Correlation of Comorbidity with Severity of COVID-19 Patient Based On Immunogenomic Phase: A Literature Review

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Abstract

COVID-19 is a disease with high mortality rates with various clinical severity (mild, severe, and critical) during three different immunogenomic phase (initial, propagating and complicating) based on one of the clinicogenomic mechanism, renin angiotensin aldosterone system. Patients with pre-existing comorbidity was reported with higher susceptibility, prevalency, and worsening outcomes such as acute respiratory distress syndrome. Individual immune system factors could contribute to susception, duration, severity and reinfection of the disease, hence why probing the comorbidities associated with COVID-19 is a comprehensive approach to reveal the biological phenomenone cuasing varying disease severity levels across COVID-19 patients. The desired goal of this literature review was to describe the correlation of comorbidity with severity of COVID-19 patient based on the three immunogenomic phases.

Keywords : COVID-19; SARS CoV-2; Comorbidity; Immunogenomic phase; Internal Medicine

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) that causes coronavirus disease (COVID-19) is a global pandemic in Indonesia with a high mortality rate that originated in Wuhan, China, and spread fast throughout the world. The COVID-19 epidemic was deemed a public health emergency of global concern by the World Health Organization. It has been established that the COVID-19 infection begins to develop 14 days after the crucial encounter. [1] The clinical severity and mortality rates of the infection could vary among the affected cases. COVID-19 patient is classified as three different clinical courses : mild (asymptomatic, mild pneumoniae), severe (present with dyspnea, hypoxia, or >50 percent lung involvement on the imaging within 24-48 hours), and critical (quite poor clinical course such as respiratory failure, shock, or multi organ dysfunction. [2] According to Turk et al. (2020), the renin-angiotensin-aldosterone system is one of the clinicogenomic mechanisms that has particular characteristics in relation to the COVID-19 infection's initial, propagating, and complicating phases. At the beginning of the infection, SARS CoV-2 displayed strong expression in the ACE2 and Aminopeptidase N (ANPEP) genes (12-24 hours). [3]

Several meta-analyses identified that individuals with pre-existing conditions such as type 2 diabetes melitus, hypertension and chronic kidney disease are more vulnerable to COVID-19 infection. Meta-analysis of the data extracted from the included studies suggested that diabetes and CAD/CVD were prevalent in 10% and 8% of the patients, respectively. [4] Hypertension was higher (3%) of chronic pulmonary disease. [5] Compared to patients without comorbidities, patients with comorbidities have greater negative outcomes. Patients with COVID-19 who have a history of hypertension, obesity, chronic obstructive pulmonary disease, diabetes, or cardiovascular disease have the worst prognosis and may experience worsening outcomes such

acute respiratory distress syndrome (ARDS) or pneumonia. [6] Comparative research across different coronaviruses indicates parallels in immunological pathogenesis, as well as entry and pathogenesis of SARS CoV-2, SARS, and MERS in numerous areas of multi-organ involvement and systematic vasculitis. Patients who required ICU care (n = 36) were significantly older (median age, 66 years [IQR, 57-78] vs 51 years [IQR, 37-62]; P .001) than patients who did not require ICU care (n = 102). They were also more likely to have underlying comorbidities, such as hypertension (21 [58.3%] vs 22 [21.6%], diabetes (8 [22.2%] vs 6 [5. [8] Patients with COVID-19 may take longer to heal depending on their immunity. [9] The individual immune system factors include genetics (HLA genes), age, gender, nutritional status, neuroendocrine immune regulation, and physical status contribute to susception of viral infection, duration, severity of the disease, and the reinfection. [10] Probing the comorbidities associated with SARS CoV-2 infection is a comprehensive approach to reveal the biological phenomenon causing varying disease severity levels across COVID-19 patients. [5]

1. Methodology

The primary databases utilized to retrieve the salient medical literature presented in this review were PubMed, ScienceDirect and Google Scholar. The following search term were used both separately and in combination included : “COVID-19”, “Coronavirus”, “SARS CoV-2”, “Comorbidity”, “Severity”, “Predictor”, “Prognostic”, “Immunogenomic”, “Immunity”, and “Outcome”. These were articles in English.

2. Immunogenomic Phase

Initial phase includes asymptomatic or pre-symptomatic disease of COVID-19 disease. After an incubation period of around 5.2 days, the symptoms occur. Respiratory forms of COVID-19 infection involves upper respiratory system first, then proceeds to lower respiratory system. Generally patient admitted with upper respiratory tract viral infection (mild fever, dry cough, sore throat, oropharyngeal mucositis, nasal congestion, malaise, headache and muscle pain. Intestinal forms of COVID-19 patient includes smell and taste disorder (anosmia and dysgeusia) [11], nausea and diarrhea [12]. SARS CoV-2 bind to their target cells through angiotensin converting enzyme (ACE2) which expressed in epithelial cells of the lung, intestine, kidney and blood vessels. ACE2 expression is substantially increased in type 1 diabetes, type 2 diabetes and hypertension patient who are treated with ACE inhibitors and angiotensin II type-1 receptor blockers (ARBs). The treatment upregulates ACE2, which would facilitate infection with COVID-19. [12]. The current work demonstrates that individuals with secondary diseases that might directly influence the RAS system, such as COVID-19, differ in their expression of the gene ACE2 (diabetes, hypertension, cardiovascular disease, etc.) [13, 14, 15]

Propagating phase involve several system, including respiratory, cardiovascular, hematopoietic, renal system and others. Moderate to severe pneumoniae can occur. Severe dyspnea, respiratory distress, tachypnea (>30 breaths/min) and hypoxia (SpO2 <90% on room air) with fever that must be evaluated cautiously. [3] Numerous cardiological symptoms in COVID-19 could be caused by the disease's hypercoagulable condition, which has been linked to microvascular occlusion. Multiple organ involvement in COVID-19 suggests that endothelial damage resulting in visceral vasculopathy may be the trigger for the disease. [16]. Coronary artery plaques may become unstable as a result of direct myocardial injury caused by hemodynamic disturbance or hypoxia, inflammatory myocarditis, stress cardiomyopathy, microvascular dysfunction or thrombosis due to hypercoagulability, or cytokine storm. [17] Biventricular cardiomyopathy occurred in approximately 7-33% of critically ill patient. [18] In COVID-19 patients, the Virchow triad's three components are all present,

causing hypercoagulability. The SARS CoV-2 virus's direct invasion of endothelium cells has the potential to produce endothelial damage, followed by immobilization that may result in blood flow stagnation. [19] The activation and accumulation of platelets brought on by lung injury may result in thrombocytopenia. [20] A study concludes that respiratory infections are common and one of the leading causes of morbidity and mortality. [21] The thrombotic microangiopathy and microcirculatory impairment due to the endothelial cell injury could be aggravated by liver dysfunction. [22] Epithelial response occurs through activating EGF receptors (EGFR) combined with toll like receptors (TLR). Downregulation of EGFR can prevent early immune response against the infection. [23] Insulin growth factor 2 receptor (IGFR2) is used for intracellular transport of lysosomal enzymes, transforming growth factor beta activation, and degrading IGF2IGF2R dysfunction likely makes it easier for viruses to enter cells through endocytosis. [24] Acute kidney injury (AKI), hematuria, and proteinuria are three symptoms of kidney illness. In COVID-19, renal complications were associated with greater mortality. [25] Patients with end-stage renal illness and kidney transplant recipients had higher COVID-19 mortality rates than non-recipients. A more severe type of COVID-19 can affect patients with chronic kidney illness, and these patients have a greater mortality rate. [26]

Throughout the clinical course of COVID-19, the illness spreads throughout the body, damaging the respiratory, cardiovascular, gastrointestinal, bone marrow and hematopoietic, renal, hepatic, and other systems. [3] Severe COVID-19 patients may develop acute respiratory distress syndrome during the complicating phase, which manifests as breathing difficulties and low blood oxygen levels. [27] Sepsis, which is characterized by organ dysfunction and fatal organ failure brought on by an imbalanced host response to infection, is another clinical picture. Numerous organ failures, such as the respiratory system (severe dyspnea and hypoxemia), the renal system (reduced urine production), the cardiovascular system (tachycardia), and the neurological system, can be driven on by uncontrolled inflammation (altered mental status). [3] Septic shock could occur if the negative clinical trajectory worsens.

3. Presence of comorbidities and clinical characteristics and outcomes of COVID-19

According to current findings, individuals who have diabetes, hypertension, and cardiovascular disease frequently have COVID-19. According to Singh et al., there are 21%, 11%, and 7% patients with hypertension, diabetes, and CVD, respectively. [28] The prognosis is worsened for elderly adults and for those of any age who have concomitant conditions like diabetes and hypertension. According to a meta analysis study, the most common underlying conditions among hospitalized COVID-19 patients were hypertension, cardiovascular disease, and chronic kidney disease. [8] Diabetes patients have higher rates of morbidity and mortality, which are linked to more hospital and intensive care unit admissions. [6] A two to three times higher risk of severe to critical illness and hospital mortality is significantly associated with COVID-19 patients who have pre-existing diabetes (commonly type 2 DM). [30] Diabetes is linked to a higher risk and severity of SARS CoV-2 infection due to a number of various factors, including elevated ACE-2 expression, elevated furin, reduced t-cell activity, and elevated IL-6. For COVID-19 patients with diabetes, special therapy is necessary, requiring glycemic control (insulin delivery) and continuous blood glucose testing. [31]

A study by Liu H. et al. found a high correlation between previous chronic disease and greater disease severity (OR 3.5, 95% CI 1.78 to 6.9). Pre-existing conditions include diabetes, hypertension, coronary artery disease (CAD), and chronic lung illness all improve the chance of disease progression. [4] Common chronic conditions include endothelial dysfunction, the proinflammatory state, and changes in the innate immune response may be etiologically related to the etiology of COVID-19. Vascular inflammation

and systemic oxidative stress are both exacerbated by diabetes and hyperglycemia. Both local and systemic inflammation are relevant to the vascular endothelial dysfunction associated with chronic illnesses. [32] Activation of innate immunity complement pathway may negatively impact vascular endothelial function in hypertension [33], where increased anti-inflammatory IL-10 expression from the adaptive immune response blunt the adverse effects on endothelial function of angiotensin II associated hypertension [34]

On admission, the severe group had more leucocytes, neutrophils, AST, LDH, CK, PT, INR, D-dimer, CRP, IL-6, ferritin, NLR, and PLR, while having lower lymphocytes. [21] According to Kermali et al., severe COVID-19 was linked to an increase in NLR, CRP, LDH, IL-6, and a decrease in lymphocyte. [35] Based on a study by Liu et al., the severity of COVID-19 was strongly associated with the levels of IL-6, CRP, LDH, and ferritin at the time of admission. [36] In severe or critical patients, compared with mild or moderate cases, the levels of LDH were 1.5 times greater (p 0.001) while the levels of prealbumin were lower (p 0.001). [37Poor prognostic indicators for COVID-19 include increased neutrophil counts, decreased lymphocyte counts, increased MPV, anemia with anisocytosis, in conjunction with obesity, chronic renal failure, COPD, cardiovascular disorders, and age > 60. [38] In patients with diabetes who presented with various comorbidities, D-dimer, alanine aminotransferase, aspartate aminotransferase, albumin, and lactic dehydrogenase were significant. [39] Due to an increased risk of pulmonary embolism, elevated D-dimer was linked to disease severity and mortality. [40] There are distinctive biochemical and hematologic differences between severe and non-severe conditions, and these associations between markers of inflammation (ANC, IL-6, ferritin, CRP, and albumin), a subpar adaptive immune response (ALC), intravascular coagulation (D-dimer), and tissue damage (LDH, hsTroPI) have been found in a meta-analysis. [41] These pathways are most likely the ideal possibilities for treatment with drugs like heparin or tocilizumab (an IL-6 inhibitor to target inflammation) (to target coagulation). [42] Higher Neutrophil to Lymphocyte Ratios (NLR) and lower absolute monocyte counts (AMC) are linked to higher mortality. Similar findings were reported in a study by Yang et al. (2020), which led to the conclusion that elevated NLR can be used as a prognostic factor and is an independent prognostic biomarker for COVID-19 patients. As a result, these results were recommended as beneficial tools to assess prognosis and assess the severity of clinical symptoms in COVID-19 patients. [44] NLR, platelet count, and red blood cell distribution width were the three primary predictors of in-hospital death that Bellan et al. (2020) discovered (RDW). [45] Patients with severe COVID-19 disease showed a considerable rise in NLR levels (SMD=2.404, 95%CI=0.98-3.82). [46]

4. Conclusion

COVID-19 causes global pandemic with high mortality rate, is classified as three different clinical course (mild, severe and critical). The renin angiotensin aldosterone system as one of the clinicogenomics mechanism has particular characteristic in relation to immunogenomic phases. Therefore, COVID-19 patients with pre-existing condition related to RAA system (type 2 DM, hypertension, kidney disease) are more susceptible, greater negative outcomes, and requires more time to heal depending on their immunity.

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