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Systemic immune-inflammation index, serum albumin, and fibrinogen impact prognosis in castration-resistant prostate cancer patients treated with first-line docetaxel

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Abstract

Purpose To evaluate the prognostic value of pretreatment plasma systemic immune-inflammation index (SII), albumin, and fibrinogen levels in metastatic castration-resistant prostate cancer (mCRPC) patients treated with first-line docetaxel and to screen out the patients with the greatest risk for poor prognosis.

Methods The plasma SII, albumin, and fibrinogen levels were examined before treatment and analyzed with patient clinicopathological parameters and overall survival (OS). The survival analysis was performed using the Kaplan–Meier method, and prognostic factors were assessed using the Cox proportional hazard regression model.

Results The incidences of elevated SII level, hypoproteinemia, and hyperfibrinogenemia were 52.51%, 25.14%, and 27.93%, respectively. SII level was associated with neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) ($P<0.001$). Albumin level was found closely correlated with ECOG PS ($P=0.006$), PLR ($P=0.042$), and hemoglobin ($P=0.009$), but not other parameters. Elevated plasma fibrinogen level was significantly associated with Eastern Cooperative Oncology Group performance status (ECOG PS) ($P=0.009$), visceral metastases ($P<0.001$), and PLR ($P=0.001$). In multivariate Cox regression model, visceral metastases SII (HR 2.133, 95% CI 1.163–3.913; $P=0.014$), albumin (HR 0.540, 95% CI 0.307–0.949; $P=0.032$), and fibrinogen (HR 1.888, 95% CI 1.069–3.335; $P=0.029$) were further confirmed to be the independent prognostic factors for OS. Of the three target parameters, we found that patients with none abnormalities of the three parameters showed the best prognosis, and patients with at least any two abnormalities of them showed markedly worse prognosis than patients with any one abnormalities of the three parameters ($P<0.001$).

Conclusions Pretreatment SII, albumin, and fibrinogen are independent prognostic factors in mCRPC patients treated with first-line docetaxel. Moreover, the combined use of SII, albumin, and fibrinogen levels may help us to identify the high-risk populations for treatment decisions.

Keywords SII · D-dimer · Fibrinogen · CRPC · Prognosis

Introduction

Prostate cancer is the most common cancer and the third cause of cancer-related death among males worldwide currently [1]. Androgen deprivation therapy (ADT) is the standard treatment for locally advanced or metastatic prostate cancer or patients with early disease who are not eligible for local regional therapies. Although the initial higher response rate of ADT, most patients ultimately progress to metastatic castration-resistant prostate cancer (mCRPC), which means a more aggressive, relapsed, and deadly stage [2, 3]. For many years, docetaxel has considered as the only effective drug for first-line treatment of mCRPC patients according to TAX327 study results [4]. However, in the last 7 years, several new agents have been found to prolong the median overall survival (OS) in patients with mCRPC, including enzalutamide, abiraterone acetate, cabazitaxel, radium-223, and sipuleucel-T [4–9]. mCRPC, the therapeutic landscape of which has

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been significantly evolved by the above-mentioned new treatments, is still a heterogeneous disease with obvious variability of prognosis and treatment response between individuals. Moreover, survival estimation and therapeutic effect prediction are significantly important for patient counseling, personalizing treatment in daily clinical practice, and planning of follow-up. Owing to these, in the absence of reliable molecular markers, it is crucial to identify prognostic clinical risk factors of mCRPC treated with each available therapy.

It is clear that the inflammation of the microenvironment plays a vital role in different biological stages of tumor development and progression by influencing the proliferation and migration of tumor cells, promoting angiogenesis and metastasis, and weakening responses to anticancer therapies [10]. Meanwhile, it is increasingly recognized that the immune system is significant in cancer surveillance and elimination [11]. Thus, several biomarkers and hematological indices representative of systemic immune-inflammatory responses have been verified as prognostic factors in various cancers recently, such as NLR and PLR [12–14]. In patients with mCRPC, some studies have shown that NLR could predict prognosis when treated with docetaxel, cabazitaxel, abiraterone, or enzalutamide [15–18]. Systemic immune-inflammation index (SII), a novel inflammatory index defined as platelet (P) × neutrophil (N)/lymphocyte (L), was first described by Hu et al. [19] and can comprehensively reflect the balance of host immune and inflammatory status. Recently, SII has emerged as a powerful prognostic index in hepatocarcinoma [19], renal cell cancer [20], colorectal cancer [21], gastric cancer [22], and prostate cancer [23]. However, no studies have confirmed whether SII can impact prognosis in mCRPC patients treated with first-line docetaxel.

Increasing evidence indicates that the nutritional status of patients with malignant tumors is an important factor affecting survival outcomes [24]. It is well accepted that nutrition is an indispensable factor of immune responses. Malnutrition, which leads to impair the immune system and suppress immune functions, is highly universal and tends to reduce response to treatment and shorten overall survival among patients with cancer [25, 26]. Moreover, it can contribute to tumor development through the suppression of tumor immunity [27]. Furthermore, hypoalbuminemia, one of the protein energy malnutrition, is associated with the immunodeficiency of cell-mediated mechanisms, such as macrophage activation and granuloma formation, which is critical in the host protection against infection or cancer [28, 29]. Thus, serum albumin, which is commonly used as an indicator of nutritional status, has been widely studied about its relation with the survival of cancer patients and proven to be a significant prognostic factor for some cancers [30–32], including prostate cancer [33].

Coagulation and fibrinolysis disturbances are often observed in cancer [34]. Although the prothrombotic state with cancer has been recognized for a long time, the mechanism underlying this phenomenon is still poorly understood. Some research thought that tumor cells can release tissue factor, procoagulant molecules, and proinflammatory cytokines which can activate the coagulation system leading to hemostatic abnormalities [35]. Meanwhile, markers of coagulation activation are strong predictors of cancer survival [34]. Fibrinogen, a 340-kDa glycoprotein, is one of the most prominent markers of coagulation activation. There is growing evidence that fibrinogen level is increased in various cancer patients and thought as a factor for poor prognosis of them [36–39]. In addition, there are potential correlation among inflammation, nutritional status, and coagulation–fibrinolysis disturbance in cancer patients. Fibrinogen always enhanced in response to inflammatory disorders and hyperfibrinogenemia with malignant tumor is probably an event for inflammatory response caused by tumor progression [40]. The excessive secretion of some inflammatory cytokines can have diverse effects related to malnutrition and cachexia, and malnutrition in turn suppress immune functions which is crucial in the host defenses against cancer. Some studies have revealed the prognostic significance of inflammation, nutritional status, and coagulation–fibrinolysis makers in prostate cancer patients as previously mentioned, but to our knowledge, an investigation evaluating prognostic values of the correlative three factors synchronously in mCRPC patients treated with first-line docetaxel has not been reported and the combined effects of them on prognosis are still unknown.

In our present study, we assessed the relationship between clinicopathological factors and pretreatment SII/albumin/fibrinogen levels in mCRPC patients treated with first-line docetaxel. Then, we investigated the ability of pretreatment SII/albumin/fibrinogen levels to predict OS of these patients. Furthermore, we evaluated the combined effects of the three parameters on prognosis and then screened out the patients with the highest risk for poor prognosis.

Patients and methods

Patients

The study was approved by the ethics committee of The Second Hospital of Tianjin Medical University. All mCRPC patients who treated at our hospital and received first-line docetaxel between 2010 and 2018 were included in this retrospective study. All of the patients had pathologically diagnosed prostate carcinoma. According to the EAU-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer in 2017, the definition of CRPC is as follows: castrate serum

testosterone < 50 ng/dL or 1.7 nmol/L plus either; (a) biochemical progression: three consecutive rises in PSA 1 week apart resulting in two 50% increase over the nadir, and a PSA > 2 ng/mL or, (b) radiological progression: the appearance of new lesions: either two or more new bone lesions on bone scan or a soft-tissue lesion using RECIST (response evaluation criteria in solid tumors). The process of treating patients after the diagnosis of CRPC in our clinical practice is generally summarized as follows: After patients are diagnosed as CRPC, ADT will be continued to maintain castrate serum levels of testosterone (< 50 ng/dL), and at the same time, the level of PSA will be continually monitored. When PSA doubling time (PSADT) > 10 months, observations or other secondary hormone therapy can be selected; when PSADT ≤ 10 months, patients can be treated with other secondary hormone therapy, rather than apalutamideu or enzalutamideu which is not listed in China so far. If the level of PSA still increases after this treatment, imaging will be performed to find whether metastases exist. Change or maintain current treatment and continue monitoring will be selected when no metastases are found. Once diagnosed as mCRPC, patients can be treated with docetaxel, abiraterone, clinical trial, and other secondary hormone therapy in China. In our clinical practice, most mCRPC patients select docetaxel as the first-line treatment due to the expensiveness of abiraterone. The patients in our research were exactly those who were diagnosed as mCRPC and treated with docetaxel as the first-line therapy.

When available, the following clinical and pathological characteristics have been collected for each patient: age, Gleason score, treatment start date, ECOG PS, sites of metastasis (bones, lymph nodes, and viscera), PSA, ALP, LDH, albumin, Hb, NLR, PLR, SII, fibrinogen, and courses of docetaxel. Date of disease progression/death/last visit for alive patients was collected as follow-up information. Due to the potential confounding effect of corticosteroids on NLR/PLR/SII, when premedication was made with dexamethasone, we considered the test performed within 2 months before the first administration of docetaxel as baseline blood sample, instead of the test obtained on the same day or a few days before the initiation of chemotherapy. In addition, patients with inflammatory diseases, autoimmune diseases, cerebrovascular diseases, coagulation-related diseases, and other tumors or those lost to follow-up were excluded.

Statistical analysis

Statistical analysis was performed using *t* tests and Chi-square tests for continuous and categorical data, respectively. Outcome measure was overall survival (OS). OS was defined as the time from the date of the beginning of the treatment with docetaxel to the time of last follow-up or death. The Kaplan–Meier method was used to calculate OS. The log-rank test was used to compare the outcome of different categories for each prognostic factor. Univariate analysis was conducted to assess the prognostic role of the parameters under consideration. Then, multivariate analysis was performed on variables that were identified as statistically significant by univariate analysis to assess the independence of different prognostic factors, using the Cox proportional hazards model. All statistical analyses were performed using SPSS 21.0 statistical software (SPSS Inc, Chicago, IL, USA). *P* values less than 0.05 were considered statistically significant.

Results

One hundred and seventy-nine mCRPC patients treated with the first-line docetaxel at our hospital were included in the study. Main baseline characteristics of the patients are presented in Table 1.

The median age of the 179 patients was 70 years (range 51–88 years). The ECOG PS of most patients ($n = 138$) was 0–1, presenting better performance status. When patients were diagnosed with PCa, the median of PSA level was 62.89 ng/ml (range 4–12,614 ng/ml), and 93 patients (51.96%) had distant metastases. 48 patients (26.82%) received local radical surgery or radiotherapy after diagnosis. Then, most patients undergone traditional ADT (four patients selected castration plus abiraterone after being diagnosed as metastatic castration-naive disease) and finally progress to CRPC, which presented 108 patients (60.34%) with bone metastases and 40 patients (22.35%) with visceral metastases. The median time of ADT to initiation of docetaxel treatment was 18 months (range 2–120 months) and the median duration of docetaxel treatment was 5 months (range 1–16 months).

The SII value of 94 patients was above 535. The median level of plasma albumin and fibrinogen were 43.40 g/L (range 33.60–67.10 g/L) and 3.35 g/L (range 1.85–6.91 g/L), respectively. After a median follow-up of 24 months (range 2–118 months), death occurred in 45 patients.

Relationship between clinicopathological parameters and plasma SII/albumin/fibrinogen level in mCRPC

We analyzed the relationship between clinicopathological parameters and plasma SII/albumin/fibrinogen levels, and the results are shown in Table 2. NLR ($P < 0.001$) and PLR ($P < 0.001$) were associated with SII levels, which was easily understood according to the definition of the there parameters. A significant relationship was not observed between SII level and other clinicopathological parameters. Plasma albumin level was found closely correlated

Table 1 Patients' baseline characteristics

Number of patients	179
Demographics	
Age, years, median (range)	70 (51–88)
ECOG PS	
0	65
1	73
2	41
At PCa diagnosis	
Gleason score	
≤7	42
>7	137
PSA at diagnosis, ng/ml, median (range)	62.89 (4.00–12,614.00)
Local tumor in prostate	78
Lymph node metastases	8
Distant metastases	93
Disease characteristics	
Local tumor in pelvic cavity	44
Bone	108
Any visceral	40
Lymph node	5
Blood value	
Serum PSA, ng/ml, median (range)	36.08 (0.03–2251.00)
Serum ALP, UI/l, median (range)	99.30 (46.90–1257.90)
Serum LDH, UI/l, median (range)	191.90 (142.30–2490.70)
NLR	
≤3	104
>3	75
PLR	
≤210	46
>210	133
SII	
≤535	85
>	94
Serum albumin, g/L, median (range)	43.40 (33.60–67.10)
Hemoglobin, g/dl, median (range)	131.00 (86.00–160.00)
Plasma fibrinogen, g/L, median (range)	3.35 (1.85–6.91)
Prior local radical surgery or radiotherapy	48
Time parameters	
Start of ADT to initiation of docetaxel treatment, months, median (range)	18 (2–120)
Duration of docetaxel treatment, months, median (range)	5 (1–16)

with ECOG PS ($P = 0.006$), PLR ($P = 0.042$) and hemoglobin ($P = 0.009$), but not other parameters. In addition, elevated plasma fibrinogen level was significantly associated with ECOG PS ($P = 0.009$), visceral metastases ($P < 0.001$), and PLR ($P = 0.001$) but not with age, Gleason score, and other blood values.

Prognostic role of clinicopathological parameters, SII, albumin, and fibrinogen level in univariate analysis

We assessed the prognostic values of the pretreatment SII, albumin, fibrinogen levels, and other baseline

Table 2 Relationship between clinicopathological parameters, SII (≤535 vs > 535), albumin value (≤40 g/L vs > 40 g/L), and fibrinogen level (2–4 g/Lvs > 4 g/L) in the 179 CRPC patients treated with first-line docetaxel

Variable	*n*	SII		*P*	Albumin, g/L		*P*	Fibrinogen, g/L		*P*
		≤535	> 535		≤40	> 40		≤4	> 4	
Age (years)				0.705			0.366			0.774
≤70	90	44	46		20	70		64	26	
> 70	89	41	48		25	64		65	24	
ECOG PS				0.379			0.006			0.009
0 or 1	138	68	70		28	110		106	32	
2	41	17	24		17	24		23	18	
Gleason score				0.709			0.820			0.093
≤7	42	21	21		10	32		26	16	
> 7	137	64	73		35	102		103	34	
Visceral metastases				0.474			0.093			0.000
Absent	139	68	71		39	100		111	28	
Present	40	17	23		6	34		17	23	
Serum PSA, ng/ml				0.156			0.575			0.341
≤36.08	90	38	52		21	69		62	28	
> 36.08	89	47	42		24	65		67	22	
Serum ALP, UI/l				0.709			0.071			0.093
≤160	137	64	73		30	107		103	34	
> 160	42	21	21		15	27		26	16	
Serum LDH, UI/l				0.477			0.527			0.687
≤250	126	62	64		30	96		94	32	
> 250	53	23	30		15	38		35	18	
NLR				0.000			0.272			0.303
≤3	104	70	34		23	81		78	26	
> 3	75	15	60		22	53		51	24	
PLR				0.000			0.042			0.001
≤210	132	82	50		28	104		104	28	
> 210	47	3	44		17	30		25	22	
Hemoglobin, g/dl				0.223			0.009			0.202
≤12.0	52	21	31		20	32		34	18	
> 12.0	127	64	63		25	102		95	32	
Prior local radical surgery or radiotherapy				0.789			0.114			0.069
Yes	48	22	26		8	40		37	11	
No	131	63	68		37	94		92	39	
Start of ADT to initiation of docetaxel treatment, months				0.498			0.413			0.105
≤18	90	45	45		25	65		60	30	
> 18	89	40	49		20	69		69	20	
Duration of docetaxel treatment, months				0.877			0.519			0.488
≤5	100	48	52		27	73		70	30	
> 5	79	37	42		18	61		59	20	

characteristics in the patients with mCRPC included in our study, as shown in Table 3. As for SII, median OS was 42 months in patients with low SII versus 27 months in those with high SII [hazard ratio (HR) 2.879, 95% confidence interval (95% CI) 1.659–4.996, and $P < 0.001$]. Kaplan–Meier curves of OS according to SII category are shown in Fig. 1a. Patients with high serum albumin level (> 40 g/L) had a significantly improved OS of 42 months as opposed to 22 in patients with low serum albumin levels (≤40 g/L) (HR 0.409, 95% CI 0.245–0.683, $P < 0.001$; Fig. 1b). Compared with hyperfibrinogenemia, normal plasma fibrinogen levels (2–4 g/L) owned a better OS (21

Table 3 Prognostic role of baseline characteristics: univariate analysis for overall survival

Baseline characteristics	Median, m	*P*	HR (95% CI)
SII		< 0.001	2.879 (1.659–4.996)
≤ 535	42		
> 535	27		
Serum albumin, g/L		< 0.001	0.409 (0.245–0.683)
≤ 40	22		
> 40	42		
Plasma fibrinogen, g/dL		< 0.001	2.931 (1.768–4.859)
≤ 4	49		
> 4	21		
Age, years		0.787	0.933 (0.566–1.540)
≤ 70	31		
> 70	38		
ECOG PS		< 0.001	3.055 (1.824–5.114)
0–1	49		
2	22		
Gleason score		0.181	0.701 (0.416–1.180)
≤ 7	30		
> 7	42		
Visceral metastases		0.009	1.988 (1.184–3.340)
Absent	42		
Present	25		
Serum PSA, ng/ml		0.949	0.984 (0.601–1.612)
≤ 36.08	38		
> 36.08	42		
Serum ALP, UI/L		0.181	1.427 (0.847–2.404)
≤ 160	42		
> 160	30		
Serum LDH, UI/L		0.003	2.149 (1.291–3.576)
≤ 250	42		
> 250	27		
NLR		0.008	1.944 (1.187–3.184)
≤ 3	42		
> 3	28		
PLR		0.811	0.935 (0.541–1.618)
≤ 210	38		
> 210	42		
Hemoglobin, g/dL		0.177	0.707 (0.428–1.169)
≤ 12.0	31		
> 12.0	42		
Prior local radical surgery or radiotherapy		0.066	1.603 (0.970–2.650)
Yes	42		
No	30		
Start of ADT to initiation of docetaxel Treatment, months		0.031	0.570 (0.342–0.950)
≤ 18	31		
> 18	42		
Duration of docetaxel treatment		0.864	0.957 (0.580–1.578)
≤ 5	38		
> 5	42		

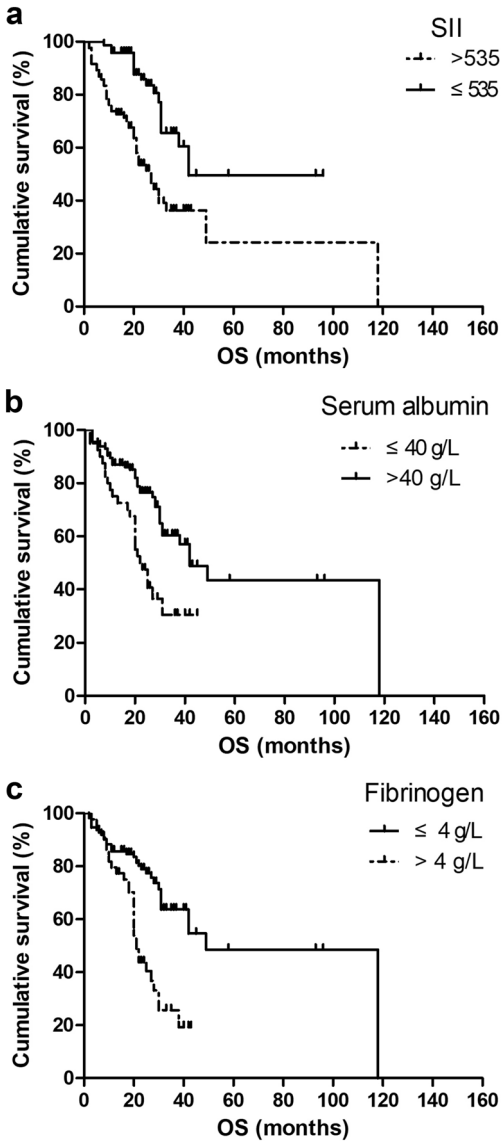

Fig. 1 Cumulative survival curves for OS according to pretreatment plasma SII, albumin, and fibrinogen levels by Kaplan–Meier method in the 179 patients with CRPC. **a**–**c** OS for plasma SII ($P<0.001$), albumin ($P<0.001$), and fibrinogen levels ($P<0.001$)

vs 49 months, HR 2.931, 95% CI 1.768–4.859, $P<0.001$; Fig. 1c).

In addition, ECOG PS (49 vs 22 months, HR 3.055, 95% CI 1.824–5.114, $P<0.001$), visceral metastases (42 vs 25 months, HR 1.988, 95% CI 1.184–3.340, $P=0.009$), serum LDH (42 vs 27 months, HR 2.149, 95% CI 1.291–3.576, $P=0.003$), NLR (42 vs 28 months, HR 1.944, 95% CI 1.187–3.184, $P=0.008$), and start of ADT to initiation of docetaxel treatment (31 vs 42 months, HR 0.570, 95% CI 0.342–0.950, $P=0.031$) were significantly associated with OS in the univariate analysis.

Although median OS were longer in patients with prior local radical surgery or radiotherapy, this difference did not reach statistical significance. In detail, median OS was 42 months in patients with prior local radical surgery or radiotherapy versus 30 months in those without prior local therapies (HR 1.603, 95% CI 0.970–2.650, $P=0.066$). OS were not found significant difference according to baseline age, Gleason score, serum PSA, ALP, PLR, hemoglobin level, and duration of docetaxel treatment.

Prognostic role of clinicopathological parameters, SII, albumin, and fibrinogen level in multivariate analysis

We performed multivariate analysis on the factors that were statistically significant in the univariate analysis, and the results are shown in Table 4. Multivariate evaluation of plasma SII, albumin, and fibrinogen level considered ECOG PS, visceral metastases, serum LDH, NLR, and start of ADT to initiation of docetaxel treatment. In the Cox proportional hazard model, ECOG PS (HR 2.555, 95% CI 1.437–4.543, $P=0.001$), visceral metastases (HR 1.827, 95% CI 1.060–3.149, $P=0.030$), and serum LDH (HR 1.727, 95% CI 1.016–2.934, $P=0.043$) were significantly associated with OS. Of the three target parameters, SII confirmed an independent impact on OS (HR for SII lower than 535 vs SII > 535: 2.133, 95% CI 1.163–3.913; $P=0.014$). Serum albumin level also showed an independent prognostic role on OS (HR for albumin lower than 40 g/L vs albumin > 40 g/L: 0.540, 95% CI 0.307–0.949; $P=0.032$).

Table 4 Prognostic role of baseline characteristics: multivariate analysis for overall survival

Baseline characteristics	Category	*P*	HR (95% CI)
ECOG PS	0–1 vs 2	0.001	2.555 (1.437–4.543)
Visceral metastases	Absent vs present	0.030	1.827 (1.060–3.149)
Serum LDH	≤ 250 vs > 250 UI/l	0.043	1.727 (1.016–2.934)
NLR	≤ 3 vs > 3	0.936	1.022 (0.598–1.748)
Start of ADT to initiation of docetaxel treatment	≤ 18 vs > 18 months	0.652	0.879 (0.503–1.539)
SII	≤ 535 vs > 535	0.014	2.133 (1.163–3.913)
Serum albumin	≤ 40 vs > 40 g/L	0.032	0.540 (0.307–0.949)
Plasma fibrinogen	≤ 4 vs > 4 g/dl	0.029	1.888 (1.069–3.335)

Finally, plasma fibrinogen was confirmed to be an independent prognostic factor for OS (HR for fibrinogen lower than 4 g/dL vs > 4 g/dL: 1.888, 95% CI 1.069–3.335; $P = 0.029$).

Combined effects of SII, albumin, and fibrinogen level on prognosis

To identify the combined effects of plasma SII, albumin, and fibrinogen level on prognosis, we further grouped the patients as follows: group 1, patients with normal plasma SII, albumin and fibrinogen levels; group 2, patients with high plasma SII level or low albumin or hyperfibrinogenemia; group 3, patients with any two or three abnormalities of plasma SII, albumin, and fibrinogen levels. The result demonstrated that there were 52 patients with normal plasma SII, albumin, and fibrinogen levels, that 77 patients had an abnormality for 1 of the 3 parameters, that 50 patients showed an abnormality for 2 or 3 of the 3 parameters. We then assessed the combined prognostic values of plasma SII, albumin, and fibrinogen levels. We found that group 1 showed a markedly longer OS than group 2 did ($P < 0.001$) and group 2 showed a statistically longer OS than group 3 did ($P < 0.001$), as shown in Fig. 2.

Discussion

The treatment landscape of mCRPC who progressed on prior treatment with ADT has dramatically changed in the last few years, due to the approval of several new therapeutic agents, such as abiraterone, cabazitaxel, and enzalutamide [4]. However, docetaxel remains a standard treatment for most of these patients. A crucial problem remains in patients with mCRPC treated with first-line docetaxel, that is the lack of prognostic and predictive biomarkers which can be easily obtained and aid in patient counseling and clinical decision-making in the stratification of patient risk [4]. In our present study, we explored the prognostic value of pretreatment SII/albumin/fibrinogen levels in patients with mCRPC treated with first-line docetaxel.

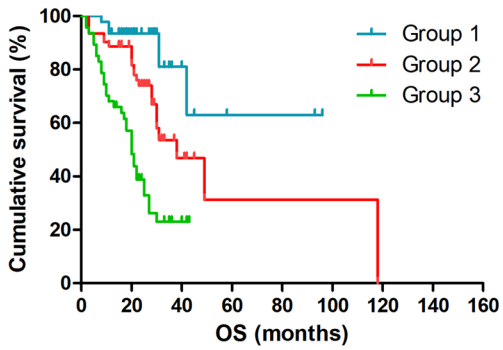

Fig. 2 Combined effect of plasma SII, albumin, and fibrinogen levels on OS using the Kaplan–Meier method. Group 1, patients with normal plasma SII, albumin, and fibrinogen levels; group 2, patients with any one abnormality of plasma SII, albumin, and fibrinogen levels; group 3, patients with any two or three abnormalities of plasma SII, albumin, and fibrinogen levels. Group 1 showed a markedly longer OS than group 2 did ($P < 0.001$) and group 2 showed a statistically longer OS than group 3 did ($P < 0.001$)

From the results of our study, we can see that the incidence of high SII level, low albumin, and hyperfibrinogenemia was 52.51%, 25.14%, and 27.93%, respectively, in the patients with mCRPC. We found that plasma SII was associated with NLR and PLR levels, which was easily understood according to the definition of the there parameters. Serum albumin level was found closely correlated with ECOG PS, and it appeared that decreased albumin level was clinically relevant events at the patients with high ECOG PS. The percentage of low albumin level in patients with raised PLR was higher than that in patients with lower PLR, which estimated that patients with low albumin may had stronger systemic immune-inflammatory responses. The patients with decreased albumin had lower hemoglobin, which may be explained by the common raw materials for synthesis of the proteins. In addition, the percentage of hyperfibrinogenemia in patients with high ECOG PS was much higher than that in those with low ECOG PS. There was also a significant relationship between hyperfibrinogenemia and visceral metastases in the cohort study, which can be understood by the theory that the patients with advanced stage usually are in the state of hypercoagulability. Moreover, the percentage of hyperfibrinogenemia in patients with high PLR was higher than those with low PLR. This estimated that patients with hyperfibrinogenemia may have more intense systemic immune-inflammatory responses, which confirmed the relationship between fibrinolytic system and inflammatory responses. The three parameters were then identified as independent prognostic factors for OS in the Cox proportional hazard model.

Due to tumor hypoxia, tissue injury, and necrosis, the body can launch the nonspecific inflammatory responses. Conversely, inflammatory responses of the microenvironment can influence the proliferation of tumor cells, promote angiogenesis, and reduce responses to anticancer agents, through the production of inflammatory cytokines and chemokines, which ultimately give rise to the development and progression of cancer [10]. Recently, several scores can be used to assess the systemic inflammatory responses in cancer patients, such as CRP, NLR, PLR, SII, etc. Previous studies have shown that elevated NLR and PLR at the baseline were associated with worse prognosis in resected and advanced cancers [41, 42].

However, SII, being defined as platelet × neutrophil/lymphocyte, perhaps can reflect the systemic inflammatory responses more comprehensively than other indexes.

Previous basic studies have shown that platelets can support the adhesion of circulating tumor cells (CTCs) to microvascular endothelium and promote metastasis [43]. Neutrophils can enhance cell arrest in microvessels and promote tumor-related angiogenesis via secreting cytokines and chemokines [44]. Recent evidence indicates that both platelets and neutrophils can create a defensive barrier around CTCs, facilitating CTCs to evade the host's immune surveillance [45, 46]. Lymphocytes can induce cytotoxic cell death and inhibit tumor proliferation and migration through secreting cytokines, such as IFN-g and TNF-a, leading to the host immune response to malignancy [47]. High SII means thrombocythemia, neutrophilia, or lymphopenia, suggesting an elevated nonspecific inflammatory status and weak adaptive immune response in patients. All of these might cause more tumor cells escaping from immune surveillance, increasing the peripheral CTCs level, and finally promoting tumor infiltrating and metastasis. Based on the above, compared to PLR and NLR, SII could be a more objective marker that reflects the association among cancer, immunity, and inflammation. In our present study, we found that both higher SII and NLR were associated with shorter OS in patients with mCRPC ($P < 0.001$ and $P = 0.008$, respectively). However, only SII was finally identified as the independence prognostic factor in multivariate analysis, similar to many other cancers [19–23].

It is well known that patients with advanced cancer are usually in the state of malnutrition due to the tumor chronic exhaustion and deficiency of intake. In addition, systemic inflammation in cancer is associated with malnutrition and cachexia, with muscle mass loss, which increases morbidity [48]. As inflammation, malnutrition can also promote tumor progression through affecting the host's immune functions. Several studies have shown that protein energy malnutrition is associated with the cell-mediated immunodeficiency, such as macrophage activation and granuloma formation, which is crucial in the host protection against cancer [28, 29]. Decreased albumin at diagnosis may indicate an undernourished status in addition to a suppressed immune system [49]. Therefore, serum albumin is commonly used to evaluate nutritional status and hypoproteinemia has been proven to be a factor significantly associated with poor prognosis in many cancers [30–33]. Consistent with previous studies, patients in the lower albumin group were with a shorter OS in our study, which further confirmed the correlation between nutritional status and prognosis in mCRPC patients.

Fibrinogen, as the marker of coagulation activation in cancer, probably elevate due to the inflammatory response during tumor progression or the increased synthesis by tumor cells themselves [50]. Fibrinogen has been proved to participate in several tumor biological behaviors such as proliferation, invasion, and metastasis via promoting tumor angiogenesis and supporting the sustained adhesion of tumor cells [51, 52]. Moreover, fibrinogen can help platelets to adhere to tumor cells through β3-integrins, which are expressed on the surface of human cancer cells. In turn, platelets promote more fibrinogen to aggregate around tumor cells, and finally form the dense fibrin layers that protect tumor cells from natural killer cell cytotoxicity [53]. Furthermore, Steinbrecher et al. had demonstrated the interaction between cancer cell-expressed integrins and fibrinogen in an inflammation-driven animal model of colorectal cancer [54]. Hyperfibrinogenemia have been identified as an important prognostic factor in several malignancies, such as tract urothelial carcinoma, endometrial cancer, and prostate cancer [37–41]. In accordance with the above-mentioned experimental studies and recent clinical research, our study also demonstrated that elevated fibrinogen was an independent prognostic factor for OS in patients with mCRPC treated with first-line docetaxel.

As mentioned above, there are potential correlation among immune inflammation, nutritional status and coagulation–fibrinolysis disturbance in cancer patients. Inflammation can induce malnutrition and coagulation–fibrinolysis disturbance. Elevated inflammatory cells, platelets, and fibrinogen can act corporately to protect tumor cells from immune surveillance. Malnutrition affects the host's immune system and is associated with cell-mediated immunodeficiency, which is important to host protection against cancer. Evaluating the status of immune inflammation, nutrition, and coagulation–fibrinolysis in cancer patients comprehensively can perhaps predict the prognosis more accurately than considering one single factor. For these reasons, we further grouped the patients according to the levels of SII, albumin, and fibrinogen. We found that patients with at least any two abnormalities of SII, albumin, and fibrinogen levels showed a markedly worse prognosis than patients with any one abnormality of the three parameters. And patients with none abnormalities of the three parameters showed the best prognosis. It means that elevated SII, albumin, and fibrinogen act together to contribute to the poor prognosis of mCRPC synergistically. However, which factor plays a more important role in tumor progression has not yet been confirmed. The mechanisms connecting SII, albumin, fibrinogen, and cancer cells are complicated and require further study. The measurement of SII, albumin, and fibrinogen levels requires only small plasma aliquots and less invasive technique. Therefore, the application of the three parameters for predicting oncological outcome in clinical practice was considered as being time- and cost-efficient. Our study first evaluated prognostic values of the correlative three factors synchronously in mCRPC patients treated with first-line docetaxel and found that the three parameters could predict prognosis for clinical practice. Thus, we propose the use of the three parameters in evaluation of the prognosis in patients with mCRPC for clinical decisions.

In conclusion, pretreatment SII, albumin, and fibrinogen can partly reflect the status of immune inflammation, nutrition, and coagulation–fibrinolysis, respectively, and all of them are independent prognostic factors in mCRPC patients treated with first-line docetaxel. Moreover, the combined use of SII, albumin, and fibrinogen levels may help us to identify the high-risk populations for treatment decisions.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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