UNIVERSIDAD DE MURCIA

FACULTAD DE MEDICINA

Papel Pronóstico de Nuevos Métodos de Valoración de la Función Renal en Insuficiencia Cardiaca Aguda y Síndrome Coronario Agudo sin Elevación del Segmento ST

D. Pedro José Flores Blanco

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Doctorando: D. Pedro José Flores Blanco

Doctorado: Ciencias Clínicas en Medicina

Directores: Doctor Sergio Manzano Fernández

Profesor Dr. Mariano Valdés Chávarri

El contenido de la presente tesis constituye un compendio de tres trabajos previamente publicados siendo la aportación del doctorando la siguiente:

1) Comparison of risk prediction with the CKD-EPI and MDRD equations in acute decompensated heart failure. *Manzano-Fernández S, Flores-Blanco PJ, Pérez-Calvo JI, Ruiz-Ruiz FJ, Carrasco-Sánchez FJ, Morales-Rull JL, Galisteo-Almeda L, Pascual-Figal D, Valdés M, Januzzi JL.* J Card Fail 2013;19:583-591.

Diseño del estudio, recogida de datos, análisis estadístico y redacción de manuscrito.

2) Cystatin C-based CKD-EPI equations and N-terminal pro-B-type natriuretic peptide for predicting outcomes in acutely decompensated heart failure. *Flores-Blanco PJ, Manzano-Fernández S, Pérez-Calvo JI, Pastor-Pérez FJ, Ruiz-Ruiz FJ, Carrasco-Sánchez FJ, Morales-Rull JL, Pascual-Figal D, Galisteo-Almeda L, Januzzi JL.* Clin Cardiol 2015;38:106-113.

Diseño del estudio, recogida de datos, análisis estadístico y redacción de manuscrito.

3) Major bleeding risk prediction using Chronic Kidney Disease Epidemiology Collaboration and Modification of Diet in Renal Disease equations in acute coronary syndrome. *Flores-Blanco PJ, López-Cuenca Á, Januzzi JL, Marín F, Sánchez-Martínez M, Quintana-Giner M, Romero-Aniorte AI, Valdés M, Manzano-Fernández S.* Eur J Clin Invest 2015;45:385-393.

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Índice de Contenidos

1. Introducción

Epidemiología de las enfermedades cardiovasculares.

Las enfermedades cardiovasculares (ECV) constituyen la principal causa de muerte en el mundo. Se estima que aproximadamente un 30% de todas las defunciones (15,6 millones) fueron causadas por ECV en 2010.[1] En Europa, donde la mayoría de los países son considerados de renta elevada, las ECV son responsables de hasta un 46% de todas las muertes. Sin embargo, existe una gran variabilidad entre los diferentes países, con un claro gradiente norte-sur, con mayores tasas observadas en los países del norte.[2] Particularmente España se encuentra entre los países con tasas más bajas de ECV, junto con otros países del área mediterránea como Francia e Italia. En 2012, las ECV causaron en España 122.097 defunciones, lo que supone el 30,3% del total, siendo la primera causa de muerte en mujeres (con una tasa de 282,2 defunciones por cada 100.000 habitantes) y la segunda, sólo por detrás del cáncer, en varones (con una tasa de 239,4 defunciones por cada 100.000 habitantes).[3]

Todos estos datos resaltan la importancia de las ECV y justifican el extraordinario esfuerzo realizado y que sigue realizándose en investigación para mejorar el conocimiento sobre la etiopatogenia, pronóstico y tratamiento de las ECV. Dentro de este marco, en las últimas décadas la comunidad científica está tomando conciencia progresiva del importante papel de la enfermedad renal en el pronóstico de las ECV. Cada vez disponemos de más datos que señalan que incluso el deterioro leve de la función renal tiene relación directa con el aumento del riesgo cardiovascular.[4,5] Todo ello está llevando a considerar los marcadores de deterioro de la función renal como verdaderos centinelas del riesgo cardiovascular.

Enfermedad renal y cardiovascular

Actualmente está claramente establecido que existe una importante relación entre enfermedad renal y ECV. Los pacientes con función renal disminuida tienen más riesgo de complicaciones cardiovasculares,[3] siendo la ECV la principal causa de muerte.[6] Más de la mitad de los pacientes con enfermedad renal avanzada mueren por causa cardiovascular, lo que supone una mortalidad hasta 30 veces más elevada que en la población general.[7,8] Además, los pacientes con enfermedad renal crónica muestran mayor prevalencia de ECV, como insuficiencia cardiaca, cardiopatía isquémica, arritmias ventriculares, fibrilación auricular, hipertrofia ventricular izquierda, rigidez arterial y calcificación valvular.[9] Por otro lado, la prevalencia de enfermedad renal entre los pacientes con patología cardiovascular es muy elevada y tiene carácter pronóstico al margen de la presencia de otros factores de riesgo cardiovascular, como la hipertensión arterial, la diabetes mellitus, la hipercolesterolemia o el hábito tabáquico.[4]

Dentro del amplio espectro de la patología cardiovascular, la cardiopatía isquémica y la insuficiencia cardiaca, por su alta prevalencia, su elevada morbimortalidad y su gran impacto socioeconómico, se sitúan como dos de los principales grupos de ECV en nuestro medio. El valor pronóstico de la enfermedad renal ha sido ampliamente demostrado en ambas patologías cardiovasculares. A continuación se exponen algunos datos que resaltan la importancia de la disfunción renal como marcador de riesgo en pacientes con insuficiencia cardiaca y cardiopatía isquémica.

Insuficiencia cardiaca

- En pacientes con insuficiencia cardiaca avanzada, la función renal alterada es un factor predictor de mortalidad más potente que la fracción de eyección del ventrículo izquierdo o la clase funcional según la escala *New York Heart Association* (NYHA).[10]

- Un subanálisis del estudio *Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity* (CHARM) demostró que el riesgo de muerte, muerte cardiovascular y hospitalización por insuficiencia cardiaca aumentaba de forma independiente y significativa conforme disminuía el filtrado glomerular, tanto en pacientes con función sistólica deprimida como preservada.[11] Un estudio español que exploró el impacto de la disfunción renal en pacientes del mismo perfil obtuvo similares conclusiones.[12]

- En un estudio prospectivo multicéntrico con más de 1.000 pacientes hospitalizados por insuficiencia cardiaca aguda, el empeoramiento de la función renal durante el ingreso (definido como un aumento > 0,3 mg/dL en la concentración de creatinina sérica) ocurrió en un 27% de los pacientes y se asoció de forma independiente a mayor mortalidad; complicaciones intrahospitalarias como shock, infarto de miocardio, ictus y desarrollo de fibrilación auricular; y mayor duración de la estancia hospitalaria.[13]

Cardiopatía isquémica

- El estudio *Valsartan in Acute Myocardial Infarction Trial* (VALIANT) incluyó a pacientes con disfunción ventricular o insuficiencia cardiaca tras un infarto agudo de miocardio. Todos los eventos cardiovasculares importantes, como

la mortalidad cardiovascular total, el infarto de miocardio, la insuficiencia cardiaca y el accidente cerebrovascular, estuvieron en estrecha relación con el grado de disfunción renal. La incidencia de dichos eventos se duplicó o triplicó en pacientes con filtrado glomerular < 45 mL/min/1,73m^2 respecto a los que tenían un filtrado glomerular > 75 mL/min/1,73m^2.[14] El estudio *Survival and Ventricular Enlargement* (SAVE), con un diseño similar, obtuvo los mismos resultados.[15] Los estudio *Heart Outcomes and Prevention Evaluation* (HOPE) y *Prevention of Events with ACE inhibition* (PEACE), esta vez en pacientes con cardiopatía isquémica crónica, también obtuvieron las mismas conclusiones.[16,17]

- Las complicaciones hemorrágicas tras un síndrome coronario agudo, con un impacto negativo en el pronóstico de estos pacientes,[18] son más frecuentes en los pacientes con función renal alterada.[19]

- Tras un procedimiento de revascularización coronaria percutánea, la mortalidad se relaciona directamente, y de forma independiente, al grado de disfunción renal.[20,21] En un estudio realizado en la Clínica Mayo que incluyó 5.327 pacientes sometidos a intervencionismo coronario percutáneo, la mortalidad anual fue del 1,5%, 3,6%, 7,8% y 18,3% entre los pacientes con aclaramiento de creatinina ≥ 70 mL/min, 50-69 mL/min, 30-49 mL/min y < 30 mL/min, respectivamente.[21]

- En pacientes sometidos a cirugía de revascularización coronaria, la presencia de insuficiencia renal es uno de los factores predictores independientes más potentes relacionados con la morbimortalidad postoperatoria.[22]

A pesar de todos los datos de los que disponemos que avalan la estrecha relación entre enfermedad renal y cardiovascular, no existe un total acuerdo sobre la fisiopatología de esta compleja asociación.[23] La hipótesis más generalizada establece la asociación entre enfermedad renal y cardiovascular sobre la base de la elevada prevalencia de factores de riesgo cardiovascular en ambas patologías, la mayor agresividad de los mismos a la hora de alterar la función de los órganos diana y la presencia de alteraciones concomitantes que crean un ambiente propicio para el desarrollo y progresión de ambas afecciones, como la disfunción endotelial generalizada, el desequilibrio de los sistemas de coagulación y fibrinolisis y la inflamación crónica.

En un intento de esquematizar la intrincada fisiopatología de esta relación surge el concepto de "síndrome cardiorrenal", entendido éste como una condición fisiopatológica en la que la disfunción primaria de un órgano, ya sea aguda o crónica, da lugar a la disfunción secundaria del otro.[24] Se han definido 5 tipos de síndrome cardiorrenal: 1) Tipo I o síndrome cardiorrenal agudo: deterioro agudo de la función cardiaca que produce daño renal agudo; 2) Tipo II o síndrome cardiorrenal crónico: alteraciones crónicas de la función cardiaca que causan enfermedad renal crónica progresiva y permanente; 3) Tipo III o síndrome renocardiaco agudo: deterioro agudo de la función renal que causa alteraciones cardiacas agudas; 4) Tipo IV o síndrome renocardiaco crónico: enfermedad renal crónica que contribuye al empeoramiento de la función cardiaca y/o aumento del riesgo de acontecimientos cardiovasculares; y 5) Tipo V o síndrome cardiorrenal secundario: condición sistémica, como sepsis o diabetes mellitus, que causa disfunción renal y cardiaca simultáneamente.

Evaluación de la función renal en el paciente cardiovascular

Si bien el valor pronóstico de la enfermedad renal en la ECV es conocida desde hace tiempo, ha sido en las últimas décadas cuando se ha hecho más evidente la importancia de su correcta evaluación, sobre todo a raíz de estudios que han demostrado que esta relación directa entre función renal y acontecimientos cardiovasculares aparece ya en fases de disfunción renal moderada, e incluso, leve.[4,5,25] La evaluación precisa de la función renal permite por tanto identificar precozmente a los pacientes con riesgo elevado de acontecimientos cardiovasculares, con la finalidad de mejorar su pronóstico mediante una intervención precoz de diagnóstico y tratamiento. Además, posibilita la monitorización estrecha de ciertas intervenciones como el ajuste de fármacos y la prevención de nefrotoxicidad por diversos agentes en pacientes de alto riesgo. Una mala estimación de la función renal puede llevar a que un paciente no reciba el tratamiento cardioprotector adecuado a su riesgo, lo que conlleva un aumento de mortalidad.[26,27]

Podemos decir que cuanto más precisa ha sido nuestra capacidad para evaluar la función renal, más relevancia ha ido adquiriendo la enfermedad renal como factor pronóstico en el paciente con ECV. Todo lo expuesto anteriormente trae a primer plano la importancia del método utilizado para evaluar la disfunción renal.

La creatinina ha sido clásicamente la sustancia endógena más utilizada para la evaluación de la función renal. No obstante, la concentración de creatinina se ve afectada por diversos factores (masa muscular, sexo, raza, tipo de alimentación), además de otros relacionados con la propia filtración de

creatinina, como la secreción tubular, la producción y la excreción extrarrenal.[28,29] Dadas las desventajas de la creatinina plasmática como marcador de deterioro renal han sido múltiples los métodos propuestos para conocer la función renal, tanto invasivos como no invasivos. Algunos de ellos han quedado relegados al ámbito de la investigación exclusivamente, mientras que otros se utilizan en ocasiones muy concretas. Dada su relativa sencillez, en la actualidad, las fórmulas de estimación del filtrado glomerular constituyen el método más usado en la práctica clínica habitual. Además del filtrado glomerular estimado, la determinación de albuminuria también permite el diagnóstico de disfunción renal y tiene valor pronóstico en la patología cardiovascular.[30,31] Ambos parámetros, disminución del filtrado glomerular y albuminuria, tienen efecto sinérgico como factor predictor de riesgo cardiovascular.[32,33]

Existen diferentes formulas para estimar el filtrado glomerular en un determinado paciente. Todas ellas incorporan una serie de variables que intentan solventar las carencias de la creatinina plasmática como único marcador de función renal. Sin embargo, su precisión no es constante en todos los escenarios y sigue habiendo situaciones en las que no tenemos un método fiable para conocer el grado de deterioro renal real del paciente. La primera fórmula ampliamente utilizada para estimar la función renal fue la ecuación de Cockroft-Gault.[34] Ésta se obtiene a partir de cuatro parámetros: concentración sérica de creatinina, edad, peso y sexo. La fórmula estima el aclaramiento renal por lo que debe ser ajustada a la superficie corporal para hablar de tasa de filtración glomerular. Posteriormente, fue desarrollada la fórmula abreviada derivada del estudio *Modification of Diet in Renal Disease* (MDRD) que utiliza

otros cuatro parámetros: concentración sérica de creatinina, edad, sexo y raza.[35]

La comparación entre las ecuaciones de Cockroft-Gault y MDRD es controvertida. Existen estudios con resultados opuestos, aunque parece que la mayoría son favorables a la ecuación MDRD, especialmente cuando el filtrado glomerular es < 60mL/min/1,73m^2.[36] No obstante, sabemos que en paciente con función renal normal o casi normal, la ecuación MDRD puede subestimar la función renal, especialmente en mujeres.[35] En la mayoría de los análisis comparativos realizados se constata que la ecuación de Cockroft-Gault sobreestima el filtrado glomerular un 10-15%.[37] Sin embargo, en poblaciones con insuficiencia renal terminal parece que la ecuación de Cockroft-Gault es la más precisa.[38]

Más recientemente, el grupo *Chronic Kidney Disease Epidemiology Collaboration* (CKD-EPI) publicó una nueva ecuación con los mismos cuatro parámetros que la ecuación MDRD en un intento de disminuir el sesgo o subestimación que ésta última produce, sobre todo, con filtrados glomerulares > 60 mL/min/1,73m^2.[39,40]

Basado en todo lo expuesto previamente, el documento de consenso de la Sociedad Española de Nefrología y la Sociedad Española de Medicina Familiar y Comunitaria recomienda estimar el filtrado glomerular utilizando las ecuaciones CKD-EPI o MDRD y no utilizar la creatinina sérica como único parámetro para evaluar la función renal.[41]

Biomarcadores y nuevos métodos de evaluación de la función renal

En las últimas décadas, la cistatina C ha surgido como un marcador más sensible de disfunción renal incipiente que la creatinina.[42-44] Esta proteína básica procedente de todas las células nucleadas presenta una tasa de síntesis muy estable y su bajo peso molecular y bajo punto isoeléctrico permite que se elimine casi exclusivamente por filtración glomerular. Posteriormente es metabolizada en el túbulo renal, sin que medie reabsorción ni secreción tubular. Su concentración no parece estar influida por la edad, el sexo o la ingesta de proteínas y presenta una mayor sensibilidad a pequeños cambios en el filtrado glomerular. Son todas estas características las que la aproximan mucho a lo considerado como marcador ideal de función renal y las que la han identificado como uno de los mejores marcadores para evaluar el filtrado glomerular.

Habida cuenta de la relación entre enfermedad renal y riesgo cardiovascular y la mayor sensibilidad de la cistatina C comparada con la creatinina para detectar leves descensos del filtrado glomerular, han sido múltiples las investigaciones que han analizado el valor pronóstico de la cistatina C en diferentes poblaciones de pacientes con ECV.

A continuación se exponen de forma resumida algunos de los datos más relevantes del valor pronóstico de la cistatina C en pacientes con insuficiencia cardiaca y cardiopatía isquémica.

Insuficiencia cardiaca

- En pacientes ambulatorios con insuficiencia cardiaca crónica, la cistatina C es mejor predictor de mortalidad en el seguimiento que la creatinina.[45,46]

- En pacientes ingresados por insuficiencia cardiaca aguda, la cistatina C es mejor predictor de mortalidad e ingreso por insuficiencia cardiaca en el seguimiento que otros parámetros de función renal y su valor pronóstico es independiente a otros biomarcadores como la fracción N-terminal del propéptido natriurético cerebral (NT-proBNP) o la troponina.[47,48]

Cardiopatía isquémica

- En pacientes ambulatorios con cardiopatía isquémica crónica, los valores elevados de cistatina C plasmática predicen la mortalidad por todas las causas, eventos cardiovasculares y desarrollo de insuficiencia cardiaca, tanto en pacientes con filtrado glomerular disminuido como normal según la ecuación MDRD.[49,50]

- En pacientes con síndrome coronario agudo, la concentración plasmática de cistatina C al ingreso se relaciona de forma directa con la mortalidad y eventos cardiovasculares mayores durante la hospitalización y en el seguimiento. Además, la capacidad discriminativa de la cistatina C es superior al resto de parámetros de función renal.[51-56] Más aún, su valor pronóstico se ha demostrado complementario al potente score de *Global Registry of Acute Coronary Events* (GRACE).[57,58] y a otros biomarcadores como la troponina.[59] Por último, los valores elevados de cistatina C se relacionan con incidencia superior de sangrado mayor intrahospitalario[60] y en el seguimiento.[61]

Todos estos estudios obtienen resultados similares: los valores plasmáticos de cistatina C se relacionan con una mayor tasa de eventos cardiovasculares, mejorando la capacidad discriminativa de otros marcadores de función renal

alterada. Sin embargo, todavía no sabemos a ciencia cierta si la relación entre cistatina C y eventos cardiovasculares se debe simplemente a que la cistatina C es mejor marcador de función renal que la creatinina sérica o a que existen factores independientes del filtrado glomerular que afectan a las concentraciones de dicha proteína y están además relacionados con el riesgo cardiovascular. En este sentido, se ha descrito la correlación positiva entre valores plasmáticos de cistatina C, de proteína C reactiva y fibrinógeno, y eventos cardiovasculares; sugiriendo que la cistatina C es en parte un marcador inflamatorio.[62] Sin embargo, otros estudios no apoyan esta hipótesis, pues han demostrado que los niveles de cistatina C se mantenían estables a las 6 semanas de sufrir un síndrome coronario agudo, mientras que marcadores inflamatorios (proteína C reactiva e interleucina-6) y de estrés parietal o necrosis miocitaria (NT-proBNP y troponina) descendían progresivamente.[63]

Recientemente, el grupo CKD-EPI ha publicado dos nuevas ecuaciones (una basada en cistatina C y otra que agrupa a ésta con la creatinina) que han demostrado mayor precisión en la estimación del filtrado glomerular.[64-66] Sin embargo, aún queda por dilucidar si su mayor capacidad para estimar la función renal se acompaña de una mejor discriminación en el pronóstico de los pacientes.

Por tanto, se plantea como objetivo de esta tesis explorar el valor pronóstico de las nuevas ecuaciones para estimar la función renal basadas en cistatina C en dos poblaciones de pacientes muy prevalentes en la práctica clínica hospitalaria habitual, como son los pacientes con insuficiencia cardiaca aguda y con síndrome coronario agudo sin elevación del segmento ST. En los primeros,

no se ha estudiado previamente el valor pronóstico de estas ecuaciones, por lo que el objetivo principal será analizar si dichas ecuaciones predicen adecuadamente la mortalidad y el reingreso por insuficiencia cardiaca. Además, se comparará el valor de estas ecuaciones con los métodos hasta ahora utilizados para valorar la función renal, como las ecuaciones basadas en creatinina, y se estudiará si la información aportada es complementaria a otros marcadores pronósticos establecidos, como los péptidos natriuréticos. En los pacientes con síndrome coronario agudo se ha comunicado recientemente una mejor predicción de la mortalidad con estas ecuaciones comparadas con otras basadas en creatinina.[67] Sin embargo, no se han estudiado de forma específica en el subgrupo de pacientes con síndrome coronario agudo sin elevación del segmento ST y en ningún caso se ha analizado previamente su valor pronóstico en términos de complicaciones hemorrágicas. El objetivo será por tanto evaluar si estas nuevas ecuaciones predicen adecuadamente la aparición de complicaciones hemorrágicas mayores en pacientes con síndrome coronario agudo sin elevación del segmento ST, comparándolas con otros métodos de evaluación de la función renal. De forma complementaria, se analizará su valor pronóstico en términos de mortalidad en este subgrupo concreto de pacientes con síndrome coronario agudo.

Esta investigación permitirá conocer el valor pronóstico de estas nuevas ecuaciones de estimación de la función renal basadas en cistatina C en pacientes con insuficiencia cardiaca aguda y síndrome coronario agudo sin elevación del segmento ST. Al mismo tiempo, con los resultados obtenidos se aportarán nuevos datos que ampliarán nuestro conocimiento y entendimiento de los mecanismos que vinculan la enfermedad renal con la ECV.

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2. Objetivos

Los objetivos de la presente tesis fueron:

1. En pacientes ingresados por insuficiencia cardiaca aguda:

- Analizar el valor pronóstico de las nuevas ecuaciones para la estimación del filtrado glomerular basadas en cistatina C para la predicción de mortalidad y reingreso por insuficiencia cardiaca.
- Comparar el valor pronóstico de dichas ecuaciones con otros métodos utilizados habitualmente en la práctica clínica habitual, como las ecuaciones basadas en creatinina.
- Evaluar si la información pronóstica aportada por dichas ecuaciones es complementaria e independiente a otros factores pronósticos establecidos en insuficiencia cardiaca aguda, como los péptidos natriuréticos.

2. En pacientes ingresados por síndrome coronario agudo:

- Analizar el valor pronóstico de dichas ecuaciones para la predicción de complicaciones hemorrágicas.
- Comparar el valor pronóstico de dichas ecuaciones con otros métodos utilizados habitualmente en la práctica clínica habitual, como las ecuaciones basadas en creatinina.
- Evaluar si la información pronóstica aportada por dichas ecuaciones es independiente a otros factores de riesgo hemorrágico establecidos en síndrome coronario agudo.

3. Publicaciones

Artículo 1: Comparison of Risk Prediction Using the CKD-EPI Equations and the MDRD Study Equation in Patients with Acutely Decompensated Heart Failure.

Publicado en: Jounal of Cardiac Failure.

Abstract

Background: Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations estimate glomerular filtration rate (eGFR) more accurately than the Modification of Diet in Renal Disease (MDRD) equation. The aim of this study was to evaluate whether CKD-EPI equations based on serum creatinine (SCr) and/or cystatin C (CysC) predict risk for adverse outcomes more accurately than the MDRD equation in a hospitalized cohort of patients with acute decompensated heart failure (ADHF).

Methods: A total of 526 subjects with ADHF were studied. Blood was collected within 48 hours from admission. eGFR was calculated with the use of MDRD and CKD-EPI equations. The occurrences of mortality and heart failure (HF) hospitalization were recorded.

Results: Over the study period (median 365 days [interquartile range 238-370]), 305 patients (58%) died or were rehospitalized for HF. Areas under the receiver operator characteristic curves for CKD-EPI$_{CysC}$ and CKD-EPI$_{SCr-CysC}$ equations were significantly higher than that for the MDRD equation, especially in patients with > 60 mL/min/1.73m^2. After multivariate adjustment, all eGFR

equations were independent predictors of adverse outcomes ($P < 0.001$). However, only CKD-EPI$_{CysC}$ and CKD-EPI$_{SCr\text{-}CysC}$ equations were associated with significant improvement in reclassification analyses (net reclassification improvements 10.8% and 12.5%, respectively).

Conclusion: In patients with ADHF, CysC-based CKD-EPI equations were superior to the MDRD equation for predicting mortality and/or HF hospitalization especially in patients with > 60 mL/min/1.73m^2, and both CKD-EPI equations improved clinical risk stratification.

Key words: *Acute heart failure, prognosis, CKD-EPI, MDRD.*

URL: *http://dx.doi.org/10.1016/j.cardfail.2013.05.011*

Artículo 2: Combination of Cystatin C-based CKD-EPI Equations and N-Terminal Pro-B-Type Natriuretic Peptide for Predicting Outcomes in Acutely Decompensated Heart Failure.

Publicado en: Clinical Cardiology.

Abstract

Background: In patients with acute decompensated heart failure (ADHF), both natriuretic peptides and renal impairment predict adverse outcomes. Our aim was to evaluate the complementary prognosis role of N-terminal pro-B-type natriuretic peptide (NT-proBNP) and the newly developed Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations based on cystatin C (CysC) for glomerular filtration rate (GFR) estimation in ADHF patients. The aim of this study was to evaluate whether renal impairment assessed by CysC-based CKD-EPI equations and natriuretic peptides have complementary prognostic value in ADHF patients.

Methods: The study included 613 consecutive patients presenting with ADHF. At admission, plasma levels of NT-proBNP and CysC were determined. The GFR was estimated using CysC-based CKD-EPI equations. The primary endpoint was death from any cause and heart failure readmission.

Results: During the median follow-up of 365 days (interquartile range, 227–441 days), 323 patients (0.65 %patient-year) died or were readmitted for heart failure. After multivariate adjustment, estimated GFR < 60 mL/min/1.73m^2 and

NT-proBNP > 3251 pg/mL were independent predictors of adverse outcomes (*P* < 0.01). The combination of GFR < 60 mL/min/1.73m^2 and NT-proBNP > 3251 pg/mL was associated with the highest risk of adverse outcomes. Furthermore, reclassification analyses demonstrated that use of both NT-proBNP and CysC-based CKD-EPI equations resulted in improving the accuracy for adverse outcomes prediction.

Conclusions: In patients with ADHF, the combination of NT-proBNP with estimated GFR using CysC-based CKD-EPI equations better predicts outcomes than either parameter alone and adds valuable complementary prognosis information to other established risk factors.

Key words: *Acute heart failure, prognosis, kidney, natriuretic peptides.*

URL: *http://dx.doi.org/10.1002/clc.22362*

Artículo 3: Major bleeding risk prediction using Chronic Kidney Disease Epidemiology Collaboration and Modification of Diet in Renal Disease equations in non ST segment elevation acute coronary syndrome

Publicado en: European Journal of Clínical Investigation.

Abstract

Background: Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations estimate glomerular filtration rate more accurately than the Modification of Diet in Renal Disease (MDRD) Study equation. Our aim was to evaluate whether CKD-EPI equations based on serum creatinine (SCr) and/or cystatin C (CysC) predict risk for major bleeding (MB) more accurately than the MDRD Study equation in patients with non-ST-segment elevation acute coronary syndromes (NSTE-ACS).

Methods: Three hundred and fifty consecutive subjects with NSTE-ACS (68±12 years, 70% male) were studied. Glomerular filtration rate was estimated using the CKD-EPI and MDRD Study equations. The primary endpoint was the occurrence of MB during the follow-up, which was defined according to the Bleeding Academic Research Consortium Definition criteria as bleeding types 3–5.

Results: During the median follow-up of 589 days (interquartile range, 390–986), 27 patients had MB (0.04% events per person year). Patients with MB had worse kidney function parameters, regardless of the estimating equation used ($P < 0.001$). After multivariate Cox regression adjustment, both CysC-based CKD-EPI equations were independent predictors of MB ($CKD\text{-}EPI_{SCr\text{-}CysC}$ per mL/min/1.73 m^2, HR = 0.973 (95% CI 0.955-0.991; $P = 0.003$) and $CKD\text{-}EPI_{CysC}$ per mL/min/1.73m^2, HR = 0.976 (95% CI 0.976-0.992; $P = 0.003$), while the $CKD\text{-}EPI_{SCr}$ and MDRD equations did not achieve statistical significance. Both

CKD-EPI$_{SCr-CysC}$ and CKD-EPI$_{CysC}$ were associated with a significant improvement in MB risk reclassification.

Conclusions: In this cohort of NSTE-ACS patients with relatively preserved renal function, both CysC-based CKD-EPI equations improved ability to predict risk for MB and were superior to other equations for this application.

Key words: *Acute coronary syndrome, hemorrhage, prognosis, kidney.*

URL: *http://dx.doi.org/10.1111/eci.12418*

4. Conclusiones

Las conclusiones de esta tesis son las siguientes:

1. En pacientes ingresados por insuficiencia cardiaca aguda, el filtrado glomerular estimado a través de las ecuaciones basadas en cistatina C tiene valor pronóstico independiente para la predicción de mortalidad o reingreso por insuficiencia cardiaca en el seguimiento a medio-largo plazo.
2. En pacientes ingresados por insuficiencia cardiaca aguda, el filtrado glomerular estimado a través de las ecuaciones basadas en cistatina C predice mejor que la ecuación MDRD la mortalidad o el reingreso por insuficiencia cardiaca aguda en el seguimiento, especialmente en pacientes con función renal relativamente preservada.
3. En pacientes ingresados por insuficiencia cardiaca aguda, el filtrado glomerular estimado a través de las ecuaciones basadas en cistatina C añade información pronóstica complementaria al NT-proBNP.
4. En pacientes ingresados por insuficiencia cardiaca aguda, la combinación del filtrado glomerular estimado a través de las ecuaciones basadas en cistatina C y el fragmento NT-proBNP añade información pronóstica a otros factores de riesgo establecidos.
5. En pacientes ingresados por insuficiencia cardiaca aguda, el filtrado glomerular estimado a través de las ecuaciones basadas en cistatina C comparado con la ecuación MDRD mejora la estratificación pronóstica.
6. En pacientes ingresados por un síndrome coronario agudo sin elevación del segmento ST, el filtrado glomerular estimado a través de las ecuaciones basadas en cistatina C tiene valor pronóstico independiente para la predicción de sangrado mayor en el seguimiento a medio-largo plazo.

7. En pacientes ingresados por un síndrome coronario agudo sin elevación del segmento ST, el filtrado glomerular estimado a través de las ecuaciones basadas en cistatina C predice mejor que la ecuación MDRD el sangrado mayor en el seguimiento, especialmente en pacientes con función renal relativamente preservada.

8. En pacientes ingresados por un síndrome coronario agudo sin elevación del segmento ST, el filtrado glomerular estimado a través de las ecuaciones basadas en cistatina C mejora la estratificación pronóstica respecto al sangrado mayor en el seguimiento a medio-largo plazo.

5. Apéndice

Artículo no publicado

Prognosis assessment of estimated glomerular filtration rate by the new Chronic Kidney Disease Epidemiology Collaboration equations in comparison with the Modification in Diet of Renal Disease equation in non-ST segment elevation acute coronary syndromes.

Pedro J. Flores-Blanco[1], MD; Ángel López-Cuenca[2] MD, PhD; Miriam Gómez-Molina[1] , MD; Francisco Marín[1,3] MD, PhD; Marianela Sánchez-Martínez[1], MD; Miriam Quintana-Giner[1]; Ana I. Romero-Aniorte[1]; Mariano Valdés[1,3] MD, PhD; and Sergio Manzano-Fernández[1,3] MD, PhD.

[1]Department of Cardiology, Hospital Universitario Virgen de la Arrixaca, Murcia, Spain. [2]Department of Cardiology, Hospital de la Vega Lorenzo Guirao, Cieza, Murcia, Spain. [3]University of Murcia, School of Medicine, Department of Cardiology, Murcia, Spain.

Address for correspondence:

Pedro J Flores-Blanco, MD. Division of Cardiology, University Hospital Virgen de la Arrixaca, School of Medicine, University of Murcia, Carretera Madrid Cartagena s/n, CP 30120, Murcia, Spain Tel: +34 968369445. e-mail: pedrofb1986@gmail.com

Abstract

Background: Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations estimate glomerular filtration rate (GFR) more accurately than the Modification of Diet in Renal Disease (MDRD) equation. The aim of this study was to evaluate whether these new CKD-EPI equations improve the risk stratification of patients with non-ST segment elevation acute coronary syndromes (NSTE-ACS), and assess if they add complementary information to the Global Registry of Acute Coronary Events (GRACE) risk score.

Methods: 350 subjects (age 68±12 years, male 70%) with NSTE-ACS were studied. Estimated GFR was calculated using the MDRD equation and new CKD-EPI equations based on serum creatinine (SCr) and/or cystatin C (CysC) concentrations obtained within 48 hours of hospital admission. The primary endpoint was the occurrence of all cause death during the follow-up.

Results: Over the study period (median 648 days [interquartile range 236 to 1,042], 31 patients died (0.05% events per person-year). Decedents had poorer renal function parameters ($P < 0.001$). Both CysC-based CKD-EPI equations had the highest areas under the ROC curve for the prediction of all-cause mortality. After multivariate adjustment, only CysC-based CKD-EPI equations were independent predictors of all-cause mortality ($CKD\text{-}EPI_{CysC}$, per mL/min/1.73m2: HR 0.975 [95%CI 0.956-0.994], $P = 0.009$; $CKD\text{-}EPI_{SCr\text{-}CysC}$, per mL/min/1.73m2: HR 0.978 [95%CI 0.961-0.995], $P = 0.012$). Reclassification analyses showed that all CKD-EPI equations added complementary prognostic information to the MDRD equation, but only CysC-based CKD-EPI equations improved the predictive accuracy of the GRACE risk score.

Conclusion: In patients with NSTE-ACS, CysC-based CKD-EPI equations improved clinical risk stratification for mortality and added complementary prognostic information to the GRACE risk score.

Key words: *Acute coronary syndrome, prognosis, kidney.*

Introduction

Renal dysfunction is common in patients with non-ST-segment acute coronary syndrome (NSTE-ACS) and is associated with adverse in-hospital and long-term outcomes.[1] Current clinical guidelines for the management of NSTE-ACS patients recommend the use of estimated glomerular filtration rate (eGFR) equations to assess renal function.[2] One of the most widely used is the abbreviated Modification of Diet in Renal Disease (MDRD) equation, which uses only four variables: serum creatinine (SCr) concentration, age, sex, and race.[3] The prognostic value of this equation in NSTE-ACS patients has been validated in numerous studies.[4-6] However, it is increasingly recognized that the reliability and accuracy of this equation decreases in extremes of glomerular filtration rate, mainly above 60 mL/min/1.73m^2.[7-9]

In recent years, cystatin C (CysC) has emerged as a potential alternative to SCr for estimating renal function. In previous studies, it has consistently shown to be a better mortality risk marker than SCr in NSTE-ACS patients.[10-12] However, the lack of CysC-based equations has limited its clinical use. More recently, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) group has proposed three alternative equations to estimate GFR;[13-15] these newer equations apply different coefficients to the same four variables used in the MDRD equation (CKD-EPI$_{SCr}$ equation), add CysC values (CKD-EPI$_{CysC}$ equation), or combine it with SCr (CKD-EPI$_{SCr-CysC}$ equation). These new CysC-based CKD-EPI equations have been reported to estimate GFR more accurately than the MDRD equation[16] and its use is currently recommended as a confirmatory test for renal dysfunction, namely in patients with “normal” creatinine level, muscle wasting or chronic illness.[17] However, despite its better

performance to assess renal function, studies in the area of ACS are still scarce.

Therefore, given the importance of renal function for predicting outcomes in patients with NSTE-ACS, the aim of the present study was to evaluate the performance of the new CKD-EPI equations in predicting all-cause mortality during follow-up in patients admitted for NSTE-ACS, and to compare them with the MDRD equation. Additionally we intended to determine the added value of these equations in risk stratification compared to the Global Registry of Acute Coronary Events (GRACE) risk score.

Method

The study population consisted of 350 consecutive patients admitted to one tertiary Spanish hospital from September 2006 to August 2013 with an established final diagnosis of high risk NSTE-ACS. The diagnosis of high risk NSTE-ACS was established on the basis of current guidelines.[2] The study protocol conforms to the ethical principles outlined in the Declaration of Helsinki and the local ethics committee approved the study. Written informed consent was obtained from each patient at inclusion.

We excluded patients on chronic renal function replacement therapy and those with evidence of hepatic dysfunction; concomitant neoplasia, infectious, connective tissue or inflammatory disease; deep vein thrombosis, pulmonary embolism; recent (< 1 month) surgery or trauma; as well as, patients taking immunosuppressant agents. Patients who refused or were incapable of giving informed consent were also excluded.

Blood samples were collected for all patients within 48 hours from admission, processed, and stored at -80ºC until the study analysis. Baseline clinical characteristics and data about in-hospital management were prospectively recorded. Echocardiography was also performed on all patients before hospital discharge. Left ventricular ejection fraction (LVEF) was measured according to the biplane Simpson's method. All patients received standard management as recommended by contemporary guidelines. During the entire hospitalization period, clinical management decisions about each patient were made by the responsible cardiologist, who was unaware of the patient's CysC concentrations.

We calculated eGFR using the MDRD equation[3] and the CKD-EPI equations.[13-15] Determination of CysC levels was performed using a BN ProSpec analyser (Dade Behring GmbH, Liederbach, Germany). The intra-assay and interassay coefficients of variation for CysC were 2.5% and 2.0%, respectively. For each patients the GRACE 6-month post-discharge mortality risk score were calculated.[18]

All patients were clinically followed during a median of median 648 days [interquartile range (IQR) 236 to 1,042]. The study endpoint was all-cause mortality during follow-up. Death was ascertained from available medical records and death certificates. If hospital records were ambiguous or unavailable, patients' families were interviewed through telephone contact.

Continuous variables were tested for a normal distribution by the Kolmogorov-Smirnov test. Normally distributed data are presented as the mean ± standard deviation (SD) and non-normally distributed data as the median

[IQR]. Categorical variables are expressed as percentages. Categorized analyses were performed according to the presence of death during the follow-up. Differences in baseline characteristics were compared using the Student *t*-test or the Mann-Whitney *U*-test for continuous variables and the chi-square test for categorical variables.

We assessed the discriminative performance of each equation by calculating the area under each receiver operating characteristic curve (AUC). We calculated hazard ratios (HRs) derived from the Cox regression analysis to identify predictors of mortality during follow-up. The independent effect of eGFR equations on prognosis was calculated using a Cox multivariable regression analysis, incorporating covariates with *P* values < 0.10 in the univariable analysis. Linearity assumption was tested using Martingale residuals. Log-cumulative hazard plots, time-dependent covariates, and Schoenfeld residuals were used to evaluate adherence of the Cox proportional hazard assumptions. Moreover, the improvement in predictive accuracy of using the new CKD-EPI equations over the MDRD equation and the GRACE risk score was evaluated by calculating the net reclassification improvement (NRI) as described by Pencina et al.[19] All *P* values < 0.05 were accepted as statistically significant. Statistical analysis was performed using SPSS version 15.0 (SPSS, Inc., Chicago, Illinois).

Results

Clinical characteristics of the study population are shown in Table 1. The mean eGFR was 79 ± 23 mL/min/1.73m^2, 83 ± 26 mL/min/1.73 m^2, 74 ± 21

mL/min/1.73m^2 and 78 ± 24 mL/min/1.73m^2 according to the CKD-EPI$_{SCr-CysC}$, CKD-EPI$_{CysC}$, CKD-EPI$_{SCr}$ and MDRD equations, respectively (Table 2).

Over the study period, 31 patients died (0.05% events per person-year). Table 1 presents the distribution of clinical characteristics and laboratory parameters in accordance to the occurrence of death. Decedents were older, less likely to be smokers and more often had chronic heart failure. At admission, their clinical status was poorer, with higher Killip class and higher heart rate. Moreover, they had higher SCr and CysC concentrations, lower hemoglobin concentrations and lower LVEF. The GRACE 6-month mortality risk score were higher among died patients (139 ± 22 vs. 107 ± 28; $P < 0.001$). There were no differences between groups with respect to the in-hospital management and treatment at discharge. Regarding renal function (Table 2), patients who died had lower eGFR regardless of the equation used.

Figure 1 shows the all-cause mortality rate according to eGFR categories using the different equations. A stepwise increase in mortality rate was seen with declining eGFR category for all equations. Both CysC-based CKD-EPI equations provided the highest all-cause mortality rate in patients with eGFR < 30 mL/min/m^2. Moreover, the MDRD equation did not show difference between the all-cause mortality rates in the two lowest eGFR categories.

The discriminatory power of each equation was assessed by calculating the AUC for the study endpoint. As shown in Table 3, both CysC-based CKD-EPI showed the highest AUCs, and both were statistically higher than the MDRD AUC.

Table 4 details the univariate and multivariate Cox regression analysis for the prediction of the study endpoint. All equations were associated with all-cause mortality. However, after multivariate adjustment (incorporating age, hemoglobin concentration, LVEF and the GRACE 6-month mortality risk score) only both CysC-based CKD-EPI equations remained as independent predictors of the study endpoint.

The addition of all CKD-EPI equations to the MDRD equation was associated with a significant improvement in the predictive accuracy, reflected particularly in the percentage of no-events correctly reclassified (Table 5). We performed another reclassification analysis to assess whether the addition of the equations to the GRACE 6-month mortality risk score improved the predictive accuracy. The results are shown in Table 6. Only both CysC-based CKD-EPI equations added complementary prognostic information to the GRACE risk score.

Finally, Kaplan–Meier survival analyses showed the complementary prognosis value of all equations and the GRACE 6-month mortality risk score for the prediction of all-cause mortality. As detailed in Figure 2, patients with a GRACE risk score < 118 (low and intermediate risk) and an eGFR ≥ 60 mL/min/1.73m^2 had the lowest risk to experience adverse outcomes regardless of the equation used (all log-rank test $P < 0.001$). Interestingly, patients with GRACE risk score ≥ 119 (high risk) and eGFR < 60 mL/min/1.73m^2 using both CysC-based CKD-EPI showed the lowest survival rate.

Discussion

Accurate assessment of renal function plays a major role in NSTE-ACS patients. In the present study, all eGFR equations showed good performance in predicting of all-cause mortality in patients with NSTE-ACS. Interestingly, both CysC-based CKD-EPI equations had the highest overall discriminative power and outperformed the most widely used eGFR equation, the MDRD equation. Compared with the MDRD equation, all CKD-EPI equations accurately reclassified a significant percentage of patients into more appropriate risk category. However, only both CysC-based CKD-EPI equations are independent predictors after multivariate adjustment and add predictive value to the most widely used prognostic score in these patients, the GRACE risk score. Our study provides evidence that the use of CysC-based equations improves the role of eGFR in risk categorization, as judged by the risk of death from any cause. The highest performance of the CysC-based CKD-EPI equations highlights the value of CysC as a prognostic marker in ACS patients.

The SCr has long been the basis for calculating the eGFR. However, despite standardization, eGFR based on SCr remain relatively imprecise owing to variation in non-GFR determinants of SCr.[20] In recent years CysC has arisen as an interesting marker of renal function. CysC is a low molecular non-glycosylated protein which is synthesized by all nucleated cells and released into the blood at a relatively constant rate. It is freely filtered by the glomerulus, reabsorbed and catabolized in the proximal tubular cells without secretion, and does not appear in the urine.[21] Compared to SCr, it is less affected by age, sex, muscle mass or diet.[22] Liver disease, hyperthyroidism and high doses of corticosteroids have been described to increase its production.[23-26] In our study,

patients with these characteristics were excluded. Therefore, given its properties, it has been proposed as a more reliable marker of renal function than SCr.[21]

The prognostic role of CysC has been studied specifically in NSTE-ACS patients. Although the precise mechanism remains to be clarified, elevated levels of plasma CysC have been associated with adverse outcomes in these patients, including in-hospital cardiovascular adverse outcomes,[12] long-term mortality[10-11] and bleeding complications.[27] In these studies, the accuracy in predicting adverse outcomes of elevated CysC values outperformed other widely used parameters for estimating renal function (SCr or SCr-based equation). However, despite the favourable properties of CysC, the lack of CysC-based eGFR equations has limited its use in clinical practice. More recently, the Chronic Kidney Disease Epidemiology Collaboration group has developed a newer eGFR equations based on CysC values.[13-15] Compared to SCr-based equations, CysC-based equations provides a more precise and accurate eGFR in patients with near-normal renal function.[16] Therefore, the use of CysC-based equations is currently recommended to confirm the presence of renal dysfunction.[17]

Recent studies have focused on evaluating the prognostic value of these new equations in different clinical scenarios. Our group has previously demonstrated that both CysC-based equations outperformed the MDRD equations for predicting adverse outcomes (death and heart failure readmission) in acute heart failure patients.[28] In patients with acute myocardial infarction, Abu-Assi et al.[29] reported that both CysC-based CKD-EPI equations were the most accurate for predicting in-hospital mortality rather than the MDRD

and CKD-EPI$_{SCr}$ equations. Almeida et al.[30] found that the CKD-EPI$_{CysC}$ equation revealed the highest discriminative performance in predicting long-term mortality in patients with ACS and added predictive value to the GRACE risk score. However, unlike this study, we have focused on patients with NSTE-ACS. These patients tend to be older, have more co-morbidity (including worse renal function) and have worse long term prognosis, compared with ST-segment elevation ACS patients.[31] Therefore, accurate long-term risk stratification of NSTE-ACS patients is even more crucial.

We consider that given that CysC seems to be a better prognostic marker of renal dysfunction, along with the well-established value of renal dysfunction in NSTE-ACS patients, may explain our study results. However, some studies have confirmed the relationship between CysC and cardiovascular disease independently of renal function.[32] In this perspective, it has been postulated that cystatin C is also a marker of ongoing inflammatory process and atherosclerosis, which could explain its role in cardiovascular risk. In this way, Acuña et al.[12] reported a positive correlation between elevated CysC concentrations and high-sensitivity C-reactive protein and fibrinogen. Moreover, CysC concentration is also related to the prevalence of cardiovascular disease, even in patients without established chronic kidney disease.[33] Other study reported that high concentration of CysC were independently associated with cardiovascular risk factors, such as age, body mass index, low high-density lipoprotein cholesterol, and smoking, even in individuals without chronic kidney disease or microalbuminuria.[34] Therefore, it remains unknown whether the prognostic advantage of these CysC-based eGFR equations may be related not only to a more precise measurement of kidney function but also to an

association with non-renal factors such as inflammation and atherogenesis. Unfortunately, our study was not specifically designed to address this issue.

Our study has several limitations. The relatively small size of our single-centre sample and the lack of direct measure of GFR should be considered the main limitations of this research, especially because these new eGFR equations have not been completely validated in the setting of ACS. It is also noteworthy that this study was conducted in an entirely Caucasian population, so our results cannot be extrapolated to mixed race populations. The blood samples to measure SCr and CysC were collected during the first 48 hours from hospital admission and may not reflect a steady state of renal function. Furthermore, we did not have serial renal function measurements during follow-up or a group of patients with which to externally validate our results.

In conclusion, the new CKD-EPI equations based on CysC provides and apparently improved method for assessing long-term all-cause mortality risk in patients admitted to a NSTE-ACS, compared with the SCr-based eGFR equations. Moreover, these new equations improved the predictive value of the GRACE risk score. These results further highlight the value of CysC-based equations as a risk stratification tool in NSTE-ACS patients and support future research to achieve a better understanding of the mechanisms of renal dysfunction on cardiovascular outcomes and provide additional therapeutic options to reduce the risk in these patients.

Table 1: Study population clinical characteristics in the whole population and as a function of the occurrence of death.

Variables	Whole population n = 350	Events n = 31	No events n = 318	*P* Value
Age (y)	68 ± 12	80 ± 7	67 ± 11	< 0.001
Male	244 (70)	17 (55)	227 (71)	0.055
Body Mass Index (kg/m^2)	29 ± 4	30 ± 7	29 ± 4	0.442
Medical history				
Current smoking	91 (26)	3 (10)	88 (28)	0.029
Hypertension	277 (79)	28 (90)	249 (78)	0.114
Diabetes mellitus	167 (48)	19 (61)	148 (47)	0.117
Hyperlipidemia	219 (63)	21 (68)	198 (62)	0.547
LVEF (%)	60 [56-65]	54 [40-60]	60 [53-65]	0.004
Previous ACS	127 (37)	15 (48)	112 (35)	0.212
Previous PCI	107 (31)	13 (42)	94 (30)	0.154
Previous CABG	27 (8)	5 (16)	22 (7)	0.078
Chronic heart failure	15 (4)	5 (16)	10 (3)	0.006
Atrial fibrillation/flutter	36 (10)	4 (13)	32 (10)	0.544
Previous stroke	33 (10)	2 (6)	31 (10)	0.753
Peripheral artery disease	29 (8)	4 (13)	25 (8)	0.309
COPD	31 (9)	3 (10)	28 (9)	0.871
Clinical status at admission				
SBP (mmHg)	145 ± 28	145 ± 27	142 ± 33	0.966
Heart rate (beats/min)	80 ± 20	88 ± 21	79 ± 19	0.029
Killip class ≥ II	41 (12)	10 (32)	31 (10)	< 0.001
In-hospital procedures and treatments				
Coronary angiography	309 (89)	25 (81)	284 (89)	0.146
LM or 3-VD*	86 (28)	10 (40)	76 (27)	0.157
Femoral access*	120 (39)	11 (44)	109 (38)	0.580
Radial access*	220 (71)	17 (68)	203 (71)	0.713
Use of IIbIIIa GPI	17 (5)	0 (0)	17 (5)	0.382
PCI	213 (61)	16 (52)	197 (62)	0.260
Drug-eluting stent	159 (45)	12 (39)	147 (46)	0.373
Bare-metal stent	73 (21)	7 (23)	66 (21)	0.845
CABG	27 (8)	2 (6)	25 (8)	0.780
Medical treatment	109 (31)	13 (42)	96 (30)	0.178

Table 1: Study population clinical characteristics in the whole population and as a function of the occurrence of death (*cont*).

Variables	Whole population n = 350	Events n = 31	No events n = 318	*P* Value
Risk Scores				
GRACE	110 ± 29	139 ± 22	107 ± 28	< 0.001
Laboratory parameters				
Hemoglobin (g/dL)	14 ± 2	13 ± 2	14 ± 2	0.010
SCr (mg/dL)	0.95 [0.83-1.11]	1.16 [0.90-1.46]	0.94 [0.82-1.10]	< 0.001
CysC (mg/dL)	0.87 [0.73-1.08]	1.14 [0.98-1.76]	0.86 [0.72-1.04]	< 0.001
BUN (mg/dL)	39 [32-49]	49 [41-81]	38 [31-47]	< 0.001
Treatment at discharge†				
β-Blocker	307 (88)	25 (89)	282 (89)	1.000
ACE inhibitors / ARA	301 (87)	24 (86)	277 (87)	0.768
Aldosterone Antagonists	22 (6)	2 (7)	20 (6)	0.679
Statin	334 (97)	26 (93)	308 (97)	0.563
Aspirin	335 (97)	27 (96)	308 (97)	0.825
2P2y12 inhibitor	290 (84)	22 (79)	268 (84)	0.419
Anticoagulation	25 (7)	2 (7)	23 (7)	1.000

Data are expressed as mean ± SD, median [quartiles] and number (%). 3-VD denotes three vessel disease, ACE, angiotensin-converting enzyme; ACS, acute coronary syndrome; ARA, angiotensin-receptor blocker; COPD, chronic obstructive pulmonary disease; CABG, coronary artery bypass graft; CysC, cystatin C; GRACE, Global Registry of Acute Coronary Events; GPI, glycoprotein inhibitor; LM, left main; LVEF, left ventricular ejection function; PCI, percutaneous coronary intervention; SCr, serum creatinine; SBP, systolic blood pressure; and PCI, percutaneous coronary intervention.

* Referred to patients undergoing coronary angiography.

† Referred to patients alive at discharge (347 patients).

Table 2: Estimated glomerular filtration rate in the whole population and as a function of the occurrence of death.

Variables	Whole population n = 350	Events n = 31	No events n = 318	*P* Value
$CKD\text{-}EPI_{Scr\text{-}CysC}$ (mL/min/1.73m^2)	79 ± 23	54 ± 21	83 ± 24	< 0.001
$CKD\text{-}EPI_{Scr\text{-}CysC}$ < 60 mL/min/1.73m^2	69 (20)	17 (55)	52 (16)	< 0.001
$CKD\text{-}EPI_{CysC}$ (mL/min/1.73m^2)	83 ± 26	55 ± 24	89 ± 28	< 0.001
$CKD\text{-}EPI_{CysC}$ < 60 mL/min/1.73m^2	67 (19)	19 (61)	48 (15)	< 0.001
$CKD\text{-}EPI_{SCr}$ (mL/min/1.73m^2)	74 ± 21	53 ± 19	78 ± 20	< 0.001
$CKD\text{-}EPI_{SCr}$ < 60 mL/min/1.73m^2	83 (24)	18 (58)	65 (20)	< 0.001
MDRD (mL/min/1.73m^2)	78 ± 24	58 ± 20	80 ± 23	< 0.001
MDRD < 60 mL/min/1.73m^2	73 (21)	15 (48)	58 (18)	< 0.001

Data are expressed as mean ± SD, median [quartiles] and number (%). CKD-EPI denotes Chronic Kidney Disease Epidemiology Collaboration; MDRD, Modification of Diet in Renal Disease; other abbreviations as in Table 1.

Table 3. Performance of estimated glomerular filtration rate equations for prediction of death according to kidney function status.

Variable	AUC (95% CI)	Cut-off point value (mL/min/1.73m^2)	Sensitivity (95% CI)	Specificity (95% CI)	PPV	NPV	*P* Value[†]
CKD-EPI$_{SCr-CysC}$							
All patients	0.82 (0.77-0.86)	66.88	0.74 (0.55-0.88)	0.77 (0.72-0.81)	0.24	0.97	< 0.05
eGFR ≥ 60 mL/min/1.73m^2	0.78 (0.72-0.82)	87.79	1.00 (0.77-1.00)	0.49 (0.43-0.55)	0.09	1.00	< 0.05
eGFR < 60 mL/min/1.73m^2	0.71 (0.59-0.81)	34.42	0.47 (0.23-0.72)	0.92 (0.82-0.98)	0.67	0.84	0.18
CKD-EPI$_{CysC}$							
All patients	0.82 (0.77-0.86)	69.97	0.77 (0.60-0.90)	0.73 (0.68-0.78)	0.22	0.97	< 0.05
eGFR ≥ 60 mL/min/1.73m^2	0.71 (0.66-0.77)	97.27	1.00 (0.74-1.00)	0.51 (0.47-0.57)	0.08	1.00	0.10
eGFR < 60 mL/min/1.73m^2	0.66 (0.53-0.77)	31.57	0.42 (0.20-0.67)	0.94 (0.83-0.99)	0.73	0.80	0.26
CKD-EPI$_{SCr}$							
All patients	0.77 (0.74-0.83)	65.83	0.77 (0.59-0.90)	0.68 (0.63-0.73)	0.19	0.97	0.08
eGFR ≥ 60 mL/min/1.73m^2	0.74 (0.68-0.79)	81.52	0.92 (0.64-1.00)	0.55 (0.49-0.61)	0.10	0.99	< 0.05
eGFR < 60 mL/min/1.73m^2	0.65 (0.54-0.75)	44.69	0.78 (0.52-0.93)	0.58 (0.46-0.71)	0.34	0.91	0.22
MDRD							
All patients	0.75 (0.70-0.79)	68.90	0.74 (0.55-0.81)	0.68 (0.62-0.73)	0.18	0.96	-
eGFR ≥ 60 mL/min/1.73m^2	0.69 (0.63-0.74)	76.42	0.69 (0.41-0.89)	0.69 (0.63-0.74)	0.12	0.97	-
eGFR < 60 mL/min/1.73m^2	0.72 (0.60-0.81)	48.38	0.93 (0.68-1.00)	0.50 (0.37-0.63)	0.33	0.97	-

AUC denotes area under the curve; eGFR, estimated glomerular filtration rate; PPV, positive predictive value; NPV, negative predictive value; other abbreviations as in Table 1 and 2.

[†] Comparison between MDRD Study equation and the other equations.

Table 4. Cox regression risk analysis for prediction of death.

Variables	Univariate		Multivariate	
	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value
$CKD\text{-}EPI_{Scr\text{-}CysC}$ (per mL/min/1.73m^2)	0.952 (0.937-0.968)	< 0.001	0.978 (0.961-0.995)	0.012
$CKD\text{-}EPI_{CysC}$ (per mL/min/1.73m^2)	0.957 (0.943-0.971)	< 0.001	0.975 (0.956-0.994)	0.009
$CKD\text{-}EPI_{SCr}$ (per mL/min/1.73m^2)	0.955 (0.939-0.972)	< 0.001	-	-
MDRD (per mL/min/1.73m^2)	0.960 (0.944-0.977)	< 0.001	-	-

Adjusted for age, hemoglobin (g/dL), LVEF (%) and GRACE 6-month mortality risk score. CKD-EPI and MDRD equations were tested separately and multivariable. CI denotes confidence interval; other abbreviations as in Table 1.

Table 5: Evaluating added predictive ability of adding CKD-EPI equations to MDRD for prediction of mortality using reclassification indexes.

	NRI	*P* Value	% no events correctly reclassified	% events correctly reclassified
MDRD + CKD-EPI$_{SCr-CysC}$	24%	< 0.001	27%	-3%
MDRD + CKD-EPI$_{CysC}$	26%	0.003	26%	0%
MDRD + CKD-EPI$_{SCr}$	20%	0.013	23%	-3%

NRI denotes Net Reclassification Improvement; other abbreviations as in Table 1.

Table 6: Evaluating added predictive ability of adding eGFR equations to GRACE risk score for prediction of mortality using reclassification indexes.

	NRI	*P* Value	% no events correctly reclassified	% events correctly reclassified
GRACE + CKD-EPI$_{SCr-CysC}$	18%	0.051	15%	3%
GRACE + CKD-EPI$_{CysC}$	18%	0.047	15%	3%
GRACE + CKD-EPI$_{SCr}$	13%	0.097	3%	10%
GRACE + MDRD	7%	0.328	7%	0%

Abbreviations as in Table 1 and 5.

Figure 1: Rates of all-cause mortality according to estimated glomerular filtration rate categories using different equations. CKD-EPI denotes Chronic Kidney Disease Epidemiology; CysC, cystatin C; MDRD, Modification of Diet in Renal Disease, and SCr, serum creatinine.

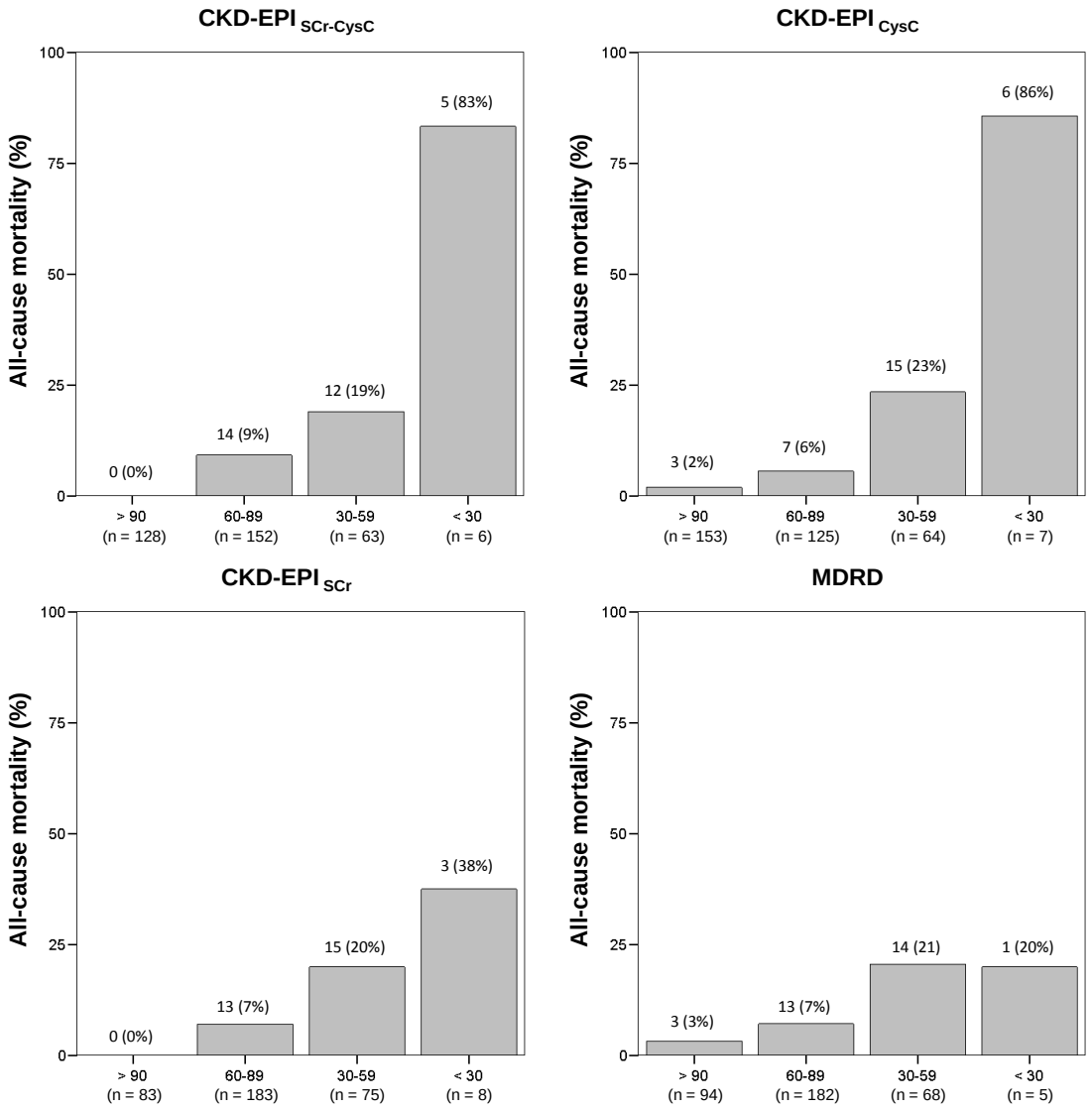
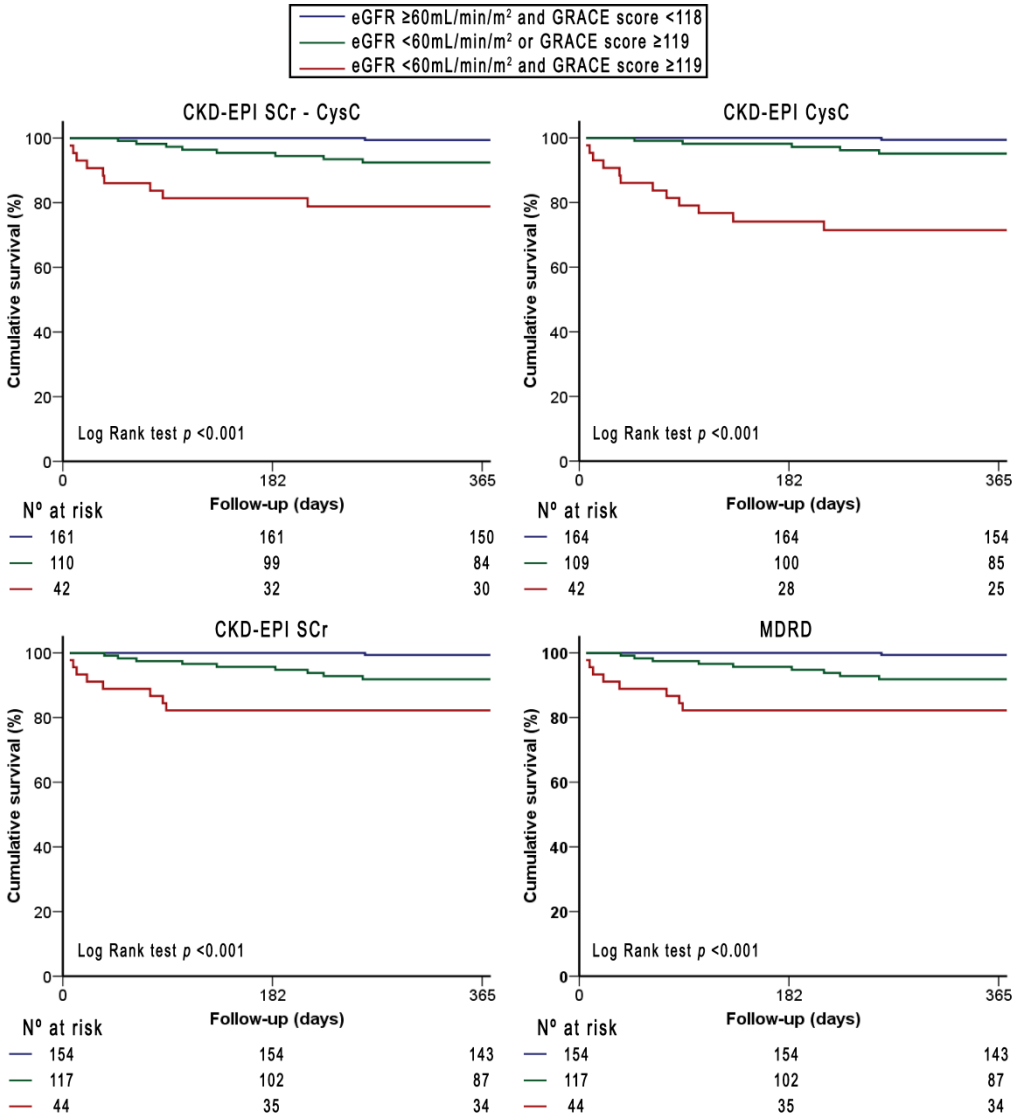


Figure 2: Kaplan-Meier survival curves for death as a function of glomerular filtration rate estimated using different equations and GRACE 6-month postdischarge risk score. CKD-EPI denotes Chronic Kidney Disease Epidemiology; CysC, cystatin C; MDRD, Modification of Diet in Renal Disease, and SCr, serum creatinine.



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Cartas de aceptación de las publicaciones

Artículo 1

De: "Journal of Cardiac Failure" <schristiansen@hfsa.org>
Fecha: 21 de mayo de 2013 20:18:36 GMT+02:00
Para: sergiomanzanofernandez@gmail.com
Asunto: Your Submission 135402R1

Ref.: Ms. No. 135402R1
Title: Comparison of Risk Prediction Using the CKD-EPI Equations and the MDRD Study Equation in Acutely Decompensated Heart Failure
Journal of Cardiac Failure

Dear Dr. Manzano-Fernández,

Your above revised manuscript has now been reviewed and I am pleased to inform you that it is accepted for publication in the Journal of Cardiac Failure.

The copyright agreement will be sent to you with the galley proofs from the publisher.

Thank you for submitting this interesting article to the Journal.

Sincerely,

Gary S. Francis, M.D.
Editor-in-Chief

Articulo 2

29-Oct-2014

Dear Mr. Flores-Blanco,

Your manuscript entitled "Combination of Cystatin C-based CKD-EPI Equations and N-Terminal Pro-B-Type Natriuretic Peptide for Predicting Outcomes in Acutely Decompensated Heart Failure" has been accepted for publication in Clinical Cardiology in its current form.

Your article cannot be published until you have signed the appropriate license agreement. Within the next few days you will receive an email from Wiley's Author Services system which will ask you to log in and will present you with the appropriate license for completion.

Thank you for your fine contribution.

Sincerely,

Prof. A. John Camm
Clinical Cardiology
jcamm@sgul.ac.uk, ppotts@sgul.ac.uk

Referee(s)' Comments to Author:

Review Editor's Comments to Author:
Review Editor
Comments to the Author:
(There are no comments.)

Artículo 3

04-Feb-2015

Dear Dr. Flores-Blanco

I am pleased to confirm that your paper has been accepted for publication in the European Journal of Clinical Investigation.

Your article cannot be published until the publisher has received the appropriate signed licence agreement. Within the next few days the corresponding author will receive an email from Wiley's Author Services system which will ask them to log in and will present them with the appropriate licence for completion.

It is important that all electronic artwork has been supplied to the editorial office in the correct format and resolution (TIFF, EPS or PDF: 300 dpi for photographic images, 600 dpi for line art). For further assistance please go to http://www.blackwellpublishing.com/bauthor/illustration.asp.

Your paper will now be passed to the production department and proofs will follow in due course.

Proofs will be sent via e-mail as an Acrobat PDF (portable document format) file. The e-mail server must be able to accept attachments up to 4 MB in size. Acrobat Reader will be required in order to read this file.

Please inform the Editorial Office of a change in address.

Proofs will be posted if no e-mail address is available, but this will inevitably lead to a delay in publication.

Thank you for supporting the European Journal of Clinical Investigation!

Yours sincerely

Dr. John P. A. Ioannidis
Editor in Chief

Índices de impacto de las publicaciones

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☐	1	J CARD FAIL	1071-9164	3876	3.065	3.632	0.408	98	5.5	0.01183	1.243

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Artículo 2

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☐	1	CLIN CARDIOL	0160-9289	3040	2.586	2.380	0.664	107	6.3	0.00765	0.810

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Artículo 3

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				Total Cites	Impact Factor	5-Year Impact Factor	Immediacy Index	Articles	Cited Half-life	Eigenfactor® Score	Article Influence® Score
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