Universitat de Barcelona

Estudio observacional de variables clínicas de pacientes operados de cirugía cardíaca y evaluación de su influencia sobre el pronóstico vital

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"ESTUDIO OBSERVACIONAL DE VARIABLES CLÍNICAS DE PACIENTES OPERADOS DE CIRUGÍA CARDÍACA Y EVALUACIÓN DE SU INFLUENCIA SOBRE EL PRONÓSTICO VITAL"

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"La unidad en la variedad, y la variedad en la unidad es la ley suprema del universo" (Isaac Newton, 1642-1727).

"Cridem qui som i que tothom ho escolti. [...] que tot està per fer i tot és possible" (poema Ara mateix, Del llibre "L'àmbit de tots els àmbits", Miquel Martí i Pol, 1929-2003)

"[...] El amor lo vence todo." (Carta a los Corintios. San Pablo).

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PRODUCCIÓN CIENTÍFICA EN RELACIÓN CON LA TESIS

1. **Publicaciones internacionales realizadas.**

   - **Lopez-Delgado JC**, Esteve F, Javierre C, Perez X, Torrado H, Carrio ML, Rodríguez-Castro D, Farrero E, Ventura JL. **Short-term independent mortality risk factors in patients with cirrhosis undergoing cardiac surgery.** *Interact Cardiovasc Thorac Surg*. 2013 Mar; 16(3):332-338. doi: 10.1093/icvts/ivs501.

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   - **Lopez-Delgado JC**, Esteve F, Torrado H, Rodríguez-Castro D, Carrio ML, Farrero E, Javierre C, Ventura JL, Manez R. **Influence of acute kidney injury on short- and long-term outcomes in patients undergoing cardiac surgery: risk factors and prognostic value of a modified RIFLE classification.** *Crit Care*. 2013 Dec 13;17(6):R293.

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   - **Lopez-Delgado JC**, Esteve F, Javierre C, Torrado H, Carrio ML, Rodríguez-Castro D, Farrero E, Ventura JL, Manez R. **Predictors of long-term mortality in patients with cirrhosis undergoing cardiac surgery.** *J Cardiovasc Surg (Torino)*. 2014 Mar 18. [Epub ahead of print]

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2. **Trabajos en proceso editorial.**

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- **Lopez-Delgado JC**, Esteve F, Javierre C, Torrado H, Rodriguez-Castro D, Carrio ML, Farrero E, Skaltsa K, Ventura JL, Mañez R. **Evaluation of serial arterial lactate levels over short and long-term mortality in patients after cardiac surgery.** *PLoS One*.
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3. Comunicaciones a Congresos.

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- Conferenciante invitado en **11th INTERCEPT (INTERnational Course on Extracorporeal Perfusion Technologies) and Outcome Meeting**. Milan, April 3rd - 5th , 2014. **JC. Lopez-Delgado** (Barcelona). Session VII The forgotten organs - sons of a lesser god **"Liver cirrhosis and cardiac surgery"**. Ver programa en http://www.intercepteurope.org/intercept.php
- Capítulo de Libro ***Diet & Nutrition in Critical Care*** "Magnesium and cardiac surgery in the critical care setting". Editorial ***Springer®***.

ABREVIATURAS

UCI: Unidad de Cuidados Intensivos.

EuroSCORE: European System for Cardiac Operative Risk Evaluation.

APACHE: Acute Physiology and Chronic Health Evaluation.

SAPS: Simplified Acute *Physiology Score. Sequential.*

SOFA: *Organ Failure Assessment.*

IMC: Índice de Masa Corporal.

AKI: Acuyte Kidney Injury.

PaO2/FIO2: Presión parcial de oxígeno arterial/ Fracción inspirada de oxígeno.

CEC: circulación extracorporeal.

HUB: Hospital Universitari de Bellvitge.

CEIC: *Comité d' Ètica i Assajos Clínics de Hospital Universitari de Bellvitge.*

LA: Lactato arterial.

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1. RESUMEN DEL PROYECTO

Antecedentes del tema: La supervivencia en postoperados de cirugía cardíaca es un parámetro básico de la indicación y calidad de la cirugía realizada. La mayor parte de los *scores* pronósticos específicos (Parsonnet score, *European System for Cardiac Operative Risk Evaluation* (EuroSCORE),…etc.) sólo tienen en cuenta variables preoperatorias. La mayor parte de estudios se centran, por su mayor facilidad y rapidez, en el pronóstico en la fase hospitalaria, cuando, en general y para el paciente, es claramente más importante el pronóstico a largo plazo, que es el que realmente puede validar la operación, ya que simplemente sobrevivir a ella no puede implicar suficientemente que su elección fue correcta.

Hipótesis: La complejidad de la cirugía realizada hace que las fases operatoria y postoperatoria en UCI sean fundamentales para la supervivencia de estos pacientes. Algunas variables han sido estudiadas y se ha descrito su capacidad para predecir/precisar la mortalidad a corto plazo. No obstante, siguen sin conocerse los factores postoperatorios que tienen un mayor impacto, incluso en la supervivencia a largo plazo. Los *scores* pronósticos no asociados clásicamente a cirugía cardíaca y sí al paciente crítico, tales como el *Acute Physiology and Chronic Health Evaluation* (APACHE), el *Simplified Acute Physiology Score* (SAPS) y el *Sequential Organ Failure Assessment* (SOFA), junto con las variables postoperatorias, podrían tener una gran utilidad a la hora de evaluar el pronóstico de los pacientes de cirugía cardíaca.

Objetivos: Evaluar el impacto de diversas variables, preoperatiorias (como la cirrosis y el Índice de Masa Corporal (IMC)) y postoperatorias (grado de disfunción renal o *Acute Kidney Injury (AKI),* los niveles de lactato arterial y el cociente Presión parcial de oxígeno arterial/ Fracción inspirada de oxígeno (PaO2/FIO2), sobre el pronóstico a corto y largo plazo en postoperados de cirugía cardíaca en una UCI de tercer nivel. En algunas poblaciones específicas, evaluar los *scores* pronósticos y su utilidad en el pronóstico de dichos pacientes, especialmente a largo plazo.

Metodología: Las variables han sido estudiadas según su correspondencia a un órgano o sistema. Se realizó una recogida de variables en la base de datos de la unidad de

postoperados de cirugía cardíaca en el servicio de Medicina Intensiva del Hospital Universitari de Bellvitge, desde enero de 2004 hasta junio de 2010, con un seguimiento de la mortalidad a largo plazo.

Resultados: Las variables postoperatorias, tales como el lactato arterial, la PaO2/FIO2, y el desarrollo de *AKI*, así como las variables preoperatorias, tales como el grado de disfunción hepática y el IMC, tienen en su mayoría un impacto pronóstico claro e importante a corto plazo en el postoperado de cirugía cardíaca y en la mayoría de casos en la supervivencia a largo plazo de dichos pacientes. Asimismo, en su mayoría son predictores asociados a la morbilidad. Los *scores* pronósticos de UCI y/o específicos para una determinada población (como los pacientes con hepatopatía) tendrían un mejor poder predictivo que aquellos diseñados para cirugía cardíaca.

2. INTRODUCCIÓN

La mortalidad y la morbilidad hospitalarias de los pacientes operados de cirugía cardíaca han ido disminuyendo a pesar de su envejecimiento progresivo y su complejidad creciente [1, 2].

Valorar la calidad asistencial de la cirugía cardíaca realizada en un hospital requiere compararla con la de otros centros, pero resulta difícil por las diferencias existentes en la selección de los pacientes estudiados y la gran heterogeneidad. El EuroSCORE y el Parsonnet son *scores* específicos para estimar el riesgo en cirugía cardíaca. Sin embargo, su poder predictivo disminuye en determinadas poblaciones, llegando a no ser válido. Además, no tiene en cuenta variables intraoperatorias como el tiempo de circulación extracorpórea (CEC), ni variables postoperatorias [3]. El desarrollo de las *scores* de mortalidad locales basados en las características epidemiológicas podría mejorar la predicción de la mortalidad a corto y largo plazo.

La población de pacientes que se someten a cirugía cardíaca es cada vez más heterogénea. Con la tendencia hacia una mayor longevidad, los pacientes tienden a presentar una mayor morbilidad y sufren enfermedades crónicas con mayor frecuencia [4]. Los *scores* específicos de cirugía cardíaca evalúan sólo el estado preoperatorio de los pacientes, y pueden ser inexactos en el caso de complicaciones quirúrgicas. Los *scores* propios de la UCI (APACHE, SAPS y SOFA entre otros) llegan a reflejar el estado crítico del paciente, incluyendo enfermedades crónicas en su evaluación [5, 6]. Sin embargo, no son específicos para la cirugía cardíaca y requieren 24 horas para el cálculo. En definitiva, los médicos tienen pocas herramientas disponibles para evaluar el pronóstico inmediato tras la cirugía cardíaca y su predicción, con el cambio progresivo en las características esta población, supone un desafío.

La cirrosis hepática se ha convertido en un factor de riesgo importante para la cirugía cardíaca debido a la mayor morbilidad y mortalidad que estos pacientes pueden sufrir en comparación con el resto de población sometida a cirugía cardíaca [7]. A pesar de que la población de pacientes cirróticos que son sometidos para cirugía cardíaca es pequeño y las recomendaciones provienen de pequeñas series, se prevé un incremento de incidencia de esteatohepatitis no alcohólica, especialmente en los países occidentales dónde los factores de riesgo para esta enfermedad son los mismos que para la patología

cardiovascular, y en consecuencia de pacientes cirróticos que serán sometidos a este tipo de cirugía [8].

La obesidad es un factor de riesgo para el desarrollo de *diabetes mellitus*, hipertensión arterial y enfermedad cardiovascular [9]. La obesidad y un IMC elevado son han sido considerados factores de riesgo para la cirugía cardíaca, teniéndose en cuenta para la estratificación del riesgo de muerte perioperatoria [10, 11]. Sin embargo, algunos informes han mostrado una mejor tasa de supervivencia en pacientes con sobrepeso y obesos en comparación con aquellos con IMC normal cuando son sometidos a cirugía cardíaca (*obesity paradox*). Por otro lado, la obesidad se asocia con una mayor morbilidad en la UCI desde el punto de vista respiratorio e infeccioso [12, 13]. Debido a las contradicciones existentes en la literatura queda por dilucidar la influencia real del IMC en la mortalidad de pacientes sometidos a cirugía cardíaca.

El desarrollo de *AKI* tras la cirugía cardíaca adulta se asocia con una mayor morbilidad y mortalidad, con una incidencia entre el 1% hasta el 30% dependiendo de la definición utilizada [14-17] y que conduce a la terapia de reemplazo renal (TRR) del 1% al 5% de los casos [18]. Recientemente ha sido validada una escala *RIFLE* (*risk, injury, failure, loss of kidney function, and end-stage renal failure*) modificada para la evaluación del AKI en los pacientes sometidos a cirugía cardíaca, objetivándose una mejor predictibilidad [16]. La función cardíaca tiene una estrecha relación con la función renal, y viceversa, reflejando esta última con la diuresis la situación hemodinámica del paciente en la mayoría de casos [19]. Asimismo, la imposibilidad de adecuar el balance hídrico es un factor importante en el pronóstico de estos pacientes, por lo que la prevención en el desarrollo de *AKI* es fundamental tras la cirugía cardíaca [20].

La PaO2/FIO2 es un indicador del estado de oxigenación y uno de los criterios diagnósticos para el síndrome de *Distress* respiratorio agudo en adultos (SDRA) [21-24]. Una baja PaO2/FIO2 se ha asociado con una mayor mortalidad y estancia hospitalaria en pacientes ingresados en la UCI [25-27]. Durante la cirugía se producen alteraciones del intercambio gaseoso secundario a varios factores (atelectasias, reacción inflamatoria pulmonar provocada por la cirugía, p.ej.), lo que puede llevar a una disfunción pulmonar postoperatoria incluso en pacientes sin lesión pulmonar preexistente. A pesar de la optimización en la ventilación mecánica durante y después de la cirugía, una PaO2/FIO2 en rangos inferiores puede ser reflejo de una disfunción pulmonar persistente que puede influir en el pronóstico de los pacientes [28].

Una concentración de lactato arterial elevado es común tras de la cirugía cardíaca, siendo un marcador de insuficiencia cardíaca asociado a una mayor morbi-mortalidad [29-32]. Su fisiopatología ha sido relacionada con un desequilibrio entre el transporte y las necesidades de oxígeno, aunque recientemente se ha especulado aumento de la producción de lactato a través del metabolismo aeróbico [33]. A pesar que un lactato superior a 3mmol/l durante el postoperatorio ha sido asociado a una mayor mortalidad, su valor como herramienta pronóstica no ha sido totalmente estudiado.

La supervivencia de los postoperados de cirugía cardíaca es un parámetro de calidad de la cirugía realizada. Sin embargo, este aspecto no se ha estudiado suficientemente, suponiendo un área de especial interés para la investigación clínica por las múltiples implicaciones que de ello se derivan. Lo mismo ocurre con las variables postoperatorias.

A pesar que el postoperatorio de cirugía cardíaca se realiza mayoritariamente en UCIs, los *scores* pronósticos de medicina intensiva son raramente publicados, impidiendo una comparación real de los resultados de los diferentes centros hospitalarios.

3. HIPÓTESIS DE TRABAJO, UNIDAD TEMÁTICA Y OBJETIVOS

La complejidad de la cirugía realizada hace que el postoperatorio de cirugía cardíaca en UCI sea fundamental para la supervivencia de estos pacientes. Hay múltiples variables descritas para predecir la mortalidad a corto plazo. No obstante, en muchos casos, siguen sin conocerse los factores postoperatorios que tienen un impacto mayor en la supervivencia a largo plazo. Los *scores* de UCI, como el APACHE, SAPS y SOFA podrían tener un claro interés a la hora de evaluar el pronóstico y la supervivencia de estos pacientes [34, 35].

En nuestros diferentes estudios analizamos una serie de variables clínicas de pacientes operados de cirugía cardíaca, en su mayoría sometidos a CEC, con diversas patologías y evaluamos las correlaciones con el pronóstico a corto y largo plazo, mostrando entre ellos una unidad temática concreta y coherente respecto a la hipótesis planteada en esta tesis.

El objetivo principal del estudio es evaluar la posible influencia de diversas variables, especialmente postoperatorias, sobre el pronóstico a corto y largo plazo en postoperados de cirugía cardíaca en una UCI especializada de tercer nivel de un hospital universitario.

Como objetivos secundarios, en los diferentes estudios realizados, se han evaluado la influencia y capacidad predictiva de los *scores* pronósticos utilizados habitualmente.

4. METODOLOGÍA

El Hospital Universitari de Bellvitge (HUB) es un centro hospitalario y universitario de titularidad pública, construido en 1972 en el término municipal de L´Hospitalet de Llobregat (Barcelona), que pertenece al Institut Català de la Salut y está acreditado como centro hospitalario de 3er nivel. Es centro hospitalario de referencia para una población de 1.300. 000 personas y de más de 2 millones para algunas especialidades.

La UCI 3-2 del servicio de Medicina Intensiva del HUB era, en el periodo de estos estudios, la especializada en el control postoperatorio agudo de los pacientes operados de Cirugía Cardíaca en nuestro hospital. En el periodo de estudio se ingresaban en ella alrededor de 450 pacientes al año, siendo entre 15 y 20 de ellos transplantados cardíacos. Estos últimos no se incluyeron por su heterogeneidad y la particular naturaleza de su fisiopatología respecto al resto de los pacientes.

Los datos fueron recogidos en la base de datos de la unidad de manera sistemática y prospectiva. Se recogieron datos de filiación, epidemiológicos, antecedentes médico-quirúrgicos de los pacientes, tipo de cirugía, datos operatorios y datos postoperatorios. Respecto a este último apartado, se realizó especial énfasis en las variables que fueron recogidas de manera sistemática en el postoperatorio y que se corresponden con las de control habitual que establece el protocolo del Servicio de Medicina Intensiva. No se realizó ningún procedimiento añadido para completar los datos del estudio. Dichas variables se asocian a diversos órganos y sistemas que influyen en el pronóstico de nuestros pacientes, siendo básicamente respiratorias (PaFiO2), renales (creatinina), hematológicas (hemograma y coagulación), marcadores de daño cardíaco (troponina I), y marcadores de perfusión tisular (lactato). Asimismo, se recogieron las complicaciones y las necesidades terapéuticas (necesidad de terapia de reemplazo renal, tiempo en ventilación mecánica, etc.).

La naturaleza de los estudios realizados es observacional y la base de datos incluía 3092 pacientes consecutivos operados de cirugía cardíaca desde enero de 2004 hasta junio de 2010. Se realizó un seguimiento de 2592 de ellos hasta enero de 2013, mediante el *Registre Central de Persones Assegurades*, siendo el seguimiento promedio de 7,5±3,5 años.

El estudio de variables se realizó según su correspondencia a un órgano o sistema. Por ejemplo, la proporción entre la presión parcial de oxígeno en sangre arterial y la

fracción inspirada de oxígeno (PaFiO2) es un marcador indirecto de la oxigenación y secundariamente de la función pulmonar. En otras ocasiones, se evaluó de forma genérica la función de un órgano, como es el caso de la función hepática [2].

Los aspectos fundamentales y las variables asociadas que se han estudiado en este proyecto son:

- Pacientes cirróticos operados de cirugía cardíaca: implicaciones en la mortalidad a corto y largo plazo, y variables asociadas.
- Influencia de la PaFiO2 seriada postoperatoria como marcador pronóstico de mortalidad a corto y largo plazo en cirugía cardíaca.
- La lactatemia como marcador pronóstico de la mortalidad a corto y largo plazo en postoperados de cirugía cardíaca.
- Comprobación de un posible mejor pronóstico en pacientes obesos sometidos a cirugía cardíaca (*obesity paradox* [36]) y evaluación del IMC en el pronóstico de la cirugía cardíaca.
- Impacto del desarrollo de daño renal agudo o *AKI* en el pronóstico tras cirugía cardíaca.

4.1. Análisis estadístico

La distribución de las variables cuantitativas se expresó con la media y la desviación estándar, y las diferencias entre ellas se analizaron con el test de la *t de Student* o el de la *U* de Mann-Whitney. Las diferencias entre los grupos se compararon con el análisis de la varianza y la corrección de Bonferroni. Las que no seguían una distribución normal se expresaron como mediana (intervalo intercuartílico) y las diferencias entre grupos, con la prueba no paramétrica de Kruskal-Wallis. Las variables cualitativas se expresaron como valor absoluto y porcentaje, y las diferencias entre ellas se analizaron con el test de la χ^2.

Se estimó el riesgo preoperatorio mediante los análisis estadísticos anteriormente descritos. Los análisis de regresión multivariable contemplaron la regresión logística y la regresión de Cox para determinar si potenciales variables pronósticas se asociaban o no con la mortalidad a corto y largo plazo, respectivamente. Los diferentes modelos relacionan las variables seleccionadas, tanto preoperatorias como postoperatorias, con la mortalidad con un nivel de significación P=<0,1 en el análisis univariable.

En todos los casos, el test de Kolmogorov-Smirnov fue evaluado para valorar la distribución normal de la población y las diferentes variables continuas estudiadas para garantizar los resultados de los modelos de regresión. La curva ROC (*Receiver Operating Curve*) se utilizó para evaluar los valores de corte de los *scores* para la mortalidad a corto y largo plazo, teniendo en cuenta las diferentes áreas bajo la curva.

La supervivencia se estimó durante el seguimiento de todos los pacientes a partir del alta hospitalaria mediante curvas de Kaplan-Meier.

Los datos se analizaron con el programa PASW statistics 13.0 (SPSS Inc., Chicago, Illinois, USA).

Respecto a análisis estadísticos más específicos, en variables continuas se requirió la colaboración de la Dra. K. Skaltsa (Departament de Salut Pública, Universitat de Barcelona) para la búsqueda de puntos de corte asociados a mayor mortalidad basándonos en análisis coste-función [37, 38]. El ANOVA de medidas repetidas fue utilizado para diferenciar las diversas concentraciones séricas de lactato arterial entre grupos de pacientes. Asimismo, el cálculo del área bajo la curva fue usado para estimar la intensidad en la producción de niveles de lactato. Por último, señalar que el *propensity score* se usó para ajustar las variables preoperatorias e intraoperatorias en la evaluación de la *obesity paradox* en nuestra población.

4.2. Aspectos éticos

Los diferentes estudios realizados recibieron la aprobación ética necesaria del CEIC (*Comité d' Ètica i Assajos Clínics de Hospital Universitari de Bellvitge*) para la realización de los mismos y para la recogida de variables en la base de datos clínicos anteriormente mencionada. En ningún momento han sido utilizados datos personales de los pacientes para el mencionado estudio, ni para otros derivados de la misma base de datos.

5. RESULTADOS

5.1. Publicaciones internacionales: resumen, comentarios y publicación original.

• Lopez-Delgado JC, Esteve F, Javierre C, Perez X, Torrado H, Carrio ML, Rodríguez-Castro D, Farrero E, Ventura JL. **Short-term independent mortality risk factors in patients with cirrhosis undergoing cardiac surgery**. *Interact Cardiovasc Thorac Surg*. 2013 Mar; 16(3):332-338. doi: 10.1093/icvts/ivs501.
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Resumen: La cirrosis hepática es un factor de riesgo para la aquellos pacientes que requieren cirugía cardíaca. A pesar de que se ha identificado un peor pronóstico según el grado de cirrosis, no se han identificado factores pronósticos postoperatorios en esta población específica ni determinado qué *scores* son mejores predictores de mortalidad.
Estudiamos 58 pacientes cirróticos sometidos a cirugía cardíaca entre 2004 y 2009. 42 (72%) fueron sometidos a cirugía valvular, 9 (16%) a revascularización coronaria y 7 (12%) a cirugía combinada. 34 (58%) fueron clasificados como Child-Turcotte-Pugh clase A, 21 (36%) como clase B y 3 (5%) como clase C.
La mortalidad hospitalaria fue del 12% (n=7). Los pacientes con Child B y Child C mostraron peor supervivencia hospitalaria (Log-rank test, P=0.035). El análisis univariante objetivó las siguientes variables asociadas a la mortalidad a corto plazo: *International Normalized Ratio* (1.5±0.24 vs 2.2±0.11, P<0.001), plaquetas preoperatorias (171±87 vs 113±52 $l \cdot nl^{-1}$, P=0.031), hemoglobina preoperatoria (11.8±1.8 vs 10.2±1.4 $g \cdot dl^{-1}$, P=0.021), necesidad de concentrados de hematíes (2±3.4 vs 8.5±8 unidades, P<0.001), PaO2/FiO2 12h tras ingreso en UCI (327±84 vs 257±78, P=0.04), presión venosa central inicial (11±3 vs 16±4 mmHg, P=0.02) y niveles de lactato arterial 24h tras ingreso en UCI (1.8±0.5 vs 2.5±1.3 mmol l^{-1}, P=0.019). El análisis multivariable reveló a la presión venosa central inicial como el único factor independiente asociado a mortalidad hospitalaria (P=0.027). La curva ROC mostró al MELD (*Model for End-Stage Liver Disease*) como el *score* con mejor poder predictivo en esta población (AUC: 90.5±4.4%; sensibilidad: 85.7%; especificidad: 83.7%).

Comentarios: Se aprecia que en pacientes bien seleccionados y sin otras graves comorbilidades, a pesar de grados ligeros o moderados de cirrosis hepática los resultados hospitalarios de la cirugía cardíaca pueden ser buenos. También se valoran los diferentes *scores* y se identifica la presión venosa central al ingreso en UCI como el único factor predictivo independiente de mortalidad intrahospitalaria.

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Short-term independent mortality risk factors in patients with cirrhosis undergoing cardiac surgery

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Abstract

OBJECTIVES: Cirrhosis represents a serious risk in patients undergoing cardiac surgery. Several preoperative factors identify cirrhotic patients as high risk for cardiac surgery; however, a patient's preoperative status may be modified by surgical intervention and, as yet, no independent postoperative mortality risk factors have been identified in this setting. The objective of this study was to identify preoperative and postoperative mortality risk factors and the scores that are the best predictors of short-term risk.

METHODS: Fifty-eight consecutive cirrhotic patients requiring cardiac surgery between January 2004 and January 2009 were prospectively studied at our institution. Forty-two (72%) patients were operated on for valve replacement, 9 (16%) for a CABG and 7 (12%) for both (CABG and valve replacement). Thirty-four (58%) patients were classified as Child-Turcotte-Pugh class A, 21 (36%) as class B and 3 (5%) as class C. We evaluated the variables that are usually measured on admission and during the first 24 h of the postoperative period together with potential operative predictors of outcome, such as cardiac surgery scores (Parsonnet, EuroSCORE), liver scores (Child-Turcotte-Pugh, model for end-stage liver disease, United Kingdom end-stage liver disease score) and ICU scores (acute physiology and chronic health evaluation II and III, simplified acute physiology score II and III, sequential organ failure assessment).

RESULTS: Seven patients (12%) died in-hospital, of whom 5 were Child-Turcotte-Pugh class B and 2 class C. Comparing survivors vs non-survivors, univariate analysis revealed that variables associated with short-term outcome were international normalized ratio (1.5 ± 0.24 vs 2.2 ± 0.11, $P < 0.0001$), presurgery platelet count (171 ± 87 vs 113 ± 52 l nl^{-1}, $P = 0.031$), presurgery haemoglobin count (11.8 ± 1.8 vs 10.2 ± 1.4 g dl^{-1}, $P = 0.021$), total need for erythrocyte concentrates (2 ± 3.4 vs 8.5 ± 8 units, $P < 0.0001$), PaO_2/FiO_2 at 12 h after ICU admission (327 ± 84 vs 257 ± 78, $P = 0.04$), initial central venous pressure (11 ± 3 vs 16 ± 4 mmHg, $P = 0.02$) and arterial blood lactate concentration 24 h after admission (1.8 ± 0.5 vs 2.5 ± 1.3 mmol l^{-1}, $P = 0.019$). Multivariate analysis identified initial central venous pressure as the only independent factor associated with short-term outcome ($P = 0.027$). The receiver operating characteristic curve showed that the model for end-stage Liver disease score had a better predictive value for short-term outcome than other scores (AUC: $90.5 \pm 4.4\%$; sensitivity: 85.7%; specificity: 83.7%), although simplified acute physiology score III was acceptable.

CONCLUSIONS: We conclude that central venous pressure could be a valuable predictor of short-term outcome in patients with cirrhosis undergoing cardiac surgery. The model for end-stage liver disease score is the best predictor of cirrhotic patients who are at high risk for cardiac surgery. Sequential organ failure assessment and simplified acute physiology score III are also valuable predictors.

Keywords: Liver cirrhosis • Cardiac surgery • Short-term outcome • Mortality scores

INTRODUCTION

Liver cirrhosis (LC) is a major preoperative risk factor in general surgery, especially in cardiac surgery, and the outcome is strongly related to the severity of liver disease in those patients [1]. While in patients without advanced cirrhosis, cardiac surgery can be done safely, the risk of mortality is higher in patients with Child-Turcotte-Pugh (CTP) class B and C or with a model for end-stage liver disease score (MELD) >13 [1, 2]. Preoperative total plasma bilirubin, cholinesterase concentrations, the European system for cardiac operative risk evaluation (EuroSCORE), and the cardiopulmonary bypass (CPB) time have all been identified as potential predictors of mortality after cardiac surgery in those patients [3]. However, evidence comes mainly from several small studies; due to the lack of evidence from larger pools of data, postoperative risk factors remain unidentified.

At the same time, the option of liver transplantation as a treatment for patients with LC has produced an increase in survival rate and the evaluation of concomitant cardiac diseases, which increase post-liver transplantation complications, is crucial for

preoperative risk assessment [4]. Thus, cardiac surgery is increasing in those patients awaiting liver transplantation.

Consequently, identifying independent cardiac surgery postoperative risk factors for these patients is an area of interest if we want to optimize post-surgical management and improve outcome, especially post-surgical short-term outcome. In this study, we also wanted to evaluate different score systems to identify the best predictors of mortality.

MATERIALS AND METHODS

This study is a prospective single-centre observational study performed between January 2004 and January 2009. Data were included from 58 patients of 2825 (2.05%) consecutive patients with LC who underwent cardiac surgery in our hospital. The study was approved by the Institutional Ethics Committee. All of the patients had previously granted permission for their medical records to be used for research purposes.

LC was confirmed either by a liver biopsy or by clinical, laboratory and radiographical findings showing impaired hepatic function and portal hypertension. The CTP classification score was calculated for each patient (CTP A: 7 points; CTP B: 8–10 points; CTP C >11 points); 58.6% ($n = 34$) were classified as class A, 36.2% ($n = 21$) as class B and 5.2% ($n = 3$) as class C.

We evaluated demographical data and comorbidities, treatment before surgery, bedside variables currently measured during the first 24 h of postoperative clinical care and complications/mortality during their admission. We calculated different prognosis scores for each patient: cardiac surgery scores (Parsonnet and EuroSCORE), liver scores (CTP, MELD and United Kingdom end-stage liver disease (UKELD)), ICU scores (sequential organ failure assessment (SOFA), acute physiology and chronic health evaluation (APACHE II and III) and simplified acute physiology score (SAPS II and III). Finally, survival of the different CTP groups was shown to allow a comparison with previous studies.

Cardiac surgical procedures were performed in all patients using median sternotomy, standard cardiopulmonary bypass (CPB) with moderate hypothermia (34°C) and antegrade cardioplegia. A mean aortic pressure of >60 mmHg was maintained during surgery. For revascularization, we used the internal thoracic artery (or bilateral if possible) and saphenous vein grafts. Bypass graft flow was assessed for each graft by Doppler transit time flowmetry. Protamine was administered to reverse heparin according to standard practice. For CABG surgery, aspirin was routinely administered within the first 6 h after surgery following local protocol.

Statistical analysis

Statistical analysis was carried out using PASW statistics 13.0 (SPSS, Inc., Chicago, IL, USA). Data are expressed as mean ± standard deviation. We analyzed differences in data between survivors and non-survivors. For the comparisons between the two groups, the Mann–Whitney *U*-test was used or, when appropriate (after applying the one-sample Kolmogorov–Smirnov test), the two-sample *t*-test was used. The χ^2 test was used to evaluate categorical prognostic factors. A multivariate analysis was carried out using Cox regression model to show independent risk mortality factors for short-term outcome. Finally, the survival analysis of the CTP group was carried out with the Kaplan–Meier estimator for comparison with previous studies. Receiver operating characteristic (ROC) curve analyses were applied to determine optimal cut-off values of the different scores for short-term outcome and to further evaluate the predictive power between them, considering the differences of the areas under the empirical ROC curves. A *P*-value of 0.05 was considered statistically significant in all cases.

RESULTS

Forty-one patients (70.7%) were operated on for valve replacement, 10 (17.2%) for CABG, 6 of them off-pump, and 7 (12.1%) were both CABG and valve replacement. Only 3 patients underwent urgent surgery for CABG and there were no mortalities. All valve replacement operations were isolated: 34 (70.83%) were mitral valve and 14 (29.17%) aortic. None of the patients had previously undergone cardiac surgery.

Aetiologies for LC were predominantly infective hepatitis in 37.9% (hepatitis C, 31% ($n = 18$); hepatitis B, 6.9% ($n = 4$)), alcohol-induced in 34.48% ($n = 20$) and both hepatitis C and alcohol-induced in 13.8% ($n = 8$). The other were cryptogenic cirrhosis/others (13.8% ($n = 8$)) and in 10 patients, it was because of hepatocellular carcinoma.

The preoperative characteristics of the patients, including treatment before surgery, presented differences between groups in platelet and haemoglobin counts (see Table 1). Three patients were admitted previously at the cardiology department for acute myocardial infarction and underwent urgent cardiac surgery during the same admission. None of them died and their postoperative course did not differ from the other patients. Six patients (10.3%) were treated with aspirin before going into theatre. None of them died and there was no significant increase in terms of postoperative bleeding or the requirement for blood products. Despite there being a considerable prevalence of preoperative risk factors in these patients in terms of LC complications due to end-stage liver disease, there was no significant difference between survivors and non-survivors.

There were no differences in intraoperative data, such as CPB time and aortic cross-clamping (ACC), between groups (see Table 2). Differences in postoperative data were observed for arterial oxygen pressure of O_2 and the fraction of inspired oxygen ratio (PaO_2/FiO_2), which was higher in survivors, while central venous pressure (CVP) on admission and 24 h after admission and arterial lactate (AL) 24 h after admission were all lower in survivors. With regard to postoperative morbidities, patients who died required a large amount of erythrocyte concentrates during admission, but there were no differences in terms of post-surgical bleeding. They also required a longer period on mechanical ventilation, and had a greater need for renal replacement therapies (RRT) and an increased the need for vasopressors.

The median ICU stay was 9 ± 10 days, with a difference between groups (7.7 ± 1 in the survival group vs 13 ± 5 in the non-survival group, $P = 0.002$). However, the median hospital stay was 34 ± 20 days, and there were no differences between groups (21 ± 3 vs 14.8 ± 5.6 days).

Mortality was 12.1% ($n = 7$); 5 patients were CTP class B and 2 class C. The class C died of multi-systemic organ failure (MSOF), and the class B MSOF (3 patients) and septic shock (2). Short-term survival evaluated by Kaplan–Meier in Fig. 1 showed differences between CTP class groups (log-rank test, $P = 0.035$).

Table 1: Demographics and baseline data

	All patients (*n* = 58)	Survivors (*n* = 51)	Non-survivors (*n* = 7)	*P*
Sex (male)	69% (40)	70.6% (36)	57.1% (4)	0.66
Age (years)	64.9 ± 11.6	64.6 ± 9.6	66.9 ± 10.3	0.92
Body mass index (kg m^{-2})	27 ± 4.2	27.6 ± 4.6	26.6 ± 4.2	0.54
Hypertension	56.9% (33)	54.9% (28)	71.4% (5)	0.68
Diabetes mellitus	32.8% (19)	33.3% (17)	28.6% (2)	0.99
Dyslipidaemia	34.5% (20)	33.3% (17)	42.9% (3)	0.68
Chronic renal insufficiency	8.6% (5)	7.8% (4)	14.3% (1)	0.12
Renal failure (on dialysis)	19% (11)	19.60% (10)	14.3% (1)	0.60
Creatinine before surgery (mmol l^{-1})	114.4 ± 100.8	106.4 ± 93.7	170.3 ± 136.3	0.15
Previous stroke	12.1% (7)	12.1% (7)	0%	0.23
Chronic obstructive pulmonary disease	17.2% (10)	17.6% (9)	14.3% (1)	0.85
Active smokers	19% (11)	19.6% (10)	14.3% (1)	0.64
Active alcohol consumption	3.4% (2)	3.9% (2)	0%	0.84
Previous atrial fibrillation	31% (18)	33.3% (17)	14.3% (1)	0.78
Previous myocardial infarction	12.1% (7)	11.8% (6)	14.3% (1)	0.53
NYHA class III-IV	34.5% (20)	35.3% (18)	28.6% (2)	0.58
On B-blockers	39.7% (23)	41.2% (21)	28.6% (2)	0.69
On statins	25.9% (15)	25.50% (13)	28.6% (2)	0.92
Ascites (moderate to severe)	69% (40)	70.6% (36)	57.1% (4)	0.45
Oesophageal varices	31% (18)	25.5% (13)	71.4% (5)	0.26
Variceal bleeding	17.2% (10)	17.6% (9)	14.3% (1)	0.14
Encephalopathy	34.5% (20)	33.3%(17)	42.9% (3)	0.32
Hypertrophic cardiomyopathy	31% (18)	31.4% (16)	28.6% (2)	0.68
Dilated cardiomyopathy	27.6% (16)	27.5% (14)	28.6% (2)	0.91
Left ventricular ejection fraction (%)	60.3 ± 11.2	59.3 ± 11.7	62.6 ± 10.1	0.71
Pulmonary arterial pressure (mmHg)	48.7 ± 15.4	48.6 ± 15.6	49.4 ± 14.7	0.58
Haemoglobin before surgery (g dl^{-1})	11.67 ± 1.82	11.8 ± 1.8	10.2 ± 1.05	**0.02**
Platelet count before surgery (1 nl^{-1})	164 ± 85	171 ± 87	113 ± 52	**0.03**
International normalized ratio before surgery	1.5 ± 0.83	1.45 ± 0.15	1.85 ± 0.76	0.18

NYHA: New York Heart Association classification. Results are expressed as mean ± standard deviation or percentage.

Some scores revealed significant differences between groups: only SAPS II and III and SOFA showed a significant predictive power similar to that of UKELD and CTP. However, the other ICU scores and cardiac surgery scores were not as useful (Table 3). In order to compare differences between potential preoperative (liver and cardiac surgery scores) and postoperative (ICU scores) predictions, predictors of outcome for short-term survival were analysed using the ROC curve. The MELD score was the most predictive for in-hospital mortality. The optimal cut-off level for the MELD score was 18.5, with a sensitivity of 85.7% and a specificity of 83.7% (Fig. 2).

To evaluate preoperative and postoperative predictors of death for all patients, a multivariate analysis was conducted (See Table 4). We included those univariate factors that showed significant differences between groups in a Cox regression model. After risk adjustment, the multivariate analysis revealed initial CVP as the only independent factor associated with short-term outcome.

DISCUSSION

The most important finding of the current study was that in terms of predicting short-term mortality, both the CVP and the SAPS III and SOFA postoperative scores proved effective. We also confirm that the MELD score is the most effective predictor for the short-term outcome of these patients and that the CTP is a valuable score.

In view of the complexity of the procedure, the postoperative morbidity and mortality rates reported in the literature are considerably higher for cirrhotic patients undergoing cardiac surgery. [1]. The mortality risk in CTP class B patients is around 32.2% and increases to 66.6% in CTP class C patients [2]; even when there is a minimal degree of impaired liver function in combination with elective surgery, the incidence of complications significantly increases [5]. Careful patient selection is critical to improve surgical outcome in patients with cirrhosis [6]; however, there is a lack of factors that can be used to identify the mortality risk in those patients, especially after surgery. The lower incidence of comorbidities, the low number of urgent procedures and the low mortality rate found highlight the importance of our aim to select and prepare those patients for surgery carefully. Despite the differences in haemoglobin and platelets, the groups of survivors and non-survivors were comparable in almost all presurgery risk factors except the grade of liver disease. The major need for erythrocyte concentrates and RRT needs in non-survivors can be explained by initial presurgical lower haemoglobin, post-surgical INR differences and larger ICU admission and presence of MSOF as a cause of mortality, respectively. In any case, the risk of mortality increases with the deterioration of liver function [1–6].

In this scenario, INR progressively worsens during cirrhosis, also reflecting the current status of end-stage liver disease [7]. The replenishment of vitamin K-dependent factors beyond a normal INR has not proven its efficacy; however, individualized heparin and protamine dosing, antifibrinolytic drug administration,

Table 2: Intraoperative and postoperative data

	All patients ($n = 58$)	Survivors ($n = 51$)	Non-survivors ($n = 7$)	*P*
Intraoperative data				
Isolated CABG	15.5% (9)	15.7% (8)	14.3% (1)	0.95
Isolated valve surgery	72.4% (42)	72.50% (37)	71.4% (5)	0.97
CABG + valve surgery	12.1% (7)	11.76% (6)	14.3% (1)	0.78
Fluid balance during surgery (ml)	1325 ± 850	1250 ± 980	1350 ± 785	0.58
Aortic cross-clamping time (min)	72 ± 44	74 ± 41	69 ± 50	0.85
Cardiopulmonary bypass time (min)	107 ± 37	106 ± 48	108 ± 53	0.35
Postoperative data and major postoperative complications				
Ventilation time (days)	5.3 ± 10.2	3.16 ± 7.7	21 ± 12	**0.01**
PaO_2/FiO_2 on admission	287 ± 95	293 ± 93	245 ± 110	0.28
PaO_2/FiO_2 12 h after admission	318 ± 86	327 ± 84	257 ± 78	**0.04**
PaO_2/FiO_2 24 h after admission	307 ± 75	315 ± 70	253 ± 96	0.23
MAP on admission (mmHg)	83 ± 15	85 ± 15	74 ± 18	0.72
MAP 24 h after admission (mmHg)	80 ± 10	80 ± 9	75 ± 11	0.51
CVP on admission (mmHg)	12 ± 3.6	11.4 ± 3	16.5 ± 4.4	**0.02**
CVP 24 h after admission (mmHg)	12.5 ± 3.6	12 ± 2.8	16.3 ± 6	**0.002**
Need of vasoactive drugs (h)	165 ± 197	112 ± 109	490 ± 304	**0.016**
Low cardiac output syndrome	31% (18)	34% (17)	14.3% (1)	0.25
Perioperative myocardial infarction	7.1% (4)	6.1% (3)	14.3% (1)	0.18
Arterial lactate on admission (mmol l^{-1})	2.6 ± 1.4	2.45 ± 1.3	3.6 ± 1.5	0.22
Arterial lactate 24 h after admission (mmol l^{-1})	1.9 ± 0.7	1.8 ± 0.5	2.5 ± 1.3	**0.02**
Creatinine 24 h after surgery (mmol l^{-1})	129 ± 108	118 ± 101	207 ± 138	0.15
Urine output first 24 h (ml)	1860 ± 650	1920 ± 570	1444 ± 1066	0.28
Need for renal replacement therapy	8.9% (5)	2% (1)	57.1% (4)	**<0.0001**
Albumin (g l^{-1})	27 ± 4	27.9 ± 4	27.8 ± 4.5	0.97
International normalized ratio on admission	1.8 ± 0.32	1.5 ± 0.24	2.2 ± 0.11	**<0.0001**
Drainage loss first 12 h (ml)	464 ± 308	446 ± 299	595 ± 369	0.34
Major bleeding	1.7% (1)	2% (1)	0%	0.85
Re-exploration	19% (11)	21.6% (11)	0%	0.15
Erythrocyte concentrates (units)	3 ± 4.6	2 ± 30.4	8.5 ± 8	**<0.0001**

CABG: coronary artery bypass graft; PaO_2/FiO_2: arterial partial pressure of O_2 and fraction of inspired oxygen ratio; MAP: mean arterial pressure; CVP: central venous pressure. Results are expressed as mean ± standard deviation or percentage.

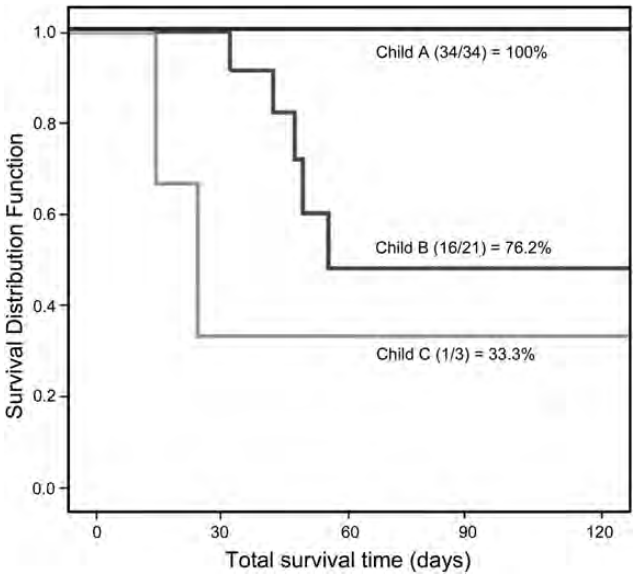


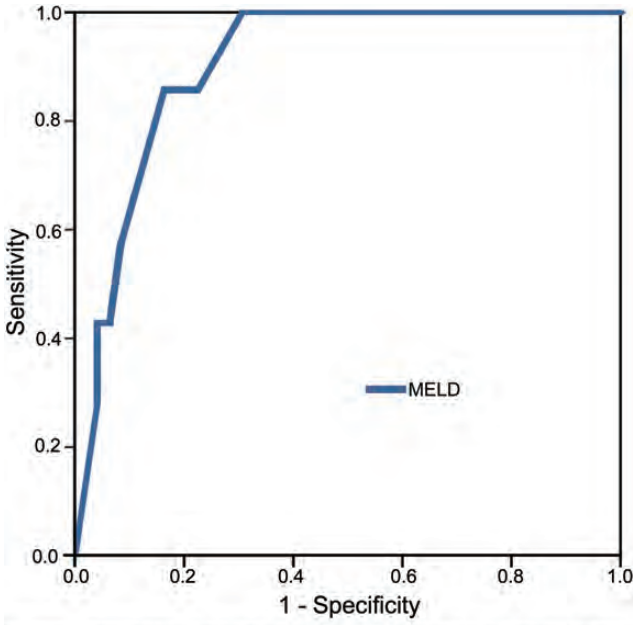
Figure 1: Short-term survival rate according to Child-Turcotte-Pugh score.

minimization of blood loss and dilution, and minimal CPB time could still potentially help achieve surgical homeostasis [8]. All these efforts are reflected in our results, in that drainage loss was similar between the groups despite postoperative INR differences.

Table 3: Evaluation scores for risk assessment

	All patients ($n = 58$)	Survivors ($n = 51$)	Non-survivors ($n = 7$)	*P*
SAPS II	25.2 ± 10.4	24 ± 9.4	33.7 ± 14	**0.02**
SAPS III	45.9 ± 10.8	44.7 ± 10.4	54.7 ± 10.4	**0.045**
APACHE II	13.9 ± 4.4	13.5 ± 4.1	16.8 ± 6	0.19
APACHE III	56.6 ± 18	55.2 ± 17.7	66.7 ± 19	0.17
SOFA	5.41 ± 2.72	6.6 ± 2.7	9.4 ± 1.8	**0.005**
EuroSCORE	6.48 ± 3	6.2 ± 2.9	8.8 ± 3.7	0.12
Parsonnet score	9.43 ± 6.42	9.2 ± 6.4	11.4 ± 6.8	0.43
MELD	16 ± 5.4	15 ± 4.57	23 ± 5.4	**0.005**
UKELD	49.8 ± 4	49.6 ± 4	52.6 ± 3.3	**0.044**
CTP class A	58.6% ($n = 34$)	66.7% ($n = 34$)	0%	**<0.0001**
CTP class B	36.2% ($n = 21$)	31.4% ($n = 16$)	71.4% ($n = 5$)	**<0.0001**
CTP class C	5.2% ($n = 3$)	2% ($n = 1$)	28.6% ($n = 2$)	**0.045**

SAPS: simplified acute physiology score; APACHE: acute physiology and chronic health evaluation; SOFA: sequential organ failure assessment; EuroSCORE: European system for cardiac operative risk evaluation; MELD: model for end-stage liver disease score; UKELD: United Kingdom end-stage liver disease; CTP: Child-Turcotte-Pugh. Results are expressed as mean ± standard deviation or percentage.



	AUC± SD %(95% CI)	Cut-off levels	Sensitivity	Specificity	*P* value
SAPS III	74.8±8.8 (57.5-92.1)	50.5	71.4%	73.5%	**0.035**
SOFA	80.2 ± 7.2 (66 - 94)	7.5	85.7%	59.2%	**0.01**
MELD	90.5 ± 4.4 (81.9-99.1)	18.5	85.7%	83.7%	**0.001**

Figure 2: ROC curve for MELD. Comparison of AUC for MELD, SAPS III and SOFA scores. AUC: area under curve; ROC: receiver operating characteristic curve; SAPS: simplified acute physiology score; SOFA: sequential organ failure assessment; MELD: model for end-stage liver disease score; NS: non-statistically significant. Results are expressed as mean ± standard deviation or percentage.

Table 4: Multivariate analysis-dependent variable deceased during admission

	Hazards ratio (95% CI)	*P*
Age	0.99 (0.94–1.036)	0.69
Platelets before surgery	0.96 (0.79–1.164)	0.68
Haemoglobin before surgery	1.13 (0.65–1.97)	0.66
INR after surgery	0.65 (0.17–2.51)	0.53
CVP on admission	0.88 (0.78–0.98)	**0.027**
SOFA score	1.02 (0.86–1.195)	0.82
AL 24 h after admission	0.81 (0.60–1.094)	0.17
PaO_2/FiO_2 12 h	1.00 (0.99–1.004)	0.91
MELD score	0.96 (0.87–1.068)	0.48

PaO_2/FiO_2: arterial partial pressure of O_2 and fraction of inspired oxygen ratio; AL: arterial lactate; INR: international normalized ratio; CVP: central venous pressure; SOFA: sequential organ failure assessment; MELD: model for end-stage liver disease score.

Hyperlactataemia in the ICU, which is caused mainly by shock, is associated with increased mortality and is more frequent when respiratory and/or renal failures are/is present [9]. It predicts postoperative mortality after cardiac surgery with a maximum lactate threshold of ≥4.4 mmol l^{-1} in the first 10 h after operation [10]. Arterial lactate tends to be higher in non-survivors, though it could be a reflection of a presurgery poorer liver function or an exacerbation of liver dysfunction in the setting of CPB.

Arterial partial pressure of O_2 and fraction of inspired oxygen ratio (PaO_2/FiO_2) is a new marker for outcome in some types of cardiac surgery [11]. Hypoxaemia depicted by low PaO_2/FiO_2 is common after CPB, and is associated with different variables, which are preoperative factors (age, obesity, chest X-ray with alveolar oedema 1 h after surgery, decreased baseline PaO_2/FiO_2, previous myocardial infarction), operative factors (emergency surgery, prolonged CPB) and postoperative factors (low cardiac output syndrome (LCOS), renal failure, persistent hypothermia 2–6 h after surgery, requirement for re-exploration). A lower PaO_2/FiO_2 ratio correlated significantly with the time required to carry out extubation and also to lung injury. However, in these patients, it had minimal effect on the postoperative clinical course [12]. Although PaO_2/FiO_2 12 h after admission was lower in non-survivors, it did not have an independent significant impact on the outcome of surgery.

Central venous pressure (CVP) is used almost universally to guide fluid therapy in hospitalized patients. Some authors argue that there is a very poor relationship between CVP and blood volume as well as the inability to predict the haemodynamic response to a fluid challenge, being a good indicator of blood volume only at the extreme values [13]. Nevertheless, the conditions that influence CVP are well known, and as such, CVP remains a useful tool for evaluating haemodynamic status if it is performed under controlled conditions. CVP has the great advantage of being able to be measured at the patient's bedside without the need of invasive methods [14]. Dynamic evaluation of CVP could be a reliable predictor of fluid responsiveness in patients under mechanical ventilation, similar to the variation of arterial pulse pressure after cardiac surgery [15]. The proper use of CVP requires a good understanding of the waveform because higher values and CVP tracing are concordant with rhythm disorders, tricuspid regurgitation, cardiac tamponade, cardiac restriction and decreased thoracic compliance [16]. Limitations of CVP as a surrogate variable of preload are caused by the influence of intrathoracic and intra-abdominal pressures. However, these limitations do not impair the importance of CVP as the downstream pressure of the systemic venous system [15, 16]. We found CVP on admission to be the only independent factor for short-term outcome in the multivariate analysis. We hypothesize that CVP could be a surrogate marker of underscored right ventricular failure, which can ultimately explain the higher mortality, but we cannot confirm our suspicions [17]. However, non-survivors did not receive larger amount of fluids in the operating theatre and did not have higher incidences of low cardiac output syndrome, which could have biased the CVP measurement.

Although EuroSCORE is widely accepted in Europe as a valuable score in cardiac surgery, in some populations, it does not have acceptable discriminatory ability. The development of local mortality risk scores corresponding to local epidemiological characteristics may improve the prediction of outcome [18]. In addition, it does not take into account surgical prognosis factors such as CPB time, and there is a lack of postoperative factors to determine short-term mortality [19]. Furthermore, the Parsonnet score does not consider specific liver variables. However, some authors suggest that it can be used to predict 3-month mortality, prolonged length of stay and specific postoperative complications such as renal failure, sepsis and respiratory failure in the whole context of cardiac surgery [20]. Because mortality in cirrhotic patients undergoing cardiac surgery is associated with liver function, liver scores such as the MELD or CTP score are

associated with outcome [1–3]. Our results confirm that the MELD score most reliably identifies cirrhotic patients at high risk for cardiac surgery, with better results than in previous studies [1]. In our study, the MELD values are higher than in previous studies, which is likely due to the high number of patients awaiting liver transplantations. With regard to CTP class scores, mortality was higher in postoperative cardiac surgery in patients with a CTP score of class C [1–3, 6]. With a lack of a large data series in previous research or a significant number of CTP class C patients described in the literature, there is no basis for comparison. The UKELD score can be used as a local score for end-stage liver disease, but unlike the MELD, it has never been evaluated in cardiac surgery. It evaluates sodium as well as INR, creatinine and bilirubin, identifying cirrhotic patients with the poorest quality of life and the highest complication rates [21]. The results for UKELD were statistically significant in the univariate analysis, though the ROC analysis raised doubts about its clinical relevance. ICU scores such as SOFA have been previously evaluated in cardiac surgery for the same purpose [22]. We also evaluated other ICU scores such as SAPS and APACHE. SAPS scores provided an estimate of the risk of death without having to specify a primary diagnosis, including liver failure and cardiac insufficiency grade [23]. Furthermore, higher SAPS scores have been associated with a poor quality of life, with the worst outcome occurring both before and after general surgery [24]; additionally, a higher mortality rate was found in elderly patients (>70 years) who required dialysis after cardiac surgery [25]. In our series, SAPS III provided an acceptable level of sensitivity and specificity, comparable with MELD results of other series [1]. APACHE scores were not found to be valuable tools.

Our study presents certain limitations. The most important are that it was a single-centre observational study. Results should be viewed cautiously due to the low number of patients and events. However, we have shown a larger number of patients than any other study of this kind to date, and observed a low mortality rate despite the level of end-stage liver disease.

We conclude that cardiac surgery can be performed safely in CTP class A and in some class B patients. Regarding CTP class C patients, due to the higher mortality in these patients, we think that liver function should be optimized prior to cardiac surgery, perhaps even performing liver transplantation. Indeed, synchronous surgery has modestly improved survival in some patients with cirrhosis when cardiac surgery is needed [4]. We recommend proper preoperative selection of patients and apply careful operative and postoperative management, especially in terms of fluid balance, in order to increase the short-term survival rate. A higher CVP at ICU admission may make physicians aware of a patient's prognosis, but its efficacy as a valuable predictor of short-term outcome must be shown in future studies. MELD score and postoperative ICU scores such as SAPS III and SOFA can be used to predict short-term outcome in those patients. In our opinion, in the setting of end-stage liver disease and cardiac surgery, postoperative evaluation is as important as preoperative evaluation in terms of predicting short-term outcome.

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Conflict of interest: none declared.

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eComment. The prognostic role of the MELD score in cardiac surgery patients with cirrhosis

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doi:10.1093/icvts/ivt024

We read with great interest the recent article from Lopez-Delgado and colleagues [1], addressing the very relevant issue of risk prediction of short-term outcome in cirrhotic patients undergoing cardiac surgery. However, we believe that some aspects of the article require further comment.

The Model for End-stage Liver Disease (MELD) score has gained increased popularity over recent years in predicting the risk of mortality in patients with liver cirrhosis undergoing cardiac surgery. We agree that the MELD score improves prognostic assessment of those cirrhotic patients who are at an extraordinary high risk for major postoperative complications and in-hospital mortality after conventional cardiac surgery. Crucially, the mean preoperative MELD score is usually significantly lower among survivors compared to non-survivors. In a recent article [2], our group showed that in 57 cirrhotic patients, those with a MELD score of 13.5 points or higher had a significantly higher risk of dying within 30 days of cardiac surgery (mortality: 56%) than patients with a MELD score less than 13.5 (mortality: 9%) with a sensitivity of 82.0% and a specificity of 78.5%. With an even better discriminative power, Lopez-Delgado and colleagues [1] demonstrate the prognostic strength of the MELD score for in-hospital mortality with a cut-off value of 18.5. In this study of 58 patients who underwent cardiac surgery, predominantly for isolated primary valve replacement (71%), the overall mortality rate was 12% at 4 months. This figure consisted exclusively of in-hospital mortality, without any further documentation of deaths in the early period after discharge from the cardiac surgery clinic. These promising results are inconsistent with our data [2] and those of another recently published retrospective study of 109 such patients from Germany [3], in which the overall in-hospital mortality was found to be 29.8% and 26%, respectively. Unfortunately, the work of Lopez-Delgado and colleagues [1] focused only on short-term outcome, with a follow-up of just four months. Therefore, their work contributes no additional knowledge to this field, as they simply did not incorporate a long enough follow-up period to enable comparison with other studies in this area. In addition, the authors state that," … the MELD values are higher than in previous studies, which is likely due to the high number of patients awaiting liver transplantation … " It would be interesting to know if and how many of these cirrhotic patients indeed underwent liver transplantation after successful cardiac surgery, and particularly whether this institutional strategy could have influenced short-term survival. Clarity on this specific issue and a better longitudinal data collection would add important information to the study. However, irrespective of early outcomes achieved, it is clear that 1-year survival rate drops significantly in cirrhotic patients considered to be at elevated operative risk. In our study [2] and according to the MELD score, 1-year survival was 23.8% with MELD score >13.5 as compared to 74.6% with MELD score <13.5. Roughly 75% of our high-risk cirrhotic population died after conventional cardiac surgery, despite adherence to strict preventive and postoperative management strategies, and expert consultation before and up to one year after surgery. Disappointingly, cardiac surgery in such individuals is performed before liver transplantation candidacy and often on an emergency basis with little if any impact on long-term survival.

Although liver cirrhosis alone is not considered a contraindication for surgery, cirrhotic patients with a high preoperative MELD score, in whom life expectancy per se is also limited by non-cardiac comorbidities, should be treated with caution. In this sub-group of cirrhotic patients, we believe that conventional cardiac surgery should not be performed.

Conflict of interest: none declared

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ORIGINAL ARTICLES - Adult Cardiac:
Juan Carlos Lopez-Delgado, Francisco Esteve, Casimiro Javierre, Xose Perez, Herminia Torrado, Maria L. Carrio, David Rodríguez-Castro, Elisabet Farrero, and Josep Lluís Ventura

Short-term independent mortality risk factors in patients with cirrhosis undergoing cardiac surgery

Interact CardioVasc Thorac Surg (2013) 16(3): 332-338 first published online December 12, 2012 doi:10.1093/icvts/ivs501

Abstract Full Text (HTML) Full Text (PDF)

eReply. Re: The prognostic role of the MELD score in cardiac surgery patients with cirrhosis

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Hospital Universitari Bellvitge, Barcelona, Spain

We thank P. Tossios, A. Karatzopoulos, and M. Thielmann for their comments and suggestions. Long-term outcome is becoming increasingly important today in decision-making regarding health care interventions. Risk prediction in cirrhotic patients undergoing cardiac surgery is a good example. In our article we focused on post-operative predictors of short-term outcome [1]. We agree that there is a need for a report on follow-up and on long-term outcome.

The Model for End-stage Liver Disease (MELD) score improves the prognostic assessment of these patients but has never been compared with other ICU scores applying a long-term perspective. Indeed, the emergence of hidden non-alcoholic fatty liver disease in Western countries, which has the same risk factors as cardiovascular disease, and the fact that cardiovascular diseases are a common cause of mortality in liver cirrhosis raise doubts about the appropriateness of MELD for evaluating long-term outcome in cirrhotic patients undergoing cardiac surgery [2]. A scoring system, which includes a cardiovascular and/or multi-organ approach seems more reasonable in addition to the liver assessment, which the MELD score offers because life expectancy is no longer limited only by non-cardiac comorbidities [2].

Tossios and associates mentioned that our in-hospital mortality is low compared with other studies. This may be due to the fact that in our institution, when these patients need cardiac surgery, we apply strict selection criteria after consultation with hepatologists, surgeons, cardiologists, anaesthesiologists and the intensive care team. This institutional strategy, based on a multi-team approach, has produced excellent results and does not only apply to these patients.

In our preliminary long-term results, the 1-year survival rate fell in cirrhotic child A (from 100% to 94%) and B (from 76.2% to 71%). Using a MELD score cut-off of 13.5 to compare with other studies [3], the 1-year survival was 76% with MELD score > 13.5, compared to 95% with MELD score < 13.5. If we use our optimal cut-off value of 18.5, 1-year survival was 95% with MELD score > 18.5 compared to 50% with MELD score < 18.5, which has a better discriminative power.

In our opinion, patients should be carefully evaluated prior to surgery after consultation with a variety of specialists in order to avoid high mortality. We believe that liver transplantation should be considered in certain patients before cardiac surgery. However, more research is needed to establish when, and in which clinical situations it is indicated.

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Conflict of Interest:
None declared

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eComment. The prognostic role of the MELD score in cardiac surgery patients with cirrhosis

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Interactive CardioVascular and Thoracic Surgery doi:10.1093/icvts/ivt024

We read with great interest the recent article from Lopez-Delgado and colleagues [1], addressing the very relevant issue of risk prediction of short-term outcome in cirrhotic patients undergoing cardiac surgery. However, we believe that some aspects of the article require further comment.

The Model for End-stage Liver Disease (MELD) score has gained increased popularity over recent years in predicting the risk of mortality in patients with liver cirrhosis undergoing cardiac surgery. We agree that the MELD score improves prognostic assessment of those cirrhotic patients who are at an extraordinary high risk for major postoperative complications and in-hospital mortality after conventional cardiac surgery. Crucially, the mean preoperative MELD score is usually significantly lower among survivors compared to non-survivors. In a recent article [2], our group showed that in 57 cirrhotic patients, those with a MELD score of 13.5 points or higher had a significantly higher risk of dying within

30 days of cardiac surgery (mortality: 56%) than patients with a MELD score less than 13.5 (mortality: 9%) with a sensitivity of 82.0% and a specificity of 78.5%. With an even better discriminative power, Lopez-Delgado and colleagues [1] demonstrate the prognostic strength of the MELD score for in-hospital mortality with a cut -off value of 18.5. In this study of 58 patients who underwent cardiac surgery, predominantly for isolated primary valve replacement (71%), the overall mortality rate was 12% at 4 months. This figure consisted exclusively of in-hospital mortality, without any further documentation of deaths in the early period after discharge from the cardiac surgery clinic. These promising results are inconsistent with our data [2] and those of another recently published retrospective study of 109 such patients from Germany [3], in which the overall in-hospital mortality was found to be 29.8% and 26%, respectively. Unfortunately, the work of Lopez-Delgado and colleagues [1] focused only on short-term outcome, with a follow-up of just four months. Therefore, their work contributes no additional knowledge to this field, as they simply did not incorporate a long enough follow-up period to enable comparison with other studies in this area. In addition, the authors state that, "...the MELD values are higher than in previous studies, which is likely due to the high number of patients awaiting liver transplantation..." It would be interesting to know if and how many of these cirrhotic patients indeed underwent liver transplantation after successful cardiac surgery, and particularly whether this institutional strategy could have influenced short-term survival. Clarity on this specific issue and a better longitudinal data collection would add important information to the study. However, irrespective of early outcomes achieved, it is clear that 1-year survival rate drops significantly in cirrhotic patients considered to be at elevated operative risk. In our study [2] and according to the MELD score, 1-year survival was 23.8% with MELD score > 13.5 as compared to 74.6% with MELD score < 13.5. Roughly 75% of our high-risk cirrhotic population died after conventional cardiac surgery, despite adherence to strict preventive and postoperative management strategies, and expert consultation before and up to one year after surgery. Disappointingly, cardiac surgery in such individuals is performed before liver transplantation candidacy and often on an emergency basis with little if any impact on long-term survival.

Although liver cirrhosis alone is not considered a contraindication for surgery, cirrhotic patients with a high preoperative MELD score, in whom life expectancy per se is also limited by non-cardiac comorbidities, should be treated with caution. We believe that conventional cardiac surgery should not be performed in this sub-group of cirrhotic patients.

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Submit response

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• Lopez-Delgado JC, Esteve F, Javierre C, Torrado H, Carrio ML, Rodríguez-Castro D, Farrero E, Ventura JL, Manez R. **Predictors of long-term mortality in patients with cirrhosis undergoing cardiac surgery**. *J Cardiovasc Surg (Torino).* 2014 Mar 18. [Epub ahead of print]

Resumen: La supervivencia a largo plazo de los pacientes cirróticos sometidos a cirugía cardíaca está pobremente descrita en la literatura científica. Tampoco han sido estudiados qué *scores* son mejores predictores de mortalidad a largo plazo. Realizamos un seguimiento en aquellos pacientes que no fallecieron en el hospital (n=51) para estudiar dichos elementos en nuestra población durante 4 años aproximadamente.

La mortalidad durante el seguimiento fue del 23.5% (n=12). El análisis univariante objetivó las siguientes variables asociadas a mejor supervivencia: niveles de lactato arterial 24h tras ingreso en UCI (1.7±0.4 *vs*. 2.1±0.7 mmol·l-1, P=0.03) y volumen de orina en las primeras 24 h (2029±512 *vs*. 1575±627 mL, P=0.03). La curva ROC mostró al SAPS III como el *score* con mejor poder predictivo a largo plazo en esta población (AUC: 77.4±0.76%; sensibilidad: 83.3%; especificidad: 64.9%, P=0.005). El análisis multivariable reveló al SAPS III (P=0.02) y el volumen de orina en las primeras 24h como el único factor independiente asociado a la mortalidad a largo plazo (P=0.02). La supervivencia global en toda la muestra (n=59) fue peor según el grado de hepatopatía (82.4% para Child A, 47.6% para Child B y 33.3% para Child C; P=0.001).

Comentarios: En un seguimiento postoperatorio de alrededor de 4 años se observa que la supervivencia en los pacientes cirróticos postcirugía cardíaca es bastante buena, especialmente en los con Child A, en los que es algo superior al 82%. El volumen de orina en las primeras 24 h es el mejor predictor de mortalidad a largo plazo. Estos datos justifican, en pacientes cirróticos razonablemente seleccionados, la práctica de las operaciones cardíacas.

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Predictors of long-term mortality in patients with cirrhosis undergoing cardiac surgery

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***Aim*. Little is known regarding the long-term outcome in cirrhotic patients undergoing cardiac surgery. The objective of this study was to identify preoperative and postoperative mortality risk factors and to determine the best predictors of long-term outcome.**

***Methods*. Fifty-eight consecutive cirrhotic patients requiring cardiac surgery between January 2004 and January 2009 were prospectively studied at our institution. Seven patients (12%) died. A complete follow-up was performed in the whole survival group until November 2012 (mean 46 ± 28 months). Variables usually measured on admission and during the first 24h of the postoperative period were evaluated together with cardiac surgery scores (Parsonnet, EuroSCORE), liver scores (Child-Turcotte-Pugh, Model for End-Stage Liver Disease, United Kingdom end-stage Liver Disease score), and ICU scores (Acute Physiology and Chronic Health Evaluation II and III, Simplified Acute Physiology Score II and III, Sequential Organ Failure Assessment).**

***Results*. Twelve patients (23.5%) died during follow-up; six were Child class A and six class B. Comparing survivors *vs*. non-survivors using univariate analysis, variables associated with better long-term outcome were lower arterial lactate 24 h after admission (1.7±0.4 *vs*. 2.1±0.7 mmol·l^{-1}, P=0.03) and higher urine output in the first 24 h (2029±512 *vs*. 1575±627 mL, P=0.03). The receiver operating characteristic curve showed that the Simplified Acute Physiology Score III score had the best predictive value for long-term outcome (AUC: 77.4±0.76%; sensitivity: 83.3%; specificity: 64.9%, P=0.005). Multivariate analysis identified Simplified Acute Physiology Score III score (P=0.02) and urine output in the first 24 h (P=0.02) as independent factors associated with long-term outcome. Long-term survival was 82.4% for Child A, 47.6% for Child B and 33.3% for Child C (P=0.001).**

***Conclusion*. Long-term survival in cirrhotic patients requiring cardiac surgery is a more valuable prognostic measure than short-term survival. Urine output in the first 24h may be a valuable predictor of long-term outcome in these patients. The Simplified Acute Physiology Score III is also useful.**

KEY WORDS: Liver - Cardiac surgical procedures - Kidney - Liver cirrhosis.

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Liver cirrhosis (LC) represents a major preoperative risk factor in cardiac surgery, and long-term outcomes in cirrhotic patients are also related to the severity of their liver disease.[1] However, complications after cardiac surgery, especially during Intensive Care Unit (ICU) stay, may produce sequelae that can influence long-term survival.[2] Data on this issue are scarce and the postoperative risk factors that influence long-term outcome are poorly understood. At the same time, the option of liver transplantation before or after cardiac surgery has increased the survival rate in those patients.[3] In previous work we identified independent postcardiac surgery risk factors for short-term mortality in these patients.[4] In the present study we again assessed postsurgical variables, together with cardiac, liver and ICU prognosis scores, in order to identify the best predictors of long-term outcome.

Materials and methods

This study is a prospective, single-centre, observational study performed between January 2004 and January 2009. Fifty-eight patients with liver cirrhosis, out of a total of 2825 (2.%) consecutive patients undergoing cardiac surgery in our hospital, had a short-term mortality of 12% (N.=7). Data were included from the whole survival group (N.=51) with complete follow-up until November 2012, with a mean follow-up of 46±28 months (follow-up range: 18 to 89 months). The follow-up study was approved by the Institutional Ethics Committee. All patients had previously granted permission for their medical records to be used for research purposes. The follow-up was performed using the Catalan Health Central Registry (*Registre Central de Persones Assegurades*, RCA).

LC was confirmed either by a liver biopsy or by clinical, laboratory, and radiographic findings showing impaired hepatic function and portal hypertension. The Child-Turcotte-Pugh (CTP) classification score was calculated for each patient (CTP A, 5-6 points; CTP B, 7-9 points; CTP C >11 points); 66.7% (N.=34) were classified as class A, 31.4% (N.=16) as class B and 2% (N.=1) as class C.

We evaluated demographic data and comorbidities, treatment before surgery, bedside variables currently measured during the first 24 h of postoperative clinical care and complications/mortality during admission. We calculated different prognosis scores for each patient: cardiac surgery scores (Parsonnet and EuroSCORE), liver scores (CTP, MELD and United Kingdom end-stage Liver Disease [UKELD]), ICU scores (Sequential Organ Failure Assessment, SOFA), Acute Physiology and Chronic Health Evaluation (APACHE II and III) and Simplified Acute Physiology Score (SAPS II and III).

Cardiac surgical procedures were performed in all patients using median sternotomy, standard cardiopulmonary bypass (CPB) with moderate hypothermia (34 °C) and anterograde cardioplegia. We used a priming solution with albumin in combination with crystalloid fluid for CBP. A mean aortic pressure of >60 mmHg was maintained during surgery. For revascularization we used the internal thoracic artery (or bilateral if possible) and saphenous vein grafts. Bypass graft flow was assessed for each graft by Doppler transit time flowmetry. Protamine was administered to reverse heparin according to standard practice. For CABG surgery, aspirin was routinely administered within the first 6 h after surgery following the local protocol.

Statistical analysis

Statistical analysis was carried out using PASW statistics 13.0 (SPSS Inc., Chicago, IL, USA). Data are expressed as means (or medians for non-parametric values) ± standard deviation. We analyzed differences in data between survivors and non-survivors using the Mann-Whitney *U* test or, when appropriate (after applying the one-sample Kolmogorov-Smirnov test), the two-sample *t*-test. The χ^2-test was used to evaluate categorical prognostic factors. A multivariate analysis was carried out using a Cox regression model to show independent risk mortality factors for long-term outcome. Finally, the survival analysis of the CTP group was carried out with the Kaplan-Meier estimator for comparison with previous studies. Receiver operating characteristic (ROC) curve analyses were applied to determine optimal cut-off values of the different scores for short-term outcome and to compare their predictive power, considering the differences of the areas under the empirical ROC curves. A P value < 0.05 was considered statistically significant in all cases.

Results

Thirty-seven patients (72.5%) were operated for valve replacement, eight (15.8%) for CABG, six of them off-pump, and six (11.7%) for both CABG and valve replacement. The three patients undergoing urgent surgery for CABG did not show fatal outcome during follow-up. Of the valve replacement operations, 31 (72.1%) were for mitral valve and twelve (27.9%) for aortic valve. None of the patients had previously undergone cardiac surgery.

Aetiologies for liver cirrhosis were predominantly alcohol-induced in 37.2% (N.=19), infective hepatitis in 36.8% (hepatitis C, 31.2% [N.=16]; hepatitis B, 5.8% [N.=3]), and both hepatitis C and alcohol-induced in 9.8% (N.=5). The origin was unknown in the remaining 20.2% (N.=8).

Prior to surgery, the groups presented only differences in terms of dyslipidemia. One of the three patients admitted for acute myocardial infarction (AMI), who underwent urgent cardiac surgery during

the same admission, died due to AMI two years after surgery. Although these patients presented a high number of preoperative risk factors in terms of LC complications due to end-stage liver disease, there was no significant difference between survivors and non-survivors regarding demographics and baseline data, except dyslipidemia rates which were higher in survivors (Table I).

There were no differences in intraoperative data, such as CPB time and aortic cross clamping (ACC), between the groups (Table II). A biological and a mechanical valve replacement was performed in 26 patients (60%) and 17 patients (40%), respectively. No statistical difference regarding valve characteristics was found in terms of survival and outcome. Differences in postoperative data were observed for arterial lactate 24 h after admission, which was higher in non-survivors, while urine output in the first 24 h was higher in survivors. With regard to postoperative morbidity, no differences were found (Table II).

The median ICU stay was 7.1±7.7 days, without any difference between groups (7.2±8.5 days in the survival group *vs.* 6.8±4.6 days in the non-survival group, P=0.86). Nor were there differences in median hospital stay (33.8±21.3 days, 32.1±22.9 days in the survival group *vs.* 39.4±14.4 days in the non-survival group, P=0.30). Mortality was 23.5% (N.=12); six patients were CTP class A and six class B. Ten patients died of cardiovascular causes, eight from AMI and two from arrhythmias related to dilated cardiomyopathy. The other two patients died of septic shock in the setting of cirrhotic complications.

We did not find differences regarding months of follow-up between the groups and the analysis of long-term survival in the follow-up group (N.=51) did not identify differences. However, long-term survival in the whole group (N.=58) evaluated by Ka-

TABLE I.—*Demographics and baseline data.*

	All patients (N.=51)	Survivors (N.=39)	Non-survivors (N.=12)	P value
Sex (male/female)	36/15	28/11	8/4	0.49
Age (years)	64.9±8	63.6±10	67.8±7.6	0.24
Body Mass Index ($kg \cdot m^{-2}$)	27±4.8	27±4.4	27±5.6	0.96
Hypertension	55% (28)	56.4% (22)	50% (6)	0.75
Diabetes Mellitus	33% (17)	30.8% (12)	41.7% (5)	0.50
Dyslipidemia	33% (17)	41% (16)	8.3% (1)	0.04
Chronic renal insufficiency	7.8% (4)	5.1% (2)	16.6% (2)	0.99
Creatinine before surgery ($mmol \cdot L^{-1}$)	135±95	106±54	157±180	0.13
Previous stroke	13.7% (7)	10.2% (4)	25%(3)	0.18
COPD	17.6% (9)	20.5% (8)	8.3% (1)	0.66
Active smokers	19.6% (10)	23% (9)	8.3% (1)	0.54
Active alcohol consumption	4% (2)	5.1% (2)	0%	0.35
Previous atrial fibrillation	33.3% (17)	30.8% (12)	41.7% (5)	0.69
Previous myocardial infarction	11.7% (6)	15.4% (6)	0%	0.31
NYHA class III-IV on discharge	17.6% (9)	15.4% (6)	25% (3)	0.18
On B-Blockers	41.2% (21)	46.2% (18)	25% (3)	0.31
On statins	25.5% (13)	30.8% (12)	8.3% (1)	0.15
Ascites (moderate to severe)	70.6% (36)	76.9% (33)	50% (6)	0.42
Oesophageal varices	25.5% (13)	25.6% (10)	25%(3)	0.89
Variceal bleeding	17.6% (9)	22.5% (7)	16.6% (2)	0.75
Encephalopathy	33.3%(17)	30.8% (12)	41.7% (5)	0.38
Hypertrophic cardiomyopathy	31.4% (16)	30.8% (12)	33% (4)	0.92
Dilated cardiomyopathy	27.5% (14)	25.6% (10)	33% (4)	0.71
LVEF (%)	58±12	60±10	56±15	0.44
PAP (mmHg)	49±17	46±15	53±16	0.31
Albumin before surgery ($g \cdot L^{-1}$)	35±4.5	33±5.5	34±6.5	0.78
Haemoglobin before surgery ($g \cdot dL^{-1}$)	11.8±1.8	11.9±1.8	11.5±1.5	0.52
Platelet count before surgery ($1 \cdot nL^{-1}$)	171±87	162±75	198±117	0.33
INR before surgery	1.45±0.15	1.5±0.24	1.58±0.26	0.34

COPD: chronic obstructive pulmonary disease; NYHA: New York Heart Association classification; LVEF: left ventricular ejection fraction; PAP: pulmonary arterial pressure; INR: International Normalized Ratio. Results are expressed as mean± standard deviation or percentage.

TABLE II.—*Intraoperative and postoperative data.*

	All patients (N.=51)	Survivors (N.=39)	Non-survivors (N.=12)	P value
Intraoperative data				
Isolated CABG	15.7% (8)	12.8% (5)	25% (3)	0.68
Isolated valve surgery	72.5% (37)	82% (32)	41.6% (5)	0.25
CABG + valve surgery	11.8% (6)	7.7% (3)	25% (3)	0.18
Aortic valve replacement	37.2% (19)	35.9% (14)	41.6% (5)	0.78
Mitral valve replacement	47% (24)	43.6% (17)	58.3% (7)	0.85
Fluid balance during surgery (mL)	1250±980	1450±670	1125±985	0.58
ACC time (min)	74±41	73±39	78±47	0.77
CPB time (min)	106±48	104±44	110±60	0.76
Postoperative data and major postoperative complications				
Ventilation time (days)	3.2±7.7	3.8±8.7	1.1±1.5	0.07
PaO_2/FiO_2 on admission	293±93	298±95	275±87	0.45
PaO_2/FiO_2 12 h after admission	327±84	336±95	288±78	0.16
PaO_2/FiO_2 24 h after admission	315±70	322±69	290±66	0.19
PaO_2/FiO_2 24 h on ICU discharge	310±74	319±56	289±80	0.26
MAP on admission (mmHg)	85±15	85±15	83±14	0.52
MAP 24 h after admission (mmHg)	80±9	80±9	79±9	0.57
MAP 48 h after admission (mmHg)	79±8	80±11	77±6	0.21
CVP on admission (mmHg)	11.4±3	11.4±3	11.4±3.1	0.98
CVP 24 h after admission (mmHg)	12±2.8	12±3.1	11.7±1.9	0.66
CVP 48 h after admission (mmHg)	12.6±3	12±3.7	13.7±3.5	0.57
Need of vasoactive drugs (h)	112±109	115±112	105±102	0.89
LCOS	34% (17)	35.9% (14)	25% (3)	0.75
PMI	6.1% (3)	5.1% (2)	8.3% (1)	0.95
AL on admission ($mmol \cdot L^{-1}$)	2.45±1.3	2.3±1.2	2.6±1.5	0.56
AL 24h after admission ($mmol \cdot L^{-1}$)	1.8±0.5	1.7±0.4	2.1±0.7	0.03
Creatinine 24h after surgery ($mmol \cdot L^{-1}$)	118±101	111±66	166±181	0.12
Urine output first 24 h (mL)	1920±570	2029±512	1575±627	0.03
Need for RRT	2% (1)	2.5% (1)	0%	0.95
Albumin ($g \cdot L^{-1}$)	27.9±4	28.2±4	27±3.6	0.97
INR on admission	1.5±0.24	1.4±0.56	1.6±0.11	0.85
Drainage loss first 12 h (mL)	446±299	468±325	371±182	0.2
Major bleeding	2% (1)	0%	8.3% (1)	0.95
Re-exploration	6.1% (3)	2.5% (1)	16.6% (2)	0.85
Erythrocyte concentrates (Units)	2.x±3.4	2.1±3.6	2.2±2.6	0.97

CABG: coronary artery bypass graft; ACC: aortic cross clamping; CPB: cardiopulmonary bypass; PaO_2/FiO_2: arterial partial pressure of O_2 and fraction of inspired oxygen ratio; LCOS: Low Cardiac Output Syndrome; PMI: perioperative myocardial infarction; AL: arterial lactate; RRT: renal replacement therapy; INR: International Normalized Ratio. Results are expressed as mean±standard deviation or percentage.

plan-Meier (Figure 1) showed differences between Child class groups (log-rank test, P=0.001).

In order to compare differences between potential preoperative (liver and cardiac surgery scores) and postoperative (ICU scores) predictions, predictors of outcome for long-term survival were studied using univariate analysis and the ROC curve (Table III). The SAPS III score presented differences between groups in the univariate analysis and had better predictive value for long-term outcome than other scores (AUC: 77.4±0.76%; sensitivity: 83.3%; specificity: 64.9%, P=0.005).

A multivariate analysis was conducted to evaluate preoperative and postoperative predictors of death for all patients (Table IV). We included the univariate factors which showed significant differences between groups in a Cox regression model. After risk adjustment, the multivariate analysis revealed urine output in the first 24 h and SAPS III to be independent factors associated with long-term outcome.

Comments

The most important finding of the current study was that in terms of predicting long-term mortality, both urine output in first 24 h and the SAPS III post-

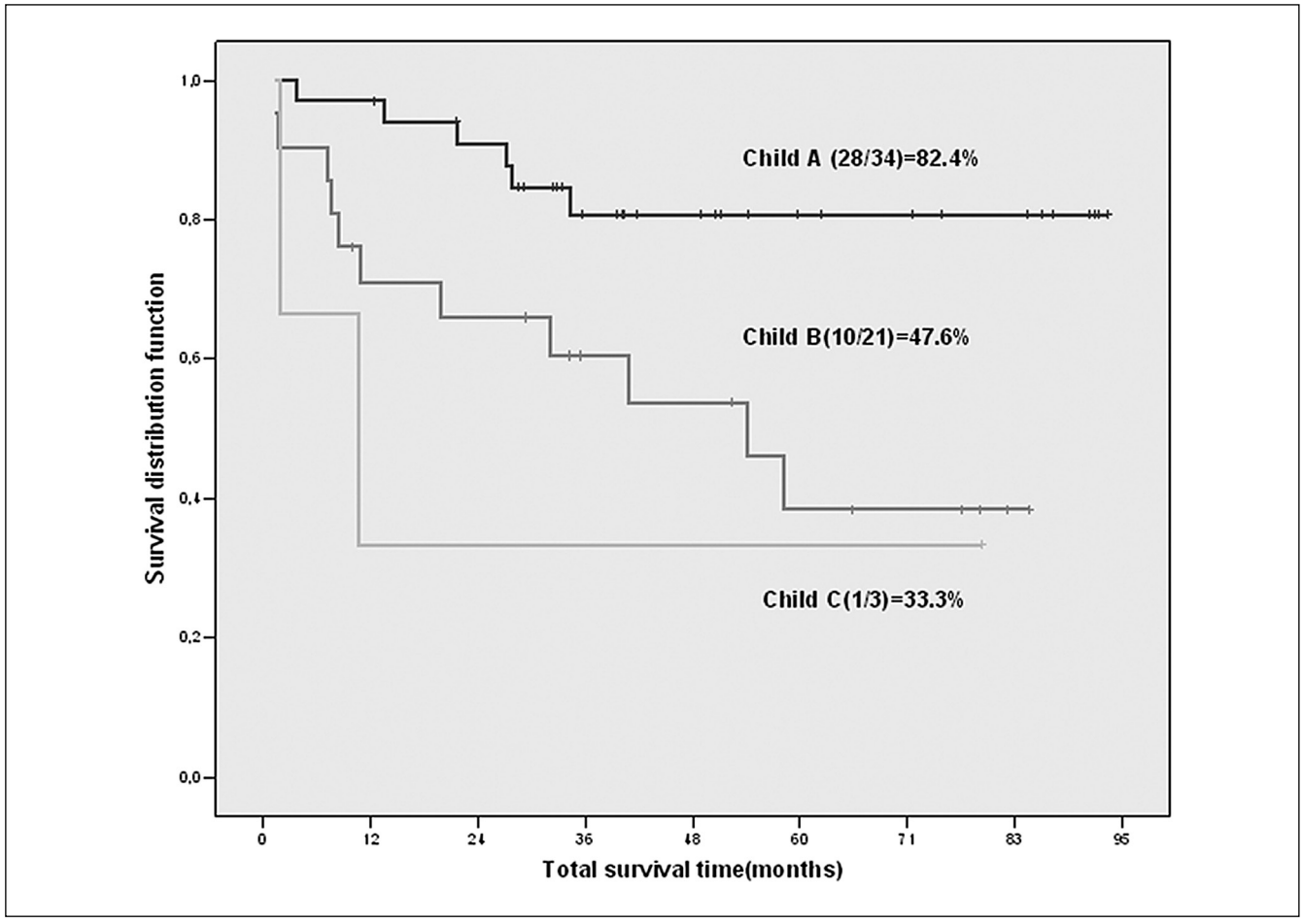

Figure 1.—Long-term survival rate according to Child-Turcotte-Pugh score.

TABLE III.—*Evaluation scores for risk assessment.*

	All patients (n = 51)	Survivors (n = 39)	Non-survivors (n = 12)	*P* value
SAPS II	24 ± 9.4	22.7 ± 8.8	28.1 ± 10.5	0.13
SAPS III	44.7 ± 10.4	44.7 ± 10.4	54.7 ± 10.4	0.002
APACHE II	13.5 ± 4.1	13.1 ± 3.5	14.6 ± 5.6	0.39
APACHE III	55.2 ± 17.7	53.5 ± 17.3	60.5 ± 18.6	0.26
SOFA	6.6 ± 2.7	6.3 ± 2.7	7.3 ± 2.6	0.28
EuroSCORE	6.2 ± 2.9	5.8 ± 2.9	7.2 ± 2.3	0.09
Parsonnet score	9.2 ± 6.4	8.9 ± 6.1	9.9 ± 7.3	0.67
MELD	15 ±4.57	14 ± 4.8	15.± 3.5	0.45
UKELD	49.6 ± 4	49.3 ± 4.2	49.8 ± 3.1	0.67
CTP class A	66.7% (n = 34)	71.8% (n = 28)	50% (n = 6)	0.28
CTP class B	31.4% (n = 16)	25.7% (n = 10)	50% (n = 6)	0.16
CTP class C	1.9% (n = 1)	2.5% (n = 1)	0%	0.85

SAPS = Simplified Acute Physiology Score. APACHE = Acute Physiology and Chronic Health Evaluation. SOFA = Sequential Organ Failure Assessment. EuroSCORE = European system for cardiac operative risk evaluation. MELD = Model for End-Stage Liver Disease score. UKELD =United Kingdom en-stage Liver Disease. CTP = Child-Turcotte-Pugh.
Results are expressed as mean ± standard deviation or percentage.

TABLE IV.—*Multivariate analysis - dependent variable deceased during follow-up.*

	Hazards ratio (95% CI)	*P* value
Age	1.022 (0.951 - 1.098)	0.55
SAPS III score	1.088 (1.011 - 1.170)	**0.02**
AL 24 h after admission	1.426 (0.511 - 3.976)	0.49
Urine output first 24 h (mL)	0.395 (0.173 - 0.903)	**0.02**

SAPS = Simplified Acute Physiology Score. AL= Arterial Lactate.

operative score proved effective. Surprisingly, liver scores such as the MELD or CTP scores were not effective predictors of long-term outcome.

The postoperative morbidity and mortality rates reported in the literature are high for cirrhotic patients undergoing cardiac surgery, especially in the long term. Mortality rates are extremely high in some series, with overall mortality ranging from 40% to 70% at approximately six years. Comparing patients according to CTP score, mortality ranged from 45% to 80%, in the Child A group and from 25% to approximately 50% in the Child B group and was extremely high in the Child C group.[1, 2, 4-7] Careful patient selection is critical in order to improve surgical outcome in patients with LC;[6] however, few factors can be used to identify the long-term mortality risk in these patients. The low incidence of comorbidities, urgent procedures and mortality rate found highlights the importance of the strategy for patient selection and preparation prior to surgery. The survival of the only Child class C patient is attributed to the performance of a liver transplantation after recovery from cardiac surgery. The Liver Unit at our hospital performed a strict control of liver function during follow-up, which explains the lower mortality due to liver-related causes.

Theoretically, the risk of mortality increases with the deterioration of liver function [6] but we did not find any increase in mortality directly related to impaired liver function. Indeed, the major causes of death during follow-up were cardiovascular. The emergence of an underscored non-alcoholic fatty liver disease or non-alcoholic steatohepatitis in western countries, which have the same risk factors for cardiovascular disease, together with a common cause of chronic liver disease may explain the ineffectiveness of liver function and liver scores in predicting long-term outcome.[8] In addition, cardiovascular diseases are a common cause of mortality in LC because the severity of liver injury and inflammation is strongly associated with an increased cardiovascular risk and an atherogenic lipid profile.[9]

Arterial lactate tended to be higher in non-survivors. We think this may reflect a poorer cardiovascular or liver function prior to surgery or an exacerbation of liver dysfunction in the setting of CPB. Hyperlactatemia predicts postoperative mortality after cardiac surgery with a maximum lactate threshold of ≥4.4 $mmol \cdot l^{-1}$ in the first 10 h after operation.[10]

Oliguria may be a feature of acute kidney injury (AKI) and renal dysfunction, a complication which is frequently present after cardiac surgery and which has a strong influence on overall survival.[11, 12] In addition, fluid overload has also been identified as an independent predictor of increased mortality in critically ill patients, especially after major surgery. Oliguria leads to positive fluid balance, resulting in vital organ edema.[13] In our previous report we found worse short-term survival in those patients with higher central venous pressure, which is related to volume status.[4] The relationship between renal function and cardiac output is well known,[14] and so our results are concordant with known physiopathology. In addition, urine output is used, together with serum creatinine, for staging patients at the RIFLE (risk, injury, failure, loss of kidney function, and end-stage renal failure) classification or acute kidney injury network criteria class, which evaluate the extent of AKI.[15] It seems that there is a trend towards a worst postoperative and even preoperative creatinine in the non-survivors group, which may hide an emerging hepatorenal syndrome (HRS) within this group. Cirrhotic cardiomyopathy is characterized by suboptimal ventricular contractile response to stress, diastolic dysfunction and QT interval prolongation, being clinically relevant during stressful conditions, such as surgery, and potentially may play a role in the pathogenesis of HRS.[16] In the same way, HRS occurs in conjunction with microcirculatory dysfunction in other organs, including the heart.[17] Finally, we have to keep in mind that renal function and development of AKI after adult cardiac surgery is associated with higher morbidity and mortality, even

in long-term scenario.[18] We hypothesized that urine output in the first 24 h, which is a main component of fluid balance in the first 24 h, may be a surrogate marker of renal function, which can ultimately explain the higher long-term mortality with lower urine output in the first 24 h.

In certain populations such as cirrhotic patients cardiac surgery scores do not have acceptable discriminatory ability, and the development of local mortality risk scores corresponding to local epidemiologic characteristics may improve the prediction of outcome.[6] Short- and long-term mortality in cirrhotic patients undergoing cardiac surgery is usually associated with liver function and so liver scores such as the MELD or CTP score have been related to outcome.[1-5] However, our results show that liver scores (MELD, UKELD and CTP class scores), cardiac surgery scores (EuroSCORE and Parsonnet score) and some ICU scores (APACHE and SOFA) do not reliably identify cirrhotic patients at high risk of poor long-term outcome. However, the SAPS III score includes items related to liver function, such as bilirubin, platelets and the presence of LC, and items related with renal function, such as creatinine, with higher scores being related to worse outcomes both before and after general surgery.[19, 20] The inclusion of renal and liver variables within SAPS III score could explain why it provided an acceptable level of sensitivity and specificity for evaluating long-term outcome in our series.

Limitations of the study

Our study presents certain limitations. The most important is its single-centre, observational design. The results should be treated with caution because the number of patients and events is not particularly large; however, the sample size was greater than those of other studies and the mortality rate observed was low despite a high percentage of end-stage liver disease.

Conclusions

We conclude that cardiac surgery has acceptable long-term outcomes in CTP class A and some class B patients. Liver function should be optimized prior to cardiac surgery in CTP class C and some class B patients, due to the lower long-term survival, and liver transplantation should be considered.[3, 4] If appropriate follow-up of the liver function is performed after cardiac surgery, liver function has a low influence on outcome in those patients. Regarding the type of valve surgery (biological *versus* mechanical) used in those patients, we think it should be evaluated individually: based on the aetiology of cirrhosis and the future need for liver transplantation, the potential interference in INR monitoring due to anticoagulant therapy together with its potential for hemorrhagic complications, and life expectancy of the patient. Lower urine output in the first 24 h following surgery may be a valuable predictor of long-term outcome in patients with LC undergoing cardiac surgery. However, its value as a predictor of long-term outcome must be demonstrated in future studies. We recommend proper preoperative selection of patients together with careful operative and postoperative management, especially in terms of fluid balance, in order to increase the long-term survival rate.

Albumin, as priming solution for CPB, seems to have a more favourable profile in terms of bleeding, although this remains controversial.[21, 22] The Simplified Acute Physiology Score III may be a good predictor of long-term outcome after cardiac surgery in these patients. In our opinion, in the setting of end-stage liver disease and cardiac surgery, postoperative evaluation may be as important as preoperative evaluation for predicting long-term outcome.

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Resumen: El desarrollo de daño renal agudo o *Acute Kidney Injury* (*AKI*) está asociado a un peor pronóstico en el paciente crítico en general, incluidos los postoperados de cirugía cardíaca. La escala *RIFLE* (*risk, injury, failure, loss of kidney function, and end-stage renal failure*) modificada mejora el poder predictivo del *AKI* en pacientes sometidos a cirugía cardíaca.

Estudiamos 2940 pacientes sometidos a cirugía cardíaca entre enero 2004 y julio 2009 con el fin de objetivar factores de riesgo para *AKI* postoperatorio, junto con la influencia del grado de *AKI* según la escala *RIFLE* modificada en la mortalidad hospitalaria y su supervivencia a largo plazo.

La incidencia de *AKI* fue del 14% (n=409). Identificamos un mayor tiempo de circulación extracorpórea, una mayor necesidad de drogas vasoactivas y un mayor lactato arterial a las 24 h tras ingresar en UCI como predictores de *AKI*. Una peor supervivencia se asoció a un mayor grado de *AKI* según la escala *RIFLE* con un seguimiento medio de 6.9±4.3 años: 74.9% para el subgrupo *RIFLE risk* group, 42.9% para el subgrupo *RIFLE injury*, y 22.3% para el subgrupo *RIFLE failure* (P <0.001). El desarrollo de *AKI* durante el postoperatorio en grado de severidad *injury* y *failure* se asoció de manera independiente a una mayor mortalidad.

Comentarios: En una gran muestra de pacientes postcirugía cardíaca y con un seguimiento promedio de casi 7 años se determinan las variables, sobre todo postoperatorias, que se asocian a *AKI* y se cuantifica su importante correlación con la mortalidad, tanto a corto como a largo plazo.

CRITICAL CARE

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Influence of acute kidney injury on short- and long-term outcomes in patients undergoing cardiac surgery: risk factors and prognostic value of a modified RIFLE classification

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Abstract

Introduction: The development of acute kidney injury (AKI) is associated with poor outcome. The modified RIFLE (risk, injury, failure, loss of kidney function, and end-stage renal failure) classification for AKI, which classifies patients with renal replacement therapy needs according to RIFLE failure class, improves the predictive value of AKI in patients undergoing cardiac surgery. Our aim was to assess risk factors for post-operative AKI and the impact of renal function on short- and long-term survival among all AKI subgroups using the modified RIFLE classification.

Methods: We prospectively studied 2,940 consecutive cardiosurgical patients between January 2004 and July 2009. AKI was defined according to the modified RIFLE system. Pre-operative, operative and post-operative variables usually measured on and during admission, which included main outcomes, were recorded together with cardiac surgery scores and ICU scores. These data were evaluated for association with AKI and staging in the different RIFLE groups by means of multivariable analyses. Survival was analyzed via Kaplan-Meier and a risk-adjusted Cox proportional hazards regression model. A complete follow-up (mean 6.9 ± 4.3 years) was performed in 2,840 patients up to April 2013.

Results: Of those patients studied, 14% (n = 409) were diagnosed with AKI. We identified one intra-operative (higher cardiopulmonary bypass time) and two post-operative (a longer need for vasoactive drugs and higher arterial lactate 24 hours after admission) predictors of AKI. The worst outcomes, including in-hospital mortality, were associated with the worst RIFLE class. Kaplan-Meier analysis showed survival of 74.9% in the RIFLE risk group, 42.9% in the RIFLE injury group and 22.3% in the RIFLE failure group (P <0.001). Classification at RIFLE injury (Hazard ratio (HR) = 2.347, 95% confidence interval (CI) 1.122 to 4.907, P = 0.023) and RIFLE failure (HR = 3.093, 95% CI 1.460 to 6.550, P = 0.003) were independent predictors for long-term patient mortality.

Conclusions: AKI development after cardiac surgery is associated mainly with post-operative variables, which ultimately could lead to a worst RIFLE class. Staging at the RIFLE injury and RIFLE failure class is associated with higher short- and long-term mortality in our population.

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Introduction

The development of acute kidney injury (AKI) after adult cardiac surgery is associated with higher morbidity and mortality [1-3]. AKI develops in 1% to 30% of these patients, depending on the definition used for AKI [4], and leads to renal replacement therapy (RRT) in 1% to 5% [5]. Previous reports have studied risk factors associated with the occurrence of AKI, mainly focusing on factors measurable before surgery [6,7] or during the perioperative period [1]. However, postoperative management in the intensive care unit (ICU) could also be relevant for the occurrence of AKI after cardiac surgery. In addition, factors that are measurable postoperatively may indicate AKI development, suggesting appropriate strategies to prevent or limit AKI.

The RIFLE (Risk, Injury, Failure, Loss of kidney function, and End-stage renal failure) classification indicates AKI severity based on changes in serum creatinine (sCr) relative to the baseline condition, its association with short-term mortality after cardiac surgery having been validated previously [8-10]. Recently, a modification of the RIFLE classification by staging all patients with acute need for RRT in the failure class F showed an improvement of the predictive value for AKI in patients undergoing cardiac surgery, being superior to acute kidney injury network criteria (AKIN) if there is no correction of sCr for fluid balance, which leads to over-diagnosis of AKI [3]. In addition, data on long-term survival after AKI in these patients are scarce despite the need for such information.

The aim of this study was: (1) to identify the risk factors for AKI, especially regarding postoperative variables, and the predictive value for AKI of preoperative and postoperative scores; and (2) to evaluate the long-term mortality risk associated with a modified RIFLE classification after cardiac surgery in a large single-center cohort of patients with no history of chronic kidney disease, together with an evaluation of the variables that influence staging in the different RIFLE groups.

Methods

This study was a retrospective study of prospectively collected data from 2,940 consecutive patients undergoing different types of cardiac surgery between January 2004 and July 2009 at our institution. We excluded those with preoperative renal failure requiring dialysis (n =24) or chronic kidney disease (CKD) (n = 144). Heart-transplant patients (n = 124) were also excluded due to the higher AKI rates reported in previous studies, which may lead to bias [2]. Definition of CKD was based on the Society of Thoracic Surgeons' national cardiac surgery database definitions, which is defined as a serum creatinine value of 2.0 mg/dL (176.8 mmol · L-1) or greater.

The study was approved by the Institutional Ethics Committee of our hospital (Comité d' Ètica i Assajos Clínics de Hospital Universitari de Bellvitge (CEIC); Ethics and Clinical Assays Committee of Hospital Universitari de Bellvitge). Informed consent was waived due to the observational nature of our study. The follow-up was performed using the Catalan Health Central Registry (*Registre Central de Persones Assegurades*, RCA). A complete follow-up was performed in 2,840 patients up to April 2013.

Data on and during ICU admission were extracted from the medical registry of each patient in real time using a standardized questionnaire and collected in a database for analysis purposes. Recent myocardial infarction (AMI) was defined as an AMI that required admission to the hospital during the last month before surgery or an AMI that did not allow discharge from the hospital before surgery. The other definitions used for this study were based on the Society of Thoracic Surgeons' national cardiac surgery database definitions [11].

Preoperative data (demographic data, comorbidities and treatment before surgery), operative data and postoperative variables usually measured on and during admission, which included main outcomes, were recorded together with cardiac surgery scores (Parsonnet, European System for Cardiac Operative Risk Evaluation (EuroSCORE)) and ICU scores (Acute Physiology and Chronic Health Evaluation (APACHE) II and III, Simplified Acute Physiology Score (SAPS) II and III).

AKI was defined according to the RIFLE classification [8-10]. The baseline sCr is based on the preoperative analysis 24 h before surgery. Patients who met the RIFLE criteria for AKI were classified as "AKI", whereas those who did not were classified as "no AKI". Patients with AKI were stratified according to the RIFLE class; all patients with acute RRT were assigned to failure class F [3]. We measured the patients' sCr at admission, 6 h, 12 h and 24 h postoperatively and a minimum of twice per day during their stay in the ICU based on our unit protocols.

The operations were performed by the same group of cardiac surgeons during the study period. Cardiac procedures were performed in all patients using median sternotomy, standard cardiopulmonary bypass (CPB) with moderate hypothermia (34°C) and antegrade cardioplegia. A mean aortic pressure of >60 mmHg was maintained during surgery. For revascularization, we used the internal thoracic artery (or bilateral if possible) and saphenous vein grafts. Bypass graft flow was assessed for each graft by Doppler transit time flowmetry. Protamine was administered to reverse heparin according to standard practice. For coronary artery bypass graft (CABG) surgery, aspirin was routinely administered within the first 6 h after surgery following the local protocol. In all patients the decisions regarding postoperative ICU management were made by the attending physician.

Statistics

Statistical analysis was conducted using PASW statistics 13.0 (SPSS Inc., Chicago, IL, USA). Data are expressed as mean ± standard deviation. In order to evaluate differences regarding risk factors for AKI we analyzed differences between groups that were determined according to the presence of AKI after cardiac surgery. For comparisons between groups the Mann–Whitney *U* test was used or, when appropriate, the two-sample *t*-test. The χ^2-test was used to evaluate categorical prognostic factors. A multivariate analysis was carried out using a stepwise logistic regression model to identify independent risk factors for AKI after cardiac surgery after adjusting for preoperative and postoperative scores. Receiver operating characteristic (ROC) curve analyses were applied to check the optimal cut-off values of the different scores for AKI diagnosis and to further evaluate the predictive power between them, considering the differences between the areas under the empirical ROC curves (AUC). ANOVA was used to compare differences in characteristics and outcome differences between different RIFLE class groups (*P* shown in tables) and subsequent *post hoc* tests (Bonferroni tests) were used to determine significant differences in the various pairwise comparisons (*P* shown in results). This was confirmed by means or a multivariate analysis after adjusting for preoperative

Table 1 Univariate analysis of preoperative data associated with the presence of AKI after cardiac surgery

	All patients (*n* = 2,940)	Non-AKI patients (*n* = 2,531; 86%)	AKI patients (*n* = 409; 14%)	*P*-value
Sex (male)	64.0% (1,881)	64.4% (1,631)	61.1% (250)	0.20
Sex (female)	36.0% (1,059)	35.6% (900)	38.9% (159)	0.20
Age (years)	64.5 ± 11.6	64.0 ± 11.8	67.7 ± 9.8	**<0.001**
Hypertension	62.8% (1,846)	62.1% (1,570)	67.5% (276)	**0.03**
Dyslipidemia	50.5% (1,484)	51.4% (1,301)	44.9% (183)	**0.01**
Diabetes mellitus	8.2% (241)	7.9% (200)	10% (41)	0.14
BMI ($kg \cdot m^{-2}$)	28.1 ± 4.3	28.4 ± 4.3	27.9 ± 4.5	0.90
Peripheral vascular disease	8.9% (263)	7.9% (200)	15.4% (63)	**<0.001**
sCr before surgery ($mmol \cdot L^{-1}$)	95.8 ± 59.8	94.0 ± 60.0	101.0 ± 56.0	**0.045**
Previous stroke	5.6% (165)	5.2% (131)	8.3% (34)	**0.015**
COPD	12.0% (354)	11.6% (294)	14.7% (60)	0.08
Active smokers	15.5% (458)	15.8% (402)	13.7% (56)	0.29
Previous Atrial fibrillation	23.9% (703)	22.5% (569)	32.8% (134)	**0.045**
Previous myocardial infarction	15.4% (454)	16.0% (404)	12.2% (50)	0.055
Recent myocardial infarction	11.1% (325)	11.0% (278)	11.5% (47)	0.73
NYHA class III-IV	15.3% (450)	15.3% (389)	14.9% (61)	0.79
On B-Blockers	41.0% (1,204)	41.8% (1,057)	35.9% (147)	**0.026**
On statins	41.2% (1,212)	42.6% (1,078)	32.8% (134)	**<0.001**
On aspirin	44.4% (1,306)	45.7% (1,156)	36.7% (150)	**0.001**
On diuretics	47.6% (1,398)	46.0% (1,165)	57.0% (233)	**<0.001**
Hypertrophic cardiomyopathy	30.9% (910)	31.2% (790)	29.3% (120)	0.35
Dilated cardiomyopathy	20.4% (600)	20.1% (508)	22.5% (92)	0.34
LVEF (%)	60.2 ± 11.9	60.1 ± 11.8	60.3 ± 12.2	0.83
PAP (mmHg)	45.9 ± 15.7	45.3 ± 15.0	48.0 ± 17.0	**0.003**
Hemoglobin before surgery ($g \cdot dL^{-1}$)	12.9 ± 1.7	13.0 ± 1.6	12.4 ± 1.9	**<0.001**
Platelet count before surgery($1 \cdot nL^{-1}$)	215 ± 68	217 ± 67	206 ± 76	**0.005**
EuroSCORE	5.9 ± 3.0	5.6 ± 2.7	7.7 ± 3.5	**0.015**
Parsonnet score	11.5 ± 7.3	10.9 ± 6.8	14.5 ± 9.3	**0.001**
Past cardiac surgery	9.4% (277)	8.4% (213)	15.6% (64)	**<0.001**

BMI, Body Mass Index; COPD, Chronic Obstructive Pulmonary Disease; NYHA, New York Heart Association classification; LVEF, Left ventricular ejection fraction; PAP, Pulmonary arterial pressure; sCr, serum creatinine;. Data are mean ± standard deviation or percentage.
Boldface data are statistically significant (*P* <0.05).

Table 2 Univariate analysis of intraoperative and postoperative data associated with the presence of AKI after cardiac surgery

	All patients (*n* = 2,940)	Non-AKI patients (*n* = 2,531; 86%)	AKI patients (*n* = 409; 14%)	*P*-value
Intraoperative data				
Isolated CABG	32.1% (945)	33.6% (851)	23.0% (94)	**0.005**
Isolated valve surgery	51.6% (1,518)	51.8% (1,311)	51.6% (207)	0.85
CABG + valve surgery	6.9% (203)	6.2% (158)	11.0% (45)	**<0.001**
Other cardiac surgery	9.4% (274)	8.4% (211)	15.4% (63)	**<0.001**
Emergent surgery	5.1% (149)	3.9% (99)	12.2% (50)	**<0.001**
Number of bypass	2.3 ±0.9	2.3 ± 0.8	2.2 ± 0.9	0.68
ACC time (minutes)	73 ± 29	72 ± 28	87 ± 37	**<0.001**
CPB time (minutes)	113 ± 41	109 ± 37	135 ± 55	**<0.001**
Postoperative data				
Ventilation time (hours)	50 ± 127	36 ± 96	139 ± 229	**<0.001**
PaO_2/FiO_2 ratio on admission	331 ± 98	334 ± 96	315 ± 106	**0.001**
PaO_2/FiO_2 ratio 12 h after admission	311 ± 89	316 ± 87	278 ± 93	**<0.001**
PaO_2/FiO_2 ratio 24 h after admission	307 ± 77	314 ± 72	270 ± 90	**<0.001**
Reintubation	1.1% (31)	0.8% (21)	2.5% (10)	**0.001**
Tracheostomy	1.3% (38)	0.8% (19)	4.7% (19)	**0.001**
Need of vasoactive drugs (hours)	103 ± 141	82 ± 110	195 ± 210	**<0.001**
LCOS	41.6% (1,223)	36.3% (920)	74.1% (303)	**<0.001**
PMI	11.8% (346)	10% (252)	23% (94)	**<0.001**
IABP support	7.8% (230)	6.1% (155)	18.3% (75)	**<0.001**
Atrial fibrilation	39.4% (1,158)	36.1% (913)	59.9% (245)	**<0.001**
AL on admission ($mmol \cdot L^{-1}$)	2.3 ± 1.4	2.2 ± 1.2	3.1 ± 2.3	**<0.001**
AL 24 h after admission ($mmol \cdot L^{-1}$)	1.9 ± 1.0	1.8 ± 0.7	2.6 ± 1.9	**<0.001**
sCr peak after surgery ($mmol \cdot L^{-1}$)	114.3 ± 80.8	99.0 ± 62.0	205.0 ± 113.0	**<0.001**
Albumin 48 h after surgery ($g \cdot L^{-1}$)	28.2 ± 3.7	28.4 ± 3.6	26.5 ± 4.1	**<0.001**
Hemorrhage-related re-exploration	3.5% (103)	2.6% (66)	9.0% (37)	**<0.001**
Pericardial tamponade	0.7% (22)	0.4% (11)	2.7% (11)	**<0.001**
Drainage loss first 12 h (mL)	393 ± 301	377 ± 275	496 ± 414	**<0.001**
Major bleeding	3.6% (109)	2.6% (66)	10.5% (43)	**<0.001**
Re-exploration	1.6% (48)	0.8% (21)	5.1% (27)	**<0.001**
Need for blood products (units)	1.6 ± 3.0	1.4 ± 2.5	3.3 ± 4.6	**<0.001**
Stroke	1.4% (42)	0.9% (24)	4.4% (18)	**<0.001**
Septicemia	6.6% (195)	4.0% (102)	22.7% (93)	**<0.001**
SAPS II	24.2 ± 9.6	22.8 ± 8.3	32.3 ± 12.8	**<0.001**
SAPS III	39.9 ± 10.4	38.6 ± 9.4	48.4 ± 12.3	**<0.001**
APACHE II	12.3 ± 4.6	11.6 ± 4.0	16.1 ± 6.3	**<0.001**
APACHE III	49.9 ± 18.5	47.0 ± 15.0	67.0 ± 24.0	**<0.001**
Mean Pre-ICU stay (days)	7.0 ± 13.0	6.7 ± 8.6	8.7 ± 28.8	0.15
Mean ICU stay (days)	7.5 ± 11.0	6.2 ± 7.7	15.2 ± 20.3	**<0.001**
Mean hospital stay (days)	24.6 ± 22.5	22.8 ± 15.7	36.1 ± 44.5	**<0.001**
In-hospital mortality	6.0% (177)	2.4% (60)	28.6% (117)	**<0.001**

ACC, Aortic cross clamping; AL, Arterial lactate; APACHE, Acute Physiology and Chronic Health Evaluation; CABG, Coronary artery bypass graft; CPB, Cardiopulmonary bypass; IABP, intra-aortic balloon pump; LCOS, Low Cardiac Output Syndrome; PaO_2/FiO_2, Arterial partial pressure of O_2 and fraction of inspired oxygen ratio; PMI, Perioperative myocardial infarction; SAPS, Simplified Acute Physiology Score; sCr, serum creatinine. Data are mean ± standard deviation or percentage. Boldface data are statistically significant (P <0.05).

and postoperative scores. In all cases, the Kolmogorov-Smirnov test was used to check the normal distribution of our population and to assess the goodness-of-fit of the final regression models. Survival analysis was carried out with the Kaplan-Meier estimator for the different RIFLE class groups. A proportional hazards Cox regression model was used to evaluate the effect of AKI and RIFLE class groups on survival. A two-tailed *P*-value <0.05 was considered statistically significant.

Results

Risk factors and scores prediction of AKI

The results of the univariate analysis of preoperative, intraoperative and postoperative data are shown in Tables 1 and 2. The 14% of patients ($n = 409$) who were diagnosed with AKI were older and more likely to have associated comorbid conditions and postoperative complications with a higher risk prediction for in-hospital mortality based on preoperative and postoperative scores than those without AKI.

In Table 3, we compare the results of the multivariate analysis of AKI based on different variable categories included in each analysis. We performed an adjustment for these scores in order to avoid the influence of severity of illness at the time of cardiac surgery and/or ICU admission. The preoperative data (older age, presence of peripheral vascular disease, higher pulmonary arterial pressure in preoperative echocardiography, and lower hemoglobin before surgery), intraoperative data (higher cardiopulmonary bypass (CPB) time and emergent surgery), and postoperative data (a longer need for vasoactive drugs and higher arterial lactate 24 h after admission) were associated with the occurrence of AKI when we analyzed these different variable categories separately. However, when assessing all data collected simultaneously, only postoperative variables and a higher CPB time were associated with the occurrence of AKI.

Table 3 Logistic regression model - dependent variable presence of AKI

	Odds ratio (95% CI)	*P*-value
Preoperative data		
Age	1.038 (1.021 to 1.055)	**<0.001**
Presence of peripheral vascular disease	1.403 (0.991 to 1.987)	**0.003**
PAP (mmHg)	1.012 (1.002 to 1.022)	**0.020**
Hemoglobin before surgery ($g \cdot dL^{-1}$)	0.856 (0.783 to 0.936)	**0.001**
Intraoperative data		
CPB time (minutes)	1.013 (1.010 to 1.016)	**<0.001**
Emergent surgery	1.273 (1.168 to 1.444)	**<0.001**
Postoperative data		
Need of vasoactive drugs (hours)	1.005 (1.001 to 1.008)	**0.001**
AL 24 h after admission	1.530 (1.293 to 1.819)	**<0.001**
All data		
Need of vasoactive drugs (hours)	1.003 (1.002 to 1.004)	**<0.001**
AL 24 h after admission	1.810 (1.300 to 2.015)	**<0.001**
CPB time (minutes)	1.012 (1.002 to 1.028)	**0.025**

AL, Arterial lactate; CPB, Cardiopulmonary bypass; PAP, Pulmonary arterial pressure; sCr, Serum creatinine.
Boldface data are statistically significant (*P* <0.05).

When we assessed the ability of cardiac surgery and ICU scores to predict AKI (see Table 4), we found that cardiac surgery scores were poor predictors of AKI development whereas ICU scores were fair predictors based on the ROC curve.

Differences between RIFLE groups

The differences between RIFLE groups showed a comparable univariate association of the majority of outcome variables with worse outcome according to increased severity of AKI (see Tables 5 and 6). Preoperative variables showed lower hypertension rates in the RIFLE risk (RIFLE-R) group compared with the RIFLE failure (RIFLE-F) group and lower diabetes mellitus rates compared with the RIFLE injury (RIFLE-I) group. The RIFLE-F group suffered from higher CPB times compared with RIFLE-R (Bonferroni *post hoc P* <0.001) during cardiac surgery. Postoperative variables showed higher albumin levels 48 h after cardiac surgery in the RIFLE-R (P <0.001) and RIFLE-I ($P = 0.019$) groups when compared with RIFLE-F. The RIFLE-F and RIFLE-I groups showed a longer need for vasoactive drugs (P <0.001 in both groups) and higher in-hospital mortality rates ($P = 0.001$ and $P = 0.003$, respectively) when compared with the RIFLE-R group. Finally, the RIFLE-R group showed lower Low Cardiac Output Syndrome (LCOS) and septicemia rates compared with the RIFLE-F group. All these comparisons were confirmed later by means of the logistic regression model adjusted for risk prediction scores (see Table 7).

Mortality and survival analysis

A Cox proportional hazards model for patients' in-hospital mortality demonstrated that staging at RIFLE-I (hazard ratio (HR) = 2.347, 95% confidence interval (CI) 1.122 to 4.907, $P = 0.023$) and RIFLE-F (HR = 3.093, 95% CI 1.460 to 6.550, $P = 0.003$) were independent predictors for patient mortality. Other factors associated with an increased risk of death included older age (HR = 1.080, 95% CI 1.036 to 1.126, P <0.001), diabetes mellitus (HR = 1.376, 95% CI 1.178 to 1.795, $P = 0.01$), longer time on vasoactive drugs (HR = 1.003, 95% CI 1.001 to 1.004, P <0.001) and suffering a stroke after cardiac surgery (HR = 1.130, 95% CI 1.045 to 1.376, P <0.001).

We performed a complete follow-up in order to evaluate long-term mortality in 2,840 patients. Mean follow-up was 6.9 ± 4.3 years. Kaplan-Meier plots, shown in Figures 1 and 2, illustrated that patients with AKI and a higher

Table 4 Comparison of AUC for ICU and cardiac surgery scores for AKI prediction

	AUC ± SD% (95% CI)	Cut-off levels	Sensitivity	Specificity	*P*-value
APACHE II	71.0 ± 2.4 (66.4 to 75.6)	13.5	67.1%	64.7%	**<0.001**
APACHE III	75.8 ± 2.2 (71.4 to 80.1)	54.5	73.0%	67.1%	**<0.001**
SAPS II	72.3 ± 2.3 (67.7 to 76.9)	26.5	67.8%	65.7%	**<0.001**
SAPS III	72.0 ± 2.2 (67.6 to 76.3)	42.5	70.4%	61.9%	**<0.001**
EuroSCORE	67.6 ± 2.3 (63.0 to 72.2)	5.5	71.1%	53.8%	**<0.001**
Parsonnet	61.9 ± 2.5 (57.0 to 66.8)	11.5	61.8%	54.6%	**<0.001**

APACHE, Acute Physiology and Chronic Health Evaluation; AUC, Area under curve; EuroSCORE, European system for cardiac operative risk evaluation; SAPS, Simplified Acute Physiology Score.
Boldface data are statistically significant (P <0.05).

Table 5 Differences in preoperative data between AKI subgroups based on RIFLE classification

	AKI patients (*n* = 409)	RIFLE risk (*n* = 226; 55.2%)	RIFLE injury (*n* = 87; 21.3%)	RIFLE failure (*n* = 96; 23.5%)	*P*-value
Sex (male)	61.1% (250)	58.8% (133)	57.5% (50)	69.8% (67)	0.12
Sex (female)	38.9% (159)	41.2% (93)	42.5% (37)	30.2% (29)	0.13
Age (years)	67.7 ± 9.8	67.3 ± 10.0	68.1 ± 10.4	68.1 ± 8.9	0.68
Hypertension	67.5% (276)	62.8% (142)	69.0% (60)	77.1% (74)	**0.042**
Dyslipidemia	44.9% (183)	39.4% (89)	46.0% (40)	56.3% (54)	**0.02**
Diabetes mellitus	10.0% (41)	7.5% (17)	17.2% (15)	9.4% (9)	**0.036**
BMI ($kg \cdot m^{-2}$)	27.9 ± 4.4	27.8 ± 4.3	28.2 ± 4.1	27.9 ± 5.3	0.77
Peripheral vascular disease	15.4% (63)	13.3% (30)	14.9% (13)	20.8% (20)	0.22
sCr before surgery ($mmol \cdot L^{-1}$)	101 ± 56	86 ± 31	91 ± 30	115 ± 48	**<0.001**
Previous stroke	8.3% (34)	7.5% (17)	10.3% (9)	8.3% (8)	0.72
COPD	14.7% (60)	14.2% (32)	17.2% (15)	13.5% (13)	0.74
Active smokers	13.7% (56)	10.2% (23)	19.5% (17)	16.6% (16)	0.43
Previous atrial fibrillation	32.8% (134)	31.4% (71)	31.0% (27)	37.5% (36)	0.61
Previous myocardial infarction	12.2% (50)	11.5% (26)	13.8% (12)	12.5% (12)	0.85
Recent myocardial infarction	11.5% (47)	8.8% (20)	14.9% (13)	14.6% (14)	0.17
NYHA class III-IV	14.9% (61)	15.1% (34)	14.9% (13)	14.6% (14)	0.82
On B-blockers	35.9% (147)	35.4% (80)	41.4% (36)	32.3% (31)	0.42
On statins	32.8% (134)	29.2% (66)	39.1% (34)	35.4% (34)	0.21
On aspirin	36.7% (150)	34.1% (77)	41.4% (36)	38.5% (37)	0.44
On diuretics	57.0% (233)	52.7% (119)	63.2% (55)	61.5% (59)	0.14
Hypertrophic cardiomyopathy	29.3% (120)	27.8% (63)	27.5% (24)	34.3% (33)	0.37
Dilated cardiomyopathy	22.5% (92)	20.8% (47)	25.3% (22)	23.9% (23)	0.65
LVEF (%)	60.0 ± 12.2	60.8 ± 11.7	58.7 ± 13.7	60.7 ± 11.8	0.41
PAP (mmHg)	48.0 ± 17.0	46.4 ± 16.9	51.9 ± 16.7	52.0 ± 16.9	0.07
Hemoglobin before surgery ($g \cdot dL^{-1}$)	12.4 ± 1.9	12.7 ± 1.8	12.2 ± 1.8	12.1 ± 2.1	**0.009**
Platelet count before surgery ($1 \cdot nL^{-1}$)	206 ± 76	206 ± 77	206 ± 75	205 ± 73	0.98
EuroSCORE	7.7 ± 3.5	7.1 ± 3.0	7.9 ± 3.6	8.8 ± 4.0	**0.028**
Parsonnet score	14.5 ± 9.3	13.1 ± 7.7	14.3 ± 7.8	18.5 ± 12.8	**<0.001**
Past cardiac surgery	15.6% (64)	17.3% (39)	11.5% (10)	15.6% (15)	0.45

AKI, Acute Kidney Injury; BMI, Body Mass Index; COPD, Chronic Obstructive Pulmonary Disease; LVEF, Left ventricular ejection fraction; NYHA, New York Heart Association classification; PAP, Pulmonary arterial pressure; sCr, serum creatinine. Data are mean ± standard deviation or percentage.
Boldface data are statistically significant (P <0.05).

Table 6 Differences in intraoperative and postoperative data between AKI subgroups based on RIFLE classification

	AKI patients (*n* = 409)	RIFLE risk (*n* = 226; 55.2%)	RIFLE injury (*n* = 87; 21.3%)	RIFLE failure (*n* = 96; 23.5%)	*P*-value
Intraoperative data					
Isolated CABG	23% (94)	22.1% (50)	26.4% (23)	21.9% (21)	0.87
Isolated valve surgery	51.6% (207)	51.3% (116)	49.4% (43)	50.0% (48)	0.82
CABG + valve surgery	11% (45)	12.8% (29)	4.6% (4)	12.5% (12)	0.32
Other cardiac surgery	15.4% (63)	13.7% (31)	19.5% (17)	15.6% (15)	0.68
Emergent surgery	12.2% (50)	9.3% (21)	7% (8)	22.9% (22)	**0.004**
Number of bypass	2.29 ± 0.92	2.3 ± 0.9	2.5 ± 0.8	2.1 ± 1.0	0.21
ACC time (minutes)	87 ± 37	81 ± 32	96 ± 41	92 ± 39	**0.004**
CPB time (minutes)	135 ± 55	123 ± 44	147 ± 64	151 ± 62	**<0.001**
Postoperative data					
Ventilation time (hours)	139 ± 229	84 ± 176	204 ± 264	209 ± 268	**<0.001**
PaO_2/FiO_2 ratio on admission	315 ± 106	325 ± 105	320 ± 85	310 ± 115	**0.01**
PaO_2/FiO_2 ratio 12 h after admission	278 ± 93	300 ± 85	290 ± 105	270 ± 96	**0.003**
PaO_2/FiO_2 ratio 24 h after admission	270 ± 90	295 ± 78	259 ± 91	221 ± 94	**<0.001**
Reintubation	2.5% (10)	1.8% (4)	3.4% (3)	3.2% (3)	0.08
Tracheostomy	4.7% (19)	4.1% (9)	8.0% (7)	3.2% (3)	**0.01**
Need of vasoactive drugs (hours)	195 ± 210	137 ± 149	242 ± 207	267 ± 274	**<0.001**
LCOS	74.1% (303)	62.4% (141)	87.3% (76)	89.5% (86)	**<0.001**
PMI	23.0% (94)	14.6% (33)	28.7% (25)	37.5% (36)	**<0.001**
IABP support	18.3% (75)	15.9% (36)	16.0% (14)	26.1% (25)	**0.04**
Atrial fibrilation	59.9% (245)	52.2% (118)	64.4% (56)	74.0% (71)	**<0.001**
AL on admission ($mmol \cdot L^{-1}$)	3.1 ± 2.3	3.1 ± 2.2	2.9 ± 3.3	3.3 ±2.5	0.11
AL 24 h after admission ($mmol \cdot L^{-1}$)	2.6 ± 1.9	2.2 ±1.3	2.7 ± 1.7	3.3 ± 2.7	**<0.001**
sCr peak after surgery ($mmol \cdot L^{-1}$)	205 ± 113	143 ± 52	214 ± 72	342 ± 126	**<0.001**
Albumin 48 h after surgery ($g \cdot L^{-1}$)	26.5 ± 4.1	27.0 ± 3.4	26.0 ± 3.5	24.0 ± 5.0	**<0.001**
Hemorrhage-related re-exploration	9.0% (37)	5.3% (12)	13.8% (12)	13.5% (13)	**0.014**
Pericardial tamponade	2.7% (11)	2.2% (5)	2.3% (2)	4.2% (4)	0.59
Drainage loss first 12 h (mL)	496 ± 414	448 ± 368	523 ± 498	581 ± 422	**0.026**
Major bleeding	10.5% (43)	10.1% (23)	10.3% (9)	11.4% (11)	0.65
Re-exploration	5.1% (27)	4.4% (10)	4.6% (4)	13.5% (13)	**0.001**
Need for blood products (Units)	3.3 ± 4.6	2.6 ± 4.2	4.23 ± 4.9	4.3 ± 4.9	**0.001**
Stroke	4.4% (18)	3.1% (7)	3.4% (3)	8.3% (8)	0.09
Septicemia	22.7% (93)	13.2% (30)	27.5% (24)	40.6% (39)	**<0.001**
SAPS II	32.3 ± 12.8	27.7 ± 9.5	34.4 ± 13.0	40.9 ± 14.4	**<0.001**
SAPS III	48.4 ± 12.3	44.1 ± 9.9	49.2 ± 11.5	56.9 ± 13.2	**<0.001**
APACHE II	16.1 ± 6.3	13.7 ± 4.3	17.0 ± 6.8	20.9 ± 7.1	**<0.001**
APACHE III	67.0 ± 24.0	58.4 ± 17.4	69.6 ± 23.4	86.0 ± 27.5	**<0.001**
Mean Pre-ICU stay (days)	8.7 ± 28.8	6.2 ± 7.8	7.7 ± 9.3	15.7 ± 57.3	**0.023**
Mean ICU stay (days)	15.2 ± 20.3	12.0 ± 15.8	18.0 ± 22.8	20.3 ± 25.4	**0.001**
Mean hospital stay (days)	36.1 ± 44.5	31.5 ± 34.2	38.5 ± 32.0	44.6 ± 68.0	**0.046**
In-hospital mortality	28.6% (117)	10.6% (24)	42.5% (37)	58.3% (56)	**<0.001**

ACC, Aortic cross clamping; AL, Arterial lactate; APACHE, Acute Physiology and Chronic Health Evaluation; CABG, Coronary artery bypass graft; CPB, Cardiopulmonary bypass; IABP, Intra-aortic balloon pump; LCOS, Low Cardiac Output Syndrome; PaO_2/FiO_2, Arterial partial pressure of O_2 and fraction of inspired oxygen ratio; PMI, Perioperative myocardial infarction; SAPS, Simplified Acute Physiology Score; sCr, Serum creatinine. Results are expressed as mean ± standard deviation or percentage. Boldface data are statistically significant ($P < 0.05$).

Table 7 Differences between RIFLE groups in a logistic regression model

	Odds ratio (95% CI)	*P*-value
RIFLE risk vs RIFLE failure		
Hypertension	1.299 (1.098 to 1.916)	**0.034**
Cardiopulmonary bypass time (minutes)	1.014 (1.003 to 1.025)	**0.014**
Need of vasoactive drugs (hours)	1.003 (1.000 to 1.006)	**0.004**
Albumin 48 h after surgery ($g \cdot L^{-1}$)	0.858 (0.764 to 0.964)	**0.010**
Low cardiac output syndrome	1.144 (1.039 to 1.534)	**0.004**
Septicemia	1.078 (1.019 to 1.321)	**<0.001**
In-hospital mortality	1.856 (1.198 to 3.028)	**0.001**
RIFLE risk vs RIFLE injury		
Diabetes mellitus	1.323 (1.116 to 1.901)	**0.031**
Need of vasoactive drugs (hours)	1.002 (1.000 to 1.004)	**0.045**
In-hospital mortality	1.656 (1.360 to 2.980)	**0.003**
RIFLE injury vs RIFLE failure		
Albumin 48 h after surgery ($g \cdot L^{-1}$)	0.896 (0.828 to 0.969)	**0.006**

Boldface data are statistically significant (P <0.05).

RIFLE class had worse long-term survival over the follow-up period (see also Table 8). The long-term survival was similar regardless of type of surgery, as shown in Figure 3A, B. A Cox proportional hazards model of patient mortality demonstrated that AKI in isolated coronary artery bypass graft (CABG) procedures (HR = 3.706, 95% CI 2.012 to 6.875, P <0.001) and valve surgery procedures (HR = 2.713, 95% CI 1.980 to 5.250, P <0.001) was an independent predictor of mortality in these surgical groups. We observed a long-term global mortality of 11.74% (n = 313/2,665), after excluding patients who died in-hospital and those who survived but in whom follow-up could not be performed. In addition, in the long-term scenario mortality was 10.6% in non-AKI patients (n = 253/2,384), 21.4% (n = 60/281) in AKI patients, 15.9% (n = 31/195) in RIFLE-R, 25% (n = 12/48) in RIFLE-I, and 44.7% (n = 17/38) in RIFLE-F (P <0.001).

Discussion

This study shows the key importance of postoperative factors, which can be easily monitored, for predicting the occurrence of AKI after cardiac surgery. Thus, a prompt intervention in the postoperative management in the ICU, especially avoiding additional renal insults and optimizing volume status, may help to some extent to prevent a higher progression of perioperative AKI, and the occurrence of the worst outcomes, including in-hospital mortality, is associated with the worst RIFLE class. We also demonstrated that scoring systems based only on variables known preoperatively, such as the Parsonnet and EuroSCORE, which have been proposed for the assessment of AKI developing after adult cardiac surgery [12], are worse predictors than ICU scores, which mainly included variables known postoperatively. Finally, a modified RIFLE classification is associated with long-term mortality, especially when staging within the RIFLE-I and RIFLE-F groups.

Although sCr is not always a perfect surrogate of renal function, it continues to be a basic measurement for the classification and diagnosis of AKI [8]. A ≥10% reduction in the sCr level may predict significantly lower AKI risk, whereas a ≥10% increase may predict significantly higher AKI risk compared with the reference category, reflecting the fact that minimal changes in sCr can increase mortality after cardiac surgery [4,13]. Novel biomarkers, such as neutrophil gelatinase-associated lipocalin and cystatin C, have been correlated with the duration and severity of AKI and the duration of ICU stay after adult cardiac surgery, and have been identified as independent predictors of AKI, being superior to conventional biomarkers [14]. However, due to its availability and widespread use, sCr continues to be a more valuable and accepted tool for AKI diagnosis worldwide.

Hyperlactatemia in the ICU is associated with increased mortality, being more frequent when renal failure is present [15]. It predicts postoperative mortality after cardiac surgery with a maximum lactate threshold of ≥4.4 $mmol \cdot L^{-1}$ in the first 10 h after operation [16]. During CPB the kidneys may suffer from an imbalance between oxygen supply and oxygen needs, resulting in inadequate oxygen delivery that is associated with lactate production [17]. The duration of CPB, which is a surrogate of the complexity of the procedure or of unexpected intraoperative problems, and its related variables, such as pressures and flows, have also been associated with AKI [1,18,19]. This may explain why higher arterial lactate values, which are ultimately a surrogate marker of tissue hypoperfusion, and a longer CPB duration,

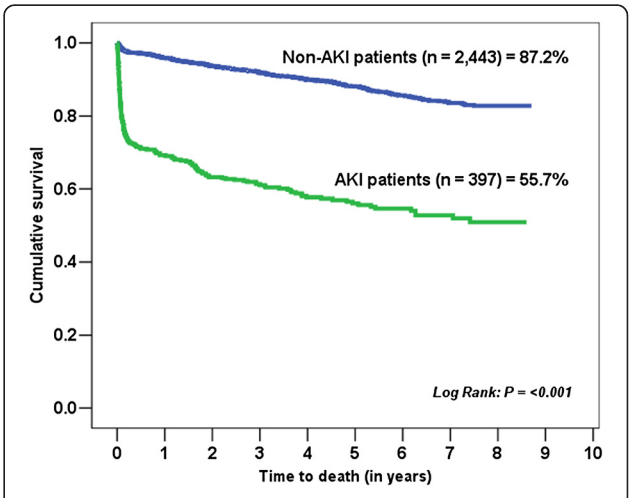

Figure 1 Kaplan-Meier survival curves for the presence of AKI.

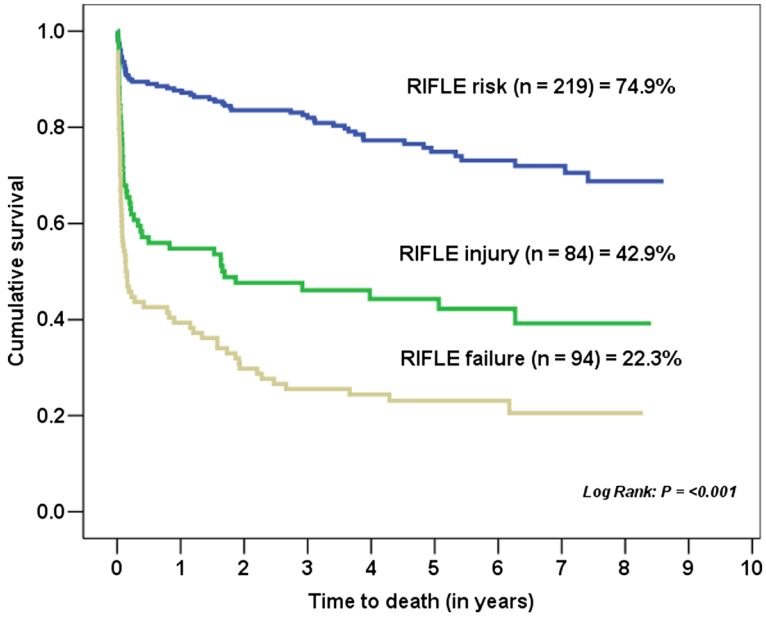

Figure 2 Kaplan-Meier survival curves for the different AKI groups.

were associated with the occurrence of AKI. In addition, oxygen delivery depends on an appropriate hemoglobin level [17], being consistent with our finding that lower hemoglobin before surgery was associated with AKI. Previous studies that found preoperative anemia, hemodilution and perioperative red blood cell transfusions to be associated with AKI are also consistent with this finding [19,20]. As a consequence, intraoperative avoidance of the extremes of anemia, especially during CPB, and avoidance of transfusion in patients with hemoglobin levels >8 $g \cdot dL^{-1}$, may be helpful strategies in order to decrease AKI in patients undergoing cardiac surgery [21,22].

Despite the relationship between heart failure and renal insufficiency, even in the acute scenario [23], there is a lack of studies associating heart failure variables and/or related variables with AKI after cardiac surgery [24]. The postoperative use of norepinephrine in postoperative cardiac surgery patients and the postoperative use of vasoactive drugs in those with sCr <60 $mL \cdot minute^{-1} \cdot 1.73\ m^{-2}$ has been associated with AKI [19]. We hypothesized that a longer requirement for vasoactive drugs, even with a higher RIFLE class, is a variable concerning the perioperative drug management of patients, and could be a surrogate marker of unresolved postoperative cardiac or vascular dysfunction.

We confirmed the association of worse outcomes, including in-hospital mortality, with a worse RIFLE class, which may ultimately contribute to AKI. Limited CPB duration and adequate cardiac output are of key importance in order to avoid AKI development [25]. Hypoalbuminemia also increased the risk for infection in cardiac surgery patients, which itself is an important risk factor for mortality after cardiac surgery [26]. Sepsis can induce cardiac dysfunction *per se* [27], being associated with AKI and mortality after cardiac surgery [28,29]. As a result, our findings are concordant with the literature in relation to the associated AKI factors described above.

The RIFLE classification provides a useful tool for identifying patients with AKI after cardiac surgery and as a consequence those at risk of death, even in the long-term scenario [1-4], being superior to the classical postoperative renal failure definition in identifying such patients [11]. The present report is the first detailing the important association between long-term mortality after cardiac surgery and RIFLE-I and RIFLE-F classes in a large, single-center cohort, defined by a modified RIFLE

Table 8 Survival rates during follow-up for the different AKI groups

RIFLE class	1-year	2-years	3-years	4-years	5-years	6-years	7-years	8-years	9-years
Risk	88%	84%	82%	77%	75%	73%	72%	68%	68%
Injury	55%	48%	46%	45%	45%	42%	39%	39%	39%
Failure	39%	30%	25%	24%	23%	23%	20%	20%	20%

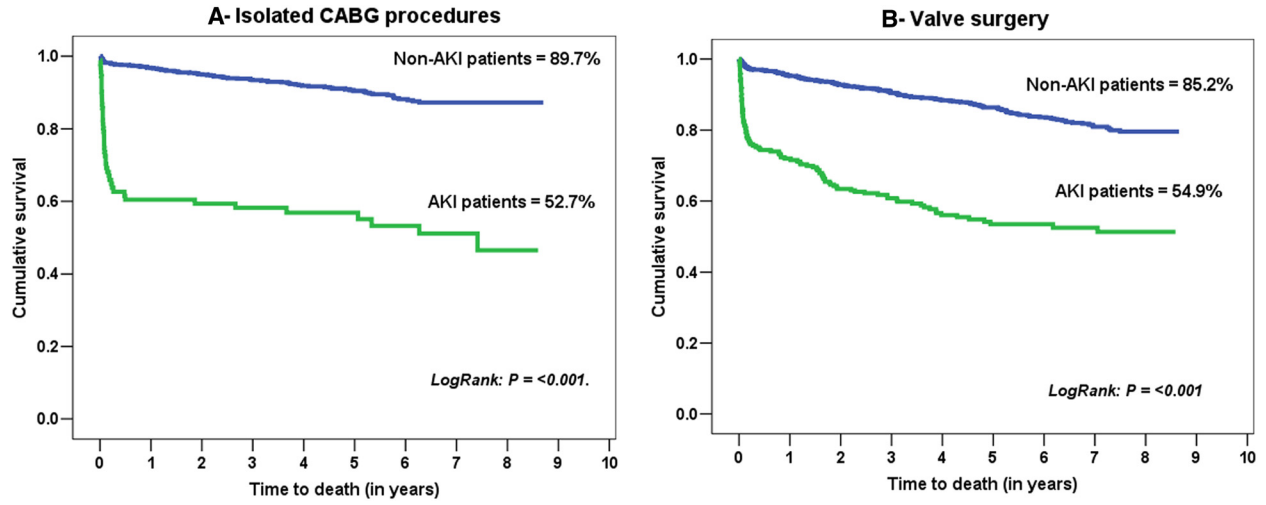

Figure 3 Kaplan-Meier survival curves for AKI patients stratified by individual surgery type (A and B).

classification [3]. We have also shown that AKI is an independent predictor of outcome regardless of type of surgery, being more important in isolated CABG procedures, as previously reported, but with greater influence over valve surgery compared with other studies [2]. Peripheral vascular disease leads to endothelial dysfunction, which is associated with renal insufficiency and contributes to cardiovascular mortality [30]. We hypothesized that a higher influence of arteriosclerosis in CABG patients is also associated with peripheral vascular disease and with vascular damage in renal vessels, which ultimately predisposes to AKI.

Renal blood flow and clearance function can remain impaired for a prolonged period of time after an episode of AKI, despite apparent normalization of sCr [31]. Indeed, several studies have indicated that there is ongoing progressive damage after AKI that results in a decrease in the capillary density of peritubular capillaries, a process known as "rarefaction" that can be linked to the development of chronic kidney disease, often with a delayed increase in sCr [32]. We can only hypothesize that the development of chronic kidney disease is one of the potential mechanisms that exposes these patients to increased cardiovascular morbidity and mortality [33]. Although comparisons among other studies remain difficult due to the different definitions and incidence of AKI, our survival rates for both AKI and non-AKI groups are comparable with other studies [2].

Our study presents certain limitations. The most important is that it was a single-center observational study. Unfortunately, we were not able to collect information on the cause of death and progression of kidney disease either. Among the strengths of this study are the large sample size, the prospective entry of all data elements into the database and the use of the finest statistical models together with systematic risk assessment using preoperative and postoperative scores, which are not shown in contemporary studies, even since the widespread use and importance of risk score stratification during the last decades. Furthermore, this investigation was conducted at a large tertiary referral hospital with a high level of complexity and all types of surgery, and all patients underwent surgery with CPB.

Conclusions

In summary, the cause of AKI in the postoperative period, which is usually multifactorial, could be associated to a large extent with postoperative variables. In most cases, such variables lead to worse RIFLE staging when AKI occurs. The occurrence of AKI, especially staging at the RIFLE-I and RIFLE-F class, is associated with higher long-term mortality in our population.

The identification of postoperative AKI predictors could be of great clinical value, suggesting management changes that could prevent or reduce the impact of AKI itself and guiding ICUs in allocating resources for postoperative care before more severe complications occur. In addition, on the basis of this and previous studies [2,31-33], we suggest that patients suffering AKI after cardiac surgery should be closely followed in order to detect progressive renal damage beyond the acute episode, despite apparent normalization of sCr.

Key messages

- The occurrence of AKI in the postoperative period of cardiac surgery continues to be a crucial factor which influences the outcome these patients, even from the long-term perspective.

- AKI development after cardiac surgery is associated with postoperative variables, which ultimately could lead to a worse RIFLE class.
- Staging at the RIFLE injury and RIFLE failure class is associated with higher short- and long-term mortality in our population.
- The identification of postoperative AKI predictors could help clinicians in order to prevent the impact of AKI itself and guiding ICUs in allocating resources for postoperative care.

Abbreviations

AKI: Acute kidney injury; AKIN: Acute kidney injury network criteria; AMI: Acute myocardial infarction; APACHE: Acute Physiology and Chronic Health Evaluation; CABG: Coronary artery bypass graft; CKD: Chronic kidney disease; CPB: Cardiopulmonary bypass; EuroSCORE: European System for Cardiac Operative Risk Evaluation; ICU: Intensive care unit; LCOS: Low cardiac output syndrome; RIFLE: Risk, injury, failure, loss of kidney function, and end-stage renal failure; RRT: Renal replacement therapy; SAPS: Simplified acute physiology score; sCr: serum creatinine.

Competing interests

There is no funding support or conflicts of interest for the present paper.

Authors' contributions

JCLD was involved in the conception and design of the research, and performed statistical analysis and wrote the paper. FE performed statistical analysis and wrote the paper. HT was involved in the coordination and the acquisition of data. DRC contributed to the acquisition of data, especially in terms of follow-up. MLC and EF contributed to the design of the research and acquisition of data. CJ performed statistical analysis and interpretation of data. JLV was involved in the conception, design of the research and interpretation of data. RM was involved in the design of the research and supervised the writing of the present manuscript. All authors read and approved the final version of this manuscript.

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CRITICAL CARE

LETTER

Severity of post-cardiac surgery acute kidney injury and long-term mortality: is chronic kidney disease the missing link?

Helmut Schiffl

See related research by Lopez-Delgado *et al.*, http://ccforum.com/content/17/6/R293

While the retrospective cohort study by Lopez-Delgado and colleagues [1] suggests a strong association of the RIFLE classification and long-term mortality of acute kidney injury (AKI) after post-cardiac surgery, it has a number of limitations. The numbers of patients with pre-existing chronic kidney disease (CKD) or with non-recovery of renal function, *de novo* CKD or progression of CKD to stage V are not given. The authors used an obsolete definition of CKD and a modified RIFLE classification system for definition and grading of AKI.

Taken together, numerous studies underscore the strong association between AKI and *de novo* CKD. Severity, duration and frequency of AKI as well as age, comorbidities and pre-existing CKD are known risk factors for the development and/or progression of CKD [2]. Careful analyses of the cumulative mortality curves reported by Lopez-Delgado and colleagues or by our group [3] revealed a triphasic pattern. In the early phase, survival rates drop steeply due to critical illness, followed by a phase of smaller decline (caused by patient characteristics and development of CKD) and later on by a flatter survival curve attributable to the high cardiovascular mortality of progressive CKD [4].

Physicians need to consider the long-term sequels of severe AKI. Lopez Delgado and colleagues's study provides further arguments for an early follow-up of survivors of AKI by nephrologists.

Authors' response

Juan C Lopez-Delgado, Francisco Esteve, Casimiro Javierre and Josep L Ventura

We thank the authors for their comments and suggestions. Risk prediction in patients who suffer from post-operative AKI after cardiac surgery is becoming increasingly important today in decision-making regarding health care interventions. Thus, we agree that follow-up and long-term outcomes need to be reported as accurately as possible, especially for those patients who do not recover (totally or partially) renal function.

Nowadays, the definition of CKD is evolving and there are no definitive criteria [5,6]. In addition, development of risk scores for AKI corresponding to specific patient populations, such as cardiac surgery patients, is lacking [7]. However, Englberger and colleagues [8] have provided an approach with a modified RIFLE score.

We must keep in mind the close relationship between renal and cardiac function. The development of a cardiorenal syndrome after cardiac surgery is one of the major causes of AKI [9]. As a consequence, the second phase with a smaller decline in survival rates could be caused not only by development of *de novo* CKD but also by poor cardiac function after cardiac surgery.

In our opinion, patients with AKI should be evaluated after surgery not only by nephrologists, but even by a team including different specialities to provide a multidisciplinary approach.

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Abbreviations
AKI: Acute kidney injury; CKD: Chronic kidney disease.

Competing interests
The authors declare that they have no competing interests.

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Resumen: El cociente PaO2/FIO2 (Presión parcial de oxígeno arterial/ Fracción inspirada de oxígeno) es un indicador ampliamente usado en las UCIs para valorar el estado de la función respiratoria del paciente crítico. Aunque los *scores* pronósticos de cirugía cardíaca y de UCI predicen la mortalidad, los primeros no tienen en cuenta variables quirúrgicas, mientras que los segundos requieren 24h, en su gran mayoría, para ser calculados. En definitiva, disponemos de pocos instrumentos para dar un pronóstico con mayor exactitud durante las primeras 24h y, por tanto, tomar las decisiones asistenciales más adecuadas.

Estudiamos 2725 pacientes sometidos a cirugía cardíaca entre 2004 y 2009 con el fin de objetivar la utilidad del cociente PaO2/FIO2 como predictor pronóstico.

El cociente PaO2/FIO2 fue diferente en todas sus mediciones (0h, 3h, 6h, 12h y 24h) entre supervivientes y no supervivientes durante las primeras 24h (P <0.001). La PaO2/FIO2 a las 3h fue el mejor predictor de mortalidad basado en el área bajo la curva, dando un punto de corte óptimo según el análisis de coste-efectividad de 222 (95% Intervalo de Confianza (CI): 202-242). Se dividió la muestra en 3 grupos: Grupo 1, con PaO2/FIO2>242; Grupo 2, con PaO2/FIO2 de 202 hasta 242; y Grupo 3, con PaO2/FIO2<202. El Grupo 3 presentó una mayor mortalidad intra-UCI y mayores complicaciones respiratorias. La presencia de una PaO2/FIO2<202 3h tras el ingreso en UCI fue identificado como un predictor de mortalidad intra-UCI (OR: 1.364; 95% IC: 1.212-1.625, P<0.001) y fue asociado a una peor supervivencia intrahospitalaria (88.8% vs. 95.8%; *Log rank* P=0.002. *Adjusted Hazard ratio*: 1.48; 95% IC: 1.293–1.786; P=0.004).

Comentarios: En una gran muestra de pacientes postcirugía cardíaca se objetiva cómo una simple determinación gasométrica puede identificar pacientes de alto riesgo en el postoperatorio inmediato, siendo tan importante como los *scores* utilizados habitualmente y de obtención más precoz. El análisis coste-efectividad pone de

relevancia la utilidad de la PaO2/FIO2 como predictor pronóstico, siendo una herramienta estadística con amplia aplicabilidad.

BMC Anesthesiology

RESEARCH ARTICLE Open Access

Evaluation of the PaO2/FiO2 ratio after cardiac surgery as a predictor of outcome during hospital stay

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Abstract

Background: The arterial partial pressure of O2 and the fraction of inspired oxygen (PaO2/FiO2) ratio is widely used in ICUs as an indicator of oxygenation status. Although cardiac surgery and ICU scores can predict mortality, during the first hours after cardiac surgery few instruments are available to assess outcome. The aim of this study was to evaluate the usefulness of PaO2/FIO2 ratio to predict mortality in patients immediately after cardiac surgery.

Methods: We prospectively studied 2725 consecutive cardiac surgery patients between 2004 and 2009. PaO2/FiO2 ratio was measured on admission and at 3 h, 6 h, 12 h and 24 h after ICU admission, together with clinical data and outcomes.

Results: All PaO2/FIO2 ratio measurements differed between survivors and non-survivors ($p < 0.001$). The PaO2/FIO2 at 3 h after ICU admission was the best predictor of mortality based on area under the curve ($p < 0.001$) and the optimum threshold estimation gave an optimal cut-off of 222 (95% Confidence interval (CI): 202–242), yielding three groups of patients: Group 1, with PaO2/FIO2 > 242; Group 2, with PaO2/FIO2 from 202 to 242; and Group 3, with PaO2/FIO2 < 202. Group 3 showed higher in-ICU mortality and ICU length of stay and Groups 2 and 3 also showed higher respiratory complication rates. The presence of a PaO2/FIO2 ratio < 202 at 3 h after admission was shown to be a predictor of in-ICU mortality (OR:1.364; 95% CI:1.212-1.625, $p < 0.001$) and of worse long-term survival (88.8% vs. 95.8%; Log rank $p = 0.002$. Adjusted Hazard ratio: 1.48; 95% CI:1.293–1.786; $p = 0.004$).

Conclusions: A simple determination of PaO2/FIO2 at 3 h after ICU admission may be useful to identify patients at risk immediately after cardiac surgery.

Keywords: Cardiac surgery, Cardiopulmonary bypass, PaO2/FIO2 ratio, Outcomes, Long-term survival

Background

In critically ill patients the PaO2/FIO2 ratio is an indicator of oxygenation status and is one of the diagnostic criteria for acute respiratory distress syndrome in adults (ARDS) [1-4]. A low PaO2/FiO2 value has been associated with increased mortality and hospital stay in patients admitted to the intensive care unit (ICU) [5-8]. The PaO2/FiO2 ratio is widely used in ICUs because it quickly and easily provides data on the oxygenation status of critically ill patients. Its values are included in ICU prognostic scores [9,10]. During surgery, atelectasis may cause intraoperative gas exchange abnormalities, which may be increased by inflammation triggered by the surgery itself, leading to postoperative lung dysfunction even in patients without preexisting lung injury. Despite protective mechanical ventilation during and after surgery, including recruitment maneuvers, a lower PaO2/FiO2 may be a reflection of a persistent lung dysfunction which can influence outcome [11].

The population of patients who undergo cardiac surgery is heterogeneous. With the trend towards greater

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longevity, patients are likely to be older and to present higher rates of comorbidities such as chronic heart or respiratory failure [12]. The cardiac surgery scores habitually used to predict short-term postoperative mortality (Parsonnet, European System for Cardiac Operative Risk Evaluation (EuroSCORE)) are objective and relatively simple [13,14]; however, they evaluate preoperative status and may become inaccurate in the case of surgical complications. ICU scores (Acute Physiology and Chronic Health Evaluation (APACHE) II and III, Simplified Acute Physiology Score (SAPS) II and III) [9,10] are not specific for cardiac surgery and both require 24 hours for calculation. Other than their clinical judgment, physicians have few tools available for assessing outcome immediately after cardiac surgery.

The aim of this study was to evaluate the usefulness of the PaO2/FIO2 ratio for predicting mortality in patients after cardiac surgery in order to provide a potential tool and value for immediate postoperative assessment. We also aimed to test the value of the PaO2/FIO2 ratio to assess respiratory complications.

Methods

A prospective single-center observational study was conducted in a 10-bed cardiac surgery ICU at a 900-bed referral university hospital. The data were collected between January 2004 and January 2009. During the study period 2725 consecutive patients underwent various types of cardiac surgery. PaO2/FIO2 ratios after ICU admission were obtained for 2701 patients and these data were used for the subsequent analysis. Heart-transplant patients ($n = 98$) were not included, due to their particular physiopathology.

The local clinical research ethics committee (Comité d'Ètica i Assajos Clínics de Hospital Universitari de Bellvitge) approved the study protocol. Informed consent was waived because of the observational nature of the study and because all procedures were routine.

The PaO2/FiO2 ratio was measured at ICU admission, and after 3 h, 6 h, 12 h and 24 h, together with clinical data and outcomes. Data on and during ICU admission were extracted from the medical registry of each patient in real time using a standardized questionnaire and stored in a database for analysis. The definitions used for this study were based on the Society of Thoracic Surgeons' national cardiac surgery database definitions [15]. In all the patients admitted to our cardiac surgery ICU we recorded demographic data (including risk factors for cardiovascular disease), diagnostic category, preoperative conditions, type of surgery (valvular, coronary or both) and characteristics (cardiopulmonary bypass (CBP) and aortic clamping times), respiratory complications, length of ICU and hospital stay, and mortality in the ICU and hospital. Outcome scores were also calculated for each patient: cardiac surgery scores (Parsonnet and EuroSCORE) and ICU scores (APACHE II and III, and SAPS II).

Both the clinical and laboratory data obtained are based on the internal postoperative protocol in place when this study was performed. Arterial blood gas analyses were performed at our hospital's local laboratory, which meets the International Organization for Standardization quality standards (ISO 9001:2000).

The operations were performed by the same group of cardiac surgeons. Cardiac procedures were performed in all patients using median sternotomy, standard CPB with moderate hypothermia (34°C) and antegrade cardioplegia. A mean aortic pressure of > 60 mmHg was maintained during surgery. Intraoperative ventilatory strategies were based on an individual approach according to the patient's previous respiratory status. Volume-controlled ventilation with a tidal volume of around 8 $mL \cdot kg^{-1}$ and a minimum PEEP were used to provide adequate ventilation and oxygenation, to prevent atelectasis and to maintain inspiratory plateau pressure <30 cmH_2O. Minimum FiO2 was used to guarantee adequate oxygenation, even in the presence of CPB. All ventilatory parameters were modified in accordance with intraoperative analyses. For revascularization the internal thoracic artery was used (or bilaterally if possible) and saphenous vein grafts. Bypass graft flow was assessed for each graft by Doppler transit time flowmetry. Protamine was administered to reverse heparin, in accordance to standard practice. For Coronary Artery Bypass Graft (CABG) surgery, aspirin was routinely administered within the first 6 h after surgery following the local protocol. In all patients, decisions regarding postoperative ICU management were made by the attending physician. Patients were treated according to hemodynamic parameters, urine output, metabolic markers of tissue perfusion, such as arterial lactate levels and venous oxygen saturation, and an individual mechanical ventilation approach was performed in accordance with respiratory status.

Statistical analyses

Statistical analysis was conducted using PASW statistics 13.0 (SPSS Inc., Chicago, Illinois, USA). Differences regarding PaO2/FIO2 ratios between survivors and non-survivors were evaluated by means of repeated measures analysis of variance. Receiver operating characteristic (ROC) curve analyses were applied to evaluate the predictive power between different PaO2/FIO2 ratio values and considering the differences of the areas under the empirical ROC curves (AUC). In order to determine optimal cut-off values of the best predictive PaO2/FIO2 ratio value, optimum threshold estimation was applied.

The optimum threshold was estimated by means of an adequately weighed cost function, which was then minimized [16]. A confidence interval was also estimated for this threshold, such that patients with values below the

lower confidence interval limit were predicted to be non-survivors, patients with values above the upper confidence interval limit were predicted to be survivors, and values between the two limits were considered as inconclusive. Prognostic indexes, such as sensitivity and specificity and the likelihood ratio for survival were also calculated.

We thus studied all the data based on groups generated from previous analyses. For comparisons between groups, post-hoc exploratory analysis comparing different baseline and clinical characteristics was performed. ANOVA (P shown in tables) with post-hoc Bonferroni correction (P shown in results) was applied in order to evaluate any differences between the three groups for the quantitative samples with a normal distribution (e.g., TnI, ICU stay in hours, etc.). For qualitative variables (e.g., mortality), the χ^2-test test was used. These differences were confirmed by means of multivariate analysis after adjusting for preoperative and postoperative scores. The multivariate analysis was a proportional hazards Cox regression model to evaluate the effect of staging in the different three groups of PaO2/FIO2 ratio at 3 h and the differences between the subgroups. Variable selection was performed stepwise and a variable remained in the model if the *p*-value was <0.1. Model fit was assessed through checking residual normality, the existence and influence of outliers, and goodness-of-fit.

Finally, we evaluated the PaO2/FIO2 ratio as a mortality risk factor after cardiac surgery analysing differences between survivors and non-survivors. For this purpose we categorized PaO2/FIO2 ratios. For comparisons between groups the Mann–Whitney *U* test was used or, when appropriate, the two-sample *t*-test. The χ^2-test was used to evaluate qualitative variables. Multivariate analysis was performed based on the previous methods. Survival analysis was carried out with the Kaplan-Meier estimator and confirmed by means of the proportional hazards Cox regression model. The normality of the quantitative samples was checked by means of the one-sample Kolmogorov-Smirnov test in all cases, if necessary. Data are expressed as mean ± standard deviation. A two-tailed p value < 0.05 was considered statistically significant.

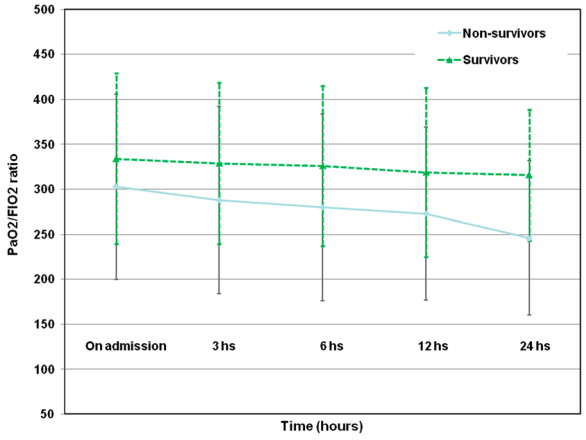

Figure 1 PaO2/FiO2 ratio levels curve of different measurements between survivors and non-survivors.

Results

PaO2/FIO2 ratios were higher in survivors than non-survivors (see Figure 1 and Table 1). ROC curve analysis showed that the PaO2/FIO2 ratio at 3 h after ICU admission was the best predictor of ICU mortality, and was also better than cardiac surgery scores. When comparing ROC curves of the PaO2/FIO2 ratio at 3 h with ICU scores, there were only slight differences, except in the case of APACHE II which was considerably higher (see Figure 2 and Table 2).

The optimum threshold estimation explored the value of the PaO2/FIO2 ratio at 3 h after admission as a predictor of hospital mortality, giving an optimal cut-off of 222 (95% Confidence interval (CI):202–242). On the basis of the confidence interval limits, patients were classified into three groups: patients with a PaO2/FIO2 ratio >241, corresponding to a high expectation of survival (Group 1); patients with a PaO2/FIO2 ratio between 202 and 241, corresponding to an inconclusive outcome (Group 2); and patients with a PaO2/FIO2 ratio <202, corresponding to low expectation of survival (Group 3). The results showed 2195 patients with a PaO2/FIO2 ratio >241, 257 with a ratio between 202 and 241, and 249 with a ratio <202. The accuracy indexes of sensitivity and specificity were 82%

Table 1 PaO2/FiO2 ratio levels curve of different measurements between survivors and non-survivors

	Survivors (n = 2569; 95.1%)	Non-survivors (n = 132; 4.9%)	*P*
PaO2/FIO2 ratio on admission	334 ± 95	303 ± 103	***0.001***
PaO2/FIO2 ratio at 3 h	329 ± 90	288 ± 104	***<0.001***
PaO2/FIO2 ratio at 6 h	326 ± 89	280 ± 104	***<0.001***
PaO2/FIO2 ratio at 12 h	319 ± 94	273 ± 96	***0.008***
PaO2/FIO2 ratio at 24 h	316 ± 73	246 ± 86	***<0.001***

PaO2/FiO2 ratio: Arterial partial pressure of O2 and fraction of inspired oxygen ratio.

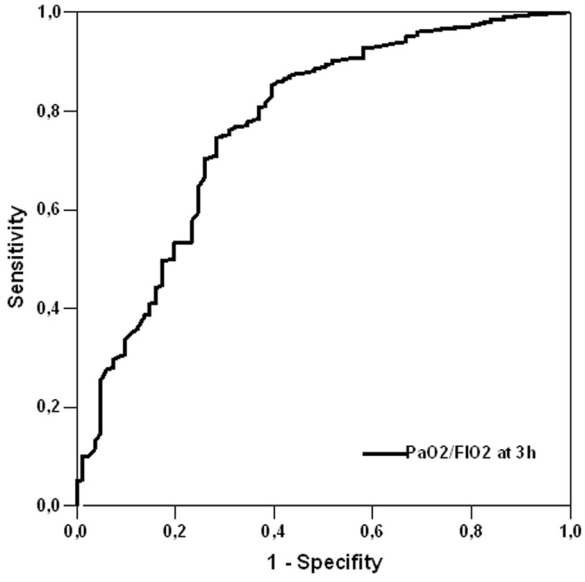

Figure 2 Receiver operating characteristic curve analysis for PaO2/FIO2 at 3 h.

and 21% respectively, and the predictive value for in hospital survival was 96%. The likelihood ratio for survival was 1.23 (95% CI:1.09-1.39) and for the outcome death was 0.41 (95% CI:0.29-0.58). These results indicate that survival is more likely in a patient with a PaO2/FIO2 ratio higher than 242, and death is more likely in a patient with a ratio lower than 202.

Baseline demographic and clinical characteristics of different groups (preoperative, intraoperative, and postoperative) are shown in Table 3. Regarding the preoperative data, Group 2 had a higher percentage of males (Bonferroni post-hoc: $p < 0.001$). The incidence of chronic obstructive bronchopulmonary disease (COPD) was higher in Group 3 (21.7%) than in either Group 2 (17.5%) or Group 1 (9.9%) ($p < 0.001$). There was a higher percentage of smokers in Group 2 (28.4%) than in Group 3 (26.5%) and Group 1 (19.8%) ($p < 0.001$). Group 3 patients tended to have higher body mass indices than patients in both groups 2 and 3, although the difference was not significant. Patients in Group 3 had higher preoperative creatinine levels and more chronic renal failure (CRF) than those in the other two groups ($p = 0.001$). As well, TnI levels were higher in Group 3 than among patients in the other two groups ($p < 0.001$). Scores on all the prognostic systems (Parsonnet and EuroSCORE, SAPS II, APACHE II, APACHE III) were likewise higher in Group 3.

Regarding outcomes, the mean ICU stay in Group 3 was 4.1 days longer than in Group 2 ($p = 0.002$) and 6.1 days longer than in Group 1 ($p < 0.001$). Similarly, the hospital stay in Group 3 was 7 days longer by than in Group 2 and 8.1 days longer than in Group 1 (both $p < 0.001$). Group 3 showed significantly greater in-ICU mortality ($\chi^2 = 25.2$, $p < 0.001$) and in-hospital mortality ($\chi^2 = 26.2$, $p < 0.001$) compared with the other two groups. The differences between groups in terms of mortality and length of stay are represented in Figure 3. In-ICU mortality was 320% higher in patients with a PaO2/FIO2 ratio <202 than in patients with a PaO2/FIO2 ratio >241. The same pattern was observed for in-hospital mortality, which was 280% higher in patients with a PaO2/FIO2 ratio <202 compared with those with a ratio > 241. In addition, both ICU and hospital stay were longer in patients with a ratio <202 than in those with a ratio > 241: longer by 6 days for ICU stay and by 8 days for hospital stay. Finally, regarding respiratory complications, Group 2 and 3 also showed higher rates (see Table 4) with the exception of diaphragmatic paresis and hemothorax.

Multivariate analysis (see Table 5) confirmed higher tracheal reintubation rates in Groups 2 and 3 than in Group 1; higher Acute Pulmonary Edema in Group 3

Table 2 Comparison of area under curve (AUC) for the different PaO2/FIO2 ratios and scores

	AUC ± SD% (95% CI)	Cut-off levels	Sensitivity	Specificity	*P* value
PaO2/FIO2 ratio on admission	58.8 ± 8.8 (54.6 - 66.9)	314	63%	58%	***0.001***
PaO2/FIO2 ratio at 3 h	77.2 ± 2.9 (71.2 - 82.8)	255	81%	69%	***<0.001***
PaO2/FIO2 ratio at 6 h	67.3 ± 3.2 (60.9 - 73.6)	301	61%	68%	***<0.001***
PaO2/FIO2 ratio at 12 h	71.1 ± 3.2 (64.9 - 77.6)	265	70%	64%	***<0.001***
PaO2/FIO2 ratio at 24 h	63.4 ± 3.3 (57.0 - 69.8)	300	62%	57%	***<0.001***
EuroSCORE	71.1 ± 4.4 (62.5 - 79.7)	6.5	69.4%	56.3%	***<0.001***
Parsonnet	68.7 ± 5.1 (58.8 - 78.7)	12.5	63.9%	66.4%	***<0.001***
SAPS II	78.5 ± 4 (70.6 - 86.4)	27.5	80.6%	70%	***<0.001***
APACHE II	82 ± 3.9 (74.4 - 89.6)	13.5	72.2%	63.3%	***<0.001***
APACHE III	79.6 ± 4.5 (70.8 - 88.4)	51.5	75%	62.1%	***<0.001***

PaO2/FiO2 ratio: Arterial partial pressure of O2 and fraction of inspired oxygen ratio. EuroSCORE: European system for cardiac operative risk evaluation. SAPS: Simplified Acute Physiology Score. APACHE: Acute Physiology and Chronic Health Evaluation.
Results are expressed as mean ± standard deviation or percentage.
Comparison of area under curve (AUC) for the different PaO2/FIO2 ratios and scores.

Table 3 Baseline demographic and clinical characteristics (preoperative, intraoperative, and postoperative) of patients

	PaO_2/FIO_2 ratio > 241 (*n* = 2195)	PaO_2/FIO_2 ratio 202-241 (*n* = 257)	PaO_2/FIO_2 ratio < 202 (*n* = 249)	*p* value
Preoperative data				
Age	65.3 (11.1)	66.1 (9.6)	66.0 (10.2)	*0.392*
BMI ($kg{\cdot}m^{-2}$)	27.9 (8.5)	28.8 (4.2)	29.7 (17.5)	*0.09*
Gender *(% male)*	60.1	73.5	72.7	***< 0.001***
HBP (%)	61.8	67.7	66.7	***<0.001***
IDDM (%)	8.2	9.3	8.0	*0.867*
NIDDM (%)	17.5	17.9	18.1	*0.748*
DLP (%)	51.2	56.4	47.8	*0.354*
Smokers (%)	19.8	28.4	26.5	***<0.001***
Vasculopathy (%)	8.4	8.9	9.6	*0.947*
COPD (%)	9.9	17.5	21.7	***<0.001***
CRF (%)	4.1	5.1	10.4	***<0.001***
Ejection fraction (%)	60.7 (11.5)	58.7 (13.0)	60.0 (11.9)	*0.06*
Preoperative haematocrit (%)	39.5 (4.9)	40.5 (5.0)	38.8 (6.0)	***<0.001***
Preoperative platelets ($x10^6$/L)	216423 (67126)	213470 (60195)	219409 (79665)	*0.615*
Preoperative creatinine *(μmol/l)*	91.8 (48.5)	94.6 (37.1)	107.9 (80.8)	***<0.001***
Parsonnet	10.8 (6.4)	11.5 (8.0)	13.8 (9.9)	***<0.001***
EuroSCORE	5.2 (2.8)	5.5 (3.2)	6.2 (3.6)	***0.006***
Surgical group				
CABG (%)	28.6	35.8	31.1	*0.145*
Valve (%)	62.7	55.3	60.7	*0.145*
CABG + Valve (%)	8.7	8.9	8.2	*0.145*
CPB time *(min)*	109.9 (36.4)	115.1 (37.6)	118.6 (40.7)	***<0.001***
Cross-clamping time *(min)*	71.9 (26.6)	73.2 (24.6)	76.0 (29.7)	*0.07*
Main Postoperative data				
SAPS II	22.8 (8.9)	26.4 (9.0)	29.3 (10.4)	***<0.001***
APACHE II	11.7 (4.2)	13.0 (4.8)	14.7 (5.4)	***<0.001***
APACHE III	47.6 (16.2)	52.8 (18.5)	60.8 (20.7)	***<0.001***
Blood lactate at ICU admission *(mmol/L)*	2.3 (5.6)	2.3 (1.2)	2.4 (1.4)	*0.960*
TnI at ICU admission *(μg/L)*	6.5 (7.0)	7.0 (11.8)	9.4 (25.5)	***<0.001***
Need for blood products (units)	1.8 (2.5)	1.4 (2.8)	1.9 (3.1)	*0.17*
ICU stay (days)	6.4 (9.2)	8.48 (11.6)	12.5 (15.1)	***<0.001***
Hospital stay (days)	23.6 (19.5)	24.7 (18.0)	31.7 (23.0)	***<0.001***
In-ICU exitus (%)	2.6	4.7	8.4	***< 0.001***
In-hospital exitus (%)	4	6.2	11.2	***<0.001***

PaO2/FiO2 Arterial partial pressure of O2 and fraction of inspired oxygen ratio, *HBP* High blood pressure, *IDDM* Insulin-dependent diabetes mellitus, *NIDDM*, Non-insulin-dependent diabetes mellitus, *DLP* Dyslipidaemia, *COPD,* Chronic obstructive pulmonary disease, *CRF* Chronic renal failure, *BMI* Body Mass Index, *EuroSCORE* European system for cardiac operative risk evaluation, *SAPS* Simplified Acute Physiology Score, *APACHE* Acute Physiology and Chronic Health Evaluation, *CPB* Cardiopulmonary bypass, *CABG* Coronary artery bypass graft, *TnI* Troponin I, Data expressed as mean (SD).

wthan Group 1; and the highest need for tracheostomy in Group 3. It also confirmed that Group 3 had the highest in-ICU mortality and ICU length of stay, and higher CRF and COPD rates than in group 1.

When we categorized the presence of a PaO2/FIO2 ratio <202 at 3 h after admission, we confirmed its value as a predictor of in-ICU mortality (OR: 1.364; 95% CI: 1.212-1.625, $p < 0.001$). Kaplan-Meier plots, shown in Figure 4,

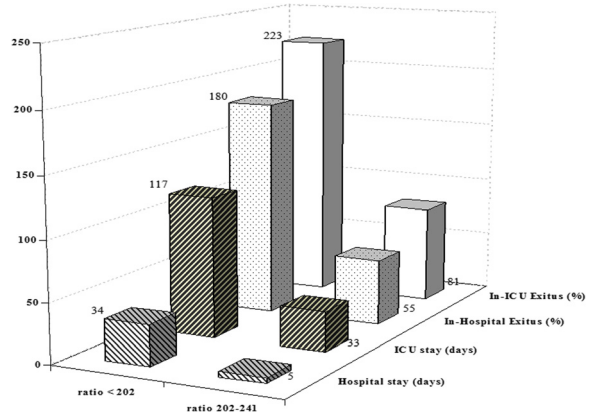

Figure 3 Percentage of exitus and stay in PaO_2/FiO_2 ratio <202 group and PaO_2/FiO_2 ratio 202–241 group, compared to PaO_2/FiO_2 ratio >241 group.

illustrated that patients with PaO2/FIO2 ratio <202 at 3 h after admission had the poorest long-term survival over the hospital stay (Log rank test: $p = 0.002$), which was confirmed by means of multivariate analysis (Adjusted Hazard ratio: 1.48; 95% CI:1.293 − 1.786; $p = 0.004$).

Discussion

Using a new method, the optimum threshold estimation criterion, this study highlights the value of the PaO2/FIO2 ratio as a prognostic indicator after cardiac surgery. The main findings of our study are the association between higher in-ICU mortality and length of stay with lower PaO2/FIO2 ratios.

PaO2/FIO2 values were lower in non-survivors than in survivors. Furthermore, the ratio has been reported to be a predictor of mortality in critically ill patients, particularly in patients with acute lung injury and in ARDS [5-7]. Low values of the PaO2/FIO2 ratio may be due to pathological conditions, primarily those of a respiratory nature (atelectasis, ARDS, acute pulmonary edema, pneumonia, etc.), as well as to alterations in hemodynamic status (cardiogenic shock, septic shock, etc.), or even both.

Immediately after cardiac surgery it is easy for physicians to detect a low PaO2/FIO2 ratio which can be swiftly corrected using general ICU procedures, such as appropriate analgesia, correcting tracheal tube placement if needed, or increasing PEEP to correct intraoperative atelectasis [8]. The same applies to hemodynamic disturbances. These potentially reversible causes may confound the immediate evaluation of the patient's status performed on admission. Hence, the PaO2/FIO2 ratio 3 h after ICU admission is the most useful for prognosis purposes.

The so-called "fast-track", modifying anesthetic techniques and postoperative sedation protocols, may allow for early tracheal extubation and, therefore, early ICU discharge without a significant increase in morbidity or mortality when correctly applied [17,18]. However, readmission after this procedure, though infrequent, produces a catastrophic increase in both mortality and the length of ICU stay [19,20]. In our view, the use of the PaO2/FiO2 ratio may help to minimize these types of events if specific strategies for weaning from mechanical ventilation are developed for patients at risk.

Several scoring systems are used to predict outcome in patients undergoing cardiac surgery, notably the Parsonnet score and the EuroSCORE [13,14], while for patients admitted to ICUs the SAPS II, APACHE II, and APACHE III are used [9,21]. Although the Parsonnet score and EuroSCORE are useful for determining the outcome of patients undergoing cardiac surgery they are both based on preoperative variables and so do not evaluate intraoperative or postoperative

Table 4 Respiratory data and complications during ICU admission after cardiac surgery

	PaO_2/FIO_2 ratio > 241 ($n = 2195$)	PaO_2/FIO_2 ratio 202-241 ($n = 257$)	PaO_2/FIO_2 ratio < 202 ($n = 249$)	*p* value
Mechanical ventilation (hours)	35 (101)	59 (136)	125 (200)	***<0.001***
Hours until tracheal extubation	27.5 (74.1)	42.8 (86.9)	70.5 (122.9)	***<0.001***
Maximum PEEP needs	3.4 (1.4)	4.4 (4.7)	5.7 (2.5)	***<0.001***
Pneumonia	0.2	1.2	0.4	***0.046***
Hemothorax	0.2	0	0.4	*0.57*
Pneumothorax	2.2	3.9	6	***0.001***
Acute Pulmonary Edema	5.4	6.6	15.7	***<0.001***
Tracheostomy	4.1	6.2	17.7	***<0.001***
Tracheal reintubation	2.6	2.3	5.2	***0.003***
Diaphragmatic paresis	0.5	0.8	1.2	*0.43*
Pleural effusion	6.6	10.9	16.5	***<0.001***

PEEP: positive end expiratory pressure. Data expressed as mean (SD).

Table 5 Differences between subgroups according PaO_2/FIO_2 ratio at 3 h after surgery in a multivariate analysis

	Hazard ratio (95% CI)	*P value*
PaO_2/FIO_2 ratio > 241 subgroup vs. **PaO_2/FIO_2 ratio 202–241** subgroup		
Preoperative haematocrit (%)	1.080 (1.054 - 1.108)	***<0.001***
Tracheal reintubation	5.338 (1.938 – 14.707)	***0.001***
ICU stay (days)	1.972 (1.959 - 1.985)	***<0.001***
In-ICU exitus	1.348 (1.185 - 1.654)	***0.001***
PaO_2/FIO_2 ratio > 241 subgroup vs. **PaO_2/FIO_2 ratio < 202** subgroup		
Acute pulmonary edema	1.636 (1.418 - 1.968)	***0.035***
Tracheal reintubation	2.649 (1.147 - 6.116)	***0.022***
Need of tracheostomy	2.121 (1.015 - 4.432)	***0.046***
ICU stay (days)	1.961 (1.951 - 1.971)	***<0.001***
In-ICU exitus	1.332 (1.206 - 1.536)	***<0.001***
PaO_2/FIO_2 ratio 202–241 subgroup vs. **PaO_2/FIO_2 ratio < 202** subgroup		
Chronic obstructive pulmonary disease	1.031 (1.006 - 1.056)	***0.015***
Chronic renal failure	1.847 (1.371 - 2.207)	***0.005***
Need of tracheostomy	2.371 (1.301 - 4.322)	***0.005***
ICU stay (days)	1.489 (1.319 - 1.602)	***<0.001***
In-ICU exitus	1.190 (1.078 - 1.459)	***<0.001***

conditions and/or complications. SAPS II, APACHE II, and APACHE III are useful in determining the outcome of ICU patients, but they are only available 24 h after ICU admission and require the determination of several physiopathological variables and analytical parameters, including the PaO2/FIO2 ratio. Therefore, in the immediate postoperative period physicians lack a prognostic tool other than their own clinical judgment. In addition, cardiac surgery patients constitute a specific population of ICU patients with low mortality and short length of stay; it is therefore crucial to detect the ones who are at risk of postoperative complications and/or death, especially considering the increase in aging and comorbidities in previous years [22].

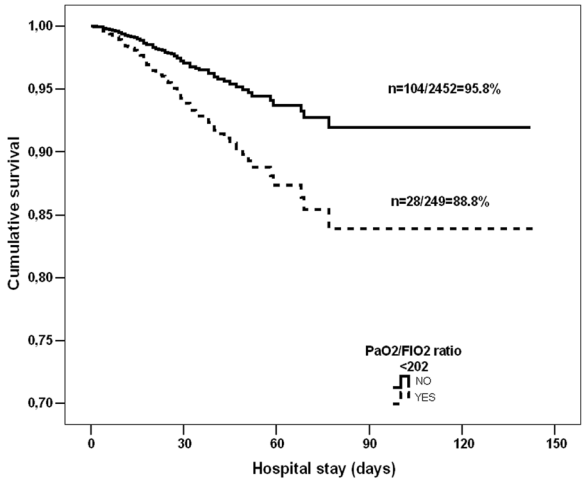

Figure 4 Kaplan-Meier survival curves for PaO2/FIO2 ratio <202 at 3 h subgroup.

The presence of preoperative organ dysfunction adversely affects outcome after cardiac surgery [23]. Minimal changes in preoperative kidney function are associated with a substantial increase in the risk of mortality and morbidity following cardiac surgery, even when increases in serum creatinine levels are minimal [24]. In addition, during Cardiopulmonary Bypass (CPB) the kidneys may suffer from an imbalance between oxygen supply and oxygen needs, resulting in inadequate oxygen delivery that can be associated with worsening of renal function [25]. In addition, the presence of COPD entails a variable degree of airway inflammation which may be aggravated by CPB [26]. Both COPD and CRF show a consistent trend of increasing frequency of postoperative complications with advanced disease [23]; the higher incidences of both chronic diseases in the PaO2/FIO2 group with the worst survival may be related to this.

Respiratory complications are frequent reasons for ICU readmission and increase length of stay and mortality [27]. In consequence, our findings for respiratory complications are not surprising, especially if we consider PaO2/FIO2 ratio as a reflection of respiratory status. Tracheal reintubation worsens outcomes, increasing both complications and mortality [28]. The higher risk of tracheal reintubation in the groups with lower PaO2/FIO2 ratios may promote the use of the ratio as an assessment tool in tracheal extubation and/or weaning strategies. Early tracheostomy in patients who require prolonged mechanical ventilation after cardiac surgery is associated with decreased length of

stay, morbidity, and mortality [27,28]. We suggest this strategy in the case of a persistently low PaO2/FIO2 ratio after an individual approach.

It was not the purpose of our study to differentiate between causative conditions of low PaO2/FIO2 ratio. Our results do not specifically address the cause of a low PaO2/FIO2 ratio in patients after cardiac surgery (which may represent a limitation of the study), but serve to evaluate the outcome in this scenario. Our study has other limitations as well. The most important is that it was a single-centre, observational study. However, it was conducted at a large tertiary referral hospital with a high level of complexity which performs all types of cardiac surgery and has a referral population of almost 2 million. Among the strengths of this study are its large sample size (the largest to date in studies addressing the postoperative PaO2/FIO2 ratio) and the prospective design. Our results may be clinically relevant, since a simple determination of PaO2/FIO2 ratio may provide very important information for determining outcome, both in terms of mortality and length of stay, in the immediate postoperative care of cardiac surgery patients. In addition, this strategy may be applicable in other post-cardiac surgery ICU settings because all the procedures and measurements are routine in clinical practice and easy to obtain.

Conclusions

In summary, the PaO2/FIO2 ratio may be useful for identifying cardiac surgery patients at risk in the immediate postoperative period. PaO2/FIO2 ratios are lower in patients at risk, and the values at 3 h after admission are the most useful in terms of predicting in-ICU outcome. Respiratory complications are more frequent with PaO2/FIO2 ratios lower than 241. A simple determination of PaO2/FIO2 ratio at 3 h may provide important information about patient status. Physicians should be alert to the presence of low values, especially PaO2/FIO2 ratios at 3 h below 202.

Key messages

- The PaO2/FIO2 ratio may be useful to identify at risk cardiac surgery patients in the immediate postoperative period.
- The PaO2/FIO2 ratio at 3 h after ICU admission has the highest prediction power in terms of outcome.
- Respiratory complications are more frequent when the PaO2/FIO2 ratio at 3 h is lower than 241 and poor outcome when the ratio below 202.

Abbreviations

PaO2/FiO2 ratio: Arterial partial pressure of O2 and fraction of inspired oxygen ratio; ARDS: Respiratory distress syndrome in adults; ICU: Intensive care unit; EuroSCORE: European system for cardiac operative risk evaluation; APACHE: Acute physiology and chronic health evaluation; SAPS: Simplified acute physiology score; CPB: Cardiopulmonary bypass; CABG: Coronary artery bypass graft; COPD: Chronic obstructive bronchopulmonary disease.

Competing interests

The authors declare that they have no competing interest.

Authors' contributions

FE was involved in the conception and design of the research, as well as performed statistical analysis and wrote the paper. JCLD performed partial statistical analysis and wrote the paper. CJ performed statistical analysis and interpretation of data. KS supervised and performed statistical analysis. DRC and HT were involved in the coordination and the acquisition of data. MLC and EF contributed to the design of the research and acquisition of data. JLV was involved in the conception, design of the research and interpretation of data. RM and ADP were involved in the design of the research and supervised the writing of the present manuscript. All authors read and approved the final version of this manuscript.

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5.2. Trabajos en curso de publicación internacional: resumen, comentarios y trabajo enviado.

• Lopez-Delgado JC, Esteve F, Javierre C, Torrado H, Carrio ML, Rodriguez-Castro D, Farrero E, Mañez R, Ventura JL. **The influence of Body Mass Index on outcomes in patients undergoing cardiac surgery: does it really exist the obesity paradox?** *PLoS One*.

Resumen: La obesidad influencia de manera notable la estratificación y planificación de la cirugía cardíaca. Algunos estudios han objetivado mejores resultados en la población obesa en comparación con la población con Índice de Masa Corporal (IMC) normal respecto a la mortalidad y supervivencia. Esta paradoja es aún objeto de controversia.

Estudiamos 2499 pacientes entre 2004 y 2009 con el objetivo de cuantificar la influencia del IMC sobre la mortalidad y morbilidad en cirugía cardíaca, y la existencia de la paradoja en la población. Para ello se dividieron los pacientes según el IMC: IMC normal (18.5-24.9 kg·m-2; n=523; 21.4%), sobrepeso (25-29.9kg·m-2; n=1150; 47%), obesos (≥30-≤34.9kg·m-2; n=624; 25.5%) y obesidad mórbida (≥35kg·m-2; n=152; 6.2%).

Tras ajustar las variables preoperatorias y intraoperatorias (mediante *propensity score*), una peor oxigenación y mejor estado nutricional, reflejados por una peor PaO2/FiO2 a las 24h y unos niveles de albúmina a las 48h más elevados respectivamente, fue observado en pacientes con mayor IMC. Los pacientes obesos mostraron mayor riesgo para infarto peroperatorio (OR: 1.768; 95% CI: 1.035-3.022; p=0.037) y sepsis (OR: 1.489; 95% CI: 1.282-1.997; p=0.005). La mortalidad hospitalaria fue del 4.8% (n=118) y la mortalidad a un año del 10.1% (n=252). No hubo diferencias en la mortalidad hospitalaria entre grupos. Los pacientes con sobrepeso mostraron una mejor supervivencia a 1 año comparados con la población normal (91.2% vs. 87.6%; Log Rank: p= 0.029).

Comentarios: A pesar de la mayor morbilidad en pacientes obesos, no hay diferencias en la mortalidad, por lo que no podemos atribuir un efecto protector a la presencia de la obesidad en pacientes sometidos a cirugía cardíaca.

Estado: Enviado pendiente de segunda revisión.

PLOS ONE

THE INFLUENCE OF BODY MASS INDEX ON OUTCOMES IN PATIENTS UNDERGOING CARDIAC SURGERY: DOES THE OBESITY PARADOX REALLY EXIST?

--Manuscript Draft--

Manuscript Number:	PONE-D-14-25556R1
Article Type:	Research Article
Full Title:	THE INFLUENCE OF BODY MASS INDEX ON OUTCOMES IN PATIENTS UNDERGOING CARDIAC SURGERY: DOES THE OBESITY PARADOX REALLY EXIST?
Short Title:	Effect of Body Mass Index after cardiac surgery.
Corresponding Author:	Juan Carlos Lopez-Delgado, MD Hospital Universitari Bellvitge L'Hospitalet de Llobregat, Barcelona SPAIN
Keywords:	Body mass index; cardiac surgery; Obesity; intensive care unit; postoperative outcomes; in-hospital mortality; long-term mortality.
Abstract:	Purpose: Obesity influences risk stratification in cardiac surgery in everyday practice. However, some studies have reported better outcomes in patients with a high body mass index (BMI): this is known as the obesity paradox. The aim of this study was to quantify the effect of diverse degrees of high BMI on clinical outcomes after cardiac surgery, and to assess the existence of an obesity paradox in our patients. Methods: A total of 2499 consecutive patients requiring all types of cardiac surgery with cardiopulmonary bypass between January 2004 and February 2009 were prospectively studied at our institution. Patients were divided into four groups based on BMI: normal weight (18.5-24.9 kg•m-2; n=523; 21.4%), overweight (25-29.9kg•m-2; n=1150; 47%), obese (≥30-≤34.9kg•m-2; n=624; 25.5%) and morbidly obese (≥35kg•m-2; n=152; 6.2%). Follow-up was performed in 2379 patients during the first year. Results: After adjusting for confounding factors, patients with higher BMI presented worse oxygenation and better nutritional status, reflected by lower PaO2/FiO2 at 24h and higher albumin levels 48h after admission respectively. Obese patients showed a higher risk for Perioperative Myocardial Infarction (OR: 1.768; 95% CI: 1.035-3.022; p=0.037) and septicaemia (OR: 1.489; 95% CI: 1.282-1.997; p=0.005). In-hospital mortality was 4.8% (n=118) and 1-year mortality was 10.1% (n=252). No differences were found regarding in-hospital mortality between BMI groups. The overweight group showed better 1-year survival than normal weight patients (91.2% vs. 87.6%; Log Rank: p= 0.029. HR: 1.496; 95% CI: 1.062-2.108; p= 0.021). Conclusions: In our population, obesity increases Perioperative Myocardial Infarction and septicaemia after cardiac surgery, but does not influence in-hospital mortality. Although we found better 1-year survival in overweight patients, our results do not support any protective effect of obesity in patients undergoing cardiac surgery.
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	Vibeke Videm, Prof Head of Departmen / Consultant, St Olav's University Hospital. vibeke.videm@ntnu.no She investigates mechanisms for complications following open-heart surgery and how they can be prevented, especially on mechanisms for how inflammation contributes to arteriosclerosis and cardiovascular disease,
Opposed Reviewers:	
Response to Reviewers:	Dear Rasheed Ahmad, Ph.D. PLOS ONE Academic Editor, We enclose a rebuttal letter responding to each point raised by you and the reviewers, together with a clean revised manuscript and a marked-up copy of the changes made from the previous article. Only specific changes have been marked due to the major revision needed. We would like to thank all the reviewers for their comments, which have helped us to make significant improvements in this manuscript. Since major revision was recommended, we have repeated the statistical analysis, based on the comments of reviewer #3. As a result, the aim and methods of the paper have undergone some changes and the results and discussion sections have been thoroughly re-written. The manuscript has been reviewed in full by a native English speaker (Prof. Michael Maudsley, from the Language Services of the Universitat de Barcelona - maudsley@ub.edu). Our financial disclosure has not changed since the previous submission. We also confirm that electronic health records were de-identified or anonymized prior to use. This point is now stated in the Methods section. Review Comments to the Author. Reviewer #1: While some speculation in the discussion is acceptable, attributing immunosupression to obesity as an explanation for increased infectious complications probably goes too far. It is unclear if there were differences in emergent patients versus elective, did duration of CPB matter? The speculations regarding infectious complications have been deleted in view of the reviewer's comment. Emergency patients have been omitted from the analysis, in accordance with the recommendations of reviewer #3 (see below). Although we do not provide specific analyses within the manuscript, in our preliminary analyses we found that duration of CPB did not influence mortality in BMI groups. Reviewer #2: This is a prospective observational study, aimed to evaluate the prognostic implication of BMI in patients undergoing cardiac surgery procedures with the aid of extracorporeal circulation. The study is well written. Main findings were that though higher BMI was associated with increased rates of respiratory related morbidity and risk of septicemia during ICU stay, BMI exerted no effect on early and late survival. These results are largely confirmatory of current knowledge on the topic. I have a main concern on that the authors should comment on: The study should be checked again as it appears not to have the statistical power to detect the differences shown. Indeed the very low incidence of morbidity in obese patients and the relatively low incidence of highly complex surgical procedures could be due to selection biases of a mono center study. This concern about the very low incidence of morbidity and the relatively low incidence of highly complex surgical procedures in obese patients is underlined in the discussion. We note that this may be a potential limitation of the study. However, propensity score analysis offsets some of those limitations, adding statistical power to detect the differences in outcomes. In addition, multivariate analysis still showed similar results. We are a referral hospital and cases are discussed in detail prior to surgical procedures. Long, highly complex surgical procedures are evaluated by a multi-specialist committee. We stress that our study is one of the largest carried out to date. In addition, we describe our data in great detail: unusually in a study of this area, we do not focus only on mortality but on morbidities as well.

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Additional Information:	
Question	**Response**
Financial Disclosure Please describe all sources of funding that have supported your work. A complete funding statement should do the following:	The authord received no specific funding for this work.

Include **grant numbers and the URLs** of any funder's website. Use the full name, not acronyms, of funding institutions, and use initials to identify authors who received the funding. **Describe the role** of any sponsors or funders in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. If they had no role in any of the above, include this sentence at the end of your statement: "*The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.*" If the study was **unfunded**, provide a statement that clearly indicates this, for example: "*The author(s) received no specific funding for this work.*" * typeset	
Competing Interests You are responsible for recognizing and disclosing on behalf of all authors any competing interest that could be perceived to bias their work, acknowledging all financial support and any other relevant financial or non-financial competing interests. Do any authors of this manuscript have competing interests (as described in the PLOS Policy on Declaration and Evaluation of Competing Interests)? **If yes**, please provide details about any and all competing interests in the box below. Your response should begin with this statement: *I have read the journal's policy and the authors of this manuscript have the following competing interests:* **If no** authors have any competing interests to declare, please enter this statement in the box: "*The authors have declared that no competing interests exist.*" * typeset	The authors have declared that no competing interests exist.

Ethics Statement You must provide an ethics statement if your study involved human participants, specimens or tissue samples, or vertebrate animals, embryos or tissues. All information entered here should **also be included in the Methods section** of your manuscript. Please write "N/A" if your study does not require an ethics statement.	The study was approved by the Institutional Ethics Committee of our hospital (Comité d' Ètica i Assajos Clínics de Hospital Universitari de Bellvitge). Our Institutional Ethics Comittee waived the need to consent.
Human Subject Research (involved human participants and/or tissue) All research involving human participants must have been approved by the authors' Institutional Review Board (IRB) or an equivalent committee, and all clinical investigation must have been conducted according to the principles expressed in the Declaration of Helsinki. Informed consent, written or oral, should also have been obtained from the participants. If no consent was given, the reason must be explained (e.g. the data were analyzed anonymously) and reported. The form of consent (written/oral), or reason for lack of consent, should be indicated in the Methods section of your manuscript. Please enter the name of the IRB or Ethics Committee that approved this study in the space below. Include the approval number and/or a statement indicating approval of this research.	
Animal Research (involved vertebrate animals, embryos or tissues) All animal work must have been conducted according to relevant national and international guidelines. If your study involved non-human primates, you must provide details regarding animal welfare and steps taken to ameliorate suffering; this is in accordance with the recommendations of the Weatherall report, "The use of non-human primates in research." The relevant guidelines followed and the committee that approved the study should be identified in the ethics statement. If anesthesia, euthanasia or any kind of	

animal sacrifice is part of the study, please include briefly in your statement which substances and/or methods were applied. Please enter the name of your Institutional Animal Care and Use Committee (IACUC) or other relevant ethics board, and indicate whether they approved this research or granted a formal waiver of ethical approval. Also include an approval number if one was obtained. **Field Permit** Please indicate the name of the institution or the relevant body that granted permission.	
Data Availability PLOS journals require authors to make all data underlying the findings described in their manuscript fully available, without restriction and from the time of publication, with only rare exceptions to address legal and ethical concerns (see the PLOS Data Policy and FAQ for further details). When submitting a manuscript, authors must provide a Data Availability Statement that describes where the data underlying their manuscript can be found. Your answers to the following constitute your statement about data availability and will be included with the article in the event of publication. **Please note that simply stating 'data available on request from the author' is not acceptable.** ***If, however, your data are only available upon request from the author(s), you must answer "No" to the first question below, and explain your exceptional situation in the text box provided.*** Do the authors confirm that all data underlying the findings described in their manuscript are fully available without restriction?	Yes - all data are fully available without restriction
Please describe where your data may be found, writing in full sentences. **Your answers should be entered into the box below and will be published in the form you provide them, if your manuscript is accepted.** If you are copying our sample text below, please ensure you replace any instances of XXX with the appropriate details.	All relevant data are within the paper.

If your data are all contained within the paper and/or Supporting Information files, please state this in your answer below. For example, “All relevant data are within the paper and its Supporting Information files.” If your data are held or will be held in a public repository, include URLs, accession numbers or DOIs. For example, “All XXX files are available from the XXX database (accession number(s) XXX, XXX)." If this information will only be available after acceptance, please indicate this by ticking the box below. If neither of these applies but you are able to provide details of access elsewhere, with or without limitations, please do so in the box below. For example: “Data are available from the XXX Institutional Data Access / Ethics Committee for researchers who meet the criteria for access to confidential data.” “Data are from the XXX study whose authors may be contacted at XXX.” * typeset	
Additional data availability information:	

To whom it may concern/ Editorial team,

On behalf of my co-authors, I submit the enclosed manuscript for consideration by the **PLOS ONE Journal**. It has not been published in this or a substantially similar form (in print or electronically, including on a web site), nor accepted for publication elsewhere, nor is it under consideration by another publication. None of the authors have any possible conflicts of interest (including financial or other relationships). Appropriate Ethics Committee approval has been obtained for the research reported (written committee documents will be supplied on request).

By means of this letter all the authors confirm that they have read and approved the paper, meet the criteria for authorship as established by the International Committee of Medical Journal Editors, believe that the paper represents honest work, and are able to verify the validity of the results reported.

The manuscript explores the so-called "obesity paradox" in cardiac surgery, reported previously in several publications. Its existence is not confirmed by our study; in fact we call the obesity paradox" into question in all types of cardiac surgery. We also explore related complications based on body mass index classification. This prospective observational study was carried out on a large sample and (rather unusually, even though we live in the risk assessment era) takes into account a variety of risk scores.

From your list of referees we would like to recommend Chiara Lazzeri as a reviewer for the present manuscript. Dr Lazzeri has great expertise in the area of intensive cardiac care and is ideally qualified to assess the strengths of our paper and to suggest potential improvements and revisions.

Long-term outcome is becoming increasingly important today in decision-making regarding health care interventions, especially with a view to maximizing healthcare resources. This is why our research focuses more on long-term outcomes than on ICU/short-term outcomes.

This study has been carried out as part of the PhD of the corresponding author.

We hope that our approach to the issue of obesity – focusing on medical rather than surgical aspects – will be of interest to you. We thank you for the opportunity to submit this report and look forward to hearing from you.

Sincerely,

Juan Carlos Lopez-Delgado
Hospital Universitari de Bellvitge
Intensive Care Department -Servei de Medicina Intensiva
C/Feixa Llarga s/n.08907.L'Hospitalet de Llobregat. Barcelona. Spain.
juancarloslopezde@hotmail.com / jlopez@bellvitgehospital.cat

Dear Rasheed Ahmad, Ph.D. PLOS ONE Academic Editor,

We enclose a **rebuttal letter** responding to each point raised by you and the reviewers, together with a clean revised manuscript and a marked-up copy of the changes made from the previous article. Only specific changes have been marked due to the major revision needed.

We would like to thank all the reviewers for their comments, which have helped us to make significant improvements in this manuscript. Since major revision was recommended, we have repeated the statistical analysis, based on the comments of reviewer #3. As a result, the aim and methods of the paper have undergone some changes and the results and discussion sections have been thoroughly re-written.

The manuscript has been reviewed in full by a native English speaker (Prof. Michael Maudsley, from the Language Services of the Universitat de Barcelona - maudsley@ub.edu).

Our financial disclosure has not changed since the previous submission. We also confirm that electronic health records were de-identified or anonymized prior to use. This point is now stated in the Methods section.

Review Comments to the Author.

Reviewer #1: **While some speculation in the discussion is acceptable, attributing immunosupression to obesity as an explanation for increased infectious complications probably goes too far. It is unclear if there were differences in emergent patients versus elective, did duration of CPB matter?**

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These results are largely confirmatory of current knowledge on the topic.

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Title: THE INFLUENCE OF BODY MASS INDEX ON OUTCOMES IN PATIENTS UNDERGOING CARDIAC SURGERY: DOES THE OBESITY PARADOX REALLY EXIST?

Short title: Influence of Body Mass Index after cardiac surgery.

Authors: Juan C Lopez-Delgado[1], Francisco Esteve[1], Rafael Manez[1], Herminia Torrado[1], Maria L. Carrio[1], David Rodríguez-Castro[1], Elisabeth Farrero[1], Casimiro Javierre[2], Josep L Ventura[1].

Affiliations:

[1]Hospital Universitari de Bellvitge, Intensive Care Department, IDIBELL (Institut d'Investigació Biomèdica Bellvitge; Biomedical Investigation Institute of Bellvitge), C/Feixa Llarga s/n. 08907, L'Hospitalet de Llobregat, Barcelona, Spain.

[2] Department Physiological Sciences II, University of Barcelona, Barcelona, Spain.

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Sources of financial support: None.

Conflicts of interest and disclosures: None of the authors have any conflicts of interest to report regarding the present paper.

ABSTRACT

Purpose: Obesity influences risk stratification in cardiac surgery in everyday practice. However, some studies have reported better outcomes in patients with a high body mass index (BMI): this is known as the obesity paradox. The aim of this study was to quantify the effect of diverse degrees of high BMI on clinical outcomes after cardiac surgery, and to assess the existence of an obesity paradox in our patients.

Methods: A total of 2499 consecutive patients requiring all types of cardiac surgery with cardiopulmonary bypass between January 2004 and February 2009 were prospectively studied at our institution. Patients were divided into four groups based on BMI: normal weight (18.5-24.9 $kg \cdot m^{-2}$; n=523; 21.4%), overweight (25-29.9$kg \cdot m^{-2}$; n=1150; 47%), obese (≥30-≤34.9$kg \cdot m^{-2}$; n=624; 25.5%) and morbidly obese (≥35$kg \cdot m^{-2}$; n=152; 6.2%). Follow-up was performed in 2379 patients during the first year.

Results: After adjusting for confounding factors, patients with higher BMI presented worse oxygenation and better nutritional status, reflected by lower PaO_2/FiO_2 at 24h and higher albumin levels 48h after admission respectively. Obese patients showed a higher risk for Perioperative Myocardial Infarction (OR: 1.768; 95% CI: 1.035-3.022; *p*=0.037) and septicaemia (OR: 1.489; 95% CI: 1.282-1.997; *p=0.005*). In-hospital mortality was 4.8% (n=118) and 1-year mortality was 10.1% (n=252). No differences were found regarding in-hospital mortality between BMI groups. The overweight group showed better 1-year survival than normal weight patients (91.2% vs. 87.6%; Log Rank: *p*= 0.029. HR: 1.496; 95% CI: 1.062-2.108; *p*= 0.021).

Conclusions: In our population, obesity increases Perioperative Myocardial Infarction and septicaemia after cardiac surgery, but does not influence in-hospital mortality. Although we found better 1-year survival in overweight patients, our results do not support any protective effect of obesity in patients undergoing cardiac surgery.

Keywords: Body mass index; cardiac surgery; Obesity; ntensive care unit; postoperative outcomes; in-hospital mortality; long-term mortality.

INTRODUCTION

Obesity is a risk factor for the development of diabetes mellitus, hypertension and coronary artery disease [1]. Morbid obesity (defined as ≥1.5 ideal weight) and body mass index (BMI) are included in the Parsonnet system and in the Society of Thoracic Surgeons' model for stratification of the risk for perioperative death [2, 3]. Since mortality risk factors of cardiac surgery and their incidence in obese patients are largely the same as in patients with normal BMI [4, 5], a similar outcome seems likely. However, some reports have shown a better survival rate in overweight and obese patients than in those with normal BMI. This is currently known as the obesity paradox [6, 7]. Indeed, increased BMI alone is not related to an increased perioperative risk in non-cardiac surgery [8] and extreme obesity is not more closely associated with poor survival than normal weight in the intensive care unit (ICU) [9].

On the other hand, obesity is associated with increased morbidity in the ICU. It markedly increases the risk of pulmonary and airway complications [10] and hampers tracheal intubation, mechanical ventilation and weaning, which requires specific ventilatory settings due to the mechanical and inflammatory alterations observed in this condition [11, 12]. In addition, obese patients more frequently develop ICU-acquired infections [13]. As a result, obesity is still regarded as a risk factor for adverse outcomes in the ICU.

The aim of this study was to quantify the effect of diverse degrees of higher BMI on clinical outcomes (morbidity, in-hospital mortality and 1-year mortality) after cardiac surgery and to assess the existence of an obesity paradox in our patients.

METHODS

Data from this prospective study were collected from 2499 consecutive patients undergoing different types of cardiac surgery between January 2004 and February 2009 at our institution. The patients were divided into four groups based on BMI: normal weight (18.5-24.9 $kg \cdot m^{-2}$; n=523; 21.4%), overweight (25-29.9$kg \cdot m^{-2}$; n=1150; 47%), obese (≥30-≤34.9 $kg \cdot m^{-2}$; n=624; 25.5%) and morbidly obese (≥35$kg \cdot m^{-2}$; n=152; 6.2%). [1-6]. The underweight group (n=24) was excluded from the study due to the low number of patients and events. Emergency (n=124) and redo (n=265) cases were excluded since they might have introduced a strong bias.

The study was approved by the Institutional Ethics Committee of our hospital (Comité d'Ètica i Assajos Clínics, Hospital Universitari de Bellvitge). Due to the observational

nature of the study, the Ethics Committee waived the need for consent. The follow-up was performed using the Catalan Health Central Registry (*Registre Central de Persones Assegurades*, RCA). A complete follow-up for evaluating 1-year mortality was performed in 2379 patients (95.2% of our study population).

Data on and during ICU admission were extracted from the medical registry of each patient in real time using a standardized questionnaire and were entered into a database for analysis. Electronic health records were de-identified prior to use. Recent acute myocardial infarction (AMI) was defined as an AMI that required admission to the hospital during the month before surgery or one that prevented discharge from the hospital before surgery. The other definitions used for this study were based on the Society of Thoracic Surgeons' national cardiac surgery database definitions [14].

Preoperative data (demographic data, co-morbidities and treatment before surgery), operative data and postoperative variables usually measured on and during admission (including main outcomes) were recorded together with cardiac surgery scores (Parsonnet, European System for Cardiac Operative Risk Evaluation (EuroSCORE) and ICU scores (Acute Physiology and Chronic Health Evaluation (APACHE) II and III, Simplified Acute Physiology Score (SAPS) II and III).

The operations were performed by the same group of cardiac surgeons throughout the study period. Cardiac procedures were performed in all patients using median sternotomy, standard cardiopulmonary bypass (CPB) with moderate hypothermia (34ºC) and antegrade cardioplegia. A mean aortic pressure of > 60mmHg was maintained during surgery. Protamine was administered to reverse heparin, in accordance with standard practice. In all patients, decisions regarding postoperative ICU management were made by the attending physician.

Statistical analysis

Statistical analysis was conducted using PASW statistics 13.0 (SPSS Inc., Chicago, Illinois, USA). Data are expressed as mean ± standard deviation. ANOVA was used to compare differences in characteristics and outcome differences between BMI groups, and a subsequent post-hoc test (Bonferroni test) was used to determine significant differences in the various pairwise comparisons. In all cases, the Kolmogorov-Smirnov test was used to assess the normal distribution of our population and the goodness-of-fit of the final regression models.

A propensity score analysis was used to adjust for preoperative and operative confounding factors in order to minimize baseline differences between the BMI groups.

The probability given by the propensity score was included in the different multivariate analyses. A stepwise logistic regression model was used to confirm differences between BMI groups. The BMI groups were included within the models, and the normal weight group was used as control. Survival analysis was carried out with the Kaplan-Meier estimator for the different BMI groups. A proportional hazards Cox regression model was used to evaluate the effect of staging in a BMI group on 1-year survival. A two-tailed *p*-value of 0.05 was considered statistically significant.

RESULTS

The median BMI of the whole sample was 28.2±4.1 $kg \cdot m^{-2}$ (range 18.7 - 50 $kg \cdot m^{-2}$). There was a low proportion (0.67%; n=19) of morbidly obese subjects with a BMI≥40$Kg \cdot m^{-2}$.

The preoperative characteristics of the patients, including treatment before surgery, are shown in **Table 1**. Univariate analyses showed higher rates of cardiovascular risk factors such as hypertension, diabetes mellitus, dyslipidaemia and hypertrophic cardiomyopathy in higher BMI groups compared with normal weight patients, as well as a higher proportion of treatment on β-blockers, statins and aspirin. Chronic obstructive pulmonary disease rates were higher in the obese groups. Patients in the normal group were likely to be younger than those who were overweight. Haemoglobin before surgery was lower in normal BMI than in the overweight and obese groups. Patients treated with aspirin did not experience a significant increase in postoperative bleeding or requirement for blood products.

The operative characteristics are shown in **Table 2.** There was a higher proportion of isolated valve surgery in the normal group, and a higher proportion of Coronary Arterial Bypass Graft in the higher BMI groups. Surgeries also included in the analysis were: pericardial surgery 0.8% (n=18), congenital cardiac surgery 1.8% (n=45), aortic surgery 2.7% (n=66), and cardiac tumours 1.4% (n=35).

Differences in postoperative data were observed between BMI groups (**Table 2**). Obese groups (obese and morbidly obese) were more likely to be ventilated >24h, suffer from perioperative AMI and septicaemia compared with the normal weight group. Regarding episodes of septicaemia, the main aetiologies were: deep sternal wound infection 0.04% (n=1), mediastinitis 0.12% (n=3), pneumonia 4.8% (n=12), and bacteraemia 3.3% (n=82). Higher BMI groups had lower arterial oxygen pressure values and lower fraction of inspired oxygen ratio (PaO_2/FiO_2) measurements, without any influence on

tracheal extubation or respiratory complications. In contrast, they showed higher albumin blood levels 48h after surgery.

The mean ICU stay was longer in the obese groups than in the normal weight group, while the pre-ICU stay in hospital was shorter in the obese groups. In-hospital mortality was 4.8% (n=118). Patients died mainly of multiple organ failure (n=83; 71%), heart failure (n=29; 23.9%) and septic shock (n=6; 5.1%). No differences were found regarding in-hospital mortality and its causes. Out of 2379 patients, 2139 survived. 1-year mortality was 10.1% (n=240).

The differences between groups after adjusting for preoperative and postoperative confounding factors using a propensity score analysis are shown in **Table 3**. No differences in hospital mortality were found between normal weight patients and the higher BMI group. However, the obese group showed higher perioperative AMI and septicaemia compared with normal weight patients. Higher BMI groups were more likely to have worse PaO_2/FiO_2 measurements in the first 24h after cardiac surgery and higher albumin blood levels 48h after surgery.

1-year survival was 89.9%: 87.6% (n=62/502) for the normal BMI group, 91.2% (n=98/1119) for the overweight group, 89.7% (n=63/609) for the obese group and 88.6% (n=17/149) for the morbidly obese. When we analyzed long-term outcome, the overweight group showed better 1-year survival than the normal weight group when evaluated by Kaplan-Meier survival analysis (**Figure 1**), and confirmed by a proportional hazards Cox regression model (HR: 1.496; 95% CI: 1.062-2.108; p= 0.021).

DISCUSSION

Previous studies have postulated the existence of an obesity paradox in terms of in-hospital and long-term mortality after cardiac surgery [6, 7, 15], despite the association of obesity with higher rates of cardiovascular risk factors and risk of death in the general population [16]. However, after adjusting for preoperative and operative confounding factors, the present study did not find that obesity had protective effect; nor did obesity exert any influence over in-hospital mortality, despite higher morbidities during the ICU stay in the higher BMI groups, especially in obese patients. On the other hand, overweight patients showed better 1-year survival.

Our findings challenge those of previous studies supporting the obesity paradox after cardiac surgery. In those studies, obese patients tended to be referred for surgical

revascularization at a younger age than normal BMI patients due to earlier development of coronary artery disease [6, 7]; this, together with the high levels of care provided in postoperative follow-up, may explain their better survival. Conceivably, the obesity paradox may result from direct comparisons of the study groups which produced a study bias due to incorrect risk adjustments. To minimize the risk of this bias, we performed a propensity score analysis in order to correct for confounding factors [17]. Consistent with epidemiological studies, we found higher cardiovascular risk factor rates in the higher BMI groups, including hypertrophic cardiomyopathy [16]. This condition and obesity itself are associated with diastolic dysfunction and lower coronary microvascular density in the obese population, which may increase the risk of heart failure [18, 19]. In addition, obese patients are more likely to be receiving preoperative statin treatment, which is associated with lower biochemical parameters of inflammatory response and myocardial damage following cardiac surgery [20]. Obese patients tend to receive more aggressive cardioprotective medication regimens, as was the case in our patients, and may also receive improved in-hospital management owing to the perceived increased risk. Thus, all these preoperative factors, together with the particular baseline differences between groups in each population studied and the operative variables shown in the univariate analysis, have to be taken into account in order to perform a propensity score analysis. In addition to these conditions, obese patients have a greater number of atherosclerotic lesions in coronary arteries, even at a younger age, than the normal body weight or overweight population [21, 22]. They suffer from low-grade chronic inflammation, which is also related to atherosclerosis and endothelial dysfunction [23, 24]. In consequence, the higher rates of perioperative AMI that we found in the obese might be explained by preoperative risk factors and obesity itself.

Cardiac surgery involves a systemic inflammatory response syndrome with the accumulation of both pro- and anti-inflammatory cytokines, which may lead to a worse outcome [25]. Peripheral adipose tissue has been shown to produce soluble cytokine receptors such as tumour necrosis factor receptors, which are believed to neutralize the harmful effects of cytokines in the myocardium [26]. Lower systemic vascular resistance, plasma renin activity and renin-angiotensin responses, lower levels of atrial natriuretic peptides, and an attenuated sympathetic nervous system are pathophysiological changes in obese patients that can balance the risk that obesity itself represents [27]. This may also explain why overweight and obesity are not associated

with higher all-cause and cardiovascular mortality rates in patients with heart failure [28]. At the same time, overweight and obese patients had higher postoperative albumin levels, which may reflect a preserved or increased lean body mass [29]. The correct functioning of the immune response system depends on the metabolic response system, and vice versa. As a result, the overweight and the obese have sufficient nutritional reserve and a more efficient metabolic state, and a better inflammatory and immune response to surgery [30]. This offers a possible explanation for the potential survival benefit in overweight groups in our population.

Higher septicaemia in obese patients is not a new finding. Sepsis is an important risk factor for mortality after cardiac surgery, which produces a sepsis-induced cardiac dysfunction per se [31, 32]. A BMI>30 $kg \cdot m^{-2}$ has been associated with increased sternal wound infection and saphenous vein harvest site infection [33]. Obesity and diabetes (which itself has a high incidence in obesity) are independent predictors of infection in patients undergoing CABG [34]. Although a high BMI is associated with a higher rate of ICU-acquired urinary tract, pulmonary, ICU-acquired catheter and blood stream infections, it seems to reduce the risk of death from septic shock [13, 35, 36]. Finally, hypoalbuminaemia also increases the risk of infection in cardiac surgery patients [37]. In spite of the lower postoperative albumin levels, normal BMI patients showed lower rates of septicaemia compared with the obese group. We hypothesised that obese patients have higher visceral adiposity, which is associated with chronic inflammation and can aggravate the stress of surgery, leading to an abnormal response in a septic scenario [29, 30].

Obesity is frequently associated with hypoxaemia (reflected by a low PaO_2/FIO_2) after CPB [38] and with a longer time on mechanical ventilation in ICU, especially when BMI is $\geq 40 kg \cdot m^{-2}$ [13]. A lower PaO_2/FIO_2 ratio correlated with the time required to carry out extubation and also with lung injury as a marker for outcome in some types of cardiac surgery [39, 40]. In obesity, end-expiratory lung volume is decreased, leading to impairment in the mechanics of the respiratory system, lung, and chest wall, as well as gas-exchange. Thus, recruitment maneuvers added to PEEP are crucial to improve oxygenation and compliance without causing adverse effects on the respiratory function [8, 9]. This may reflect the lack of influence over mortality despite worse oxygenation after admission in the higher BMI groups.

Our study presents certain limitations. The most important is that it was a single-centre observational study. We found a very low incidence of morbidity in obese patients and a

relatively low incidence of highly complex surgical procedures which may be due both to the selection bias inherent in a single-centre study and to the optimal postoperative management provided. Among the strengths of this study are the large sample size, which exceeds that of other contemporary studies [7, 15] and the prospective nature of the data. Furthermore, this investigation was conducted at a large tertiary referral hospital with all the patients that underwent surgery with CPB, which makes the study population more homogeneous. In addition, our mortality rates are similar to those reported in other series.

In conclusion, we found higher perioperative AMI and septicaemia after cardiac surgery in our obese population. Worse oxygenation and better nutritional status were also observed in patients with higher BMI, reflected by a lower PaO_2/FiO_2 at 24h and higher albumin levels 48h after admission respectively. However, there was no difference between groups in terms of in-hospital mortality. Although we found a better 1-year survival in overweight patients, our results do not support a protective effect of obesity in patients undergoing cardiac surgery. Therefore, our findings do not support the obesity paradox concept, which, in our view, may be the result of study biases. Further studies are needed to examine this issue in greater depth.

Author Contributions: JCLD was involved in the conception and design of the research, performed the statistical analysis and wrote the paper. FE performed statistical analysis and wrote the paper. HT was involved in the coordination and the acquisition of data. DRC contributed to the acquisition of data, especially in terms of follow-up. MLC and EF contributed to the design of the research and acquisition of data. CJ performed statistical analysis and interpretation of data. JLV was involved in the conception, design of the research and interpretation of data. RM was involved in the design of the research and supervised the writing of the present manuscript. All authors read and approved the final version of this manuscript.

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Figure 1. Kaplan-Meier survival curves comparing normal vs. overweight BMI groups.

Table 1. Distribution of preoperative variables according Body Mass Index group.

	Studied group (n = 2449)	Normal weight BMI = 18.5-24.9 $kg \cdot m^{-2}$ (n = 523; 21.4 %)	Overweight BMI = 25-29.9 $kg \cdot m^{-2}$ (n = 1150; 47 %)	Obese BMI = 30-34.9 $kg \cdot m^{-2}$ (n = 624; 25.5 %)	Morbidly obese BMI ≥ 35 $kg \cdot m^{2}$ (n = 152; 6.2 %)	*p*-value
Sex (male/female)	1600 / 849	344 / 179	800 / 350	389 / 235	67 / 85	*0.15*
Age (years)	65.1 ± 11.4	63.8 ± 13.7	65.6 ± 11	65.4 ± 10.2	63.5 ± 10.2	***0.012*** A
Hypertension	64.8% (1588)	46.1% (241)	65.6% (754)	76.3% (476)	77% (117)	***<0.001*** A,B,C
Diabetes Mellitus	17.9% (438)	13.6% (71)	17.8% (205)	20.2% (126)	23.7% (36)	***0.006*** A,B,C
Dyslipidemia	52.5% (1285)	39.2% (205)	54.5% (627)	58.5% (365)	57.9% (88)	***<0.001*** A,B,C
Peripheral vascular disease	9.4% (229)	9.8% (51)	9.4% (108)	9.3% (58)	7.9% (12)	*0.92*
Chronic renal insufficiency	4.7% (114)	5.5% (29)	4.7% (54)	4.2% (26)	3.3% (5)	*0.59*
Renal Failure (on Dialysis)	0.8% (20)	1.3% (7)	0.9% (10)	0.3% (2)	0.7% (1)	*0.69*
Creatinine before surgery ($mmol \cdot L^{-1}$)	95 ± 61	99 ± 81	95 ± 58	93 ± 45	88 ± 56	*0.22*
Previous Stroke	5.2% (127)	5.2% (27)	5.8% (67)	4.2% (26)	4.6% (7)	*0.49*
COPD	12.1% (296)	10.1% (53)	10.7% (123)	15.4% (96)	15.8% (24)	***0.03*** B,C
Active smokers	22.9% (562)	26.4% (138)	22% (253)	21.6% (135)	23.7% (36)	*0.45*
Previous Atrial Fibrillation	21.9% (538)	22% (115)	23.5% (271)	19.4% (121)	20.4% (31)	*0.87*
Previous Myocardial Infarction	17% (417)	14.3% (75)	18.4% (212)	16.8% (105)	16.4% (25)	*0.22*
Recent Myocardial Infarction	10.8% (264)	12.2% (64)	10.4% (120)	10.9% (68)	7.9% (12)	*0.45*
On B-Blockers	43.6% (1067)	36.7% (192)	44.3% (510)	46.8% (292)	48% (73)	***0.03*** A,B,C
On statins	44.6% (1093)	35.4% (185)	45.7% (525)	49.5% (309)	48.7% (74)	***0.001*** A,B,C
On Aspirin	48.3% (1183)	41.5% (217)	48.5% (558)	52.6% (328)	52.6% (80)	***0.01*** A,B,C
On diuretics	45.3% (1110)	44.9% (235)	44% (506)	46.2% (288)	53.3% (81)	*0.28*
Hypertrophic cardiomyopathy	33.6% (823)	23.9% (125)	34.9% (402)	37.5% (234)	40.8% (62)	***0.001*** A,B,C
Dilated cardiomyopathy	20.4% (500)	22.4% (117)	19.8% (228)	21.1% (132)	15.1% (23)	*0.23*
LVEF (%)	60.3 ± 11.8	59.7 ± 13	60.5 ± 11.6	60.7 ± 11.5	60.5 ± 10.7	*0.53*
Hemoglobin before surgery ($g \cdot dL^{-1}$)	13.1 ± 1.6	12.8 ± 1.6	13.2 ± 1.6	13.2 ± 1.7	13 ± 1.6	***0.003*** A,B
Platelet count before surgery ($1 \cdot nL^{-1}$)	217 ± 69	222± 71	214 ± 66	218 ± 65	224 ± 69	*0.061*
EuroSCORE	5.4 ± 2.5	5.7 ± 2.6	5.4 ± 2.6	5.1 ± 2.4	5.5 ± 2.3	*0.17*
Parsonnet score	10.3 ± 5.9	11 ± 6.4	9.9 ± 5.8	10.3 ± 5.9	10.2 ± 4.8	***0.02*** A

COPD = Chronic Obstructive Pulmonary Disease; NYHA = New York Heart Association classification; LVEF = Left ventricular ejection fraction; EuroSCORE = European system for cardiac operative risk evaluation.

Results are expressed as mean ± standard deviation or percentage. Statistical results correspond to ANOVA *p* values. Bonferroni post hoc testing with statistical significant differences: [A] between Normal weight and overweight subgroup; [B] between Normal weight and obese subgroup; [C] between Normal weight and morbidly obese subgroup.

Table 2.Distribution of intraoperative and postoperative variables according BMI group.

	Studied group (n = 2449)	Normal weight BMI = 18.5-24.9 kg·m^{-2} (n = 523; 21.4 %)	Overweight BMI = 25-29.9 kg·m^{-2} (n = 1150; 47 %)	Obese BMI = 30-34.9 kg·m^{-2} (n = 624; 25.5 %)	Morbidly obese BMI ≥ 35 kg·m^{2} (n = 152; 6.2 %)	*p*-value
Intraoperative data						
Isolated CABG	35.7% (874)	29.7% (155)	37.4% (430)	38% (237)	34.2% (52)	***0.02*** A,B,C
Isolated valve	50% (1225)	54.7% (286)	47.5% (546)	49% (306)	57.2% (87)	***0.01*** A,B,C
CABG+valve	7.6% (186)	8% (42)	8.2% (95)	7.1% (44)	3.3% (5)	*0.35*
Other cardiac surgery	6.7% (164)	7.6% (40)	6.9% (79)	5.9% (37)	5.3% (8)	*0.54*
Number of bypass	2.3 ± 0.8	2.3 ± 0.9	2.3 ± 0.8	2.3 ± 0.9	2.5 ± 0.8	*0.30*
CPB time(min)	110 ± 39	107 ± 37	111 ± 41	112 ± 39	109 ± 33	*0.24*
ACC time(min)	72 ± 29	71 ± 28	72 ± 30	73 ± 28	70 ± 21	*0.59*
Postoperative data						
SAPS III	39 ± 10	39 ± 10	39 ± 10	38 ± 10	38 ± 8	*0.29*
APACHE III	48 ± 17	48 ± 17	48 ± 17	48 ± 16	49 ± 15	*0.99*
Ventilation time (hours)	41 ± 113	36 ± 99	35 ± 96	52 ± 135	64 ± 165	*0.07*
Prolonged ventilation (>24 h)	17.8% (438)	15.1% (79)	16.9% (195)	20% (125)	25.6% (39)	***0.001*** B,C
PaO2/FiO2 ratio 3 h after admission	327 ± 91	353 ± 93	327 ± 89	310 ± 85	311 ± 107	***<0.001*** A,B,C
PaO2/FiO2 ratio 24 h after admission	311 ± 73	335 ± 73	312 ± 71	296 ± 71	288 ± 76	***<0.001*** A,B,C
Reintubation	1% (26)	0.9% (5)	1.3% (15)	0.8% (5)	0.6% (1)	*0.75*
Tracheostomy	1% (24)	0.3% (2)	0.9% (11)	1.1% (7)	2.6% (4)	*0.45*
Need of vasoactive drugs (h)	91 ± 125	88 ± 110	85 ± 107	96 ± 147	113 ± 181	*0.14*
LCOS	39.2% (960)	39% (204)	37.1% (427)	41.7% (260)	45.4% (69)	*0.19*
PMI	12% (293)	11.8% (62)	11.1% (127)	13.5% (84)	13.2% (20)	***0.03*** B,C
IABP support	7.5% (185)	6.8% (36)	7.7% (89)	7.7% (48)	7.9% (12)	*0.45*
Atrial Fibrilation	35% (857)	34.9% (183)	36.8% (424)	31.6% (197)	34.8% (53)	*0.37*
Creatinine peak after surgery(mmol·L^{-1})	110 ± 76	112 ± 92	110 ± 75	111 ± 66	102 ± 66	*0.62*
Acute Renal Failure	7.8% (192)	7.1% (37)	7.4% (85)	9.5% (59)	7.2% (11)	*0.38*
Albumin 48h after surgery (g·L^{-1})	28 ± 3.5	27 ± 3.5	28 ± 3.4	28.7 ± 3.7	28.5 ± 3.4	***0.001*** A,B, C
Hemorrhage-related reexploration	3.4% (83)	3.8% (20)	4.2% (48)	2.1% (13)	1.3% (2)	*0.08*
Pericardial tamponade	0.6% (15)	0.8% (4)	0.5% (6)	0.8% (5)	0	*0.65*
Drainage loss first 12 h (mL)	383 ± 287	392 ± 251	395 ± 307	364 ± 286	344 ± 235	*0.08*
Re-exploration	1.3% (32)	0.6% (3)	1% (12)	2.4% (15)	1.3% (2)	*0.42*
Need for blood products (Units)	1.1 ± 1.7	1.2 ± 1.8	1.1 ± 1.7	1.1 ± 1.5	1 ± 1.7	*0.28*
Stroke	1.5% (36)	2.1% (11)	1.3% (15)	1.3% (8)	1.3% (2)	*0.60*
Septicemia	4% (98)	3.8% (20)	2.6% (30)	5.6% (35)	8.5% (13)	***0.03*** B,C
Mean Pre-ICU stay	6.7 ± 8.5	7.8 ± 9.2	6.8 ± 8.4	6 ± 8.2	6.3 ± 7.6	***0.002*** B

in hospital (days)						
Mean ICU stay (days)	6.6 ± 8.9	6.7 ± 9.3	6 ± 7.1	7.4 ± 11.3	7.8 ± 9.3	***0.007*** [B,C]
Mean hospital stay (days)	23 ± 16.5	24 ± 18	22 ± 15	23 ± 18	24 ± 14	*0.09*
In-hospital mortality	4.8% (118)	5.2% (27)	4.4% (51)	5.4% (34)	3.9% (6)	*0.73*

SAPS = Simplified Acute Physiology Score; APACHE = Acute Physiology and Chronic Health Evaluation; CABG = coronary artery bypass graft; ACC = Aortic cross clamping; CPB = cardiopulmonary bypass. PaO2/FiO2 = Arterial partial pressure of O2 and fraction of inspired oxygen ratio; LCOS = Low Cardiac Output Syndrome; PMI = Perioperative Myocardial Infarction; IABP = intra-aortic balloon pump.

Results are expressed as mean ± standard deviation or percentage. Statistical results correspond to ANOVA *p* values. Bonferroni post hoc testing with statistical significant differences: [A] between Normal weight and overweight subgroup; [B] between Normal weight and obese subgroup; [C] between Normal weight and morbidly obese subgroup.

Table 3. Final models of multivariable analysis adjusted by a propensity score showing differences between Body Mass Index groups.

	Odds ratio (95%CI)	*p*-value
Differences between normal and overweight groups		
Age	1.010 (0.999 - 1.020)	*0.086*
PaO2/FiO2 ratio 3 h after admission	0.998 (0.997- 1.000)	***0.037***
PaO2/FiO2 ratio 24 h after admission	0.996 (0.994 - 0.998)	***<0.001***
Albumin 48 h after surgery	1.072 (1.031 - 1.115)	***<0.001***
In-hospital mortality	1.160 (0.564 – 2.387)	*0.687*
Differences between normal and obese groups		
Perioperative Myocardial Infarction	1.768 (1.035 - 3.022)	***0.037***
PaO2/FiO2 ratio 24 h after admission	0.992 (0.989 - 0.995)	***<0.001***
Albumin 48 h after surgery	1.132 (1.069 - 1.198)	***<0.001***
Mean ICU stay	1.020 (0.999 - 1040)	*0.058*
Septicemia	1.489 (1.282 - 1.997)	***0.005***
In-hospital mortality	1.146 (0.498 - 2.635)	*0.75*
Differences between normal and morbidily obese groups		
Albumin 48 h after surgery	1.138 (1.051 - 1.233)	***0.002***
PaO2/FiO2 ratio 24 h after admission	0.991 (0.987 - 0.994)	***<0.001***
In-hospital mortality	2.435 (0.578 – 10.249)	*0.225*

Figure 1
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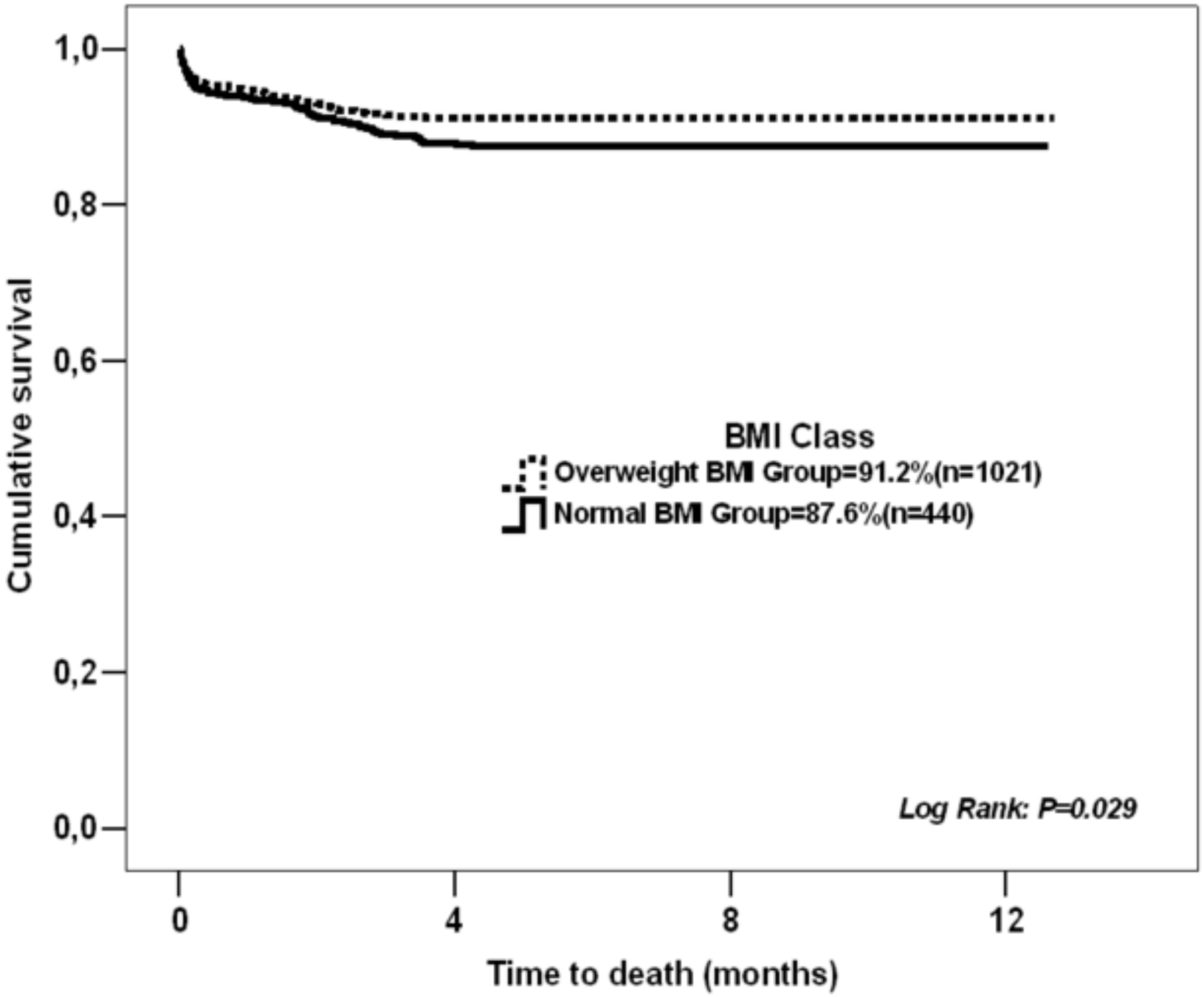

• Lopez-Delgado JC, Esteve F, Javierre C, Torrado H, Rodriguez-Castro D, Carrio ML, Farrero E, Skaltsa K, Ventura JL, Mañez R. **Evaluation of serial arterial lactate levels over short and long-term mortality in patients after cardiac surgery.** *PLoS One*.

Resumen: El lactato arterial (LA) elevado es frecuente en el postoperatorio de cirugía cardíaca y su elevación se asocia a mal pronóstico, a pesar de no estar detalladamente estudiado en estos pacientes.

Estudiamos 2935 pacientes sometidos a cirugía cardíaca con el fin de objetivar la utilidad del LA en el postoperatorio de cirugía cardíaca.

La mortalidad hospitalaria y a largo plazo (seguimiento de 6.3±1.7 años) fue del 5.9% y del 11.7% respectivamente. El LA fue diferente en todas sus mediciones (0h, 6h, 12h y 24h) entre supervivientes y no supervivientes durante las primeras 24h (P<0.001). La presencia de un LA >3.0 mmol·L^{-1} fue un predictor para mortalidad hospitalaria (Odds ratio (OR): 1.468; 95% Intervalo de confianza (95% IC): 1.239–1.739; P<0.001) y para la mortalidad a largo plazo (Hazard ratio (HR): 1.511; 95% IC: 1.251–1.825; P<0.001). El antecedente de un infarto de miocardio reciente y sufrir un mayor tiempo de CEC fueron predictores de un LA >3.0 mmol·L^{-1}. El patrón dinámico del LA fue similar en supervivientes y no supervivientes pero con mayores valores en no supervivientes (ANOVA de medidas repetidas, P<0.001). Asimismo, el área bajo la curva objetivó mayores niveles de LA en los no supervivientes (80.9±68.2 vs. 49.71±25.8mmol·l^{-1}·h^{-1}; P=0.038). Aquellos pacientes que presentaron un LA >3.0 mmol·L^{-1} y su pico se objetivó a las 24h tuvieron peor supervivencia (79.1% vs. 86.7–89.2%; *Log Rank*: P=0.03) comparados con aquellos que presentaron su pico al ingreso, a las 6h o a las 12h durante el postoperatorio.

Comentarios: Con respecto a lo anteriormente publicado en la literatura, nuestros resultados objetivan una dinámica parecida de la curva de lactato arterial entre supervivientes y no supervivientes, con mayores valores en estos últimos, lo cual podría sugerir un mecanismo similar para la producción y aclaramiento del lactato pero con una mayor acumulación en los no supervivientes. . También se objetiva que el pico de lactato arterial a las 24h del postoperatorio inmediato en aquellos pacientes con LA >3.0 mmol·L^{-1} está asociado a un peor pronóstico hospitalario y a largo plazo.

Estado: Enviado.

PLOS ONE

EVALUATION OF SERIAL ARTERIAL LACTATE LEVELS AS A PREDICTOR OVER SHORT AND LONG-TERM MORTALITY IN PATIENTS AFTER CARDIAC SURGERY.

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Short Title:	Arterial Lactate and outcome after cardiac surgery
Corresponding Author:	Juan Carlos Lopez-Delgado, MD Hospital Universitari Bellvitge L'Hospitalet de Llobregat, Barcelona SPAIN
Keywords:	cardiac surgery; hyperlactatemia; Area under the curve; postoperative care; in-hospital; long-term mortality.
Abstract:	Purpose: Although hyperlactataemia is common after cardiac surgery, its value as a prognostic marker is not entirely clear. The aim of the present study was to determine whether serial arterial lactate (AL) measurements after cardiac surgery can predict postoperative outcome. Methods: Prospective, observational study in a surgical ICU in a tertiary-level university hospital, including 2935 consecutive patients. AL was measured on ICU admission, and 6, 12 and 24h after surgery, together with clinical data and outcomes including in-hospital and long-term mortality. Results: In-hospital and long-term mortality (mean follow-up 6.3±1.7 years) were 5.9% and 11.7% respectively. In comparison with survivors, non-survivors showed higher mean AL values in all measurements (P<0.001). Hyperlactataemia (AL >3.0mmol/L) was a predictor for both in-hospital mortality (Odds ratio (OR): 1.468; 95% Confidence Interval (95% CI): 1.239-1.739; P<0.001) and long-term mortality (Hazard ratio (HR): 1.511; 95% CI: 1.251-1.825; P<0.001). Recent myocardial infarction and longer cardiopulmonary bypass time were predictors of hyperlactataemia. The pattern of AL dynamics was similar in survivors and non-survivors, but non-survivors presented higher AL values, as confirmed by repeated measures analysis of variance (P<0.001). The area under the curve also suggested higher levels of AL in non-survivors (80.9±68.2 vs. 49.71±25.8mmol*l-1*h-1; P=0.038). Patients with hyperlactataemia were divided according to their timing of peak arterial lactate, with higher mortality and worse survival in those in whom AL peaked at 24h compared with other groups (79.1% vs. 86.7-89.2%; Log Rank test: P=0.03). Conclusions: The dynamics of the postoperative AL curve in patients undergoing cardiac surgery is similar in survivors and non-survivors, though non-survivors present higher values. This suggests a similar mechanism of hyperlactataemia in both groups, albeit with a higher production or lower clearance of AL in non-survivors. The presence of hyperlactataemia, especially a peak at 24hhyperlactataemia, is associated with higher in-hospital and long-term mortality in those patients.
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Competing Interests You are responsible for recognizing and disclosing on behalf of all authors any	The authors have declared that no competing interests exist

competing interest that could be perceived to bias their work, acknowledging all financial support and any other relevant financial or non-financial competing interests. Do any authors of this manuscript have competing interests (as described in the PLOS Policy on Declaration and Evaluation of Competing Interests)? **If yes**, please provide details about any and all competing interests in the box below. Your response should begin with this statement: *I have read the journal's policy and the authors of this manuscript have the following competing interests:* **If no** authors have any competing interests to declare, please enter this statement in the box: "*The authors have declared that no competing interests exist.*" * typeset	
Ethics Statement You must provide an ethics statement if your study involved human participants, specimens or tissue samples, or vertebrate animals, embryos or tissues. All information entered here should **also be included in the Methods section** of your manuscript. Please write "N/A" if your study does not require an ethics statement. **Human Subject Research (involved human participants and/or tissue)** All research involving human participants must have been approved by the authors' Institutional Review Board (IRB) or an equivalent committee, and all clinical investigation must have been conducted according to the principles expressed in the Declaration of Helsinki. Informed consent, written or oral, should also have been obtained from the participants. If no consent was given, the reason must be explained (e.g. the data were analyzed anonymously) and reported. The form of consent (written/oral), or reason for lack of	The study was approved by the Institutional Ethics Committee of our hospital (Comité d' Ètica i Assajos Clínics de Hospital Universitari de Bellvitge). Our Institutional Ethics Committee waived the need to consent due to the observational nature of our study. The follow-up was performed using the Catalan Health Central Registry (Registre Central de Persones Assegurades, RCA).

consent, should be indicated in the Methods section of your manuscript. Please enter the name of the IRB or Ethics Committee that approved this study in the space below. Include the approval number and/or a statement indicating approval of this research. **Animal Research (involved vertebrate animals, embryos or tissues)** All animal work must have been conducted according to relevant national and international guidelines. If your study involved non-human primates, you must provide details regarding animal welfare and steps taken to ameliorate suffering; this is in accordance with the recommendations of the Weatherall report, "The use of non-human primates in research." The relevant guidelines followed and the committee that approved the study should be identified in the ethics statement. If anesthesia, euthanasia or any kind of animal sacrifice is part of the study, please include briefly in your statement which substances and/or methods were applied. Please enter the name of your Institutional Animal Care and Use Committee (IACUC) or other relevant ethics board, and indicate whether they approved this research or granted a formal waiver of ethical approval. Also include an approval number if one was obtained. **Field Permit** Please indicate the name of the institution or the relevant body that granted permission.	
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Additional data availability information:	

To whom it may concern,

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All authors send this letter as confirmation that they have read and approved the paper, have met the criteria for authorship as established by the International Committee of Medical Journals Editors, believe that the paper represents honest work, and are able to verify the validity of the results reported.

The manuscript explores for the first time the area under the curve of serial arterial lactate levels in cardiac surgery. Arterial lactate is a well-known mortality predictor. What is new is the different analysis we performed in order to evaluate the prognosis role that arterial lactate has. We call in question this in all types of cardiac surgery, exploring also the predictors of hyperlactatemia in the immediate postoperative course of these patients. It is a prospective observational study with larger sample size and the research has tended into account different risk scores, which is uncommon despite we live in the risk assessment era.

We would like to recommend from your list as editor of the present manuscript Giovanni Landoni who has great expertise in the field of intensive care and could assess the strengths and potential improvements/ revisions within our paper. We would be honoured if he could be our editor.

We would like to underline that long-term outcome is becoming increasingly important today in decision-making regarding health care interventions, especially if we want to maximize healthcare resources. This is the reason because our research team is focusing on long-term outcome results more than ICU/short-term outcome. This work has been done as a part of PhD of corresponding author.

The manuscript has been reviewed in full by a native English speaker (Prof. Michael Maudsley, from the Language Services of the Universitat de Barcelona - maudsley@ub.edu).

We hope I will be of your interest and our more medical and less surgical approach to the issue of obesity will not disappoint yours. Thank you for the opportunity of submitting this report.

If you need further information, please contact corresponding author,

Sincerely,

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Title: EVALUATION OF SERIAL ARTERIAL LACTATE LEVELS AS A PREDICTOR OVER SHORT AND LONG-TERM MORTALITY IN PATIENTS AFTER CARDIAC SURGERY.

Short title: Arterial Lactate and outcome after cardiac surgery.

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ABSTRACT

Purpose: Although hyperlactataemia is common after cardiac surgery, its value as a prognostic marker is not entirely clear. The aim of the present study was to determine whether serial arterial lactate (AL) measurements after cardiac surgery can predict postoperative outcome.

Methods: Prospective, observational study in a surgical ICU in a tertiary-level university hospital, including 2935 consecutive patients. AL was measured on ICU admission, and 6, 12 and 24h after surgery, together with clinical data and outcomes including in-hospital and long-term mortality.

Results: In-hospital and long-term mortality (mean follow-up 6.3±1.7 years) were 5.9% and 11.7% respectively. In comparison with survivors, non-survivors showed higher mean AL values in all measurements (P<0.001). Hyperlactataemia (AL >3.0mmol/L) was a predictor for both in-hospital mortality (Odds ratio (OR): 1.468; 95% Confidence Interval (95% CI): 1.239–1.739; P<0.001) and long-term mortality (Hazard ratio (HR): 1.511; 95% CI: 1.251–1.825; P<0.001). Recent myocardial infarction and longer cardiopulmonary bypass time were predictors of hyperlactataemia.

The pattern of AL dynamics was similar in survivors and non-survivors, but non-survivors presented higher AL values, as confirmed by repeated measures analysis of variance (P<0.001). The area under the curve also suggested higher levels of AL in non-survivors (80.9±68.2 vs. 49.71±25.8mmol·l^{-1}·h^{-1}; P=0.038). Patients with hyperlactataemia were divided according to their timing of peak arterial lactate, with higher mortality and worse survival in those in whom AL peaked at 24h compared with other groups (79.1% vs. 86.7–89.2%; Log Rank test: P=0.03).

Conclusions: The dynamics of the postoperative AL curve in patients undergoing cardiac surgery is similar in survivors and non-survivors, though non-survivors present higher values. This suggests a similar mechanism of hyperlactataemia in both groups, albeit with a higher production or lower clearance of AL in non-survivors. The presence of hyperlactataemia, especially a peak at 24hhyperlactataemia, is associated with higher in-hospital and long-term mortality in those patients.

Keywords: cardiac surgery;hyperlactatemia;Area under the curve;postoperative care;in-hospital;long-term mortality.

INTRODUCTION

Hyperlactataemia is a common occurrence after cardiac surgery, and is a marker of circulatory failure which is associated with poorer outcomes [1-4]. It mainly appears to be related to an imbalance between oxygen delivery and needs (type A hyperlactataemia) during cardiopulmonary bypass (CPB) and/or after cardiac surgery [4]. Lactate production increases in cells as a result of anaerobic glycolysis. Organ dysoxia mainly occurs in peripheral and non-vital tissues, being more severe as a result of inadequate cardiac output [2]. However, a considerable body of evidence has shown that hyperlactataemia may be due to increased aerobic lactate production [5]. Confounding variables such as the presence of liver cirrhosis may lower lactate clearance rates, and the presence of hyperlactataemia should be interpreted with caution and on a case-to-case basis.

Preoperative stratifications such as the EuroSCORE [6] and the Parsonnet score [7] do not take into account the morbidity and mortality produced by intraoperative and postoperative factors [8]. Thus, patient prognosis during the initial postoperative period may differ significantly from the preoperative estimation. Hyperlactataemia, defined according to a threshold of 3 mmol/L [3, 4], is associated with intraoperative complications and therefore with postoperative outcome [1, 4]. Serial arterial blood lactate levels (AL) have also been evaluated in paediatric cardiac surgery, with similar results [9]. However, the dynamics of the AL curve and the impact of the timing of hyperlactataemia on postoperative outcome, and even long-term mortality, have not yet been evaluated. Furthermore, the incremental Area under the Curve (AUC), which has been used to evaluate endocrinological factors such as glucose [10] and cortisol levels [11], and is a reflection of changes over time in the intensity of a measured factor, has not been used to date to assess AL levels in adult cardiac surgery.

The aim of our study was to determine whether serial arterial lactate (AL) measurements after cardiac surgery can predict postoperative outcome. We evaluated the dynamics, intensity and timing of AL levels during the immediate postoperative period, together with predictors of hyperlactataemia (AL levels>3mmol/L), to determine whether they can serve as a tool for postoperative assessment.

MATERIALS AND METHODS

This study was a post-hoc analysis of a prospective study of 2935 consecutive patients undergoing different types of cardiac surgery between January 2004 and December 2009 at our university hospital. Heart-transplant patients (*n*=134, off-pump coronary artery bypass (CABP) patients (*n*=185), and patients with liver dysfunction (*n*=62) were excluded due to the different physiopathology of AL production under these conditions [1].

The study was approved by the Institutional Ethics Committee of our hospital (Comité d' Ètica i Assajos Clínics, Hospital Universitari de Bellvitge). Due to the observational nature of the study, the Ethics Committee waived the need for consent. The follow-up was performed using the Catalan Health Central Registry (*Registre Central de Persones Assegurades*, RCA). The hospital records data were de-identified and analyzed anonymously. A complete follow-up was performed in 2837 patients up to May 2013, with a mean follow-up of 6.3±1.7 years.

AL was measured on ICU admission, at 6, 12 and 24h after surgery, together with clinical data and outcomes. Data on and during ICU admission were extracted from the medical registry of each patient in real time using a standardized questionnaire and recorded in a database for analysis. Recent acute myocardial infarction (AMI) was defined as an AMI that required admission to the hospital during the month before surgery or an AMI that did not allow discharge from the hospital before surgery. Long-term mortality was defined as mortality during the follow-up period. Major bleeding was defined as an output from chest drainages more than 300 mL during 3h the first 24h after surgery. The other definitions used for this study were based on the Society of Thoracic Surgeons' national cardiac surgery database definitions [12]. Preoperative data (demographic data, comorbidities and treatment before surgery), operative data and postoperative variables were usually measured on and during admission, and included main outcomes. Cardiac surgery scores (Parsonnet, European System for Cardiac Operative Risk Evaluation (EuroSCORE)) and ICU scores (Acute Physiology and Chronic Health Evaluation (APACHE) II and III, Simplified Acute Physiology Score (SAPS) II and III) were recorded for risk assessment. Hyperlactataemia was defined as an arterial lactate concentration >3.0mmol/L, in accordance with the previous literature [1-4]. Patients with

hyperlactataemia were classified into subgroups based on the time when the AL level peaked.

All operations were performed by the same group of cardiac surgeons during the study period. Cardiac procedures were performed in all patients using median sternotomy, standard CPB with moderate hypothermia (34ºC) and antegrade cardioplegia. A mean aortic pressure of >60mmHg was maintained during surgery. For revascularization the internal thoracic artery was used (or bilateral if possible) along with saphenous vein grafts. Bypass graft flow was assessed for each graft by Doppler transit time flowmetry. Protamine was administered to reverse heparin, in accordance with standard practice. For CABG surgery, aspirin was routinely administered within the first 6h after surgery following the local protocol. In all patients, decisions regarding postoperative ICU management were made by the attending physician. Patients were treated according to haemodynamic parameters, urine output and metabolic markers of tissue perfusion, such as AL levels and venous oxygen saturation. A strict glycaemic protocol was applied during and after cardiac surgery based on local protocols, even for non-diabetic patients.

Statistical analyses

Statistical analysis was conducted using PASW statistics 13.0 (SPSS Inc., Chicago, Illinois, USA). Data are expressed as mean ± standard deviation. In order to evaluate AL as a mortality risk factor after cardiac surgery, we analysed differences between survivors and non-survivors. For comparisons between groups the Mann-Whitney *U* test was used or, when appropriate, the two-sample *t*-test. The χ^2-test was used to evaluate categorical prognostic factors. A multivariate analysis was carried out using a stepwise logistic regression to identify AL as a risk factor for in-hospital mortality after cardiac surgery and for evaluating the predictors for hyperlactataemia. Proportional hazards Cox regression model was used to evaluate long-term mortality after adjusting for the time of follow-up period. We performed adjustment for age, cardiac surgery and ICU scores in order to avoid the influence of the severity of illness at the time of cardiac surgery and/or ICU admission. We tested for interactions between the variables that we introduced into all the multivariate analyses, in order to avoid destabilization of the different analyses.

The difference in AL curve between survivors and non-survivors was evaluated by means of repeated measures analysis of variance. The difference in incremental AUC between

groups was calculated using a computerized method (Simpson's integration) by integrating all measurements up to 24h. ANOVA was used to compare differences in characteristics and outcome between different hyperlactataemia subgroups (based on timing of peak AL) (*P* shown in tables) and subsequent post hoc tests (Bonferroni tests) were used to determine and confirm significant differences in the various pairwise comparisons (*P* shown in results). These differences were confirmed via multivariate analysis after adjusting for preoperative and postoperative scores. In all cases, the Kolmogorov-Smirnov test and D'Agostino-Pearson omnibus normality test was used to check the normal distribution of our population and to assess the goodness-of-fit of the final regression models. Survival analysis was carried out using the Kaplan-Meier estimator for the different hyperlactataemia groups in patients in whom follow-up was completed. A two-tailed *P* value<0.05 was considered statistically significant.

RESULTS

Evaluation of AL as a risk factor for in-hospital and long-term mortality

In-hospital mortality was 5.9%. The results of the univariate analysis of preoperative, intraoperative and postoperative data comparing survivors and non-survivors revealed higher comorbidity and complications in the non-survivors, including higher mean values in all serial AL measurements (**Table 1** and **2**).

Causes of in-hospital mortality were: 6.3% haemorrhage-related (*n*=11); 40.2% cardiac-related (*n*=70), which includes 5.7% postoperative AMI (*n*=10) and 1.7% cardiac rupture (*n*=3); 35% Multiorgan failure (*n*=61); 11% sepsis (*n*=19); 5.2% mesenteric ischaemia (*n*=9); and 2.3% stroke (*n*=4). The multivariate analysis for mortality showed that hyperlactataemia at any time was a predictor for in-hospital (Odds ratio (OR): 1.468; 95% Confidence Interval (95% CI): 1.239–1.739; *P*<0.001) and long-term mortality (Hazard ratio (HR): 1.511; 95% CI: 1.251–1.825; *P*<0.001).

Evaluation of predictors of hyperlactataemia after cardiac surgery

The results of the univariate analysis of preoperative, intraoperative and postoperative data comparing patients with normal lactate and those with hyperlactataemia revealed higher comorbidity and complication rates in the latter subgroup (**Tables 3** and **4)**. The preoperative data (recent AMI), intraoperative data (higher CPB time) and postoperative

data (higher creatinine peak after surgery) were found to be statistically significant predictors of hyperlactataemia. In contrast, intra-aortic balloon pump (IABP) support appeared to protect against the occurrence of hyperlactataemia (**Table 5**).

Evaluation of dynamics and intensity of AL after cardiac surgery

The AL dynamics (**Figure 1**) was similar in survivors and non-survivors, but with higher values in non-survivors, as confirmed by repeated measures analysis of variance between groups (P<0.001). The AUC of AL also suggested higher AL production in non-survivors than in survivors: 80.9±68.2 vs. 49.71±25.8 $mmol \cdot l^{-1} \cdot h^{-1}$ (P=0.038).

Evaluation of timing of AL peak in patients with hyperlactataemia after cardiac surgery

Patients with hyperlactataemia were divided according to the timing of peak AL (on admission, or at 6, 12 or 24h after surgery). The differences found by the univariate analysis of preoperative, intraoperative and postoperative data between hyperlactataemia subgroups are shown in **Tables 6** and **7**.

Preoperative variables confirmed higher haemoglobin before surgery in the 6h (Bonferroni post hoc P=0.001) and 12h (P<0.001) subgroups, and higher left ventricular ejection fraction (P=0.02) in the 6h subgroup compared with the group with peak AL levels on admission. The latter had a higher incidence of recent AMI than the 12h subgroup (P=0.015), and the 24h subgroup had higher chronic renal insufficiency than the 6h subgroup (P=0.002). Regarding intraoperative variables, those in whom hyperlactataemia peaked on admission suffered longer CPB times compared with those with peaks at 6, 12 and 24h (P< 0.001). Postoperative variables showed higher mortality risk in all subgroups compared with the 24h subgroup (P< 0.001). A higher risk for reintubation and Low Cardiac Output Syndrome (LCOS) was also apparent in the 24h subgroup compared with the 6h subgroup (P=0.035 and P<0.001 respectively), along with a higher risk for LCOS compared with the 12h subgroup (P<0.001). All these comparisons were later confirmed by the logistic regression model adjusted for risk prediction scores (**Table 8**). No differences were found between the 6h and 12h subgroups.

We observed a long-term global mortality of 11.7% (n=313/2663) with a mean follow-up of 6.3±1.7 years, after excluding patients who died in-hospital and those who survived

but in whom follow-up could not be performed. In the long-term scenario mortality was highest in the 24h AL peak subgroup (*n*=14/67; 20.9%; *P*=0.001) compared with the other subgroups (peak at admission subgroup 12.4% (*n*=29/233); peak at 6h subgroup 13.3% (*n*=70/526); peak at 12h subgroup 11.07% (*n*=36/325)). A Cox proportional hazards model of patient mortality demonstrated that the subgroup with peak AL at 24h had a higher mortality risk than other groups (HR: 1.769; 95% CI: 1.572–2.033; *P* <0.001). Kaplan-Meier plots (**Figure 2)** illustrated that patients in the 24h AL peak subgroup had worse survival over the follow-up period. The overall survival of AL subgroups on admission, and 6h and 12h after admission was similar to that of patients without hyperlactataemia (*n*=1573; 85.7% survival).

DISCUSSION

Using methods that have not been evaluated previously in the cardiac surgery population, this study underlines the importance of serial measurements of AL levels and production, in order to assess its value as a prognostic marker after cardiac surgery. The main findings of our study are the association between mortality and higher AL production, from both the dynamics and the intensity/quantitative perspective and the occurrence of peak AL at 24h in patients with hyperlactataemia, even in terms of long-term mortality.

AL levels can be influenced by several factors. Poorer liver function pre-surgery or an exacerbation of liver dysfunction in the setting of CPB may reduce AL clearance [13]. During heart transplantation, the mechanisms of AL production may be more influenced by cold/warm ischaemia times [14]. Off-pump CABG surgery also leads to lower AL release, suggesting a mechanism associated with the cellular inflammatory response [15]. This explains why we excluded subgroups of these patients from the study.

Hyperlactataemia predicts in-hospital postoperative mortality after cardiac surgery with a maximum AL threshold of $\geq$4.4mmol·L^{-1} in the first 10h or >3mmol·L^{-1} in the first 12 h post-operation [2, 3]. It has been postulated that its association with central venous oxygen saturation could be used to identify patients with occult hypoperfusion and subsequently guide haemodynamic optimization [16]. However, the ideal AL threshold for assessing mortality risk is not yet known. The pattern of AL dynamics seems to be similar in survivors and non-survivors, which suggests a similar mechanism of

hyperlactataemia. However, the AUC showed differences in AL between groups, with higher AL values in non-survivors, suggesting a higher intensity of AL production and/or lower AL clearance in this group. Variations related to the method used in estimating AUC do not seem to be clinically relevant [10]. Although AUC has not previously been used for AL analysis in clinical practice, it is advantageous from both a statistical and biological point of view. Statistically, it simplifies the analysis by creating a single summary response from multiple measurements, increasing the power of testing without sacrificing the information contained in the multiple measurements. Biologically, it incorporates the intensity and sensitivity contained in repeated measurements into the statistical analysis [11].

Low oxygen delivery and impairment of tissue oxygen utilization during CPB are the most likely causes of hyperlactataemia and can exert deleterious effects on different organs, especially on renal function, during the early postoperative period [17, 18]. At the same time, hyperlactataemia in the ICU is more frequent when renal failure is present. Kidneys are responsible for 30% of lactate metabolism via gluconeogenesis or complete oxidation, but unlike the liver, the kidney's ability to remove lactate is increased by acidosis [5]. The duration of CPB may be a surrogate of the complexity of the procedure or of unexpected intraoperative problems, with procedures requiring prolonged CPB being more likely to cause hyperlactataemia, together with acute kidney injury [19]. This may explain why a longer CPB duration was associated with the occurrence of hyperlactataemia. On the other hand, the finding of a higher creatinine peak after surgery as a predictor of hyperlactataemia is not clinically relevant.

AMI may contribute significantly to decreasing cardiac function in patients with hibernating myocardium. Despite cardioplegic protection, ischaemic-reperfusion states can lead to a variable degree of myocardial stunning during cardiac surgery [20]. This scenario can contribute to a low left ventricular ejection fraction after cardiac surgery, which is a risk factor for hyperlactataemia [1]. IABP support can contribute to haemodynamic stabilization, in particular for non-elective surgery, and is a safe option to support heart failure in cardiac surgery [21]. Thus, our finding that recent AMI is a predictor and IABP is a protective factor for hyperlactataemia was not unexpected.

Regarding the physiopathology of AL production, the dominant paradigm suggests anaerobic mechanisms while recent findings suggest an increased aerobic AL production secondary to adrenergic stimulation [5]. Stimulation of β-adrenergic receptors increases plasma glucose concentration, thereby increasing the substrates for glycolysis and AL production [5]. During CPB, impaired perfusion can provoke the release of stress hormones and cytokines, leading to insulin resistance and increased glucose production. This produces a glucose excess that is degraded to lactate by the glycolytic pathway, and also increases AL production [22]. This reinforces the need for an aggressive strategy of monitoring glycaemia during and after cardiac surgery.

Hyperlactataemia between 6 and 16h after surgery has been shown to be a better predictor of mortality than at 24h [3]. However, we found higher mortality with later hyperlactataemia, which may be a reflection of prolonged tissue hypoperfusion even after surgery (hypoperfusion and/or increased O_2 utilization occurs during the postoperative period [23]) or of insufficient correction of haemodynamic injury despite adequate treatment. Higher work-of-breathing related to lung injury, pulmonary oedema or an attempt to compensate metabolic acidosis increases pulmonary lactate levels [24]. Norepinephrine has also been associated with higher AL levels [3] and reintubation is mainly dependent on cardiac variables [25]. In consequence, the higher rates of LCOS and reintubation that we found in patients with hyperlactataemia at 24h were expected.

Our study presents certain limitations. The most important is that it was a single-centre observational study. The higher hyperlactataemia rates and postoperative complications such as perioperative AMI compared with previous studies could be a point of criticism [1-3]. Serial AL measurements refer only to the first 24h: thus, AUC could be underestimated in the 24h peak group, and this might mean that the real AUC in this group could explain the poor outcome rather than the late peak itself. However, this investigation was conducted at a large tertiary referral hospital with a high level of complexity, as reflected in our patients' higher preoperative and postoperative scores and comorbidities. Among the strengths of this study are the large sample size for the assessment of postoperative AL and the prospective data collection. AL levels can be helpful in the immediate postoperative period when cardiac surgery scores cannot evaluate surgical injury and when it is too early for ICU evaluation [7]. Furthermore, all

patients underwent surgery with CPB, and AL levels are simple and quick to obtain in most institutions, which make our results more homogeneous and more easy to compare.

In summary, the dynamics of the AL curve seems to be similar in survivors and non-survivors, but values in non-survivors are higher, which suggests a similar mechanism underlying the development of hyperlactataemia. AUC measurement of the AL dynamic curve can reflect a higher intensity of AL production and/or lower AL clearance, and may be useful for prognosis purposes. Having a 24h hyperlactataemia peak was associated with higher in-hospital and long-term mortality in patients undergoing cardiac surgery. We found that recent AMI and longer CPB time were predictors of hyperlactataemia and that IABP support was a protective factor. We think that evaluation of serial AL in the postoperative period and recognition of hyperlactataemia is crucial to address prognosis and guide haemodynamic treatment, especially in high-risk patients. Correction of risk factors for hyperlactataemia, such as a reduction in CPB time, together with prompt and aggressive monitoring and treatment at the bedside could control or prevent this condition and substantially improve the prognosis.

Author Contributions: JCLD was involved in the conception and design of the research. He also performed statistical analysis and wrote the paper. FE performed statistical analysis and wrote the paper. CJ performed statistical analysis and interpretation of data. HT and DR were involved in the coordination and the acquisition of data. DRC contributed to the acquisition of data, especially in terms of follow-up. MLC and EF contributed to the design of the research and acquisition of data. KS supervised the adequacy of statistical analysis, including the different multivariate analyses with an adjustment for prognosis scores. JLV was involved in the conception, design of the research and interpretation of data. RM was involved in the design of the research and supervised the writing of the present manuscript. All authors have read and approved the final version of this manuscript.

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Figure 1. Dynamics of arterial lactate levels curve of different measurements between survivors and non-survivors (*P<0.001*).

Figure 2. Kaplan-Meier survival curves for the different hyperlactatemia timing groups.

Table 1. Preoperative variables according in-hospital survivors and non-survivors groups.

	All patients (n=2935)	Survivors (n=2761; 94.1%)	Non-survivors (n=174; 5.9%)	*P*
Sex (male)	63.9% (1876)	94.2% (1768)	5.8% (108)	*0.63*
Sex (female)	36.1% (1059)	93.7% (993)	6.3%(66)	
Age (years)	64.5±11.6	64.2±11.6	69.9±9.7	***<0.001***
BMI ($Kg \cdot m^{-2}$)	28±4.3	27.9±4.2	27.9±4.6	*0.93*
Hypertension	62.8% (1844)	62.0 % (1713)	75.3% (131)	***<0.001***
Diabetes Mellitus	25.5% (748)	24.9% (689)	33.9% (59)	***0.01***
Dyslipidemia	50.5% (1483)	50.3% (1388)	54.6% (95)	*0.27*
Peripheral vascular disease	8.9% (262)	8.3% (230)	18.4% (32)	***<0.001***
Chronic renal insufficiency	5.3% (156)	4.7% (129)	15.5% (27)	***<0.001***
Renal Failure (on Dialysis)	0.8%(24)	0.8%(21)	1.7%(3)	*0.16*
Creatinine before surgery ($mmol \cdot l^{-1}$)	96±60	95±59	119±66	***<0.001***
Previous Stroke	5.7 % (166)	5.5% (152)	8.0% (14)	*0.17*
COPD	11.0 % (352)	11.6% (321)	17.8% (31)	***0.021***
Active smokers	23.1% (678)	23% (636)	24.1% (42)	*0.46*
Previous Atrial Fibrillation	23.9% (701)	23.4% (646)	25.8% (45)	*0.35*
Previous Myocardial Infarction	15.5% (454)	15.2% (420)	19.5% (34)	*0.13*
Recent Myocardial Infarction	11.1% (325)	10.6% (292)	19.0% (33)	***0.002***
NYHA class III-IV	41.7% (1225)	41.7% (1152)	41.9% (73)	*0.92*
On B-Blockers	41% (1204)	41.1% (1134)	40.2% (70)	*0.87*
On statins	41.3% (1212)	41.3% (1141)	40.8% (71)	*0.93*
On Aspirin	44.5% (1306)	44.5% (1230)	43.7% (76)	*0.87*
On diuretics	47.6% (1396)	46.6% (1286)	63.2% (110)	*0.001*
Hypertrophic cardiomyopathy	31% (909)	30.6% (847)	35.6% (62)	*0.26*
Dilated cardiomyopathy	20.4% (600)	20.2% (558)	24.1% (42)	*0.29*
LVEF (%)	60±12	59±13	60±11	*0.31*
PAP (mmHg)	46±16	45±16	49±16	*0.05*
Hemoglobin before surgery ($g \cdot dL^{-1}$)	13±1.7	13±1.7	12±1.9	***0.01***
Platelet count before surgery($1 \cdot nl^{-1}$)	215±68	216±68	206±74	*0.07*
Emergent Surgery	5.0% (148)	4.5% (124)	13.8% (24)	***<0.001***
Past Cardiac surgery	9.4% (276)	9.2% (253)	13.2% (23)	*0.08*
EuroSCORE	6.3±3.5	5.7±2.8	8.5±3.7	***<0.001***
Parsonnet score	11.5±4.4	11.2±7.1	15.3±9.6	***<0.001***

COPD=Chronic Obstructive Pulmonary Disease. BMI=Body Mass Index. COPD=Chronic Obstructive Pulmonary Disease. NYHA= New York Heart Association classification. LVEF= Left ventricular ejection fraction. PAP= Pulmonary arterial pressure. EuroSCORE= European system for cardiac operative risk evaluation. Results are expressed as mean± standard deviation or percentage.

Table 2. Postoperative and intraoperative data according in-hospital survivors and non-survivors groups.

	All patients (n=2935)	Survivors (n=2761; 94.1%)	Non-survivors (n=174; 5.9%)	*P*
Intraoperative data				
Isolated CABG	32.2% (945)	32.4% (895)	28.7% (50)	*0.16*
Isolated valve surgery	51.6% (1515)	51.8% (1431)	48.3% (84)	*0.65*
CABG + valve surgery	6.9% (203)	6.7% (185)	10.3% (18)	*0.09*
Other cardiac surgery	9.3% (272)	9.1% (250)	12.6% (22)	*0.16*
Number of bypass	2.3±1.0	2.3±0.9	2.1±0.8	*0.12*
CPB time (min)	112±41	111±39	121±22	***0.001***
ACC time (min)	74±30	75±25	79±36	*0.07*
Postoperative data				
APACHE II	12.3±4.6	11.8±4.1	19.2±7.1	***<0.001***
APACHE III	50±18.5	48.0±16.0	79.5±28.5	***<0.001***
SAPS II	24.0±9.6	23.3±8.4	39.0±14.7	***<0.001***
SAPS III	40.0±10.5	39±9.6	52.6±13.6	***<0.001***
Ventilation time (hours)	50±127	39±98	89±161	***<0.001***
PaO2/FiO2 ratio 3hs after admission	321±91	326±93	276±112	***<0.001***
PaO2/FiO2 ratio 12hs after admission	3112±90	315±87	249±99	***<0.001***
PaO2/FiO2 ratio 24hs after admission	308±77	312±73	234±93	***<0.001***
Reintubation	1.1% (31)	0.9%(25)	3.4%(6)	***0.01***
Tracheostomy	1.3%(38)	1.1%(29)	5.2%(9)	***0.005***
Need of vasoactive drugs(hs)	103±140	90±115	237±266	***<0.001***
LCOS	41.6%(1221)	38.8%(1072)	85.6%(149)	***<0.001***
PMI	11.8%(346)	10.3%(285)	35.1%(61)	***<0.001***
IABP support	7.9%(231)	6.7%(186)	27%(47)	***<0.001***
Atrial Fibrilation	39.3%(1154)	37.7%(1042)	64.4%(112)	***<0.001***
Creatinine peak after surgery($mmol \cdot l^{-1}$)	114±81	106±70	232±129	***<0.001***
Acute Renal Failure	9.7%(285)	6.4%(178)	61.5%(107)	***<0.001***
Need for RRT	2%(59)	0.8%(22)	21.3%(37)	***<0.001***
Albumin 48h after surgery ($g \cdot L^{-1}$)	28±4	28±4.1	25±4.8	***<0.001***
Hemorrhage-related reexploration	3.5%(103)	3%(83)	11.5%(20)	***<0.001***
Pericardial tamponade	0.7%(22)	0.6%(17)	2.9%(5)	***0.008***
Drainage loss first 12h (ml)	393±301	385±285	530±481	***<0.001***
Major bleeding	4.4%(116)	3.6%(98)	10.3%(18)	***0.001***
Re-exploration	1.5%(44)	1.2%(35)	5.2%(9)	***<0.001***
Need for blood products (Units)	1.1±1.7	1.1±1.9	2.3±2.5	***0.01***
Stroke	1.4%(42)	1%(28)	8%(14)	***<0.001***
Septicemia	7.1%(195)	4.7%(130)	37.3%(65)	***<0.001***
Mean ICU stay (hours)	127±151	117±127	294±318	***0.03***
Mean hospital stay (days)	24.5±21.3	23.7±17.3	35.7±52.6	***<0.001***

CABG=coronary artery bypass graft. ACC= Aortic cross clamping. CPB=cardiopulmonary bypass. SAPS=Simplified Acute Physiology Score. APACHE= Acute Physiology and Chronic Health Evaluation.

PaO2/FiO2= Arterial partial pressure of O2 and fraction of inspired oxygen ratio. LCOS= Low Cardiac Output Syndrome. PMI= Perioperative Myocardial Infarction. IABP= intra-aortic balloon pump. AL=Arterial Lactate. RRT=Renal Replacement Therapy. Results are expressed as mean± standard deviation or percentage.

Table 3. Preoperative data according postoperative hyperlactatemia (lactate≥3.0mmol/L) in any time.

	All patients (n=2935)	Normal lactate levels (n=1625; 55.4%)	hyperlactatemia (n=1310; 44.6%)	*P*
Sex (male)	63.9% (1876)	70.1% (1139)	56.3% (737)	***0.01***
Sex (female)	36.1% (1059)	29.9% (486)	43.7% (573)	
Age (years)	64.5±11.6	64±12	65±11	***0.002***
BMI ($Kg \cdot m^{-2}$)	28±4.3	28±4.3	28±4.1	*0.19*
Hypertension	62.8% (1844)	63% (1024)	62.6% (820)	*0.84*
Diabetes Mellitus	25.5% (748)	27.4% (451)	22.7% (297)	***0.004***
Dyslipidemia	50.5% (1483)	52.5% (853)	48.1% (630)	***0.02***
Peripheral vascular disease	8.9% (262)	9.7% (158)	7.9% (104)	*0.10*
Chronic renal insufficiency	5.3% (156)	5.8% (95)	4.7% (61)	*0.18*
Renal Failure (on Dialysis)	0.8%(24)	0.8% (14)	0.8% (10)	*0.82*
Creatinine before surgery ($mmol \cdot l^{-1}$)	96±60	97±69	93±44	*0.06*
Previous Stroke	5.7% (166)	4.4% (71)	7.3% (95)	***0.01***
COPD	11% (352)	13.8% (226)	9.6% (126)	***<0.001***
Active smokers	23.1% (678)	24.1% (392)	21.8% (286)	*0.78*
Previous Atrial Fibrillation	23.9% (701)	21% (340)	27.5% (361)	***<0.001***
Previous Myocardial Infarction	15.5% (454)	17.1% (277)	13.5% (177)	***0.01***
Recent Myocardial Infarction	11.1% (325)	12.8% (207)	9% (118)	***0.001***
NYHA class III-IV	41.7% (1225)	41.2% (669)	42.4% (556)	*0.35*
On B-Blockers	41% (1204)	43.1% (698)	38.5% (506)	***0.01***
On statins	41.3% (1212)	45.7% (743)	36% (471)	***<0.001***
On Aspirin	44.5% (1306)	47.2% (765)	41.3% (541)	***0.02***
On diuretics	47.6% (1396)	45.8% (743)	49.8% (653)	***0.03***
Hypertrophic cardiomyopathy	31% (909)	32.7% (488)	34.8% (421)	*0.25*
Dilated cardiomyopathy	20.4% (600)	21.9% (356)	18.7% (245)	*0.30*
LVEF (%)	60±12	59±12	61±12	***0.01***
PAP (mmHg)	46±16	45±15	46±16	*0.35*
Hemoglobin before surgery ($g \cdot dL^{-1}$)	13±1.7	12.9±1.7	13±1.7	*0.49*
Platelet count before surgery($1 \cdot nl^{-1}$)	215±68	216±67	214±69	*0.45*
Emergent Surgery	5% (148)	4.2% (69)	6% (79)	***0.03***
Past Cardiac surgery	9.4% (276)	8.2% (134)	10.8% (142)	***0.02***
EuroSCORE	6.3±3.5	5.5±2.6	6.5±3.3	***0.001***
Parsonnet score	11.5±4.4	11±4.5	12.1±4.8	***0.02***

COPD=Chronic Obstructive Pulmonary Disease. BMI=Body Mass Index. COPD=Chronic Obstructive Pulmonary Disease. NYHA= New York Heart Association classification. LVEF= Left ventricular ejection fraction. PAP= Pulmonary arterial pressure. EuroSCORE= European system for cardiac operative risk evaluation. Results are expressed as mean± standard deviation or percentage.

Table 4. Postoperative and intraoperative data according postoperative hyperlactatemia (lactate≥3.0mmol/L) in any time.

	All patients (n=2935)	Normal lactate levels (n=1625; 55.4%)	hyperlactatemia (n=1310; 44.6%)	*P*
Intraoperative data				
Isolated CABG	32.2%(945)	35.7%(578)	28%(367)	***0.001***
Isolated valve surgery	51.6%(1515)	50.2%(814)	53.5%(701)	*0.10*
CABG + valve surgery	6.9%(203)	5.7%(94)	8.3%(109)	***0.02***
Other cardiac surgery	9.3%(272)	8.5%(139)	10.2%(133)	***0.01***
Number of bypass	2.3±1	2.3±0.9	2.3±0.8	*0.85*
CPB time (min)	112±41	105±34	121±46	***0.001***
ACC time (min)	74±30	69±25	79±32	***0.03***
Postoperative data				
APACHE II	12.3±4.6	11.6±4	13±5.3	***0.001***
APACHE III	50±18.5	47.1±15.5	53.5±21.2	***0.001***
SAPS II	24±9.6	23±8.4	25.7±10.8	***0.01***
SAPS III	40±10.5	38.3±9.4	42.3±11.4	***0.005***
Ventilation time (hours)	50±127	38±101	66±153	***0.001***
PaO2/FiO2 ratio 3hs after admission	308±77	304±92	304±92	*0.70*
PaO2/FiO2 ratio 12hs after admission	312±90	324±93	322±96	*0.18*
PaO2/FiO2 ratio 24hs after admission	321±91	331±97	332±100	*0.68*
Reintubation	1.1%(31)	0.3%(5)	2%(26)	***0.02***
Tracheostomy	1.3%(38)	1%(16)	1.7%(22)	***0.01***
Need of vasoactive drugs(hs)	103±140	88±120	118±158	***<0.001***
LCOS	41.6%(1221)	36.6%(595)	47.8%(626)	***<0.001***
PMI	11.8%(346)	7.7%(124)	16.9%(222)	***<0.001***
IABP support	7.9%(231)	6.9%(99)	10.1%(132)	***<0.001***
Atrial Fibrilation	39.3%(1154)	35.5%(575)	44.1%(579)	***<0.001***
Creatinine peak after surgery($mmol \cdot l^{-1}$)	114±81	106±83	123±77	***<0.001***
Acute Renal Failure	9.7%(285)	6.2%(100)	14.1%(185)	***<0.001***
Need for RRT	2%(59)	1.2%(19)	3.1%(40)	***0.001***
Albumin 48h after surgery ($g \cdot L^{-1}$)	28±4	28.5±3.5	27.7±3.9	***0.01***
Pericardial tamponade	0.7%(22)	0.3%(5)	1.3%(17)	***0.03***
Drainage loss first 12h (ml)	393±301	376±266	414±335	***0.001***
Major bleeding	4.4%(116)	3.1%(50)	5%(66)	***0.04***
Re-exploration	1.5%(44)	1.6%(26)	1.3%(18)	*0.09*
Need for blood products (Units)	1.1±1.7	0.9±1.6	1.5±2.2	***0.001***
Stroke	1.4%(42)	1%(16)	2%(26)	***0.03***
Septicemia	7.1%(195)	6.6%(86)	8.3%(109)	***0.001***
Mean ICU stay (hours)	167±251	156±224	207±297	***<0.001***
Mean hospital stay (days)	24.5±21.3	22.8±19.4	26.6±23.3	***<0.001***
In-hospital mortality	5.9%(174)	3.7%(61)	8.6%(113)	***<0.001***

CABG=coronary artery bypass graft. ACC= Aortic cross clamping. CPB=cardiopulmonary bypass. SAPS=Simplified Acute Physiology Score. APACHE= Acute Physiology and Chronic Health Evaluation. PaO2/FiO2= Arterial partial pressure of O2 and fraction of inspired oxygen ratio. LCOS= Low Cardiac

Output Syndrome. PMI= Perioperative Myocardial Infarction. IABP= intra-aortic balloon pump. AL=Arterial Lactate. RRT=Renal Replacement Therapy. Results are expressed as mean± standard deviation or percentage.

Table 5. Logistic regression model – dependent variable having postoperative hyperlactatemia (lactate≥3mmol/L) any time.

	Odds ratio (95% CI)	*P*-value
Age	1.018 (0.997-1.038)	*0.088*
Recent Myocardial Infarction	1.519 (1.107-2.086)	***0.010***
Cardiopulmonary bypass (min)	1.392 (1.132-1.711)	***<0.001***
Intra-aortic Balloon Pump suport	0.430 (0.252-0.735)	***0.002***
Creatinine peak after surgery($mmol \cdot l^{-1}$)	1.008 (1.005.1.010)	***<0.001***

Table 6. Preoperative variables according postoperative hyperlactatemia peak timing after surgery.

	On admission (*n*=271; 20.7%)	At 6hs (*n*=582; 44.4%)	At 12h (*n* = 336; 27.9%)	At 24hs (*n* = 91; 7 %)	*ANOVA P value*
Sex (male)	55% (149)	53.4% (311)	59.3% (217)	65.9% (60)	*0.07*
Sex (female)	45% (122)	46.6% (271)	40.7% (149)	34.1% (31)	*0.07*
Age (years)	63.3±11.6	65.2±11.2	66.7±10.1	66.5±11.3	***0.001***
Hypertension	59% (160)	63.9% (372)	62.3% (228)	65.9% (60)	*0.50*
Dyslipidemia	49.8% (135)	48.6% (283)	46.4% (170)	46.2% (42)	*0.82*
Diabetes Mellitus	27.7% (75)	21% (122)	20.8% (76)	26.4% (24)	*0.09*
BMI ($kg \cdot m^{-2}$)	28±4.6	28±4	27.5±4.1	27.5±4.6	*0.29*
Peripheral vascular disease	7% (19)	7.6% (44)	7.7% (28)	14.3% (13)	*0.14*
Chronic renal insufficiency	6.6% (18)	3.1% (18)	4.1% (15)	11% (10)	***0.003***
Renal Failure (on Dialysis)	0.7% (2)	0.7% (4)	09% (3)	1.1% (1)	*0.35*
sCr before surgery ($mmol \cdot L^{-1}$)	99±42	90±31	92±49	107±81	***0.001***
Previous Stroke	5.2% (14)	7.2% (42)	8.5% (31)	8.8% (8)	*0.41*
COPD	10.7% (29)	8.4% (49)	34% (9.3)	15.4% (14)	*0.18*
Active smokers	20.6% (56)	21.8% (127)	24.7% (83)	22% (20)	*0.84*
Previous Atrial Fibrillation	26.2% (71)	28.4% (165)	27.6% (101)	25.3% (23)	*0.11*
Previous Myocardial Infarction	14% (38)	13.2% (77)	14.2% (52)	11% (10)	*0.86*
Recent Myocardial Infarction	14% (38)	8.6% (50)	5.5% (20)	11% (10)	***0.002***
NYHA class III-IV	40.2% (109)	42.6% (248)	44.6% (150)	42.8% (39)	*0.45*
On B-Blockers	36.5% (99)	38.7% (225)	40.2% (147)	37.4% (34)	*0.82*
On statins	31% (84)	35.7% (208)	40.4% (148)	31% (34.1)	*0.10*
On Aspirin	39.1% (106)	43.3% (252)	40.2% (147)	39.6% (36)	*0.61*
On diuretics	49.4% (134)	50.7% (295)	48.4% (177)	50.5% (46)	*0.91*
Hypertrophic cardiomyopathy	29.3% (72)	36.8% (197)	35.2% (119)	37.2% (32)	*0.21*
Dilated cardiomyopathy	19.6% (48)	16.4% (88)	25.7% (87)	25.6% (22)	***0.02***
LVEF (%)	59±13	62±11	60±12	59±11	***0.007***
PAP (mmHg)	48±17	46±17	45±15	45±13	*0.49*
Hemoglobin before surgery($g \cdot dL^{-1}$)	12.5±1.9	13.1±1.6	13.2±1.6	12.9±1.9	***0.001***
Platelet count before surgery($1 \cdot nL^{-1}$)	224±73	216±72	206±606	210±743	***0.017***
EuroSCORE	8.2±3.5	5.9±3	5.7±2.7	7±3	***<0.001***
Parsonnet score	15.7±10	11±6.5	11.3±6.4	11.8±6.8	***<0.001***
Past Cardiac surgery	14.8% (40)	10.3% (60)	9.6% (35)	7.7% (7)	*0.11*
Emergent Surgery	20.7% (56)	2.1% (12)	1.6% (6)	4.4% (4)	***<0.001***

BMI, Body Mass Index; sCr, serum creatinine; COPD, Chronic Obstructive Pulmonary Disease; NYHA, New York Heart Association classification; LVEF, Left ventricular ejection fraction; PAP, Pulmonary arterial pressure. Data are mean± standard deviation or percentage.

Table 7. Intraoperative and postoperative variables according postoperative hyperlactatemia peak timing after surgery.

	On admission (*n*=271; 20.7%)	At 6hs (*n*=582; 44.4%)	At 12h (*n* = 336; 27.9%)	At 24hs (*n* = 91; 7 %)	*ANOVA P value*
Intraoperative data					
Isolated CABG	24.4% (66)	29.2% (170)	28.1% (103)	30.8% (28)	*0.09*
Isolated valve surgery	46.1% (125)	55.3% (322)	56% (205)	53.8% (49)	*0.08*
CABG + valve surgery	8.9% (24)	8.9% (52)	8.2% (30)	3.3% (3)	***0.03***
Other cardiac surgery	20.7% (56)	6.5% (38)	7.7% (28)	8.3% (11)	***0.001***
Number of bypass	2.1±0.9	2.2±0.6	2.1±0.7	2.5±0.5	*0.12*
CPB time (min)	144±52	115±42	116±45	114±43	***<0.001***
ACC time (min)	92±36	76±30	77±32	75±30	***<0.001***
Postoperative data					
APACHE II	14±6.1	12.4±4.5	13.1±5.7	14.3±5.7	***<0.001***
APACHE III	57±24	50±18	54±21	59±24	***<0.001***
SAPS II	27.7±11.6	24.2±9.6	26±11.7	28±11	***<0.001***
SAPS III	44±11.1	40.4±9.9	42.8±11.8	44.5±14.6	***0.001***
Ventilation time (hours)	110±207	45±115	63±148	78±168	***<0.001***
PaO2/FiO2 ratio 3hs after admission	283±95	312±88	311±95	283±88	***<0.001***
PaO2/FiO2 ratio 12hs after admission	296±98	321±90	328±92	306±94	***<0.001***
PaO2/FiO2 ratio 24hs after admission	305±110	336±92	346±101	332±100	***<0.001***
Reintubation	1.5% (4)	1.7% (10)	1.4% (5)	7.8% (7)	***0.04***
Tracheostomy	3% (8)	1.4% (8)	1.4% (5)	1.1% (1)	*0.11*
Need of vasoactive drugs(hs)	157±192	99±122	112±159	126±191	***<0.001***
LCOS	63.1% (171)	42.6% (248)	44.3% (149)	63.7% (58)	***<0.001***
PMI	19.2% (52)	16% (93)	16.4% (60)	18.7% (17)	*0.65*
IABP support	14.8% (40)	8.8% (51)	7.6% (28)	14.3% (13)	***0.01***
Atrial Fibrilation	50.6% (137)	38% (221)	48.1% (176)	48.4% (44)	***0.03***
Creatinine peak after surgery($mmol \cdot l^{-1}$)	132±81	113±56	124±86	158±111	***<0.001***
Acute Renal Failure	17% (46)	10.3% (60)	13.7% (50)	31.9% (29)	***<0.001***
Need for RRT	3.3% (9)	1.9% (11)	2.7% (10)	11% (10)	***<0.001***
Albumin 48h after surgery ($g \cdot L^{-1}$)	26.7±5	28.1±3.4	28.2±3.5	27.3±4.2	***<0.001***
Pericardial tamponade	1.5% (4)	1% (6)	1.6% (6)	1.1% (1)	*0.86*
Drainage loss first 12h (ml)	440±344	397±338	423±344	417±242	*0.33*
Major bleeding	4.4% (12)	4.5% (26)	6% (22)	6.6% (6)	*0.61*
Re-exploration	1.1% (3)	1.2% (7)	1.8% (6)	2.2% (2)	*0.29*
Need for blood products (Units)	1.8±2.3	1.5±2.2	1.4±2.1	1.7±2.2	*0.08*
Stroke	1.8% (5)	1.5% (9)	2.2% (8)	4.4% (4)	*0.33*
Septicemia	1.3% (35)	5.8% (34)	7.1% (24)	17.6% (16)	***<0.001***
Mean ICU stay (hours)	264±320	188±283	191±275	227±377	***0.003***
Mean hospital stay (days)	32.2±33.5	24.6±18.5	25.5±19.2	27.3±26.4	***<0.001***
In-hospital mortality	10% (27)	5.5% (32)	8.2% (30)	26.4% (24)	***<0.001***

CABG, coronary artery bypass graft; ACC, Aortic cross clamping; CPB, cardiopulmonary bypass; PaO_2/FiO_2, Arterial partial pressure of O_2 and fraction of inspired oxygen ratio; LCOS, Low Cardiac Output Syndrome; PMI, Perioperative Myocardial Infarction; IABP, intra-aortic balloon pump; sCr, serum creatinine; AL, Arterial Lactate; SAPS, Simplified Acute Physiology Score; APACHE, Acute Physiology and Chronic Health Evaluation. Results are expressed as mean± standard deviation or percentage.

Table 8. Differences between subgroups according postoperative hyperlactatemia peak timing after surgery in a logistic regression model.

	Odds ratio (95 % CI)	*P value*
Hyperlactatemia **on admission** vs Hyperlactatemia at **6hs**		
Cardiopulmonary bypass time (min)	0.987 (0.983 – 0.991)	***<0.001***
Hemoglobin before surgery($g \cdot dL^{-1}$)	1.187 (1.070 - 1.317)	***0.001***
Left ventricular ejection fraction	1.018 (1.002 - 1.034)	***0.026***
Hyperlactatemia **on admission** vs Hyperlactatemia at **12hs**		
Recent Myocardial Infarction	2.549 (1.132 -5.738)	***0.024***
Hemoglobin before surgery ($g \cdot dL^{-1}$)	1.293 (1.145 - 1.459)	***<0.001***
Cardiopulmonary bypass time (min)	0.978 (0.969 - 0.987)	***<0.001***
Hyperlactatemia **on admission** vs Hyperlactatemia at **24hs**		
Cardiopulmonary bypass time (min)	0.983 (0.976 - 0.990)	***<0.001***
In-hospital mortality	1.206 (1.093 - 1.458)	***<0.001***
Hyperlactatemia at **6hs** vs Hyperlactatemia at **24hs**		
Chronic renal insufficiency	1.259 (1.094 - 1.715)	***0.009***
Low Cardiac Output Syndrome	3.233 (1.019 - 9.259)	***0.036***
Reintubation	2.595 (2.081-3.050)	***0.011***
In-hospital mortality	1.257 (1.103- 1.624)	***0.003***
Hyperlactatemia at **12hs** vs Hyperlactatemia at **24hs**		
In-hospital mortality	1.244 (1.130 - 1.456)	***<0.001***
Low Cardiac Output Syndrome	2.153 (1.011 - 4.860)	***0.040***

Figure 1
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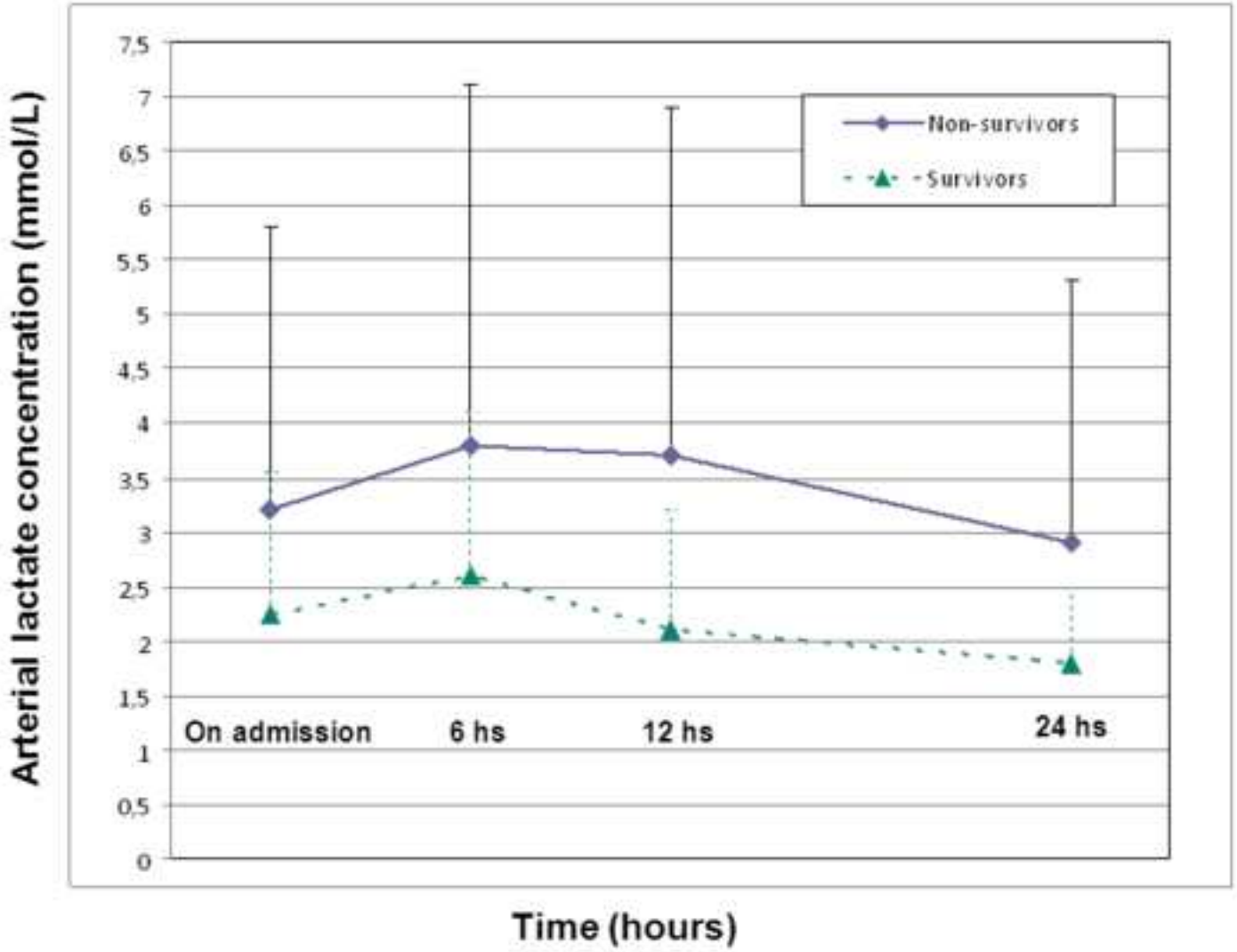

	All patients (n=2935)	Survivors (n=2761; 94.1%)	Non-survivors (n=174; 5.9%)	P
AL on admission(mmol·l^{-1})	2.3±1.3	2.24±1.3	3.2±2.6	<0.001
AL 6hs after admission (mmol·l^{-1})	2.7±1.7	2.6±1.5	3.8±3.3	<0.001
AL 12hs after admission (mmol·l^{-1})	2.5±1.4	2.1±1.1	3.7±3.2	<0.001
AL 24hs after admission (mmol·l^{-1})	1.9±0.9	1.8±0.7	2.9±2.4	<0.001

Figure 2
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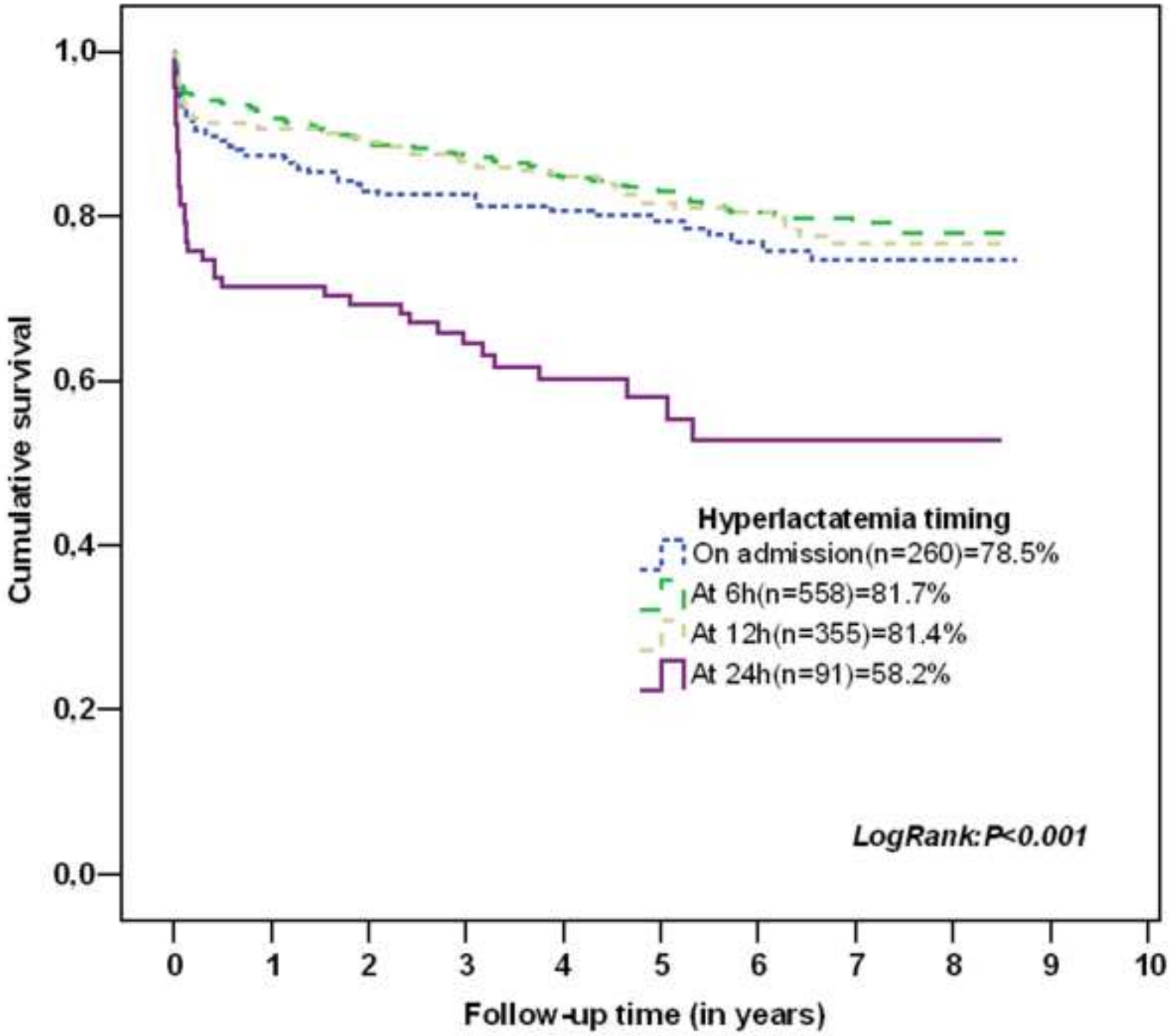

• Lopez-Delgado JC, Esteve F, Javierre C, Ventura JL, Mañez R, Farrero E, Torrado H, Rodriguez-Castro D, Carrio ML. **The influence of cirrhosis in cardiac surgery outcomes.** *World J Hepatol*. (Review article under invitation for *World Journal of Hepatology (WJH)* 6th Anniversary Special Issues (4): Cirrhosis).

Resumen: La cirrosis hepática se ha convertido en un factor de riesgo importante para la cirugía cardíaca debido a la mayor morbilidad y mortalidad que estos pacientes pueden sufrir en comparación con la población general de cirugía cardíaca. La presencia de factores que contribuyen a un mayor riesgo y peores resultados quirúrgicos, tales como: coagulopatía, desnutrición, inmunodepresión, miocardiopatía, disfunción renal y pulmonar, deben tenerse en cuenta para la evaluación quirúrgica cuando la cirugía es necesaria, junto con el grado de la enfermedad hepática y sus complicaciones primarias. Las características fisiopatológicas asociadas que representa la cirrosis hepática tienen una gran influencia en el desarrollo de complicaciones durante la cirugía cardíaca y el curso postoperatorio. En consecuencia, se necesita un enfoque más específico en la evaluación de la atención de estos pacientes si queremos mejorar sus resultados postoperatorios. En este artículo se revisa la fisiopatología y el pronóstico de los pacientes cirróticos sometidos a cirugía cardíaca en las diferentes series publicadas en la literatura.

Comentarios: Dado que los pacientes con cirrosis hepática han aumentado sus posibilidades de supervivencia en los últimos 20 años, son considerados más frecuentemente para cirugía cardíaca. De hecho, debido al incremento en los países occidentales de enfermedad del hígado graso no alcohólico y la esteatohepatitis no alcohólica es posible que esta población se incremente en la cirugía cardíaca, especialmente si consideramos que los factores de riesgo son comunes en la génesis de la enfermedad cardiovascular y el desarrollo de este tipo de enfermedad hepática crónica. La información publicada en la literatura es pequeña y las recomendaciones provienen de pequeñas series. Por lo tanto, es fundamental revisar los problemas que suponen estos pacientes con el fin de mejorar su pronóstico, siendo la presente revisión un reflejo de las experiencias acumuladas en la literatura.

Estado: Pendiente de revisión.

Title: THE INFLUENCE OF CIRRHOSIS IN CARDIAC SURGERY OUTCOMES.

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ABSTRACT

Liver cirrhosis has evolved an important risk factor for cardiac surgery due to the higher morbidity and mortality that these patients may suffer compared with general cardiac surgery population. The presence of contributing factors for a poor outcome, such as coagulopathy, a poor nutritional status, an adaptive immune dysfunction, a degree of cirrhotic cardiomyopathy, and a degree of renal and pulmonary dysfunction, have to be taken into account for surgical evaluation when cardiac surgery is needed, together with the degree of liver disease and its primary complications. The associated pathophysiological characteristics that liver cirrhosis represents have a great influence in the development of complications during cardiac surgery and the postoperative course. In consequence, a more specific approach is needed in the assessment of care of these patients if we want to improve their management. In this article, we review the pathophysiology and outcome prediction of cirrhotic patients who underwent cardiac surgery.

Core tip: Since liver cirrhotic patients have increased their chance of survival in the last 20 years due to the advances in their medical care, which includes liver transplantation, they have been increasingly considered for cardiac surgery. Indeed, there is an expected rise of cirrhotic patients within the cardiac surgical population due to the increasing rates of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis, especially in western countries. Cardiovascular risk factors are the same for the development of cardiomyopathy and this type of chronic liver disease. Despite cirrhosis is usually not a recognized risk factor within the risk scores for cardiac surgery, it is well known that the pathophysiological characteristics of cirrhosis have the potential for a higher surgical risk and poor prognosis in the perioperative course. The population of cirrhotic patients who are referred for cardiac surgery is small and recommendations come from small series. Thus, there is a challenge in order to improve the outcome of these patients based on advances in procedures for cardiac surgeons and clinical perioperative management for physicians.

INTRODUCTION

Despite liver cirrhosis (LC) is not included within the most important cardiac surgery scores, such as European system for cardiac operative risk evaluation (EuroSCORE) or Parsonnet, it is considered a major preoperative risk factor in cardiac surgery (CS), and the outcome is strongly related to the severity of liver disease in those patients [1]. The risk of mortality is higher compared with patients without cirrhosis, especially with advanced liver disease [2, 3].

The different anatomical and pathophysiological characteristics that cirrhosis represents have a significant influence in their perioperative course. Mortality has been widely studied among different series in the literature. It is recommended that CS can be done safely in patients with Child-Turcotte-Pugh (CTP) class B and C or with a higher model for end-stage liver disease score (MELD) with a cut-off ranging from 13 to 18 [1-5]. However, complications involving different features from the basis of different pathophysiological conditions are poorly described. Thus, further understanding is necessary to significantly modulate the current surgical results, and definitive recommendations and indications for CS in the cirrhotic population have to be reviewed. The understanding and evaluation of different score systems is also an area of interest to identify patients at risk. This review summarizes the influence of LC in CS based on current literature, including their clinical implications from a pathophysiological point of view. This is important since the advancement in the medical management and life expectancy of LC has lead to the increased eligibility of those patients for CS in the past decades.

METHODS

The review of the indexed articles of series of patients with LC who underwent CS was performed by means of Medline 1950 to March 2014 using the OVID interface. Only one manuscript was excluded from general LC analysis because it included patients from a past described series [2]. The present review aim to select manuscripts addressing outcome based on the degree of LC, such as MELD and/or CTP scores. Almost all the selected studies were retrospective, with only two of prospective profile [5, 6]. The selection of articles addressing the pathophysiology of cirrhotic patients and the implications in CS was done based on the importance, the availability (open access), the latest publication and the citation of the manuscripts. Note that morbidities are not

reported in detail in all the series and that the cause of death is reported in only approximately 60% of the dead patients.

RESULTS AND DISCUSSION

Epidemiology of LC in CS

The frequency of LC patients who are referred for CS is low because of their compromised health status and poor expected survival. On the other hand, in recent years, increased longevity has contributed to the increased incidence of hepatocellular carcinoma and coronary artery disease in cirrhotic patients [7].

Demographic characteristics of the series described in the literature and its aetiologies are showed in **Table 1**. The aetiology of LC in those patients seems to be linked with the aetiology of LC in the general population and geographical differences: alcoholic LC is more frequent in western series while viral LC is more frequent in Asian series. One major problem is the absence of series from other countries or regions, such as Arabic countries or India.

The aetiology of LC is expected to change due to the global obesity epidemic, which is associated with the increasing prevalence of metabolic syndrome. In consequence, a large cohort of patients that will develop NASH-/NAFLD-related LC is expected in CS [8]. In future series, we would have to consider the emergence of this phenomenon, which have the same risk factors of cardiovascular disease.

Pathophysiological considerations of LC in CS

The estimation of liver functional reserve and the identification of coexisting pathophysiological disorders associated with LC are key issues in the evaluation of those patients before CS.

The occurrence of portal hypertension in LC leads to variceal bleeding, ascites and spontaneous bacterial peritonitis, and hepatic encephalopathy. Patients with LC are at higher risk of liver-related complications during the postoperative course of CS [9]. In **Table 2** and **Table 3** we show respectively the postoperative complications and the mortality causes of these patients. Morbidities are poorly studied in the majority of the series and LC predisposes to other complications in CS in addition to those liver-related complications. However, mortality is higher when liver-related complications occur.

Regarding the diagnosis of LC, despite liver biopsy remains the “gold standard”, it is not imperative in clinical practice due to the advances in laboratory tests and imaging tools, such as abdominal ultrasound, computed tomography and magnetic resonance imaging [10]. It would be advisable to perform a preoperative evaluation of liver

function in patients at risk with confirmed or suspected liver disease in order to stage the severity. The indocyanine green plasma disappearance rate (ICG-PDR) is useful for assessing hepatic functional reserve and perfusion in the setting of CS. A lower preoperative ICG-PDR value (e.g. below 8.2%/min) is an independent predictor for mortality after CS and a marker of prolonged ICU treatment [11, 12].

Coagulopathy

Coagulopathy is a routine concern during CS, because the liver is the principal source of coagulation protein synthesis, including thrombopoietin, coagulation factors (II, V, VII, IX, X, XI, and XII), anticoagulation protein C, protein S, and antithrombin. In LC there is a decrease in both pro- and anti-coagulants. Thrombocytopenia secondary due to poor nutritional status, hypersplenism and bleeding from varices may adversely influence bleeding problems. However, primary haemostasis may not be defective in LC and a low platelet count, if not severe, should not necessarily be considered as an automatic index of an increased risk of bleeding [13].

Prothrombin time-derived international normalized ratio (PT-INR) is used to assess bleeding risk, prognosis in MELD score and to guide treatment of coagulation disturbances in clinical practice. The lack of improvement of PT-INR to the administration of vitamin K may reflect a poor hepatic reserve and a worse prognosis in CS of LC patients. Despite PT-INR provides a good measure of liver function, it only measures the activity of procoagulants. Thromboelastography provides better assessment of patient's degree of coagulopathy and offers information enabling immediate transfusion therapy, being useful in CS for guiding transfusion therapy [14]. Thus, correction of severe thrombocytopenia and replenishment of vitamin K storages is mandatory before surgery, together with the assessment of coagulopathy status before and during surgery. Despite bleeding is a major concern during CS, it has shown an incidence of only 30% of significant postoperative bleeding and a low mortality (**Table 2** and **3**).

Immune dysfunction

Infections are an important cause of death in hospitalized cirrhotic patients, especially in the presence of advanced clinical stages of LC, and most of these are nosocomial infections [15]. The presence of an innate and adaptive immune dysfunction in LC, the so called cirrhosis-associated immune dysfunction syndrome, predisposes to an increased occurrence of systemic infections, having a simultaneous substantial impact on the development of liver dysfunction. Paradoxically, depression and overstimulation

of immune system exist, and result in an enhanced susceptibility to acute inflammatory processes. There is also a shift towards the persistence of inflammation leading to the progression of LC and the development of different complications, such as portal hypertension and hepatic encephalopathy [16-18]. Sepsis is an important cause of mortality when is produced after CS leading to multy-system organ failure, especially regarding short-term outcome [5]. In addition, the surgical invasiveness that cardiac surgery represents is an added risk factor for infections susceptibility, especially when cardiopulmonary bypass (CPB) is used [19]. Septic problems range from 11% to 58% of the postoperative complications in these patients, being the main cause of known death together with liver-related repercussions (**Table 2** and **3**).

Poor nutritional status

Nutritional status of LC is poor and the correct functioning of the immune and metabolic response systems is dependent on each other [20]. As a result, LC patients do not have a sufficient nutritional reserve and may be functioning in a worse efficient metabolic state with an inadequate inflammatory and immune response to surgery. Preoperative serum albumin levels can be used to quantify nutritional status and underlying disease, with levels of albumin$<25 g \bullet L^{-1}$ being independently associated with an increased risk of reoperation for bleeding [20]. Hypoalbuminaemia, a current condition is LC, also increased the risk of infection in CS patients [21]. Sepsis is an important risk factor for mortality after CS, which produces a sepsis-induced cardiac dysfunction per se [22]. Higher blood transfusion requirements after CS, which are associated with poor outcome, are also associated with an increased risk of infection at multiple sites, suggesting a system-wide immune response [23]. The lack of response to the preoperative nutritional support may be considered a surrogate marker of minimal hepatic reserve and poor prognosis in CS of LC patients.

Cardiac dysfunction

The evaluation of cardiovascular dysfunction in LC is crucial and it should be addressed preoperatively. The emergence of an underscored NASH/NAFLD, especially in western countries, has the same risk factors for cardiovascular disease, together with a common cause of chronic liver disease [24]. In addition, cardiovascular diseases are a common cause of mortality in LC because the severity of liver injury and inflammation is strongly associated with an increased cardiovascular risk and an atherogenic lipid profile [25]. LC is associated with peripheral arterial vasodilatation, and activation of sodium and water retentive pathways which produces blood volume expansion and

redistribution within the splanchnic bed. Thus, the resting hyperdynamic circulatory state with increased cardiac output is a response to splanchnic arterial vasodilatation. These changes increase with the progression of liver disease leading to cardiac failure. Cirrhotic cardiomyopathy develops a variety of progressive clinical manifestations being characterized by diastolic dysfunction, impaired inotropic and chronotropic incompetence leading to a suboptimal ventricular contractile response during stressful conditions, such as CS [26]. Thus, hemodynamic postoperative management is crucial after CS and higher Central Venous Pressure is associated with worse short-term outcome [5]. It seems that the assessment of preoperative cardiac function, even from a dynamic point of view with a dobutamine stress echocardiography, may play a role in the indication for CS and postoperative management in the setting of LC. Cirrhotic cardiomyopathy may also play a role in the pathogenesis of hepatorenal syndrome (HRS) or the development of Acute Kidney Injury (AKI) in LC [27].

If we exclude recurrent diseases, graft loss resulting from technical complications, and malignancies, cardiac complications are the most common after liver transplantation (LT). More than 50% of cirrhotic patients undergoing LT show a degree of cardiac dysfunction [26]. There is a greater risk of cardiac deaths and ischemic events in LT patients as compared to age- and sex-matched population [28]. A history of coronary artery disease, prior stroke, postoperative sepsis, and increased interventricular septal thickness are risk predictors of early postoperative adverse cardiac outcomes, such as myocardial infarction, after LT. These patients benefit from the use of perioperative β-blockers regardless of their risk profile [29]. Theoretically, the same could be applied to cirrhotic patients who underwent CS, especially if we tend into account that those who underwent LT are patients with advanced cirrhosis. Cardiac dysfunction due to LC is poorly addressed after CS in those patients because the disease overlaps with other scenarios, such as low cardiac output syndrome.

Acute kidney Injury

Oliguria is a feature of AKI and renal dysfunction, a complication which is frequently present after CS and which has a strong influence on morbidity and mortality, even in long-term scenario [30]. It leads to a positive fluid balance, resulting in vital organ edema [31]. Having an appropriate renal function is closely related with a good cardiac output performance [32]. LC leads to development of renal dysfunction and HRS which occurs in conjunction with microcirculatory dysfunction in other organs, including the heart and the peripheral vascular bed [33]. Lower urine output in the first 24 h following

surgery may be a valuable predictor of long-term outcome in patients with LC undergoing cardiac surgery [34]. It is difficult to compare AKI rates between series due to the differences in AKI definitions. However, assessment of preoperative renal function is of paramount importance due to the higher incidence of AKI after CS in those patients. AKI can be present in almost 80% of LC patients after CS and approximately 50% of them will need renal replacement therapies (**Table 2**).

Pulmonary dysfunction

Ascites and fluid overload may cause or aggravate pulmonary function due to atelectasias and pulmonary edema. The end-expiratory lung volume can be decreased, leading to impairment in the mechanics of the respiratory system, lung and chest wall, as well as gas-exchange. Thus, initial use of moderate Positive End Expiratory Pressure is an advisable approach to improve oxygenation and compliance without causing adverse effects in the respiratory function [35].

In advanced LC, hepatopulmonary syndrome, portopulmonary hypertension and hepatic hydrothorax are typical pulmonary complications. Whereas hepatopulmonary syndrome and portopulmonary hypertension represent pulmonary vascular diseases, the development of hepatic hydrothorax is associated with the presence of ascites and phrenic lesions. For severe hepatopulmonary syndrome and refractory hepatic hydrothorax, LT is the treatment of choice. In severe portopulmonary hypertension specific medical treatment is indicated. In selected patients, besides intravenous prostanoids, oral endothelin receptor antagonists and phosphodiesterase type-5 inhibitors are possible treatment options [36, 37]. These complications need to be screened in CS candidates, especially those with medical past history of respiratory failure and/or moderate or advanced LC patients because pulmonary complications can achieve an incidence of about 30% (**Table 2**).

Pathophysiological considerations of CS

CS involves a systemic inflammatory response with the accumulation of both pro-and anti-inflammatory cytokines, which may be clinically irrelevant but may also lead to a worse outcome in many cases. Poor hepatosplanchnic perfusion affects intestinal mucosa, predisposing to endotoxemia, proinflammatory cytokine release, and the systemic inflammatory response syndrome [38]. Contact activation of factor XII by the extracorporeal circuit stimulates inflammation by the activation of the intrinsic coagulation pathway, kallikrein, and complement, worsening the coagulopathy status of

LC [39]. In addition, those physiologic risks associated with all major CS procedures (e.g anesthesia, large volume transfusion) are amplified in the presence of LC due to the immunologic and metabolic higher demands that CPB imposes to the liver. The hemodynamics of CPB are non-physiological, with nonpulsatile flow and low cardiac output, leading to the ischemia-reperfusion hepatic injury. There is a decrease of the hepatic perfusion of approximately 20% and of the hepatic arterial blood flow of 20-45% through vasoconstriction during CPB, resulting in an imbalanced oxygen supply [40]. However, we have taken into account that haemodilutional anaemia produced during CPB, even when below to a haematocrit of 20%, does not impair hepatic function and perfusion [12]. In consequence, perioperative strategies that minimize or avoid, such as off-pump CS [3], the duration of CPB and transfusion requirements together with higher perfusion flow rates ($\geq$ 2.3L·min^{-1}), the addition of pulsatile perfusion, and more efficient circuits have a beneficial effect on hepatic function reducing injury and improving organ perfusion [41, 42]. Albumin, as priming solution for CPB, could have a more favourable profile in terms of bleeding in this scenario [43]. Operative characteristics of cirrhotic patients undergoing CS described in the literature are shown in **Table 4**.

Predictors of outcome in LC patients undergoing CS

The survival and long-term outcomes of LC patients who underwent CS are related to the severity of their liver disease and also with the complications after cardiac surgery; especially those produced during ICU stay [34]. Higher preoperative total plasma bilirubin, low preoperative serum cholinesterase concentrations, prolonged CPB time, central venous pressure, preoperative and postoperative thrombocytopenia, operative time, age have all been identified as potential predictors of mortality after CS in those patients [5, 44].

Although European system for cardiac operative risk evaluation (EuroSCORE) is widely accepted in Europe as a valuable score in CS, in some populations, it does not have acceptable discriminatory ability in this field. In addition, it does not take into account surgical prognosis factors such as CPB time [45]. The development of local mortality risk scores corresponding to local epidemiological characteristics or a specific patient's population may improve the prediction of outcome and LC patients may benefit from it [46]. Furthermore, the Parsonnet score does not consider specific liver variables. Because mortality in cirrhotic patients undergoing CS is associated with liver function, liver scores such as the MELD or CTP score are associated with outcome [1].

MELD score most reliably identifies cirrhotic patients at high risk for CS. With regard to CTP class scores, mortality is higher in patients with a CTP score of class B and C [1, 5]. ICU scores such as simplified acute physiology score (SAPS) III provide an acceptable level of sensitivity and specificity, comparable with MELD results of other series, even in the long-term scenario [1, 5, 47]. The postoperative long-term mortality rates reported in the literature are high for cirrhotic patients undergoing CS ranging from 40% to 70% at approximately six years. Comparing patients according to CTP score, mortality ranged from 45% to 80% in the Child A group and from 25% to approximately 50% in the Child B group and is extremely high in the Child C Group [1, 2, 3, 5]. In **Table 5** we show a summary of the existing series published in the literature, describing the associated in-hospital mortality based on CTP score. In consequence, CS can be performed safely in CTP class A and in some class B patients or with a MELD with a cut-off ranging from 13 to 18 [1, 3-5]. Regarding CTP class C patients, due to the higher mortality in these patients, liver function should be optimized prior to CS, even performing LT.

CONCLUSIONS

There are physiological characteristics of LC and properties of CS itself that predispose to complications in cirrhotic patients undergoing CS. The occurrence of organ related dysfunctions is crucial at the development of post-CS complications and outcome, being closely related with preoperative status and the degree of surgical injury. Apart from the degree of liver disease, evaluation of cardiovascular function, immune and nutritional status, renal function, degree of coagulopathy, and pulmonary function need to be also evaluated in order to perform an adequate prognosis, including postoperative management, and surgical approach. This is especially important in those patients with high risk profile, such as Child B and C, and/or high MELD. Since advanced LC represents a contraindication for CS, LT may be considered before CS in those patients.

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Table 1. Demographic characteristics of cirrhotic patients undergoing cardiac surgery (**A**) and liver cirrhosis aetiologies by region (**B**).

A.

	Country	Age (years)	Sex (Male)	Liver cirrhosis aetiology					Mean MELD/ Mean CTP
				Alcohol	Viral (Hep.B/ Hep.C)	PBC/ autoinmune	Congestive	Others	
Klemperer et al. [48]	USA	65 ± 8.3	11 (84.6%)	10	2	1	-	-	NA
Suman et al. [49]	USA	63.6 ± 12.6	27 (61.3%)	11	6 (3/3)	2	2	23	11.5± 4.2 / 6.29
Filsoufi et al. [9]	USA	58±10	20 (74%)	8	18 (5/13)	1	1	4	14.2±4.2 / NA
Lin et al. [51]	China	56	14 (77.7%)	5	13	-	-	-	NA/ NA
Ann et al. [44]	China	53±13	10 (41.6%)	1	15	-	7	1	NA/ NA
Hayashida et al. [50]	Japan	64±12	11 (61.1%)	3	12	1	1	1	NA/ NA
Murashita et al. [52]	Japan	69.9±9.4	5(41.6%)	NA	NA	NA	NA	NA	NA/ 6.3
Morisaki et al. [45]	Japan	69±8.5	31(73.8%)	5	27(1/26)	2	7	7	11.8 ±6/ 5.9 ±1.6
Sugimura et al. [55]	Japan	61.1±11.2	11(84.6%)	4	4 (0/4)	1	1	1	8.6±2.5/ 6.7±2
Morimoto et al. [56]	Japan	69.8±9.4	21(65%)	7	25(17/8)	-	-	-	11.5±5.1/ 7.2±1.9
Thielmann et al. [1]	Germany	62±10	38(66.7%)	NA	NA	NA	NA	NA	13±6 /NA
Gundling et al.[3]	Germany	65.4±11.7	33(70.2%)	25	6(3/3)	1	1	14	NA/ NA
Arif et al. [54]	Germany	64±10	82(75.2%)	60	6	3	7	33	11.6±5.1/ 6.4±1.5
Bizouarn et al. [6]	France	58.8±13.9	8(66.7%)	7	2	2	-	1	NA/ NA
Vanhuyse et al. [53]	France	65 ±11	26(76%)	20	11	2	-	1	12±3.5/NA
Lopez-Delgado et al. [5]	Spain	64.9±11.6	10(69%)	20	30(4/26)	-	-	8	16 ±5.4/ NA

Hep: Hepatitis; PBC: Primary Biliary Cirrhosis MELD: Model for End-Stage Liver Disease; CTP: Child-Turcotte-Pugh; NA: Not available.

B.

Region	LC Etiology					Total
	Alcohol	Viral	PBC/ autoinmune	Congestive	Others	
USA	29 (32.6%)	26 (29.2%)	4 (4.5%)	3 (3.4%)	27 (30.3%)	89
China	6 (14.3%)	28 (66.6%)	-	7 (16.8%)	1 (2.3%)	42
Japan	19 (17.4%)	68 (62.4%)	4 (3.6%)	9 (8.3%)	9 (8.3%)	109
Germany	75 (51%)	12 (8.2%)	4 (2.7%)	9 (6.1%)	47 (32%)	147
France	27 (60%)	13 (28.8%)	4 (9%)	-	1 (2.2%)	45
Spain	20 (34.5%)	30 (51.7%)	-	-	8 (13.8%)	58
Total (EU)	122 (48.8%)	55 (22%)	8 (3.2%)	9 (3.6%)	56 (22.4%)	250
Total (Asia)	25 (16.5%)	96 (63.5%)	4 (2.6%)	16 (10.8%)	10 (6.6%)	151

Table 2. Postoperative complications of cirrhotic patients undergoing cardiac surgery.

	Morbidities	RI-AKI	RRT needs	Sepsis	Pulmonary	Bleeding	Liver
Klemperer et al. [39]	44% (7)	23% (3)	-	38% (5)	30% (4)	30% (4)	23% (3)
Suman et al. [41]	-	13% (6)	-	11% (5)	-	-	12 (27%)
Filsoufi et al. [9]	52% (14)	15% (4)	15% (4)	18% (5)	22% (6)	7% (2)	15% (4)
Lin et al. [42]	50% (9)	5% (1)	-	22% (4)	6% (1)	22% (4)	11% (2)
Ann et al. [34]	75% (18)	29% (7)	-	17% (4)	29% (7)	25% (6)	12% (3)
Hayashida et al. [43]	66.7% (12)	28% (5)	-	33% (6)	28% (5)	17% (3)	22% (4)
Murashita et al. [42]	75% (9)	-	-	-	-	-	-
Morisaki et al. [35]	31.7% (13)	-	-	-	-	-	-
Sugimura et al. [46]	77% (10)	15% (2)	15% (2)	23% (3)	15% (2)	-	8% (1)
Morimoto et al. [47]	53% (17)	9% (3)	-	9% (3)	29% (10)	26% (9)	11% (4)
Thielmann et al. [1]	-	39% (22)	39% (22)	9% (5)	-	28% (16)	14% (8)
Arif et al. [45]	>50%	53% (58)	24% (26)	58% (63)	9% (10)	-	-
Bizouarn et al. [40]	58% (7)	-	-	25% (3)	-	-	33% (4)
Vanhuyse et al. [44]	-	21% (7)	-	50% (17)	9% (3)	18% (6)	12% (4)
Lopez-Delgado et al. [3]	43.1% (25)	79% (46)	9% (5)	21% (12)	-	2% (1)	-
Ranges	31-77%	5-79%	9-39%	11-58%	6-30%	2-30%	8-23%

RI-AKI: Renal Insufficiency or Acute Kidney Injury; RRT: Renal Replacement Therapies.

Table 3. Mortality[1] causes of cirrhotic patients undergoing cardiac surgery.

	Liver	Sepsis	Bleeding	Cardiovascular	Other
Klemperer et al. [48]	4				
Filsoufi et al. [9]	3	2	1		1-Bowel ischaemia
Lin et al. [51]	1				
Ann et al. [44]		5	1		
Hayashida et al. [50]	1	2			1
Sugimura et al. [55]	1				
Morimoto et al. [56]	1	2	2		2
Thielmann et al. [1]	8	5	1	2	1-Bowel ischaemia
Gundling et al.[3]	2	2		3	2
Bizouarn et al. [6]	1				
Vanhuyse et al. [53]	4	3			1 ; 1-Bowel ischaemia
Lopez-Delgado et al. [5]	1	6			
Total	38.5% (27)	38.5%(27)	7.1% (5)	7.1% (5)	8.6% (6)

[1]Thirty-day mortality or in-hospital mortality.

Table 4. Operative characteristics of cirrhotic patients undergoing cardiac surgery.

	Mean CPB (min)	Urgent-Emergent	Type of surgery					
			CABG	Valve surgery	CABG + Valve	Aortic	Other	Off Pump (% Mortality)
Klemperer et al. [48]	102	9 (69.2%)	6	4	3	-	-	-
Suman et al. [49]	114±48	1 (2.3%)	16	16	10	-	2	-
Filsoufi et al. [9]	142±68	4 (15%)	8	12	-	3	4	5 (0 %)
Lin et al. [51]	138	-	4	13	1	-	-	2
Ann et al. [44]	160±53	7 (29.1%)	2	19	2	1	-	-
Hayashida et al. [50]	151±63	3 (16.7%)	6	9	1	1	1	3 (0%)
Murashita et al. [52]	147± 41	0	3	9	-	-	-	2
Morisaki et al. [45]	157±50	7 (16.7%)	11	20	5	2	4	5
Sugimura et al. [55]	242±77	6 (46.1%)	1	7	1	3	1	3
Morimoto et al. [56]	145±98	7 (22%)	6	18	2	6	-	6
Thielmann et al. [1]	125±55	10 (18%)	24	11	19	-	3	2
Gundling et al.[3]	101±43	-	21	14	9	-	3	-
Arif et al. [54]	-	23 (21%)	55	36	10	2	6	-
Bizouarn et al. [6]	85	-	1	10	2	-	-	-
Vanhuyse et al. [53]	100±66	2 (6%)	13	20	-	-	-	1
Lopez-Delgado et al. [5]	107±37	3 (5.1%)	9	42	7	-	-	6 (0%)

CPB: Cardiopulmonary bypass; CABG: Coronary Artery Bypass Graft.

Table 5. Short-term mortality[1] based on Child-Turcotte-Pugh (CTP) class.

	Year	CTP A		CTP B		CTP C		Total		
		Deaths	Patients	Deaths	Patients	Deaths	Patients	Deaths	Patients	Average
Klemperer et al. [48]	1998	0	8	4	5	-	-	4	13	31%
Bizouarn et al. [6]	1999	0	10	1	2	-	-	1	12	8.3%
Suman et al. [49]	2004	1	31	5	12	1	1	7	44	15.9%
Hayashida et al. [50]	2004	0	10	2	7	1	1	3	18	16.6%
Lin et al. [51]	2005	1	13	0	4	0	1	1	18	5.5%
Ann et al. [44]	2007	1	17	4	6	1	1	6	24	25%
Filsoufi et al. [9]	2007	1	10	2	11	4	6	7	27	26%
Murashita et al. [52]	2009	3	6	1	6	-	-	4	12	33%
Morisaki et al. [45]	2010	0	30	4	12	-	-	4	42	9.5%
Thielmann et al. [1]	2010	6	39	7	14	4	4	17	57	29.8%
Gundling et al.[3]	2010	2	33	7	14	-	-	9	47	19.1%
Vanhuyse et al. [53]	2012	4	22	3	10	2	2	9	34	26.4%
Arif et al. [54]	2012	15	74	14	29	3	6	32	109	29.3%
Sugimura et al. [55]	2012	0	7	1	5	0	1	1	13	7.7%
Lopez-Delgado et al. [5	2013	0	34	5	21	2	3	7	58	12%
Morimoto et al. [56]	2013	2	14	3	21	-	-	5	35	14.3%
Total mortality (deaths / patients = average)		36 / 358 = 10.05%		63 /179 = 35.2%		18 / 26 = 69.2%		117 / 563 = 20.8%		

[1]Thirty-day mortality or in-hospital mortality. CTP: Child-Turcotte-Pugh score.

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Resumen: A pesar que la cirrosis hepática no se encuentra en ningún *score* pronóstico, es un factor de riesgo importante para la cirugía cardíaca. El grado de la enfermedad hepática y de las características fisiopatológicas asociadas deben tenerse en cuenta si queremos mejorar el pronóstico de estos pacientes sometidos a cirugía cardíaca. Su predictibilidad en términos de morbimortalidad es aún más compleja debido a sus características fisiopatológicas, en comparación con otras poblaciones de cirugía cardíaca. Un equipo multidisciplinar, que incluyera hepatólogos entre otros especialistas, debería participar activamente en la evaluación y atención de estos pacientes.

Comentario: En la presente revisión se han pretendido analizar brevemente los factores asociados a la fisiopatología del paciente cirrótico que deben tener una especial consideración a la hora de someter estos pacientes a cirugía cardíaca. También se analizan brevemente las series publicadas en la literatura.
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Influence Over Outcome of Liver Cirrhosis in Cardiac Surgery: An Overview of the Pathophysiological Considerations and Review of the Literature

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ABSTRACT

Liver cirrhosis has evolved an important risk factor for cardiac surgery since those patients have been considered for intervention due to advances in their medical care, which ultimately has increased their survival. The degree of liver disease and the associated pathophysiological characteristics have to be into consideration if we want to improve the management and outcome of these patients in cardiac surgery. The prediction of outcome is even more crucial compared with other cardiac surgery populations and hepatologists should be closely involved in the assessment of care of these patients. The current understandings of the pathophysiology and outcome prediction are discussed below, together with a review of the series reported in the literature.

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INTRODUCTION

Liver cirrhosis (LC) is a major preoperative risk factor in general surgery, especially in cardiac surgery, and the outcome is strongly related to the severity of liver disease in those patients.[1] While in patients without advanced cirrhosis, cardiac surgery can be done safely, the risk of mortality is higher in patients with Child-Turcotte-Pugh (CTP) class B and C or with a higher model for end-stage liver disease score (MELD) with a cut-off ranging from 13 to 18.[1-3]

The advancement in the medical management and life expectancy of LC has lead to the increased eligibility of those patients for cardiac surgery in the past decades. Indeed, increased longevity has contributed to the increased incidence of hepatocellular carcinoma and coronary artery disease in cirrhotic patients.[4] More than 50% of cirrhotic patients undergoing liver transplantation (LT) show a degree of cardiac dysfunction.[5] This is the so called cirrhotic cardiomyopathy, which is characterized by suboptimal ventricular contractile response to stress, diastolic dysfunction and QT interval prolongation, being clinically relevant during stressful conditions, such as cardiac surgery, and potentially may play a role in the pathogenesis of hepatorenal syndrome (HRS) or the development of Acute Kidney Injury (AKI) in LC [6]. In addition, we have to keep in mind that renal function and development of AKI after adult cardiac surgery is associated with higher morbidity and mortality, even in long-term scenario [7]. At the same time, the option of LT as a treatment for patients with LC has produced an increase in survival rate and the evaluation of concomitant cardiac diseases, which increase post-LT complications, is crucial for preoperative risk assessment.[8]

Consequently, the understanding of physiopathology, the identification of independent cardiac surgery postoperative risk factors and evaluation of different score systems to identify the best predictors of mortality in cirrhotic patients who underwent cardiac surgery is an area of interest if we want to optimize post-surgical management and improve their outcome. However, evidence comes mainly from several small studies; due to the lack of evidence from larger prospective pools of data, more studies are still needed for this purpose. We review briefly the existing literature on the clinical implications and pathophysiology of cirrhotic patients who underwent cardiac surgery.

METHODS

The review of the indexed articles of series of patients with LC who underwent cardiac surgery was performed by means of Medline 1950 to March 2014 using the OVID interface. Only one manuscript was excluded from general LC analysis because it included patients from a past described series.[9] The present review aim to select manuscripts addressing outcome based on the degree of LC, such as MELD and/or CTP scores. Of the selected studies, all of them were retrospective, with only two prospective studies.[3,10] The selection of articles addressing the pathophysiology of cirrhotic patients and the implications in cardiac surgery was done based on importance, the availability (open access), the latest publication and the citation of the manuscripts.

RESULTS AND DISCUSSION

Pathophysiological considerations of LC in cardiac surgery.

The occurrence of portal hypertension in LC leads to variceal bleeding, ascites and spontaneous bacterial peritonitis, and hepatic encephalopathy. Patients with LC are at higher risk of liver-related complications during the postoperative course of cardiac surgery.[11] However, LC predisposes to other complications in cardiac surgery in addition to their classical complications. Some considerations must be done for their understanding in the cardiac surgical scenario.

Coagulopathy is a routine concern during cardiac surgery. The liver is the principal source of coagulation protein synthesis, including thrombopoietin, coagulation factors (II, V, VII, IX, X, XI, and XII), anticoagulation protein C, protein S, and antithrombin. In LC there is a decrease in both pro- and anti-coagulants. Prothrombin time-derived international normalized ratio (PT-INR) is used to assess bleeding risk, prognosis in MELD score and to guide treatment of coagulation disturbances in clinical practice. The lack of improvement of PT-INR to the administration of vitamin k may reflect a poor hepatic reserve and prognosis in cardiac surgery of LC patients. Despite PT-INR provides a good measure of liver function, it only measures the activity of procoagulants. Thromboelastography provides better assessment of patient's degree of coagulopathy and offers information enabling immediate transfusion therapy, being useful in cardiac surgery guiding transfusion therapy.[12]

The presence of an innate and adaptive immune dysfunction in LC, the so called cirrhosis-associated immune dysfunction syndrome, predisposes to an increased occurrence of systemic infections, having simultaneous substantial impact on the development of liver dysfunction. Paradoxically, depression and overstimulation of immune system exist, and result in an enhanced susceptibility to acute inflammatory processes. However, there is also a shift towards persistence of inflammation leading to progression of liver fibrosis and development of different complications, such as portal hypertension and hepatic encephalopathy.[13-15] Sepsis is an important cause of mortality when is produced after cardiac surgery leading to multy-system organ failure, especially regarding short-term outcome .[3]

Nutritional status of LC is poor and the correct functioning of the immune and metabolic response systems is dependent on each other.[16] As a result, LC patients do not have a sufficient nutritional reserve and may be functioning in a worse efficient metabolic state with a inadequate inflammatory and immune response to surgery. Preoperative serum albumin levels can be used to quantify nutritional status and underlying disease, with levels of albumin<25g·L-1 being independently associated with an increased risk of reoperation for bleeding.[16] Hypoalbuminaemia, a current condition is LC, also increased the risk of infection in cardiac surgery patients.[17] Sepsis is an important risk factor for mortality after cardiac surgery, which produces a sepsis-induced cardiac dysfunction per se.[18] Higher blood transfusion requirements after cardiac surgery, which are associated with poor outcome, are also associated with an increased risk of infection at multiple sites, suggesting a system-wide immune response.[19] The lack of response to the preoperative nutritional support is a surrogate marker of minimal hepatic reserve and poor prognosis in cardiac surgery of LC patients. The evaluation of cardiovascular dysfunction in LC is crucial and it should be addressed during the preoperative, operative and postoperative cardiac surgery. There is an emergence of an underscored non-alcoholic fatty liver disease or non-alcoholic steatohepatitis in western countries, which have the same risk factors for cardiovascular disease, together with a common cause of chronic liver disease.[20] In addition, cardiovascular diseases are a common cause of mortality in LC because the severity of liver injury and inflammation is strongly associated with an increased cardiovascular risk and an atherogenic lipid profile.[21] LC is associated with peripheral arterial vasodilatation, which is a reflection of reduced arterial compliance. At the same time, activation of sodium and water retentive pathways produces blood volume expansion and redistribution of this volume in splanchnic bed. Thus, the resting hyperdynamic circulatory state with increased cardiac output is a response to splanchnic arterial vasodilatation. These changes increase with the progression of liver disease leading to cardiac failure. Cirrhotic cardiomyopathy develops a variety of progressive clinical manifestations being characterized by diastolic dysfunction, impaired contractility and inotropic and chronotropic incompetence.[5] Hemodynamic postoperative management is crucial after cardiac surgery and higher Central Venous Pressure is associated with worse short-term outcome in LC.[3] It seems that the assessment of preoperative cardiac function, even from a dynamic point of view with dobutamine stress echocardiography, may play a role in the indication for cardiac surgery and postoperative management in the setting of LC.

If we exclude recurrent disease, graft loss resulting from technical complications, and malignancies, cardiac complications are the most common after LT. There is a greater risk of cardiac deaths and ischemic events in LT patients as compared to age- and sex-matched population.[22] A history of coronary artery disease, prior stroke, postoperative sepsis, and increased interventricular septal thickness are risk predictors of early postoperative adverse cardiac outcomes, such as myocardial infarction, after LT. These patients benefit from the use of perioperative β-blockers regardless of their risk profile.[23] Theoretically, the same could be applied to cirrhotic patients who underwent cardiac surgery, especially if we tend into account that those who underwent LT are patients with advanced cirrhosis.

Oliguria is a feature of AKI and renal dysfunction, a complication which is frequently present after cardiac surgery and which has a strong influence on overall survival.[7] It leads to positive fluid balance, resulting in vital organ edema.[24] Having an appropriate renal function is closely related with a good cardiac output performance.[25] LC leads to development of

renal dysfunction and HRS, which is related with cardiac dysfunction, and HRS occurs in conjunction with microcirculatory dysfunction in other organs, including the heart and the peripheral vascular bed.[26] Lower urine output in the first 24 h following surgery may be a valuable predictor of long-term outcome in patients with LC undergoing cardiac surgery.[27]

Ascites and fluid overload may cause or aggravate pulmonary function in patients with LC due to atelectasias and pulmonary edema. In advanced LC, hepatopulmonary syndrome, portopulmonary hypertension and hepatic hydrothorax are typical pulmonary complications. Whereas hepatopulmonary syndrome and portopulmonary hypertension represent pulmonary vascular diseases, the development of hepatic hydrothorax is associated with the presence of ascites and phrenic lesions. For severe hepatopulmonary syndrome and refractory hepatic hydrothorax, LT is the treatment of choice. In severe portopulmonary hypertension specific medical treatment is indicated. In selected patients, beside intravenous prostanoids, oral endothelin receptor antagonists and phosphodiesterase type-5 inhibitors are possible treatment options.[28, 29] These complications need to be screened in cardiac surgery candidates, especially those with medical past history of respiratory failure and/or moderate or advanced LC patients.

Pathophysiological considerations of cardiac surgery over LC.

Cardiac surgery involves a systemic inflammatory response with the accumulation of both pro-and anti-inflammatory cytokines, which may be clinically irrelevant but may also lead to a worse outcome in many cases. Poor hepatosplanchnic perfusion antagonizes intestinal mucosal injury, predisposing to endotoxemia, proinflammatory cytokine release, and the systemic inflammatory response syndrome.[30] Contact activation of factor XII by the extracorporeal circuit stimulates inflammation by the activation of the intrinsic coagulation pathway, kallikrein, and complement worsening the coagulopathy status of LC.[31] In addition, those physiologic risks associated with all major cardiac surgical procedures (e.g anesthesia, large volume transfusion) are amplified in the presence of LC due to the immunologic and metabolic higher demands that Cardiopulmonary bypass (CPB) imposes for the liver. The hemodynamics of CPB is nonphysiologic with nonpulsatile flow and low cardiac output, leading to ischemia-reperfusion hepatic injury. There is a decrease hepatic perfusion by approximately 20% and hepatic arterial blood flow by 20-45% through vasoconstriction during CPB resulting in an imbalanced oxygen supply.[32] Perioperative strategies that minimize or avoid the duration of CPB and transfusion requirements together with higher perfusion flow rates ($\geq$ 2.3L/min), the addition of pulsatile perfusion, and more efficient circuits have a beneficial effect on hepatic function reducing injury and improving organ perfusion.[33, 34] There is a potential benefit when revascularization surgery is performed off-pump.[7] Albumin, as priming solution for CPB, could have a more favourable profile in terms of bleeding in this scenario.[35]

Predictors of outcome in LC patients undergoing cardiac surgery.

The survival and long-term outcomes of LC patients who underwent cardiac surgery are related to the severity of their liver disease and also with the complications after cardiac surgery, especially those produced during ICU stay.[27] Higher preoperative total plasma bilirubin, low preoperative serum cholinesterase concentrations, prolonged CPB time, central venous pressure[3] preoperative and postoperative thrombocytopenia, operative time, age[8] have all been identified as potential predictors of mortality after cardiac surgery in those patients.

Table 1: Associated in-hospital mortality of patients with LC who undergo cardiac based on Child-Turcotte-Pugh (CTP) score.

	Year	CTP A		CTP B		CTP C		Total		%
		Death	Pat.	Death	Pat.	Death	Pat.	Death	Pat.	
Klemperer et al. [40]	1998	0	8	4	5	-	-	4	13	31%
Bizouarn et al.[10]	1999	0	10	1	2	-	-	1	12	8.3%
Suman et al.[41]	2004	1	31	5	12	1	1	7	44	15.9%
Hayashida et al.[42]	2004	0	10	2	7	1	1	3	18	16.6%
Lin et al. [43]	2005	1	13	0	4	0	1	1	18	5.5%
Ann et al.[8]	2007	1	17	4	16	1	1	6	24	25%
Filsoufi et al.[11]	2007	1	10	2	11	4	6	7	27	26%
Murashita et al. [44]	2009	3	6	1	6	-	-	4	12	33%
Morisaki et al.[36]	2010	0	30	4	12	-	-	4	42	9.5%
Thielmann et al.[1]	2010	6	39	7	14	4	4	17	57	29.8%
Gundling et al.[39]	2010	2	33	7	14	-	-	9	47	19.1%
Vanhuyse et al. [45]	2012	4	22	3	10	2	2	9	34	26.4%
Arif et al. [46]	2012	15	74	14	29	3	6	32	109	29.3%
Sugimura et al.[47]	2012	0	7	1	5	0	1	1	13	7.7%
Lopez-Delgado et al. [3]	2013	0	34	5	21	2	3	7	58	12%
Morimoto et al. [48]	2013	2	14	3	21	-	-	5	35	14.3%
Total mortality (deaths / patients = average)		36 / 358 = 10.05%		63 / 179 = 35.2%		18 / 26 = 69.2%		117 / 563 = 20.8%		

Although European system for cardiac operative risk evaluation (EuroSCORE) is widely accepted in Europe as a valuable score in cardiac surgery, in some populations, it does not have acceptable discriminatory ability. In addition, it does not take into account surgical prognosis factors such as CPB time.[36] The development of local mortality risk scores corresponding to local epidemiological characteristics may improve the prediction of outcome and LC patients are a good example of it.[37] Furthermore, the Parsonnet score does not consider specific liver variables. Because mortality in cirrhotic patients undergoing cardiac surgery is associated with liver function, liver scores such as the MELD or CTP score are associated with outcome.[1] MELD score most reliably identifies cirrhotic patients at high risk for cardiac surgery. With regard to CTP class scores, mortality is higher in patients with a CTP score of class B and C.[1, 3] ICU scores such as simplified acute physiology score (SAPS) III provide an acceptable level of sensitivity and specificity, comparable with MELD results of other series, even in the long-term scenario.[1, 3, 38] The postoperative long-term mortality rates reported in the literature are high for cirrhotic patients undergoing cardiac surgery ranging from 40% to 70% at approximately six years. Comparing patients according to CTP score, mortality ranged from 45% to 80%, in the Child A group and from 25% to approximately 50% in the Child B group and is extremely high in the Child C Group.[1, 3, 9, 39] In Table 1 we show a summary of the existing series published in the literature, describing the associated in-hospital mortality based on CTP score. In consequence, cardiac surgery can be performed safely in CTP class A and in some class B patients. Regarding CTP class C patients, due to the higher mortality in these patients, liver function should be optimized prior to cardiac surgery, even performing LT before cardiac surgery.

CONCLUSIONS

There are physiological characteristics of LC and properties of cardiac surgery that predispose to complications in cirrhotic patients undergoing cardiac surgery. Apart from the degree of liver disease, cardiovascular and heart function is of paramount importance at the management and outcome during cardiac surgery. However, immune and nutritional status, renal function, degree of coagulopathy, and pulmonary function need to be also evaluated in order to perform an adequate prognosis. The occurrence of organ related dysfunctions is crucial at the development of post-surgical complications and outcome, being closely related with preoperative status and the degree of surgical injury. Individual evaluation of those patients should be done before surgery, especially in those with high risk profile (e.g. Child B and C, high MELD). However, postoperative evaluation and ICU management is as important as preoperative evaluation in terms of predicting outcome, especially in the long-term.

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Ver programa en http://www.intercepteurope.org/intercept.php

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This supplement issue of the official ESICM/ESPNIC journal *Intensive Care Medicine* contains abstracts of scientific papers presented at the 26th Annual Congress of the European Society of Intensive Care Medicine.

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INTRODUCTION. In previous studies it seems that statins could be a protective factor of developing acute kidney injury (AKI) in cardiac surgery.

OBJECTIVES. We tried to confirm this protective effect with a high quality analysis.

METHODS. Prospective, observational and multicentre study of patients admitted in ICU after major cardiac surgery in 13 hospitals of Spain.

AKI was defined as double levels of creatinine if it was normal previously, or above 3.5 mg/dl if it was between 1.2 and 2.2 or need for renal replacement therapy (RRT).

We used Chi square test and student-t test for univariate analysis and binary logistic regression for multivariate analysis, with p value <0.05.

A propensity score-matched analysis was performed to compare AKI in patients treated or not with statins previous major cardiac surgery.

RESULTS. We included 7,276 patients and AKI was developed in 9.6 % of global population. 8.5 % of 3,749 patients treated with statins developed AKI and 10.7 % of 3,527 non treated (p = 0.002; OR 0.78, 95 % CI 0.67–0.91). After adjusted with logistic regression by EuroSCORE, bypass time and previous renal failure, statins continue being protective OR 0.82, 95 % CI (0.7–0.96).

In the propensity score-matched patient population realized in 3,056 (1,528 with statins and 1,528 without), AKI was 10.8 % in patient without statins and 9.9 % in patients with statins, OR 0.91 (0-72–1.11). After adjustment by EuroSCORE, bypass time and previous renal failure, OR was very similar 0.93 (0.73–1.18).

CONCLUSIONS. Although multivariate analysis suggests a protective effect for statins in terms of AKI after cardiac surgery, when we adjusted with a propensity score analysis, protective effect is rejected.

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0544

EFFECT OF BODY MASS INDEX IN OUTCOME OF PATIENTS UNDERGOING CARDIAC SURGERY

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INTRODUCTION. Obesity is not considered a risk factor for higher mortality after cardiac surgery. Some reports have documented a better outcome in patients with higher body mass index(BMI) compared with those with normal BMI despite higher comorbidities in obese patients.

OBJECTIVES. The aim of this study is to quantify the effect of BMI on clinical outcomes after cardiac surgery.

METHODS. 2844 consecutive patients requiring all types of cardiac surgery between January 2004 and February 2008 were prospectively studied at our institution. The patients were divided based on BMI ranges: normal (BMI $\geq$ 18.5–24.9 kg m^{-2}; n = 644; 22.6 %), overweight (BMI $\geq$ 25–29.9 kg m^{-2}; n = 1,320; 46.4 %) and obese (BMI $\geq$ 30 kg m^{-2}; n = 856; 30.2 %). Preoperative, operative and postoperative data including main outcomes were recorded together with cardiac surgery scores(Parsonnet,EuroSCORE) and ICU scores(APACHE,SAPS). ANOVA and Bonferroni post hoc analysis were used to compare differences between BMI groups. Multivariable analyses compared the risk of outcomes between different BMI groups after adjusting for case-mix. A complete follow-up was performed in 2,592 patients until January 2013.

RESULTS. In higher BMI groups there were higher cardiovascular risk factors rates, such as hypertension [odds ratio (OR) 3.51; 95 % confidence interval (CI) 2.58–4.78 for obese. OR 1.87 (95 % CI 1.46–2.40) for overweight; $P = < 0.001$], diabetes (OR 2.05; 95 % CI 1.16–3.63 for obese; $P = 0.013$. OR 1.53; 95 % CI 1.20–1.96 for overweight; *$P = 0.001$*) and including hypertrophic cardiomyopathy(OR 2.29; 95 % CI 1.66–3.16 for obese. OR 1.69; 95 % CI 1.29–2.21 for overweight; $P = < 0.001$) compared with normal BMI patients. Respiratory-related morbidities were shown with higher BMI patients, such as a worst oxygenation reflected by lower PaO_2/FiO_2 12hs after admission in higher BMI groups (OR 0.95; 95 % CI 0.92–0.99 for obese; $P = < 0.001$. OR 0.90; 95 % CI 0.85–0.95 for overweight; *$P = < 0.001$*) and longer ventilation times in obese (OR 0.97; 95 % CI 0.94–0.98; $P = 0.007$), and higher risk for septicaemia in obese compared with normal (OR 1.30; 95 % CI 1.06–1.60; $P = 0.012$) and overweight (OR 1.15; 95 % CI 1.03–1.28; $P = 0.007$) BMI groups.

In-hospital mortality was 5.6 % (n = 160) and long-term mortality was about was 11.95 % (n = 310) during the follow-up (6.2 ± 4.1 years). No mortality and survival differences were shown between BMI groups.

CONCLUSIONS. Despite higher respiratory-related morbidities with higher BMI and higher septicaemia with obese during ICU stay, there is not any BMI related influence over in-hospital mortality and long-term survival after cardiac surgery.

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0545

PREOPERATIVE HEMOGLOBIN-A1C AS A PREDICTOR FOR INFECTION POST CORONARY BYPASS SURGERY

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INTRODUCTION. Diabetes is a widely recognized risk factor for coronary artery disease and is associated with increased early and late mortality after myocardial revascularization in patients with multivessel disease(1). HbA1c refers to glucose bound hemoglobin A molecule. The hemoglobin A1c (HbA1c) test can provide an assessment of average blood glucose control during the 60–90 days (2–3 months) prior to the test [8–13]. Recent evidence suggests that hyperglycemia plays a significant role in the development of postoperative infections [2–5].

OBJECTIVES. To determine the prevalence of elevated Hemoglobin A1c levels, a marker of glycemic control in patients presenting for coronary artery bypass surgery, whether poorly controlled diabetes (high HbA1C) is a risk factor for infections and, if so, Is good preoperative glycemic control HbA1c levels <7 % is associated with decreased postoperative infections and Whether any protocol might improve outcome in diabetic patients.

METHODS. Retrospective observational study using KFAFH-JEDDAH data base. From January 2006 to December 2008, including 712 patients underwent coronary artery bypass surgery (CABG) + valve surgery. Among them, 478 patients (76.13 %) were diabetic and 234 (32.86 %) were nondiabetic, with primary outcomes were infectious complications, including pneumonia, wound infection, urinary tract infection, or sepsis.

RESULTS. The multivariable model includes age, sex, operation length and HbA1c levels were significantly associated with postoperative infections. An HbA1c level of more than 7 % was significantly associated with increased infectious complications with an adjusted odds ratio of 5 (95 % confidence interval, 2.7–9.3) and a P value of £0.001.

CONCLUSIONS. Good preoperative glycemic control (HbA1c levels <7 %) is associated with a decrease in infectious complications post CABG.

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0546

SYSTEMIC INFLAMMATORY RESPONSE TO ANESTHESIA: A COMPARISON OF FOUR DIFFERENT TECHNIQUES

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INTRODUCTION. Surgical injury induces systemic endocrine, metabolic and immune-inflammatory responses, activated by primary immune system and afferent neural stimuli from the surgical area. An increase of counter-insulin hormones, cytokines and catecholamines characterizes the post-operative hyper-metabolic phase [1]. Anesthesia can influence these responses [2].

OBJECTIVES. The aim of this study was to evaluate the post-operative systemic inflammatory response to four different anesthetic techniques: "blended" anesthesia (regional neural blockade plus general anesthesia, B), balanced anesthesia (Ba), TIVA (totally intra-venous anesthesia) and inhalational anesthesia (I).

METHODS. A preliminary retrospective study was conducted. We collected data from patients who underwent elective laparoscopic left hemicolectomy performed for colorectal cancer between January and December 2012. Patients who underwent emergency surgery, "open" surgery and surgery performed for inflammatory bowel diseases were excluded. Patients were divided in four groups depending on the anesthetic technique used for the surgery. Serum levels of glucose, leukocyte count and temperature were collected at different times to evaluate the systemic inflammatory response: before induction (T0), at the end of the surgery (T1, only for blood glucose levels), at 24 (T24) and 48 (T48) h from induction. Glucose variability, determined as the ratio of standard deviation to mean glucose levels at T0, T1, T24 and T48, was used to evaluate the degree of insulin resistance in each patient. Data were subjected to analysis of variance (differences were considered significant when P values were <0.05).

RESULTS. Thirty-two patients were eligible for the study: seven were included in the "B" group, nine in the "Ba" group, eight in the "TIVA" group and eight in the "I" group. Median blood glucose values (mg/dl) were statistically significant at T1 (I 122.5; Ba 100; TIVA 97.5; B 94.5; p < 0,05), T24 (I 135; Ba 114; TIVA 117.5; B 97.5; p < 0,05) and T48 (I 145; Ba 117.5; TIVA 123; B 105; p < 0,05). Median temperature values (°C) were statistically significant at T48 (I 37.3; Ba 37; TIVA 36.9; B 36.85; p < 0,05). Median leukocyte count values (n × 10^6/l) were statistically significant at T24 (I 1,250; Ba 9,000; TIVA 8,550; B 7,300; p < 0,05) and T48 (I 12,750; Ba 10,500; TIVA 9,250; B 7,600; p < 0,05). The difference among mean glucose variability values (mean %) was statistically significant (I 18.6; Ba 8.9; TIVA 11.8; B 5.1; p < 0.05).

CONCLUSIONS. Our preliminary data show that "blended" anesthesia seems to be able to modulate the systemic inflammatory response. A statistically significant difference appears also between anesthetic techniques using opioids, balanced and TIVA, and the inhalational anesthesia.

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0547

EFFECTS OF SYSTEMATIC LUNG RECRUITMENT IN POST-OPERATIVE STANDARD CARDIAC SURGERY : A PILOT STUDY

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INTRODUCTION. Cardiac surgery with extracorporeal circulation is associated with inflammation, leucocytes and platelets activation, leading to lung capillary leak and micro embolizations. This may prolong the duration of mechanical ventilation and increase the incidence of pulmonary complications.

OBJECTIVES. To evaluate the impact of systematic lung recruitment on postoperative gas exchange and morbidity after standard on-pump cardiac surgery.

METHODS. Prospective, randomized, single centre pilot study, including 100 consecutive patients admitted in ICU after cardiac surgery. Pre- and post-operative shocks and emergencies were excluded. Patients were included in the immediate postoperative period, still anesthetized, when hemodynamically stable and eligible for extubation. They were randomized for high PEEP application (35 cmH_2O during 45 s) or not (control group). Then, a physician blinded of the randomization applied standard protocols and collected the hemodynamic and ventilation variables at hours 1, 6, 12 and 24.

RESULTS. Of the 100 patients included into the study, 49 were recruited and 51 were not. The two groups were not different in terms of age, gender, BMI, LVEF, type of surgery, postoperative lung compliance, blood pressure, blood gas and lactate. However, in the

0705
THE EARLY BENEFITS OF A SEPSIS UNIT IN A TEACHING HOSPITAL. RESULTS FROM THE FIRST 100 SEVERE AND SEPSIS SHOCK PATIENTS TREATED

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INTRODUCTION. The mortality of severe sepsis and septic shock remains unacceptably high. The development of a multidisciplinary sepsis rapid response team (Sepsis unit) based on SSC could improve the survival of these patients and could also diminish their length of stay.

OBJECTIVES. The aims of this study were to describe the principal characteristics of the first patients treated by a Sepsis unit and to analyse the possible early benefits in terms of mortality and length of stay after the implementation of this unit in a teaching hospital.

METHODS. During a 4 months period, 100 severe sepsis and septic shock patients in a teaching hospital were prospectively evaluated, clinical and microbiological variables were recorded. Two different periods were analyzed in order to analyse the possible differences in mortality rates and length of stay. Period A: From 22-November-2102 to 15-January-2013 when a electronic check list to guide the management of these patients was applied without active interventions of sepsis team and Period B: From 16-January-2013 to 23-February-2013 when Sepsis team began to work actively. A univariate analysis was performed to define the possible differences between to periods using SPSS package (15.0). Statistical significance was considered when p value < 0.05.

RESULTS. Among 140 electronic activations 100 of them corresponded to severe sepsis (72) and septic shock (28). Their mean APACHE II and SOFA score were 17.04 ± 7.02 and 5.20 ± 3.19 respectively. The most frequent sources of infections were the respiratory focus (43 %), urinary (29 %) and abdominal (17 %). Global mortality was 22 %. The principal place of activation was ER in the 85 % of the cases. Only 27 % of patients were admitted in ICU. The number of activations was higher in period B (43 vs. 57). Length of stay was 9.15 ± 10.44 days. The global mortality rate was lower in period B without statistical significance (23.3 vs 21.1 %) whereas the length of stay dramatically diminished in a significant way also in Period B (11.1 ± 13 vs 6.79 ± 7 days, $p = 0.03$). No differences in APACHE II and SOFA scores were found between two periods.

CONCLUSIONS. These preliminary results showed a clear an early benefit of a sepsis unit in terms of detection, mortality and length of stay.

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SURVIVING SEPSIS: THE MANAGEMENT OF SEPSIS, EMERGENCY DEPARTMENT RAIGMORE HOSPITAL

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INTRODUCTION. Surviving sepsis campaign has recommended early administration of antibiotics within 1 h as each hour delay associated to increase of mortality[1]. This is a departmental audit performed in Emergency Department (ED) Raigmore Hospital to assess and to improve the compliant of timely management of septic patient.

OBJECTIVES. The objectives is to improve early recognition of septic patient and instigate timely investigation, improve the delivery time of antibiotics to septic patient in ED and to maintain a continuous education and feedback to ED staffs on management of sepsis.

METHODS. The data was collected retrospectively from reviewing clinical notes of patient who were diagnosed sepsis. First round of audit was carried out in November 2011 to assess percentage of antibiotics given, time of antibiotics given from the time a patient was triaged and percentage of lactate measured. 'Think sepsis even with SEWs (Scottish early warning sign) 0 or 1' campaign was introduced.

After 3 months, 2nd set of results were presented and we introduced the sepsis board which was updated monthly on above three measures. A sepsis trolley was also introduced (resuscitation items including Highland antimicrobial prescription guidelines). Following that a 3rd set of data was collected.

RESULTS. The results following the 3rd cycle of audits showed the time of antibiotics given has improved significantly from mean time of 104 min in December 2011 to 72.6 min in July 2012. The antibiotic that was administered within 1 h has improved from initial <20 % to average of 47 %. Lactate measurements have improved and maintained at above 70 % in July 2012.

CONCLUSIONS. 'Sepsis six bundle' is relatively difficult to achieve within one hour of patient presenting to ED. However, the duration of antibiotics given and percentage of lactate measured has significantly improved with above interventions. The cause of delay is usually due to uncertainty of diagnosis. Continuous education is essential to improve and maintain the standard of sepsis management. Think sepsis even if patient has low SEWS score but appear unwell. A common broad spectrum antibiotic could be considered as an attempt to avoid delay in antibiotics given due to uncertainty of which antimicrobial regimen is appropriate. The regimen should be reviewed daily for potential de-escalation and prevent resistance.

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0707
RISK FACTORS FOR ICU-ACQUIRED GRAM-NEGATIVE INFECTIONS

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INTRODUCTION. Infections due to multidrug-resistant Gram-negative bacteria have become a common problem in ICUs [1]. Antagonistic interactions between fungi and bacteria have been reported: *Candida albicans* can inhibit the virulence and the viability of human pathogens such as *P. aeruginosa* and *A. baumannii* [2]. The suppression of fungal growth could therefore lead to a higher risk of bacterial infections.

OBJECTIVES. Endpoint of this study was to determine the risk factors for ICU-acquired Gram-negative infections, with particular attention to the possible role of an antifungal therapy.

METHODS. A preliminary retrospective case–control study was conducted. We collected data from all patients admitted to ICU between January and December 2011. Patients admitted for <48 h were excluded. Patients who developed a Gram-negative, ICU-acquired infection were included in the study group, all the other patients were included in the control group. A preliminary analysis was conducted using χ^2 test for categorical data and t test for continuous data. Univariate logistic regression was used to confirm preliminary significant associations and to determine the odds ratio of found risk factors (OR). Outcome data, such as ICU mortality and length of stay and duration of mechanical ventilation, were collected from all patients.

RESULTS. Out of 193 enrolled patients, 15 (7.8 %) developed an ICU-acquired, Gram-negative infection; 40 % of patients who developed a ICU-acquired infection due to Gram-negative bacteria already had an infection on ICU admission ($p < 0.0001$, OR = 2.22, 95 % CI 1.03–3.40) and 60 % of patients with a Gram-negative ICU-acquired infection had been treated with antifungal drugs ($p < 0.0001$, OR = 2.30, 95 % CI 1.17–3.44). Outcome data showed a significantly higher ICU-mortality rate in patients with Gram-negative infections than in the control group (77.3 vs 14.6 %), and a higher length both of ICU stay and mechanical ventilation (24.07 ± 21.91 days vs 5.01 ± 402 days and 17.5 ± 17.23 days vs 2.15 ± 3.48 days respectively).

CONCLUSIONS. Our preliminary data show that infection on admission and antifungal therapy are significantly associated with a higher risk of Gram-negative ICU-acquired infections. The real need of an antifungal therapy should always be carefully evaluated, and its unnecessary use should be avoided.

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Cardiac surgical intensive care: 0708–0721

0708
EFFECTS OF RED BLOOD CELL TRANSFUSION ON MODERATE ANEMIA IN POST-OPERATIVE CARDIAC SURGERY: A COHORT STUDY

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INTRODUCTION. Transfusion criteria are not consensual in non-bleeding patients with moderate anemia (NBMA). Several studies have suggested that transfusing patient with moderate anemia can be detrimental in ICU.[1]

OBJECTIVES. To evaluate the impact on mortality and morbidity of transfusing NBMA patients in the immediate postoperative period of cardiac surgery.

METHODS. Retrospective, single center, cohort study, including 2,608 patients admitted in ICU after the end of the Aprotinin use. For all these patients, 85 items investigating the pre-, peri-, and post-operative status were available, including the logistic EuroSCORE (EuroSCORE), the length of stay (LOS), the duration of mechanical ventilation (MV), the post-operative Troponin IC serum concentration (Troponin). "Non-bleeding" was defined as total peri-operative blood transfusion ≤4 units. "Moderate anemia" was defined as hemoglobin rate nadir >75 g/L. The 30-days mortality was the primary outcome. Secondary outcomes were the postoperative occurrence of three composite indices of: (1) left ventricle dysfunction (LVD), (2) infection, (3) ischemic complication.

RESULTS. Of the 2,160 NBMA patients, 1,016 (47 %) received a blood transfusion. Transfusion was associated with higher mortality, OR = (4.1–1.2), $p < 0.0001$. The probability of transfusion was higher according to female gender (71 vs. 38 % for males), age (71.5 vs. 65.3), EuroSCORE (10.1 vs. 4.5), combined surgery (69 vs. 45 % for other interventions), duration of the extra corporeal circulation (65 vs. 58 min), Troponin (7.2 vs. 5.2 mg/L) and MV (7.7 vs. 15.1 h), all $p < 0.0001$. When all peri-operative items were included into a logistic regression, mortality was only linked to the EuroSCORE OR = (1.09–1.03), $p = 0.0003$, the MV OR = (1.01–1.00), $p = 0.006$, and the Troponin OR = (1.2–4.1), $p = 0.01$. The number of transfused red blood cells units was not linked to the ischemic composite index but was linked to infectious complications, OR = (1.34–1.05), $p = 0.0002$, in combination with LOS, OR = (1.12–1.05), $p < 0.0001$, body mass index OR = (1.08–1.03), $p = 0.0009$, and Troponin OR = (1.02–1.00), $p = 0.02$. The number of transfused red blood cells units was also linked with LVD, with OR = (1.65–1.01), $p < 0.0001$, in combination with preoperative LVEF OR = (1.07–1.03), $p < 0.0001$, Troponin OR = (1.07–1.02), $p < 0.0001$ and EuroSCORE OR = (1.05–1.02), $p < 0.002$.

CONCLUSIONS. In this large retrospective study in the postoperative period of cardiac surgery, restrictive blood transfusion in NBMA patients did not independently predict death, or ischemic complications, but predicted postoperative left ventricle dysfunction and infections.

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0709
5-YEAR MORTALITY IN CARDIAC-SURGERY PATIENTS WITH POSTOPERATIVE HEART FAILURE TREATED WITH LEVOSIMENDAN: PROGNOSTIC EVALUATION OF NT PRO-BNP AND C-REACTIVE PROTEIN AND CLINICAL RISK FACTORS

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OBJECTIVES. The aim of this study was to determine clinical risk factors for 5-year mortality in cardiac-surgery patients with perioperative myocardial dysfunction treated with levosimendan and if there is any relationship with NTpro-BNP and C-reactive protein (CRP) levels.

METHODS. Prospective observational study.

A group of 30 cardio surgical patients, 12 men and 18 women, with postoperative heart failure dependent on inotropic support, received levosimendan at the standard dose 0.1 mcg/kg/min during 24 h without a loading dose.

All of them underwent elective surgery, 20 valve replacement, 8 coronary artery bypass grafting, 1 aortic surgery and 1 aortic valve replacement plus bypass grafting.

The mean age was 64.7 ± 11.8 years.

The APACHE II was 13.2 ± 3.3 and EuroSCORE 8.2 ± 4.3.

NT pro-BNP and CRP serum levels were measured before levosimendan administration, and 48 h and 7 days later.
Hemodynamic parameters were recorded.
Statistical analysis was performed using SPSS 13.0.
We made the follow-up at 5 years for dead or alive.
RESULTS. One patient died during hospital stay.
The 5-year mortality in the study group was 12.1 % (n = 11). The NT pro-BNP levels showed no significant changes during the study, nor were associated with 5-year mortality. CRP levels changed over the period of 7 days:
we found a significant decrease between CRP pretreatment and on day 7 (172 ± 79 vs 94 ± 64 mg/L, P (t student: 5.00) = < 0.001) and between CRP 48 h post-treatment and on day 7 (144 ± 88 vs 94 ± 64 mg/L, P (t student: 2.97) = 0.006). In the univariate analysis, dilated cardiomyopathy 26.3 vs 72.7 %, P = 0.05), lower systolic blood pressure (132 ± 15 vs 120 ± 9 mmHg; P = 0.003), higher central venous pressure (CVP) at 48 h after treatment (11 ± 4 vs. 14 ± 2 mmHg, P = 0.02) and a decrease in CRP on day 7 (109 ± 73 vs 61 ± 34 mg/L, P = .03) were associated with increased 5-year mortality. In Cox regression the presence of dilated cardiomyopathy (HR = 36.909 [95 % CI 1.901–716 0.747], P = 0.017), a higher PVC 24 h after levosimendan administration (HR = 2.686 [95 % CI 1,383–5,214], P = 0.004) and lower CRP levels on day 7 (HR = 0.963 [95 % CI 0933–0994], P = 0.021) were found to be risk factors for 5-year mortality.

Table 1 NT pro-BNP levels

NT pro-BNP pg/ml	All patients n 30	Survivors n 18	Non Survivors n 11	p value
Pre treatment	29,300 ± 11,572	41,683 ± 14,784	10,081 ± 8,533	NS
48 h	7,716 ± 9,364	7,734 ± 11,146	8,059 ± 6,133	NS
7 days	6,868 ± 7,175	6,563 ± 7,740	7,709 ± 6,716	NS

CONCLUSIONS. In cardiac-surgery patients with postoperative heart failure, the presence of dilated cardiomyopathy, a higher CVP and lower CRP levels on day 7 after levosimendan administration were associated with 5-year increased mortality. Although NT pro-BNP levels showed no significant changes, there was a trend to higher initial levels in survivors, suggesting that sicker patients benefit more from levosimendan treatment in terms of survival.
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0710
A COMPARISON OF HEMODYNAMIC EFFECTS OF ETOMIDATE-MIDAZOLAM AND KETAMINE-MIDAZOLAM FOR ANESTHESIA INDUCTION IN CORONARY ARTERY BYPASS GRAFTING SURGERY

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INTRODUCTION. The stable hemodynamic profile of etomidate makes this drug the agent of choice for anesthesia induction during CABG. However, the undesirable effect of etomidate on steroid synthesis in adrenal glands has given rise to the search for an appropriate alternative for anesthesia induction during CABG.
OBJECTIVES. The aims of this study were to compare the effects of anesthesia induction with ketamine-midazolam or etomidate-midazolam combinations on hemodynamic parameters and adrenal suppression in CABG.
METHODS. 40 adult patients undergoing CABG were randomly allocated into two groups for this prospective randomized double-blinded study. Anesthesia was induced with ketamine 1 mg/kg in ketamine group (n = 20) and with etomidate 0.3 mg/kg in etomidate group. All patients also received midazolam 0.025 mg/kg during anesthesia induction. Standard opioid-based anesthesia maintenance, cardiopulmonary bypass (CPB), and surgical technique were used in all patients. Intra- and post-operative hemodynamic parameters including systolic, diastolic, and mean arterial pressures and heart rate were recorded. In order to investigate the etomidate induced adrenal suppression blood cortisol levels were measured before anesthesia, 5 min after anesthesia induction, and during rewarming (at 35 °C). In addition, at postoperative days 1 and 4 adrenocorticotropic hormone (ACTH) stimulation tests were performed
RESULTS. The groups were not significantly different in terms of demographic features except for a higher number of females in ketamine group than etomidate group (9/11 vs 1/19, p = 0.04). This difference was due to the randomization. Intra- and post-operative hemodynamic parameters were not significantly different between the groups (p > 0.05). However, compared with their matching baseline values, the systolic, diastolic, and mean arterial pressures significantly decreased in both groups (p < 0.05). Despite similar baseline measurements, cortisol levels were significantly higher 5 min after induction, during rewarming, and after ACTH stimulation test at postoperative day 1 in group ketamine than group etomidate (p < 0.05). Cortisol levels were similar in both groups after postoperative day 4 ACTH stimulation test (p > 0.05). The groups were not significantly different in terms of duration of surgery, intraoperative usage of inotropic/vasopressor use, intraoperative use of fluids and blood products, duration of postoperative mechanical ventilation, frequency of postoperative delirium, and intensive care unit and hospital lengths of stay (p > 0.05).
CONCLUSIONS. Ketamine-midazolam combination is an acceptable alternative to etomidate-midazolam combination in terms of hemodynamic stability. Compared with ketamine-midazolam combination, etomidate-midazolam combination significantly decreased cortisol levels during the intraoperative and early postoperative periods.

0711
INCIDENCE AND RISK FACTORS FOR SERIOUS DIGESTIVE COMPLICATIONS AFTER CARDIAC SURGERY

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OBJECTIVES. To study the incidence and risk factors of serious gastrointestinal complications (CDG) after major cardiac surgery (CCM).
MATERIALS AND METHODS. Retrospective study of patients admitted to ICU after CCM from January 2005 to June 2010. Variable recorded: age, sex, type of CCM, priority, type of CDG (bleeding, liver disease, intestinal ischemia, pancreatitis, cholecystitis), preoperative risk factors (obesity, smoking, high blood pressure, heart failure [HF], EuroSCORE, renal failure [RF], treatment with antiplatelet therapy, anticoagulant therapy and inotropic intravenous treatment [IV]), perioperative complications (myocardial infarction [IMP], surgery for bleeding) and mortality. Descriptive analysis by percentage for qualitative variables and mean or median for quantitative variables. Univariate test for qualitative variables and quantitative variables χ^2, student t test or Mann–Whitney test. Multivariate analysis using logistic regression model. Null hypothesis was rejected for alpha error = 0.05. Relative risk by odds ratio (OR) and confidence interval (95 %).
RESULTS. We included 3,242 patients after CCM, medium age 66 ± 12; 62.2 % male patients. 42 patients (1.3 %) had CDG: 30 hemorrhagic (71.4 %), 5 pancreatitis (11.9 %), 5 cholecystitis (11.9 %), 8 liver disease (19 %), hemoperitoneum (2.4 %), intestinal ischemia (2.4 %). Univariate analysis showed higher incidence of CDG: obesity OR 2.1 (1.1–4), p = 0.018, high blood pressure OR 3.3 (1.4–7.4), p = 0.002; EuroSCORE p = 0.001; RF OR: 3. (2–7), p = 0.001; inotropic IV p = 0.01 OR 6.3 (2.5–15.3); Heparin Na p = 0.007 OR 3.16 (1.3–7.6), CI p = 0.038 OR 2.1 (1.2–5.5) p priority = 0.004 OR 2.8 (1.3–5.7), IMP p = 0.001 OR 4.1 (1.8–9), surgery for bleeding p = 0.002 OR: 3.6 (1.5–8.7). The regression model were associated independently with CDG: Obesity p = 0.044 OR 2.05 (1.04–4); RF p = 0.046 OR 2.13 (1.04–4.3); inotropic IV: p = 0.047 OR 3.18 (1.09–9.2); IMP p = 0.004 OR 3.9 (1.7–9.1) and EuroSCORE p = 0.01 OR 1.17 (1.06–1.2). The total mortality was 1 %. The mortality of patients with CDG was 33 % and 2 deaths were directly caused of digestive complication. The CDG is associated with higher mortality p = 0.001 OR 6.8 (3.5 to 13.2).
CONCLUSIONS. 1. Incidence of CDG after CCM is low. 2. Independent risk factors are high EuroSCORE, obesity, RF, previous treatment with inotropic and IMP. 3. CDG are associated with increased mortality, but are a direct cause of death in some cases.

0712
DOES APROTININ INFLUENCE OUTCOMES IN REDO CARDIAC SURGERY

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INTRODUCTION. Redo cardiac surgery is associated with a high risk of numerous complications including the risk of bleeding. Serine protease inhibitors tranexamic acid and aprotinin are the two most commonly used agents worldwide to prevent bleeding after cardiac surgery. There have been numerous studies comparing the effects of these agents and have failed to ascertain a superior pharmacological effect of one agent over the other. A large multicentre trial in the middle of last decade highlighted the risks associated with the use of aprotinin. The use of aprotinin has since reduced significantly and is used only some centres for high risk cardiac surgery. Administration of aprotinin in our regional cardiothoracic centre located in the north of England is restricted to use in redo cardiac surgery where a high risk of post-operative bleeding is anticipated. We designed the study to analyse the effects of aprotinin in our patients.
OBJECTIVES.
To study the frequency of Aprotinin utilization.
To study and compare the incidence of renal failure with patients who did not receive Aprotinin.
To study the effect of co-morbidity and other confounding factors in the development of renal failure.
To study the incidence of post-operative renal failure and mortality in both groups of patients.
METHODS. Retrospective analysis of case notes of all elective redo cardiac surgery in Freeman Hospital over 3 years. The data was collected on a proforma. The patients were grouped into those who received Aprotinin versus those who had alternate drug, tranexamic acid. The data was analysed using Microsoft excel spread sheet.
RESULTS. A total of 97 redo surgeries were performed during the period. Aprotinin was administered in 45 patients. The most common surgery performed was Aortic valve replacement with CABG. Patient demographics in both groups including age, sex height and weight were comparable in both group. Co-morbidities, length of surgery, bypass time and aortic cross clamp time were comparable in both groups. No significant difference was observed between the groups with respect to renal failure, need for replacement therapy or mortality. This was true of even in the subset of patients with premorbid renal failure. A significant difference in favour of aprotinin was noted for the requirement of blood and blood products perioperatively.
CONCLUSIONS. Use of aprotinin was not associated with increased risk of renal failure and death in redo cardiac surgery in Freeman Hospital. The need for blood and blood products was reduced peri-operatively in patients who were administered Aprotinin.
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0713
PREDICTIVE MODEL FOR LONG-STAY IN ICU AFTER CARDIAC SURGERY

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INTRODUCTION. The prolonged stay Care Unit (ICU) is associated with higher mortality rates and it will include an important consumption care resources [1]. In cardiac surgery is now recognized as an important component of outcome evaluation [2] and may influence decision-making in the management of this patients.
OBJECTIVE. Analyze the perioperative risk factors of very prolonged ICU stay and survival at hospital discharge in patients undergoing cardiac surgery.
PATIENTS AND METHODS. We reviewed patients after cardiac surgery admitted in a cardiovascular ICU of a tertiary University Hospital for 5 consecutive years (Jan 2007–Dec 2011), following the analysis of data collected prospectively. It was classified as very prolonged stay in ICU if exceed 20 days of admission. We analyzed the variables pre, intra and postoperative, by univariate and multivariate analysis, and we built a logistic regression model in which assessed its capacity of discriminate in the odds requested and the sensitivity and specificity in classifying the model. Survival at discharge was analyzed by Kaplan–Meier curve. Independent risk factors were expressed by OR (CI 95 %).
RESULTS. Of the 2,929 patients treated, 119 (4.1 %) were admitted to the ICU more than 20 days. In univariate analysis statistically significant variables associated (p < 0.05) with prolonged stay were: age > 70 years, hypertension, chronic obstructive pulmonary disease (COPD), chronic renal failure, obesity, NYHA functional class III/IV, urgent surgery, valve surgery and aortic arch, cardiogenic shock, postoperative critical condition, CPB time, ischemia time, EuroSCORE, vasoactive support >24 h, prolonged intubation, re-operation,

35 REUNIÓ SOCIETAT CATALANA
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ÀMBIT MÈDIC: COMUNICACIONS ORALS

OM7- Avaluació de nivells seriats de lactat arterial en el postoperatori de cirurgia cardíaca.

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Objectius: Determinar el valor pronòstic del lactat arterial (LA) en el postoperatori immediat de cirurgia cardíaca.

Mètodes: Estudi prospectiu i observacional en una UCI quirúrgica d´un hospital universitari nivell 3. Es van incloure 2935 pacients. Vam mesurar el lactat a l´ingrés, a les 6h, 12h i 24h després de l´ ingrés a UCI, conjuntament amb les dades clíniques, complicacions i mortalitat a curt i llarg termini (seguiment mitjà 6.3 ± 1.7 anys).

Resultats: La mortalitat va ser d´ un 5.9%. El no-supervivents comparats amb els supervivents tenien nivells més alts (P<000.1) en totes les mesures de LA (mmol•l-1): 3.2±2.6vs.2.24±1.3 a l´ingrés, 3.8±3.3vs.2.6±1.5 a les 6h, 3.7±3.2vs.2.1±1.1 a les 12h i 2.9±2.4vs.1.8±0.7 a les 24h després de l´ ingrés a UCI. Un LA elevat (LA>3.0mmol•l-1) va ser predictor de mortalitat a curt termini/ hospitalària (Odds ratio(OR): 1.468; 95% Confidence Interval (95% CI):1.239-1.739) i a llarg termini (Hazard ratio(HR):1.511; 95% CI:1.251-1.825). L´infart de miocardi recent (OR:1.519; 95% CI: 1.107-2.086;P=0.01), la cardiomiopatia dilatada (OR:1.392;95% CI:1.132-1.711;P=0.002), un elevat temps de Circulació Extracorpòrea (OR:1.010;95% CI:1.008-1.013;P<0.001) i un pic de creatinina elevat després de la cirurgia (OR:1.008;95% CI:1.005-1.010; P<0.001) van ser predictors d´ un LA elevat.

Les corbes del LA van seguir patrons similars entre no-supervivents i supervivents, amb valors més elevats entre els no-supervivents confirmat per l´ anàlisi de mesures repetides de variància (P<000.1). L´ àrea sota la corba del LA també suggereix una major intensitat en els seus nivells en el grup de no-supervivents (80.9±68.2vs.49.71±25.8mmol•l-1•h-1; P=0.038). Els pacients amb LA elevat van ser dividits segons el moment en el qual es produïa el valor més alt de LA, objectivant-se una major mortalitat en aquells que tenien uns nivells més elevats a les 24h del postoperatori, confirmat mitjançant l´ anàlisi multivariable i una pitjor supervivència comparat amb la resta de grups (58.2%vs.78.5-81.7%; Log Rank test:P<0.001)

Conclusions: La dinàmica de les corbes del LA entre no-supervivents i supervivents amb valors mitjans més elevats en els no-supervivents, suggereix uns mecanismes similar de producció del LA però una major producció i/o menor aclariment del mateix. El pic de LA elevat a les 24h després de la cirurgia està associat a una major mortalitat a curt i llarg terme en aquests malalts.

MAGNESIUM AND CARDIAC SURGERY IN THE CRITICAL CARE SETTING

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List of all abbreviations used in the manuscript:

Mg: Magnesium; ATP: Adenosine triphosphate; ICU: Intensive Care Unit; AMI: myocardial infarction; $MgSO_4$: magnesium sulphate; SAH: subarachnoid haemorrhage; AF: Atrial fibrillation; CABG: coronary artery bypass surgery.

ABSTRACT

Magnesium (Mg) is an important intracellular ion with electrophysiological properties. It is essential for optimal metabolic cell function. Serum Mg is a poor predictor of body stores, as less than 1% of total body Mg is found in serum. Ionized Mg assessment, the active portion of Mg, may be a more useful indicator than total serum Mg assessment.

Hypomagnesaemia is common in the cardiac surgical population and correlates with higher incidence of cardiac arrhythmias and major adverse cardiac events. However, the role of Mg in preventing postoperative arrhythmias – especially atrial fibrillation – is controversial. There is moderate evidence that intravenous Mg therapy, particularly low doses administered before cardiac surgery, will reduce the postoperative incidence of atrial fibrillation.

Hypomagnesaemia is also common in hospitalized patients. It is especially prevalent in the critically ill, and correlates with worse clinical outcomes. Mg has proven effective for treating Torsade de Pointes, eclampsia, and preeclampsia. Other therapeutic applications such as adjunctive therapy in acute asthma exacerbations, acute coronary syndromes, acute cerebral ischaemia and postoperative pain control are under discussion. Mg has a low adverse effects profile and multiple theoretical advantages, including its low cost.

Key Words: Magnesium; intensive care; cardiac surgery; acute coronary syndromes; asthma; acute cerebral ischaemia; pain control; postoperative care; arrhythmia; atrial fibrillation.

INTRODUCTION

Magnesium (Mg) is a bivalent ion, the fourth most common mineral salt in the human organism and the second most frequent intracellular cation after potassium. However, its plasma concentrations do not give an accurate indication of the Mg pool in the organism; less than 1% of the total body Mg is represented by the plasma/serum levels.

Mg is involved in the regulation of various ion channels and phosphorylation reactions, and serves as a cofactor in many enzyme systems. Mg-dependent enzyme systems include the ones associated with the membrane pumps that generate the voltage gradient across the cell membranes; therefore, Mg plays an important role in the activity of electrically excitable tissue (White, 1989).

As a calcium antagonist, Mg reduces intracellular calcium accumulation, thus altering the calcium channel function. This process improves adenosine triphosphate (ATP) availability and reduces ATP utilization, optimizing cellular energy resources (Shattock, 1987). Mg also regulates the movement of calcium into vascular smooth muscle cells, and therefore plays a central role in maintaining the contractile heart function and peripheral vascular tone (Tong, 2005).

Dysmagnesaemia, and in particular hypomagnesaemia, is one of the most common electrolyte abnormalities in hospitalized patients. This disturbance is especially prevalent in the critically ill.

The physiology of magnesium

The adult human body contains approximately 0.3 g of Mg per kg of body weight, i.e., an average of 24 g of Mg (1 mol or 2000 mEq). Mg is distributed principally between bone (53%), intracellular compartments of muscle (27%) and soft tissues (19%). Very small amounts are found in erythrocytes (0.5%) and in serum (approximately 0.3%). Serum Mg is divided into three fractions: ionized (65%, the active form), bound to proteins (27%, mainly to albumin), and bound to anions such as citrate and phosphate (8%).

The estimated average daily Mg requirement is between 300 and 400 mg in adults. Rich sources of Mg in the diet are cereals and legumes (**Table 1**). From 30 to 50% of ingested Mg is absorbed, principally from the jejunum and the ileum. This proportion increases to 70% in the states of Mg deficiency.

The excretion and control of serum Mg are carried out by the kidneys. It is filtered in the glomerulus and reabsorbed predominantly in the ascending limb of the loop of

Henle. The reabsorption is stimulated by the parathyroid hormone (PTH), hypothyroidism, intravascular volume depletion, hypocalcaemia, and so on; conversely, it is inhibited in the presence of hypercalcaemia, intravascular volume expansion, metabolic acidosis, phosphate depletion, diuretics, etc. However, the main regulating factor is the intracellular concentration of Mg.

Most intracellular Mg binds to adenosine triphosphate (ATP) and is in equilibrium with free Mg ions. Therefore, the displacement of free Mg helps to regulate ATP deposits. ATP is crucial for almost all metabolic reactions, and so the preservation of normal serum Mg concentration is essential for maintaining adequate reserves of this important nucleotide. Mg intervenes in the activation of membrane calcium-ATPase and sodium-potassium ATPase involved in transmembrane ion exchanges during depolarization and repolarization phases. It is considered to act as a regulator of different ion channels. Calcium and Mg concentrations are related to each other and their interaction also depends on temperature. Under normothermic conditions, the Mg concentrations required are dependent on the calcium concentration; high calcium requires high Mg, and vice versa. However, temperature influences the ion balance; the calcium required for a given Mg concentration is reduced by hypothermia (Maruyama, 2013; Takemoto, 1992).

The clinical effects of Mg derive from its main action as a physiological antagonist of the calcium channel: it is involved in the maintenance of vascular muscle tone (myocardial, brain, lung) through the regulation of calcium levels. Mg deficiency may increase the release of calcium from the sarcoplasmic reticulum and increase calcium channel binding, which may in turn raise intracellular calcium levels with vascular smooth muscle contraction. Mg is also an antagonist of N-methyl-D-aspartate (NMDA) receptors; in the central nervous system it appears to play a role in protecting against ischaemic damage.

Measurement of magnesium

The determination of total serum Mg by molecular absorption spectrophotometry is accurate and easy to perform. It is used routinely in clinical practice. However, owing to the intracellular nature of this ion, there is a disparity between its intracellular and serum levels; equilibrium between these tissue pools is achieved very slowly, which suggests that serum Mg concentrations do not reflect true body stores (Elin, 1994) or a clinically relevant deficiency. Other concentrations have been studied in attempts to

obtain better assessments of true Mg deficiencies, namely intracellular and ionized serum Mg concentrations. Because of the long mean life of Mg and its slow turnover, erythrocytic Mg may be a better indicator of deficiency.

Another indicator of Mg status is urinary Mg excretion, which is useful to distinguish between renal and non-renal causes of hypomagnesaemia. In the presence of hypomagnesaemia, high urinary excretion suggests that increased renal loss is the mechanism of Mg depletion, whereas low urinary excretion suggests gastrointestinal or other causes. Studies of urinary Mg excretion after a loading test can help to diagnose Mg deficiency when magnesaemia is normal: subjects without deficiency excrete more than 60-70% of Mg input, whereas subjects with deficiency excrete less than 50% (Dubé, 2003).

Mg units are commonly expressed in mmol, mEq or mg. A method of conversion is shown in **Table 2**. Normal Mg concentration, assuming normal distribution, has a reference range from 0.7 to 1.1 mmol/L (although these numbers may vary slightly depending on the laboratory).

Magnesium disturbances

The main aetiologies of hypomagnesaemia are deficient supply and increased gastrointestinal or renal losses. The common causes of magnesium deficiency are listed in **Table 3**. Patients are usually asymptomatic when serum Mg concentration is > 0.5 mmol/L, although the severity of symptoms may not correlate with serum Mg levels. Clinical manifestations of hypomagnesaemia are described in **Table 4**. When present, it is frequently associated with hypokalaemia and hypocalcaemia.

Hypomagnesaemia has been demonstrated in between 7% and 20% of hospitalized patients and it is associated with higher mortality and longer hospital stay (Wolf, 2014). It usually coexists with other electrolyte disturbances, particularly hypokalaemia or hypophosphataemia and, to a lesser extent, with hypocalcaemia, in which more than 40% of patients are affected (Soave, 2009). The prevalence of hypomagnesaemia in critically ill adult patients ranges between 14% and 61%. In the few studies that have measured ionized Mg, the prevalence of hypomagnesaemia was much lower (10-18%). This overestimation of hypomagnesaemia may be related to the decreased serum protein concentrations in critical illnesses. Another likely explanation for the high prevalence of hypomagnesaemia assessed by total serum Mg is a shift from extracellular to

intracellular compartments of the body in which the concentration of ionized Mg, in contrast to total serum Mg, usually remains unchanged (Escuela, 2005; Soliman, 2003).

Hypermagnesaemia is less common than hypomagnesaemia; its prevalence is between 4% and 14%, and it is mostly due to acute or chronic renal failure, or a higher Mg intake (e.g. cathartics or in the treatment of eclampsia); also occurs in rhabdomyolysis due to release of Mg from disintegrating muscle. It is clinically well tolerated and severe manifestations are uncommon (**Tabla 5**). Under the conditions that lead to hypermagnesaemia, Mg administration is contraindicated.

APPLICATIONS TO THE CRITICAL CARE SETTING

The importance of regulating electrolytes such as potassium in the intensive care unit (ICU) is well recognized. Potassium levels are measured frequently, especially in patients with cardiovascular disease. In contrast, measurement of electrolytes such as Mg, calcium and phosphate is much less common.

Critically ill patients tend to present Mg depletion. The condition is multifactorial: it may be due to deficient intake, increased losses, or redistribution in the body. Losses may be renal or extrarenal (**Table 3**). The critical patient may lose Mg through the nasogastric tube or if they have diarrhoea or enteric fistulas. Gastric aspirate contains about 0.5 mmol/L of Mg and intestinal fluid about 7 mmol/L. However, the most common and important loss mechanism is via the kidney. The kidney may decrease Mg reabsorption due to acute tubular necrosis or tubulointerstitial disease; diuretics stimulate excretion, and other drugs such as aminoglycosides, amphotericin B or cyclosporine may reversibly injure tubules. Sometimes the origin is abnormal distribution, e.g. in pancreatitis hypocalcaemia and hypomagnesaemia is produced due to chelation of calcium and Mg in the necrotic areas of the pancreas. Total parenteral nutrition is another predisposing factor; purportedly, the change of anabolism to catabolism increases Mg needs and input inside the cell.

Hypomagnesaemia in critical illness correlates with higher mortality and worse clinical outcomes in the ICU (Tong, 2005). It is associated with longer mechanical ventilation support (Aglio, 1991; England, 1992), more rhythm disorders, and higher mortality (Rubeiz, 1993; Chernow, 1989). Mg deficiency is associated with increased ventricular ectopy and may raise the risk of sudden unexpected death. When associated with other electrolyte disorders such as hypokalaemia, it is usually refractory to isolated potassium supplementation until the magnesium deficiency is corrected. This relation may be due

to underlying disorders that cause both Mg and potassium loss. In addition, renal potassium losses are increased in hypomagnesaemic patients. The role of Mg in transmembrane potassium transport systems accounts for this phenomenon (Fawcett, 1999; Tong, 2005).

Hypermagnesaemia have been associated with mortality. The main factor in this association could be the development of acute renal failure, a major cause of hypermagnesaemia and a frequent complication in critically ill patients. Mg has proven effective for treating eclampsia, preeclampsia, and polymorphic ventricular tachycardia associated with prolonged QT (Torsade de Pointes) and for treatment of arrhythmias associated with digitalis toxicity. It is also recommended for managing rapid atrial fibrillation if it is associated with factors for hypomagnesaemia and kypokalaemia, such as the use of diuretics. It also plays a role in other clinical conditions as adjuvant treatment in acute coronary syndromes, asthma, acute cerebral ischaemia, and pain control.

Acute coronary syndromes

Hypomagnesaemia is common in coronary artery disease and/or chronic heart failure. Mg is thought to exert its anti-ischaemic protective effect by influencing the high-energy phosphate content of the myocardium. Its supplementation improves myocardial metabolism and inhibits calcium accumulation and myocardial cell death (Shechter, 2010). It was recently demonstrated that a Mediterranean diet is associated with increased serum Mg levels, and that this diet may be cardioprotective (Bahreini, 2009).

Mg acts through multiple pathways to produce its benefits in these patients. It regulates haemodynamic function by improving vascular tone, peripheral vascular resistance, afterload and cardiac output, and even reduces cardiac arrhythmias (Shechter, 2010). By improving the lipid metabolism profile, it reduces vulnerability to oxygen-derived free radicals. It enhances the human endothelial function and inhibits platelet function, including platelet aggregation and adhesion, and so its physiological and natural effects may be similar to those of adenosine-diphosphate inhibitors such as clopidogrel (King, 2009).

The data regarding its use in patients with acute myocardial infarction (AMI) are conflicting. Mg treatment in the acute phase of AMI appeared favourable in the LIMIT-2 trial, but the ISIS-4 trial conducted the following year with a substantially larger

sample did not find improvements in the clinical outcome in the group treated with Mg (Woods, 1994; Lancet, 1995). In the MAGIC-trial, administration of Mg to high-risk patients with AMI had no effect on mortality and did not improve clinical outcome (Antman, 2002). However, despite the negative results Mg may be an adjunctive therapy option in selected AMI patients, such as older samples, in the presence of left ventricular dysfunction and/or chronic heart failure, or in patients who are unsuited for reperfusion therapy (Shechter, 2005).

Asthma

Mg influences the smooth muscle function of the bronchi by means of calcium-dependent mechanisms: hypomagnesaemia causes their contraction, and hypermagnesaemia their relaxation. The use of Mg sulphate ($MgSO_4$) is one of the adjunctive therapies available during asthma exacerbations. The use of intravenous $MgSO_4$ (in addition to β_2-agonists and systemic steroids) in the treatment of acute asthma appears to produce benefits in the form of improved pulmonary function in both children and adults, and also in reducing the number of hospital admissions for children (Shan, 2013). As regards the use of inhaled $MgSO_4$ in addition to inhaled β_2-agonists there is currently no clear evidence of improved pulmonary function or reduced hospital admissions; however, some small trials suggest a possible improvement in pulmonary function in adults with severe asthma exacerbations (defined as peak expiratory flow rate or FEV_1<50% predicted) (Powell, 2012).

Acute cerebral ischaemia

Mg deficit is one of the bases for hypoxia in brain cells in acute or chronic stroke, which leads to their subsequent death. In addition to its anti-platelet function described above Mg contributes to the energy balance. In experimental models, it reverses cerebral vasospasm and reduces infarct volume in subarachnoid haemorrhage (SAH). Thus, Mg administration may help to reduce cerebral ischaemic events after aneurysmal SAH (van der Bergh, 2005). However, although initial pilot studies showed a reduction in clinical deterioration due to delayed cerebral ischaemia, current data did not suggest that Mg might improve clinical outcome (Wong, 2013).

Pain control

Mg reduces catecholamine release and thus allows better control of the adrenergic response during painful manoeuvres such as intubation. Perioperative Mg administration may reduce the need for intraoperative anaesthetics and relaxant drugs in both general and loco-regional anaesthesia and may also allow reductions in postoperative analgesia dosage (Dube, 2003). It exerts anti-nociceptive effects by blocking the N-methyl-D-aspartate receptor and the associated ion channels, thus preventing the central sensitization caused by peripheral nociceptive stimulation (Soave, 2009). Addition of Mg to bupivacaine in thoracic paravertebral block also improves the analgesic effect in patients undergoing thoracic surgery (Ammar, 2014).

Pre-eclampsia and eclampsia

Eclampsia is defined as the onset of convulsions in women who have either gestational hypertension or pre-eclampsia. Mg sulphate is the treatment of choice for the prevention and treatment of seizures in eclampsia with level of evidence I. Large, randomized clinical trials have demonstrated the superiority of $MgSO_4$ over phenytoin and diazepam and the efficacy of $MgSO_4$ in reducing the risk of seizure and, possibly, the risk of maternal death. Mg may prevent seizures by interacting with NMDA receptors in the central nervous system.

Pre-eclampsia is a pregnancy-specific disease characterised by de-novo development of concurrent hypertension and proteinuria, sometimes progressing into a multiple organ dysfunction. The underlying mechanism of pre-eclampsia is multifactorial. Pathological placental blood flow, endothelial activation, oxidative stress and generalised inflammation are strongly associated with this systemic disease. Women with severe preeclampsia should be considered for $MgSO_4$ prophylaxis during initial stabilisation and peripartum. Four grams should be administered intravenously over 15 min in severe pre-eclampsia (or 5 min if actively seizing) followed by an infusion of 1 g/h for 24 h. This should be maintained for 24 h following delivery of the baby or from the last seizure (Arulkumaran, 2013). This regimen does not need testing of blood concentrations of Mg because clinical effect can be monitored with deep tendon reflexes in patients with normal renal function (Steegers, 2010).

APPLICATIONS TO CARDIAC SURGERY

Patients undergoing cardiac surgery with cardiopulmonary bypass (CPB) are at high risk of electrolyte depletion, especially hypomagnesaemia. The aetiology appears to be

multifactorial: increased incidence of pre-surgery hypomagnesaemia, haemodilution, increased urinary excretion and intracellular shift, induced by a combination of CPB and decreased body temperature during surgery (hypothermia-induced diuresis and intracellular shift). Citrate toxicity in blood transfusion may also contribute to decreasing Mg after cardiac surgery.

Hypomagnesaemia has been well documented in cardiac surgical patients, with rates ranging from 12% to 44% (Polderman, 2004; Pasternak, 2006; Carrió, 2012). Low serum Mg levels correlate with major adverse cardiac events and with the all-cause mortality rate as long as a year after surgery (Booth, 2003). Hypomagnesaemia is an independent risk factor for postoperative atrial fibrillation (AF) and increases atrial myocardial excitability. Mg concentration has been shown to decline after cardiopulmonary bypass and does not recover to preoperative levels until three to five days after surgery, a period that parallels the time frame for postoperative AF. Although it correlates with the increased incidence of cardiac arrhythmias after cardiac surgery, its role in preventing postoperative AF has been a subject of much debate. Therefore, practices involving the perioperative use of Mg in adult cardiac surgery vary widely (Roscoe, 2003).

Postoperative atrial arrhythmias, fundamentally AF, are the most common complications following cardiac surgery. Their incidence ranges from 11% to 54%, while the incidence of ventricular arrhythmias is between 2% and 13%. In surgery combining CABG and valve surgery, the incidence of atrial arrhythmias may be above 50% (Hogue, 2000). Postoperative AF is associated with an increased risk of heart failure, myocardial infarction, increased length of ICU and hospital stay, healthcare costs, and, less frequently, with post-operative stroke and mortality (Khalpey, 2012). The effects of Mg for arrhythmogenic potential (**Table 6**) have been widely studied and are the rationale for Mg administration in these patients (Stiles, 2007; Ince, 2001).

Mg treatment has been associated with a decrease in ventricular dysrhythmias (England, 1992; Caspi, 1995; Shiga, 2004). With regard to AF, several studies have used Mg as a prophylactic agent following CABG. However, the results are inconsistent: some authors report that levels are maintained or suggest a small benefit (Treggiari-Venzi, 2000; Kaplan, 2003; Hazelrigg, 2004; Geertman, 2004), but others report a reduction in the incidence of AF (Fanning, 1991; Colquhoun, 1993; Nurözler, 1996; Toraman, 2001). Few studies have specifically addressed the ability of Mg to prevent atrial arrhythmias after heart valve surgery. Two clinical trials involving CABG and valve

surgery found that Mg prophylaxis immediately after surgery does not reduce the incidence of AF (Cook, 2009; Carrio, 2012). The studies measured serum Mg levels all agree that normomagnesaemia affords protection from arrhythmias (Rostron, 2005).

Table 7 summarizes the main double blind, placebo-controlled, randomized clinical trials that have analysed the effect of Mg on post cardiac surgery atrial arrhythmias.

Overall, the meta-analyses have shown that Mg reduces the risk of AF after cardiac surgery, but the heterogeneity of the design of the trials included limits the impact of their conclusions (Shiga, 2004; Burgess 2006). A recent meta-analysis that evaluated twenty studies concluded that the effect of Mg in reducing postoperative supraventricular arrhythmias was significant when examined by lower-quality studies but not in higher-quality studies, and stresses that this difference was probably responsible for the controversial findings reported in the literature (De Oliveira, 2012). However, another recent meta-analysis of only seven double blind, placebo-controlled randomized clinical trials (RCT) after CABG reported that Mg prophylaxis decreased the incidence of postoperative AF by 36% (Gu, 2012).

It appears that preoperative Mg administration is more effective in preventing postoperative AF than intra- or postoperative supplementation. When cumulative doses are analysed it seems that lower doses significantly reduce postoperative AF, whereas moderate to higher doses are less effective (Henyan, 2005; Miller, 2005). At the same time, Mg appears to be more effective in trials with CABG surgery alone than when CABG was combined with valve surgery (Miller, 2005).

A recent meta-analysis (Cook, 2013) including only those RCTs that studied AF as a primary endpoint showed no beneficial effect of Mg in the prevention of postoperative AF. However, the majority of these RCTs did not administer Mg preoperatively.

Mg has a synergistic effect with other antiarrhythmic drugs such as amiodarone. This reduces the need for prolonged use of these potent agents, thus decreasing their side effects and costs (Cagli, 2006). However, the use of Mg supplementation may not offer any additive effect to perioperative beta-blockers in preventing AF (Wu, 2013).

Most of the meta-analysis found that the use of prophylactic Mg does not significantly affect the length of hospital stay or mortality (Shiga, 2004; Miller, 2005; Wu, 2013).

In summary, there is moderate evidence that IV Mg therapy, particularly in low doses initiated before cardiac surgery reduces the postoperative incidence of AF. The major advantage of this approach is that therapy is very unlikely to be associated with adverse effects in patients without renal dysfunction. Thus, patients who have a contraindication

to beta-blocker therapy and to amiodarone therapy may be considered for prophylactic therapy to prevent postoperative AF with Mg.

The European Association for Cardiothoracic Surgery (Dunnig, 2006) and the Canadian Cardiovascular Society (Mitchell, 2010) have recommended prophylaxis with IV $MgSO_4$ in their guidelines (Conditional Recommendation, Moderate-Quality Evidence). The guidelines published in 2011 by the Society of Thoracic Surgeons (Fernando, 2011) for the prophylaxis and management of AF associated with general thoracic surgery recommend Mg supplementation to augment the prophylactic effects of other medications (Class IIa recommendation, Level of evidence B). However, the guidelines published also in 2011 by the American College of Cardiology/American Heart Association/European Society of Cardiology do not mention in its recommendations the use of IV Mg for prevention of postoperative AF.

Other applications in cardiac surgery

Recent studies have shown the potential benefits of Mg cardioplegia, since it provides superior cardioprotection with lower and slower ischaemic contracture compared to hyperkalaemic cardioplegia and represents a safe way to protect the heart. This issue is particularly important in view of the growing numbers of elderly patients, especially octogenarians, in the cardiac surgery population (Mayurama, 2013).

Neurocognitive decline is frequent after cardiac surgery and persists in a significant number of patients (Martin, 2008). There is a growing interest in developing strategies to prevent neurologic dysfunction in these patients. Mg is thought to provide neuroprotection by preserving the cellular energy metabolism, blocking the N-methyl-D-aspartate receptor, reducing the inflammatory response, and inhibiting platelet activation. Thus, some authors advocate Mg use as a neuroprotective agent in order to reduce postoperative cognitive dysfunction. So far, however, few randomized clinical trials have been conducted, and the results have been mixed: Mg administration improved short-term postoperative neurologic function after cardiac surgery (Bhudia, 2006) but a recent study did not report positive results (Mathew, 2013).

Finally, Mg may play a role as adjunctive therapy in the management of postoperative pain. It shortens postoperative time for tracheal extubation and reduces postoperative pain scores by IV infusion during elective CABG surgery (Ferasatkish, 2008).

GUIDELINES AND PROTOCOLS

Mg dosage for replacement therapy is not well determined, and recommendations vary. There are no formal guidelines regarding its therapeutic use – only the recommendations described in **Table 8**.

Critical care patients usually require Mg supplements, mainly administered by IV due to the need for rapid administration or to contraindication of the oral route, which is the first choice. Oral administration of 5-15 mmol/day is enough to correct moderate deficits, while an oral intake ranging from 15 to 28 mmol/day is necessary for severe deficits. The most common treatment option is to give 25 mmol of IV $MgSO_4$ as a continuous infusion for between eight and 24h (Dubé, 2003). In severe hypomagnesaemia 4-8 mmol of $MgSO_4$ can be given over 20 min. This can be followed by 4-8 mmol over six to eight hours and repeated as needed. It has been recommended that one should limit intravenous Mg replenishment to 50 mmol in 24 hours except in severe life-threatening hypomagnesaemia although about 50% of IV Mg will be excreted into the urine even in the presence of Mg deficiency (Sue, 2008). Each vial of 10 ml of $MgSO_4$ 10% has 1 g of Mg salt, which is equivalent to 98 mg of elemental Mg. Other presentations include magnesium chloride ($MgCl_2$). Each vial of 10 ml 10% $MgCl_2$ has 1 g of Mg salt, which is equivalent to 118 mg of elemental Mg (**Table 2**).

Serum or ionized Mg levels and renal function monitoring is mandatory during treatment. Rarely there are instances of normal or high serum Mg in patients with depletion of total body Mg. This suggests that serum Mg is a reasonable guide to decide that total body Mg levels are low but not ideal for determining the degree of depletion. Fortunately, in the absence of decreased glomerular filtration, administered Mg is readily excreted when serum Mg concentration is greater than 0.83 mmol/L suggesting that repletion of Mg is safe in almost all patients with Mg concentration less than 0.63-0.71 mmol/L (Sue, 2008).

Treatment should be stopped if hypotension or bradycardia develops or if the deep tendon reflexes disappear. These reflexes disappear with hypermagnesaemia, but usually only at very high toxic levels. Replacement doses of Mg in patients with renal insufficiency should be reduced, and serum Mg must be monitorized carefully.

Dietary intake of approximately 5 mg/kg per day (about 300 mg) of Mg is required for normal Mg balance. Mg supplementation is not usually required in patients eating a reasonable diet or who are receiving enteral feeding formulas. Parenteral nutrition solutions should provide about 12 mmol/day (about 300 mg/day) of Mg.

In the case of clinically significant hypermagnesaemia, current treatment comprises Mg restriction intake, hydration, calcium salts, loop diuretics and even dialysis if needed. Calcium, administered IV in doses of 100-200 mg over 1-2 hours, has been reported to provide temporary improvement in signs and symptoms of hypermagnesaemia.

Summary Points

- Magnesium is an essential mineral salt, the second most abundant intracellular bivalent cation in the body. It has electrophysiological properties, and is essential for optimal metabolic cell function.
- Hypomagnesaemia is common in the general population and hospital patients, especially in the elderly. It is highly prevalent in critically ill patients and has potential implications for critical care and postoperative cardiac surgery scenarios.
- As one third of serum magnesium is protein bound, hypoproteinaemia may result in lower total Mg concentrations even though ionized Mg values are normal. Ionized Mg assessment may be more useful than total serum Mg assessment, because it is independent of any variation in transport protein levels.
- Magnesium sulphate is effective for treating eclampsia and preeclampsia, Torsade de Pointes, and for managing arrhythmias associated with digitalis toxicity.
- Magnesium may be effective as adjunctive therapy in acute asthma exacerbations, acute coronary syndromes, acute cerebral ischaemia, and postoperative pain control.
- Low blood magnesium levels correlate with increased incidence of atrial fibrillation after cardiac surgery.
- Preventive use of magnesium sulphate in cardiac surgery is controversial. IV Mg therapy, initiated before cardiac surgery, will reduce the postoperative incidence of atrial fibrillation, but intraoperative and postoperative use of Mg is less effective. A high value in this recommendation is placed on the low probability of adverse effects of Mg.
- Magnesium administration has no effect on ICU and hospital mortality or on length of stay.

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Table 1. Food sources of magnesium

Food	*Mg (in mg per each 100g of food)*
Almonds, peanuts, snails	250
Soya	242
Chickpeas, white beans, peas, hazelnuts, pistachios, walnuts	150
Corn	120
Chocolate	100
Brown bread	91
Lentils	78
Crawfish, prawns, shrimps, chard	76
Mashed potato	69
Dates	59
Pasta	57
Milk chocolate, spinach, canned sardines, clams, cockles, razor clams, cheese (Gruyere, Emmental)	50
Raisins, dried plums	40
"Manchego" cheese	39
Chestnuts	36
Cookies	32
Rabbit	25

Partially adapted from "Dietary Supplement Fact Sheet: Magnesium" of the NIH Office of Dietary Supplements. http://ods.od.nih.gov/factsheets/magnesium.asp.

Table 2. Conversion for Mg units

Serum Mg concentration. Molecular weight = 24.3		
1.7-2.64 mg/dL	0.7-1.1 mmol/L	1.4-2.2 mEq/L
Number of moles = mass(g)/molecular weight		Number of Eq= number of moles x valence
1.7mg/dL = 17 mg/L	17/24.3 = 0.7 mmol/L	0.7x2 = 1.4 mEq/L
2.64=26.4 mg/L	26.4/24.3 = 1.1 mmol/L	1.1x2 = 2.2 mEq/L

- 1g of magnesium sulphate ($MgSO_4$) is equal to 4.06 mmol, 8.12 mEq or 98mg of elemental Mg
- 1g of magnesium chloride ($MgCl_2$) is equal to 4.5 mmol, 9 mEq or 118mg of elemental Mg

Table 3. Causes of Mg deficiency

1. Reduced dietary intake:
   - Malnutrition
   - Chronic alcoholism
2. Gastrointestinal disorders
   - Decreased absorption: malabsorption, chronic pancreatic insufficiency, short bowel syndrome, inflammatory bowel disease
   - Increased losses: diarrhoea, vomiting, enteric or biliary fistulas, acute pancreatitis, prolonged nasogastric suction, laxative abuse
3. Increased renal losses
   - Congenital or acquired tubular defects
   - Diabetes mellitus
   - Drug-induced: diuretics, angiotensin converting enzyme inhibitors, aminoglycosides, amphotericin, cyclosporine, cisplatin, pentamidine.
   - Hypercalcaemia
   - Hyperaldosteronism
   - Hypoparathyroidism
   - Chronic alcoholism
4. Others
   - Increased requirements (growth, pregnancy)
   - Loss through burned skin

Table 4. Clinical manifestations related with hypomagnesaemia

Cardiovascular

• Hypertension
• Sinus tachycardia
• Arrhytmias: supraventricular tachycardias, Torsade de pointes, ventricular arrhytmias
• ECG changes:
  • Nonspecific T-wave changes
  • U waves
  • Prolonged QT, PR and QU interval
  • Repolarization alternans

Neuromuscular
• Fasciculations • Muscle weakness • Tetany • Hyperreflexia - occasionally hyporeflexia • Muscle cramps / spasms • Chvostek and Trosseau signs
Central Nervous System
• Tremors • Athetosis • Ataxia • Nystagmus • Seizures
Other

- Psychiatry: depression, irritability, psychotic behavior, apathy, emotional liability.
- Vertigo
- Insomnia
- Digestive: anorexia, nausea.

Table 5. Effects of Mg for arrhythmogenic potential

• Increases the threshold for electrical excitation of myocardial cells
• Increases sinus node recovery times (at high doses)
• Slows the atrioventricular conduction and intra-atrial conduction times
• Slow pathway conduction in patients with dual AV nodal physiology
• Prolongs atrioventricular conduction and atrial refractoriness
• Prolongs the atrial cycle in chronic atrial fibrillation
• Stabilizes cardiac repolarization in ischaemic cardiomyopathy/ congestive heart failure

Table 8. Common Mg dosages for recognized therapeutic use in Critical Care

Indication	***Dosage schedule***
• Adjunctive therapy of atrial fibrillation	IV 1 to 5 g initial dose over 1-30 minutes (min) [1].
• Torsade de Pointes	IV 2 g bolus over 1-5 min.; second bolus 5-15 min. later if necessary. IV continuous infusion of 3-20 mg/min for 48 hours until the QT interval is <0.50 seconds [1].
• Acute severe asthma exacerbation • Inadequate initial response to broncho-dilating inhalation treatment	1.2-2g IV infusion over 20 min. / IV 25 to 75 mg/kg [2].
• Eclampsia • Pre-eclampsia	IV 4-6 g bolus over 15-20 min.; then 1-2 g per hour [3].

[1] *Adapted from European Society of Cardiology guidelines (2012).*

[2] *Adapted from British Thoracic Society guidelines (2012).*

[3] *Adapted from WHO recommendations for Prevention and treatment of pre-eclampsia and eclampsia (2011).*

6. DISCUSIÓN GLOBAL

El principal beneficio de este proyecto es la evaluación de variables clínicas, especialmente las postoperatorias, como factores de riesgo y potenciales predictores de mortalidad a corto e incluso a largo plazo, así como demostrar qué *scores* son los que tienen un mayor poder predictivo en nuestra población de postoperados. Esto no tan sólo tiene implicaciones a nivel terapéutico y social, sino también a nivel de distribución de recursos, lo cuál es muy importante en un sistema sanitario dónde parece que cada vez van a haber menos recursos y mayores necesidades.

También tiene una aplicabilidad en la práctica clínica, tanto desde el punto de vista pronóstico cómo desde el punto de vista operatorio, tanto en la realización de pruebas complementarias incluidas en nuestro protocolo cómo en la indicación quirúrgica de determinadas poblaciones. Un ejemplo del primer aspecto es la determinación del momento en que la concentración de la lactatemia tiene mayor implicación pronóstica, con lo que podrían ajustarse mejor las determinaciones de lactato arterial . Un ejemplo del segundo aspecto, lo podemos encontrar en nuestros resultados relativos a cirróticos sometidos a cirugía cardíaca: se requiere una valoración meticulosa de los cirróticos Child B antes de someterlos a intervención, mientras que en los Child C se debería plantear el transplante hepático previo a la cirugía cardíaca, debido a la elevada mortalidad que supone dicha cirugía con una función hepática terminal [2].

Las variables pre y postoperatorias tienen una influencia importante en la supervivencia a largo plazo en pacientes postoperados de cirugía cardiaca, siendo predictores válidos de mortalidad, incluso con mayor poder predictivo que las variables preoperatorias en la mayoría de los casos. La influencia de dichas variables no había sido estudiada en su total profundidad, y fundamentalmente en la gran mayoría de las publicaciones a corto plazo [39, 40]. Del mismo modo, los *scores* pronósticos de UCI (APACHE y SAPS) y/o aquellos que son específicos de una población con una patología concreta especial confirmarían su mejor poder predictivo sobre la mortalidad a corto y largo plazo en comparación con los específicos asociados previamente a la cirugía cardíaca (Parsonnet y EuroSCORE), ya que estos últimos tienen en cuenta sólo factores preoperatorios y fueron diseñados para un pronóstico a corto plazo, valorando básicamente el riesgo quirúrgico inmediato [3, 4]. Los *scores* pronósticos no diseñados para postoperatorios de cirugía cardíaca, reflejan complicaciones que suceden al paciente durante la cirugía y

valoran en gran medida la habilidad del equipo quirúrgico [41]. Un ejemplo de ello en nuestros resultados, el mejor poder predictivo de los *scores* hepáticos y de UCI respecto al EuroSCORE y al Parsonnet en pacientes cirróticos sometidos a cirugía cardíaca [2]. Por la importancia que de ello se deriva, en los diferentes estudios realizados se ha mostrado especial atención a los *scores* pronósticos para incrementar la comparabilidad de resultados con otros centros.

En nuestras series hemos confirmado una mayor mortalidad en los pacientes cirróticos según el grado de disfunción hepática cuando son sometidos a cirugía cardíaca. La presencia de factores como coagulopatía, desnutrición, disfunción inmune adaptativa, miocardiopatía, y disfunción renal y pulmonar, deben tenerse en cuenta para la evaluación pre-quirúrgica cuando la cirugía cardíaca es necesaria en el paciente cirrótico, junto con el grado de la enfermedad hepática y sus complicaciones primarias. Las características fisiopatológicas asociadas que representa la cirrosis hepática tienen una gran influencia en el desarrollo de complicaciones durante la cirugía cardíaca y el curso postoperatorio. En consecuencia, se necesita un enfoque más específico en la evaluación de la atención de estos pacientes si queremos mejorar sus resultados.

Nuestros resultados no apoyaron el concepto *obesity paradox*, que puede ser el resultado de sesgos en los diferentes estudios publicados. Sin embargo, hay una mayor incidencia de IAM perioperatorio y septicemia tras la cirugía cardiaca en la población obesa. No hubo diferencia entre los grupos de IMC en términos de mortalidad hospitalaria. La mejor supervivencia a 1 año en pacientes con sobrepeso no apoya un efecto protector de la obesidad en los pacientes sometidos a cirugía cardíaca.

El desarrollo de *AKI* en el período postoperatorio, de causa multifactorial en la mayoría de casos, podría estar asociada en gran medida con las variables postoperatorias. Una peor clasificación en la escala *RIFLE*, especialmente en *injury* o *failure*, se asocia con una mayor mortalidad a largo plazo. Dado el elevado impacto en términos de morbi-mortalidad tanto a corto como a largo plazo que esto supone, el desarrollo de estrategias para la prevención de los factores de riesgo es básico para mejorar no tan sólo la incidencia de *AKI* en estos pacientes sino los resultados de la cirugía en general.

El cociente PaO2/FIO2 puede ser útil para la identificación de pacientes de cirugía cardíaca con mal pronóstico en el postoperatorio inmediato. Valores más bajos, especialmente a las 3h tras el ingreso en la UCI, son los más útiles en términos de predicción de resultados y las complicaciones respiratorias son más frecuentes con

PaO2/FIO2 inferiores a 241. Asimismo, la evaluación de otra variable continua como el lactato arterial ha demostrado en el postoperatorio ser fundamental para abordar el pronóstico y guiar el tratamiento hemodinámico, especialmente en pacientes de alto riesgo con valores elevados a las 24h tras el ingreso en UCI.

La mejoría del estudio pronóstico de variables en el postoperatorio inmediato las convierte en herramientas a pie de cama que ayudan al clínico en la toma de decisiones e influyen en la supervivencia de sus pacientes. Sin lugar a dudas, una mejor precisión pronóstica conlleva una mejoría en establecer el grado de vigilancia y cuidados que requiere cada paciente, y en consecuencia, los recursos destinados. La mayor precisión en el pronóstico a largo plazo tiene obvias e importantes ventajas, tanto desde el punto de vista clínico del paciente a nivel individual como desde el punto de vista sanitario y social.

7. CONCLUSIONES FINALES

- Se ha conseguido determinar la asociación de diversas variables clínicas, muchas susceptibles de modificación, con la mortalidad postcirugía cardíaca, tanto hospitalaria como a largo plazo.
- Se han cuantificado variables clínicas y determinados *scores* que ayudan a la selección objetiva de las indicaciones de cirugía cardíaca en pacientes afectos de cirrosis hepática y a precisar su expectativa de mortalidad, tanto hospitalaria como a largo plazo. Además se han realizado dos trabajos de revisión detallando los aspectos fisiopatológicos fundamentales en este subgrupo de pacientes que influyen en el desarrollo de la cirugía cardíaca.
- Se ha profundizado en el estudio de las implicaciones pronósticas del grado de daño renal (*AKI*) postcirugía cardíaca, tanto a corto como a largo plazo.
- Se ha realizado un análisis de las implicaciones pronósticas de las diferentes PaO2/FiO2 obtenidas en el postoperatorio inmediato.
- Se ha objetivado la ausencia de un mejor pronóstico en pacientes obesos en nuestra muestra, al contrario que otras series publicadas en la literatura, evaluándose los diferentes grados de Índice de Masa Corporal y su influencia en el diagnóstico.
- Se ha realizado un análisis detallado de las posibles implicaciones pronósticas de las variaciones de la concentración plasmática de lactato arterial postcirugía cardíaca.
- En todos los estudios se han detallado los *scores* pronósticos, algo infrecuente en los trabajos publicados en la literatura.

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9. *ADDENDUM*

9.1. Escrito sobre el Impact Factor y/o categorización de las publicaciones. Explicación de la participación del doctorando en los diversos trabajos, de los cuales ninguno ha sido utilizado para otra tesis doctoral.

A la atención de la Comisión del Programa de Doctorado de Medicina

20 de septiembre de 2014

El Ldo. Juan Carlos López Delgado presenta la siguiente tesis para su evaluación y obtención del título de Doctor en Medicina por la Universitat de Barcelona. Consta de las publicaciones aceptadas con las siguientes características:

1. Short-term independent mortality risk factors in patients with cirrhosis undergoing cardiac surgery. ***Interact Cardiovasc Thorac Surg***. 2013. *Impact Factor* (***IF***)**: 1.109** . Categorización: CARDIAC & CARDIOVASCULAR SYSTEMS *97/125* (**4º cuartil)**. (Primer autor)
2. Influence of acute kidney injury on short- and long-term outcomes in patients undergoing cardiac surgery: risk factors and prognostic value of a modified RIFLE classification. ***Crit Care***. 2013. ***IF*****: 5.04** . Categorización: CRITICAL CARE MEDICINE 5/27 **(1º cuartil)**. (Primer autor)
3. Predictors of long-term mortality in patients with cirrhosis undergoing cardiac surgery. ***J Cardiovasc Surg (Torino)***. 2014. ***IF*****: 1.365**. Categorización: SURGERY 103/202 **(3º cuartil)**; CARDIAC & CARDIOVASCULAR SYSTEMS 83/125 **(3º cuartil)**; PERIPHERAL VASCULAR DISEASE 51/65 **(4º cuartil)** . (Primer autor).
4. Evaluation of the PaO2/FIO2 ratio after cardiac surgery as a predictor of outcome during hospital stay. ***BMC Anesthesiol***. ***IF*****: 1.33**. Categorización: ANESTHESIOLOGY 22/29 **(3º cuartil)**. (Segundo autor).
5. Influence Over Outcome of Liver Cirrhosis in Cardiac Surgery: An Overview of the Pathophysiological Considerations and Review of the Literature. ***Annals of Gastroenterology & Hepatolog.*** Revista internacional divulgativa.

9.2. Explicación de la participación del doctorando en los diversos trabajos, de los cuales ninguno ha sido utilizado para otra tesis doctoral.

El Ldo. Juan Carlos López Delgado ha participado de manera activa en todos los aspectos del desarrollo y realización de la presente tesis doctoral. Durante su residencia participó en la inclusión de datos en la base de datos de la UCI 3-2 – encargada de recibir los postoperados de cirugía cardíaca – durante la rotación en dicha unidad. Asimismo, realizó el seguimiento de todos los pacientes incluidos en la base de datos. Los análisis estadísticos han sido realizados por el autor de la tesis bajo la supervisión de sus directores , excepto en el artículo relativo a la PaFiO2 en el que la Dra. K. Skaltska realizó el análisis coste-función y el Dr.F. Esteve participó en su análisis estadístico. La redacción de los diferentes artículos ha sido realizada por el doctorando de manera significativa, con las correcciones de los Dres.C. Javierre y J.L. Ventura. En el caso del artículo relativo a la PaFiO2 el doctorando ha prestado un apoyo significativo al Dr.F. Esteve en la redacción y análisis estadístico. El Dr. Mañez ha participado en la corrección de los artículos de revisión de manera importante. El doctorando ha enviado, respondido y corregido la correspondencia relativa a la publicación y proceso editorial de todos los artículos publicados y/o enviados.

Las publicaciones utilizadas durante el desarrollo de esta tesis doctoral no se han utilizado (ni en forma impresa ni electrónica, incluyendo en un sitio web) para la publicación de otras tesis.

Los directores han leído y aprobado el documento, certifican que se han cumplido los criterios de autoría y creen que el documento representa un trabajo honesto, verificando la validez de la resultados obtenidos.

Fdo.: Juan Carlos López Delgado