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A CASE-CONTROL STUDY OF HEMATOLOGICAL ANALYSIS ON DIABETES AND COVID-19 SEVERITY

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ABSTRAK

Penelitian ini menyelidiki hubungan antara komorbiditas diabetes dan tingkat keparahan COVID-19 di RS Muhammadiyah Palembang, dengan fokus pada parameter hematologi sebagai prediktor komplikasi penyakit. Dengan menggunakan desain kasus-kontrol dengan 61 orang responden, data demografi, klasifikasi keparahan COVID-19, dan profil hematologi dianalisis. Hasil penelitian menunjukkan tingkat prevalensi diabetes melitus di antara pasien COVID-19 sebesar 32,8% dan penderita diabetes mengalami tingkat komplikasi klinis sedang sampai tinggi. Analisis hematologi menunjukkan variasi parameter seperti kadar hemoglobin, jumlah trombosit, dan rasio neutrofil terhadap limfosit antara pasien COVID-19 diabetes dan non-diabetes. Temuan ini menggarisbawahi pentingnya intervensi yang disesuaikan untuk individu penderitas diabetes yang terinfeksi COVID-19 dan menyoroti potensi parameter hematologi dalam memprediksi tingkat keparahan penyakit. Studi ini menunjukkan perlunya penelitian multisenter berskala besar untuk memvalidasi temuan dan memberikan informasi kepada praktik klinis berbasis bukti dalam menangani pasien COVID-19 dengan komorbiditas diabetes melitus.

ABSTRACT

A Case-Control Study Of Hematological Analysis On Diabetes And Covid-19 Severity. This study investigates the relationship between diabetes comorbidity and COVID-19 severity in Muhammadiyah Palembang Hospital, focusing on hematological parameters as potential predictors of disease progression. Utilizing a case-control design with 61 respondents, demographic data, COVID-19 severity classifications, and hematological profiles were analyzed. Results reveal a prevalence rate of diabetes mellitus among COVID-19 patients at 32.8%, with diabetic individuals experiencing higher rates of moderate clinical complications. Hematological analysis demonstrates variations in parameters such as hemoglobin levels, platelet counts, and neutrophil-to-lymphocyte ratio between diabetic and non-diabetic COVID-19 patients. These findings underscore the importance of tailored interventions for diabetic individuals infected with COVID-19 and highlight the potential of hematological parameters in predicting disease severity. The study suggests the need for larger-scale, multicenter research to validate findings and inform evidence-based clinical practice in managing COVID-19 patients with comorbid diabetes mellitus.

INTRODUCTION

COVID-19 has brought new difficulties to global public health systems, not only as a contagious illness but also by increasing pre-existing health inequities and introducing complicated interactions with numerous comorbidities, all of which have a significant impact on disease severity and outcomes.[1] Research on the influence of comorbidities on COVID-19 outcomes has revealed the complexities of patient reactions across disease phases, as well as the need to understand these linkages to improve patient care.[2] Diabetes has been shown in several investigations to impair the clinical course and prognosis of COVID-19 patients.

The study discovered that COVID-19 patients with diabetes had increased mortality and comorbidities, necessitating more acute care after discharge.[3] A statewide Polish study discovered diabetes to be an independent risk factor for COVID-19 in-hospital mortality, with the risk varying by age group.[4] A multicenter study discovered that diabetes patients had higher long-term mortality than non-diabetics, despite comparable readmission and reinfection rates.[5] The French CORONADO study found that diabetes was associated with a worse COVID-19 prognosis, regardless of age or comorbidities, particularly in terms of invasive mechanical ventilation or death.[6] Diabetes produced more severe innate immune cell dysfunction and organ damage in COVID-19 patients in early 2020 and 2021, demonstrating immune system deterioration in response to SARS-CoV-2 infection.[7] A study of US healthcare systems found that type 1 and type 2 diabetes increased the likelihood of COVID-19 infection and poor outcomes, with the risk rising with diabetes severity.[8] Japanese researchers looked at how undiagnosed diabetes and prediabetes affect COVID-19 outcomes, revealing a wide spectrum of glucose metabolism issues that influence COVID-19 severity.[9] A comprehensive review found that diabetes can exacerbate COVID-19, which can change glucometabolic.[10] Severe COVID-19 was associated with hypertension, poor glycemic control, older age, and male sex in diabetics in Indonesia.[11] Finally, pancreatic beta cells exhibit angiotensin-converting enzyme 2 receptors, which might result in hyperglycemia in SARS-CoV-2 patients with or without diabetes, aggravating their prognosis.[12]

Diabetes, particularly poor glycemic control, raises the risk of serious COVID-19 outcomes, such as death. A study found that diabetes is linked to COVID-19 severity, implying that hematological indicators may predict disease development.[13–15] Elevated C-reactive protein, D-dimer, ferritin, and lactate dehydrogenase levels suggest a severe infection in COVID-19 patients with diabetes.[16] Hematological markers and the neutrophil-lymphocyte count ratio (NLR) show the inflammatory response and may predict disease progression.[11]

A comprehensive counterexample may be a diabetic patient with modest COVID-19 symptoms and normal hematological profiles, demonstrating that not all diabetic people are at high risk of developing serious disease. This shows that variables other than diabetes and hematological characteristics may have a major impact on the severity of COVID-19 in diabetic individuals. This study addresses the complex relationship among diabetes, hematological indicators, and COVID-19 outcomes to improve clinical care and public health strategies during the pandemic.

METHODS

This case-control study used the medical records of adult inpatients from Muhammadiyah Palembang Hospital who were diagnosed with COVID-19 during the period of March 1, 2020, to November 30, 2023. The individuals in question were one with less of 65 years of age, with the

purposive sampling to include diabetes resulted in 61 participants. The patient was excluded based on the presence of a single comorbidity, rather than specifically diabetes or multiple comorbidities. Polymerase chain reaction (PCR) was used to detect the presence of SARS-CoV-2 in nasopharyngeal swabs. The Faculty of Medicine at Universitas Muhammadiyah Palembang awarded the ethical clearance number 166/EC/KBHKI/FK-UMP/XI/2023. Co-morbid diabetes mellitus was the primary exposure variable in this study, whereas COVID-19 severity is the outcome variable. Patients with COVID-19 and a history of diabetes were chosen to establish a representative sample for research into diabetes comorbidity and COVID-19 severity.

The WHO classified severe COVID-19 as an oxygen saturation level below 93% while breathing in room air, a respiratory rate more than 30 breaths per minute, and symptoms of severe respiratory distress (such as the use of extra muscles or the inability to complete full sentences). Mild COVID-19 patients presented with COVID-19 symptoms but no shortness of breath, dyspnea, or abnormal chest imaging. Hence, moderate illness was defined as lower respiratory tract disease (clinical assessment/abnormal chest imaging) with oxygen saturation of at least 95% in room air.[17]

Hematological indicators were used to determine the severity of COVID-19 in diabetics. Several variables include hemoglobin, the neutrophil-lymphocyte ratio, platelets, leucocytes, lymphocytes, and erythrocyte sedimentation rate (ESR). According to World Health Organization (WHO) criteria, anemia is defined as a hemoglobin level of less than 13 g/dL for men and less than 12 g/dL for women.[18] Following to current studies, the usual NLCR range in healthy people was 0.78 to 3.53, with 3.3 functioning as the ideal cut-off value for identifying individuals with severe COVID.[19] The normal range of platelet was 150.000-400.000 cell/µL.[20] Leucocyte counts were within the usual range of 4200-11.000 /µL.[21] The amount of lymphocytes collected was within the normal range of 20-50%.[22] The erythrocyte sedimentation rate was less than 10 millimeters per hour, which is considered normal for a healthy person.[23]

Univariate and bivariate analyses were performed to investigate the distributions and associations of simultaneous diabetes, COVID-19 severity, and hematological markers. Frequencies, means, and standard deviations provide a summary of the research population and variables. The statistical software Statistical Package for the Social Sciences (SPSS) was utilized due to its comprehensive range of statistical tools. Independent Samples t-test was to compare of means between two separate groups, whether statistically significant disparity between case-control groups. Mann-Whitney test was used to investigate categorical and continuous variable connections. The rationale for using the independent sample t-test is to compare the means of different groups or circumstances, particularly when the data meets normality criteria. The Mann-Whitney test was selected as an additional non-parametric approach. The value of this technique stems from its capacity to be employed even when the data does not follow a normal distribution, ensuring the precision and dependability of the analysis. To control for any possible confounding factors, we employed stratification and matching methods. The data were categorized according to major criteria that might influence the results, such as severity and the existence of comorbidities. By doing many analyses on subgroups, we can determine if the core findings are consistent across categories, ensuring that the results are not unfairly impacted by variables that might bias the conclusion. Subjects were occasionally matched based on key confounding characteristics. Participants in the treatment groups were matched according to the severity of their sickness and any other medical issues they had.

RESULTS

The demographic profile of the study participants revealed that the majority were male, constituting 31 individuals (50.8%) of the total sample. Moreover, approximately two-thirds (67.2%) of the respondents fell within the age range of 40 to 65 years. In terms of the temporal distribution of COVID-19 cases, the year 2022 recorded the highest prevalence, with 27 comments (44.3%) confirming it as the most prevalent year. Among the COVID-19 patients, 41 individuals (67.2%) did not have comorbid diabetes, while diabetes mellitus was present in 20 out of the total 61 COVID-19 patients, accounting for a prevalence rate of 32.8%. Notably, 11 individuals (55%) with the highest number of underlying health conditions, including diabetes mellitus, experienced moderate clinical complications. Conversely, a majority of COVID-19 patients without diabetes, namely 21 individuals (51.2%), experienced minor clinical effects. All RT-PCR findings for COVID-19 patients were positive, confirming the presence of the virus in all cases (See Table 1).

Table 1. Frequency and Percentage Distribution of Respondent Characteristics (n=61)

Characteristic	Category	Frequency	Percent. (%)
Gender	Male	31	50,8
	Female	30	49,2
Age (year)	0-39	20	32,8
	40-65	41	67,2
Confirmed year	2020	14	23
	2021	20	32,8
	2022	27	44,3
COVID-19	With DM	20	32,8
	Without DM	41	67,2
Severity with DM	Low	2	10
	Moderate	11	55
	Severe	7	35
Severity without DM	Low	21	51,2
	Moderate	20	48,8
	Severe	0	0
RT-PCR	Positive	61	100
	Negative	0	0%

In terms of hematological parameters, individuals with comorbidity diabetes mellitus exhibited a lower average hemoglobin level (9.6 g/dL) with a standard deviation (SD) of 1.58 g/dL compared to those without comorbidity. The average platelet count was 217 × 10^3/µL, with an SD of 70.04 × 10^3/µL, while the average leukocyte count was 10.95 × 10^3/µL, with an SD of 3.32 × 10^3/µL. Additionally, the average lymphocyte count was lower at 8.1%, with an SD of 4.61%, whereas the average neutrophil-to-lymphocyte ratio (NLR) was higher at 18.5, with an SD of 39.06. Individuals with concomitant diabetes mellitus also exhibited a higher average erythrocyte sedimentation rate (ESR) of 55.15 mm/hour, with an SD of 40.26 mm/hour, compared to those without diabetes (See Table 2).

Table 2. Frequency Distribution and Normality test of Hematological Parameters (n=61)

Variables (Mean ± SD)	With DM (n=20)	p-value	Without DM (n=41)	p-value
Hemoglobin	9.6 ± 1.58	0.200	11.4 ± 1.91	0.200
Platelets	217 ± 70.04	0.200	321 ± 128.2	0.200
Leukocytes	10.95 ± 3.32	0.200	8.7 ± 3.63	0.200
Lymphocytes	8.1 ± 4.61	1.32	21.63 ± 12.4	0.062
NLR	18.5 ± 39.06	0.000	5.3 ± 5.54	0.000
LED	55.15 ± 40.26	0.024	23.5 ± 17.17	0.015

The normality test results for hemoglobin, platelets, leukocytes, and lymphocytes indicated p-values larger than 0.05, suggesting a normal distribution of data and justifying the use of the Independent Sample T-test for further investigation. Conversely, the normality test of NLR, ESR, and clinical symptoms yielded p-values of less than 0.05, indicating a non-normal distribution of data and prompting the application of the Mann-Whitney test. Statistical analyses revealed significant differences in the levels of hemoglobin, platelets, leukocytes, and lymphocytes between COVID-19 patients with and without comorbid diabetes mellitus. Furthermore, the Mann-Whitney U test demonstrated significant differences in NLR, ESR values, and clinical symptoms between COVID-19 patients with and without concomitant diabetes mellitus. However, the RT-PCR test yielded a significance value of 1,000 ($p > 0.05$), indicating no significant difference in RT-PCR results between COVID-19 patients with and without comorbid diabetes mellitus, as both groups had the same average rank (See Table 3).

Table 3. Independent Sample T-Test and Mann-Whitney test of With DM and Without DM (n=61)

Variables	Independent Sample T-Test	p-value	Mann-Whitney test	p-value
Hemoglobin	32,8%	0,001	-	-
Platelets	32,8%	0,021	-	-
Leukocytes	32,8%	0,041	-	-
Lymphocytes	32,8%	0,001	-	-
NLR	-	-	32,8%	0,000
LED	-	-	32,8%	0.019
Clinicals	-	-	32,8%	0,000
RT-PCR	-	-	32,8%	1,000

DISCUSSIONS

The prevalence of diabetes mellitus among COVID-19 patients, especially 32.8% among those who passed on, demonstrated the importance of comorbidities such as diabetes in determining the outcomes of COVID-19 disease.[3] This is consistent with a substantial amount of evidence demonstrating that diabetic mellitus (DM) significantly affects the severity of COVID-19 illness. A retrospective cohort study found that people with diabetes who caught COVID-19 succumbed at a higher rate, had more problems after discharge, and were more likely to be admitted to specialized care facilities than people without diabetes.[5] Furthermore, a second study found that people with diabetes mellitus (DM) had a higher long-term mortality rate than those without DM, highlighting the considerable impact of diabetes on COVID-19 outcomes.[24] A meta-analysis found data supporting the assumption that COVID-19 survivors had a 66% higher risk of acquiring diabetes. Furthermore, the severity of diabetes, as indicated by characteristics such as

insulin usage and poor blood sugar management, has been associated with an increased risk of developing COVID-19 and having more severe outcomes.[16] According to studies, diabetes affects more than 20% of COVID-19 patients globally, with a 7.3% mortality rate. This strengthens the link between diabetes and the severity of COVID-19. Inadequate blood sugar control, high blood pressure, advanced age, and male gender are all risk factors for the severity of COVID-19 in patients with type 2 diabetes mellitus (T2DM).[11] These findings highlight the need to identify diabetes as a major risk factor for severe COVID-19 illness. This emphasizes the need to carefully manage diabetes individuals throughout the epidemic.

The interaction between diabetes mellitus (DM) and COVID-19 has a significant impact on the duration and implications of the infection, showing a combined effect that complicates the severity of illness in diabetics. According to studies, persons with diabetes are more susceptible to experiencing severe COVID-19 symptoms and have a higher risk of dying. Diabetic individuals often have more severe symptoms and require more frequent admission to critical care units than non-diabetic patients.[14] This susceptibility is exacerbated by the increased incidence of major infections in diabetics due to immune system dysregulation.[25] The fatality rate among COVID-19 patients with diabetes is much greater demonstrating the critical role of diabetes in the severity of COVID-19 infection.[16] Individuals with diabetes are more likely to acquire COVID-19 and are more vulnerable to negative outcomes due to alterations in their immunological and inflammatory responses.[26]

Diabetics are more likely to have impaired innate immune cells, resistant blood coagulation problems, and organ damage when infected with SARS-CoV-2, complicating their prognosis.[7] Poor glycemic control, hypertension, and an increased neutrophil-lymphocyte ratio are associated with the severity of COVID-19 in diabetics.[11] Diabetes incidence increases in proportion to the severity of the illness, contributing significantly to the severity and fatality rates linked with COVID-19.[24] Diabetes patients who catch COVID-19 reveal more severe symptoms as well as abnormalities in their blood and metabolic markers. When compared to those without diabetes, these alterations include lower levels of hemoglobin, calcium, and alkaline phosphate and greater levels of glucose, potassium, and cardiac troponin.[14] This suggests that diabetes exacerbates the severity of COVID-19, necessitating closer monitoring of these variables to assess the condition's progression and adjust treatment options. Furthermore, the significance of hematological indicators in connection to COVID-19 goes beyond the presence of diabetes. The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have been identified as markers for discriminating between moderate and severe COVID-19.[27] Furthermore, alterations in red blood cell distribution width (RDW) and platelet indices have been associated to COVID-19 mortality, indicating that they may serve as prognostic indications.[28] To summarize, the findings as prospective indicators of the severity of the disease, thus highlighting the importance of precisely evaluating and managing people with diabetes and COVID-19.[29]

The relationship between diabetes, COVID-19, and hematological indicators is complex and variable, as seen by the different findings of various studies. The research underlines the significance of addressing the highlighted limitations, such as restricted sample sizes and single-center designs, by conducting larger-scale, multicenter investigations with longitudinal follow-up. This is required to have an in-depth understanding of the relationships between diabetes, COVID-19, and hematological markers.

CONCLUSIONS

In conclusion, this study contributes to the growing body of evidence on the relationship between diabetes mellitus, COVID-19 severity, and hematological parameters. Our findings underscore the observed alterations in all hematological parameters among diabetic COVID-19 patients suggest potential mechanisms underlying disease progression and provide valuable insights for clinical management.

Furthermore, recommendation can inform future research and clinical practice. Firstly, there is a need for larger-scale, multicenter studies to validate our findings and further elucidate the complex interplay between diabetes, COVID-19, and hematological parameters. Longitudinal studies with comprehensive follow-up are essential for assessing disease progression and long-term outcomes in diabetic individuals infected with COVID-19.

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