Universitat Autònoma de Barcelona

Evaluation of the Prevalence and Risk Factors for Undernutrition in Hospitalized Dogs and Cats

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TO ACCESS THE DOCTOR'S DEGREE WITHIN THE ANIMAL PRODUCTION DOCTORATE PROGRAM OF THE DEPARTMENT OF ANIMAL AND FOOD SCIENCE

Bellaterra, 2019

FACULTAT DE VETERINÀRIA

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They certify that:

The PhD work entitled "Evaluation of the Prevalence and Risk Factors for Undernutrition in Hospitalized Dogs and Cats", presented by Jenifer Molina for being qualified for the Degree of Doctor in Veterinary Medicine, has been made under his direction and, considering it finalized, authorize its presentation to be judged by the corresponding commission.

And for the record, we sign the present document in Bellaterra, October 25th, 2019.

Dr. Cecilia Villaverde Haro

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This PhD work has been completed thanks to the partial funding of Affinity PetCare and the Hospital Clinic Veterinari of the Universitat Autònoma of Barcelona.

Agradecimientos

Quiero agradecer a mis directoras Cecilia Villaverde y Marta Hervera por enseñarme con entrega y paciencia, pero sobretodo por enseñarme el respeto nuestra profesión y nuestro esfuerzo diario por crear un servicio de calidad. Gracias también por enseñarme a hacer las cosas dando el 100% de uno mismo. Nunca dejaré de aprender de vosotras. Gracias también a mi tutora de tesis, Susana, por siempre confiar en que acabaría esta tesis y darme ánimos en los últimos momentos.

Gracias a mi marido, Álvaro, por su paciencia durante éste duro período de tesis y por enseñarme que nunca hay que rendirse y que lo que hace poderoso al ser humano es su fuerza interior. Gracias por darme la energía positiva necesaria para llevar el día a día, no podría haber imaginado un mejor compañero de vida.

Gracias a mi hijo, Darío, con sólo 1 añito y casi sin hablar ha sido mi inspiración y mi fuerza para acabar esta tesis. No sé cuántas veces habré mirado sus fotos en un descanso para recobrar fuerzas y seguir escribiendo.

Gracias a mis padres, Antonio y Luisa, por esforzarse para darme una educación y unos principios, sois el mejor ejemplo de que las cosas se consiguen con esfuerzo y trabajo.

Gracias a Mariola, por darme el contacto de dos buenas compañías de petfood para hacer mis prácticas de campo, creo que ahí es donde realmente empezó toda mi andadura por el mundo de la nutrición hasta llegar dónde estoy hoy.

Gracias a mis compañeros del hospital, por ayudarme a recoger los datos para realizar esta tesis. Especialmente gracias al personal de UCI (Luis, Carlos, Maribel y Erika), por dejarme campar a mis anchas para recoger los datos necesarios.

Gracias a Edgar, el súper estadístico que me ha ayudado a que esta tesis sea posible. Finalmente tenemos la estadística de gatos! Salut! ☺

Gracias a mis primeros compañeros de despacho, Roger y Víctor por hacerme reir en el día a día de la UAB, que no es poco! Y gracias también los compis del segundo despacho, especialmente a Sergi y Inma, por darme ánimos y compartir penas cuando lo hemos necesitado.

Gracias a Rosa y Olga, por las charlas en el laboratorio y por los pasillos y por ayudarme en el laboratorio y con la gestión diaria de material siempre que lo he necesitado.

Gracias Julia, por ayudarme con las gestiones necesarias para poder entregar esta tesis y explicarme todas las triquiñuelas, no estando presencialmente en la UAB ha sido aún más importante tú trabajo.
Gracias a todas las personas que me crucé, de un modo u otro, durante el tiempo que estuve en la UAB por ser siempre tan amables conmigo.

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Summary

The nutritional support (NS) in hospitalized dogs and cats is increasingly being recognized as a key point in their treatment. This concern has arisen together with the trend in human intensive care medicine, where nutrition is already recognized as an effective tool for improving the patient health status. Undernutrition has been suggested to decrease the effectiveness of the medical treatment in hospitalized veterinary patients and worsen outcome. The prevalence of the problem is unknown and current estimates situate it between 25% to 65%, using a variety of indicators. There is also a lack of data regarding risk factors for malnutrition in hospitalized animals, but vomiting, regurgitation, abdominal pain, incorrect nutritional plans, *Nil per os* (NPO, medical fasting) orders, and patient's anorexia have been suggested.

Studies in human patients have reported that NS is effective in improving the hospitalized patient health status and in reducing the hospitalization length (HL). However, despite a scattered numbre of studies with a small number of patients showing positive effects of NS on HL and health outcomes, there is still a lack of research backing its importance in veterinary medicine. The optimal time to implement NS in hospitalized veterinary patients is still not well defined either.

We hypothesized that undernutrition is frequent in veterinary patients, and that an appropriate nutritional status can help improve the outcome of the veterinary hospitalized patients.

Therefore, the main **objectives** of the present thesis (**Chapter 2**) were to assess the prevalence of undernutrition defined as loss of body condition score (BCS) and body weight (BW), to identify risk factors associated with undernutrition throuought hospitalization period, and to study the association of the nutritional status with the outcome and HL in hospitalized dogs and cats in a university teaching hospital.

In **Chapter 3** we explain the **material and methods** we used for achieving these objectives. A prospective cohort study was carried out in the hospitalization ward of a veterinary teaching hospital in Spain (Fundació Hospital Clínic Veterinari, Universitat Autònoma de Barcelona). Data from patients was collected, during 9 months in dogs and during one year in cats, throughout 2013 and 2014. All dogs and cats with a HL longer than 24 h were included. Data collected from each animal included signalment, clinical signs at admission (anorexia, vomiting, and diarrhea),

reason for hospitalization, diagnostics, fasting order at admission, nutritional evaluation at admission and for each day of the hospitalization period [BCS, muscle condition score (MCS), and BW(kg)], HL (days), daily food type and intake (Energy intake (EI)) (grams), type of nutritional intervention, and outcome (discharge or death). Clinicians from the admitting service obtained histories and performed physical examination of the patients prior to hospitalization, giving a severity index to each patient (physical status score –PSS) as described by Brunetto et al. (2010). The presence of weight loss, loss of appetite, vomiting, and diarrhea during the month before hospitalization was also identified by the clinicians during the anamnesis. Once the patient was hospitalized, researchers performed most of the nutritional evaluation including BCS and MCS measures in order to avoid confounding factors.

Chapter 4 shows the results regarding the prevalence and risk factors of undernutrition in the **canine** population of patients. The BCS and BW changes were modeled using multiple linear regression and outcome was modeled using logistic regression. The risk factors studied were EI, HL, initial BW (iBW) and BCS (iBCS), age, sex, severity of clinical signs, admitting service, fasting or other nutritional interventions, and the presence of anorexia, vomiting or diarrhea at admission. Most of the dogs (52.6%) consumed less than 25% of their estimated resting energy requirements (RER) and only 6.8% of the dogs met these requirements. The majority of hospitalized dogs maintained their BCS (78.2%) and BW (77%) during hospitalization. Older patients ($P=0.040$), higher iBCS ($P < 0.001$), and vomiting at admission ($P=0.030$) were associated with a decrease of BCS status during hospitalization. BCS was also decreased in patients with low EI, particularly in patients with HL over 3 days ($P < 0.001$). Both longer HL ($P < 0.001$) and vomiting at admission ($P = 0.004$) were also associated with a decrease in BW. Dogs that consumed their estimated RER during hospitalization period [$P < 0.001$; odds ratio (OR) 0.95, 95% CI: 0.92 to 0.98], and had a higher iBCS [$P < 0.001$; OR 0.39, 95% CI: 0.22 to 0.63] had a lower odds for dying. Anorexia at admission [$P < 0.001$; OR 5.67, 95% CI: 2.23 to 15.47] was associated with a higher risk of death.

Chapter 5 shows results of prevalence and risk factors of undernutrition in the **feline** population of patients. Data were collected from 120 hospitalized cats and outcome was available for all of them. The BCS and BW changes were modeled using multiple linear regression and outcome was modeled using logistic regression. The risk factors studied were EI, HL, iBW and iBCS, age, sex, severity of clinical signs, admitting service, fasting or other nutritional interventions, and the presence of anorexia, vomiting or diarrhea at admission. Although only the 9.2% of cats met their RER, most of the hospitalized cats maintained their BW and BCS during hospitalization, and most cats (90.4%) were discharged alive. The main variables identified as undernutrition risk factors in this study were iBCS, HL, and decreased EI during hospitalization. Regarding the outcome, lower EI during hospitalization was associated with higher odds for dying [P=0.05; OR 1.19, 95% CI: 1 to 1.08]. Cats with no reported weight loss before admission had lower odds of dying [P<0.001; OR 0.29, 95% CI: 0.07 to 1.16].

Results from the present study in a population of hospitalized dogs and cats in a university teaching hospital setting showed that decreased energy intake (EI) is very common during hospitalization and in some cases results in loss of BW and BCS, and it is also associated with a worse outcome. Age, HL, decreased EI, and, vomiting at admission have been identified as risk factors for undernutrition in dogs while HL, decreased EI and, diarrhea at admission are the main risk factors in cats.

Resumen

El soporte nutricional (NS) en perros y gatos hospitalizados se reconoce cada vez más como un punto clave en su tratamiento. Esta preocupación ha surgido junto con la tendencia en la medicina de cuidados intensivos en humana, donde la nutrición ya es reconocida como una herramienta efectiva para mejorar el estado de salud del paciente. Se ha sugerido que la desnutrición disminuye la efectividad del tratamiento médico en pacientes veterinarios hospitalizados y empeora el desenlace clínico. Se desconoce la prevalencia del problema y las estimaciones actuales lo sitúan entre el 25% y el 65%, utilizando una variedad de indicadores.

También hay una falta de datos con respecto a los factores de riesgo de desnutrición en animales hospitalizados, pero los vómitos, la regurgitación, el dolor abdominal, los planes nutricionales incorrectos, las órdenes de *nil per os* (NPO, ayuno médico) y anorexia del paciente, se han sugerido como posibles factores de riesgo.

Los estudios en humana han reportado que el NS es eficaz para mejorar el estado de salud del paciente hospitalizado y para reducir la duración de la hospitalización (HL). Sin embargo, a pesar de un número disperso de estudios con un pequeño número de pacientes que muestran efectos positivos de NS sobre HL y desenlace clínico, todavía hay una falta de investigación que respalde su importancia en medicina veterinaria. El momento óptimo para implementar el NS en pacientes veterinarios hospitalizados tampoco está bien definido.

Presumimos que la desnutrición es frecuente en pacientes veterinarios, y que un estado nutricional adecuado puede ayudar a mejorar el resultado de los pacientes veterinarios hospitalizados.

Por lo tanto, los **objetivos** principales de la presente tesis (**Capítulo 2**) fueron evaluar la prevalencia de desnutrición, definida como la pérdida de la puntuación de la condición corporal (BCS) y el peso corporal (BW), identificar los factores de riesgo asociados con la desnutrición durante el período de hospitalización y estudiar la asociación del estado nutricional con el resultado y el HL en perros y gatos hospitalizados en un hospital veterinario universitario.

En el **Capítulo 3** explicamos el **material y métodos** que utilizamos para lograr estos objetivos. Se realizó un estudio de cohorte prospectivo en la sala de hospitalización de un hospital veterinario universitario en España (Fundació Hospital Clínic

Veterinari, Universitat Autònoma de Barcelona). Se recogieron datos de pacientes, durante 9 meses en perros y durante un año en gatos, durante 2013 y 2014. Se incluyeron todos los perros y gatos con un HL de más de 24 h. Los datos recopilados de cada animal incluyeron reseña, signos clínicos al ingreso (anorexia, vómitos y diarrea), razón de hospitalización, diagnóstico, orden de ayuno al ingreso, evaluación nutricional al ingreso y para cada día del período de hospitalización [BCS, puntaje de condición muscular (MCS) y BW (kg)], HL (días), tipo e ingesta diaria de alimentos (Ingesta energética (EI)) (gramos), tipo de intervención nutricional y desenlace clínico (alta o muerte). Los médicos del servicio de admisión obtuvieron historiales y realizaron un examen físico de los pacientes antes de la hospitalización, dando un índice de gravedad a cada paciente (puntaje de estado físico –PSS) como lo describen Brunetto et al. (2010) La presencia de pérdida de peso, pérdida de apetito, vómitos y diarrea durante el mes anterior a la hospitalización también fue identificada por los médicos durante la anamnesis. Una vez que el paciente fue hospitalizado, los investigadores realizaron la mayor parte de la evaluación nutricional, incluidas las medidas de BCS y MCS para evitar factores de confusión.

El **Capítulo 4** muestra los resultados con respecto a la prevalencia y los factores de riesgo de desnutrición en la **población canina** de pacientes. Los cambios BCS y BW se modelaron mediante regresión lineal múltiple y el resultado se modeló mediante regresión logística. Los factores de riesgo estudiados fueron EI, HL, BW inicial (iBW) y BCS inicial (iBCS), edad, sexo, gravedad de los signos clínicos, servicio de ingreso, ayuno u otras intervenciones nutricionales, y la presencia de anorexia, vómitos o diarrea al ingreso . La mayoría de los perros (52.6%) consumieron menos del 25% de sus requerimientos estimados de energía en reposo (RER) y solo el 6.8% de los perros cumplieron con estos requisitos. La mayoría de los perros hospitalizados mantuvieron su BCS (78.2%) y BW (77%) durante la hospitalización. Los pacientes mayores ($P = 0.040$), con iBCS más alto ($P < 0.001$) y vómitos al ingreso ($P = 0.030$) se asociaron con una disminución de la BCS durante la hospitalización. El BCS también disminuyó en pacientes con bajo EI, particularmente en pacientes con HL mayor de 3 días ($P < 0.001$). Tanto un HL más largo ($P < 0.001$) como los vómitos al ingreso ($P = 0.004$) se asociaron con una disminución del BW. Perros que consumieron su RER durante el período de hospitalización [$P < 0.001$; odds ratio (OR) 0.95, IC 95%: 0.92 a 0.98], y tenía un iBCS más alto [$P < 0.001$; O 0,39; IC del 95%:

0,22 a 0,63] tenían una probabilidad menor de morir. Anorexia al ingreso [P <0,001; O 5.67, IC 95%: 2.23 a 15.47] se asoció con un mayor riesgo de muerte.

El **Capítulo 5** muestra los resultados de la prevalencia y los factores de riesgo de desnutrición en la **población felina** de pacientes. Se recopilaron datos de 120 gatos hospitalizados y el desenlace clínico estuvo disponible para todos ellos. Los cambios de BCS y BW se modelaron mediante regresión lineal múltiple y el resultado se modeló mediante regresión logística. Los factores de riesgo estudiados fueron EI, HL, iBW e iBCS, edad, sexo, gravedad de los signos clínicos, servicio de ingreso, ayuno u otras intervenciones nutricionales, y la presencia de anorexia, vómitos o diarrea al ingreso. Aunque solo el 9.2% de los gatos consumieron al menos su RER, la mayoría de los gatos hospitalizados mantuvieron su BW y BCS durante la hospitalización, y la mayoría de los gatos (90.4%) fueron dados de alta con vida. Las principales variables identificadas como factores de riesgo de desnutrición en este estudio fueron iBCS, HL, y disminución de EI durante la hospitalización. Con respecto al desenlace clínico, un menor EI durante la hospitalización se asoció con mayores probabilidades de morir [P = 0.05; O 1.19, IC 95%: 1 a 1.08]. Los gatos sin pérdida de peso informada antes de la admisión tenían menores probabilidades de morir [P <0,001; O 0.29, IC 95%: 0.07 a 1.16].

Los resultados del presente estudio en una población de perros y gatos hospitalizados en un hospital veterinario universitario mostraron que la disminución de la EI es muy común durante la hospitalización y, en algunos casos, resulta en la pérdida de BW y BCS y se asocia a un peor pronóstico. La edad, el HL, la disminución del EI y los vómitos al ingreso se han identificado como factores de riesgo para la desnutrición en los perros, mientras que el HL, la disminución del EI y la diarrea al ingreso son los principales factores de riesgo en los gatos.

Resum

El suport nutricional (NS) en gossos i gats hospitalitzats es reconeix cada vegada més com un punt clau en el seu tractament. Aquesta preocupació ha sorgit juntament amb la tendència en la medicina de vigilància intensiva a humana, on la nutrició ja és reconeguda com una eina efectiva per a millorar l'estat de salut del pacient. S'ha suggerit que la desnutrició disminueix l'efectivitat del tractament mèdic en pacients veterinaris hospitalitzats i empitjora el desenllaç clínic. Es desconeix la prevalença del problema, però les estimacions actuals la situen entre el 25% i el 65%, utilitzant una varietat d'indicadors.

També hi ha una falta de dades respecte als factors de risc de desnutrició en animals hospitalitzats, però els vòmits, la regurgitació, el dolor abdominal, els plans nutricionals incorrectes, les ordres de *nil per os* (NPO, dejuni mèdic) i anorèxia del pacient, s'han suggerit com a possibles factors de risc.

Els estudis a humana han reportat que el NS és eficaç per a millorar l'estat de salut del pacient hospitalitzat i per a reduir la durada de l'hospitalització (HL). No obstant això, malgrat un nombre dispers d'estudis amb un petit nombre de pacients que mostren efectes positius de NS sobre HL i desenllaç clínic, encara hi ha una falta de recerca que recolzi la seva importància en medicina veterinària. El moment òptim per a implementar el NS en pacients veterinaris hospitalitzats tampoc està ben definit.

Presumim que la desnutrició és freqüent en pacients veterinaris, i que un estatus nutricional adequat pot ajudar a millorar el resultat dels pacients veterinaris hospitalitzats.

Per tant, els **objectius** principals de la present tesi (**Capítol 2**) van ser avaluar la prevalença de desnutrició, definida com la pèrdua de la puntuació de la condició corporal (BCS) i el pes corporal (BW), identificar els factors de risc associats amb la desnutrició durant el període d'hospitalització i estudiar l'associació de l'estat nutricional amb el resultat i el HL en gossos i gats hospitalitzats en un hospital veterinari universitari.

En el **Capítol 3** expliquem el **material i mètodes** que utilitzem per a arribar a aquests objectius. Es va realitzar un estudi de cohort prospectiu a la sala d'hospitalització d'un hospital veterinari universitari a Espanya (Fundació Hospital Clínic Veterinari, Universitat Autònoma de Barcelona). Es van recollir dades de pacients, durant 9 mesos en gossos i durant un any en gats, durant 2013 i 2014. Es van incloure tots els

gossos i gats amb un HL de més de 24 h. Les dades recopilades de cada animal van incloure ressenya, signes clínics a l'ingrés (anorèxia, vòmits i diarrea), raó d'hospitalització, diagnòstic, ordre de dejuni a l'ingrés, avaluació nutricional a l'ingrés i per a cada dia del període d'hospitalització [BCS, puntuació de condició muscular (MCS) i BW (kg)], HL (dies), tipus i ingesta diària d'aliments (Ingesta energètica (EI)) (grams), tipus d'intervenció nutricional i desenllaç clínic (alta o mort). Els metges del servei d'admissió van obtenir historials i van realitzar un examen físic dels pacients abans de l'hospitalització, donant un índex de gravetat a cada pacient (puntuació d'estat físic –PSS) com ho descriuen Brunetto et al. (2010). La presència de pèrdua de pes, pèrdua d'apetit, vòmits i diarrea durant el mes anterior a l'hospitalització també va ser identificada pels metges durant l'anamnesi. Una vegada que el pacient va ser hospitalitzat, els investigadors van realitzar la major part de l'avaluació nutricional, incloses les mesures de BCS i MCS per a evitar factors de confusió.

El **Capítol 4** mostra els resultats respecte a la prevalença i els factors de risc de desnutrició en la **població canina** de pacients. Els canvis BCS i BW es van modelar mitjançant regressió lineal múltiple i el resultat es va modelar mitjançant regressió logística. Els factors de risc estudiats van ser EI, HL, BW inicial (iBW) i BCS inicial (iBCS), edat, sexe, gravetat dels signes clínics, servei d'ingrés, dejuni o altres intervencions nutricionals, i la presència d'anorèxia, vòmits o diarrea a l'ingrés . La majoria dels gossos (52.6%) van consumir menys del 25% dels seus requeriments estimats d'energia en repòs (RER) i només el 6.8% dels gossos van complir amb aquests requisits. La majoria dels gossos hospitalitzats van mantenir el seu BCS (78.2%) i BW (77%) durant l'hospitalització. Els pacients d’edat avançada (P = 0.040), amb iBCS més alt (P <0.001) i vòmits a l'ingrés (P = 0.030) es van associar amb una disminució de la BCS durant l'hospitalització. El BCS també va disminuir en pacients amb baix EI, particularment en pacients amb HL superior a 3 dies (P <0.001). Tant un HL més llarg (P <0.001) com els vòmits a l'ingrés (P = 0.004) es van associar amb una disminució del BW. Gossos que van consumir el seu RER durant el període d'hospitalització [P <0.001; odds ràtio (OR) 0.95, IC 95%: 0.92 a 0.98], i tenien un iBCS més alt [P <0.001; O 0,39; IC del 95%: 0,22 a 0,63] tenien una probabilitat menor de morir. Anorèxia a l'ingrés [P <0,001; O 5.67, IC 95%: 2.23 a 15.47] es va associar amb un major risc de mort.

El **Capítol 5** mostra els resultats de la prevalença i els factors de risc de desnutrició en la **població felina** de pacients. Es van recopilar dades de 120 gats hospitalitzats i el desenllaç clínic va estar disponible per a tots ells. Els canvis de BCS i BW es van modelar mitjançant regressió lineal múltiple i el resultat es va modelar mitjançant regressió logística. Els factors de risc estudiats van ser EI, HL, iBW i iBCS, edat, sexe, gravetat dels signes clínics, servei d'ingrés, dejuni o altres intervencions nutricionals, i la presència d'anorèxia, vòmits o diarrea a l'ingrés. Encara que només el 9% dels gats van consumir almenys el seu RER, la majoria dels gats hospitalitzats van mantenir el seu BW i BCS durant l'hospitalització, i la majoria dels gats (90.4%) van ser donats d'alta amb vida. Les principals variables identificades com a factors de risc de desnutrició en aquest estudi van ser iBCS, HL, disminució de EI durant l'hospitalització i pèrdua de pes abans de l'ingrés. Respecte al desenllaç clínic, un menor EI durant l'hospitalització es va associar amb majors probabilitats de morir [P = 0.05; O 1.19, IC 95%: 1 a 1.08]. Els gats sense pèrdua de pes informada abans de l'admissió tenien menors probabilitats de morir [P <0,001; O 0.29, IC 95%: 0.07 a 1.16].

Els resultats del present estudi en una població de gossos i gats hospitalitzats en un hospital veterinari universitari van mostrar que la disminució del EI és molt comuna durant l'hospitalització i, en alguns casos, resulta en la pèrdua de BW i BCS, i s'associa a un pitjor pronòstic. L'edat, el HL, la disminució del EI i els vòmits a l'ingrés s'han identificat com a factors de risc per a la desnutrició en els gossos, mentre que el HL, la disminució del EI i la diarrea a l'ingrés són els principals factors de risc en els gats.

CHAPTER 1. LITERATURE REVIEW

1.1. General introduction

The importance of adequate nutrition in hospitalized animals is increasingly being recognized (Remillard et al., 2001; Brunetto et al., 2010;). Hypermetabolism, reduced appetite, and loss of energy and nutrients (attributable to vomits, diarrhoea, and polyuria) are common in critically-ill animals, and can predispose these patients to malnutrition (Chan, 2004). Malnourished critically ill patients have a higher risk of morbidity and mortality (Barker et al., 2011; Lew et al., 2016). Malnutrition can be defined as the state of suboptimal nutritional status caused by an inadequate, unbalanced, or excessive consumption of nutrients that compromise to the host physically and mentally (Gagne and Wakshlag, 2015), and can increase morbidity and mortality in critically ill patients. Undernutrition is defined as an unbalance between energy intake (EI) and the energy necessary to maintain body functions, also associated to decreased provision of nutrients. In hospitalized patients, undernutrition is the most common disorder and most of the studies in the literature have focused on malnutrition particularly associated to decreased energy and nutrient intake. Therefore, the present work is using the term malnutrition as a synonym of undernutrition.

Lack of knowledge on identifying malnutrition and of well-defined hospital protocols to institute nutritional support (NS) have been described as the main barriers to achieve an adequate nutrition status in hospitalized human patients (Annetta et al., 2015), and the same situation could be true in veterinary medicine.

We have limited information on the prevalence of malnutrition in veterinary medicine mainly due to the lack of agreement on how to identify or measure it. There is consequently limited data regarding the most important risk factors for malnutrition in hospitalized animals. The identification of the risk factors is important to find a better prevention option for this problem. There is also a lack of research backing the importance of NS and the optimal time to implement it in hospitalized veterinary patients (Chan and Freeman, 2006). This review will focus on pathophysiology, risk factors and diagnostic of malnutrition and the effect of nutritional intervention in hospitalized patients.

1.2. Pathophysiology of malnutrition in hospitalized patients

1.2.1. Effects of under nutrition

The metabolic response to undernutrition is different in healthy animals (simple starvation) than in critically ill animals (stress starvation). Simple starvation is defined as physiological metabolic changes that occur when an otherwise healthy animal does not have access to food, whereas stress starvation is induced by anorexia or hyporexia associated to illness and the capacity of the organism to respond to starvation is altered by the disease. Therefore, it is not possible to completely base the nutritional approach of the ill patient on the model of the healthy starved patient (Delaney et al., 2006).

Simple starvation

In the postprandial period in healthy animals, exogenous dietary nutrients are used to meet immediate metabolic and energy needs, thus sparing endogenous fuels stored as glycogen and adipose tissue. After these needs are met, replenishment of glycogen reserves (in the liver and muscle) takes place. Any excess of energy in the form of carbohydrate, fat or protein is then converted to triglycerides for storage as fat in adipose tissue, muscle and liver tissue (Delaney et al., 2006; Hand et al., 2010; Gagne and Wakshlag, 2015).

Animals undergoing food deprivation require endogenous fuels and nutrients to meet immediate metabolic requirements. Endogenous glucose will be employed within the first 4-5 hours of food deprivation, and afterwards glycogen reserves will break down to provide energy for an additional 12-24 hours (figure 1.1). Insulin is down regulated, which leads to a decrease in the conversion of thyroxine (T4) to triiodothyronine (T3), resulting in a general metabolism rate reduction (Saker and Remillard, 2010). Furthermore, while glycogen stores are quickly depleted, stimulation of lean body mass catabolism begins to occur mediated by the influence of counter regulatory hormones, such as glucagon and endogenous glucocorticoids. The amino acids alanine and glutamine, obtained from lean tissue, are used towards gluconeogenesis in the liver and kidney, respectively (Welborn and Moldawer, 1997). The increase in glucagon stimulates muscle and fat catabolism, mobilizing fatty acids from adipose stores (Gagne and Wakshlag, 2015).

There is a shift over time from mixed fuels to fatty acids as a primary fuel source, and, as food deprivation continues, the metabolic rate continues to decrease (Saker and Remillard, 2010). By the third day of food deprivation, in all mammals, the basal metabolic rate decreases to promote conservation of resources (particularly lean body mass) for long-term survival. Thus, the type of energy fuel used by the animal depends on the length of food deprivation and the amount of fuel stores available (Saker and Remillard, 2010).

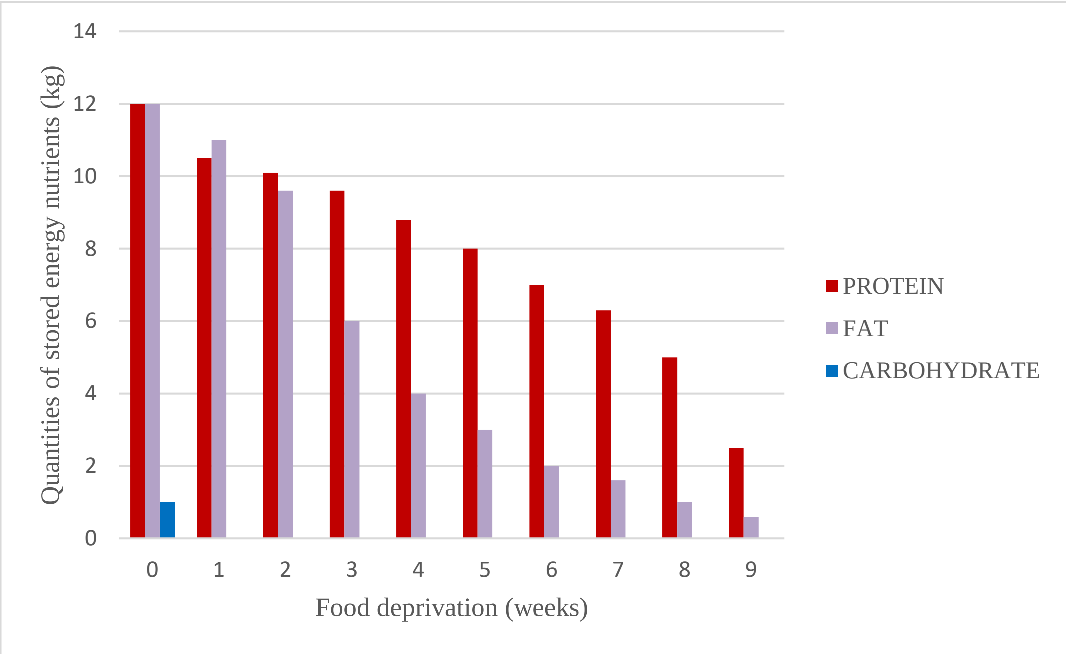


Figure 1.1. Utilization of nutrient stores during simple starvation (Saker and Remillard, 2010).

Maintaining normoglycemia is a priority. Omnivores, like the dog, achieve this via glycogenolysis and gluconeogenesis during the first 2 days of starvation. A decrease in blood glucose below 120 mg/dl decreases activity of hepatic glucokinase which in turn leads to activation of hepatic glycogenolysis, and the liver becomes a net exporter of glucose (figure 1.2). When hepatic glycogen stores are depleted, gluconeogenesis will be the main source of blood glucose. Carnivores like the cat depend mainly on gluconeogenesis for maintenance of blood glucose levels owing to their reduced hepatic glycogen storage, due in part, to lower glycogen synthase and glucokinase activities (Engelking and Anwer, 1992).

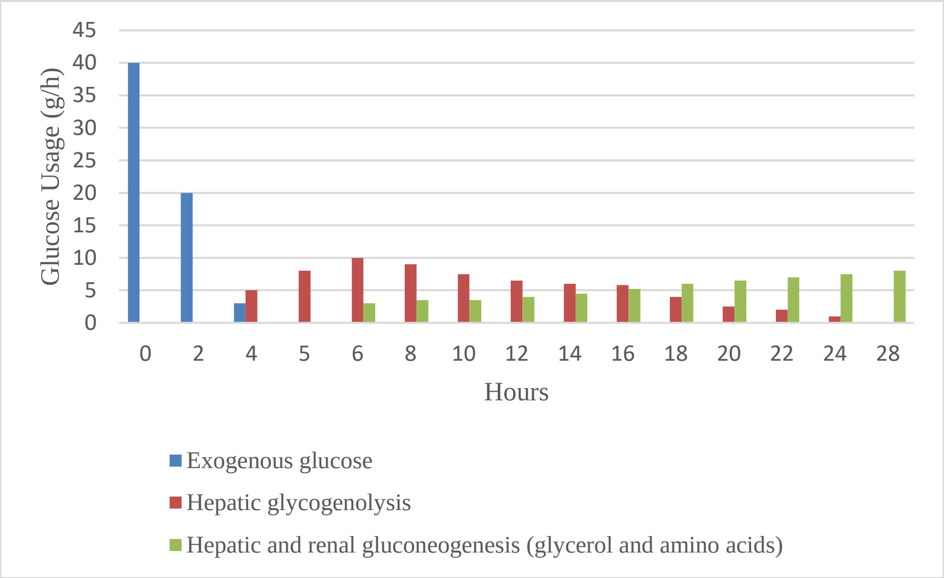


Figure 1.2. Utilization of glucose during the first day of starvation (Saker and Remillard, 2010).

Gluconeogenesis, mediated by glucagon and glucocorticoids, is carried out predominately in the liver and kidneys using substrates resulting from the catabolism of adipose tissue (glycerol) and lean tissue (glycogenic amino acids, lactic acid and pyruvate). Moreover, the Cory cycle and the alanine cycle in the liver will help conserve circulating glucose for glucose-dependent tissues, even though they require energy to do so. Both lactate and alanine generated in peripheral tissues can be carried in the circulation to the liver, where they serve as substrates for hepatic gluconeogenesis. The glucose produced from these precursors, can be transported from the liver and carried back to peripheral tissues for energy generation (McGrane, 2006).

In the Cory cycle (figure 1.3), lactate generated from pyruvate, the end product of glycolysis, is released mainly from muscle or red blood cells and transported to the liver, where is converted back to pyruvate and can be used to synthesize glucose. This glucose is then recirculated to muscle or red blood cells (McGrane, 2006). In this process, the NADH generated in skeletal muscle during glycolysis is used for the reduction of pyruvate to lactate.

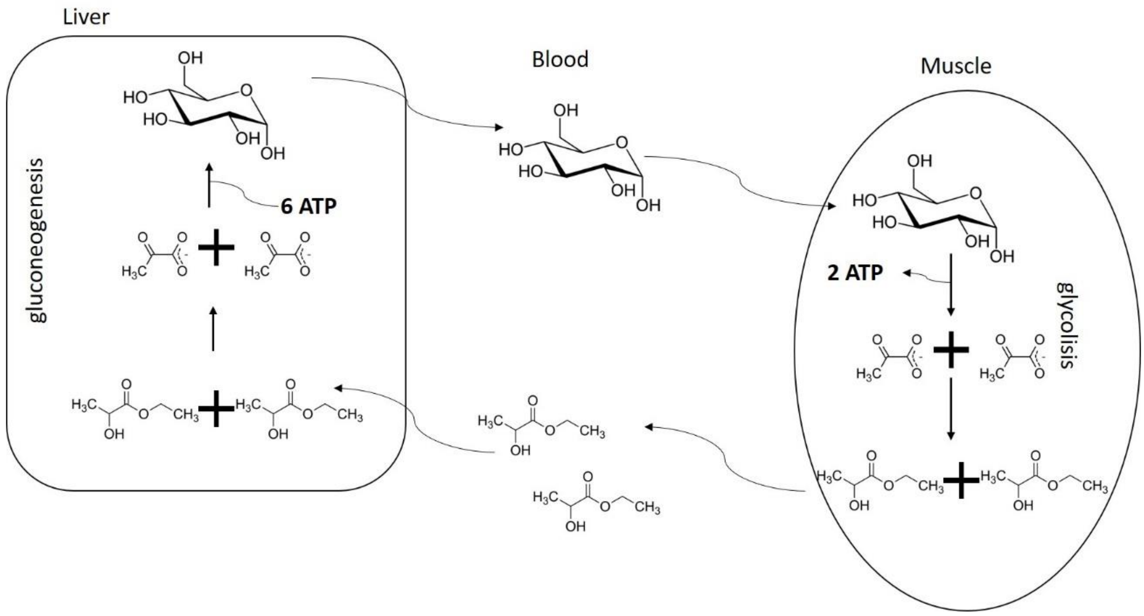


Figure 1.3. Re-utilization of glucose during the Cory cycle.

The alanine cycle involves the hepatic deamination of alanine to pyruvate, which serves as substrate for hepatic gluconeogenesis. The resulting glucose is then sent back into circulation. In the alanine cycle, unlike the Cory cycle, the NADH generated in skeletal muscle during glycolysis is available for mitochondrial electron transport and ATP production (McGrane, 2006).

The recycled glucose coming from these cycles does not contribute significantly to the net amount of glucose used by the brain; this tissue relies on gluconeogenesis from glycerol and amino acids. This situation is not desirable, because the utilization of endogenous amino acids will lead to an important muscle and protein loss from the body (Watford, 2006). An alternative fuel for the brain at this time are ketone bodies, synthesized in the liver from the partial oxidation of long-chain fatty acids obtained from triglycerides in adipose stores. The hydrolysis of triglycerides to provide fatty acids is mediated by hormone sensitive lipase, stimulated by glucagon.

Ketone bodies are water soluble and have a very wide distribution within the body, being also able to diffuse across cell membranes (Saker and Remillard, 2010). In consequence, they act to serve as a direct source of energy for vital organs such as the brain (McKenna et al., 2005; Schönfeld and Reiser, 2013). Ketosis in food deprivation is an appropriate physiologic response and does not lead to severe ketoacidosis except in diabetic dogs and cats (Stojanovic and Ihle, 2011).

Ketone body production is maintained until adipose tissue is depleted. Once the fat reserves have been exhausted, the animal will die.

Stress starvation

In contrast to patients undergoing simple starvation, ill patients may have access to food but have a decreased (hyporexia) to non-existent (anorexia) food intake. In these patients, there is a release of inflammatory mediators and stimulation of the sympathetic nervous system. This stimulation may induce a hypermetabolic state, which increases the body energy expenditure and proteolysis, leading to a negative energy and nitrogen balance (Tisdale, 2000; Inui, 2011). There is no adaptative reduction of the metabolic rate. All this results in loss of lean body mass, which impairs the patient's strength, immune function, wound healing, and negatively affects overall survival (Gagne and Wakshlag, 2015).

General neuroendocrine responses and local mediators create a hypermetabolic state. This response has been described as an acute phase followed by an adaptive phase (Popp and Brennan, 1983). The acute phase is characterized by catabolism and generally occurs within the first 24 to 72 hours. The decreased exogenous nutrients provision in the face of increased energy and nutrient demands leads to a negative energy and nitrogen balance. Some of the cytokines stimulating this hypermetabolic state include tumour necrosis factor (TNF-α), interleukin 1 (IL-1β), interleukin 6 (IL-6), and interferon ϒ (IFN-ϒ) (Inui, 2011). This phase will continue until the neuroendocrine stimuli and cytokine mediators are removed. The loss of 25 to 30% of lean body mass has been associated with reduced heart muscle mass and function, decreased pulmonary function, diminished respiratory drive, and compromised immune function, leading to higher mortality rates of these patients (Matthews and Fong, 1993). The adaptive phase, in surviving patients, is characterized by increased metabolic rate, nitrogen gain and normal body temperature and may last for several days, weeks or years. Specific disease states will affect the type and/or degree of metabolic and hormonal alterations in the patient.

1.2.2. Effects of overfeeding

Refeeding syndrome

Metabolic derangements that can occur in the refeeding process in a patient after an extended period of complete anorexia or severe malnutrition are called refeeding syndrome (RS) (Kraft, et al., 2005). In human medicine, RS can be observed within the first 2 to 5 days after initiation of feeding, but signs can be identified from hours to days after refeeding starts (Hofer et al., 2014). At the moment, RS is primarily identifiable by electrolyte imbalances, fluid disturbances, and/or life-threating complications, such as respiratory failure (Matthews et al., 2017). Risk of RS is significantly higher in elderly and geriatric patients (Matthews et al., 2017; Pourhassan et al., 2017).

Refeeding syndrome is believed to result when enteral (EN) or parenteral nutrition (PN) is provided to starved or severely malnourished patients, leading to changes and redistribution of fluid and electrolyte that cannot be accommodated by the weakened cardiovascular system (Skipper, 2012; Matthews et al., 2017). These patients have low insulin and high glucagon concentrations plus lack of exogenous nutrients. As a result, they have activated gluconeogenesis and proteolysis. The malnutrition has also resulted in a depletion of intracellular vitamin and electrolyte supplies (Boateng et al., 2010), that may not be identified analytically.

After initiation of NS in these patients, there is a sudden increase in blood glucose and insulin concentrations, leading to an overwhelming shift in electrolytes with increased sodium and water retention and extracellular volume expansion (McCray et al., 2005). The potential clinical consequences are volume overload with risk for heart failure and peripheral oedema, as well as transcellular shift and redistribution of phosphate, potassium, and magnesium with life-threatening complications such as spasm, or cardiac arrhythmias (Crook et al., 2001; Boateng et al., 2010).

Upon refeeding, there is increased utilization of phosphorus and magnesium to drive metabolic pathways of substrates and to act as co-factors for adenosine triphosphate (ATP) synthesis. This increased intracellular need, in conjunction with cotransport of potassium into the cell with insulin-driven glucose uptake, results in the further depletion of extracellular electrolytes.

The metabolic derangements seen in RS include severe hypophosphatemia, hypomagnesemia, hypokalemia, hyponatremia, hypocalcemia, hyperglycemia and vitamin deficiencies (Skipper, 2012). In human medicine, having limited consensus, hypophosphatemia is still considered the key sign in the diagnosis of RS, as the most common and consistent abnormality (Matthews et al., 2017). The ensuing depletion in phosphate results in neuromuscular, cardiovascular, and respiratory compromise.

Arrhythmias could be induced by hypokalemia in combination with hypocalcemia and hypomagnesemia. Hyperglycemia has been observed more commonly in critically ill dogs, although a case report in a cat diagnosed with RS stated also hypoglycaemia as a metabolic derangement (De Avilla and Leech, 2016).

Thiamine deficiency is an important component of the RS in people and has been reported in hospitalized cats with hepatic lipidosis (Brenner et al., 2011). Thiamine is a cofactor in many enzymatic reactions involved in carbohydrate metabolism and signs of thiamine deficiency include ataxia, vestibular dysfunction and visual disturbances. Upregulation of carbohydrate metabolism may also explain the increased demand for magnesium and thiamine, which then leads to neurological and neuromuscular complications (Kraft et al., 2005; Skipper, 2012).

Although there are no agreed guidelines for identification of patients at high risk for developing RS in veterinary medicine as there are in human medicine, some authors have suggested daily monitorization of body weight (BW), urine output, serum electrolytes (phosphorous, potassium, magnesium and calcium), haematocrit, serum glucose, and cardiovascular and respiratory function (Gagne and Wakshlag, 2015). It is recommend that NS not be introduced prior to correction of fluid and electrolyte imbalances and start gradually after that (Gagne and Wakshlag, 2015; De Avilla and Leech, 2016).

Other effects of overfeeding

Overfeeding may also lead to functional changes in some body organs (Havala and Shronts, 1990). The main affected ones are the gastrointestinal and cardiopulmonary system, although the liver and kidney can also be impacted (Havala and Shronts, 1990; Mauldin et al. 2001). Metabolic complications described include hyperglycaemia, hyperlipidaemia, azotemia and acidosis (Klein et al, 1998). Some patients can show volume intolerance after long periods of anorexia.

Within hours to days from the refeeding initiation, intestinal mucosa, liver, heart and kidney are restored gradually, while skeletal muscle is restored the last (Havala and Shronts, 1990). Diarrhoea, due to a reduced intestinal surface area (Steiner et al., 1968) decreased enzyme activity and hypoalbuminemia is a common complication of enteral refeeding (Knudsen et al., 1968).

During refeeding, the basal metabolic rate is increased, leading to an increased oxygen consumption, carbon dioxide production, and minute ventilation. Consequently, cardiopulmonary effort is increased, and in the long term, the inability of the heart and lungs to provide adequate oxygenation may result in respiratory and/or cardiac failure (Weinsier and Krumdieck, 1981).

1.2.3. Energy and nutrient requirements in hospitalized dogs and cats

Knowledge of energy requirements is needed in order to prevent both under and overnutrition. Energy requirements determine how much food an animal needs in order to maintain an adequate BW (see section 1.6). Energy requirements in dogs and cats can be established by measuring energy expenditure or estimated using formulas.

1.2.3.1. Measurement

Calorimetry is the measurement of the heat produced by the individual. Because animals do not store heat, the quantity of heat lost from the animal is equal to the quantity produced. Calorimetry allows measurement of the heat lost (heat production), that can be measured directly (direct calorimetry) or estimated from respiratory exchange (indirect or respiratory calorimetry) (Blaxter, 1989; Levine and Morgan, 1990). In human medicine, respiratory calorimetry is the most common method to calculate a patient's energy requirements. This can be done in hospitalized individuals in order to tailor the energy provision (Parker et al., 2017). Indirect calorimetry in veterinary medicine is usually reserved for research settings and is not commonly used in daily practice.

1.2.3.2. Estimation

Different formulas have been obtained empirically for the estimation of energy requirements in different physiological stages and for different activity levels in dogs and cats (National Research Council, 2006; Hand et al., 2010). Most of these equations have been obtained from populations of healthy individuals.

These equations are based in the metabolic body weight of dogs ($Kg^{0.75}$) and cats ($Kg^{0.67}$). Some equations calculate the daily energy requirements (DER) directly (National Research Council, 2006) and others first estimate resting energy requirements (RER) and then apply a factor according to species, life stage and activity (Hand et al., 2010). The RER (Kleiber, 1961) represents the energy requirement for an animal in a thermoneutral environment, without performing physical exercise and includes energy needed for digestion, absorption and metabolism of food (heat increment) and recovery from previous physical activity. It can be calculated by the estimate formula RER = 70 x $(BW_{kg})^{0.75}$.

Energy requirements of hospitalized animals

There is almost no data about the energy requirements in disease conditions. This can be due to the difficulty in performing prospective studies with a high number of patients and during enough time to extract reliable conclusions, and to the variability among different diseases and severity situations. A limited number of studies in dogs in the post-operative stage have been conducted in this area (Ogilvie et al, 1996; Walton et al, 1996) with respiratory calorimetry. These studies suggested that energy requirements of hospitalized dogs were close to their RER.

Some authors have recommended multiplying the RER by an illness factor based on the severity of underlying disease (Richardson and Davidson, 2003; Mauldin, 2012), assuming that the hypermetabolic state in critically ill patients will increase energy needs. Although illness factors have been used in the past in hospitalized animals, it is now recognized that they can overestimate the requirements of a convalescing and inactive veterinary patients (Chan, 2004). In human medicine, the European Society for Clinical Nutrition and Metabolism Guidelines on Enteral Nutrition advises against providing more than approximately basal energy requirements, especially in the acute phase of critical illness (Kreymann et al., 2006).

Given the probable increased risk of complications when ill animals are overfed, and the lack of evidence that feeding above energy requirements is beneficial in these cases, the current recommendation for calculating the energy needs in ill cats and dogs is to start at RER. Afterwards, the amount fed can be increased or decreased depending on the animal’s tolerance and BW trends (Chan, 2015).

Nutrient requirements in hospitalized animals

There is a lack of research on the effect of critical illness on nutrient requirements, thus, most recommendations are empirical, and the assumption is that the nutrient requirements are at least equal to those of healthy dogs and cats (National Research Council, 2006). Nutrient needs are important for diet selection (see Section 1.6.2).

The best macronutrient profile for hospitalized patients is unknown, and will likely vary for each patient. Usually (except in some particular cases) diets recommended are energy and nutrient dense in order to maximize energy and nutrients provision in patients that are frequently hypo/anorectic. These diets are complete and balanced for healthy adults, meaning that they include all macro and micronutrients (vitamins and minerals) required by healthy dogs and cats (National research council, 2006).

Common convalescence diets and their macronutrient content are presented in table 1.1.

	Protein	Fat	Carbohydrates	Caloric Content
Royal Canin Veterinary Diet Convalescence Instant (powder)	9.7	5.8	4.9	1.2 (reconstituted)
Royal Canin Veterinary Diet Recovery (can)	11.7	6	2.3	1.1
Royal Canin Veterinary Diet Recovery (liquid)	9.4	5.4	6	1
Hill's Prescription Diet a/d (can)	9.1	6.9	2.7	1.1
Specific Veterinary Diet Intensive Support (can)	9.4	5.9	3.1	1.3
Purina Pro Plan Veterinary Diet CN (can)	9.7	6.7	1	1.1

Table 1.1. Macronutrient content (expressed in g/100 kcal) and calorie content (expressed in kcal/ml or kcal/g) of the main convalescence diets in the European market for dogs and cats.

Protein

Adequate provision of protein is important to ensure lean body mass maintenance and organic functions. The recommended level of protein in malnourished dogs is of 4 g/100 kcal as a starting point, when there is no identified loss of protein. In cats, a minimum of 6 g/100 kcal of protein is recommended (Gagne and Wakshlag, 2015). Most diets for hospitalized patients provide amounts well above this minimum.

Fat

Fat is a concentrated source of palatable energy and the vehicle to provide essential fatty acids (Wakshlag and Kallfelz, 2006). Moreover, hospitalized patients with a history of decreased food intake are already using fat (endogenous) as a fuel. Diets formulated for hospitalized patients usually provide 5-7.5 g/100 kcal.

Carbohydrates

Carbohydrates are a convenient and easily assimilated energy source. The amount of digestible carbohydrates in the diets formulated for hospitalized dogs and cats is low and ranges from 1.5 g/100 kcal to 11 g/100 kcal (Becvarova, 2015). This reduced amount can be explained by the lower calorie content that this macronutrient has compared to fat (3.5 kcal ME/g of carbohydrate vs. 8.5 kcal ME/g of fat). In animals that are at risk of malnutrition, the use of high-energy dense foods is important. Lowering the amount of carbohydrates in the diet could be beneficial for patients with insulin resistance, hyperglycaemia and respiratory distress, because of decreased CO_2 production from carbohydrate metabolism (Gagne and Wakshlag, 2015) but there is still a lack of data in this regard.

Others

Specific nutrients have been proposed to promote healing and recovery are usually added to the critical care formulas. However, the research behind their efficacy is still lacking.

1. Arginine: essential amino acid functioning as an intermediary in the urea cycle. Protein catabolism is increased in malnourished animals, which could accelerate the urea cycle, creating an increased arginine demand. Despite this, no conclusive scientific data is present regarding arginine supplementation effectiveness in hospitalized canine patients (Kalil et al., 2006; Chan et al., 2009; Larsen, 2012).

2. Glutamine: non-essential amino acid, considered a conditionally essential amino acid during time of stress in some species (Buchman, 1999; Lacey and Wilmore, 1990). Glutamine is an energy source for enterocytes and lymphocytes, and is important for nucleotide biosynthesis (Mobrahan, 1992; Buchman, 1999). Most of the diets high in protein (convalescence diets) supply the adequate amount of glutamine, being the addition of glutamine to a complete and balance convalescence diet questionable at this time.

3. Branched-chain amino acids (BCAA): Leucine, isoleucine and valine. These amino acids are metabolized in the muscle, are used with the objective of improving nitrogen balance, and spare lean body mass in malnourished patients. Some data suggests that oral and parenteral administration of BCAA decreases the severity of anorexia and improves protein accretion and albumin synthesis in human cancer patients (Cangiano et al., 1996). Currently there is no evidence of benefits of adding BCAA in canine and feline patients already eating high protein diets.

4. Omega 3 fatty acids: Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). These fatty acids displace arachidonic acid from cell membranes, reducing the

formation of proinflammatory eicosanoids. Moreover, eicosanoids derived from EPA (series 3 prostaglandins and series 5 leukotrienes) are less pro inflammatory vs those originating from arachidonic acid. These fatty acids have also been proposed to downregulate TNF-α, IL-1β, and IL-6 synthesis in inflammatory cells (National Research Council, 2006). As reported in one study (Freeman, 2009), omega-3 fatty acids can also have a positive effect combating cardiac cachexia, and could have potentially beneficial effects in patients with cachexia of other origin, but data is still missing.

5. Vitamins: B-vitamins are coenzymes required in the citric acid cycle, being necessary for glucose, protein, and fat metabolism (National Research Council, 2006). Most pet foods contain adequate amounts of B-vitamins, but when the patient is not eating for an extended amount of time, these vitamins can be supplemented, even parenterally. Fat soluble vitamins can be stored in the liver thus there is no need for parenteral supplementation, however, after an extended amount of time presenting anorexia/hyporexia, excessive loss of fat stores occur and parenteral supplementation should be considered (Gagne and Wakshlag, 2015).

1.3. Malnutrition in human medicine

1.3.1. Prevalence of malnutrition

Malnutrition (referring to both under and overnutrition) in hospitalized people is a common concern associated with poor clinical outcomes (Ridley et al., 2015). According to studies around the world, malnutrition is present in about half of hospitalized patients (Ordoñez et al., 2013; Ridley et al., 2015), but tends to be undetected and incorrectly addressed because it is not considered a high-priority clinical issue, and nutritional evaluation is still far from being routinely implemented in hospitalized patients (Tsaousi et al., 2014). This situation was also showed in the study conducted by McWhirter and Pennington (1994). In this study, between 40-50% of 500 patients admitted to a university hospital had some degree of undernutrition, but only 23% of the patients had ever been through a minimal nutritional assessment (weighed) and in less than 50% the information of nutritional state was reported in their medical history. Furthermore, only 10 patients (2%) were referred for dietetic advice, and these patients had an average of 7.9% weight gain, while the rest had an average weight loss of 5.4%. Moreover, Annetta et al. (2015)

reported that only 41% of the patients admitted to the hospital were receiving a nutritional assessment.

1.3.2. Diagnosis of malnutrition

The European Society of Clinical Nutrition and Metabolism (ESPEN) selected a group of clinical scientists to provide a consensus statement, setting criteria for the diagnosis of malnutrition and define a unified international terminology (Cederholm et al., 2015). The common malnutrition screening tools and measures available until that time were inappropriate in critical illness, preventing an accurate assessment of weight and other anthropometric assessments (Ridley et al., 2015). Additionally, some screening tools require answers to questions that are impossible to obtain in patients who are ventilated or sedated and which are often unknown to relatives. Other well-known body composition assessment techniques, such as bioelectrical impedance analysis, were also considered unreliable in critical illness due to altered hydration status. Biochemical markers have long been considered a potential way to identify and measure nutrition status as it changes during hospitalisation but were also unreliable in critical illness due to variability resulting from underlying disease. Such markers might include albumin or other proteins with a shorter half-life which are frequently altered in critical illness, making their interpretation difficult (Ridley et al., 2015).

In the consensus of Cederholm et al. (2015), the experts agreed that subjects at risk of malnutrition should be identified by validated screening tools. A unanimous consensus was reached to advocate two options for the diagnosis of malnutrition, particularly undernutrition: body mass index (BMI) (<18.5 kg/m^2 to define malnutrition) or a combination between unintentional weight loss and either a reduced BMI or a low fat free mass index. Unintentional weight loss is defined as >10% of usual body weight in an undetermined period of time or >5% over 3 months.

1.3.3. Hospitalization length (HL) and clinical outcome

The high prevalence of malnutrition and the insufficient food intake during hospitalization leads to an increased risk of in-hospital mortality (Lainscak, 2014). In general, malnourished patients have a worse treatment response and increased rate of complications, showing longer hospital stays and poorer outcomes (higher mortality) compared to well-nourished patients (Ordoñez et al., 2013; Tsaousi et al., 2014; Lew et al., 2016). A significantly increased HL was associated with medical fasting (nil per os, NPO) in one study (Halvorson et al., 2013). In another study conducted in Spain (Villalobos et al., 2014) the patients diagnosed with malnutrition had a higher HL (31.7 days) compared with other patients (9.5 days). The death rate for these patients was 5 times higher compared with the mean, and the number of urgent re-hospitalization was increased by 1.9 times. Another study in children (Bechere et al., 2015) also revealed a higher HL in children with excess of BW compared with children with normal BW. Therefore, poor nutritional status is an important prognosticator of HL in acute care patients. The economic consequence of this health outcome is substantial.

1.3.4. Nutritional intervention

Recent retrospective (Ordoñez et al., 2013; Lainscak et al., 2014) and prospective (Calleja et al., 2014; Tsaousi et al., 2014) studies in human patients have stressed that a correct NS is important for improving patient's health status and for reducing the HL. This has a positive effect on the patient, who will return home earlier, but also for the hospital, which will save costs. In a study done in 1996, Fisher and Opper reported that having a specialized nutrition team support resulted in more patients meeting their daily nutritional requirements.

When considering the need for assisted nutrition, the route of nutrition delivery is an important topic to be covered when starting nutrition therapy for intensive care unit patients. Both the route of nutrition and the best time to start likely depend on many factors, including patient characteristics and disease state. Enteral nutrition is cheaper and more physiological than PN, but it remains controversial whether enteral feeding protocols are effective in improving important outcomes vs parenteral ones. Li et al. (2017) found that the implementation of EN feeding protocol marginally reduced HL and was able to increase the proportion of EN feeding, but failed to reduce 28-day mortality or the duration of mechanical ventilation. In another randomized controlled trial (Doig et al., 2013) 1372 patients were included to determine whether providing early PN to critically ill adults, where early EN was contraindicated, altered their outcomes compared with standard care. The use of PN did not affect day-60 mortality or HL and early PN resulted in significantly fewer days of invasive ventilation, with no harmful effects.

The timing of NS also needs to be carefully considered. Although there is no global consensus, meta-analisis show that early nutrition support (defined as a standard formula commenced within 24 hours of intensive care admission) lead to reduced mortality and hospitalization complications compared with delayed enteral intake (Tian et al., 2018). Although in some specific situation some studies fail to find a clear benefit of early nutrition support, no clear negative effects on outcome or complications have been reported (Koretz et al., 2007; Reintam et al., 2017). Moreover, latest meta-analysis in critically ill patients with gastrointestinal diseases and burn injured demonstrate improvements in clinical outcomes with early enteral feeding (Feng et al., 2017; Pu et al., 2018; Zhang et al., 2019).

1.4. Malnutrition in hospitalized veterinary patients

1.4.1. Prevalence of malnutrition

There are very few studies assessing malnutrition prevalence in hospitalized animals in veterinary medicine. Brunetto et al., (2010) in a retrospective study, and Chandler and Gunn-Moore (2004) and Remillard et al. (2001), in two prospective studies, estimated a prevalence of malnutrition in veterinary hospitalized patients (specifically dogs and cats) ranging between 25% and 65%. These authors used different methods to assess malnutrition (see 1.4.2).

1.4.2. Diagnosis of malnutrition

There is no standardized method to identify and diagnose malnutrition. Nutritional status in veterinary medicine is mostly assessed on the basis of classical factors such as BW, body condition score and plasma albumin concentration. The study of Remillard et al. (2001) identified malnutrition using energy balance and body condition score (BCS) of canine hospitalized patients. A daily neutral or positive-energy balance (> 95% RER) was achieved for only 27% of the 821 days of hospitalization per dog (dog-days).

The study from Chandler and Gunn-Moore (2004) assessed the nutritional status of dogs and cats at admission to a veterinary teaching hospital, based on clinical history, BCS (using the 9-point scale system), and serum albumin concentrations. The percentage of dogs and cats with a BCS below ideal was 34.7% and 53.3% respectively, and recent weight loss had been reported in 45.8% of dogs and 53.3% of cats. The results showed no significant positive correlation between serum albumin concentration and BCS in dogs. In contrast, there was a positive correlation between serum albumin concentration and BCS in cats. Many of the dogs with decreased serum albumin concentration had gastrointestinal disease or a hepatopathy that accounted for a loss of or failure to synthesize albumin rather than lack of protein intake; but the exact reason why albumin is a potentially better indicator of poor nutritional status in cats than in dogs is not known. In addition, there were significant associations in both species between a BCS <5 and decreased appetite and between a BCS <5 and recent weight loss.

Some authors have tried to identify other biomarkers of malnutrition in veterinary patients, such as serum proteins like insulin-like growth factor I (IGF-I) and creatine kinase. Serum IGF-I showed good correlation with nutritional status, as defined by BW and EI, in healthy animals (Maxwell et al., 1998; Maxwell et al., 1999), but has only been examined in research studies and has not been applied widely to clinical patients. Serum creatine kinase concentration was assessed as a marker of nutritional status in cats (Fascetti et al., 1997). In this study, creatine kinase was higher in hospitalized anorectic cats compared to healthy controls, and decreased with NS. However, it is also subject to changes with disease states.

Rapid turnover proteins such as transferrin (Tf) are used as dynamic nutritional biomarkers in human medicine (Ingenbleek et al., 1975; Kuvshinoff et al., 1993). Nakajima et al. (2014) evaluated the clinical usefulness of Tf as nutritional assessment marker by measuring plasma Tf concentrations in malnourished dogs before and after nutritional treatment. Post treatment plasma Tf concentrations were significantly higher than those of pre-treatment. The authors concluded that plasma Tf concentration was related to nutritional condition and would be a candidate for novel nutritional assessment marker in dogs although further research is needed. Apart from these biomarkers, Chan et al. (2009) reported that critically ill dogs had altered amino acid profiles. Critically ill dogs had significantly lower concentrations of alanine, arginine, citrulline, glycine, methionine, proline, and serine but significantly higher concentrations of lysine and phenylalanine compared with control group (healthy dogs). Concentrations of arginine, isoleucine, leucine, serine, valine, and total BCAA were significantly higher in survivors compared with no survivors. Consequently, the amino acid profile could also be an instrument for the diagnosis and prediction of the outcome in hospitalized dogs. In the same study, median C-reactive protein concentrations were significantly higher in the critically ill dogs compared with controls.

However, despite encouraging results in small powered studies, there are no standardized biomarkers to diagnose malnutrition in veterinary medicine at this time.

1.4.3. Risk factors of undernutrition in hospitalized dogs and cats

Due to the difficulty in diagnosing malnutrition in a standardized manner, identifying patients at risk is very important, to ensure early intervention and prevent the problem if possible. Some of the proposed risk factors for malnutrition in hospitalized animals are listed below (Chan and Freeman, 2006; Saker and Remillard, 2010; Perea, 2012). However, evidence is very scarce since there are only a few clinical studies assessing risk factors of undernutrition in ill dogs and cats.

- Anorexia: **Anorexia** is defined as the total loss of appetite and **hyporexia** is defined as a reduction in appetite. Both can occur for numerous reasons (Forman, 2010), and a complete nutritional assessment of the patient should be carried out to find the likely cause (see section 1.6). These patients are using endogenous lean and adipose tissue as an energy and anabolic substrates and when this state is prolonged, the loss of functional protein will result in a negative protein balance. Comparing the current EI with the theoretical energy requirement, we can evaluate the necessity of implementing assisted nutrition (EN or PN). Days of anorexia or hyporexia is one of the most important malnutrition risk factors in veterinary medicine (Gagne and Wakshlag, 2015).

- Vomiting and diarrhoea: These result in nutrient losses and are usually accompanied by hyporexia or anorexia.

- Insufficient EI: The two main reasons why dogs can be found in a negative energy balance during hospitalization, as reported by Remillard et al. (2001), are rejection of the offered food (hypo and anorexia) and NPO. Moreover, the same study identified that, out of 1000 written orders in respect to feeding, fewer than 20% were complete and accurate, which can contribute to an inadequate EI. In human medicine, studies have found a positive relationship between a proper EI and survival (Halvorson et al., 2013; Calleja et al., 2014; Tsaousi et al., 2014).

- Life stage: Energy and nutrient needs are different depending on the animal life stage (adult, lactating female, gestating female, puppy, etc.). Therefore, the risk of undernutrition will potentially be higher in the most energy demanding physiological stages (Burger, 1994¸McDonald, 1995; Schroeder and Smith, 1995).
- Age: advanced age has been proposed as a risk factor for malnutrition in companion animals (Weber et al., 2003; Fahey et al., 2008), as well as in humans (Calleja et al., 2014; Tsaousi et al., 2014). This may be due to changes in intestinal function or other aspects such as the presence of periodontal disease (Hirai, 2013) or impairment in the immune function.
- HL: a longer stay in the hospital can worsen malnutrition status and it is associated with a worse prognosis in human patients (Halvorson et al., 2013; Calleja et al., 2014; Tsaousi et al., 2014).
- Diseases: inflammation, trauma, neoplasia, facial/oral injures, gastrointestinal tract dysfunction, liver disease, or pancreatic disease can cause anorexia, as well as pain, fear and other components of emotional stress (Saker and Remillard, 2010).

1.4.4. Nutritional status and clinical outcome

Brunetto et al. (2010), in a retrospective study with 467 dogs and 50 cats, found that disease severity was negatively associated with hospital outcome and EI, and that EI was positively associated with hospital discharge alive. They also found that the patients' outcome was related to BCS, with discharge (alive) rates of 73% for animals with low BCS, and 84.7% for those with ideal or high BCS. Most of the dogs consumed more than 66% of their maintenance energy requirements (MER), which lead to a higher number of discharges compared with the animals that were consuming less energy during the hospitalization period.

In the study of Remillard et al. (2001), there were significant relationships between EI and disease severity, outcome and PSS, and outcome and caloric intake. Patients with milder disease had higher EI and were more likely to be discharged whereas patients with more severe disease were less likely to meet their energy needs and be discharged alive from the hospital. In this study, it is difficult to separate the effect of disease severity and decreased EI on outcome.

1.4.5. Nutritional intervention

Michel and Higgins (2006) investigated the percentage of prescribed EN (tube feeding) that was delivered in a small animal teaching hospital, as well as the percentage of the RER that was delivered to the patients, and the reasons why animals were under or overfed. All dogs and cats that underwent tube feeding were included in the study conducted during 5 months in 2003. Twenty-five animals (23 cats and 2 dogs) were enrolled in the study. Animals received a median of 91% (range: 68–100%) of their prescribed feeds/day and a median of 90% (range: 36–133%) of goal feeds/day. Nausea or vomiting and conflict with other treatments were the most common recorded reasons for incomplete meals. The study concluded that both prescribed and goal feeds were delivered with a good rate of success. Additionally, the nutritional intervention by the Nutrition Support Service improved the likelihood that the prescribed feeding plan would meet the animal's estimated RER.

One small prospective study (Mohr et al., 2003) found that early enteral feeding in growing dogs with acute parvovirosis (within 12 hours of admission) resulted in earlier resolution of clinical signs, better growth and improvements in indirect measures of gut barrier function compared to late enteral feeding (on average 50 hours after admission). A retrospective study (Liu et al., 2012) evaluated nutritional status and the effect of NS in dogs with septic peritonitis. The route of nutrition was also taken in account, being EN (voluntary or assisted tube feeding) and central PN the two early NS options studied. The authors concluded that early NS, defined as consistent caloric intake initiated within 24 hours post-surgery, in dogs with septic peritonitis was associated with a shorter HL in septic dogs compared to feeding more than 24 hours after surgery. In another retrospective study (Brunetto et al., 2010) a higher hospital discharge was reported in the voluntary feeding group, intermediate in those that received intensive nutritional care (forced feeding, enteral support, and parenteral support groups), and lower for the fasting group.

Regarding the types of nutritional intervention, Chan et al., (2002) reviewed the medical records of all dogs and cats receiving PPN between 1994 and 1999 in a veterinary teaching hospital to obtain signalment, reasons for use of PPN, duration of PPN administration, duration of hospitalization, complications, and mortality. A total of 80 dogs and 47 cats were included in the study. The most common underlying diseases were pancreatitis, gastrointestinal disease, and hepatic disease. Median duration of hospitalization was 7 days, with a median time of hospitalization before initiation of PPN of 2.8 days and median duration of PPN administration of 3.0 days. In the 127 animals receiving PPN, 72 complications occurred, most of them were metabolic (hyperglycaemia, hiperlipidemia, and hyperbilirubinemia), and were classified as mild and did not require discontinuation of PPN. The 73.2% of the patients were discharged. The study found that patients receiving supplemental EN had higher survival rates than the ones receiving only PPN, suggesting that enteral nutrition support, even partial, can be important in hospitalized dogs and cats.

1.5. Nutritional evaluation

Per the above, identification of the malnourished (or at risk) patient is complex due to the lack of standardized criteria in companion animals. Some authors have suggested that some of the indicators that the clinician may identify include unintentional weight loss (>10% in less than 3 months), poor hair coat quality, muscle wasting, inadequate wound healing, hypoalbuminemia, lymphopenia and coagulopathies. However, these abnormalities are not specific to malnutrition and often can occur late in the disease process (Chan and Freeman, 2006, Freeman et al., 2011).

Loss of lean and fat mass could be a great indicator of altered nutritional status. Loss of muscle mass can be associated with aging (sarcopenia) and certain disease states (cachexia), both associated with increased morbidity and mortality (Freeman, 2012). Muscle loss adversely affects strength, immune function, wound healing, and, is independently associated with mortality in humans (Gulsvik et al., 2009; Von Haehling et al., 2009). There are objective measures of body composition like dual energy X-ray absorptiometry (DEXA), stable isotope dilution, and bioelectric impedance. However, these methods are not commonplace in clinical practice due to expense and complexity and are restricted to the research setting. Therefore, indirect, subjective methods like BCS and muscle condition score (MCS) have been developed.

These factors can be identified performing a nutritional assessment. The World Small Animal Veterinary Association (WSAVA) has proposed that the nutritional assessment be the 5th vital sign in the routine physical examination (Freeman et al., 2011). This should be performed in every patient at every visit and, in hospitalized patients, daily. This assessment currently includes signalment, BW, BCS, MCS, complete dietary history and basic analytical parameters (Freeman et al., 2011). A patient with advanced malnutrition will not be very complex to recognize, since parameters such as BCS or MCS will be clearly altered (figure 1.4). The challenge is to identify patients at risk or at earlier stages.

Figure 1.4. Canine patient showing advanced signs of malnutrition

1.5.1. Initial nutritional evaluation (screening)

The initial screening helps to differentiate pets that are healthy and without risk factors (additional nutritional assessment not needed) from pets that have some nutritional risk factors and should be evaluated more in depth (extended nutritional evaluation) (figure 1.5).

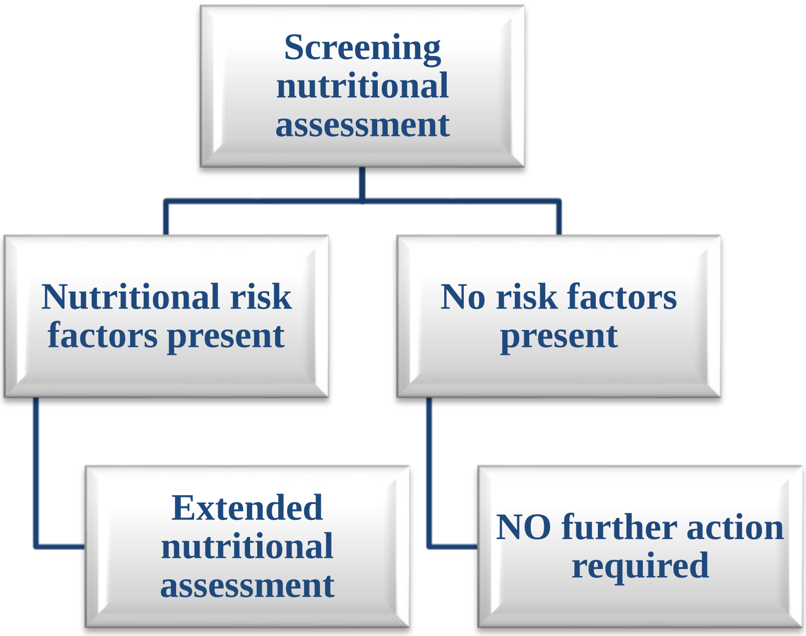


Figure 1.5. The **Screening evaluation** performed on every patient in order to see if there is any nutritional risk factor present. An **Extended evaluation** is performed when one or more nutrition-related risk factors are found or suspected based on the screening evaluation. *(Freeman et al. (2011)).*

Nutritional screening includes information from signalment, routine history taking and physical examination. Information collected should include assessment of factors specific to the **animal**, the **diet,** and the **feeding management/environment**.

1.5.1.1. Animal

Age, life stage, activity, appetite, and nutrient sensitive disorders are animal factors obtained from the signalment and history that should be collected. On the physical exam, any alterations should be noted and the veterinary team should assess BW, BCS, and MCS in a consistent manner, to evaluate the current status and changes over time.

1.5.1.1.1. Body weight (BW)

During the hospitalization period, BW should be measured at least once per day, at the same time of the day and with the same scale in order to minimize variability (figure 1.6). Some medical procedures and conditions can alter BW in a small period of time, such as rehydration or surgery processes (extracting the uterus, extracting a tumour, adding a bandage, etc.). These should be taken in account in order to interpret correctly the BW.

Figure 1.6. Cat weighted at home with a special scale. The animal was calm and with all the body inside the scale.

1.5.1.1.2. Body condition score (BCS)

The BCS is a subjective, semi-quantitative method that uses visual and tactile clues to indirectly estimate body fat (figure 1.7). The most common scales are the 5-point and the 9-point ones (Laflamme, 1997; German et al., 2006; Hand et al., 2010). On the 9-point scale, a BCS of 4 and 5 (only 5 in cats) is considered ideal, between 1 and 3 is considered underweight (or emaciation) and a BCS between 6 and 9 indicates overweight. This method has been validated with an objective measurement of body fat (DEXA) in dogs (Laflamme, 1997) and in cats (Laflamme, 1997(b)).

Figure 1.7. Body Condition Score System in dogs and cats. *Global Nutrition Committee Toolkit provided courtesy of the World Small Animal Veterinary Association*

1.5.1.1.3. Muscle condition score (MCS)

The MCS aims to evaluate the muscle mass (figure 1.8). This is a subjective method that includes visual examination and palpation of 4 muscle groups: over the temporal bones, scapulae, lumbar vertebrae and pelvic bones.

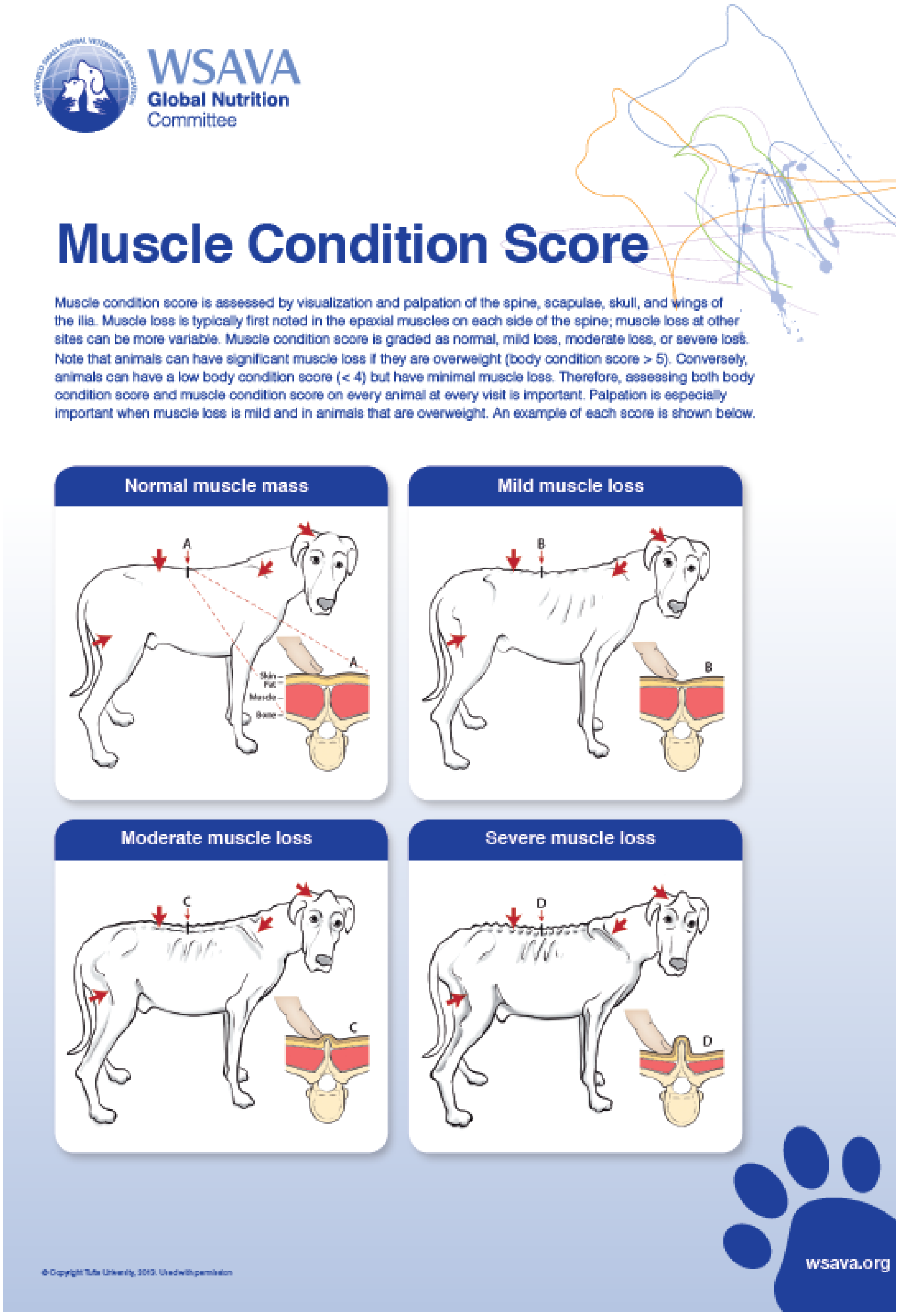


Figure 1.8. Muscle condition score system in dogs and cats. *"Provided courtesy of the World Small Animal Veterinary Association (WSAVA). Available at the WSAVA Global Nutrition Committee Nutritional Toolkit website: http://www.wsava.org/nutrition-toolkit. Accessed June 29, 2016. Copyright Tufts University, 2014."*

The MCS has been used without validation, but a recent prospective study (Freeman et al., 2019) has attempted to validate it in dogs using ultrasonographic measurements as the objective measure. The study used 40 dogs and the MCS correlated with several ultrasound measurements, including the vertebral epaxial muscle score (VEMS), which has also been proposed as a good indicator of lean body mass in dogs (Freeman et al., 2017). These results are very encouraging, since ultrasound is available in many clinics and VEMS could substitute MCS as a more objective estimate of muscle wasting.

1.5.1.1.4. Appetite

The total daily caloric intake should be estimated in patients with decreased or absent appetite. The assessment should entail a review of the medical history to rule out environmental stressors, unpalatable food, anosmia, or side effects of medications (Buffington et al., 2004). A complete physical examination should be performed, and appropriate diagnostic tests carried out to identify disease processes. Some geriatric patients with mild cognitive dysfunction can have no other identifiable cause of hyporexia (Gagne and Wakshlag, 2015).

1.5.1.2. Diet

Specific dietary factors, such as safety and appropriateness of the diet, should be evaluated before starting a nutritional plan. The information collected should include name of the diet, type, and amounts fed. Problems related to dietary factors are referred to as diet-induced disorders (e.g., nutrient imbalances, contamination, etc.).

1.5.1.3. Environment and feeding method

Feeding aspects include the frequency, timing, location and method of feeding, while environmental factors include space and quality of the pets’ surroundings. Problems related to feeding and environmental factors are referred to as feeding-related and environment-related disorders (e.g., over- or underfeeding, excessive use of treats, poor husbandry, competitive eating, or lack of appropriate environmental stimulation).

1.5.2. Extended nutritional evaluation

The extended evaluation is performed when one or more nutrition-related risk factors are found or suspected based on the screening evaluation. The importance of an extended nutritional evaluation (figure 1.9) increases as the number of risk factors and their severity increases (Freeman et al., 2011).

Changes in food intake or behaviour should be examined, taking in account the amount of food eaten, chewing or swallowing problems, nausea, vomiting, regurgitation, or other problems limiting the food intake. The skin and hair condition should also be examined in more detail, paying attention to the type of hair (dry, easily plucked hair), and skin (thin, dry, or scaly). Minimum laboratory testing should be done, including a complete blood count, urinalysis, biochemistry profile, faecal culture.

Once we have a complete dietary, animal, and environment evaluation, we can set up a nutritional plan according to the patient's needs.

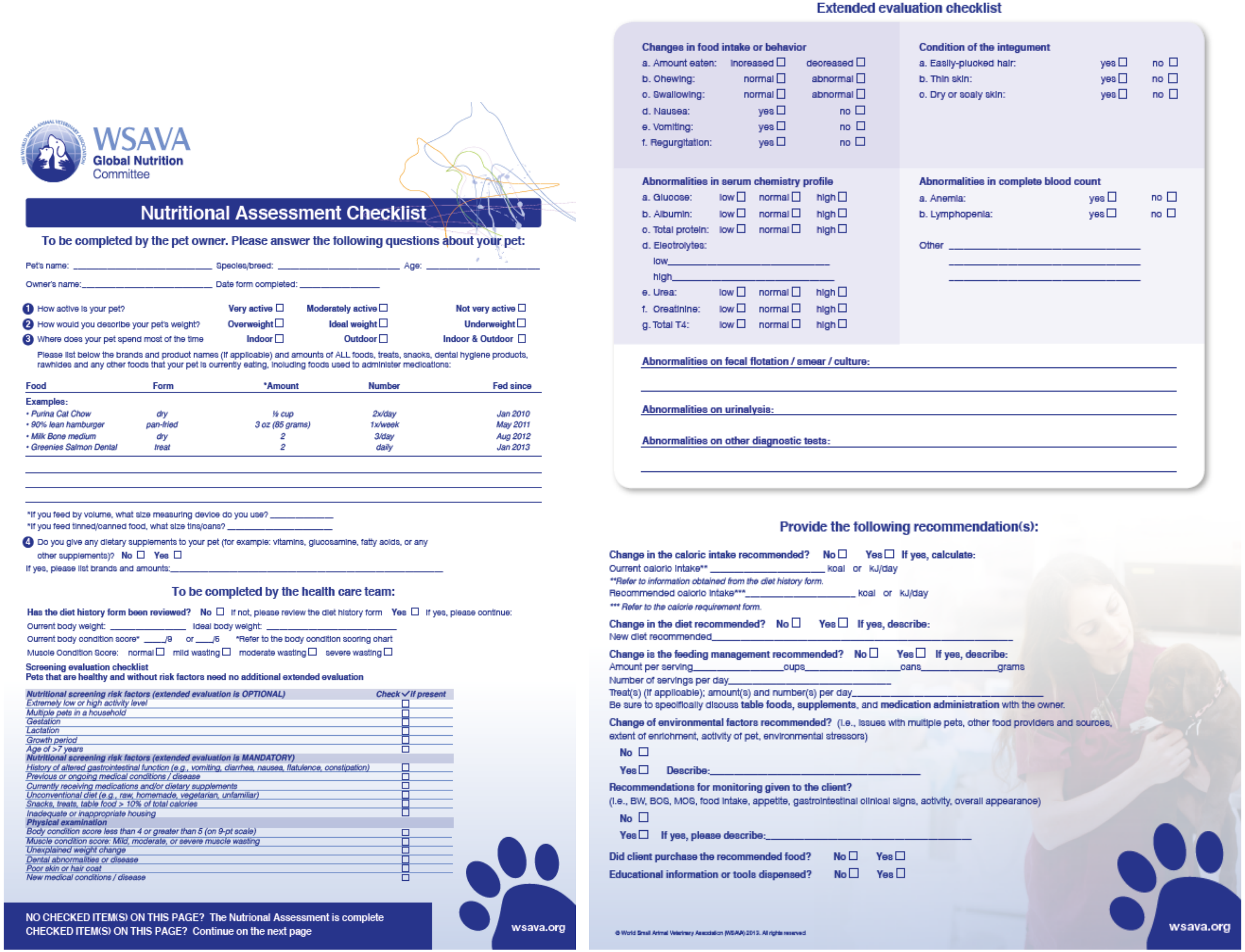
1.6. Nutritional support in hospitalized veterinary patients: current recommendations

Despite the lack of standardized definitions and protocols, recommendations have been made by different authors (Chan et al., 2004, Delaney et al., 2006) regarding NS in hospitalized patients, based on the limited available evidence. The provision of the necessary amount of energy and nutrients is the main objective in the sick patient in order to prevent or correct possible nutritional deficiencies, minimize metabolic disorders, prevent protein catabolism and maintain the correct functions of the organs. Following the trends in human medicine, the old paradigm of "the patient will eat when she/he feels better" has been replaced by "the patient will feel better sooner if nutrition is provided as soon as possible" (Chandler, 2004).

1.6.1. When to start the nutritional support

Specific circumstances should be considered in order to identify the perfect moment for implement the NS in veterinary patients once the patient has been stabilized and is properly hydrated, ideally with no acid base or electrolyte imbalances:

- **Anorexia**. Although the ideal time to start the NS has not been stablished yet, some authors proposed that assisted feeding should be started after 3 to 5 days of anorexia and no later (Chan and Freeman 2006, Freeman et al., 2011). In some disease processes, like parvovirosis in young dogs (Mohr et al, 2003), starting within the 1st day of admission is indicated.



WSAVA Global Nutrition Committee

Nutritional Assessment Checklist

To be completed by the pet owner. Please answer the following questions about your pet:

Pet's name: ____ Species/breed: ____ Age: ____

Owner's name: ____ Date form completed: ____

1. How active is your pet? **Very active** ☐ **Moderately active** ☐ **Not very active** ☐
2. How would you describe your pet's weight? **Overweight** ☐ **Ideal weight** ☐ **Underweight** ☐
3. Where does your pet spend most of the time **Indoor** ☐ **Outdoor** ☐ **Indoor & Outdoor** ☐

Please list below the brands and product names (if applicable) and amounts of ALL foods, treats, snacks, dental hygiene products, rawhides and any other foods that your pet is currently eating, including foods used to administer medications:

Food	Form	*Amount	Number	Fed since
Examples:				
• *Purina Cat Chow*	*dry*	*½ cup*	*2x/day*	*Jan 2010*
• *90% lean hamburger*	*pan-fried*	*3 oz (85 grams)*	*1x/week*	*May 2011*
• *Milk Bone medium*	*dry*	*2*	*3/day*	*Aug 2012*
• *Greenies Salmon Dental*	*treat*	*2*	*daily*	*Jan 2013*

*If you feed by volume, what size measuring device do you use? ____

*If you feed tinned/canned food, what size tins/cans? ____

4. Do you give any dietary supplements to your pet (for example: vitamins, glucosamine, fatty acids, or any other supplements)? **No** ☐ **Yes** ☐

If yes, please list brands and amounts: ____

To be completed by the health care team:

Has the diet history form been reviewed? **No** ☐ If not, please review the diet history form **Yes** ☐ If yes, please continue:

Current body weight: ____ Ideal body weight: ____

Current body condition score* ____/9 or ____/5 *Refer to the body condition scoring chart

Muscle Condition Score: normal ☐ mild wasting ☐ moderate wasting ☐ severe wasting ☐

Screening evaluation checklist
Pets that are healthy and without risk factors need no additional extended evaluation

Nutritional screening risk factors (extended evaluation is OPTIONAL)	***Check ✓ if present***
Extremely low or high activity level	☐
Multiple pets in a household	☐
Gestation	☐
Lactation	☐
Growth period	☐
Age of >7 years	☐
Nutritional screening risk factors (extended evaluation is MANDATORY)	
History of altered gastrointestinal function (e.g., vomiting, diarrhea, nausea, flatulence, constipation)	☐
Previous or ongoing medical conditions / disease	☐
Currently receiving medications and/or dietary supplements	☐
Unconventional diet (e.g., raw, homemade, vegetarian, unfamiliar)	☐
Snacks, treats, table food > 10% of total calories	☐
Inadequate or inappropriate housing	☐
Physical examination	
Body condition score less than 4 or greater than 5 (on 9-pt scale)	☐
Muscle condition score: Mild, moderate, or severe muscle wasting	☐
Unexplained weight change	☐
Dental abnormalities or disease	☐
Poor skin or hair coat	☐
New medical conditions / disease	☐

NO CHECKED ITEM(S) ON THIS PAGE? The Nutrional Assessment is complete
CHECKED ITEM(S) ON THIS PAGE? Continue on the next page

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Extended evaluation checklist

Changes in food intake or behavior
a. Amount eaten: increased ☐ decreased ☐
b. Chewing: normal ☐ abnormal ☐
c. Swallowing: normal ☐ abnormal ☐
d. Nausea: yes ☐ no ☐
e. Vomiting: yes ☐ no ☐
f. Regurgitation: yes ☐ no ☐

Condition of the integument
a. Easily-plucked hair: yes ☐ no ☐
b. Thin skin: yes ☐ no ☐
c. Dry or scaly skin: yes ☐ no ☐

Abnormalities in serum chemistry profile
a. Glucose: low ☐ normal ☐ high ☐
b. Albumin: low ☐ normal ☐ high ☐
c. Total protein: low ☐ normal ☐ high ☐
d. Electrolytes:
low ____
high ____
e. Urea: low ☐ normal ☐ high ☐
f. Creatinine: low ☐ normal ☐ high ☐
g. Total T4: low ☐ normal ☐ high ☐

Abnormalities in complete blood count
a. Anemia: yes ☐ no ☐
b. Lymphopenia: yes ☐ no ☐

Other ____

Abnormalities on fecal flotation / smear / culture: ____

Abnormalities on urinalysis: ____

Abnormalities on other diagnostic tests: ____

Provide the following recommendation(s):

Change in the caloric intake recommended? **No** ☐ **Yes** ☐ **If yes, calculate:**
Current caloric intake** ____ kcal or kJ/day
***Refer to information obtained from the diet history form.*
Recommended caloric intake*** ____ kcal or kJ/day
**** Refer to the calorie requirement form.*

Change in the diet recommended? **No** ☐ **Yes** ☐ **If yes, describe:**
New diet recommended ____

Change is the feeding management recommended? **No** ☐ **Yes** ☐ **If yes, describe:**
Amount per serving ____ cups ____ cans ____ grams
Number of servings per day ____
Treat(s) (if applicable); amount(s) and number(s) per day ____
Be sure to specifically discuss **table foods, supplements**, and **medication administration** with the owner.

Change of environmental factors recommended? (i.e., issues with multiple pets, other food providers and sources, extent of enrichment, activity of pet, environmental stressors)
No ☐
Yes ☐ **Describe:** ____

Recommendations for monitoring given to the client?
(i.e., BW, BCS, MCS, food intake, appetite, gastrointestinal clinical signs, activity, overall appearance)
No ☐
Yes ☐ **If yes, please describe:** ____

Did client purchase the recommended food? **No** ☐ **Yes** ☐
Educational information or tools dispensed? **No** ☐ **Yes** ☐

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Figure 1.9. Nutritional Assessment Checklist. *Global Nutrition Committee Toolkit provided courtesy of the World Small Animal Veterinary Association*

- **BCS**. A BCS at or lower than 3 out of 9 is an indicator to implement NS.
- **BW**. An involuntary loss of BW between 5 and 10% (not attributed to water loss) is an indicator of the necessity of implementing an adequate NS strategy for the patient.

The presence of other risk factors, such as young age or elderly, obesity in cats (with a high risk for hepatic lipidosis), and ongoing nutrient losses (such as hypoalbuminemia, vomiting and diarrhoea) should also be factored in when deciding when to start feeding.

1.6.2. What to feed: diet choice

There is a lack of information on nutrient requirements in disease states, therefore, the clinician should assume at least similar requirements compared to a healthy patient. A complete and balanced commercial food adequate for species and lifestage is the first choice, which can be customized according to the patient's preferences and disease. If the commercial balanced diets are not palatable, unbalanced homemade diets can be offered in the short term in order to provide energy and protein, despite deficiencies in macronutrients, vitamins and essential minerals. If the homemade diet is fed for longer than 1 week, the recommendation is to balance it by contacting to an expert (Remillard, 2008; Cave, 2012).

1.6.3. How much to feed: energy needs

The initial recommended goal is to feed RER. The amount should be increased progressively, starting with 25% or 33% of the RER, and rising according to the animal tolerance, up to 100% in about 3-4 days, to minimize adverse effects. The severity of the patient's condition and tolerance to the food will determine the frequency of administration. A common recommendation is to divide the food in 3 to 6 times a day, depending on each specific case, taking in account the volume administered in each administration. As dietary tolerance increases, the number of administrations per day can be reduced.

1.6.4. Feeding route

Voluntary oral feeding should be initiated as soon as possible, and can be stimulated by offering highly palatable foods, creating a relaxed environment or facilitating the access to the food (flat bowls, create an area where the animal feels safe, etc.). The use of drugs (such as mirtazapine and capromorelin) for enhancing appetite can be useful (Quimby and Lunn, 2013), even though its effects are not predictable and are often insufficient, so they are not always effective (Agnew and Korman, 2014; Ferguson et al., 2016). Forced feeding is not recommended in any case in order to avoid the adverse effects it can cause, as aspiration pneumonia or food aversion (Larsen, 2012).

In patients that will not or cannot eat their requirements voluntarily, assisted feeding is indicated, either enteral or parenteral. The route selected will be influenced by medical and nutritional status of the patient, functionality of the intestinal tract, nutritional needs, availability of diets, and the advantages and disadvantages presented by each route.

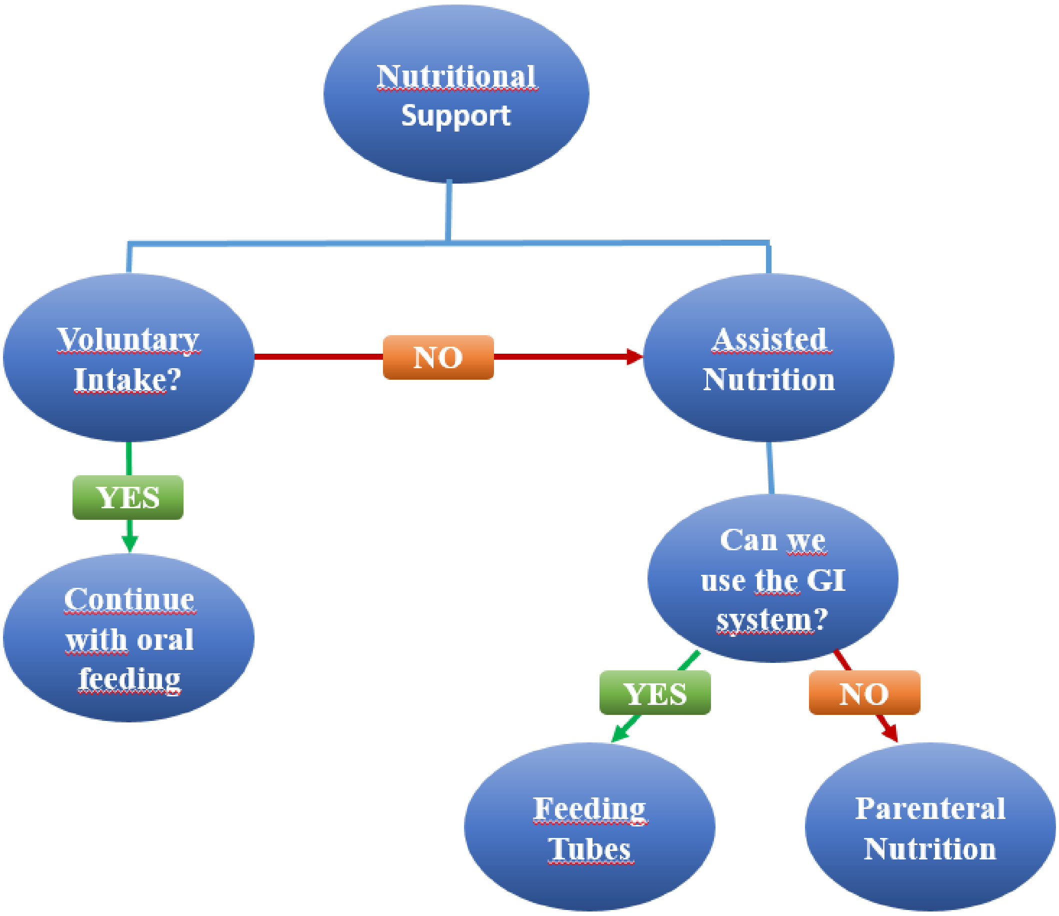

Figure 1.10. Nutritional support options in veterinary patients

1.6.4.1. Enteral nutritional support

This is the recommended route because it is considered more physiological, cheaper and safer, and can promote intestinal mucosal integrity, potentially reducing the risk of intestinal bacteria translocation and subsequent sepsis (Gagne and Wakshlag, 2015) although there is a paucity of data on the effects of assisted feeding on intestinal barrier function.

	Nasoesphageal/ Nasogastric	Esophagostomy	Gastrostomy	Jejunostomy
Duration	Short term (<7 days)	Medium term (Weeks-months)	Long term (Months)	Very short term (Days)
Diameter (French)	<8	10-20	>20	<8
Diet type	Liquid	Slurry	Slurry	Liquid
Advantages	Cheap, not invasive, does not require anaesthesia. Does not require special equipment	Placed easily using short anaesthesia. Home management possible.	Bigger diameter of the tube that allows feeding more dense slurries. Home management possible.	Allows for enteral nutrition in situations where pre-gastric feeding is not possible.
Disadvantages	Short term (7-10 days). Small diameter, only liquid diets, require hospitalization.	Invasive, requires anaesthesia.	Invasive, requires anaesthesia.	Invasive, requires anaesthesia. Small diameter, only liquid diets, require hospitalization.
Complications	Aspiration pneumonia, epistaxis.	Stoma infection, tube migration	Stoma infection, tube migration, spleen rupture, peritonitis	Peritonitis and tube migration

Table 1.2. Main characteristics of the most commonly used feeding tubes (nasoenteral, esophagostomy, gastrostomy and jejunostomy)

Enteral nutrition is performed with feeding tubes and the most commonly used are nasoenteral, esophagostomy, gastrostomy and jejunostomy ones (Remillard et al., 2001; Delaney et al., 2006; Gagne and Wakshlag, 2015). A short summary of their characteristics is presented in table 1.2.

1.6.4.2. Parenteral nutritional support

Parenteral nutrition is always intravenous and can be peripheral or central, depending on where the venous catheter is positioned. It is expensive and has many technical requirements, as the solution should be prepared under strict sterile conditions (figure 1.11). For this reason, this type of nutritional support is reserved to situations where the gastrointestinal tract cannot be used due to medical or surgical causes.

Figure 1.11. Parenteral nutritional support. Sterile bag containing the parenteral solution to be administered to the animal.

The most common complications associated with parenteral nutrition are hyperglycaemia, hyperlipidaemia and RS. Other adverse effects that can be seen during PN infusion are thrombophlebitis, septicaemia, microvilli atrophy-bacterial translocation, and paralytic ileus. In order to minimize most of these complications, an intensive care and monitoring should be planned.

1.6.5. Follow up

An advanced nutritional evaluation, including BW, BCS, MCS, appetite, amount of food ingested voluntarily or administered via feeding tube and tolerance to nutrition must be monitored daily in order to ensure the maintenance or the increase, depending on each specific situation, of the animal's BW.

CHAPTER 2. HYPOTHESIS AND OBJECTIVES

The nutritional support in hospitalized animals is described as an important part of the therapy and limited research shows that nutritional support can improve the outcome in hospitalized and critically ill dogs and cats. However, the published information shows that in countries like USA and UK not all patients receive a nutritional assessment and a nutritional plan during their hospital stay. This could be related to a lack of agreement on what is malnutrition and how to identify it.

Additionally, there is scarce data on the actual prevalence of malnutrition and the described malnutrition risk factors, important for patient selection and prevention, are mostly theoretical and extrapolated from human medicine.

The **hypothesis** of the study is that the prevalence of undernutrition in hospitalized dogs and cats, in a veterinary teaching hospital in Spain, would be similar to what has been described before in other countries and that undernutrition would negatively affect outcome.

The main **objectives** of the present study were:

1. To assess the prevalence of undernutrition, defined as loss of BCS and BW, and the percentage of energy requirements consumed in hospitalized dogs and cats.
2. To study the effect of the nutritional status on outcome in hospitalized dogs and cats.
3. To identify main risk factors associated with undernutrition in hospitalized dogs and cats.

CHAPTER 3. EXPERIMENTAL DESIGN

A prospective observational study was carried out in the hospitalization ward of the Veterinary Teaching Hospital Fundació Hospital Clínic Veterinari (FHCV) (Universitat Autònoma de Barcelona - Spain). Data was collected throughout one year (from April 2013 to April 2014) in cats and throughout 9 months (from April 2013 to January 2014) in dogs.

All patients admitted to the hospitalization unit of the FHCV throughout the study with HL periods over 24 hours and under 20 days were included in the study.

In the hospitalization unit of the FHCV dogs and cats were housed separately, having the cats and the dogs their own hospitalization ward space. Dogs and cats were allocated in individual cages.

Animal care and use protocol was approved by the Animal Protocol Review Committee of the Universitat Autònoma de Barcelona, and owner consent was obtained to enrol each patient in the study.

Data was collected in a daily basis from all the patients in the study using a standard form, shown in the figure 3.1. Data collected during the study period for each patient was:

- Signalment: patient’s name, age, gender, breed, and physiological status.
- Clinical signs at admission: anorexia, vomiting, and diarrhoea.
- Clinical service admitting the patient.
- Diagnostics.
- Severity score (PSS).
- Fasting order at admission.
- Daily nutritional evaluation: BCS, MCS, and BW (kg).
- Type of nutritional intervention.
- Daily food type and intake (grams).
- HL (days).
- Outcome: discharge or death.

Clinicians from the admitting services obtained anamnesis and performed physical examination of the patients prior to hospitalization.

The presence of weight loss, loss of appetite, vomiting, and diarrhoea one month prior to admission were also identified by the veterinarian who admitted the patient at the time that anamnesis was performed. Presence of vomiting, anorexia, diarrhoea and BW loss before admission (at presentation) was asked from the client. This data was collected using the form in figure 3.2.

The reasons for hospitalization and diagnostics were summarized according the service in charge of the patient as one of the following: surgery, internal medicine, neurology, ophthalmology, traumatology, emergency and critical care.

In order to evaluate the severity score of the patient, the PSS, described by Brunetto et al. (2010), was used. The PSS was classified with a 5-point scale where “1” indicated a normal animal with no organic disease, “2” mild systemic disease, “3” severe systemic disease (limiting activity but not incapacitated), “4” incapacitating systemic disease that is a constant threat to life, and “5” a moribund animal (not expected to live 24 hours with or without any type of intervention).

The BCS (figure 1.7) was assessed by the 9 point scale where 4-5 is ideal, <4 is underweight and >5 is overweight (Laflamme, 1997a; Laflamme, 1997b). In cats, only 5 was considered ideal.

The MCS (figure 1.8) was assessed using a 4-point scale where 3 is normal muscle mass, 2 is mild muscle wasting, 1 is moderate muscle wasting, and 0 is severe muscle wasting (Freeman et al., 2011). Due to the subjectivity of these measurements, the same researcher (Jenifer Molina) performed all BCS and MCS measures during the study period in order to obtain reliable results.

Nutritional intervention was defined as purposefully planned actions decided by the Nutrition Service intended to meet energy and nutrient requirements of a hospitalized animal and was classified as “Yes/No”. These interventions included feeding plans for voluntary oral feeding and enteral and parenteral nutrition support. All throughout the hospitalization period, the clinician in charge of the case had the chance of asking the Nutrition Service of the FHCV for a nutritional plan. In that case, the Nutrition Service calculated the specific requirements, food type, and food amounts for the dog/cat daily and stablished nutritional support orders for the patient. If the clinician in charge of the case decided not to ask for Nutrition Service intervention as mentioned above, this service did not issue any orders for that patient. The Nutrition Service participation with specific nutritional support orders in a patient was recorded as Yes (nutritional intervention completed) or No (no action from the Nutrition Service).

The average theoretical energy requirements were calculated every day for each dog and cat using the RER formula: RER (kcal/day)=70 x $BW^{0.75}$, according to the daily recorded BW. The daily EI was expressed as the average percentage of the RER consumed by the patient; calculated by dividing total EI (kcal/day) by RER (kcal/day) and multiplying this by 100. All dogs/cats were offered initially a complete and balanced commercial diet decided by the clinician in charge of the case or by the Nutrition Service (if consulted). If the patient refused the initial food offered, the hospitalization ward staff offered alternative commercial options with different textures and flavours. If none were accepted, they offered uncompleted homemade food, mainly composed by steamed white rice and boiled chicken breast.

In the cases where the Nutrition Service was not asked for a nutrition support plan, the hospitalization ward staff offered food, without considering estimated requirements, and recorded food type and amount in the study forms (figure 3.1).

For patients that were anorexic or with an EI below RER after 3 days of hospitalization, the Nutrition Service suggested assisted feeding (placement of a feeding tube or parenteral nutrition), but the final decision of assisted nutrition intervention was made by the clinician in charge of the case.

The amount of food consumed by the animals was recorded every day. The main researcher visited the hospitalization ward 3 times per day (morning, midday and, afternoon) in order to help the nurses to weight and offer the food to the animals. One hour later, the food was removed and weighted, in order to see the food intake of the animal at each meal. The total amount of food consumed during each day was calculated for each patient after discharge or death and, using the energy density of the food(s) consumed, was used to calculate the average daily EI as a proportion of RER.

Results of bloodwork performed throughout hospitalization period according to the clinician in charge of the case criteria were also recorded.

DATE	BW	Neutered Yes / No
IDENTIFICATION Nº	BCS MCS	
NAME	AGE	
BREED	GENDER	

If the animal has enetered today:
Time of entry:
Blood sample: Yes / No

TIME	9	10	11	12	13	14	15	16	17	18	19	20	21
DIET: complete name, brand & type.													
OFFERED AMOUNT: grams or fractions of the cans													
LEFT AMOUNT: grams or fractions of the cans													
APPETITE (YES /NO)													
BLOOD ANALYTICS	Alb= Prot= Gluc= Na= K= Cl= P= Ca= BUN= TG= Col= ALT= AST= Creat= Hto= PT= PTT= Fibr= D-dim= CBC tot=												
VOMIT/DIARRHEA													
HISTORY/DIAGNOSTIC													

Figure 3.1. Hospitalization data collection sheet. Recorded data per day per each animal hospitalized enroled in the study. The form was keeped in the hospitalization ward with pationts clinical record and filled by the main researcher (Jenifer Molina) or the hospitalization ward staff (in case they give more food to the animal out of the hours of researcher ward attendance)

Patient's name	
Identification number	
Age	
Gender	
Breed	
Neutered Yes/ No	
BW one year ago (Kg)	

BW lost during the last month?	Yes / No
In case that yes, BW lost	Kg

	normal	diminished	increased	absent
Appetite during the last month				
In case that absent or diminished, specify the number of days since this happen				

CURRENT DIET	Yes/No	Name	Daily amount (g)
Comercial Diet			
Treats			
Homemade diet			

USUAL DIET / PREVIOUS DIET	Yes/No	Name	Daily amount (g)
Comercial Diet			
Treats			
Homemade diet			

Figure 3.2. Form aimed to owners data collection regarding prior admittance period . The form was given to each owner at the time of admision. The form was filled by the owner and the veterinarian in charge of anamnesis performance in order to make sure that the owner comprehended correctly the form, and to check that the information given by the owner was correct.

3.1. Statistical analysis

Data were analyzed using R 3.1.0 (R core team, RRID: SCR_001905) in dogs and SAS 9.4 (Cary, NC) in cats. The animal was considered the experimental unit for all analyses. Descriptive statistics were performed for continuous and categorical variables. Change in BCS (BCS at admission minus BCS at discharge or death), relative BWchange [(BW at admission—BW at discharge or death)/BW at admission] during hospitalization, and outcome were considered as dependent variables. The main independent variables studied were EI and HL. The models also included as independent variables iBW, iBCS, age, sex, PSS, service admiting the patient, fasting order at admission, nutritional intervention and, the presence of anorexia, vomiting or diarrhoea at admission.

Regression models, linear for BCS and BW change and logistic for outcome, were used. Each predictor variable was included as a single fixed factor. Variables with P values under 0.25 in this univariable analysis were selected to build the multivariable model.

Before entering the variables into a multivariable model, bivariate Pearson's and Spearman's correlations and Chi-square analysis were performed among independent variables in order to assess collinearity. Collinearity was also assessed by bivariate analysis showing a significant association and $r > 0.70$. In case of collinearity, the variable with the highest association with the dependent variable was entered in the model. When both variables presented similar associations with the dependent variable the selection was based on clinical criteria. Collinearity of the complete model was tested using the variance inflation factor (VIF).

Linearity of the responses to each independent variable was checked graphically. The BCS change and BW change models were built using multiple linear regression with manual stepwise selection procedure.

The outcome model was built using logistic regression with manual stepwise selection procedure and results are presented as Odds ratio (OR) and the 95% confidence interval (CI). All two-way interactions between significant variables in the multivariable models were tested.

Model fit was assessed with the Akaike information criterion (AIC) and adjusted r^2. Alpha level for determination of significance was 0.05.

CHAPTER 4. EVALUATION OF THE PREVALENCE AND RISK FACTORS FOR UNDERNUTRITION IN HOSPITALIZED DOGS

Related Open Access article:

Molina, J., Hervera, M., Manzanilla, E.G., Torrente, C., Villaverde, C. 2018. Evaluation of the Prevalence and Risk Factors for Undernutrition in Hospitalized Dogs. Front Vet Sci. Aug 29; 5: 205.

doi: 10.3389/fvets.2018.00205.

4.1. Introduction

Nutritional support in hospitalized animals is key to prevent malnutrition via delivery of adequate calories and nutrients, preventing nutritional deficiencies, metabolic disorders, protein catabolism, and maintaining the correct organ functions (Chan, 2004). The lack of knowledge and well defined hospital protocols have been described as the main barriers to adequate nutrition in hospitalized human patients (Annetta et al., 2015) and the same situation is found in veterinary medicine. To identify malnutrition, a daily nutritional evaluation of hospitalized patients should be completed including BW, BCS, MCS, dietary information, and environmental assessment (Freeman et al., 2011b).

Retrospective (Lainscak et al., 2014; Ordoñez et al., 2013) and prospective (Calleja et al., 2014; Tsaousi et al., 2014) studies in human patients have reported that nutritional support is effective in improving the hospitalized patient status and reducing the HL. There is a lack of research backing the importance of nutrition support in veterinary medicine, although enteral feeding has been shown to be positive in dogs with acute gastrointestinal disease (Mohr et al., 2003; Will et al., 2005), early nutritional support has been associated with decreased HL in septic dogs (Liu et al., 2012) and one study found an association between low EI during hospitalization and a negative outcome (Remillard et al., 2001). Another issue that has not been well defined is the best time to implement nutritional support in veterinary patients (Chan and Freeman, 2006).

The objectives of this prospective study were to assess the prevalence of malnutrition defined by loss of BCS and BW, to identify risk factors associated with malnutrition, and to study the effect of the nutritional status on outcome in hospitalized dogs.

4.2. Results

Data were collected prospectively during 9 months from hospitalized dogs with a HL longer than 24 hours in a veterinary teaching hospital in Spain. Data were collected (see Chapter 3) from 500 dogs and outcome was available for all 489 dogs; BCS change was recorded for a total of 445 dogs; and dogs were weighed by the hospitalization ward staff at discharge for 358 animals.

A detailed description of dependent and independent variables is presented in tables 4.1 and 4.2. The median age of the dogs was 6 years old (range: 2 months – 17 years) and the gender distribution was: 149 (30.5%) entire females, 104 (21.3%) spayed females, 193 (39.5%) entiremales, and 43 (8.8%) neutered males. The mean iBW and iBCS ± the standard deviation were 15.7 ± 12.5 kg and 5 ± 0.9 respectively.

Variable	n	Mean	SD[a]	Median	Minimum	Maximum
Dependent variables						
Body Weight Change, kg	358	-0.2	0.5	-0.1	-2.2	2.2
Body Condition Score change	445	-0.1	0.4	0	-2	2
Independent variables						
Age, years	481	6	4.3	6	0.16	17
Initial Body Weight, kg	489	15.7	12.5	12	0.4	75
Initial Body Condition Score	470	5	0.9	5	1	8
Initial Muscle Condition Score	470	3	0.6	3	0	3
Energy intake, %RER	487	34.5	36.7	23.9	0	210.8
Hospitalization length, days	489	4.1	2.8	3	1	20

Table 4.1. Descriptive statistics for continuous dependent and independent variables for the hospitalized dogs. [a] SD = Standard deviation.

Variable	n	Category: Frequency (percentage)
Dependent		
Outcome	489	Discharge: 453 (92.6%) Death: 36 (7.4%)
Independent		
Sex	488	Entire Female: 149 (30.5%) Entire Male: 192 (39.4%) Spayed Female: 104 (21.3%) Neutered Male: 43 (8.8%)
Physical status score	470	1: 67 (14.3%) 2: 86 (18.3%) 3: 180 (38.3%) 4: 130 (27.6%) 5: 7 (1.5%)
Service in charge of the patient	482	Surgery: 22 (4.6%) Internal Medicine: 176 (36.5%) Neurology: 144 (29.9%) Ophthalmology: 46 (9.5%) Traumatology: 21 (4.4%) Emergency and Critical Care: 73 (15.1%)
Fasting ordered by clinician	488	Yes: 152 (31.1%) No: 336 (68.9%)
Nutritional intervention	489	Yes: 152 (31.1%) No: 337 (68.9%)
Anorexia at admission	473	Yes: 153 (32.3%) No: 320 (67.7%)
Vomiting at admission	482	Yes: 79 (16.4%) No: 403 (83.6%)
Diarrhoea at admission	482	Yes: 40 (8.3%) No: 442 (91.7%)

Table 4.2. Descriptive statistics for categorical dependent and independent variables.

Regarding the nutritional status of the dogs, 77% of the hospitalized dogs maintained their BW during hospitalization, 16% lost BW and only 7% increased it. Gain or loss of BW was defined as a change of at least 5% from the patient's iBW. Similarly, most dogs (78.2%) maintained their BCS during hospitalization, while 18.4% lost, and 3.4% gained BCS. The median EI of hospitalized dogs was 23.9% of their RER ranging from 0 to 211%. Most of the dogs (52.6%) consumed less than 25% of their RER, whereas 22.4% consumed between 25 and 50%, and 18.2% consumed between 50 and 100%. Only 6.8% of the dogs consumed their RER or more. Therefore, most hospitalized dogs did not meet their energy requirements. Hospitalization ranged from 1 to 20 days with a median value of 3 days and 92.6% of the animals were discharged alive. The details for the distribution of patients within PSS categories and clinical services and the proportion of animals with anorexia, vomiting, diarrhea, fasting and nutritional intervention are presented in table 4.2. Table 4.3 summarizes the associations between each risk factor and the dependent variables. Sex and diarrhea did not show association with any of the dependent variables. EI, HL, and PSS showed associations with the three dependent variables. The rest of covariates showed associations with 1 or 2 of the dependent variables.

Variable	Change of [a]BCS Mean+/- SE[c]	Change of [b]BW Mean+/-SE[c]	Outcome Death/Discharge, (%)[d]
Sex			
Entire Female	-0.10 +/- 0.02	-0.16 +/- 0.05	13/136 (8.7%)
Entire Male	-0.12 +/- 0.03	-0.14 +/- 0.05	11/181 (5.7%)
Spayed Female	-0.06 +/- 0.03	-0.08 +/- 0.05	6/98 (5.8%)
Neutered Male	-0.11 +/- 0.04	-0.23 +/- 0.12	6/37 (14.0%)
p-value	P = 0.603	P = 0.886	P = 0.271
Physical status score			
1	-0.02 +/- 0.02	0.01 +/- 0.07	2/65 (3.0%)
2	0.01 +/- 0.04	-0.10 +/- 0.08	4/82 (4.7%)
3	-0.14 +/- 0.04	-0.13 +/- 0.04	11/169 (6.1%)
4	-0.14 +/- 0.04	-0.24 +/- 0.05	13/117 (10.0%)
5	-0.17 +/- 0.11	-0.13 +/- 0.08	3/4 (42.8%)
p-value	P = 0.003	P = 0.054	P < 0.001
Service in charge of patient			
Surgery	-0.11 +/- 0.05	0.03 +/- 0.23	2/20 (9.1%)
Internal Medicine	-0.15 +/- 0.03	-0.09 +/- 0.05	19/157 (10.8%)
Neurology	-0.12 +/- 0.03	-0.22 +/- 0.04	7/137 (4.9%)
Ophthalmology	0.03 +/- 0.06	-0.05 +/- 0.06	1/45 (2.2%)
Traumatology	0.02 +/- 0.06	-0.14 +/- 0.06	0/21 (0.0%)
Emergency and Critical Care	-0.08 +/- 0.03	-0.21 +/- 0.08	6/67 (8.2%)
p-value	P = 0.032	P < 0.001	P = 0.208
Fasting ordered by clinician			
Yes	-0.12 +/- 0.02	-0.22 +/- 0.05	30/306 (8.9%)
No	-0.07 +/- 0.03	-0.16 +/- 0.08	6/146 (3.9%)
p-value	P = 0.140	P = 0.383	P = 0.002
Nutritional intervention			
Yes	-0.07 +/- 0.02	-0.16 +/-0.03	10/142 (6.6%)
No	-0.17 +/- 0.03	-0.09 +/- 0.05	26/311 (7.7%)
p-value	P = 0.009	P = 0.739	P = 0.795
Anorexia at admission			
Yes	-0.08 +/- 0.02	-0.13 +/- 0.03	25/128 (16.3%)
No	-0.14 +/- 0.04	-0.12 +/- 0.06	8/312 (2.5%)
p-value	P = 0.134	P = 0.926	P < 0.001
Vomiting at admission			
Yes	-0.21 +/- 0.06	-0.15 +/- 0.03	5/74 (6.3%)
No	-0.08 +/- 0.02	-0.14 +/- 0.07	31/372 (7.7%)
p-value	P = 0.004	P = 0.082	P = 0.407
Diarrhoea at admission			
Yes	-0.14 +/- 0.09	-0.15 +/- 0.03	32/36 (47.0%)
No	-0.10 +/- 0.02	-0.06 +/- 0.09	4/410 (9.7%)
p-value	P = 0.454	P = 0.498	P = 0.567

Table 4.3. Effects of the studied categorical risk factors for each of the dependent variables using univariable analysis. [a] BCS: body condition score. [b] BW: body weight. [c] SE= Standard error. [d] Indicate the percentage of deaths for every category of each independent variable.

The multivariable analysis (table 4.4) showed that older patients (P = 0.041), higher iBCS (P < 0.001) and vomiting at admission (P = 0.019) were associated to more severe BCS loss during hospitalization. There was also an interaction between HL and EI (P < 0.001) showing that a higher EI was associated with less BCS loss but only for HL longer than 3 days (figure 4.1).

	Estimate	[a] SE	p-value
ΔBCS (n=445)			
Intercept	0.4970	0.0936	<0.001
Hospitalization length (days)	-0.0820	0.0092	<0.001
Energy Intake (%RER)	-0.0017	0.0006	0.007
Age	-0.0074	0.0036	0.041
Initial BCS	-0.0562	0.0165	<0.001
Vomiting at admission	-0.0973	0.0411	0.019
Hospitalization length (days)* Energy Intake (%RER)	0.0007	0.0001	<0.001
ΔBW (n=358)			
Intercept	-0.0229	0.0075	0.003
Hospitalization length (days)	-0.0035	0.0009	<0.001
Energy Intake (%RER)	0.0002	0.0007	0.008
Initial BW (Kg)	0.0008	0.0003	0.002
Vomiting at admission	0.0372	0.0128	0.004
Initial BW (Kg)*vomiting at admission	-0.0013	0.0059	0.033
OUTCOME (n=489)	[b] OR	95% CI [c]	
Initial BCS	0.39	0.22, 0.63	<0.001
Energy Intake (%RER)	0.95	0.92, 0.98	<0.001
Anorexia at admission	5.67	2.23, 15.47	<0.001
Hospitalization length (days)	1.19	0.96, 1.45	0.092

Table 4.4. Risk factors of the multivariable analysis for each dependent variable, body condition score change (ΔBCS), body weight change (ΔBW) and outcome. [a] SE= Standard error, [b] OR= Odds ratio; for continuous variables the OR indicate variation per unit, [c] CI= Confidence interval.

Vomiting at admission, iBWand HL affected also BW change. Longer HL was associated with a greater loss of BW during hospitalization (P < 0.001). An interaction between iBW and vomiting (P = 0.033) was described, showing that vomiting was a risk factor for greater BW loss but mainly in heavier dogs.

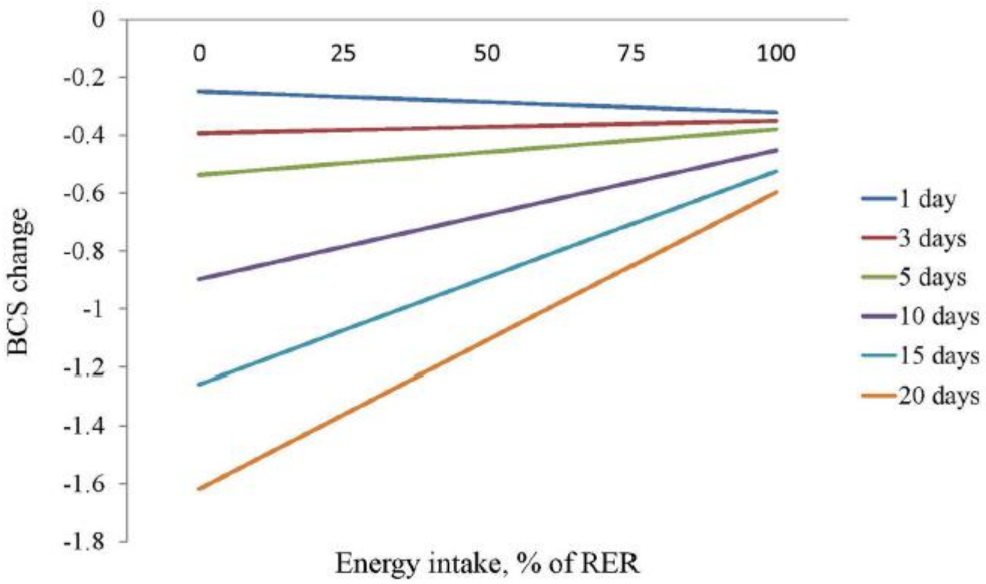

Figure 4.1. Estimation of the effect of the energy intake, measured as percentage of resting energy requirements, on BCS of dogs with different hospitalization lengths.

Finally, the variables associated with outcome were iBCS, EI, anorexia at admission, and HL (table 4.4). A higher iBCS and EI were related to lower odds of dying. In particular, the odds of dying were 61% lower for the fattier dog when 2 dogs differed in 1 unit of iBCS ($P < 0.001$; OR 0.39, 95% CI: 0.22 to 0.63) and were 5% lower when 2 dogs differed in 1% of EI ($P < 0.001$; OR 0.95, 95% CI: 0.92 to 0.98). On the other hand anorexia at admission and longer HL were related to higher odds of dying. Dogs reporting anorexia at admission were at 5.67 greater odds of dying than those not presenting it ($P < 0.001$; OR 5.67, 95% CI: 2.23 to 15.47) and a dog was at 1.19 greater odds of dying than a dog with a HL 1 day shorter ($P = 0.092$; OR 1.19, 95% CI: 0.96 to 1.45).

4.3. Discussion

There is a need to increase the body of knowledge in nutrition of hospitalized dogs and develop adequate protocols (Chan &Freeman 2006). The present study builds on the results of the only 3 studies available in this area (Remillard et al., 2001; Chandler at al., 2004; Brunetto et al., 2010) adding new risk factors of high interest, i.e. the presence of anorexia, vomiting and diarrhea at admission, and using a larger sample size. To the authors' knowledge, this is the largest prospective study assessing the prevalence of undernutrition and its risk factors in hospitalized dogs.

The present study assessed undernutrition in two ways: change of BCS and relative change of BW. We used both measures because BW can be rapidly affected by other aspects besides nutrition (such as fluid changes) and BCS is a much more consistent measure over short periods of time. It is estimated that there needs to be a 10-15% change in BW to see a change in one BCS unit (Laflamme, 1997). If we consider loss of more than 5% of BW and loss of BCS as undernutrition, the prevalence of undernourished dogs during hospitalization in this study was close to 20%. Brunetto et al. (2010) reported similar results; using BCS change, the prevalence of undernourished dogs was around 20%. However they reported 46 % prevalence using BW change, a higher proportion than in the present study, probably because they considered 2% as their cut-off value for a significant change in BW. If we apply such cut-off to the present study the percentage of undernourished dogs is almost 40%, however the authors consider that 2% may be too low of a cut-off because such variation may be the consequence of changes in hydration or meals.

Regarding the EI, 96% of the dogs did not meet their estimated energy requirement. This suggests that most of the hospitalized population were at risk of undernutrition and might have resulted in BW and BCS losses with longer HL. Previous studies found lower percentages; 65% for (Brunetto et al., 2010) and 73% for (Remillard et al., 2001), respectively. In the case of Brunetto et al. the proportion of animals gaining weight was also higher than in our case (40 vs.7%), which might be related to the higher number of animals that met their estimated energy requirements. The difference with Remillard et al. (2001) could be due to a difference in experimental units. We used the average EI of all the hospitalization period while Remillard et al. used the daily EI per dog. Dogs that had an average negative energy balance during the hospitalization period may actually meet their requirements some of the days.

The undernutrition risk factors identified in this study were consistent within the different undernutrition estimators. EI and HL were significant in all three models and vomiting at admission and iBCS were significant in 2 models as shown in table 4.4.

As expected, EI was positively associated and HL negatively associated with BW and BCS change. There was an interaction between HL and EI, based on the results of the BCS model, showing that EI becomes critical in preventing loss of BCS in animals with HL longer than 3 days. Patients are able to maintain their body mass for a few days even facing anorexia, however NS would be needed in patients with expected

HL of 3 days or longer, as it has been proposed as a general rational rule in veterinary practice (Owen et al., 1979; Chan&Freeman 2006). We also found that

The EI was positively associated with a better outcome, a finding also reported by Brunetto et al. (2010) and Remillard et al. (2001) as well as in human medicine (Calleja et al., 2014; Lainscak et al., 2014; Lew et al., 2016;). We did not find an association between PSS and BW or BCS change or outcome, which suggests that the protective effect of EI is not associated with disease severity. However, the small number of animals that died or were euthanized, plus the lack of a standardized objective severity index (King et al., 2001) in our study limits the interpretation of these findings.

An association was found between iBCS and BCS change during hospitalization. Heavier dogs at admission lost more BCS than did thin dogs. We hypothesize that veterinarians may pay more attention to the NS of thin animals compared to heavier dogs, because they appear to be at immediate nutritional risk. However, BW change, which is a more objective measure, was not related to iBCS. Despite this finding, iBCS was positively correlated with discharge as also reported (Brunetto et al., 2010). Rather than reflecting a protective effect of obesity, we believe this finding supports that underweight dogs are at higher risk of dying than dogs with adequate body stores. In some cases, this lower BCS may be related to the course of disease before admission and here a more accurate measure of disease severity may be needed.

Vomiting at admission was also associated with a deterioration of nutritional status measured as BCS and BW change. In the case of BW change, vomit had an interaction with iBW, showing differences in vomiting effects on BW depending on dog size. In the present study, iBW was included as a measure of the size of the animal to avoid loss of information by categorization. In a closer look to the relationship between iBW and BW change, dogs heavier than 35 kg at admission appeared to lose more weight during hospitalization, especially when vomiting was present. We hypothesize that the food amount offered by the hospitalization ward personnel was smaller in large dogs than in the small ones, especially if vomiting was their reason for hospitalization, or that a specific cause of admission was typical of this group. Unfortunately, our data cannot verify the hypothesis.

Future research should study the nutritional requirements of hospitalized dogs of extreme body size for a more accurate nutritional support.

Age was identified as a risk factor for undernutrition only for BCS change. Older dogs had a higher BCS loss than the younger patients. This could be due partly to the potential effect of aging on digestive physiology (Fahey et al., 2008), thus ultimately affecting nutrient digestibility (Weber et al., 2003). Nevertheless, several studies have failed to demonstrate differences in macronutrient digestibility between young and old healthy dogs (Burkholder 1999, Swanson et al., 2004) and some have even reported an increased nutrient apparent fecal digestibility in older dogs (Sheffy et al., 1985). Higher severity of disease or comorbidities could be another explanation for the greater BCS loss in older dogs however; our data cannot confirm this hypothesis either.

In this sense, older dogs may suffer of frailty making them more vulnerable to stressors or disease than younger dogs (Hua et al., 2016). Some of the risk factors included in this study such as anorexia or iBCS are related to frailty and this concept could easily be included in future research by using one of the numerous available tools.

Finally, anorexia at admission was associated with higher risk of death, which may be related to its high correlation to severity of disease. During the statistical analysis, anorexia had a better correlation to outcome than severity, which is why it was kept in the model. It seems clear that anorexia is a main risk factor for death, reinforcing the need of nutritional support in those patients during the hospitalization period.

The clinical service in charge of the patient was initially included in the study as a representation of the nature of the type illness. However this variable had multiple associations to other risk factors and was finally not included in the models. The specific protocols used in each clinical service can be very different between hospitals and these results may not be fully valid for other hospitals. These protocols are also a potential source of bias because some departments may be more likely to recommend nutritional support than others.

CHAPTER 5. PREVALENCE AND RISK FACTORS FOR UNDERNUTRITION IN HOSPITALIZED CATS AT A VETERINARY TEACHING HOSPITAL IN SPAIN

5.1. Introduction

The risk of undernutrition (defined as involuntary loss of BCS and/or BW or decreased EI) reported in hospitalized dogs and cats stresses the potential importance of the nutritional intervention in these patients (Remillard et al., 2001; Brunetto et al., 2010; Molina et al., 2018).

There is a paucity of data available describing risk factors for undernutrition in hospitalized cats (Chan and Freeman, 2006; Larsen, 2012) and a lack of standarized protcols to identidy and treat malnutrition. Although retrospective (Lainscak et al., 2014; Ordoñez et al., 2013) and prospective (Calleja et al., 2014; Tsaousi et al., 2014) studies in human patients have reported that an adequate nutritional status and NS support are effective in improving the hospitalized patient status and reducing the HL, there is a lack of research backing their importance in cats. The present study (see Chapter 4) showed the effect of an adequate EI on outcome in a canine population of hospitalized patients.

A retrospective study in cats fed with central PN (Pyle et al., 2004) reported a higher mortality rate in the cats maintained that had multiple concurrent diseases associated with a poor prognosis compared to cats with milder disease; and indicators of poor prognosis related to the nutritional status included a history of weight loss and hypoalbuminemia (other risk factors included hyperglycemia at 24 hours following PN administration and chronic renal failure). One study with cats with pancreatitis (Nivy et al. 2018) found that anorexia during hospitalization was associated with a negative outcome.

This study aims to evaluate the prevalence of undernutrition in hospitalized cats, estimated with the proportion of RER met by EI, BW and BCS; and to determine the risk factors that affect their nutritional status (BCS, BW change) and their association with the final outcome.

5.2. Results

Data were collected prospectively during 12 months from hospitalized cats with a HL longer than 24 hours in a veterinary teaching hospital in Spain (see Chapter 3). Data was collected from 120 hospitalized cats and outcome was available for all of them; BCS (9-point scale) was recorded for 112 cats, weight at discharge for 101 cats, and age for 111 cats. A detailed description of dependent and independent variables is presented in tables 5.1 and 5.2.

Variable	N	Mean	SD	Median	Minimum	Maximum
Dependent variables						
Body weight change, kg	101	-0.05	0.22	0.00	-0.80	0.70
Body Condition Score change	112	-0.09	0.36	0.00	-2	1
Independent variables						
Age, years	111	6.7	4.9	6.0	0.16	16
Initial Body Weight, kg	120	3.7	1.3	3.70	0.64	8.4
Initial Body Condition Score	120	4.3	1.2	4	2	8
Initial Muscle Condition Score	120	2.3	0.8	2	1	3
Energy intake, %RER	120	33.8	40.6	19.8	0	186.2
Hospitalization length, days	120	3.9	2.4	3	2	15

Table 5.1. Descriptive statistics for continuous dependent and independent variables for the hospitalized cats. SD = Standard deviation.

The median age of the cats was 6 years old, ranging from 2 months to 16 years. Gender distribution was: 17.5% entire females, 33.3% spayed females, 22.5% entire males, and 26.7% neutered males. The mean iBW and iBCS were 3.7 (+/- 1.3) kg and 4.3 (+/- 1.2) respectively.

Regarding the nutritional status of the cats, the median BCS at admission was 4/9, which is considered underweight. The percentage of cats with an iBCS below 5 was 62.7%. During hospitalization, 61.4% of the hospitalized cats maintained their BW, 25.7% lost BW and only 12.9% increased it. Gain or loss of BW was defined as a change of at least 5% from the patient's iBW. Similarly, most cats (78.6%) maintained their BCS during hospitalization, while 17.0% lost, and 4.4% gained BCS. From the ones that gained BCS during the hospitalization period, around half of the cats gained 0.5 points, and the other half 1 point in the BCS scale score. More than half of the cats (54.2%) consumed less than 25% of their RER, whereas 24.9% consumed between 25 and 50%, and 11.7% consumed between 50 and 100%. Only 9.2% of the cats consumed their RER or more. Consequently, 90.8% of the cats did not meet their estimated energy requirements. The median EI, during the complete hospitalization period, was 19.8% of their RER, ranging from 0 to 186.2%. Hospitalization ranged from 2 to 15 days with a median value of 3 days and 90.4% of the animals were discharged alive. The details for the distribution of patients within PSS categories and clinical services and the proportion of animals with anorexia, vomiting, diarrhoea, fasting and nutritional intervention are shown in table 5.2.

Variable	N	Category: Frequency (percentage)	
Dependent			
Outcome	120	Discharge: 108 (90.0%) Death: 12 (10.0%)	
Independent			
Sex	120	Entire Female: 21 (17.5%) Entire Male: 27 (22.5%) Spayed Female: 40 (33.3%) Neutered Male: 32 (26.7%)	
Physical status score	117	1: 9 (7.7%) 2: 17 (14.5%) 3: 49 (41.9%) 4: 38 (32.5%) 5: 4 (3.4%)	
Service in charge of the patient	120	Surgery: 10 (8.3%) Internal Medicine: 69 (57.5%) Neurology: 6 (5.0%) Ophthalmology: 6 (5.0%) Traumatology: 6 (5.0%) Emergency and Critical Care: 23 (19.2%)	
Fasting ordered by clinician	120	Yes: 71 (59.2%)	No: 49 (40.8%)
Nutritional intervention	116	Yes: 44 (37.9%)	No: 72 (62.1%)
Anorexia at admission	115	Yes: 67 (58.3%)	No: 48 (41.7%)
Weight loss pre-admission	114	Yes: 56 (49.1%)	No: 58 (50.9%)
Vomiting at admission	120	Yes: 20 (16.7%)	No: 100 (83.3%)
Diarrhoea at admission	120	Yes: 10 (8.3%)	No: 110 (91.7%)

Table 5.2. Descriptive statistics for categorical dependent and independent variables in cats.

Table 5.3 summarizes the associations between each risk factor analysed and the dependent variables. Regarding BCS change, diarrhoea at admission (P=0.026), was associated with higher BCS loss on the univariate analysis. The multivariable analysis (table 5.4) showed that a higher iBCS was associated with a greater BCS loss during hospitalization (P=0.04). In this analysis, HL trended towards significance (P=0.075), suggesting that a longer HL could be potentially associated with BCS loss.

Variable	Change of [a]BCS Mean+/- SE[c]	Change of [b]BW Mean+/-SE[c]	Outcome Death/Discharge, (%)[d]
Sex			
Entire Female	-0.08 +/- 0.09	-0.004 +/- 0.014	3/18 (14.3%)
Entire Male	-0.07 +/- 0.07	-0.008 +/- 0.013	2/25 (7.4%)
Spayed Female	-0.09 +/- 0.06	-0.004 +/- 0.011	5/35 (12.5%)
Neutered Male	-0.11 +/- 0.07	-0.031 +/- 0.012	2/30 (6.3%)
p-value	P = 0.989	P = 0.332	P = 0.704
Physical status score			
1	-0.06 +/- 0.13	-0.016 +/- 0.024	0/9 (0.0%)
2	-0.10 +/- 0.09	-0.003 +/- 0.018	1/16 (5.9%)
3	-0.10 +/- 0.05	-0.014 +/- 0.010	4/45 (8.2%)
4	-0.09 +/- 0.06	-0.012 +/- 0.011	7/31 (18.4%)
5	0.00 +/- 0.21	-0.000 +/- 0.064	0/4 (0.0%)
p-value	P = 0.992	P = 0.985	P = 0.306
Department in charge of patient			
Surgery	-0.06 +/- 0.12	-0.016 +/- 0.020	0/10 (0.0%)
Internal Medicine	-0.09 +/- 0.05	-0.013 +/- 0.008	8/61 (11.6%)
Neurology	-0.20 +/- 0.16	-0.090 +/- 0.031	2/4 (33.3%)
Ophthalmology	-0.17 +/- 0.15	0.025 +/- 0.031	1/5 (16.7%)
Traumatology	-0.00 +/- 0.15	0.018 +/- 0.031	0/6 (0.0%)
Emergency and Critical Care	-0.07 +/- 0.08	-0.006 +/- 0.014	1/22 (4.3%)
p-value	P = 0.938	P = 0.118	P = 0.208
Fasting ordered by clinician			
Yes	-0.08 +/- 0.04	-0.003 +/- 0.010	3/44 (6.4%)
No	-0.10 +/- 0.05	-0.018 +/- 0.008	9/64 (12.3%)
p-value	P = 0.758	P = 0.236	P = 0.289
Nutritional intervention			
Yes	-0.11 +/- 0.06	-0.006 +/- 0.010	6/38 (13.6%)
No	-0.07 +/- 0.04	-0.016 +/- 0.009	6/66 (8.3%)
p-value	P = 0.626	P = 0.464	P = 0.363
Anorexia at admission			
Yes	-0.10 +/- 0.04	-0.016 +/- 0.008	10/57 (14.9%)
No	-0.08 +/- 0.05	-0.003 +/- 0.010	2/46 (4.2%)
p-value	P = 0.752	P = 0.334	P = 0.063
Weight loss pre-admission			
Yes	-0.09 +/- 0.05	-0.020 +/- 0.009	9/47 (16.1%)
No	-0.09 +/- 0.05	-0.004 +/- 0.009	3/55 (5.2%)
p-value	P = 0.942	P = 0.207	P = 0.058
Vomiting at admission			
Yes	-0.13 +/- 0.08	-0.021 +/- 0.014	4/16 (20.0%)
No	-0.08 +/- 0.04	-0.010 +/- 0.007	8/92 (8.0%)
p-value	P = 0.573	P = 0.509	P = 0.103
Diarrhoea at admission			
Yes	0.15 +/- 0.11	-0.011 +/- 0.020	1/9 (10.0%)
No	-0.11 +/- 0.03	-0.012 +/- 0.007	11/99 (10.0%)
p-value	P = 0.026	P = 0.950	P = 0.999

Table 5.3. Effects of the studied categorical risk factors for each of the dependent variables using univariable analysis (cats). [a] BCS: body condition score. [b] BW: body weight. [c] SE= Standard error. [d] Indicate the percentage of deaths for every category of each independent variable.

As for BW change, a longer hospitalization period (P<0.001) was associated with higher BW loss (table 5.4). Change in BW was also affected by the EI (P=0.006), where a higher EI was associated with weight stability.

Finally, regarding outcome, a lower EI during hospitalization was associated with higher odds of dying (P=0.05; OR 1.19, 95% CI: 1 to 1.08). Weight loss at the moment of admission was also associated with the outcome: cats that were reportedly weight stable had lower odds of dying (P<0.001; OR 0.29, 95% CI: 0.07 to 1.16).

	Estimate	[a] SE	p-value
BCS change (n = 112)			
Intercept	0.2526	0.1356	0.065
Hospitalization length (days)	-0.0243	0.0135	0.075
Initial BCS	-0.0575	0.0277	0.040
BW change (n = 101)			
Intercept	---	---	>0.500
Hospitalization length (days)	-0.0061	0.0016	<0.001
Energy Intake (%RER)	0.0004	0.0001	0.006
OUTCOME (n = 111)	[b] OR	95% CI [c]	
Weight loss pre-admission	0.29	0.07, 1.16	<0.001
Energy Intake (%RER)	1.04	1.00, 1.08	0.050

Table 5.4. Risk factors of the multivariable analysis for each dependent variable; body condition score change, body weight change and outcome (survival). [a] SE= Standard error. [b] OR= Odds ratio; for continuous variables the OR indicate variation per unit. [c] CI= Confidence interval.

5.3. Discussion

The scientific data available about the nutritional status of hospitalized cats is limited. There are some studies in the area (Pyle et al., 2004; Chandler and Gunn-Moore, 2004; Brunetto et al., 2010; Nivy et al., 2018), but to the authors' knowledge, this is the largest prospective study assessing the prevalence of undernutrition and its risk factors in hospitalized cats. The study from Pyle et al (2004) is retrospective and focuses only on risk factors for outcome in cats receiving PN. The study of Chandler and Gunn-Moore (2004) is prospective, includes 60 cats, but does not look at BW and BCS evolution during hospitalization, and they only look at parameters on admission (BCS, reported weight loss and food intake, and serum albumin). The study of Brunetto et al (2010) is the most complete, and looks at BCS, BW, EI with the limitations of being retrospective and presenting the data for dogs (n=467) and cats (n=55) together. Finally, Nivy et al (2018) looked at the prognostic factors of feline pancreatitis. Even though they looked at some variables related to nutritional status (anorexia during hospitalization and PN provision), they did not assess BW, BCS or EI.

Regarding EI, 90.8% of the cats did not meet their estimated energy requirement and the median EI was only 19.8% of their RER during hospitalization. This suggests that most of the hospitalized population were at risk of undernutrition and might have suffered further BW and BCS losses with longer HL, which was a median of 3 days. In the study of Brunetto et al. (2010), 42.5% of the patients did not meet their RER, which is much lower percentage compared to the present study. This can be due to different statistical unit used in the study as in that study dogs and cats were considered (together) as the statistical unit, meanwhile in our study cats were considered independently. Another potential explanation is the feeding management of the patients: in their study all cats (and dogs) received an assessment by the Nutrition Service and had a feeding plan established, as opposed to our study, where NS was only initiated if requested by the admitting clinical service. No other repported data of EI during hospitalization in cats is available.

Despite the low EI, most cats managed to maintain a stable BW and BCS. Accoridng to BCS and BW losses, the prevalence of undernutrition in our population was 17.0-25.7%. The values differ because BW is faster indicator of negative energy balance, since it is estimated that a BW change of 10-15% has to be noted in order to observe a variation in the 9-point scale BCS (Laflamme, 1997). However, BW can also be affected by other factors, like hydration status and, to minimize this error, in the present sudy only fluctuations of 5% or more of BW were considered significant. Chandler and Gunn-Moore (2004) did not look at BW and BCS changes during hospitalization, but on admission 53.3% of their feline patients had a BCS <5 on the 9-point scale, which is considered underweight; and 56.7% of cats had reported weight loss. In our study, 62,7% of cats had a BCS below 5, and 49.1% had reported weight loss at admission, which are comparable. Brunetto et al (2010) report that 19.3% of their population presented a low BCS, but those included dogs and cats.

The difference might also be institutional and relate to the type of diseases the hospitalized patients presented. They did look at BW changes in their study and, despite reporting higher EI, the percentage of patients (canine and feline) that lost weight was higher than our study at 46.6%. This can be attributed to the fact that they used a 2% BW variation from iBW, whereas in the current study we used 5%. If we used a cut-off of 2% with our data, the proportion of cats with weight loss would increase to 34.1%.

The main undernutrition (loss of BW and BCS) risk factors identified in this study were iBCS, EI, and HL. Diarrhoea, which can result in nutrient and energy losses, was also associated to BW loss, but only on the univariate analysis. The iBCS was significant in the BCS model, but not the BW. Heavier cats at admission lost more BCS than did thin cats, which could be due to veterinarians being more proactive with NS in thin animals, because they appear to be at a more immediate nutritional risk. Another possibility relates to the fact that BCS is a subjective measure, and the operator might detect more differences in cats wth higher BCS than in underweight cats. Energy intake was positively, and HL negatively, associated to BW change. Greater EI was associated with a lower BW change, what means that patients that consumed more energy had a more stable BW during hospitalization, as expected. Those cats that were hospitalized during longer periods showed further loss of BW. In our model, EI was only significant for BW change, and not BCS, which can be explained by the fact that BCS changes are slower to respond than BW changes.

Regarding outcome, EI and weight loss at admission were associated with outcome as shown in table 5.4. A lower EI during hospitalization was associated with higher probabilities of having a negative outcome (death). This result agrees with Nivy et al. (2018), where very low EI (reported only as “anorexia during hospitalization”) was more frequently seen in nonsurvivors cats with pancreatitis. This is also in agreement with Brunetto et al. (2010), where EI was positively associated with hospital discharge in dogs and cats. These findings were also reported in human medicine (Calleja et al., 2014; Lainscak et al., 2014; Lew et al., 2016). An inadequate nutritional status assessed with Subjective Global Assessment (SGA, anthropometry, and biochemical parameters was related with higher HL (Calleja et al., 2014; Lew et al. 2016). Fatal outcomes were seen in the study of Lainscak et al. (2014) when the EI was dramatically decreased (nothing eaten or not allowed to eat). Malnutrition, diagnosed by nutrition assessments (SGA), was also associated with a higer risk of hospital mortality (Lew et al. 2016).

Weight loss at admission was associated with a higher risk of death. Similar results were reported in the retrospective study of Pyle et al. (2004) with cats undergoing central PN. History of weight loss (as well as hyperglycemia at 24 hours following PN administration, hypoalbuminemia, and chronic renal failure), another indicator of malnutrition, was related with poor prognosis in that study.

The severity of the disease, measured as PSS, did not have an effect on the BW and BCS change or on the outcome in the present study, and no association was found between EI and PSS. Therefore, the positive association between EI and nutritional status and outcome is potentially independent of the severity of the disease. This suggests that having an adequate nutritional plan to achieve and adequate EI should always be a priority independently of disease severity. However, the small number of animals that died or were euthanized, plus the lack of a standardized objective severity index (King et al., 2001) in our study limits the interpretation of these findings. Moreover, nutritional intervention was not significant in any of our models, which can be due to a small sample size and the small number of patients that received assisted feeding.

The clinical service in charge of the patient was initially included in the study as a representation of the nature of the type illness. However this variable had multiple associations to other risk factors and was finally not included in the models. The specific protocols used in each clinical service can be very different between hospitals and these results may not be fully valid for other hospitals. These protocols are also a potential source of bias because some departments may be more likely to recommend nutritional support than others.

The main limitations of the present study were the low number of patients who died or were euthanized (10%), the limited number of enteral and parenteral nutrition support cases, the lack of an objective measure of severity (such as APPLE: acute patient physiologic and laboratory evaluation) and the fact that this is a single center study. The number of cats that die or receive nutritional support may differ between hospitals due to differences in protocols and in the type of animals that are hospitalized. For example, Brunetto et al. (Brunetto 2010) reported a similar mortality (7%) to the current study, while Nivy et al. (2018) and Pyle et al. (2004) reported mortalities of 22.3% and 52% respectively. However, the patients in Nivy et al. (2018) were only cats with pancreatitis patients, and the severity of this disease can be higher than others in the general population (Watson., 2015). The population in the Pyle et al (2004) study was receiving PN, and the majority of the animals that required this type of nutritional intervention where diagnosed with pancreatitis (Chan et al., 2002; Queau et al., 2011). Moreover, according some studies (Chan et al., 2002; Queau et al., 2011), parenteral nutrition tends to be used in patients with higher severity index, as they are not capable to tolerate the oral or tube feeding. Therefore, the high mortality in the study of Pyle et al. (2004) may be due to the selected population. Although comparison is not possible, the present study includes patients with a wider range of PSS scores with expected better outcomes. In any case, multi-centric studies would provide a higher sample size and less bias and would be of great interest.

CHAPTER 6. GENERAL DISCUSSION

Our study reported the nutritonal status during hospitalization of dogs and cats. A larger number of dogs (n=500) were hospitalized during the study period, compared with cats (n=120), even though the recruitment window was larger in cats (12 months) vs dogs (9 months). In Spain, the dog is the preferred pet to have at home: 30.6% of Spanish households have a dog, while only 13.3% have a cat (Grupo AeI, 2019). Another reason that can explain this large difference is that cats can get very stressed in the hospitalization ward (Grupo AeI, 2019), and, as a consequence, hospitalization is less common than in dogs. Owners can be more reluctant to bring the cat to the hospital (Habacher et al., 2010) to avoid the stressful situation for the cat and for themselves. In Spain, 85% of the households that have a dog have visited the vet in the last year, and this number idecrease to 66% for cat households (Grupo AeI, 2019). Regarding sexual status, 60.0% of cats and 30.1% of dogs were spayed or neutered, in alignment with the country statistics where 79.7% of cats and 48.6% of dogs are desexed (Grupo AeI, 2019).

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The present work highlights the high proportion of hospitalized dogs and cats not meeting their estimated energy requirement during the hospitalization period (on average, 93.2% and 90.8%, respectively) in a veterinary teaching hospital setting. These values are higher than the 73.2% reported in a canine population (Remillard et al, 2001) in a multi-centric study, measured on a daily basis; and higher than the 65% average reported by Brunetto et al (2010) in a mixed canine and feline population. However, Brunetto used the mainteinance energy requirement as goal instead of RER. When using RER, the percentage of patients nor meeting energy needs was lower at 42.5%. The differences can be due to differing hospital protocols: for example, in the study of Brunetto et al (2010) the food was offered twice per day, and if the animal was not consuming their MER after 48 hours, and the orced feeding was unsuccessful, assited enteral nutrition was placed. It can also be explained by different patient population and reasons for admission, but, in all cases, the proportion of patients not reaching their estimated RER is high. This suggests that hospitalized patients are at risk of undernutrition wich, our study suggests, can affect outcome.

Incidence of undernutrition in the present work, defined as a loss of ≥ 5% BW or loss of BCS during hospitalization, was 16.0-18.4% among hospitalized dogs, and 17.0-25.7% among hospitalized cats. Those findings agree with what was reported in the prospective study in humans by Tsaousi et al., 2014, where they described a prevalence of 21.4% in acute hospital care setting. They measured this using a Malnutrition Universal Screening Tool, based on low BMI or recent unintentional weight loss. Our results are lower than those reported by Brunetto et al (2010), that reported weight loss in 46.6% of their feline and canine hospitalized population in Brazil, but this can be due to the different cut-off for weight loss, which was 2%, compared to 5% in our study. They did not report changes in BCS and they did not separate the results from dogs and cats which complicates comparisons. No other studies in veterinary medicine report BW and BCS evolution during hospitalization.

If we define nutritional risk as the percentage of hospitalized dogs or cats consuming less than the 25% of their RER during hospitalization, the population at-risk in the present study is proportion is 52.6% in dogs, and 54% in cats. The percentage of patients where nutritional intervention was requested from the Nutrition Service was slightly higher in cats (37.9%) than in dogs (31.1%). In dogs, EI was also potentially affected by body size (figure 6.1). Larger dogs tended to eat a smaller percentage of their RER compared to smaller ones. This could be the result of underestimation of needs for big dogs if a specific RER was not calculated in these cases and the amount was eyeballed.

Cats lost, on average more BW (25.7%) than dogs (16%), even though there was a similar population at-risk in both species. However, the patients that lost BCS was very similar (18.4 in dogs and 17.0 in cats), which is a more solid, although subjective and slow to respond, indicator of undernutrition. According to these results, we suggest that NS in hospitalized patients shares limitations and problems in human and veterinary medicine.

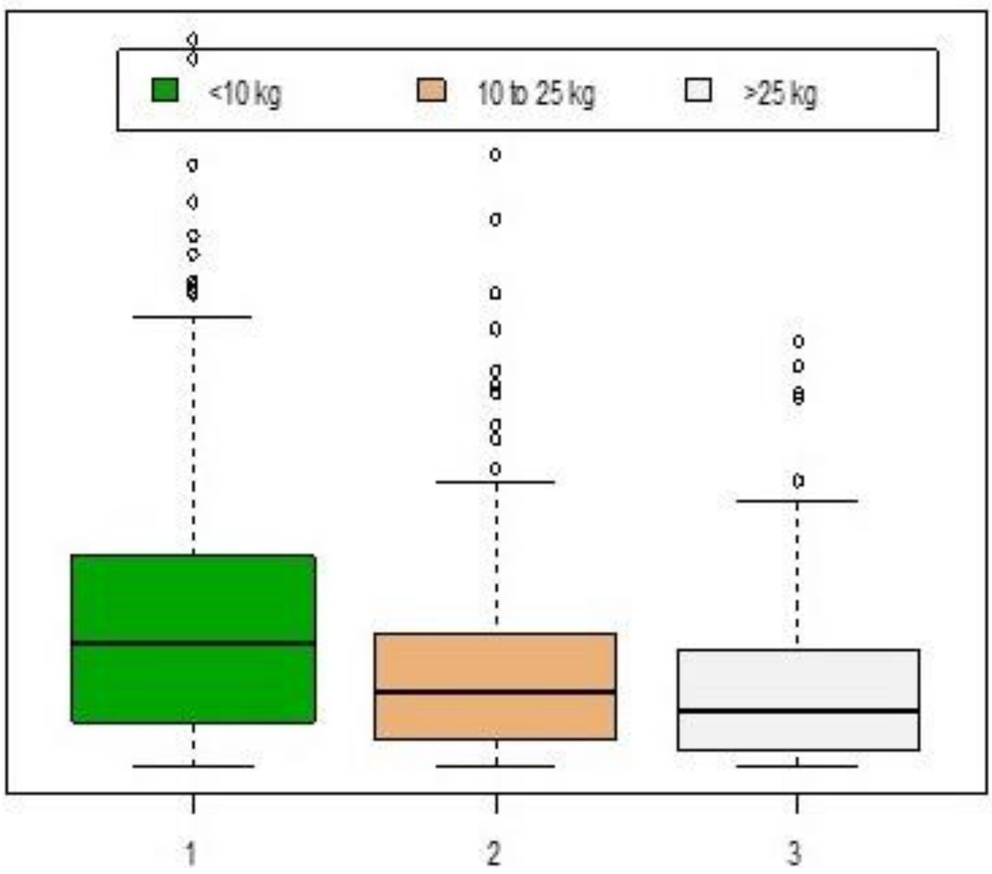

Figure 6.1. Relationship between body size and EI (as percentage of RER) in dogs.

The present study was performed in only one center where no standarized nutritional protocol for hospitalized patients was set up, and the Nutrition Service developed feeding plans only on request by the primary veterinarian oin the case. This lack of standarized procedure could have affected the nutritional status of our patients. For example, all patients in the study from Brunetto et al (2010) were assigned a feeding plan and they reported a higher percentage of patients meeting their RER. They do not report the percentag of patients eating <25% RER, so we cannot compare the populations at-risk in more detail. However, in our study, nutritional intervention was only significant for BCS change in dogs in the univariate analysis but was not a significant factor in any of our undernutrition models or in outcome for either species. A larger sample size and information for multiple centers will be needed to clarify the importance of specific NS in reducing undernutrition risk.

Food intake and, therfore, EI, can be affected by many reasons in hospitalized patients. In the present study, the feeding schedule was the same for dogs and cats. The veterinary technicians always offered food 3 times per day, always during the light hours and at the same time every day However, the feeding behaviour and physiology between cats and dogs is different and a species-specific approach could be beneficial. Feral cats are solitary hunters and use to seek small preys (mice, birds, etc.), while dogs used to hunt in pack and medium-sized to lare preys. In the studies done in laboratory conditions, dogs eat fewer, larger, and more variable sized meals than cats. Dogs can eat 1-2 meals per day (morning/evening for example), while cats tend to eat multiple times/day. Moreover, cats can eat during the light period as well as during the dark one, while dogs usually eat during the light period (NRC, 2006). The present study could not assess the effect of pain and stress on EI, BW or BCS, both of those could affect EI. Stress is a determinant factor that affects EI in hospitalized patients (Epstein et al., 2015) and hospitalization is a stressful situation in itself due to unknown environment, illness, unpleasant and painfull manipulations, and interactions with unknown humans. Future studies should investigate if a more customized approach to accommodate different feline and canine feding behaviour plus pain and stress management can positively affect EI and nutritional status.

One study in people (Barton et al., 2000) in a University hospital in the UK was reported a continuing weight-loss in hospitalized patients, which was suggested to be caused by the low EI of the patients. The hospital menu provided did meet nutritional requirements of the patients, but more than 40% of the food was refused, resulting in energy and protein intakes lower than the 80% of the recommendations. Similarly, we found that the amount offered to the animal could usually meet their requirements, but the food was refused in many cases. Remillard et al (2001) identified food refusal as the main reason to negative energy balance in dogs per day (44% of the cases). The same study also identified NPO as a reason for dogs not to meet their energy requirements on a daily basis (34% of the dog-days on negative energy balance). In our study, 31% of dogs and 59% of cats had initial NPO orders for a variety of reasons including the need for anaesthesia or diagnostic procedures. We did not analyze energy intake on a daily basis, rather we presented an average, therefore we cannot really compare our results, but NPO did not have an effect on malnutrition or outcome models in our study. This may be due to the fact that it was limited in time and had little effect on overall EI.

Regarding undernutrition risk factors, EI was positively associated, and HL negatively associated, with BW and BCS change in both species. As hypothesized, a higher provision of calories was associated with weight and body condition stability and decreased calorie intake was associated with weight loss. And patients with a longer HL had a more marked weight loss compared to patients with shorter hospitalization periods. According to our results, a dog has a higher risk of dying (1.19 greater odds) per each day of longer HL (P = 0.092; OR 1.19, 95% CI: 0.96 to 1.45). In canine patients, we found an interaction between HL and EI, which suggested that EI is strongly associated to BCS maintenance in patients with HL of 3 days or longer. This interaction was not found in feline patients, maybe due to the smaller sample size we had for this species. This result sugests that at-risk patients, particularly dogs, that do not meet their energy requirements (RER) are able to maintain their BCS during the first 3 days of hospitalization, but a decreased EI is associated with a reduction of BCS with longer hospitalization periods (see figure 4.1). The theoretical recommendation currently available in veterinary medicine recommends implementing assited nutrition after 3 days of anorexia (and 5 of hyporexia), prior to further compromise of their nutritional status (Chan and Freeman, 2006; Freeman et al., 2011). Our study confirm this approach, setting up the limit in 3 days, as from this day onwards the BCS loss is markedly increased. The study from Remillard et al (2001) showed that, of all dogs that did not meet their calorie goals, incomplete orders were responsible for a negative energy balance in almost a quarter of the days. Due to the prospective nature of the current study and the specific form used to collect the data, completeness of feeding orders could not be assessed without bias, therefore, it is unknown which percentage of the population in the present study received inadequate orders. All of this stresses the importanve, as previously mentioned, of having an initial complete dietary history plus adequate records of EI during hospitalization to help decide when the assisted nutrition should be implemented.

In both species, iBCS was correlated negatively with BCS change, meaning, dogs and cats with higher iBCS lost more body condition than thinner patients. We have mentioned before that a potential explanation is that patients with lower BCS might be considered at more immediate risk by the attending clinician and therefore shown a more proactive approach in regards to NS. Another possibility relates to the fact that BCS is a subjective measure, and the operator might detect more differences in patients with higher BCS than in underweight ones. The use of more objetive measures of body composition (rather than BCS) would have provided more accurate and reliable data, unfortunately, those methods were not available, due to cost and complexity.

Vomting was identified as a risk factor for undernutrition in dogs, using both BW and BCS, which could be related to higher nutrient and energy losses caused by this clinical sign. We did not identify this in cats, although the percentage of patients with vomiting at admission was similar in both species (16.4% in dogs and 16.7% in cats). This lack of effect could be explained by the small sample size in cats or to different characteristics of the process between the patients (frequency, volume, response to medication, etc). Diarrhoea, another clinical sign associated with energy losses, was identified as a risk factor in cats only in the univariate analysis, but not when included in the multivariate analysis.

Age was identified as a risk factor in dogs, where older patients showed more severe BCS loss during hospitalization. This has also been described in elderly human patients (Tsaousi et al., 2014). In this study, an impaired nutritional status in elderly hospitalized humans was identified as an independent predictor of prolonged HL and increased mortality. We would have expected the same result in cats, since it has been reported that the aging cat population has a higher incidence of underweight, loss of muscle mass and loss of BCS (Laflamme and Gunn-Moore, 2014) but did not see it, which could be again related to the small sample size or to a different senior population in our hospital compared to other institutions. There are no other studies in veterinary medicine that have assessed the effect of age on nutritional status and outcome in hospitalized patients.

Regarding the outcome, there are also similarities between human and veterinary medicine. The present study, the variables associated with outcome in dogs were iBCS, EI, anorexia at admission, and HL. In cats, the variables were EI and weight loss at admission.

In both species, EI during hospitalization affected both nutritional status and outcome, possibly independently of the severity status of the patient. In both populations, a lower EI was associated with higher odds of dying. Moreover, dogs that had reported anorexia at admission had 5.67 greater odds of dying than those not presenting it. In dogs, additionally, higher iBCS was associated with better outcome.

In particular, the odds of dying were 61% lower for heavier dogs, when 2 dogs differed in 1 BCS unit. Similar to our results, both Remillard et al (2001) and Brunetto et al (2010) reported an association of lower EI with worse outcome. As for BCS, even though Remillard et al (2201) did not find an effect of BCS on outcome, our results are similar to Brunetto et al (2010), who also identified lower BCS with a worse outcome in their mixed population of dogs and cats. This association could reflect a protective effect of obesity but we believe this shows that dogs with undernutrition are at higher risk of dying than dogs with adequate body stores. The set up of a proper nutritional intervention with the objective of increasing the animal EI should be in the primary list of the clinicians for managing any illness. However, we require further research in the form of interventional studies to evaluate the effect of NS on EI and outcome.

This effect of iBCS on outcome was not identified in cats, however, cats with reported weight loss at admission had higher odds of dying than those that did not, again supporting the importance of an adequate nutritional status to achieve success during hospitalization and disease. Weight loss is one of the key historical nutrition assessment indicators, which has been associated with long-term mortality in numerous human studies (Hiesmayr et al., 2009; Jensen et al., 2010). Clinical significance is determined both by the degree and duration of weight loss (Zekry et al., 2013). Therefore, the identification of history of weight loss is an important point, especially in feline medicine that should be addressed during the initial veterinary appointment. Recording weights at every appointment will help identify any concerning weight trends in our patients.

Nutritional status can affect outcome due to its importance for adequate immune system function (Satyaraj, 2011). Both nutrient provision and adequate immunity are essential to sustain life and to promote adequate recovery. Consequently, nutrient metabolism and immunity have co-evolved organ systems and signaling pathways. This close relationship means that chronic nutrient deficiencies or excesses can negatively impact immune health and consequently overall health (Satyaraj, 2019). Additional studies with a larger population of both dogs and cats, the use of more objetive measuires of body composition (rather than BCS) and a more accurate measure of severity to confirm the effect of body composition and EI on nutritional status and outcome in both species.

The PSS, our index of severity, was significant in dogs in the univariate analysis for both nutritional status and outcome, however, it did not have an effect on the multivariate models in our study. Dogs and cats in our population presented with a very simlar PSS distribution (figure 6.2), most dogs and cats were admitted with a PSS of 3 followed by 4, 2, 1 and 5. The percentage of cats that entered with PSS 3, 4, and 5 was slightly higher in cats than in dogs. Dogs use to express their discomfort in a more evident way, being less active, crying or trying to stay closer to family members. Cats use to be more elusive, hiding themselves sometimes, ans this make more difficult for the owner to realize of the real physical status of the cat. One of the most common signs seen in painful cats is the lack of grooming (Epstein et al., 2015). Other secondary behaviour as defecating outside the litter box, should make us suspect that something is happening (Epstein et al., 2015). Therefore, we can hypothetizise that the higher percentage of cats in PSS of 3, 4, and 5 at admission, may be due to the longer time that the owner takes to realize clinical situation of the cat or the reluctancy to stress the cat by a veterinary visit as mentioned above.

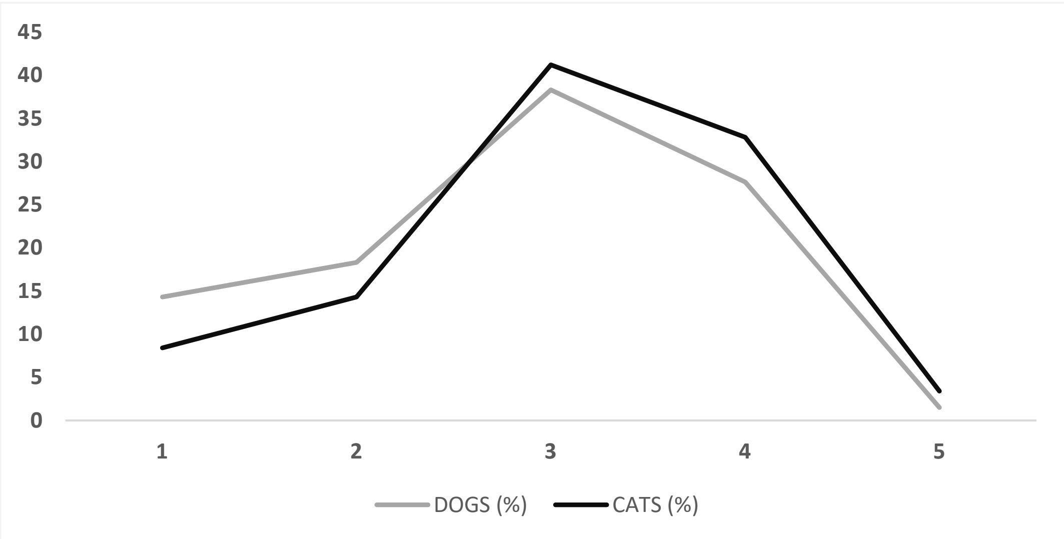

Figure 6.2. Classification of dogs and cats by their Physical Status Score (PSS) at the moment of hospitalization.

This lack of effect of PSS on nutritional status and outcome was unexpected and different from Remillard et al (2001) and Brunetto et al (2010), where severity of the disease was associated with worse outcomes, and severity was also associated with energy balance. This difference could reflect the different populations among the countries and the type of institutions. Additionally, individual parameters associated with severity (like EI, anorexia, weight loss) better explained the results compared to an overall index, which is why PSS was not included in any of our models. Using a more objetive and standarized severity index would have been a better way to assess the effect of disease severity on nutritional status and outcome. This could not be done in the present study due to the great variability in the approach to cases by each primary clinician and we used a subjective measure of severity (PSS) to be able to compare our results to those obtained by Brunnetto et al. (2010) and Remillard et al. (2001). However, future studies should include more objective measures of severity like the APPLE (Hayes et al., 2010) in order to study the actual effect of physiological status on EI and outcome.

In the present study, it was not possible to accurately assess the effect of assisted nutrition on nutritional status or outcome due to a low sample size. It is noteworthy that, despite the high number of dogs and cats eating below their RER during the hospitalization period, the number of assisted nutrition interventions (EN or PN) was low, suggesting that this type of intervention was not a top priority for clinicians when they have to manage hospitalized patients. In human medicine, studies suggest that the sooner the patients are nourished (voluntarly or through feeding tube), the better recovery and shorter HL they will have (Herbert et al., 2018). This is specially important in order to vacate beds for other patients that may need them and to save costs of hospitalization. In human medicine, even though the situatio is still not ideal, assisted feeding during hospitalization (manly by feeding tube placements) is encouraged. A cluster-randomized controlled trial (Martin et al., 2004) showed that patients with an assisted nutritional intervention received significantly more days of enteral nutrition (6.7 v. 5.4 per 10 patient-days), and had a significantly shorter HL (25 v. 35 days) compared to no intervention.

Other limitations of the present study were the low number of patients who died or were euthanized, which could limit the reliability of our outcome model. The number of dogs and cats that die or receive nutritional support may differ between hospitals due to differences in protocols and characteristics of population treated. Brunetto et al. (2010) study reported a similar mortality to our population (7%) but Remillard et al. (2001), the only multi-centric study, reported a mortality of 16%. Studies with a higher sample size and from different hospitals would be of great interest. We already mentioned the lack of an objective measure of body composition, limited number of enteral and parenteral nutrition support interventions, and the lack of an objective severity scale.

The current study has showed the importance of adeuate energy intake and nutritional status on preventing malnutrition and improving outcome in both dogs and cats and stresses the importance of performing nutritional evaluation in hospitalized patients to identify those patients at risk. Ideally, future studies should be multi-centric and incorporate more objective measures of body composition and disease severity and be powered enough to be able to assess the effect of nutritional intervention. More objective mesures of energy requirements, when indirect calorimetry becomes cheaper and more practical, will also provide necessary information about energy needs and allow for a more individualized approach. We did not assess laboratory analysis values as malnutrition risk markers, because it was outside the scope of the study, but future studies could incorporate these in order to provide additional information and allow for faster and more accurate nutritional assessment.

CHAPTER 7. CONCLUSIONS

Based on the results presented in Chapters 4 and 5, in a population of hospitalized dogs and cats in a veterinary teaching hospital, the main following conclusions can be derived:

1. The prevalence of undernutrition in dogs and cats, measured as loss of body weight and body condition score, was between 16.0 and 25.7%. The prevalence of patients at risk of malnutrition, defined as patients receiving less than 25% of their energy requirements, was above 50% in both species.
2. In dogs and cats, energy intake during hospitalization was positively correlated with an adequate nutritional status and outcome. In dogs, the effect of energy intake on nutritional status was seen in patients with hospitalization periods of 3 days or longer.
3. In dogs and cats, hospitalization length was negatively associated with nutitional status, with long hospitalization periods associated with increased losses of weight and body condition.
4. Old age and vomiting at admission were identified as risk factors for undernutrition in dogs, but not in cats
5. Energy intake was associated with lower odds of dying in both species. In dogs, but not in cats, hospitalization length and anorexia at presentation were associated with higher odds of dying. whereas higher initial body condition score was associated with lower odds of dying. In cats, weight loss at admission was assocaited with higher odds of dying.

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ABBREVIATIONS

AIC: Akaike information criterion

APPLE: acute patient physiologic and laboratory evaluation

ATP: Adenosine triphosphate

BCAA: Branched-chain amino acids

BCS: Body condition score

BMI: Body mass index

BW: Body Weight

CI: Confidence interval

CKD: Chronic kidney disease

CO_2: Carbon dioxide

DER: Daily energy requirements

DEXA: Dual energy X-ray absorptiometry

DHA: Docosahexaenoic acid

EEN: Early enteral Nutrition

EI: Energy intake

EN: Enteral nutrition

EPA: Eicosapentaenoic acid

ESPEN: European Society of Clinical Nutrition and Metabolism

FHCV: Veterinary Teaching Hospital Fundació Hospital Clínic Veterinari

HL: Hospitalization length

iBCS: Initial BCS

IBD: Inflammatory bowel disease

iBW: Initial BW

ICU: Intensive Care Unit

IFN-ϒ: Interferon ϒ

IGF-I: Insulin-like growth factor I

IL-1β: Interleukin-1

IL-6: Interleukin 6

kcal: kilocalorie

kg: kilogram

LT: Leukotriene

MCS: Muscle condition score

MER: Maintenance energy requirements

NADH: nicotinamide adenine dinucleotide (NAD) + hydrogen (H).

NPO: Nil per os

NS: Nutritional support

OR: Odds ratio

PD: Prescription Diet

PG: Prostaglandins

PN: Parenteral nutrition

PPN: Partial parenteral nutrition

PSS: Physical Status Score

RER: Resting Energy Requirements

RS: Refeeding syndrome

SD: Standard deviation

SE: Standard error

SGA: Subjective Global Assessment

Tf: Transferrin

TNF-α: Tumour necrosis factor

TPN: Total Parenteral Nutrition

VD: Veterinary Diet

VEMS: Vertebral epaxial muscle score

VIF: Variance inflation factor

WSAVA: World Small Animal Veterinary Association

ΔBW: BW change

ΔBCS: BCS change

2,3-DPG: 2,3-diphosphoglyverate

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