Original Paper

Kidney & Blood Pressure Research

Kidney Blood Press Res 2012;35:489–496
DOI: 10.1159/000338306

Received: June 9, 2011
Accepted: March 22, 2012
Published online: June 14, 2012

Relationship between Myeloid-Related Protein 8/14 and Survival of Chinese Peritoneal Dialysis Patients

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Key Words
Inflammation · Renal failure · Cardiovascular disease · Myeloid-related protein 8/14

Abstract
Background: Myeloid-related protein 8/14 (MRP8/14) is released by cells of myeloid lineage upon inflammatory challenges. Experimental data suggested that MRP8/14 is important in the initiation and progression of inflammation and cardiovascular diseases. We examined the relation between serum MRP8/14 level and cardiovascular disease in Chinese peritoneal dialysis (PD) patients. ***Methods:*** We studied 102 new PD patients (58 males, mean age 57.3 ± 11.9 years). Baseline serum MRP8/14 was determined and grouped to quartiles for analysis. All patients were then followed for an average of 23.9 ± 6.9 months. ***Results:*** There was a trend of lower 3-year cardiovascular event-free survival for patient quartiles with high serum MRP8/14 levels (log-rank test, p = 0.064). The 3-year actuarial survival was significantly lower for quartile groups with higher MRP8/14 levels (96.0, 94.7, 72.9, and 62.5% for quartiles 1–4, respectively, p = 0.003). Cox regression analysis showed that serum MRP8/14 level and Kt/V were independent predictors of actuarial survival; in this model, every 1 μg/ml increase in serum MRP8/14 level confers a 25.1% increase in risk of death (95% confidence interval, 1.3–54.4%, p = 0.037). There was no significant difference in technique survival between the MRP8/14 quartile groups. ***Conclusion:*** A high baseline serum MRP8/14 level was associated with a lower actuarial survival in Chinese PD patients. The pathogenic role of MRP8/14 in the cardiovascular disease of PD patients needs further investigation.

Introduction

Peritoneal dialysis (PD) is the first-line renal replacement therapy in Hong Kong [1, 2]. Most PD patients can enjoy an impressive survival rate and an excellent quality of life during the treatment [2]. However, PD is known to cause inflammation and oxidative stress, which may aggravate atherosclerotic lesions [3–7]. In fact, cardiovascular disease is the major cause of morbidity and mortality in PD patients [8, 9]. Glucose, glucose degradation products and advanced glycation end products in the PD solutions are probably the major causative factors of inflammation in PD process [10–13]. However, the exact pathogenic mechanism of accelerated atherosclerosis and systemic inflammation in PD remains unclear.

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Myeloid-related protein 8/14 (MRP8/14) is a 24-kDa heterodimer of 2 calcium-binding proteins MRP8 (also called S100A8) and MRP14 (also called S100A9) [14, 15]. Cells of myeloid origin (neutrophils and monocytes), epithelial cells and platelets are the sources of MRP8 and MRP14 [16–18]. Upon cell activation such as contacted with inflamed endothelium, MRP8 and MRP14 associate to form the MRP8/14 complex, which is then transported to the cell membrane and secreted to the extracellular environment [19–21]. There is a wealth of experimental data suggesting that MRP8/14 is important in the initiation and progression of the inflammatory process [22–27]. Some clinical studies also demonstrated a link between MRP8/14 expression and cardiovascular diseases [28–31]. However, the contribution of MRP8/14 to the systemic inflammation and cardiovascular disease in PD patients has not been explored. In the present study, we examined the relation between serum MRP8/14 levels and the risk of cardiovascular events and mortality of Chinese PD patients.

Methods

Study Population

From April 2007 to September 2008, we studied 104 consecutive new PD patients. All patients were started with 2-liter PD exchanges three times a day. Those who were unlikely to survive for 6 months, who planned to have elective living donor transplant or who would be transferred to other renal centers within 6 months were excluded. The presence of diabetes, hypertension, and a history of cardiovascular disease were recorded. Hypertension was defined according to the Joint National Committee VII criteria [32]. The definition of cardiovascular disease has been described previously [33]. Serum MRP8/14 protein and C-reactive protein (CRP) levels were measured at the initiation of dialysis when patients were free of peritonitis and any other acute infection or inflammation for at least one month. CRP was quantified by our in-house high-sensitivity assay. This study was approved by the Clinical Research Ethical Committee of the Chinese University of Hong Kong. Informed consent was obtained from all the patients.

MRP8/14 Assay

Baseline serum samples were obtained from clotted bloods of the patients and stored at –85°C until the assays started. MRP8/14 enzyme-linked immunoabsorbant assay kits were purchased from Bühlmann Laboratories AG (Schönenbuch, Switzerland). The assay was done according to the instruction supplied with the kit. The limit of detection of the assay was lower than 0.4 μg/ml. The intra-assay and inter-assay coefficients of variation were 4.3 and 5.8%, respectively. Two patients were subsequently excluded from the study because they were unexplained outliers of serum MRP8/14 levels.

Clinical Follow-Up

All patients were followed until March 2010. The clinical management and dialysis regimen were decided by individual nephrologists and not affected by the study. Primary end point was hospital admission for pulmonary edema, unstable angina, or coronary intervention. Secondary end points included actuarial survival, technique survival, and peritonitis-free survival. Censoring events for actuarial survival included transfer to long-term hemodialysis, kidney transplant, recovery of renal function, loss to follow-up, and transfer to other dialysis centers. Technique survival was defined as being alive and remaining on PD.

Statistical Analysis

Statistical analysis was performed by SPSS for Windows software version 15.0 (SPSS Inc., Chicago, Ill., USA). Data were expressed as mean ± standard deviation. Comparisons between groups were performed by the χ^2 test, Student's t test or one-way analysis of variance as appropriate. Regression analysis was used to investigate the correlation between two parameters. Serum MRP8/14 levels were grouped into quartiles 1–4 (with increasing MRP8/14 levels) for analysis. Kaplan-Meier analysis and the log rank test were used to explore the effect of MRP8/14 quartiles on the clinical end points. In addition to MRP8/14 quartiles, we also added baseline residual glomerular filtration rate (GFR), total Kt/V, serum albumin, subjective global assessment, Charlson's comorbidity score, age, and diabetic status into the Cox proportional hazard model to look for independent predictors of clinical outcome. Backward stepwise analysis was applied to remove insignificant variables. A p value below 0.05 was considered statistically significant. All probabilities were two tailed.

Results

We analyzed the results of 102 patients. The demographic and baseline clinical information of the patients in different quartiles are summarized and compared in table 1. Peritoneal transport, dialysis adequacy and nutritional status are compared in table 2. In short, all the baseline clinical and laboratory parameters were highly comparable among the 4 quartile groups except for the dialysate-to-plasma creatinine ratio at 4 h and weekly total Kt/V, where a slight difference was shown. There was no significant difference in the use of antihypertensive drugs or blockers of the renin-angiotensin system between the groups (details not shown). The average serum CRP level was 3.43 ± 2.68 mg/l. Serum MRP8/14 levels did not correlate with CRP levels ($p = 0.9$); there was no significant difference in serum CRP levels between MRP8/14 quartile groups (details not shown). However, there was a modest but statistically significant inverse correlation between serum MRP8/14 level and residual GFR ($r = -0.298$, $p = 0.004$).

Table 1. Baseline clinical and demographic data

	MRP8/14 quartile			
	1	2	3	4
Patients	25	26	25	26
MRP8/14, μg/ml*	1.28 ± 0.34	2.46 ± 0.35	3.70 ± 0.51	7.53 ± 2.91
Males/females	16/9	15/11	13/12	14/12
Age, years	53.3 ± 10.6	57.5 ± 10.8	60.7 ± 11.8	57.8 ± 13.7
Body height, cm	164.4 ± 9.0	161.3 ± 6.2	158.2 ± 9.0	159.8 ± 8.3
Body weight, kg	64.1 ± 15.8	66.2 ± 12.1	58.8 ± 11.6	65.6 ± 14.3
Body mass index	23.6 ± 5.2	25.4 ± 4.5	23.4 ± 3.3	25.5 ± 4.0
Renal diagnosis				
Glomerulonephritis	11 (44.0)	7 (26.9)	5 (20.0)	9 (34.7)
Diabetic nephropathy	5 (20.0)	12 (46.2)	9 (36.0)	11 (42.3)
Polycystic kidney	5 (20.0)	1 (3.9)	1 (4.0)	0 (0.0)
Hypertensive nephrosclerosis	1 (4.0)	1 (3.9)	3 (12.0)	2 (7.6)
Obstructive uropathy	0 (0.0)	3 (11.5)	1 (4.0)	0 (0.0)
Others/unknown	3 (12.0)	2 (7.6)	6 (24.0)	4 (15.4)
Comorbid conditions				
Coronary heart disease	3 (12.0)	6 (23.1)	2 (8.0)	3 (11.5)
Cerebrovascular disease	5 (20.0)	3 (11.5)	2 (8.0)	7 (26.9)
Peripheral vascular disease	1 (4.0)	0 (0.0)	0 (0.0)	1 (3.8)
Charlson's comorbidity index	4.4 ± 2.1	5.3 ± 2.4	5.2 ± 1.9	5.5 ± 2.8

* $p < 0.001$ between the groups. Figures in parentheses indicate percentages.

Table 2. Baseline peritoneal transport, dialysis adequacy and nutritional status

	MRP8/14 quartile			
	1	2	3	4
Patients	25	26	25	26
Peritoneal transport				
D/P creatinine at 4 h*	0.59 ± 0.11	0.56 ± 0.13	0.49 ± 0.16	0.57 ± 0.11
MTAC creatinine, ml/min/1.73 m^2	7.85 ± 4.06	7.09 ± 3.72	5.91 ± 4.26	7.25 ± 3.75
Dialysis adequacy and nutritional status				
Weekly total Kt/V*	2.29 ± 0.72	2.16 ± 0.52	2.46 ± 0.78	1.91 ± 0.49
Residual GFR, ml/min/1.73 m^2	5.36 ± 3.82	4.46 ± 2.85	4.03 ± 3.79	2.66 ± 2.41
Serum albumin, g/l	35.1 ± 3.8	34.0 ± 3.6	35.7 ± 3.8	33.7 ± 5.4
NPNA, g/kg/day	1.11 ± 0.28	1.14 ± 0.32	1.20 ± 0.32	1.13 ± 0.25
FEBM, %	37.9 ± 9.2	37.8 ± 7.5	43.9 ± 12.7	43.1 ± 10.9

D/P = Dialysate-to-plasma ratio; MTAC = mass transfer area coefficient; NPNA = normalized protein nitrogen appearance; FEBM = fat-free edema-free body mass.

* $p < 0.05$ between the groups.

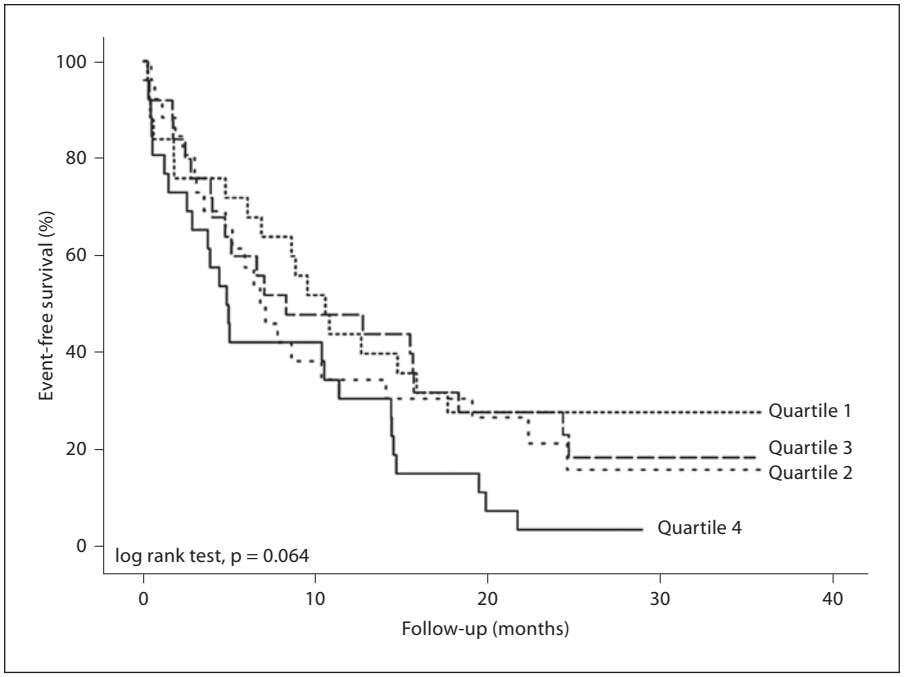

Fig. 1. Kaplan-Meier plot of event-free survival for PD patients with different MRP8/14 quartiles.

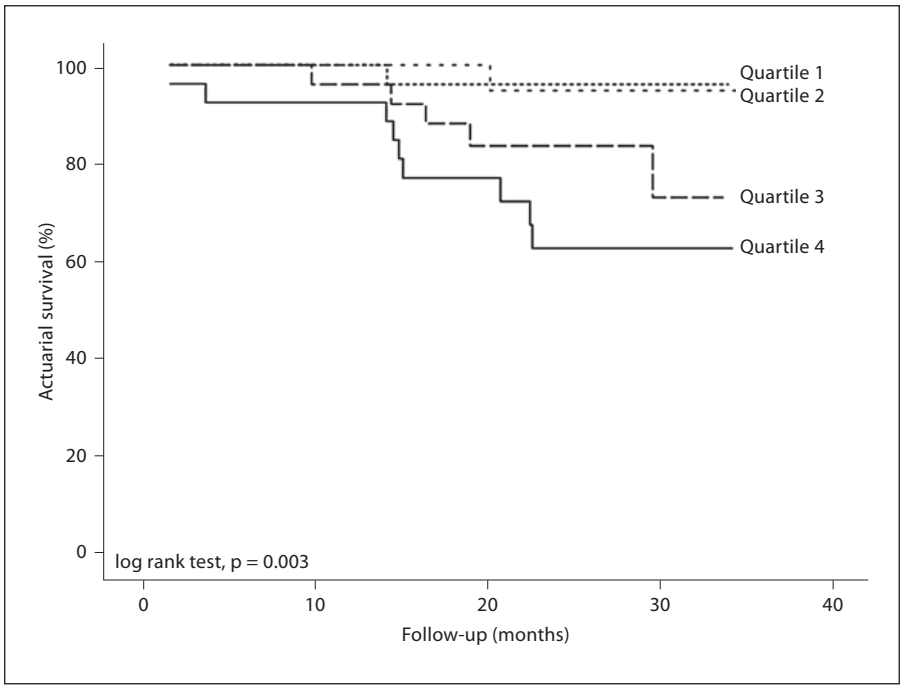

Fig. 2. Kaplan-Meier plot of actuarial survival for PD patients with different MRP8/14 quartiles.

Primary End Point

The average follow-up was 23.9 ± 6.9 months. During the study period, 84 patients (82.4%) developed the primary end point. There was a trend of lower 3-year event-free survival for groups with higher serum MRP8/14 levels (28.0, 16.2, 18.7, and 3.8% for quartiles 1–4, respectively; log rank test, p = 0.064; fig. 1). However, the difference did not reach statistical significance.

Secondary End Points

During the follow-up period, 16 (15.7%) patients died. The causes of death were acute coronary syndrome (6

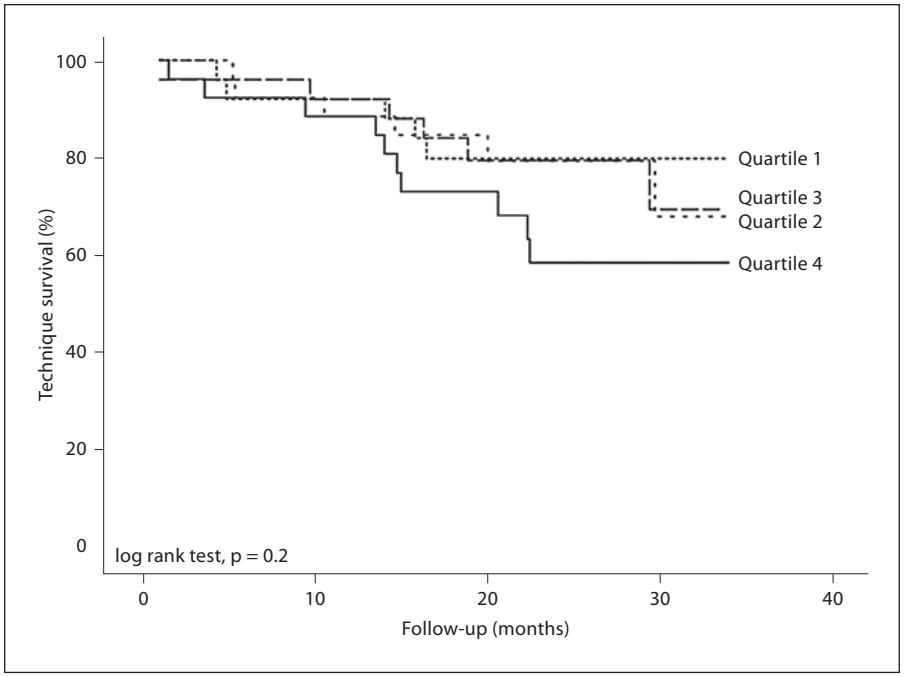

Fig. 3. Kaplan-Meier plot of technique survival for PD patients with different MRP8/14 quartiles.

Table 3. Multivariate analysis by Cox model for actuarial survival

	AHR	95% CI	p value
MRP8/14 level	1.251	1.013–1.544	0.037
Kt/V	0.110	0.015–0.818	0.031
Presence of preexisting diabetes	7.567	0.941–60.848	0.057

AHR = Adjusted hazard ratio; CI = confidence interval.

cases), sudden cardiac death (5 cases), malignancy (2 cases), non-peritonitis infections (1 case), termination of dialysis (1 case) and suicide (1 case). The 3-year actuarial survival was significantly lower for quartile groups with higher MRP8/14 levels (96.0, 94.7, 72.9, and 62.5% for quartiles 1–4, respectively; p = 0.003; fig. 2). Multivariate Cox regression analysis also showed that serum MRP8/14 level and Kt/V were independent predictors of actuarial survival (table 3). In this model, every 1 μg/ml increase in serum MRP8/14 level confers a 25.1% increase in risk of death (95% confidence interval, 1.3–54.4%, p = 0.037).

During the study period, another 8 patients had kidney transplantation, 3 changed to hemodialysis and 1 was transferred to another center. There was no significant difference in the 3-year technique survival between the MRP8/14 level groups (79.8%, 68.0, 69.4, and 58.5% for quartiles 1–4, respectively; p = 0.2; fig. 3). There was also no difference in the 3-year peritonitis-free survival between the MRP8/14 level groups (67.6, 54.7, 71.4, and 43.7% for quartiles 1–4, respectively; p = 0.26).

Discussion

To the best of our knowledge, this study is the first to investigate the effect of baseline serum MRP8/14 levels on the clinical outcome of PD patients. In essence, we found that patients having higher baseline serum MRP8/14 had significantly higher all-cause mortality and a marginally higher risk of cardiovascular events.

The exact mechanism that a high serum MRP8/14 level confers an increase in mortality risk is not clear. Most previous clinical reports pointed out that MRP8/14 is a sensitive marker of acute inflammation in other clinical conditions, such as Kawasaki disease, acute myocardial infarction, and kidney transplant rejection. In addition, Frosch et al. [21] demonstrated that monocytes secreted MRP8/14 after contact with inflamed endothelium. In return, MRP8/14 stimulates endothelial cells to ex-

press various inflammatory factors [26], and is essential for the migration of neutrophils to the site of inflammation [24].

Our result agrees with previous reports in non-renal failure patients. A number of previous studies showed that higher MRP8/14 levels correlated with a higher incidence of cardiovascular events [28, 29, 31]. Taken together, available evidence suggests that MRP8/14 is important in the initiation and progression of inflammation and atherosclerosis. It should be noted that a high baseline MRP8/14 level is associated with excess mortality risk throughout the 3 years of study period rather than being limited to the early months after dialysis (see fig. 1), suggesting that MRP8/14 reflects the degree of background systemic inflammatory state rather than being a direct precipitating factor of immediate infection episode or cardiovascular event.

On the other hand, the relationship between MRP8/14 and peritoneal inflammation has not been explored. As mentioned previously, PD solutions are inflammatory stimuli to the peritoneal cells [34, 35]. In vitro studies indicated that activated endothelial cells could cause cellular release of MRP8/14 [19–21]. In addition, low-grade endotoxemia is common in PD patients and may be related to cardiovascular diseases [36, 37]. In vitro, lipopolysaccharide could induce MRP8/14 production by monocytes [38, 39]. The relation between MRP8/14 and inflammation is therefore particularly complex in PD patients.

Although MRP8/14 is related to inflammation, our result does not show any correlation between serum MRP8/14 and CRP levels. This observation is consistent with the finding of Burkhardt et al. [30] who showed that CRP levels were not significantly different between diabetic nephropathy patients with MRP8/14 levels below and above the median value. Morrow et al. [29] found that serum CRP levels of patients with acute coronary syndrome were only weakly correlated with MRP8/14 levels. Furthermore, serum MRP8/14 has been reported to be a more sensitive marker than CRP. For example, Ikemoto et al. [40] showed that serum MRP8/14 appeared earlier than CRP in a patient with partial small intestine transplant rejection. Patients with acute ST-segment elevation myocardial infarction had significantly higher serum levels of MRP8/14, but not CRP, than patients with stable coronary artery disease [18]. In our cohort, the CRP levels did not differ between the 4 MRP8/14 quartile groups. Our study indirectly suggests that baseline serum MRP8/14 may be more sensitive than serum CRP as a prognostic marker of PD patients.

There are a number of inadequacies of our present study. First, because of the limitation in the original design of the study, we had the baseline but not any follow-up MRP8/14 levels, which may shed light on the role of serum MRP8/14 level for serial monitoring. Similarly, we did not compare the serum MRP8/14 levels before and after PD was started; although PD is unlikely to remove substantial amount of MRP8/14 protein from the serum, it remains possible that the procedure of PD per se induces some low-grade inflammation or macrophage activation, resulting in an increase in serum MRP8/14 levels. Secondly, we did not explore the relationship between serum MRP8/14 level and other inflammatory markers (for example, serum interleukin-6 or circulating endothelial progenitor cell), and the relation between MRP8/14 and systemic inflammation has not been clearly worked out.

Last but not least, the sample size of our study was limited. It could be estimated that a significant difference in the rate of cardiovascular events could only be detected if the sample size is increased to over 200 patients.

In conclusion, baseline serum MRP8/14 level was associated with all-cause mortality and probably cardiovascular events in Chinese PD patients. The mechanism through which MRP8/14 leads to excessive mortality and cardiovascular disease deserves further investigation.

Acknowledgements

This study was supported in part by the CUHK research accounts 6901031 and 7101215, and the Richard Yu Peritoneal Dialysis Research Fund.

Disclosure Statement

The authors declare no conflict of interest.

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