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High C-reactive protein to albumin ratio and the short-term survival prognosis within 30 days in terminal cancer patients receiving palliative care in a hospital setting

A retrospective analysis

Sang-Yhun Ju, MD, PhD[a,*], Soo-Jin Ma, MD, PhD[b]

Abstract

Survival estimates are very important to patients with terminal cancer. The C-reactive protein (CRP)/albumin ratio is associated with cancer outcomes. However, few studies have investigated the dose-response association in terminal cancer patients. Therefore, we aimed to evaluate the association between the CRP/albumin ratio and mortality in terminal cancer patients using a longitudinal analysis. We retrospectively investigated the electronic medical records of 435 inpatients with terminal cancer admitted to the palliative care unit of Yeouido St. Mary's Hospital between October 8, 2015, and January 17, 2018. In total, 382 patients with terminal cancer were enrolled in the study. The serum CRP/albumin ratio measured at admission had a linear dose-response relationship with the risk of death among the terminal cancer patients (*P* for linearity = .011). The multivariate analyses showed that the CRP/albumin ratio was an independent prognostic factor (Model 1, CRP/albumin ratio $>48.53 \times 10^{-4}$: HR = 2.68, 95% CI = 1.82–3.93; Model 2, tertile 2: HR = 1.91, 95% CI = 1.31–2.82 and tertile 3: HR = 3.66, 95% CI = 2.24–5.97). The relationship between a high CRP/albumin ratio and poor survival was a flat L-shape for survival time with an inflection point at approximately 15 days, while the relationship was not significant in terminal cancer patients who survived beyond 30 days. This study demonstrated that high CRP/albumin ratios are significantly and independently associated with the short-term survival prognosis of terminal cancer patients within 30 days.

Abbreviations: CI = confidence interval, CRP = C-reactive protein, ECOG = Eastern Cooperative Oncology Group, EMRs = electronic medical records, GPS = Glasgow prognostic score, IRB = Institutional Review Board, LDH = lactate dehydrogenase, NLR = neutrophil/lymphocyte ratio, ROC = receiver operating characteristic, SBP = systolic blood pressure.

Keywords: albumin, cancer, cohort study, C-reactive protein, death, palliative care

1. Introduction

Survival estimates are very important to patients with terminal cancer.[1] Patients who are admitted to palliative care hospitals and their families wish to know how much longer they have to live, and this topic is important for reorienting their priorities, particularly as they approach the end of life.[1–3] However, physicians may experience difficultly in identifying terminal cancer patients with a short survival period. Published reviews have shown that clinicians' predictions of survival are inaccurate and unreliable in advanced cancer.[4,5] A recent meta-analysis showed that clinicians' accuracy in prognostic estimates varied from 23% to 78% in a palliative care setting.[6]

There are various prognostic tools, such as the palliative prognostic score, palliative prognostic index, and palliative performance scale.[7] Although these prognostic tools have been validated, their clinical utility is limited due to their complexity and subjectivity.[7] In a systematic review of candidate biomarkers in body fluids for the prediction of the risk of death in cancer patients, 7 prognostic biomarkers, namely, the lymphocyte count, white blood cell count, and serum levels of albumin, sodium, C-reactive protein (CRP), urea and alkaline phosphatase, were supported by Grade A evidence.[8]

Increased levels of serum CRP in all stages of tumor growth have been associated with a poor prognosis.[9,10] Amano et al divided the serum CRP levels into four groups to predict patient outcomes and clearly demonstrated an inverse dose-response relationship between CRP and patient survival.[9] Furthermore, low levels of albumin measured at admission are associated with increased short-term and long-term mortality.[11] It is well known that as the inflammation process progresses, the essential protein components of the body gradually decrease, leading to increased

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mortality in advanced cancer patients.[12] A meta-analysis of studies involving 4582 tumor patients demonstrated that a high CRP/albumin ratio is associated with a worse survival in various cancers and that this association is consistently significant independent of the cutoff value, cutoff value selection, treatment method, country, sample size, stage and cancer type.[13] Recently, a cross-sectional study explored the association between the CRP/albumin ratio and clinical outcomes in terminal cancer and non-cancer patients.[14] This study suggested that the CRP/albumin ratio was beneficial in the prediction of short-term survival within two weeks. Whether this association applies to terminal cancer patients with a longer survival is unclear. Moreover, few studies have focused on the dose-response association of the CRP/albumin ratio and mortality in terminal cancer patients. Thus, we aimed to elucidate the association between mortality and the CRP/albumin levels in terminal cancer patients using a longitudinal analysis.

2. Methods

2.1. Study design and patient selection

We retrospectively exploited data from electronic medical records (EMRs), including CRP, albumin and other clinical variables. The EMR data were obtained from an observational, longitudinal database at Yeouido St. Mary's Hospital; this database has been previously described in detail.[15] This study was approved by the Institutional Review Board (IRB) of Yeouido St. Mary's Hospital (approval number: SC18RESI008; approval date: July 24, 2018). As this study was a retrospective review of EMRs, the requirement for informed consent was waived by the IRB.

In total, 435 inpatients with terminal cancer admitted between October 8, 2015 and January 17, 2018 were screened and considered eligible for this study if they were aged older than 20 years, they and/or their families had been informed of their illness being terminal cancer that has progressed to the end stage, and no curative treatment could be provided by their physicians. All patients signed a DNR (do-not-resuscitate) order and accepted a referral to the palliative care ward. The exclusion criteria were as follows: death within a day of admission and a blood test not being conducted. Therefore, 382 inpatients (87.8%) with terminal cancer were enrolled in the study (Fig. 1).

2.2. Data collection

The patients' clinical information, including age, sex, Eastern Cooperative Oncology Group (ECOG) status, survival status, survival days, primary cancer site, systolic blood pressure (SBP), existence of dyspnea, metastasis and serum levels of CRP, albumin, neutrophil and lymphocyte fractions (%), lactate dehydrogenase (LDH), hemoglobin, creatinine and sodium, was collected from EMRs. The CRP/albumin ratio and neutrophil/lymphocyte ratio (NLR) were calculated, and both ratios were derived based on the same blood sampling. We defined the survival time as the period from the day of evaluation to the day of death.

2.3. Statistical analyses

The continuous variables are expressed as medians with interquartile ranges, and the categorical variables are expressed as counts and percentages. The cutoff values of the CRP/albumin ratio and NLR were analyzed by a survival significance analysis using Cutoff Finder.[16] A receiver operating characteristic (ROC) curve was generated by plotting the sensitivity value against the false-positive rate (1-specificity). We assessed the predictive value of life expectancy < 30 days based on 2×2 tables. The patients were also stratified into tertiles (tertile 1, 0.077×10^{-4} to less than 12.7×10^{-4}; tertile 2, 12.9×10^{-4} to less than 41.81×10^{-4}; and tertile 3, 42.17×10^{-4} to less than 194.4×10^{-4}) based on the CRP/albumin ratio distribution. A Kaplan-Meier analysis with a log-rank test was used to assess the differences in the median survival time among the groups. The individual effect of each variable on the association with mortality was first tested in a univariate Cox regression model. Then, all covariates with $P < .1$ were tested in a multivariate Cox proportional hazards model. Notably, CRP, albumin and the CRP/albumin ratio were

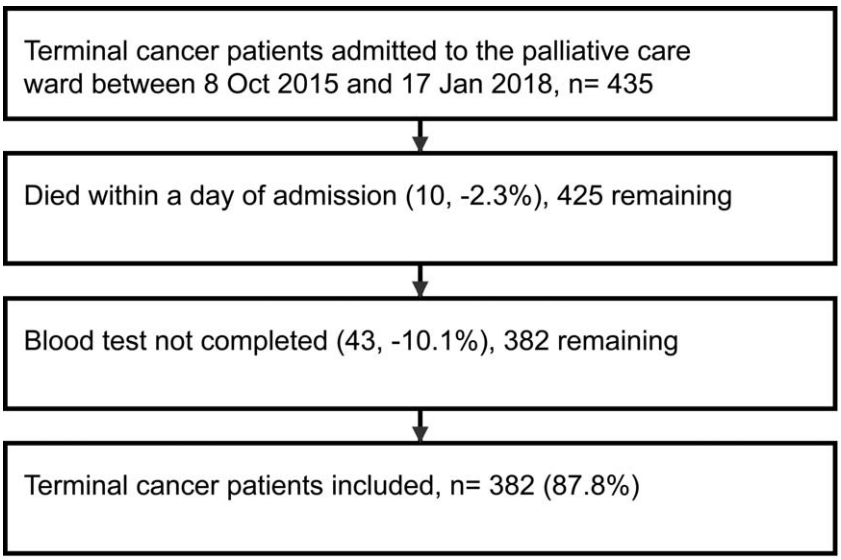

Figure 1. Flow chart of the participant selection process.

separately evaluated in a multivariate Cox proportional hazards model. A log-log plot was used to determine whether the Cox proportional hazards assumptions of each variable were confirmed. If a violation of the proportional hazards assumption was observed, a time-varying coefficient was created for the covariate. We performed a dose-response analysis using the restricted cubic splines approach to further explore whether the associations between the serum CRP/albumin levels and risk or death were linear or nonlinear (STATA mkspline command). P values $<.05$ were considered statistically significant. The statistical analyses were performed using STATA 15.0 (StataCorp, College Station, TX).

3. Results

Using Cutoff Finder in the survival significance analysis, we classified the patients as having a low CRP/albumin ratio (n = 270, 70.68%) or a high CRP/albumin ratio (n = 112, 29.32%) using the cutoff value of 48.53×10^{-4} (Supplementary Figure 1A, http://links.lww.com/MD/D868: distribution of the CRP/albumin ratios in all 382 patients; Supplementary Fig. 1B, http://links.lww.com/MD/D868: hazard ratios of overall survival independent of the cutoff point for CRP/albumin in patients with terminal cancer). Regarding the NLR, a cutoff of 4.104 was found to be optimal for overall survival using a ROC curve analysis, and this value also yielded the lowest log-rank P value ($P<.05$) in the survival analysis. The patients were divided into the following two groups based on this cutoff value (Table 1): NLR < 4.104 (n = 73, 19.11%) and NLR ≥ 4.104 (n = 309, 80.89%). Using a cutoff value of 48.53×10^{-4} for the CRP/albumin ratio, life expectancy was assuming to be < 30 days, yielding an area under the curve (AUC) of 0.641 (95% CI 0.602–0.680), a sensitivity of 36.5% (95% CI 30.9%–42.4%), a specificity of 91.8% (95% CI, 84.4–96.4%), a positive predictive value (PPV) of 92.9% (95% CI, 86.4%–96.9%), a negative predictive value of 33.0% (95% CI, 27.4–38.9%), a positive likelihood ratio of 4.42 (95% CI, 2.24–8.74), and a negative likelihood ratio of 0.692 (95% CI, 0.622–0.770).

Of the 382 patients, 295 (77.23%) died within 119 days of admission to the palliative care ward. The overall median survival was 21 days. Table 1 shows the clinical characteristics of the patients included in the study and the median survival according to their characteristics. The median age was 70 years (IQR, 19 years), and 191 (50.00%) patients were male. The most common cancer sites were gastrointestinal organs (n = 219, 57.33%), followed by thoracic neoplasms (n = 81, 21.20%). A performance status of ECOG ≥ 3 was observed in 260 patients (68.6%). Dyspnea was observed in 132 patients (34.55%). Metastasis was observed in 328 patients (85.86%). The median systolic pressure was 120 mmHg. In contrast to the patients with a low CRP/albumin ratio, the patients with a high CRP/albumin ratio had a shorter median survival time (12 vs 27 days, $P<.001$). Additionally, the other factors significantly associated with a shorter overall survival included a high NLR, ECOG status, albumin, CRP, LDH and existence of dyspnea. However, factors, including age, sex, primary cancer site, metastasis, SBP, creatinine, serum sodium and hemoglobin, were not significantly associated with overall survival.

In the univariate regression analyses (Table 2), the CRP/albumin ratio was significantly associated with mortality in the terminal cancer patients ($P<.001$), but age, sex, primary cancer site, SBP, metastasis, creatinine and hemoglobin were not associated with mortality. The other factors associated with mortality included the ECOG status ($P=.013$), dyspnea ($P<.001$), CRP ($P<.001$), albumin ($P<.001$), LDH ($P=.001$), serum sodium ($P=.003$) and NLR ($P<.001$).

Table 1

Median survival time by demographic and clinical characteristics.

Variables	Cases	Proportion	Median survival	*P
	n	%	days (95% CI)	
Age; median, IQR (year)	70, 19			
<70	191	50.00	20 (15–25)	.275
≥70	191	50.00	22 (18–26)	
Sex				
Female	187	48.95	22 (17–26)	.332
Male	195	51.05	21 (16–25)	
Primary cancer, n %				
Gastrointestinal cancer	219	57.33	19 (16–24)	.991
Thoracic neoplasm	81	21.20	24 (13–29)	
Urogenital neoplasm	55	14.40	21 (15–26)	
Head and neck neoplasm	10	2.62	24 (14– —)	
Hematologic malignancy	9	2.36	24 (7–37)	
Other cancer	8	2.09	20 (5– —)	
ECOG				
<3	122	31.94	26 (23–31)	.011
≥3	260	68.06	19 (16–21)	
Dyspnea				
No	250	65.45	24 (21–29)	<.001
Yes	132	34.55	16 (11–18)	
Metastasis				
No	54	14.14	28 (21–34)	.054
Yes	328	85.86	20 (16–23)	
SBP, median, IQR (mmHg)	120, 27			
<120	210	54.97	23 (17–26)	.533
≥120	172	45.03	21 (16–24)	
†CRP, median, IQR (mg/L)	66.9, 107.9			
<94.05	233	60.99	29 (24–33)	<.001
≥94.05	149	39.01	13 (11–16)	
†Albumin, median, IQR (g/dL)	2.83, 0.82			
<2.715	168	43.98	14 (12–16)	<.001
≥2.715	214	56.02	28 (25– 32)	
†CRP/albumin ratio				
Median, IQR ($\times 10^{-4}$)	25, 45.3			
<48.53	270	70.68	27 (24–31)	<.001
≥48.53	112	29.32	12 (9–15)	
†NLR, median, IQR	8.58, 9.37			
<4.104	73	19.11	33 (28–38)	<.001
≥4.104	309	80.89	18 (15–21)	
LDH, median, IQR, (IU/L)	644.5, 623			
<644.5	191	50.00	26 (21–30)	.001
≥644.5	191	50.00	18 (14–22)	
Creatinine, median, IQR (mg/dL)	0.71, 0.63			
<0.71	193	50.52	21 (17–24)	.614
≥0.71	189	49.48	21 (16–26)	
Sodium, median, IQR (mmol/L)	132, 7			
<132	194	50.79	18 (14–22)	.299
≥132	188	49.21	24 (20–27)	
Hemoglobin, median, IQR (g/dL)	10.4, 2.7			
<10.4	196	51.31	21 (17–24)	.647
≥10.4	186	48.69	22 (16–26)	

CI = confidence interval, ECOG = Eastern Cooperative Oncology Group, HR = hazard ratio, IQR = interquartile ratio, NLR = neutrophil to lymphocyte ratio, SBP = systolic blood pressure.

* P value by a log rank test using the Kaplan-Meier method.

† Optimal cutoff value with a minimum P value using a log-rank test (http://molpath.charite.de/cutoff/).

Table 2

Univariate Cox regression analysis of mortality in patients with terminal cancer.

Variables	HR	95% CI	*P*
Age, year			
<70	1		
≥70	0.88	0.70–1.11	.285
Sex			
Female	1		
Male	1.12	0.89–1.41	.342
Primary cancer site			
Gastrointestinal cancer	1		
Thoracic neoplasm	1.01	0.77–1.34	.924
Urogenital neoplasm	1.00	0.70–1.43	.989
Head and neck neoplasm	0.84	0.40–1.80	.645
Hematologic malignancy	1.17	0.63–2.32	.646
Other cancer	0.92	0.42–1.95	.818
ECOG			
<3	1		
≥3	1.40	1.07–1.83	.013
Dyspnea			
No	1		
Yes	1.58	1.25–2.00	<.001
Metastasis			
No	1		
Yes	1.37	0.99–1.90	.06
SBP (mmHg)			
<120	1		
≥120	1.07	0.85–1.35	.542
*CRP (mg/L)			
<94.05	1		
≥94.05	3.01	2.07–4.38	<.001
Albumin (g/dL)			
≥2.715	1		
<2.715	1.97	1.56–2.48	<.001
*CRP/Albumin ratio ($\times 10^{-4}$)			
<48.53	1		
≥48.53	3.17	2.17–4.63	<.001
Tertile 1	1		
Tertile 2	2.20	1.51–3.21	<.001
Tertile 3	4.63	2.88–7.44	<.001
NLR			
<4.104	1		
≥4.104	1.97	1.43–2.71	<.001
LDH (IU/L)			
<644.5	1		
≥644.5	1.46	1.16–1.84	.001
Creatinine (mg/dL)			
<0.71	1		
≥0.71	0.96	0.76–1.21	.716
*Serum sodium (mmol/L)			
≥132	1		
<132	1.76	1.21–2.56	.003
Hemoglobin (g/dL)			
<10.4	1		
≥10.4	0.95	0.75–1.20	.654

tertile 1, 0.077×10^{-4} to less than 12.7×10^{-4}; tertile 2, 12.9×10^{-4} to less than 41.81×10^{-4}; and tertile 3, 42.17×10^{-4} to less than 194.4×10^{-4}.

CI = confidence interval, CRP = C-reactive protein, ECOG = Eastern Cooperative Oncology Group, HR = hazard ratio, LDH = lactate dehydrogenase, NLR = neutrophil to lymphocyte ratio.

* Proportional hazards assumption not met: a time-varying coefficient was produced.

The variables that were significant ($P < .1$) in the univariate analysis were included in the multivariate Cox regression analysis of mortality (Table 3). The multivariate analysis revealed that the CRP/albumin ratio was an independent predictor of mortality.

Table 3

Multivariate Cox regression analysis of mortality in patients with terminal cancer.

	Model 1			Model 2		
Variables	HR	95% CI	*P* value	HR	95% CI	*P* value
ECOG						
<3	1			1		
≥3	1.29	0.98–1.69	.073	1.31	1.00–1.72	.055
Dyspnea						
No				1		
Yes	1.31	1.02–1.68	.031	1.27	0.99–1.62	.058
Metastasis						
No	1			1		
Yes	1.14	0.82–1.59	.443	1.09	0.78–1.53	.604
LDH (IU/L)						
<644.5	1					
≥644.5	1.27	1.00–1.61	.055	1.27	1.00–1.62	.048
*Serum sodium (mmol/L)						
≥132	1					
<132	1.46	1.00–2.13	.050	1.44	0.98–2.10	.062
*CRP/Albumin ratio ($\times 10^{-4}$)						
<48.53	1					
≥48.53	2.68	1.82–3.93	<.001			
Tertile 1				1		
Tertile 2				1.91	1.31–2.82	.001
Tertile 3				3.66	2.24–5.97	<.001
NLR						
<4.104	1			1		
≥4.104	1.63	1.17–2.27	.004	2.42	1.08–2.14	.016

Tertile 1, 0.077×10^{-4} to less than 12.7×10^{-4}; tertile 2, 12.9×10^{-4} to less than 41.81×10^{-4}; and tertile 3, 42.17×10^{-4} to less than 194.4×10^{-4}.

CI = confidence interval, CRP = C-reactive protein, ECOG = Eastern Cooperative Oncology Group, HR = hazard ratio, NLR = neutrophil to lymphocyte ratio.

* Proportional hazards assumption not met: a time-varying coefficient was produced.

The patients with a high CRP/albumin ratio ($\geq 48.53 \times 10^{-4}$) had a 2.7-fold higher risk of death than those with a low CRP/albumin ratio ($< 48.53 \times 10^{-4}$) in Model 1 (HR = 2.68, 95% CI = 1.82–3.93; Fig. 2A). The NLR ($P = .004$) and dyspnea ($P = .031$) were also independently associated with mortality. Using the first tertile of the CRP/albumin ratio as a reference in Model 2, the HR of the patients in the second and third tertiles of the CRP/albumin ratio were 1.91 (95% CI, 1.31–2.82) and 3.66 (95% CI, 2.24–5.97), respectively, indicating that a higher CRP/albumin ratio is independently associated with an increased risk of death (Fig. 2B). The NLR ($P = .016$) and LDH ($P = .048$) were also independently associated with mortality. Moreover, other factors, such as ECOG, metastasis and serum sodium, were not related to the risk of mortality in this analysis. In addition, the multivariate analysis showed that CRP and albumin were significantly associated with mortality (Model 3, Supplementary Table 1, http://links.lww.com/MD/D868). The HRs of high CRP (≥94.05 mg/L) and low albumin (<2.715 g/dL) were 2.15 (95% CI, 1.44–3.20) and 1.53 (95% CI, 1.18–1.97), respectively.

The cubic spline curves showed a gradual increase in the risk of death as the CRP/albumin ratio increased, but there was no statistically significant nonlinearity between the CRP/albumin ratio and the risk of death (*P* for nonlinearity = .092). However, there was a significant linear relationship between the risk of death and the CRP/albumin ratio (P for linearity = 0.011). In the linear fitted model, compared with the lowest CRP/albumin ratio (0.05×10^{-4}), the estimated HRs were 1.14 (95% CI, 1.10–1.18) for 10×10^{-4}, 1.49 (95% CI, 1.35–1.65) for 30×10^{-4}, 2.22

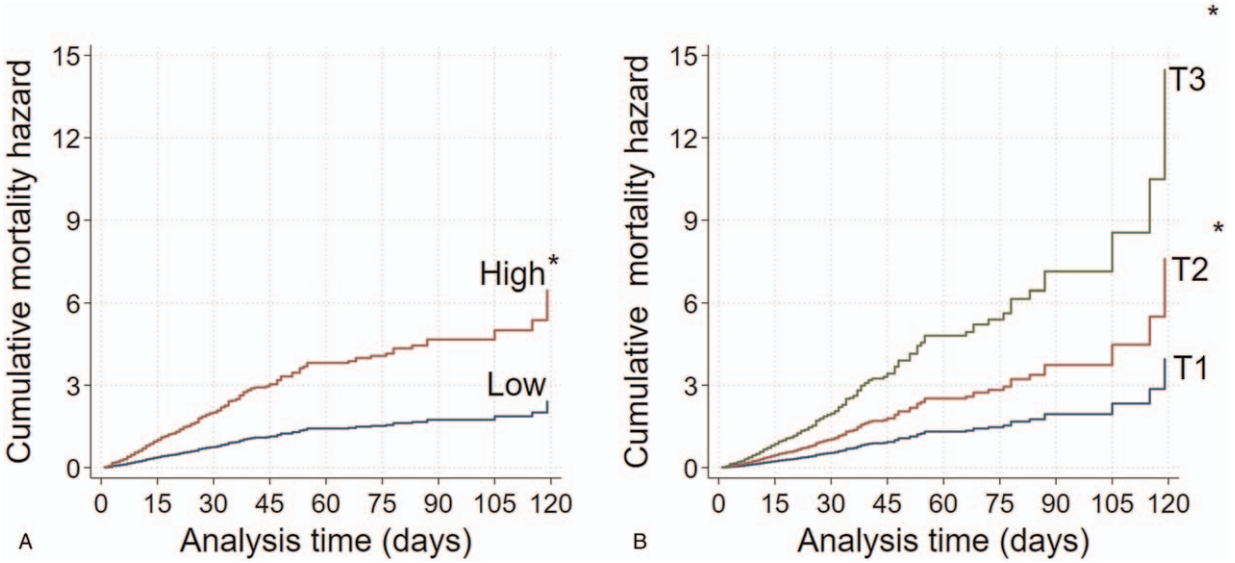

Figure 2. Cumulative mortality hazard plot over time (in days) based on the CRP/albumin ratio. (A) Comparison of overall mortality in patients with a high CRP/albumin ratio vs. low CRP/albumin ratio. (B) Comparison of overall mortality in patients according to the tertiles of the CRP/albumin ratio. All analyses were adjusted for dyspnea, metastasis, the ECOG status, serum sodium, LDH and the neutrophil/lymphocyte ratio. The HR of a high CRP/albumin ratio was significantly higher than that of a low CRP/albumin ratio (HR = 2.68, $P < .001$). The cumulative mortality hazard was significantly high in the highest tertile ($P < .001$). The HR of the highest tertile was significantly higher than that of the lowest tertile (HR = 2.24, $P < .001$). T1, 0.077×10^{-4} to less than 12.7×10^{-4}; T2, 12.9×10^{-4} to less than 41.81×10^{-4}; and T3, 42.17×10^{-4} to less than 194.4×10^{-4}. CRP/albumin ratio is treated as a time-varying covariate in this analysis. ECOG = Eastern Cooperative Oncology Group, T1 = tertile 1, T2 = tertile 2, T3 = tertile 3. $^{*}P < .001$ by Wald test.

(95% CI, 1.81–2.72) for 60×10^{-4}, 3.77 (95% CI, 2.69–5.30) for 100×10^{-4}, and 7.34 (95% CI, 4.42–12.20) for 150×10^{-4} (Fig. 3).

In a time-dependent Cox model, after adjustment for ECOG, dyspnea, metastasis, serum sodium, NLR, and LDH, the hazard plot for the patients with a high CRP/albumin ratio ($\geq 48.53 \times 10^{-4}$) compared with the patients with a low CRP/albumin ratio ($< 48.53 \times 10^{-4}$) showed a flat L-shape with an inflection point approximately 15 days after hospitalization (Fig. 4). The estimated HRs were 3.02 (95% CI, 1.87–4.88) at 3 days, 2.06 (95% CI, 1.58–2.69) at 10 days, 1.64 (95% CI, 1.22–2.22) at 20 days, 1.45 (95% CI, 1.01–2.09) at 30 days, 1.12 (95% CI, 0.71–1.97) at 60 days and 1.04 (95% CI, 0.57–1.93) at 90 days.

4. Discussion

The serum CRP/albumin ratio at admission to palliative care was a simple biomarker for predicting the risk of mortality in terminal

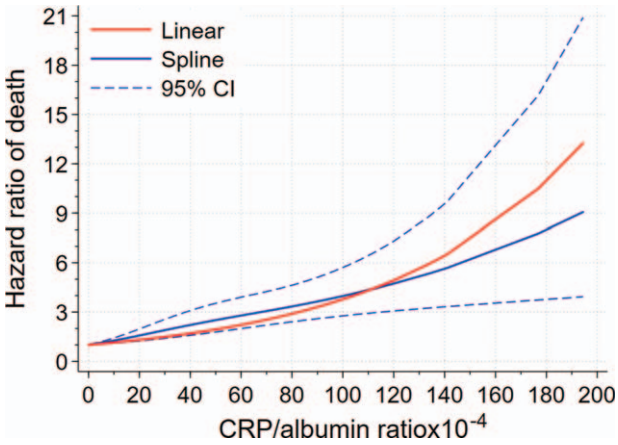

Figure 3. Dose-response relationship between the serum CRP/albumin ratio and hazard ratio (HR) of death estimated by a Cox-proportional hazards regression. The blue solid and dashed lines represent the estimated HRs and their 95% confidence intervals using a restricted cubic spline model (P for nonlinearity = .092). The red solid line represents the estimated HRs using a linear model (P for linearity = .011).

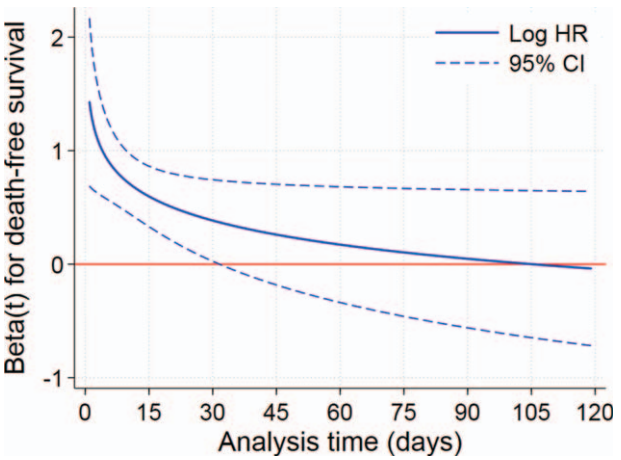

Figure 4. Plots of the hazard functions for the terminal cancer patient after hospitalization. The estimated time dependent Beta(t) coefficient for the patients with high CRP/albumin ratio ($\geq 48.53 \times 10^{-4}$) compared with the patients with the low CRP/albumin ($< 48.53 \times 10^{-4}$) from a Cox model after adjustment (ECOG, metastasis, dyspnea, NLR, serum sodium, and LDH). The solid blue curve represents estimates the log hazard ratio for mortality free survival. The blue dashed line shows the 95% CI around the regression line. The red solid line indicates a reference line. CRP = C-reactive protein, ECOG = Eastern Cooperative Oncology Group, HR = hazard ratio, LDH = lactate dehydrogenase, NLR = neutrophil to lymphocyte ratio.

cancer patients within 119 days of follow-up. The serum levels of the CRP/albumin ratio measured at admission were associated with the risk of death in terminal cancer patients. The serum CRP/albumin ratio measured at admission showed a linear dose-response relationship with the risk of death in terminal cancer patients. Notably, the results remained essentially unchanged after controlling for potential confounding factors, such as the NLR, ECOG, dyspnea, metastasis, serum sodium and LDH. Therefore, these data suggest that the CRP/albumin ratio could be an independent biomarker for predicting death in terminal cancer patients admitted to a hospital for palliative care. However, the overall median survival of the terminal cancer patients was 21 days. The relationship between a high CRP/albumin ratio and poor survival was a flat L-shape for survival time with an inflection point at approximately 15 days, while it was not significant in terminal cancer patients surviving beyond 30 days. These findings are consistent with a previously reported finding linking the CRP/albumin ratio to short-term survival within two weeks in cancer and noncancer patients.[14] In addition, we observed that the CRP/albumin ratio was a useful independent predictor of the short-term survival prognosis within 30 days in terminal cancer patients.

Several mechanisms might help explain the association between high levels of CRP to albumin ratio and the shortened survival in terminal cancer patients.[12] Proinflammatory cytokines, such as interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), can induce CRP production in the liver and contribute to systemic inflammation, which can lead to the gradual loss of important protein components in the body and subsequent death in cancer patients.[17] A chronic systemic inflammatory response results in the clinical features of cancer cachexia, that is, the progressive loss of weight.[18] The serum albumin concentration is negatively correlated with weight loss, while the serum CRP concentration is known to be positively correlated with weight loss.[12] Hypoalbuminemia has been suggested to predict the progressive decline of patients with advanced cancer.[12,18] The serum albumin levels at later stages of tumorigenesis could be significantly decreased by TNF-induced increases in the permeability of the microvasculature and the suppression of albumin synthesis induced by IL-I and IL-6, whereas no or slight hypoalbuminemia occurs at the beginning of the disease.[12,13] Serum CRP levels have been associated with progressive stages of cancer and terminal cancer patients.[10,17] The higher the tumor stage, the greater the inflammatory response, and the higher the serum CRP levels.[9] These results support the notion that terminal cancer is related to a systemic inflammatory response and malnutrition, resulting in the death of the patient. Additionally, terminal cancer patients lack sufficient metabolic capability to respond to anti-inflammatory drugs and nutritional supplementation due to the spread of the disease state and multi-organ dysfunction.

Several previous meta-analyses investigating the cutoff values of the CRP/albumin ratio in relation to the prognosis of patients reported that the cutoff values differed among studies, thus reflecting differences in the characteristics of the patients across studies.[13,19,20] In this study, we evaluated the CRP/albumin ratio as a prognosis index of survival in terminal cancer inpatients. The 30-day mortality prediction by a CRP/albumin ratio cutoff value of 48.53×10^{-4} is considered to have moderate accuracy with an AUC of 0.641 according to a ROC analysis and a PPV of 92.9%. Further investigation is needed to clarify the optimal cutoff values of the serum CRP/albumin ratio for predicting death in terminal cancer patients in various settings, such as hospitalization, home and consultation-based palliative care. The present analysis was not conducted separately using training and test datasets. Given that a general cutoff value for the CRP/albumin ratio has not been previously determined, we concluded that it could be better to present data cutoff values in many patients. Thus, this study focuses on presenting hospital data cutoff values as a training data set.

The Glasgow prognostic score (GPS) and modified GPS, which merges the elevated level of CRP (>1.0 mg/dL) and the lowered level of albumin (<3.5 g/dL), are prognostic scores for cancer patients.[21–23] However, most patients in the present study had high levels of CRP and low levels of albumin (CRP ≥ 1 mg/dL, n = 373, 97.64%; albumin < 3.5 g/dL, n = 329, 86.13%; Supplementary Table 2, http://links.lww.com/MD/D868). Thus, the two prognostic scores might be inappropriate because terminal cancer inpatients who are no longer receiving curative treatment are in a severe condition approaching death. In contrast, the CRP/albumin ratio is based on the levels of CRP and albumin, resulting in a continuous value; thus, this ratio can reflect the inflammatory and nutritional status of patients at all stages of cancer. The plausible mechanism of the independent value of the CRP/albumin ratio in terminal cancer is likely to be complex. CRP and albumin can be considered valid markers of systemic inflammation and components of the criteria for cancer cachexia.[18] In a systematic review, serum CRP and albumin were reported to have prognostic values of the systemic inflammatory response in patients with advanced cancer.[17] It may be possible to combine CRP and albumin into a single index to predict death in terminal cancer patients. Furthermore, the CRP/albumin ratio can be calibrated based on how well the predicted probability of survival based on this prognostic model matches real data.[24]

This study was applied only in terminal cancer patients at a single palliative care facility and is not applicable to all terminally ill patients. We excluded 10 (2.3%) patients who died within a day of admission to avoid the impact of left censored data and 43 (10.1%) patients who had missing CRP and albumin data, which could have affected our outcome regarding the CRP/albumin ratio. Nevertheless, the present study provides insight as this study is the first to analyze the dose-response relationship between the CRP/albumin ratio and mortality in terminal cancer inpatients. In conclusion, this study demonstrated that high levels of the CRP/albumin ratio are significantly and independently associated with the risk of mortality in terminal cancer patients hospitalized for palliative care.

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