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NUMBER 005-01: Early warning Signs/indicators for severe COVID-19

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2. **RESEARCH DOMAIN:** COVID-19‘diagnosis and Case management

3. **TITLE:** Early warning Signs/indicators for severe COVID-19

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5. **BACKGROUND**

Coronavirus disease 2019 (COVID-19) was first identified in Wuhan, China, in December 2019. Although previous studies have described the clinical aspects of COVID-19, few studies have focused on the early detection of severe COVID-19 [1]. Patients with severe novel coronavirus disease (COVID-19) can likely develop comorbidities, which can lead to irreversible organ damage and, eventually, death. However, early indicators of disease progression remain unclear [2]. Therefore, this policy Brief aimed to identify the predictors of severe COVID-19 and to compare clinical features between patients with severe COVID-19 and those with less severe COVID-19 and then provide a basis for improved prognostic prediction and disease management. The evidence presented originates from a systematic review of primary studies on early warning signs of severe COVID-19 disease.

6. **SEARCH STRATEGY / RESEARCH METHODS**

A systematic search of databases was conducted between 13th and 19th August 2020 for relevant available articles from 1 December to 19 August 2020. Relevant studies in English that reported on early warning signs of severe COVID-19 in patients were included if they provided COVID-19 clinical outcomes and compared severe covid-19 and non-severe covid-19 Patients. In addition, manual search for articles referenced in the primary studies was undertaken. French language studies were not included and these were not relevant to the subject matter but also few and small. The exclude articles did not report on COVID-19 and did not provide laboratory data on COVID-19 Patients.

The systematic search identified 78 potential studies but only 16 met the inclusion criteria. Study quality was assessed using van Tulder criteria. The research conducted to a meta-analysis because of the homogeneity of the participants, interventions, comparators and outcomes. Four databases: PUBMED, WHO COVID-19, IRIS (WHO Institutional Repository for Information Sharing) and Google Scholar were used to pull out papers completed or ongoing.

7. **SUMMARY OF GLOBALLY PUBLISHED LITERATURE RELATED TO THE SUBJECT**

1°. **COVID-19 Symptoms and signs.**

All studies report that Clinical manifestations of COVID-19 if there are include: fever, fatigue, dry cough, diarrhea, chest tightness and shortness of breath. Fever is the most common clinical manifestation of COVID-19, followed by cough (3, 4) and most patients with severe COVID-19 developed fever, cough, dyspnea and markedly decline in oxygen saturation, which are the early clinical manifestations of ARDS.

2°. **Demographic patients’ characteristics and Underlying comorbidities.**
All studies shown that elderly male patients with comorbidities such as diabetes, hypertension, heart disease cancer and are at the highest risk of SARS-Cov-2 infection [5]. Patients aged 60 or more years are about 2 times more likely to develop severe COVID-19 compared to those below 60 years (OR: 1.6; P-value 0.03).

In one study 14% who deteriorated were older, more likely to be smokers and equally likely to have diabetes compared to those who improve. Older age was found to be a risk factor for Acute Respiratory Distress Syndrome (ARDS) and death in a single-center study of 201 patients [14].

Existing comorbidities are also a major risk factor for progression to severe COVID-19. Over 70% of the patients had underlying diseases. The proportions of patients with diabetes and heart disease were significantly higher in the severely and critically ill group than in the mild and moderately ill group (p-value < 0.01). Patients with underlying chronic illnesses such as hypertension, diabetes and chronic obstructive pulmonary disease are twice as likely to develop severe COVID-19 than those without underlying chronic illnesses (OR: 1.5; p-value: 0.04).


Several biomarkers have also been proposed as early indicators of severe COVID-19 [6, 7]. For example, it has been reported that high levels of interleukin 6 (IL-6) and lactic acid in the blood can independently predict the progression of COVID-19 to severe disease [8]. However, an elevated lactate dehydrogenase (an enzyme that catalyzes the interconversion of lactic and pyruvic acids) level in the blood, a sign of early myocardial infarction, may reduce the effectiveness of lactic acid as an early warning sign of severe COVID-19 because patients with high levels of lactate dehydrogenase tend to have low levels of lactic acid. Consequently, an elevated lactate dehydrogenase in the blood has also been proposed as an early warning sign of severe COVID-19 [9]. Furthermore, higher C-reactive protein (CRP) and progressive decrease in the absolute lymphocyte count have also been observed in severe COVID-19 patients [10,11]. Patients with IL-6 ≥ 30 ng/L are twice as likely to develop severe COVID-19 than Patients with Low level of IL. and all cases had a decreased lymphocyte count on admission; patients in the severe group had even lower absolute lymphocyte values (OR = 2.426, P = 0.010) [12].

4° Blood cells count.

Blood cell counts are also an important indicator of severe COVID-19. One study reported that patients with severe COVID-19 often had abnormally high levels of white blood cells, and abnormally low levels of lymphocytes and platelets [13].

The assessment of following parameters linked to platelet (PLTs) function and activity are: PLT fraction, mean volume, distribution width, aggregation, reticulated PLTs, PLT-derived microparticles (PMPs) combined with D-dimer, and a combination of PMPs, PLTs distribution width, PLTs count, and D-dimer could lead to a great deal of information on the hyper-activation of coagulation and on the development of thrombosis and microthrombosis in COVID-19 patients.

6 studies have shown that immature platelet fraction can be effectively used as marker of PLTs activation and increased risk of thrombosis. Larger PLTs contain more dense granules, produce more thromboxane A2, platelet factor A and beta-thromboglobulin, and are consequently more reactive with greater prothrombotic potential than smaller PLTs. Moreover, increased immature PLT fraction can predict a decrease in PLT count during coagulopathy. A key marker of PLTs activation for COVID-19 patients could also be the PLTs distribution width that has been reported to be increased in venous thrombosis as well as in several hypercoagulative state, such as in cardiovascular diseases. An additional PLTs parameter
particularly active in thrombus formation is the reticulated PLTs that reflect increased PLTs consumption during the thrombosis progression and/or prelude to the development of thrombosis. In fact, reticulated PLTs may reflect an increased PLT turnover in the setting of a normal PLTs count and this aspect could be of critical importance in the early diagnosis of COVID-19. Another efficient parameter that can be also combined with PLT distribution width, PLTs count, and D-dimer is the PLT-derived microparticles (PMPs) that play a critical role in thromboembolism through direct cell-to-cell contact interactions or release of active components.

8 SUMMARY OF AFRICA-SPECIFIC LITERATURE ON THE SUBJECT

None identified

9 POLICY FINDINGS

- The studies show that there are clear early warning signs of severe COVID-19 that health care providers can use as a guide for timely instituting measures to reduce the risk of death among COVID-19 patients. The most common clinical manifestations of COVID-19 are: fever, fatigue, dry cough, diarrhea, chest tightness and shortness of breath and most patients with severe COVID-19 developed fever, cough, dyspnea and markedly decline in oxygen saturation, which are the early clinical manifestations of Acute Respiratory Distress Syndrome.

- The results of studies indicate that demographic characteristics and behavior such as older age, male and more likely to be smokers are the risk factor for severe COVID-19.

- The same studies reported that Blood cells counts (WBC count, lymphocyte count, platelet count) deserve closely monitor, the increase of WBC, decrease of absolute lymphocytes and platelets could serve as early warning laboratory manifestations for severe COVID-19. Furthermore, the alteration of PLTs parameters in association with the prolonged prothrombin time, increase of D-dimer, and decrease of fibrinogen in COVID-19 patients are of key importance to diagnose and/or monitoring the worsening of coagulation. In the most serious form, this worsening of coagulation leads to an inadequate blood supply to different organs and contributing to multiple organ failure/dysfunction, thus giving rise to disseminated intravascular coagulation (DIC) disease [15].

- The risk of developing severe COVID-19 in patients with a serum CRP of ≥65.08 mg/L is 8.9 times than in patients with a serum CRP≤65.08 mg/L. At elevated concentrations, CRP, which is an acute-phase protein, is correlated with an increased risk of organ failure and death for patients admitted to the Intensive Care Unit. Further, prolonged periods of high CRP concentrations are associated with adverse outcomes.

- A decreased lymphocyte counts on admission, and an increased concentration of serum CRP could serve as early warning signs in patients who are at risk of developing severe COVID-19.

- A strong recommendation for clinicians to closely monitor bio-markers such as IL-6, Lactate dehydrogenase and serum ferritin as markers for potential progression to critical illness when they are high, moreover high lactate dehydrogenase levels are also associated with tissue injury occurring in various diseases, including pulmonary disorders such as pneumonia, and liver and kidney dysfunctions; therefore, corresponding treatments should be taken timeously to prevent further deterioration of the disease. Similarly, as COVID-19 can also cause pneumonia as well as
heart, liver, kidney, and other organ dysfunctions, the patients may die from heart failure, shock, acute respiratory distress syndrome, arrhythmia, or renal failure [16].

In conclusion, age and laboratory indicators, such as elevated lactate dehydrogenase, procalcitonin and D-dimer increase, are early predictors of severe COVID-19. Shortness of breath at admission, past histories of diabetes and heart disease, and abnormalities in some indicators, such as low absolute lymphocyte count, low CD4 percentage and CRP increase, indicate that the patient is already severely ill or has a significant risk of progressing to severe conditions. Moreover, coagulation function disorder is also an early indicator of the disease progression to severe. All these could serve as early warning manifestations in patients who are at risk of severe COVID.

10 ONGOING RESEARCH IN THE AFRICAN REGION
Not found

11 AFRO RECOMMENDATIONS FOR FURTHER RESEARCH
There is a need to carry out other studies to have fairly clear evidences on warning signs for severe COVID-19; interactions between COVID-19 and underlying disease, coagulation disorders and COVID-19 deserve further attention and clarification in the African Region. WHO/AFRO encourages producing and sharing scientifically research and knowledge related to COVID-19 for early prevention, diagnosis and treatment.
REFERENCES


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