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Immunological Investigations
A Journal of Molecular and Cellular Immunology

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/iimm20

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To cite this article: Kheir Eddine Kerboua (2020): NLR: A Cost-effective Nomogram to Guide Therapeutic Interventions in COVID-19, Immunological Investigations, DOI: 10.1080/08820139.2020.1773850

To link to this article: https://doi.org/10.1080/08820139.2020.1773850

IMMUNOLOGICAL INVESTIGATIONS
https://doi.org/10.1080/08820139.2020.1773850

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NLR: A Cost-effective Nomogram to Guide Therapeutic Interventions in COVID-19

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ABSTRACT

COVID-19 exhibits a non-yet elucidated heterogeneity dominated by mild form of the illness. Nevertheless, mortality is frequent among patients with a delayed innate immune response that suddenly exacerbates during the second week after admission leading to a lethal over inflammation. Therefore, this rapid and unpredictable deterioration requires timely prediction of COVID-19 refractoriness and critical illness. The two biomarkers readily available in routine laboratories, blood lymphocytes and neutrophil counts, are expected to provide an accurate clinical tool to incline reasonable medication and care because lymphopenia marks immune exhaustion while neutrophilia demonstrates the immunological exuberation. Meanwhile, combining the two parameters as a Neutrophil-to-lymphocyte ratio (NLR) helps to constitute a powerful predictive and prognostic nomogram. This scoring tool allows clinicians to stratify COVID-19 severities on admission and guide early interventions to accelerate recovery and shorten the course of disease in order to alleviate the shortage of medical resources and reduce mortality.

KEYWORDS

SARS-CoV-2; Covid-19; refractory patients; nomogram; neutrophil-to-lymphocyte ratio; risk stratification

Introduction

The distinct clade from the ß-coronavirus, SARS-CoV-2 is the third fatal coronavirus among the seven that we're able to break from bats to humans but with more respiratory tropism compared with SARS-CoV and MERS-CoV. It causes COVID-19 that is erupting worldwide dramatically and intensified by the human-to-human transmission and yet unavailable specific therapeutic agents or vaccines (Cascella et al. 2020). Since the outbreak in Wuhan, COVID-19 patients are showing a wide clinical heterogeneity with 5% to 20% of positive patients developing the severe form of COVID-19 and received intensive care because of cardiac, renal or respiratory distress injuries (Bansal 2020). This situation highlights the need to identify refractoriness in order to prioritize patients and focus more on patients with bad prognosis by anticipating hyperinflammation. The ultra-rapid course of the second week from the onset of symptoms necessitates to identify, on admission, the factors that may affect COVID-19 progression and determine patients at risk of poor clinical outcome. The question that emerged was how laboratory medicine could efficiently contribute to manage the care of patients with suspected or confirmed SARS-CoV-2 infection. Obviously, accurate individualized assessment by using circulating biomarkers resulting from systematic inflammatory response might help in attributor appropriate

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supportive care and reducing unnecessary or inappropriate health-care utilization. Interestingly, peripheral white blood cell (WBC) subsets counts are the potential candidates to follow the inflammatory dynamics of COVID-19 allowing close surveillance for those who would have a worse prognosis (Yang et al. 2020).

Pathophysiology kinetics of COVID-19

Growing evidence supports that the pathogenetic kinetics of COVID-19 is probably following two phases with two opposite immune reactions indicating an immune response imbalance during the course of this disease. The longitudinal analyses of Jing Liu et al. (2020a) along 16 days from the admission revealed that the severe group has a sustained increase in neutrophil count while lymphocyte count follows two-step dynamics; T cells show a constant decrease during the first week but gradually increase during the second week to reach a comparable level to that of the mild patients. Therefore, the determination of the patient's immunological phase is essential to decide when to use of immunosuppressant drugs, antagonists of cytokines or blockers of the complement system because immunosuppression during the first phase of the disease might result in aggravated illness through a delayed viral clearance (Chen et al. 2020a; Liu et al. 2020a).

Earlier after the infection, SARS-CoV-2 promotes its viral survival via mitigating type I IFN and hampering T lymphocytes (Li et al. 2020). Even in the cases where neutrophil counts cannot reveal an obvious difference between severe COVID-19 patients and mild cases, longitudinal studies highlighted that the degree of lymphopenia correlates with the intensity of proinflammatory cytokine storm and disease severity (Liu et al. 2020a; Song et al. 2020). Although lymphocyte subsets were shown to be decreased when the levels of interleukin-6 (IL-6) and IL-10 increased in severe cases, significant positive correlations were found in the mild group suggesting that IL-6 and IL-10 can be used to predict immune function imbalance and the transition from mild to severe form of the disease (Liu et al. 2020a; Wan et al. 2020). It was worth noting that the slow or meager response to the virus at the onset is a common feature of the patients who will have a severe disease (Mo et al. 2020). Any immunosuppression at this stage could be detrimental but antiviral strategies that target the virus or enhance antiviral immunity are highly warranted. Lymphopenia was shown in all the COVID-19 cohorts published so far with varying frequencies (63% (Huang et al. 2020), 80.0% (Zhou et al. 2020a), 82.1% (Guan et al. 2020)) but it was not so frequent in children patients (Chang et al. 2020; Qiu et al. 2020). Noteworthily that this lymphopenia was more observed in severe patients at the onset of the disease compared to mild patients 84.6% *versus* 44.4% (Liu et al. 2020a). Its levels are around 0.8×10^9/L in severe cases compared to non-severe cases (1.0×10^9/L) (Qin et al. 2020) and can get reduced to less than 5% within 2 weeks after disease onset (Tan et al. 2020). This lymphocyte deficiency might be caused by a direct effect of the virus, pro-inflammatory cytokines IL6, exosomes from inflammatory tissues or elevated blood lactic acid levels (Fischer et al. 2007; Liao et al. 2002; Shenoy et al. 2020; Xu et al. 2020).

The second phase of the disease is arguably dominated by the immune pathology, mainly the cytokine release syndrome (CRS), which may lead to shock, tissue damage, coagulopathy, respiratory failure and multiple organ failure (Cao 2020). Alarmingly, this late inflammatory state is associated with the persistence of lymphopenia contrasted by neutrophilia and elevated levels of CRP and coagulation parameters (Tang et al. 2020).

Furthermore, acute respiratory distress syndrome (ARDS) and organ injury during CoVs infections correlate with the extensive lung's infiltration of neutrophils and increased neutrophil counts in the peripheral blood of refractory patients (Channappanavar and Perlman 2017; Mo et al. 2020). Even in the absence of bacterial co-infection, the magnitude of increase in neutrophils counts observed during this immunopathological phase still reflects the inflammatory responses intensity (Liu et al. 2020b; Chang et al. 2020; Zhou et al. 2020b). Indeed, IL-8 and IL-17 are potent cytokine for neutrophil chemotaxis and may be potential targets for immunotherapy of COVID-19 (Crispim et al. 2020). Conforming to this fact, identifying the subgroup of patients with ongoing inflammation allows to focus the medical intervention on the inflammation rather than the viral replication. On admission, the absolute counts of neutrophils were shown to be significantly higher in the peripheral blood of the severe patients than those of the mild patients. The kinetic analyses of neutrophil changes in COVID-19 from the disease onset to at least 2 weeks later emphasize significant increases in the severe group compared to the mild group (Liu et al. 2020b). While COVID-19 non-survivors began to have an increase in their neutrophils counts beyond $6x10^9$/L from the 7th day of admission (Wang et al. 2020), the range observed in severe disease spans an interval from 4.3×10^9/L up to$10.\ 6 \times 10^9$/L (4.3×10^9/L (Qin et al. 2020); 7.1×10^9/L (Chen et al. 2020b); 10.6×10^9/L. (Huang et al. 2020). Hence, prolonged inflammation is behind the lethality of coronavirus and could help explain the escalated risk of the correlation between comorbidities and COVID-19 severity. Besides, it has been reported that rapid progression was more likely to occur in elders with comorbidities (Qin et al. 2020); it seems to be due to constitutive low-grade inflammation and not to weaker immune functions since corona fatality is higher among patients with inflammatory conditions.

NLR to determine the pathophysiologic phase of COVID-19

The likelihood of severe COVID-19 is more striking with higher levels of inflammation on admission (Yuan et al. 2020). At present; the screening panel for hyperinflammation includes mainly a bunch of inflammatory markers like elevated levels of D-Dimers, ferritinemia and serum IL-6 that could suffer from frequent shortage in many laboratories unlike the routine complete blood count (CBC) test. Clearly, the majority of early warning models for predicting the severity of the disease and adverse outcome are based on the three cells measured by CBC test, namely platelets, neutrophils and lymphocytes. The usual CBC interpretation, stating that neutrophilia is more likely to be associated with bacterial infections whereas the viral infections induce mainly increases in lymphocyte counts, could lead to misinterpretation in coronaviruses infections, certain autoimmune diseases such as polymyositis and dermatomyostis and other inflammatory diseases like acute coronary syndrome, ischemic stroke and cerebral hemorrhage (Zhu 2004; Liu et al. 2020b; Tamhane et al. 2008; Celikbilek et al. 2014; Lattanzi et al. 2019). Obviously, neutrophilia in parallel to lymphopenia is characterizing COVID-19 (Liu et al. 2020b; Wang et al. 2020). In this way, Li Tan et al. (2020) have developed a time-lymphocyte model to predict COVID-19 progression as patients with lym%>20% are in recovery while patients with lym% <5% need intensive care. But considering this indicator independently of the innate exuberation to guide immunosuppression seems to be unwise. During the first fortnight of February of 2020, Liu J. and his collaborators (2020b) proposed through

a prospective single-center study the nomogram « Neutrophil-to-lymphocyte ratio » (NLR), quickly calculated from a routine laboratory test by dividing the absolute neutrophil count by the lymphocyte count on admission, taken in million per liter, for an effective screening for COVID-19 patients with severe form and to predict outcomes and guide access to intensive care unit. Almost all published studies show that NLR tends to be higher in severe cases of COVID-19 that are likely to have higher neutrophil count contrasted by lower lymphocyte count in comparison to nonsevere group (Qin et al. 2020; Zhang et al. 2020). Often, optimum cut-off values to distinguish high NLR (NLR^{hi}) from low NLR (NLR^{lo}) are of particular concern because laboratory reference value still yet no unified and receiving operator curve (ROC) analyses are needed for the calculation. Despite the cut-off value that could lead to high false-positive rates, it still acceptable in the setting of COVID-19 in order to minimize risks of missed diagnosis. The proposed cut-off spectrum went from 3 to 6 (3.04 (Zhang et al. 2020); 3.13 (Liu et al. 2020b); 3.3 (Yang et al. 2020); 5.0 (Liu et al. 2020d); 5.5 (Qin et al. 2020) to 5.87 (Song et al. 2020)). Hence, combining age greater than 49.5 or 50 years old with NLR^{hi} generates four different strata and leads to improved prediction and, thereby closely attending patients at risk of severe form (Yang et al. 2020; Song et al. 2020, Liu et al. 2020d). Meanwhile, it predicts transform into severe cases in less than a week, while those did not meet the both criteria of age>50 and NLR^{hi} would be discharged at approximately 13.5 days. Furthermore, based on the data from three centers, Yuan et al. (2020) have developed a nomogram with higher AUC than the Liu's one (0.914/0.856 vs 0.849). This difference is thought to be linked to the including of increased LDH and C-reactive protein (CRP) since CRP was significantly associated with refractory patients (Liu et al. 2020c). Inflammation-related biomarkers like CRP and the baseline IL-6 have a moderate to high correlation with NLR and are significantly associated with hospitalization days and unfavorable aspects of COVID-19 pneumonia (Quartuccio et al. 2020; Zhu et al. 2020; Terpos et al. 2020; Gong et al. 2020; Ye et al. 2020).

On the other hand, to improve outcome predictions in COVID-19, further CBC-based models were addressed, ordered according to their clinical relevance into lymphocyte-to-CRP ratio, platelet-to-lymphocyte ratio and derived NLR ratio (d-NLR, the denominator is WBC count minus neutrophil count) (Lagunas-Rangel 2020). But, NLR was shown to exhibit the highest specificity and sensitivity for illness severity compared to either lymphocyte-to-monocyte (MON), platelet-to-lymphocyte ratio (PLR) or CRP (Yang et al. 2020). Additionally, a longitudinal study of Jing Liu and colleagues (2020) has established no significant differences in monocyte counts between the severe and non-severe groups during the 2 weeks after the disease. Also, other researchers had included NLR in a more complex multiparameter diagnostic model to strengthen early warning score (COVID-19 EWS) or by using only CD8 + T cells subset in the neutrophil-to-CD8 + T cell ratio (N8 R) (Liu et al. 2020d; Song et al. 2020). Definitely, a meta-analysis including 828 patients, conducted to investigate the predictive values of NLR in patients with COVID-19, has shown that NLR increases significantly in severely ill patients (SMD = 2.404, 95% CI = 0.98–3.82) (Lagunas-Rangel 2020). Moreover, Liu et al. (2020d) have shown that NLR could be an independent predictor of mortality. After converting NLR to a categorical variable of tertiles, they have shown that the risk of in-hospital mortality is higher by 8% for each unit increase in NLR (Liu et al. 2020d). This risk is independent of other predictors of in-hospital death such as older age, high level of D-dimer and comorbidities.

Guide the therapeutic intervention by NLR

Indeed, the two phase-based kenetics of COVID-19 allow to interfere with immunological dynamics only during the latest immunopathology phase and not in the early immunocompromized stage to anticipate transfer to intensive care unit and prevent in-hospital death. Analyses of data summarized above show that COVID-19 patients can be grouped according to their different inflammatory kinetics. Indeed, mild patients can be identified by the normal or slight changes of cells counts during the course of the disease in comparison with the severe form characterized by substantial cell count changes and rapid clinical deterioration. Obviously, the pathophysiology of severe COVID-19 is summarized in imbalanced inflammation and antiviral immunity and that COVID-19 might damage lymphocytes in parallel to exuberation of immunologic storm during the immunopathologic phase of the disease. Importantly, it was speculated that the course of T cells in patients with a favorable outcome reached its decrease peak within the first week and then gradually recover to a comparable level of the mild disease in the third week to modulate cytokines production (Liu et al. 2020b). However, refractory COVID-19 patients showed an obvious difference (Mo et al. 2020). Thus, pointing out the immune imbalance of patients on admission would be pivotal to distinguish patient with a severely impaired immune response from those with intense inflammatory response to decide when to dampen the inflammatory process before the onset of respiratory failure or to reinforce antiviral immunity.

Besides, knowing that during the severe phase neutrophil tends to rise contrasted by the lymphocyte count falling, surveillance of NLR is helpful for both the early screening of critical illness of COVID-19 and providing timely therapeutic intervention (Liu et al. 2020b; Qin et al. 2020). Additionally, the loss of T cells in the severe illness may aggravate the magnitude of cytokine storm that reaches their peaks when T cell counts drop to their lowest levels. Nonetheless, the reversibility of T cell kinetics correlates with the cytokine levels reversibility in peripheral blood (Liu et al. 2020a). In the absence of immune-modulating T cell therapy, it is meaningful to alleviate this overinflammation by dampening proinflammatory cytokines when reliable markers are available to indicate the timepoint for the therapeutic intervention. NLR can also be used to assess immunosuppression treatment like methylprednisolone and cell normalization in patients who have recovered or are recovering (Chen et al. 2020b; Liu et al. 2020b; Zheng et al. 2020).

Patients with NLR^{hi} have more chance of being developing immunologic storm. So far researches of COVID-19 are focused on whether the NLR can serve as a valuable indicator to help in the decision to target the immune system. Weak NLR shows a considerable lymphocyte count which is rather good prognosis but an elevated NLR is a reflection of lymphocytes depression in parallel to an exaggeration of innate immunity and predicted poor outcome. Several evidences are pointing that T cells are more affected by SARS-CoV-2, and tend to be more hampered in severe cases (Qin et al. 2020). For instance, a patient with NLR^{lo} has a good prognosis and cannot be a candidate for treatment with Tocilizumab or Eculizumab because cytokine blockade contributes to further T lymphocyte damage that causes patients to deteriorate (Liu et al. 2017). Also, based on the tow phase-based model, non-refractory patients have been shown to have proinflammatory cytokines reaching their peaks at the end of the first week after the disease onset and IL-6 levels start natural reductions at the day 16 (Liu et al. 2020a). In severe cases, knowing that ARDS results from inflammation and microvascular thrombosis that is propagated by deregulated

Neutrophil-Extracellular-Traps (NETs), Yu Zuo et al. speculated that antagonizing IL-6 trans-signaling could be effective indirect strategies for targeting neutrophils in severe COVID-19 (Zuo et al. 2020). On the other hand, increasing neutrophil could indicate bacterial co-infection and can early warn the administration of antibiotics. Many studies have generated data compatible with the current inexpensive and easy-to-use predictor index. Furthermore, to select patients for plasmatherapy, Zhang et al. (2020) proposed to combine NLR^{hi} with anti-SARS-CoV-2 IgG to predict secondary antibody-mediated organ damage that is associated with mechanical ventilation in a percentage exceeding 40%. This retrospective investigation has also shown that NLR^{hi} patients had higher TH1 cytokines levels such as IL6 and TNF-a (72.3%) and they appeared to be difficult to recover because mortality occurs regardless of their neutralizing IgG levels (Zhang et al. 2020). In alignment with the evidence of NLR-age model, four strata could be generated based on the description of thresholds that defines them. At a time where intensive resources available for severe cases are scarce, this risk stratification makes it possible to better manage medical resources and to focus monitoring on the fourth stratum with NLR^{hi} and age >50 yrs old (age ^{hi}) while NLR^{lo}/age^{lo} could be treated in a community hospital or even home isolation. Patients belonging to strata NLR^{hi}/Age^{lo} are at low risk of bad prognosis in contrast to those with NLR^{lo}/age^{hi} who are at moderate risk and necessitate respiratory monitoring and supportive care (Liu et al. 2020d).

Concluding remarks

The extent of the variability in inducing inflammatory reactions in COVID-19 is not yet elucidated but it is largely accepted that it is likely due to the degree of the immune disturbance governed by epigenomic signature and microbiota dysbiosis. As the main battlefield on the first stage, indicators of COVID-19 outcome are unmet need to distinguish severe from non-severe patients. However, the practice has shown that detection of patients prone to severe form of COVID-19 remains problematic and implementing early risk stratification management will enable better management via alleviating the shortage of intensive medical resources and thus significantly reduce mortality rates. Widely used as a prognosis marker of bacterial infections and tumors, NLR has reignited more interest in the COVID-19 pneumonia management process. Consistent with the recent reports, the hypothesis that elevated NLR could be an independent prognostic biomarker in COVID-19 is gaining interest among scholars. Although it includes easy-to-get laboratory parameters, one caveat is still challenging that consists in determining the applicable thresholds that had the highest of sensitivity and specificity and the largest of AUC on the ROC curve. The cumulative data reviewed and analyzed in this paper prompt large diffusion of this considerable nomogram for early warning and further optimization of its performance via re-evaluation in additional multi-center and multi-ethnic studies.

Acknowledgments

I am very thankful to Prof. Bachir Kerboua and my student Maroua Benzouada for their constructive comments on improving the language, grammar, and readability of this paper.

Disclosure statement

The author declares that he has no conflict of interest.

Funding

This work was supported by the General Directorate of Research and Technology Development, Ministry of Higher Education and Scientific Research of Algeria.

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