Metabolic Syndrome, Malnutrition, and its Associations with Cardiovascular and All-cause Mortality in Hemodialysis Patients: Follow-Up for Three Years

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ABSTRACT. Metabolic disorder contributes to the increase in the mortality rate of patients on hemodialysis (HD). The aim of this study was to estimate the prevalence of metabolic syndrome (MS) and malnutrition in patients on maintenance HD and to evaluate their influence on cardiovascular and all-cause mortality during the follow-up. We carried out a prospective cross-sectional study in which we enrolled 100 patients from a single center who had been followed up for three years. Collected data included demographic characteristics, detailed medical history, clinical variables, MS variables, nutritional status, and laboratory findings. The outcomes were the occurrence of a cardiovascular event and cardiovascular or all-cause mortality during the follow-up period. The Statistical Package for the Social Sciences software was used for statistical analysis. Whereas 50% of patients had MS, 23% showed evidence of malnutrition. Patients with MS were older and had more preexisting cardiovascular diseases (CVDs). All patients were followed for 36 months. During this time, 19 patients with MS and 14 patients without MS died (38% vs. 28%; P = 0.19), most frequently of CVD. Mean survival time was 71.52 ± 42.1 months for MS group versus 92.06 ± 65 months for non-MS group, but the difference was not significant. MS was related with a higher cardiovascular mortality, while malnutrition was significantly associated with all-cause mortality. Our data showed that MS was not related to cardiovascular or all-cause mortality in HD patients and did not influence survival. The independent risk factors for all-cause mortality were older age, preexisting CVD, and malnutrition.

Introduction

Despite the advent of maintenance hemodialysis (HD) therapy for end-stage chronic renal failure, the mortality among patients on HD remains high.1,2 Cardiovascular disease
(CVD) is the main cause of morbidity and causes more than 50% of the deaths in chronic HD patients. Metabolic syndrome (MS) is considered as an interconnected clinical, biochemical, and metabolic disorder which manifests by increased blood pressure, large waist circumference, high triglyceride level, reduced high-density lipoproteins (HDLs) cholesterol, and elevated fasting blood glucose. The prevalence of MS depends on many factors, such as the definition of MS used, country of origin, and urban or rural environment. It has been reported to range from 30% to 84% in various studies worldwide and is associated with higher mortality and morbidity in the general population.

However, some risk factors for CVD in the general population have not been associated with a poor prognosis among patients on HD. Different studies suggest an association between nutrition and clinical outcome in (HD patients assuming that malnutrition may contribute to mortality. However, few scientific reports are focusing on the prevalence and incidence of MS and malnutrition in HD patients during the follow-up. The purpose of our study is to estimate the prevalence of MS and malnutrition among HD patients in the first place and then, to evaluate the relationship between the MS, malnutrition, and mortality (cardiovascular and all-cause) in HD patients during a follow-up of three years.

Patients and Methods

Study design
This was a prospective cross-sectional study.

Patients
Of a series of 210 filed HD cases studied from January 2013 to December 2016, we included in this study all patients on HD for more than three months.

All patients required regular HD sessions for 4 h, three times a week. Blood flow was generally 300 mL/min with a dialysate flow of 500 mL/min. Patients were dialyzed with high-flux polysulfone membranes with bicarbonate-buffered dialysate. All patients received regular doses of standard heparin before an HD session.

Exclusion criteria were nonregular dialysis patients, patients with acute or chronic hepatic failure, acute infections, and clinical instabilities.

Variables
Collected data included detailed medical history and clinical variables [age, sex, body mass index (BMI), waist circumference, predialysis systolic blood pressure, etiology of end-stage renal disease, preexisting CVD, presence or not of diabetes, high blood pressure and ischemic cardiopathy, seniority on dialysis, and erythropoietin stimulating agent treatment].

MS was defined using the modified National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria. It was defined by three or more of the following: fasting plasma glucose of at least 110 mg/dL (6.1 mmol/L), serum triglycerides of at least 150 mg/dL (1.7 mmol/L), serum HDL cholesterol <40 mg/dL (1.04 mmol/L), blood pressure of at least 130/85 mm Hg or use of antihypertensive drugs and waist circumference >102 cm in men and >88 cm in women.

Each patient nutritional status was assessed by subjective global assessment (SGA) methods (A = normal nutrition, B = mild malnutrition, C = severe malnutrition). The SGA includes six subjective assessments, three based on the patient’s history of weight loss, incidence of anorexia and incidence of vomiting, and three based on the physical findings of muscle wasting, presence of edema, and loss of subcutaneous fat. Laboratory findings including HDL cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol, total cholesterol, phosphorus, calcium, parathyroid hormone, hemoglobin, and nutritional and inflammatory markers such as serum albumin and C-reactive protein were measured in all patients using standard methodologies at the biochemistry department. Urea reduction ratio was used to evaluate the adequacy of HD treatment.

Follow-up
Patients were classified based on the presence or absence of MS and were prospec-
tively followed for 36 months or until the patient died or had a renal transplant if this event occurred before. In case of patient death, the primary cause of death was recorded.

**Statistical Analyses**

Statistical analysis was performed using the IBM SPSS Statistics for Windows version 21.0 (IBM Corp., Armonk, NY, USA) for Windows. Data were expressed as percentage, mean and standard deviation. Different comparisons between groups of HD patients with MS and without MS and groups of survivors and dead patients were performed using Student’s t-test and Chi-square test, according to statistical significance at $P <0.05$. A Cox regression model was performed to determine risk factors for mortality. The Kaplan–Meier test was used for the analysis of survival.

**Results**

**Clinical and laboratory characteristics of the study population**

One hundred HD patients were recruited and followed for 36 months. The mean age was 62 ± 11 years and 60% of patients were men. Fifty patients (50%) had MS according to NCEP criteria. Demographic, clinical, and laboratory characteristics of the study population are shown in Table 1. In the MS versus the non-MS group, significant differences in sex and prevalence of preexisting CVD were observed. Patients with MS were older and had significantly higher BMI. There were fewer patients with malnutrition (by SGA) in MS group but the difference was not significant (Table 1).

**All-cause mortality, cardiovascular mortality, and metabolic syndrome**

All patients were followed for 36 months. During this time, 19 patients with MS and 14 patients without MS died (38% vs. 28%; $P = 0.19$), most frequently of CVD (Table 2).

**Kaplan–Meier analysis of survival**

Patients with MS developed more CVD than those without MS. The all-cause mortality rate was higher in patients with MS than in patients without MS, but the difference was not significant (Figures 1 and 2).

**Comparison between survivors and non-survivors**

To study more the risk factors for mortality, the 100 patients were reclassified according to survival and death, and the clinical and laboratory characteristics were compared between these two groups (Table 3). Compared to surviving patients, there were more patients

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**Table 1. Demographic, clinical, and laboratory characteristics of the study population.**

|                      | All patients (n=100) | MS (n=50) | Without MS (n=50) | $P$  |
|----------------------|----------------------|-----------|-------------------|------|
| Age (years)          | 53.5±17.09           | 59.7±13.38| 47.3±18.24        | <0.0001|
| Female               | 60                   | 24 (48)   | 36 (72)           | 0.014 |
| Preexisting CVD      | 44                   | 28(56)    | 16 (32)           | 0.016 |
| Seniority on dialysis (months) | 50.67±53.94          | 41.54±40.45| 59.8±63.84        | 0.09  |
| BMI (kg/m²)          | 24.93±4.99           | 27.11±4.77| 22.7±4.23         | <0.001|
| Malnutrition (B, assessed by SGA) | 23                  | 8 (16)    | 15 (30)           | 0.09  |
| Hemoglobin (g/dL)    | 8.16±2.01            | 7.8±1.8   | 8.5±2.16          | 0.08  |
| Serum albumin (g/L)  | 36.25±7.32           | 35.78±6.56| 36.68±8.01        | 0.55  |
| Total cholesterol (mmol/L) | 3.91±1.14            | 3.91±1.21 | 3.91±1.07         | 0.99  |
| PTH (pg/mL)          | 368.91±252.38        | 358.34±194.01| 375.69±292.92    | 0.75  |
| URR (%)              | 71.13±11.69          | 68.88±12.27| 73.33±10.81       | 0.1   |
| CRP (mg/L)           | 9.35±9.88            | 8.52±8.13 | 10.23±11.5        | 0.46  |

Data are mean ± standard deviation or number (%). MS: Metabolic syndrome, CVD: Cardiovascular disease, SGA: Subjective global assessment, BMI: Body mass index, PTH: Parathyroid hormone, URR: Urea reduction ratio, CRP: C-reactive protein.
Table 2. Comparison of causes of death between metabolic syndrome and nonmetabolic syndrome groups

|                              | All patients (n=100) | MS (n=50) | Non-MS (n=50) | P    |
|------------------------------|----------------------|-----------|---------------|------|
| All-cause mortality, n (percentage of total) | 33                   | 19 (38)   | 14 (28)       | 0.19 |
| Cause of death, n (percentage of deaths)   |                      |           |               |      |
| CVD                                        | 17 (51.51)           | 10 (52.63)| 7 (28)        | 0.42 |
| Malnutrition                              | 4 (12.12)            | 2 (10.52) | 2 (14.28)     | 0.69 |
| Other causes                               | 12 (36.36)           | 7 (36.84) | 5 (35.71)     | 0.38 |
| Total survival time (months), mean±SD      | 81.79±55.37          | 71.52±42.1| 92.06±64.84   | 0.064|

MS: Metabolic syndrome, CVD: Cardiovascular disease, SD: Standard deviation.

Figure 1. Kaplan–Meier analysis of cardiovascular disease occurs in patients with and without metabolic syndrome.

Figure 2. Kaplan–Meier survival analysis of all-cause mortality in patients with and without metabolic syndrome P = 0.19.
with malnutrition (B, assessed by SGA) in the dead patient group (Table 3). However, the percentage of patients with MS was higher among the dead patients group, but the difference was not significant.

Factors associated with all-cause and cardiovascular mortality using multivariate Cox regression analysis

Variables that were significantly associated with all-cause and cardiovascular mortality were included in the multivariate regression model. Age and malnutrition were significantly and independently associated with all-cause mortality. The presence of preexisting CVD and low HDL was significantly and independently associated with cardiovascular mortality (Table 4).

Discussion

CVDs are the major cause of morbidity and mortality of HD patients. In the general population, MS is associated with a higher risk of CVD. Overall, the relationship between MS and cardiovascular or all-cause mortality in HD patients has not been determined. The present study demonstrates that MS defined according to the NCEP-ATPIII criteria was present in more than 50% of our patients, which is consistent with many studies. In the present work as well as in many studies, the lipid profile of HD patients was unique and classically characterized by the predominance of hypertriglyceridemia, low HDL cholesterol, and high LDL cholesterol. However, when we classified the patients

### Table 3. Comparison of clinical and laboratory characteristics between surviving and dead patients.

|              | Survived (n=67) | Dead (n=33) | P  |
|--------------|----------------|-------------|----|
| Diabetes     | 13 (19.40)     | 11 (33.33)  | 0.1|
| SBP          | 132.69±19.64   | 133.33±22.45| 0.88|
| Waist circumference (cm) | 93.66±14.63 | 96.21±13.89 | 0.85|
| Malnutrition | 8 (11.94)      | 15 (45.45)  | <0.0001|
| Serum albumin (g/L) | 36.73±7.41 | 35.21±7.15 | 0.35|
| Triglycerides (mmol/L) | 1.95±1.00 | 1.66±0.68 | 0.13|
| HDL-C (mmol/L) | 1.01±0.34 | 0.93±0.26 | 0.25|
| MS           | 31 (46.26)     | 19 (57.57)  | 0.19|

Data are mean ± standard deviation or number (%). MS: Metabolic syndrome, CVD: Cardiovascular disease, SBP: Systolic blood pressure, BMI: Body mass index, HDL-C: High-density lipoprotein cholesterol, CRP: C-reactive protein.

### Table 4. Factors associated with all-cause, cardiovascular mortality, and cardiovascular events.

| Variable       | All-cause mortality | Cardiovascular mortality | Cardiovascular events |
|----------------|---------------------|--------------------------|-----------------------|
|                | OR (CI=95%)         | P                        | OR (CI=95%)          | P                        |
| Malnutrition   | 8.01 (2.61–24.61)   | <0.0001                  | -                     | -                        |
| Age            | 1.05 (1.01–1.08)    | 0.03                     | -                     | -                        |
| Preexisting CVD| -                   | 4.34 (1.37–13.71)        | 0.01                  | -                        |
| Components of MS|                    |                          |                       |                         |
| Low HDL-C      | -                   | 12.35 (1.47–103.21)      | 0.02                  | -                        |
| Obesity        | -                   | -                        | -                     | 3.83 (1.21–12.1)         | 0.022 |
| HBP            | -                   | -                        | -                     | 10.74 (1.32–87.09)       | 0.026 |

OR: Odds ratio, CI: Confidence interval, MS: Metabolic syndrome, CVD: Cardiovascular disease, HDL-C: High-density lipoprotein cholesterol, HBP: High blood pressure.
into groups based on the NCEP/ATP III criteria and performed a prospective study focusing on the relationship between MS and cardiovascular or all-cause mortality in HD patients, we found that MS did not increase the mortality risk in HD patients which is concordant with others studies.19

Some reasons could explain the nonsignificant influence of MS on CVD and all-cause mortality among our HD patients. First, our follow-up time was relatively short and our sample size, coming from a single-center, was relatively small. Second, the preexisting CVD, which was powerfully associated with cardiovascular and all-cause mortality, might affect patients’ survival over the short-term whereas MS might influence patients’ survival in the long time. The assessment of nutritional status was generally based on the measurement of serum albumin levels,9,20 but in a few studies, nutritional status was evaluated with SGA or total body nitrogen.10,21 In our study, the nutritional status was evaluated with both SGA and the serum albumin levels. The prevalence of malnutrition in our HD patients was 23%. In the literature reports, the prevalence of malnutrition in HD patients was very different; it ranged from 23% to 73%.22 Differences depend specifically on the country, urban or rural environment, and the composition of the study population (sex and age). The role of nutrition as a mortality factor has not been obviously established. In our study, there were more patients with malnutrition in the dead patient group than in the surviving group. It is consistent with Stolic et al who reported that malnutrition increased the risk of mortality in HD patients compared with MS.23,24

Conclusion

Unlike malnutrition, MS was not linked to cardiovascular or all-cause mortality in our HD patients and did not influence survival rate. The independent risk factors for mortality were older age, preexisting CVD, and malnutrition.

Conflict of interest: None declared.

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