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The Diagnostic and Predictive Role of Neutrophil-Lymphocyte Ratio, Lymphocyte-Monocyte Ratio, Platelet-Lymphocyte Ratio and C-Reactive Protein in Diabetic and Nondiabetic COVID-19 Patients

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Abstract

Background: Coronavirus disease 2019 (COVID-19) infection is more severe in diabetic cases due to abnormality in hematological and inflammatory markers. This study was conducted to determine the values of neutrophil-lymphocyte ratio (NLR), lymphocyte-monocyte ratio (LMR), platelet-lymphocyte ratio (PLR) and C-reactive protein in COVID-19 diabetic and COVID-19 nondiabetic patients, with a specific focus on associating these markers with disease severity and mortality.

Methods: A descriptive study was done by collecting hematological and inflammatory laboratory parameters of COVID-19 diabetic patients (n = 123) and COVID-19 nondiabetic patients (n = 124) retrospectively at King Fahad Medical City, Saudi Arabia.

Results: Compared with nondiabetics, patients with diabetes were older, and their mean values of white blood cells (9.16; 8.22), monocytes (7.68; 7.08), and eosinophils were high (0.69; 0.26), and lymphocytes were low (17.65; 18.77). The NLR, LMR, PLR, C-reactive protein and D-dimer were higher, with statistical significance for NLR (P = 0.05) and PLR (P = 0.005). Diabetic COVID-19 cases had longer hospital stay (17 days), higher intensive care admissions (28.5%), and a higher mortality rate (11.4%). The percentage of diabetic COVID-19 patients with comorbidities was higher. Multinomial logistic regression analysis was performed controlling for age and sex, and we obtained odds ratio for several factors. The association for NLR, LMR, PLR and D-dimer with mortality and severity was not statistically significant.

Conclusions: The results obtained from this research identified that NLR, LMR, PLR, C-reactive protein, and D-dimer were higher in COVID-19 diabetic patients than COVID-19 nondiabetic patients.

Keywords: COVID-19; Diabetes; C-reactive protein; Severity; Mortality; Lab parameters

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Introduction

Coronavirus was recognized by the World Health Organization (WHO) and declared as a pandemic on January 12, 2020, and is known to cause common cold and severe acute respiratory syndrome (SARS) depending mainly on the hosts' inflammatory response [1, 2].

The majority of patients with symptomatic infections demonstrate mild disease (with or without pneumonia). About 15-20% of the patients with symptomatic infections progress to severe disease (dyspnea, hypoxia, or > 50% lung involvement) [3]. Severe disease can affect healthy individuals of all age groups; however, it chiefly encompasses adults of advanced age or people with certain comorbidities, such as hypertension, cancer, obesity, diabetes mellitus, chronic lung disease, and chronic kidney disease. According to International Diabetic Federation report 2021, prevalence rate of diabetes mellitus in Saudi Arabia is 17.7% [4]. Many patients with diabetes mellitus were affected by coronavirus disease 2019 (COVID-19) during the pandemic across Saudi Arabia. A large, retrospective, 3-month study done on 7,260 COVID-19 patients in Riyadh from May 2020 to July 2020, reported that 920 (12.6%) had type 2 diabetes mellitus [5]. Another cross-sectional study performed in Riyadh in 2020, including 458 COVID-19 patients, revealed that 62 (13.6%) patients were found to have type 2 diabetes mellitus [6]. Many studies have shown that patients with diabetes and severe COVID-19 had a severe inflammatory response and were more likely to have higher mortality compared to nondiabetics [7-10]. These abnormalities in hematological and inflammatory markers in diabetic COVID-19 patients need to be diagnosed early, and prompt treatment with

anticoagulants should be initiated to prevent morbidity [11].

Severe COVID-19 disease cases exhibit increased leukocyte, neutrophil, eosinophil, and monocyte count than those with non-severe disease and necessitate intensive care unit (ICU) level of care. The lymphocyte-monocyte ratio (LMR), neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), D-dimer, and C-reactive protein are easily obtained from a complete blood picture with a differential profile. The NLR, LMR, PLR, and C-reactive protein have been selected because in recent studies these factors are reported to measure the degree of systemic inflammation and indicate prognosis in COVID-19 cases [12]. Also, as inflammation progresses in COVID-19, changes in the levels of many cells such as lymphocytes, monocytes, neutrophils, and platelets cause subsequent change in relevant indices such as NLR, PLR, and LMR, as well as serum acute phase proteins such as C-reactive protein. Henry et al showed that patients with severe COVID-19 had significantly higher white blood cell (WBC) and lower platelet and lymphocyte counts than non-severe cases [13].

Type 2 diabetes is more prevalent (20%) among COVID-19 patients, and diabetic patients are more prone to be affected severely and are vulnerable to death than nondiabetic COVID-19 patients. Li et al reported that the mortality rate for diabetic patients with COVID-19 was 14.5%, which is higher than nondiabetic patients (5.7%) [14]. So, patients with COVID-19 and diabetes need extra care [14]. There is very limited evidence on the clinical characteristics and outcomes of hospitalized COVID-19 patients with or without diabetes mellitus in Saudi Arabia in particular [15-17].

Alahmari et al conducted a retrospective study in Saudi Arabia and reported that more than 70% had mild-to-moderate symptoms; 45% had either diabetes or hypertension with the median length of hospital stay being 7.00 days (interquartile range (IQR): 3 - 11) [15].

Abujabal et al in 2023 collected retrospective data on socio-demographics, medical history, biomarkers, and disease outcomes from five hospitals and health institutions in Saudi Arabia and reported that common presentation of COVID-19 in their study was pneumonia, and the presence of abnormal inflammatory biomarkers (D-dimer, C-reactive protein, troponin, lactate dehydrogenase (LDH), ferritin, and WBC) were significantly associated with unstable COVID-19 disease [16].

Alguwaihes et al conducted a single-center study in Saudi Arabia and revealed that the most prevalent comorbidities in COVID-19 patients were diabetes mellitus (68.3%), hypertension (42.6%) and obesity (42.2%). During hospitalization, 77 (17.5%) patients died, thus indicating that diabetes mellitus patients had a higher death rate (20.5% versus 12.3%; P = 0.04) and lower survival time (P = 0.016) than non-diabetes mellitus [17].

Our study will measure NLR, LMR, PLR, C-reactive protein and D-dimer in the Saudi population as they may differ from published values in different populations. In addition, we will predict which factors are associated with disease progression and mortality, thus enabling the clinicians to apply them in the investigation and treatment of COVID-19 diabetic disease states before it devastates their life.

The aim of the study was to determine the values of NLR, LMR, PLR, D-dimer and C-reactive protein in COVID-19 diabetic and COVID-19 nondiabetic patients and to associate them with disease severity and mortality.

Materials and Methods

It was a descriptive retrospective study, and the study population were patients at King Fahad Medical City, with COVID-19 and diabetes, and COVID-19 patients without diabetes (total n = 247).

The inclusion criteria were all type 2 diabetic patients > 18 years old with COVID-19 (n = 123 out of 126 total reported) (irrespective of duration of diabetes, and with hemoglobin A1c (HbA1c) > 6.5%) and nondiabetic patients with COVID-19 (n = 124 out of total 133 reported).

Diabetic patients with prior hematological and thromboembolic disorders and patients with incomplete records were excluded.

Study setting

Only retrospective data were collected from King Fahad Medical City medical records between March and December 2020.

Data collection

Sample size

The study involved a sample size of 247 participants. The sample size calculation was performed with a significance level of 0.05% and a power of 80%, using the Sealed Envelope website [18].

Data collection procedure

Laboratory parameters such as hemoglobin, HbA1c, total WBC count, differential count, NLR, LMR, PLR, C-reactive protein, D-dimer from medical records at King Fahad Medical City were retrospectively collected before low-molecular-weight heparin (LMWH) was given. The data were obtained from medical records as needed, according to sample size calculated and available cases during that period after requesting information of cases from the Infection Control Department according to selection criteria mentioned above (COVID-19 patients with and without diabetes). Type 2 diabetic patients > 18 years old with COVID-19 (n = 123 out of 126 total reported) (irrespective of duration of diabetes, and with HbA1c > 6.5%) and nondiabetic patients with COVID-19 (n = 124 out of total 133 reported), both males and females, were selected. Records with incomplete information were excluded.

Data analysis

Data were transferred to EXCEL and analyzed in SPSS ver-

Table 1. Demographic Features of Patients With COVID-19 Infection With Diabetes Mellitus (N = 123) and COVID-19 Infection Without Diabetes Mellitus (N = 124)

Characteristics	COVID-19 cases with type 2 diabetes (n = 123)	COVID-19 cases without type 2 diabetes (n = 124)	P value
Average age	61 years	50 years	< 0.0001*
Gender			
Male	70 (56.9%)	97 (78.2%)	< 0.0001*
Female	53 (43.1%)	27 (21.8%)	< 0.0001*
Comorbidities	103 (83.7%)	45 (36.2%)	< 0.0001*
ICU admission	35 (28.5%)	30 (24.2%)	0.002*
Length of hospital stay (average days)	17 days	13 days	0.067
Mortality	14 (11.4%)	12 (9.7%)	< 0.0001*
LMWH given	113 (91.9%)	116 (93.5%)	0.045*

*P < 0.05. COVID-19: coronavirus disease 2019; ICU: intensive care unit; LMWH: low-molecular-weight heparin.

sion 26. Descriptive statistics like mean and standard deviation values were calculated for the normally distributed variables, while independent samples *t*-test was used to compare between the groups. NLR was calculated by dividing neutrophil count by lymphocyte count, LMR by dividing lymphocyte count by monocyte count, and PLR by dividing platelet count by lymphocytes. P value of < 0.05 was considered of statistical significance. COVID-19 was classified into mild disease (according to the criteria in previous studies (with or without pneumonia)) and severe disease (dyspnea, hypoxia, or > 50% lung involvement), by a consultant clinician working in the Diabetic Center [3].

Multinomial logistic regression analysis controlled for age and sex was done to detect predictive factors for severity and mortality of illness.

Ethical approval

The Institutional Review Board (IRB) approval was obtained (IRB number: 22-420) from the IRB Committee at King Fahad Medical City, Saudi Arabia. All the data collected were kept confidential in a password protected document, and its contents were not disclosed to people not participating in the study. The study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration.

Results

Compared with nondiabetics, patients with diabetes were older, and their average/mean values of WBC (9.16; 8.22 × 10^9 cells/L), monocytes (7.68; 7.08 × 10^9 cells/L), and eosinophils (0.69; 0.26 × 10^9 cells/L) were higher, and lymphocytes were lower (17.65; 18.77 × 10^9 cells/L). Diabetic COVID-19 cases had a longer stay in the hospital (17 days), had higher ICU admissions (28.5%), with comorbidities (83.7%), and a higher mortality rate (11.4%) (Table 1).

The NLR, LMR, PLR, C-reactive protein and D-dimer were higher with statistical significance for NLR (P = 0.05) and PLR (P = 0.005) (Table 2).

Association with mortality and severity

Multinomial logistic regression analysis was performed controlling for age and sex, and we obtained odds ratio (OR) for several factors. However, the association for NLR, LMR, PLR and D-dimer with mortality (Table 3) and severity (Table 4) was not clinically significant.

Discussion

COVID-19 patients with diabetes have received extra consideration, due to severity of cases and higher mortality rate. In the present study, we identified hematologic and inflammatory markers such as NLR, LMR, PLR, C-reactive protein, and D-dimer in COVID-19 patients with and without type 2 diabetes mellitus in Saudi population and their association with severity and mortality of the disease.

In our study, majority of the patients affected with COVID-19 and diabetes were males. This is similar to the study conducted by Alguwaihes et al, where males were more than females in the ratio of 2:1, indicating a biological risk for COVID-19 [17]. Since the spread of the pandemic all across the world from 2020, many studies have been conducted revealing that blood parameters like NLR, LMR, PLR, D-dimer and C-reactive protein, apart from other factors, are higher in COVID-19 cases, and these heightened levels have been identified as predictors for various outcomes, including disease severity, hospital admission, ICU admission, intubation, and mortality [19-22].

Guo et al in 2020 reported that the presence of diabetes has been associated with the poorer survival of COVID-19 cases with a hazard ratio (HR) of 3.17 (95% confidence interval (CI): 1.93 - 5.20) even after adjusting for age and other

Table 2. Lab Parameters of Patients With COVID-19 Infection With Diabetes Mellitus (N = 123) and COVID-19 Infection Without Diabetes Mellitus (N = 124)

Characteristics (reference range)	COVID-19 cases with type 2 diabetes (n = 123)	COVID-19 cases without type 2 diabetes (n = 124)	P value
Hb, g/dL (> 13 in males, > 12 in females)	13.02 (2.25)	13.76 (1.97)	0.079
WBC, × 10^9 cells/L (4.5 - 11)	9.16 (8.51)	8.22 (5.04)	0.091
Neutrophils, × 10^9 cells/L (2.0 - 8.0)	74.32 (13.02)	75.62 (15.79)	0.449
Lymphocytes, × 10^9 cells/L (1.0 - 4.8)	17.65 (11.22)	18.77 (14.14)	0.097
Monocytes, × 10^9 cells/L (0.30 - 0.90)	7.68 (13.93)	7.08 (7.72)	0.700
Eosinophils, × 10^9 cells/L (- 0.5)	0.69 (1.92)	0.26 (0.550)	< 0.0001
Basophil count, × 10^9 cells/L (0.02 - 0.05)	0.28 (0.274)	0.28 (0.243)	0.264
Platelets, × 10^9 cells/L (150 - 400)	252.80 (96.64)	236.65 (98.17)	0.380
NLR (0.3 - 2.1)	7.36 (8.64)	6.40 (4.78)	0.052*
LMR (2.97 - 4.83)	3.76 (6.66)	3.41 (3.41)	0.258
PLR (36.63 - 172.68)	24.75 (30.82)	19.20 (15.55)	0.005*
D-dimer, mg/L (< 0.50)	3.24 (10.01)	2.96 (8.17)	0.571
C-reactive protein, mg/L (< 10)	117.35 (88.33)	108.19 (83.97)	0.207

*P < 0.05. COVID-19: coronavirus disease 2019; Hb: hemoglobin; WBC: white blood cell; NLR: neutrophil-lymphocyte ratio; LMR: lymphocyte-monocyte ratio; PLR: platelet-lymphocyte ratio.

comorbidities (HR = 1.53, 95% CI: 1.02 - 2.30) [19].

In our study among 123 COVID-19 diabetic patients, 83.7% had comorbidities, making their average stay in the hospital more than 2 weeks, with a greater number of admissions in ICU and higher mortality rate. Zhang et al conducted a study and revealed that COVID-19 patients with diabetes and secondary hyperglycemia were classified as more critical and had about 2 - 5-fold greater composite outcomes risk compared with controls, as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection releases increased amounts of glucocorticoids and catecholamines, further elevating blood glucose and causing hyperglycemia, leading to release of the proinflammatory monocytes, augmenting platelet reactivity, ultimately contributing to increased number of deaths in diabetic individuals [20].

In a study conducted by Liu et al of 134 COVID-19 patients with diabetes, correlation analysis between inflammatory markers and prognosis revealed that age, NLR, and LMR were correlated with COVID-19 severity in type 2 diabetics. In multivariate regression analysis after controlling for the relevant confounding factors, COVID-19 diabetes patients with higher NLR had more severity, and longer duration of hospital stay [21]. Varikasuvu et al in 2020 reported that the levels of C-reactive protein (standardized mean difference (SMD) = 0.53, CI: 0.20 - 0.86, P = 0.002), and D-dimers (SMD = 0.54, CI: 0.16 - 0.91, P = 0.005) were significantly higher in diabetic COVID-19 cases as compared to nondiabetic COVID-19 patients, signifying that diabetic COVID-19 patients are more susceptible to coagulation dysfunction and inflammatory storm [22].

In another study by Yang et al, elevated NLR and age were considerably related with illness severity. The binary logistic analysis revealed increased NLR (HR: 2.46, 95% CI: 1.98 - 4.57) and age (HR: 2.52, 95% CI: 1.65 - 4.83) as independent factors for poor clinical consequence of COVID-19 [23].

In severe COVID-19 cases, there is dysregulation of im-

Table 3. Multinomial Regression Analysis Controlling for Age and Sex to Know the Impact of Lab Parameters on COVID-19 Mortality

Variable	P value	OR (95% confidence interval)
NLR	0.967	1.003 (0.889 - 1.130)
LMR	0.223	1.047 (0.972 - 1.128)
PLR	0.087	1.030 (0.996 - 1.065)
D-dimer	0.078	0.961 (0.920 - 1.004)
C-reactive protein	0.048*	0.996 (0.992 - 1.000)

*P < 0.05. COVID-19: coronavirus disease 2019; OR: odds ratio; NLR: neutrophil-lymphocyte ratio; LMR: lymphocyte-monocyte ratio; PLR: platelet-lymphocyte ratio.

Table 4. Multinomial Regression Analysis Controlling for Age and Sex to Know the Impact of Lab Parameters on COVID-19 Severity

Variable	P value	OR (95% confidence interval)
NLR	0.557	0.973 (0.889 - 1.065)
LMR	0.827	0.994 (0.939 - 1.052)
PLR	0.310	1.013 (0.988 - 1.038)
D-dimer	0.248	1.018 (0.988 - 1.050)
C-reactive protein	0.163	0.997 (0.993 - 1.001)

COVID-19: coronavirus disease 2019; OR: odds ratio; NLR: neutrophil-lymphocyte ratio; LMR: lymphocyte-monocyte ratio; PLR: platelet-lymphocyte ratio.

mune pattern characterized by constant cytokine release and hyperinflammation. In addition, abnormalities in biochemical, hematological, immune, and inflammatory biomarkers lead to lymphocytopenia, decreased monocyte and eosinophil counts, and elevated neutrophil counts. Taj et al in 2021 revealed that leukocytosis, neutrophilia and increased NLR, as well as C-reactive protein had a major relationship with the disease severity and was highest in patients with critical disease [24]. Other studies have also associated elevated C-reactive protein with disease severity and mortality [25-27].

Lee et al reported that the mean LMR, PLR, and mean platelet volume (MPV) were 5.31 (1.68), 132.40 (43.68), and 10.02 (0.79), respectively and recommended that patients with age < 50 years old and NLR ≥ 3.13 at low risk should be kept in general isolation ward. Patients with age ≥ 50 and NLR < 3.13 patients at moderate risk, should be admitted to isolation ward with respiratory monitoring and supportive care. Patients with age ≥ 50 and NLR ≥ 3.13 at high risk should be actively transferred to ICU [3]. Liao et al in their study also demonstrated high NLR as a prognosticator for severity and mortality of SARS-CoV-2 infection [27]. Kurt et al in their study reported that the risk of COVID-19 was significantly correlated to the NLR level (adjusted OR: 1.438, P = 0.012) [11].

In our study, the NLR, LMR, PLR, C-reactive protein and D-dimer were higher in COVID-19 patents with diabetes. It has been reported that SARS-CoV-2 infects circulating immune cells, promotes inflammation and intensifies apoptosis of lymphocytes, leading to lymphocytopenia, and thus altering NLR and LMR with the severity of COVID-19 [28]. The C-reactive protein released in hyperinflammatory state is regulated by proinflammatory cytokines, chiefly by interleukin-6 (IL-6), which is elevated in most COVID-19 patients, thereby affecting the disease severity and prognosis [29].

Various studies have reported that in COVID-19 cases there is an upsurge in inflammatory and hyper coagulation status as compared to non-COVID-19 cases. Moreover the presence of chronic diseases like type 2 diabetes mellitus further affects the degree of inflammatory and coagulation dysfunction in COVID-19 [30-33]. Expression of angiotensin-converting enzyme 2 (ACE2) is more concerted in epithelial cells of the lung, intestine, kidney, and blood vessels, thereby affecting these organs more than the other organs [34, 35].

There are certain limitations to our study, as the sample size is not huge in this retrospective study, selection bias might have occurred. Also, the duration of diabetes mellitus was not recorded, and if known it would definitely have added value to the study.

Despite the limitations, the findings of the present study are robust, and add value to the limited literature on COVID-19 patients with diabetes in this region. It is one of the very few studies conducted in Saudi population to comprehensively compare several factors among COVID-19 patients with and without diabetes. Emerging biomarkers are not routinely assessed, such as N-terminal-pro-brain natriuretic peptide, high-sensitivity troponin (hs-troponin), and triglyceride-glucose (TyG) index were not taken into account [36, 37].

Due to incomplete documentation of certain values, and limited accuracy of medical records in retrospective studies, it is advisable to conduct prospective studies with larger sample size and multiple medical centers across the region that could probably add more information to the existing knowledge regarding predicting factors of severity and mortality in COVID-19 patients. Also, treatment options that prevent progress of the disease need exploration, especially in patients with associated comorbidities that could shorten the life span of the patients.

Conclusions

The results obtained from this research indicated that NLR, LMR, PLR, C-reactive protein, and D-dimer were higher in COVID-19 diabetic patients compared to COVID-19 nondiabetic patients.

In summary, diabetes mellitus is highly prevalent among COVID-19 patients in Riyadh, Saudi Arabia. While the age of diabetes mellitus patients is higher, with longer duration of stay, a greater number of ICU admissions, and a higher mortality rate than non-diabetes mellitus patients, other factors such as elevated C-reactive protein appear to be more significant predictors of mortality. Diabetic COVID-19 patients with comorbidities on admission are more likely to receive intensive care.

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Conflict of Interest

The authors have no conflict of interest to disclose.

Informed Consent

The informed consent was waived by the IRB since we only used the patient results without identification.

Author Contributions

Raneem Salem and Ayesha Nuzhat conceptualized this study, did the formal analysis and investigation, wrote the original draft, read the manuscript, and approved it. Majd Aldeen Kallash contributed to the review of patients' data and final review of the manuscript.

Data Availability

The data presented in the study are available on request from the corresponding author during submission or after publication.

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