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Review Article

Could homocysteine, angiotensin and alamandine be used as potential biomarkers in management of COVID-19?

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ABSTRACT

The corona virus is now known as the severe acute respiratory syndrome corona virus 2 (SARS-CoV-2). Risk predictors and novel predictors associated with COVID-19 is required to enable the risk stratification, guide interventional studies to target patients at enhanced risk of developing severe disease risk and optimize the allocation of limited human and technical resources in the ongoing pandemic all over the globe. The present review focused on potential laboratory biomarkers associated with COVID-19. We carried out an electronic search in Medline (PubMed central), Scopus, Web of Science and using the keywords laboratory, biomarkers, novel biomarkers, corona virus 2019 or COVID-19. We observed that limited data were found that related to homocysteine and angiotensin II in COVID-19 patients. Hence original research on these novel biomarkers which associated with the complication of COVID-19 might be given new clues especially that mediate anti-inflammatory and anti-fibrotic effects leading to cardiovascular, renal-protective actions. The present review proposed by the available literature, these predictors might be the potent biomarkers to improve management of corona virus. Further, large cohort studies will be required to support conclusions of present review.

Keywords: COVID-19, Homocysteine, Angiotensin, Alamandine

INTRODUCTION

WHO declared that in response to corona virus disease 2019 (COVID-19) pandemic serious situation, it a public health crisis of global concern on 30 January 2020 and called for mutual efforts of all countries in the globe to prevent the rapid spread of corona virus. In the present battle against COVID-19 situations, the emergency requirement is urgent detection of clinical and laboratory biomarkers of disease progression towards severe and fatal forms.[1,2] It was reported that the early biomarkers such as interleukin-6 (IL-6), D-dimers, C-reactive protein (CRP) and white cell count (WCC), lactate dehydrogenase (LDH), platelet count, cardiac troponin and renal markers in COVID-19.[3] In previous reports, reported that procalcitonin and platelet count as potential predictors of COVID-19 severity.[4,5] Previous studies from other countries (China, Singapore in 2020) reported that early biomarkers and their crucial role in patients with COVID-19. Although, biomarkers like homocysteine and angiotensin established in cardio-vascular disease risk in other diseased conditions. However, potential utility of these biomarkers in severity of COVID-19 and association with their complications not known.[6-15] Research is going on these current laboratory biomarkers of COVID-19 but yet Indian studies were not found related to novel laboratory biomarkers in patients with COVID-19. Hence the

present review initiative to guide further studies to target potential predictors of COVID-19 in who were at increased risk of developing severe illness due to complications and their utility for timely management of disease.

Material and methods

Search data extraction

The present study was searched an electronically in Medline (PubMed central), Scopus, Web of Science and using the keywords laboratory biomarkers, biomarkers, corona virus 2019 or COVID-19 between 2019 to till date (November 2020). The reference list of all recognized study articles was scrutinized with the aim of identifying additional potentially suitable studies.

DISCUSSION

In SARS- CoV-2, signs and symptoms may appear in the incubation period of two to fourteen days after exposure. Common signs and symptoms were fever, cough and tiredness. Other symptoms can include loss of taste or smell, shortness of breath, muscle aches, chills, sore throat, runny nose, headache, chest pain and conjunctivitis. Moreover, the severities of COVID-19 symptoms can extent from mild to severe. These subjective clinical symptoms can be interpreted more confidently with the use of laboratory biomarkers. These might be provided objective values throughout the progression of the COVID-19 disease.[2] In future, categorizing patients COVID-19 into mild, moderate and severe or critical ill subjects becomes more defined, allowing for earlier interventions.[3] Previous literature explores the significance of different laboratory biomarkers in the disease pathogenesis of COVID-19 and assesses how their levels vary depending on the severity of the disease. By doing these investigations so, which predominantly helps to clinicians to identify the group of patients and predict prognosis and mortality. Current huge research is going on laboratory biomarkers to identifying of COVID-19 in all over the globe. It was found that the CRP, IL-6, WCC, LDH, D-dimers, platelet count, cardiac troponin and renal markers as early biomarkers in COVID-19 and these biomarkers were incorporated as routine investigations in clinical set up for COVID-19 screening profile (Table 1).[2,3] In previous reports, reported that procalcitonin and platelet count as potential predictors of COVID-19 severity.[4,5] However, with greater than before volume of COVID-19 reports now available, it has enabled a more wide-ranging analysis of laboratory data that is urgently needed by the medical as well as scientific communities. The present review focused to enlighten the new path for ongoing research and discussed about laboratory potential biomarkers of COVID-19 positive patients, which might be useful to assess how their levels vary depending on the severity of the COVID-19 disease and complications.[4,5]

Homocysteine and COVID-19

Homocysteine (Hcy) discovered in 1932 and it was reported that high plasma levels of Hcy significantly increase the incidence of vascular damage in large and small vessels, increased levels above the 90th percentile are associated with increased risk of degenerative and cause the atherosclerotic mechanisms in the coronary, cerebral and peripheral circulatory systems.[6-9] Contradictory to the above, though Hcy is an effective cardiovascular disease (CVD) marker, however the cardiovascular complications are critical in hospitalized in patients with COVID-19, it has not been adopted and well-studied and published prospective studies focused on laboratory markers useful for clinical evaluation of COVID-19. Earlier research proposed that the definition of hyper homocysteinemia differs between studies.[10] This was defined as a medical condition characterized by an abnormally high level of Hcy in the blood (>15 µmol/l).[11] The total fasting Hcy levels in plasma of healthy individuals is low, between 5.0 and 15.0 µmol/l when measure with the use of high-performance liquid chromatography, but 5.0-12.0 µmol/l when immunoassay methods are used. When the level is between 16 and 30 µmol/l, it is classified as moderate, 31-100 µmol/l is considered as intermediate and a value >100 µmol/l is classified as severe hyperhomocysteinemia.[12,13] The previous research was found to have associations of hyperhomocysteinemia to cardiovascular disease, diabetes, CKD and fatty liver disease.[10,11,14] The study done by Ponti et al preliminary clinical observations in a COHORT of 40 patients suggested that routine determination of plasma Hcy as a potential marker for severe disease in SARS-CoV-2 patients. This laboratory test can be easily performed on blood EDTA samples at diagnosis.[15] Very recently Omer et al comment on an article: homocysteine as a potential predictor of cardiovascular risk in patients with COVID-19. They proposed that B-vitamins could medication of choice in the treatment when harmful hyperhomocysteinemia coexisting with COVID-19. Finally, they were encouraging other professionals on making future efforts, as well as investigations and discussions about this topic.[16] Very recent short communication published in dermatologic therapy journal explained that role of Hcy mediated trans-sulfuration pathway in COVID-19 infection. They proposed that vitamins (vitamin B6, folic acid and vitamin B12) should be merged in the treatment regimen for corona virus infections to suppress complications, as the virus mediates altered host cell metabolism. However, further interventional studies will be required to conclude the beneficial effects of vitamins association with Hcy mediated trans-sulfuration pathway in COVID-19 infection.[17]

Very recent data demonstrated a predictive value of Hcy (in addition with age, MLR and the period from onset of disease to hospital admission) for severe pneumonia on chest computer tomography at the first week from COVID-19 patients, but did not report on additional

organ involvement. They opined that MLR was significantly higher in imaging progression patients compared to imaging progression-free ones. Allocation preliminary observations on potential biomarkers for severe disease during a pandemic can lead to rapid enhancement of current knowledge and significant benefit for patients.[18]

Angiotensin-II

Angiotensin converting enzyme (ACE2) is a type-I transmembrane metallocarboxy peptidase with homology to ACE, functions as a regulator of the renin-angiotensin system (RAS), modulating endogenous levels of angiotensin (Ang) I and Ang II. Animal models were reported that Ang II levels were found to be significantly increased in the kidneys, hearts and plasma of ACE2 null mice.[14] The level of Ang II was also significantly increased in the avian influenza-A infected patients, indicating that Ang II is a biomarker for lethality in flu infections.[19,20] It was reported that a strong correlation has been found between increases in IL-6 and vascular macrophage accumulation and the degree of endothelial dysfunction produced by Ang II.[21] Animal study model reported that ACE2 and Ang-(1-7) infusion were shown to be protective via down regulation of RhoA/Rho kinase (ROCK) pathway. This ROCK pathway is deeply involved in changes of vascular tone and structure leading to hypertension and cardiovascular-renal remodeling, and it has a relevant role in the induction of lung fibrosis.[22]

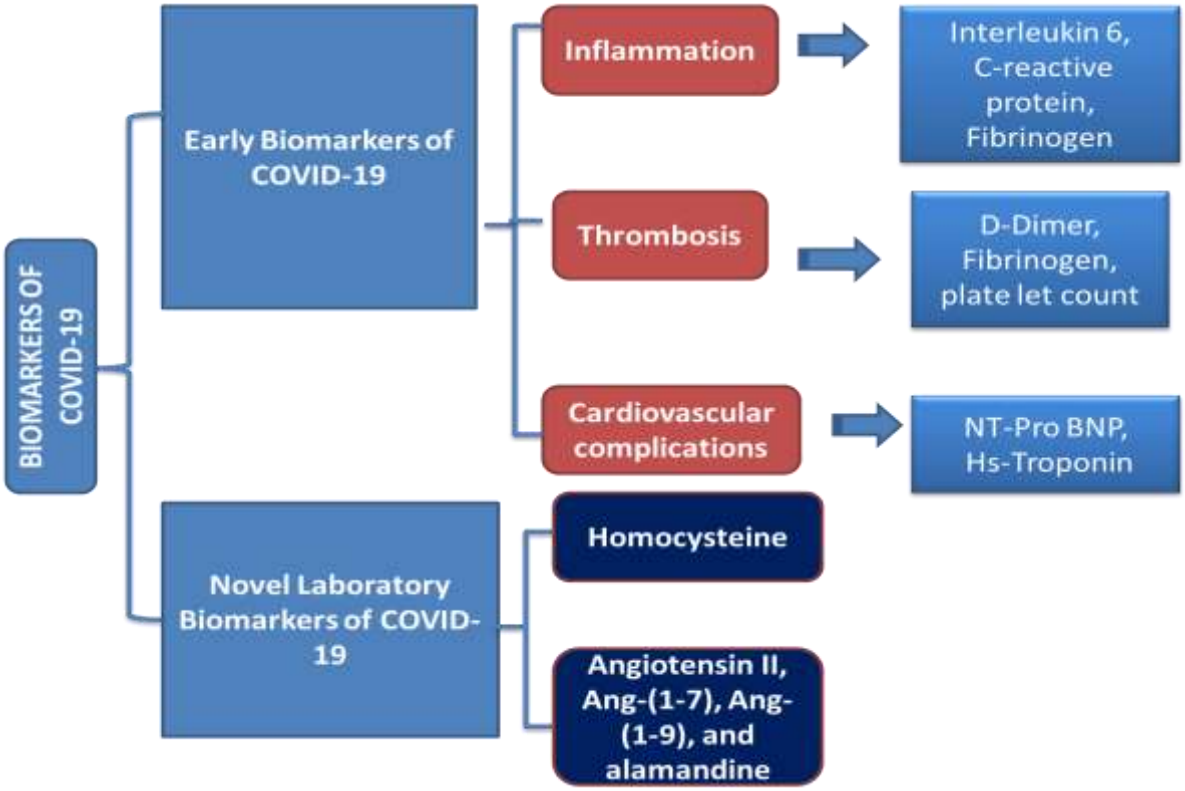

Figure 1: Blood biomarkers in patients with COVID-19.

Table 1: Changes in levels of predictors in patients with severe or fatal COVID-19.

Parameters	Changes in levels of laboratory biomarkers COVID-19
Hematologic biomarkers	Elevated: WBC count, neutrophil count, Decreased: lymphocyte count, platelet count, eosinophil count, hemoglobin
Biochemical biomarkers	Elevated: alanine aminotransferase, aspartate aminotransferase, total bilirubin, blood urea nitrogen, creatinine, creatine kinase, lactate dehydrogenase, myoglobin, creatine kinase-MB, cardiac troponin I Decreased: albumin
Coagulation biomarkers	Elevated: prothrombin time and D-dimer
Inflammatory biomarkers	Elevated: erythrocyte sedimentation rate, CRP, serum ferritin, PCT, IL-2R, IL-6, IL-8, IL-10

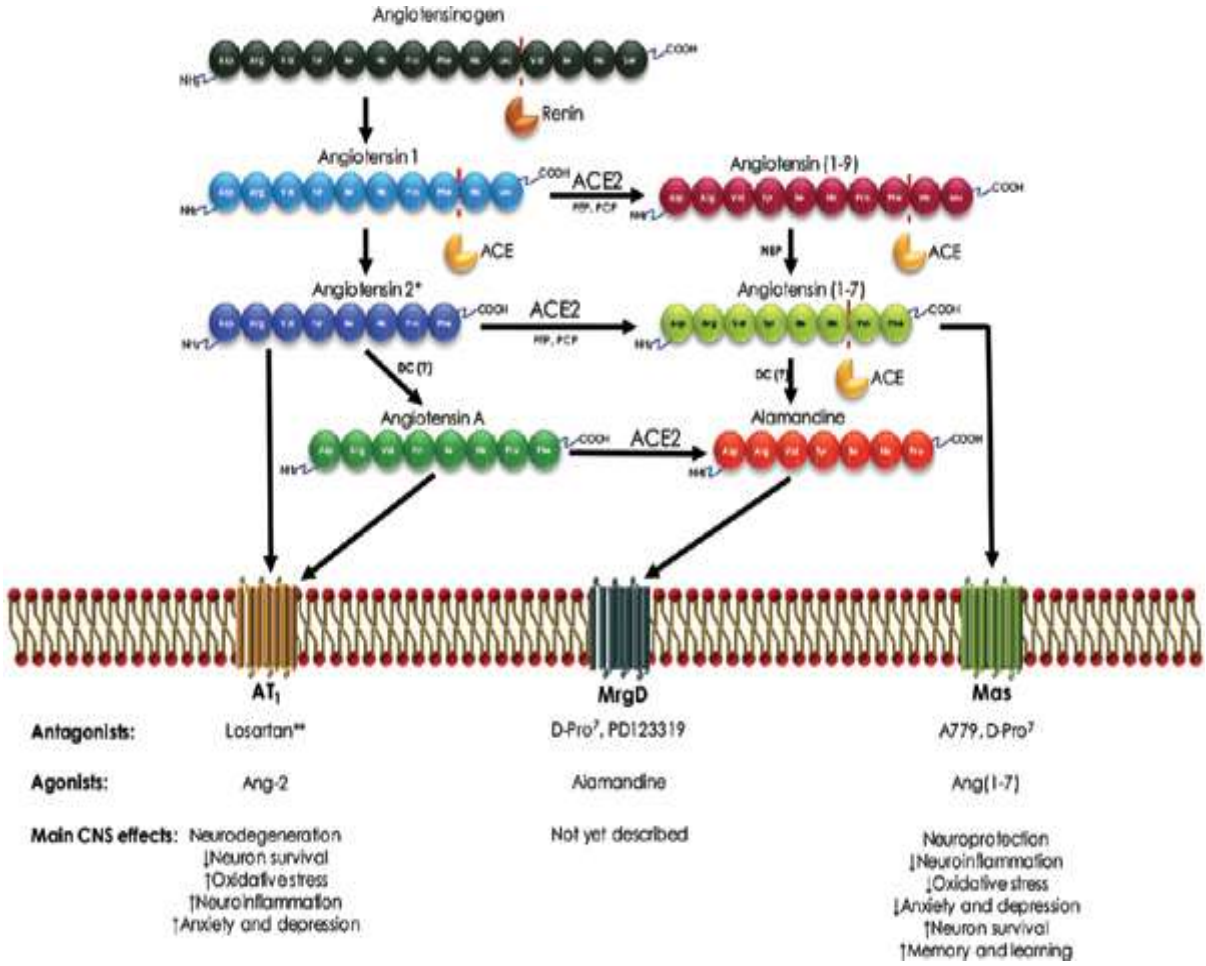

Figure 2: Molecular mechanisms of alamandine.

Angiotensin-(1-7), Angiotensin-(1-9)

ACE converts Ang II to Ang-(1-7) and Ang I to Ang (1-9). Ang-(1-7) and Ang-(1-9) produce biological effects through the mas receptor (MasR) and AT2 receptor (AT2R), respectively. The available literature showed that Ang-(1-7) induces regional and systemic vasodilation, diuresis and natriuresis. Ang-(1-9) increases nitric oxide (NO) bioavailability by stimulating bradykinin (BK) release.[23] Hence, activation of these pathways mediates anti-inflammatory and anti-fibrotic effects leading to cardiovascular, renal-protective actions, and acute lung injury protection.[24,25]

Molecular perspective of alamandine and COVID-19

Alamandine is produced by the action of ACE2 on Ang-A through a decarboxylation reaction on Ang-(1-7) in the N-terminal aspartate amino acid residue. Alamandine as like Ang-(1-7), which effect on vasodilation and antifibrosis.[26] It modulates peripheral and central blood pressure regulation and cardiovascular remodeling.[27] Philosophical theory information from related corona viruses suggests that SARS-CoV-2 infection may down regulate ACE2, that leads to fulminant myocarditis. The Ang II level in the plasma samples from SARS-CoV-2 infected patients was markedly higher and linearly associated with viral load and lung injury. Up to date, there are no data regarding Ang-(1-7), Ang-(1-9) and alamandine plasma levels in COVID-19 patients.[28] The present study suggested that there was an urge to conduct large cohort and interventional research to innovate novel biomarkers that associated with the pathways that mediate anti-inflammatory and anti-fibrotic effects leading to cardiovascular, renal-protective actions (Figure 2).

CONCLUSION

The present review proposed from the current available data that the following bio markers mainly the loss of ACE2 function, elevated level of Hcy, Ang-II and lower levels of Ang-(1-7), Ang-(1-9) and alamandine in severely infected patients with COVID-19 might be novel predictors to improve management of COVID-19 infection. Genomics and large COHORT interventional clinical trials will be required to conclude the present review opinions and the biomarkers association with

commodities of COVID-19 might be given clues for novel pathological mechanisms for pharmacological interventions.

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