

Inflammatory markers for predicting severity, mortality, and need for intensive care treatments of a patient infected with covid-19: a scoping review



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ABSTRACT

Introduction: Numerous types of inflammatory markers are used by health workers to predict the patients infected with COVID-19 condition. However, fewer studies have identified the specific inflammatory markers to predict the severity, mortality, and need for intensive care treatments among patients infected with COVID-19. Thus, this scoping review aimed to evaluate and grouping the inflammatory markers related to severity, mortality, and need for intensive care treatments.

Methods: Electronic databases were discovered for studies by elaborating specific proposed keywords related to types of inflammatory markers for predicting the severity, mortality, and need for intensive care treatments of patients infected with COVID-19. Authors independently comprised the literature search, evidence evaluation, and article extraction until the types of inflammatory markers for predicting the severity, mortality, and need for intensive care treatments of patients infected with COVID-19 are discovered.

Results: 8 of 133 identified articles were included. These articles summarized that the mean of thrombocyte volume-to-platelet count ratio (MPV/PLT), the C-reactive protein/albumin ratio (CAR), prognostic nutritional index (PNI) and lymphocyte to C-reactive protein ratio (LCRP) were significant in predicting mortality. Lymphocyte-to-monocyte ratio (LMR) and Lymphocyte-to-CRP ratio (LCR) were inversely correlated with disease severity. The systemic-immune-inflammation index (SII) and platelet-to-lymphocyte ratio (PLR) findings were statistically significant in predicting disease severity and the need for intensive care treatments. Moreover, Elevated C-reactive protein (CRP), lymphocyte-to-CRP ratio (LCR), and neutrophil-to-lymphocyte ratio (NLR) were statistically significant in predicting the disease severity, need for intensive care treatment, and mortality.

Conclusion: Each of the inflammatory markers has specificity in predicting the severity, mortality, and need for intensive care treatments among patients infected with COVID-19. These predictors can be used by health professionals, particularly nurses in providing the best clinical decisions and nursing care to COVID-19 patients.

Keywords: COVID-19, inflammatory markers, mortality, intensive care treatment.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a respiratory infectious disease caused by an agent of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).¹⁻³ In December 2019, the initial spread of the virus occurred in Wuhan China until it became a global problem throughout the world.^{1,4,5} This situation encourages WHO to declare a pandemic situation in March 2020. Recently, the number of people who died due to COVID-19 worldwide was 6.23 million.⁶

Mild, moderate, to severe were

various kinds of responses in patients with COVID-19.⁷⁻⁹ It was reported that 15–20% of severe cases became critical. Those critical condition need ICU during treatment period.¹⁰ Determining the severity of a person's condition plays a major role in determining the patient's emergency condition so that the risk of death can be prevented.¹⁰⁻¹⁴

The severity of the COVID-19 patient's condition is closely related to the patient's mortality rate.^{10,12,15} It turns out that the study shows that the severity, lightness, and risk of death of COVID-19 patients can

be predicted by the hyperinflammatory response experienced by the patient.^{11,14} The indicator to determine the hyperinflammation can be seen from the value of the inflammatory parameters which is indicated by the patient's laboratory test results.^{15,16} Studies show that inflammatory parameters are closely related to the severity of COVID-19 patients.^{10,16} Another study showed evidence that inflammatory parameters can also detect how big the risk of death of a patient is to determine the criteria for whether the patient needs to receive intensive care

treatment or not.^{10,12,13} Many study results show the types of inflammatory markers for COVID-19 patients. Therefore, it is important to discover and group the types of inflammatory markers that are closely related to severity, mortality, and intensive care treatment. as a result, the grouping of patients based on the level of emergency can be done in the hospital. Thus, the purpose of this scoping review was to evaluate and group inflammatory markers related to severity, mortality, and need, d for intensive care treatments.

METHODS

Identifying The Purpose And Research Question

The patients infected with COVID-19 from a variety of countries, all of inflammatory markers that has been assessed for severity, mortality, and the need for intensive care treatments in COVID-19 patients were belong in to this review. Our scoping review using question “what are the specific types of inflammatory markers for predicting the severity, mortality, and need for intensive care treatment among COVID-19 infected patients?”

Identifying Relevant Literature

Using the Boolean logic operators “AND” and “OR,” we combined the keywords: inflammatory markers, inflammatory indexes, severity, mortality, need for intensive care, and COVID-19. In this study, EBSCO Host engine searches included Pubmed, MEDLINE Complete, MEDLINE With Full Text, Academic Search Complete, Professional Development Collection, OmniFile Full Text Select (H.W. Wilson), and APA PsycArticles. All relevant article that included in our requirements were then reviewed (Figure 1).

Selecting Studies

Inclusion criteria for this study were the studies published in English between March 2019 and April 2022 that used inflammatory markers to predict severity, mortality, and the need for an ICU in COVID-19 patients. Exclusion criteria, on the other hand, included articles that were not aligned with inflammatory markers that focused on predicting severity, mortality, and the need for an ICU in

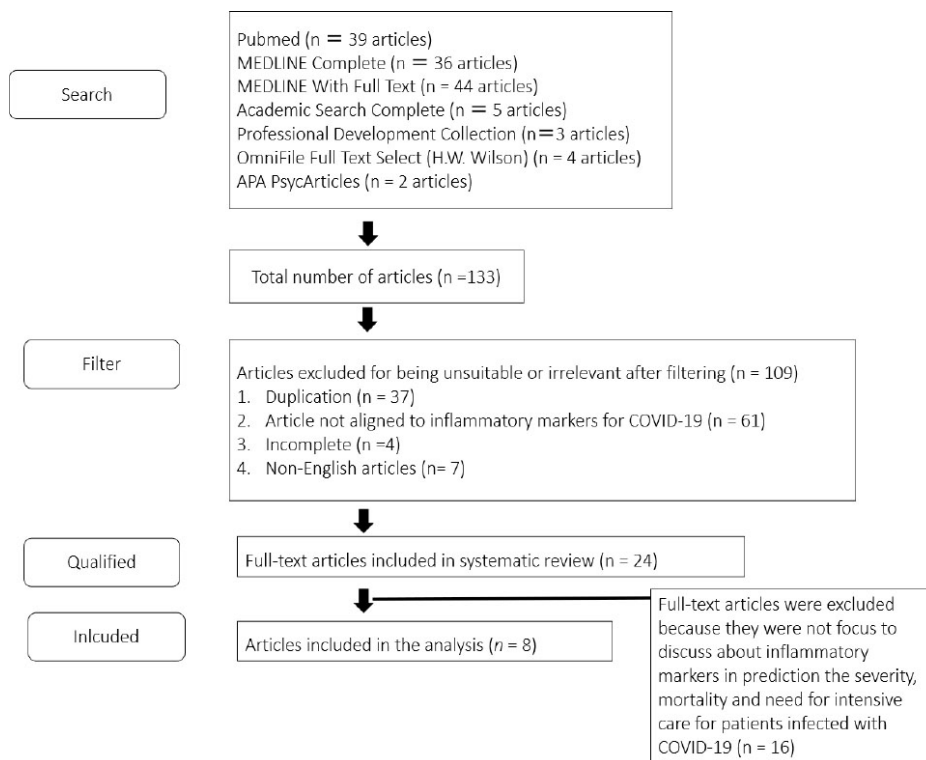


Figure 1. Flowchart of identified relevant literature.

patients infected with COVID-19, as well as articles that were incomplete. As a result, 8 of the 133 identified articles were included. Table 1 displays the extraction data.

Charting The Data

In this study, we found a large number of the articles. Meanwhile, screening has been done for several step according to the flowchart thus we found the article related to the topic. The authors assisted in the analysis of this review’s data, where themes and subthemes were identified and coded across all retrieved articles Table 2.

Collating, Summarizing, And Reporting The Results

We described inflammatory markers for predicting the severity of COVID-19 infection in this study. Following that, researchers concentrated on inflammatory markers to predict the mortality of COVID-19 patients. The third sub-topic would be inflammatory markers for predicting the severity and need for intensive care treatments of COVID-19 patients, and the final sub-topic would be inflammatory markers for predicting the severity, mortality, and need for intensive care treatments of COVID-19 patients.

RESULTS

Inflammatory Markers For Predicting Severity Of Patients Infected With COVID-19

Lymphocyte-to-Monocyte ratio (LMR) and Lymphocyte-to-CRP ratio (LCR) were identified as inflammatory markers for predicting the severity of patients infected with COVID-19.^{13,16} According to the Turan D *et.al* the patient was in severe and mild condition and a part of that was in ICU. There was a high sensitivity (92.31), but low specificity (49.30) for the prognostic predictors in COVID-19 ($p \leq 0.14$).¹³ Other research has assessed LMR and LCR parameters but did not analyze the sensitivity and specificity. Both parameters showed a lower mean value in dead patients rather than in ICU ($p < 0.001$).¹⁶ Thus, it means that the higher mean of LMR and LCR value, the better the patient’s condition.

Inflammatory Markers For Predicting Mortality Of Patients Infected With COVID-19

Thrombocyte volume-to-platelet count ratio (MPV/PLT), the C-reactive protein/albumin ratio (CAR), prognostic nutritional index (PNI), and lymphocyte

Table 1. Data extraction according to the inclusion criteria.

No	Author	Purpose	Methods	Results	Suggestion
1.	Acar et al (2021) ¹⁵	To predict mortality in hospitalized patients with a diagnosis of COVID-19	Single-center cohort study	Inflammatory parameters (LRCP, SII, and NLR) were linked to disease severity and could be used as potential COVID-19 risk factors.	Multicentre studies are needed for further studies
2.	Aciksari et al (2021) ¹⁴	To investigate the prognostic value of systemic inflammatory biomarkers including CAR, PNI, NLR, LMR, PLR in patients with severe COVID-19	Single-center, retrospective study	For the severe COVID-19 infection could be predicted by the CAR, PNI, and NLR independently. In addition, PLR and LMR known to be a prognostic marker.	Further studies would provide additional information to this underexamined field of research
3.	BG et al (2021) ¹²	To examine the prognostic value of normal and derived NLR, LMR, PLR, and MPV/PLT ratios in patients with COVID-19.	Retrospective cross-sectional study	NLR was found in 60% of the population and was significantly higher in disease survivors. The PLR followed the same pattern. In contrast, even though the LMR followed the trend as well, this parameter did not have any significant relationship with COVID-19. The NLR and MPV/PLT also shown linear results in mortality aspect.	Further studies are needed with larger sample sizes and larger studies
4.	Carpio-Orantes et al (2021) ¹⁹	To correlate the NLR, PLR, and SII with COVID-19 severity	A descriptive, analytical, and retrospective study	INL, IPL, and IIS are indices that can be used as predictors of severity and hospital outcome in patients with COVID-19 pneumonia. Second, they can indicate a serious inflammatory process and a loss of immune system homeostasis, which can lead to severe clinical conditions and a poor prognosis.	More research is needed to explore the relationship between the rates analyzed in other populations affected by COVID-19.
5.	Singh et al (2021) ¹¹	To investigate the role of NLR and PLR in predicting the disease progression	The single-center study, the prospective observational study	The reduction NLR ration in the first and third days of survivor group were reported. It lowest than the no survivors group. In contrast, PLR parameter did not significant in both groups for disease severity and mortality aspect.	Similar research with a bigger sample and a lot of centre involve are needed.
6.	Turan et al (2021) ¹³	To determine the usefulness of the SII, LCR, PLR, and MPV/PLT values compared with the commonly used laboratory parameters of absolute lymphocyte count, NLR, and CRP, as prognostic biomarkers of COVID-19	Single-center and retrospective study	In predicting disease severity, mortality rate, and the needs of ICU an enhancement of CRP, NLR, reduction of lymphocyte counts could be considered. Those parameters were statistically significant, and mortality. The SII and PLR parameter also established a significant results in predicting disease severity and the need for intensive care, while the LCR value predicted all three outcomes. The MPV/PLT ratio was only significant in predicting mortality.	More comprehensive studies with larger patient groups are needed to further assess
7.	Waris et al (2021) ¹⁰	To explore novel inflammatory markers NLR, PLR as a valuable marker in predicting the severity and outcome of COVID-19 infection as they were previously reported in different infections and inflammatory conditions	Retrospective cross-sectional study	PLR, NLR, and LMR demonstrated a significant link. These blood parameters could be used as a biomarker for COVID-19 prognosis and severity.	Moreover, futher investigation of the topic is urgently needed to provide optimal management to patients during the COVID-19 pandemic

No	Author	Purpose	Methods	Results	Suggestion
8.	Asghar et al (2020) ¹⁶	To utilize the hematological parameters in predicting the prognosis and mortality in COVID-19 patients	Single-center, retrospective, observational study	In severe condition NLR and PLR levels were tend to be increase. In contrast, LMR and LCR levels were tend to decrease when predicting the disease severity and mortality.	Further studies are needed to predict overall mortality or therapeutic benefits

Table 2. Review concepts, themes, and subthemes.

Sub-topic	Major themes	Subthemes	Authors
Inflammatory markers for predicting the severity of patients infected with COVID-19	1. Inflammatory markers 2. The severity of patients infected with COVID-19	• LMR • LCR	Turan (2021), ¹³ Asghar (2020), ¹⁶
Inflammatory markers for predicting mortality of patients infected with COVID-19	1. Inflammatory markers 2. Mortality of patients infected with COVID-19	• MPV/PLT • CAR • PNI • LCRP	Açıksarı (2021), ¹⁴ Acar (2021), ¹⁵ BG (2021), ¹²
Inflammatory markers for predicting severity and needs for intensive care treatments of patients infected with COVID-19	1. Inflammatory markers 2. Severity and needs for intensive care treatments of patients infected with COVID-19	• SII • PLR	Acar (2021), ¹⁵ Asghar (2020), ¹⁶
Inflammatory markers for predicting severity, mortality, and needs for intensive care treatments of patients infected with COVID-19	1. Inflammatory markers 2. Severity, mortality, and needs for intensive care treatments of patients infected with COVID-19	• CRP • LCR • NLR	Turan (2021), ¹³ Asghar (2020), ¹⁶ Açıksarı (2021), ¹⁴ Waris (2021), ¹⁰

to C-reactive protein ratio (LCRP) were identified as inflammatory markers for predicting mortality of patients infected with COVID-19.^{12,14,15} The MPV/PLT also had a significant association with mortality. In general, the mean of MPV/PLT was 0.00052 ± 0.0005 . This parameter established that the non-survivor group had a lower mean value rather than the survivor group. Meanwhile, the mean difference did not have a significant association ($p=0.14$).¹² Acıksarı G *et al.*, assessed the different parameter (CAR and PNI). Both parameters had different results. The CAR value was higher in the nonsurvivor group rather than in the survivor group. Meanwhile, the PNI value is higher in the survivor group rather than in the nonsurvivor group. Meanwhile, both parameters were significant in predicting mortality among COVID-19 patients.¹⁴ Other parameters have been assessed, such as LCRP both in survivor and nonsurvivor groups. It showed a higher mean value in the survivor group rather than in the non-survivor group ($p \leq 0.05$).¹⁵ We can conclude that all parameters had different pattern values in each group, but those parameters have been associated with mortality rates in COVID-19 patients.

Inflammatory Markers For Predicting Severity And Needs For Intensive Care Treatments Of Patients Infected With COVID-19

The systemic-immune-inflammation index (SII) and platelet-to-lymphocyte ratio (PLR) were identified as inflammatory markers for predicting severity and needs for intensive care treatments of patients infected with COVID-19.^{14,15} The PLR parameter had cut off was ≥ 312 , AUC = 0.63, CI 95% 0.56-0.69, p -value = 0.019 for predicting a mortality rate among severe patient's condition. The survivor group had a lower value rather than the non-survivor. The comparison of both parameters had a significant association with COVID-19 ($p=0.019$). Meanwhile, this study did not assessed the ICU needs of the patient.¹⁴ According to the Acar E *et al.*, study, the mean difference of PLR in the ICU compare within the ward patient showed a higher value among the survivor group rather than the non-survivor. This difference had a significant relationship ($p \leq 0.05$). A similar pattern was also established in the SII value from both groups ($p \leq 0.05$).¹⁵

Inflammatory Markers For Predicting Severity, Mortality, And Needs For Intensive Care Treatments Of Patients Infected With COVID-19

Elevated C-reactive protein (CRP), lymphocyte-to-CRP ratio (LCR), and neutrophil to lymphocyte ratio (NLR) were identified as inflammatory markers for predicting severity, mortality, and needs for intensive care treatments of patients infected with COVID-19.^{10,13,14,16} The NLR value got higher in the worsening condition. This could figure the patient COVID-19 severity. It showed a significant relationship with severity of COVID-19 severity ($p < 0.001$).¹⁰ Other research from ROC analysis CRP, LCR and NLR could predict the disease severity [(CRP $p=0.002$; AUC 0.749; sensitivity=54.55; specificity=91.78), (LCR $p < 0.001$; AUC 0.766; sensitivity=89.29; specificity=53.57), (NLR $p=0.001$; AUC=0.755; sensitivity=100.0; specificity=43.84)], ICU needs [(CRP $p < 0.001$; AUC 0.841; sensitivity=76.92; specificity=78.87), (LCR $p < 0.001$; AUC 0.746; sensitivity=92.31; specificity=49.30), (NLR $p < 0.001$; AUC=0.808; sensitivity=61.54; specificity=85.92)], and

mortality rate [(CRP $p=0.002$; AUC 0.749; sensitivity=54.55; specificity=91.78), (LCR $p=0.029$; AUC 0.696; sensitivity=45.45; specificity=90.41), (NLR $p<0.001$; AUC=0.755; sensitivity=100.0; specificity=43.84)].¹³ In line with the previous study, NLR could be a parameter to predict mortality and disease severity.¹⁴

DISCUSSION

Although the lungs are the primary organ of infection,²⁰ COVID-19 is now recognized as a multisystemic infection involving the hematological and immune systems. As a result, identifying inflammatory markers in disease progression and treating patients early is critical. The current study discovered several inflammatory markers that predict severity, mortality, and the need for intensive care treatments in COVID-19 patients.

One study found that LMR and LCR are related to the severity of COVID-19 disease. A serum complete blood count with a differential profile was used to calculate the LMR value. It performs relative lymphopenia and monocytosis. Lymphopenia in COVID-19 patients is linked to the virus's ability to infect T-cells via the angiotensin-converting enzyme 2 (ACE2, receptor and differentiation cluster protein (CD)147-spike.^{21,22} The levels of CD3+, CD4+, and CD8+ T lymphocytes were lower in the final condition, while regulatory T cells were higher. Increased pro-inflammatory cytokines in T-cell lymphopenia may predispose severe COVID-19 patients to cytokine storm, resulting in increased lymphocyte apoptosis and multi-organ failure.

Lower levels of CD4+ and CD8+ T lymphocytes were found to be associated with disease severity, which may lead to low LMR.^{23,24} Previous research has found that patients with severe COVID-19 disease have lower LMR values than those with less severe disease. Patients with severe COVID-19 disease have lymphocytopenia and monocytosis, and they are more likely to develop ARDS and require ICU care than those with less severe disease.^{25,26} LCR, in addition to LMR, is an inflammatory marker capable of distinguishing the severity of COVID-19-infected patients of varying severity.²⁷ LCR is a newly developed

inflammatory score that reflects systemic inflammation status in cancer patients by taking lymphocyte counts and CRP into account.²⁸ Previous research discovered that the LCR was significantly lower in severe cases, implying that this marker could reflect the severity of COVID-19 disease.²⁹ Lower LCR levels in severe patients may be due to fewer lymphocytes, which leads to immune dysfunction and reflects the patients' severe systemic inflammatory response.^{30,31} LCR was found to be lower in severe patients than in mild/moderate patients, consistent with previous research.^{32,33} Lower LCR counts in severe patients are thought to be due in part to their relatively higher viral load levels, which may contribute to lower lymphocyte count levels and higher CRP levels when compared to mild/moderate patients. This is consistent with the trend of SARS-CoV-2 viral load reported in previous studies, it was observed that the LCR in the critically ill group remained low.²⁷

The mortality rate among COVID-19 patients has been established in several studies. Those studies have identified four important inflammatory factors such as MPV/PLT, CAR, LCRP), and NLR. A study in Turkey found that MPV is positively correlated with the severity and mortality of COVID-19 patients.³⁴ Platelets play many important roles in hemostasis, the coagulation cascade, maintaining vascular integrity, neo-angiogenesis, inflammatory response, innate immunity, and tumor biology. Previous research conducted by Aciksari *et.al.*, highlighted that CAR, PNI and LCRP are several inflammatory parameters that are important in predicting mortality in COVID-19 patients.³⁵ These inflammatory parameters are more closely related to mortality prognosis compared to PLR and LMR. This is in line with the study of BG *et al* which explained that LMR and PLR did not have a significant relationship in predicting death in COVID-19 patients.¹² In addition, a study investigated by Singh *et al* found that NLR inflammatory parameters better predict severity and mortality among COVID-19 patients compared to PLR.¹¹ NLR could predict the sepsis condition. Other inflammatory marker such as MPV/PLT ratio established

the significant results in the mortality rate assessment COVID-19. Previous studies has been investigated other parameter. It was a PNI for COVID 19 patients' prognosis. It behave as a prognosis marker for COVID-19 independently. Hypoalbuminemia also can be suspected for the severe inflammation in our body. Cytokine storm was behind the condition. It was often found in COVID-19 patient. Thus, it could be a parameter for predicting disease severity in COVID 19 patients.³⁵

Several inflammatory markers were also determined to predict severity and need for intensive care including high CRP, NLR, SII, PLR values, and lower absolute lymphocyte count values. These inflammatory markers were statistically significant in predicting the severity and need for intensive care. CRP is an inflammatory marker that is regulated by proinflammatory cytokines, especially interleukin-6 (IL-6). The active inflammatory process will result in hypoalbuminemia. Therefore, elevated CRP levels are often associated with hypoalbuminemia. Furthermore, inflammatory markers of NLR in peripheral blood are associated with several diseases involving systemic inflammatory processes and may show prognostic value such as in cardiovascular disease, autoimmune disease, malignant tumors, and infectious diseases.³⁶ For patients with COVID-19, in addition to severe pulmonary lesions, the increased NLR reflects the severity of COVID-19 and the patient's immune status. A previous retrospective study analyzed NLR in differentiating severe patients and predicting mortality in COVID-19 patients.^{37,38} NLR was also included as a variable in the clinical risk score to predict the occurrence of critical illness in hospitalized patients with COVID-19.³⁹ In addition, a study conducted by Chan defined that the inflammatory marker PLR was higher among severe COVID-19 patients. compared with non-severe patients and is emphasized as an important indicator for patients requiring intensive care.⁴⁰ In addition to the above parameters to describe the inflammatory process that occurs, the SII parameter can also be used. SII is estimated based on lymphocyte, neutrophil, and platelet counts.³⁵ Previous

studies have shown that SII is important for predicting the prognosis of tumors and other inflammatory diseases.^{41,42} This is in line with a study conducted by Nalban that found significantly higher levels of SII in the ICU than in the ICU with non-ICU COVID-19 patients. This increase is associated with an increase in the number of neutrophils and a decrease in the number of lymphocytes.³⁵

CONCLUSION

In COVID-19 patients, each inflammatory marker predicts severity, mortality, and the need for intensive care. MPV/PLT, CAR, PNI, and LCRP were all found to be significant predictors of death. LMR and LCR were related to disease severity in an inverse manner. The SII and PLR findings predicted disease severity and the need for ICU in a statistically significant way. CRP, LCR, and NLR were also found to be statistically significant in predicting disease severity, the need for intensive care, and mortality. This study cannot be generalized due to the limitations of inflammatory marker studies in predicting severity, mortality, and intensive care needs among COVID-19 patients.

CONFLICT OF INTEREST

The author declared that there was no conflict of interest in publishing this article.

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ETHICAL APPROVAL

None.

AUTHOR CONTRIBUTION

All authors were in charge of data collection, supervision, and writing the original draft. The final version of the manuscript was reviewed by all authors.

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