OPEN ACCESS Freely available online
http://www.banglajol.info/index.php/BJID/index
Original Article
Bangladesh Journal of Infectious Diseases
December 2024, Volume 11, Number 2, Page 102-107
ISSN (Online) 2411-670X
ISSN (Print) 2411-4820
DOI: https://doi.org/10.3329/bjid.v11i2.75290

Leukocyte Glucose Index as Significant Marker of Poor Prognosis in COVID-19 Patients with Hyperglycemia

Marwan S.M. Al-Nimer[1], Talar A. Merza[2], Thaqeef M. Jawad[3], Ismail I. Latif[4]

[1]Emeritus Professor of Clinical Pharmacology, Department of Clinical Pharmacology and Therapeutics, College of Medicine, University of Diyala, Baqubah, Iraq; [2]Assistant Professor (Clinical Pharmacy), Department of Clinical Pharmacy, College of Pharmacy, Hawler Medical University, Erbil, Iraq; [3]Assistant lecturer, Department of Chemistry, College of Science, University of Wasit, Wasit, Iraq; [4]Professor of Immunology, Department of Microbiology, College of Medicine, University of Diyala, Baqubah, Iraq

Abstract

Background: Both diabetes mellitus (DM) and stress hyperglycemia (SH) are common findings in complicated or critically ill COVID-19 patients. **Objective:** This retrospective study aims to assess leukocyte glucose index (LGI) as a prognostic marker for the outcome of COVID-19 patients. **Methodology**: This retrospective study was conducted at the College of Medicine, University of Diyala, Iraq. Patients with COVID-19 were randomly allocated. A primary outcome of this study was clinical outcomes in terms of surviving or not surviving. **Results**: 187 patients in total were included in the study and divided into three groups. Group I (n = 45) survived patients, Group II (n = 90) survived patients with complications, and Group III (n = 52) non-survived patients. The baseline data showed significant differences between Groups III, I, and II. The median values of LGI were significantly ($p < 0.001$) higher in Group III (2.911) compared with Group I (1.754) and Group II (1.728). The odds ratio of DM, SH, and LGI (a cutoff value of 1.5) as a risk of mortality is 2.361, 7.333, and 4.842, respectively. **Conclusion:** Leukocyte glucose index is a worse marker for COVID-19 patients with overt diabetes or stress hyperglycemia. [*Bangladesh Journal of Infectious Diseases, December 2024;11(2):102-107*]

Keywords: COVID-19; Mortality; Leucocyte glucose index; Diabetes mellitus; Stress hyperglycemia

Correspondence: Marwan S.M. Al-Nimer, *MD, PhD,* Emeritus Professor of Clinical Pharmacology, Department of Clinical Pharmacology and Therapeutics, College of Medicine, University of Diyala, 32001 Baqubah, Iraq. Email: alnimermarwan@ymail.com; Cell No.: +964 790 260 0291; ORCID: https://orcid.org/0000-0002-5336-3353

Introduction

Researchers identified the risk factors, severity, and mortality of COVID-19. Zhang et al[1] in their review, summarized the risk factors that contributed to the severity of COVID-19: old age (> 70 years), male sex with a lower immunity and normal testosterone levels, associated chronic diseases like hypertension, diabetes mellitus, chronic obstructive lung diseases, bronchial asthma and factors related to the delay of health care services. The relationship between diabetes mellitus and COVID-19 is running in a vicious cycle, i.e., diabetes patients are at risk of developing COVID-19, diabetic complications, and a high incidence of mortality[2-4]. It has been reported that 21.6% of elderly patients

infected with SARS-CoV-2 were diabetic, and 28.4% had dysglycemia, characterized by fasting plasma glucose of 5.6-6.9 mmoL[5]. Hyperglycemia in COVO-19 patients is attributed to many etiological factors, including the stress induced by viral infection, using corticosteroids, dysfunction of adipose tissue, or direct destruction of β-pancreatic cells[6]. During the pandemic COVID-19, stress hyperglycemia was defined as a fasting plasma glucose level of more than 7mmoL/L (more than 125 mg/dL) on the admission of non-diabetic COVID-19 patients, and it is significantly associated with an increased risk of thromboembolism[7].

Furthermore, the researchers were working on the circulation biomarkers to identify COVID-19 patients with a poor prognosis. Biomarkers were related to hematological indices, inflammatory factors, hormones, antioxidants, nutrients and so one[8-9]. It has been reported that leukopenia is a feature of COVID-19 patients in 20.0% to 40.0%, while leukocytosis occurs in 3.0% to 24.0%, and lymphocytopenia is a strong associated risk factor[10]. In-hospital admissions of COVID-19 have poor prognostic outcomes if they are hypertensive or have higher values of neutrophil-to-lymphocyte ratio (NLR) and N-terminal pro B- type natriuretic peptide[11]. A cutoff value of 6.82 indicated poor prognostic clinical outcomes after adjusting the characteristic demographic characteristics of the patients[12]. However, the NLR is considered a decision-making process for recovered patients with COVID-19 pneumonia[13]. Higher percentages of morbidity and mortality of COVI-19 illness are associated with a higher platelet-to-lymphocyte ratio (PLR) on admission, as a mean difference between a critically ill patient and survival of 66.10 was reported[14].

In one systematic review and meta-analysis that included 71 studies, it has been found that the discriminators of survival and progression outcomes of COVID-19 are the blood cell counts, which include relative neutrophilia, lymphocytopenia and thrombocytopenia, as well as a higher NLR value on admission[15]. The leukocyte glycemic index (LGI) was evaluated in 109 COVID-19 adult patients, and it has been found that LGI is a biomarker of severe COVID-19, particularly in diabetic females[16].

The markers of severity included biomarkers related to hematological and respiratory diseases. So, combining the total leukocyte and plasma glucose levels on admission will improve the diagnostic accuracy of LGI as a prognostic marker.

The rationale for this study is to COVID-19-induced stress hyperglycemia in patients without overt diabetes. Therefore, this study aimed to assess the LGI as a biomarker of COVID-19 severity and mortality in diabetic patients and non-diabetic patients who showed stress hyperglycemia.

Methodology

Study Design and Population: This retrospective study was performed at the College of Medicine, University of Diyala, Baqubah, Iraq. This study was conducted in the governorate, and all subjects were of Arab ethnicity.

Study Procedure: The data from the patient's records was collected from three hospitals. Participants were included if they had (i) a COVID-19 proved by polymerase chain reactions; (ii) clinical and laboratory evidence of COVID-19; (iii): the demographic characteristics included age, sex, and a history of diabetes mellitus treated with oral hypoglycemic agents at the time of admission; (iv) the laboratory investigations included a complete blood count (determined by the Coulter machine), inflammatory markers (erythrocyte sedimentation rate and C-reactive protein), and plasma glucose level at the time of admission into the hospital. Participants were excluded if they had (i) a negative or unavailable laboratory test of COVID-19 polymerase reactions; (ii) an incomplete laboratory investigation.

In total, the data of 187 patients was extracted for analysis. The primary outcome is the last event of COVID-19, whether they survived without complications and discharged from the hospital within 7 days (Group I, n = 45), had complications with a stay duration in the hospital up to 4 weeks (Group II, n = 90), or not survived despite their management (Group III, n = 52).

Definition of Pathological Conditions: Stress hyperglycemia is defined as a plasma glucose >180mg.dL^{-1} in non-diabetic patients who were admitted to the hospital due to the concurrent illness[17], while most researchers used a fasting plasma glucose of >125 mg/dL as an indication of stress-induced hyperglycemia. A leukocyte counts of >10^9/L indicates leukocytosis. LGI is a novel prognostic biomarker whose higher value is linked with disease severity and poor prognostic outcomes.

Blood Biochemistry, Hematological and Inflammatory Indices Examination: All the biochemical variables were done in the laboratories

of the hospitals. Blood samples were collected from participants, and serum or plasma samples were analyzed on the same day. The anticoagulant EDTA whole blood was collected for a complete blood count measurement and erythrocyte sedimentation rate. The biochemistry measurements included plasma glucose and serum C-reactive protein.

Calculating the indices

LGI=

$$\frac{\textbf{Total Leucocytes } (\times 10^9\ .L^{-1} \times \textbf{plasma glucose } (mg.dL^{-1})}{1000}$$

Neutrophil-to-lymphocyte ratio (NLR)

$$= \frac{\textbf{Neutropil count}}{\textbf{Lympcyte count}}$$

Derived neutrophil-to-lymphocyte ratio (dNLR)

$$= \frac{\textbf{Neutrophi count}}{\textbf{Total leukocyte count} - \textbf{Neutrophil count}}$$

Platelet-to-lymphocyte ratio (PLR)

$$= \frac{\textbf{Platelet count}}{\textbf{Lymphocyte cound}}$$

Statistical Analysis: Statistical analyses were carried out using SPSS 25 (IBM Corp., Armonk, NY, USA). The sample size was calculated by using the margin of error (α error = 0.05, β = 0.2, the power is 0.8), two tails, and a 95% confidence interval. The Shapiro-Wilk test was used to evaluate the normality assumption of quantitative variables. Categorized and continuous data are presented as numbers (percentages) and medians (25th–75th percentiles).

For comparing baseline characteristics between groups, the Mann-Whitney U test was used for continuous data. To enable comparisons between groups in the LGI, the patients were sub-grouped into diabetes and non-diabetes patients, and the later sub-group was further grouped according to plasma glucose level (a cutoff value of 180 mg.dL^{-1}) into stress and non-stress hyperglycemia. In addition, the odds ratio with a 95% confidence interval was calculated for each sub-group to report the risk of mortality in COVID-19 patients. A p-value of < 0.05 was considered statistically significant.

Results

the median values of age, CRP, and ESR in Group I were significantly lower than the corresponding values in Groups II and III. There were non-significant differences between groups in the PLR, dNLR, PCT, MPV, and hemoglobin median values. A significantly higher leukocyte count and plasma glucose values were observed in Group III compared with Groups I and II. Known cases of T2D were present in 33.3% (15 out of 45), 50% (45 out of 90), and 65.4% (34 out of 52) in Groups I, II, and III, respectively (Table 1).

Figure I showed a significantly (p <0.001) higher median value of LGI in Group III (2.911) compared with Groups I (1.754) and II (1.728). Stress hyperglycemia (PG > 180 mg.dL^{-1}) was identified in 10% (3 out of 30), 13.3% (6 out of 45), and 50.0% (9 out of 18) for Groups I, II, and III, respectively. Plasma glucose of >125 mg/dL is found in 24 (53.3%), 45 (50%), and 43 (82.7%) for Groups I, II, and III, respectively. Leukocytosis was found in 31(68.9%), 56 (62.2%), and 42 (80.8%) for Groups I, II, and III, respectively.

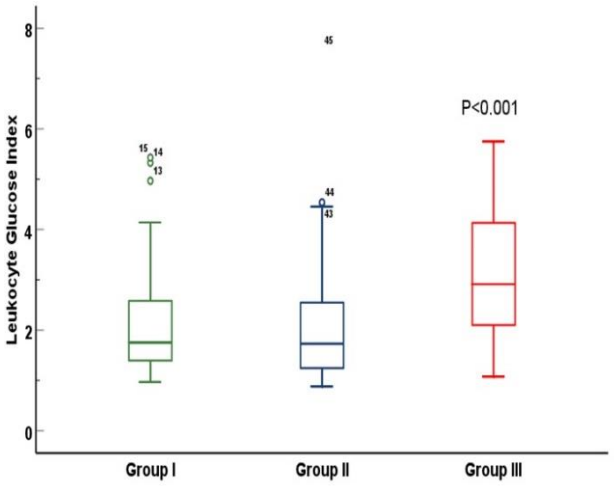

Figure I: Boxplot showed a significantly higher leukocyte glucose index in COVID-19 patients. Group I: Uncomplicated survival, Group II: survived with complications, and Group III: non-survival

Figure II showed the highly significant difference in the LGI between non-survival (Group III) and survival (Groups I and II). In each group, the median value of LGI was significantly higher in patients with diabetes and non-diabetes who concurrently showed stress hyperglycemia.

The calculated odds ratios with a 95% confidence interval for mortality are 2.361 (1.215 to 4.589, p = 0.011); 7.33 (2.306 to 23.323, p <0.001); and 4.842 (2.036 to 11.514, p <0.001) for the risk factors of diabetes mellitus, stress hyperglycemia, and LGI value (a cutoff value of 1.5).

Table 1: Results of Inflammatory Markers, Hematological Indices, and Plasma Glucose-Related Biomarkers

Variables	Group I (n=45)	Group II (n=90)	Group III (n=52)	*p1*-value	*p2*-value	*p3*-value
Age, years	50 (38, 60)	62 (53, 70)	70 (60, 72.8)	<0.001	0.001	0.965
ESR, $mm.h^{-1}$	55 (43.2, 73.3)	67.9 (51.1, 87.1)	75.5 (61.3, 92.4)	0.030	<0.001	0.048
CRP mg.-1L	49.0 (30.9, 89.8)	87.7 (40.6, 141.2)	85.5 (54.2, 159.4)	0.046	0.003	0.249
RDW, %	12.9 (12.35, 13.6)	12.9 (12.3, 13.7)	13.45 (12.63,14.18)	0.953	0.088	0.033
NLR	10.7 (8.4, 15.0)	11.56 (8.28,15.07)	14.18 (8.93, 18.92)	0.609	0.029	0.048
dNLR	6.09 (3.62, 8.66)	6.25 (4.28, 9.03)	6.22 (3.94, 8.59)	0.490	0.834	0.610
PLR ($\times 10^{9} \cdot L^{-1}$)	237.1 (181.8,377.1)	261.6 (187.1, 375.0)	244.5 (165.0, 364.8)	0.874	0.734	0.509
Platelet,%	0.210 (0.170,0.270)	0.190 (0.138, 0.253)	0.200 (0.133, 0.250)	0.199	0.438	0.768
MPV, fL	8.80 (8.40, 9.30)	9.10 (8.28, 9.70)	9.05 (8.43, 9.78)	0.327	0.411	0.961
LGI	1.754 (1.367, 2.607)	1.728 (1.244, 2.559)	2.911 (2.099, 4.149)	0.629	<0.001	<0.001
Hemoglobin, $g.dL^{-1}$	12.9 (11.65,15.35)	13.4 (12.2, 14.4)	13.8 (12.1, 14.4)	0.220	0.181	0.748
Leukocytes ($\times 10^{9} \cdot L^{-1}$)	12.26 (8.65,15.35)	11.50 (8.50, 14.78)	16.0 (12.55, 19.38)	0.321	0.004	<0.001
Plasma glucose, $mg.dL^{-1}$	137 (97.8, 194.0)	126.0 (98.5, 191.5)	210.5 (153.5, 301.8)	0.668	<0.001	<0.001

A *p*-value was calculated using independent samples Mann-Whitney U test. *p1*= comparison between Groups I and II, *p2*: comparison between Group I and III, and *p3* comparison between Groups II and III. ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, RDW: red distribution width, NLR: neutrophil-to lymphocyte ratio, dNLR: derived neutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio, MPV: mean platelet volume.

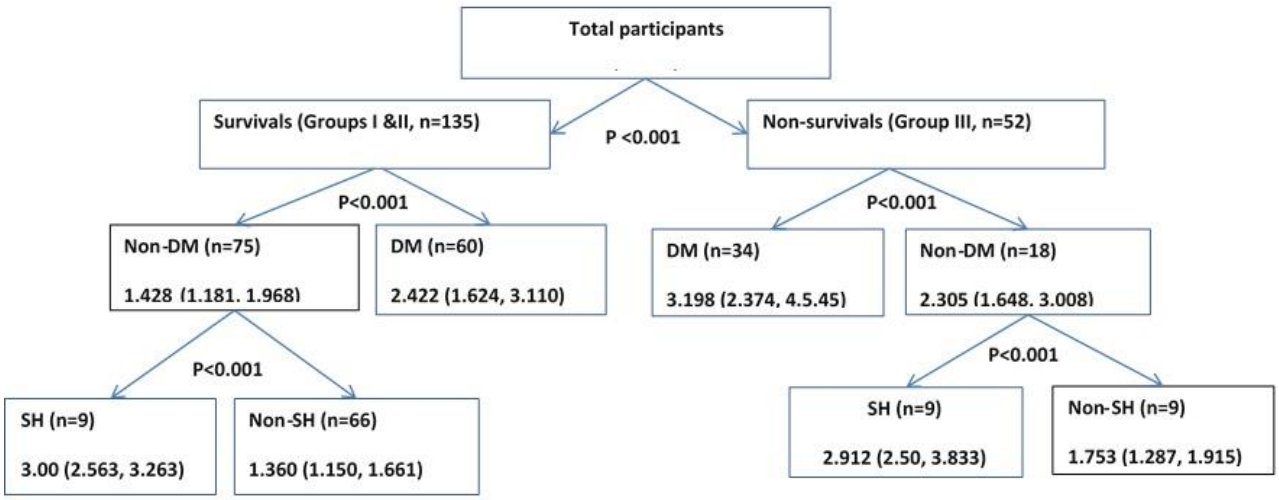

Figure II: Comparison in the median values of leukocyte glucose index (25th, 75th percentiles) between survival and non-survivals COVID-19 patients taking into considerations the associated diabetes mellitus and stress hyperglycemia in non-diabetes mellitus. DM: diabetes mellitus, SH: stress hyperglycemia. The results are expressed as median (25th, 27th percentiles)

Discussion

The results of this study showed that higher plasma glucose is a risk factor for mortality in COVID-19 patients. Three risk factors, including diabetes mellitus, stress hyperglycemia, and a LGI of 1.5, are potentially prognostic factors. The results of this study agree with previous studies that diabetes mellitus is a risk factor for severe COVID-19 and mortality[18]. Diabetic patients are more prone to cytokine storms because their immunity is compromised and they have already had elevations of inflammatory biomarkers[19]. Hyperglycemia was reported in non-diabetic COVID-19 patients, and it

was considered a bad prognostic biomarker and linked to insulin resistance or the destruction of pancreatic β-cells by virus overload[6]. A higher percentage of hyperglycemia is found among Group III, a result agrees with other studies that found hyperglycemia at admission in patients with COVID-19 is a risk factor for poor clinical prognosis compared with normoglycemic patients[20]. Stress hyperglycemia mediated a number of pathological conditions that ultimately led to a poor clinical outcome. One of these conditions is a risk of thromboembolism, which is significantly associated with stress hyperglycemia[8]. Arrieta et al. reported that stress hyperglycemia was found in critically ill patients, was associated with a long stay in the intensive care unit, and required large doses of infusion[21].

In this study, the LGI is a significant marker for severe COVID-19, mortality, and stress hyperglycemia. Patients with LGI > 1.5 are at risk of death by 4.842 times the survival rate. The optimal cutoff of LGI for severe COVID-19 is 1.764, which was reported with a sensitivity and specificity of 77.8% and 72.3%, respectively, while a lower cutoff value is reported in this study[16]. The discrepancy in the cutoff value is related to the study design, as the Ramos-Hernández study was carried out on survivals and assessed clinical features and biomarkers[16]. Significantly higher NLR values in Group III compared with Groups I and II agreed with previous studies that the NLR value is considered a decision-making factor for the clinical outcome of COVID-19. The dNLR values showed non-significant differences between the survival and non-survival COVID-19 patients, which is not in agreement with the Qiu et al. study, which found the dNLR is a significant prognostic biomarker in 2645 patients infected with COVID-19 Omicron BA.2[22]. The non-significant changes in the platelet indices are attributed to wide variations in the platelet count in each group.

The strength of this study is to use a biomarker, which is a combination of plasma glucose and total white blood cells represented by LGI, which are both elevated in poor prognostic outcomes. This study is a preliminary report; therefore, the small sample size is a limitation of the study, but it did not bias the results.

Conclusion

The risk factor for mortality in COVID-19 patients is the glucose molecule, whether in diabetes or non-diabetes patients, which can be interpreted in terms of hyperglycemia or the calculation of the leukocyte glucose index. A cutoff value of 1.5 can explain the worse prognosis in COVID-19 with diabetes mellitus or stress hyperglycemia.

Acknowledgment
None

Conflict of Interest
The author declare that they have no competing interests to declare

Financial Disclosure
The author did not receive any funding.

Contribution to authors:
Conception; Design; Funding; Materials; Data Collection and/or Processing; Analysis and/or Interpretation; Literature; Review, Writing; and Critical Review: M, Al-N. All authors reviewed and approved the final manuscript.

Data Availability
Any questions regarding the availability of the study's supporti ng data should be addressed to the corresponding author, who can provide it upon justifiable request.

Ethics Approval and Consent to Participate
Ethics approval and consent to participate: Not applicable. The study carried out in the College of Medicine, University of Diyala. Iraq

How to cite this article: Al-Nimer MSM, Merza TA, Jawad TM, Latif II. Leukocyte Glucose Index as Significant Marker of Poor Prognosis in COVID-19 Patients with Hyperglycemia. Bangladesh J Infect Dis 2024;11(2):102-107

ORCID
Marwan S.M. Al-Nimer:
https://orcid.org/0000-0002-5336-3353
Talar A. Merza: https://orcid.org/0000-0002-9849-2773
Thaqeef M. Jawad: https://orcid.crg/0009-0008-1762-0587
Ismail I. Latif: https://orcid.org/0000-0003-0668-7539

Article Info
Received on: 17 September 2024
Accepted on: 2 November 2024
Published on: 3 December 2024

References

1. Zhang JJ, Dong X, Liu G.H, Gao Y.D. Risk and protective factors for COVID-19 morbidity, severity, and mortality. Clin Rev Allergy Immunol. 2023;64 (1):90-107
2. Sharma P, Behl T, Sharma N, Singh S, Grewal AS, Albarrati A, Albratty M, Meraya AM, Bungau S. COVID-19 and Diabetes: Association intensify risk factors for morbidity and mortality. Biomed Pharmacother. 2022;151:113089

3. Zhou Y, Chi J, Lv W, Wang Y. Obesity and diabetes as high-risk factors for severe coronavirus disease 2019 (Covid-19). Diabetes Metab Res Rev. 2021;37(2):e3377
4. Zhang T, Mei Q, Zhang Z, Walline JH, Liu Y, Zhu H, Zhang S. Risk for newly diagnosed diabetes after COVID-19: a systematic review and meta-analysis. BMC Med. 2022; 20(1): 444
5. Li H, Tian S, Chen T, Cui Z, Shi N, Zhong X, Qiu K, Zhang J, Zeng T, Chen L, Zheng J. Newly diagnosed diabetes is associated with a higher risk of mortality than known diabetes in hospitalized patients with COVID-19. Diabetes Obes Metab. 2020;22(10):1897-906
6. Gerganova A., Assyov Y., Kamenov Z. Stress hyperglycemia, diabetes mellitus and COVID-19 infection: risk factors, clinical outcomes and post-discharge implications. Front Clin Diabetes Healthc. 2022;3:826006
7. Calvisi SL, Ramirez GA, Scavini M, Da Prat V, Di Lucca G, Laurenzi A, Gallina G, Cavallo L, Borio G, Farolfi F, Pascali M, Castellani J, Lampasona V, D'Angelo A, Landoni G, Ciceri F, Querini PR, Tresoldi M, Piemonti L. Thromboembolism risk among patients with diabetes/stress hyperglycemia and COVID-19. Metabolism. 2021;123:154845
8. Mermutluoğlu Ç, Dursun R, Aktar F, Dayan S, Çelen MK, Kadiroğlu AK., İnci E, Karagöz R, Kuyumcu M, Özcan N, Tekin R. Evaluation of inflammatory and hematological parameters in patients diagnosed with COVID-19. J Infect Dev Ctries. 2022;16(10):1564-9
9. Coronel PMV, Pereira IC, Basilio DCLS, Espinoça IT, de Souza KFS, Ota RSN, de Almeida EB, Paredes-Gamero EJ, Wilhelm Filho D, Perdomo RT, Parisotto EB. Biomarkers of oxidative stress and inflammation in subjects with COVID-19: Characterization and prognosis of the disease. Microb Pathog. 2023;184:106339
10. Yazdani AN., Abdi A, Velpuri P, Patel P, DeMarco N, Agrawal DK, Rai VA. A review of hematological complications and treatment in COVID-19. Hematol Rep. 2023;15(4):562-77
11. Dong YM, Sun J, Li YX, Chen Q, Liu QQ, Sun Z, Pang R, Chen F, Xu BY, Manyande A, Clark TG, Li JP, Orhan IE, Tian YK, Wang T, Wu W, Ye DW. Development and validation of a nomogram for assessing survival in patients with COVID-19 Pneumonia. Clin Infect Dis. 2021;72(4):652-60
12. Prozan L, Shusterman E, Ablin J, Mitelpunkt A, Weiss-Meilik A, Adler A, Choshen G, Kehat O. Prognostic value of neutrophil-to-lymphocyte ratio in COVID-19 compared with Influenza and respiratory syncytial virus infection. Sci Rep. 2021;11(1):21519
13. Buonacera A, Stancanelli B, Colaci M, Malatino L. Neutrophil to lymphocyte ratio: an emerging marker of the relationships between the immune system and diseases. Int J Mol Sci. 2022;23 (7):3636
14. Sarkar S, Kannan S, Khanna P, Singh AK. Role of platelet-to-lymphocyte count ratio (PLR), as a prognostic indicator in COVID-19: A systematic review and meta-analysis. J Med Virol. 2022;94(1):211-21
15. Zinellu A, Mangoni AA. A systematic review and meta-analysis of the association between the neutrophil, lymphocyte, and platelet count, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio and COVID-19 progression and mortality. Expert Rev Clin Immunol. 2022;18(11):1187-202
16. Ramos-Hernández WM, Soto LF, Del Rosario-Trinidad M, Farfan-Morales CN, De Jesús-González LA., Martínez-Mier G, Osuna-Ramos JF, Bastida-González F, Bernal-Dolores V, Del Ángel RM, Reyes-Ruiz JM. Leukocyte glucose index as a novel biomarker for COVID-19 severity. Sci Rep. 2022;12(1):14956
17. Vedantam D, Poman DS, Motwani L, Asif N, Patel A, Anne KK. Stress-induced hyperglycemia: consequences and management. Cureus. 2022;14(7):e26714
18. Singh AK, Khunti K. COVID-19 and Diabetes. Annu Rev Med. 2022;73:129-47
19. Lagunas-Rangel FA, Chávez-Valencia V. Laboratory findings that predict a poor prognosis in COVID-19 patients with diabetes: A meta-analysis. Endocrinol Diabetes Nutr (Engl Ed). 2021;68(7):520-2
20. Singh AK, Singh R. At-admission hyperglycemia is consistently associated with poor prognosis and early intervention can improve outcomes in patients with COVID-19. Diabetes Metab Syndr. 2020;14(6):1641-4
21. Arrieta F, Martinez-Vaello V, Bengoa N, Rosillo M, de Pablo A, Voguel C, Pintor R, Belanger-Quintana A, Mateo-Lobo R, Candela A, Botella-Carretero JI. Stress hyperglycemia and osteocalcin in COVID-19 critically ill patients on artificial nutrition. Nutrients. 2021;13(9):3010
22. Qiu W, Shi Q, Chen F, Wu Q, Yu X, Xiong L. The derived neutrophil to lymphocyte ratio can be the predictor of prognosis for COVID-19 Omicron BA.2 infected patients. Front Immunol. 2022;13:1065345