




Systemic Immune-Inflammation Index and Risk of Diabetes and Prediabetes Two Years Post-COVID-19: A Retrospective Cohort Study

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Abstract

Background: Post-COVID-19 metabolic complications, such as diabetes, are linked to systemic inflammation. The Systemic Immune-Inflammation Index (SII) may help predict these outcomes; however, evidence from non-Western populations remains limited.

Methods: In this retrospective cohort study, 2,060 COVID-19 patients hospitalized in 2020 in Iran were followed for two years. SII was calculated and categorized as normal or elevated. The incidence of diabetes and prediabetes was assessed using fasting blood sugar (FBS) and HbA1c levels. Linear regression analyses were conducted to examine associations between SII and metabolic outcomes, adjusting for potential confounders.

Results: Among participants, 73.4% remained normoglycemic, 7.5% developed prediabetes, and 19.1% developed diabetes. Linear regression analysis demonstrated a statistically significant but modest positive association between SII and FBS levels ($\beta = 0.018$; 95% CI: 0.004–0.032; $P = 0.011$). Other inflammatory markers showed no significant associations.

Conclusion: Elevated SII was modestly associated with higher fasting blood sugar levels two years after COVID-19 infection. Although the effect size was small, these findings suggest that systemic inflammation may play a role in long-term glycemic dysregulation, underscoring the importance of metabolic follow-up in individuals with heightened post-COVID inflammatory profiles.

Keywords: Systemic Immune-Inflammatory, Diabetes, Prediabetes, Cohort

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Introduction

In late 2019, the world witnessed the emergence of COVID-19, caused by the SARS-CoV-2 virus, which rapidly escalated into an unprecedented global pandemic (1). Initially recognized for its association with acute respiratory syndromes, the disease gradually revealed a broader impact on multiple organ systems, including the heart, kidneys, liver, and nervous system (2-4). Among the notable consequences of COVID-19 is the heightened risk of metabolic disorders, particularly diabetes and prediabetes, as reported across numerous studies (5, 6). This association appears especially pronounced among patients who

experienced severe forms of the disease or who had pre-existing metabolic risk factors such as obesity, hypertension, or cardiovascular disease (5, 6). Given the escalating global burden of diabetes as one of the most prevalent chronic conditions, understanding the underlying mechanisms of this relationship and identifying prognostic markers for early intervention are of critical importance (3).

Systemic inflammation, a hallmark of COVID-19 pathogenesis, plays a central role in the development of metabolic complications (7). This inflammation, often charac-

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↑What is “already known” in this topic:

Post-COVID-19 metabolic complications, such as new-onset diabetes and prediabetes, have been linked to systemic inflammation. The Systemic Immune-Inflammation Index (SII) is a biomarker that has been associated with COVID-19 severity and metabolic disturbances in several populations.

→What this article adds:

This study is among the first to investigate the association between SII and long-term glycemic outcomes in a Middle Eastern cohort. It shows that elevated SII during initial hospitalization is independently associated with higher fasting blood sugar levels of two years post-COVID-19, highlighting its potential as a prognostic marker for long-term metabolic risk assessment.

terized by the so-called cytokine storm, involves elevated levels of pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- α), and interferon-gamma (IFN- γ) (8, 9). These cytokines can exacerbate insulin resistance and disrupt glucose homeostasis, thereby increasing the risk of developing diabetes or advancing prediabetes (8, 9). Moreover, evidence suggests that COVID-19 may directly or indirectly affect pancreatic beta cells, leading to persistent glycemic disturbances. Such metabolic effects have been observed not only during the acute phase of infection but also over extended periods following recovery, underscoring the need to investigate the long-term consequences of COVID-19 (10-14).

The Systemic Immune-Inflammation Index (SII) (calculated by multiplying the neutrophil-to-lymphocyte ratio by the platelet count) has emerged as a promising marker for assessing systemic inflammation and immune response (15, 16). Due to its simplicity and accessibility, SII has demonstrated significant prognostic value in various inflammatory conditions, including cancers, cardiovascular diseases, and viral infections such as COVID-19 (17, 18).

In COVID-19 patients, elevated SII levels have been associated with disease severity, intensive care unit admission, and adverse outcomes (19). However, the potential role of SII in predicting long-term metabolic complications, particularly diabetes and prediabetes, remains underexplored. This knowledge gap is particularly notable in non-Western populations, such as Iran, where local data are scarce.

Diabetes and prediabetes impose substantial economic and social burdens on healthcare systems and markedly diminish patients' quality of life. Reports indicate a 1.6- to 1.7-fold increase in the risk of new-onset diabetes following COVID-19, especially within the first three to six months after recovery (20, 21). This elevated risk is particularly evident among patients who experienced intense inflammation during the acute phase of illness. Early identification of at-risk individuals could enable preventive interventions such as regular blood glucose monitoring and management of metabolic risk factors (22-24). Besides SII, other inflammatory markers, such as erythrocyte sedimentation rate (ESR), white blood cell count (WBC), and neutrophil-to-lymphocyte ratio (NLR), also hold value in assessing systemic inflammation (22). Compared to other commonly used inflammatory markers such as the NLR, C-reactive protein (CRP), or ESR, the SII offers a more comprehensive measure of both immune and inflammatory status by incorporating neutrophils, lymphocytes, and platelets into a single index. While markers like NLR and CRP reflect certain aspects of inflammation, SII is considered superior in capturing the dynamic balance between immune response and systemic inflammation. Emerging evidence suggests that SII may outperform traditional markers in predicting disease severity and adverse outcomes in conditions such as COVID-19, cardiovascular disease, and cancer. Given its broader scope and prognostic value, this study focused on investigating the association between SII and the incidence of diabetes and prediabetes two years after COVID-19 infection among patients

hospitalized at Kowsar Hospital in Sanandaj. In addition, other inflammatory markers (e.g., WBC, ESR, and NLR) and clinical variables (such as fasting blood glucose, liver enzymes, and serum creatinine) were analyzed to gain a comprehensive understanding of the role of systemic inflammation in post-COVID metabolic outcomes. In light of the growing burden of diabetes in the post-pandemic era, the study aimed to generate local evidence to support more effective monitoring and intervention strategies for COVID-19 survivors, particularly among high-risk groups such as older adults and individuals with pre-existing metabolic risk factors.

Methods

Study Design and Setting

This retrospective cohort study was conducted at Kowsar Hospital, affiliated with Kurdistan University of Medical Sciences in Sanandaj, Iran. The study aimed to investigate the association between the SII and the incidence of diabetes and prediabetes two years after COVID-19 infection. Patients hospitalized with confirmed COVID-19 in 2020 were followed up until 2022. Baseline data were obtained from medical records, and follow-up clinical assessments were performed at the hospital's outpatient clinic. This was a non-matched cohort study, and no matching criteria were applied.

Study Population and Eligibility Criteria

The study population included all patients admitted to Kowsar Hospital in 2020 with a confirmed diagnosis of COVID-19, verified by clinical symptoms and a positive PCR test. Patients were eligible if they had complete baseline clinical and laboratory data, including fasting blood sugar (FBS), glycated hemoglobin (HbA1c), and inflammatory markers (SII, ESR, white blood cell count, lymphocyte count, neutrophil count, and platelet count). Patients were excluded if they declined participation or had incomplete follow-up data. Follow-up was conducted through in-person outpatient glycemic assessments or via telephone interviews to confirm glycemic status and overall health.

Sampling and Sample Size

Using convenience sampling, 2,058 patients meeting the inclusion criteria were enrolled from an estimated 2,000 eligible patients admitted in 2020. A review of medical records confirmed that all 2,058 patients had complete data. The sample size, encompassing all eligible patients, ensured sufficient statistical power for the analysis.

Outcomes and Study Variables

The primary outcomes were the incidence of diabetes (defined as fasting blood sugar [FBS] ≥ 126 mg/dL, HbA1c $\geq 6.5\%$, or self-reported diagnosis) and prediabetes (FBS 100–125 mg/dL or HbA1c 5.7–6.4%) within two years post-COVID-19. The main predictor was the SII, calculated as neutrophils \times platelets \div lymphocytes. Independent variables included age, arterial oxygen saturation level, length of hospital stay, hemoglobin, red blood cell volume, hemoglobin per red blood cell, lactate dehydro-

genase (LDH) level, and serum creatinine level. Due to data limitations, variables such as corticosteroid use, body mass index (BMI), and smoking status were not available for adjustment. However, the available clinical and laboratory variables were incorporated into the regression models to partially account for disease severity and patient health status.

Data Collection and Assessment Methods

Data was extracted from medical records and outpatient assessments using a standardized checklist capturing demographic details, clinical parameters, and laboratory indices. For patients without a prior diabetes diagnosis, FBS and HbA1c were measured using standardized laboratory methods; otherwise, self-reported diabetes diagnoses were accepted. The SII was categorized as normal (<390) or high (≥ 390) (25). To minimize bias, data extraction and quality control were performed systematically, and assessment methods were consistent across all patient groups. Data collection was conducted by the research team in coordination with hospital management, following ethical approvals.

Statistical Analysis

All analyses were performed using STATA version 18. Continuous variables were summarized using means, standard deviations (SD), and 95% confidence intervals (CIs). Differences in means across glycemic status categories (normoglycemic, prediabetes, and diabetes) were assessed using one-way analysis of variance (ANOVA), followed by pairwise t-tests with Tukey's correction for multiple comparisons. Linear regression models were used to examine the association between the systemic immune-inflammation index (SII) and glycemic measures, adjusting for potential confounders such as age and sex. Adjust-

ed regression coefficients with corresponding 95% CIs were reported. These findings remained consistent after adjusting for age and sex. Missing data (<5%) were handled using listwise deletion, with minimal impact on the overall results.

Ethical Considerations

The study was approved by the Ethics Committee of Kurdistan University of Medical Sciences and authorized by the university's Research Council. Informed consent was obtained for the use of clinical data and participation in glycemic assessments. Data were anonymized and stored confidentially, adhering to the Declaration of Helsinki.

Results

A total of 2,058 participants were included in this retrospective cohort study, with a mean follow-up period of two years post-COVID-19 diagnosis. The cohort was characterized by a diverse range of clinical and demographic variables, as summarized in Table 1. Of the participants, 73.47% (n=1,512) were classified as normoglycemic, 7.48% (n=154) had prediabetes, and 19.05% (n=392) were diagnosed with diabetes. Regarding the Systemic Immune-Inflammatory Index (SII), 32.55% (n=670) of participants had normal SII values, while 67.45% (n=1,388) exhibited abnormal SII levels (Table 1).

Clinical and Hospitalization Characteristics

Table 1 provides a detailed distribution of key variables, including recurrent hospitalization, reinfection, chest CT scan findings, intubation status, and vaccination status. Recurrent hospitalization occurred in 30.47% (n=627) of the cohort, while 51.41% (n=1,058) had no recurrent hospitalizations, and 18.12% (n=373) were missing or other

Table 1. Distribution of Variables in Patient Groups Based on Chest CT Scan, Intubation, and Vaccination Status

Variable	Classification	Count (n)	Percentage (%)
Recurrent Hospitalization	No	1058	51.41
	Yes	627	30.47
	Other / Missing	373	18.12
	Total	2058	100
Recurrent Infection (Reinfection)	No	1766	85.81
	Yes	292	14.19
	Total	2058	100
Chest CT Scan Group	No Lung Involvement	249	12.10
	Up to 25% Lung Involvement	1194	58.02
	Up to 50% Lung Involvement	388	18.85
	Above 50% Lung Involvement	227	11.03
	Total	2058	100
Intubation (Endotracheal Tubing)	Not Performed	1938	94.12
	Performed	121	5.88
	Total	2059	100
Vaccination Status	Not Vaccinated	928	45.09
	Vaccinated	757	36.78
	Other / Missing	373	18.12
	Total	2058	100
Diabetes	Normal	1512	73.47
	Prediabetes	154	7.48
	Diabetes	392	19.05
	Total	2058	100
SII categories	Normal	670	32.55
	Abnormal	1388	67.45
	Total	2058	100

statuses. Reinfection was reported in 14.19% (n=292) of participants, with the majority (85.81%, n=1,766) experiencing no reinfection (Table 1). Chest CT scan results, available for 2,039 participants, revealed varying degrees of lung involvement: 12.10% (n=249) had no lung involvement, 58.02% (n=1,194) had up to 25% lung involvement, 18.85% (n=388) had up to 50% involvement, and 11.03% (n=227) had greater than 50% lung involvement. Intubation was performed in 5.88% (n=121) of participants, while 94.12% (n=1,938) did not require endotracheal tubing. Vaccination status showed that 45.09% (n=928) were unvaccinated, 36.78% (n=757) were vaccinated, and 18.12% (n=373) had missing or other vaccination statuses (Table 1).

Laboratory and Clinical Variables

Table 2 presents descriptive statistics for laboratory and clinical variables. The mean fasting blood sugar level was 98.9 mg/dL (SD, 1.39; 95% CI, 96.2-101.6). Hematological parameters included a mean hemoglobin level of 13.01 g/dL (SD, 9.0; 95% CI, 12.82-13.19), total white blood cell count of 13,050.7 cells/ μ L (SD, 1947.4; 95% CI, 9227.3-16,874.2), lymphocyte level of 2498.1 cells/ μ L (SD, 481.5; 95% CI, 1552.7-3443.5), and neutrophil level of 10,706.9 cells/ μ L (SD, 1475.09; 95% CI, 7810.9-13,602.9) (Table 2). Inflammatory markers included a mean erythrocyte sedimentation rate (ESR) of 27.554 mm/h (SD, 0.513; 95% CI, 26.547-28.560) and lactate dehydrogenase (LDH) level of 709.5 U/L (SD, 13.01; 95% CI, 683.9-735.07). Liver function tests showed mean alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels of 31.8 U/L (SD, 11.0; 95% CI, 30.24-33.4) and 26.7 U/L (SD, 7.65; 95% CI, 25.4-28.1), respectively. The mean serum creatinine level was 1.34 mg/dL (SD, 4.0; 95% CI, 1.25-1.42), and the mean length of hospital stay was 3.58 days (SD, 11.0; 95% CI, 3.35-3.81) (Table 2).

Comparison of Laboratory Variables Across Glycemic Status

Table 3 presents comparisons of laboratory variables among diabetes, prediabetes, and normoglycemic groups

using ANOVA and post-hoc tests. Significant differences were observed for WBC, neutrophil, platelet, and ESR levels (all $P < 0.01$), with a trend toward significance for SII ($P = 0.069$). No significant differences were found for ALT ($P = 0.329$) or AST ($P = 0.243$). The diabetes group exhibited markedly higher mean WBC levels (23,076.61 cells/ μ L; SD, 2966.51) compared to the normoglycemic (8893.07 cells/ μ L; SD, 1089.60) and prediabetes (7926.39 cells/ μ L; SD, 4739.58) groups ($F = 10.41$, $P = 0.001$). Post-hoc tests confirmed significant differences between diabetes and normoglycemic groups (mean difference, 14,183.54 cells/ μ L; $P = 0.001$) and diabetes and prediabetes groups (mean difference, 15,150.22 cells/ μ L; $P = 0.019$), but not between normoglycemic and prediabetes groups ($P = 0.978$). Neutrophil levels followed a similar pattern, with the diabetes group showing a higher mean (18,316.99 cells/ μ L; SD, 2257.69) than the normoglycemic (7535.35 cells/ μ L; SD, 834.87) and prediabetes (7104.75 cells/ μ L; SD, 3592.83) groups ($F = 2.91$, $P = 0.001$). Post-hoc comparisons indicated significant differences between diabetes and normoglycemic (mean difference, 10,781.64 cells/ μ L; $P = 0.001$) and diabetes and prediabetes (mean difference, 11,212.25 cells/ μ L; $P = 0.008$) groups, with a modest difference between normoglycemic and prediabetes groups (mean difference, -430.61 cells/ μ L; $P = 0.033$) (Table 3).

Platelet levels were significantly higher in the diabetes group (218,392.01 cells/ μ L; SD, 8605.01) compared to the normoglycemic (181,547.4 cells/ μ L; SD, 3324.40) and prediabetes (182,932.80 cells/ μ L; SD, 14,176.82) groups ($F = 8.92$, $P = 0.003$). Post-hoc tests showed a significant difference between diabetes and normoglycemic groups (mean difference, 36,844.56 cells/ μ L; $P = 0.001$), but not between diabetes and prediabetes ($P = 0.924$) or normoglycemic and prediabetes ($P = 0.672$) groups. ESR was also elevated in the diabetes group (34.39 mm/h; SD, 2.89) compared to the normoglycemic (26.00 mm/h; SD, 5.19) and prediabetes (32.74 mm/h; SD, 4.66) groups ($F = 15.04$, $P = 0.001$). Post-hoc analyses confirmed significant differences between diabetes and normoglycemic (mean difference, 8.39 mm/h; $P = 0.001$) and normoglycemic and prediabetes (mean difference, 6.74 mm/h; $P = 0.009$) groups,

Table 2. Descriptive Statistics and 95% Confidence Intervals for Laboratory and Clinical Variables

Variable	Mean \pm SD	95% Confidence Interval
Age	60.72 \pm 27.0	59.4 - 62.04
Arterial Oxygen Saturation Level	34.0 \pm 17.0	29.0 - 36.0
Length of Hospital Stay	3.58 \pm 11.0	3.35 - 3.81
Hemoglobin	13.01 \pm 9.0	12.82 - 13.19
Red Blood Cell Volume	85.7 \pm 3.0	85.18 - 86.3

Table 4. Linear Regression Model Results

Predictor	Coefficient (β)	Std. Error	P-value	95% Confidence Interval	Model results
SII	0.0180	0.0071	0.011	0.0041 to 0.0319	F (6, 1499): 5.19
NLR	0.0254	0.2226	0.909	-0.4112 to 0.4620	Prob > F: 0.0000
PLR	0.0217	0.0088	0.014	0.0045 to 0.0389	R-squared: 0.0204
Neutrophils	0.0012	0.0013	0.346	-0.0013 to 0.0037	Adj R-squared: 0.0164
Lymphocytes	0.0013	0.0013	0.322	-0.0012 to 0.0038	
WBC	-0.0011	0.0013	0.367	-0.0036 to 0.0013	
Constant	90.6406	1.5315	<0.001	87.6365 to 93.6448	

SII: Systemic Immune-Inflammation Index, NLR: Neutrophil-to-Lymphocyte Ratio, PLR: Platelet-to-Lymphocyte Ratio, Adjusted Coefficients (Age and Gender)

Table 3. Comparison of Laboratory Variables Among Diabetes, Prediabetes, and Healthy Groups (Mean \pm SD, ANOVA and Post-hoc Results)

Variable	Group	Mean \pm SD	Square sum	F Value	P Value	Post-hoc Comparison	Mean Difference \pm SD	P Value
ALT	Diabetes	29.41 \pm 1.53	10.76	1.12	0.329	Diabetes vs Healthy	-0.361 \pm 1.632	0.244
	Healthy	29.77 \pm 5.62				Diabetes vs Prediabetes	-3.291 \pm 2.889	0.824
	Prediabetes	32.70 \pm 2.45				Healthy vs Prediabetes	2.928 \pm 2.513	0.490
AST	Diabetes	25.57 \pm 1.22	5.38	1.41	0.243	Diabetes vs Healthy	0.63 \pm 1.30	0.491
	Healthy	24.94 \pm 0.44				Diabetes vs Prediabetes	-2.64 \pm 2.29	0.484
	Prediabetes	28.22 \pm 1.94				Healthy vs Prediabetes	3.28 \pm 1.99	0.228
WBC	Diabetes	23076.61 \pm 2966.51	10.38	10.41	0.001	Diabetes vs Healthy	14183.54 \pm 3160.29	0.001
	Healthy	8893.07 \pm 1089.60				Diabetes vs Prediabetes	15150.22 \pm 5591.41	0.019
	Prediabetes	7926.39 \pm 4739.58				Healthy vs Prediabetes	-966.67 \pm 4863.22	0.978
Lymphocyte	Diabetes	4940.98 \pm 1246.47	10.32	10.23	0.001	Diabetes vs Healthy	3123.47 \pm 813.43	0.001
	Healthy	1817.50 \pm 813.43				Diabetes vs Prediabetes	3651.98 \pm 1433.94	0.011
	Prediabetes	1289.01 \pm 904.78				Healthy vs Prediabetes	-528.51 \pm 246.47	0.672
Neutrophil	Diabetes	18316.99 \pm 2257.69	5.98	2.91	0.001	Diabetes vs Healthy	10781.64 \pm 2407.11	0.001
	Healthy	7535.35 \pm 834.87				Diabetes vs Prediabetes	11212.25 \pm 4243.30	0.008
	Prediabetes	7104.75 \pm 3592.83				Healthy vs Prediabetes	-430.61 \pm 368.56	0.033
Platelet	Diabetes	218392.01 \pm 8605.01	10.32	8.92	0.003	Diabetes vs Healthy	36844.56 \pm 224.85	0.001
	Healthy	181547.4 \pm 3324.40				Diabetes vs Prediabetes	35459.18 \pm 583.98	0.924
	Prediabetes	182932.80 \pm 14176.82				Healthy vs Prediabetes	1385.38 \pm 162.49	0.672
ESR	Diabetes	34.39 \pm 2.89	7.32	15.04	0.001	Diabetes vs Healthy	8.39 \pm 1.67	0.001
	Healthy	26.00 \pm 5.19				Diabetes vs Prediabetes	2.97 \pm 1.65	0.579
	Prediabetes	32.74 \pm 4.66				Healthy vs Prediabetes	6.74 \pm 2.59	0.009
SII	Diabetes	254.13 \pm 22.06	6.93	2.67	0.069	Diabetes vs Healthy	-49.66 \pm 13.22	0.088
	Healthy	303.78 \pm 8.10				Diabetes vs Prediabetes	-10.00 \pm 13.92	0.962
	Prediabetes	264.13 \pm 35.29				Healthy vs Prediabetes	-39.65 \pm 28.44	0.517

but not between diabetes and prediabetes ($P=0.579$) (Table 3).

For SII, the normoglycemic group had a higher mean (303.78; SD, 8.10) than the diabetes (254.13; SD, 22.06) and prediabetes (264.13; SD, 35.29) groups, though the difference was not statistically significant ($F=2.67$, $P=0.069$). Post-hoc tests showed a trend toward a difference between diabetes and normoglycemic groups (mean difference, -49.66; $P=0.088$), but no differences between diabetes and prediabetes ($P=0.962$) or normoglycemic and prediabetes ($P=0.517$) groups. Fasting blood sugar levels, as reported in Table 2, were not compared in Table 3 but showed a gradient across groups in descriptive analyses: diabetes (125.6 mg/dL; SD, 2.1), prediabetes (108.3 mg/dL; SD, 1.7), and normoglycemic (92.4 mg/dL; SD, 1.2) (Table 3).

Linear Regression Results

Table 4 presents the results of the linear regression model assessing the association between inflammatory markers and glycemic levels, adjusted for age and sex. The SII was significantly associated with glycemic levels ($\beta=0.0180$, 95% CI: 0.0041 to 0.0319, $P=0.011$), indicating a positive relationship. Similarly, the PLR also showed a statistically significant association ($\beta=0.0217$, 95% CI: 0.0045 to 0.0389, $P=0.014$). Although SII and PLR showed statistically significant associations with glycemic levels, the effect sizes were extremely small. The overall model explained only about 2% of the variance in glycemic levels ($R^2=0.0204$; adjusted $R^2=0.0164$), indicating that these inflammatory markers have very lim-

ited explanatory value. Therefore, these findings should be interpreted with considerable caution, as the statistical significance does not translate into meaningful clinical relevance. Additional factors not captured in this model likely play a far more substantial role in determining glycemic status.

Discussion

This study examined the link between the SII and the development of diabetes and prediabetes two years after COVID-19 infection among hospitalized patients in Sanandaj. The findings highlight the potential role of systemic inflammation in post-COVID metabolic disorders, with elevated inflammatory markers, such as WBC, neutrophils, platelets, and ESR, observed in patients who developed diabetes. These results align with prior evidence suggesting that heightened inflammation contributes to adverse outcomes in COVID-19 patients, particularly those with diabetes (26, 27). Elevated WBC and neutrophil counts in the diabetes group suggest a more robust inflammatory response, possibly leading to cytokine storm activation (28). This inflammatory cascade may exacerbate insulin resistance and impair glucose homeostasis, ultimately increasing the risk or severity of diabetes (5, 29, 30).

Unexpectedly, the lymphocyte count was also higher in the diabetes group, contrasting with the typical lymphocytopenia seen during the acute phase of COVID-19 (29, 31). This discrepancy may relate to the timing of blood sampling, as samples could have been collected during

recovery or after the use of immunomodulatory therapies (e.g., corticosteroids). Previous studies have shown that while lymphocytopenia is common during the acute phase, lymphocyte counts may normalize or even rise during recovery (32). Further investigation into the timing of sampling and the treatment history is necessary to confirm this observation. ESR, as a non-specific marker of inflammation, was also significantly higher in the prediabetes and diabetes groups compared to the normal group. This aligns with the concept of chronic low-grade inflammation in both conditions (12, 29, 33). Combined with other markers like CRP, ESR may help identify individuals at risk of metabolic complications. However, the absence of CRP data in this study is a limitation, as CRP has been previously reported as a key mediator in the link between inflammation and diabetes (1, 28, 29, 32).

This study aimed to examine the association between the SII and FBS levels two years after COVID-19. Linear regression analysis revealed a statistically significant but weak positive association between SII and FBS. Contrary to expectations, other inflammatory markers, including NLR, WBC, neutrophils, and lymphocytes, were not significantly associated with glycemic levels. Interestingly, the mean SII was slightly lower in participants with diabetes compared to normoglycemic individuals, although this difference was not significant after adjustment. These findings differ from previous studies that reported stronger associations between SII and COVID-19-related metabolic outcomes. Possible explanations include the generally normal SII levels in the study population, the timing of biomarker assessment after the acute inflammatory phase, limited variability in FBS values, and potential confounding by medications, disease severity, or comorbidities. Further prospective studies with larger and more diverse cohorts are needed to clarify the clinical relevance of SII in post-COVID metabolic risk stratification (22, 26, 34-37).

No significant differences in ALT and AST levels were observed between the normal, prediabetic, and diabetic groups. These results are consistent with prior reports suggesting that liver enzyme levels in COVID-19 patients are generally within normal or mildly elevated ranges and do not indicate acute liver injury. Some studies have also reported mild elevations in liver enzymes in COVID-19 patients, consistent with our findings (5, 38, 39). The lack of difference across diabetic statuses may reflect moderate disease severity or the absence of underlying liver disease in the study population. Nonetheless, long-term monitoring of liver function is recommended for at-risk patients (e.g., those with diabetes or hepatotoxic medication exposure). Serum creatinine levels (mean: 1.34 mg/dL) were within the normal range but approached the upper limit, supporting the recommendation for close renal function monitoring in patients with prolonged hospitalization or comorbidities. COVID-19 may impair kidney function via systemic inflammation or direct renal damage. Fasting blood sugar (FBS) averaged 98.9 mg/dL, also within normal limits but near the threshold for prediabetes, possibly indicating patients at risk of glycemic progression.

This study has various strengths. The large cohort

(n=2060) from Kowsar Hospital in Sanandaj provides reliable data on post-COVID-19 metabolic outcomes, improving generalizability across similar populations. A comprehensive examination of inflammatory markers (WBC, neutrophils, platelets, and ESR) in conjunction with SII allowed for a detailed investigation of the role of systemic inflammation in diabetes and prediabetes.

There are several limitations to consider. The retrospective design may introduce selection bias, limiting causal inference. The small prediabetes sample (n=154) possibly lowered the statistical power to identify the link between SII and prediabetes. Inconsistent SII measurements across analyses (e.g., mean=1280.97 vs. <390) may indicate methodological or reporting differences, complicating interpretation. Uncontrolled variables, such as corticosteroid use, obesity, or illness severity, could have affected inflammatory marker levels. The lack of CRP data and imprecise sampling schedule (acute vs. recovery period) further limits complete inflammatory study. These variables underline the importance of exercising caution when interpreting findings.

Conclusion

This study underscores a potential link between systemic inflammation, reflected in elevated WBC, neutrophils, platelets, and ESR, and increased diabetes risk two years after COVID-19. While the SII demonstrated a statistically significant association with fasting blood glucose, its predictive strength was limited. These findings support routine monitoring of inflammatory and glycemic markers in COVID-19 survivors, particularly those with underlying metabolic risk factors. Future prospective studies with larger, standardized cohorts and broader biomarker panels (e.g., C-reactive protein) are needed to better define the prognostic value of SII and guide strategies for preventing post-COVID-19 metabolic complications.

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Conflict of Interests

The authors declare that they have no competing interests.

Authors' Contributions

All authors contributed substantially to the conception, design, data collection, analysis, and interpretation of the study. E.R. and N.B. conceptualized and supervised the project. L.S. and N.M. contributed to data acquisition and clinical interpretation. S.D. and P.M. performed data management and statistical analysis. All authors reviewed, revised, and approved the final manuscript.

Ethical Considerations

The study adhered to all institutional and national ethical standards for research involving human data. The da-

taset used in the present analysis was derived from a previously approved thesis project conducted at Kurdistan University of Medical Sciences. The proposal was approved by the Ethics Committee of Kurdistan University of Medical Sciences under the code IR.MUK.REC.1401.451 (February 28, 2023). All patient information used in the current study was anonymized, and no identifiable data were accessed or reported.

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Data Availability

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request and subject to institutional data-sharing policies.

AI Use Statement

Artificial intelligence tools were used solely for language editing, clarity improvement, and formatting of the manuscript. All analyses, interpretations, and conclusions were performed by the authors, and the AI tools had no role in data analysis or scientific decision-making.

References

- Jalilova A, Ata A, Demir G, Işıklar H, Atik Altınok Y, Özens S, et al. The Effect of the SARS-CoV-2 Pandemic on Presentation with Diabetic Ketoacidosis in Children with New Onset Type 1 Diabetes Mellitus. *J Clin Res Pediatr Endocrinol*. 2023;15(3):264-7.
- Hajiasgharzadeh K, Jafarlou M, Mansoori B, Dastmalchi N, Baradaran B, Khabbazi A. Inflammatory reflex disruption in COVID-19. *Clin Exp Neuroimmunol*. 2022.
- Hirani D, Salem V, Khunti K, Misra S. Newly detected diabetes during the COVID-19 pandemic: What have we learnt? *Best Pract Res Clin Endocrinol Metab*. 2023;37(4):101793.
- Hu Z, Youn HM, Quan J, Lee LLS, Mak IL, Yu EYT, et al. The indirect impact of the COVID-19 pandemic on people with type 2 diabetes mellitus and without COVID-19 infection: Systematic review and meta-analysis. *Prim Care Diabetes*. 2023;17(3):229-37.
- Han M, Ma K, Wang X, Yan W, Wang H, You J, et al. Immunological Characteristics in Type 2 Diabetes Mellitus Among COVID-19 Patients. *Front Endocrinol*. 2021;12:596518.
- Hanif S, Ali SN, Hassanein M, Khunti K, Hanif W. Managing People with Diabetes Fasting for Ramadan During the COVID-19 Pandemic: A South Asian Health Foundation Update. *Diabet Med : a journal of the British Diabetic Association*. 2020;37(7):1094-102.
- Kaivola J, Nyman TA, Matikainen S. Inflammasomes and SARS-CoV-2 Infection. *Viruses*. 2021;13(12).
- Pietro Paolo M, Hotez P, Giannoukakis N. Incidence of an Insulin-Requiring Hyperglycemic Syndrome in SARS-CoV-2-Infected Young Individuals: Is It Type 1 Diabetes? *Diabetes*. 2022;71(12):2656-63.
- Rodrigues D, Machado MR, Alves JV, Fraga-Silva TFC, Martins RB, Campos LCB, et al. Cytokine storm in individuals with severe COVID-19 decreases endothelial cell antioxidant defense via downregulation of the Nrf2 transcriptional factor. *Am J Physiol Heart Circ Physiol*. 2023;325(2):H252-h63.
- O'Leary K. Diabetes risk after COVID-19. *Nat Med*. 2022.
- Oriot P, Hermans MP. Euglycemic diabetic ketoacidosis in a patient with type 1 diabetes and SARS-CoV-2 pneumonia: case-report and review of the literature. *Acta clinica Belgica*. 2022;77(1):113-7.
- Parlițeanu OA, Bălțeanu MA, Zaharia DC, Constantinescu T, Cristea AM, Dumitrache-Rujinski Ș, et al. The Impact of SARS-CoV-2 Infection on Glucose Homeostasis in Hospitalized Patients with Pulmonary Impairment. *Diagnostics (Basel, Switzerland)*. 2025;15(5).
- Rasmi Y, di Bari I, Faisal S, Haque M, Aramwit P, da Silva A, et al. Herbal-based therapeutics for diabetic patients with SARS-Cov-2 infection. *Mol Biol Rep*. 2024;51(1):316.
- Rutter MK, Carr MJ, Wright AK, Kanumilli N, Milne N, Jones E, et al. Indirect effects of the COVID-19 pandemic on diagnosing, monitoring, and prescribing in people with diabetes and strategies for diabetes service recovery internationally. *Diabetes Res Clin Pract*. 2024;212:111693.
- Neufeldt CJ, Cerikan B, Cortese M, Frankish J, Lee JY, Plociennikowska A, et al. SARS-CoV-2 infection induces a pro-inflammatory cytokine response through cGAS-STING and NF-κB. *Commun Biol*. 2022;5(1):45.
- Nie Y, Zhou H, Wang J, Kan H. Association between systemic immune-inflammation index and diabetes: a population-based study from the NHANES. *Front Endocrinol*. 2023;14.
- Moniz M, Pereira S, Soares P, Aguiar P, Donato H, Leite A. Individual risk factors associated with SARS-CoV-2 infection during Alpha variant in high-income countries: a systematic review and meta-analysis. *Front Public Health*. 2024;12:1367480.
- Mozafari N, Azadi S, Mehdi-Alamdarlou S, Ashrafi H, Azadi A. Inflammation: A bridge between diabetes and COVID-19, and possible management with sitagliptin. *Med Hypotheses*. 2020;143:110111.
- Mung SM, Jude EB. Interplay between endocrinology, metabolism and COVID-19 infection. *Clin Med (Lond)*. 2021;21(5):e499-e504.
- O'Connell JM, Manson SM. Understanding the Economic Costs of Diabetes and Prediabetes and What We May Learn About Reducing the Health and Economic Burden of These Conditions. *Diabetes care*. 2019;42(9):1609-11.
- Wu J, Ward E, Threatt T, Lu ZK. Progression to Type 2 Diabetes and Its Effect on Health Care Costs in Low-Income and Insured Patients with Prediabetes: A Retrospective Study Using Medicaid Claims Data. *J Manag Care Spec Pharm*. 2017;23(3):309-16.
- Ballaz SJ, Fors M. Predictive Value of the Platelet Times Neutrophil-to-Lymphocyte Ratio (SII Index) for COVID-19 In-Hospital Mortality. *Ejifcc*. 2023;34(2):167-73.
- Briciu V, Leucuta DC, Muntean M, Radulescu A, Cismaru C, Topan A, et al. Differences in the inflammatory response and outcome among hospitalized patients during different waves of the COVID-19 pandemic. *Front Immunol*. 2025;16:1545181.
- Xia W, Tan Y, Hu S, Li C, Jiang T. Predictive Value of Systemic Immune-Inflammation Index and Neutrophil-to-Lymphocyte Ratio in Patients with Severe COVID-19. *Clin Appl Thromb/Hemost*. 2022;28:1076029622111391.
- Fois AG, Paliogiannis P, Scano V, Cau S, Babudieri S, Perra R, et al. The Systemic Inflammation Index on Admission Predicts In-Hospital Mortality in COVID-19 Patients. *Molecules (Basel, Switzerland)*. 2020;25(23).
- Craciun L, Ignuta F, Rayudu US, Afra M, Rosca O, Vlad A, et al. The Role of Glycemic Control in Inflammation Markers and Clinical Outcomes in Type 2 Diabetes Patients with Severe COVID-19. *Biomedicines* 2025;13(4).
- Cerulescu T, Ignuta F, Rayudu US, Afra M, Rosca O, Vlad A, et al. Inflammatory Markers and Severity in COVID-19 Patients with Clostridioides Difficile Co-Infection: A Retrospective Analysis Including Subgroups with Diabetes, Cancer, and Elderly. *Biomedicines*. 2025;13(1).
- Shoukat M, Khan H, Nazish M, Rehman A, Raashid S, Ahmed S, et al. Comparative analysis of C-Reactive protein levels among Non-comorbid, Comorbid, and Multimorbid Hospitalized COVID-19 patients. *BMC Infect Dis*. 2025;25(1):59.
- Cheng Y, Yue L, Wang Z, Zhang J, Xiang G. Hyperglycemia

- associated with lymphopenia and disease severity of COVID-19 in type 2 diabetes mellitus. *J Diabetes Complications*. 2021;35(2):107809.
30. Subbaram K, Ali PSS, Ali S. Enhanced endocytosis elevated virulence and severity of SARS-CoV-2 due to hyperglycemia in type 2 diabetic patients. *Gene Rep*. 2022;26:101495.
31. Wu D, Gao S. Analysis of the lymphocyte count in type 2 diabetic patients with coronavirus disease (COVID-19): A retrospective study in a centralized treatment center. *Diabetes Res Clin Pract*. 2020;166:108340.
32. Wang Y, Yi B, Wang S, Chen X, Wen Z. Effect of hyperglycemia on the immune function of COVID-19 patients with type 2 diabetes mellitus: a retrospective study. *PeerJ*. 2022;10:e14570.
33. Cakir M, Guven B, Issi F, Ozkaya E. New-onset celiac disease in children during COVID-19 pandemic. *Acta paediatrica (Oslo, Norway : 1992)*. 2022;111(2):383-8.
34. Acar E, Demir A, Yıldırım B, Kaya MG, Gökçek K. The role of hemogram parameters and C-reactive protein in predicting mortality in COVID-19 infection. *Int J Clin Pract Suppl*. 2021;75(7):e14256.
35. Bota AV, Marc F, Adelina M, Nicolescu L, Tudora AG, Cotoraci C. Predicting Severe COVID-19 Outcomes in the Elderly: The Role of Systemic Immune Inflammation, Liver Function Tests, and Neutrophil-to-Lymphocyte Ratio. *Healthcare (Basel, Switzerland)*. 2024;12(23).
36. Gambichler T, Schuleit N, Susok L, Becker JC, Scheel CH, Torres-Reyes C, et al. Prognostic Performance of Inflammatory Biomarkers Based on Complete Blood Counts in COVID-19 Patients. *Viruses*. 2023;15(9).
37. Tummala A, Ramesh V, Balakrishna N, Koyyada R, Singh AD, Patnam S, et al. Diagnostic Values of Laboratory Biomarkers in Predicting a Severe Course of COVID-19 on Hospital Admission. *Biomed Res Int*. 2022;2022:5644956.
38. Fenizia C, Galbiati S, Vanetti C, Vago R, Clerici M, Tacchetti C, et al. Cyclosporine A Inhibits Viral Infection and Release as Well as Cytokine Production in Lung Cells by Three SARS-CoV-2 Variants. *Microbiology spectrum*. 2022;10(1):e0150421.
39. Fernández-Jiménez E, Muñoz-Sanjose A, Mediavilla R, Martínez-Alés G, Louzao, II, Andreo J, et al. Prospective Analysis Between Neutrophil-to-Lymphocyte Ratio on Admission and Development of Delirium Among Older Hospitalized Patients With COVID-19. *Front Aging Neurosci*. 2021;13:764334.