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Prognostic value of REDS, SOFA, and D-dimer in critically ill COVID-19 patients with sepsis

Прогностички значај РЕДС, СОФА и Д-димера код критично оболелих пацијената од ковида 19 са сепсом

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SUMMARY

Introduction/Aim Early identification of high-risk patients with COVID-19-associated sepsis is essential for timely intervention and optimal ICU resource allocation.
This study aimed to evaluate and compare the prognostic performance of the REDS (Risk-stratification of Emergency Department Sepsis) and SOFA (Sequential Organ Failure Assessment) scores, alongside D-dimer levels, in predicting 28-day mortality among critically ill patients.

Methods A retrospective analysis was conducted on 163 critically ill adult patients with confirmed COVID-19 and sepsis (Sepsis-3 criteria) admitted to the intensive care unit of a tertiary center between November 2020 and May 2022. REDS, SOFA, and D-dimer values were assessed within 24 hours of ICU admission. Predictive value was evaluated using ROC analysis, logistic regression, and CHAID decision tree modeling.

Results The overall 28-day mortality rate was 65.6%. REDS (AUC = 0.690) and SOFA (AUC = 0.680) demonstrated moderate predictive ability, while D-dimer showed lower accuracy (AUC = 0.632). REDS > 2 had the highest sensitivity (80.2%), and SOFA >4 had the highest specificity (56.1%). Both REDS and SOFA were identified as independent mortality predictors. CHAID analysis recognized REDS as the strongest discriminator, stratifying mortality risk into three distinct groups (42.9%, 66.1%, and 84.5%).

Conclusion REDS and SOFA scores provide meaningful prognostic value in patients with COVID-19–related sepsis. REDS demonstrated a slight advantage and may serve as a simple and effective bedside tool for early risk stratification in clinical practice and future viral pandemics.

Keywords: COVID-19, sepsis; REDS score; SOFA score; prognosis; mortality

САЖЕТАК

Увод/Циљ Рано препознавање пацијената са високим ризиком од смртног исхода код ковида 19–повезане сепсе од суштинског је значаја за правовремену интервенцију и оптималну расподелу ресурса у Јединици интензивног лечења (ЈИЛ). Циљ рада био је да се процени и упореди прогностичка вредност РЕДС (Скор за стратификацију ризика сепсе на одељењу хитне помоћи) и СОФА (скору процене секвенцијалног попуштања органа) скорова, заједно са нивоом Д-димера, у предикцији 28-дневног морталитета код тешко оболелих пацијената.

Методе Ретроспективна анализа обухватила је 163 одрасла пацијента са потврђеним ковидом 19 и сепсом (критеријуми Сепса-3), лечених у ЈИЛ терцијарног центра у периоду од новембра 2020. до маја 2022. РЕДС, СОФА и Д-димер процењени су у року од 24 сата од пријема у ЈИЛ. Прогностичка вредност анализирана је помоћу *ROC* анализе, логистичке регресије *CHAID* моделовања стабла одлуке.

Резултати Укупна 28-дневна смртност износила је 65,6%. РЕДС (*AUC* = 0,690) и СОФА (*AUC* = 0,680) показали су умерену предиктивну способност, док је Д-димер имао нижу тачност (*AUC* = 0,632). РЕДС > 2 имао је највећу сензитивност (80,2%), док је СОФА > 4 показао највећу специфичност (56,1%). РЕДС и СОФА идентификовани су као независни предиктори смртности. *CHAID* анализа издвојила је РЕДС као најјачи дискриминатор, који је стратификовао пацијенте у три групе ризика са стопама смртности од 42,9%, 66,1% и 84,5%.

Закључак РЕДС и СОФА скорови имају значајну прогностичку вредност код пацијената са ковидом 19-повезаном сепсом. РЕДС је показао благу предност и може послужити као једноставан и ефикасан алат за рану стратификацију ризика у клиничкој пракси и будућим вирусним пандемијама.

Кључне речи: ковид 19; сепса; РЕДС скор; СОФА скор; прогноза; морталитет

INTRODUCTION

Critically ill patients with COVID-19 and sepsis remain among the most vulnerable in intensive care units (ICUs), with persistently high mortality rates despite advances in supportive care [1,

2, 3]. The convergence of viral pneumonia, immune dysregulation, and sepsis-induced multiorgan failure creates complex clinical scenarios, underscoring the urgent need for reliable early prognostic tools [4]. Timely risk stratification is essential to inform therapeutic decisions, optimize resource allocation, and improve patient outcomes. While numerous studies have explored individual biomarkers and severity scores, there is still no consensus on the most effective approach for early mortality prediction in this high-risk group [5, 6, 7]. Notably, the REDS scoring system has been shown to be a simple and objective tool for risk stratification in patients with suspected sepsis, although these studies did not include patients with COVID-19 [8].

This study provides novel insights by directly comparing the prognostic performance of three early indicators – the SOFA score, REDS score, and D-dimer levels – within the first 24 hours of ICU admission in COVID-19 patients with sepsis. Unlike prior research that typically assessed single markers or lacked rigorous validation, our study integrates multiple established tools and employs advanced statistical techniques, including bootstrap-adjusted multivariate logistic regression and CHAID decision tree modeling, to enhance predictive power and internal validity [9, 10, 11].

The most notable finding is the potentially valuable prognostic role of the REDS score in predicting 28-day mortality, supported by ROC analysis, multivariate models, and decision tree classification. A simplified model based on REDS thresholds effectively stratified patients into clinically relevant risk groups, supporting its utility in ICU triage and early management. The use of bootstrap validation further mitigates limitations common to retrospective studies, such as small sample size and data skewness, enhancing the robustness of our conclusions.

This study was conducted in critically ill COVID-19 patients with sepsis. While the findings provide valuable insights for this specific population, their applicability to future pandemics

caused by similar viral pathogens remains to be investigated. Given the challenges posed by comorbidities, immunosuppression, and variable vaccine responsiveness, our results underscore the potential importance of accurate, evidence-based prognostic tools in guiding clinical decisions. The objective of this study was to assess and compare the prognostic accuracy of the SOFA score, REDS score, and D-dimer levels in predicting 28-day mortality, using comprehensive and statistically rigorous methodologies. These findings contribute to the expanding literature on multidimensional and machine learning–assisted approaches in critical care and support further external validation in larger, diverse cohorts.

METHODS

This retrospective observational study was conducted at the Institute for Pulmonary Diseases of Vojvodina, within the Clinic for Intensive Care Medicine and Pulmonary Vascular Diseases, Department for Intensive Care and Intoxications Level 3. The study population included 163 critically ill patients with confirmed COVID-19 and sepsis who were admitted to the Intensive Care Unit between November 2020 and May 2022.

Eligibility criteria included adult patients (≥ 18 years) with COVID-19 confirmed via RT-PCR or rapid antigen testing using nasopharyngeal swabs. All patients met Sepsis-3 criteria, requiring documented or suspected infection and an acute increase of ≥ 2 points in the Sequential Organ Failure Assessment (SOFA) score [12]. To minimize confounding, we excluded individuals with advanced immunocompromised states (e.g., HIV/AIDS, transplant recipients, active cancer, autoimmune diseases), as well as pregnant or breastfeeding women.

Demographic, clinical, and laboratory data were collected from medical records within the first 24 hours of ICU admission. Variables necessary for calculating the SOFA and REDS scores

were extracted from documentation and verified by two independent reviewers. Laboratory tests, including D-dimer levels, were performed using the VIDAS® D-Dimer Exclusion II assay (BioMérieux, Marcy-l'Étoile, France), which is based on an ELFA (enzyme-linked fluorescent assay) technique and analyzed on the VIDAS 3 platform.

The primary outcome was 28-day all-cause mortality. Statistical analyses were performed using SPSS Version 26.0 (IBM Corp., Armonk, NY), MedCalc Statistical Software v20.2 (MedCalc Software Ltd., Ostend, Belgium). A two-tailed p-value < 0.05 was considered statistically significant.

Statistical Analysis

Continuous variables were summarized as medians with interquartile ranges (IQR), while categorical variables were presented as frequencies and percentages. The distribution of continuous variables was assessed using the Shapiro-Wilk test. Between-group comparisons were conducted using the Mann–Whitney U test for non-normally distributed data and the Chi-square or Fisher's exact test for categorical variables, depending on expected cell frequencies. To evaluate the discriminatory power of the SOFA score, REDS score, and D-dimer levels for predicting 28-day mortality, receiver operating characteristic (ROC) curve analyses were performed. The Youden index was applied to determine optimal cut-off values for each marker. Diagnostic performance was assessed through sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), each with corresponding 95% confidence intervals. Multivariate logistic regression analysis was conducted to identify independent predictors of 28-day mortality, with internal validation performed through bootstrapping (1,000 iterations) to improve model robustness and minimize overfitting. Model calibration was assessed using the Hosmer–Lemeshow goodness-of-fit test by comparing observed and expected mortality across deciles of predicted risk. Additionally, a Chi-squared Automatic

Interaction Detector (CHAID) decision tree analysis was employed to explore variable interactions and stratify mortality risk groups based on REDS, SOFA, and D-dimer, allowing identification of key thresholds and clinically relevant decision nodes.

Ethics: The study protocol received ethical approval from the Ethics Committee of the Institute for Pulmonary Diseases of Vojvodina (No. 9-II/3, February 24, 2022) and the Faculty of Medicine, University of Novi Sad (No. 01-39/190/1, May 13, 2022).

RESULTS

In this study involving 163 critically ill COVID-19 patients with sepsis, the prognostic performance of three early clinical indicators – SOFA score, REDS score, and D-dimer levels—was evaluated within the first 24 hours of ICU admission for their ability to predict 28-day mortality. In this cohort, the prevalence of comorbidities varied, with hypertension (55.8%) and diabetes mellitus (27%) being the most common (Figure 1). Although patients with malignancy exhibited the highest mortality rate (90.9%), this did not reach statistical significance ($p = 0.062$), likely due to the small subgroup size. Other comorbidities such as COPD, cardiovascular disease, and diabetes showed elevated mortality proportions but without statistically significant differences between survivors and deceased. The absence of significant associations may reflect limited statistical power or heterogeneous effects of individual comorbidities on 28-day outcomes. Overall, these findings suggest that while comorbid conditions are prevalent in critically ill patients, their isolated impact on short-term mortality requires further investigation in larger cohorts to clarify their prognostic value.

Receiver operating characteristic (ROC) curve analysis demonstrated moderate discriminative ability across all three parameters (Figure 2). The REDS score yielded the highest Youden

index (0.293; 95% CI: 0.148–0.403), followed by the SOFA score (0.288; 95% CI: 0.162–0.420) and D-dimer (0.255; 95% CI: 0.132–0.377). The optimal cut-off values identified were REDS >2, SOFA >4, and D-dimer >1425 μg/L. Notably, the confidence interval for D-dimer's cut-off value was wide (1028–8253 μg/L), indicating potential variability in its discriminatory capacity.

D-dimer (AUC = 0.632) shows modest predictive value, slightly better than chance. SOFA (AUC = 0.680) performs better with moderate accuracy. REDS (AUC = 0.690) is the best among the three, though only marginally superior to SOFA (Table 1). All models have AUCs between 0.6 and 0.7, indicating weak to moderate predictive power. Based on the ROC analysis for this sample, although none of the scores are strong predictors on their own, both REDS and SOFA demonstrated statistically significant differences between survivors and non-survivors ($p < 0.001$), highlighting their value as useful prognostic tools within a comprehensive clinical assessment.

In terms of diagnostic accuracy, REDS >2 demonstrated the highest sensitivity (80.2%) and negative predictive value (71.3%), while SOFA > 4 achieved the highest specificity (56.1%) and positive predictive value (75.5%). D-dimer > 1425 μg/L showed a sensitivity of 76.5%, specificity of 49.1%, PPV of 73.6%, and NPV of 52.9% (Table 2). Despite the observed differences in point estimates, the overlapping confidence intervals for the Youden index suggest that none of the three markers was statistically superior in isolation.

In our research, three REDS parameters showed statistically significant associations with mortality outcomes (Table 3). Patients with GCS < 15 had over 75% mortality, indicating a strong correlation between severe neurological impairment and death. Similarly, approximately 80% of patients with lactate levels ≥ 4 mmol/L did not survive, underscoring the prognostic importance of elevated lactate. Furthermore, more than 85% of patients exhibiting refractory

hypotension combined with lactate ≥ 2.1 mmol/L died, highlighting this combination as a potent clinical marker of high mortality risk. Among the eight REDS components, these variables demonstrated the most pronounced and significant differences between survivors and non-survivors, while other parameters such as systolic blood pressure < 100 mmHg and albumin < 27 g/L showed no significant discrimination (Figure 3). Despite variability in individual component performance, the composite REDS score exhibited superior discriminatory ability (AUROC = 0.69, $p < 0.001$) by integrating all variables, supporting its role as a comprehensive bedside risk stratification tool. These findings suggest that while certain REDS components have stronger individual prognostic value, the aggregate score remains the preferred measure for clinical application and may benefit from further optimization in future studies.

In the multivariate logistic regression model, both the REDS and SOFA scores were identified as independent predictors of mortality (Table 4). Each 1-point increase in the REDS and SOFA scores was associated with a 22% increase in the odds of death (OR = 1.22, $p \leq 0.05$ for both). Male sex was also independently associated with increased mortality risk (OR = 2.78, $p = 0.029$). Other variables, including hypertension, diabetes, cardiovascular disease, chronic obstructive pulmonary disease, and allergies, were not statistically significant predictors in the adjusted model. Logistic regression analysis and combined ROC curves further supported the enhanced prognostic utility when these variables were used in tandem.

To assess the predictive value of clinical variables for mortality in critically ill COVID-19 patients with sepsis, a logistic regression analysis was performed using the bootstrap method with 1000 samples (Table 5). This approach allowed for a more robust estimation of the model parameters, reducing potential bias and improving the reliability of confidence intervals in small and potentially non-normally distributed datasets.

The use of bootstrap logistic regression represents a novel methodological aspect of this study, ensuring more stable estimates of the regression coefficients and confidence intervals compared to traditional methods. This technique enhances statistical robustness, particularly in clinical datasets with skewed distributions and heterogeneous patient populations. Our findings confirm the independent prognostic significance of both the SOFA and REDS scores, while D-dimer did not reach statistical significance in the multivariate model.

The calibration of the predictive model was evaluated across deciles of predicted mortality risk using the Hosmer–Lemeshow goodness-of-fit test, which yielded $p > 0.05$ for the overall model ($\chi^2 = 11.285$; df = 8; $p = 0.186$). This indicates that there was no statistically significant difference between the observed and expected mortality rates across all risk deciles (Table 6). The observed and expected mortality frequencies, as presented in Table 6, demonstrate satisfactory model calibration and internal validity, supporting its ability to stratify patients reliably across the full spectrum of disease severity. Such adequate calibration strengthens the model's clinical applicability by ensuring stable and trustworthy risk estimates that can aid early decision-making, optimize resource allocation, and guide individualized management strategies in critically ill patients.

The CHAID decision tree analysis was employed to identify the most relevant predictors of 28-day mortality in critically ill patients. Among the evaluated variables—SOFA score, REDS score, and D-dimer – only the REDS score remained in the final model, highlighting its important predictive value within this cohort (Figure 4) . The resulting tree had a simple structure with one major split (depth = 1), dividing patients into three terminal nodes based on REDS score thresholds. Mortality rates increased progressively across these groups, from 42.9% in patients with REDS ≤2, to 66.1% in those with scores between 2.1–4.0, and reaching 84.5% in those with scores >4.0. This stratification demonstrates the REDS score's strong

discriminatory ability and practical clinical utility for early risk assessment. The simplicity of the model enhances its applicability in real-time decision-making; however, the absence of internal or external validation limits the ability to generalize these findings beyond the current sample and warrants further evaluation in broader patient populations.

DISCUSSION

This study provides important insights into the prognostic performance of early clinical indicators – SOFA score, REDS score, and D-dimer – in critically ill COVID-19 patients with sepsis. Consistent with prior research, our findings show that while none of these markers alone achieves ideal accuracy, the REDS score demonstrates the highest sensitivity and negative predictive value (NPV), underscoring its value as an effective initial triage tool to identify low-risk patients. This aligns with the intended role of rapid assessment tools for early deterioration, highlighting their broader clinical applicability in patients with sepsis and the potential to improve timely interventions and resource allocation [7, 9, 11].

Conversely, the SOFA score exhibited superior specificity and positive predictive value (PPV), reinforcing its utility in confirming patients at higher mortality risk. These complementary characteristics suggest that SOFA and REDS scores serve distinct but synergistic roles in risk stratification [12–15]. The D-dimer, despite moderate sensitivity, showed wide confidence intervals around cut-off points, reflecting biological variability and highlighting the challenges of relying on coagulation markers alone for prognostication in this context. This observation resonates with emerging literature documenting inconsistent predictive utility of D-dimer across heterogeneous COVID-19 cohorts [16–19].

Importantly, the overlapping confidence intervals for the Youden indices emphasize that these markers are best utilized in combination rather than isolation, supporting a multimodal prognostic strategy. Clinically, a REDS score >2 may serve as an early alert prompting closer monitoring and resource allocation, whereas a SOFA score >4 could guide escalation of care decisions. Incorporation of D-dimer into composite models may add incremental value but requires further validation [20, 21].

Our multivariate logistic regression analysis substantiates the independent prognostic significance of both REDS and SOFA scores, with each point increase correlating with a 22% rise in mortality odds, even after adjustment for key comorbidities. This reinforces the robustness of these scores as bedside tools reflecting organ dysfunction severity rather than mere comorbidity burden. Interestingly, common comorbidities including hypertension and diabetes were not independently predictive, suggesting their effects may be mediated through clinical deterioration captured by these scoring systems [22]. Male sex emerged as an additional independent risk factor, consistent with documented sex disparities in COVID-19 outcomes [23].

The CHAID decision tree analysis further illustrates the clinical utility of the REDS score by stratifying patients into clear mortality risk groups based on simple thresholds. In the era of precision medicine, such machine-learning–based models offer scalable, interpretable tools to augment clinician judgment and tailor management strategies [24]. Our findings support integrating decision tree models with validated scores like REDS to enhance real-time ICU triage, ultimately improving individualized care and resource optimization.

Calibration analysis is an important step in evaluating predictive models across diverse clinical populations [25, 26]. For example, it has been applied in neurological patients, and in our study, the model showed good alignment between observed and predicted 28-day mortality across

risk deciles in critically ill COVID-19 patients with sepsis, supporting its potential reliability for early clinical decision-making.

During the COVID-19 pandemic, careful prioritization of emergency and elective cases became a critical aspect of hospital management, with clear guidelines emphasizing that only urgent, non-deferrable cases should be treated immediately to reduce hospital crowding and protect both patients and healthcare staff [27]. The identification of effective laboratory biomarkers that could stratify patients at risk of developing severe forms of the disease is imperative to ensure they receive prompt medical treatment [28]. In this context, the implementation of relatively simple and rapidly applicable scoring systems such as REDS and SOFA can facilitate the early identification of high-risk patients, enabling clinicians to prioritize treatment and optimize outcomes. These tools, together with biomarker such as D-dimer may play an important role in guiding appropriate and timely therapy in patients with severe forms of COVID-19 and sepsis.

Limitations of this study include its retrospective design, single-center setting, and modest sample size, which may affect generalizability. The absence of external validation warrants cautious interpretation and underlines the need for prospective, multicenter studies to confirm and refine these predictive models.

CONCLUSION

This study demonstrates that among critically ill COVID-19 patients with sepsis, the REDS score is a robust and independent predictor of 28-day mortality, outperforming both SOFA score and D-dimer levels in risk stratification. The application of CHAID decision tree analysis further confirms the REDS score's practical utility in categorizing patients into distinct

mortality risk groups, facilitating timely clinical decision-making. Bootstrap-validated logistic regression reinforces the reliability of these findings despite the retrospective design and sample size limitations. These results support the integration of the REDS score into ICU protocols to improve early identification of high-risk patients and optimize resource allocation.

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REFERENCES

1. Lavrentieva A, Kaimakamis E, Voutsas V, Bitzani M. An observational study on factors associated with ICU mortality in Covid 19 patients and critical review of the literature. Sci Rep. 2023;13(1):7804. [DOI:10.1038/s41598-023-34613-x] [PMID: 37179397]
2. Llitjos JF, Carrol ED, Osuchowski MF, Bonneville M, Scicluna BP, Payen D, et al. Enhancing sepsis biomarker development: key considerations from public and private perspectives. Crit Care. 2024;28(1):1–15. [DOI: 10.1186/s13054-024-05032-9] [PMID: 39003476]
3. Van den Berg M, van Beuningen FE, ter Maaten JC, Bouma HR. Hospital-related costs of sepsis around the world: A systematic review exploring the economic burden of sepsis. J Crit Care. 2022;71:154096. [DOI: 10.1016/j.jcrc.2022.154096] [PMID: 35839604]
4. Duncan CF, Youngstein T, Kirrane MD, Lonsdale DO. Diagnostic Challenges in Sepsis. Curr Infect Dis Rep. 2021;23(12):22. [DOI: 10.1007/s11908-021-00765-y] [PMID: 34720754]
5. Heubner L, Hattenhauer S, Güldner A, Petrick PL, Rößler M, Schmitt J, et al. Characteristics and outcomes of sepsis patients with and without COVID-19. J Infect Public Health. 2022;15(6):670–6. [DOI: 10.1016/j.jiph.2022.05.008] [PMID: 35617831]
6. Thodphetch M, Chenthanakij B, Wittayachamnankul B, Sruamsiri K, Tangsuwanaruk T. A comparison of scoring systems for predicting mortality and sepsis in the emergency department patients with a suspected infection. Clin Exp Emerg Med. 2021;8(4):289–95. [DOI: 10.15441/ceem.20.145] [PMID: 35000356]
7. Sivayoham N, Mara HO, Turner NT, Sysum K, Wicks G, Mason O. Validation of the REDS score in hospitalised patients who deteriorated and were admitted to the intensive care unit — a retrospective cohort study. BMJ Open Qual 2025;14(1): e003054. [DOI: 10.1136/bmjoq-2024-003054] [PMID: 39762056]
8. Sivayoham N, Hussain AN, Shabbo L, Christie D. An observational cohort study of the performance of the REDS score compared to the SIRS criteria, NEWS2, CURB65, SOFA, MEDS and PIRO scores to risk-stratify emergency department suspected sepsis. Ann Med. 2021;53(1):1863–74. [DOI: 10.1080/07853890.2021.1992495] [PMID: 34686088]
9. Sheerin T, Dwivedi P, Hussain A, Sivayoham N. Performance of the CURB65, NEWS2, qSOFA, SOFA, REDS, ISARIC 4C, PRIEST and the Novel COVID-19 Severity Scores, Used to Risk-Stratify Emergency Department Patients with COVID-19, on Mortality – An Observational Cohort Study. COVID. 2023;3(4):555–66. [DOI: 10.3390/covid3040040]
10. Kumar MCH, Chabba SK, Udasimath S, Ravishankar G, Sushma MKM, Gadwal NV. Study of Inflammatory Markers - CRP , D-dimer , and Ferritin in COVID- 19 Positive patients - A Retrospective Study. European Journal of Cardiovascular Medicine (EJCM) 2025;5(15):699–703. [DOI : 10.5083/ejcm/25-05-128]
11. Rahmoun M Al, Sabaté-elabbadi A, Guillemot D, Brun-buisson C, Watier L. Impacts of the COVID-19 pandemic on sepsis incidence, etiology and hospitalization costs in France: a retrospective observational study. BMC Infec Dis. 2025;25:627 [DOI: 10.1186/s12879-025-11000-7] [PMID: 40301806]
12. Esmaeili Tarki F, Afaghi S, Rahimi FS, Kiani A, Varahram M, Abedini A. Serial SOFA-score trends in ICU-admitted COVID-19 patients as predictor of 28-day mortality: A prospective cohort study. Heal Sci Reports. 2023;6(5):1–8. [DOI: 10.1002/hsr2.1116] [PMID: 37152236]
13. Lee HJ, Ko BS, Ryoo SM, Han E, Suh GJ, Choi SH, et al. Modified cardiovascular SOFA score in sepsis: development and internal and external validation. BMC Med. 2022;20(1):1–15. [DOI:10.1186/s12916-022-02694-6] [PMID: 36482459]
14. Sherak RAG, Sajjadi H, Khimani N, Tolchin B, Jubanyik K, Taylor RA, et al. SOFA score performs worse than age for predicting mortality in patients with COVID-19. PLoS One. 2024;19:1–12. [DOI: 10.1371/journal.pone.0301013] [PMID: 38758942]
15. Munim FA, Yusof AM, Cheah SK, Khazrul M, Abd N, Rahiza W, et al. SOFA Score Trends in Predicting Mortality in Critically Ill COVID-19 Patients. COVID 2025;5(9):154. [DOI: 10.3390/covid5090154]
16. Dumache R, Muresan CO, Maria S, Laitin D, Ivanovic N, Chisalita A, et al. COVID-19 Organ Injury Pathology and D-Dimer Expression Patterns: A Retrospective Analysis. Diagnostics. 2025;15(15):1860 [DOI: 10.3390/diagnostics15151860]
17. Benfathallah B, Boutagayout A, Hassani AC, Ihazmade H. Dynamic Relationship Between High D-Dimer Levels and the In-Hospital Mortality Among COVID-19 Patients: A Moroccan Study. COVID. 2025;5(8):116 [DOI:10.3390/covid5080116]
18. Akerman M, Joseph DA. Role of peak D-dimer in predicting mortality and venous thromboembolism in COVID-19 patients. Science Progress. 2025;108(1):1–19. [DOI: 10.1177/00368504241247982]
19. Bozorgmehr R, Shams N, Akbarniakhan H, Alirezaei T. D-dimer Levels as a Prognostic Inpatient Mortalit y Indicator in COVID-19 Patients: Insights from a Cross-Sectional Study. Int Jour of Cardiovas Prac. 2025;10(2): e162064. [DOI:10.5812/intjcardiovascpract-162064]

20. Reddy V, Reddy H, Gemnani R, Kumar S, Acharya S. Navigating the Complexity of Scoring Systems in Sepsis Management: A Comprehensive Review. Cureus. 2024;16(2):e54030. [DOI: 10.7759/cureus.54030] [PMID: 38481909]
21. Silingardi M, Zappulo F, Dormi A, Pizzini AM, Donadei C, Cappuccilli M, et al. Is COVID-19 Coagulopathy a Thrombotic Microangiopathy? A Prospective, Observational Study. Int J Mol Sci. 2025;26(11):5395. [DOI: 10.3390/ijms26115395]
22. König S, Vaskyte U, Boesing M, Lüthi-corridori G, Leuppi JD. The Role of Comorbidities in COVID-19 Severity. Viruses. 2025;17(7):957. [DOI: 10.3390/v17070957] [PMID: 40733574]
23. Kaim A, Shetrit SB, Saban M. Women Are More Infected and Seek Care Faster but Are Less Severely Ill: Gender Gaps in COVID-19 Morbidity and Mortality during Two Years of a Pandemic in Israel. Healthcare 2022, 10(12), 2355 [DOI: 10.3390/healthcare10122355] [PMID: 36553879]
24. Mohammadi-Pirouz Z, Hajian-Tilaki K, Haddat-Zavareh MS, Amoozadeh A, Bahrami S. Development of decision tree classifcation algorithms in predicting mortality of COVID-19 patients. International Journal of Emergency Medicine. 2024;17:126 [DOI: 10.1186/s12245-024-00681-7] [PMID: 39333862]
25. Poopipatpab S, Weerayutwattana R, Nuchpramool P, Phairatwet P. Evaluation of physiological severity scores for predicting COVID-19 disease progression: a retrospective study. BMC Infect Di. 2025;25(1):758. [DOI: 10.1186/s12879-025-11127-7] [PMID: 40419986]
26. Lee YS, Han S, Lee YE, Cho J, Choi YK, Yoon SY, et al. Development and validation of an interpretable model for predicting sepsis mortality across care settings. Scientific reports Nature. 2024;14(1):13637. [DOI: 10.1038/s41598-024-64463-0] [PMID: 38871785]
27. Ozturan B, Okay E, Yildiz Y, Iyetin Y, Demiroglu M, Ozkan K. Management of resources for orthopedic oncology and trauma patients during the COVID-19 pandemic – a retrospective cohort study. Srp Arh Celok Lek. 2022;150(3–4):138–42. [DOI: 10.2298/SARH210318027O]
28. Radojičić B, Dolić M, Taušan Đ, Radojičić M, Mišović M. Comparison of baricitinib and tocilizumab in clinical outcome among hospitalized patients with severe form of COVID-19 – our experiences. Srp Arh Celok Lek. 2025 (Online First) [DOI: 10.2298/SARH250108083R]

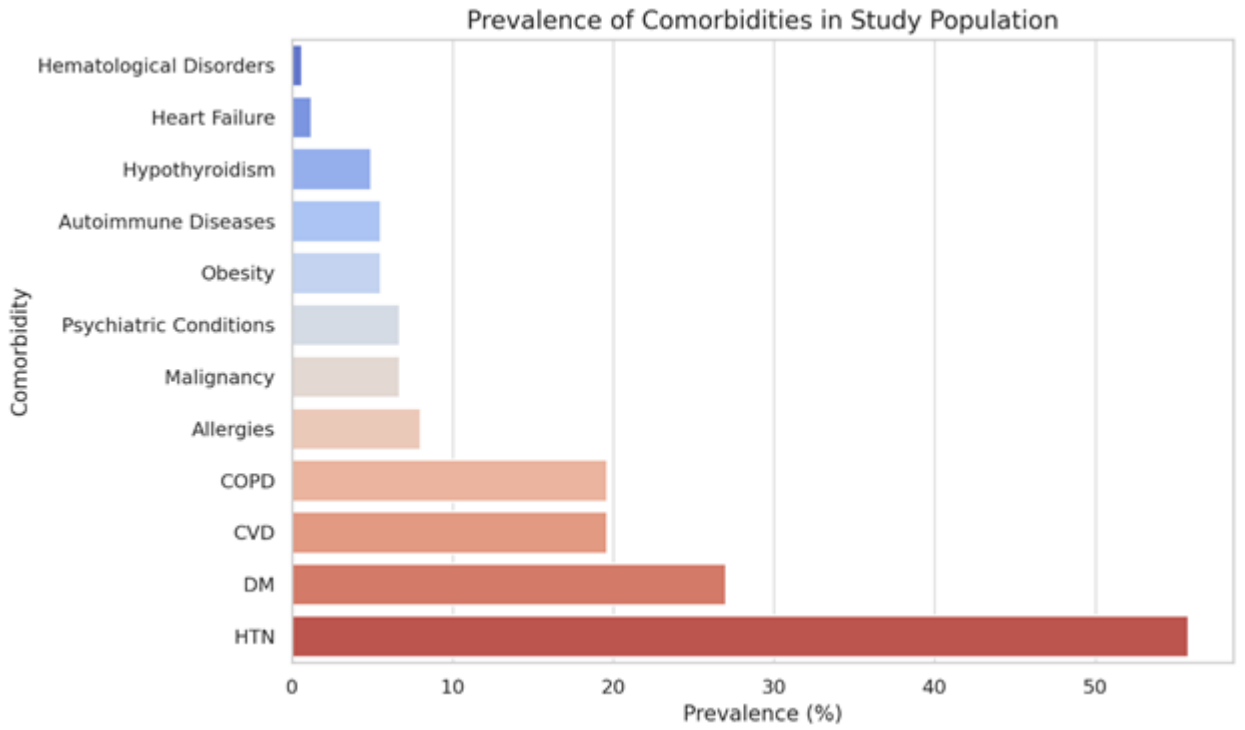

Figure 1. Prevalence of comorbidities in the patient cohort, with hypertension (HTN) (55.8%) and diabetes mellitus (DM) (27%) as the most frequent conditions; cardiovascular disease (CVD) and chronic obstructive pulmonary disease (COPD) rank third and fourth in prevalence, respectively; this distribution highlights the common occurrence of multiple underlying diseases that may influence patient prognosis and clinical management

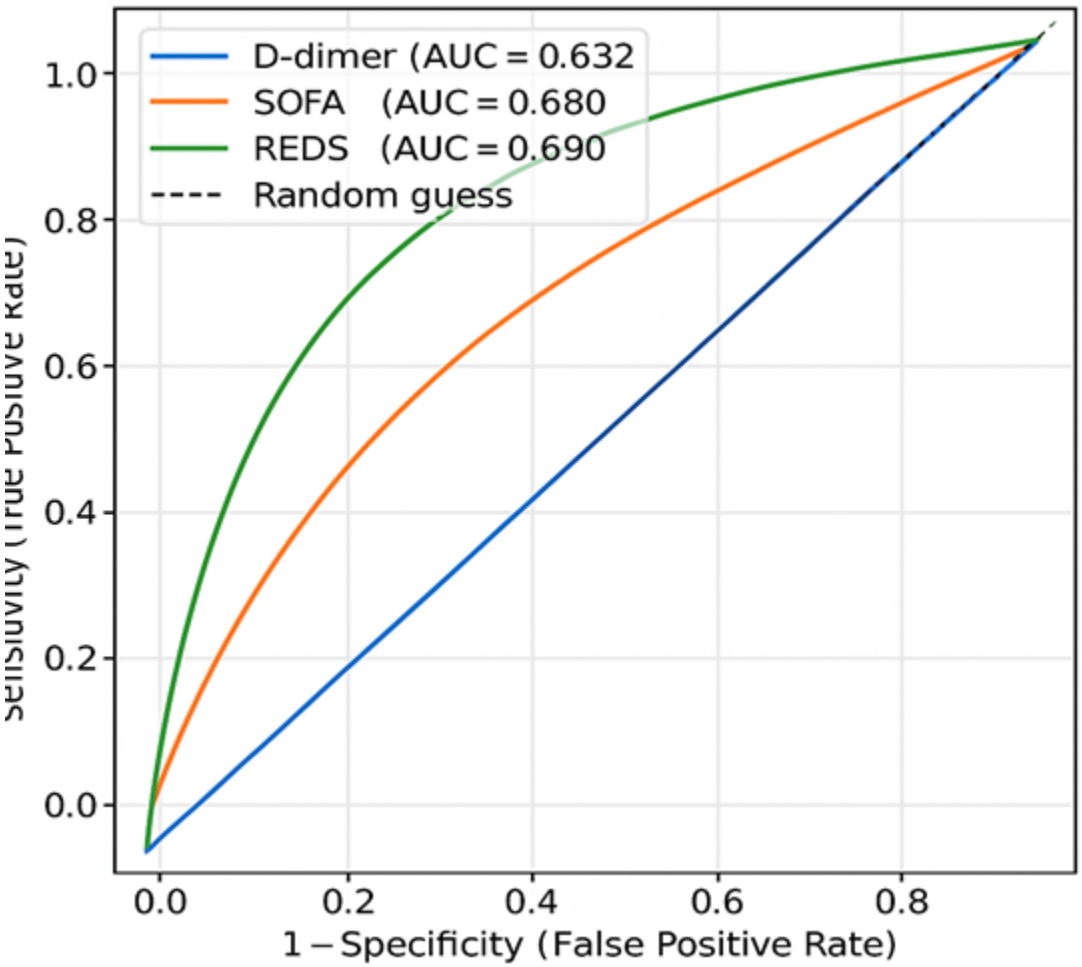

Figure 2. ROC curves for D-dimer, sequential organ failure assessment (SOFA), and risk-stratification of emergency department sepsis (REDS) scores showing their predictive accuracy for 28-day mortality; AUC values indicate the discriminative performance of each tool

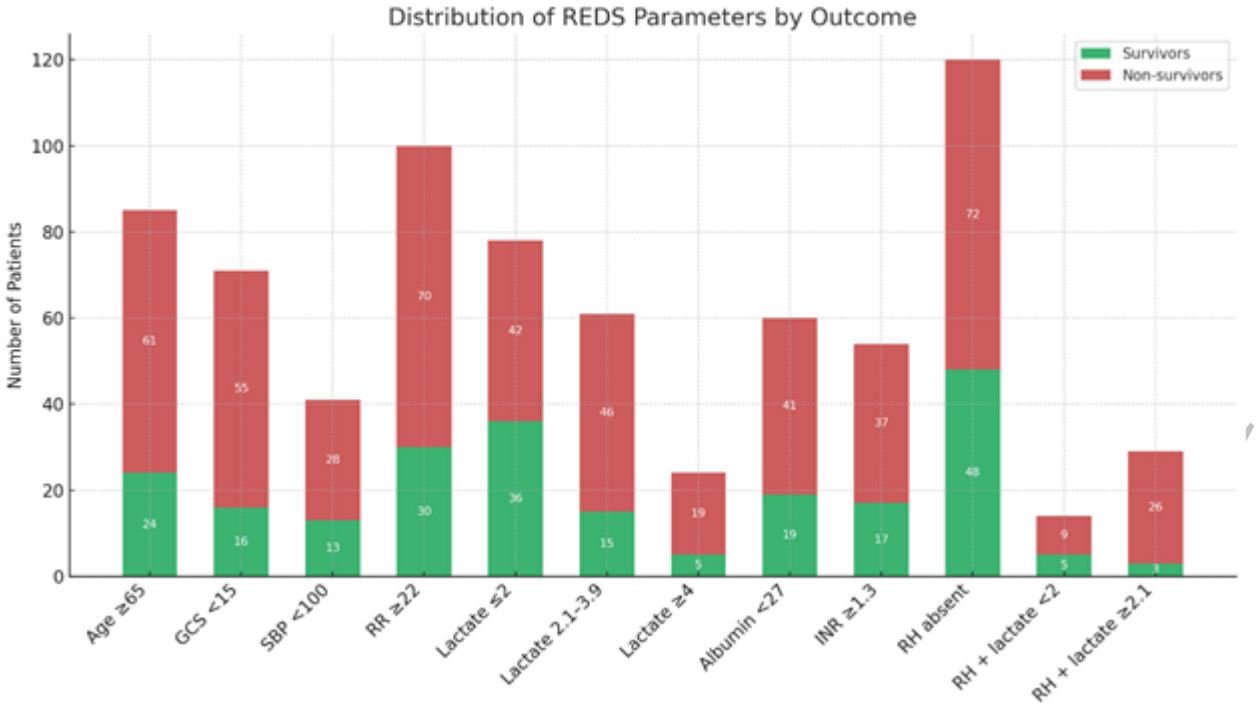

Figure 3. Distribution of risk-stratification of emergency department sepsis (REDS) parameters by outcome; lactate values are expressed in mmol/L, and albumin in g/L; GCS – Glasgow coma scale; SBP – systolic blood pressure; RR – respiratory rate; INR – international normalized ratio; RH – refractory hypotension

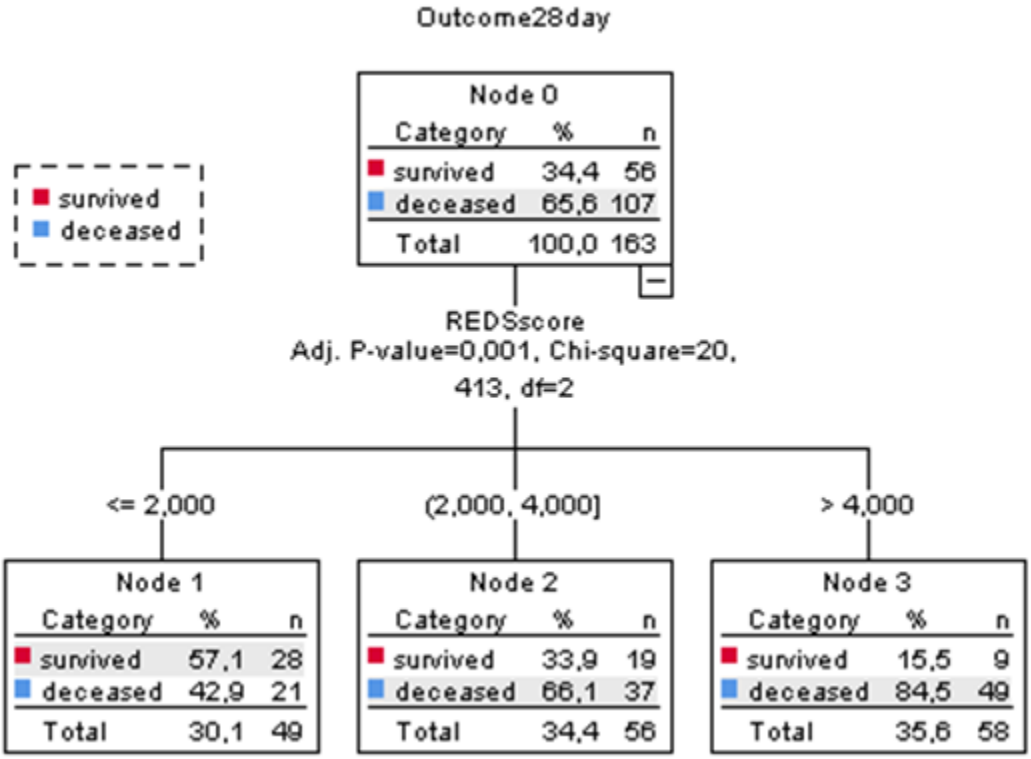

Figure 4. Decision tree model stratifying 28-day mortality outcomes using risk-stratification of emergency department sepsis (REDS) score

Table 1. AUC ROC curve analysis for D-dimer, sequential organ failure assessment (SOFA) and risk-stratification of emergency department sepsis (REDS) scores for predicting 28-day mortality

Parameters	AUC ROC	SE	95% CI for AUC ROC	p
D-dimer	0.632	0.047	0.551–0.707	**0.005**
SOFA	0.680	0.042	0.603–0.751	**< 0.001**
REDS	0.690	0.043	0.613–0.760	**< 0.001**

SE – standard error; CI – confidence interval; p – probability that AUC differs from 0.5 (no discrimination); all AUC values between 0.6–0.7 indicate moderate discrimination; p-values indicate significance of AUC versus 0.5 (no discrimination)

Table 2. Optimal cut-off, sensitivity, specificity, PPV and NPV for D-dimer, SOFA and REDS

Parameters	Youden index	95% CI Youden index	Optimal cut-off value	95% CI for cut-off value	SENS (%)	SPEC (%)	PPV	NPV
D-dimer	0.25	0.13-0.37	> 1425	> 1028 - > 8253	76.47	49.09	73.6	52.9
SOFA	0.28	0.16-0.42	> 4	> 3 - < 6	72.64	56.14	75.5	52.5
REDS	0.29	0.14-0.40	> 2	> 1 - < 4	80.19	49.12	61.2	71.3

CI – confidence interval; SENS – sensitivity; SPEC – specificity; PPV – positive predictive value; NPV – negative predictive value; SOFA – sequential organ failure assessment; REDS – risk-stratification of emergency department sepsis

Table 3. Individual REDS parameters: comparison between survivors and non-survivors (n = 163)

REDS Component	Survivors n = 56	Non-survivors n = 107	χ^2 (df)	p
Age ≥ 65 years	24 (42.9%)	61 (57.0%)	2.95 (1)	0.086
GCS < 15	16 (28.6%)	55 (51.4%)	7.79 (1)	**0.005**
SBP < 100 mmHg	13 (23.2%)	28 (26.2%)	0.17 (1)	0.680
RR ≥ 22/min	30 (53.6%)	70 (65.4%)	2.18 (1)	0.140
Lactate (categorical: ≤ 2 / 2.1–3.9 / ≥ 4 mmol/L)	36 (64.3%) / 15 (26.8%) / 5 (8.9%)	42 (39.3%) / 46 (43.0%) / 19 (17.8%)	9.34 (2)	**0.009**
Albumin < 27 g/L	19 (34.5%)	41 (38.7%)	0.27 (1)	0.607
INR ≥ 1.3	17 (30.9%)	37 (34.9%)	0.26 (1)	0.610
Refractory hypotension + lactate: — RH absent — RH + lactate < 2 — RH + lactate ≥ 2.1	48 (85.7%) 5 (8.9%) 3 (5.4%)	72 (67.3%) 9 (8.4%) 26 (24.3%)	9.12 (2)	**0.010**

REDS – risk-stratification of emergency department sepsis; GCS – Glasgow coma scale; SBP – systolic blood pressure; RR – respiratory rate; INR – international normalized ratio; RH – refractory hypotension; ;lactate values are categorized as ≤ 2.0, 2.1–3.9, and ≥ 4.0 mmol/L; albumin < 27 g/L and INR ≥1.3 indicate hypoalbuminemia and coagulopathy, respectively; refractory hypotension in combination with elevated lactate (≥ 2.1 mmol/L) reflects the highest circulatory risk subgroup; χ^2 values with degrees of freedom (df) were used to assess the association between each REDS component and 28-day mortality

Table 4. Logistic regression summary table – multivariate model

Variable	B (Beta)	p	Exp(B) (OR)	Interpretation
SOFA score	0.204	0.024	1.226	Each 1-point increase in SOFA raises death risk by 22.6%
D-dimer	0.000	0.050	1.000	Marginally significant; very weak or negligible effect
REDS score	0.203	0.050	1.225	Each 1-point increase in REDS raises death risk by 22.5%
Sex (Male)	1.018	0.012	2.766	Males have 2.77 times higher risk of death compared to females
HTN	0.391	0.332	1.479	Not significant when adjusted for other variables
DM	0.147	0.755	1.159	Not significant
CVD	0.073	0.883	1.075	Not significant
COPD	0.724	0.145	2.062	Not statistically significant
Allergies	1.042	0.162	2.834	Not statistically significant

Logistic regression analysis of predictors of mortality in critically ill COVID-19 patients; B – regression coefficient; Exp(B) – odds ratio (OR); p-values ≤ 0.05 are considered statistically significant; in the multivariate logistic regression model, each 1-point increase in sequential organ failure assessment (SOFA) or risk-stratification of emergency department sepsis (REDS) scores was associated with an approximately 22% increase in the odds of 28-day mortality (OR = 1.226 for SOFA and OR = 1.225 for REDS; p ≤ 0.05 for both); male sex was also identified as an independent predictor of mortality, with males having nearly 2.8 times higher risk compared to females; other comorbidities [hypertension (HTN), diabetes mellitus (DM), cardiovascular disease (CVD), chronic obstructive pulmonary disease (COPD), allergies] did not show statistically significant associations with mortality in the multivariate model

Table 5. Multivariate logistic regression with bootstrap (1000 samples)

Variable	B (Coefficient)	Std. Error	p (Sig. 2-tailed)	95% CI – Lower	95% CI – Upper
SOFA score	0.188	0.077	**0.005**	0.044	0.355
D-dimer	0.000	0.000	0.143	0.000	0.000
REDS score	0.195	0.107	**0.049**	0.014	0.448
Constant	-1.421	0.525	**0.003**	-2.527	-0.447

(Outcome: in-hospital mortality) – multivariate logistic regression with bootstrap resampling (1000 samples) identified sequential organ failure assessment (SOFA) and risk-stratification of emergency department sepsis (REDS) scores as independent predictors of mortality in critically ill COVID-19 patients with sepsis; the 95% confidence intervals for SOFA and REDS excluded zero, supporting their prognostic relevance

Table 6. Observed *vs*. expected 28-day mortality by deciles of predicted risk

Decile of Predicted Probability	Observed Deaths (n)	Total Patients (n)	Observed Mortality (%)	Expected Deaths (n)	Expected Mortality (%)
1 (lowest risk)	5	16	31.3	10.5	65.6
2	5	16	31.3	10.5	65.6
3	10	17	58.8	11.2	65.9
4	10	16	62.5	10.5	65.6
5	9	16	56.3	10.5	65.6
6	15	17	88.2	11.2	65.9
7	11	16	68.8	10.5	65.6
8	15	17	88.2	11.2	65.9
9	14	16	87.5	10.5	65.6
10 (highest risk)	13	16	81.3	10.5	65.6
Total	107	163	65.6	107	65.6

The table displays the observed and expected mortality within each decile of predicted death probability; the "observed mortality (%)" column shows the actual mortality rate in each decile, while the "expected mortality (%)" reflects the model's predicted mortality; consistency between observed and expected mortality across deciles indicates good calibration of the predictive model

