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Research Article

The Clinical Usefulness of C-Reactive Proten and Ferritin Level to Albumin Ratios in Triaging, Stratifying, Diagnosing, Following, and Assessing Covid-19 Infected Hospitalized Patients

"Moh'd Nour" Mahmoud Bani Younes; Ph[1], Amani Daoud Alshawabkeh; PharmD[1], Zahra Amjad AL-Masalha ; PharmD[2] ,Eman Feras Awwad; PharmD[2] & Tariq Mohammad Al Tarabsheh; PharmD[1]

[1]Clinical Pharmacy Department, King Hussein Medical Hospital, Royal Medical Services, Amman, Jordan
[2]Clinical Pharmacy Department, The University of Jordan, Amman, Jordan

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Abstract: Coronavirus is now known as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the resulting disease is called coronavirus disease 2019 (COVID-19). The World Health Organization (WHO) declared the novel coronavirus outbreak a global pandemic in March 2020. Despite rigorous global containment and quarantine efforts, the incidence of COVID-19 continues to rise, with more than 2,973,347 laboratory-confirmed cases and over 206,018 deaths worldwide. Currently, no specific medication is recommended to treat COVID-19 patients. However, governments and pharmaceutical companies are struggling to quickly find an effective drug to defeat the coronavirus. In this review article we summarize the usefulness of C-reactive protein as positive phase protein and albumin as negative phase protein as investigator of mortality for COVID-19 patient. Relying on C-reactive protein level to albumin level ratio over either albumin or C-reactive protein alone. Ferritin level also may be good predictor for morbidity and mortality but it is affected by iron overload and existing stress condition in COVID-19 patient result in deviation in ferritin level to be higher than expected. Ratio of ferritin to albumin is useful in determining the mortality, risky, diagnostic, following, determination in many illnesses. In our article we will focus in the possibility of the clinical usefulness of C-reactive protein and ferritin level to albumin ratios in triaging, stratifying, diagnosis, following and assessing COVID-19 infected hospitalized patients.

Keywords: C-Reactive Protein to Albumin Ratio; Ferritin level to Albumin Ratio; Triaging and Stratifying; Diagnosing and Following; Assessing COVID-19 Infected Hospitalized Patients; Positive and Negative Acute Phase Reactant; SARS-CoV-2.

INTRODUCTION

Coronavirus (CoV) is a large family of positive-sense, single-stranded RNA viruses that belong to the Nidovirales order. The order includes Roniviridae, Arteriviridae, and Coronaviridae families (Fehr & Perlman, 2015). The Coronaviridae family is subdivided into Torovirinae and Coronavirinae subfamilies (Fehr & Perlman, 2015). Coronavirinae is further subclassified into alpha-, beta-, gamma-, and delta-COVs (Fehr & Perlman, 2015). Phylogenetic clustering accounts for the classification of these subtypes of viruses. Their viral RNA genome ranges from 26 to 32 kilobases in length (Lu *et al*., 2020). They can be isolated from different animal species. These include birds, livestock, and mammals such as camels, bats, masked palm civets, mice, dogs, and cats (Lu *et al*., 2020). The widespread distribution and infectivity of COV make it an important pathogen. Deep sequencing studies and lab investigations have identified the culprit as a new strain of COV (Chen *et al*., 2020). The repeated emergence and outbreaks of CoVs indicate a public health threat. This suggests the possibility of animal-to-human and human-to-human transmission of newly emerging CoVs. The ongoing changes in ecology and climate make future emergence of such infections more likely (Chen *et al*., 2020). Laboratory findings specific to COVID-19 include elevated prothrombin time, LDH (lactate dehydrogenase), D-dimer, ALT, C-reactive protein (CRP), and creatine kinase. In the early stages of the disease, a marked reduction in CD4 and CD8 lymphocytes can also be noted (Y. Wang *et al*., 2020). Patients in the intensive care unit have shown higher levels of interleukin (IL) 2, IL-7, IL-10, GCSF (granulocyte colony-stimulating factor), IP10 (interferon gamma-induced protein 10), MCP1 (monocyte chemotactic protein 1), MIP1A (macrophage inflammatory protein alpha), and TNF-α (tumor necrosis factor-α) (Huang *et al*., 2020). They also

***Corresponding Author:** "Moh'd Nour" Mahmoud Bani Younes Email: panasomycine@hotmail.com

displayed other abnormal findings indicative of coagulation activation, cellular immune deficiency, myocardial injury, renal injury, and hepatic injury (Y. Wang *et al*., 2020). In critical patients, amylase and D-dimer levels are significantly elevated (Huang *et al*., 2020). However, blood lymphocyte counts progressively decreased (Cascella *et al*., 2020). Common to non-survivors are the elevations in ferritin, neutrophil count, D-dimer, blood urea, and creatinine levels (D. Wang *et al*., 2020). Elevations in procalcitonin levels are not a feature of COVID-19. Therefore, an elevated level of procalcitonin may suggest an alternative diagnosis such as bacterial pneumonia. Levels of CRP correlate directly with disease severity and progression. Diagnoses gold standard is positive for the SARS-CoV-2 by the polymerase chain reaction PCR test for nucleic acid in respiratory or blood samples, or viral gene sequencing shows high homogeneity to the known SARS-CoV-2 in respiratory or blood samples. At present, the only way of infection confirmation is by nucleic acid testing but early testing of CRP and ferritin levels of symptomatic patients can be helpful in early treatment and isolation before diagnosis is confirmed.

Acute phase reactants are inflammatory markers and mediators that either increase or decrease in case of tissue damage or inflammatory state. If they increase, they are classified positive APR and if decrease then negative APR. Positive APR includes C reactive protein, erythrocyte sedimentation rate (ESR) and ferritin. Negative APR includes albumin, transferrin, and retinol binding protein. C-reactive protein, ferritin and albumin are visceral proteins mostly synthesized in the liver. Poor protein and energy intake, impaired liver synthetic function as well as inflammatory status result in low circulating levels of visceral proteins like albumin. They are used clinically to identify infections. There main function is to prevent spread of acute infection by activating the immune system and complement pathway. Positive APR are key components in the anti-infection host response. In this article we will discuss the clinical usefulness of C-reactive protein and ferritin level to albumin ration in triaging, stratifying, diagnosis, following and assessing COVID-19 infected hospitalized patients.

DISCUSSION

COVID-19 could attack the ß chain of hemoglobin (Hgb) releasing iron to the blood causing iron overload. This iron overload pose harmful effects on the body as iron is a strong oxidizing agent (Zhou *et al*., 2020). This in turn trigger compensatory protective mechanisms to reduce its toxicity. These compensatory mechanisms including but not excluded to increase in serum ferritin level, hyperproduction of new RBCs, and monocytosis. The rate of iron release exceeds the capacity of the protective mechanisms, exposing the body to iron toxicity that will stimulate monocytes in an excessive manner, increase C-reactive protein to albumin ratio (CRP: ALB), increase ferritin level which will place the body in severe stress condition. Cells react to stress due to inflammation, producing large amounts of serum ferritin to bind free iron ions to reduce damage. That was noticed after biochemical examination indexes of 99 patients with novel coronavirus pneumonia, and the report also reflected the abnormal phenomenon of hemoglobin-related biochemical indexes of patients (Liu *et al*., 2020). Ferritin is a major iron binding protein that exists in both intracellular and extracellular compartments in most living organisms. Ferritin subfamilies including the unbound, iron free form of apoferritin, the iron-bound form of holoferritin, and simply ferritin, are composed of 24 subunits comprised of ferritin H-chains and ferritin L-chains with a hollow spherical cage (W. Wang *et al*., 2010). Not only does serum ferritin act as a critical marker of iron storage and delivery (Fisher *et al*., 2007), recent studies have also demonstrated that elevated serum ferritin levels are indicative of pathological processes in immunosuppression (Fargion *et al*., 1991), angiogenesis (Coffman *et al*., 2009), and proliferation (Alkhateeb *et al*., 2013). Serum ferritin is a marker of morbidity and mortality in hemodialysis patients also (Kalantar-Zadeh *et al*., 2001).There is an association between severity of the disease and development of ARDS versus high C-RP and high ferritin was highly seen in COVID-19. We can rely on ferritin and C-RP mainly and low albumin to differentiate between severe cases and non- sever cases. In a retrospective study, in comparison between moderate and severe cases, sever cases had higher levels of C-RP, ferritin and D-dimer and lower levels of albumin according to patients laboratory baseline characteristics seen in Tongji Hospital, Wuhan.

Albumin is the most abundant protein in human serum. It has been used for decades as an indicator of malnutrition in patients in clinically stable conditions (review and meta-analysis) (S. *et al*., 2015). Serum albumin concentrations decrease with increasing age by approx. by 0.1 g/L per year; however, age itself is not a cause of distinct hypoalbuminemia. There is a clear relationship between serum albumin concentrations and all-cause mortality in elderly subjects (Corti, 1994). In patients with a hip fracture, albumin levels below 35 g/L were associated with higher rates of post-operative complications such as sepsis and higher overall mortality. Significant loss of muscle mass has been observed in elderly people with low albumin levels. Inflammatory states and in particular, high concentrations of the cytokines IL-6 and TNF-alpha, were two of the main factors causing low levels of serum albumin (S. *et al*., 2015). Systemic inflammation not only reduces albumin synthesis but increases its catabolic and promotes its transcapillary escaping rate (TCER). Acute exacerbation of the respiratory disease induced by COVID-19 can be early predicted using elevated CRP and ferritin to albumin ratio. In a similar scenario, influenza virus infection

higher CRP levels, corresponds to more severe symptoms and higher mortality risk and this conclusion can be extrapolated on coronavirus 2019 infection setting.

CRP and ESR inflammatory biomarkers correlates well with COVID-19 disease severity when evaluated using computed tomography CT and high CRP indicates lung complication and progression of injury. Thus can be used in severity evaluation whenever CT usage is limited. Even in early stages of the disease CRP is positively associated with higher lung damage and higher severity disease. Mentioning that CRP has higher sensitivity than ESR toward inflammatory status we can rely on CRP to determine and predict the severity of lung injury. A simple, quick, and accessible parameter is needed to confirm treatment response and predict mortality in ICU patients. C-reactive protein (CRP) is an acute-phase protein that is produced following stimulation by various cytokines in response to infection, ischemia, trauma, and other inflammatory conditions (Thijs & Hack, 1995). High CRP levels have been studied in relation to prognosis and mortality in critically ill patients (K.M. *et al*., 2008) (Ho *et al*., 2006) (Villacorta *et al*., 2007) (Ö. *et al*., 2012). On the other hand, low serum albumin is known to be associated with poor prognosis and mortality (Artero *et al*., 2010) (Goldwasser & Feldman, 1997). Based on this knowledge, we speculated that the ratio of CRP to albumin could be used as a predictive marker for mortality. Recently, the CRP/albumin ratio, a combination of markers for systemic inflammation and nutritional status, has been extensively studied as an independent prognostic marker in patients with infection, malignancy, and other diseases.(Kim *et al*., 2015) (Ranzani *et al*., 2013) (Mao *et al*., 2017) (Wei *et al*., 2015).

The most important strategy to decrease morbidity and mortality of the disease is early detection, early isolation, and early identification of severe cases. This must be done using any useful strategy including acute phase reactants measurements to defeat the pandemic. Early diagnosis of infections is a major challenge especially in emergent situation. Acute phase reactants are valuable in diagnosing bacterial and viral infection. CRP is the most sensitive marker for infection suspicion and ferritin to albumin ration can support the evidence, too. It is suggested in literature to use iron level and hemoglobin to differentiate between viral and bacterial infection referring to study conducted in 2019. A linear relationship between ferritin concentration and acute phase reactants is seen in inflammatory status but presence of additional factor affecting iron stores and ferritin this suggest a further increase in ferritin level and deviates from the linear increase of acute phase reactants. In iron dysregulated metabolism pathway as seen in COVID-19 serum ferritin level can be adjusted by measuring CRP and albumin. Moreover, CRP and ferritin both measurements helps in finding patients at higher risk for systematic inflammation induced organ failure and who have higher mortality risk. This can be extrapolated on COVID-19 patients who have a complication of sepsis and organ failure. For monitoring and follow-up chest X-ray is performed. High CRP, ferritin, D-dimer and low albumin all indicates poor prognosis. Close monitoring of platelet count and ferritin is recommended in severe disease and can predict progression to critical illness in COVID-19. Also, presence of hypercoagulability state and disseminated intravascular coagulation DIC is commonly seen in pneumatic and sever cases. Monitoring WBC count and ferritin helps in identification of potential progression to critical illness. Reduction in CRP and ferritin levels can indicate infection eradication and suppression of inflammatory status.

CONCLUSION

In COVID-19, high CRP, high ferritin, and low albumin can be considered as a tool for early recognition of severe cases. And we suggest usage of Ferritin: ALB Ratio as it is likely to be more prognosticative than using each parameter alone or the CRP: ALB Ratio in COVID-19 infected hospitalized patients. These clinical diagnostic ratios may be an effective, lower-cost bedside point of care modalities, realistic, reliable, and early discriminative prognosticators with reasonable sensitivities, specificities, performances, and accuracies. The CRP: ALB Ratio and Ferritin: ALB Ratio (Preferred and more selective than CRP: ALB in case of COVID-19 infection) may be used as an additional or more readily available red flag assessment tool for triaging, stratifying, diagnosing, following, and assessing COVID-19 and other viral or bacterial infections in near future. Further clinical research is needed to validate the proposed laboratory measurements.

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