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# Metabolic syndrome predicts mortality in non-diabetic patients on continuous ambulatory peritoneal dialysis

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## Abstract

**Background.** Metabolic syndrome is associated with higher morbidity and mortality in the general population, but the corresponding effects in patients on dialysis have not been clearly defined. In this study, we prospectively investigated the effect of metabolic syndrome and its individual components on outcome in non-diabetic peritoneal dialysis (PD) patients.

**Method.** The study subjects included 106 stable non-diabetic PD patients who had been on PD for >3 months. We measured baseline characteristics, blood pressure, fasting blood glucose, lipid profiles and high-sensitivity CRP (hsCRP), and defined metabolic syndrome using the modified National Cholesterol Education Program (Adult Treatment Panel III) criteria. Mortality, technical failure and hospitalization were evaluated during the follow-up period.

**Results.** Metabolic syndrome was present in 50 patients (47.2%), and these showed higher baseline hsCRP levels (0.67; 95% CI: 0.50–0.94 versus 1.78 mg/dl; 95% CI: 1.21–2.57; $P < 0.001$). Patients with metabolic syndrome experienced significantly lower 5-year survival rates than patients without (90% versus 67%, $P = 0.02$), although these groups did not differ in peritonitis rates, technical failure or hospitalization. A Cox proportional hazards analysis identified the following as predictors of mortality: metabolic syndrome (RR: 3.39; 95% CI: 1.16–9.94; $P = 0.02$),

baseline albumin (RR: 0.06; 95% CI: 0.01–0.30; $P = 0.001$) and baseline hsCRP levels (RR: 1.14; 95% CI: 1.07–1.22; $P < 0.001$).

**Conclusion.** Metabolic syndrome is prevalent and is a risk factor influencing long-term survival in non-diabetic PD patients.

**Keywords:** inflammation; metabolic syndrome X; mortality; peritoneal dialysis

## Introduction

Metabolic syndrome arises from a constellation of derangements that includes hypertension, atherogenic dyslipidaemia, central obesity and insulin resistance, and in the general population, presents a significant risk for morbidity [1]. Studies support a positive association of metabolic syndrome with cardiovascular complications, development of type 2 diabetes and incidence of some malignancies [2,3]. Metabolic syndrome may also increase the risk for both cardiovascular and all-cause mortality in the general population [4]. Relative mortality risks vary widely, however, among the diverse study populations [5], and the impact of metabolic syndrome on overall mortality in some patient groups remains in question [4].

Metabolic syndrome promotes the development of chronic kidney disease, and insulin resistance has been noticed as a result of impaired renal function; hence, patients with end-stage renal disease (ESRD) show a high prevalence of metabolic syndrome [6,7]. Among patients with ESRD, the prevalence may be especially high in those on peritoneal dialysis (PD), because of the glucose load from the dialysate [8,9].

Although diabetes increases the risk for cardiovascular and overall mortality in both the general population and dialysis patients [10,11], some traditional risk factors, including higher body mass index (BMI), increased serum cholesterol levels and hypertension, may not be related to or even partially protect dialysis patients from these events, an example of 'reverse epidemiology' [12]. However, no study has investigated the combined effects of these traditional risk factors on mortality in patients on PD. In this study, we prospectively determined the effect of metabolic syndrome, an interrelated group of traditional risk factors, on mortality in non-diabetic PD patients.

## Subjects and methods

### *Patient population*

For this prospective observational study, we recruited 106 prevalent continuous ambulatory PD patients, who had maintained PD for >3 months, from a single Korean dialysis centre and followed them at Yonsei University Health System in Seoul, Korea. We excluded patients who were younger than 18 years of age, had overt infections during the last 3 months prior to study enrollement or had a history of malignancy or other chronic inflammatory disease (e.g. rheumatoid arthritis or systemic lupus erythaematosus). To reduce confounding effects from glucose and lipid metabolism, we also excluded diabetic patients.

A senior nursing clinician obtained the demographic data through an interview. The BMI was calculated as the weight (kg) divided by the height squared ($m^2$). Nursing staff measured the systolic blood pressure (SBP) and diastolic blood pressure (DBP) using standard mercury sphygmomanometers on the right arm of seated participants who had rested for at least 5 min. To simulate the actual dialysis condition, all patients had a full abdomen at the time of sampling. Blood samples for laboratory measurements were drawn from the antecubital vein after the first 2 h of PD exchange with 1.5% dextrose dialysate in an overnight fasting state. The preceding overnight dwell was regulated to 1.5% dextrose dialysate to standardize the glucose load. All participants gave their informed consent prior to study entry.

### *Laboratory measurements*

Plasma was separated from blood within 30 min and stored at −70°C until analysis. Fasting blood glucose was determined by the glucose oxidase method. Serum total cholesterol, HDL cholesterol and TG concentrations were measured by enzymatic colorimetry using an autoanalyser (Hitachi 7150, Hitachi Ltd, Tokyo, Japan). Low-density lipoprotein (LDL) cholesterol was calculated using the Friedwald formula. High-sensitivity C-reactive protein levels were determined using a BN II analyser (Dade Behring, Newarkand, Del.) by a latex-enhanced immunoephelometric method.

### *Diagnosis of metabolic syndrome*

The National Cholesterol Education Program (Adult Treatment Panel III) [13] bases the diagnosis of metabolic syndrome on the presence of three or more of the following: (1) SBP ≥ 130 mmHg and/or DBP ≥ 85 mmHg, (2) serum TG ≥ 150 mg/dl, (3) serum HDL cholesterol <40 mg/dl in men or <50 mg/dl in women, (4) fasting plasma glucose ≥110 mg/dl and (5) abdominal obesity. We based abdominal obesity on BMI rather than on waist circumference, because of instilled dialysate in the peritoneal cavity, and classified participants with a BMI ≥ 25 $kg/m^2$ as centrally obese in accordance with the Western Pacific Region of the World Health Organization (WPRO) criteria [14]. The modified ATP III definition used in this study has been determined to be more accurate than the WHO criteria for the diagnosis of metabolic syndrome in Asians [15].

### *Follow-up and endpoints*

Patients were classified based on the presence or absence of metabolic syndrome and prospectively followed from January 2004 until death, transfer to an alternative dialysis method, or December 2008. Only one patient was lost during follow-up, and we excluded his data from the analysis. The dates for transfer to haemodialysis (HD), renal transplantation and death were defined as endpoints. Death during PD and within 3 months after conversion to HD was regarded as PD-related mortality. Clinical outcomes were specified for mortality, technical failure, hospitalization and peritonitis. Hospitalizations for vascular access formation or renal transplantation were excluded from the analysis. Patients who transferred to HD or transplantation were censored for the patient survival analysis, while death and transplantation were censored for technique failure.

### *Statistical analysis*

Statistical analysis was performed using SPSS for Windows, version 13.0 (SPSS Inc., Chicago, IL, USA). All data were expressed as means ± SD. For analysis of the log-normally distributed TG and high-sensitivity C-reactive protein (hsCRP) values, we used the natural log values. Geometric means for all log-normally distributed continuous variables were calculated and reported with 95% confidence intervals (CI), while duration of PD with median values and ranges. To compare differences between patients with and without metabolic syndrome, Student's *t*-test or the Mann–Whitney U-test was used for continuous variables and the chi-square test for categorical variables. hsCRP levels across the numbers of metabolic syndrome components were compared by the *P*-value for the trend test. Cox proportional hazards analysis was performed to determine risk factors for mortality and technique failure. The assumption of proportionality was assessed through the analysis of Schoenfeld residuals of the covariates introduced in the models. Survival between patients with and without metabolic syndrome was compared using Kaplan–Meier analysis and a log-rank test. *P*-values < 0.05 were considered statistically significant.

**Table 1.** Clinical characteristics of subjects

| | |
|---|---|
| Age (years) | 51.6 ± 9.9 |
| Gender (male) | 49 (46.2) |
| Duration of PD (months) | 83.4 (6.7–210.6) |
| Primary kidney disease | |
| Hypertension | 24 (22.6) |
| Glomerulonephritis | 27 (25.5) |
| Others | 13 (12.3) |
| Unknown | 42 (39.6) |

PD, peritoneal dialysis; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.
Data are expressed as mean ± SD or geometric mean (95% CI), and median value (range) is expressed for duration of PD.

## Results

### *Patient characteristics*

The baseline patient characteristics are shown in Table 1. The mean age was 51.6 ± 9.9 years, 49 patients (46.2%) were male and the median PD duration was 83.4 (6.7–210.6).

### *Comparison between patients with and without metabolic syndrome*

Patients were divided into two groups based on the presence or absence of metabolic syndrome, which was present in 50 patients (47.2%). The hsCRP concentrations (0.67; 95% CI: 0.50–0.94 versus 1.78 mg/dl; 95% CI: 1.21–2.57; $P < 0.001$) were significantly higher in the metabolic syndrome group, while the SBP (139.3 ± 18.5 versus 144.9 ± 12.1 mmHg, $P = 0.07$) and DBP (83.0 ± 9.9 versus 86.0 ± 9.1 mmHg, $P = 0.10$) did not differ significantly between the two groups (Table 2).

### *hsCRP levels according to the number of metabolic syndrome components*

When the subjects were divided into six groups according to the number of metabolic syndrome components, hsCRP levels increased significantly as the number of components increased ($P$ for trend < 0.001, Figure 1). In contrast, the numbers of metabolic syndrome components had no impact on technical failure rates ($P = 0.27$), hospitalization days ($P = 0.58$) and mortality rates ($P = 0.73$).

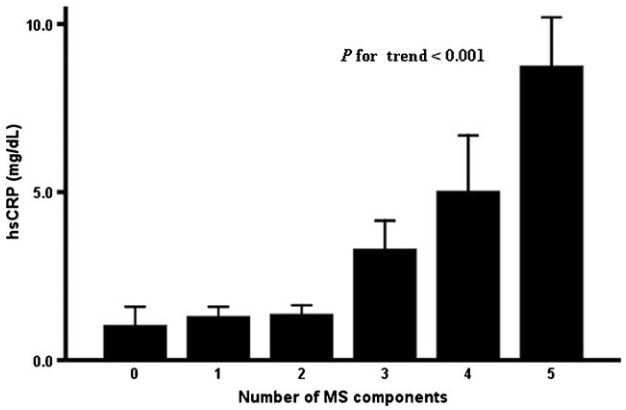


**Fig. 1.** hsCRP levels according to the number of metabolic syndrome components. Each bar shows the mean and its standard error. hsCRP levels increased in parallel with the number of metabolic syndrome components ($P$ for trend <0.001). MS, metabolic syndrome.

**Table 3.** Causes of death

| | Number of deaths (%) |
|---|---|
| Cardiovascular disease | 6 (40.0) |
| Malignancy | 3 (23.1) |
| Infection | 3 (23.1) |
| Gastrointestinal haemorrhage | 2 (15.3) |
| Unknown | 1 (7.7) |

### *Clinical outcomes with respect to metabolic syndrome*

During the follow-up period, 15 patients died. The most common cause of death was cardiovascular disease (40.0%), followed by malignancy (23.1%) and infection (23.1%) (Table 3). The 5-year survival rates were significantly lower in patients with metabolic syndrome compared to those without metabolic syndrome (67% versus

**Table 2.** Comparison of clinical and biochemical parameters in patients with and without metabolic syndrome

| | Without MS ($n = 56$) | With MS ($n = 50$) | $P$-value |
|---|---|---|---|
| Age (years) | 50.7 ± 9.5 | 52.6 ± 10.1 | 0.33 |
| Gender (male) | 30 (53.6) | 19 (38.0) | 0.12 |
| Duration of PD (months) | 78.9 (19.1–205.8) | 84.6 (6.7–210.6) | 0.89 |
| BMI (kg/m$^2$) | 22.9 ± 2.6 | 25.4 ± 3.0 | <0.001 |
| SBP (mmHg) | 139.3 ± 18.5 | 144.9 ± 12.1 | 0.07 |
| DBP (mmHg) | 83.0 ± 9.9 | 86.0 ± 9.1 | 0.10 |
| Fasting glucose (mg/dl) | 88.6 ± 13.5 | 98.3 ± 17.2 | 0.001 |
| Albumin (g/dl) | 3.5 ± 0.4 | 3.5 ± 0.4 | 0.44 |
| hsCRP (mg/dl) | 0.67 (0.50–0.94) | 1.78 (1.21–2.57) | <0.001 |
| Total cholesterol (mg/dl) | 183.7 ± 38.3 | 199.1 ± 36.2 | 0.04 |
| TG (mg/dl) | 101.1 (89.6–117.8) | 177.1 (150.4–206.1) | <0.001 |
| HDL cholesterol (mg/dl) | 47.7 ± 11.4 | 41.2 ± 13.3 | 0.008 |
| LDL cholesterol (mg/dl) | 114.0 ± 30.0 | 112.1 ± 40.0 | 0.81 |

MS, metabolic syndrome; PD, peritoneal dialysis; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.
Data are expressed as mean ± SD or geometric mean (95% CI), and median value (range) is expressed for duration of PD.

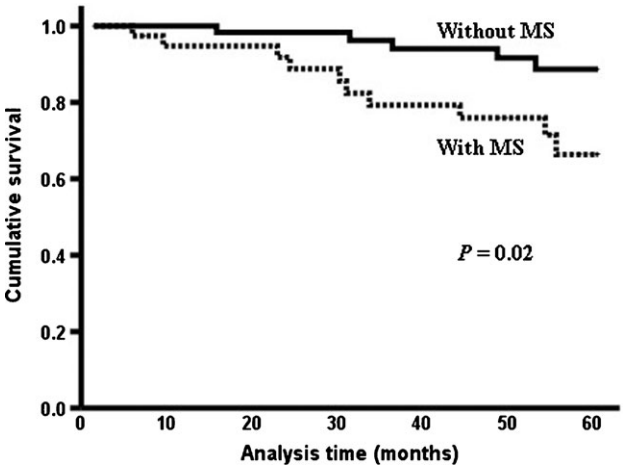


**Fig. 2.** Survival in patients with and without metabolic syndrome. Patients with MS showed significantly lower survival rates than PD patients without MS (5-year survival 90% versus 67%). MS, metabolic syndrome.

**Table 4.** Clinical outcomes according to the presence of metabolic syndrome

| | Without MS | With MS | *P*-value |
|---|---|---|---|
| Hospitalization (days/patient-years) | 6.4 ± 14.4 | 9.4 ± 18.6 | 0.35 |
| Hospitalization (times/patient-years) | 0.5 ± 0.6 | 0.7 ± 1.2 | 0.34 |
| Peritonitis (times/patient-years) | 0.4 ± 0.7 | 0.7 ± 1.4 | 0.22 |
| Technique survival at 5 years (%) | 71% | 63% | 0.66 |
| Patient survival at 5 years (%) | 90% | 67% | 0.02 |

MS, metabolic syndrome.
Data are mean ± SD.

90%, $P = 0.02$) (Figure 2). However, the groups did not differ in hospitalization days (9.4 ± 18.6 versus 6.4 ± 14.4 days/patient-years, $P = 0.35$), peritonitis rates (0.7 ± 1.4 versus 0.4 ± 0.7 times/patient-years, $P = 0.22$) or technical survival (63% versus 71%, $P = 0.66$) (Table 4).

### *Predictive value of metabolic syndrome components on mortality*

To determine the association between individual metabolic syndrome components and mortality, Cox proportional hazards analysis was performed and revealed that hypertension (RR: 7.04; 95% CI: 0.79–62.59; $P = 0.08$), high triglycerides (RR: 1.07; 95% CI: 0.32–3.61; $P = 0.91$), low HDL cholesterol (RR: 2.36; 95% CI: 0.76–7.34; $P = 0.14$), high glucose levels (RR: 1.27; 95% CI: 0.28–5.80; $P = 0.76$) and high BMI (RR: 1.17; 95% CI: 0.41–3.38; $P = 0.77$) did not predict mortality when adjusted for age, sex, albumin and haematocrit levels (Table 5).

**Table 5.** Predictive value of individual metabolic syndrome components on mortality (Cox proportional hazards analysis)

| | RR | 95% CI | *P* |
|---|---|---|---|
| High blood pressure (versus not) | 7.04 | 0.79–62.59 | 0.08 |
| High triglycerides (versus not) | 1.07 | 0.32–3.61 | 0.91 |
| Low HDL cholesterol (versus not) | 2.36 | 0.76–7.34 | 0.14 |
| High glucose (versus not) | 1.27 | 0.28–5.80 | 0.76 |
| High BMI (versus not) | 1.17 | 0.41–3.38 | 0.77 |

RR, relative risk; CI, confidence interval; BMI, body mass index.
Adjusted for age, sex, albumin and haematocrit.

**Table 6.** Predictive value of variables other than metabolic syndrome components on mortality (univariate Cox proportional hazards analysis)

| | RR | 95% CI | *P* |
|---|---|---|---|
| Age (per 1-year increase) | 1.15 | 1.07–1.23 | <0.001 |
| Gender (male) | 1.18 | 0.43–3.25 | 0.75 |
| Serum albumin (g/dl) | 0.06 | 0.01–0.30 | 0.001 |
| Haematocrit (%) | 0.96 | 0.87–1.06 | 0.40 |
| hsCRP (mg/dl) | 1.14 | 1.07–1.22 | <0.001 |
| Metabolic syndrome | 3.39 | 1.16–9.94 | 0.02 |

RR, relative risk; CI, confidence interval.

**Table 7.** Metabolic syndrome as an independent predictor of death (multivariate Cox proportional hazards analysis)

| | RR | 95% CI | *P* |
|---|---|---|---|
| Model 1 | | | |
| Metabolic syndrome | 3.83 | 1.11–13.20 | 0.03 |
| Model 2 | | | |
| Metabolic syndrome | 3.03 | 0.80–11.46 | 0.10 |

RR, relative risk; CI, confidence interval.
Model 1: adjusted for age, sex, albumin, haematocrit and dialysis duration.
Model 2: model 1 plus hsCRP.

### *MS as a predictor of patient survival*

Univariate Cox regression analysis revealed increases in mortality risk with older age (RR: 1.15; 95% CI: 1.07–1.23; $P < 0.001$), hypoalbuminaemia (RR: 0.06; 95% CI: 0.01–0.30; $P = 0.001$), high hsCRP levels (RR: 1.14; 95% CI: 1.07–1.22; $P < 0.001$) and the presence of metabolic syndrome (RR: 3.39; 95% CI: 1.16–9.94; $P = 0.02$) (Table 6). The predictability of metabolic syndrome for mortality remained significant even after adjustment was made for age, sex, dialysis duration and albumin and haematocrit levels (RR: 3.83; 95% CI: 1.11–13.20; $P = 0.03$) (Table 7). Moreover, metabolic syndrome was still a significant predictor for mortality even after adjusting for each of the individual components of metabolic syndrome: hypertension (RR: 3.04; 95% CI: 1.03–10.51; $P = 0.04$); high triglycerides (RR: 5.55; 95% CI: 1.36–12.65; $P = 0.02$); low HDL cholesterol levels (RR: 3.77; 95% CI: 1.05–13.50; $P = 0.03$); high glucose levels (RR: 5.63; 95% CI: 1.51–21.00; $P = 0.01$) and high BMI (RR: 4.66; 95% CI: 1.12–19.30; $P = 0.03$). The proportional hazards assumption held reasonably for all ($P > 0.05$) covariates of the model.

## Discussion

In the present study, we showed that metabolic syndrome is a factor influencing long-term survival in non-diabetic PD patients.

In the general population, metabolic syndrome and its constituent components are known to increase risk for adverse effects [3], including cardiovascular disease and type 2 diabetes [4]. Epidemiologic studies have also linked metabolic syndrome to cancer risks [2]. Evidence increasingly suggests, however, that some components of metabolic syndrome, including hypertension, hyperlipidaemia and obesity, may favourably influence outcome in ESRD patients [16–18].

Recent studies associate metabolic syndrome with hospitalization and severe coronary artery disease in HD patients [19,20]. Reports also show a relationship between metabolic syndrome and inflammation in patients on HD [21]. The outcome of PD patients with metabolic syndrome, however, remains unclear. Although HD and PD patients both develop chronic hypervolaemia and inflammation, the relationship between these risk factors and outcome may differ between these two treatment methods. The likely role of glucose from the dialysate in causing dyslipidaemia and weight gain in PD patients also supports a different strength of association between metabolic syndrome and outcome in HD and PD [22,23].

It is well known that metabolic syndrome is strongly associated with cardiovascular diseases, which mainly contributes to the death in these patients. In the present study, the most common cause of death was cardiovascular disease, which was in concordance with most other previous studies [3,4], but it accounted for only 40% of mortality. Recently, accumulating evidences have revealed that there is a close link between metabolic syndrome and malignancies in the general population [2]. However, this linkage has not yet been proved in PD patients. Considering that death due to malignancies was the second common cause of death in this study, we surmise that malignancy may contribute to the poor outcome in PD patients with metabolic syndrome.

The results of the present study show that metabolic syndrome is an independent factor for patient survival while the individual components of metabolic syndrome lacked the power to predict mortality. We assume that in combination, these factors synergistically influence the 5-year mortality. Recently, Zambon *et al.* sought the impact of metabolic syndrome on mortality in an elderly population, whose survival rates, like those of dialysis patients, are lower than in the general population [24]. Among the individual components of metabolic syndrome, they found that only hyperglycaemia increased the mortality risk, whereas metabolic syndrome as a whole independently predicted all-cause mortality. This supports our speculation.

Since diabetes is closely associated with hyperlipidaemia and hypertension, and is a strong risk factor for cardiovascular and all-cause mortality, data analysis that includes diabetic patients may confound the effect of metabolic syndrome *per se* on mortality. We therefore excluded diabetic patients from this study to test the independent effect of metabolic syndrome. Previous studies with non-diabetic patients have shown that metabolic syndrome predicts all-cause mortality but not cardiovascular events [4]. This supports our findings, which correlate with the relatively low incidence of cardiovascular mortality in non-diabetic patients.

Accumulating evidence has shown that metabolic syndrome, inflammation and atherosclerosis are closely related [25,26]. In the general population and in ESRD patients, inflammation markers such as CRP are associated with metabolic syndrome and mortality [27,28]. We also observed significantly higher hsCRP levels in patients with metabolic syndrome. Moreover, the significance of metabolic syndrome and hsCRP in predicting mortality disappeared after adjusting for hsCRP and metabolic syndrome, respectively. These findings indicate that metabolic syndrome and inflammation are interrelated and do not impose separate risks for mortality.

The results of the present study showed that the overall survival rates of the patients were 80.3%. Even though the survival rates were higher compared to Western countries, they were comparable with the results of a previous study on 1656 PD patients treated in our institute, which revealed that the 5- and 10- year survival rates of non-diabetic PD patients were 81.4% and 62.7%, respectively [29]. We surmise that the specific characteristics of patients (only non-diabetic patients), relatively younger age, and the ethnic difference may in part contribute to this superior survival rates in this study [30–32].

In the present study, the assessment of metabolic syndrome was made only at a single time point, so it was impossible to determine the onset of metabolic syndrome. In addition, we regarded this time point as a baseline for the analysis of the patients' survival and did not take into account the fact that the patients without metabolic syndrome also had a possibility of developing metabolic syndrome during the follow-up period. In spite of these limitations, we suppose it noteworthy that the results of this study revealed metabolic syndrome as a significant and independent predictor for mortality in PD patients.

In summary, metabolic syndrome is prevalent even in non-diabetic PD patients, and is associated with overall mortality in this group.

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*Conflict of interest statement*. None declared.

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