Review article

Predictors in mortality risk stratification in patients with chronic kidney disease on hemodialysis

Predictores en la estratificación de riesgo de mortalidad en pacientes con enfermedad renal crónica en hemodiálisis

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ABSTRACT

Introduction: The identification of predictors of mortality in patients with chronic kidney disease on hemodialysis, which allows the identification of early treatment to patients at higher risk of death, it is necessary in practice current clinic.

Objective: To describe the predictors of mortality in patients with disease chronic kidney on hemodialysis.

Methods: A bibliographic review of the theoretical foundations on the Mortality risk stratification in patients with chronic kidney disease on hemodialysis. The resources available through Infomed (PubMed, PubMed Central, SciELO, Web of Science, Scopus, Ebsco, Clinical Key), as well as Google Scholar. The search strategies were: "chronic kidney disease OR renal insufficiency OR end-stage renal disease and hemodialysis and mortality and predictors OR predictive models".

Development: Chronic kidney disease mortality risk stratification in hemodialysis is complex, taking into account that there are numerous traits that can influence the outcome end of patients. Multiple variables have an implication in the classification of the risk of the patient, which depend on the history, the clinical evolution of the disease, paraclinical results and adherence to hemodialysis.

Conclusions: The predictors in the risk stratification of Mortality in patients with chronic kidney disease on hemodialysis. These Predictors do not act in isolation, but rather interact with each other to influence the patient prognosis. The comprehensive and systematic evaluation, which integrates these variables can help personalize treatment and improve clinical outcomes.

Key words: end-stage renal disease; hemodialysis; mortality; predictors.

RESUMEN

Introducción: La identificación de predictores de mortalidad en los pacientes con enfermedad renal crónica en hemodiálisis, que permitan reconocer de manera temprana a los pacientes con mayor riesgo de fallecer, resulta necesaria en la práctica clínica actual.

Objetivo: Describir los predictores de mortalidad en los pacientes con enfermedad renal crónica en hemodiálisis.

Métodos: Se realizó una revisión bibliográfica de los sustentos teóricos sobre la estratificación de riesgo de mortalidad en los pacientes con enfermedad renal crónica en hemodiálisis. Se utilizaron los recursos disponibles a través de Infomed (PubMed, PubMed Central, SciELO, Web of Science, Scopus, Ebsco, Clinical Key), así como Google académico. Las estrategias de búsquedas fueron: "*chronic kidney disease OR renal insufficiency OR end-stage renal disease and hemodialysis and mortality and predictors OR predictive models*".

Desarrollo: La estratificación de riesgo de mortalidad de enfermedad renal crónica en hemodiálisis es compleja, al tener en cuenta que existen numerosos rasgos que pueden influir en el desenlace final de los pacientes. Múltiples variables tienen implicación en la clasificación del riesgo del paciente, las cuales dependen de los

antecedentes, la evolución clínica de la enfermedad, los resultados paraclínicos y la adherencia a la hemodiálisis.

Conclusiones: Se describieron los predictores en la estratificación de riesgo de mortalidad en los pacientes con enfermedad renal crónica en hemodiálisis. Estos predictores no actúan de forma aislada, sino que interactúan entre sí para influir en el pronóstico del paciente. La evaluación integral y sistemática, que integra estas variables puede ayudar a personalizar el tratamiento y mejorar los resultados clínicos.

Palabras clave: enfermedad renal crónica; hemodiálisis; mortalidad; predictores.

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Introduction

Chronic kidney disease (CKD) has become the third cause of mortality in the world, the one with the highest rise and it is estimated that by 2040 it will be the fifth cause of years of life potentially lost. Worldwide, around 850 million people live with kidney disease, of these, 4 million receive renal replacement therapies (RRT) for a crude rate of 298.4 patients per million inhabitants.[1]

According to *Ríos* and others[2] from 2000 to 2019, the incidence and prevalence of CKD in United States of America (USA) increased by 41.8% (92,660 patients) and 118.7% (783 594 patients) respectively and hemodialysis (HD) patients have a higher mortality than the rest of the population. It is estimated that mortality one year after the start of RRT, is 21.7%, which generates a high impact on medical care.

In Cuba, during the year 2023, CKD was the thirteenth cause of higher mortality. 1,203 deaths were reported, for a crude rate of 11.7 and adjusted 5.6.[3]

Mortality from CKD in Cuba has increased considerably compared to previous years, so it is a scientific necessity to carry out research that contributes to early

identification of prognostic factors. He population aging and the increase in diseases such hypertension (HTN) and diabetes, are important challenges for Cuba in order to obtain better results in the kidney health of individuals.

The approach to stratification of mortality risk in patients with CKD in iterated HD, using traditional predictive models, presents numerous limitations, which leads to the development of complications, progression of disease and mortality, which has limited its use in clinical practice. Furthermore, it report challenges linked to interpretability, applicability, reproducibility, generalization, discrimination, calibration and limitation in pattern detection complex.

CKD is a medical condition that affects a large number of people throughout the world and HD treatment carries a significant risk of mortality. Given this situation, it is necessary to determine potential mortality predictors that allow early identify patients at higher risk of dying, in order to improve your clinical care and increase your chances of survival.

Taking into account the previous comments, the objective of this research was to describe the predictors of mortality in patients with kidney disease chronic on hemodialysis.

Methods

A theoretical investigation was carried out in the existing national and international bibliography about mortality risk stratification in patients with CKD on HD, from February 6 to 15, 2023, with which a bibliographic review was prepared. The resources available through Infomed (PubMed, PubMed Central, SciELO, Web of Science, Scopus, Ebsco, Clinical Key), as well as Google academic.

The search strategies were: "chronic kidney disease OR renal insufficiency OR end-stage renal disease AND hemodialysis AND mortality AND predictors OR predictive models". The methods applied were induction-deduction, analysis-synthesis and historical-logical, which allowed a pertinent assessment and interpretation of the topic under investigation.

The inclusion criteria taken into account were that the articles were published in peer-reviewed scientific journals and in English or Spanish. Articles that did not provide access to the full text were excluded those who did not present a URL electronic address.

Finally, the search provided 101 articles, of which 34 were discarded for not being meet the inclusion criteria. 67 articles were cited, 94.03% of the latest five years.

Development

The CKD mortality risk stratification process in HD is complex, taking into account that there are numerous variables that can influence the outcome end of patients. In general, these variables can be interpreted in differently in different scenarios. Multiple variables have an implication in the determination of the patient's risk, which depend on the patient's history, clinical evolution of the disease, paraclinical results and adherence to HD.[4,5]

Past medical history

Age

In recent years, the population of patients over 65 years of age with CKD in HD. The quality of life of older adults with CKD has a great impact, and the multidimensional study of the evolution of the geriatric patient on HD presents its limitations. Age is a variable with important prognostic implications in the mortality stratification of nephropathic patients, so the majority of MP include it.[6]

Mayrink and others[7] in a longitudinal and exploratory evaluation that included 97 HD patients, with a mean follow-up of 32 months, the mean age was 50.93 ± 14.10 years and revealed statistical significance (ß = -0.096 and p = 0.024). In it Cox regression analysis, older age than the median identified showed a risk of 1.05 times more likely to die.

Miao and others[8] in a series of cross-sectional and prospective cohorts that included patients from China and USA, included people over 65 years of age and demonstrated that older patients had worse levels of biomarkers related to kidney disease and mortality was higher.

Meyer and others[9] analyzed 375 patients with a mean age of 77.5 ± 6.1 years, with the objective of establishing a geriatric evaluation scale contextualized to the patient with CKD. The values of the multidimensional prognostic index developed are were significantly associated with mortality at three, six and 12 months (p = 0.001), independent of age.

Scientific evidence suggests that elderly patients on HD meet a high burden of comorbidities, in addition to limited functional status that may be responsible for higher mortality rates compared to young patients.

Sex

Previous investigations[10,11] show that unlike women, men are diagnosed with CKD in more advanced stages, they present more diseases associated and start RRT later. All these aspects taken together, make the male sex have a higher risk of mortality and complications, especially cardiovascular events. However, in other reviews the results have not been so conclusive and women with greater vascular risk are outlined global chronic.

Men with CKD on HD have a higher risk of developing events major cardiovascular events that cause mortality. The sex risk difference is based in part on cardiometabolic comorbidities and risk factors pre-existing traditional cardiovascular. The protective effect of the female gender decreases with progression of kidney disease, increasing age and appearance of DM.[12]

Hypertension

HTN is a common risk factor for cardiovascular diseases (CVD) and kidneys. Together with diabetes, it is the main cause of CKD. The increase in numbers of blood pressure, associated with the years of evolution of HTN, generates

vasoconstriction and endothelial dysfunction, which promotes the progression of kidney damage, appearance of future complications and mortality.[13]

HTN is considered a major risk factor for mortality due to cardiovascular in CKD. *Zhang* and others[14] carried out a meta-analysis (MA) where they included 20,059 patients from 10 randomized controlled studies. The authors concluded that the intensive control of blood pressure levels reduced the incidence of events cardiovascular events in patients exposed to HD (relative risk: 0.69; 95% CI: 0.53 - 0.90 and p = 0.01).

Yanai and others[15] postulate that cardiovascular events are serious complications and frequent that increase the risk of mortality in nephropathic patients in stage pre-dialysis and dialysis. The authors indicated that blockade of the renina-angiotensin-aldosterone system was effective in reducing mortality in 8,322 patients. The pharmacological group with the best results was the antagonists of the mineralocorticoid receptors.

The results analyzed reinforce that control of the figures is vitally important. Blood pressure and appropriate pharmacological treatment in patients with HTN, with a view to stratifying the risk of mortality in patients on HD. The variability of blood pressure is highly correlated with mortality from cardiovascular causes in patients with renal dysfunction.

Diabetes

Diabetes is the main cause of CKD grade 5 worldwide. HD patients present early albuminuria and progressive decrease in glomerular filtrate rate (GFR). It is estimated that about 40% of patients with type 2 diabetes develops kidney damage in the first 10 years of disease evolution metabolism and that mortality on dialysis is higher.[16]

The evidence available from clinical guidelines recommends the appropriate management of blood pressure numbers and good metabolic control guided by hemoglobin levels glycosylated between 6.5% and 8%. In addition to the use of enzyme inhibitors angiotensin II converter or angiotensin receptor antagonists. In

recent guidelines, a sodium glucose cotransporter 2 inhibitor drug is added that has potential effects on preserving renal function and offers cardiovascular protection.[17]

Saputro and others[18] carried out an MA where 18 studies with 366 210 were included diabetic patients with CKD on HD. The researchers developed predictive models based on 46 mathematical equations with the aim of predicting the final phase of the disease and mortality. The predictors were age, sex, GFR, body mass index (BMI) and glycosylated hemoglobin levels. These results are subjected to internal and external validations.

Clinical evolution of the disease

Cardiovascular disease

CVD is the leading cause of mortality in patients with kidney disease. The patients with chronic kidney dysfunction present vascular calcification, atherosclerosis advanced and valve stiffness. These phenomena are capable of promoting the development of left ventricular hypertrophy, heart failure, arrhythmias and cardiac arrest. The control of cardiorenal syndrome encourages better survival outcomes.[19]

Yang and others[20] in a MA that included six investigations, of which three were randomized controlled trials showed that the administration of inhibitors renin-angiotensin system, significantly reduced mortality from all causes in patients with CKD. It was concluded that although some group's pharmacological drugs can reduce the risk of cardiovascular death, more are needed evidence to prove it.

The frequency of CVD in patients with CKD on HD is higher than previously thought. Know the different scales for estimating cardiovascular risk do not include kidney function among the aspects to be evaluated. Since the diagnosis of kidney disease in its early stages, strategies must be designed to reduce the incidence of mortality due to cardiovascular causes.

Zhu and others[21] in a research that constructed an predictive model for the presence and severity of coronary artery calcification in patients with CKD

depending on the cardiac computed tomography, reported that, of the 3,701 patients included, 943 (25.5%) had calcification. This was associated with the development of events major cardiovascular events and mortality.

Wolff and others[22] in a series that included 1,374 HD patients evaluated the incidence of non-fatal and fatal serious adverse cardiovascular events during a median follow-up of 26 months. Disease of the significant coronary arteries in 886 individuals. Although the prevalence of CVD was high in patients undergoing percutaneous coronary intervention or graft of coronary artery bypass, there was an 18% reduction in the risk of death for all causes (p = 0.003).

On the other hand, a research that included 336,182 patients who started HD in 2021, carried out by *Sakuma* and others[23] investigated the association of risk factors with the CVD mortality rate. The mortality rate from CVD is correlated positively with systolic blood pressure (r = 0.3127 and p = 0.0324) and diastolic blood pressure (r = 0.3378 and p = 0.0202). The researchers suggested that, among other measures, optimal blood pressure management can reduce mortality on dialysis.

Dyslipidemia

Dyslipidemia in kidney disease generates persistent inflammation, a condition that it causes other comorbidities and increases the risk of mortality. *Wang* and others[24] conducted an MA that included 7,921 participants concluded that the treatment of dyslipidemia with statins achieved a decrease in C-reactive protein levels and that, an important anti-inflammatory effect was exerted, to delay the progress of the kidney disease, evade complications and avoid mortality.

Sung and others[25] conducted a cohort investigation with the objective of evaluating the mortality risks in patients with hypercholesterolemia and CKD. Three were compared cohorts of patients with normal kidney function, established CKD and kidney failure chronicle. Patients on HD were the group with the highest mortality, those who used statins had a reduced risk of mortality of 32%.

Lee and others[26] performed an analysis in which 136 events were reported major cardiovascular diseases in patients on HD, a higher incidence was obtained in those patients with high lipoprotein values.

There is still limited understanding of how dyslipidemia contributes to development of progression and mortality in CKD, the truth is that the dysfunction of the system endothelial and oxidative stress are involved in the pathogenesis of kidney damage mediated by dyslipidemia. Over a period of 10 years, indicators were evaluated biochemical tests of 8,053 patients with CKD. Individuals with dyslipidemia had higher risk of death (RR: 1.264 and $p < 0.007$).[27]

Cerebrovascular diseases

Cerebrovascular diseases (CD) frequently complicate the prognosis of the patient with CKD on HD. They are associated with worse severity, cognitive impairment important and healthcare expenses. The start time in HD is a vulnerable period for acute stroke, since the 30-day period before and after from the start of dialysis, is associated with a three-fold increase in the risk of stroke transient ischemic or recurrent stroke.[28]

Shinya and others[29] revealed significant CD trends in patients followed in HD. The incidence rate in the first year after starting dialysis was 22.6%. According to the multivariate analysis, diabetic nephropathy was the risk factor significant, to trigger CD (OR = 2.63; $p = 0.032$).

In HD, significant progression of atherosclerosis with strong calcification occurs induced by calcium/phosphorus metabolic abnormality due to secondary hyperparathyroidism. This vascular calcification can cause different CD that cause morbidity and mortality. The incidence of stroke in the population on dialysis, is 2 to 10 times higher than the general population and is reported between 12.4 and 74.0 per thousand patients per year.[30]

In patients on supportive HD, intracerebral hemorrhage is one of the main causes of mortality among stroke subtypes. It is not at all clear whether, along with

traditional cardiovascular risk factors, risk factors unique to the uremic environment may contribute to the risk of mortality from CVD.[31]

Malnutrition

HD patients tend to experience malnutrition due to excessive intake inadequate food, diseases of the digestive tract, food restrictions, medications that alter nutrient absorption, inadequate dialysis and comorbidities. Nutritional status is related to quality of life and mortality of patients on periodic HD.[32]

Yaparak and others[33] performed a prospective longitudinal investigation in 334 patients in HD, with the aim of investigating malnutrition as a possible indicator of mortality. The following were analyzed: the geriatric nutritional risk index, the inflammation due to malnutrition and the prognostic nutritional index. Through the use of four different models and logistic regression analysis, it was shown that the best mortality indicator was the malnutrition index.

Malnutrition is considered a negative prognostic factor in HD, with an estimated frequency of 50%. Poor nutritional status is a risk factor for reduced immunity causing the development of infections and pro-inflammatory state, which favors the appearance of comorbidities and complications.[34]

Anemia

Anemia is a recognized prognostic factor of mortality in HD patients. *Kim* and others[35] in a single-center retrospective series that included 582 patients with CKD in maintenance HD, evaluated the association of distribution width of red blood cells with adverse effects and mortality. During the median follow-up of 3.1 years, 165 cardiovascular events and 124 deaths were reported. The Cox regression showed that low levels of red blood cells presented significance statistic (HR: 1.66; p = 0.03).

Wittbrodt and others[36] characterized 22,720 patients with CKD in an investigation retrospective longitudinal study conducted in USA. 23.3% of patients presented anemia, the prevalence of this was higher in HD patients (72.8%) and was

associated a higher rate of hospitalizations, complications during the dialysis procedure, progression of kidney disease and increased mortality.

Anemia in patients with CKD has a multifactorial cause, but the use of agent's erythropoietin stimulants and iron supplements have a considerable impact in survival outcomes.

Hemoglobin, whether in patients with or without anemia, is associated with an increase in interdialytic complications and in-hospital mortality. In 1999, *Asmar* and others[37] revealed that hemoglobin levels between 12 and 13 were related to better survival in HD patients. The study of dialysis outcomes and patterns of practice suggested maintaining hemoglobin above 11 g/dL. A later essay, of treatment to reduce cardiovascular events in HD revealed greater harm in elevated hemoglobin levels and influenced international guidelines on anemia to recommend a hemoglobin of 11 to 12 g/dL in patients with CKD.

Peripheral arterial disease

Peripheral arterial disease (PAD) at the beginning of HD is a variable that must be considered in the monitoring and follow-up of patients. *Morooka* and others[38] in a study that included 1,524 patients at the time of initiation of RRT, they compared mortality rates of patients with or without PAD. After a median of follow-up of 814.5 days, 33.80% died *vs.* 17.00% (p = 0.001). After although adjustment for confounding factors was performed, PAD continued to be considered an independent risk factor for mortality.

Since 1916 there have been reports of the association between PAD and mortality in HD patients. Multivariable-adjusted relative risks range from 2.9 to 7.1 for all causes of mortality and others due to cardiovascular causes, respectively. At the same time, PAD is associated with other traditional cardiovascular risk factors such as: diabetes, dyslipidemia, HTN and smoking, which shadow the prognosis of the patient.[39]

PAD is associated with an increased risk of cardiovascular morbidity and mortality in dialysis patients. Prolongation of the corrected QT interval in electrocardiogram,

raises suspicion of major cardiovascular events such as myocardial infarction, stroke and cardiovascular death. In Conclusion, symptomatic PAD is related to all-cause mortality in incident patients on HD.[40]

Cancer

As life expectancy and survival have lengthened in patients with CKD, has increased the prevalence of cancer in patients who start HD. The high frequency of deaths from causes other than primary cancer and the decreased life expectancy in HD makes implementation of measures impossible optimal treatment strategies.[41]

Chen and others[42] analyzed a retrospective cohort of 639 patients who started HD, with the aim of investigating the incidence of cancer in these patients and identify if this was considered a prognostic factor. 9.08% were diagnosed with cancer at a median follow-up of 5.22 years. Digestive malignancy was the most common, followed by urological tumors and lung cancer. Of all the deaths during the follow-up period, 11.33% were attributed to direct cause of neoplasia and the cumulative survival rate in the first year of diagnosis of the cancer was 58.73%.

In an MA, conducted by *Lees* and others[43] which included data from five clinical trials and a population cohort of 32,057 individuals, there was a trend toward greater risk of cancer incidence and a significant increase in cancer death among HD patients. Death from cancer represents between 14% and 39% of all deaths in RRT.

Paraclinical results

Creatinine and glomerular filtration rate

Glomerular filtration rate can only be measured accurately in experimental models. In humans it is determined from the clearance of low molecular weight substances such as creatinine, which are excreted by the kidney through the glomerular component. There are different estimation formulas, among them, the Cock-Croft and Gault equation, Modification Diet in Renal Disease and Chronic Kidney Disease

Epidemiology Collaboration. The use of each one is recommended according to different criteria.[44]

Liangjing and others[45] in a prospective cohort in 18,298 patients with diabetes without history of CKD, they used the Modification Diet in Renal Disease formulas and Chronic Kidney Disease Epidemiology Collaboration to estimate GFR in a model kidney failure risk equation. In summary, 132 patients developed CKD stage 5 after 12 years and mortality one year after starting HD was high.

Both formulas were accurate in the prediction model. In general, the formulas to estimate the GFR require the figures of creatinine and these present variability depending on diet, muscle mass and disorders in secretion and excretion.

To determine possible errors in creatinine measurements and overcome biases In calculating the GFR, *Carrero* and *Elinder*[46] carried out during the years 2006 to 2019 mega research project SCREAM (for its acronym derived from *The Stockholm CREAtinine Measurements*). Motivated by the high prevalence of a "silent" disease and the high mortality rates. It was analyzed the creatinine values of 1.8 million people. It was concluded that, although the Creatinine had limitations, the estimate of GFR exceeded them.

The SCREAM project[46] constitutes a reference at an international level, for the clinical epidemiology in HD for the findings shown. These results achieved generalize in different cohorts and the model used was implemented in future population studies. The direct relationship was determined between the increase in numbers of creatinine and decreased GFR with all-cause mortality.

Albumin

Albumin is the main plasma protein with high solubility. Among his functions: regulates vascular osmotic pressure, helps in the transport of substances endogenous and exogenous, it is also considered a vital extracellular antioxidant.[47] The detriment of their values, has been identified as an important factor dependent mortality in patients receiving HD.

Zeng and others[48] investigated the association between albumin concentrations plasma concentration and the risk of cardiac arrest in patients with kidney disease followed in HD. In the 4,990 patients studied, for every 1 g/dL increase in albumin, was associated with a 68% decrease in the risk of cardiovascular mortality. A study carried out in patients with CKD on HD from the province of Las Tunas, Cuba between in 2016 and 2019, it was reported that albumin less than 35 g/L was a prognostic factor mortality (p = 0.000; HR: 3.468; CI: 1.760 - 5.879).[7]

Lee and others[49] explored optimizing the prediction of 2-year mortality of patients with CKD on HD by associating serum growth differentiation factor-15 and albumin. The researchers concluded that the highest quartile of the index prognosis was associated with mortality (p = 0.000; HR: 8.468; CI: 2.981 - 24.054). It was recommended that both isolated albumin and the association in the proposed index discriminated the risk of mortality.

Xie and others[50] in a retrospective cohort investigation that included 1,954 Chinese patients on HD demonstrated by Cox regression that the risk of all-cause mortality was associated with decreased albumin values. Individuals with a decrease between 9.36 and 12.79 had an HR of 0.731; while those with loss values greater than 12.79 revealed HR of 1.705. The competing risk analysis revealed significant differences for mortality due to all causes $p < 0.001$.

Urea

In HD patients, urea levels, specifically, the kinetic distribution of urea, offers better explanatory hypotheses related to mortality. Although several cardiovascular risk factors are known traditional, in the patient with kidney disease, uremic toxins overlap pathogenic vascular changes. The urea figures are related in a way directly with the quality and adequacy of optimal dialysis. The constant monitoring of the urea in the renal patient on RRT would estimate their clinical outcome.

Laville and others[51] in a cohort of 2,507 HD patients, with the aim of to determine whether urea levels were associated with CVD and death, they divided the sample in three tertiles according to urea figures and used risk models Cox proportional.

The results of the study suggested that the highest values High urea levels were predictors of CVD, HR: 1.93, and of mortality, HR: 1.31.

An analysis of longitudinal data from a retrospective cohort of patients incidents in HD, carried out by *Okazaki* and others[52] showed that deceased patients they presented creatinine, GFR and urea levels of 609.96 ± 256.36 mmol/L; 7.9 mL/min/1.73m^2 and 18.66 mmol/L respectively. Living individuals showed levels at 397.8 ± 150.28 mmol/L; 9.10 mL/min/1.73m^2 and 27.13 mmol/L respectively, the three parameters were associated with specific mortality.

Hyperkalemia

Potassium disorders are the most common electrolyte alteration in patients in HD. Hyperkalemia in HD patients can trigger arrhythmias fatal heart attacks. Although the serum potassium level prior to HD is a factor known risk of modifiable mortality, sometimes this risk can underestimate yourself. Failure to comply with dietary potassium restrictions and acidosis metabolism increases the risk of hyperkalemia.[53]

The optimal serum potassium level before HD is unknown. There are no trials randomized controlled trials that examined the target potassium level before dialysis. It is a survivor bias to include only prevalent patients in HD and non-incident, when evaluating the role of potassium in mortality.[53]

Rooij and others[54] performed a multicenter prospective cohort investigation, investigated the relationship between serum potassium level prior to dialysis and death. 1,117 incident HD patients were included and followed for six months. It was concluded that there was a "U-shaped relationship" between the serum potassium level and mortality.

Hemodialysis Adherence

Late start of hemodialysis

Early mortality after starting the HD program is high, so, in our opinion, of the authors, prior nephrological care and early initiation of the dialytic procedure in CKD

patients are of great importance. The different therapeutic measures performed in the pre-dialysis stage, as well as the timely initiation of HD, are associated with greater survival.

Nee and others[55] analyzed a retrospective cohort of 1,256,640 patients who they started supportive HD. The highest frequency of mortality was reached between the fourth and eighth week of start of RRT. Lower mortality rates were shown in six, nine and 12 months of follow-up in patients who started the treatment program HD early.

Fu and others[56] conducted a nationwide cohort study in the Netherlands with the objective of identifying the optimal GFR level to begin HD. Of the 10 290 patients with advanced CKD, 3,822 started HD, 4,160 died and 2,446 presented CVD. Those patients who started RRT with GFR between 15 - 16 mL/min/1.73m^2 presented a 5.1% lower absolute risk of mortality at five years and 2.9% lower risk of cardiovascular events compared to patients with GFR between 6 - 7 mL/min/1.73m^2.

Adherence to HD is an element of great importance, to evaluate rigorous medical interventions aimed at improving dialysis outcomes. A MA performed by *Sousa* and others[57] with the objective of exploring the criterion validity of the influential variables in adherence to HD, showed that there was a force of medium-high association in those patients who started the procedure late dialytic.

An MA that included 13 studies, carried out by *Jia* and others[58] investigated the evidence available regarding the optimal initiation of maintenance dialysis. Nine investigations focused on optimal GFR, five showed no association between GFR and mortality or other adverse outcomes, two studies revealed that the initiation of HD with higher GFR levels had a poor prognosis and two showed higher GFR with better prognosis.

Excessive interdialysis weight gain

Another variable that must be monitored in prevalent HD patients is excessive interdialysis weight gain (EIWG). Those patients who present an increase of

interdialysis weight greater than 4.5% of total body weight, are considered as excessive interdialytic weight gain EIWG.[59]

An EIWG can cause complications such as HTN, acute pulmonary edema, increased of morbidity and even mortality from all cardiovascular causes. The main cause of EIWG is excessive intake of liquids and/or food. It is estimated that between 30-60% of HD patients do not follow a restriction regimen liquids.[60] People on HD should be consistently warned to limit the salt consumption, to help control thirst and, consequently, reduce intake of liquids.

Miyasato and others[61] examined the association between EIWG with mortality and rapid decline EIWG was divided into seven categories. The most EIWG categories high rates were associated with a higher risk of adverse outcomes. The risk quotient multivariate-adjusted in residual kidney function. The retrospective cohort formed for 41,650 patients, the snapshot of all-cause mortality in the group with gain over 5% was 1.26; 95% CI: 1.06 - 1.28.

Sepsis

The development of sepsis in patients on repeated HD has been a prognostic factor traditionally established, it is one of the most serious and deadly complications. There is geographic variability regarding this variable as a cause of death. Despite of the material resources allocated to the treatment of patients on RRT, sepsis it is an element of great importance in the prognosis of patients in dialysis's unit.

Locham and others[62] conducted a review with the objective of reporting the incidence and prognosis of sepsis in patients on HD. In a cohort that included a total of 870 571 patients, 29.8% developed sepsis. This was associated with three-fold increase higher odds of mortality (OR: 3.16; 95% CI: 3.11 - 3.21; $p < 0.001$). One-year mortality after sepsis among survivors was 21%. The incidence rate of sepsis was 12.66 episodes per hundred people per year.

Sepsis and bacterial infections are very common in patients with CKD stage 5 and after CVD, it is the second leading cause of death. 8% of patients with septic shock

receive chronic dialysis. Patient mortality in septic HD is much higher than that of those patients without evidence of infection (47.65%).[63]

Although mortality in HD is high, detailed information on long-term causes of death are limited. To overcome this limitation, *Hiyamuta* and others[64] carried out a multicenter study for 10 years that included 3,528 patients followed in HD, in Japan. Infectious diseases were the second cause of mortality, with 25.8%, only surpassed by CVD.

Vascular access

One of the elements responsible for mortality in HD is the type of access vascular. The highest incidence of deaths in patients with catheters is recognized centrovenous (CVC), compared to those with arteriovenous fistula (AVF) or grafts. His previous approach is due to the association of infections and complications cardiovascular diseases in patients with CVC. The policy on vascular access in the patients on HD, is to promote the use of an AVF or arteriovenous grafts, in case of that there is no severe heart failure, ischemia of the limb induced by the limited access or prognosis.[65]

Although AVF can cause deleterious effects on the structure and heart function, such as: increased cardiac output, ventricular hypertrophy left, alterations in diastolic function and risks of arrhythmias, which contribute to cardiovascular dysfunction, its use is essential.

Laham and others[66] conducted a retrospective cohort investigation in 503 patients with the objective of evaluating survival with early onset, versus late start in HD taking into account the type of vascular access used. It was demonstrated that the group that started HD with CVC had a poor survival rate compared to those patients with AVF ($p < 0.001$). The multivariate analysis revealed CVC as an independent mortality factor.

Vascular access is a prerequisite for maintenance HD and establishing effective and functional long-term access is important to improve the patient's prognosis.

International guidelines recommend AVF autologous as the first option compared to CVC with the aim of achieving better adherence to HD.[67]

In general, there are other variables with marked interest for the prediction of mortality in patients with CKD on HD, among them are calcium levels, phosphorus and parathyroid hormone, which are related to the development of alterations of bone and mineral metabolism. Furthermore, biomarkers related to chronic inflammation such as elevated C-reactive protein and proinflammatory cytokines are associated with mortality. Sarcopenia, time on renal replacement therapy and psychosocial factors also influence death from all causes.

Conclusions

Predictors in mortality risk stratification were described in patients with chronic kidney disease on hemodialysis. These predictors do not act in isolation, but rather interact with each other to influence the patient's prognosis. Comprehensive and systematic evaluation, which integrates these predictors, can help personalize treatment and improve clinical outcomes.

Recomendations

Scientific evidence in the stratification of mortality risk in patients with chronic kidney disease on hemodialysis are extensive and constantly evolution. The authors recommend, for future reports, including other variables related to biochemical and metabolic parameters, indicators dependent on hemodialysis and psychosocial factors.

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Conflict of interest

Authors declare that they have no conflict of interest.