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Serum level of high mobility group box protein-1 and prognosis of patients with end-stage renal disease on hemodialysis and peritoneal dialysis

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Abstract

To investigate serum level of high mobility group box protein-1 (HMGB1) and prognosis of patients with end-stage renal disease (ESRD) on hemodialysis (HD) and peritoneal dialysis (PD).

This prospective cohort observational study included a total of 253 ESRD patients who came to our hospital for HD or PD from February 2013 to February 2015. Enzyme linked immunosorbent assay (ELISA) method was used to detect the serum level of HMGB1, interleukin (IL-6), IL-8, and tumor necrosis factor-alpha (TNF-α). The kidney disease quality of life short form (KDQOL-SF) and kidney disease targeted area (KDTA) was applied for evaluating the quality of life. Kaplan–Meier (K–M) curve was performed for survival time.

Serum level of HMGB1 in patients on HD was higher than PD. HMGB1 levels were gradually decreased with the treatment of HD or PD. Furthermore, HMGB1 was positively correlated with IL-6 and TNF-α. Moreover, patients with higher HMGB1 had more complications than patients with lower HMGB1, but there was no difference for the survival rate. In addition, the quality of life was associated with different dialysis methods.

The serum level of HMGB1 and prognosis of ESRD patients was associated with different dialysis methods.

Abbreviations: BMI = body mass index, CAD = coronary artery disease, CCI = Charlson comorbidity Index, CKD = Chronic kidney disease, ESRD = end-stage renal disease, HD = hemodialysis, HMGB1 = high mobility group box protein-1, IL-10 = interleukin-10, IL-6 = interleukin-6, KDQOL-SF = kidney disease quality of life short form, KDTA = kidney disease targeted area, KDTA = kidney disease-targeted areas, PD = peritoneal dialysis, SF-36 = Short-Form 36 Health Survey, TNF-α = tumor necrosis factor-alpha, VEGF = endothelial growth factor.

Keywords: hemodialysis, high mobility group box protein-1, peritoneal dialysis, prognosis

1. Introduction

Chronic kidney disease (CKD) has become a public health problem worldwide that is characteristic with high treatment costs and poor prognosis.[1] Recently, cardiovascular complications are the most common cause of morbidity and mortality for patients with end-stage renal disease (ESRD),[2] besides, systemic inflammation in ESRD patients has proved to be correlated with coronary artery disease (CAD).[3] The aim of treatment for various chronic diseases is to control symptom and improve the quality of life and survival time rather than complete cure. Therefore, chronic dialysis therapy, including hemodialysis (HD) and peritoneal dialysis (PD), has been identified as the effective therapy that remarkably prolonged the lives of ESRD patients in clinic.[4] However, both HD or PD strategies may influence the patients' quality of life. Thus, to assess and predict the prognosis and impact factors of HD and PD is important.

Though HD and PD have been conducted as renal replacement therapies for patients with end-stage renal disease, chronic kidney disease and dialysis therapy have great impact on the quality of life of patients, including functioning and well-being.[5] Hence, Short-Form 36 Health Survey (SF-36) and kidney disease-targeted areas (KDTA) are usually performed in the follow-up survey after therapy.[6–8] Subsequently, the complications, including arteriovenous fistula occlusion, peritonitis, pulmonary infection, and so on, were also considered as a measure of prognosis for ESRD patients.[9] As reported in a research on elderly patients, the incidence of low estimated glomerular filtration rate, acute kidney injury, presence of congestive heart failure, and high baseline proteinuria were the risk factors for CKD progression.[10] However, up to now, limited studies the difference of prognosis for ESRD patients on HD and PD. And different effects of inflammation response on prognosis between ESRD patients who receive HD and PD are rarely reported.

The inflammation condition is an important factor in ESRD patients with HD or PD. In previous researches, it was found inflammatory factors like IL-6, IL-8, C reactive protein, and TNF-α were increased in patients with HD or HD compared with

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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healthy control.[11,12] In recent years, more new inflammation-related factors are found. High mobility group box protein-1 (HMGB1) is a kind of nuclear protein binding to DNA that acts as a co-factor for gene transcription.[13] Subsequently, HMGB1 is also considered as late pro-inflammatory cytokine released from apoptotic cells and acts as a damage-associated molecular pattern molecule (DAMP).[14] As is known to all, inflammatory cytokines, including vascular endothelial growth factor (VEGF), interleukin (IL)-6, interleukin (IL)-10 as well as HMGB1, have been identified as markers or pathogenic mediators for the severity of sepsis.[15] As stated in a previous study, downregulated HMGB1 and TRL4 in spinal cord could inhibit the pain induced by chronic pancreatitis in rats.[16] In addition, Andersson et al[17] suggested that HMGB1 could be a therapeutic target against inflammatory diseases. HMGB1 was found to be correlated with renal function in chronic kidney disease.[18] Another report indicated that HMGB1 was elevated in CKD patients, and overexpressed HMGB1 could worsen sepsis as well as sepsis-induced acute kidney injury.[19] However, there is no research focusing on the difference of serum level of HMGB1 between ESRD patients treated with HD and PD.

In the present study, we conducted a prospective cohort observational study to investigate serum level of HMGB1 and prognosis of patients with end-stage renal disease (ESRD) on HD and PD. This study might provide clinical evidence for role of HMGB1 in patients with end-stage renal disease.

2. Materials and methods

2.1. Subjects and treatment

This prospective cohort observational study enrolled 253 patients with end-stage renal disease (ESRD) from February 2013 to February 2015 who went to our hospital for HD or PD. All the patients that met inclusion criteria were consecutively included just before the start of dialysis treatment during the study period. The inclusion criteria of ESRD patients with HD or PD were as follows: the patients should meet the diagnostic criteria of K/DOQI clinical practice guidelines for ESRD with glomerular filtration rate (GFR) <15 mL/min or the level of serum creatinine (Scr) $>707\,\mu$mol/L[20]; the individuals were required over 18 years old; the patients had received HD or PD 2 to 3 times/wk for at least 3 months; there were no serious infection and other complications during the study; the patients could communicate, understand the purpose of the study. The therapy for ESRD patients on HD or PD was as follows: the patients on HD received dialysis 3 to 4 times every week with 4 hours for each session; for the patients on PD, dialysate of 2000 mL was exchanged 3 to 4 times a day with 4 hours for each time. The dialysis therapy must last for at least 3 months. Written informed consent was obtained from all patients. The present study was approved by The First People's Hospital of Fuyang Hangzhou.

2.2. Data collection and assessment

Both demographic and clinical data were collected at the start of chronic dialysis. Demographic data included the age, sex, employment, and marital status. The clinical data were as follows: body mass index (BMI), primary renal diseases (classified according to the codes of the European Dialysis and Transplantation Association–European Renal Association), comorbidity, serum albumin, hemoglobin, dialysis adequacy (i.e., Kt/V), Charlson comorbidity Index (CCI), residual renal function parameters, and so on. The CCI refer to an age-modified score of severity and number of comorbidities that prognosticated for mortality of ESRD patients. The kidney disease quality of life (QoL) short form (KDQOL-SF) was used to evaluate the quality of life. Briefly, KDQOL-SF consist of kidney disease targeted area (KDTA), which included the symptoms/problem list (SPL, 12 items), effect of kidney disease (EKD, 8 items), work status (WS, 2 items), burden of kidney disease (BKD, 4 items), quality of social interaction (QSI, 3 items), cognitive function (CF, 3 items), sleep quality (Sleep, 4 items), social support (Sos, 2 items), sexual function (SexF, 2 items), and the Short-Form (SF-36), which included the physical function (PF, 10 items), Pain (pain, 2 items), role-physical (RP, 4 items), emotional well-being (EWB, 5 items), role-emotional (RE, 3 items), social function (SocF, 2 items), general health (GH, 5 items), and energy/fatigue (Energ, 4 items). A lower CCI suggested that the patient had few comorbidities. The follow-up lasted for 5 years from admission to the last follow-up or death.

2.3. Enzyme linked immunosorbent assay (ELISA)

The level of HMGB1, IL-6, IL-8, and TNF-α was detected by ELISA method at the month of 0, 1, 2, 3, 6. In brief, peripheral venous blood samples were collected from all the ESRD patients and devaluated by using commercial ELISA kits (Human IL-6 ELISA Kit, ab178013; Human IL-8 ELISA Kit, ab214030; Human TNF alpha ELISA Kit, ab181421. All purchased from Abcam, Cambridge, MA; Human High HMGB1 ELISA Kit, #MBS2021229, purchased from San Diego, CA).

2.4. Statistical analysis

Statistical analysis was conducted using the SPSS 20.0 (SPSS Inc., Chicago, USA). Continuous data were expressed by mean ± SD if they were normally distributed, otherwise, they were expressed by median (range). Comparison between 2 groups was made using the Student t test or Mann–Whitney U test, while comparison among ≥3 groups was performed by one-way analysis of variance (ANOVA) followed by Tukey post hoc test. Chi-square test was applied to compare the rates. In addition, Kaplan–Meier (K–M) curve was performed for survival analysis and Spearman analysis was also used for the correlation analysis. A P-value $<.05$ was considered to be statistically significant.

3. Results

3.1. Basic characteristics for all participants

A total of 280 ESRD patients were enrolled in this study, but 27 patients were excluded with missing data. So, 253 ESRD patients were involved in the present study, including 151 cases on HD and 102 cases on PD. The basic characteristics of all patients in 2 groups were shown in Table 1. There were no significant differences found in 2 groups for the basic characteristics.

3.2. The dynamic changes of HMGB1 and its correlation with inflammatory factors

Then, we further detected the serum level of HMGB1, IL-6, IL8, and TNF-α in 2 groups. It was observed that the serum level of HMGB1, IL-6, IL-8, and TNF-α was decreased in a time-dependent manner in 2 groups. Subsequently, the serum level of HMGB1, IL-6, IL8, and TNF-α in HD group was gradually

Table 1

Characteristics at baseline of ESRD patients in HD and PD group.

Variables	HD, n = 151	PD, n = 102	*P*
Age, y	56.47 ± 16.99	59.73 ± 17.33	.139
Female, n (%)	70 (46.36)	52 (50.98)	.470
BMI, kg/m^2	23.11 ± 3.64	22.28 ± 3.27	.066
Married, n (%)	135 (89.40)	89 (87.25)	.599
Employed, n (%)	30 (19.87)	31 (30.39)	.055
Primary kidney disease			
Glomerulonephritis, n (%)	82 (54.30)	49 (48.04)	.328
Renal vascular disease, n (%)	20 (13.25)	15 (14.71)	.741
Diabetes mellitus, n (%)	32 (21.19)	19 (18.63)	.618
Others, n (%)	17 (11.26)	19 (18.63)	.100
Comorbidity (CCI)			
CCI ≤ 2, n (%)	105 (69.54)	66 (64.71)	.421
2 < CCI < 5, n (%)	31 (20.53)	30 (29.41)	.105
CCI ≥ 5, n (%)	15 (9.93)	6 (5.88)	.252
Serum albumin, g/L	47.08 ± 7.46	46.50 ± 6.27	.505
Dialysis adequacy, Kt/V, week	1.87 ± 0.264	1.82 ± 0.16	.056
Plasma creatinine, μmol/L	600.24 ± 119.38	594.37 ± 115.23	.698
Urea nitrogen, mmol/L	23.98 ± 3.78	23.77 ± 3.89	.661

BMI = body mass index; CCI = Charlson comorbidity Index; ESRD = end-stage renal disease; HD = hemodialysis; PD = peritoneal dialysis.

higher than PD at 1, 2, 3, and 6 months after the admission, but no difference was found at the admission ($P < .05$, Fig. 1). We further analyzed the correlation between the level of HMGB1 with L-6, IL8, and TNF-α at 3rd month. It showed that the level of HMGB1 was positively correlated with the level of IL-6 and TNF-α in 2 groups ($P < .05$, Table 2), but there was no significant correlation between HMGB1 and IL-8.

3.3. Dialysis method was associated with the score of SF-36 and KDTA

Then, the SF-36 result showed that PD patients scored higher on Energy than HD patient ($P < .05$), but there was no significant difference in the other 7 fields. Moreover, KDTA result revealed that the Symptom/problems list and Work status in HD patients scored lower than PD patients, however, social support and sleep quality in HD patients scored higher than PD patients ($P < .05$, Table 3).

3.4. Different dialysis methods affected clinical outcomes of ESRD patients

Finally, we investigated the incidence of complication during therapy and survival rate of ESRD patients and the relationship with HMGB1. The patients in either groups were divided into

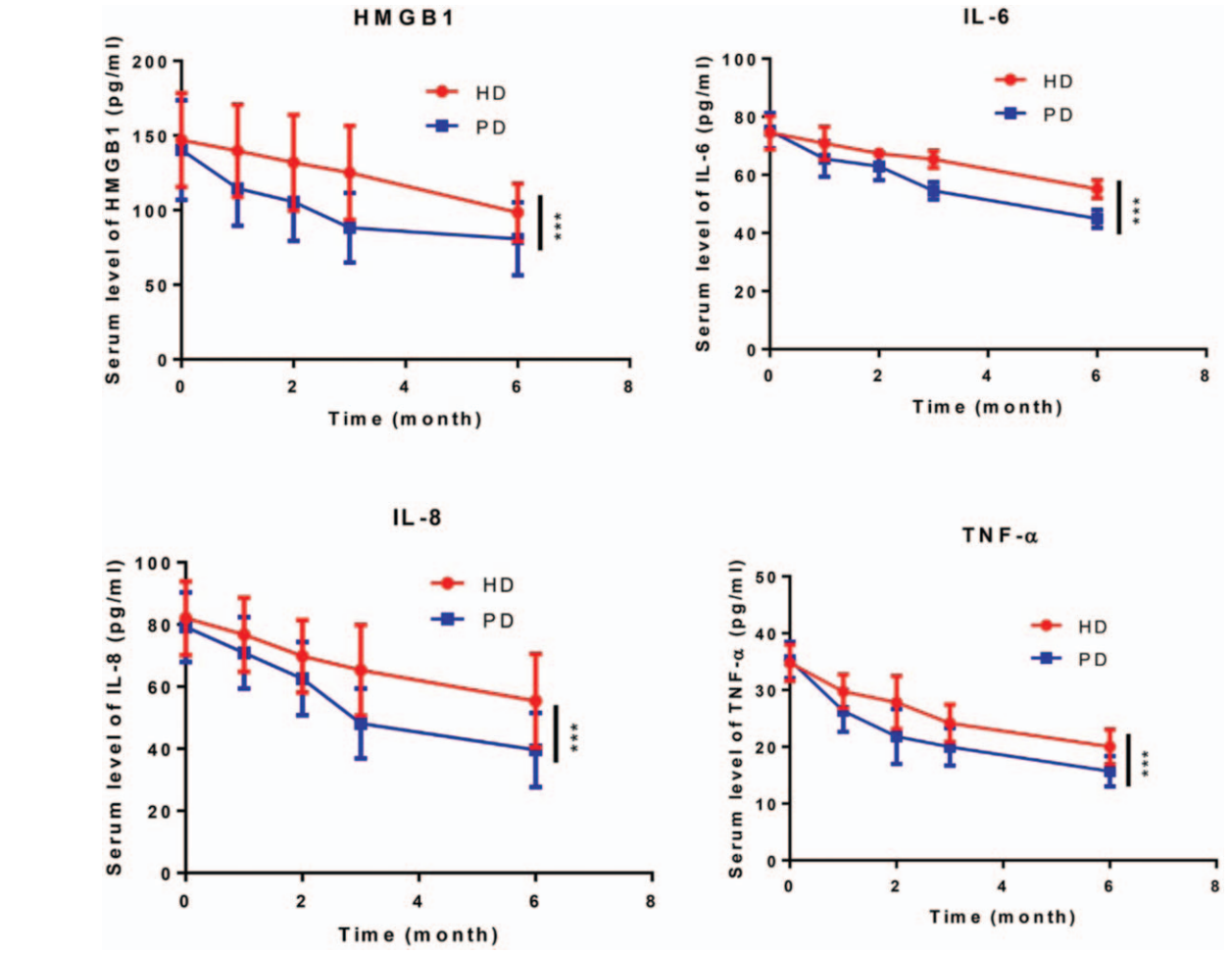

Figure 1. The serum level of HMGB1, IL-6, IL8, and TNF-α in HD group and PD group. HD = hemodialysis; HMGB1 = high mobility group box protein-1; IL = interleukin; PD = peritoneal dialysis.

Table 2

The correlation between HMGB1 with inflammatory factors.

	HMGB1 (HD)	HMGB1 (PD)
IL-6		
Pearson correlation	0.210	0.202
P	.010	.042
IL-8		
Pearson correlation	–0.027	0.124
P	.741	.215
TNF-α		
Pearson correlation	0.174	0.195
P	.033	.049

HD = hemodialysis; HMGB1 = high mobility group box protein-1; IL = interleukin; PD = peritoneal dialysis.

Table 3

Descriptive summary of KDQOL-SF scale score.

KDQOL-SF parameters	HD, n = 151	PD, n = 102	*P*
36-Item Health Survey scales			
Physical function	58.99 ± 18.19	56.36 ± 15.81	.223
Role-physical	44.81 ± 13.93	47.42 ± 12.44	.121
Pain	52.54 ± 17.65	55.97 ± 19.11	.150
General health	34.28 ± 10.96	35.60 ± 12.74	.394
Emotional well-being	55.86 ± 9.76	53.71 ± 11.01	.112
Role-emotional	56.85 ± 12.91	54.57 ± 13.70	.184
Social function	65.13 ± 14.24	63.92 ± 11.19	.452
Energy /fatigue	51.77 ± 10.86	58.74 ± 11.39	.000
Kidney disease-targeted areas (KDTA)			
Symptom/problems list	67.32 ± 10.72	71.99 ± 11.09	.001
Effects of kidney disease	41.35 ± 13.25	42.50 ± 13.51	.503
Burden of kidney disease	56.07 ± 13.58	57.40 ± 16.42	.500
Work status	34.64 ± 13.92	44.28 ± 14.77	.000
Cognitive function	66.75 ± 12.50	69.64 ± 11.52	.064
Quality of social interaction	70.07 ± 11.59	67.61 ± 11.55	.098
Sexual function	45.70 ± 13.99	49.33 ± 18.39	.093
Sleep quality	55.87 ± 15.05	45.55 ± 15.39	.000
Social support	63.83 ± 14.04	56.15 ± 12.44	.000

KDQOL-SF = kidney disease quality of life short form; HD = hemodialysis; PD = peritoneal dialysis.

HMGB1 high/low groups according to the mean values of serum HMGB1 when admission. As shown in Table 4, incidence ration of heart failure and arteriovenous fistula occlusion in HD group was higher than PD group, but the incidence of peritonitis in HD group was significantly lower than PD group ($P < .05$). Besides, we noticed that the incidence ration of heart failure in HMGB1 high group was higher than HMGB1 low group in patients on HD and PD. Moreover, the incidence rate of arteriovenous fistula occlusion in HMGB1 high group was higher than HMGB1 low group in patients on PD, and the incidence rate of peritonitis in HMGB1 high group was higher than HMGB1 low group in patients on HD ($P < .05$). Nevertheless, K–M curve suggested that there was no obviously difference of survival time between HP patients and PD patients (Fig. 2).

4. Discussion

End-stage renal disease refers to the end stage of various chronic kidney diseases with the incidence rate as high as 1/100,000.[21] Blood purification is usually used in clinical treatment that can effectively alleviate the related symptoms, prolong the life duration, and improve the quality of life.[22] However, there are persistent micro inflammation in ESRD patients on dialysis, which is related to the biocompatibility of dialysate membrane, endotoxin in dialysate, and immune disorder of chronic kidney disease.[23] In the present study, we demonstrated that the serum level of HMGB1 was lower in ESRD patients on HD than PD, and the level of which is positive correlated with IL-6 and TNF-α. Moreover, blood purification method affected the quality of life and the clinic outcomes of patients.

Role of HMGB1 has been reported to be involved in inflammatory responses and chemotaxis of pro-inflammatory cells in several diseases.[24] As reported in the study of Massey et al,[25] HMGB1-Receptor for advanced glycation end products (RAGE) signaling had an impact on neuroinflammation and organic dust-induced microglial activation. Another research on a mouse model of nonalcoholic fatty liver disease revealed that HMGB1-mediated innate immune signaling could be inhibited by FBXW7 to suppress hepatic inflammation.[26] Besides, HMGB1 was proved to bind to receptors on cell membranes, including TLR2/4 and RAGE, to induce inflammation and participate in pathological mechanism in a variety of kidney diseases.[27] Zhu et al[28] also pointed out that HMGB1 was closely related to kidney diseases and could be considered as a therapeutic target/agent against many kidney diseases, for instance, glomerulonephritis, diabetic nephropathy, lupus nephritis, acute kidney injury, and renal allograft rejection. Moreover, endogenous HMGB1 was found to promote ischemia-reperfusion injury (IRI) through Toll-like receptor 4

Table 4

The incidence of complications between HMGB1 high/low groups of ESRD patients.

	HD, n = 151				PD, n = 102			
Complications	**HMGB1 high (n = 79)**	**HMGB1 low (n = 72)**	**Total**	P_1	**HMGB1 high (n = 49)**	**HMGB1 low (n = 53)**	**Total**	P_2
Heart failure	30 (38.0)	15 (20.8)	45 (29.8)*	.021	7 (14.3)	1 (1.9)	8 (7.8)	.020
Arteriovenous fistula occlusion	27 (34.2)	9 (12.5)	36 (23.8)*	.002	0 (0)	0 (0)	0 (0)	–
Peritonitis	0 (0)	0 (0)	0 (0)	–	17 (34.7)	9 (17.0)	26 (25.5)*	.041
Pulmonary infection	2 (2.5)	1 (1.4)	3 (2.0)	.615	1 (2.0)	1 (1.9)	2 (2.0)	.955
Digestive tract bleeding	11 (13.9)	12 (16.9)	23 (15.2)	.639	8 (16.3)	7 (13.2)	15 (14.7)	.657
Subcutaneous hemorrhage	3 (3.8)	4 (5.6)	7 (4.6)	.608	3 (6.1)	3 (5.7)	6 (5.9)	.921
Cerebral infarction	8 (10.1)	7 (9.7)	15 (9.9)	.934	6 (12.2)	8 (15.1)	14 (13.7)	.676

ESRD = end-stage renal disease; HD = hemodialysis; HMGB1 = high mobility group box protein-1; PD = peritoneal dialysis.

* *P* value was calculated between total complication rate of ESRD patients on HD and PD.

P_1 value was calculated between HMGB1 high/low groups of patients on HD.

P_2 value was calculated between HMGB1 high/low groups of patients on PD.

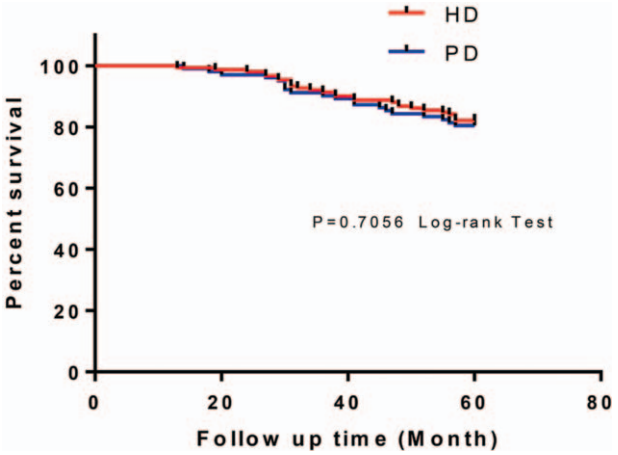

Figure 2. K–M curve for survival time in patients on HD and PD. HD = hemodialysis; K–M = Kaplan–Meier; PD = peritoneal dialysis.

pathway, but HMGB1 inhibitor could provide obvious protection for IRI.[29] However, there are rare studies reported the role of HMGB1 in ESRD patients on hemodialysis and peritoneal dialysis. In the present study, we for the first time demonstrated that the serum level of HMGB1 is higher in ESRD patients on HD compared with PD, besides, the level of HMGB1 decreased in a time-dependent manner. We also found that the serum level of HMGB1 was positively correlated with IL-6 and TNF-α.

Quality of life (QOL) is very essential for evaluating the prognosis of ESRD patients. Sleep disorder usually affect most aspects of life for ESRD patients.[30] As reported in the study of Malekmakan et al,[31] patients on peritoneal dialysis had lower rate of poor sleep quality than patients on hemodialysis. However, another report indicated that QOL was almost the same between patients on HD and PD, but the patients on PD scored lower than HD in terms of Pain.[32] In this study, we found that PD patients scored higher on Energy than HD patient in SF-36 survey, besides, HD patients scored lower than PD patients on Symptom/problems list and Work status, but HD patients scored higher in terms of social support and Sleep quality.

A system review showed that there was difference of the survival rate between patients on HD and PD.[33] Another study also demonstrated that survival rate of patients on HD and PD was similar in the first 3 years.[34] In this study, we also found that there was no obvious difference between 5-year survival of patients on HD and PD. As stated in the research of Voskamp et al,[35] symptoms could impact the quality of life that affected clinic outcomes of elderly CKD on stage 4/5 patients. We also found that the total complication rate of ESRD patients on HD was higher than PD. Moreover, the patients with higher HMGB level had more complications.

There are some limitations for the present research. First the sample size of this study is limited. Secondly, we didn't investigate the serum level of HMGB1 in health controls, partly because it is reported that HMGB1 was hardly to detect in healthy individuals.[18,36] Furthermore, several important serum markers were not detected to evaluate the prognosis of ESRD patients.

5. Conclusion

In summary, we investigated the serum HMGB1 level of ESRD patients on HD and PD, and analyzed the correlation between different dialysis methods with prognosis. We found that serum level of HMGB1 was higher in ESRD patients on HD than PD, which was positively correlated with the serum level of IL-6 and TNF-α. Moreover, patients on HD had more complications than PD, especially for heart failure and arteriovenous fistula occlusion and ESRD patients with higher HMGB1 level might have more complications. However, there was no difference for the survival rate. In addition, the quality of life was associated with different dialysis methods.

Author contributions

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Resources: Xiangdong Kong.
Software: Linyan Chen.
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Validation: Gaoping Chen.
Writing – original draft: Linyan Chen.
Writing – review & editing: Xiangdong Kong.

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