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C-Reactive Protein: A Biomarker for Mortality Assessment in Cancer-Related Infections

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ABSTRACT

Introduction: Infection is a common complication in cancer patients. Plasma C-reactive protein (CRP) levels can be used to assess disease activity in inflammatory and infectious conditions. This study aimed to determine the role of CRP level in predicting mortality in patients with cancer and infectious complications.
Methods: This was a prospective study of solid and hematological cancer patients over 18 years of age undergoing hospital treatment. We used the Kaplan-Meier curve to obtain the median and overall survival. Cox regression analysis was used to determine the hazard ratio (HR) of CRP level in predicting mortality.
Results: This study encompassed 40 participants. Analysis utilizing Kaplan-Meier curves demonstrated increased mortality among individuals with elevated C-reactive protein (CRP) concentrations compared to those with lower levels. The risk of death for patients with high CRP was 11.07 times greater (95% confidence interval (CI) 3.13 – 39.10; p<0.001). Subsequent to adjusting for other factors in a multivariate analysis, CRP levels exhibited an adjusted hazard ratio of 2.00 (95% CI 1.33 – 11.98; p=0.048).
Discussion: Examining CRP levels at the time of diagnosis not only has a role as an inflammatory biomarker but can also help clinicians determine the severity of infection.
Conclusion: The mortality risk in cancer patients experiencing infectious complications can be predicted using plasma CRP measurements.

Keywords: C-reactive protein, cancer, infection, mortality.

INTRODUCTION

Infection is a common cause of mortality in cancer patients. The mortality rate due to infection in cancer patients is approximately 60%. A retrospective study of 151,440 patients with cancer found that pneumonia and sepsis were the leading causes of infection-related mortality in the last 40 years. Prostate and breast cancers are the most common cancers associated with infectious complications. The highest incidence of septicemia is observed in hematological cancers.[1] A study of 496 solid and hematological cancer patients found that gram-negative bacteria caused 72.8% of infections, with a mortality rate of 22%. However, it can reach 70% when patients do not receive adequate antibiotics.[2]

C-reactive protein (CRP) is an acute-phase protein whose levels increase in the plasma in response to infection, inflammation,

malignancy, and tissue damage. In clinical practice, examination of plasma CRP levels is often used to diagnose and assess disease activity in inflammatory and infectious conditions.[3,4] Hepatocytes synthesize CRP, the transcription of which is regulated by inflammatory cytokines such as interleukin (IL)-6 and IL-1. Plasma CRP concentrations increase within six hours after acute stimuli such as infection and inflammation. The role of CRP in infection is yet to be fully understood. C-reactive protein can bind to the phospholipid components of microorganisms and facilitate phagocytosis by macrophages.[3]

Increased plasma CRP levels in malignancies are associated with larger tumor sizes and distant metastases.[5] Plasma CRP levels are associated with poor prognosis in solid cancers, including non-squamous lung cell carcinoma (NSLCC),[6] small cell lung cancer,[7] pancreatic neuroendocrine neoplasia,[8,9] colorectal cancer,[10] head and neck squamous cell carcinoma,[11] and osteosarcoma.[12] Plasma CRP levels can also predict mortality in hematologic cancers such as multiple myeloma,[13] diffuse large B-cell lymphoma (DLBCL),[14,15] classical Hodgkin's lymphoma (HL),[16] and primary central nervous system lymphoma (PCNSL).[17] Inflammatory factors, such as CRP, have significant clinical value in assessing the severity and prognosis.[18] High levels of C-reactive protein are a significant risk factor for mortality in patients with infectious complications.[19-21]

This study aimed to examine the correlation between C-reactive protein (CRP) levels and survival rates, with the objective of establishing this biomarker as a potential indicator of mortality risk in cancer patients experiencing infectious complications.

MATERIALS & METHODS

Study design

This prospective study aimed to determine the differences in mortality based on CRP levels at the 28-day follow-up. Sampling was performed at Professor Ngoerah Hospital from June 2022 to January 2023 using consecutive sampling techniques. Patients with autoimmune diseases, steroid or immunosuppressant therapy, liver cirrhosis, end-stage chronic kidney disease, pregnancy, and mortality not related to infectious complications were excluded from this study. After blood sampling, the patient was treated according to the standard treatment for infectious complications and underlying disease, followed by follow-up to determine mortality.

Sample collection

Upon admission, the patient provided blood specimens for analysis. Three milliliters of venous blood sample was placed in a sample tube and centrifuged. Plasma CRP levels were measured using the Human CRP CLIA Kit E-CL-H0043 reagent (Elabscience, United States) using the sandwich chemiluminescence immunoassay (CLIA) method. Plasma CRP levels were reported as mg/dL.

Data analysis

Plasma CRP levels were categorized as high if they were above the cut-off obtained through receiver operator curve (ROC) analysis and normal/low if they were below or equal. The median and overall survival based on CRP levels were obtained using Kaplan-Meier curve analysis. The log-rank test (Mantel-Cox) was used to compare the survival distributions of the two groups. Bivariate Cox regression analysis was used to obtain the hazard ratio (HR) and multivariate time-independent Cox regression analysis was used to determine the adjusted HR. All data were analyzed using SPSS version 25.0. Statistical significance was set at $p < 0.05$.

RESULTS

Sample characteristics

This study included 40 patients, 22 (55%) of whom had solid cancer. There were significant differences in CRP levels between survivors and non-survivors. Significant differences were also found

based on septic shock and hemoglobin and albumin levels (Table 1).

Table 1. Sample characteristics

	Median (interquartile range)		
Variable	**Survive (n = 23)**	**Non-survival (n = 17)**	**p-value**
Age, years	49.0 (18 - 84)	53.00 (22 - 83)	0.479
Age category			
<60 years	17 (73.9)	12 (70.6)	1,000
≥60 years old	6 (26.1)	5 (29.4)	
Sex, n (%)			
Female	12 (52.2)	6 (35.3)	0.348
Male	11 (47.8)	11 (64.7)	
Type of cancer, n (%)			
Solid cancer	14 (60.9)	8 (47.1)	0.523
Hematological cancer	9 (39.1)	9 (52.9)	
Underlying disease, n (%)			
Without underlying disease	16 (69.6)	10 (58.8)	0.521
With underlying disease	7 (30.4)	7 (41.2)	
Septic shock, n (%)			
Without septic shock	22 (95.7)	9 (52.9)	0.02*
With septic shock	1 (4.3)	8 (47.1)	
Hemoglobin level, gr/dL	9.96 (1.74)	8.16 (1.73)	0.002*
White blood cell counts, $x10^3\mu L$	11.24 (0.02 – 38.16)	3.05 (0.02 – 369.39)	0.547
Platelet count, $x10^3\mu L$	172 (3 – 693)	70 (4 – 378)	0.109
Albumin level, gr/dL	3.14 (1.91 – 4.40)	2.63 (1.41 – 3.53)	0.025*
Serum creatinine, mg/dL	0.91 (0.41 – 4.24)	1.46 (0.49 – 8.50)	0.061
CRP level, mg/dL	60.10 (31.04)	152.32 (65.85)	<0.001*

***: statistically significant**

Optimal cut-off plasma CRP levels in predicting mortality

We found an optimal cut-off plasma CRP level of >97.75 mg/dL in predicting mortality in cancer patients complicated by infection (Figure 1 and Table 2).

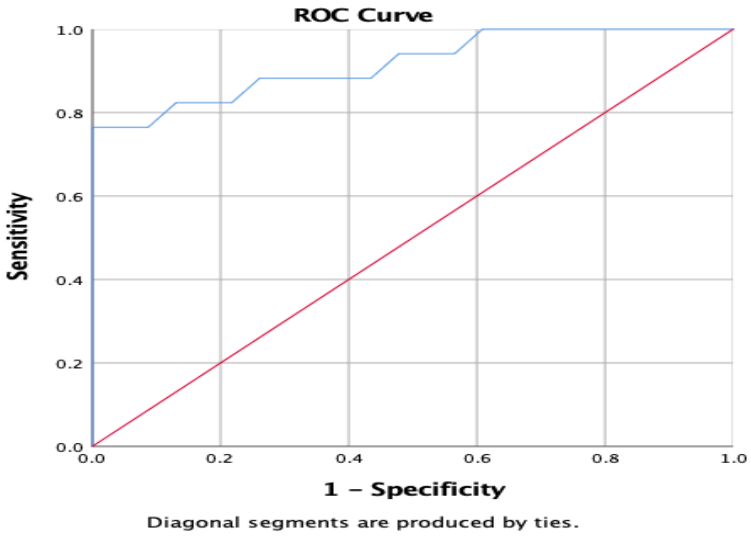

Figure 1. ROC analysis of CRP levels in predicting mortality in cancer patients with infectious complications

Table 2. The optimal cut-off value of CRP levels in predicting mortality in cancer patients with infectious complications

Variable	Cut-off	Sensitivity (%)	Specificity (%)	AUC	95%CI	p-value
CRP level (mg/dL)	>97.75	82.4	87.0	0.918	0.827 – 1.000	0.003*

***: statistically significant; AUC: area under the curve**

Differences in survival based on plasma CRP levels

Kaplan-Meier analysis demonstrated significant differences in survival patterns between individuals with elevated C-reactive protein (CRP) concentrations and those with CRP levels within or below the normal range. The median survival in subjects with high CRP levels was eight days, which means that mortality occurred in 50% of subjects within eight days of follow-up. In subjects with normal/low CRP levels, the mortality rate did not reach 50% at 28 days of follow-up. The overall survival (OS) in subjects with high CRP was 17.6%, while that in the normal/low CRP group was 87.0% (Figure 2 and Table 3).

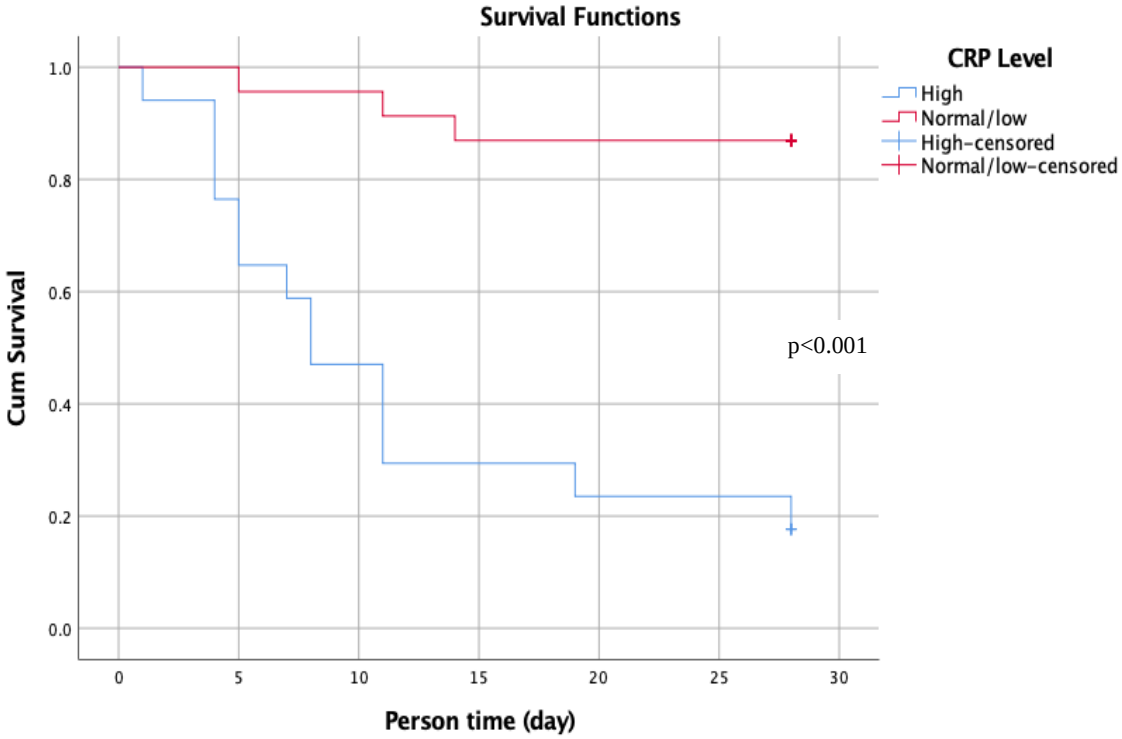

Figure 2. Differences in survival based on plasma CRP levels

Table 3. Differences in median and overall survival based on plasma CRP levels

CRP levels	95%CI	Median (days)	95%CI	Overall survival (%)
High	7.65 – 17.05	8.0	4.77 – 11.23	17.6
Normal/low	1.29 – 23.11	-	-	87.0
All subjects	16,743 – 23,257	-	-	57.5

Hazard ratio (HR) and Adjusted HR of plasma CRP levels

The hazard ratio for high plasma CRP levels is 11.07 (95% CI 3.13 – 39.10), p<0.001, on bivariate analysis. On multivariate analysis, high plasma CRP levels and septic shock remained statistically significant with an adjusted HR of 2.00 (95% CI 1.33 – 11.98), p=0.045, and 5.32 (95% CI 1.60 – 17.59), p=0.006) (Table 4).

Table 4. Hazard ratio (HR) and adjusted HR of plasma CRP levels

Variable	Hazard ratio (95% CI)	p-value	Adjusted HR (95% CI)	p-value
High CRP levels (>97.5 mg/dL)	11.07 (3.13 – 39.10)	<0.001*	2.00 (1.33 – 11.98)	0.048*
Septic shock	5.71 (2.14 – 15.26)	0.001*	5.32 (1.60 – 17.59)	0.006*
Low albumin levels (<3 gr/dL)	2.37 (0.93 – 7.50)	0.56	2.31 (0.66 – 8.10)	0.189
Low hemoglobin levels (<10 gr/dL)	5.77 (1.31 – 25.34)	0.02*	3.11 (0.59 -16.48)	0.182

***: statistically significant**

DISCUSSION

Our study found significant differences in CRP levels between survivors and non-survivors of cancer with infectious complications. These results are similar to those of Devran et al., who found significant differences in CRP levels between survivors and non-survivors.[21] Plasma CRP levels are a laboratory test that can be used to diagnose and monitor the severity of infections, such as lactate levels.[3] Plasma CRP levels are not only associated with the severity and extent of cancer but are also related to cancer pathogenesis.[4] Evidence shows that increased circulating CRP levels correlate with prognosis independent of tumor stage.[22] Plasma CRP level can be a prognostic indicator in solid[23] and hematologic[19] cancers. Changes in CRP levels observed during serial examinations are also valid prognostic indicator.[20,24]

In the survival analysis using the Kaplan-Meier curve, we found higher mortality in patients with high CRP levels than in those with normal or low CRP levels. These results are similar to Devran et al.'s study, which found that CRP levels >100 mg/dL were found to be a risk factor for mortality with an odds ratio (OR): 3.76, (95% CI 1.68-8.40, p <0.001).[21] High initial plasma CRP level is a significant risk factor for mortality in patients with cancer infectious complications.[19] Examining CRP levels at the time of diagnosis not only plays a role as an inflammatory biomarker but can also help clinicians determine the severity of infection and cancer progression so that it can guide the provision of therapy.[4] Mortality in patients with cancer complicated by infection can be reduced by early antibiotic therapy.[19] Plasma CRP level examination is suitable for clinical practice because it is a simple examination, provides fast results, and is inexpensive.

This study had several limitations, including its restriction to a single center and the lack of sequential measurements of plasma CRP levels to evaluate their association with mortality.

CONCLUSION

Cancer patients with infectious complications and high CRP levels have higher mortality rates than patients with normal or low CRP levels. The initial plasma CRP level can be used as a predictor of mortality in patients with cancer complicated by infection. Further multicenter prospective studies are required to confirm these findings.

Declaration by Authors

Ethical Approval: This study was approved by the Ethics Commission of the Faculty of Medicine, Udayana University (approval: 350/ UN14.2.2.VII.14/ LT/ 2022). The patients or their families voluntarily stated their willingness to participate in the study and signed informed consent forms.

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Conflict of Interest: The authors declare that they have no conflicts of interest.

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