

Exploring the Predictive Value of Inflammatory Biomarkers in COVID-19 Patients: A Prospective Cohort Study in Malang, Indonesia

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Abstract: The objective of this study was to assess the predictive value of inflammatory biomarkers in COVID-19 patients, namely the CRP/albumin ratio (CAR), interleukin 6 (IL-6), IL-6/lymphocyte ratio (IL-6/LY), and neutrophil/lymphocyte ratio (NLR). A prospective cohort study was conducted between January to June 2021 at Dr. Saiful Anwar General Hospital, Malang, East Java, Indonesia. CRP and albumin levels were measured using COBAS C6000. IL-6 was measured using the enzymatic chemiluminescence immunoassay (ECLIA) method and NLR was calculated based on flow cytometry evaluation of neutrophil and lymphocyte. Patient outcomes were obtained from medical records. Out of the 102 COVID-19 patients, 60 were non-survivors. The findings revealed that the area under the receiver (AUC) for CAR, IL-6, IL-6/LY, and NLR were 0.71, 0.77, 0.75, and 0.65, respectively. Kaplan-Meier curve analysis demonstrated significant differences between the groups stratified by these cut-off values. Notably, CAR and IL-6 exhibited the most accurate predictive values for mortality in COVID-19 patients. These findings suggest that CAR and IL-6 may serve as valuable biomarkers for predicting mortality in COVID-19 patients. Importantly, CAR offers an advantage over IL-6 as it is relatively more affordable, making it a viable option even if COVID-19 becomes endemic.

Keywords: CAR; IL-6; IL-6/LY; mortality; COVID-19

■ INTRODUCTION

The global healthcare system has faced unprecedented challenges over the past three years due to the COVID-19 pandemic caused by SARS-CoV-2 infection. The management of critically ill patients in intensive care settings poses significant difficulties in developing predictive models due to the unpredictable nature of COVID-19 outcomes, especially in developing countries such as Indonesia.

In Indonesia, the mortality rate among COVID-19 patients, especially those in critical condition, remains relatively high. According to the Indonesian Ministry of

Health, the country's COVID-19 patient mortality rate stands at 3.9%. According to this, Indonesia has the eighth-highest number of COVID-19 cases in Asia. Although severe COVID-19 cases have a higher death rate, there are currently no commonly used prognostic tools for estimating in-hospital mortality [1-2].

The inflammatory process is essential to the development of COVID-19. Cytokine storms or hyperinflammatory situations can be brought on by the immune system's activation of cytokines and chemokines, which can result in life-threatening organ malfunction and severe lung damage. Individual

differences in the degree of the inflammatory response lead to some patients' reactions being more pronounced than those of other patients. This emphasizes the value of individualized treatment plans that take into account each patient's particular immune response and inflammatory profile. Furthermore, gaining a deeper understanding of the inflammatory mechanisms involved in COVID-19 can facilitate the development of novel therapies that specifically target these processes. This holds the potential for more effective treatments and improved outcomes for patients [3-4].

One of the pro-inflammatory cytokines that exhibit an increase in COVID-19 patients is IL-6. Previous research has demonstrated a significant disparity in IL-6 levels between patients receiving intensive care treatment and those receiving standard care [3]. This elevation of IL-6 stimulates the production of acute-phase reactants, including CRP, by hepatocytes. CRP, as an acute phase reactant, plays a crucial role in the complement system and phagocytosis during the body's immune response to pathogenic infections. Numerous studies have indicated elevated CRP levels in patients with severe pneumonia, showing a correlation with the extent of inflammation. Conversely, inflammatory conditions lead to a reduction in albumin levels, which correlates with the deterioration of symptoms in COVID-19 patients [5]. The adaptive immune response also contributes to the SARS-CoV-2 infection. Severe cases of COVID-19 commonly exhibit a decline in lymphocyte count, particularly in the CD8+ subset [6-7]. Additionally, an upsurge in neutrophil count in COVID-19 patients is often associated with bacterial or fungal infections, frequently observed in these patients [8-10]. The utilization of inflammatory marker parameters, such as CAR, IL-6, IL-6/LY, and NLR, is expected to assist in the management of COVID-19 patients, given the pivotal role of the inflammatory process in their disease progression.

■ EXPERIMENTAL SECTION

Materials

In this study, various materials were utilized for different purposes. Samples from the naso- and oropharynx were collected to confirm the diagnosis of

COVID-19 in patients. Serum from peripheral blood was used to measure CRP, albumin, and IL-6 levels. Additionally, plasma EDTA samples were obtained to measure the counts of neutrophils and lymphocytes.

Instrumentation

Several instrumental methods were employed for different measurements. The Sysmex XN-1000 series was utilized to measure neutrophil and lymphocyte counts. The COBAS Chemistry system was used to measure CRP and albumin levels. Additionally, the Elecsys series, specifically the ECLIA, was employed to measure IL-6 levels. Furthermore, medical records were also utilized in the study to determine the outcomes of the patients.

Procedure

The procedures can be divided into several steps. Firstly, the study obtained approval (Approval No. 400/011/K.3/302/2021) from the Saiful Anwar General Hospital's ethics committee, ensuring ethical conduct. All participants in the study provided informed consent and met the requirements of the Declaration of Helsinki. The minimum age requirement for participants was 20 years. It took place from January to June 2021. Patients with a history of cancer, liver illness, hemostatic dysfunction, autoimmune diseases, or heart failure were excluded.

The diagnosis of COVID-19 was confirmed using the RT-PCR method. Following the patients' discharge from the hospital, their medical records were examined to determine their outcomes. On the first day of admission, peripheral blood samples were collected to measure CAR, IL-6, IL-6/LY, and NLR. Data analysis was performed using IBM SPSS Statistics 26. Initially, independent t-tests and chi-square tests were conducted to examine the characteristics of the study subjects. Receiver operating characteristic (ROC) analysis was then carried out to determine the area under the curve (AUC) and the cut-off for each variable. Additionally, a survival analysis utilizing Kaplan-Meier curves and Hazard Ratio (HR) was employed to create a predictive model for COVID-19 patients.

■ RESULTS AND DISCUSSION

Since COVID-19 was deemed a global public health emergency three years ago, it has posed ongoing difficulties for patient care. Numerous reasons, including the introduction of novel viral variations that contribute to recurrent waves of infection, can be blamed for these ongoing medical issues. In addition, the clinical course of the illness is highly unpredictable and challenging to predict, particularly in critically ill individuals. Hyperinflammation is the fundamental pathogenic process causing SARS-CoV-2 infection to progress to severe symptoms, such as acute respiratory distress syndrome, multiple organ failure, and lethal consequences [11]. A total of 102 COVID-19 patients were included in this study, with 39 subjects (38.23%) were female and 63 subjects (61.76%) were male. The mean age of the patients was 57.51 ± 14.05 years. Data collection was completed at the end of the study period.

Based on Table 1, the p-value for CAR, IL-6, IL-6/LY, and NLR, which were examined in this study, was found to be < 0.05 , indicating a significant difference in the median value between the survivor and non-survivor groups. However, no statistically significant differences were found in the parameters of sex, age, albumin, and lymphocyte count.

The development of a panel of standard laboratory tests is essential for patient risk assessment, optimum

clinical care, and the effective use of medical resources. In this study, we sought to determine the prognostic value of inflammatory biomarkers in predicting COVID-19 patients' in-hospital mortality. Inflammatory markers such as CAR, IL-6, the IL-6/LY ratio, and NLR have the potential to be used as predictors of in-hospital mortality for COVID-19 patients, according to our data. These results offer the foundation for the creation of a prognostic scoring system that can efficiently stratify the risk of COVID-19 patients who are critically ill.

Our study indicated that there was a substantial increase in CRP, CAR, IL-6, IL-6/LY, WBC, neutrophils, and NLR in the non-survivor group compared to the survivor group. This study was aligned with other studies that have also demonstrated higher levels of CRP, CAR, and IL-6 in severe COVID-19 cases and an association between increased CRP levels and disease severity or poor outcomes [10-11]. In addition, IL-6 was found to be a strong independent predictor of mortality in a retrospective examination of severely ill COVID-19 patients who were admitted to the intensive care unit (ICU). Similar to this, cohort research focusing on sick patients with SARS-CoV-2 infection showed that elevated baseline levels of both IL-6 and CRP were significantly related to illness progression and increased death within a 60-day window [9]. Therefore, it has been demonstrated that excessive CRP levels can predict the

Table 1. Demographic data of the subject

Variables	Survivors (n = 42)	Non-Survivors (n = 60)	p.s
Sex			
Male	24 (58.06%)	39 (65.00%)	
Female	18 (41.93%)	21(35.00%)	0.643 ^a
Age(year)*	54.29 ± 15.07	59.50 ± 13.15	0.105 ^b -
CRP (mg/dL) [#]	3.94 (2.19–7.45)	12.06 (7.94–18.41)	0.000 ^c -
Albumin (g/dL)*	3.50 ± 0.50	3.29 ± 0.54	0.078 ^b -
CAR [#]	1.50 (0.68–3.68)	4.29 (2.23–6.71)	0.001 ^c -
IL-6 (pg/mL) [#]	24.08 (14.25–80.12)	111.55 (52.03–269.23)	0.000 ^c -
Lymphocyte count (cells/mm ³) [#]	1210 (770–1680)	1040 (702.50–1382.50)	0.319 ^c -
IL-6/LY [#]	26.26 (9.59–71.6)	106.57 (41.85–292.11)	0.000 ^c -
Leukocyte count (cells/mm ³) [#]	8880 (6660–12250)	11640 (8025–18045)	0.021 ^c -
Neutrophil count (cell/mm ³) [#]	6360 (4190–10000)	9820 (5872.50–16165)	0.011 ^c -
NLR [#]	5.59 (3.02–9.94)	8.59 (4.81–16.76)	0.000 ^c -

*mean (\pm SD); #median (Q1-Q3)

severity and mortality of COVID-19, but low albumin levels are linked to higher mortality. It is possible to state that albumin levels in COVID-19 patients are predominantly affected by this fact, which is directly associated with the hyperinflammatory states that are frequently discovered in severe cases. Therefore, a CRP-to-albumin ratio might offer greater performance.

The optimal cut-off for each parameter (Table 2) was determined using ROC analysis (AUROC), with COVID-19 patient mortality being used as the comparison, where 0 represents survivors, and 1 represents non-survivors. Fig. 1 shows the area under the receiver operating characteristic curve (AUROC) for each variable. It is evident that IL-6 has the highest AUROC value in predicting mortality in COVID-19 patients, with a value of 0.77. Following IL-6, IL-6/LY, CAR, and NLR had AUROC values of 0.75, 0.71, and 0.65, respectively.

Fig. 2 shows the survival curves, indicating that individuals with elevated levels or ratios of the studied parameters exhibit lower survival rates compared to those with lower levels or ratios. After performing the logistic regression test, HR values of 7.706, 14.131, 0.807, and 1.926 were obtained for CAR, IL-6, IL-6/LY, and NLR, respectively.

In this study, ROC curve analysis showed IL-6 has the highest AUROC value in predicting death in COVID-19 patients, with a value of 0.77. Following IL-6, IL-6/LY, CAR, and NLR had AUROC values of 0.75, 0.71, and 0.65, respectively. These findings are comparable with those of a prior study, which also established the predictive usefulness of these inflammatory markers in COVID-19 patients. IL-6 shows a strong correlation and the greatest performance in predicting the severity and death of COVID-19 patients [12]. The study conducted by Zhou et al. [13] indicated that people who were seriously ill with COVID-19 had increased levels of IL-6. This conclusion

was similarly observed in a study by El-Shabrawy et al. [14], albeit with a different cut-off value of 32.3 pg/mL. Similarly, a different study with a lower cut-off value of 26.09 pg/mL revealed equivalent sensitivity. According to these findings, our study also found that people with severe and very severe COVID-19 cases had considerably higher IL-6 levels than those with mild to moderate instances [13-14].

In COVID-19 patients with severe disease, elevated IL-6 levels are frequently seen. This is related to a hyperinflammatory condition brought on by excessive synthesis of pro-inflammatory cytokines, such as IL-6. The IL-6 level in our investigation had a cut-off value of 47.5 pg/mL, showing potential as a predictor of mortality with a sensitivity of 80%, a PPV of 83.3%, and an AUROC value of 77.3% (95% CI: 66–88.6%; $p = 0.000$). A study by El-Shabrawy et al. [14] revealed a cut-off value of 32.3 pg/mL, and our results were in agreement with that study's findings. A level of IL-6 greater than 25 pg/mL is regarded as a risk factor for fatal illness. IL-6 levels could therefore be a potential indicator of serious

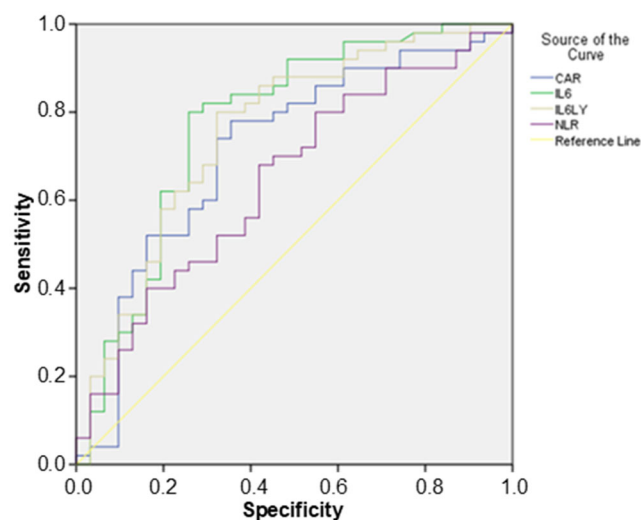


Fig 1. ROC Curve of CAR, IL-6, IL-6/LY, and NLR

Table 2. CAR, IL-6, IL-6/LY, NLR cut-off values and performance in determining mortality

Variables	Cut off	units	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
CAR	2.70	ratio	74	67.7	78.7	61.8	71.6
IL-6	47.50	pg/mL	80	74.2	83.3	69.7	77.8
IL-6/LY	39.30	ratio	80	67.7	80.0	67.7	75.3
NLR	5.59	ratio	68	58.1	72.3	52.9	64.2

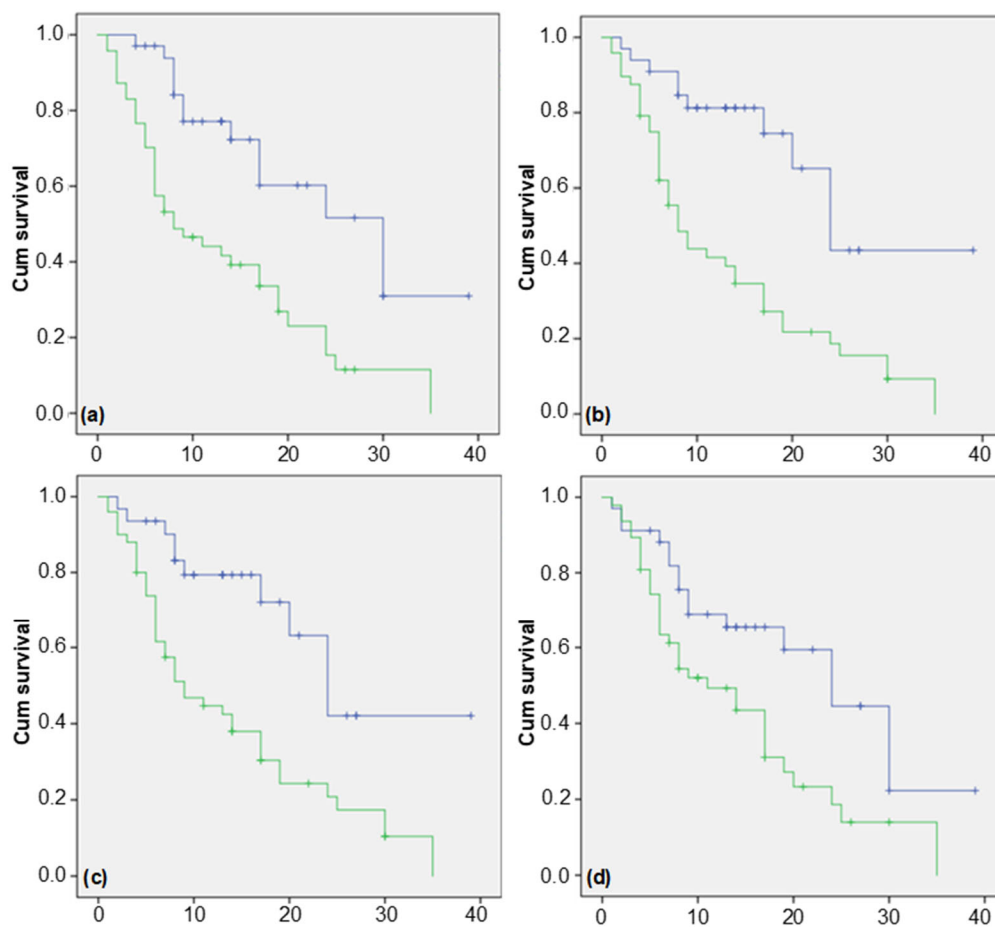


Fig 2. CAR, IL-6, IL-6/LY, and Kaplan-Meier curves NLR's blue line designates the group above the cut-off, and its green line designates the group below the cut-off

illness and mortality. Sabaka et al. [15] also included IL-6 value > 24 pg/mL to screen COVID-19 individuals at risk of worsening, particularly those requiring supplemental oxygen due to hypoxemia [14-15].

The predictive value of IL-6/LY in COVID-19 mortality is consistent with that of IL-6. IL-6/LY is a new marker used to predict worsening symptoms and mortality in COVID-19 patients [16]. The hyperinflammatory process associated with severe COVID-19 symptoms leads to an increase in inflammatory markers, including IL-6, and a decrease in lymphocyte count, particularly the T lymphocyte subset. The combination of these markers has been reported to have better clinical value in describing hyperinflammatory condition and immune system dysfunction [16-17]. In this study, the optimal cut-off value for IL-6/LY was 39.3, with an AUROC of 75.5%

(95% CI: 64.3–86.8%; $p = 0.000$) and a sensitivity and PPV of 80%. This value is higher than that reported in several other studies, possibly due to differences in the population of research subjects. For instance, a study limited to patients with severe COVID-19 treated in the ICU reported a cut-off value of 2.5 for IL-6/LY, whereas another study with a more heterogeneous population from asymptomatic to severe symptoms found a higher cut-off value of 19 [18-19].

This study indicated that NLR has the lowest predictive value for mortality compared to other markers. NLR has been frequently utilized to screen for systemic inflammatory illnesses such as ischemic heart disease and acute pancreatitis, and it has also been extensively investigated in COVID-19 as a predictor of severity and death [20]. High NLR values have been associated with greater severity of the disease. In this

study, the NLR cut-off value was determined to be 5.59, with an AUROC value of 64.6% (95% CI: 52.3–76.9%; $p = 0.028$) and a positive predictive value of 72.3%. A study by Bellan et al. [21], which discovered an NLR cut-off value of 4.68 as a predictor of death in COVID-19 patients [21], reported a similar value. Increased neutrophil counts or decreased lymphocyte counts can also contribute to increased NLR [22]. Neutrophils play several roles in the infection process, including the formation of NETs, which are known to be associated with hyperinflammatory conditions that can lead to a cytokine storm. However, an increase in neutrophils can also be caused by a bacterial infection. In contrast, the depletion of CD8+ T cells, which are frequently present in severe cases of COVID-19, is the key factor contributing to the decrease in the number of lymphocytes in COVID-19 [21-22]. The fact that data were only gathered once during the patient's initial hospital admission is one of the study's shortcomings. This restriction may have an impact on how well the mortality predictors function, particularly for the IL-6/LY and NLR parameters. Serial studies of these variables may offer a more thorough understanding of their functions in predicting patient outcomes because it is known that the levels of these inflammatory biomarkers fluctuate throughout the progression of COVID-19 disease.

The research findings have several implications for developing countries. First, CAR and IL-6 may be useful biomarkers for predicting mortality in COVID-19 patients in developing countries. This is important because developing countries often have limited access to sophisticated medical equipment and expertise. CAR and IL-6 are relatively simple and inexpensive biomarkers that can be measured using widely available assays.

CAR may be a more cost-effective option for predicting mortality in COVID-19 patients in these settings. Second, the findings suggest that CAR and IL-6 may be useful for identifying patients who are at high risk of mortality from COVID-19. This information could then be used to prioritize these patients for early treatment or admission to the ICU. This could help to improve their chances of survival.

■ CONCLUSION

Our study demonstrated that inflammatory biomarkers, such as CAR, IL-6, the IL-6/LY ratio, and NLR, were predictive of in-hospital mortality in COVID-19 patients. Following IL-6/LY, CAR, and NLR as the best predictors of mortality, IL-6 had the highest AUROC value. These findings imply that routine monitoring of these inflammatory biomarkers may help to better classify COVID-19 patients' risks, particularly for those with severe disease. CAR, which performs as well as IL-6, is relatively simple, inexpensive, and easy to measure. Therefore, it has the potential to serve as a promising biomarker for patient stratification, not only in COVID-19 but also in other hyperinflammatory diseases.

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■ AUTHOR CONTRIBUTIONS

Agustin Iskandar contributed to the conceptualization of the study, methodology design, visualization of data, and writing of the original draft. Hambiah Hari Oki was involved in data collection, analysis of the data, and contributed to the review and editing of the manuscript. Catur Suci Sutrisnani played a role in methodology development, database management, and contributed to the review and editing of the manuscript. Novi Khila Firani contributed to the review and editing of the manuscript. Nur Samsu was responsible for data visualization, validation of results, and contributed to the review and editing of the manuscript. Agustina Tri E provided supervision throughout the study and contributed to the review and editing of the manuscript. Edi Widjajanto contributed to result validation, provided supervision, and contributed to the review and editing of the manuscript. All authors have made significant contributions to the article, have

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■ REFERENCES

- [1] WHO, 2021, *COVID-19 Weekly Epidemiological Update*, <https://covid19.who.int/>, accessed on March 20, 2023.
- [2] Indonesian Ministry of Health, 2023, *COVID-19 Distribution Map*, <https://covid19.go.id/peta-sebaran>, accessed on February 5, 2023.
- [3] Zeng, F., Huang, Y., Guo, Y., Yin, M., Chen, X., Xiao, L., and Deng, G., 2020, Association of inflammatory markers with the severity of COVID-19: A meta-analysis, *Int. J. Infect. Dis.*, 96, 467–474.
- [4] Mazzoni, A., Salvati, L., Maggi, L., Capone, M., Vanni, A., Spinicci, M., Mencarini, J., Caporale, R., Peruzzi, B., Antonelli, A., Trotta, M., Zammarchi, L., Ciani, L., Gori, L., Lazzeri, C., Matucci, A., Vultaggio, A., Rossi, O., Almerigogna, F., Parronchi, P., Fontanari, P., Lavorini, F., Peris, A., Rossolini, G.M., Bartoloni, A., Romagnani, S., Liotta, F., Annunziato, F., and Cosmi, L., 2020, Impaired immune cell cytotoxicity in severe COVID-19 is IL-6 dependent, *J. Clin. Invest.*, 130 (9), 4694–4703.
- [5] Wang, L., 2020, C-reactive protein levels in the early stage of COVID-19, *Med. Mal. Infect.*, 50 (4), 332–334.
- [6] Huang, W., Li, C., Wang, Z., Wang, H., Zhou, N., Jiang, J., Ni, L., Zhang, X.A., and Wang, D.W., 2020, Decreased serum albumin level indicates poor prognosis of COVID-19 patients: Hepatic injury analysis from 2,623 hospitalized cases, *Sci. China Life Sci.*, 63 (11), 1678–1687.
- [7] Soy, M., Keser, G., Atagündüz, P., Tabak, F., Atagündüz, I., and Kayhan, S., 2020, Cytokine storm in COVID-19: Pathogenesis and overview of anti-inflammatory agents used in treatment, *Clin. Rheumatol.*, 39 (7), 2085–2094.
- [8] Yuki, K., Fujiogi, M., and Koutsogiannaki, S., 2020, COVID-19 pathophysiology: A review, *Clin. Immunol.*, 215, 108427.
- [9] Borges, L., Pithon-Curi, T.C., Curi, R., and Hatanaka, E., 2020, COVID-19 and neutrophils: The relationship between hyperinflammation and neutrophil extracellular traps, *Mediators Inflammation*, 2020, 8829674.
- [10] Didangelos, A., 2020, COVID-19 hyperinflammation: What about neutrophils?, *mSphere*, 5 (3), e00367-20.
- [11] Rabaan, A.A., Al-Ahmed, S.H., Garout, M.A., Al-Qaaneh, A.M., Sule, A.A., Tirupathi, R., Mutair, A.A., Alhumaid, S., Hasan, A., Dhawan, M., Tiwari, R., Sharun, K., Mohapatra, R.K., Mitra, S., Emran, T.B., Bilal, M., Singh, R., Alyami, S., Moni, M.A., and Dhama, K., 2021, Diverse immunological factors influencing pathogenesis in patients with COVID-19: A review on viral dissemination, immunotherapeutic options to counter cytokine storm and inflammatory responses, *Pathogens*, 10 (5), 565.
- [12] Pál, K., Molnar, A.A., Huțanu, A., Szederjesi, J., Branea, I., Timár, Á., and Dobreanu, M., 2022, Inflammatory biomarkers associated with in-hospital mortality in critical COVID-19 patients, *Int. J. Mol. Sci.*, 23 (18), 10423.
- [13] Zhou, J., He, W., Liang, J., Wang, L., Yu, X., Bao, M., and Liu, H., 2021, Association of interleukin-6 levels with morbidity and mortality in patients with coronavirus disease 2019 (COVID-19), *Jpn. J. Infect. Dis.*, 74 (4), 293–298.
- [14] El-Shabrawy, M., Alsadik, M.E., El-Shafei, M., Abdelmoaty, A.A., Alazzouni, A.S., Esawy, M.M., and Shabana, M.A., 2021, Interleukin-6 and C-reactive protein/albumin ratio as predictors of COVID-19 severity and mortality, *Egypt. J. Bronchol.*, 15 (1), 5.
- [15] Sabaka, P., Koščálová, A., Straka, I., Hodosy, J., Lipták, R., Kmotorková, B., Kachlíková, M., and Kušnířová, A., 2021, Role of interleukin 6 as a predictive factor for a severe course of Covid-19: Retrospective data analysis of patients from a long-term care facility during Covid-19 outbreak, *BMC Infect. Dis.*, 21 (1), 308.
- [16] Liu, B., Li, M., Zhou, Z., Guan, X., and Xiang, Y., 2020, Can we use interleukin-6 (IL-6) blockade for coronavirus disease 2019 (COVID-19)-induced

- cytokine release syndrome (CRS)?, *J Autoimmun.*, 111, 102452.
- [17] Liu, X., Wang, H., Shi, S., and Xiao, J., 2022, Association between IL-6 and severe disease and mortality in COVID-19 disease: A systematic review and meta-analysis, *Postgrad. Med. J.*, 98 (1165), 871–879.
- [18] Masotti, L., Grifoni, E., Pelagalli, G., Cioni, E., Mattaliano, C., Cioffi, E., Mattaliano, C., Cioffi, E., Maggi, F., Pinto, G., Madonna, E.M., Micheletti, I., Gelli, A.M.G., Ciambotti, B., Mannucci, A., Bello, R., Cei, F., Dolenti, S., Tarquini, R., Montenora, I., Spina, R., and Vanni, S., 2022, Prognostic role of Interleukin-6/lymphocytes ratio in SARS-CoV2 related pneumonia, *Int. Immunopharmacol.*, 103, 108435.
- [19] Rotundo, S., Borelli, M., Scaglione, V., Lionello, R., Biamonte, F., Olivadese, V., Quirino, A., Morrone, H.L., Matera, G., Costanzo, F.S., Russo, A., Trecarichi, E.M., Torti, C., and IDTM UMG COVID-19 Group, 2023, Interleukin-6/lymphocyte as a proposed predictive index for COVID-19 patients treated with monoclonal antibodies, *Clin. Exp. Med.*, 1–7.
- [20] Palladino, M., 2021, Complete blood count alterations in COVID-19 patients: A narrative review, *Biochem. Med.*, 31 (3), 030501.
- [21] Bellan, M., Azzolina, D., Hayden, E., Gaidano, G., Pirisi, M., Acquaviva, A., Aimaretti, G., Aluffi Valletti, P., Angilletta, R., Arioli, R., Avanzi, G.C., Avino, G., Balbo, P.E., Baldon, G., Baorda, F., Barbero, E., Baricich, A., Barini, M., Barone-Adesi, F., Battistini, S., Beltrame, M., Bertoli, M., Bertolin, S., Bertolotti, M., Betti, M., Bobbio, F., Boffano, P., Bogliione, L., Borrè, S., Brucoli, M., Calzaducca, E., Cammarata, E., Cantaluppi, V., Cantello, R., Capponi, A., Carriero, A., Casciaro, G.F., Castello, L.M., Ceruti, F., Chichino, G., Chirico, E., Cisari, C., Cittone, M.G., Colombo, C., Comi, C., Croce, E., Daffara, T., Danna, P., Della Corte, F., De Vecchi, S., Dianzani, U., Di Benedetto, D., Esposto, E., Faggiano, F., Falaschi, Z., Ferrante, D., Ferrero, A., Gagliardi, I., Galbiati, A., Gallo, S., Garavelli, P.L., Gardino, C.A., Garzaro, M., Gastaldello, M.L., Gavelli, F., Gennari, A., Giacomini, G.M., Giacone, I., Gai Via, V., Giolitti, F., Gironi, L.C., Gramaglia, C., Grisafi, L., Inserra, I., Invernizzi, M., Krenghli, M., Labella, E., Landi, I.C., Landi, R., Leone, I., Lio, V., Lorenzini, L., Maconi, A., Malerba, M., Manfredi, G.F., Martelli, M., Marzari, L., Marzullo, P., Mennuni, M., Montabone, C., Morosini, U., Mussa, M., Nerici, I., Nuzzo, A., Olivieri, C., Padelli, S.A., Panella, M., Parisini, A., Paschè, A., Patrucco, F., Patti, G., Pau, A., Pedrinelli, A.R., Percivale, I., Ragazzoni, L., Re, R., Rigamonti, C., Rizzi, E., Rognoni, A., Roveta, A., Salamina, L., Santagostino, M., Saraceno, M., Savoia, P., Sciarra, M., Schimmenti, A., Scotti, L., Spinoni, E., Smirne, C., Tarantino, V., Tillio, P.A., Tonello, S., Vaschetto, R., Vassia, V., Zagaria, D., Zavattaro, E., Zeppegno, P., Zottarelli, F., and Sainaghi, P.P., 2021, Simple parameters from complete blood count predict in-hospital mortality in COVID-19, *Dis. Markers*, 2021, 8863053.
- [22] Tadesse, Z., Bekele Bayissa, A., Diriba, T., Chernet, N., Tsegaye, S., and Tsega, M., 2022, Neutrophil-to-lymphocyte ratio and cut-off values as predictor of severity and mortality in COVID-19 patients in millennium COVID-19 care center, Addis Ababa, Ethiopia, *Int. J. Gen. Med.*, 15, 6739–6755.