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Original Paper

A Comparison of Systemic Inflammation-Based Prognostic Scores in Patients on Regular Hemodialysis

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Key Words
Albumin · C-reactive protein · Hemodialysis · Prognosis

Abstract
Background/Aims: Systemic inflammation-based prognostic scores have prognostic power in patients with cancer, independently of tumor stage and site. Although inflammatory status is associated with mortality in hemodialysis (HD) patients, it remains to be determined as to whether these composite scores are useful in predicting clinical outcomes. ***Methods:*** We calculated the 6 prognostic scores [Glasgow prognostic score (GPS), modified GPS (mGPS), neutrophil-lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR), prognostic index (PI) and prognostic nutritional index (PNI)], which have been established as a useful scoring system in cancer patients. We enrolled 339 patients on regular HD (age: 64 ± 13 years; time on HD: 129 ± 114 months; males/females = 253/85) and followed them for 42 months. The area under the receiver-operating characteristics curve was used to determine which scoring system was more predictive of mortality. ***Results:*** Elevated GPS, mGPS, NLR, PLR, PI and PNI were all associated with total mortality, independent of covariates. If GPS was raised, mGPS, NLR, PLR and PI were also predictive of all-cause mortality and/or hospitalization. GPS and PNI were associated with poor nutritional status. Using overall mortality as an endpoint, the area under the curve (AUC) was significant for a GPS of 0.701 (95% CI: 0.637–0.765; $p < 0.01$) and for a PNI of 0.616 (95% CI: 0.553–0.768; $p = 0.01$). However, AUC for hypoalbuminemia (<3.5 g/dl) was comparable to that of GPS (0.695, 95% CI: 0.632–0.759; $p < 0.01$). ***Conclusion:*** GPS, based on serum albumin and highly sensitive C-reactive protein, has the most prognostic power for mortality prediction among the prognostic scores in HD patients. However, as the determination of serum albumin reflects mortality similarly to GPS, other composite combinations are needed to provide additional clinical utility beyond that of albumin alone in HD patients.

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Introduction

It has been documented that the presence of systemic inflammatory response is associated with poor outcome in a variety of diseases. In patients with cancer, the acute-phase protein markers of the systemic inflammatory response, namely serum C-reactive protein (CRP) and albumin used as standard thresholds (>1.0 mg/dl for conventional CRP and <3.5 g/dl for albumin), have been combined to form a cumulative, inflammation-based prognostic score [1] termed Glasgow prognostic score (GPS) (table 1). The GPS was then refined, termed the modified GPS (mGPS) (table 1), to reflect the observation that hypoalbuminemia without an elevated CRP was rare and that hypoalbuminemia on its own was not associated with survival prognosis in cancer patients [2]. GPS/mGPS, being simple to measure, routinely available and well standardized around the world, has subsequently been the subject of prognostic studies in many cancer patients over the last decade [1–3].

Other hematological components of the systemic inflammatory response have been combined to form inflammation-based prognostic scores associated with survival in cancer patients (table 1). The neutrophil-lymphocyte ratio (NLR), a combination of circulating neutrophil and lymphocyte counts, is a determinant of clinical outcomes [4, 5]. The platelet lymphocyte ratio (PLR), a combination of circulating platelet and lymphocyte counts, has been related to prognosis [6, 7]. The combination of CRP and white blood cell (WBC) count in a prognostic index (PI) has been associated with survival in patients with lung cancer [8]. In addition, the prognostic nutritional index (PNI), which is composed of serum albumin and total lymphocyte count within the equation, has been associated with mortality [9].

In patients with chronic kidney disease (CKD), increased CRP is associated with progression of arteriosclerosis, cardiovascular events and mortality [10–12]. Both lower lymphocyte and higher neutrophil counts are related to mortality in prevalent dialysis patients [13–15]. An increased blood monocyte count is also associated with cardiovascular mortality in hemodialysis (HD) patients [16]. Hypoalbuminemia is a strong risk factor for mortality in HD patients [17]. Thrombocytosis (>30 × 10^4/μl) is associated with poor nutritional status as well as all-cause and cardiovascular mortality in HD patients [18]. It is of considerable interest to examine the prognostic value of combined parameters including CRP, albumin, neutrophil, lymphocyte and platelet counts. However, there was no study to compare the prognostic power of the scoring system in the CKD population.

We hypothesized that the systemic inflammation-based scores, including GPS, mGPS, NLR, PLR, PI and PNI, would be useful in predicting clinical outcomes in HD patients. We compared the prognostic value of these scores adjusted for covariates and assessed whether GPS contributed substantially more to prediction models than serum albumin and highly sensitive CRP (hs-CRP), an individual component of GPS.

Patients and Methods

Study Population

The study population consisted of 339 adult patients who had been undergoing regular HD and gave their consent to participate in the study conducted at Maruyama Hospital and Maruyama Clinic (Hamamatsu, Japan). The patients had been in a stable condition, and no participant had advanced cancer, active collagen disease or active infections. All patients had been subjected to regular HD with bicarbonate buffer (30 mEq/l) at a dialysate flow rate of 500 ml/min for 3.5–5 h 3 times per week. None of the patients reused the dialyzer, and neither bacteria nor pyrogen was grown in the dialysate prepared from water obtained by reverse osmosis. By an endotoxin removal filter, the endotoxin concentration dropped below 0.020 EU/ml.

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Table 1. Assessment of systematic inflammation-based prognostic scores

Prognostic score	Criteria	Score
GPS	CRP ≤1.0 mg/dl and albumin ≥3.5 g/dl	0
	CRP >1.0 mg/dl or albumin <3.5 g/dl	1
	CRP >1.0 mg/dl and albumin <3.5 g/dl	2
mGPS	CRP ≤1.0 mg/dl	0
	CRP >1.0 mg/dl and albumin ≥3.5 g/dl	1
	CRP >1.0 mg/dl and albumin <3.5 g/dl	2
NLR	neutrophil count:lymphocyte count <5:1	0
	neutrophil count:lymphocyte count ≥5:1	1
PLR	platelet count:lymphocyte count <150:1	0
	platelet count:lymphocyte count 150–300:1	1
	platelet count:lymphocyte count >300:1	2
PI	CRP ≤1 mg/dl and WBC count ≤11,000/μl	0
	CRP ≤1 mg/dl and WBC count >11,000/μl	1
	CRP >1 mg/dl and WBC count ≤11,000/μl	
	CRP >1 mg/dl and WBC count >11,000/μl	2
PNI	albumin (g/dl) × 10 + 0.005 × total lymphocyte count (/μl) ≥45	0
	albumin (g/dl) × 10 + 0.005 × total lymphocyte count (/μl) <45	1

Blood Sampling and Laboratory Examinations

Blood samples were drawn from the arterial site of the arteriovenous fistula at the start of each dialysis session every 2 days. Absolute WBC subtype counts were calculated by multiplying total WBC quantitated as cells/μl^{-1} of blood by the percentages of subtypes. Serum electrolytes, urea nitrogen, creatinine, albumin, transthyretin (TTR), total cholesterol and triglyceride were measured by standard laboratory techniques using an autoanalyzer. Intact parathyroid hormone was determined by immunoradiometric assay, and hs-CRP was measured by latex photometric immunoassay (Wako Junyaku, Tokyo, Japan). Efficacy of dialysis and normalized protein catabolic rate (PCR) were assessed based on the delivered dose of dialysis (Kt/V for urea) using a single-pool urea kinetic model. We also examined the use of therapeutic drugs such as statins, angiotensin-converting enzyme inhibitor (ACEI) and angiotensin receptor blocker (ARB).

After the construction of basal GPS, mGPS, NLR, PLR, PI and PNI as described in table 1, we followed all patients for the next 42 months.

Statistical Analysis

Values were expressed as means ± SD. Survival or hospitalization was calculated from the study entry to death or hospital admission for any cause. The Kaplan-Meier estimate following a log-rank test was used to analyze the relationship between prognostic scores and overall survival.

Cox proportional hazards model multivariate regression analysis was used to correct for age, sex, diabetes, time on HD, history of cardiovascular disease (CVD), Kt/V for urea and ACEI/ARB treatment and to determine the relationship between patient characteristics, GPS, mGPS, NLR, PLR, PI and survival. To determine whether one of the independently significant variables was more predictive than the others, we conducted receiver-operating characteristic (ROC) analyses and calculated the area under the curve (AUC) [19]. The analysis was performed using SPSS 17.0 software (SPSS Inc., Chicago, Ill., USA).

Table 2. Clinical and laboratory parameters in all patients (n = 339)

Parameters	Means ± SD	Median (range)
Age, years	64±13	65 (20–92)
Time on HD, months	129±114	97 (2–426)
Male gender, %	75	
Diabetes, %	26	
Past history of CVD, %	25	
ACEI/ARB treatment, %	27	
Statin treatment, %	6	
Serum urea nitrogen, mg/dl	61.1±14.1	60.5 (18.9–112.6)
Creatinine, mg/dl	11.49±3.03	11.36 (3.01–20.01)
Calcium, mg/dl	8.9±0.9	8.9 (6.5–11.2)
Phosphorus, mg/dl	5.7±1.5	5.7 (2.1–12.6)
Total cholesterol, mg/dl	151±36	148 (71–271)
Triglyceride, mg/dl	109±68	92 (26–501)
HDL cholesterol, mg/dl	47±15	45 (23–114)
LDL cholesterol, mg/dl	88±29	84 (27–212)
Albumin, g/dl	3.6±0.4	3.6 (2.4–4.5)
TTR, mg/dl	29±9	28 (7–55)
hs-CRP, mg/dl	0.38±0.83	0.10 (0.00–5.22)
WBC count, /μl	5,740±1,920	5,460 (1,980–23,320)
Neutrophil count, /μl	3,940±1,670	3,650 (1,220–21,640)
Lymphocyte count, /μl	1,260±534	1,180 (338–3,851)
Hemoglobin, g/dl	10.5±1.1	10.5 (4.7–15.8)
Platelet count, $\times 10^4$/μl	17.1±5.6	16.7 (3.0–39.6)
Kt/V for urea	1.44±0.25	1.41 (0.43–2.19)
Normalized PCR, g/kg/day	0.91±0.17	0.92 (0.38–1.50)
Intact parathyroid hormone, pg/ml	279±238	221 (6–1,291)
NLR	3.6±2.3	3.1 (0.8–21.3)
PLR	153±72	136 (35–641)
PNI	42.0±5.5	42.0 (26.2–62.4)

Results

Clinical Profiles

The characteristics of 339 HD patients are summarized in table 2. The average age was 64 years with a median time on HD of 97 months. The underlying kidney diseases were chronic glomerulonephritis (n = 188), diabetic nephropathy (n = 61), benign nephrosclerosis (n = 23), autosomal-dominant polycystic kidney disease (n = 21), rapidly progressing glomerulonephritis (n = 5), malignant hypertension (n = 3), others (n = 18) and unknown (n = 20).

Inflammation-Based Prognostic Scores

Of the 339 patients, 209 (61.6%) had a GPS of 0, while 107 (31.6%) and 23 (6.8%) patients showed a GPS of 1 and 2, respectively. With regard to mGPS, 30 (8.9%) patients had a score of 1 and 2 (table 3).

In 47 (13.9%) patients, NLR had been categorized as score 1, and there were 137 (40.4%) and 10 (2.9%) patients who had a PLR score of 1 and 2, respectively. The PI scores classified a total of 32 (9.4%) patients into score 1 and 2. PNI classification disclosed that 234 (69.0%) patients had score 1 (table 3).

Table 3. Prevalence of inflammation-based prognostic scores

Prognostic score		Patients
GPS	0	209 (61.6%)
	1	107 (31.6%)
	2	23 (6.8%)
mGPS	0	309 (91.1%)
	1	7 (2.1%)
	2	23 (6.6%)
NLR	0 (<5:1)	292 (86.1%)
	1 (≥5:1)	47 (13.9%)
PLR	0 (<150:1)	192 (56.7%)
	1 (150–300:1)	137 (40.4%)
	2 (≥300:1)	10 (2.9%)
PI	0	307 (90.6%)
	1	31 (9.1%)
	2	1 (0.3%)
PNI	0 (≥45)	105 (31.0%)
	1 (<45)	234 (69.0%)

Association of Nutritional Parameters with Inflammation-Based Prognostic Scores

Serum TTR was significantly higher in patients with a GPS of 0 (31.6 ± 8.1 mg/dl) when compared to those with a GPS of 1 (23.6 ± 6.2 mg/dl) and a GPS of 2 (23.8 ± 9.7 mg/dl) ($p < 0.01$). In the patients with an mGPS of 2, a significantly lower TTR was found than in those with an mGPS of 0 (23.8 ± 9.7 vs. 29.0 ± 8.4 mg/dl, $p < 0.01$). An increased PI score was related to a decreased TTR (23.4 ± 9.9 vs. 29.1 ± 8.5 mg/dl, $p < 0.01$). A raised PNI score was also associated with a reduced TTR (26.3 ± 7.9 vs. 33.5 ± 7.9, $p < 0.01$) and a normalized PCR (0.89 ± 0.18 vs. 0.95 ± 0.17 g/kg/day, $p < 0.01$). In contrast, NLR and PLR were not associated with serum TTR and normalized PCR.

Clinical Outcomes

Two patients were transferred to other dialysis clinics during the follow-up, so we finally assessed the relationship between the inflammation-based prognostic scores and clinical outcomes in the 337 HD patients.

During the 42-month follow-up, 98 (29.1%) patients died, 58 (59.2%) of them due to CVD. Other causes of death were sudden death (n = 21), cerebrovascular disease (n = 12), chronic heart failure (n = 10), acute myocardial infarction (n = 9), intestine ischemia (n = 4) and others (n = 2). Twenty-three out of 98 (28.6%) patients died due to infectious diseases such as pneumonia (n = 11), sepsis (n = 7), infectious gangrene of the lower limbs (n = 2) and others (n = 3). Furthermore, death was also caused by cancer (n = 6), advanced age (n = 4), uremia (n = 2), hepatic failure (n = 3) and others (n = 3).

Sixty-four patients were admitted to hospital during the follow-up. The causes of admission were as follows: peripheral arterial disease (n = 13), orthopedic diseases (n = 10), coronary artery disease (n = 8), gastrointestinal disease (n = 6), cancer (n = 5), infectious disease (n = 5), cerebrovascular disease (n = 4) and others (n = 13).

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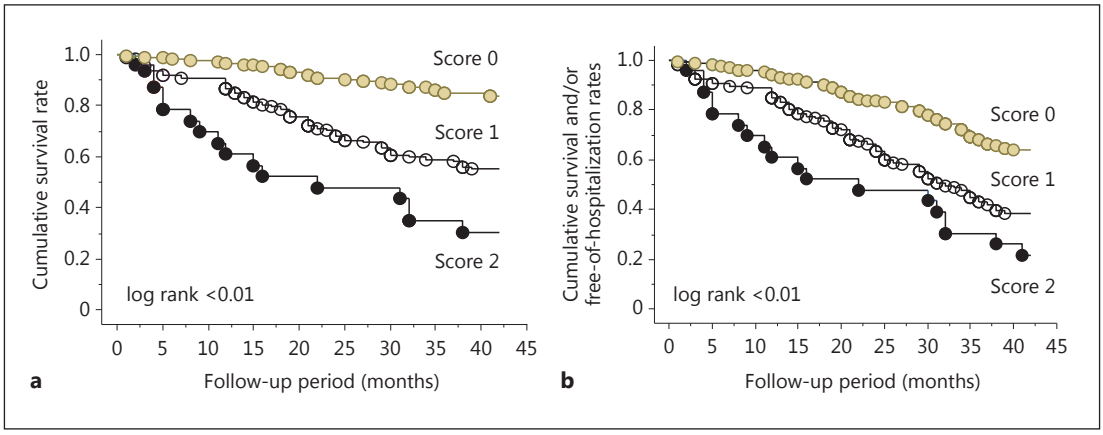

Fig. 1. Relationship between GPS and survival and/or hospitalization. The Kaplan-Meier analysis revealed that the cumulative survival (**a**) and the cumulative survival and/or free-of-hospitalization (**b**) rates were significantly higher in HD patients with a score of 0 when compared to those with a score of 1 and 2.

Table 4. Kaplan-Meier analyses in the inflammation-based prognostic scores

Prognostic score		Cumulative survival rate	χ^2	p
GPS	0	83.6%	60.3	<0.01
	1	55.1%		
	2	30.4%		
mGPS	0	73.6%	31.7	<0.01
	1	85.7%		
	2	30.4%		
NLR	0 (<5:1)	72.8%	4.3	0.04
	1 (≥5:1)	59.6%		
PLR	0 (<150:1)	75.8%	5.8	0.06
	1 (150–300:1)	65.0%		
	2 (≥300:1)	60.0%		
PI	0	73.2%	11.3	<0.01
	1	48.4%		
	2	NA		
PNI	0 (≥45)	86.4%	17.0	<0.01
	1 (<45)	64.1%		

NA = Not applicable.

Relationship between Prognostic Scores and Clinical Outcomes

Kaplan-Meier analyses revealed that, in GPS, the survival rate was significantly higher in patients with a score of 0 (83.6%) than in those with a score of 1 (55.1%) and 2 (30.4%) ($p < 0.01$, fig. 1). Elevated mGPS, NLR, PI and PNI scores were also associated with a reduced overall survival (table 4). In contrast, PLR did not relate to cumulative survival.

Cox hazards analysis revealed that increased GPS, mGPS, NLR, PLR, PI and PNI values were associated with total mortality after adjustment for covariates (table 5). Raised GPS, mGPS, NLR, PLR and PI values were also independently predictive of mortality and/or hospitalization (table 5).

Table 5. Cox hazards analyses for clinical outcomes

Score		n	All-cause mortality		All-cause mortality/hospitalization	
			RR (95% CI)	p	RR (95% CI)	p
GPS	0	207	1		1	
	1	107	2.12 (1.34–3.37)	<0.01	1.58 (1.11–2.25)	0.01
	2	23	4.62 (2.50–8.52)	<0.01	2.52 (1.48–4.30)	<0.01
mGPS	0	307	1		1	
	1	7	0.43 (0.06–3.11)	0.40	1.36 (0.55–3.37)	0.50
	2	23	3.19 (1.83–5.57)	<0.01	2.11 (1.27–3.52)	<0.01
NLR	0	306	1		1	
	1	31	1.96 (1.14–3.37)	0.01	1.72 (1.09–2.69)	0.02
PLR	0	190	1		1	
	1	137	1.37 (0.91–2.07)	0.13	1.30 (0.94–1.79)	0.11
	2	10	3.48 (1.21–9.96)	0.02	2.77 (1.18–6.49)	0.02
PI	0	306	1		1	
	1	31	1.96 (1.14–3.37)	0.01	1.72 (1.09–2.69)	0.02
	2	0	NA	NA	NA	NA
PNI	0	103	1		1	
	1	224	2.07 (1.16–3.70)	0.01	1.31 (0.89–1.93)	0.18

Cox proportional hazards model multivariate regression analysis was used to adjust for case-mix covariates including age, sex, diabetes, time on HD, history of CVD, Kt/V urea and ACEI/ARB treatment.

NA = Not applicable.

Table 6. Area under the ROC curve

Prognostic score	Area under the ROC curve	p	95% CI
Overall mortality			
GPS	0.701	<0.01	0.637–0.765
mGPS	0.561	0.08	0.491–0.632
NLR	0.550	0.15	0.480–0.620
PLR	0.538	0.27	0.469–0.607
PI	0.567	0.05	0.499–0.636
PNI	0.616	<0.01	0.553–0.768
Overall mortality and/or hospitalization			
GPS	0.640	<0.01	0.587–0.706
mGPS	0.554	0.09	0.492–0.616
NLR	0.551	0.11	0.489–0.613
PLR	0.524	0.45	0.462–0.586
PI	0.563	<0.05	0.502–0.625
PNI	0.573	0.02	0.511–0.634

When overall mortality was used as an endpoint, AUC was 0.701 (95% CI: 0.637–0.765; $p < 0.01$) for GPS, and 0.616 (95% CI: 0.553–0.768; $p < 0.01$) for PNI (table 6). The AUC values for overall mortality and/or hospitalization were 0.640 (95% CI: 0.587–0.706; $p < 0.01$) for GPS, 0.563 (95% CI: 0.502–0.625; $p < 0.05$) for PI and 0.573 (95% CI: 0.511–0.634; $p = 0.02$) for PNI (table 6).

Comparison of AUC between GPS and Its Components

We examined the best values of serum albumin and hs-CRP to find the highest sensitivity and specificity for total mortality based on the peak and cutoff points. The cutoff for albumin was unchanged at 3.5 g/dl (sensitivity 0.748, specificity 0.643), while the cutoff value for hs-CRP was decreased to 0.17 mg/dl (sensitivity 0.602, specificity 0.697).

AUC was 0.695 (95% CI: 0.632–0.759; $p < 0.01$) for hypoalbuminemia (<3.5 g/dl), which was almost identical to GPS (AUC 0.701). In contrast, a cutoff value of hs-CRP ≥1.0 mg/dl did not relate to total mortality (AUC 0.559, 95% CI: 0.489–0.630; $p = 0.09$). When we applied the best cutoff (>0.17 mg/dl), AUC was increased to 0.649 (95% CI: 0.583–0.716; $p < 0.01$).

Discussion

In this study, we showed that increased GPS, mGPS, NLR, PLR, PI and PNI values were associated with all-cause mortality during the 42-month follow-up of patients on regular HD. Elevated GPS, mGPS, NLR, PLR and PI values were also related to overall death and/or hospitalization. ROC analyses revealed that GPS was the most predictive among the scores examined. GPS was also associated with serum TTR. However, GPS did not surpass serum albumin alone as a predictor of mortality.

Recent studies have demonstrated that inflammation-based prognostic scores are useful in predicting cardiovascular risk. A higher NLR was associated with increased arterial stiffness and severe coronary artery disease [20, 21]. An elevated NLR was related to clinical outcomes in patients with ST-segment elevation myocardial infarctions undergoing primary coronary intervention [22]. An increased PLR was also a predictor of total mortality in patients with non-ST-segment elevation myocardial infarction [23]. Higher NLR and PLR scores were related to limb survival in patients with critical limb ischemia [24].

In CKD patients, both NLR and PLR scores were positively correlated with inflammatory markers such as hs-CRP and inteleukin-6 [25, 26]. Elevated NLR scores (≥5:1) were independently associated with all-cause and cardiovascular mortality in peritoneal dialysis patients [27], and a lower PNI score (<40) was related to a 5-year mortality in incident peritoneal dialysis patients [28]. In the current study, we confirmed that increased NLR (≥5:1) and PLR (≥300:1) scores as well as decreased PNI (<45) scores were independently associated with overall mortality and/or hospitalization in HD patients.

Recently, the Glasgow Inflammation Outcome Study [29] compared the impact of the inflammation-based prognostic scores on cancer-specific survival in approximately 9,000 cancer patients. The researchers found that mGPS and PI had a more prognostic value when compared to GPS, NLR, PLR and PNI. In the present study, we found that GPS was the most useful score for predicting all-cause mortality and hospitalization in HD patients.

The GPS is based on two components, namely hypoalbuminemia (<3.5 g/dl) and elevated CRP (>1.0 mg/dl). In HD patients, serum CRP and albumin levels are known to be important parameters in improving mortality prediction [12]. However, phase 3 of the Dialysis Outcome and Practice Pattern Study (DOPPS) [13] did not identify any CRP threshold below which mortality rate leveled off, indicating that the lower the CRP in HD patients the better. Recently, the classification of CRP using a cutoff value of 0.5 mg/dl has allowed a more precise discrimination between high-risk patients and normal patients than using 1.0 mg/dl in patients with colon cancer [30]. It has also been reported that AUC for cancer-specific survival increased from 0.695 to 0.734 by administering 0.3 mg/dl of hs-CRP instead of 1.0 mg/dl of conventional CRP [31]. In this study, the best hs-CRP cutoff for mortality prediction was 0.17 mg/dl. However, ROC analyses revealed that AUC for this cutoff was smaller than that for GPS (0.649 vs. 0.701), indicating that albumin contributed exclusively to the predictive power of GPS.

In HD patients, interleukin-6 has the strongest independent association of mortality when compared with other acute-phase reactants such as hs-CRP, serum amyloid A and albumin at single time points [32]. Therefore, future research efforts should be directed at elucidating suitable components that have additional clinical utility beyond that of albumin alone and establishing whether any such markers are truly more predictive of mortality in dialysis patients than others.

There are some limitations to the current study. First, we determined the inflammation-based prognostic scores only at baseline; a time-averaged score may be a more proper method for predicting clinical outcomes than a single determinant. Second, we analyzed only a small-sized sample. Finally, we did not compare the inflammation-based prognostic parameters with other established nutritional scores such as the malnutrition-inflammation score [33] and the geriatric nutritional risk index [34].

In summary, we showed that the inflammation-based prognostic scores, which are well established as predictors of outcome in cancer patients, are associated with mortality and/or hospitalization in HD patients. In particular, an elevated GPS can predict mortality most strongly compared to other scores. However, as the determination of serum albumin reflects mortality risk similarly to GPS, other composite combinations are needed to provide additional clinical utility beyond that of albumin alone in HD patients.

Disclosure Statement

None of the authors has any conflict of interest to disclose.

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