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Clinical-nutritional, inflammatory and oxidative stress predictors in hemodialysis mortality: a review

Predictores clínico-nutricionales, inflamatorios y de estrés oxidativo en la mortalidad por hemodiálisis: una revisión

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ABSTRACT

The evaluation of clinical-nutrition status is essential to increase life quality and improve clinical outcomes of patients in hemodialysis (HD). In the absence of a gold standard, the goal of this integrative review was to present and discuss the latest scientific literature on the ability of clinical-nutritional indicators and inflammatory and oxidative stress markers to predict morbidity and mortality in HD. In this context, the lean and fat mass indexes have become good predictors of mortality in HD individuals, regardless of BMI. Subjective scoring systems have been more sensitive to malnutrition, and altogether anthropometric indicators may result in an early detection of mortality risk in this population. On the other hand, inflammation in HD, as assessed by C-reactive protein, is not only related to cardiometabolic alterations, but it is also one of the key-points in the development of malnutrition, exacerbated by

the state of oxidative stress, which has been identified in this group by the increase of the serum levels of gamma-glutamyl transferase and malondialdehyde.

Key words: Chronic kidney disease. Malnutrition. Hemodialysis. Oxidative stress. Inflammation. Mortality.

RESUMEN

La evaluación del estado clínico-nutricional es esencial para aumentar la calidad de vida y mejorar los resultados clínicos de los pacientes en hemodiálisis (HD). En ausencia de un patrón oro, el objetivo de esta revisión integrativa fue presentar y discutir la literatura científica más reciente sobre la capacidad de indicadores clínico-nutricionales, y marcadores de estrés oxidativo e inflamatorio, en la predicción de morbilidad y mortalidad en HD. En este contexto, los índices de masa grasa y grasa se han convertido en buenos predictores de mortalidad en individuos con HD, independientemente del IMC. Los sistemas de puntuación subjetiva han sido más sensibles a la desnutrición y, en conjunto, los indicadores antropométricos pueden resultar en una detección temprana del riesgo de mortalidad en esta población. Por otro lado, la inflamación en HD, evaluada por la proteína C reactiva, no solo se relaciona con alteraciones cardiometabólicas, sino que también es uno de los puntos clave en el desarrollo de la desnutrición, exacerbada por el estado de estrés oxidativo, que ha sido identificado en este grupo por el aumento de los niveles séricos de gamma-glutamyl transferasa y malondialdehído.

Palabras clave: Enfermedad renal crónica. Desnutrición. Hemodiálisis. Estrés oxidativo. Inflamación. Mortalidad.

INTRODUCTION

End-stage renal disease (ESRD), as well as hemodialysis (HD), treatment are marked by clinical-nutritional conditions that increase morbidity and mortality and reduce life quality of patients with this chronic disease (1-3). In this sense, hypoalbuminemia, which is also affected by inflammation status and age, is not able to accurately reflect the nutritional state (4). In turn, body mass index (BMI) has been associated with

better prognosis of individuals in HD, which is known as "reverse epidemiology" (5-7). This relationship is influenced by characteristics such as age, inflammation and related-comorbidities (8). In addition, subjective global assessment may help predict mortality, when properly applied (9).

On the other hand, the progressive deterioration of renal function leads to physiological dysfunctions such as changes in cellular energy metabolism, protein catabolism, insulin resistance and synthesis of mediators of inflammation and oxidative stress (10-12). Still, the complex inter-relationship among nutritional indicators and inflammatory and oxidative markers remains the object of investigation on the premise to get better prediction of mortality in patients with ESRD in HD (13).

Overall, the objective of this integrative review was to present and discuss the latest scientific literature on the ability of clinical-nutrition indicators, and inflammatory and oxidative stress markers to predict morbidity and mortality in HD individuals.

STUDY CHARACTERISTICS AND SELECTION CRITERIA

A review search was carried out from the databases LILACS, Medline, PubMed, SciELO and BIREME, using the keywords "hemodialysis and mortality", "chronic renal failure", "ESRD", "biochemical markers", "inflammatory markers", "oxidative stress markers", "anthropometric evaluation", "nutritional status", "subjective evaluation", combined with " mortality". Publications carried out from 2010 to 2016 with HD individuals were included.

From the selected articles, a reverse search was carried out for studies whose titles would be eligible. Subsequently, the abstracts were read to ensure compliance with the inclusion criteria and then each article was entirely read to confirm its eligibility. Cohort studies with adults and elderly individuals in HD treatment were included. Articles that were not published in full or those presented as tutorials, editorials, news, letters or comments, reviews and experimental testing were excluded. In addition, studies of acute renal disease, chronic kidney disease under conservative treatment or treatment with peritoneal dialysis, transplantation and nephrotic syndrome were excluded.

During the initial selection process, 155 articles were found, from which 108 were excluded, as shown by figure 1. Selected papers are related to anthropometric

indicators (four studies), subjective global assessment (five studies), oxidative stress markers (two studies), and inflammatory markers (four studies) as predictors of mortality in HD individuals.

CLINICAL-NUTRITIONAL PREDICTORS AND MARKERS OF INFLAMMATION AND OXIDATIVE STATE OF THE STUDY

The 15 selected studies used as anthropometric indicators, BMI, waist circumference (WC), skinfold thickness, arm circumference (AC), Mid-arm circumference (MAC), mid-arm muscle circumference (MAMC) lean tissue index (LTI) and fat tissue index (FTI) and total body fat (TBF), assessed by bioelectrical impedance analysis (BIA). Subjective methods to nutritional assessment were: Subjective Global Assessment (SGA), Modified Subjective Global Assessment (mGSA), Objective Score of Nutrition on Dialysis (OSND), International Society of Renal Nutrition and Metabolism (ISRNM), Malnutrition-Inflammation Score (MIS) and Geriatric Nutritional Risk Index (GNRI).

Hemoglobin, albumin, calcium, phosphorus, parathyroid hormone (PTH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, total cholesterol (TC), triglycerides (TG), uric acid, urea, creatinine, Kt/V urea (Kt/V), ferritin and transferrin were used as metabolic markers.

The oxidative stress markers used in the studies were plasma concentrations of gamma-glutamyltransferase (GGT), nitric oxide (NO) and malondialdehyde (MDA); while the inflammatory markers were plasma concentrations of C-reactive protein (CRP), interleukin-6 (IL-6), tumor-necrosis factor alpha (TNF- α) and their receptors (TNFR1 and TNFR 2).

The articles were separated in accordance with categories of predictors of mortality in HD as follows: anthropometric indicators, subjective scores, oxidative stress and inflammation markers (Tables I to IV).

ANTHROPOMETRIC INDICATORS ON MORTALITY IN HD INDIVIDUALS

Studies show that protein-energy malnutrition is present in a range of 23% to 76% of individuals in HD (14). Unlike the general population, a higher BMI in these individuals was associated with better survival, fact presented as reverse epidemiology in the literature (15). However, BMI measures did not present differences between lean and

fat mass, making it difficult to quantitatively understand which components of body composition are related to survival in HD individuals with ESRD (16). In order to evaluate body compartments, the studies use the Body Composition Monitor (BCM) based on spectroscopic bioimpedance (BIS). Bioimpedance methodologies, the BCM expresses body composition as a three-compartment model, providing overhydration, lean tissue index (LTI), and fat tissue index (FTI), whereby LTI and FTI are the respective tissue masses normalized to height squared. Also, LTI and FTI percentiles (< 10th percentile [low]; 10th-90th percentile [normal]; and > 90th percentile [high]) relative to an age- and sex-matched healthy population are supplied. The three-compartment model of the BCM has been validated against standard reference methods for assessment of fluid status and body composition in dialysis patients. Castelhana et al. (17) have indicated LTI and FTI reference values (10th and 90th percentiles), adjusted for age and sex, in which lean tissue below the 10th percentile was associated with higher mortality in HD (OR: 1.57). Similarly, considering age, sex and diabetes *mellitus*, higher percentage of lean body mass was associated with better survival (18,19) in HD individuals for the same population.

Moreover, Rosenberger et al. (20) evaluated the relationship between scarcity of lean tissue (expressed as LTI below the 10th percentile) and survival in HD. The possible causes to worse survival (21,22) included malnutrition and inflammation signal (21) as lean mass stocks uremic toxins, in which case, the smaller amount of lean tissue could indicate a higher concentration of uremic toxins in the blood (21,23).

The relation of muscle mass and increased mortality caused by infections in HD individuals is well known, since subjects with ESRD develop an acquired immune deficiency that may be exacerbated in those with low muscle mass and hypoalbuminemia (24). In this sense, Marcellid et al. (16) had found that body composition by multifrequency bioimpedance and LTI and FTI between the 10th and 90th percentiles were associated with improved survival, while the low LTI and FTI, and especially the combination of both, were associated with increased mortality, regardless of BMI.

Other anthropometric and body composition indicators do not qualify as common practices. TBF and simple anthropometric measures, such as MAC, AC and triceps skinfold thickness (TSF) are generally used (25,26). Stosovic et al. (27) found that the

TBF, TSF, AC and MAC were independent predictors of mortality for individuals in HD. The predictive values of all these anthropometric indicators for mortality were similar, except for BMI. When these indicators were altogether tested, the AC was the indicator with the greatest power to predict mortality and showed an average reduction of 8.0% in the proportional mortality risk.

Furthermore, the reduction of muscle mass in this population (28) is associated with hypoalbuminemia and PEM, which indicate inflammatory conditions (29). Su et al. (24) have reported that the decline in lean body mass over time, estimated by MAC and skinfold measurements were associated with higher risk of all specific causes of mortality in HD individuals. These relationships were particularly strong in those with BMI < 25 kg/m².

It is noteworthy that BMI values for individuals in HD are usually higher than for general population, although many of them may present LTI values below percentile 10 (30), suggesting that body composition related to lean tissue is more important than BMI isolated. In addition, interventions to keep lean and fat mass suitable are favorable for survival in population with ESRD. Thus, AC measure and the body fat distribution (as LTI and FTI) were altogether promissory predictors of morbidity and mortality in HD, reinforcing the importance of lean and fatty tissues in evaluating the survival of HD patients independently of BMI, making them (mainly AC) good indicators in clinical practice.

SUBJECTIVE SCORES ON MORTALITY IN HD INDIVIDUALS

In this sense, SGA is a simple method for assessing the nutritional status in many patients, including those with ESRD. Vogt and Caramori (31) had presented prevalence of malnutrition of 26.3% by SGA, 25.2% for MIS (MIS > 8) and 28.8% by criteria based on ISRN, and malnutrition evaluated by SGA and MIS was able to predict mortality in a period of 15.5 ± 5.4 months. The study of Zuidewijnet et al. (32) highlighted the SGA and MIS, after comparing eight evaluation tests of nutritional risk, as better predictors of mortality. As results, these studies show the impact of changes in scores of SGA and MIS on clinical outcomes and mortality risk. Another study has shown that an 1-point increase in SGA, 12 months after dialysis, was independently associated with an increase of 34% in all-cause mortality risk when tested with albumin, CRP, and BMI

(33). The same finding was discussed by Chan et al. (34), after adjusting for all variables including age, sex, HD time, serum albumin, body mass index and smoking. In addition, they observed that the SGA, considering mild malnutrition (B) and moderate (C) independently predicts mortality.

The study of Beberashvili et al. (35) has found significant associations with hospitalization and mortality in individuals in HD through a comprehensive OSND scoring system. Both variables were significantly correlated with inpatient days and frequency, as well as lean and fat body mass, MIS, blood pressure and IL-6 values (35,36). The results found by Beberashvili et al. (37) indicate that MIS had reliability and good concurrent and predictive validity (37).

Even so, these scoring systems should be considered as complementary clinical markers of malnutrition state, while application of SGA and MIS could result in early detection of malnutrition compared to metabolic and inflammatory markers, or classic anthropometric indicators (38). Therefore, SGA and MIS may represent good tools for application in clinical practice, as they may contribute to an early identification of malnutrition.

OXIDATIVE STRESS MARKERS ON MORTALITY IN HD

The presence of oxidative stress, as well as anthropometric and subjective evaluation, has been related to the increase in morbidity and mortality in cardiac surgical patients, critically ill and renal patients requiring HD (39,40).

In HD individuals, increased oxidative stress results from an imbalance between pro-oxidant activity and anti-oxidant systems, more intensely, contributing to increased morbidity and mortality (41,42). Diabetes *mellitus*, advanced age, inflammation, excess of uremic toxins, bio-incompatibility of dialysis membranes (43) and intravenous iron therapy (44) are the main causes of increased pro-oxidant activity in these individuals (42).

Excess of oxygen reactive species (ROS) can produce cellular damage, interacting with biomolecules (proteins, lipids and nucleic acids) and, thus, have negative effects on tissue function and structure. ROS can react with polyunsaturated fatty acids that produce lipid hydro peroxides. MDA, a linolenic acid product of decomposition of the main final oxidation reactions of polyunsaturated fatty acids, is a useful indicator to

evaluate oxidative damage (45,46). MDA can still interact with DNA and proteins, and can lead to mutagenic and cytotoxic effects and, possibly, is involved in the pathogenesis of various diseases, such as atherosclerosis (47). Low MDA values, which suggest a lower intensity of oxidative stress, are associated with better survival (45).

Rusu et al. (48) observed that the increase in MDA is associated with a higher ratio of albumin corrected calcium (cCA). It is known that elevated cCA is a predictor of mortality, since hypercalcemia and increased ROS can act synergistically in aggravating the severe vascular lesions found in HD individuals. MDA has a high predictive value for the mortality of these individuals and is related to the survival of this population, especially when associated with cardiovascular diseases.

GGT (49), a recognized biomarker for liver disease, was another marker of oxidative stress presented as a predictor of mortality in HD individuals. It is an enzyme with important role in the extracellular catabolism of glutathione, a representative intracellular antioxidant (50). GGT-mediated oxidative stress may be involved in the formation of coronary atherosclerotic plaques and endothelial dysfunction (51-53).

In this sense, oxidative stress may play an important role in the pathogenesis of atherosclerosis and cardiovascular risk in ESRD, thus contributing to the increase in mortality. More studies are necessary to identify potential biomarkers in these people. Still, an early evaluation through GGT and MDA may contribute to a better monitoring of oxidative stress presence, which is common among individuals with chronic kidney disease.

INFLAMMATORY MARKERS ON MORTALITY IN HD INDIVIDUALS

Inflammation has recently been recognized as an essential component in ESRD in HD, playing a unique role in its pathophysiology and is responsible, in part, by CVD mortality and all other causes (54). Moreover, inflammation is related to the development of PEM and other comorbidities. In fact, the increase in release or activation of pro-inflammatory cytokines such as IL-6 or TNF- α , as well as acute phase protein CRP, may suppress appetite, cause muscle proteolysis and hypoalbuminemia (55). Furthermore, PEM and inflammation contribute independently to hypoalbuminemia and thus increase the risk for mortality in ESRD in HD (56).

Inflammation is often present in individuals in HD, and the use of central venous catheter has been linked to chronic inflammatory state (57). Faria et al. (58) have found that its use as vascular access for HD procedure was independently associated with mortality in patients with high concentrations of CRP and low triglycerides.

In this context, the inflammation as assessed by CRP is present between 30% and 60% of American north and Europeans individuals in dialysis (59). In addition, values of CRP higher than 5 mg/L (60) or 10 mg/L (61,62) have been positively associated to cardiovascular mortality. Inflammatory markers such as TNF- α and CRP are powerful independent predictors of risk for atherosclerosis, cardiovascular disease and mortality in HD individuals (63). The study of Nakagawa et al. (64) has shown that TNF- α and CRP were positively associated with the causes of cardiovascular mortality, after adjusting for age and sex. When stratified by GNRI, TNF- α and CRP were positively associated with all-cause mortality, only in malnourished individuals. This is supported by the finding of Carlsson et al. (65), concerning the slightly higher values of TNFR 1 and 2 in subjects with malnutrition. However, inflammation can elevate risk of mortality in patients with ESRD in HD by increasing cardiovascular risk and malnutrition.

Thus, the inflammation in individuals in HD, particularly evaluated by the CRP, is not only related to the cardiovascular alterations, including atherosclerosis, but it is also one of the key points in the development of PEM, stimulated by the oxidative stress. This fact can be reversed through a better follow-up of these individuals through PCR, TNF- α , IL-6, identifying the evolution of inflammation and providing better nutritional support, aiming to improve the clinical picture of the individual with ESRD in HD.

CONCLUSIONS

In the absence of a gold standard to assess the mortality risk of HD individuals, application of one of the subjective methods together with adiposity and lean mass indicators, and CRP concentration in the clinical-nutritional practice could offer more accurate mortality risk in this population. Although oxidative stress biomarkers in ESRD are important, more studies are necessary to identify a recognized oxidative stress marker as a mortality predictor in HD.

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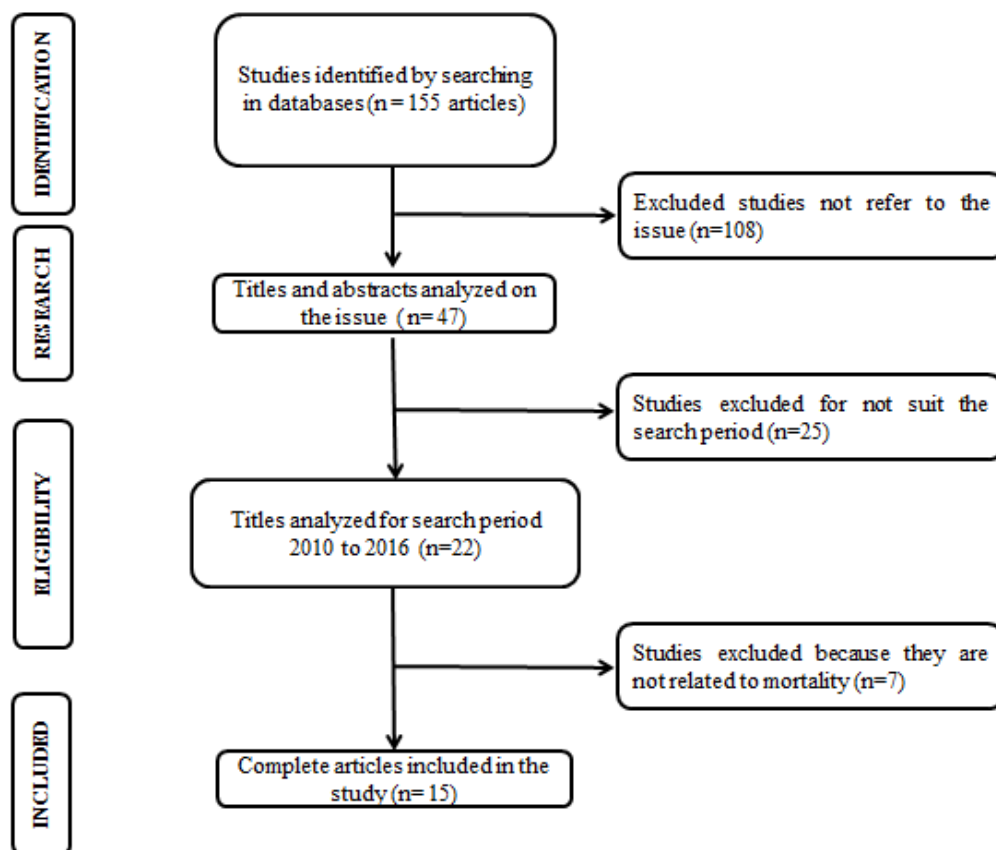


Figure 1. Flowchart showing selected studies for this review (2010-2016).

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Table I. Comparative studies of anthropometric predictors in the mortality of hemodialysis patients (cohort studies, 2010-2016)

<i>Author/Year</i>	<i>Sample</i>	<i>Method /Studied variables</i>	<i>Main results</i>
Castellano et al., 2016 (17)	6,325 patients 57 HD units in Spain January 2012 to December 2014 Average age: 67 years 37% women	Body fat distribution variables: LTI; FTI	The presence of the LTI < 10 th percentile was independently associated with increased risk of death even after adjusting for other factors such as moisture and HD time
Marcelli et al., 2015 (16)	37,345 patients 380 HD units in 17 European countries April 2006 to December 2012 Average age: 62 years 57% men	Body fat distribution variables: LTI; FTI Anthropometric variable: BMI	There was lower mortality in individuals in the percentiles > 10 for LTI and < 90 considering FTI of a healthy population
Su et al., 2013 (24)	1,846 patients 15 HD units in the US March 1995 to October 2000 Average age: 58 years 43% men	Anthropometric variables: MAC AC, BMI, TSF, BSF, SSF	Reduction in the values of AC and skinfold thickness was significantly associated with mortality from all causes and cardiac outcomes, especially those with BMI ≤ 25 kg /m ²
Stosovic et al., 2010 (27)	242 patients 1 HD unit in Serbia 1994-2004 Average age: 52 years old 53% men	Anthropometric variables: TSF, BSF, MAMC, MAC BMI Metabolic variables: albumin, creatinine, K / tV, urea Inflammatory variable: CRP	MAC was better predictor of mortality than other anthropometric, metabolic and inflammatory measures evaluated

AC: arm circumference; BMI: body mass index; BSF: bicipital skinfold; CRP: C-reactive protein; FTI: fat tissue indices; HD: hemodialysis; LTI: lean tissue indices; MAC: mid-arm circumference; MAMC: mid-arm muscle circumference; TSF: triceps skinfold; SSF: subscapular skinfold.

Table II. Comparative studies of subjective predictors in the mortality of hemodialysis patients (cohort studies, 2010-2016)

<i>Author/Year</i>	<i>Sample</i>	<i>Method/Studied variables</i>	<i>Main results</i>
Vogt; Caramori, 2016 (31)	163 patients HD Centre in Botucatu (Brazil) July to December 2012 Average age: 58 years 54.6% men	Subjective variables: SGA, ISRNM, MIS Anthropometric variables: MAC, BMI Metabolic variables: serum albumin, the total iron binding capacity and transferrin	SGA and MIS were predictors of all-cause mortality when associated with other parameters
Kwon et al., 2016 (33)	914 patients 36 HD centers in Korea November 2008 to February 2014 Average age: 60 years 62% men	Subjective variable: SGA Anthropometric variable: BMI Metabolic variable: albumin Inflammatory variable: CRP	The changes in nutritional status evaluated by SGA during the first year of HEMO were associated with all-cause mortality
Chan et al., 2012 (34)	167 patients HD unit in Sydney (Australia) August 2000 to July 2010 Average age: 65 years 57.5% men	Subjective variable: SGA Anthropometric variable: BMI Metabolic variable: albumin	SGA Malnutrition (B and C) at the beginning of HD was associated with high mortality, regardless of BMI and serum albumin
Beberashvili et al., 2010 (35)	81 patients HD Centre in Israel 27 months Average age: 64 years 65% men	Subjective Variable: OSND Anthropometric variables: BMI, TSF, MAC Metabolic variable: albumin, transferrin and cholesterol	The OSND based on anthropometric and metabolic variables, proved to be a broader marker of all aspects of nutrition and a strong predictor of morbidity and mortality in chronic hemodialysis patients

AC: arm circumference; BMI: body mass index; HD: hemodialysis; ISRN: International Society of Nutrition and Metabolism Renal; MAC: mid-arm circumference; MIS: malnutrition-inflammation score; OSND: Objective Score of Nutrition on Dialysis; SGA: subjective global assessment; TSF: triceps skinfold.

Table III. Comparative studies of oxidative stress predictors in the mortality of hemodialysis patients (cohort studies, 2010-2016)

<i>Author/Year</i>	<i>Sample</i>	<i>Method/Studied variables</i>	<i>Main results</i>
Rusu et al., 2016 (48)	44 patients 01 HD unit in Romania 108 months (beginning in 2005) Average age: 59.79 years 44% men	Oxidative stress variables: MDA, PC, nitric oxide Metabolic variables: ceruloplasmin, albumin, creatinine, uric acid, iron profile (iron, transferrin and ferritin), lipid profile (total cholesterol, triglycerides and HDL-cholesterol), alkaline phosphatase, (iPTH) and transaminases. pre urea and post-dialysis, Kt/V, cCA inflammatory variable: CRP Anthropometric variable: BMI	MDA is a strong predictor of mortality in hemodialysis patients. It is associated with greater amount of cCA as a predictor of mortality

Park et al., 2015 (49)	1634 patients	Oxidative stress variables: gammaGT Metabolic variables: AST, ALT, alkaline phosphatase, creatinine, urea, calcium ferritin, phosphorus, albumin, triglycerides, cholesterol	The highest concentration of Gamma GT in serum was an independent risk factor for mortality from all causes and in HD patients
	31 HD units in Korea		
	April 2009 to July 2014		
	Average age: 58 years		
	61.3% men		

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; CRP: C-reactive protein; Cca: corrected calcium/albumin; GGT: gamma-glutamyltransferase; HD: hemodialysis; MDA: malondialdehyde; PC: protein carbonyls; iPTH: intact parathyroid hormone.



Table IV. Comparative studies of inflammatory predictors in the mortality of hemodialysis patients (cohort studies, 2010-2016)

<i>Author/year</i>	<i>Sample</i>	<i>Method/Studied variables</i>	<i>Main results</i>
Carlsson et al., 2015 (65)	207 patients 01 unit of HD in Stockholm October 2003 to March 2004 Average age: 66 years 56% men	Inflammatory variables: CRP, IL-6, pentraxin 3, TNF- α and TNFR1 and 2 Subjective variable: SGA Anthropometric variable: BMI Metabolic variable: albumin	sTNFRs values seem limited when associated with anthropometric, subjective and inflammatory indicators in mortality prediction
Nakagawa et al., 2015 (64)	218 patients 01 HD unit in Sapporo (Japan) March 2006 to March 2012 Average age: 59 years 57.9% men	Inflammatory variables: adiponectin, CRP and TNF- α Subjective variables: GNRI Variable body fat distribution: VFA, SFA, ,BMI	TNF- α and CRP levels during the 6-year study showed strong predictive power for all-cause mortality dependent on the nutritional status of Japanese HD
Faria et al., 2013 (58)	189 patients 01 HD unit in Portugal April 2009 to 2011 Average age: 66 years 55% men	Inflammatory variables: CRP, IL-6 and adiponectin Metabolic variables: albumin, iron, ferritin, transferrin, cholesterol, triglycerides, phosphorus, potassium, calcium, creatinine, K/tV and sodium	High levels of CRP and low triglyceride levels can predict mortality risk in individuals in HD
Bazeley et al., 2011 (60)	5061 patients HD 140 units in 10 countries 2005-2008 Average age: 62 years 59.7% men in Europe 59.8% men in Japan	Inflammatory variable: CRP Anthropometric variables: BMI Metabolic variables: albumin, ferritin,	CRP when measured with other markers (albumin, and ferritin BMI) improves the prediction of mortality

BMI: body mass index; CRP: C-reactive protein; GNRI: geriatric nutritional risk index; HD: hemodialysis; IL-6: interleukin-6; TNF- α : tumor necrosis factor-alfa; sTNFR1 and 2: tumor necrosis factor receptors 1 and 2; VFA: visceral fat area; SFA: subcutaneous fat area; SGA: Subjective Global Assessment.

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