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Research Article

The Performance Potentials of Monocyte Versus Neutrophil to Lymphocyte Ratios For Prgnosticating the Covid-19 Infected Critically Ill Mal-Nourished Patients Who are on Corticosteroides

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Abstract: The coronavirus spread rapidly throughout the country and around the world, novel coronavirus was later identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The whole world is racing to find a vaccine or a drug or repurpose already existed drugs to stop the spread of it. Almost all the health care sectors are focusing on treating the symptoms and decrease mortality. Although many repurposed drugs have succeeded to alleviate symptoms and decrease the infection burden. Inhibition of excessive inflammatory response may be an adjunct for treating COVID-19, so in some countries, addition an adjuvant corticosteroid therapy to standard antiviral treatment. Literature does not currently provide convulsive evidence for or against the use of corticosteroids in the treatment of COVID-19 patients. Typically, Corticosteroids are used to treat severe acute respiratory infections of viral etiology because of their anti-inflammatory effect. Nevertheless, when use corticosteroid, the neutrophil count is increased, other lymphocyte/leucocytes subsets are decreased. So, the monocyte -to- lymphocyte ratio (MLR) take same direction in decreasing whereas neutrophil-to-lymphocyte ratio (NLR) abnormally increased which leads to predict a worse prognosis and wrong intervention. A need to monitor the prognosis of the disease using a specific marker is feasible economic wise and health wise, as seeing the prognosis of COVID-19 give us the ability to take an action in managing the upcoming issues and precede the virus one step ahead. So, in this review article, we will discuss all available evidences regarding the prognostication performances of MLR and NLR in discrimination bacterial from viral infections, clinical infectious from clinical non-infectious cases, and COVID-19 from other viral infections. Also, in this review article, we will focus on the Corticosteroid and Mal-Nutrition-Associated Overestimation impacts on the performance potentials of MLR vs NLR for prognosticating the COVID-19 infected critically ill patients.

Keywords: COVID19, Corticosteroids; Critically ill patients; Economic and clinical impacts; Monocyte to Lymphocyte ratios; Malnutrition; Neutrophil to Lymphocyte ratios; Prognosticators.

INTRODUCTION

The pandemic COVID-19 originated from Wuhan, China. Fever is often the major and initial symptom of COVID-19, which can be accompanied by no symptom or other symptoms such as dry cough, shortness of breath, muscle ache, dizziness, headache, sore throat, rhinorrhea, chest pain, diarrhea, nausea, and vomiting. Some patients experienced dyspnea and/or hypoxemia one week after the onset of the disease. In severe cases, patients quickly progressed to develop acute respiratory syndrome, septic shock, metabolic acidosis, and coagulopathy (Yi, Y. *et al.*, 2020). COVID-19 has a huge attention due to its novel pathogenesis and its reputation of being a fatal virus, SARS-COV-2 have upgraded itself due to the special feature that Corona viruses have as they have several highly active RNA processes that aren't found in any other RNA viruses (Thiel *et al.*, 2003). The pathogenesis of SARS-COV-2 is distinctive due to long

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incubation period that ranges from 2-14 days and the inclusion of not only the respiratory system, but also other many systems in the body. There are many theories that explain the involvement of various systems in the body, the first one is the "cytokine storm hyper-inflammatory" and the second is the "radical storm hyper-oxidative". Both of these theories show a clear evidence of the immune system participation and its role and function in either eradicating the virus or exacerbating the disease status. The immune system participates with its both innate and adaptive responses. (Prompetchara, Ketloy, & Palaga, n.d.)

As for the laboratory findings, severe cases tend to have lower lymphocytes counts, higher leukocytes counts and neutrophil-lymphocyte-ratio (NLR), as well as higher monocytes (Sun, S.*et al*., 2020). NLR has taken both the levels of neutrophils and lymphocytes into account, and been proposed as a new biomarker for systemic inflammation. The high NLR results from increased neutrophil count and decreased lymphocyte count. The inflammatory response could stimulate the production of neutrophils and speed up the apoptosis of lymphocytes (Liu *et al*., 2020). Generally, higher values of NLR indicate larger probabilities for bacterial infection and low probabilities for viral infection (Are, N. *et al*., 2017). Since the monocyte will differentiate to macrophages then phagocytosis happens to get rid the free iron because the patient is under hyper oxidative stress status. High neutrophil to lymphocyte ratio (NLR) can be considered independent biomarkers for indicating poor clinical outcome as NLR specificity (63.6%) and sensitivity (88%) (Ai-Ping, Y. *et al*., 2020). **MLR** decline would constitute a more adequate clinical biomarker to monitor the evolution of COVID-19 infection and its prognosis with respect to other less specific parameters, such as NLR and PLR value (Pets, 2020). Also the monocyte: lymphocyte ratio (MLR) has been used in some studies to identify patients at risk for influenza, malaria and tuberculosis (Naess *et al*., 2017). So, coronavirus 2 is contrary to what virus NLR ratio usually is. In this review we will discuss **(MLR)** has been a more accurate prognostic biomarker than (NLR) including **(COVID 19) infected critically ill malnourished patient who are on corticosteroid.**

DISCUSSION

Many cellular components and acellular components are involved in the pathogenesis of COVID-19. Three main immune system elements that play versatile roles in SARS-COV-2. First; the monocytes become macrophages when they migrate to tissues to perform their job. Macrophage serve in different ways, they represent the antigen and release different cytokines that contribute in pro-inflammatory status and activate T-cells, they perform their job by engulfing pathogens like bacteria, debris and apoptotic cells, that explains the seen leukocytosis in bacterial infections. However leukocytosis is seen in COVID-19 due to RBCs rupture and release of free iron, so macrophages number would multiple to phagocyte free iron in a process called erythrophagocytosis. It is noteworthy that macrophages overwhelm would cause severe destruction ("Macrophages - an overview | ScienceDirect Topics," n.d.), (Guilliams *et al*., 2014). The second involved immune-component in SARS-COV-2 pathogenesis is neutrophils, their role in respiratory viral infections aren't well known although they are present and contribute in ARDS and lung injury. Many respiratory viral infections as influenza A virus have shown increased amount of neutrophil and its correlation with disease severity, neutrophils function via increasing the release of chemo-attractants and complement C5. In addition, hantavirus infections (causing Hantavirus pulmonary syndrome), Severe acute respiratory syndrome-related coronavirus (SARS-Cov) have all shown increased infiltration of neutrophils in the lung leading to a fatal ARDs (Camp & Jonsson, 2017). Third important component to be discussed is lymphocytes. It is well known that the amount of lymphocytes increase during viral infection and decrease during bacterial ones, as T-Lymphocytes exhibit their functions via cell-mediated response against virally infected cells with the help of B-lymphocytes that produce antibodies, and they mediate the production of interferons that aid in viral eradication (Denman, n.d.). While the scenario is inverted in SARS-COV-2 as we see an increase in leukocytes and a decrease in lymphocytes despite the presence of a viral infection, which will lead to over-prescription of antibiotics that will lead to major issues specially in critically ill patients, as they will suffer from antibiotic resistance and they might be infected with multi-drug resistant bacteria above SARS-COV-2 and that will lead to mortality and morbidity if they survive.(Llor & Bjerrum, 2014).

As critically ill hospitalized patients need ultimate care and continuous follow up to assess their condition that might change in any second, the follow up procedure costs a lot of money and requires long time to come up, although time factor isn't in the favor of critically ill patients specifically SARS-COV-2 patients. Therefore we are looking for a prognostic tool that is easy, less painful, cost-effective and time saving, and the best thing that achieve all these conditions is laboratory blood test. In order to assess severity and prognosis of hospital resident COVID-19 patients we need to see the ratio of either neutrophil: lymphocytes or monocytes: lymphocytes. To decide if we are going to use neutrophil: lymphocytes (NLR) or monocytes: lymphocyte (MLR), we need to set a fair comparison between these ratios and take into consideration the concomitant given drugs that might affect any components, and the patients' wasting severity degree that might lead to misleading results. First both MLR and NLR are economically feasible, both are correlated in a proportional manner with the duration of illness and both are elevated in bacterial infections according

to a clinical study that recruited 299 patients as the study has statistically shown the increase of both ratio with the prolonged disease status, a significant increase of the ratios with age increase but no difference between both genders, and both are widely available in many health care centers and require no specific equipment unlike other markers as TNF alpha, procalcitonin and IL-6. Another study included 1468 patients has concluded that the use of MLR or NLR provide better predictions and high specificity than CRP or WBCs alone in estimating septicemia in critically ill patients (Naess, Nilssen, Mo, Eide, & Sjursen, 2017),(Kusnadi, Liwang, Katu, Mubin, & Halim, 2018)

To justify the reason of selecting MLR over NLR is due to the use of corticosteroids (Cs) by COVID-19 critically infected patients and the reason behind the use of corticosteroids is the high risk of developing ARDS. Corticosteroids exert anti-inflammatory, immune-modulatory and anti-fibrotic activates. Many reports and cohort studies have demonstrated the evidence of CS in decreasing ARDS in the early stages, reduce lung injury score, organ dysfunctions and increase ventilator free days (Khilnani & Hadda, 2011). However, the use of CS has affected the ability of using NLR, thus the selection of MLR is fair and practical. Using systemic route to administer Cs as Beclomethasone, Budesonide, Dexamethasone, Fluticasone, Hydrocortisone, and Prednisolone have shown a dose-dependent inhibition of neutrophils apoptosis by which will lead to neutronphilia (Zhang, Moilanen, & Kankaanranta, 2001), while numbers of both monocytes and lymphocytes are decreased with Cs administration and peak observable effects are seen in 4-6 hours.("Immunosuppressive Therapies in Organ Transplantation," n.d.) as a result of the above mentioned reasons, we need to use a reliable biomarker with the presence of other drugs that manipulate the ratios, so the selection of MLR is due to their same directional movement, which will decrease the misleading results and minimize prescribing unneeded antibiotics.

CONCLUSION

In summary, there is an urgent necessity to find an affordable and available biomarker with good specificity to prognosticate SARS-COV-2 status in critically ill patients who are in a high risk of developing lethal complications as ARDS. Therefore our choice is MRL which needs no additional tools, only simple CBC tests then applying calculations to detect the ratio. Our aim is to unify the use of a biomarker which can be used in any healthcare system to minimize the transformation of critically ill patients to late irreversible stages. Hence a need to test the potentiality of this biomarker to serve our goals need conformations by conducting clinical trials.

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