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Research article

The value of C-reactive protein velocity (CRPv) on mortality in sepsis patients who are emergently hospitalized in the ICU: A retrospective single-center study

Ayşin Kılınç Toker [a,*], İlhami Çelik [a], Ayşe Turunç Özdemir [a], Hande Sağlam [a], Derya Koçer [b], Murat Eşlik [c], İbrahim Toker [c]

[a] Kayseri City Hospital, Department of Infectious Diseases and Clinical Microbiology, Kayseri, Turkiye
[b] Kayseri City Hospital, Department of Biochemistry, Kayseri, Turkiye
[c] Kayseri City Hospital, Department of Emergency Medicine, Kayseri, Turkiye

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ABSTRACT

Purpose: The C-reactive protein (CRP) velocity (CRPv) is an indicator of the change in CRP over time. In individuals with sepsis, the second values of CRP and CRPv have been shown to have more importance than the first CRP value measured at admission. This study examined the importance of CRPv for mortality among individuals who were hospitalized in the intensive care unit (ICU).

Methods: The study was conducted between January 2021 and December 2022. CRPv was calculated according to the change in the second CRP value compared to the first.

Results: The median age of the patients was 79 years (interquartile range (IQR), 69–85 years), and 53.2 % were male. The in-hospital mortality rate was 45.5 %. The presence of diabetes increased the odds of mortality by 2.17 times (confidence interval (CI): 1.06–4.4, p=0.032). Each increase in CRPv by 1 mg/dl/hour increased the odds of mortality by 1.07 times (CI: 1.01–1.14, p=0.015), while each one-point increase in the Sequential Organ Failure Assessment (SOFA) score increased the odds of mortality by 1.21 times (CI: 1.07–1.35, p=0.002). The SOFA score had the highest area under the curve (AUC) value for in-hospital mortality (AUC = 0.699 p=<0.001). When the SOFA was >7, its sensitivity in predicting mortality was 46.7 %, and its specificity was 85.1 %. The AUC value of CRPv in predicting mortality was 0.629 (p=0.006). When CRPv was >0.75, its sensitivity in predicting mortality was 68.2 %, and its specificity was 57 %.

Conclusion: CRPv performed well in predicting mortality and had satisfactory discriminative ability. Additionally, diabetes, SOFA score, and CRPv elevation were significant risk factors for mortality.

1. Introduction

Sepsis is a major cause of admission to the intensive care unit (ICU), and hospital mortality is approximately four times higher among patients with sepsis requiring intensive care compared to all septic patients [1]. Therefore, mortality risk stratification and

* Corresponding author.
E-mail addresses: dr.aysin@gmail.com (A. Kılınç Toker), ilhamicelik@hotmail.com (İ. Çelik), drayseturunc@gmail.com (A. Turunç Özdemir), handesglm94@gmail.com (H. Sağlam), ayder78@yahoo.com (D. Koçer), drmurateslik@gmail.com (M. Eşlik), ibrahimtoker9@gmail.com (İ. Toker).

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predictive biomarkers are needed for septic ICU patients. C-reactive protein (CRP) is an acute-phase reactant that was discovered in 1930 and has been widely used clinically in emergency departments (EDs) and ICUs to determine diagnoses, treatment response, disease severity, the need for intensive care, and short-term mortality [2,3]. Studies have shown that the initial CRP value alone is weak in predicting mortality, especially in the case of sepsis, and it has not been shown to have a cutoff value [3,4].

In a comprehensive study examining approximately 3000 patients diagnosed with sepsis, 17.5 % of the patients had an initial CRP value of <31.9 mg/L, and approximately one-fifth of them died within one week of hospitalization [5]. Because CRP is part of a dynamic and continuous inflammatory process, a single CRP measurement may lead to inaccurate or delayed treatment. It is essential to consider the CRP kinetics when determining the prognosis and treatment selection [6]. Another recent study showed that critically ill patients with sepsis and different trajectories of CRP had different in-hospital mortality rates [7].

The CRP velocity (CRPv) is calculated according to the change in the second CRP measurement compared to the first CRP measurement [8]. The importance of CRPv in terms of mortality has been investigated, especially in patients with ST-elevation myocardial infarction (STEMI), pneumonia, and bloodstream infection [9]. However, the importance of CRPv for mortality among patients with sepsis has yet to be investigated. We hypothesized that increased risk of in-hospital mortality may be associated with changes in the velocity of CRP over time in patients hospitalized in the ICU who were transferred from the emergency department (ED) due to sepsis may be an independent factor. We investigated the importance of CRPv in such patients regardless of whether the first CRP value was low or high.

1.1. Clinical importance

- Risk factors and predictors in ICU patients with sepsis are of great importance.
- CRP is a well-known and significant inflammatory biomarker that correlates with in-hospital mortality risk.
- CRPv in critically ill patients with sepsis might predict early clinical deterioration and mortality.

2. Methods

2.1. Study design and setting

This retrospective study was conducted in Kayseri City Hospital, a single-center tertiary care regional hospital. The patients examined were admitted to the ICU from the ED with a diagnosis of sepsis between January 2021 and December 2022. Patients were recruited consecutively. The study included patients whose first CRP value was taken for the first time upon admission to the ED and for a second time within the first 24 h after admission to the ICU. A total of 142 of 395 patients were excluded because their second CRP value was measured after 24 h, and 17 patients were excluded because the diagnosis of sepsis was unclear (Fig. 1).

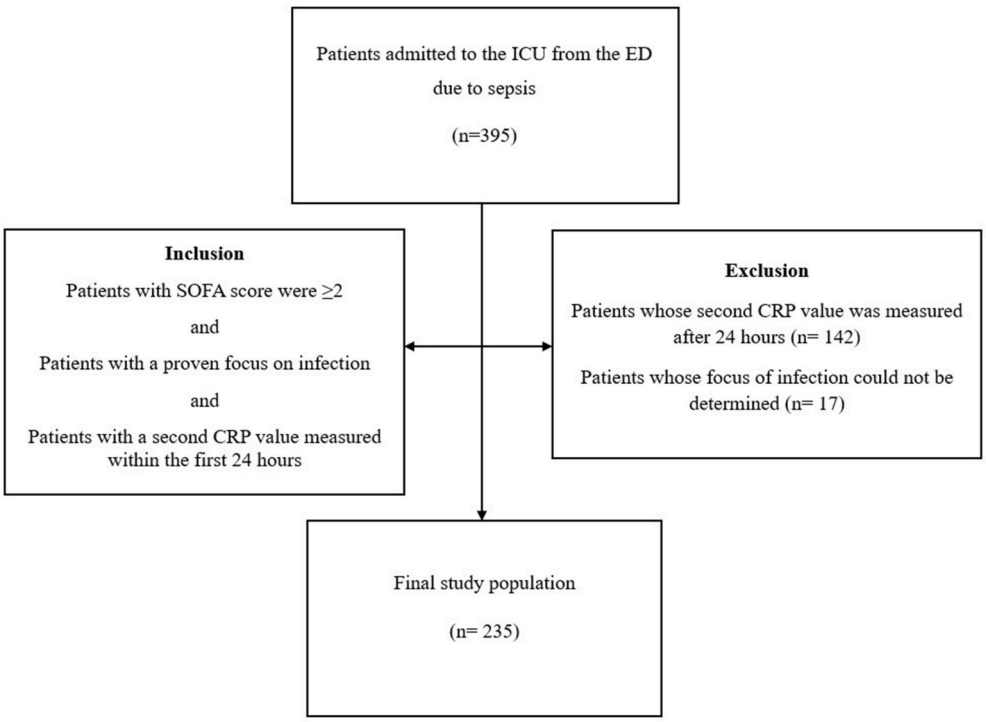

Fig. 1. Inclusion and exclusion flow chart.

According to the criteria of The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) published in 2016, a specialist in infectious diseases and microbiology diagnosed sepsis in patients who had a proven infection and a Sequential Organ Failure Assessment (SOFA) score of 2 or above [10]. The information recorded for the study comprised the patient's age, sex, comorbidities, Charlson Comorbidity Index, first and second CRP values, CRPv value, Acute Physiology and Chronic Health Evaluation (APACHE) II and SOFA scores, sources of infection, in-hospital mortality, and length of hospital.

2.2. CRPv and definition of sepsis

CRPv was calculated by dividing the difference in measurement between two values by the time difference in hours: (CRP1 - CRP2)/Δt. Sepsis was defined as life-threatening organ dysfunction resulting from inadequate host response to infection. In addition to proven infection, a SOFA score of two or higher was required for diagnosis [10].

2.3. Sample size

The sample size was computed using MedCalc software version 20 and the area under the receiver operating characteristic (ROC) curve (AUC) tab. Based on previous data, the type 1 error was selected as 0.01, the type 2 error was 0.10, the AUC was 0.72, the null hypothesis value was 0.5, and the mortality rate was 20 % [11]. Based on these values, the sample size was calculated as 210. In the study used as an example, CRP was investigated as a predictor of mortality among patients in the ICU with severe sepsis. The AUC of CRP measured at admission was 0.57, and the AUC of CRP measured on the third day was 0.72. Therefore, we estimated that the AUC of CRPv in our study could be close to 0.72 or higher.

2.4. Statistical analysis and ethics approval

Descriptive statistics are presented using numbers, percentages, the mean ± standard deviation, medians, interquartile ranges (IQRs), and minimum and maximum values. The distributions of continuous variables were assessed using the Shapiro–Wilk normality test. When comparing mortality between groups, an independent sample *t*-test was used if the data had a normal distribution, while the Mann–Whitney *U* test was used for non-normally distributed data. We compared categorical data using the chi-squared test, while risk factors for mortality were determined through multivariate binary logistic regression analysis, and the enter method was selected.

The mortality-prediction performance of continuous variables that were significant for mortality in the univariate analysis was evaluated by ROC curve analysis. Descriptive statistics included the AUC, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+), negative likelihood ratio (LR-), and 95 % confidence interval (CI). Results were considered significant in cases of $p < 0.05$. The Institutional Ethics Board of Kayseri City Hospital approved the study (Approval number: 17, decision date: 14.03.2024).

Table 1
The clinical characteristics of patients.

		In-hospital Mortality		
Variables	Total = 235	No = 128	Yes = 107	p
Age, year, median (IQR)	79 (69–85)	79 (69–85)	80 (69–85)	0,496[a]
Male	125 (53,2)	63 (49,2)	62 (57,9)	0,182
Female	110 (46,8)	65 (50,8)	45 (42,1)	
Charlson Comorbidity Index (IQR)	5 (4–7)	4 (3–6)	6 (4–8)	**<0,001**[a]
Comorbidities	174 (76,2)	89 (69,5)	90 (84,1)	**0,009**
HT	108 (46)	55 (43)	53 (49,5)	0,315
DM	83 (35,3)	37 (28,9)	46 (43)	**0,024**
CAD/CHF	60 (25,5)	29 (22,7)	31 (29)	0,269
CKD	49 (20,9)	25 (19,5)	24 (22,4)	0,586
COPD	42 (17,9)	28 (21,9)	14 (13,1)	0,080
Malignity	36 (15,3)	15 (11,7)	21 (19,6)	0,094
Trend of CRPv				
Increase	150 (63,8)	71 (55,5)	79 (73,8)	**0,004**
Decrease	85 (36,2)	57 (44,5)	28 (26,2)	
1st CRP, mg/dl	159 ± 101	155 ± 104	163 ± 99	0,577**
2nd CRP, mg/dl	179,5 ± 88	157,8 ± 71	205 ± 99	**<0,001****
CRPv, mg/dl/hour	1,19 ± 6,3	0,08 ± 5,3	2,53 ± 8,6	**0,003****
Apache 2 score	22 ± 8,7	19,4 ± 7,9	25,1 ± 8,6	**<0,001****
SOFA score	6,1 ± 3,4	5 ± 2,8	7,46 ± 3,7	**<0,001****

HT, hypertension; DM, diabetes mellitus; CAD, coroner artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic pulmonary disease; CRP, C-reactive protein; CRPv, CRP velocity; IQR, interquartile range; SOFA, Sequential Organ Failure Assessment; Apache 2, Acute Physiology and Chronic Health Evaluation 2.

[a] = Mann–Whitney *U* test, ** = The Independent Samples *t*-Test, Other P-values = Pearson's chi-squared test.

3. Results

We analyzed 235 ICU patients with sepsis, who had an average age of 79 years (IQR, 69–85 years) and comprised 53.2 % (n=125) males. The most common comorbidities were hypertension (46 %) and diabetes (35.3 %). The in-hospital mortality rate was 45.5 % (n = 107). The median length of stay in the hospital was 13 days (IQR, 7–20 days, min: 1 max: 78 days). The mean value of the first CRP measurement was 159 ± 101 mg/dl, and the second CRP measurement within 24 h was 179.5 ± 88 mg/dl. The mean CRPv was 1.19 ± 6.3 mg/dl/hour (Table 1). The primary reasons for sepsis were urinary tract infections, pneumonia, and soft tissue infections (Fig. 2).

The clinical characteristics of the patients were examined in terms of in-hospital mortality. There was a statistically significant difference in the Charlson Comorbidity Index, the presence of at least one comorbid disease, diabetes, the direction of CRPv, second CRP, CRPv, APACHE II score, and SOFA scores (p values < 0.001, 0.009, 0.024, 0.004, <0.001, 0.003, <0.001, and <0.001, respectively; Table 1). The multivariate binary logistic regression analysis evaluated risk factors affecting in-hospital mortality.

The variables that were found to be significant in univariate analyses were included in the multiple binary logistic regression model. The enter method was used to obtain the final model. The presence of diabetes, CRPv, and SOFA score were statistically significant risk factors for in-hospital mortality. A 2.17-fold increase in mortality odds was observed in the presence of diabetes (CI: 1.06–4.4, p=0.032). Each increase in CRPv of 1 mg/dl/hour increased the odds of mortality by 1.07 times (CI: 1.01–1.14, p=0.015), while each increase in SOFA score by 1 point increased the odds of mortality by 1.21 times (CI: 1.07–1.35, p=0.002; Table 2).

ROC analyses were performed on continuous variables that were found to be significant in univariate analyses in predicting mortality (second CRP, CRPv, APACHE II score, and SOFA score), and all variables were found to be statistically significant (p=0.006 for CRPv, other p values < 0.001). The SOFA score had the highest AUC of 0.699 (p < 0.001). When the SOFA score was >7, the sensitivity in predicting mortality was 46.7 %, the specificity was 85.1 %, the PPV was 72.5 %, and the NPV was 65.7 %.

The AUC of CRPv in predicting mortality was 0.629 (p = 0.006), and when CRPv was >0.75, the sensitivity was 68.2 %, the specificity was 57 %, PPV was 57 %, and NPV was 68.2 % (Table 3). In the pairwise comparison of ROC curves, there was no statistically significant difference between the variables (second CRP vs. CRPv p=0.866, second CRP vs. APACHE II p=0.289, second CRP vs. SOFA p=0.219, CRPv vs. APACHE II p=0.283, CRPv vs. SOFA p=0.204, APACHE II vs. SOFA p=0.716; Fig. 3).

4. Discussion

Two hundred thirty-five patients were examined; the median age was 79, and 53.2 % were male. The most common comorbidities were hypertension and diabetes. There was an essential difference in mortality regarding the Charlson Comorbidity Index, presence of at least one comorbidity, diabetes mellitus, direction of CRPv, second CRP, CRPv, APACHE 2, and SOFA scores. In our study, diabetes, CRPv, and SOFA score were significant risk factors for mortality. CRPv's sensitivity was 68.2 %, and specificity was 57 % in predicting mortality. It is well known that the incidence of infection and sepsis is higher among those with diabetes. Studies have found different results between diabetes and infection-related mortality. Some studies have observed that death due to sepsis increases in diabetic patients, while other studies have observed no difference, and some studies even reported fewer deaths [12]. A recent meta-analysis showed that diabetes is not associated with death in patients with sepsis but increases the risk of acute renal failure.

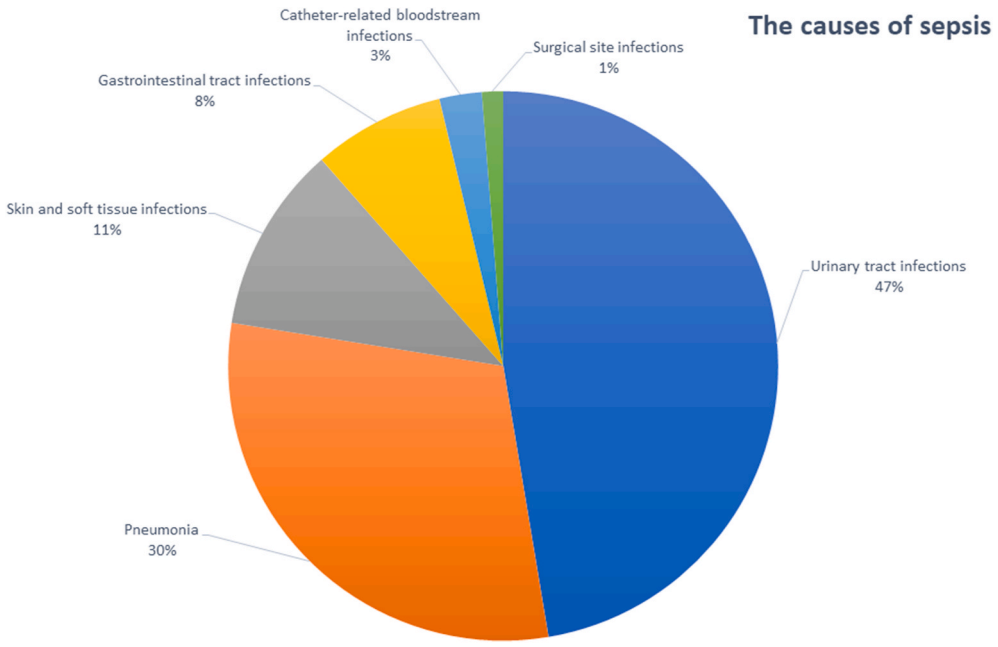

Fig. 2. The primary reasons for sepsis.

Table 2
Multivariate binary logistic regression analysis for in-hospital mortality.

	OR	95 %CI	p
Age	0,99	0,97- 1,02	0,824
Male	1,5	0,8- 2,79	0,194
Comorbidities	1,49	0,6- 3,5	0,369
Charlson Comorbidity Index	1,05	0,9- 1,2	0,405
Diabetes mellitus	2,17	1,06- 4,4	**0,032**
2nd CRP, mg/dl	1	0,99- 1	0,095
CRPv, mg/dl/hour	1,07	1,01- 1,14	**0,015**
Apache 2 score	1,04	0,99- 1,09	0,057
SOFA score	1,21	1,07- 1,35	**0,002**

CRP, C-reactive protein; CRPv, CRP velocity; SOFA, Sequential Organ Failure Assessment; Apache 2, Acute Physiology and Chronic Health Evaluation 2.

Table 3
ROC analysis for mortality.

	AUC (p-value)	Cut-off	Sensitivity	(%95 CI)	Specificity	(%95 CI)	LR+	LR-	PPV	NPV
2nd CRP	0,635 (<0,001)	>198,7	51,4	41,5–61,2	71,1	62,4–78,8	1,78	0,68	59,8	63,6
CRPv	0,629 (0,006)	>0,75	68,2	58,5–76,9	57	48- 65,7	1,59	0,56	57,0	68,2
Apache 2 score	0,687 (<0,001)	>19	73,8	64,4–81,9	53,9	44,9- 62	1,6	0,49	57,2	71
SOFA score	0,699 (<0,001)	>7	46,7	37- 56,6	85,1	77,8- 90	3,15	0,63	72,5	65,7

CRP, C-reactive protein; CRPv, CRP velocity; SOFA, Sequential Organ Failure Assessment; Apache 2, Acute Physiology and Chronic Health Evaluation 2.

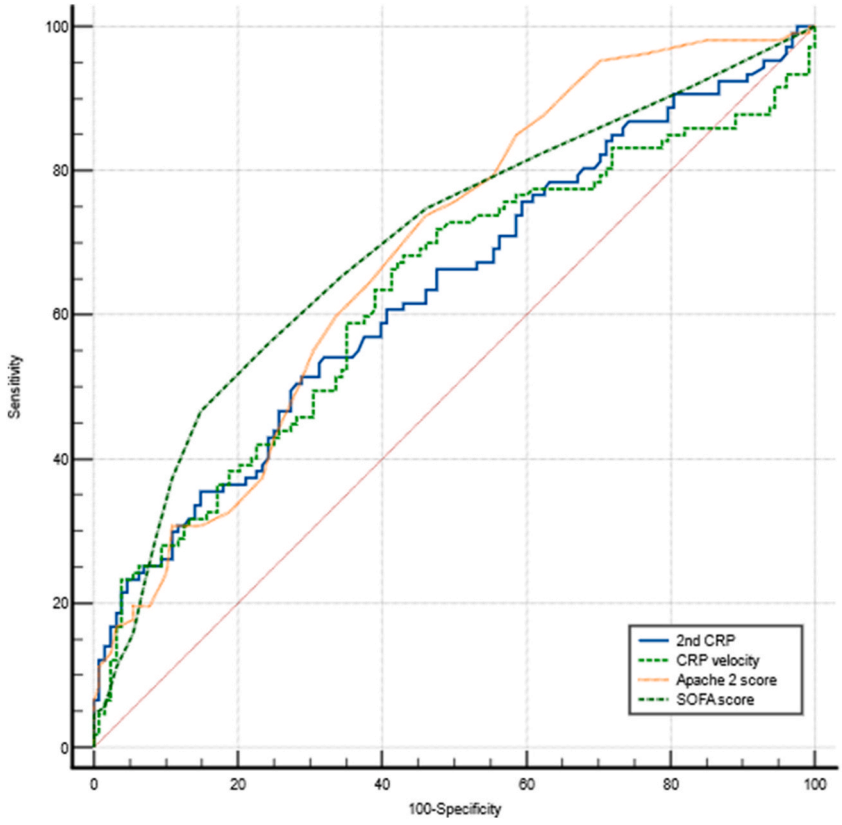

Fig. 3. The comparison of ROC curves.

It has been emphasized that high blood-sugar levels increase the risk of in-hospital death, which was independent of the presence of diabetes [13]. A comprehensive epidemiological study conducted in 2018 showed that the risk of death due to infection increased 1.8 times in people with diabetes [14]. In the present study, diabetes increased mortality risk by 2.17 times, which is consistent with the literature.

The SOFA score is a simple and easy scoring system that is widely used for adult ICU patients to assess organ failure in cases of sepsis. The SOFA score evaluates the respiratory, cardiovascular, hepatic, coagulation, renal, and central nervous systems. The score ranges from 0 to 24, and a high score in cases of sepsis is an indicator that organ dysfunction is severe [15]. Studies comparing scores for patients with sepsis, including APACHE II, have shown that the SOFA score is a better predictor of mortality [16–18]. Various cutoff values were used in these studies to predict mortality. In the present study, when the SOFA score was >7, it had a sensitivity of up to 50 % and a specificity of 85 % in predicting mortality. Additionally, we determined that each increase in SOFA score by 1 point increased the mortality risk by 1.21 times.

CRP plays a role in complement-system activation after acute inflammation, infection, and injury and is rapidly synthesized in the body. It is an acute-phase reactant that is secreted by the liver, macrophages, and fat cells. It is also a sensitive biomarker for sepsis and has a half-life of approximately 18 h. An increase in CRP compared to the initial level is associated with a poor prognosis, while a decrease is associated with a good prognosis [19]. Why is CRP velocity critical? CRPv helps to assess treatment response, detect complications, estimate prognosis, and guide clinicians. For example, in patients with an average or low first value of CRP, the second CRP value and CRPv are higher among those with acute bacterial infection than those with acute viral infection [20]. According to a study by Levinson et al., 6 % of Gram-negative bacteremia patients with baseline CRP <30 mg/L died within one week after admission to the hospital. The study also found a five-fold increase in second CRP levels in patients with a low initial CRP concentrations [21]. In addition, it has been shown that increased CRP dynamics can be used in risk stratification in this patient group, especially in cases of complement-mediated inflammation that causes tissue damage and tissue death in myocardial infarction [8]. This information in the literature emphasizes the importance of CRPv. Our study is one of the pioneering studies highlighting the importance of CRPv in sepsis patients. We showed that CRPv is a risk factor for mortality in sepsis patients, and every 1 mg/dl/hour increase increases the risk of mortality by 1.07 (CI: 1.01–1.14, p=0.015) times. CRPv also had a good AUC value (0.629); when CRPv was >0.75, the sensitivity was 68.2 %, and the specificity was 57 %. However, CRPv was a poor negative predictor (NPV = 68.2 %) in predicting mortality.

4.1. Limitations

One of the main limitations of this study is that it was conducted retrospectively in a single center. Because our study was retrospective, detailed patient-management information could not be included, which is another potential limitation. Furthermore, there was a small number of patients, and the mortality rate was higher than expected. Prospective studies are needed to evaluate the importance of CRPv in ICU patients with sepsis.

5. Conclusion

We found that diabetes, the SOFA score, and CRPv elevation were significant risk factors for mortality. The performance of CRPv in predicting mortality was good with satisfactory discriminative ability and sensitivity of up to 70 %. CRPv can be measured easily and rapidly, so it holds great potential as a valuable adjunct to established scoring systems like SOFA and APACHE II. By incorporating CRPv into these assessments, clinicians can enhance their ability to identify high-risk patients with sepsis in the ICU, which could facilitate timely and targeted interventions.

Ethics committee approval

The Kayseri City Hospital Ethics Committee approved the study (no: 17, date: 14.03.2024).

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Informed consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

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Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Ayşin Kılınç Toker: Writing – original draft, Methodology, Data curation, Conceptualization. **İlhami Çelik:** Writing – review & editing, Supervision. **Ayşe Turunç Özdemir:** Data curation, Conceptualization. **Hande Sağlam:** Data curation. **Derya Koçer:** Data curation. **Murat Eşlik:** Conceptualization. **İbrahim Toker:** Writing – original draft, Formal analysis, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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