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PREDICTIVE UTILITY OF MONOCYTE CHEMOATTRACTANT PROTEIN-1 (MCP-1) AND D-DIMER IN RISK STRATIFICATION OF SEPSIS: A PROSPECTIVE COHORT STUDY

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Abstract. *Background.* Sepsis is a severe and life-threatening clinical syndrome characterized by a dysregulated host immune response to infection. This maladaptive response promotes widespread endothelial injury and abnormalities in coagulation, often progressing to multi-organ dysfunction and death. Mortality rates remain high, highlighting the urgent need for reliable biomarkers to enable early identification of patients at high risk. Such tools are particularly valuable in low- and middle-income countries (LMICs), where access to advanced diagnostic and therapeutic resources is limited. Monocyte Chemoattractant Protein-1 (MCP-1) is a chemokine that reflects hyperactivation of the innate immune system, while D-dimer indicates activation of coagulation and fibrinolysis. Although both pathways are central to the pathophysiology of sepsis, data evaluating their combined prognostic value in LMIC settings remain scarce. This study aimed to assess the prognostic significance of MCP-1 and D-dimer, both individually and in combination, for predicting 28-day mortality in patients with sepsis. *Materials and methods.* We conducted a prospective cohort study involving 83 adult patients with newly diagnosed sepsis at Dr. Saiful Anwar General Hospital, Malang, Indonesia. Serum MCP-1 levels were measured using enzyme-linked immunosorbent assay (ELISA), and plasma D-dimer levels were determined by immunoturbidimetry at the time of diagnosis. Patients were followed for 28 days, and survival outcomes were evaluated using Kaplan–Meier survival analysis and Cox proportional hazards regression models. *Results.* Among the 83 participants, 58 patients (70%) died within 28 days. Non-survivors demonstrated significantly higher MCP-1 and D-dimer levels compared with survivors. An MCP-1 concentration ≥ 123.03 pg/mL was strongly associated with increased mortality (HR 2.664, p = 0.005). Elevated D-dimer (≥ 43.5 mg/L FEU) showed a weaker individual association, but when combined with MCP-1, predictive accuracy for mortality was significantly enhanced (HR 3.986, p = 0.037). *Conclusion.* The concurrent elevation of MCP-1 and D-dimer identifies patients with sepsis who are at markedly increased risk of death. These findings support the potential utility of integrating inflammatory and coagulation biomarkers for early risk stratification. Moreover, they highlight the central role of the inflammation–coagulation axis in sepsis pathophysiology, with particular relevance for clinical practice in resource-limited settings.

Key words: *sepsis, mortality prediction, MCP-1, D-dimer, coagulation biomarkers, resource-limited settings.*

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ПРОГНОСТИЧЕСКОЕ ЗНАЧЕНИЕ МОНОЦИТАРНОГО ХЕМОАТТРАКТАНТНОГО ПРОТЕИНА-1 (MCP-1) И D-ДИМЕРА В ОЦЕНКЕ РИСКА СЕПСИСА: ПРОСПЕКТИВНОЕ КОГОРТНОЕ ИССЛЕДОВАНИЕ

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Резюме. *Введение.* Сепсис представляет собой тяжелый жизнеугрожающий клинический синдром, характеризующийся нарушением регуляции иммунного ответа организма на инфекцию. Такой дезадаптивный ответ способствует обширному повреждению эндотелия и нарушениям коагуляции, часто прогрессирующим в полиорганную дисфункции и летальный исход. Показатели смертности остаются высокими, что подчеркивает острую необходимость в подборе надежных биомаркеров для раннего выявления пациентов высокого риска, что особенно актульно для стран с низким и средним уровнем дохода (СНСД), где доступ к передовым диагностическим и терапевтическим ресурсам ограничен. Моноцитарный хемоаттрактантный белок-1 (MCP-1) — это хемокин, отражающий гиперактивацию врожденного иммунитета, в то время как D-димер указывает на активацию коагуляции и фибринолиза. Хотя оба биологических каскада играют центральную роль в патофизиологии сепсиса, данных, оценивающих их совокупное прогностическое значение в условиях СНСД, получено недостаточно. Целью данного исследования была оценка прогностической значимости определения уровня MCP-1 и D-димера — как по отдельности, так и в сочетании — для прогнозирования 28-дневной смертности у пациентов с сепсисом. *Материалы и методы.* Было проведено проспективное когортное исследование с участием 83 взрослых пациентов с впервые диагностированным сепсисом в больнице общего профиля им. д-ра Сайфула Анвара в Маланге, Индонезия. На момент постановки диагноза уровень MCP-1 в сыворотке крови измерялся с помощью иммуноферментного анализа (ИФА), а уровень D-димера в плазме — методом иммунотурбидиметрии. Наблюдение за пациентами проводилось в течение 28 дней, а результаты выживаемости оценивались с помощью анализа выживаемости Каплана–Майера и регрессионных моделей пропорциональных рисков Кокса. *Результаты.* Из 83 участников 58 пациентов (70%) умерли в течение 28 дней. У невыживших пациентов наблюдались значительно более высокие уровни MCP-1 и D-димера по сравнению с выжившими. Концентрация MCP-1 ≥ 123,03 пг/мл была значимо связана с повышенной смертностью (ОР 2,664, p = 0,005). Повышенный уровень D-димера (≥ 43,5 мг/л ФЭЕ [фибриноген-эквивалентная единица]) сам по себе не всегда являлся неблагоприятным прогностическим признаком, однако сочетанное повышение содержания D-димера и MCP-1 являлось более точным предиктором летального исхода (ОР 3,986, p = 0,037). *Заключение.* Одновременное повышение уровня MCP-1 и D-димера позволяет выявить пациентов с сепсисом, имеющих значительно повышенный риск смерти. Указанные данные подтверждают потенциальную применимость сочетанной оценки воспалительных и коагуляционных биомаркеров для ранней стратификации риска, а также подчеркивают центральную роль оси воспаление–коагуляция в патофизиологии сепсиса, что особенно актуально для клинической практики в условиях ограниченных ресурсов.

Ключевые слова: *сепсис, прогнозирование смертности, MCP-1, D-димер, биомаркеры коагуляции, страны с ограниченными ресурсами.*

Introduction

Sepsis is a life-threatening syndrome resulting from a dysregulated host response to infection, leading to systemic inflammation, microvascular injury, and organ dysfunction. Despite advances in critical care, sepsis continues to cause substantial morbidity and mortality worldwide, with intensive care units (ICU) death rates ranging from 30% to 50% [7, 22, 26]. Among the various pathological processes in sepsis, coagulopathy has emerged as a key driver of poor outcomes, contributing to disseminated intravascular coagulation (DIC), microthrombi formation, and multiple organ failure [4, 9]. Early identification of coagulation disturbances is therefore critical for timely intervention and prognostication.

Monocyte chemoattractant protein-1 (MCP-1), also known as C–C motif chemokine ligand 2 (CCL2), is a pro-inflammatory chemokine that recruits monocytes and other immune cells to sites of infection and injury. In sepsis, excessive MCP-1 release can amplify endothelial activation and trigger procoagulant pathways, linking inflammation to thrombotic complications [4, 9]. Elevated MCP-1 levels have been associated with increased disease severity and mortality, possibly through their role in immune–coagulation crosstalk.

Similarly, D-dimer, a fibrin degradation product, serves as a marker of coagulation activation and fibrinolysis. In sepsis, elevated D-dimer levels are frequently associated with sepsis-induced coagulopathy (SIC) and the development of DIC, conditions that exacerbate organ dysfunction and increase the risk of death [21, 24, 25]. As a marker of endothelial injury and clot formation, D-dimer has shown prognostic value in assessing the severity of sepsis.

in recent years, MCP-1 and D-dimer have emerged as promising prognostic biomarkers in sepsis, offering insights into immune and coagulation pathways involved in disease progression [11, 19, 31]. Given the intertwined roles of inflammation and coagulation in sepsis progression, evaluating both MCP-1 and D-dimer may provide a more comprehensive understanding of the immunothrombotic pathways driving mortality. However, evidence on their combined prognostic utility, particularly in low- and middle-income countries, remains scarce. This prospective study aims to assess the individual and joint predictive performance of MCP-1 and D-dimer for 28-day mortality in sepsis patients in indonesia, with the goal of improving accessible, mechanism-based risk assessment in resource-limited settings.

Materials and methods

Study design. This prospective observational cohort study was conducted at Dr. Saiful anwar general hospital (RSSA), Malang, Indonesia. It is part of a larger sepsis biomarker project designed to investigate multiple pathophysiological pathways in sepsis. Each analysis within the cohort focuses on distinct biomarkers and hypotheses. The present study specifically examines MCP-1, an inflammatory chemokine, and D-dimer, a coagulation marker, in relation to 28-day mortality. Other analyses from the same cohort that evaluated different biomarkers, such as presepsin, soluble urokinase plasminogen activator receptor (supar), and procalcitonin, have been published or are under review separately, and are cited accordingly.

Sepsis diagnosis was made by the attending physicians based on Sepsis-3 criteria (2016). Patients meeting the eligibility criteria were enrolled consecutively over a one-year period. Blood samples were collected on the day of sepsis diagnosis, using residual serum from routine venous blood draws to analyze MCP-1 and D-dimer levels. All patients received standard medical care and were followed for 28 days to assess clinical outcomes. The study protocol was approved by the ethics committee of RSSA, malang (approval no. 400/235/k.3/302/2019).

Study population and eligibility criteria. The study included adult patients (≥ 18 years old) newly diagnosed sepsis based on Sepsis-3 definitions. Exclusion criteria included chronic inflammatory diseases, malignancies, or other conditions that could confound biomarker levels.

MCP-1 measurement. Serum MCP-1 levels were measured on the first day of hospitalization using the enzyme-linked immunosorbent assay (elisa) method. The analysis was performed in accordance with the MAX™ Human MCP-1/CCL2 protocol (catalog no. 430107, BioLegend Inc., USA). Results were expressed in ng/ml.

D-dimer measurement. D-dimer was quantified by immunoturbidimetric method on a “Sysmex CS2100i” analyzer with siemens innovance D-dimer reagents. The assay is based on the aggregation of polystyrene particles coated with monoclonal antibodies (clone 8d3) that react with D-dimer present in the sample.

Statistical analysis. Comparative analysis between survivors and non-survivors was performed using the Mann–Whitney U test. Receiver operating characteristic (ROC) curve analysis identified optimal cut-off values for MCP-1 and D-dimer. Survival analysis was conducted using Kaplan–Meier curves, stratified by biomarker levels based on the derived cut-offs. Hazard ratios (HRs) were calculated using cox proportional hazards regression. The proportional hazards assumption was confirmed before performing time-independent multivariate cox regression to assess the predictive value of MCP-1, D-dimer, and their combination.

A p-value < 0.05 was considered statistically significant. All statistical analyses were performed using spss version 24.0 for windows (IBM Corp., Armonk, NY, USA).

Results

Baseline characteristics. A total of 83 sepsis patients met the inclusion criteria and were enrolled. Among them, 25 patients (30.1%) survived, while 58 (69.9%) died during hospitalization. The baseline characteristics are summarized in Table 1, with comparative

Table 1. Characteristics of research subjects

Characteristics	N = 83 f (%) or median (Q_1–Q_3)
Gender	
Man	42 (50.6%)
Woman	41 (49.4%)
Age (year, mean±SD)	53.89±15.21
D-dimer (mg/L FEU)	4.81 (1.85–13.67)
MCP-1 (pg/mL)	205.61 (98.64–405.00)
Length of stay (day)	8 (4–14)
SOFA score	6 (4–8)
< 6	27 (32.5%)
≥ 6	56 (67.5%)
Outcome	
Alive (survivor)	25 (30.1%)
Died (non-survivor)	58 (69.9%)
Source of infection	
Respiratory	35 (42.2%)
Skin or joints	8 (9.6%)
Gastrointestinal tract	13 (15.7%)
Upper urinary tract	3 (3.6%)
Central nervous system	1 (1.2%)
Lower urinary tract	23 (27.7%)

Table 2. Subject characteristics based on outcomes

Characteristics	Survivor (n = 25)	Non survivor (n = 58)	p value
Gender			
Man	13 (52%)	29 (50%)	0.867[a]
Woman	12 (48%)	29 (50%)	
Age (years)			
median (Q_1–Q_3)	52 (38.5–64.5)	55 (44.75–67.25)	0.335[c]
D-dimer (mg/L FEU)			
median (Q_1–Q_3)	2.66 (1.28–6.46)	6.03 (1.98–16.58)	0.012[c]
MCP-1 (pg/mL)			
median (Q_1–Q_3)	75 (42.42–111.82)	282.27 (146.06–651.59)	0.000[c]
SOFA scores			
< 6	24 (96%)	3 (5.2%)	0.000[c]
≥ 6	1 (4%)	55 (94.8%)	
Length of stay (day)			
median (Q_1–Q_3)	7 (4.5–11.5)	10.22 (4–15.75)	0.905[c]

Note. [a]p value based on chi-square test; [b]p value based on Independent t-test; [c]p value based on Mann–Whitney U test; *$p < 0.05$; significant.

analysis between survivors and non-survivors is presented in Table 2. Gender distribution was equal in the non-survivor group (29 males, 29 females), with no significant difference. The mean age was 52 years for survivors and 55 years for non-survivors, showing no statistical significance. Median length of hospital stay was 7 days for survivors and 10.22 days for non-survivors, also not significantly different.

Biomarker levels. Both MCP-1 and D-dimer levels were significantly elevated in non-survivors compared to survivors. Median MCP-1 was 282.27 pg/ml in non-survivors and 75 pg/ml in survivors ($p = 0.000$). Likewise, median D-dimer levels were 6.03 mg/L FEU in non-survivors, compared to 2.66 mg/L FEU in survivors ($p = 0.012$).

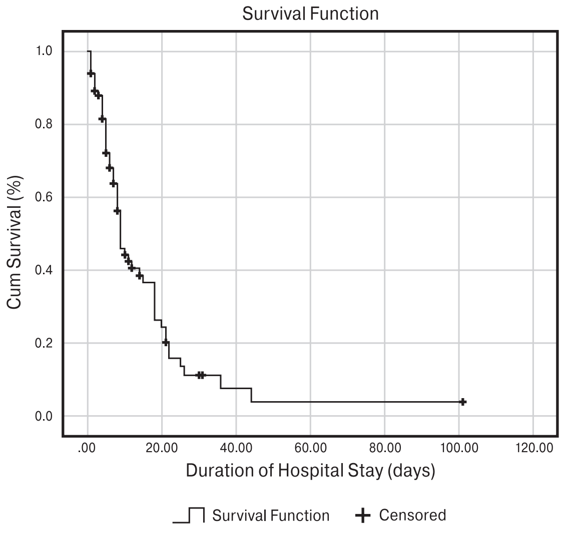

Figure 1. Overall survival analysis graph
Note. Kaplan–Meier survival analysis of 83 sepsis patients revealed a median survival time of 9 days. The survival rate sharply declined during the first two weeks of observation, with fewer than 10% of patients surviving beyond 28 days. This curve highlights the high early mortality associated with sepsis in the studied population.

Overall survival analysis. Kaplan–Meier survival analysis revealed a median survival time of 9 days for the entire cohort, indicating that 50% of patients died within this period. The survival curve also demonstrated that fewer than 10% of patients remained alive beyond day 28 (Fig. 1).

Survival analysis and risk stratification based on MCP-1. Survival analysis stratified by MCP-1 levels is shown in Fig. 2 and Table 3. The Kaplan–

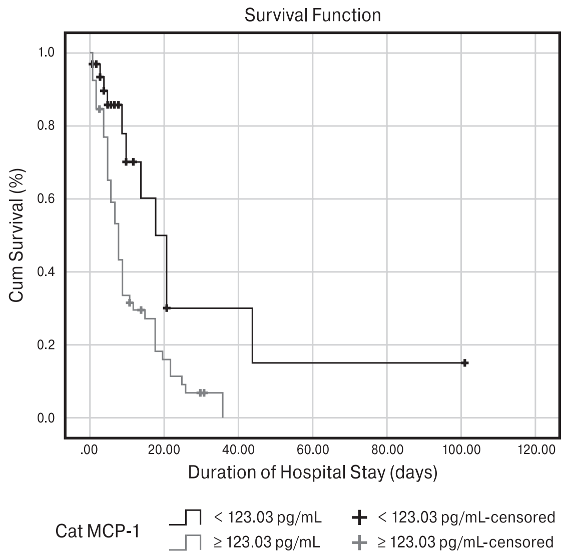

Figure 2. Kaplan–Meier survival analysis graph based on MCP-1 levels in sepsis patients
Note. Survival analysis based on MCP-1 levels using a cut-off value of 123.03 pg/ml. Patients with MCP-1 < 123.03 pg/ml (blue line) showed significantly improved survival compared to those with MCP-1 ≥ 123.03 pg/ml (green line). Median survival was 31 days in the lower MCP-1 group versus 11 days in the higher MCP-1 group. The survival curves crossed, indicating a violation of the proportional hazards assumption. This suggests that elevated MCP-1 levels are associated with a higher risk of mortality in sepsis.

Meier curves, based on the cut-off value of 123.03 pg/ml (determined via roc analysis), crossed, indicating a violation of the proportional hazards (PH) assumption. Patients with MCP-1 levels < 123.03 pg/ml had a longer median survival of 31 days, while those with levels ≥ 123.03 pg/ml had a median survival of 11 days. The hazard ratio of MCP-1 ≥ 123.03 pg/ml was 2.664 (95%CI: 1.341–5.29; p value 0.005).

Survival analysis based on D-dimer. As depicted in Fig. 3 and Table 4, survival analysis using a D-dimer cut-off of 43.5 mg/L FEU also yielded Kaplan–Meier curves that violated the PH assumption. Patients with D-dimer levels < 43.5 mg/L FEU had a median survival of 17 days, compared to 8 days for those with levels ≥ 43.5 mg/L FEU. The hazard ratio of D-dimer ≥ 43.5 mg/L FEU was 1.980 (95%CI: 0.612–6.40; p value 0.264).

Survival analysis based on combination of MCP-1 and D-dimer. A combined analysis of MCP-1 and D-dimer levels was performed based on their respective cut-off values. Patients with both MCP-1 ≥ 123.03 pg/ml and D-dimer ≥ 43.5 mg/L FEU were compared to those with either or both biomarkers below the thresholds. The Kaplan–Meier curve (Fig. 4) again violated the PH assumption. The group with elevated levels of both biomarkers had a significantly shorter median survival of 5 days, compared to 20 days in the group with lower levels of either MCP-1 or D-dimer. Patients were divided into 3 groups based on the presence of risk factors (MCP-1 and/or D-dimer levels). Table 5 showed that patients with 1 risk factor had an HR of 2.605 (95%CI: 1.306–5.196; p value 0.007), while patients with 2 risk factors had an HR of 3.986 (95%CI: 1.084–14.652; p value 0.037).

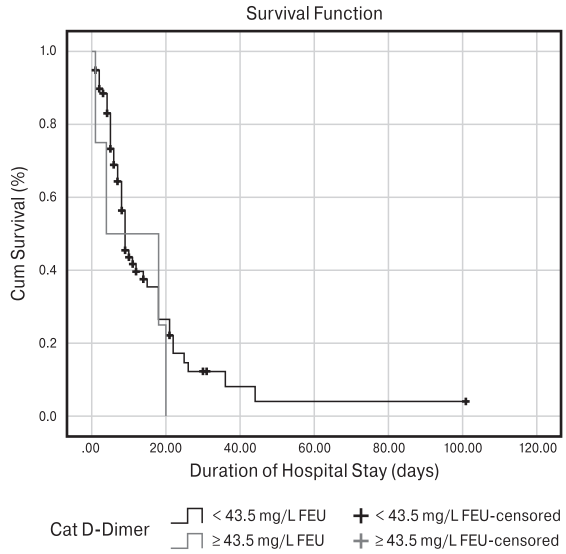

Figure 3. Kaplan–Meier survival analysis graphs based on D-dimer levels in sepsis patients

Note. Patients were divided by a D-dimer cut-off of 43.5 mg/L FEU. The blue line represents those with D-dimer < 43.5 mg/L FEU, and the green line those with D-dimer ≥ 43.5 mg/L FEU. Median survival was 17 days in the lower D-dimer group versus 8 days in the higher D-dimer group. The survival curves cross, indicating a violation of the proportional hazards assumption, but overall higher D-dimer levels are associated with increased mortality risk (AUROC 67.4%, p = 0.012).

Discussion

Baseline characteristics. This study included 83 patients diagnosed with sepsis, with an almost equal gender distribution (49.4% female, 50.6% male) and a mean age of 53.89±15.21 years. The median length of hospital stay was 8 days, and 67.5% of patients

Table 3. Survival analysis and risk stratification based on MCP-1

MCP-1	Low (< 123.03 pg/mL)	High (≥ 123.03 pg/mL)
Total subject	31	52
Amount event	11 (35.48%)	47 (90.38%)
Amount censored	20 (64.52%)	5 (9.62%)
Mean (95%CI)	31.16 (11.36–50.96)	11.05 (8.39–13.72)
Median (95%CI)	21 (14.61–27.39)	8 (6.27–9.73)
p value	0.002	
Hazard ratio (95%CI)		2.664 (1.341–5.29)
p value		0.005

Table 4. Survival analysis and risk stratification based on D-dimer

D- dimer	Low (< 43.5 mg/L FEU)	High (≥ 43.5 mg/L FEU)
Total subject	80	3
Amount event	55 (68.75%)	3 (100%)
Amount censored	25 (31.25%)	0 (0%)
Mean (95%CI)	16.58 (10.48–22.68)	8.33 (0–19.892)
Median (95%CI)	9 (7.044–10.957)	4 (0–8.801)
p value	0.223	
Hazard ratio (95%CI)		1.980 (0.612–6.40)
p value		0.254

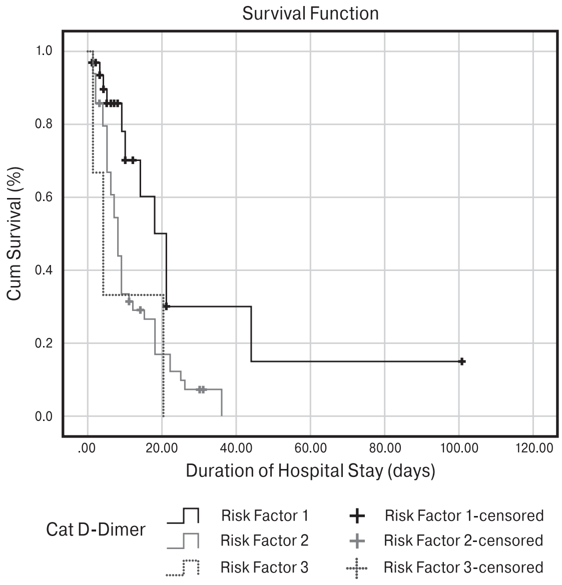

Figure 4. Kaplan–Meier survival analysis graph based on the combination of MCP-1 and D-dimer

Note. Patients were grouped by the number of elevated biomarkers: those with neither or only one elevated marker (MCP-1 < 123.03 pg/ml and/or D-dimer < 43.5 mg/L FEU; blue line) versus those with both MCP-1 ≥ 123.03 pg/ml and D-dimer ≥ 43.5 mg/L FEU (green line). Median survival was 20 days in the lower-risk group compared to 5 days in the high-risk group.

had a sofa score ≥ 6, indicating high illness severity. Overall, 69.9% (58/83) of patients died during hospitalization.

Respiratory tract infections (42.2%) and lower urinary tract infections (27.7%) were the most common sources of sepsis. This distribution aligns with common etiologies in clinical settings, where respiratory infections are frequently associated with complications such as ards and poorer outcomes [7, 18, 26]. Several characteristics of patients in this study can be seen in Table 1 below.

As shown in Table 2, D-dimer and MCP-1 levels significantly differed between survivors and non-survivors. Non-survivors had higher D-dimer levels (median: 6.03 mg/L FEU) compared to survivors (2.66 mg/L FEU, p = 0.012), reflecting possible sepsis-associated coagulopathy, which is known to be linked to mortality [10, 12]. Likewise, MCP-1 levels were significantly elevated in non-survivors (282.27 pg/ml vs 75 pg/ml, p < 0.001), indicating a stronger inflammatory response and supporting its role as a marker of immune activation and tissue injury in sepsis [1, 3, 16].

No significant age difference was found between groups (median age: 55 vs 52 years, p = 0.335), consistent with prior findings suggesting that age may not be an independent predictor of mortality in all sepsis populations [17]. Length of hospital stay was also not significantly different between groups (p = 0.905), implying that other factors like biomarker levels and illness severity may better reflect prognosis.

Crucially, 96% of survivors had sofa scores < 6, while only 5.2% of non-survivors had scores in this range (p = 0.000). This finding highlights the prognostic value of the sofa score at admission and supports its use in risk stratification among sepsis patients [27].

Survival analysis and risk stratification based on MCP-1. Kaplan–Meier analysis showed a median survival of 9 days among 83 sepsis patients, with less than 10% surviving beyond 28 days, underscoring the high early mortality risk in sepsis (Fig. 1).

Stratification by MCP-1 levels (< 123.03 pg/ml vs ≥ 123.03 pg/ml) revealed that patients with lower MCP-1 had significantly better survival (median: 31 vs 11 days; Fig. 2, Table 3), suggesting a strong association between lower inflammatory response and improved outcomes.

However, in Fig. 2 the Kaplan–Meier curve for MCP-1 violated the proportional hazards assumption, indicating the effect may not be consistent over time. The cut-off of 123.03 pg/ml yielded an auroc of 89.2% (95%CI: 81.1–97.3%, p = 0.000) for MCP-1 in predicting mortality, with 81% sensitivity and 80% specificity.

This aligns with Bozza et al., who found that MCP-1 levels > 1000 pg/ml were associated with increased mortality in severe sepsis [1]. Jansen et al. reported that MCP-1 > 1600 pg/ml upon ICU admission predicted 28-day mortality [15], and Yamamoto et al. found that levels > 1500 pg/ml were associated

Table 5. Survival analysis and risk stratification based on combination of MCP-1 and D-dimer

Variable	Group 1[a]	Group 2[b]	Group 3[c]
Total subject	31	49	3
Amount event	11 (35.5%)	44 (89.8%)	3 (100%)
Censored amount	20 (64.5%)	5 (10.2%)	0 (0%)
Mean (95%CI)	31.16 (11.36–50.96)	11, 23 (8.5–14.0)	8.33 (0–19.89)
Median (95%CI)	21 (14.6–27.4)	8 (6.32–9.68)	4 (0–8.8)
p value		0.007	
Hazard Ratio (95%CI)	1	2.605 (1.306–5.196)	3.986 (1.084–14.652)
p value		0.007	0.037

Note. [a]Group with no risk factor (MCP-1 < 123.03 pg/mL and D-Dimer < 43.5 mg/L FEU); [b]Group with 1 risk factors (MCP-1 ≥ 123.03 pg/mL or D-dimer ≥ 43.5 mg/L FEU); [c]Group with 2 risk factors (MCP-1 ≥ 123.03 pg/mL and D-dimer ≥ 43.5 mg/L FEU).

with worse outcomes [28]. Chen et al.'s meta-analysis of 805 patients also supported the prognostic utility of MCP-1, despite variability in cut-offs across studies [2].

In our cohort, survival rates on days 10, 20, and 28 were consistently higher in patients with MCP-1 < 123.03 pg/ml. Mean survival time was significantly longer for this group (31.16 days) compared to those with higher levels (11.05 days). Median survival for the lower MCP-1 group was 21 days versus 8 days for the higher group, reinforcing the prognostic significance of MCP-1. Although a specific study by Duan et al. reporting median survival times based on MCP-1 levels was not found, other studies confirm its predictive value. Matsumoto et al. observed significantly higher MCP-1 levels in non-survivors, with an AUC of 0.763 for 28-day mortality prediction [19]. A retrospective study in elderly patients showed MCP-1 had comparable prognostic performance to SOFA and APACHE II scores [8, 19]. Zhu et al. also reported a strong correlation between MCP-1 and 28-day mortality, particularly in septic shock cases [31].

Although most studies use MCP-1 to assess survival at fixed time points (e.g., 28 days), fewer report median survival, likely due to survival beyond this window. Nevertheless, the consistent association between elevated MCP-1 and mortality highlights its utility as a prognostic biomarker in sepsis.

Survival analysis and risk stratification based on D-dimer. Survival analysis based on D-dimer levels (cut-off at 43.5 mg/L FEU) revealed a mean survival of 17 days for patients with D-dimer < 43.5 mg/L FEU, compared to 8 days for those with higher levels (Fig. 3).

This supports the use of D-dimer as a biomarker for coagulopathy in sepsis and its potential role in mortality prediction. Like MCP-1, D-dimer also violated the PH assumption, indicating that the relationship between D-dimer and survival may change over the course of sep sis.

In this study, the AUC for D-dimer levels in determining mortality was 67.4% (95%CI: 55.8–79.1%, $p = 0.012$). This AUC value falls in the weak category (> 60–70%) but is statistically significant. The cut-off point was determined using the coordinates of the curve table, yielding a cut-off of 43.5 mg/L FEU with a sensitivity of 67.2% and specificity of 60%. Several studies have highlighted the prognostic value of D-dimer in predicting mortality among sepsis patients. Yunus et al. reported that a D-dimer cut-off of 57 ng/ml demonstrated good predictive performance for mortality [29].

In a cohort of 684 sepsis patients, D-dimer levels were significantly higher in non-survivors compared to survivors (2489 ng/ml vs 1475 ng/ml, $p = 0.0001$), and showed the strongest predictive value for mortality among tested biomarkers (AUC 0.68). Multivariate analysis confirmed that D-dimer was the only biomarker with a linear association with mortality, with an odds ratio of 3.03 (95%CI: 1.38–6.62) for levels above 2409 ng/ml [21]. Similarly, Schupp et al. found that D-dimer levels and DIC scores showed good diagnostic accuracy for distinguishing septic shock (AUC 0.710 and 0.739), but their prognostic performance for 30-day mortality was moderate (AUC 0.590–0.610). Very high D-dimer levels (> 30 mg/l) and DIC scores ≥ 3 were significantly associated with increased mortality risk and remained independent predictors after multivariable adjustment [23].

Across these studies, D-dimer cut-off values typically ranged from 2.5 to 4.0 mg/L FEU, with AUCs between 0.71 and 0.77 — indicating moderate to good discriminatory ability. Sensitivity values commonly fell between 70–80%, and specificity ranged from 65–70%. The variability in results likely reflects differences in patient populations, D-dimer assay methods, sepsis definitions, and outcome measures. Despite these variations, most evidence supports that D-dimer levels exceeding 3.0 mg/L FEU are associated with an increased risk of mortality in sepsis patients.

It is important to emphasize that while D-dimer is a useful biomarker for mortality prediction, it should not be used in isolation. Combining D-dimer measurements with comprehensive clinical evaluation and other prognostic markers can enhance the accuracy of risk stratification in sepsis. Our findings indicate that sepsis patients with D-dimer levels ≥ 43.5 mg/L FEU exhibited lower survival rates compared to those with levels < 43.5 mg/L FEU, particularly on days 10 and 20 of observation (Fig. 3). Patients with lower D-dimer levels (< 43.5 mg/L FEU) demonstrated better survival outcomes, with a mean survival of 16.58 days, significantly higher than the 8.33 days observed in those with elevated D-dimer levels (≥ 43.5 mg/L FEU). The median survival times also differed between the two groups. However, the HR for mortality in patients with elevated D-dimer levels was 1.980 (95%CI: 0.612–6.40), with a p-value of 0.254, indicating a non-significant association in this study (Table 4).

In a study by Zhang et al., 343 hospitalized COVID-19 patients were evaluated to assess the predictive value of D-dimer levels for in-hospital mortality. The optimal cutoff value for D-dimer was found to be 2.0 μg/ml, with a sensitivity of 92.3% and specificity of 83.3%. Of the 13 deaths during hospitalization, 12 occurred in patients with D-dimer levels ≥ 2.0 μg/ml, compared to just one death in patients with D-dimer levels < 2.0 μg/ml. This difference was statistically significant ($p < 0.001$). The hazard ratio for mortality with elevated D-dimer levels was 51.5 (95%CI: 12.9–206.7). The study concluded that D-dimer levels above 2.0 μg/ml on admission could serve as a strong predictor of in-hospital mortality, suggesting that it could be an effective early marker for improving the management of COVID-19 patients [30].

Similarly, Rodelo et al. found that the 28-day mortality rate was 77.8% in patients with D-dimer levels > 4.2 mg/l, compared to just 25% in those with levels ≤ 4.2 mg/l, although they did not provide data on median survival times [21]. These results are consistent with our findings, further supporting the link between elevated D-dimer levels and higher mortality in sepsis patients. Notably, most existing studies assess mortality based on 28- or 30-day outcomes rather than median survival time, possibly because a substantial number of patients survive beyond the observation period.

Nevertheless, elevated D-dimer levels — generally above 2.0 to 4.0 mg/L FEU — consistently correlate with poorer prognosis in sepsis patients. Differences in cut-off values and mortality rates across studies may reflect variations in patient populations, D-dimer assay techniques, and sepsis diagnostic criteria. These findings are in line with our study, which also observed significantly elevated D-dimer levels in non-survivors.

Survival analysis and risk stratification based on combination of MCP-1 and D-dimer. In the combined survival analysis of MCP-1 and D-dimer levels, patients with both biomarkers elevated above their respective cut-offs (MCP-1 ≥ 123.03 pg/ml and D-dimer ≥ 43.5 mg/L FEU) had a significantly shorter median survival of 5 days, compared to 20 days in patients with lower levels of either or both biomarkers (Fig. 4).

This highlights the value of combining inflammatory and coagulation markers to predict sepsis outcomes. The results suggest that both inflammatory and coagulatory pathways contribute to poor prognosis in sepsis, and combining biomarkers from these systems may improve risk stratification.

Table 5. showed that the survival rate of sepsis patients with one risk factor was higher than in those with two risk factors. The HR was 3.986 (95%CI: 1.084–14.652, p = 0.037), indicating that sepsis patients with both elevated D-dimer ≥ 43.5 mg/L FEU and MCP-1 ≥ 123.03 pg/ml are 3.986 times more likely to die quickly than those with lower levels of both biomarkers.

Mikuła et al. combined D-dimer with other biomarkers, finding that the D-dimer cut-off of 3570 ng/ml (3.57 mg/L FEU) had an AUC of 0.731, which increased to 0.801 when combined with other biomarkers [20]. Similarly, Innocenti et al. combined D-dimer with lactate, achieving an AUC of 0.74 [13]. Although no studies have reported combined MCP-1 and D-dimer cut-offs, combining biomarkers generally improves diagnostic accuracy. Ding et al. (2021) showed that combining ischemia-modified albumin, D-dimer, and MCP-1 improved diagnostic accuracy, with an AUC of 0.9047 in acute myocardial infarction patients [5].

The potential benefit of combining multiple biomarkers in sepsis stratification has been increasingly supported by recent evidence. While the combination of MCP-1 and D-dimer has not been extensively studied, the rationale for such an approach is strong, given that MCP-1 reflects monocyte-driven inflammation while D-dimer reflects coagulopathy. This dual representation of inflammatory and thrombotic pathways aligns with the multifactorial pathophysiology of sepsis. In our previous study, presepsin — a soluble CD14 subtype — demonstrated excellent prognostic value in sepsis, with an AUC of 0.939 for predicting 28-day mortality and a hazard ratio of 3.654 for patients with levels above 17.085 pg/ml [14]. Notably, its prognostic performance improved when interpreted in conjunction with clinical severity scores and other laboratory markers. These findings emphasize that no single biomarker sufficiently captures the complexity of sepsis. Therefore, incorporating MCP-1 and D-dimer, possibly alongside markers such as presepsin, may offer a more holistic risk assessment framework. A multimarker strategy, tailored to local resources and patient populations, could improve early risk stratification and inform timely, personalized interventions [14].

Conclusion

In conclusion, our study suggests that the combination of MCP-1 and D-dimer levels may serve as valuable biomarkers for predicting mortality in sepsis patients. Elevated levels of both biomarkers are associated with significantly shorter survival and higher mortality risk.

Additional information

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