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Avaliação e Gestão do Risco Nutricional de uma população de doentes com DRC5D

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Nutritional Risk Assessment and Management of a Population of CKD5D patients

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II. [Full Article] **Sá Martins V**, Adragão T, Aguiar L, Pinto I, Dias C, Figueiredo R, Lourenço P, Pascoal T, Pereira J, Pinheiro T, Ramião I, Velez B, Papoila AL, Borges N, Calhau C, Macário F. Prognostic Value of Malnutrition-Inflammation Score on Long-term Hemodialysis. J Ren Nutr 2021(article in press)
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III. [Abstract] **Sá Martins V**, Aguiar L, Dias C, Lourenço P, Pinheiro T, Velez B, Birne R, Borges N, Adragão T, Calhau C, Macário F. FP718 Diabetes and malnutrition Risk in hemodialysis patients. Nephrol Dial Transplant 34 (Supplement 1): i292–i304, 2019.
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I was responsible for conceptualization, methodology, study design, data collection, assembly and analysis, manuscript writing and revision.

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Alberto Caeiro

Resumo

Atualmente, a sobrecarga global de doenças plurimetabólicas, bem como o crescente envelhecimento da população, tem levado a um aumento da prevalência de doença renal crónica, com consequências sociais, económicas e na saúde publica. Portugal tem uma das prevalências mais elevadas do mundo.

A progressão da doença renal crónica levará inevitavelmente à necessidade de uma terapêutica substitutiva da função renal, nomeadamente a hemodiálise, a opção mais frequente para a maioria dos doentes com doença renal crónica estadio 5, à qual poderão ser submetidos cronicamente durante anos, até mesmo décadas.

Devido às funções metabólicas e nutricionais do rim, será expectável que o declínio e a falência da função renal, assim como o próprio impacto da terapêutica substitutiva da função renal, afetem o estado nutricional sistemicamente, tornando-se imprescindível a terapia nutricional em todos os estádios da DRC para compensar a progressão e perda da função renal.

A ideia para esta tese começou com o desafio pessoal e profissional como Diretor do Serviço de Nutrição: organizar um serviço de nutrição de uma empresa prestadora de cuidados renais que possuía 25 clínicas de hemodiálise, com mais de 3000 doentes em 2014, o que representou uma oportunidade única para definir procedimentos de intervenção nutricional alinhados com as melhores práticas disponíveis, esperando que um ambiente clínico centrado no doente, que conheça e auspicie a minimização do risco nutricional, potencie favoravelmente a gestão do estado nutricional.

Com o objetivo de determinar o perfil de risco de malnutrição e inflamação e sua associação com parâmetros clínicos rotinamente avaliados, foi aplicado o Malnutrition-Inflammation Score (MIS) numa amostra inicial de 3050 doentes em HD, 26% da população portuguesa em hemodiálise, no início deste estudo em janeiro de 2016. De modo a apurar a associação do MIS com a hospitalização e mortalidade e a definir o(s) ponto(s) de corte, acompanhamos esta amostra por um período de 48 meses. Considerando as implicações sistémicas do risco nutricional em HD, várias análises exploratórias foram realizadas para compreender a associação da diabetes, do índice de resistência à eritropoietina e do ganho de peso interdialítico com fatores, como o MIS, e com a hospitalização e a mortalidade.

Como o suporte nutricional oral intradialítico poderá ter um papel importante na provisão e reabilitação nutricional, pretendeu-se investigar, como prova de conceito, se um lanche intradialítico padronizado era adequado para compensar o impacto catabólico da hemodiálise.

Por fim, ambicionou-se contribuir para uma maior conscientização sobre o impacto do risco de malnutrição e inflamação nesta população.

No primeiro estudo, foram avaliados 2975 doentes com o MIS: 56% do género masculino, 31% diabéticos, média de idade de 66,7 ± 14,8 anos e uma prevalência de malnutrição de 50%. As comorbilidades, a antiguidade em hemodiálise, a transferrina, a capacidade funcional e a variação de peso tiveram maior impacto no incremento do risco. Uma Idade ≥ 75 anos, a diabetes, níveis baixos de fósforo, de creatinina sérica e da taxa normalizada de catabolismo proteico, e níveis altos de cálcio, de índice de resistência à eritropoietina, de Kt/V e de proteína C-reativa foram considerados preditores de risco de malnutrição e inflamação.

No seguimento de 48 meses, 2444 doentes foram analisados: 59% homens, 32% diabéticos, uma idade mediana de 71 anos, 35,8% tinham MIS<5, 35,2% morreram e 62,5% foram hospitalizados pelo menos uma vez. O MIS manteve o seu valor de prognóstico. O ponto de corte de 5 foi confirmado e novos pontos de corte foram identificados: 6,3 para todos os doentes, 6 para não diabéticos e 6.5 para diabéticos. Um maior MIS, maior Índice de comorbilidade de Charlson, e menor Kt/V, menor albumina e acesso vascular por fístula arterio-venosa ou cateter venoso central aumentaram o risco de hospitalização, enquanto uma maior idade, maior ganho de peso interdialítico, maior índice de comorbilidade de Charlson, menor Kt/V, menor albumina, menor taxa normalizada de catabolismo proteico e cateter venoso central aumentaram o risco de mortalidade.

Na análise exploratória de 1740 doentes diabéticos no início do estudo em 2016: 56,6% eram não insulinotratados e 43,4% eram insulinotratados. Os doentes insulinotratados apresentaram um risco 1.3 vezes maior de malnutrição.

Em relação à análise exploratória do índice de resistência à eritropoietina, foram incluídos 2044 doentes, com 56% do sexo masculino, 31% diabéticos, uma idade média de 68.4 ± 14.12 anos, uma média de antiguidade em hemodiálise de 105 ± 74 meses e uma média do índice de resistência à eritropoietina de 7.23 ± 7.15 (U/semana/kg)/(g/dL). O índice de resistência à eritropoietina esteve associado a um maior MIS, maior proteína C-reativa e um menor hematócrito.

Na última análise exploratória, com seguimento de 42 meses, foi analisado o ganho de peso interdialítico de 2424 doentes com: 59% homens, 32% diabéticos, 16% com um ganho de peso interdialítico > 4%, 35% de mortalidade e 63,9% com pelo menos um episódio de hospitalização. Um ganho de peso interdialítico > 4% foi associado com a antiguidade em hemodiálise, sexo masculino, maior taxa normalizada de

catabolismo proteico, maior Kt/V e índice de resistência à eritropoietina, mas não com um MIS> 5, a hospitalização e a mortalidade (por todas as causas).

Finalmente, como prova de conceito de um lanche intradialítico simples e de baixo custo como estratégia nutricional para compensar o impacto catabólico estimado do tratamento de hemodiálise, foram analisadas 488 refeições, 338 realizadas durante os turnos diurnos. Não foram registadas intolerâncias e o perfil nutricional médio foi: 378.8 ± 151.4 kcal, 13.5 ± 7.2 g proteína, 676 ± 334 mg sódio, 361 ± 240 mg potássio, 249,3 ± 143 mg fósforo, com 68% das refeições a atingirem a meta energética (316.8 kcal/tratamento) e 82% a meta proteica (7 g/tratamento). Verificou-se associação entre o turno do tratamento de hemodiálise e a ingestão de energia, proteína, lípidos, sódio, potássio e fósforo.

Por conseguinte, os trabalhos desta tese contribuíram para um melhor conhecimento da prevalência e do perfil do estado nutricional numa amostra representativa da população portuguesa com DRC estadio 5 em hemodiálise, e para uma maior sensibilização dentro e fora da organização. Mais evidências foram encontradas para apoiar a recomendação da utilização do MIS na avaliação de rotina do risco nutricional e de inflamação, bem como a confirmação do valor do ponto de corte, embora com o vislumbre de uma nova tendência para um aumento dos pontos de corte e da pertinência da estratificação do risco, considerando a patologia de base, como a diabetes, assim como a terapêutica farmacológica (insulinotratados vs não insulinotratados).

No que diz respeito ao suporte nutricional oral, o modelo de lanche intradialítico apresenta-se como uma estratégia adequada para compensar o impacto catabólico da hemodiálise, podendo ser facilmente replicado em outras clínicas.

As evidências preliminares relacionadas com o índice de resistência à eritropoietina e com o ganho de peso interdialítico, mostram que análises mais aprofundadas são necessárias e que o campo de impacto do risco nutricional e inflamatório é amplo e precisa ser abordado com a busca de mais evidências, a fim de contribuir para uma intervenção nutricional precoce e precisa.

Estes achados, que metade da população está em risco nutricional, que fatores que têm maior impacto, a confirmação da capacidade de prognóstico do MIS e do respetivo ponto de corte, a nova tendência nos pontos de corte, a possibilidade de se estratificar o risco no caso da diabetes, o impacto da malnutrição na resistência à eritropoietina e a sua associação com o ganho de peso interdialítico, confirmam a necessidade de priorizar a abordagem clínica ao risco nutricional e inflamatório. Foi evidenciado que será possível ter um modelo de lanche intradialítico eficiente e económico que compense o impacto catabólico da HD, assim como, um serviço de nutrição organizado e eficiente, capaz de reunir evidências científicas que contribuam para uma melhor prestação de cuidados nutricionais ao doente, fortalecendo as recomendações atuais, bem como estabelecendo a base para o desenvolvimento de melhores práticas que sejam replicáveis, assim como, de novas *guidelines*.

Palavras-Chave: hemodiálise, estado nutricional, inflamação, gestão risco nutricional, malnutrition-inflammation score, suporte nutricional intradialítico, diabetes, ganho de peso interdialítico, índice de resistência à eritropoietina, hospitalização, mortalidade.

Abstract

Currently, the global burden of plurimetabolic disorders as well as an ever-growing aging population has led to an increase of chronic kidney disease prevalence, with health, social and economic consequences. Portugal has one of the highest prevalence in the world.

The progression of chronic kidney disease will inevitably lead to the need of a renal replacement therapy, namely hemodialysis, the more suitable renal replacement therapy for the majority of chronic kidney disease stage 5 patients, which can undergo chronically for years, even decades.

Due to the inherent metabolic and nutritional functions of the kidney, it is expected that the decline and failure of the kidney, as well as the impact of the renal replacement therapy itself, will affect nutritional status systemically, making a medical nutritional therapy imperative in all stages to compensate for the progression and loss of the renal function.

The idea for this thesis began with the personal and professional challenge as the Head of Nutrition Care: to organize a national nutritional department of a renal services company that own 25 outpatients hemodialysis clinics with more than 3000 patients in 2014, which represented a unique opportunity to define nutritional intervention procedures aligned with the best practices available, expecting that a patient-focused clinical environment and that aims to minimize the nutritional risk would favorably enhance nutritional status management.

With the objective of determining malnutrition and inflammation risk profile and its association with routinely assessed clinical factors, the Malnutrition inflammation Score (MIS) was assessed in a sample of ~3050 patients, 26% of the

Portuguese population in hemodialysis, at this study baseline in January 2016. In order to understand its association with hospitalization and mortality, and define the cut-off(s), we followed-up this sample for 48 months. Considering the systemic implications of the nutritional risk in hemodialysis, several exploratory analysis were undertaken to understand the association of diabetes, erythropoietin resistance index and interdialytic weight gain with factors, such as MIS, and with hospitalization and mortality.

As oral nutritional support has an important role in nutritional provision and rehabilitation, we wanted to do determine, as a proof of concept, if a standardized intradialytic snack was adequate to compensate the catabolic impact of hemodialysis.

At last we aimed to contribute to greater awareness about the impact of the malnutrition and inflammation risk in this population.

In the first study, 2975 patients with a mean age of 66.7 ±14.8 years were assessed with MIS: 56% male, 31% diabetic and the prevalence of malnutrition was 50%. Comorbidities, hemodialysis vintage, transferrin, functional capacity and weight variation had the greatest impact on risk increment. Age ≥ 75 years, diabetes, low P, low serum creatinine, low normalized protein catabolic rate, high calcium, erythropoietin resistance index, Kt/V and C-reactive protein were found to be predictors of malnutrition and inflammation risk.

In the 48-month follow-up, 2444 patients were analyzed: 59% male, 32% diabetic, median age of 71 years, 35.8% had a MIS<5, 35.2% died and 62.5% were hospitalized at least once. MIS maintains its prognostic value in long-term hemodialysis patients, the cut-off of 5 was confirmed and new cut-offs were identified: 6.3 for all patients, 6 for non-diabetics and 6.5 for diabetics. A higher MIS, higher Charlson

Comorbidity Index, and lower Kt/V, lower albumin, and arterio-venous graft or central venous catheter increased the hospitalization risk, while higher age, higher interdialytic weight gain, higher Charlson comorbidity index, lower Kt/V, lower albumin, lower normalized protein catabolic rate and central venous catheter increased the mortality risk.

The exploratory analysis of 1740 diabetic patients at the baseline in 2016: 56.6% were non-insulin treated and 43.4% were insulin treated, with insulin treated patients having a 1.3-fold increased risk of malnutrition.

Concerning the erythropoietin resistance index exploratory analysis, 2044 patients were included: 56% male, 31% diabetic, a mean age of 68.4 ± 14.12 years, a mean hemodialysis vintage of 105 ± 74 months and a mean EPORI of 7.23 ± 7.15 (U/week/kg)/ (g/dL). Erythropoietin resistance index was found to be associated with higher MIS, higher C-reactive protein and lower hematocrit.

In the last exploratory analysis with a 42-month follow-up, the interdialytic weight gain of 2424 patients was analyzed: 59% male, 32% diabetic, 16% with an interdialitic weight gain >4%, 35% died and 63.9% were hospitalized at least once. An interdialytic weight gain > 4% was associated hemodialysis vintage, male gender, higher normalized protein catabolic rate, higher Kt/V, and higher erythropoietin resistance index, but not with MIS>5, hospitalization nor all-cause mortality.

Finally, as proof of concept of a simple and cost effective intradialytic snack in compensating the estimated catabolic impact of the hemodialysis treatment, we analyzed 488 meals, 338 during daytime shifts. No intolerances were registered, and the average nutritional profile was: 378.8 ± 151.4 kcal, 13.5 ± 7.2g protein, 676 ±334 mg sodium, 361 ±240 mg potassium, 249.3 ±143 mg phosphorus, with 68%

of the meals meeting the energy target (316.8 kcal/treatment) and 82% the protein target (7 g/treatment). The treatment shift was associated with energy, protein, lipids, sodium, potassium and phosphorus intakes.

This work contributed to a better knowledge of the prevalence and the profile of the nutritional status in a representative sample of the Portuguese population with stage 5 on hemodialysis chronic kidney disease, contributing to create awareness inside and outside the organization. More evidence was found to support the recommendation of MIS for routine assessment of nutritional and inflammation risk, as well as the confirmation of the cut-off, although with a new trend for a high cut-off the pertinence to stratify the risk, for diabetics, and even according to diabetic therapy. Concerning oral nutritional support, the intradialytic snack model was proven to be an adequate strategy to compensate the catabolic impact of HD and can be easily replicated in other clinics.

Preliminary evidence related to erythropoietin resistance index and interdialytic weight gain, showed that further analysis is needed and that the field of impact of the nutritional and inflammation risk is wide and needs to be addressed with the search of more evidence, in order to contribute to a more precocious and precise nutritional intervention.

The findings that half the population is at nutritional risk, which factors have the greatest impact, the confirmation of the prognostic value of MIS and cut-off, the new trend in the risk cut-off(s), the possibility to stratify the risk for diabetes, the impact of malnutrition in the erythropoietin resistance e the association with interdialytic weight gain, confirmed the need to prioritize the clinical approach to nutritional and inflammation risk. It also showed that it is possible to have a simple and cost effective intradialytic snack model that compensates the

catabolic impact of HD as well as an organized and efficient nutrition service that is able to gather scientific evidence that contributes to a better patient care, which strengthens the evidence of current recommendations, laying the ground for replicable best practices and new guidelines.

Keywords: hemodialysis, nutritional status, inflammation, nutritional risk management, malnutrition-inflammation score, diabetes, intradialitic nutritional support, interdialytic weigh gain, erythropoietin resistance index, hospitalization, mortality.

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List of Abbreviations

7-SGA – 7-point Subjective Global Assessment

AA –Amino Acids

Alb – Albumin

AVF – Arterio-Venous Fistula

AVG – Arterio-Venous Graft

BIA-MF – Bioelectrical impedance Analysis – Multifrequency

BMI – Body Mass Index

CaxP- Phosphorocalcium product

CCI – Charlson Comorbidity Index

CI – Confidence Interval

CKD – Chronic Kidney Disease

CKD5d – Chronic Kidney Disease stage 5 dialysis

CRP – C - reactive protein

CVC – Central Venous Catheter

DMS- Dialysis Malnutrition Score

EPO – Erythropoietin

EPORI – Erythropoietin Resistance Index

FFM – Fat Free Mass

GNRI – Geriatric Nutritional Risk Index

HBV – High Biological Value

HD – hemodialysis

HD vint. – Hemodialysis Vintage

HDF - Hemodiafiltration

HF – High-Flux Hemodialysis

HR – Hazards Ratio

Htc - Hematocrit

IDWG – Interdialytic Weight Gain

INS – Insulin Treated

ISRNM – International Society of Renal Nutrition and Metabolism

MIA – Malnutrition Inflammatory Atherosclerosis

MICS – Malnutrition Inflammatory Complex Syndrome

MIS – Malnutrition-Inflammation Score

NIT- Non-Insulin Treated

nPCR –normalized Protein Catabolic Rate

nPNA – normalized Protein Nitrogen Appearance

ONS – Oral Nutritional Supplementation

OR – Odds Ratio

PCreat – Serum Creatinine

PEW – Protein Energy Wasting

Pi – inorganic phosphorus

PTH – Parathormone

PTHi- Intact Parathormone

REE- Resting Energy Expenditure

RRT – Renal Replacement Therapy

SGA – Subjective Global Assessment

TBIC – Total Binding Iron Capacity

URR – Urea Removal Rate

General Introduction

Currently, the global burden of plurimetabolic disorders such as obesity, diabetes, hypertension, dyslipidemia as well as an ever-growing aging population has led to an increase of chronic kidney disease (CKD) prevalence, with health, social and economic consequences. The world prevalence of CKD was 9.1% (697.5 million people) in 2017, and increased 29.3% since 1990. (1)

The progression of CKD will inevitably lead to the need of a renal replacement therapy (RRT): maintenance hemodialysis, peritoneal dialysis or renal transplant. Renal transplant, as the RRT of choice, depends on availability of donors and criteria fulfillment. Peritoneal dialysis, could represent a good option for RRT but is not suitable to all patients, and has limited duration. Thus, maintenance hemodialysis (HD) is the more suitable RRT to the majority of CKD5 patients, which can undergo it chronically for years, even decades. (1-3)

Globally, Portugal has one of the greatest incidence and prevalence of CKD. With 12429 chronic patients as of the end of 2020, the incidence of RRT with HD was 204.02 p.m.p, the prevalence was 1209.72 p.m.p. (that increased from 953.21 p.m.p, in 2010) and 65% of patients were older than 65 years. The primary renal disease of prevalent patients was diabetes (28.6%), hypertension (13.2%), chronic glomerulosclerosis (12.8%), polycystic disease (6.4%), hypo and dysplasia (1.0%), other known diseases (19.9%) and unknown (18.2%). (2) to the inherent metabolic and nutritional functions of the kidney, it is expected that the decline and failure of the kidney will affect nutritional status systemically, making a medical nutritional therapy imperative in all CKD stages (RRT included) to compensate the progression and loss of the renal function.(4, 5)

Associated with high morbidity and mortality, and also prevalent in MHD patients, protein energy wasting is a syndrome with adverse changes in nutrition and body

composition caused by insufficient food intake (a result of anorexia, appetite mediators dysregulation, hypothalamic amino acid sensing alterations, high levels of nitrogen-based uremic toxins, dietary restrictions, depression and inability to obtain or prepare food).(6)

Other causes also have a great impact on nutritional status, namely: gastrointestinal alterations, hypermetabolism (increased resting energy expenditure, persistent inflammation, increased circulating proinflammatory cytokines, insulin resistance secondary to obesity, altered adiponectin and resistin metabolism); metabolic acidosis (decreased physical activity, anabolism and testosterone levels, resistance to growth hormone/insulin growth factor-1, low thyroid levels); multiple endocrine disorders (insulin resistance and increased glucocorticoid activity); and comorbidity and lifestyle related (diabetes, depression, congestive heart failure, coronary heart disease and peripheral vascular disease).(6-9)

The HD treatment itself also affects nutritional status due to nutrient losses to the dialysate, the dialysis-related inflammation and hypermetabolism, and loss of residual renal function.(6, 10-12)

The idea for this thesis began with the personal and professional challenge as the Head of Nutrition Care: to organize a national nutritional department of a renal services company that owns 25 outpatients hemodialysis clinics providing RRT with MHD to more than 3000 patients in 2014.

The chronicity of these patients adds some complexity on how nutrition intervention is organized and to the way that strategies and policies are designed, because, independently of their clinical condition now, there is a high probability that they might be, at some point, at nutritional risk. On the other hand, variables

such as patients' literacy, motivation, engagement, satisfaction, socio-economic situation, demanding for quality of life and even social responsibility, should also be accounted in this equation.

This represented a unique opportunity to define nutritional intervention procedures aligned with the best practices available, to define strategies and polices aiming to continuously optimize metabolic control, nutritional status, quality of life and reduce mortality risk in patients with different comorbidities, background and needs. This population is singular due to a constant and thorough surveillance that is facilitated because of MHD frequency.(5)

This setting of the nutritional care organization should enable an adequate knowledge of the population (namely assessing nutritional risk profile and the impact of malnutrition and inflammation); an individualized medical nutritional therapy; a frequent and sustained nutritional monitoring and intervention with defined targets (macro and micronutrient intake, Malnutrition-Inflammation Score (MIS), even interdialytic weight gain (IDWG) and anemia management); oral nutritional support that compensates HD associated losses; oral nutritional supplementation for nutritional rehabilitation; protocols for patients that return from hospitalization; awareness of the major nutritional issues; literacy and empowerment.(4, 5)

One might expect that a clinical environment that focuses on the patient, knows and aims to minimize the nutritional risk, would favorably enhance nutritional status management of this population.

In the 2018 meta-analysis of Carrero et al., they found that protein-energy wasting PEW was a common phenomenon across the spectrum of Acute Kidney Injury (AKI) and CKD, and that the prevalence ranged between 28-54%, a large variation even

adjusting the data, with the geographical region as the only significant moderator explaining the observed heterogeneity.(13)

The lack of homogeneity in the nutritional risk assessment tools, might also explain these variations. In 2018, there was no data available about the prevalence of malnutrition in the Portuguese maintenance HD population.(13)

This raises the first question of how to deal with a problem, if one does not know its size and causes, to further define, implement strategies and polices accordingly. Of course, we might expect it would be similar to countries with comparable demographic and comorbidity profile, however, that data was also lacking. (12)

In the 2020 KDOQI on nutrition update, recommends, for CKD5D patients, the 7-point subjective global assessment (LOE 1B) and suggests MIS for patients with CKD 5D on MHD or posttransplantation (LOE 2C), but no cut-offs are suggested.(3)

Although with a low level of evidence, related to the few studies available, MIS is a comprehensive and quantitative assessment tool, inexpensive, rapid to conduct with low inter-observer variability if applied by trained professionals, considers the intricate relation of malnutrition and inflammation, and is ideal for monitoring the nutritional risk, prevalence and evolution in individuals and on large groups of patients. When compared with more time-consuming tools such as Bioelectrical Impedance Analysis – Multifrequency and Dual Energy X-ray Absorptiometry, MIS presents itself as the adequate, feasible and pertinent choice. This data could also contribute to a greater level of evidence has referred in KDOQI update.(4, 8, 13-16)

Thus, the first step was to proceed with the nutritional assessment with MIS of a significant sample of ~3050 patients that received RRT with HD from private

provider with the convention of the National Health Service that, at the study baseline in January 2016 this representative sample corresponded to 26% of the Portuguese population in HD.

However, we must not forget that PEW onset can be insidious and that nutritional rehabilitation is very susceptible to the catabolic pressure of comorbidities, infections and hospitalizations. In line with that, we followed-up for 48 months to understand its association with hospitalization and mortality, and to define the cut-off(s) for malnutrition-inflammation risk that would help us to define nutritional intervention protocols for the whole HD or even further, to specify the risk in major groups, such as diabetics.

The systemic implications of the nutritional risk in HD are wide, and it is important to understand them. Erythropoiesis and anemia management are an important part of therapeutic intervention in HD patients, although with some evidence in the clinical practice, the malnutrition and inflammation risk are not often related with anemia management. Similarly, IDWG as a routine clinical performance measure needs to have clarified its impact, targets and association with malnutrition-inflammation risk, hospitalization and mortality. Vascular and skin integrity, as well as muscle support, are important to an adequate vascular access which are pivotal for an efficient HD treatment, and they can also be related with malnutrition.(5, 17-25)

In terms of core nutritional intervention it is very important that we assure the protein, energy, phosphorus, potassium, sodium and water intake needs but also to go further, changing the paradigm to a greater focus on micronutrient deficiencies and individual metabolic abnormalities.

Nutritional support should also play an important role on nutritional status maintenance and rehabilitation, particularly during HD treatment, because of the inherent catabolic impact of the treatment itself (during and afterwards) and the disruptive impact that it causes on patient's schedules and meals (4 hours of treatment and plus at least one to two hours for transportation). From a medical perspective, this nutritional support must be a part of the treatment because it should compensate the catabolic impact, that can ascend to 14 g of protein and 316.8 kcal per treatment, plus the meals that the patients does not eat properly, that can represent, for example, as much as 30% if he misses a lunch.(10, 26, 27) However, this is not included on the convention reimbursement contract defined by National Health System, so it is a decision of the organization to assume the financial impact of this nutritional support. So, it is expected to be delivered at an efficient cost and with the proof that it attains its purpose.

The possible options for the nutritional support are intradialytic (ID) meal/snack, commercial oral supplements and intradialytic parenteral nutrition. It is expected that ID meal/snack, as the most physiologic option, would have better tolerance and adherence. Although there are some studies that focus on nutritional support with commercial formulas or ID parenteral nutrition, there is a lack of studies with models for ID meals/snacks, so further evidence is needed for new or pre-existing models.(26-29)

Nutritional risk assessment and management of a population of CKD5D patients is an audacious work, because in the clinical practice context it never ends.

Objectives

i. To determine malnutrition and inflammation risk profile and the contribution of each component.

ii. To determine the association of routinely assessed clinical factors to malnutrition and inflammation risk.

iii. To determine MIS prognostic value on hospitalization on long-term hemodialysis.

iv. To identify which factors, such as MIS, are associated with EPORI and to assess its association with hospitalization and mortality risks.

v. To analyze the association of diabetes, namely non-insulin treated versus insulin treated, with malnutrition and inflammation risk in MHD patients.

vi. To evaluate the association of the interdialytic weight gain with other parameters, as well as with mortality and hospitalization risk.

vii. To determine, as a proof of concept, if a standardized intradialytic snack is adequate to compensate the catabolic impact of hemodialysis.

vii. To contribute to greater awareness about the impact of the malnutrition and inflammation risk in this population.

Materials, Methods and Study Designs

Materials, methods and study designs are described on each manuscript and abstract.

Manuscripts and Abstracts

Section A

Nutritional and inflammation risk assessment and predictors.

Manuscript title:
"Predictors of Nutritional and Inflammation Risk in Hemodialysis Patients"

Presentation: facsimile

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Original article

Predictors of nutritional and inflammation risk in hemodialysis patients

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SUMMARY

Background: Malnutrition and chronic inflammation are prevalent complications in hemodialysis (HD) patients. Different nutritional assessment tools are used to identify patients at risk. A composite and comprehensive malnutrition inflammation score (MIS) has been correlated with morbidity and mortality, and appears to be a robust and quantitative tool.

Objectives: Determine malnutrition risk profile in a sample of portuguese HD patients; determine the association of clinical and laboratory factors with MIS, and the impact of each parameter on MIS.

Methods and results: We performed, between September 15th of 2015 and January 31st of 2016, a cross sectional analysis of 2975 patients, representing 25% of portuguese HD patients. 59% were men (66.7 ± 14.8 years); 31% diabetic; 79% and 21% performed, respectively, high-flux HD and HDF. A MIS >5 was considered to indicate higher risk and was present in 1489 patients (50%). Amongst all parameters, comorbilities/dialysis vintage, transferrin, functional capacity, changes in body weight and decreased fat stores showed the higher impact, while albumin had one of the lowest impact on the nutritional risk.

Multivariable analysis: Higher age (>75 years, OR 1.71, $p < 0.001$), diabetes (OR 1.25, $p = 0.026$), lower P levels (OR 1.57,$p = 0.001$), higher Ca levels (OR 1.51, $p < 0.001$), higher ERI (OR 1.05, $p < 0.001$), higher Kt/V (OR 2.14, $p < 0.001$) and higher CRP (OR 1.01, $p < 0.001$) were independently associated with a higher risk of MIS>5; higher nPNA (OR 0.29, $p < 0.001$) and higher Pcreat (OR 0.88, $p < 0.001$) were associated with a risk reduction of MIS>5 (95% CI).

Conclusions: Routine clinical and analytic parameters were found to be associated with MIS range that might indicate higher risk, and may represent a simple alert sign for the need of further assessments.

1. Introduction

Malnutrition, with an inflammatory profile, is prevalent in hemodialysis (HD) patients.

A state of decreased protein body pools, with or without fat depletion, followed by a diminished functional capacity is a risk factor for poor quality of life and increased morbidity and mortality, including the cardiovascular related one [1–3]. This may be caused by an inadequate nutrient intake relative to the actual needs due to poor appetite and dietary restrictions that, depending on the severity of protein stores depletion, might or not be improved by nutritional repletion [1–3].

Protein-Energy Wasting (PEW), with a prevalence between 18% and 75% in HD patients, is a state that considers other highly prevalent factors, such as the increased energy expenditure, persistent inflammation, acidosis and multiple endocrine disorders. Those disorders, plus the impact of the HD procedure itself,

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render into a hypermetabolic state leading to the excess catabolism of muscle and fat, poor physical activity and frailty [4].

Depending on the modality of dialysis, assessment tools and criteria, PEW is correlated with a higher morbidity and mortality [3].

Inflammation is a major pathophysiological phenomenon, where normal homeostatic mechanisms are replaced by new set points that contribute to defensive or adaptive capabilities that are needed to help the body to defend against pathophysiologic insults. Because of the HD treatment nature, inflammation usually becomes prolonged and chronic and might lead to a decline in appetite, lower nutritional and energy intake, higher catabolism, endothelial damage and atherosclerosis [3]. Mutsert et al. estimated that 1 g/dL decrease of serum albumin was associated with a mortality risk increase of 47%, partly explained as a consequence of a higher inflammatory status [5].

Nutritional status and inflammation are closely intertwined in HD and may concur to the explanation of a malnutrition-associated mortality. Terms such as malnutrition inflammatory complex syndrome (MICS) and malnutrition inflammatory atherosclerosis (MIA) have been used to establish the close relation between malnutrition, inflammation, atherosclerosis and refractory anaemia, although a conclusive consensus is lacking regarding the association between PEW, chronic inflammation in CKD, cardiovascular events [3].

These frequent nutritional and inflammation issues should be considered as a priority in the agenda of healthcare providers, with a committed engagement on a nutritional assessment and status optimization as an important part of the patient's treatment [2,5].

The definition of medical and nutritional strategies to address these issues is crucial and can be rather complex, especially if the aim is to detect early warning indicators of PEW, to diagnose actual nutritional status and to identify patients at risk for complications, poor outcome and death risk. The main goal should be the assessment and intervention on these conditions, if possible or treatable, namely those in which timely interventions would have the potential to stop ongoing cachectic processes, for example, with nutritional status enhancing and anti-inflammatory interdisciplinary focused interventions [1,6].

Several methodologies have been suggested to assess the nutritional status of HD patients, ranging from the assessment of food and nutritional intake and simple anthropometric measurements, to more elaborate tools such as Subjective Global Assessment (SGA), Dialysis Malnutrition Score (DMS), Malnutrition Inflammation Score (MIS), International Society of Renal Nutrition and Metabolism (ISRNM) criteria for PEW, Geriatric Nutritional Risk Index (GNRI), Bioelectrical Impedance Analysis – Multifrequency (BIA-MF), Dual Energy X-ray Absorptiometry, amongst others [1–4,7,8].

The use of scoring tools, like MIS, has many strengths in the clinical and research setting: most are inexpensive and rapid to conduct, can be used effectively by health care providers from different disciplines, and have been found to be reproducible, valid and reliable, reflecting not only the overall nutritional status, but helping to predict the outcome. The MIS is a fully quantitative and more comprehensive tool that also reflects inflammation status, showing significant correlations with prospective hospitalization mortality, as well as all the measures of nutrition, inflammation and anaemia, superior to serum markers of protein metabolism and BIA. However, it requires clinical expertise, trained professionals for a reliable application and low interapplicant variability [1,2,6,8–11].

Currently, relevant information concerning the nutritional status profile of CKD5D patients using MIS in Portugal and in most other countries is scarce. Carrero et al. in a recent meta-analysis on the global prevalence of PEW in CKD, found a large variation and an excess heterogeneity of the data ($I^2 = 97\%$, $P < 0.001$), what could be explained by variabilities of observation, approach used to define patients with PEW (by methods other than SGA/MIS), amongst others [12].

In Portugal, the prevalence of patients with renal replacement therapy was, in 2016, 1901.9 p.m.p, totalling 12458 patients in HD [13].

The objectives of our study were to determine the malnutrition risk profile in an initial sample of 3080 patients representing 25% of the Portuguese population in HD, to evaluate the association of simple clinical and laboratory factors not included in MIS, and to identify the impact of each item on the final score.

2. Methods

2.1. Study design

This is a cross-sectional observational study performed in a group of prevalent HD patients who were submitted to an assessment of the nutritional and inflammation status at baseline.

2.2. Population

We included all 3080 patients from 25 outpatient HD clinics in Portugal. The exclusion criteria were: age <18 years, HD vintage <3 months, any disability that would affect data collection or the score assessment and patient's unwillingness to participate in the study.

2.3. Ethics

All patients had signed an informed consent authorizing the use of clinical data for medical analysis, and patient data was treated anonymously.

2.4. Nutritional and inflammation assessment

The nutritional and inflammation assessment was performed using MIS, which has 4 main areas: clinical history (changes in body weight, dietary intake, gastrointestinal symptoms, functional capacity, comorbid conditions), physical assessment (decreased fat stores and signs of muscular atrophy), BMI and laboratory results (albumin and transferrin/TBIC), in a total of 10 items, each scored from 0 (normal) to 3 (severely abnormal), summing a final score between 0 and 30 [1,7,14].

The assessment was performed between September 15th of 2015 and January 31st of 2016 in all the HD patients that fitted the inclusion criteria by a team of 6 nutritionists who had previously received specific training, during the scheduled nutritional monthly monitoring. The physical examination was made according to the SGA criteria. The information that was not directly available during the assessment was collected from patients' charts and treatment records on the electronic clinical record system.

Current dry weight and measured height were used to determine BMI.

2.5. Biochemical analysis

Biochemical results were obtained from pre and post-dialysis blood samples of the midweek day (Wednesday or Thursday), with all the laboratory analysis performed nationwide by the same methodology. Serum albumin assessment was made using the bromocresol green method. Instead of using TIBC, we chose to use transferrin values, as originally suggested: ≥200 mg/dL (score 0), 199-170 mg/dL (score 1), 169-140 mg/dL (score 2), and <140 mg/dL (score 3).

2.6. Statistical analysis

In the descriptive statistics analysis categorical variables were presented as frequencies and percentages and continuous variables, were presented by means and standard deviations or by medians and interquartile ranges. The chi-square test (χ^2) or Fisher's test (in the case of expected frequencies below 5%) was used to compare proportions between categorical variables. The non-parametric Mann–Whitney (two groups) test was used to compare independent groups against a quantitative variable.

A multivariate logistic regression model was used to assess the association strength of the explanatory factors among variables which had p-value <0.3 in the bivariate analysis and clinical relevance. The associations were expressed by an odds ratio (OR) with a 95% confidence interval (95% CI). The absence of collinearity among explanatory factors was checked in all models based on variance inflation factor and variance proportions standard procedures.

Statistical tests were performed bilaterally at a significance level of 5%, whereby a p-value <0.05 was considered statistically significant.

The statistical analysis of the data was performed using statistical software R [1], version 3.3.1. (R Core Team (2016). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.)

3. Results

We assessed 2975 patients, 59% men (66.7 ± 14.8 years); 31% diabetic; 79% and 21% performed, respectively, high-flux HD and HDF; 41% had an age ≤65 years, 23% between 66 and 74 years, and 36% were older than 74 years (Table 1). From the initial 3080 patients, 43 patients were not included for not meeting the criteria, and 62 patients rejected participating in the study.

The national average of MIS was 6.34 ± 3.8. As shown in Fig. 1, there was no normal distribution, and the scores with highest frequency were, respectively, MIS = 4, 5, 6, 7 and 3.25%, 50% and 75% of the patients had, respectively a MIS below 4, 5 and 8. The outliers (n = 125) ranged from a score of 15 (n = 37) to 24 (n = 1).

Figure 2 shows a box-plot of each of the 10 items and its contribution to the final MIS value. Comorbidities/HD vintage (A5) and transferrin (D10) had the highest impact, followed respectively by functional capacity (A4), changes in body weight (A1) and decreased fat stores (B6). The items in the lower half of impact were, albumin (D9), muscular atrophy (B7), dietary intake (A2) and BMI (C8).

Since clear cut-offs for MIS are still to be defined, we chose to categorize for this analysis, a MIS≤5 as absence of nutritional risk and a MIS>5 as a condition where nutritional risk already exists and there is a significant risk of one year-mortality. Other cut-offs have been suggested, such as higher than 7 or even higher than 9 [9,14–17].

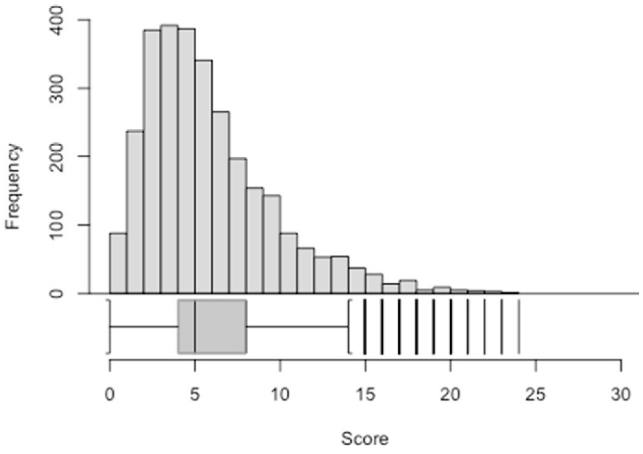

Fig. 1. Continuous score histogram and box plot (n = 2975).

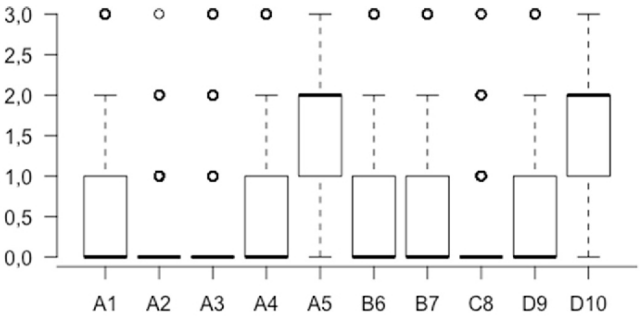

Fig. 2. Box-plot of each of the 10 items and its contribution to the final MIS value. A1- Change in body weight; A2- Dietary intake; A3- Gastrointestinal symptoms; A4- Functional capacity; A5- Comorbid cond./HD vintage; B6- Decreased fat store; B7- Muscular atrophy; C8- Body mass index; D9- Albumin; D10- Transferrin.

Nationwide, 50.1% (n = 1489) of all studied patients presented a MIS≤5 and 49.9% (n = 1486) had a MIS>5 (Table 1). We found some regional variability, in the north/center region 44.4% of the patients had a MIS>5, while in Lisbon region it was 54.5%.

Figure 3 describes the results of association tests, using chi-square test (χ^2), between categorized variables for recommended clinical ranges and a categorized MIS. Interdialytic weight gain (IDWG) does not appear to have a significant association, and it is noticeable that patients that are female, oldest, diabetic and within range to lower phosphate levels have a higher percentage of MIS>5.

Table 1
Univariable analysis: demography, diabetes and HD type.

		All patients	MIS≤5	MIS>5	p-value[a]
All patients		**2975**	**1489** (50.1%)	**1486** (49.9%)	–
Gender	male	**1758** (59.0%)	**958** (64.0%)	**800** (54.0%)	**<0.001**
Age (years)	≤65	**1221** (41.0%)	**735** (49.0%)	**486** (33.0%)	**<0.001**
	66–74	**693** (23.0%)	**356** (24.0%)	**337** (23.0%)	
	≥75	**1060** (36.0%)	**398** (27.0%)	**662** (45.0%)	
Diabetes		**931** (31.0%)	**429** (29.0%)	**320** (33.0%)	**0.026**
HD type	HF	**2349** (79.0%)	**1128** (76.0%)	**1221** (82.0%)	**<0.001**
	HDF	**626** (21.0%)	**361** (24.0%)	**265** (18.0%)	

HF-high flux HD; HDF – hemodiafiltration.
[a] Chi-square test (χ^2). Significant values (<0.05) are presented in bold.

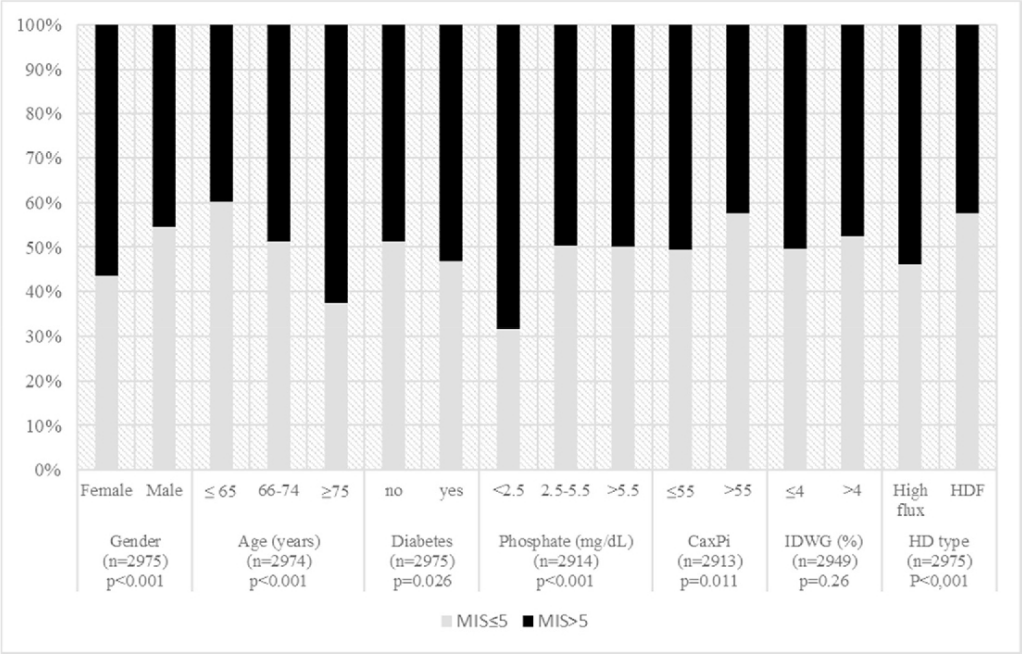

Fig. 3. Univariable analysis: Association tests between categorized variables/categorized MIS. *Pearson chi-square test (χ^2). Significant values $p < 0.05$.

To consider over time evolution of some routine clinical parameters, it was analyzed baseline values and 3-months average (t, t-1 and t-2) to lessen, in some way, any bias (Table 2). The 3-months average values were the chosen ones for the multivariable analysis. IDWG and Kt/V values referred to the same day of monthly blood samples. When multivariable logistic regression model was applied (Table 3) 2 models were considered, one with only significant variables (Model 2) and the other with also female gender, age between 66 and 74 years and IDWG>4% (Model 1) that, although in the univariable model had significant association, in the multivariable model it was not found, but have clinical relevance. It was possible to identify (Table 3, Model 2) that age ≥ 75 (OR 1.72, $p < 0.001$), diabetes (OR 1.25, $p = 0.026$); lower: P ($P < 2.5$ mg/dL) (OR 1.57, $p = 0.007$), nPNA (OR 0.29, $p < 0.001$), Pcreat (OR 0.88,

Table 2
Univariable analysis: Association between continuous variables and categorized MIS, median values (Inter-Quartile range).

		% of participants with data	MIS≤5	MIS>5	P-value[c]
Age (years)		99.97	**66** (54–75)	**70** (62–81)	<**0.001**
nPNA (g/kg)		99.43	**1.14** (0.98–1.32)	**1.03** (0.85–1.21)	<**0.001**
Pcreat (mg/dL)		98.52	**9.17** (8.7–9.64)	**9.2** (8.5–9.67)	0.387
CRP (mg/dL)		92.57	**4.4** (1.4–10.6)	**6.9** (2.1–17.3)	<**0,001**
PTHi[a] (ng/dL)		97.61	**391** (264–556)	**329** (204–497)	<**0.001**
Kt/V	baseline	95.93	**1.84** (1.66–2.08)	**1.93** (1.72–2.17)	<**0.001**
	3M av.[a]	95.93	**1.85** (1.67–2.08)	**1.93** (1.72–2.15)	<**0.001**
URR	baseline	97.68	**0.79** (0.75–0.82)	**0.81** (0.77–0.84)	<**0.001**
	3M av.[a]	97.68	**0.79** (0.76–0.82)	**0.80** (0.77–0.84)	<**0.001**
Calcium[b] (mg/dL)	baseline	97.92	**9.22** (8.9–9.6)	**9.36** (8.96–9.7)	<**0.001**
	3M av.[a]	97.92	**9.21** (8.9–9.6)	**9.33** (8.96–9.7)	<**0.001**
Phosphate (mg/dL)	baseline	97.95	**4.2** (3.5–5.1)	**3.9** (3.1–4.7)	<**0.001**
	3M av.[a]	97.95	**4.3** (3.7–5)	**3.93** (3.23–4.7)	<**0.001**
CaxPi (mg^2/dL^2)	baseline	97.92	**39.2** (32.2–47.4)	**36.2** (28.3–44.2)	<**0.001**
	3M av.[a]	97.92	**39.8** (33.4–47)	**36.5** (30.3–43.9)	<**0.001**
Weekly EPO dosage	baseline	77.92	**3000** (2000–6000)	**4000** (2000–6500)	<**0.001**
	3M av.[a]	77.92	**3000** (2000–6000)	**4000** (2000–6250)	<**0.001**
ERI	baseline	79.06	**4.34** (2.26–7.59)	**5.84** (3.04–10.26)	<**0.001**
	3M av.[a]	79.06	**4.33** (2.4–7.6)	**5.78** (3.04–10.2)	<**0.001**
HTC (%)	baseline	96.13	**34** (32–36.2)	**33.8** (31.6–36.2)	**0.031**
	3M av.[a]	96.13	**33.92** (32.23–35.87)	**33.77** (31.93–35.7)	0.059
IDWG (%)	baseline	99.09	**3.04** (2.31–3.8)	**2.88** (2.14–3.7)	**0.002**
	3M av.[a]	99.09	**3.09** (2.49–3.76)	**2.89** (2.26–3.63)	<**0.001**

nPNA, protein nitrogen appearance normalized; Pcreat, serum creatinine; CRP, C-reactive protein; URR, urea removal rate; PTHi, parathormone intact; CaxPi, phospocalcium product; EPO, erythropoietin; ERI, erythropoietin resistance index; HTC, haematocrit; IDWG, interdialytic weight gain

[a] 3 months average (baseline, t-1 and t-2) of parameters values at the monthly scheduled blood sample collection.

[b] Albumin corrected.

[c] Mann-Whitney test. Significant values (<0.05) are presented in bold.

Table 3
Uni and multivariable analysis: crude and adjusted (Model 1 and Model 2) odds ratio. Dependent variable: categorized score MIS>5. Adjusted odds ratio: multivariable logistic regression model.

		(Crude) Unadjusted			Adjusted (Model 1)			Adjusted (Model 2)		
		OR	CI 2.5%–97.5%	p-value*	OR	CI 2.5%–97.5%	p-value*	OR	CI 2.5%–97.5%	p-value*
Gender	Male	1	ref		1	ref				
	Female	1.547	1.336–1.793	**<0.001**	1.106	0.903–1.355	0.329	–		
Age	≤65	1	ref		1	ref		1	ref	
	66–74	1.432	1.186–1.728	**<0.001**	1.196	0.944–1.514	0.139	1.183	0.937–1.494	0.157
	≥75	2.516	2.125–2.981	**<0.001**	1.73	1.396–2.144	**<0.001**	1.717	1.392–2.119	**<0.001**
Diabetes	no	1	ref		1	ref		1	ref	
	yes	1.194	1.021–1.395	**0.026**	1.238	1.017–1.507	**0.033**	1.249	1.027–1.519	**0.026**
Phosphate[a]	2.5–5.5	1	ref		1	ref				
	<2.5	2.186	1.672–2.879	**<0.001**	1.586	1.15–2.204	**0.005**	1.565	1.136–2.173	**0.007**
	>5.5	0.609	0.487–0.758	**<0.001**	0.725	0.549–0.953	**0.022**	0.73	0.554–0.96	**0.025**
IDWG[a]	<4	1	ref		1	ref				
	≥4	0.896	0.741–1.083	0.258	1.052	0.825–1.342	0.685	–		
Continuous variables	nPNA	0.206	0.154–0.274	**<0.001**	0.288	0.201–0.41	**<0.001**	0.285	0.199–0.406	**<0.001**
	Calcium[a,b]	1.433	1.271–1.62	**<0.001**	1.5	1.275–1.769	**<0.001**	1.513	1.287–1.783	**<0.001**
	Pcreat	0.894	0.848–0.942	**<0.001**	0.878	0.815–0.943	**<0.001**	0.875	0.813–0.941	**<0.001**
	ERI[a]	1.048	1.035–1.062	**<0.001**	1.046	1.031–1.062	**<0.001**	1.047	1.032–1.063	**<0.001**
	Kt/V[a]	1.989	1.582–2.505	**<0.001**	1.971	1.428–2.729	**<0.001**	2.135	1.606–2.848	**<0.001**
	CRP	1.016	1.011–1.02	**<0.001**	1.011	1.006–1.017	**<0.001**	1.011	1.006–1.017	**<0.001**

OR, odds ratio estimate; CI, confidence interval; IDWG, interdialytic weight gain; nPNA, protein net appearance normalized; Pcreat, serum creatinine; ERI, erythropoietin resistance index; CRP, C-reactive protein.
Model 1: MIS ~ gender + age + diabetes + phosphate + IDWG + nPNA + calcium + Pcreat + EPO + ERI + Kt/V + CRP.
Model 2: MIS ~ age + diabetes + phosphate + nPNA + calcium + Pcreat + EPO + ERI + Kt/V + CRP (excluded all non-significant variables present in Model 1).
*Multivariable logistic regression analysis. Significant values (<0.05) are presented in bold.
[a] 3 months average (n, n−1 and n−2) of values at the monthly scheduled blood sample collection.
[b] Albumin corrected.

$p < 0.001$); and higher: Ca (OR 1.51, $p < 0.001$), ERI (EPO Resistance Index) (OR 1.05, $p < 0.001$), Kt/V (OR 2.135, $p < 0.001$) and CRP (OR 1.01, $p < 0.001$) remained significantly associated with MIS>5 in this model. Pcreat gained statistical significance in the multivariable model.

4. Discussion

K/DOQI recommends routine nutritional status assessment with SGA [8]. We chose MIS instead, a more comprehensive and fitted score that takes into account the inflammatory status, lacking only the assessment of psychosocial problems [1,6,11,14].

Significant correlations with prospective hospitalization, mortality, inflammation and anaemia have been reported. It appears to be a marker of refractory anaemia with a significant correlation to haematocrit, possibly because inflammation is associated with erythropoietin resistance and additionally, low TIBC and high ferritin levels, and are risk factors for morbidity and mortality, which supports the inclusion of serum TIBC (or transferrin) in the score [1–3,8,14,17,18].

Other associations have been found: coronary disease, health-related quality of life, sleep and depression disorders, exercise capacity and oxygen uptake. Also it is a predictor of the severity of endothelial dysfunction (positively correlated with CRP, oxidized low density lipoprotein, vascular cell adhesion molecule type-1 and soluble intercellular adhesion molecule type-1, but not with E-selectin, malondialdehyde, nitric oxide, endotelin-1 and lipoprotein(a) serum levels) [17,19,20].

In an analysis of 8 nutrition-related tests, MIS and albumin predicted mortality and infection equally well, but MIS predicted cardiovascular events better, which is particular significant in CKD5D patients setting of major causes of mortality [11,21]. The relative risk of death for each 1-unity MIS increase was found to be 1.15 (95% CI, 1.03–1.3; $P = 0.02$), while a 10-unit increase was 10.43 (95% CI, 2.28–47.64; $P = 0.002$). When predicting mortality, it was found to be superior than each of its components, considered separately or with different subversions, and being comparable to serum CRP ($r = 0.41$) and serum interleukin-6 [1,3,11,14,17].

In this study we show that it is feasible to assess a whole population with few, but trained and specialized, human resources. As a part of nutritionists' regular intervention, it had no direct impact on labour costs, since no extra human resources or hours were needed.

When compared to most studies, our study sample is very representative, corresponding to 25% of Portugal's CKD5D population, and 97.2% of patients at that baseline of a HD clinics group. There are, however, some geographic representation limitations due to clinics locations. Interestingly, when comparing north/centre, a more traditional and rural region, with the more urban Lisbon region, we found some differences on nutritional risk profile, being more severe in the latter. This may be explained by other factors, such as family and communities net support, access to foods (in rural areas families grow some of their foods) and probably also with patient's profile acceptance and adherence to the treatment and therapies.

This population is old, with an average of 66.7 ± 14.8 years, and more than one third older than 74 years, which reflects western aging trends, especially when compared with other studies where patients' average age was lower [14,15,22].

Since demography has a big impact on nutritional risk, and also due to samples heterogeneity, comparison of results might be difficult. Nevertheless, in our population MIS average and profile were somewhat lower than others [15,22].

As expected, MIS distribution was not normal and the highest concentration of score frequencies was between a MIS of 4 and 7.

The outliers, that in this study were mainly very high MIS, had a low frequency which might be related to the fact that patients with such a high risk are less prevalent at the clinics probably due to hospitalization or death.

Distribution analysis (Fig. 1) is important as a comprehensive picture of baseline nutritional risk profile and, if followed over time,

will help to understand eventual changes in response, for example, to nutritional polices, demographic changes, etc. It also helps to raise the questions of which groups should be prioritized for intervention, and what would be the cut-offs for this population.

When analysed, comorbidities/dialysis vintage and transferrin were the parameters with the biggest impact on MIS, while albumin was shown to be one with least impact. This might indicate that the overall risk in this population could be deeply related to chronic inflammation.

An unexpected low impact of the albumin and muscular atrophy in the score might be related to the fact that these patients have already been exposed to regular nutritional counselling and oral nutritional supplementation focused on serum albumin goals.

When hypothesizing strategies to diminish the risk profile, we must predict that unchangeable factors such as dialysis vintage and comorbidities will continue to have a great impact in the risk, and as patients survive or even reduce the risk, the degree of severity of those parameters will grow over time. In this study we have chosen to use the original items MIS, not excluding dialysis vintage consideration as some previous studies did, but further analysis should take into account the possibility of adjusting MIS.

On the other hand, it would be possible to address modifiable parameters with focused and transversal nutritional strategies, being ascertain whether increasing physical activity and nutritional intake may prevent or improve those conditions, for example, addressing subclinical micronutrient deficiencies; enhancing patients' intake of n-3 polyunsaturated fats, as they have an effect on inflammatory status; and assuring optimal energy intake for an increase of patients' fat stores with specific nutritional counseling and supplementation [5].

Most variables have shown higher levels of statistical significance (Table 2, Fig. 3), a female gender, a gradually higher age, higher CRP, Kt/V, URR, calcium, weekly EPO dosage and ERI, and a lower nPNA, PTHi, phosphate, CaxP, hematocrit (baseline), and IDWG were associated with higher score. However, serum creatinine and haematocrit (3M av.) and Kt/V were not associated with the categorized score. Interestingly, when comparing baseline values with 3-months average, in most cases, the differences become more noticeable with a lower inter-quartile range.

HD modality also had a significant association (Table 1 and Fig. 3), however there is a selection bias, since patients with the best profile are the ones selected to HDF.

We did not find association with heamatocrit as referred in other studies [1].

Although we used two models (1 and 2) for the analysis of multivariable logistic regression, there is little impact on the OR, with the association strength remaining almost the same. So, it is possible to identify additional predictors of higher nutritional risk: older (≥75 years), diabetic, low serum phosphate, low Pcreat, low nPNA, higher Ca, high ERI, Kt/V and CRP. These could stand as simple alert in routine assessment of patients.

There were some study limitations: inter-applicant variability was not assessed; although considered to be one of the fittest tools, MIS still has a relative degree of subjectivity; we only analyzed routine and available parameters; the chosen cut-off for risk stratification do still need further validation for this population.

Following the analysis of this baseline data, a further follow up will be conducted to study the mortality in this sample.

In summary, in this analysis evaluating a large number of HD patients we have found that higher age (>75 years, OR 1.71, $p < 0.001$), diabetes (OR 1.25, $p = 0.026$), lower P levels (OR 1.57,$p = 0.001$), higher Ca levels (OR 1.51, $p < 0.001$), higher ERI (OR 1.05, $p < 0.001$), higher Kt/V (OR 2.14, $p < 0.001$) and higher CRP (OR 1.01 $p < 0,001$) were independently associated with a higher risk of MIS>5; higher nPNA (OR 0.29, $p < 0.001$) and higher Pcreat (OR 0.88, $p < 0.001$) were associated with a risk reduction of MIS>5 (95% CI).

5. Conclusions

Applying MIS in a whole population is laborious, but feasible, as part of regular nutritional monitoring.

With the chosen cut-off, half of our population was found to be at some level of nutritional risk.

Althought MIS has shown to be one of the most comprehensive tools for nutritional assessment, additional factors related to psychossocial factors should be considered in some way in further studies, since it is expected that they would deeply affect food accessability, behaviours and patterns, and nutritional intake.

Different clinical and laboratorial parameters were associated with a MIS>5 and may represent a simple alert sign for further assessment of the presence of malnutrition and inflammation. In line with the populations nutritional risk evolution over time, this may help to define strategies to diminish this risk in more susceptible patients and to develop protocoled interventions.

6. Practical application

Assessing a whole populations' risk profile allows us to understand baseline situation and which parameters have the greatest contribution to the MIS profile. Baseline and further assessments comparisons will help to follow evolution and impact of medical and nutritional strategies on the nutritional and inflammation risk of this population. Some clinical and laboratorial parameters may represent a simple alert sign for further nutritional risk assessments.

Conflict of interest

The authors are employees of DIAVERUM – Portugal, Nova Medical School – Universidade Nova de Lisboa or Faculdade de Ciências da Nutrição e Alimentação da Universidade do Porto. There are no additional conflicts of interest. The authors alone are responsible for the content and writing the paper, and there was no funding to this study.

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Section B

Malnutrition-Inflammation Score prognostic value: a 48-month follow-up.

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ORIGINAL RESEARCH

Prognostic Value of the Malnutrition-inflammation Score in Hospitalization and Mortality on Long-term Hemodialysis

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Objective: Since its development, cumulative evidence has been found about Malnutrition and Inflammation Score (MIS/Kalantar score) prognostic value; however, there is a shortage of recent and large studies with comprehensive statistical methodologies that contribute to support a higher level of evidence and a consensual cutoff. The aim of this study was to assess the strength of MIS association with hospitalization and mortality in a nationwide cohort.

Methods: This was a historical cohort study of hemodialysis patients from 25 outpatient centers followed up for 48 months. Univariable and multivariable Cox additive regression models were used to analyze the data. The C-index was estimated to assess the performance of the final model.

Results: Two thousand four hundred forty-four patients were analyzed, 59.0% males, 32.0% diabetic, and median age of 71 years (P_{25} = 60, P_{75} = 79). During a median period of 45-month follow-up, with a maximum of 48 months (P_{25} = 31; P_{75} = 48), 875 patients presented an MIS <5 (35.8%) and 860 patients (35.2%) died. The proportion of deaths was 23.1% for patients with the MIS <5 and 41.9% if the MIS ≥5 ($P < .001$). A total of 1,528 patients (62.5%) were hospitalized with a median time to the first hospitalization of 26 months (P_{25} = 9; P_{75} = 45). A new cutoff point regarding the risk of death, MIS ≥6, was identified for this study data set. In multivariable analysis for hospitalization risk, a higher MIS, higher comorbidity index, and arteriovenous graft or catheter increased the risk, whereas higher Kt/V and higher albumin had a protective effect. In multivariable analysis for mortality risk, adjusting for age, albumin, normalized protein catabolic rate, Charlson comorbidity index, interdialytic weight gain, Kt/V, diabetes, hematocrit, and vascular access, patients with the MIS ≥6 showed a hazard ratio of 1.469 (95% confidence interval: 1.262-1.711; $P < .001$). Higher age, higher interdialytic weight gain, higher comorbidity index, and catheter increased significantly the risk, whereas higher Kt/V, higher albumin, and higher normalized protein catabolic rate (≥1.05 g/kg/d) reduced the risk.

Conclusion: Currently, when older patients are treated with advanced dialysis methods, the MIS maintains its relevant and significant association with hospitalization and mortality.

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Introduction

NUTRITIONAL STATUS ABNORMALITIES and protein energy wasting (PEW) have a great impact in the prognosis of hemodialysis (HD). Presently, the key to action is long-term planning of nutritional strategies and prevention of the nutritional risk, where the setting of chronic, older, and multicomorbidity patients represents a challenge. It is important to understand what changeable major factors contribute to this risk, how to manage nutritional status, and how to define protocols for nutritional support and other strategies to modulate patients' dietary patterns.[1-4]

The use of adequate and practical tools for screening and comprehensive assessment of the nutritional status should be a common practice for an early detection and intervention on nutrition status abnormalities.[5-7] Several scores for HD patients have been recommended, namely, a quantitative and comprehensive 10-item score, the Malnutrition-Inflammation Score (MIS), also designated the Kalantar score, that was derived from a 7-point Subjective Global Assessment (7-SGA).[8-11]

The original Kalantar-Zadeh et al. study concluded that the best model for the MIS was to complete the 7-SGA with body mass index (BMI), serum albumin, and total iron-binding capacity, retaining the intricate relationship of the nutritional status with inflammation.[8] However, in a small sample, the MIS was correlated significantly with creatinine and C-reactive protein levels and hematocrit (Htc). The whole score was superior to its components or different subversions for predicting mortality.[8]

Ho et al, in a 12-month follow-up study of 257 stable HD patients, found out that an MIS higher than 4-5 had a significant higher risk of mortality per one score increase.[12]

In a 5-year prospective cohort study with 809 patients selected from the Nutritional and Inflammatory Evaluation in Dialysis patients, Rambod et al. concluded that the MIS was associated with inflammation, nutritional status, quality of life, and a 5-year prospective mortality (with a predictability similar to serum interleukin 6 and somewhat greater than C-reactive protein). Some limitations such as selection bias, lack of data about vascular access, and HD vintage that were not being included in MIS assessment can be pointed out. A MIS ≥5 was the suggested cutoff for worst outcomes.[13]

The MIS/Kalantar score is a valid tool for longitudinal assessment of nutritional status of HD patients, with a moderate interobserver agreement and reproducibility and a good agreement with SGA.[9,14-17]

Recently, the 2020 update of KDOQI Clinical Practice Guideline For Nutrition in CKD recommends the use of 7-SGA in adults with CKD 5D as a reliable tool for assessing nutritional status and suggests the use of the MIS specifically in CKD 5 on maintenance HD or post-transplantation patients.[18] With the growth of telenutrition in kidney care, the MIS/Kalantar score is one of the core assessment tools that can be effectively implemented.[19]

Lacking a gold standard method for measuring PEW, Carrero et al. in their meta-analysis on global PEW accessed the raw patient data of the three large studies and applied the receiver operator characteristic curve analysis to predict the risk of mortality associated with the MIS. An MIS ≥5 showed the same sensitivity and specificity.[20]

Considering the recent resurgence of the interest in the MIS, there is a shortage of recent and large studies with comprehensive statistical methodologies that would contribute to support a higher level of evidence for the use of the MIS as a tool of nutritional status assessment, as well as a consensual cutoff. Most studies published in the past few years have small cohorts and follow-ups, and in some studies, the MIS is assessed retrospectively, which could add some limitations and bias to the findings.[8,12,13,21-24]

Comparing with the original and validation study population, the demography has changed; it is composed of much older individuals, submitted to a higher efficient treatment with access to pharmacological and nutritional therapy and assured by a bundled payment in many countries.[1,25] The aim of this study was to assess the strength of MIS association with hospitalization and mortality in a nationwide cohort.

Methods

Study Design

This is a historical cohort study of prevalent HD patients from 25 HD centers. The MIS was assessed at the study baseline, and patients were followed up between September 2015 and September 2019, during a median period of 45 months.[1]

Population

The initial exclusion criteria were as follows: age <18 years, HD vintage <3 months, any disability that would affect data collection, or the score assessment and the patient's unwillingness to participate in the study.

Ethics

This study was approved by the local ethics committee and follows the principles of the Declaration of Helsinki. All patients had signed an informed consent authorizing the use of clinical data for medical research, and patient data were treated anonymously.

Table 1. Patients' Demographic and Clinical Characteristics by Group (Survived/Deceased and Nonhospitalized/Hospitalized)

	Survived 1,584 (64.8%)	Deceased 860 (35.2%)	*P*-Value	Nonhospitalized 916 (37.5%)	Hospitalized 1,528 (62.5%)	*P*-Value
	P_{50} (P_{25}-P_{75})	**P_{50} (P_{25}-P_{75})**		**P_{50} (P_{25}-P_{75})**	**P_{50} (P_{25}-P_{75})**	-
MIS	**5** (3-7)	**7** (5-10)	<.001*	**5** (3-7)	**6** (4-9)	<.001*
Age (years)	**67** (56-76)	**77** (68-82)	<.001*	**69** (57-76)	**72** (62-79)	<.001*
HD vint. (months)	**62** (48-71)	**70** (61-78)	<.001*	**63** (48-73)	**66** (65-75)	<.001*
	n (%)	**n (%)**		**n (%)**	**n (%)**	
Male	**924** (58.3%)	**517** (60.1%)	.208	**529** (57.8%)	**912** (59.7%)	.184
Diabetes	**446** (28.2%)	**335** (39.0%)	<.001	**233** (25.4%)	**548** (35.9%)	<.001
MIS ≥5	**911** (57.5%)	**658** (76.5%)	<.001	**533** (58.2%)	**1,036** (67.8%)	<.001
Age (years)			<.001			<.001
≤65	**715** (45.1%)	**167** (19.4%)		**379** (41.4%)	**503** (32.9%)	‡
66-74	**422** (26.6%)	**192** (22.3%)		**225** (24.6%)	**389** (25.5%)	
≥75	**447** (28.2%)	**501** (58.3%)	†	**312** (34.1%)	**636** (41.6%)	
Vascular access			<.001			<.001
AVF	**1,317** (83.1%)	**627** (72.9%)		**786** (85.8%)	**1,158** (75.8%)	
CVC	**132** (8.3%)	**73** (8.5%)		**58** (6.3%)	**147** (9.6%)	
AVG	**135** (8.5%)	**160** (18.6%)	†	**72** (7.9%)	**223** (14.6%)	‡

AVF, arteriovenous fistula; AVG, arteriovenous graft; CVC, central venous catheter; HD vint, hemodialysis vintage; MIS, malnutrition inflammation score.

*Mann-Whitney test *P*-value; the remaining *P*-values were obtained by the chi-square test.

†age ≥75 anos and AVG vascular access were the categories that contributed most to the association between ages, vascular access, and time until death.

‡age ≤65 anos and AVG vascular access were the categories that contributed most to the association between age, vascular access, and time until hospitalization.

Data Collection

MIS Assessment

MIS baseline assessment of the patients that fitted the inclusion criteria and other data collection was performed during a 4-month period by a team of trained registered dietitian nutritionists. The MIS has 4 main areas: clinical history (changes in body weight, dietary intake, gastrointestinal symptoms, functional capacity, comorbid conditions), physical assessment (decreased fat stores and signs of muscular atrophy), BMI, and laboratory results (albumin and transferrin/total iron binding capacity), in a total of 10 items, each scored from 0 (normal) to 3 (severely abnormal), giving a final MIS between 0 and 30.[8] Physical assessment was made as per the SGA criteria.

The defined dry weight in the day of the blood sample collection and the measured height were used to determine the BMI.

Biochemistry

Baseline biochemical data were obtained on the first midweek day (Wednesday or Thursday) of the month from predialysis and postdialysis blood samples. All the laboratory analyses were performed by the same methodology. Serum albumin was assessed with the bromocresol green method, and we chose to use transferrin values as originally suggested: ≥200 mg/dL (score 0), 199-170 mg/dL (score 1), 169-140 mg/dL (score 2), and <140 mg/dL (score 3), instead of TIBC.[8]

Follow-up

Patients were followed up during a 48-month period. Data concerning patients' current status, active or deceased (and respective cause of death) and the first hospitalization episode after the MIS assessment, were collected retrospectively based on the available medical records. These records are highly reliable because of their mandatory update by the clinicians.

Statistical Analysis

Categorical data are presented as frequencies (percentages) and continuous variables as mean (standard deviation) or median (25th-75th percentile), as appropriate. Continuous variables were analyzed using the Mann-Whitney test, and categorical variables were analyzed using chi-squared or Fisher's exact tests.

Partitioning Pearson's chi-squared statistic was applied to identify which of the age and vascular access categories contributed most to the global association between each of these variables and the outcomes death and hospitalization. Univariable and multivariable additive Cox proportional hazards regression models were applied to both time until death from all causes and time until hospitalization. Variables that attained a *P*-value < .25 in the univariable analyses were candidates to the multivariable models. Crude and adjusted hazard ratios were estimated with corresponding 95% confidence intervals (CIs). Variables that presented a nonlinear association with the risk of death were modeled with smoothers (spline functions).

Table 2. Patients' Biochemical Parameters by Group (Survived/Deceased and Nonhospitalized/Hospitalized)

	Survived			Deceased				Nonhospitalized				Hospitalized			
	Median	P25	P75	Median	P25	P75	*P*-Value‡	Median	P_{25}	P_{75}	Median	P_{25}	P_{75}	*P*-Value‡
nPCR (g/kg/d)	1.12	0.95	1.3	1.01	0.83	1.19	<.001	1.11	0.94	1.29	1.06	0.89	1.25	<.001
Albumin (g/dL)	4.0	3.9	4.2	3.9	3.6	4.1	<.001	4.0	3.8	4.2	4.0	3.8	4.2	<.001
BMI (kg/m^2)	25.1	22.1	28.5	24.4	21.2	27.7	<.001	24.7	21.9	28.0	24.9	21.8	28.2	.690
CCI	6	4	7	8	6	9	<.001	6	4	8	7	5	8	<.001
Calcium* (mg/dL)	9.22	8.89	9.59	9.36	9.04	9.77	<.001	9.25	8.92	9.65	9.29	8.95	9.65	<.001
P† (mg/dL)	4.23	3.58	4.93	3.87	3.22	4.7	<.001	4.2	3.53	4.87	4.1	3.4	4.87	.075
CaxP† (mg^2/dL^2)	38.92	32.95	45.93	36.44	30.27	44.01	<.001	38.93	32.27	45.34	37.8	31.3	45.4	.076
Pcreat† (mg/dL)	9.16	8.62	9.62	9.21	8.62	9.69	.461	9.2	8.7	9.66	9.15	8.56	9.64	.225
IDWG† (%)	3.02	2.43	3.68	2.88	2.3	3.6	.004	2.98	2.42	3.66	2.96	2.37	3.66	.418
Htc† (%)	33.8	31.7	35.68	34	31.9	36.1	.32	33.8	32.2	35.63	33.9	32	35.9	.594
Kt/V†	1.89	1.7	2.13	1.88	1.69	2.08	.052	1.92	1.72	2.15	1.87	1.68	2.08	<.001
PTHi† (pg/dL)	366	243	532	339	210.5	497.3	.005	367.5	243.5	523	356	225.8	520	.041
URR† (%)	0.8	0.76	0.83	0.8	0.76	0.83	.108	0.8	0.77	0.83	0.79	0.76	0.83	<.001

BMI, body mass index; CaxP, phosphocalcium product; CCI, Charlson comorbidity index; Htc, hematocrit; IDWG, interdialytic weight; nPCR, normalized protein catabolic rate gain; P, inorganic serum phosphorus; Pcreat, plasmatic creatinine; PTHi, intact parathormone; URR, urea removal rate.

*Albumin corrected calcium, 3 months' average.

†3 months' average.

‡Mann-Whitney test *P*-value.

Cutoff values of MIS, normalized protein catabolic rate (nPCR), and serum phosphorus (P) for identifying high-risk patients were assessed using the partial function plots obtained by the additive Cox regression models. Death and hospitalization event-free survival rates were obtained using the Kaplan-Meier estimator and compared using the log-rank test. Harrell's C-index, also known as the concordance index, was used as a goodness-of-fit measure.[26] To test the proportional hazard assumption of the Cox regression models, Schoenfeld residuals were used.[27] To solve the issue of the lack of proportionality detected, continuous variables were categorized. A level of significance $\alpha = 0.05$ was considered. Data were analyzed using the statistical program R Development Core Team. R: (A language and environment for statistical computing, R Foundation for Statistical Computing, Vienna, Austria).

Results

There were 2,444 patients found eligible, 59.0% males, 32.0% diabetic, with a median age of 71 years (P_{25} = 60, P_{75} = 79), and followed up during a median period of 45 months and with a maximum of 48 months (P_{25} = 31; P_{75} = 48). All-cause mortality was observed in 860 patients (35.2%). Eight hundred seventy-five patients presented an MIS<5, corresponding to 35.8% of the study sample. A total of 1,528 patients (62.5%) were hospitalized at least once, and the median time from MIS assessment to the first hospitalization was 26 months (P_{25} = 9; P_{75} = 45). The descriptive analysis of patients' demographic characteristics, clinical characteristics, and biochemical parameters is described in Tables 1 and 2. The risks for hospitalization and mortality as per the quartiles are presented in Table S1.

Hospitalizations

The causes of the first hospitalization after baseline assessment of the MIS are described in Figure S1, and 1,528 patients were hospitalized at least once. There were 492 (56.2%) events in the group of patients with the MIS <5 (n = 875), whereas in the group with the MIS ≥5 (n = 1,569), the proportion of first hospitalization was higher (1,036 patients, 66.0%).

Multivariable analysis results, Table 3, showed that higher MIS, higher Charlson comorbidity index (CCI), and vascular access with arteriovenous graft (AVG) or central venous catheter (CVC) increased the risk of hospitalization, whereas a higher Kt/V and higher albumin had a protective effect. After adjusting for potential confounders, age, P, and nPCR did not remain in the final multivariable model.

Mortality

Regarding the suggested cutoff point 5 for the MIS, there were 202 (23.1%) events in the group of patients with the MIS <5 (n = 875), whereas in the group with the MIS ≥5 (n = 1,569), the proportion of deaths was

Table 3. Multivariable Analysis With the Cox Additive Regression Model (Time to First Hospitalization)

	Hazard Ratio Estimate	95% CI		*P*-Value
		Lower Limit	Upper Limit	
MIS*	1.162	1.035	1.306	.011
Albumin (g/dL)	0.951	0.936	0.967	<.001
CCI	1.066	1.045	1.088	<.001
Kt/V	0.843	0.775	0.916	<.001
Vascular Access†				
AVG	1.313	1.104	1.561	.002
CVC	1.534	1.322	1.780	<.001

AVG, arteriovenous graft; CCI, Charlson comorbidity index; CI, confidence interval; CVC, central venous catheter; MIS, malnutrition inflammation score.

*Reference category MIS <5.

†Reference category: vascular access by arteriovenous fistula.

higher (658 patients, 41.9%). Figure 1 presents the estimated Kaplan-Meier survival curves for this cutoff point ($P < .001$). A new cutoff point for the MIS was identified for this study data set (Figure 2C). There were 297 (24.9%) events in the group of patients with the MIS <6 (n = 1,195), whereas in the group with the MIS ≥6 (n = 1,249), the proportion of deaths was higher (563 patients, 45.1%). In the diabetic group, the cutoff point identified was 7 (Figure 2B).

To solve the issue of the lack of proportionality of nPCR (as a continuous variable) detected in the univariable model, it was categorized with the cutoff of 1.05 g/kg/d. This cutoff point was further confirmed in the multivariable analysis (Figure S2). Similar procedure was used for P, which was categorized for a cutoff 4 mg/dL (Figure S3).

In the univariable Cox regression models (Table S1), higher MIS (MIS ≥5 or MIS ≥6), higher age, higher CCI, nPCR <1.05 mg/dL, P < 4.0 mg/dL, diabetes, and CVC showed a significant increase in the risk of death, whereas higher values of interdialytic weight gain (IDWG), albumin, BMI, and Kt/V had a protective effect.

As Htc showed a nonlinear association with the risk of death, it was further modeled with smoothers (spline functions).

In multivariable analysis for mortality risk (Table 4), after adjusting for age, albumin, nPCR, CCI, IDWG, Kt/V, diabetes, Htc, and vascular access, patients with the MIS ≥6 showed a hazard ratio of 1.469 (95% CI: 1.262-1.711; $P < .001$). Higher age, higher IDWG, and higher CCI and CVC increased the risk, whereas higher Kt/V, higher albumin, and higher nPCR (≥1.05 g/kg/d) reduced the risk. Diabetes and P did not remain in the final multivariable model. Regarding the discriminative ability of the final multivariable survival model, the C-index was 0.73 (95% CI: 0.71-0.75).

The cutoff values 31.2% and 35.2% were identified for Htc (Figure S4). This figure shows that Htc values lower than 31.2% and higher than 35.2% are associated with a higher risk of death, whereas values between these two cutoff points are protective against this event.

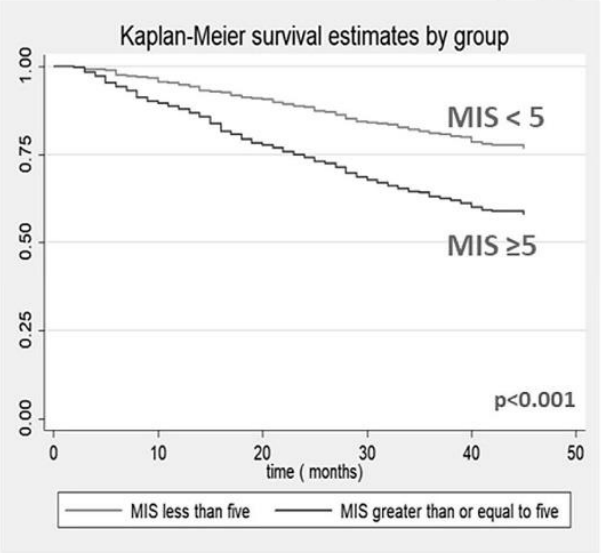

Figure 1. Kaplan-Meier survival curves estimated by MIS group (outcome: time to death). MIS, malnutrition inflammation score.

Discussion

The aim of this study was to assess the strength of MIS association with hospitalization and mortality on long-term HD. This score was developed about 2 decades ago, and there is a lack of recent and relevant studies in HD patients. The 2020 update of KDOQI Clinical Practice Guideline for Nutrition in patients with CKD suggests the use of the MIS/Kalantar score specifically in CKD 5 on HD or post-transplantation patients, but no suggested cutoffs are presented. This supports the pertinence of this study where more comprehensive statistical methodologies, a large nationwide cohort (one of the largest), and a considerable follow-up time were used to obtain a cutoff point for the MIS/Kalantar score regarding the risk of death.[18]

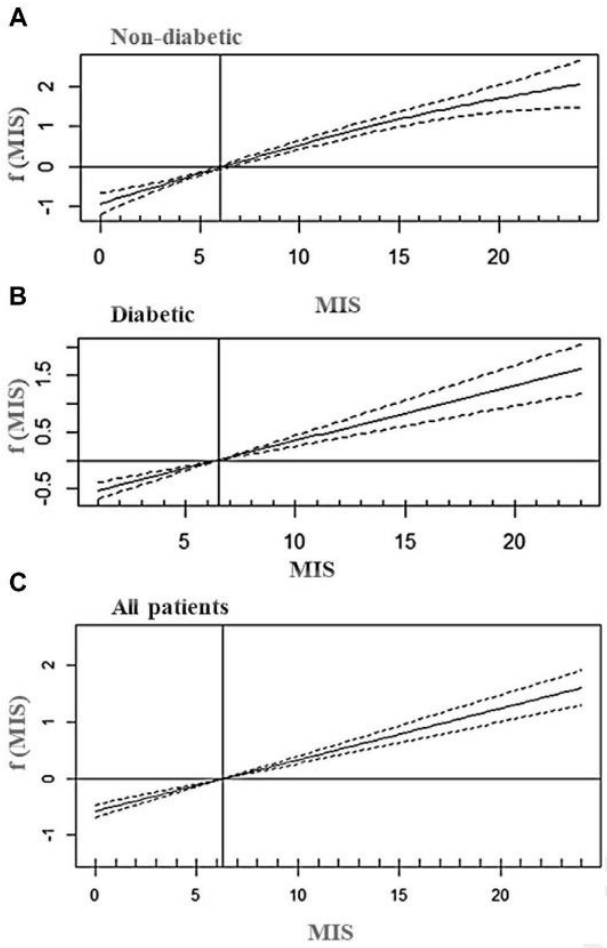

Figure 2. Fitted smooth effects of MIS on risk of death, represented by f(MIS) with a black curve, with corresponding 95 confidence intervals (dashed lines) obtained by the generalized additive Cox model. At certain observed point of MIS, a negative value of f(MIS) means that, at that point, the expected death decreases. At the contrary, if f(MIS) is positive, the expected risk of death increases. The vertical black line identifies the MIS cutoff of approximately 6 for nondiabetic patients (A), 7 for diabetic patients (B), and 6 for all patients (C).

Following the trend of this population of becoming older and with more comorbidities, there is an effort of health entities for a more thorough follow-up. This is assured by a bundled reimbursement of more efficient HD treatments, a comprehensive and coordinate care with nutritional counseling and therapy as well as medication, which is expected to have a positive impact.[1]

Concomitant with higher nutritional risk, worst parameter profile, and lower protein intake, the deceased patients (Tables 1 and 2) were older (with more than 75 years), with higher MIS, longer HD vintage, a greater proportion of patients being diabetic, and lower nPCR and IDWG. Patients who had at least one hospitalization episode after baseline assessment (Tables 1 and 2) had a similar pattern, but to a lesser extent, with higher MIS, higher proportion of patients younger than 45 and older than 75 years, and lower Kt/V, intact parathormone, and urea removal rate values.

As per the suggestion of Carrero et al. meta-analysis, we used an MIS ≥5 cutoff, as well as a nondiscretized MIS. Kaplan-Meier survival curve estimates for a cutoff of the MIS ≥5, Figure 1, clearly showed a significant difference between the two groups ($P < .001$).[20]

With this data set we found a new cutoff of 6 for the MIS regarding the risk of death (Figure 2C) that, although very similar to the established cutoff point 5, might indicate that the score for the start of a significant nutritional and inflammation risk is becoming higher. If this is the case, this interesting finding may be the result of a high-quality delivery of care with many approaches, for which the development and implementation of nutritional protocols for early intervention may also contribute.

As expected, a lower albumin and a higher CCI increased the risk of hospitalization and of death.[28-30]

In the multivariable analysis, IDWG showed an association with time until death, in accordance with previous findings, with fluid overload having a significant impact in survival mostly due to the impact in cardiovascular outcomes.[31,32] However, its relation with nutritional status and intake also needs to be clarified.

When comparing with arteriovenous fistula, CVC is associated with higher mortality, whereas an AVG did not differ. However, in previous studies, the findings reported that both had a significant association with mortality.[33-37] For hospitalization, again comparing with arteriovenous fistula, both AVG and CVC showed to be risk factors regarding time until hospitalization, as also showed in previous studies.[38,39]

The urea kinetic–based protein catabolic rate, normalized for body weight, is often interpreted as a measure of dietary protein intake; thus, during stable conditions, protein intake is similar or slightly greater than nPCR.[18,40] It is expected that the target should be the same as the recommendations for protein intake in metabolic stable HD patients: KDOQI states that should be 1.0 to 1.2 g/kg per body weight/day, whereas European Best Practice Guidelines recommend at least 1.1 g/kg ideal body weight/day or at least an nPCR of 1.0 g/kg ideal body weight/day.[18] Our findings are in accordance with these recommendations, as a cutoff of 1.05 g/kg body weight/day was identified (Figure S2).

Phosphate serum level fluctuation may also be related to nutritional intake and dietary patterns, such as protein and foods with high content and high bioavailability, so one might expect that a poor nutritional status could be concomitant with lower P. For optimal control of phosphoro-calcium metabolism, 2003 KDOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease recommend, with strong evidence, a P serum level between 3.5 mg/dL and 5.5 mg/

Table 4. Multivariable Analysis With the Cox Additive Regression Model: Time to Death

	Hazard Ratio Estimate	95% CI		*P*-Value
		Lower Limit	Upper Limit	
MIS*	**1.469**	1.262	1.711	<.001
Age (years)	**1.035**	1.027	1.043	<.001
Albumin (g/dL)	**0.938**	0.921	0.956	<.001
nPCRcat† (g/kg/d)	**1.209**	1.048	1.395	<.001
CCI	**1.122**	1.088	1.157	<.001
IDWG (%)	**1.088**	1.022	1.158	.009
Kt/V	**0.856**	0.764	0.958	.007
Vascular access‡				
AVG	1.122	0.879	1.432	.360
CVC	**1.555**	1.297	1.863	<.001

AVG, arteriovenous graft; CCI, Charlson comorbidity index; CI, confidence interval; CVC, central venous catheter; IDWG, interdialytic weight gain; MIS, malnutrition inflammation score; nPCR cat, normalized protein catabolic rate categorized.

*Reference category MIS <6.

†Reference category nPCR >1.05 g/kg/d.

‡Reference category: vascular access by arteriovenous fistula hematocrit was also included in this multivariable model having been modeled with splice (Figure 5; $P < .001$). Q16

dL. In our analysis, the cutoff of 4 found, Figure S3, is in accordance with current recommendation.[2,41]

Currently, the discussion still prevails about which would be the optimal hemoglobin levels, and consequently Htc values, that are associated with lower cardiovascular and death risk; KDIGO guidelines on anemia indicate a preferable, although not definitive, target level of 9.5-11.5 g/dL for hemoglobin (corresponding to Htc 30% to 35%) in patients treated with erythropoietin, whereas the European Best Practice Guidelines suggest 11-12 g/dL (corresponding to Htc 33% to 36%).[42-45] Findings with this data set, 31.2-35.2% (Figure S4), are coherent with the guidelines.

Reflecting the tendency in most countries, our sample was composed of much older patients. Even with the demographic differences and times of follow-up, the findings of our study, concerning hospitalization and mortality, support the conclusions of the previous studies, of Kalantar et al., Rambod et al., and Borges et al.[1,8,13,22,23]

In the recent study of Borges et al. in a smaller sample composed by younger patients and 44.4% diabetics, followed up for 18 months, a cutoff of 7 showed a high specificity to predict mortality.[23] In our study, we also found that for the diabetic patients' group, the cutoff was MIS ≥7.

The main results of our search were the confirmation that the MIS/Kalantar score maintains its prognostic value in hospitalization and mortality and the strength of the previously suggested cutoff of MIS ≥5. In addition, we found 2 new cutoffs (MIS ≥6 for all patients and MIS ≥7 for the diabetic patients); thus, it raises the question if there is a trend of an increment of the cutoff and if there might be necessary to define different cutoffs as per population, for example, for diabetic/nondiabetic patients. Further studies with wider samples are important to understand the trends of MIS/Kalantar score cutoffs, which can be achieved with the use of telenutrition in kidney care, as it can be effectively implemented, increasing the number of patients that can be routinely assessed.

Study Limitations

Although major comorbidities are considered in MIS assessment and the CCI was used in the analysis, there might be limitations in the models used for not considering those core variables alone. The fact that this is a study with a retrospective design and that there was not a comparison with other measurements of malnutrition can also be considered as a limitation.

Although the results for nPCR are solid, some limitations can be pointed out: it was not possible to account for residual renal urea clearance to correct nPCR value; overestimation can occur when protein intake is less than 1 g/kg/day, possibly due to protein catabolism; normalization of PCR to body weight can also be misleading in obese patients and/or with fluid overload. However, as nPCR estimation is automatic, it was not feasible to adjust to edema-free body weight in individuals who are <90% or >115% of standardized body weight.[18,40,45]

Even though with a considerable sample, the fact that this is a national study may affect some of the external validity of our findings, particularly in countries where HD patients' demographics are distinct or without pre-existence of continuous nutritional monitoring and support. On the other hand, in countries where the same demography and comorbidity tendency are similar, these findings may be pertinent.

Conclusion

Currently, when older patients are treated with advanced dialysis methods, the MIS maintains its relevant and significant association with mortality and hospitalization.

Practical Application

The MIS can be applied routinely as a tool for malnutrition and inflammation risk assessment and monitoring. A cutoff of MIS ≥5 should be considered for clinical intervention protocols aiming for a better nutritional status and reducing the risk of mortality and hospitalization. However, with the suggested new cutoff of MIS ≥6, further studies are needed to understand if there is a trend in the increase of the cutoff as well as the need to define other cutoffs for specific groups.

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Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1053/j.jrn.2021.11.002.

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Supplementary Tables

Table S1 - Hazard ratio for hospitalization and mortality according to the quartiles of MIS/Kalantar score.

	Quartile 1				*Quartile 2*				*Quartile 3*				*Quartile 4*			
MIS/Kalantar Score	0 - 3				4 - 6				7-8				≥9			
Frequency (n)	875				609				390				570			
		95% CI				95% CI				95% CI				95% CI		
	Hazard ratio estimate	Lower limit	Upper limit	p-value	Hazard ratio estimate	Lower limit	Upper limit	p-value	Hazard ratio estimate	Lower limit	Upper Limit	p-value	Hazard ratio estimate	Lower limit	Upper Limit	p-value
Hospitalization	1.0 (reference)				1.363	1.225	1.518	<0.001	1.412	1.276	1.562	<0.001	1.485	1.326	1.663	<0.001
Mortality	1.0 (reference)				2.096	1.790	2.454	<0.001	2.212	1.934	2.530	<0.001	2.369	2.061	2.723	<0.001

Table S2. Univariable analysis with Cox regression model: time to death.

	Hazard ratio estimate	*95% CI*		*p-value*
		Lower limit	Upper limit	
MIS/Kalantar score	1.131	1.114	1.148	<0.001
MIS≥5 [a]	2.104	1.797	2.463	<0.001
MIS≥6 [a]	2.150	1.868	2.475	<0.001
Age (years)	1.054	1.048	1.061	<0.001
nPCR [b] *(g/kg/d)*	0.757	0.716	0.799	<0.001
nPCR cat.[c] *(g/kg/d)*	1.750	1.529	2.004	<0.001
Albumin (g/dL)	0.910	0.899	0.921	<0.001
BMI (kg/m²)	0.963	0.950	0.977	<0.001
CCI	1.251	1.220	1.283	<0.001
P (mg/dL)	0.804	0.755	0.857	< 0.001
P cat. [d] *(mg/dL)*	1.469	1.285	1.680	< 0.001
IDWG (%)	0.932	0.880	0.988	0.017
Kt/V [e]	0.883	0.794	0.982	0.021
Diabetes	1.468	1.280	1.683	<0.001
Vascular access [f]				
AVG	1.143	0.875	1.456	0.281
CVC	2.116	1.779	2.518	<0.001

CI - Confidence Interval; **MIS** - malnutrition inflammation score; **nPCR** - normalized protein catabolic rate; **nPCR cat.** - normalized protein catabolic rate categorized; **BMI** - Body Mass Index; **CCI** - Charlson Comorbidity Index; **P** - inorganic serum phosphorus; **P cat** - inorganic serum phosphorus categorized; **IDWG** - interdialytic weight gain; **CVC** - central venous catether; **AVG** - arterio-venous graft.

[a] Reference category MIS < 5, and MIS<6, respectively

[b] HR estimate per 0.2mg/dl increase

[c] Reference category nPCR > 1.05 g/kg/d

[d] Reference category P> 4.0 mg/dL

e HR per each 0.5 units increase

[f] Reference category: arterio-venous fistula

Table S3. Univariable analysis with Cox regression model: time to first hospitalization after baseline.

		95% CI		
	Hazard ratio estimate	Lower limit	Upper limit	*p-value*
MIS/Kalantar score	1.057	1.044	1.071	<0.001
MIS≥5[a]	2.104	1.797	2.463	<0.001
Age (years)	1.012	1.009	1.016	<0.001
nPCR[b] *(g/kg/d)*	0.914	0.878	0.951	<0.001
nPCR Cat[c] *(g/kg/d)*	1.183	1.07	1.308	0.001
CCI	1.098	1.077	1.119	<0.001
P (mg/dL)	0.958	0.914	1.004	0.08
P Cat [d] *(mg/dL)*	1.184	1.056	1.328	0.004
Kt/V [e]	0.856	0.791	0.927	<0.001
Diabetes	1.376	1.239	1.528	<0.001
Vascular Access [f]				
AVG	1.387	1.168	1.647	<0.001
CVC	1.742	1.509	2.011	<0.001

CI - Confidence Interval; **MIS -** malnutrition inflammation score; **nPCR** – normalized protein catabolic rate; **nPCR cat.** – normalized protein catabolic rate categorized; **CCI** – Charlson Comorbidity Index; **P** – inorganic serum phosphorus; **P cat** – inorganic serum phosphorus categorized; **CVC** – central venous catether; **AVG** – arterio-venous graft.

[a] Reference category MIS < 5

[b] HR estimate per 0.2mg/dl increase

[c] Reference category nPCR > 1.05 g/kg/d

[d] Reference category P> 4.0 mg/dL

e HR estimate per each 0.5 increase

[f] Reference category: arterio-venous fistula

Supplementary Figures

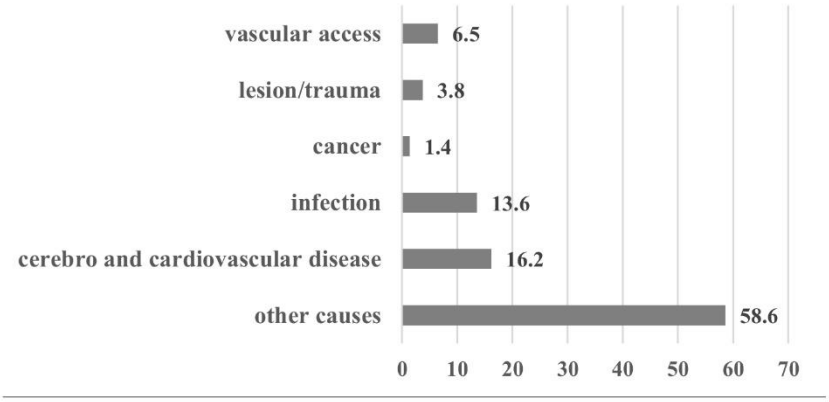

Figure S1. Main causes of first hospitalization after

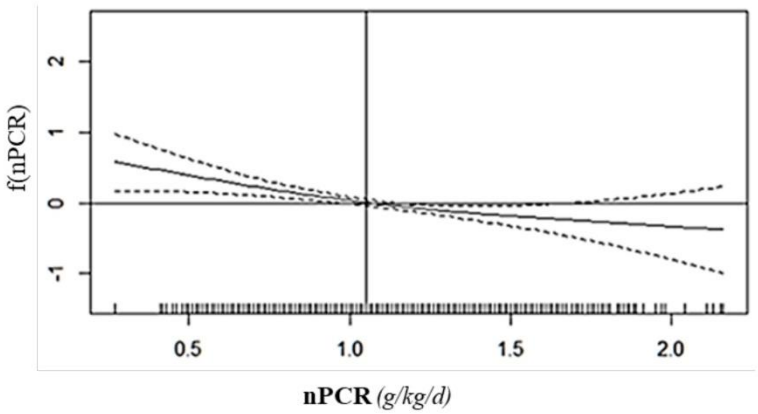

Figure S2. Fitted smooth effects of nPCR on risk of death, represented by f(nPCR) with a black curve, with corresponding 95% confidence intervals (dashed lines), obtained by generalized additive Cox model. At a certain observed point of nPCR, a negative value of f(nPCR) means that, at that point, the expected risk of death decreases. At the contrary, if f(nPCR) is positive, the expected risk of death increases. Vertical black line identifies the normalized catabolic rate cut-off at 1.05 g/kg/d.

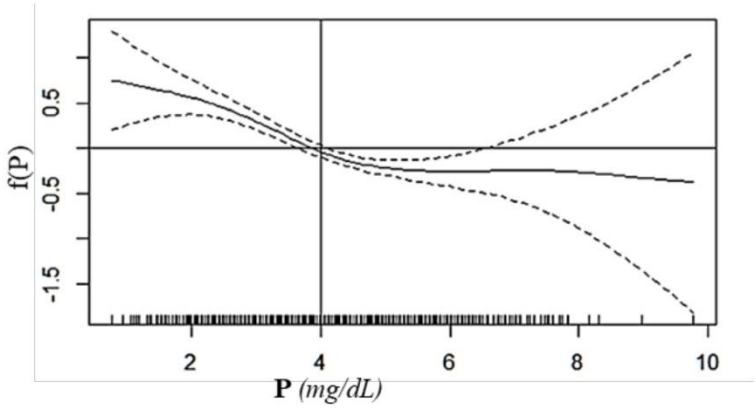

Figure S3. Fitted smooth effects of P on risk of death, represented by f(P) with a black curve, with corresponding 95% confidence intervals (dashed lines) obtained by generalized additive Cox model. These smooth effects reflect a nonlinear change of the expected survival risk considering each value of P. At a certain observed point of P, a negative value of f(P) means that, at that point, the expected risk of death decreases. At the contrary, if f(P) is positive, the expected risk of death increases. Vertical black line identifies the serum phosphorus cut-off at 4 mg/dL.

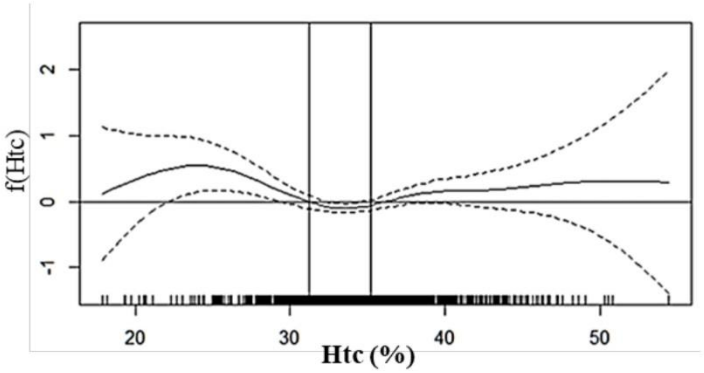

Figure S4. Fitted smooth effects of Htc on risk of death, represented by f(Htc) with a black curve, with corresponding 95% confidence intervals (dashed lines) obtained by generalized additive Cox model. These smooth effects reflect a nonlinear change of the expected survival risk considering each value of Htc. At a certain observed point of Htc, a negative value of f(Htc) means that, at that point, the expected risk of death decreases. At the contrary, if f(Htc) is positive, the expected risk of death increases. Vertical black lines identify hematocrit cut-offs at 31.2-35.2%.

Section C

Association of diabetes, non-insulin treated vs insulin treated, with malnutrition and inflammation risk.

Abstract title:
"Diabetes and malnutrition Risk in hemodialysis patients"

Presentation: facsimile

Indexed Journal: Nephrology Dialysis Transplantation, IF 5.922 (2020)

Published: June 13th, 2019

Reference:
Sá Martins V, Aguiar L, Dias C, Lourenço P, Pinheiro T, Velez B, Birne R, Borges N, Adragão T, Calhau C, Macário F. FP718 Diabetes and malnutrition Risk in hemodialysis patients. Nephrol Dial Transplant 34 (Supplement 1): i292–i304, 2019.
https://doi.org/10.1093/ndt/gfz106.FP718

Nephrology Dialysis Transplantation 34 (Supplement 1): i292–i304, 2019
doi:10.1093/ndt/gfz106

FP718 DIABETES AND MALNUTRITION RISK IN HEMODIALYSIS PATIENT

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INTRODUCTION: Diabetes is highly prevalent in hemodialysis (HD) patients (pts) as well as malnutrition. Due to the diabetes onset, pathological and metabolic nature, it would be expected to have a high impact on chronic pts' nutritional risk. We aim to analyze the association of diabetes, namely non-insulin treated (NIT) vs insulin treated (INS), with malnutrition risk in HD pts.

METHODS: Cross sectional analysis of 2975 HD patients (25% of Portuguese pts in HD), assessed between September 15th 2015 and January 31st 2016. Nutritional risk was assessed with the malnutrition-inflammation score (MIS) and when >5 indicates increased risk.

RESULTS: 1758 male (59.1%) pts; 622 (21%) pts on hemodiafiltration and 2353 (79%) on High-flux HD. All diabetic pts, 984 (33.1%), were treated, 756(25.4%) INS and 228 (7.7%) NIT. In univariate analysis diabetes was not associated with a MIS>5 (p=0.094) but ROC Curve Analysis identified the association of a MIS>6 with diabetes (AUC= 0.517±0.01; 95%CI 0.49-0.53; Sensitivity 41%; Specificity 63%).

Diabetic vs non-Diabetic pts were older (70.2±11 vs 64.9±15, p<0.001), with lower nPCR (1.07±0.27 vs 1.10±0.18, p=0.008), lower Ca (9.2±0.7 vs 9.3±0.7, p=0.014), lower P (4.05±1.2 vs 4.2±1.3, p=0.01), lower CaXP (37.8±10.9 vs 38.8±12.4, p=0.001) lower PCreat (8.6±1.5 vs 9.1±1.3, 6.6±6.8, p<0.001), lower EPO res index (6.8±6.8 vs 7.5±8.3, p=0.032), lower Kt/V (1.8±0.34 vs 1.9±0.39, p<0.001), lower PTH (389±262 vs 448±393, p<0.001), lower URR (0.778±0.08 vs 0.796±0.55,p<0.001) and lower weekly treatment duration (743±88 vs 796±114, p=0.002).

INS vs NIT pts were younger (69.7±11.4 vs 71.7±10, p<0.001), with lower nPCR (1.06±0.27 vs 1.10±0.27, p=0.008), lower EPO Res index (6.5±6.6 vs 7.7±7.9, p=0.036), higher Htc (34.1±4.4 vs 33.4±5.2, p<0.001), lower Kt/V (1.84±0.32 vs 1.85±0.31, p<0.001), and lower CRP (11.8±20.9 vs 17.7±32.4, p=0.027).

MIS>6 was associated with older age (70.1±14.3 vs 63.9±14.9, p<0.001), higher prevalence of female gender (44% vs 34%, p<0.001), diabetes (41% vs 37%, p=0.023), lower P (3.8±1.2 vs 4.31.2, p<0.001), higher Ca (9.3±0.65 vs 9.2±0.62, p<0.001), lower nPCR (1.01±0.28 vs 1.13±0.26, p<0.001), higher EPO Res index (8.7±9.2 vs 6.3±6.7, p<0.001), higher Kt/V (1.9±0.3 vs 1.8 ±0.3, p<0.001), higher URR (0.79±0.6 vs 0.78±06, p<0.001), higher CRP (15.7±25 vs 9.7±16.8p<0.001), lower prevalence of HDF (31% vs 41%, p<0.001). Analyzing separately INS and NIT pts, only INS pts had higher prevalence of MIS>6 (42% vs 37%, p=0.014).

In multivariate analysis, adjusting for age (OR 1.02, p<0.001), gender (OR 0.794, p=0.029), HDF (OR 0.797, p=0.058), Kt/V (OR 1.63, p=0.003), CRP (OR 1.01, p<0.011) and EPO Res index (OR 1.04, p<0.001), INS was associated with MIS>6 (OR 1.314; CI 1.070-1.613, p=0.006). NIT was not associated with MIS>6 (p=0.564).

CONCLUSIONS: In our population, diabetic pts treated with Insulin had a 1.3 fold increased risk of malnutrition defined as MIS>6, while diabetic pts non-insulin treated had not. A frequent and comprehensive nutritional intervention regarding a higher nutritional risk would benefit diabetic HD pts treated with Insulin.

Section D

Association of malnutrition and inflammation risk with erythropoietin resistance index.

Abstract title:
"MO901Association of Malnutrition and Inflammation with Erythropoietin Resistance Index"

Presentation: facsimile

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https://doi.org/10.1093/ndt/gfab102.002

Nephrology Dialysis Transplantation 36 (Supplement 1): i494–i501, 2021

MO901

ASSOCIATION OF MALNUTRITION AND INFLAMMATION WITH ERYTHROPOIETIN RESISTANCE INDEX

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BACKGROUND AND AIMS: Erythropoietin Resistance Index (EPORI) has been previously associated with higher risk of mortality and morbidity in hemodialysis (HD) patients (pts). The objectives of this study were to identify which factors, such as the risk of malnutrition, are associated with EPORI and to assess its association with mortality and hospitalization risk.

METHOD: Historical cohort study in a group of high-flux HD pts from 25 outpatient HD clinics, starting from a baseline group of 2975 pts. We evaluated EPORI, interdialytic weigh gain (IDWG), Malnutrition Inflammation Score (MIS) and the other parameters at the study baseline. For a better understanding of weight gain patterns, we calculated the average of the IDWG at the day of monthly blood sample collection of the previous 3 months, values >4% were considered high. A MIS>5 indicated nutritional risk.

RESULTS: We analyzed 2044 pts, 1148 (56%) males, 642 (31%) diabetic, with a mean age 68.4±14.12 years, a mean HD vintage 105±74 months and mean EPORI 7.23±7.51 (U/week/kg)/(g/dL). During a follow-up of 48 months, 719 pts (35%) died and 1291 pts (63%) were hospitalized at least once after baseline assessment, 531 pts and 400 pts were excluded because follow up was not possible and EPORI data was not available, respectively.

ROC curve analysis identified different cut-off values for EPORI in relation with all-cause mortality and hospitalizations.

UNIVARIABLE ANALYSIS: An EPORI>5 was associated with higher MIS (7.06±3.9, vs 6.02±3.48, p<0.001), higher IDWG (3.15±1.23 vs 1.26±1.09, p<0.001), lower Hematocrit (Htc) (33.26±3.17 vs 33.69±2.61, p<0.001), higher C-Reactive Protein (CRP) 14.94±24.45 vs 10.4±18.9, p<0.001), female gender (57% vs 48%, p<0.001), death (58% vs 49%, p<0.001) and hospitalization (55% vs 47%, p<0.001). When analyzing with Kaplan-Meier estimator using log-rank test to compare survival curves, mortality and hospitalizations were increased in all sub-groups with higher values for EPORI (cut-offs of 5 to 8) when compared, respectively, with lower EPORI values.

	Mortality		Hospitalizations	
	Log-Rank (x2)	p-value	Log-Rank (x2)	p-value
EPORI>5	16.663	**<0.001**	25.808	**<0.001**
EPORI>6	21.905	**<0.001**	28.847	**<0.001**
EPORI>7	23.698	**<0.001**	29.847	**<0.001**
EPORI>8	27.022	**<0.001**	44.673	**<0.001**

MULTIVARIABLE ANALYSIS: The predictors of EPORI were MIS>5 (OR 1.564, p<0.001), IDWG (OR 1.234, p< 0.001), CRP (OR 1.010, p<0.001) and Htc (OR 0.948, p<0.001).

In similar models, adjusting for MIS>5 (p<0.001), gender (p<0.001), age (p<0.001), CRP (p<0.001) and dialysis vintage (p<0.001), different EPORI cut-off values were associated with higher risk of mortality and hospitalizations.

Mortality	Hazard ratio (*HR*) estimate	95% CI		p-value
Lower limit	Upper limit			
EPORI>5	1.378	1.179	1.611	**<0.001**
EPORI>6	1.418	1.216	1.654	**<0.001**
EPORI>7	1.419	1.215	1.658	**<0.001**
EPORI>8	1.466	1.248	1.723	**<0.001**

Hospitalization	Hazard ratio (*HR*) estimate	95% CI		p-value
Lower limit	Upper limit			
EPORI>5	1.301	1.160	1.458	**<0.001**
EPORI>6	1.316	1.174	1.476	**<0.001**
EPORI>7	1.370	1.219	1.540	**<0.001**
EPORI>8	1.468	1.300	1.658	**<0.001**

CONCLUSION: In the modern hemodialysis era, higher EPORI cut-off values were associated with a progressive higher risk of mortality and of hospitalization. The modification of the EPORI predictors that are susceptible to improvement, such as the nutritional and inflammation status, may contribute for a better prognosis in this population.

Section E

Association of interdialytic weight gain with malnutrition and inflammation risk, hospitalization and mortality.

Abstract title:
"High Interdialytic Weight Gain in Hemodialysis Patients: Friend or Foe?"

Presentation: full text

Indexed Journal: Journal of Renal Nutrition, IF 3.655 (2020)

Published: March 1st, 2021

Reference:
Sá Martins V, Adragão T, Aguiar L, Dias C, Figueiredo R, Lourenço P, Pascoal T, Pereira J, Pinheiro T, Ramião I, Velez B, Borges N, Calhau C, Macário F. High interdialytic weight gain in hemodialysis patients: Friend or Foe?J Ren Nut. 2021; 31, 2: 224.
https://doi.org/10.1053/j.jrn.2021.01.018

Background: an interdialytic weight gain (IDWG) lower than 4%-4.5% of the dry weight is a target in hemodialysis (HD) patients (pts). The objective of our study was to evaluate the association of this clinical performance parameter with other parameters, as well with mortality and hospitalizations.

Methods: historical cohort study in a group of high-flux HD pts from 25 outpatient hemodialysis clinics, starting from a baseline group of 2975 pts. IDWG and Malnutrition Inflammation Score (MIS) were evaluated at the study baseline. For a better understanding of weight gain patterns, we calculated the average of the IDWG at the day of monthly blood sample collection of the previous 3 months, values >4% were considered high. A MIS>5 indicated nutritional risk.

Results: We analyzed 2424 pts (59% males; 32% diabetic, 64% with MIS>5). At the baseline 360 pts (16%) presented an IDWG>4%. During the follow-up of 48 months, 851 pts (35%) died and 1550 pts (63%) were hospitalized at least once.

Univariable analysis:

IDWG>4% was associated with HD vintage (11.3±9.7 vs 8.9±9.0 years of treatment, p<0.001) lower age (60.1±15.7 vs 69.9±12.8, p<0.001), higher P levels (4.3±1.2 vs 4.1±1.1, p<0,001), higher EPO resistance index (8.6±8.6 vs 7.1±7.7 (U/week/kg)/(g/dL), p=0.002), higher KTV (2.01±0.35 vs 1.88±0.30, p<0.001), higher URR (0.80±0.05 vs 0.78±0.05, p<0.001), longer weekly HD sessions duration (780.8±137.3 vs 743.5±95.2 min, p<0.001), male gender (21.4% vs 16.6%, p=0.003) and non-diabetic patients (2.7% vs 17%, p=0.032).

IDWG>4% was not associated with MIS>5 (19.3% vs 19.9%, p=0.746),

Multivariable analysis:

IDWG>4% was directly associated with HD vintage (OR 1.02, 95%CI: 1.01-1.03, p=0.002), male gender (OR 1.91, 95%CI: 1.46-2.50, p<0.001), nPCR (OR 2.5, 95%CI: 1.65-3.92, p<0.001), Kt/V (OR 3.17, 95%CI: 2.13-4.73, p<0.001) and EPO resistance (OR 1.03, 95%CI: 1.01-1.04, p<0.001).

Survival curves with Kaplan Meier estimator:

IDWG>4% was not associated with all-cause mortality (17.9% vs 20.3%, log rank 0.097) nor with hospitalizations (19% vs 20%, log rank 0.520).

Conclusion: IDWG is a complex parameter with many confounders. IDWG>4% was associated with different factors but it was not associated with higher risk of hospitalization and mortality. Further analysis is needed to reassess IDWG impact and which targets should be met.

Section F

Intradialytic oral nutrition support snack model for compensation of catabolic impact of hemodialysis.

Manuscript title:
"Can an intradialytic snack compensate the catabolic impact of hemodialysis?

Presentation: facsimile

Indexed Journal: Clinical Nutrition ESPEN, IF 2.38 (2020)

Published: January 8th, 2021

Reference:
Sá Martins V, Adragão T., Aguiar L, Fortes A, Costa M, Borges N, Calhau C, Macário F. Can an intradialytic snack model compensate the catabolic impact of hemodialysis? Clinical Nutrition ESPEN.2021; 42, 292-298.
https://doi.org/10.1016/j.clnesp.2021.01.018

Clinical Nutrition ESPEN 42 (2021) 292–298

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Original article

Can an intradialytic snack model compensate the catabolic impact of hemodialysis?

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SUMMARY

Background and aims: Hemodialysis (HD) has a catabolic effect caused by alterations in protein metabolism, increase in resting energy expenditure (REE) and protein needs due to inflammation, HD circuit blood and heat losses, protein losses to dialysate and HD filter membrane biocompatibility. We aim to determine, as a *proof of concept*, whether a standardized intradialytic snack model is adequate to compensate the catabolic impact of HD.

Methods: Cross sectional analysis of patients' chosen intradialytic intake according to a snack model, at the day of blood sample collection of three different months. As targets for the compensation of the catabolic impact of HD, we considered 316.8kCal (1.32 (±0.18) kcal/min − 240' of HD) for the estimated increase in REE and at least 7 g of protein losses/HD treatment.

Results: A total of 448 meals were analyzed, with 383 given during daytime shifts. No intolerances were registered. The mean nutritional profile of the daytime shifts intakes was 378.8 (±151.4) kcal, 13.5 (±7.2) g of protein, 676 (±334) mg of sodium (Na), 361.0 (±240.3) mg of potassium (K) and 249.3 (±143.0) mg of phosphates (P). We found that 68% of the meals provided an intake ≥316.8kCal and 82% a protein intake ≥ 7 g, with a significant association found between treatment shift and energy ($p < 0.028$), protein ($p < 0.028$), lipids ($p < 0.004$), Na ($p < 0.004$), K ($p < 0.009$) and P ($p < 0.039$) intakes.

Conclusions: We found that this intradialytic snack model meets the target for the treatment-related increases in protein and energy needs. Although sodium intake was found to be high, potassium and phosphate intake was considered adequate.

1. Introduction

Aiming for an adequate intake and optimal nutritional status of hemodialysis (HD) patients can be rather challenging. There is a multitude of factors that expose these patients to a higher risk of protein energy wasting (PEW), requiring a continuous effort to achieve and maintain an adequate intake of energy and protein [1,2]. There is a need for sustained, feasible and inexpensive interventions to compensate the impact of HD on metabolism and patients' eating patterns. This can be achieved by in−center meals and oral nutrition supplementation (ONS) contributes for an improvement of survival and quality of life [1,3–7].

Although some progress has occurred in the last decades, as demonstrated by Sieving coefficients <0.01, HD treatment is still not nutritionally innocuous and a HD catabolic effect may be a consequence of several factors: protein metabolism alterations; increase in resting energy expenditure (REE); inflammation

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(activation by dialysis membranes of the complement system, lower with synthetic non complement-activating membranes); protein losses to the dialysate; blood loss due to retention in the circuit and filter; HD filter membrane structure and biocompatibility; and, finally, reduction of the nutritional intake. It is estimated that high-flux HD causes a loss of 8.0 g (±2.8) g to 9.3 (±2.7) g of free amino acids (AA) to the dialysate, which contributes to an increase in protein requirements [1,4,7–12].

Ikizler et al. found that the impact of HD in whole body and forearm protein dynamics was caused by an increment in whole body proteolysis (up to 10% or 0.32 mg/kg of fat free mass (FFM)/min) and AA losses to the dialysate (0.61 (±0.002) mg/kg of FFM/min) [4]. Both factors constituted the major agents for AA decrease in plasma [4].

Whole body protein synthesis is also reduced by 72% during HD, with breakdown remaining higher by 11% in the 2 hours after HD. Overall, whole net body protein loss was increased during HD by 0.51 mg/kg of FFM/min, or approximately twofold [4].

Whole body losses during HD alone, translate to an increased loss of ~7 g of protein per dialysis period, similar to the mass of AA lost to the dialysate. For a patient with a thrice a week dialysis schedule, this protein loss would represent a loss of ~2 kg of lean mass in a span of 1 year [4,12]. In diabetics and patients with higher levels of glucocorticoids, proteolysis is potentially worsened due to the activation of the ubiquitin-proteasome system and other hormonal abnormalities (such as hypercortisolemia) [4].

The increments in energy needs are related with protein synthesis and breakdown (5 ATP/peptide formed, 1.076 kcal/g protein or 0.022kcal/FFM/h of HD), body temperature maintenance associated to heat loss in the extracorporeal circuit and to other metabolic alterations [4,11].

Energy expenditure, adjusted for FFM, increases 7% during HD and 12% during the post HD period [4]. Although macronutrients oxidation was not different during HD, post-HD rates of carbohydrates oxidation decreased 52% and lipids oxidation increased 65% compared with baseline. With no adequate compensatory protein anabolism, these processes result in a net increase in protein catabolism and REE [4,11].

In another study, Ikizler showed that HD patients have an increased REE during HD treatment of 1.32 (±0.18) kcal/min (averaged for the 4 h of HD ($p < 0.01$), versus pre-dialysis), with this effect being most pronounced during the first and second hours of HD [13].

Despite the lack of consensus, many European and South-East Asian countries still offer free meals and ONS routinely during HD, while in other countries, like the United States, there are now strict rules against food and drink intake during HD. However, even in the United States that was not the norm until a few decades ago, as serving in–center meals was considered routine practice until late 1980's [7,8].

Currently, there is, not only, a lack of reports about the best way to provide continuous nutritional support, but also an absence of universal agreement in how to compensate the deleterious impact of HD: from "one fits all" light snacks to full meals, ONS or even intradialytic parenteral nutrition. However, the positive impact and benefits of some of these models have already been described [7,14–17].

Certainly, patients' perspective on this issue should be pivotal because high levels of adherence are needed. It is important that the model for this continuous nutritional support is familiar, pleasurable, comforting, adjusted to autonomy, and readily available to all patients, while remaining nutritionally controlled. The in–center meals model fits these premises [12].

The aim of this study was to determine, as a *proof of concept*, whether a standardized continuous intradialytic snack model, delivered according to the patient's autonomy, is adequate for compensating the targets of the estimated increase in REE and protein needs related to HD treatment. As a secondary objective, we intended to analyze the nutritional profile of these meals.

2. Methods

2.1. Study design

This is a cross-sectional observational study performed in a group of prevalent HD patients with the assessment of the meals chosen to eat during the treatment in the context of an implemented snack model.

2.2. Population

We included the data of the chosen meals of 149 patients that performed HD in an outpatient HD clinic in one of the 3 to 4 daily shifts of June 22nd/23rd, October 14th/15th of 2015 and March 16th/17th of 2016. Patients that, for any clinical reason (such as dysphagia or others), were not able to choose or could not adhere to the snack model, were excluded.

2.3. Ethics

All patients signed an informed consent authorizing the use of clinical data for medical analysis, and their data was treated anonymously. This study has been approved by the local ethics committee and its procedures were in accordance to the Helsinki declaration.

2.4. Snack model and nutritional intake assessment

The in–center meal for the day shifts (Fig. 1) is an intradialytic snack with three components (drink + solid + filling): one warm or cold drink up to 200 mL, plus one or two solids with one filling per solid. For the night shifts, since they are longer, two snacks are given at the beginning of the treatment and another at the end, as a breakfast; the amount available at each snack is the same as for day shifts.

All the procedures of the food circuit are well defined: from suppliers to preparation and serving sizes, this allows traceability and assessment of the nutritional intake. Each patient is inquired at the beginning treatment about their preferences. The food choices, entirely made by the patient, were not imposed by the nutritionist. As standard, table sugar (sucrose) and jam/marmalade were not available for the diagnosed diabetics.

We analyzed the intradialytic nutritional intake of each meal.

Since ONS was prescribed to a small fraction of these patients (0.03%), it was not pertinent to this study and we did not account for its additional nutritional contribution.

In the amounts actually eaten, the nutritional composition information of the foods in terms of energy (kcal), protein (g), high biological value (HBV) protein (g), total carbohydrates (g), mono- and disaccharides (sugars) (g), lipids (g), sodium (Na) (mg), potassium (K) (mg) and phosphates (P) (mg), was based on the values declared by the manufacturer and, when not available, by the a food composition table [18]. To calculate the contribution of HBV protein, we considered all the protein amount of the animal source foods (dairy: milk, yogurt, cheeses; and turkey ham).

The targets for energy and protein intakes in order to compensate the impact of HD treatment itself, were based on the studies of Ikizler et al.: an estimated increase in REE of 316.8 kcal (1.32 (±0.18) kcal/min − 240' of HD) and at least 7 g of protein losses/HD treatment [4,12,13].

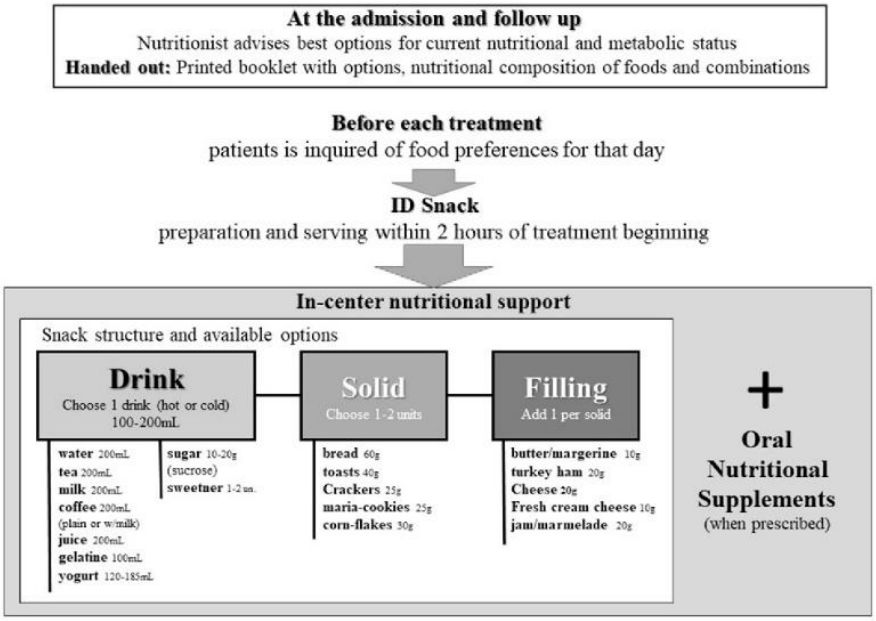


Fig. 1. Intradialytic oral nutritional support, snack model and ONS, available to all patients.

2.5. Other data

Besides gender, diabetes, swallowing ability, treatment shift and prescription of ONS, no other data was collected. The information that was not directly available during the assessment was collected from patients' chart and treatment records on the electronic clinical record system. It is mandatory that all complications during hemodialysis are registered. We analyzed all records for any related complications, such as intradialytic hypotension.

2.6. Statistical analysis

In the descriptive statistics analysis, categorical variables were presented as frequencies and percentages and continuous variables were presented by means and standard deviations or by medians and percentile ranges. The chi-square test (χ^2) was used to compare proportions between categorical variables. Analysis of Variance (ANOVA) was used to compare two or more groups of categorical variables with two or more group means. Statistical tests were performed bilaterally at a significance level of 5%, whereby a p-value <0.05 was considered statically significant. The statistical analysis of the data was performed using SPSS 24.0 (SPSS, Chicago, IL).

3. Results

A total of 448 meals were analyzed, 383 given during daytime shifts and 56 during night shifts, 165 (37.6%) were chosen by female patients and 104 (23.5%) chosen by diabetic patients and the nutritional profile mean values of day shifts are shown in Table 1 and Fig. 2.

The nutritional disparity in night shifts was due to the amount available in this snack model, up to 2 times daytime snacks.

Table 2 describes the association between treatment shift and the nutritional profile of the meals: the 1st shift shows the highest mean values for energy and almost all nutrients, except for sugars and lipids, while the 2nd shift had the lowest mean values for energy and all nutrients. The results with ANOVA reveal a significant association between the treatment shift and energy ($p < 0.028$), protein ($p < 0.028$), lipids ($p < 0.004$), Na ($p < 0.004$), K ($p < 0.009$) and P ($p < 0.039$) intake but none with HBV protein, total carbohydrates and sugars. No significant association was found between gender and diabetes with nutritional profile.

Considering the proposed targets to achieve energy and protein compensation of the HD impact (Fig. 3): 68% of the meals provided an intake $\geq$ 316.8 kcal, highest in the diabetic (72.6%) lowest in the non-diabetics (66.6%); 82% provided a protein intake $\geq$ 7 g, highest in females (86.9%) and lowest in males (79.4%), but as HBV protein is concerned, only 48% of the meals provided an intake $\geq$7 g, highest in diabetics (57.9%) and lowest in non-diabetics (44.8%).

Applying the chi-square test (χ^2), no significant association was found between these achievements and gender, diabetes or treatment shift.

No snack intolerances or incidents (such as aspiration or spilling) were registered.

The mean cost per snack was always below 1€ (~1.10$ US dollars).

4. Discussion

The nutritional therapy should aim to compensate at least some of the inherent nutritional impact of the HD treatment, so we decided to do a *proof of concept* descriptive analysis if an intradialytic snack model meets the energy and protein targets in order to compensate that catabolic impact.

Many pros and cons of in−center monitored and intradialytic meals have been discussed.

On the pros side: impact on nutritional status and clinical outcomes (with no unfavorable outcomes reported on the countries offering meals during HD); mitigation/correction of intra and post dialysis catabolism; better control of dietary P, K, Na and fluid (meal and oral nutritional supplements can be optimally prepared for the specific needs of patients, intake of P binder can be monitored and improved patient education can be achieved by simultaneous

Table 1
Nutritional profile of overall the chosen meals (day and night shifts).

	Energy (kcal)		Protein(g)		HBV[a] Protein (g)		Total Carbohydrates (g)		Sugars[b] (g)		Lipids (g)		Na (mg)		K (mg)		P[c] (mg)	
shifts	day	night	day	night	day	night	day	night	day	night	day	night	Day	night	day	night	day	night
n	383	56	383	56	383	56	383	56	383	56	383	56	383	56	383	56	383	56
Mean (SD)	378.8 (±151.4)	551.3 (±182.5)	13.5 (±7.2)	20.9 (±7.5)	5.5 (±4.8)	9.6 (±4.8)	61.9 (±23.5)	86.1 (±26.7)	16.9 (±9.7)	22.8 (±5.2)	7.9 (±5.2)	12.6 (±6.9)	676 (±335)	1040 (±360)	361.0 (±240.3)	521.6 (±307.5)	249.3 (±143.0)	395.1 (±151)
Median	399.0	556.6	13.1	21.2	4.8	9.2	67.0	88.4	16	20.3	7.4	11.3	720	1080	281.0	437.9	252.7	421.35
Minimum	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Maximum	751.3	864.0	39.4	38.3	22.4	22.0	133.1	121.5	44.7	50.0	21.2	25.6	1840	1640	948.0	1229.1	735.2	748.2
Percentiles																		
25	279.0	466.0	8.2	17.6	0.0	6.6	44.7	71.5	8.26	9.6	4.02	7.9	400	840	170.4	328.3	159.3	321.7
50	399.0	556.6	13.1	21.2	4.8	9.2	67.0	88.4	16.0	20.3	7.4	11.3	720	1080	281.0	437.9	252.7	421.4
75	487.6	686.2	18.5	25.7	8.4	13.2	77.4	107.5	24.6	33.1	10.7	18.0	880	1200	593.9	707.2	343.9	515.7

[a] HBV- high biologic value.
[b] Sugars: mono and disaccharides available in these foods – sucrose, lactose and fructose.
[c] P: organic and inorganic phosphate.

interaction with nutritionist and nephrologist while eating); increased adherence to HD treatment; improved patient satisfaction and quality of life; and relatively low costs [7,16,17].

On the cons side, the major concerns are: low blood pressure and labile circulation during food ingestion; risk of aspiration and other respiratory complications; infectious control and hygiene issues (fecal-oral transmission of infection including hepatitis A, infestation issues, food poisoning risk, food circuit may pose additional hygiene challenges); burden on dialysis staff and logistics constraints; and added expenses to HD treatment [7,16,17].

We can add another favorable reason: in countries where HD treatment is ensured by national healthcare system (or by subconventions), this meal is a measure of equity and comfort, enabling patients to have access to the same type of meal, alleviating some of the time-consuming burden of a snack preparation at home, adding the importance of meals schedule, particularly in diabetic insulin-treated patients, which have a higher nutritional risk [3,6].

Organizationally and logistically, many of the cons in the literature were inexistent in this study: no intolerances or incidents were observed in 448 meals. The whole food circuit from preparing, handling and food serving is well organized so there is an high control and low risk of infection [19,20].

Since intradialytic meals are not covered by HD treatment subconventions, there is the need to keep costs low. With this model they were reasonably low, less than 1€/snack.

4.1. Energy

The energy intake (Table 1, Figs. 2 and 3), also important to support an adequate protein metabolism, is obviously higher on the night shifts. Energy contribution was interestingly high with a mean of 378.8 (±151.4) kcal in day shifts, 75% of meals provided more than 279 kcal, and 68% met the proposed cut-off. The lowest mean intake was registered on the afternoon shifts, probably because most of the patients had lunch before the treatment, having less appetite and leading to the choice of a lighter meal; and the highest in morning shifts, probably because patients used this meal as a breakfast substitute. It is noteworthy that these values concur with the equivalent contribution of most of commercial ONS products available in our market (between 200 and 400kcal/200 mL).

4.2. Protein

The total protein intake (Table 1, Figs. 2 and 3) has met the cut-off of 7 g in 82% of meals, with a mean of 13.2 (±7.2) g and 75% of meals provided an amount higher than 8.2 g, with the same pattern between shifts.

As a key-nutrient, these values are considered positive for the premise of this study [21].

For an adequate protein synthesis an adequate contribution of HBV protein is needed. We calculated its contribution, and values were less expressive: mean 5.5 (±4.8) g in day shifts, 50% of the meals assure an intake more than 4.8 g and 25% higher than 8.4 g. If we were to apply the same target of the total protein, 7 g, to HBV protein, only 48% of the meals assure that intake. Of course this is a theoretical assumption, since there is some bias in the HBV protein calculation and protein complementarity was not taken into account.

4.3. Total carbohydrates, mono- and disaccharides

It is extremely important the control of the intake of total carbohydrates, mono- and disaccharides intake in diabetics. In this

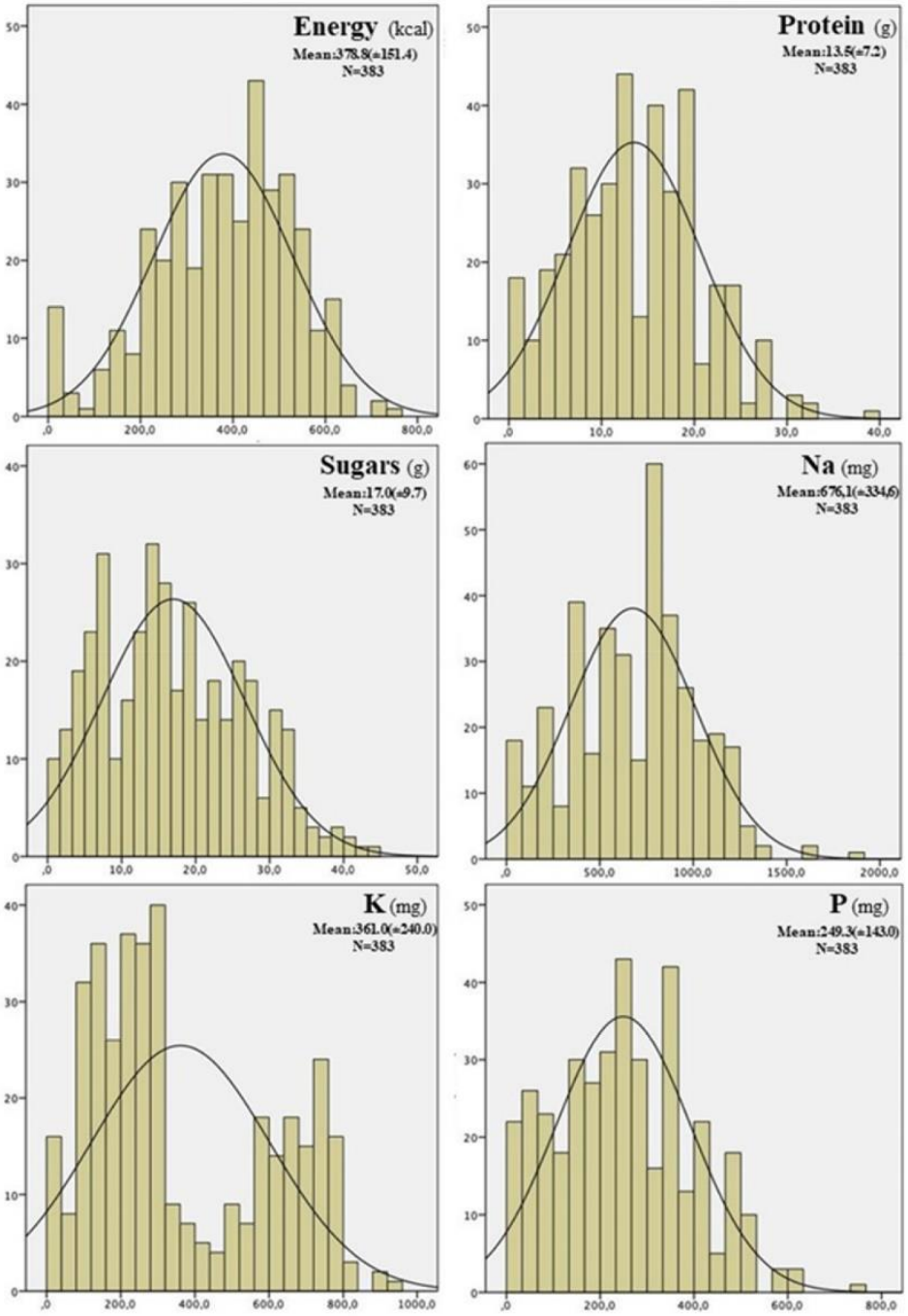


Fig. 2. Histograms of energy and some key nutrients intake of spontaneous consumptions of day shifts.

model, no foods with high sucrose or fructose content were given to diabetics, and the only intake of disaccharides intake was from the lactose present in dairy foods.

4.4. Sodium

Water balance and excessive interdialytic weight gain are common questions in this setting, so Na intake should be controlled and below the recommend 2000–2400 mg/day [22,23].

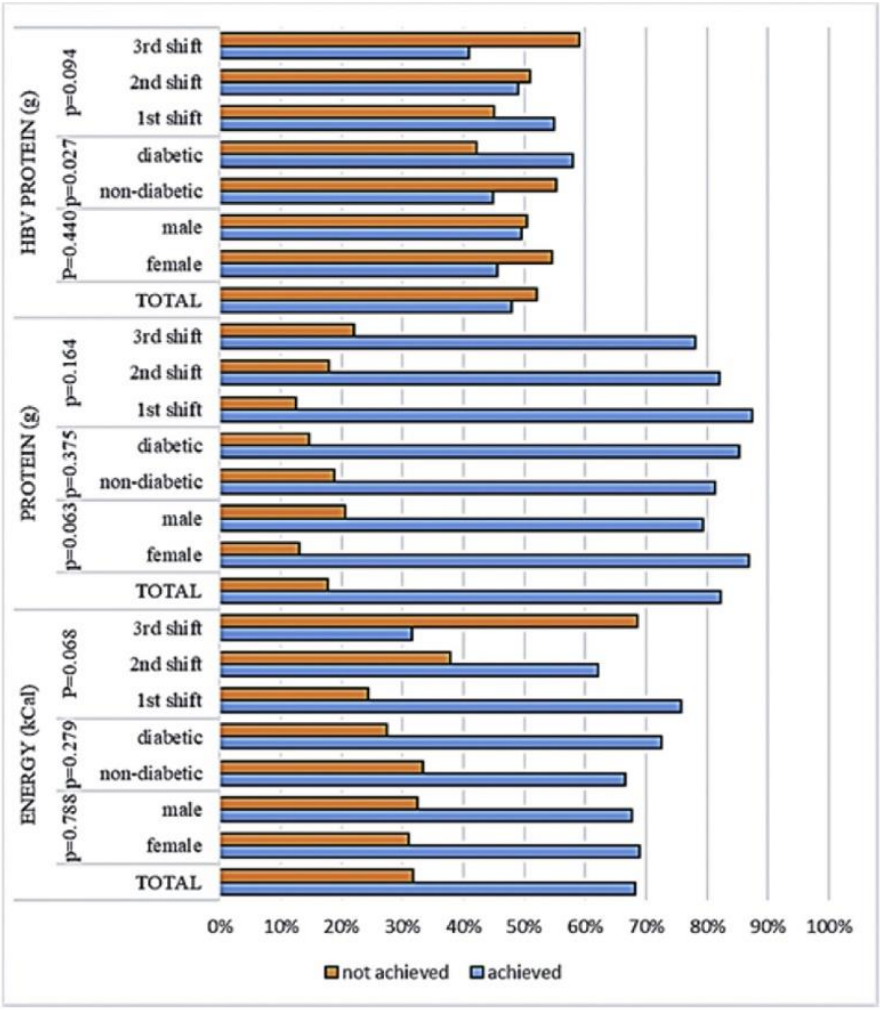
The mean Na intake (Table 1 and Fig. 2), was 676 (±334) mg on day shifts and 1040 (±360) mg on night shifts, 34% and 52% of recommendations respectively. We found that 75% of the chosen meals in day shifts assured an intake higher than 400 mg, about 20% of daily recommendations. This intake is high and it is majorly related to the contribution from food composition such as bread, ham, milk and cheese (important to achieve energy and protein intake, and that patients are fond of), no salt is added in the meal preparation, so it is a factor that depends on practices of the food industry.

Low Na options are still not available at a reasonable price or are not available at all, but as a result of legislative measures this is expected to change in the near future. A follow up is needed to correct Na contribution in this model.

Table 2
Univariable analysis: HD shift attended and nutritional profile of chosen meals.

	n	Energy (kcal)	Protein (g)	HBV[a] Protein (g)	Total Carbohydrates (g)	Sugars[b] (g)	Lipids (g)	Na (mg)	K (mg)	P[c] (mg)
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
1st shift	111	407.8 (±138.6)	15,0 (±7.2)	6,3 (±5.3)	66.3 (±20.9)	17.4 (±9.7)	8.5 (±5.2)	760 (±320)	416,2 (±256.3)	278.2 (±145.6)
2nd Shift	145	356.9 (±138.1)	12,7 (±6.3)	5.3 (±4.1)	59,6 (±22.7)	17.4 (±10.4)	6.9 (±4.5)	640 (±320)	324.6 (±207.4)	235.4 (±126.6)
3rd shift	127	378.6 (±171.1)	13,1 (±8.0)	5.3 (±5.1)	60.9 (±26.1)	16.0 (±8.6)	8.6 (±5.9)	680 (±360)	354,2 (±253.5)	239.7 (±155.4)
	p-value[d]	**0.028**	**0.028**	0.119	0.063	0.394	**0.014**	**0.004**	**0.009**	**0.039**

[a] HBV high biologic value.
[b] Sugars: mono and disaccharides available in these foods – sucrose, lactose and fructose.
[c] P: organic and inorganic phosphate.
[d] ANOVA. Significant values (<0.05) are presented in bold. 1st Shift: morning shift; 2nd shift: midafternoon shift; 3rd shift: late afternoon.



Chi-square test (χ^2). Significant values (<0.05) are presented in bold.
1st Shift: morning shift; 2nd shift: midafternoon shift; 3rd shift: late afternoon

Fig. 3. Spontaneous consumptions achievement (%) of energy and protein compensation of the HD impact with the defined targets (316.8kCal and 7 g of Protein) [4].

4.5. Potassium

The mean potassium (Table 1 and Fig. 2) contribution was 361 (±240.3) mg in day shifts, about 12% of recommendations, and 75% of the meals provided less than 593.9 mg, and half of them, below 281 mg. Overall, considering the patients' setting, these values are safe [22,23].

4.6. Phosphates

The mean phosphate (Table 1 and Fig. 2) contribution was 249.3 (±143.0) mg in day shifts, almost 33% of recommendations, 50% of the meals provided less than 252.7 mg, which was somewhat expected concerning also the high protein intake.

Apparently, these values could be considered high, however, it was not possible to adjust them to bioavailability because of the lack of data and the mix sources of the foods, organic and inorganic. We decided not to apply generic and biased values for bioavailability (that could range from 40/60% in organic P to almost 100% in inorganic P food additives). The amount of P actually absorbed will be expectably lower. The acknowledgment of P contribution from these meals would help in the decision of prescribing intradialytic P binders. At this point, further data about food composition and P bioavailability is needed [22–24].

4.7. Treatment schedule

We found (Table 2) significant associations between nutritional profile and treatment shifts, for energy, protein, lipids, Na, K and P intake but not for HBV protein, total carbohydrates and sugars. This could indicate that the treatment schedule impacts inter and intradialytic nutritional intake, and should be regarded when defining Medical Nutritional Therapy, particularly in patients with higher nutritional risk.

4.8. Study limitations

This is a descriptive and *proof of concept* study of a snack model, so no further associations with patients' factors/variables and outcomes, such as nutritional status, were studied.

Nutritional composition of food and usual serving size are regionally related, so these variations must be considered when comparing with other realities, as well as costs and availability.

Although our results show that it is possible to assure a total protein and energy intake that compensates the estimated losses in most of the chosen meals, it is not totally clear if the chosen targets are the most appropriate and if this intake would replenish those losses. Further studies are needed to relate the nutritional contribution of in–center meals with nutritional status.

Concerning the treatment shift, a selection bias could be present because of the criteria used in patients' shift allocation.

5. Conclusions

We found that this intradialytic snack model meets the target for the treatment-related increases in protein and energy needs. Although sodium intake was found to be high, potassium and phosphate intake was considered adequate.

6. Practical application

This snack model or similar models could be replicated as a strategy for compensating the nutritional impact of HD, and also as a measure of equity and enhancement of patients' comfort.

Authors' contributions

V.S.M. was responsible for study design, data collection, assembly and analysis, manuscript writing and revision, T.A. participated in data analysis, manuscript writing and revision, L.A. participated in data collection, analysis and revision, M.C. participated in data collection and assembly, A.F., N.B., C.C. and F.M. participated in manuscript writing and revision. All authors approved the final version of the manuscript.

Declaration of competing interest

The authors alone are responsible for the content and writing the paper, there was no funding to this study and there are no conflicts of interest.

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Final Discussion

This thesis is composed of 3 published manuscripts and 3 abstracts. The abstracts are related to an exploratory analysis that we made and that have interesting findings, but with time constraints we were not able to proceed with the analysis or fit in others manuscripts scope.

In the first manuscript, routine clinical and analytic parameters were found to be associated with a MIS that might indicate higher risk. With a demography characterized by older patients (one third older than 74 years) and one third with diabetes, half of the population was at nutritional and inflammation risk. Interestingly regional differences were perceivable, with higher prevalence in urban population.

Concerning the impact of each item to the risk, it was decreasingly higher from comorbidities, transferrin, functional capacity, weight variation, low fat body reserves, albumin, muscular atrophy, food consumption, to at last body mass index (BMI).

The impact of albumin and muscular atrophy items were lower than expected. This population has been exposed to nutritional counseling driven by clinical targets, and this intervention might explain these results despite the population demography.(7, 8, 14, 30)

In the multivariable analysis with two adjusted models, an age ≥ 75 years, diabetes, low P, low PCreat, low nPCR, high Ca, high EPORI, high Kt/V and high CRP were predictors of malnutrition and inflammation risk.

With these findings, our goal should be the assessment and intervention on those conditions if possible on the treatable ones, namely those in which timely interventions would have the potential to stop the ongoing cachectic processes. This can be obtained, for example, with the enhancement of nutritional status

and anti-inflammatory interdisciplinary interventions, but recognizing that unchangeable factors such as HD vintage and comorbidities will continue to have a great and negative impact.

Thus, the next step would be a practical approach defining which groups should be prioritized, focusing on modifiable factors with greatest impact on MIS, such as increasing physical activity, nutritional intake in subclinical nutrient deficiencies, increasing the intake of omega 3 fatty acids, assuring an optimal intake of energy and increasing fat stores.

At last, it was shown that is feasible to assess a whole population with few but specialized and trained human resources included as part of the nutritionists´ regular intervention. It was possible to have no direct impact on labor costs.

Since 2017, the patients treated by this organization have been yearly assessed with MIS, interrupted in 2020 and 2021 because of COVID-19 contingency strategies constraints.

In the second manuscript the aim was to assess the prognostic value of MIS in hospitalization and mortality in a 48 month follow-up.

The use of MIS was recently suggested by the 2020 KDOQI on nutrition update but with a low LOE. As our group disposes of one, and we dispose one of the wider samples used in studies of this nature, this was a very pertinent analysis to perform. (4)

Concerning the MIS cut-offs, there still is no consensus, with 5, 6, 7 even 10 to be suggested, in agreement with Carrero et al. meta-analysis findings with a cut-off of MIS≥5.(8, 30-34)

In this analysis, higher MIS, higher CCI, and lower Kt/V, lower alb, and the presence of AVG or CVC increased the hospitalization risk, while higher age, higher

IDWG, higher CCI, lower Kt/V, lower alb, lower nPCR and CVC increased the mortality risk. We found cut-offs for nPCR (1.05 g/kg/d), for P (4 mg/dL) and for HTC (31.2-35.2%) which are in line with previous findings.(4, 5, 17, 18, 35)

Our study contributed to the confirmation of the prognostic value of MIS in modern hemodialysis setting. We also confirmed the MIS cut-off 5 and identified new cut-offs in our data set: 6.3 for all patients, 6 for non-diabetics and 6.5 for diabetics, probably showing a new trend adapted to the interaction between an older dialysis populations treated with sophisticated techniques.

MIS can be used routinely as a tool for the assessment and monitoring of the malnutrition and inflammation risk and in intervention protocols/algorithms. It should aim for a nutritional status optimization that would be associated with the reduction of hospitalizations, considering a cut-off of MIS≥5 for risk assessment.

In the exploratory analysis of the diabetic patients' sample, in the first abstract, we found that there was a significant difference between insulin treated (INS) and non-insulin treated (NIT). A cut-off of MIS>6 is suggested which goes in line with the findings of the second manuscript, with INS patients having 1.3-fold increased risk of malnutrition.

Concerning EPORI exploratory analysis, in the second abstract, ROC curve analysis suggested several cut-offs associated with higher risk of hospitalization and all-cause mortality. An EPORI>5 was found to be associated with higher MIS, higher CRP and lower HTC. With further evidence needed, we might expect that the modification of EPORI predictors that are prone to improvement, such as reducing malnutrition and inflammation risk, would contribute to a better anemia management and prognosis.

The IDWG is a rather complex parameter with many associated bias and confounders, and the target is not consensual. However, in routine clinical practice a great focus is given to this parameter using a target <4% - 4.5% of IDWG. In our exploratory analysis, in the third abstract, an IDWG>4% was associated with HD vintage, male gender, higher nPCR, higher Kt/V, and higher EPORI.

However, IDWG was not associated with MIS>5, hospitalization nor all-cause mortality. This raises the question that more evidence is needed, particularly regarding the body composition data, to better understand the IDWG impact and what targets should be met.

There is a lack of consensus about intradialytic meals for many described reasons. One fact is that HD treatment itself impacts on nutritional needs and status. With our tested model, the proof of concept was possible, as showed in the last manuscript: with 68% meeting the energy target (316.8 kcal/HD) and 82% the protein target (7 g/HD). This model is already implemented in all clinics of our organization and can be easily replicated, at low cost. Our model also has the characteristic to consider patients preferences and autonomy with the range of options.

Concluding Remarks

Our main findings were:

i. the prevalence of malnutrition and inflammation in this population was 50%;

ii. the unchangeable factors, comorbidities and HD vintage, and transferrin, functional capacity and weight variation had the greatest impact on risk increment, while low fat body reserves, albumin, muscular atrophy, food consumption, and BMI, had lower impact;

iii. age ≥ 75 years, diabetes, low P, low PCreat, low nPCR, high Ca, high EPORI, high Kt/V and high CRP were predictors of malnutrition and inflammation risk;

iv. with trained, motivated and organized, but limited human resources, it was possible to nutritionally assess all patients that this organization treated;

v. twenty years after the development, MIS maintains its prognostic value in long-term hemodialysis patients, contributing to an higher level of evidence;

vi. the MIS cut-off of 5 was confirmed and new cut-offs were identified: 6.3 for all patients, 6 for non-diabetics and 6.5 for diabetics, showing a possible new trend;

vii. a higher MIS, higher CCI, and lower Kt/V, lower alb, and AVG or CVC increased the hospitalization risk, while higher age, higher IDWG, higher CCI, lower Kt/V, lower alb, lower nPCR and CVC increased the mortality risk.

viii. the cut-off found for nPCR was 1.05g/kg/d, for P was 4 mg/dL, and for HTC was 31.2-35.2%;

ix. the INS diabetic patients have a 1.3-fold increased risk of malnutrition;

x. an EPORI>5 was found to be associated with higher MIS, higher CRP and lower HTC;

xii. an IDWG>4% was associated HD vintage, male gender, high nPCR, high Kt/V, and high EPORI, but not with MIS>5, hospitalization nor all-cause mortality.

xiii. a proof of concept of a simple and cost effective snack intradialytic was possible: with 68% meeting the energy target (316.8 kcal/HD) and 82% the protein target (7 g).

Final Considerations

The search of knowledge, evidence and understanding is always a work in progress, and many questions are answered, but many more are raised.

This work contributed to a better knowledge of prevalence and profile of the nutritional status in a representative sample of the Portuguese population with CKD5D, contributing to create awareness inside and outside the organization. More evidence was found to support the recommendation of MIS for routine assessment of nutritional and inflammation risk, as well as the confirmation of the cut-off, although with a new trend for a high cut-off and the pertinence to stratify the risk, for diabetics, for example.

The exploratory analysis of diabetics (NIT vs INS), EPORI and IDWG, showed that further analyses are needed and that the field of impact of the nutritional and inflammation risk is wide and needs to be addressed with the search for more evidence, in order to contribute to a more precocious and precise nutritional intervention.

Concerning the intradialytic oral nutritional support, sustainability and efficiency in compensating the catabolic impact of HD of an intradialytic snack model was proven to be an adequate strategy, easily replicated in other clinics.

The last objective of this thesis was to create a greater awareness and inherently *a call to action* on the question of nutritional status and nutritional risk in hemodialysis patients. During the period of this doctoral program, I had the opportunity to attend and present our data in three European Renal Association-European Dialysis and Transplant Association Congresses (1 oral communication and 3 posters), two Spring Clinical Meetings (two posters) and three Encontro Renal/Portuguese Society of Nephrology (1 award for best communication on

"Nephrology and Diabetes", 2 oral communications and 1 poster). This represented an important opportunity to share and discuss our findings.

The whole spectrum of nutritional risk management is so wide that can easily represent the work for a career lifetime. Although it was embraced enthusiastically, due to the limited duration of a doctoral program, much more was left to pursue.

However, these findings confirmed the need to prioritize the clinical approach to nutritional and inflammation risk, and showed that it is possible to have an organized and efficient nutrition service able to gather scientific evidence that contributes for a better patient care, that strengthens the evidence of current recommendations, laying the ground for replicable best practices and new guidelines.

Further studies will follow.

The ones presented in this thesis are the stepping stone for continuing the much needed evidence in Renal Nutrition, and that it is a work of a lifetime dedicated to CKD5D patients' higher quality and quantity of life, that fulfills my engagement to them.

Future Fields of Investigation

i. The association of dietary patterns with clinical outcomes in HD patients;

ii. The impact of oral nutritional support with commercial oral nutritional supplements on nutritional status rehabilitation in HD patients with PEW;

iii. The assessment and management of micronutrients deficiency and metabolic abnormalities due to HD treatment;

iv. The dietary patterns and nutrient intake association with gastrointestinal function and microbiota homeostasis in HD patients.

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