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Original Article

Assessment of Leukocyte Subtypes to High-Density Lipoprotein-Cholesterol (HDL-C) Ratios as predictors of Severity and Mortality in COVID-19 Patients

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ABSTRACT

Objectives: Recently, the counts of leukocyte subtypes to HDL-C concentration ratios, including monocyte to HDL-C ratio (MHR), neutrophil to HDL-C ratio (NHR), lymphocyte to HDL-C (LHR) have been proposed as potential new indices of inflammation. This study aims to investigate the correlation between these indices with the severity and mortality of COVID-19.

Methods: This study is performed on 1224 non-vaccinated and hospitalized COVID-19 patients. The association between blood parameters and indices on admission with severity and mortality are analyzed using multivariate regression models. Receiver operating characteristic curves are used to compare the utility of different blood parameters.

Results: The severe patients and deceased groups show low level of HDL-C, high values of WBC, neutrophil, monocyte, eosinophil, WBC/HDL-C, NHR, MHR, LHR, and EHR compared with the mild and survivor groups, respectively ($P < 0.05$). Multivariate regression analysis reveals that high levels of WBC, neutrophil, WBC/HDL-C, NHR, MHR, EHR, and low levels of HDL-C are still independently associated with severity and mortality after adjusting for age, gender, and comorbidities. The correlation of LHR with severity and mortality is attenuated to insignificance. Also, patients with high eosinophil and monocyte levels have a higher risk of severe disease. According to the AUC values, the best predictors for severity are the level of WBC, neutrophil, and NHR (AUC: 0.724, 0.725, 0.724 respectively), and the best predictors for mortality are WBC/HDL-C and NHR (AUC: 0.788, 0.790 respectively).

Conclusion: In summary, low level of HDL-C and high level of WBC, neutrophil, WBC/HDL-C, NHR, MHR, and EHR which can be easily calculated from the CBC and HDL-C concentrations, may provide valuable and readily available prognostic information for severity and mortality of COVID-19.

Keywords: COVID-19,Neutrophil to HDL-C Ratio, Monocyte to HDL-C Ratio, Lymphocyte to HDL-C Ratio, CBC, WBC

Abbreviations: ARSD: acute respiratory distress syndrome; CBC: complete blood count; COPD: chronic obstructive pulmonary disease; COVID-19: coronavirus disease 2019; CVD: cardiovascular diseases; LHR: lymphocyte to HDL-C; HDL-C: high-density lipoprotein cholesterol; MHR: monocyte to HDL-C ratio; NHR: neutrophil to HDL-C ratio; WBC: white blood cell; T2D: type 2 diabetes

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Introduction

The acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic continues to cause considerable concern due to unpredictable new variants. the majority of SARS-CoV-2 infections result in mild symptoms, cases with severe disease can progress to conditions such as acute respiratory distress syndrome (ARDS), septic shock, and multi-organ failure. This has led to millions of deaths and substantial morbidity worldwide (1). Since the start of the coronavirus disease 2019 (COVID-19) pandemic, significant advances have been made in the identification of early and accessible biomarkers that indicate the prognosis of the disease (2). Studies have revealed that the severity and mortality in patients with COVID-19 are related to impaired immune response and the excessive activation of inflammatory and oxidative stress pathways (3, 4). Thus, serum biomarkers associated with the inflammatory status of patients may help clinicians identify cases with a poor prognosis at an early stage. To date, the correlation of several inflammatory biomarkers including C-reactive protein, white blood cell components, procalcitonin, and ferritin has been evaluated with COVID-19 severity (2). The leukocyte count is considered one of the simplest and most commonly used markers for assessment of the immune response and inflammation. Different white blood cell (WBC) subtypes, including neutrophils, lymphocytes, and monocytes, participate in the inflammatory processes. It has been revealed that leukocyte counts at admission, such as lymphopenia, are significantly related to mortality in COVID-19 cases (5).

In addition to its crucial role in reverse cholesterol transport, high-density lipoprotein cholesterol (HDL-C) also exhibits a multifunctional protective role, including anti-infectious, anti-inflammatory, antioxidant, and antithrombotic effects (6, 7). Low serum levels of HDL-C have been associated with a more severe COVID-19 (8). Recent studies have revealed that hematological parameters in combination with HDL-C, including monocyte to HDL-C ratio (MHR), neutrophil to HDL-C ratio (NHR), lymphocyte to HDL-C (LHR) have potential as new indices of inflammation and metabolic status. These indices may be related to metabolic syndrome (9-11), cardiovascular disease (12, 13), chronic obstructive pulmonary disease (COPD) (13), and stroke-associated pneumonia (12).

Considering the limited studies on the clinical value of leukocytes to HDL-C ratios in COVID-19 patients (14) and taking into account the availability and cost-effectiveness of these indicators, the present study was designed to investigate the association between NHR, MHR, LHR and PHR with the severity and mortality of COVID-19 patients.

Materials and Methods

Data collection

This cross-sectional research analyzed 1224 non-vaccinated confirmed COVID-19 patients admitted to Shahroud University of Medical Sciences (SHMU) hospitals between February 20, 2020, and March 20, 2021. All patients enrolled in this study were confirmed as COVID-19 cases through real-time reverse transcriptase-polymerase chain reaction (RT-PCR) testing on oro- and nasopharyngeal swab specimens. This study was approved by the Ethics Commission of SHMU (IR. SHMU-REC.1398.160) and was performed in line with the principles of the Declaration of Helsinki. All participants provided informed consent before participating in the study.

As previously described, all clinical and laboratory data of the enrolled cases were obtained from the patient's electronic medical records (15). Cases with incomplete medical records were excluded. Demographic information, comorbidities, outcomes (discharge or death), and laboratory findings were collected and verified by two independent researchers. The comorbidities assessed in the current research included type 2 diabetes (T2D), cardiovascular diseases (CVDs), kidney and liver diseases, respiratory disorders, cancers, neurological diseases, and seizures, as previously described in the study (15).

Serum sample collection was performed after 10-12 hours of fasting in the first morning following the admission of patients. The complete blood count (CBC) hematological parameters were assessed using a Sysmex hematological analyzer and HDL-C concentration was determined using calorimetric methods with commercially available kits (Biorex, Fars, Iran).

Definitions

NHR, MHR, LHR, and EHR were calculated by dividing the counts of neutrophil, monocyte, lymphocyte, and eosinophil by HDL-C concentration (in mmol/L). The formula for BMI was calculated as weight in kilograms divided by height in meters squared.

Severe disease was defined according to any of the following criteria: 1) a respiratory rate > 30/min, 2) oxygen saturation ≤ 93%, 3) patients with shock, respiratory failure requiring mechanical ventilation, or other organ failure requiring admission to the intensive care unit (ICU). The deceased cases were also categorized as severe SARS-COV-2 infected cases.

Statistical Analysis

Statistical analysis was performed using SPSS software version 23. The chi-squared, Fisher exact test, and Student's t-test were used to compare differences between two groups. The multivariate logistic regression analyses

adjusted to age, sex, and comorbidities were used to assess the correlation between markers and COVID-19 outcomes. Statistically significant differences were considered with p-values <0.05.

Results

The mean age of the 1224 confirmed COVID-19 patients in the present research was 58.67±16.24 years old. Of these, 611 (49.8 %) were male, 282 (23%) of cases had a severe form of the disease, and 88 (7.17%) died. The patients were stratified based on severity or mortality, and demographic, clinical, and laboratory data are exhibited in Table 1. In comparison with patients with mild disease and survivors, those with severe or deceased cases were older, more likely to be male, and more likely to have other comorbidities. The various comorbidities evaluated in this study included diabetes, CVD, kidney and liver disease, respiratory disorders, cancers, neurological diseases, and seizures (details have been provided in the previous research) (15).

The severe COVID-19 and deceased groups showed a low level of HDL-C, significantly increased count of WBC, neutrophil, monocyte, eosinophil, and high values of WBC/HDL-C, NHR, MHR, LHR, and EHR compared to the mild and survivor groups, respectively ($P < 0.05$). No significant differences in lymphocyte counts were found between the investigated groups **(Table 1)**.

Notably, based on multivariate regression analysis, it was found that high levels of WBC, neutrophil, WBC/HDL-C, NHR, MHR, and EHR and low level of HDL-c were still independently associated with severity and mortality after adjusting for age, gender, and comorbidities. The correlation of LHR with severity and mortality, and the association of eosinophil and monocyte with mortality were attenuated to insignificance. Also, patients with high eosinophil and monocyte levels had a higher risk for severe disease (**Table 2**).

Table 1: Demographic, clinical and Laboratory findings in COVID-19 patients based on the severity and mortality

Variables	Mild (n=942)	Severe (n= 282)	P-value	Survivor (n=1138)	Deceased (n=88)	P-value
Gender Male	455(48.2)	156(55.3)	0.021	558(49)	53(60.2)	0.027
Female	489(51.8)	126(44.7)		580(51)	35(39.8)	
Age (year)	56.10±15.81	67.29±14.65	<0.001	57.68±16.08	71.52±12.50	<0.001
Comorbidities	160 (48.2)	62 (67.4)	0.001	198 (51.2)	24 (65.9)	0.071
BMI (kg/m^2)	27.86±4.32	27.92±4.94	0.843	27.91±4.45	27.33±4.64	0.260
WBC (×10^9/L)	3.27±1.65	4.59±3.23	<0.001	3.54±1.99	5.21±3.66	<0.001
Neutrophil (×10^9/L)	2.28±1.34	3.46±2.90	<0.001	2.43±1.65	4.08±3.43	<0.001
Monocyte (×10^9/L)	0.09±0.07	0.12±0.09	<0.001	0.098±0.08	0.13±0.087	<0.001
Lymphocyte (×10^9/L)	0.82±0.51	0.91±0.73	0.058	0.84±0.56	0.89±0.69	0.49
Eosinophile (×10^9/L)	0.08±0.05	0.10±0.07	<0.001	0.08±0.06	0.10±0.06	<0.001
HDL-C(mmol/L)	0. 86±0.26	0.82±0.27	0.008	0. 87±0.26	0.73±0.27	<0.001
WBC/HDL	4.19±2.88	7.03±9.04	<0.001	4.45±3.45	9.94±13.49	<0.001
NHR	2.92±2.24	5.39±8.08	<0.001	3.15±2.90	7.88±12.21	<0.001
MHR	0.12±0.11	0.18±0.20	<0.001	0.12±0.14	0.24±0.24	<0.001
LHR	1.05±0.84	1.31±1.61	0.01	1.07±0.89	1.62±2.38	0.035
EHR	0.10±0.08	0.15±0.16	<0.001	0.10±0.09	0.19±0.22	<0.001

Data were expressed as mean ± standard deviation or number (percent).
Abbreviations: BMI, Body Mass Index; WBC, Wight Blood Cell; HDL-C, High-density lipoprotein cholesterol; NHR, Neutrophil to HDL-C ratio; MHR, Monocyte to HDL-C ratio; LHR, Lymphocyte to HDL-C; HER, Eosinophile to HDL-C ratio

Table 2: Odds ratios for severe and deceased cases associated with hematological and biochemical markers

	Severity			Mortality		
Parameters	OR(CI)	P-value	AUC*	OR(CI)	p-value	AUC*
WBC (×10^9/L)	1.17(1.09-1.25)	<0.001	0.724	1.13(1.05-1.21)	0.001	0.779
Neutrophil (×10^9/L)	1.24(1.14-1.34)	<0.001	0.725	1.17(1.08-1.27)	<0.001	0.783
Monocyte (×10^9/L)	7.81(1.43-43.31)	0.018	0.715	4.2(0.57-30.93)	0.157	0.772
Lymphocyte (×10^9/L)	1.02(0.80-1.28)	0.878	0.708	0.86(0.60-1.24)	0.433	0.770
Eosinophile (×10^9/L)	18.94(2.12-168.95)	0.008	0.712	7.87(0.30-203.71)	0.214	0.769
HDL-C (mmol/L)	0.52(0.30-.91)	0.023	0.711	0.13(0.05-0.33)	<0.001	0.779
WBC/HDL-C	1.09(1.05-1.13)	<0.001	0.722	1.09(1.05-1.13)	<0.001	0.788
NHR	1.13(1.07-1.19)	<0.001	0.724	1.11(1.06-1.16)	<0.001	0.790
MHR	5.62(2.04-15.50)	0.001	0.717	7.52(2.57-22.23)	<0.001	0.783
LHR	1.08(0.96-1.23)	0.181	0.708	1.16(0.99-1.35)	0.054	0.769
ELR	12.90(3.38-49.26)	<0.001	0.715	21.02(4.37-100.93)	<0.001	0.780

Regression models adjusted for age, gender, and comorbidities
Abbreviations: BMI, Body Mass Index; WBC, Wight Blood Cell; HDL-C, High-density lipoprotein cholesterol; NHR, Neutrophil to HDL-C ratio; MHR, Monocyte to HDL-C ratio; LHR, Lymphocyte to HDL-C; HER, Eosinophile to HDL-C ratio

In addition, the prediction for severity and mortality was also assessed using the Area Under Curve (AUC). Based on AUC, all parameters proved to be better predictors for mortality than severity. The level of WBC, neutrophil, and NHR (AUC: 0.724, 0.725, and 0.724 respectively), could significantly predict the odds of severe disease more effectively than other parameters. Also, WBC/HDL-C and NHR were the best predictors of mortality in COVID-19 patients (AUC: 0.788, 0.790 respectively) **(Table 2)**.

Discussion

Several comorbidities such as hypertension, CVD, T2D, and non-alcoholic fatty liver disease, which share chronic systemic inflammation and metabolic disturbance, as well as older age, have been recognized as the main risk factors for a poor prognosis in COVID-19 (16). The findings of this study support the view that a comorbid condition diagnosis makes COVID-19 more severe. On the other hand, some healthy young patients also showed unexpectedly high rates of poor outcomes (16). Therefore, exploring new non-invasive, fast, and cost-effective inflammatory and metabolic markers to indicate COVID-19 prognosis has been a focus of researchers. In this study, the effect of WBC count and several leukocytes to HDL-C ratios, including NHR, MHR, LHR, and HER, as potential new indices of inflammation and metabolic status on the severity and mortality of COVID-19 patients, was investigated.

The complete blood count (CBC) is a rapid, easy, and cost-effective measurement in clinical practice, providing valuable information about hematologic contents, including RBCs, WBCs, neutrophils, lymphocytes, monocytes, and platelets (17). Neutrophils and lymphocytes represent the majority of leukocytes in the body, with roles in the adaptive and innate immune systems, respectively (18, 19). Monocytes are the most important cells for pro-inflammatory cytokines production (20-22). Activated platelets also mediate inflammatory responses in some physiological and pathological conditions (23-26). Hematological markers have recently garnered attention as potential indicators for early warning, diagnosis, and risk assessment of many infectious (27) and non-infectious diseases, including hepatic cirrhosis and CVDs (28, 29). Previous studies have also highlighted the hematological parameters as potential novel biomarkers for predicting inflammation, metabolic syndrome, and T2D (30-33). It has also been demonstrated that the immune response triggered by the SARS-CoV-2 infection can lead to changes in peripheral leukocytes, such as neutrophilia (34). In this context, the current study revealed a significant increase in the total counts of WBCs, neutrophils, monocytes, and eosinophils in the severe and deceased groups when compared with the mild and survivor groups, respectively. Consistent with these results, other studies have reported a significant increase in WBC and neutrophil counts (35, 36). A meta-analysis demonstrated that leukocyte and neutrophil counts were significantly lower in COVID-19 cases compared to non-COVID-19 cases, but higher in severe patients compared to non-severe cases (37). These results have also revealed a statistically significant association between counts of WBC, neutrophil, monocyte, and eosinophil with severity of disease after adjusting for age, sex, and comorbidities. However, only the counts of WBC and neutrophils could serve as predictors of mortality after adjusting for confounding factors. Zhu et al. also showed that WBC counts at admission are significantly correlated with death in COVID-19 patients (36). A meta-analysis study demonstrated that neutrophilia at admission was also found to be significantly associated with increased odds of progression to death (38). Regarding lymphocyte counts, these results did not show a significant difference between severe and mild groups or between deceased and survivor groups. Other research demonstrated a decrease in lymphocyte counts in severe patients (35, 36, 39). Oliveira et al. also revealed that lymphocyte counts in the COVID-19 groups were not statistically different from those in the control group (39).

It is worth noting that the excessive inflammation described in SARS-COV-2 infection can persuade immune-mediated dyslipidemia, especially HDL-C reduction, through decreased production (6, 40, 41). In line with these findings, it was found that HDL-C serum concentration was statistically lower in the severe and deceased groups than in the mild and survivor groups, respectively. Studies have shown that HDL-C, a component of the lipid profile, is correlated with the function and count of neutrophils, lymphocytes, monocytes, and platelets. HDL-C has been found to mediate the activities of neutrophils, platelets, and monocytes, as well as inhibition of antigen presentation-mediated T-cell activation (42-44). Given these interactions between different blood cells and HDL-C, the combined indices including NHR, LHR, MHR, and EHR might be more reliable in reflecting the inflammation status than a single parameter. In this regard, the present study showed that NHR, MHR, and EHR values were significantly higher in severe and deceased patients than in mild and survivor patients, respectively. The result also revealed that an increase in WBC/HDL-C ratio, NHR, MHR, and EHR values on admission, were positively correlated with the severity and mortality of COVID-19 after adjusting for sex, age, and comorbidities. In support of these findings, Wang et al. indicated that higher NHR on admission was correlated with critical outcomes of COVID-19 (14). NHR has been found to be correlated with many diseases, such as metabolic syndrome (45) and CVDs (46), which are also known risk factors for severe COVID-19 (47, 48). Argun et al. also revealed that the MHR values were significantly higher in the non-survivor group compared to the survivor's group of COVID-19

patients. They also suggest that MHR can help predict the severity of COVID-19 (45). Unlike lymphocyte counts, the LHR index was higher in severe and deceased patients than in mild and survivor cases, respectively. However, LHR values could not serve as a predictor of severity or mortality when adjusted for sex, age, and comorbidities. Consistent with these findings, in Wang's study, there was no significant correlation between LHR, MHR, and PHR with COVID-19 severity (14). It is worth noting that WBC/HDL-C and NHR were the better predictors of mortality in COVID-19 patients than leukocyte count alone.

To the best of our knowledge, this study is one of the few comprehensive studies with a relatively large sample size conducted to determine the prognostic utility of leukocyte subtype to HDL-C ratios in relation to COVID-19 severity and mortality in Iranian COVID-19 patients. However, several limitations in the current study need to be considered. First, the time from the onset of symptoms to the time of hospitalization and blood sampling varied between patients, which may have caused some bias. Second, non-hospitalized cases were not included in this study. Third, although adjustments were made for several known potential confounders, the results may not have been fully adjusted for due to unmeasured or poorly measured confounders.

In conclusion, this study indicated that higher levels of WBC and neutrophil, WBC/HDL-C, NHR, MHR, ELR, and lower levels of HDL-C on admission were independently associated with the severity and mortality of COVID-19 after adjusting for confounding factors. In addition, the count of monocytes and eosinophils could predict the severity of the disease but not death in COVID-19 patients. Also, WBC/HDL-C and NHR were better predictors of mortality in COVID-19 patients than leukocyte count alone. Therefore, the count of leukocyte subtypes and the ratios of leukocyte subtypes to HDL-C, which are easily calculated from the CBC and HDL-C concentrations, may provide valuable and readily available prognostic information for clinicians when encountering patients with COVID-19 disease.

Conflict of Interest

The authors have nothing to declare.

References

1. Zinellu A, Paliogiannis P, Fois AG, Solidoro P, Carru C, Mangoni AA. Cholesterol and triglyceride concentrations, COVID-19 severity, and mortality: a systematic review and meta-analysis with meta-regression. Front Public Health. 2021;9:705916. https://doi.org/10.3389/fpubh.2021.705916
2. Zinellu A, Mangoni AA. Cystatin C, COVID-19 severity and mortality: a systematic review and meta-analysis. 2022;35(1):59-68. https://doi.org/10.1007/s40620-021-01139-2
3. Esmaeili-Nadimi A, Imanparast F, Alizadeh S, Vatannejad A, Mohaghegh P, Seyedmehdi SM, et al. Total antioxidant capacity and total oxidant status and disease severity in a cohort study of COVID-19 patients. Clin Lab. 2023;69(2). https://doi.org/10.7754/Clin.Lab.2022.220416
4. Ghahremani H, Bolandnazar K, Emamgholipor S, Hosseini H, Meshkani R. Resveratrol as a potential protective compound against metabolic inflammation. Acta Biochim Iran. 2023;1(2):50-64. https://doi.org/10.18502/abi.v1i2.14101
5. Zhu B, Feng X, Jiang C, Mi S, Yang L, Zhao Z, et al. Correlation between white blood cell count at admission and mortality in COVID-19 patients: a retrospective study. BMC Infect Dis. 2021;21(1):574. https://doi.org/10.1186/s12879-021-06277-3
6. Tanaka S, Couret D, Tran-Dinh A, Duranteau J, Montravers P, Schwendeman A, et al. High-density lipoproteins during sepsis: from bench to bedside. Crit Care. 2020;24:1-11. https://doi.org/10.1186/s13054-020-02860-3
7. Gorgani-Firuzjaee S, Meshkani R. Resveratrol reduces high glucose-induced de-novo lipogenesis through mTOR mediated induction of autophagy in HepG2 cells. Acta Biochim Iran. 2023;1(1):32-39. https://doi.org/10.18502/abi.v1i1.14063
8. Parra S, Saballs M, DiNubile M, Feliu M, Iftimie S, Revuelta L, et al. Low HDL-c levels at admission are associated with greater severity and worse clinical outcomes in patients with COVID-19 disease. Atheroscler Plus. 2023;52:1-8. https://doi.org/10.1016/j.athplu.2023.01.002
9. Chen T, Chen H, Xiao H, Tang H, Xiang Z, Wang X, et al. Comparison of the value of neutrophil to high-density lipoprotein cholesterol ratio and lymphocyte to high-density lipoprotein cholesterol ratio for predicting metabolic syndrome among a population in the southern coast of China. Diabetes Metab Syndr Obes. 2020;(13):597-605. https://doi.org/10.2147/DMSO.S238990
10. Uslu AU, Sekin Y, Tarhan G, Canakcı N, Gunduz M, Karagulle M. Evaluation of monocyte to high-density lipoprotein cholesterol ratio in the presence and severity of metabolic syndrome. Clin Appl Thromb Hemost. 2018;24(5):828-833. https://doi.org/10.1177/1076029617741362
11. Chen H, Xiong C, Shao X, Ning J, Gao P, Xiao H, et al. Lymphocyte to high-density lipoprotein ratio as a new indicator of inflammation and metabolic syndrome. Diabetes Metab Syndr Obes Targets Ther. 2019;(12):2117-2123. https://doi.org/10.2147/DMSO.S219363
12. Sun Y, Lu J, Zheng D, Qian J, Zhang H, Xing D, et al. Predictive value of monocyte to HDL cholesterol ratio for stroke-associated pneumonia in patients with acute ischemic stroke. Acta Neurol Belg. 2021;121:1575-1581. https://doi.org/10.1007/s13760-020-01418-y
13. Huang J-B, Chen Y-S, Ji H-Y, Xie W-M, Jiang J, Ran L-S, et al. Neutrophil to high-density lipoprotein ratio has a superior prognostic value in elderly patients with acute myocardial infarction: a comparison study. Lipids Health Dis. 2020;19(1):1-12. https://doi.org/10.1186/s12944-020-01238-2
14. Wang Y, Zhang J, Li H, Kong W, Zheng J, Li Y, et al. Prognostic Value of Leucocyte to High-Density Lipoprotein-Cholesterol Ratios in COVID-19 Patients and the Diabetes Subgroup. Front Endocrinol (Lausanne). 2021;12:727419. https://doi.org/10.3389/fendo.2021.727419
15. Rohani-Rasaf M, Mirjalili K, Vatannejad A, Teimouri M. Are lipid ratios and triglyceride-glucose index associated with critical care outcomes in COVID-19 patients? PLoS One. 2022;17(8):e0272000. https://doi.org/10.1371/journal.pone.0272000
16. Espejo-Paeres C, Espliguero RA, Uribarri A, Antón-Huguet B, Romero R, Fernández-Rozas I, et al. Predictors of poor prognosis in healthy, young, individuals with SARS-CoV-2 infections. Clin Microbiol Infect. 2022;28(2):273-8. https://doi.org/10.1016/j.cmi.2021.09.021
17. Agnello L, Giglio RV, Bivona G, Scazzone C, Gambino CM, Iacona A, et al. The Value of a Complete Blood Count (CBC)

for Sepsis Diagnosis and Prognosis. Diagnostics (Basel). 2021;11(10). https://doi.org/10.3390/diagnostics11101881
18. Rosales C. Neutrophils at the crossroads of innate and adaptive immunity. J Leukoc Biol. 2020;108(1):377-96. https://doi.org/10.1002/JLB.4MIR0220-574RR
19. Mazloomi S, Taghavi-Goodarzi M. The Relationship Between Chemerin Gene Polymorphism and the Incidence of Various Diseases. Acta Biochim Iran. 2023;1(2):65-70. https://doi.org/10.18502/abi.v1i2.14102
20. Seymour R, Henderson B. Pro-inflammatory-anti-inflammatory cytokine dynamics mediated by cytokine-receptor dynamics in monocytes. Math Med Biol. 2001;18(2):159-92. https://doi.org/10.1093/imammb/18.2.159
21. Jahangard R, Sadeghi SS, Vatannejad A, Meshkani R. Autophagy protects peripheral blood mononuclear cells from high glucose-induced inflammation and apoptosis. Acta Biochim Iran. 1(1):40-49.
22. Mazloom H, Alizadeh S, Pasalar P, Esfahani EN, Meshkani R. Downregulated microRNA-155 expression in peripheral blood mononuclear cells of type 2 diabetic patients is not correlated with increased inflammatory cytokine production. Cytokine. 2015;76(2):403-8. https://doi.org/10.1016/j.cyto.2015.07.007
23. Wei Y, Wang T, Li G, Feng J, Deng L, Xu H, et al. Investigation of systemic immune-inflammation index, neutrophil/high-density lipoprotein ratio, lymphocyte/high-density lipoprotein ratio, and monocyte/high-density lipoprotein ratio as indicators of inflammation in patients with schizophrenia and bipolar disorder. Front Psychiatry. 2022;13:941728. https://doi.org/10.3389/fpsyt.2022.941728
24. Cognasse F, Laradi S, Berthelot P, Bourlet T, Marotte H, Mismetti P, et al. Platelet inflammatory response to stress. Front Immunol. 2019;10:1478. https://doi.org/10.3389/fimmu.2019.01478
25. Łukasik ZM, Makowski M, Makowska JS. From blood coagulation to innate and adaptive immunity: the role of platelets in the physiology and pathology of autoimmune disorders. Rheumatol Int. 2018;38(6):959-74. https://doi.org/10.1007/s00296-018-4001-9
26. Aukrust P, Halvorsen B, Ueland T, Michelsen AE, Skjelland M, Gullestad L, et al. Activated platelets and atherosclerosis. Expert Rev Cardiovasc Ther. 2010;8(9):1297-307. https://doi.org/10.1586/erc.10.92
27. Russell CD, Parajuli A, Gale HJ, Bulteel NS, Schuetz P, de Jager CP, et al. The utility of peripheral blood leucocyte ratios as biomarkers in infectious diseases: A systematic review and meta-analysis. J Infect. 2019;78(5):339-48. https://doi.org/10.1016/j.jinf.2019.02.006
28. Milovanovic Alempijevic T, Stojkovic Lalosevic M, Dumic I, Jocic N, Pavlovic Markovic A, Dragasevic S, et al. Diagnostic accuracy of platelet count and platelet indices in noninvasive assessment of fibrosis in nonalcoholic fatty liver disease patients. Can J Gastroenterol Hepatol. 2017;2017. https://doi.org/10.1155/2017/6070135
29. Serrano CV, De Mattos FR, Pitta FG, Nomura CH, De Lemos J, Ramires JAF, et al. Association between neutrophil-lymphocyte and platelet-lymphocyte ratios and coronary artery calcification score among asymptomatic patients: data from a cross-sectional study. Mediators Inflamm. 2019;2019. https://doi.org/10.1155/2019/6513847
30. Chen T, Chen H, Xiao H, Tang H, Xiang Z, Wang X, et al. Comparison of the Value of Neutrophil to High-Density Lipoprotein Cholesterol Ratio and Lymphocyte to High-Density Lipoprotein Cholesterol Ratio for Predicting Metabolic Syndrome Among a Population in the Southern Coast of China. Diabetes Metab Syndr Obes. 2020;13:597-605. https://doi.org/10.2147/DMSO.S238990
31. Surendar J, Indulekha K, Mohan V, Pradeepa R. Association of neutrophil-lymphocyte ratio with metabolic syndrome and its components in Asian Indians (CURES-143). J Diabetes Complications. 2016;30(8):1525-9. https://doi.org/10.1016/j.jdiacomp.2016.08.006
32. Yilmaz H, Ucan B, Sayki M, Unsal I, Sahin M, Ozbek M, et al. Usefulness of the neutrophil-to-lymphocyte ratio to prediction of type 2 diabetes mellitus in morbid obesity. Diabetes Metab Syndr Clin Res Rev. 2015;9(4):299-304. https://doi.org/10.1016/j.dsx.2014.04.009
33. Taghizadeh N, Saeedi V, Haghighi L, Nourbakhsh M, Nourbakhsh M, Razzaghy Azar M. Association between Steroid Hormones and Insulin Resistance in Patients with Polycystic Ovary Syndrome. Acta Biochim Iran. 2023;1(1):26-31. https://doi.org/10.18502/abi.v1i1.14062
34. Yang L, Liu S, Liu J, Zhang Z, Wan X, Huang B, et al. COVID-19: immunopathogenesis and Immunotherapeutics. Signal Transduct Target Ther. 2020;5(1):128. https://doi.org/10.1038/s41392-020-00243-2
35. He R, Lu Z, Zhang L, Fan T, Xiong R, Shen X, et al. The clinical course and its correlated immune status in COVID-19 pneumonia. J Clin Virol. 2020;127:104361 https://doi.org/10.1016/j.jcv.2020.104361
36. Lu G, Wang J. Dynamic changes in routine blood parameters of a severe COVID-19 case. Clin Chim Acta. 2020;508:98-102. https://doi.org/10.1016/j.cca.2020.04.034
37. Soraya GV, Ulhaq ZS. Crucial laboratory parameters in COVID-19 diagnosis and prognosis: An updated meta-analysis. Med Clin (Barc). 2020;155(4):143-151. https://doi.org/10.1016/j.medcli.2020.05.017
38. Henry B, Cheruiyot I, Vikse J, Mutua V, Kipkorir V, Benoit J, et al. Lymphopenia and neutrophilia at admission predicts severity and mortality in patients with COVID-19: a meta-analysis. Acta Biomed. 2020;91(3):e2020008.
39. Oliveira DCd, Spiri BS, Schluga YC, Justus JLP, Lopes Neto FDN, Azambuja APd. Evaluation of lymphocyte count, T-cell subsets and neutrophil-to-lymphocyte ratio as early predictors for severity and outcome of COVID-19 disease-a report from a highly complex hospital in Brazil. Hematol Transfus Cell Ther. 2023;45(3):330-337. https://doi.org/10.1016/j.htct.2022.05.007
40. Golucci APBS, Marson FAL, Ribeiro AF, Nogueira RJN. Lipid profile associated with the systemic inflammatory response syndrome and sepsis in critically ill patients. Nutrition. 2018;55:7-14. https://doi.org/10.1016/j.nut.2018.04.007
41. Catapano AL, Pirillo A, Bonacina F, Norata GD. HDL in innate and adaptive immunity. Cardiovasc Res. 2014;103(3):372-383. https://doi.org/10.1093/cvr/cvu150
42. Murphy AJ, Woollard KJ, Suhartoyo A, Stirzaker RA, Shaw J, Sviridov D, et al. Neutrophil activation is attenuated by high-density lipoprotein and apolipoprotein AI in in vitro and in vivo models of inflammation. Arterioscler Thromb Vasc Biol. 2011;31(6):1333-1341. https://doi.org/10.1161/ATVBAHA.111.226258
43. Wang S-h, Yuan S-g, Peng D-q, Zhao S-p. HDL and ApoA-I inhibit antigen presentation-mediated T cell activation by disrupting lipid rafts in antigen presenting cells. Atherosclerosis. 2012;225(1):105-114. https://doi.org/10.1016/j.atherosclerosis.2012.07.029
44. Tall AR, Yvan-Charvet L. Cholesterol, inflammation and innate immunity. Nat Rev Immunol. 2015;15(2):104-116. https://doi.org/10.1038/nri3793
45. Argun D, Argun F, Basim P, Bayraktaroglu M. Monocyte-to-High-Density Lipoprotein Cholesterol Ratio: a Candidate Parameter for a Risk Assessment Model in COVID-19. Clin Lab. 2022;68(3). https://doi.org/10.7754/Clin.Lab.2022.210755
46. Kou T, Luo H, Yin L. Relationship between neutrophils to HDL-C ratio and severity of coronary stenosis. BMC Cardiovasc Disord. 2021;21:1-8. https://doi.org/10.1186/s12872-020-01771-z
47. Xie J, Zu Y, Alkhatib A, Pham TT, Gill F, Jang A, et al. Metabolic syndrome and COVID-19 mortality among adult black patients in New Orleans. Diabetes Care. 2021;44(1):188-193. https://doi.org/10.2337/dc20-1714
48. Adab P, Haroon S, O'Hara ME, Jordan RE. Comorbidities and covid-19. BMJ. 2022. https://doi.org/10.1136/bmj.o1431