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COVID-19 and Diabetes: Clinical Symptoms, Acute Kidney Injury, Inflammatory Response, and Poor Prognosis Factors

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ADE 1 Nur Özer Şensoy
AB 1 Mehmet Usta
CE 2 Emel Gürcüoğlu
F 3 Alparslan Ersoy
C 4 Mustafa Çağatay Büyükuysal

1 Department of Nephrology, Bursa City Training and Research Hospital, University of Health Sciences, Bursa, Türkiye
2 Department of Infectious Diseases, Bursa City Training and Research Hospital, University of Health Sciences, Bursa, Türkiye
3 Department of Nephrology, Bursa Uludag University Faculty of Medicine, Bursa, Türkiye
4 Department of Biostatistics, School of Medicine, Zonguldak Bulent Ecevit University, Zonguldak, Türkiye

Corresponding Author: Nur Özer Şensoy, Department of Nephrology, University of Health Sciences, Bursa City Training and Research Hospital, Bursa, Türkiye, Telephone: +905414014106, e-mail: nurozer_@hotmail.com

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Background: COVID-19 is associated with morbidity and mortality, particularly among patients with metabolic comorbidities. Diabetes mellitus may adversely affect COVID-19 outcomes. This study aimed to compare demographic, clinical, laboratory, renal, inflammatory, treatment-related, and mortality-related characteristics between COVID-19 patients with and without diabetes.

Material/Methods: This retrospective observational study included 400 hospitalized COVID-19 patients classified as diabetic or non-diabetic using hospital records. Demographic characteristics, comorbidities, clinical presentations, laboratory findings, renal function markers, acute kidney injury, treatment variables, systemic immune-inflammation index (SII), and 90-day all-cause mortality were compared. ROC analysis assessed the discriminatory ability of admission SII for predicting 90-day mortality, and multivariable logistic regression was performed.

Results: A total of 400 patients were included, including 130 with diabetes and 270 without. Patients in the diabetic group were older and had higher rates of hypertension and coronary artery disease. Respiratory symptoms and pneumonia were more frequent in the diabetic group. Renal function markers were significantly higher in the diabetic group; however, acute kidney injury, ICU admission, mechanical ventilation rates, and SII did not differ significantly between groups. During 90-day follow-up, mortality was higher in the diabetic group (15.4% vs 8.1%; *P*=0.030). In multivariable analysis, age, coronary artery disease, and SII greater than 2135.28 were associated with 90-day mortality. Admission SII showed modest discriminatory ability for predicting mortality (AUC=0.623; *P*=0.015).

Conclusions: Among patients hospitalized with COVID-19, diabetes was associated with higher comorbidity burden, respiratory involvement, altered renal function markers, and higher unadjusted 90-day mortality. Adjusted mortality was associated with age, coronary artery disease, and high admission SII.

Keywords: COVID-19 • Diabetes Mellitus • Kidney Failure, Chronic • Inflammation • Renal Insufficiency

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Introduction

The COVID-19 pandemic has profoundly affected global health, particularly among populations with chronic comorbidities [1]. Patients with conditions such as diabetes mellitus are known to experience higher morbidity and mortality due to the interplay of underlying metabolic and immunologic disturbances [2]. Persistent low-grade inflammation, impaired innate and adaptive immune responses, and metabolic instability in individuals with diabetes create a vulnerable milieu that facilitates more severe disease progression and unfavorable clinical outcomes when exposed to viral infections with multisystem involvement such as SARS-CoV-2 [3].

The presence of diabetes is a significant risk factor for the development of acute and chronic kidney disease, and the development of acute kidney injury (AKI) is a major factor increasing mortality. SARS-CoV-2 infection can also facilitate the development of AKI. Therefore, patients with COVID-19 and diabetes are at risk for developing AKI. Our knowledge of the literature on this subject is insufficient. The systemic ınflammation ındex (SII) is derived from routine hematological parameters (platelet, neutrophil, and lymphocyte counts) [4]. Because the SII can be derived from routine complete blood count tests, it has practicality and suitability for widespread clinical use, providing a composite measure of immune and inflammatory activity. The SII, which is associated with increased systemic inflammation and adverse outcomes, has been shown to be an effective and important biomarker in different patient populations [4].

In this context, the present study aimed to investigate the effect of COVID-19 on patients with diabetes, focusing particularly on the inflammatory and concomitant renal damage mechanisms associated with adverse outcomes of diabetes. By evaluating the clinical and laboratory findings in this high-risk group, we can provide a timely contribution to the medical literature on the risk stratification and management of diabetic populations during viral pandemics.

Material and Methods

This retrospective observational study was conducted at Bursa City Hospital, Department of Internal Medicine, between 2019 and 2022. Hospitalized patients diagnosed with COVID-19 were retrospectively identified through the hospital information management system. Among 427 screened patients, 400 patients with complete data were included in the study. The accuracy, completeness, and consistency of the data were carefully evaluated.

The study population was divided into 2 groups: patients with diabetes mellitus (n=130) and those without diabetes mellitus (n=270). Demographic, clinical, laboratory, renal, inflammatory, treatment-related, and mortality-related characteristics were compared between the 2 groups. Patients younger than 18 years of age, patients with incomplete medical records, and patients who completed their treatment process at another institution were excluded from the analysis.

The study was conducted with the approval of the Bursa City Hospital Ethics Committee (protocol No: 2022-14/13, 26.10.2022). Since this was a retrospective data analysis, individual patient consent was not required. The study was conducted in accordance with the Declaration of Helsinki, and patient data were anonymized before analysis.

COVID-19 diagnosis was made in accordance with the guidelines of the World Health Organization (WHO) and national health authorities, based on either reverse transcription polymerase chain reaction positivity from nasopharyngeal swab samples or characteristic clinical and radiological findings [5]. The diagnosis of diabetes mellitus was established using hospital records, including endocrinology consultation reports, documented history of antidiabetic treatment, or a previously confirmed diagnosis according to the criteria of the WHO or the American Diabetes Association [6].

AKI was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria as an increase in serum creatinine of 0.3 mg/dL or greater within 48 hours or an increase to 1.5 times or greater than the baseline value within 7 days. AKI was identified using serum creatinine measurements recorded during hospitalization. Pre-existing chronic kidney disease was recorded separately when documented in the medical records [7].

Clinical, laboratory, and radiological data were obtained from the hospital information management system. Demographic characteristics, such as age and sex; comorbidities, including hypertension, chronic kidney disease, and coronary artery disease; initial symptoms, including fever, cough, and dyspnea; and physical examination findings, including blood pressure, pulse, body temperature, and oxygen saturation, were recorded. Laboratory parameters included complete blood count parameters, biochemical and inflammatory markers, renal function markers, liver enzymes, D-dimer, and electrolyte levels. Laboratory test results obtained at admission or within the first 24 hours were considered for analysis.

Radiological data were extracted from chest radiography and/or thoracic computed tomography reports available in the hospital information management system. Pneumonia was recorded as present when the radiology report or clinical diagnosis documented COVID-19–compatible pulmonary infiltrates, ground-glass opacities, consolidation, or pneumonia.

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The variable "radiological finding" was defined more broadly as the presence of any abnormal chest imaging finding reported during the index hospitalization, including but not limited to pneumonia-compatible findings. Therefore, pneumonia represented a specific radiological and clinical diagnosis, whereas "radiological finding" represented a broader binary imaging abnormality variable.

The SII was calculated using the following formula [8]:
SII = platelet count × neutrophil count / lymphocyte count.

All parameters used for SII calculation were obtained from routine complete blood count measurements at hospital admission and expressed as absolute cell counts.

Treatment approaches, including hydroxychloroquine, favipiravir, remdesivir, antibiotics, low-molecular-weight heparin, and corticosteroids, were evaluated. In addition, intensive care unit (ICU) admission rates and duration, as well as the use and duration of noninvasive mechanical ventilation and invasive mechanical ventilation, were recorded.

The primary endpoint of the study was 90-day all-cause mortality from the date of hospital admission, compared between hospitalized COVID-19 patients with and without diabetes mellitus. Mortality status was obtained from electronic medical records and coded as death or survival during the 90-day follow-up period. Cause-specific mortality was not evaluated, because systematic cause-of-death adjudication was not performed.

Secondary endpoints included demographic and baseline clinical characteristics, comorbidities, presenting symptoms, radiological findings, renal function markers, AKI, inflammatory and hematological parameters (including SII), ICU admission and duration, need and duration of noninvasive and invasive mechanical ventilation, and treatment-related variables. Because no formal COVID-19 severity score or predefined composite severity endpoint was used in this retrospective cohort, disease severity was not analyzed as a separate scale-based outcome. Instead, measurable clinical outcome indicators were evaluated and compared between the diabetic and non-diabetic groups.

As secondary analyses, the associations of diabetes status and admission SII with 90-day all-cause mortality were evaluated.

Statistical Analysis

Statistical analyses were performed using SPSS software (IBM Corp; IBM SPSS Statistics for Windows, Version 25.0, Armonk, NY, USA). The normality of distribution for continuous variables was assessed using the Shapiro-Wilk test. Continuous variables that did not follow a normal distribution are reported as median (minimum-maximum) values, and comparisons between groups were performed using the Mann-Whitney U test. Normally distributed continuous variables are expressed as mean±standard deviation (SD), and comparisons were performed using the independent samples *t* test. Categorical variables are presented as frequencies and percentages (n [%]), and differences between groups were evaluated using the chi-square test or Fisher exact test when the expected cell counts were less than 5 in contingency tables.

All-cause mortality was evaluated over the 90-day follow-up period using Kaplan-Meier survival analysis. Patients who were alive at 90 days were censored at the end of follow-up. Survival curves were compared between the diabetic and non-diabetic groups using the log-rank test.

Receiver operating characteristic (ROC) curve analysis was performed in the overall study cohort to evaluate the discriminatory ability of admission SII for predicting 90-day all-cause mortality. The ROC analysis was not restricted to the diabetic subgroup. The state variable was 90-day all-cause mortality, coded as 1 for death and 0 for survival. The area under the ROC curve (AUC) and 95% confidence interval (CI) were calculated. The optimal SII cut-off value was determined using the Youden index. Therefore, the reported AUC, cut-off value, sensitivity, and specificity apply to the overall cohort [9,10].

To address potential confounding due to baseline imbalances between the diabetic and non-diabetic groups, multivariable logistic regression analysis was performed to identify factors independently associated with 90-day all-cause mortality. Clinically relevant variables and major baseline imbalances, including age, sex, hypertension, coronary artery disease, diabetes mellitus, and high SII category, were considered for inclusion in the model. High SII was defined according to the ROC-derived cut-off value of 2135.28. Results were reported as odds ratios (ORs) with 95% CIs. Model performance was assessed using Nagelkerke R^2. Variables not independently associated with mortality were not retained in the final model.

Analyses were performed using available data for each variable, and missing values were not imputed. Unless otherwise specified, the denominators were n=130 for the diabetic group and n=270 for the non-diabetic group. For variables with missing values, the available denominators are reported in the relevant tables.

Sample size calculation was performed based on mortality rates reported in previous studies. Mortality was assumed to be 34.3% in COVID-19 patients with diabetes and 17.7% in patients without diabetes [11]. With a diabetic to non-diabetic ratio of 1: 2, a 2-sided alpha level of 0.05, and a power of 80%, at least 79 patients with diabetes and 158 patients without diabetes were required.

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A type I error level of 5% ($P<0.05$) was considered statistically significant for all analyses. Because multiple clinical, treatment-related, and laboratory variables were compared in this exploratory observational analysis, *P* values were interpreted as nominal and should be considered hypothesis-generating rather than confirmatory. No formal adjustment for multiple comparisons was applied.

Results

The study included 400 hospitalized patients with COVID-19, who were divided into 2 groups according to diabetes status: diabetic group (n=130) and non-diabetic group (n=270). **Table 1** summarizes the demographic and baseline clinical characteristics of the study population. Patients in the diabetic group were older than those in the non-diabetic group (median age, 66.7 vs 63.6 years; $P=0.010$) and the proportion of female patients was higher in the diabetic group (47.7% vs 33.3%; $P=0.006$). Hypertension (70.0% vs 26.7%; $P<0.001$) and coronary artery disease (34.6% vs 13.7%; $P<0.001$) were also significantly more prevalent in the diabetic group, indicating a higher cardiovascular comorbidity burden. At admission, patients in the diabetic group were more frequently symptomatic (100% vs 96.3%; $P=0.034$). Dyspnea, dry cough, chest pain, and pneumonia were observed at significantly higher rates in this group. Pneumonia was more frequent among patients in the diabetic group (77.7% vs 67.0%; $P=0.029$), whereas the broader variable of any radiological finding did not differ significantly between groups (93.1% vs 87.8%; $P=0.105$). Conversely, weight loss was more frequently reported in the non-diabetic group (7.8% vs 0.8%; $P=0.004$). No significant differences were observed between the groups for the remaining presenting symptoms.

Clinical findings, complications, supportive respiratory treatments, and pharmacological treatments are presented in **Table 2**. Median systolic blood pressure was significantly higher in the diabetic group than in the non-diabetic group (130 mmHg, range 90-195 vs 120 mmHg, range 80-220; $P<0.001$). Oxygen saturation at admission, diastolic blood pressure, body temperature, and heart rate were not significantly different between groups. AKI occurred in 9 patients in the diabetic group (6.9%) and 12 patients in the non-diabetic group (4.4%), with no statistically significant difference ($P=0.298$). Similarly, arrhythmia, stroke, and thromboembolic events did not differ significantly between groups. ICU admission rates (15.4% vs 17.8%; $P=0.551$) and ICU length of stay (0 days, range 0-39 vs 0 days, range 0-85; $P=0.466$) were comparable between the 2 groups. The need for noninvasive mechanical ventilation (13.1% vs 20.0%; $P=0.090$), duration of noninvasive mechanical ventilation (0 days, range 0-46 vs 0 days, range 0-24; $P=0.094$), need for invasive mechanical ventilation (6.9% vs 8.1%; $P=0.668$), and duration of invasive mechanical ventilation (0 days, range 0-33 vs 0 days, range 0-82; $P=0.653$) were also not significantly different between groups. Treatment-related variables, including the use of hydroxychloroquine, favipiravir, remdesivir, antibiotics, low-molecular-weight heparin, acetylsalicylic acid, corticosteroids, pulse corticosteroids, convalescent plasma, and tocilizumab, were similarly distributed between the 2 groups.

Laboratory findings are shown in **Table 3**. Renal function markers, including urea, blood urea nitrogen, and creatinine, were significantly higher in the diabetic group than in the non-diabetic group (all $P<0.05$). Sodium and magnesium levels were lower in the diabetic group (both $P<0.001$), whereas potassium was higher ($P=0.019$). Glucose levels were markedly higher in the diabetic group ($P<0.001$). Among inflammatory and hematological parameters, procalcitonin ($P=0.046$), platelet distribution width ($P=0.037$), and erythrocyte sedimentation rate ($P=0.048$) were significantly higher in the diabetic group. Hemoglobin, hematocrit, mean corpuscular volume, and mean corpuscular hemoglobin were significantly lower in the diabetic group (all $P<0.05$). However, leukocyte, neutrophil, lymphocyte, monocyte, platelet count, mean platelet volume, C-reactive protein, ferritin, and D-dimer levels were not significantly different between the 2 groups. In addition, international normalized ratio ($P=0.041$), troponin T ($P<0.001$), C3 ($P=0.016$), and cortisol ($P=0.020$) values were higher, whereas free triiodothyronine was lower ($P=0.013$) in the diabetic group. The SII did not differ significantly between the 2 groups (median 1403.41, range 10.98-13272.00 vs 1257.25, range 28.59-16842.22; $P=0.413$).

No patients were lost to follow-up for the 90-day mortality assessment. Mortality was analyzed as 90-day all-cause mortality, and cause-specific mortality was not evaluated. Follow-up time was calculated from the date of hospital admission. Within 90 days after hospital admission, 42 deaths occurred in the overall cohort (10.5%), while 358 patients were alive at day 90 and were censored at the end of follow-up. In the diabetic group, 20 deaths occurred and 110 patients were censored alive at day 90. In the non-diabetic group, 22 deaths occurred and 248 patients were censored alive at day 90. Unadjusted 90-day mortality was higher in the diabetic group than in the non-diabetic group (20/130 patients, 15.4% vs 22/270 patients, 8.1%; $P=0.030$). Kaplan-Meier survival analysis demonstrated significantly lower 90-day survival among patients with diabetes compared with non-diabetic patients (log-rank $P=0.006$; (**Figure 1A, 1B**).

Figure 2 presents the ROC curve evaluating the discriminatory ability of the admission SII for predicting 90-day all-cause mortality in the overall cohort. The ROC analysis included 399 patients with available SII data, including 42 patients who died within 90 days and 357 survivors. Patients who died within 90

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Table 1. Baseline demographic and clinical comparability between groups.

Parameters	Diabetic (n=130)	Non-diabetic (n=270)	*P* value
Age	66.7 (40.4: 89.5)	63.6 (19.4: 93.5)	**0.010**[a]
Sex			
Female	62 (47.7%)	90 (33.3%)	**0.006**[b]
Male	68 (53.3%)	180 (66.7%)	
Allergy, n (%)	5 (3.8%)	8 (3%)	0.764[c]
Hypertension, n (%)	91 (70%)	72 (26.7%)	**<0.001**[b]
Chronic kidney disease, n (%)	15 (11.5%)	24 (8.9%)	0.403[b]
Coronary artery disease, n (%)	45 (34.6%)	37 (13.7%)	**<0.001**[b]
Chronic obstructive pulmonary disease, n (%)	17 (13.1%)	29 (10.7%)	0.493[b]
Congestive heart failure, n (%)	0	2 (0.7%)	>0.99[c]
Pulmonary arterial hypertension, n (%)	4 (3.1%)	5 (1.9%)	0.480[c]
Cerebrovascular accident, n (%)	10 (7.7%)	14 (5.2%)	0.370[c]
Malignancy, n (%)	7 (5.4%)	23 (8.5%)	0.265[b]
HCV positivity, n (%)	1 (0.8%)	0	0.325[c]
HBV positivity, n (%)	0	2 (0.7%)	>0.99[c]
HIV positivity, n (%)	1 (0.8%)	0	0.325[c]
COVID-19 PCR positivity	113 (86.9%)	240 (88.9%)	0.567[b]
Presence of symptoms at admission, n (%)	130 (100%)	260 (96.3%)	**0.034**[c]
Fatigue, n (%)	99 (76.2%)	181 (67%)	0.062[b]
Headache, n (%)	27 (20.8%)	46 (17%)	0.365[b]
Loss of appetite, n (%)	45 (34.6%)	92 (34.2%)	0.935[c]
Weight loss, n (%)	1 (0.8%)	21 (7.8%)	**0.004**[b]
Fever, n (%)	47 (36.2%)	89 (33%)	0.528[b]
Sore throat, n (%)	12 (9.2%)	23 (8.5%)	0.813[b]
Runny nose, n (%)	1 (0.8%)	1 (0.4%)	0.545[c]
Myalgia/arthralgia, n (%)	31 (23.8%)	51 (18.9%)	0.250[b]
Loss of taste and smell, n (%)	3 (2.3%)	3 (1.1%)	0.395[c]
Skin rash, n (%)	1 (0.8%)	2 (0.7%)	>0.99[c]
Nausea and vomiting, n (%)	15 (11.5%)	36 (13.4%)	0.605[b]
Diarrhea, n (%)	9 (6.9%)	12 (4.5%)	0.302[b]
Chest pain, n (%)	21 (16.2%)	22 (8.1%)	**0.015**[b]
Shortness of breath, n (%)	86 (66.2%)	144 (53.3%)	**0.015**[b]
Dry cough, n (%)	82 (63.1%)	140 (51.9%)	**0.034**[b]
Pneumonia, n (%)	101 (77.7%)	181 (67%)	**0.029**[b]
Speech disorder, n (%)	1 (0.8%)	10 (3.7%)	0.112[c]
Radiological finding, n (%)	121 (93.1%)	237 (87.8%)	0.105[b]

Data are presented as mean±standard deviation or median (minimum-maximum). [a] Mann-Whitney U test; [b] Chi-square test; [c] Fisher's exact test.

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Table 2. Comparison of clinical parameters between the diabetic and non-diabetic groups.

Parameters	Diabetic (n=130)	Non-diabetic (n=270)	*P* value
Oxygen saturation (%)	93 (60-100)	94 (65-100)	0.649[a]
Systolic BP (mmHg), n	130 (90-195)	120 (80-220)	<0.001[a]
Diastolic BP (mmHg), n	75 (50-108)	73 (50-120)	0.123[a]
Body temperature (°C), n	36.5 (35.5-39)	36.4 (35.6-39.8)	0.264[a]
Heart rate (bpm)	89 (60-196)	87 (55-138)	0.314[a]
Acute kidney injury, n (%)	9 (6.9%)	12 (4.4%)	0.298[b]
Arrhythmia, n (%)	13 (10%)	15 (5.6%)	0.103[b]
Stroke, n (%)	1 (0.8%)	3 (1.1%)	>0.99[c]
Thromboembolism, n (%)	2 (1.5%)	3 (1.1%)	0.662[c]
ICU admission, n (%)	20 (15.4%)	48 (17.8%)	0.551[b]
ICU length of stay (days)	0 (0-39)	0 (0-85)	0.466[a]
NIMV, n (%)	17 (13.1%)	54 (20%)	0.090[b]
NIMV length (days), n	0 (0-46)	0 (0-24)	0.094[a]
MV, n (%)	9 (6.9%)	22 (8.1%)	0.668[b]
MV length (days)	0 (0-33)	0 (0-82)	0.653[a]
Hydroxychloroquine, n (%)	12 (9.2%)	23 (8.5%)	0.813[b]
Favipiravir, n (%)	127 (97.7%)	256 (94.8%)	0.181[b]
Remdesivir, n (%)	0	2 (0.7%)	>0.99[c]
Antibiotics, n (%)	126 (96.9%)	260 (96.3%)	>0.99[c]
LMWH, n (%)	124 (95.4%)	254 (94.1%)	0.590[b]
ASA, n (%)	37 (28.5%)	70 (25.9%)	0.592[b]
Steroids, n (%)	90 (69.2%)	193 (71.5%)	0.643[b]
Pulse steroids, n (%)	17 (13.1%)	56 (20.7%)	0.063[b]
Convalescent plasma, n (%)	1 (0.8%)	1 (0.4%)	0.545[c]
Tocilizumab, n (%)	3 (2.3%)	9 (3.3%)	0.758[c]

Abbreviations: ICU; ıntensive care unit, NIMV; nonınvasive mechanical ventilation, MV; mechanical ventilation (ınvasive), LMWH; low-molecular-weight heparin, ASA; acetylsalicylic acid (aspirin). Data are presented as mean±standard deviation or median (minimum-maximum). [a] Mann-Whitney U test; [b] chi-square test; [c] Fisher exact test.

days had significantly higher SII values than survivors (median 2284.16, range 92.34-15322.67 vs 1203.95, range 10.98-16842.22; *P*=0.009). The admission SII showed statistically significant but modest discriminatory performance for 90-day mortality prediction (AUC=0.623, 95% CI: 0.573-0.670; *P*=0.015). The optimal SII cut-off value was greater than 2135.28, with 54.76% sensitivity and 69.47% specificity. Thus, this cut-off identified 54.76% of patients who died within 90 days and correctly classified 69.47% of survivors.

In multivariable logistic regression analysis for 90-day all-cause mortality, age, coronary artery disease, and high SII were retained in the final model and were associated with mortality (**Table 4**). Diabetes mellitus, hypertension, and sex were considered for inclusion in the model but were not retained as independent predictors after adjustment, because of major baseline imbalances. Each 1-year increase in age was associated with higher odds of 90-day mortality (OR 1.034, 95% CI 1.006-1.063; *P*=0.016). The presence of coronary artery disease was associated with approximately 2-fold higher odds of mortality

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Table 3. Laboratory findings in the diabetic and non-diabetic groups.

Parameters	Diabetic (n=130)	Non-diabetic (n=270)	*P* value
Urea, mg/dL	44.6 (10.7-229.9)	33.2 (9.6-287.8)	<0.001[a]
Blood urea nitrogen (BUN), mg/dL	21.1 (5-145)	15.5 (4.5-186)	<0.001[a]
Creatinine, mg/dL	0.9 (0.6-9.6)	0.9 (0.4-14.1)	0.028[a]
Sodium, mmol/L	135 (107-149)	137 (120-154)	<0.001[a]
Potassium, mmol/L	4.4 (1.4-6.2)	4.3 (3-6.1)	0.019[a]
Calcium, mg/dL	8.7 (6.4-10.8)	8.5 (6-10.6)	0.078[a]
Magnesium, mg/dL	1.9 (1.1-2.7)	2.1 (1.3-3.3)	<0.001[a]
Glucose, mg/dL	188.5 (58-615)	122.5 (6.2-582)	<0.001[a]
CRP, mg/L	65.6 (0.3-395.5)	60.7 (0-327.5)	0.163[a]
Procalcitonin, ng/mL	0.1 (0-26.7)	0.1 (0-26.4)	0.046[a]
Hemoglobin, g/dL	12.6 (6.9-17.7)	13.1 (5.2-18.4)	0.004[a]
Hematocrit,%	37.3 (20.8-50.5)	38.3 (15.9-52.6)	0.003[a]
Mean corpuscular volüme (MCV), fL	83.3 (34.9-105.5)	85.5 (27.6-106)	0.006[a]
Mean corpuscular hemoglobin (MCH), pg	28.7 (19.5-35)	29.2 (18.2-48.3)	0.019[a]
PDW, fL	12.2 (8.6-20.1)	11.9 (8.4-19.4)	0.037[a]
Erythrocyte sedimentation rate, mm/h	47 (2-123)	44 (2-140)	0.048[a]
INR	1 (0.9-2.9)	1 (0.8-2.4)	0.041[a]
Troponin T, ng/L	11.6 (3.2-3101)	9.5 (1.5-661)	<0.001[a]
AST, U/L	28 (9-147)	34 (8-325)	0.003[a]
Free triiodothyronine (fT3), pg/mL	1.7 (0.6-4.3)	1.9 (0.7-5.6)	0.013[a]
C3, mg/dL	1.3±0.3	1.2±0.3	0.016[d]
Cortisol, µg/dL	8.3 (0.3-36.3)	5.9 (0.2-57.4)	0.020[a]

Abbreviations: CRP, C-reactive protein; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; PDW, platelet distribution width; ESR, erythrocyte sedimentation rate; INR, international normalized ratio; AST, aspartate aminotransferase; fT3, free triiodothyronine. Data are presented as mean±standard deviation or median (minimum-maximum). [a] Mann-Whitney U test; [b] chi-square test; [c] Fisher exact test; d: independent samples *t* test.

(OR 2.154, 95% CI 1.035-4.483; *P*=0.040). In addition, patients with SII greater than 2135.28 had significantly higher odds of 90-day mortality compared with those with lower SII values (OR 2.577, 95% CI 1.318-5.042; *P*=0.006). The model had modest explanatory performance, with a Nagelkerke R^2 of 0.121.

Discussion

In this retrospective cohort of patients hospitalized with COVID-19, diabetes was associated with older age, a higher prevalence of hypertension and coronary artery disease, more frequent respiratory symptoms and pneumonia, and higher unadjusted 90-day all-cause mortality. Renal function markers were also higher in patients with diabetes; however, the SII did not differ significantly between the diabetic and non-diabetic groups. In contrast, patients who died within 90 days had higher SII values than survivors, and the admission SII showed statistically significant but modest discriminatory ability for 90-day mortality.

Importantly, after adjustment for major baseline imbalances and clinically relevant confounders, high SII remained associated with 90-day mortality. Age and coronary artery disease were also associated with mortality, highlighting the contribution of baseline demographic and cardiovascular risk. These findings suggest that the higher unadjusted mortality observed among patients with diabetes may be partly explained by older age and greater cardiovascular comorbidity burden rather than diabetes status alone. Therefore, diabetes should be interpreted as a marker of higher baseline risk in this cohort, while admission SII may provide additional inflammatory risk information beyond conventional clinical variables.

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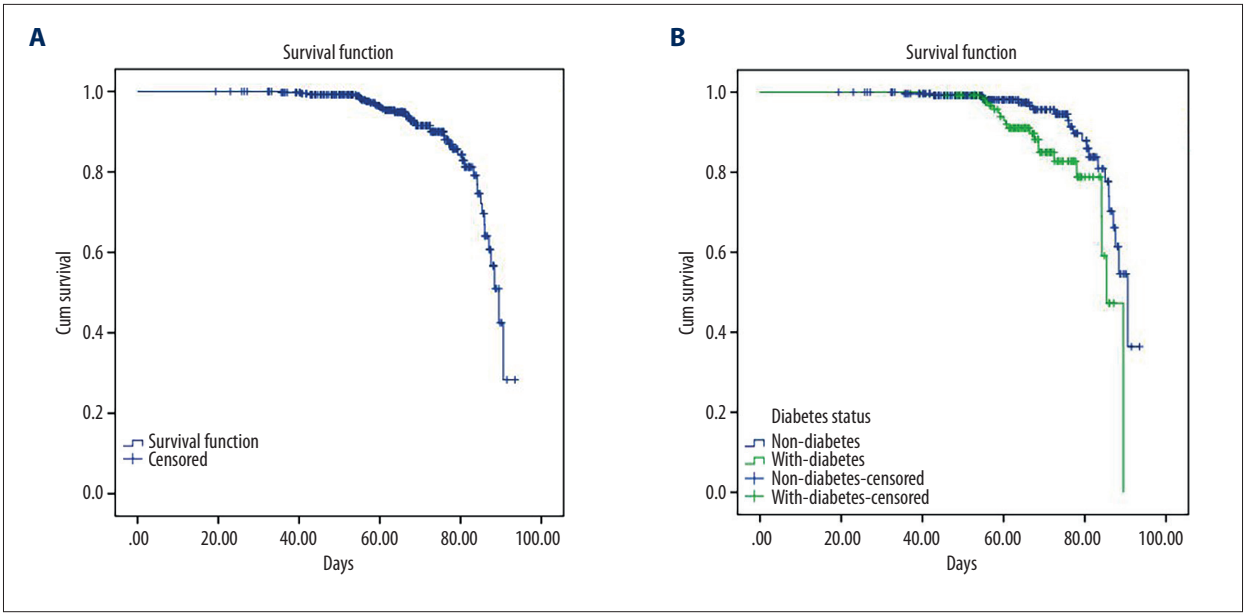

Figure 1. Kaplan-Meier survival curves for 90-day all-cause mortality. (**A**) Overall survival curve of the study cohort. (**B**) Kaplan-Meier survival curves stratified by diabetes status. Patients with diabetes had lower 90-day survival compared with non-diabetic patients. Tick marks indicate censored observations.

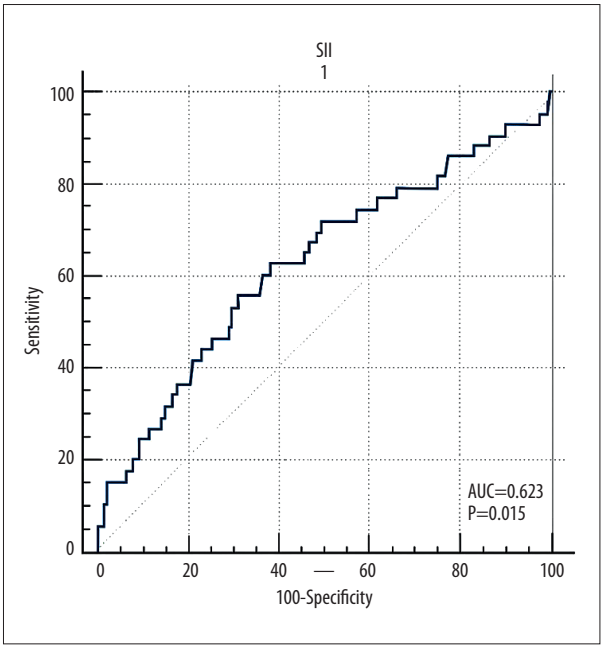

Figure 2. Receiver operating characteristic curve of admission systemic immune-inflammation index for predicting 90-day all-cause mortality in the overall cohort. Admission SII showed statistically significant but modest discriminatory ability for predicting 90-day all-cause mortality (AUC=0.623, 95% CI: 0.573-0.670; *P*=0.015). The optimal cut-off value was >2135.28, with 54.76% sensitivity and 69.47% specificity.

Diabetes is a major comorbidity in many infections, including COVID-19. Patients with diabetes may have impaired immune responses, chronic low-grade inflammation, endothelial dysfunction, and metabolic disturbances, which can contribute to unfavorable clinical outcomes. In addition, the cardiovascular and renal complications commonly associated with diabetes may increase vulnerability during acute infections. Previous studies have reported that diabetes is associated with worse prognosis and higher mortality among patients with COVID-19 [12].

Table 4. Multivariable logistic regression analysis for 90-day all-cause mortality.

Variable	B	SE	OR	95% CI	*P* value
Age, per year	0.034	0.014	1.034	1.006-1.063	0.016
Coronary artery disease	0.767	0.374	2.154	1.035-4.483	0.040
SII >2135.28	0.947	0.342	2.577	1.318-5.042	0.006

Abbreviations: B, regression coefficient; SE, standard error; OR, odds ratio; CI, confidence interval; SII, systemic immune-inflammation index. High SII was defined according to the ROC-derived cut-off value of 2135.28. Nagelkerke R^2=0.121.

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Previous studies have shown that pulmonary infections may be associated with higher mortality in patients with diabetes compared with non-diabetic individuals [13]. In our cohort, oxygen saturation at admission, ICU admission, noninvasive mechanical ventilation, invasive mechanical ventilation, and ventilatory support duration did not differ significantly between the diabetic and non-diabetic groups. These findings suggest that, although patients with diabetes had more frequent respiratory symptoms and pneumonia, several measurable severity-related outcomes were comparable between the 2 groups. However, because no formal severity score was used, these findings should not be interpreted as evidence of equivalent overall disease severity or treatment effectiveness.

In our cohort, patients with diabetes had a higher burden of cardiovascular comorbidities, including hypertension and coronary artery disease, and higher systolic blood pressure at admission. These findings are consistent with previous reports indicating that cardiovascular comorbidity is common among patients with diabetes and may contribute to clinical vulnerability during COVID-19 [3]. However, acute cardiovascular and thromboembolic complications, including arrhythmia, stroke, and thromboembolic events, did not differ significantly between the diabetic and non-diabetic groups in our study. The widespread use of low-molecular-weight heparin in both groups, in accordance with national COVID-19 management recommendations, may have contributed to the low and comparable thromboembolic event rates, although this cannot be confirmed in the present observational design [14].

In the present study, patients who died within 90 days had higher admission SII values than survivors, and the SII showed statistically significant but modest discriminatory ability for 90-day all-cause mortality. This finding is consistent with previous studies suggesting that the SII, which integrates neutrophil, lymphocyte, and platelet counts, may reflect the combined effects of systemic inflammation, immune dysregulation, and thrombo-inflammatory activation in COVID-19. Karaaslan and Karaaslan reported that higher SII was associated with mortality in hospitalized COVID-19 patients, with stronger discriminatory performance than that observed in our cohort [15]. The lower AUC in the present study may reflect differences in patient characteristics, comorbidity burden, timing of laboratory measurement, and mortality definitions. Therefore, although the SII may provide additional inflammatory risk information, its modest performance in our cohort suggests that it should be interpreted as an adjunctive marker rather than a stand-alone prognostic tool.

The 90-day follow-up period allowed assessment of mortality beyond the immediate hospitalization period. However, the present study did not systematically adjudicate the causes or timing patterns of death in relation to specific complications. Therefore, the observed mortality findings should be interpreted as 90-day all-cause mortality rather than evidence of a specific delayed complication pathway [16]. Future prospective studies with detailed cause-of-death adjudication and longitudinal inflammatory marker assessment are needed to clarify the mechanisms underlying post-acute mortality risk in patients with COVID-19 and diabetes.

An elevated SII may reflect a heightened inflammatory and thrombo-inflammatory response in patients with COVID-19 and may help identify individuals who require closer clinical observation [17]. However, given the modest discriminatory performance observed in the present study, the SII should not be interpreted as a stand-alone prognostic tool or as a direct basis for treatment intensification. Rather, the SII may be considered an adjunctive marker that could complement clinical assessment, comorbidity evaluation, vital signs, renal function, and other laboratory markers. Future prospective studies are needed to determine whether serial SII measurements or integration of SII into multivariable risk models can improve risk stratification and clinical decision-making in high-risk COVID-19 populations [18,19].

Treatment-related variables were broadly similar between the diabetic and non-diabetic groups in our cohort. Antibiotics, favipiravir, low-molecular-weight heparin, corticosteroids, pulse corticosteroids, convalescent plasma, and tocilizumab were similarly distributed between groups. The high rate of antibiotic use may reflect clinical concern for bacterial co-infection or secondary infection during the pandemic period, although microbiological confirmation and indication-specific antibiotic use were not systematically evaluated in this study [20,21]. Antiviral and corticosteroid treatments have been widely used in the management of patients hospitalized with COVID-19 [22,23]. In patients with diabetes, treatment decisions require careful consideration of metabolic control, cardiovascular risk, and renal function. However, because the present study was not designed to evaluate treatment efficacy, no causal conclusions can be drawn regarding the effect of specific therapies on mortality or other outcomes [24].

This study has several limitations. First, the retrospective and single-center design limits causal inference and generalizability. Second, although multivariable logistic regression was performed to adjust for major baseline imbalances, residual confounding cannot be excluded because of the retrospective design and the limited number of mortality events. Therefore, the associations observed in this study should not be interpreted as causal effects. Third, the SII was calculated from a single admission blood sample; therefore, dynamic changes in inflammatory status during hospitalization could not be evaluated. Fourth, mortality was analyzed as 90-day all-cause mortality, and systematic cause-of-death adjudication

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was not performed. Thus, cause-specific mortality and mechanisms of death could not be assessed. Fifth, some potentially relevant factors, including secondary infections, microbiological confirmation, treatment indications, glycemic control, and longitudinal renal function changes, were not consistently available in the medical records. In addition, multiple univariate comparisons were performed without formal adjustment for multiplicity; therefore, nominal *P* values should be interpreted cautiously and considered exploratory. Despite these limitations, the study provides real-world data on the clinical, laboratory, renal, inflammatory, treatment-related, and mortality-related characteristics of hospitalized COVID-19 patients with and without diabetes.

Conclusions

In conclusion, diabetes was associated with a higher comorbidity burden, more frequent respiratory symptoms and pneumonia, altered renal laboratory findings, and higher unadjusted 90-day all-cause mortality among patients hospitalized with COVID-19. However, age, coronary artery disease, and high admission SII were associated with 90-day mortality, after adjustment for major baseline imbalances, whereas the independent effect of diabetes was less clear. Admission SII showed statistically significant but modest discriminatory ability for mortality prediction and may provide additional inflammatory risk information as an adjunctive marker. These findings should be interpreted cautiously because of the retrospective design, modest model performance, and potential residual confounding. Larger prospective studies with serial inflammatory marker assessment and comprehensive risk models are needed to validate these results.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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