Review Article

Inflammatory Markers as Predictors of COVID-19 Severity: A Review of Literature

Richard Chinaza Ikeagwulonu[1], Mark Uchejeso Obeta[2], Henry Chukwuemeka Uro-Chukwu[3], Ngozi Immaculata Ugwu[4], Nkereuwem Sunday Etukudo[5], Reginald Obiora Ejinaka[6]

[1]Department of Medical Laboratory Services, Chemical Pathology Unit, Alex Ekwueme Federal University Teaching Hospital Abakaliki, [3]Department of Community Medicine, College of Health Science, Ebonyi State University, [4]Department of Haematology and Immunology, Faculty of Clinical Medicine, College of Health Sciences, Ebonyi State University, Abakaliki, Departments of [2]Medical Laboratory Management, [5]Haematology, and [6]Parasitology, Federal School of Medical Laboratory Science, Jos, Nigeria

Abstract

Background: COVID-19 (severe acute respiratory syndrome [SARS] COV-2), which is now a global pandemic, continues to spread across countries and continents, bringing along with it untold economic hardship and a high mortality rate. Many biochemical changes have been associated with COVID-19. This study is aimed to establish an association between various inflammatory markers and the severity of COVID-19 to provide knowledge for the clinicians and help professionals that manage the disease. **Methods:** A search in PubMed/Medline, Google scholar, and Journal Storage (JSTOR) databases was conducted from May 15, 2020 to June 15, 2020, for studies that reported serum levels of inflammatory markers in COVID-19. Search terms included a combination of "medical laboratory diagnosis, inflammatory markers, cytokines, acute-phase reactants, biomarkers and COVID-19, SARS-COV-2, and coronavirus." **Results:** Four hundred and twelve (412) articles were retrieved following the removal of duplicates, of which 15 articles were included in this study after meeting the study inclusion criteria. The included studies comprised 2828 COVID-19 positives made of 1472 (52.1%) male and 1356 (47.9%) female patients. The most prevalent laboratory finding was increased interleukin-6 (IL) (100%), erythrocyte sedimentation rate (88.9%), and procalcitonin (63.6%). Levels of ferritin, IL-2, tissue necrotic factor (TNF)-α, TNF-γ, serum amyloid A, interferon gamma, IL-4, IL-8, and IL-10 were also increased. **Conclusion:** This study provides enough evidence that inflammatory markers are associated with the severity and prognosis of COVID-19. Inflammatory markers are, therefore, necessary if not the most important assays in the management of COVID-19 patients. Patients with elevated inflammatory markers should be given adequate attention and proper management to avert deterioration.

Keywords: Acute-phase reactants, biomarkers, COVID 19, cytokines, immune-inflammatory markers, medical laboratory diagnosis, severe acute respiratory syndrome CoV-2 and coronavirus

Introduction

Severe acute respiratory syndrome (SARS) COV-2), the seventh coronavirus in history, is the causative agent of COVID-19 disease. This virus, which is now known to cause SARS took its origin from the People's Republic of China in December 2019.[1] Within a few months of onset, COVID-19 spread so fast and crossed several international borders, which led to the WHO declaring it a pandemic on March 11, 2020.[2] Despite lockdowns and restrictions in various forms of movement imposed in different countries, the disease is still rapidly spreading worldwide, probably due to lack of protective equipment[3] or due to the culture of doubts that exist in the minds of some individuals, especially among Africans who question the reality of the existence of the disease. Failure of some countries to act fast during the earlier phase of the COVID-19 has equally been attributed to the recent spike in these countries[4] as well as poor compliance with safety measures or guidelines. Intestinal, respiratory, neuronal, and hepatic diseases have all been linked to various forms of coronaviruses and SARS-CoV-2, as well as organ failure and even death in severe cases.[5,6] A

Access this article online

Quick Response Code:

Website: www.njmonline.org

DOI: 10.4103/NJM.NJM_142_20

Address for correspondence: Mr. Richard Chinaza Ikeagwulonu, Department of Medical Laboratory Services, Alex Ekwueme Federal University Teaching Hospital, Abakaliki, Ebonyi State, Nigeria. E-mail: rikeagwulonu@gmail.com

How to cite this article: Ikeagwulonu RC, Obeta MU, Uro-Chukwu HC, Ugwu NI, Etukudo NS, Ejinaka RO. Inflammatory markers as predictors of COVID-19 severity: A review of literature. Niger J Med 2020;29:548-54.

Submitted: 01-Aug-2020 **Revised:** 10-Aug-2020
Accepted: 19-Sep-2020 **Published:** 24-Dec-2020

recent study has equally reported an association between the severity of COVID-19 and some analytes such as Vitamin D.[7] In addition, COVID-19 infection has been associated with abnormally elevated levels of inflammatory markers, which could explain why infected patients are at greater risk for more severe disease and death, especially in the presence of comorbidities such as diabetes, cancer, and hypertension.[8] More severe disease in COVID-19 patients may also be as a result of a cytokine storm.[8] Although the non specific use of inflammatory markers in diagnosing serious underlying disease has been reported, their measurement can either give a marker of treatment response or be used to detect acute inflammation that might indicate a specific disease.[9] Since the outbreak of COVID-19, however, many researchers have studied changes in inflammatory markers in COVID-19-positive patients and tried to use the changes in levels of these biomarkers to predict disease severity and prognosis. The present study thus systematically reviewed all the available studies which investigated this relationship for better understanding and guide.

Methods

A literature search was conducted from May 15, 2020 for relevant publications published up to June 15, 2020, using the online databases of PubMed/Medline, Google Scholar, and JSTOR. The search strategy included a combination of "medical laboratory diagnosis, inflammatory markers, cytokines, acute-phase reactants, biomarkers and COVID-19, coronavirus, and SARS-COV-2." Snowballing of identified articles was used to identify missed articles. Primary research articles that assessed the relationship between COVID-19 disease and inflammatory markers and were published in English were included. Studies were excluded if they were newsletters, expert opinions, review articles, or commentaries and if the research outcome was not expressed in median (interquartile range [IQR]) or mean (standard deviation [SD]). The patients were classified into severe or mild cases. Severe cases are patients who are either dead or are admitted to the intensive care units (ICU), whereas patients who are not in ICU were classified as mild cases. Information extracted from selected articles included the first author name, study location, study design, disease severity criteria, among others. The entire search protocol is presented in Figure 1.

Results

The initial search of the literature yielded a total of 548 articles, which reduced to 412 articles after duplicates were removed. Following a thorough scan of the abstracts and titles, another set of 387 articles were further removed since they did not fulfill the inclusion criteria. The full texts of the remaining 25 articles were further evaluated after which ten articles were excluded either because some of the articles on biomarkers were not linked to COVID-19, or the full text was not in English and in others, the findings were not expressed in mean (SD) or median (IQR). Finally, 15 articles, which were all observational (retrospective) in design, were included in this systematic review [Figure 1] and comprised 2828 COVID-19 positive patients made of 1472 (52.1%) males and 1356 (47.9%) females. The general characteristics of the included studies are presented in Table 1. The following inflammatory markers were identified in this study: erythrocyte sedimentation rate (ESR), procalcitonin (PCT), interleukin (IL) 2, 4, 6, 8, and 10, tissue necrotic factor (TNF) gamma (ɣ) and alpha (α), ferritin, interferon-gamma (IF-ɣ), and serum amyloid A (SAA), as presented in Table 2.

Erythrocyte sedimentation rate

A total of nine studies[10-18] investigated ESR levels in the COVID-19-infected patients of which 8 (88.9%)[10,12,13-18] reported an increase in ESR among the severe cases. Three[12-14] of the eight cases with elevated ESR (37.5%) were statistically significant (P values < 0.05), whereas 5 (55.6%) were not significant (P values ≥ 0.05). Only one study[11] reported a decrease in ESR among severe cases.

Procalcitonin

Eleven of the 15 articles reviewed[10,11,13-16,18-22] assessed PCT levels in the COVID-19 infected patients, of which 7 (63.6%)[11,15,16,18-21] reported increase in PCT among the severe cases. Four[15,18,19,21] of the seven increased cases (57.1%) were statistically significant ($P < 0.05$), whereas 3[11,16,20] representing 42.9% were not statistically significant ($P \geq 0.05$). Only one study[14] reported a decrease in PCT among severe cases. Three of the studies (27.3%)[10,13,22] found no change in PCT level among the groups.

Ferritin

Changes in serum ferritin levels were investigated in four studies.[12,15,20,21] From the four studies, there was a 100% significant increase in serum ferritin in severe cases.

Tissue necrotic factor

Three studies[13,15,17] investigated TNF-α, but none of them shows a significant increase in TNF-α in severe cases. TNF-γ was reported in only one study[13] with a nonsignificant increase in its serum level in the severe case group.

Serum amyloid A

SAA was reported in two studies,[21,23] and the serum level showed an increase among the severe case group.

Interferon gamma

Zhu *et al*.[17] in their study investigated serum levels of IF-γ and reported a significant increase among the severe case group.

Interleukins

Elevated IL-6 levels were reported in eight studies with severe case groups[10,12-15,21,24] The increased serum level was significant in 75% of the studies. Three studies[13,15,17] and one study[15] that identified IL-10 and IL-8, respectively, reported a significant increase in their serum levels among the severe case groups.

IL-2 was investigated in three studies[13,15,17] and reported a 66.7% increase in its serum levels among the severe case groups.

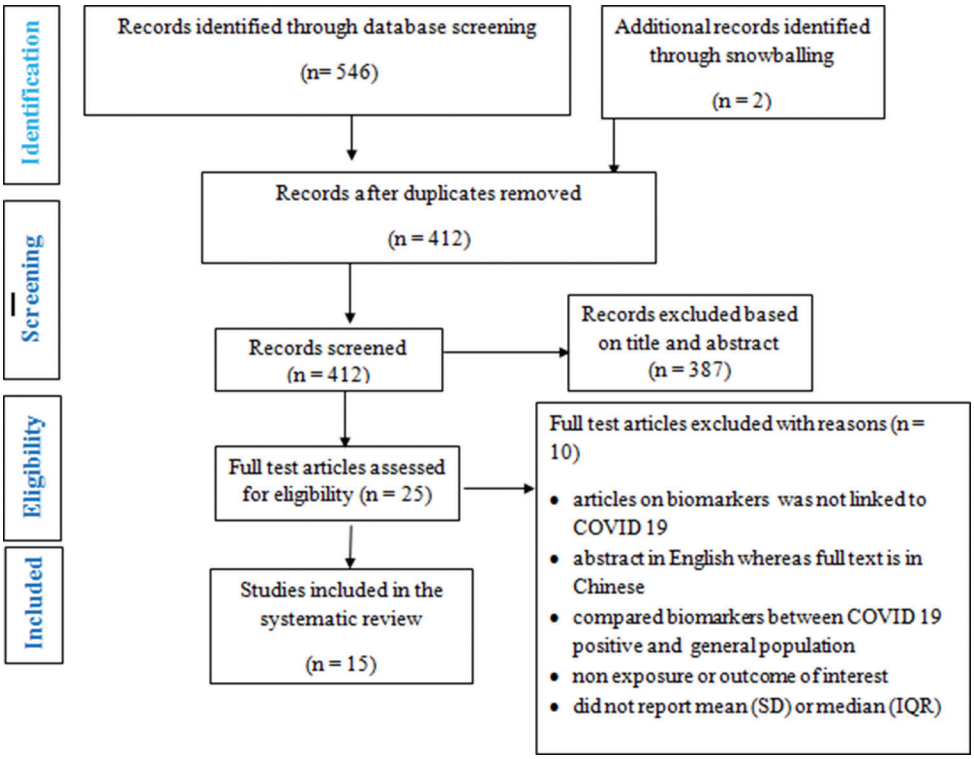

Figure 1: PRISMA flowchart of study inclusions and exclusions

Table 1: General characteristics of the studies reviewed

Author	Study design	Study location	Sample population	Age (mean/median years[a])	Gender (%)	Year of publication
10	Retrospective	China	155	54 (42–66)	Males: 86 (55.5) Females: 69 (44.5)	2020
11	Retrospective	China	78	38 (33–57)	Males: 39 (50) Females: 39 (50)	2020
12	Retrospective	Beijing China	63	47 (3–85)	Males: 37 (58.7) Females: 26 (41.3)	2020
13	Retrospective	China	298	57 (40–69)	Males: 150 (50.3) Females: 148 (49.7)	2020
14	Retrospective	Wuhan China	69	42 (35–62)	Males: 32 (46.4) Female: 37 (53.6)	2020
15	Retrospective	China	32	NA	Males: 13 (40.6) Females: 19 (59.4)	2020
16	Retrospective	Shenzhen, China	298	47 (33–61)	Males: 145 (48.7) Females: 153 (51.3)	2020
17	Retrospective	Wuhan China	28	68.6 (53–82)	Males: 21 (75) Females: 7 (25)	2020
18	Retrospective cohort	Hubei China	299	53.4±16.7	Males: 160 (53.5) Females: 139 (46.5)	2020
19	Retrospective	China	21	56.0 (50.0–65.0)	Males: 17 (81.0) Females: 4 (19.0)	2020
20	Retrospective	China	548	56	Males: 313 (57.1) Females: 235 (42.9)	2020
21	Retrospective	Zhejiang province China	645	46.7±13.82	Males: 328 (50.9) Females: 317 (49.1)	2020
22	Retrospective	China	127	50.9	Females: 82 (64.6) Males: 45 (35.4)	2020
23	Retrospective	China	148	50 (36–64)	Females: 73 (49.3) Males: 75 (50.7)	2020
24	Retrospective	Wuhan, China	19	73 (38–91)	Male: 11 (57.9) Female: 8 (42.1)	2020

Table 2: Identified major findings in reviewed studies

Author	Covid-19 detection	Disease severity	Laboratory parameter	Mean±SD		*P*	Disease severity criteria
				Serum levels in mild cases	Serum levels in severe cases		
10	Real-time RT-PCR	Severe cases: 85 Mild cases: 70	ESR IL-6 PCT	23 (13–41) 23 (9–57) 0.05 (0.05–0.05)	28 (16–51) 64 (31–165) 0.05 (0.05–0.19)	0.087 0.087 0.260	The diagnosis of pneumonia was based on clinical characteristics and chest imaging
11	Real-time RT-PCR	Mild cases: 67 Severe cases: 11	ESR PCT	31 (11–40) 0.06 (0.04–0.09)	30 (22–52) 0.12 (0.05–0.49)	0.794 0.195	The guidelines for diagnosis and management of COVID-19 (4th edition, in Chinese) by the National Health Commission of China
12	Real-time RT-PCR	8 mild cases (12.7%) 36 moderate cases (57.1%) 10 severe cases (15.9%) and 9 criticallyill (14.3%)	ESR Ferritin IL-6	5.14±4.1 0.55±0.50 5.26±1.25	52.13±37 5.08±3.29 34.09±26.	0.001 0.001 0.001	The guidelines for diagnosis and management of COVID-19 (4th edition, in Chinese) by the National Health Commission of China
13	Real-time PCR	Severe cases (those that died): 84 Mild cases those that recovered): 214	PCT	0.043 (0.027–0.065)	0.228 (0.119–0.991)	0.000	The Patients were diagnosed accord in to the World Health Organization interimguidance for COVID-19
14	Real-time PCR.	Mild cases (SpO2 ≥90% group): 55 Severe cases (SpO2 ≥90% group): 14	ESR PCT IL-6 IL-2 IL-10 IL-4 TNF a TNF-γ	17.00 (7.00–25.00) 0.13 (0.13–0.15) 6.69 (4.44–12.43) 2.63 (2.43–2.77) 4.18 (3.31–5.275) 1.95 (1.76–2.21) 2.08 (1.93–2.35) 2.19 (1.91–2.72)	30.00 (27.00–49.00) 0.13 (0.13–0.15) 51.69 (34.31–161.65) 2.77 (2.43–3.32) 6.92 (4.21–11.53) 2.26 (1.95–2.31) 2.14 (1.90–2.34) 2.23 (1.84–9.53)	0.001 0.78 <0.001 0.156 0.013 0.137 0.86 0.392	All patients with COVID-19 enrolled in this study were diagnosed and admitted in accordance with the guideline of the national health commission of China
15	Real-time PCR	The critical cases: 11 The severe cases: 10 and the mild group: 11	IL-6	2.73±1.74	Severe cases: 10.45±8.58 Critical cases: 609.04±1501.14	0.203	All diagnosis were in line with the World Health Organization diagnostic criteria and the inclusion criteria for confirmed cases
16	Real-time PCR	Mild cases: 240 (80.5%) Severe cases: 58 (19.5%)	ESR PCT IL-6	24 (13.5–42.5) 0.2 (0.16–0.24) 8.505 (4.01–16.66)	45 (28–61) 0.16 (0.13–0.18) 26.95 (12.78–46.89)	<0.001 <0.001 <0.001	The diagnosis of COVID-19 was based on the World Health Organization's interim guidanceanddiagnostic criteria were based on the recommendations by the National CDC of China
17	Real-time PCR	Mild cases (patients in isolation): 14 Severe cases (patients in ICU): 14	ESR PCT Ferrtitin IL-6 IL-2 IL-8 IL-10 TNF-α	28.6±24.0 0.03 (0.03±0.06) 555.2 (375.6–767.8) 13.0 (2.4–39.8) 677 (496–1,016) 11.0 (6.8–21.8) 5.2 (5–7.5) 9.1 (6.1–11.0)	36.9±23.6 0.31 (0.1–3.08) 1612.0 (1246.0–2290.0) 124.5 (65.1–199.9) 1538 (1214–1937) 49.1 (25.2–92.4) 14.9 (5.9–18.6) 17.1 (8.4–20.2)	0.4199 0.0006 0.0012 0.001 0.0001 0.0012 0.0057 0.0559	Diagnosis of COVID 19 was according to the New Coronavirus Pneumonia Prevention and Control Program (fifth edition) published by the National Health Commission of China
18	Real-time PCR	Mild cases (survivors): 283 Severe cases (nonsurvivors): 16	ESR PCT	35.1±25.9 0.2±0.6	45.3±25.7 0.3±0.3	0.143 0.245	diagnostic criteria was as set out by World Health Organization for COVID-19

Contd...

Table 2: Contd...

Author	Covid-19 detection	Disease severity	Laboratory parameter	Mean±SD		*P*	Disease severity criteria
				Serum levels in mild cases	Serum levels in severe cases		
19	Real-time RT-PCR	severe cases (≤93% SpO2): 11 mild cases (>93%): 10	PCT Ferrtitin	0.05 (0.04–0.06) 337.4 (286.2–1275.4)	0.18 (0.13–0.81) 1598.2 (1424.6–2036.0)	0.059 0.049	The guidelines for diagnosis and management ofCOVID-19 (6th edition, in Chinese) by the National Health Commission of China
20	Real-time RT-PCR	Mild cases (Survivors): 445 Severe cases (Non-survivors): 103	PCT Ferrtitin SAA IL-6	0.05 (0.05±0.07) 557.96 (300.78±968.50) 173.70 (61.20±249.70) 7.24 (5.58±9.78)	0.14 (0.08±0.33) 1274.80 (739.57±2000.00) 198.25 (161.45±245.25) 9.74 (7.53±13.22)	<0.001 <0.001 0.0041 <0.001	The diagnosis of COVID-19 was made based on the World Health 173Organization interim guidance
21	Real-time RT-PCR	Severe cases: 573 Mild cases: 72	PCT	0.05 (0.04–0.07)	0.05 (0.04–0.08)	0.415	The diagnosis of novelCOVID-19 was based on WHO interim guidance (World Health Organization, 2020); subtype definition of COVID-19 was according to the diagnosis and treatment scheme for SARS-CoV-2 of China (5th edition) (National Administration of Traditional Chinese Medicine, 2020).
22	Real-time RT-PCR	Mild cases: 111 (87.40) Severe groups: 16 (12.60%)	ESR IL-6 IL-2 IL-4 IL-10 TNFα Interferon-ɣ	67.00 (39.50–93.50) 3.82 (2.19–9.87) 0.93 (0.55–1.73) 1.87 (1.43–2.55) 3.13 (2.15–4.57) 1.35 (1.12–1.73) 1.24 (0.93–1.57)	89.00 (60.50–105.75) 24.11 (1.14–54.37) 0.90 (0.47–1.60) 1.99 (1.26–2.73) 6.41 (3.24–11.02) 1.48 (1.39–1.74) 1.93 (1.25–2.29)	0.083 <0.001 0.49 0.777 0.001 0.495 0.003	All patients were diagnosed according to the guidelines for diagnosis and treatment for COVID-19 (Trail Version 6)
23	Real-time RT-PCR	Severe cases: 55 (37.2%) had abnormal liver function Mild cases: 93 (4.3%) of patients with normal liver function	ESR Prothrombin time	47.5 (31.25–83.5) 0.02 (0.02–0.05)	70 (36–86) 0.06 (0.03–0.09)	0.4181 <0.0001	The clinical criteria of diagnosis and discharge were as per the standards for "Diagnosis and Treatment Scheme of New Coronavirus Infected Pneumonia" (trial version 6)
24	Real-time RT-PCR	Mild cases 11 (Survivors):Severe cases (Nonsurvivors): 8	SAA	65.7 (56.9–100.8)	95.1 (54.8–79.8)	NA	NA

NA: Not available, RT-PCR: Reverse transcription-polymerase chain reaction, SAA: Serum amyloid A, ESR: Erythrocyte sedimentation rate, PCT: Procalcitonin, IL: Interleukin, TNF: Tissue necrotic factor, SD: Standard deviation, CDC: Centers for disease control and prevention

Two studies[13,17] that reported IL-4 show that its serum levels increased nonsignificantly among the severe case groups.

Discussion

From this study, the most prevalent laboratory findings were increased IL-6 (100%) followed by ESR (88.9%) and PCT (63.6%), as seen in the previous section. In addition, 66.7% increase was seen in IL-2 in addition to a 100% increase in serum levels of ferritin, TNF-α, TNF-γ, SAA, IF-γ, IL-4, IL-8, IL-10. However, the number of studies where ferritin, TNF-α, TNF-γ, SAA, IF-γ, IL-4, IL-8, and IL-10 were reported were relatively small, comprising 4, 3, 1, 2, 1, 2, 1, and 3 articles, respectively, out of the 15 articles reviewed. About 61.2% percent (61.2%) and 53.1% increase in ESR and IL-6, respectively were reported as main findings in a similar study by Zhang *et al*.[3] and a meta-analysis of laboratory findings in COVID-19 patients also reported high ESR (41.8%).[25] A study comparing laboratory findings in COVID-19 patients with diabetes and those without diabetes reported increased serum levels of IL-6, ESR, SAA, and serum ferritin in the group with diabetes.[8]

The roles of IL-6 and TNF-α in modulating immune responses in viral infections were reported in some studies.[26,27] According to these studies, viral infections are associated with elevated levels of TNF-α and IL-6, and the level of increase is much higher in the presence of bacteria co-infection.[26,27] In line with the above reports, we reported a 100% increase in IL-6 and TNF-α among the severe case groups of COVID-19 patients. However, the present study did not account for bacteria co-infection in these patients. IL-6, when secreted in excess, works in synergy with IL-17 to promote viral persistence through inhibition of cellular apoptosis and cytotoxic T-cell function.[28]

Changes in plasma protein types, higher chances of inflammation among severe group and age have been identified by[29] as a possible reason for increased ESR levels among the severe case groups of COVID-19 patients. ESR is an essential marker of chronic inflammatory conditions and it is known to increase with age.[30] Higher levels of ESR have been associated with poorer outcomes than their lower levels.[31]

Several studies have reported the importance of PCT in infections.[32-39] Although the physiological role and mechanism behind the changes in blood levels of PCT has not been fully understood, it has been reported that IF-ᵞ secreted primarily in response to viral infections attenuate PCT[40] while in most bacterial infections, there is an increase blood level of PCT primarily due to enhanced concentrations of TNF-α, IL-1 β, or IL-6.[35,36,41] In the present study, the 63.6% increase in PCT reported in individuals with severe COVID-19 infection could be due to bacterial co-infection in these patients. Kotula *et al*.[42] reported a significant increase in PCT levels among children with viral lower respiratory tract infections who were coinfected with a bacterial infection.

Changes in serum ferritin levels have been associated with liver diseases.[43,44] Hyperferritinemia has also been associated with viral infections.[45,46] The finding in this study of a 100% increase in ferritin levels in the severe cases of COVID-19 patients could suggest that the liver of these patients has been compromised. Though the lung was the main target organ attacked by the COVID-19 virus, a recent study established an association between liver injury and COVID-19 infection.[47] A recent meta-analysis also reported hyperferritinemia in patients with severe cases of COVID 19.[29]

Elevated levels of inflammation-related biomarkers seen in this study are a pointer that organ injuries are much more serious in this group of patients. The rapid deterioration of patients with COVID-19 could eventually be the outcome due to the susceptibility of these patients to form an inflammatory storm.[8]

The main limitation of this study is the fact that all the studies were from China; however, in the absence of data from other countries, the findings from this study can still suffice. Although it is a challenge for other countries to take a cue from this type of research and practice, especially during this COVID-19 pandemic.

Conclusion

COVID-19 patients are susceptible to the inflammatory storm, and the severity of the infection correlates positively with inflammatory markers, especially IL-6, ESR, and PCT. The relationship between other biomarkers such as serum ferritin, TNF-α, TNF-γ, SAA, IF-γ, IL-4, IL-8, IL-10 requires further studies. It is, therefore, recommended that serum levels of these biomarkers should be closely monitored as a guide to assess the severity of COVID-19 patients. Randomized clinical trials and large population studies are still required to evaluate the observations in this study and also explain the mechanism of these inflammatory markers with the severity of COVID-19.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Question & answer on coronaviruses (COVID-19). World Health Organization. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus2019/question-and answers-hub/q-a-detail/q-a-coronaviruses. [Last accessed on 2020 Jun 18].
2. WHO Director-General's opening remarks at the media briefing on COVID-19-11 March 2020. Available from: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-oncovid-19. [Last accessed on 2020 Mar 11].
3. Zhang ZL, Hou YL, Li DT, Li FZ. Laboratory findings of COVID-19: A systematic review and meta-analysis. Scand J Clin Lab Invest; 2020: 1-7. doi: 10.1080/00365513.2020.1768587 [Ahead of print].
4. Obeta MU, Ejinaka RO, Ofor IB, Ikeagwulonu RC, Agbo EC, Abara US. Nigerian COVID-19 (coronavirus) patients update, the realities with medical laboratory diagnostic sites. Am J Epidemiol Infect Dis 2020;8:13-5.
5. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, *et al*. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020;382:727-33.
6. Peiris JS, Lai ST, Poon LL, Guan Y, Yam LY, Lim W, *et al*. Coronavirus as a possible cause of severe acute respiratory syndrome. Lancet 2003;361:1319-25.
7. Ikeagwulonu RC, Etukudoh NS, Obeta MU, Mgbecheta CU. Does Vitamin D serum levels affect the risk of covid 19 and its clinical outcomes? A review of literature. EAS J Med Surg 2020;2:146-151.
8. Guo W, Li M, Dong Y, Zhou H, Zhang Z, Tian C, *et al*. Diabetes is a risk factor for the progression and prognosis of COVID-19. Diabetes Metab Res Rev; 2020:e3319. DOI: 10.1002/dmrr.3319 [Ahead of print].
9. Watson J, Round A, Hamilton W. Raised inflammatory markers. BMJ 2012;344:e454.
10. Mo P, Xing Y, Xiao Y, Deng L, Zhao Q, Wang H, *et al*. Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China. Clin Infect Dis; 2020: ciaa270. Doi: 10.1093/cid/ciaa270 [Ahead of print].
11. Liu W, Tao ZW, Wang L, Yuan ML, Liu K, Zhou L, *et al*. Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease. Chin Med J (Engl) 2020;133:1032-8.
12. Sun Y, Dong Y, Wang L, Xie H, Li B, Chang C, *et al*. Characteristics and prognostic factors of disease severity in patients with COVID-19: The Beijing experience. J Autoimmun 2020;112. doi:10.1016/j.jaut.2020.102473
13. Wang Z, Yang B, Li Q, Wen L, Zhang R. Clinical features of 69 cases with coronavirus disease 2019 in Wuhan, China. Clin Infect Dis 2020;71:769-77.

14. Cai Q, Huang D, Ou P, Yu H, Zhu Z, Xia Z, *et al*. COVID-19 in a designated infectious diseases hospital outside Hubei Province, China. Allergy 2020;75:1742-52.
15. Wang F, Yang Y, Dong K, Yan Y, Zhang S, Ren H, *et al*. Clinical characteristics of 28 patients with diabetes and covid-19 in Wuhan, China. Endocr Pract 2020;26:668-74.
16. Huang J, Cheng A, Kumar R, Fang Y, Chen G, Zhu Y, *et al*. Hypoalbuminemia predicts the outcome of COVID-19 independent of age and co-morbidity. J Med Virol, 2020:jmv.26003. doi: 10.1002/jmv.26003 [Ahead of print].
17. Zhu Z, Cai T, Fan L, Lou K, Hua X, Huang Z, *et al*. Clinical value of immune-inflammatory parameters to assess the severity of coronavirus disease 2019. Int J Infect Dis 2020;95:332-9.
18. Fan Z, Chen L, Li J, Cheng X, Yang J, Tian C, *et al*. Clinical features of COVID-19-related liver functional abnormality. Clin Gastroenterol Hepatol 2020;18:1561-6.
19. Luo X, Zhou W, Yan X, Guo T, Wang B, Xia H, *et al*. Prognostic value of C-reactive protein in patients with COVID 19. Clin Infect Dis; 2020: ciaa641. doi: 10.1093/cid/ciaa641 [Ahead of print].
20. Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, *et al*. Clinical and immunological features of severe and moderate coronavirus disease 2019. J Clin Invest 2020;130:2620-9.
21. Chen R, Sang L, Jiang M, Yang Z, Jia N, Fu W, *et al*. Longitudinal hematologic and immunologic variations associated with the progression of COVID-19 patients in China. J Allergy Clin Immunol 2020;146:89-100.
22. Zhang X, Cai H, Hu J, Lian J, Gu J, Zhang S, *et al*. Epidemiological, clinical characteristics of cases of SARS-CoV-2 infection with abnormal imaging findings. Int J Infect Dis 2020;94:81-7.
23. Zhang J, Liu P, Wang M, Wang J, Chen J, Yuan W, *et al*. The clinical data from 19 critically ill patients with coronavirus disease 2019: A single-centered, retrospective, observational study. Z Gesundh Wiss; 2020:1-4. doi: 10.1007/s10389-020-01291-2 [Ahead of print].
24. Ding M, Zhang Q, Li Q, Wu T, Huang YZ. Correlation analysis of the severity and clinical prognosis of 32 cases of patients with COVID-19. Respir Med 2020;167:105981.
25. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, Villamizar-Peña R, Holguin-Rivera Y, Escalera-Antezana JP *et al*. Clinical, laboratory and imaging features of COVID-19: a systematic review and meta-analysis. Travel Med Infect Dis 2020;34:101623.
26. Zheng J, Shi Y, Xiong L, Zhang W, Li Y, Gibson PG, *et al*. The expression of IL-6, TNF-α, and MCP-1 in respiratory viral infection in acute exacerbations of chronic obstructive pulmonary disease. J Immunol Res 2017;2017:8539294.
27. Velazquez-Salinas L, Verdugo-Rodriguez A, Rodriguez LL, Borca MV. The role of interleukin 6 during viral infections. Front Microbiol 2019;10:1057.
28. Hou W, Jin YH, Kang HS, Kim BS. Interleukin-6 (IL-6) and IL-17 synergistically promote viral persistence by inhibiting cellular apoptosis and cytotoxic T cell function. J Virol 2014;88:8479-89.
29. Zeng F, Huang Y, Guo Y, Yin M, Chen X, Xiao L, *et al*. Association of inflammatory markers with the severity of COVID-19: A meta-analysis. Int J Infect Dis 2020;96:467-74.
30. Piva E, Sanzari MC, Servidio G, Plebani M. Length of sedimentation reaction in undiluted blood (erythrocyte sedimentation rate): Variations with sex and age and reference limits. Clin Chem Lab Med 2001;39:451-4.
31. Wu S, Zhou Y, Hua HY, Zhang Y, Zhu WY, Wang ZQ, *et al*. Inflammation marker ESR is effective in predicting outcome of diffuse large B-cell lymphoma. BMC Cancer 2018;18:997.
32. Meynaar IA, Droog W, Batstra M, Vreede R, Herbrink P. In critically ill patients, serum procalcitonin is more useful in differentiating between sepsis and SIRS than CRP, Il-6, or LBP. Crit Care Res Pract 2011;2011:594645.
33. Briel M, Schuetz P, Mueller B, Young J, Schild U, Nusbaumer C, *et al*. Procalcitonin-guided antibiotic use vs. a standard approach for acute respiratory tract infections in primary care. Arch Intern Med 2008;168:2000-7.
34. Schuetz P, Albrich W, Mueller B. Procalcitonin for diagnosis of infection and guide to antibiotic decisions: Past, present and future. BMC Med 2011;9:107.
35. Samsudin I, Vasikaran SD. Clinical utility and measurement of procalcitonin. Clin Biochem Rev 2017;38:59-68.
36. Lippi G, Plebani M. Procalcitonin in patients with severe coronavirus disease 2019 (COVID-19): A meta-analysis. Clin Chim Acta 2020;505:190-1.
37. Schuetz P. The role of procalcitonin for risk assessment and treatment of COVID-19 Patients. Health Management; 2020:20.
38. Gendrel D, Bohuon C. Procalcitonin, a marker of bacterial infection. Infection 1997;25:133-4.
39. Dandona P, Nix D, Wilson MF, Aljada A, Love J, Assicot M, *et al*. Procalcitonin increase after endotoxin injection in normal subjects. J Clin Endocrinol Metab 1994;79:1605-8.
40. Linscheid P, Seboek D, Nylen ES, Langer I, Schlatter M, Becker KL, *et al*. *In vitro* and *in vivo* calcitonin I gene expression in parenchymal cells: A novel product of human adipose tissue. Endocrinology 2003;144:5578-84.
41. Becker KL, Snider R, Nylen ES. Procalcitonin in sepsis and systemic inflammation: A harmful biomarker and a therapeutic target. Br J Pharmacol 2010;159:253-64.
42. Kotula JJ 3rd, Moore WS 2nd, Chopra A, Cies JJ. Association of Procalcitonin value and bacterial coinfections in pediatric patients with viral lower respiratory tract infections admitted to the pediatric intensive care unit. J Pediatr Pharmacol Ther 2018;23:466-72.
43. Kowdley KV, Belt P, Wilson LA, Yeh MM, Neuschwander-Tetri BA, Chalasani N, *et al*. Serum ferritin is an independent predictor of histologic severity and advanced fibrosis in patients with nonalcoholic fatty liver disease. Hepatology 2012;55:77-85.
44. Weismüller TJ, Kirchner GI, Scherer MN, Negm AA, Schnitzbauer AA, Lehner F, *et al*. Serum ferritin concentration and transferrin saturation before liver transplantation predict decreased long-term recipient survival. Hepatology 2011;54:2114-24.
45. van de Weg CA, Huits RM, Pannuti CS, Brouns RM, van den Berg RW, Van Den Ham HJ, *et al*. Hyperferritinaemia in dengue virus infected patients is associated with immune activation and coagulation disturbances. PLoS Negl Trop Dis 2014;8:e3214.
46. Lustbader ED, Hann HW, Blumberg BS. Serum ferritin as a predictor of host response to hepatitis B virus infection. Science 1983;220:423-5.
47. Ikeagwulonu RC, Etukudoh NS, Obeta MU, Uro-Chukwu HC, Ibanga IE. A Systematic review on use of liver function tests to assess association between liver injury and COVID 19 Disease. Int J Celiac Dis 2020;8:110-6.