Kinetics of IL-6, C-reactive Protein and Fibrinogen Levels in COVID-19 Outpatients Who Evolved to Hypoxemia

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ABSTRACT

INTRODUCTION: Despite the efficacy of the COVID-19, the search for improvements in the management of severe/critical cases continues to be important. The aim is to demonstrate the kinetics of 4 serological markers in patients with COVID-19 who evolved in hypoxemia.

METHODS: From June to December 2020, the Health Secretariat of Rondônia State, Brazil, established a home medical care service team (HMCS) that provided clinical follow-up for health professionals and military personnel with COVID-19. The clinical and laboratory monitoring was individualized at home by a nursing and medical team. In addition to laboratory parameters, C-reactive protein (CRP), interleukin-6 (IL-6), fibrinogen, and D-dimer levels were periodically taken to monitor the evolution of treatment.

RESULTS: Of 218 patients telemonitored, 48 patients needed special care by the HMCS team due to shortness of breath. Chest tomography showed multiple ground-glass shadows and lung parenchymal condensations that was compatible with secondary bacterial infection associated with leukocytosis, for which antibiotics were prescribed. The symptoms were accompanied by increases of CRP and IL-6 levels followed by fibrinogen after a few days, for which an anticoagulant therapy was included. Thirty-three patients evolved to improvements in clinical signs and laboratory results. Between the sixth and eighth day of illness, 15 patients presented signs of hypoxemia with low O_2 saturation accompanied with an increase in the respiratory rate, with some of them requiring oxygen therapy. As they did not present signs of clinical severity, but their laboratory markers showed an abrupt IL-6 peak that was higher than the increase in CRP and a new alteration in fibrinogen levels, they received a supplemental dose of anticoagulant and a high dose of corticosteroids, which resulted in clinical improvement.

CONCLUSION: Our study demonstrates that monitoring of IL-6 and CRP may identify precocious hypoxemia in COVID-19 patients and prevented the progressive deterioration of the lung injury.

KEYWORDS: SARS Virus, Coronavirus, public health, biomarkers

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Introduction

The ongoing global pandemic of coronavirus 2019 disease (COVID-19) has led to high rates of morbidity and mortality worldwide; with more than 700 million cumulative cases and more than 6.8 million deaths.[1] Currently, 9 vaccines have proven to be highly effective and safe; however, the emergence of new SARS-CoV-2 variants and the decline in the immune response over time post-vaccination is worrying and raises the need for new vaccines and vaccine boosters.[2,3] Meanwhile, mortality remains a concern despite progress in the management of ICU care. Thus, the improvement in the management of severe/critical cases is still important even in era of COVID-19 vaccine.[4]

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection causes an overactive immune response that leads to an excessive inflammatory reaction with the release of too many cytokines, a process called the "cytokine storm," which is often seen in acute respiratory distress syndrome (SARS), sepsis and multiple organ failure.[5-9] Clinical and laboratory findings of COVID-19 patients included alterations in specific biomarkers, including inflammatory and immunological parameters (CRP, procalcitonin, IL-6), hematological parameters (lymphocyte count, neutrophil-lymphocyte ratio, D-dimer, ferritin, prolonged prothrombin time, width distribution of red blood cells), cardiac (troponin, CK-MB, myoglobin), hepatic (AST, ALT, total bilirubin, albumin), and lung injury (Krebs von den Lungen-6).[10,11] Different studies have shown that high levels of IL-6 and other inflammatory biomarkers are associated with poor outcomes in patients with COVID-19.[12,13] However, the cytokine profile and kinetics of important inflammatory and thromboembolic markers in the course of the disease are still poorly understood.[11] Here, we present a retrospective longitudinal study that evaluated the dynamics of IL-6, C-reactive protein (CRP) and fibrinogen levels in outpatients with COVID-19 who evolved to hypoxemia.

Methods

Plan for early identification of COVID-19 severity

The Health Secretariat of the state of Rondônia located in the northern region of Brazil (central-western Brazilian Amazon) established a home medical care service team (HMCS) due high mortality rates in health professionals at the beginning of the COVID-19 pandemic. The cornerstone of the plan was the early identification and a severity analysis based on daily monitoring of clinical-laboratory parameters to assess the potential vulnerability of the patients. This follow-up was carried out by the HMCS team and consisted of a medical telehealth team that, when necessary, included a physical visit, and a nursing team for blood sample collection, monitoring of vital signs and medicine administration. The data demonstrated in this study were obtained from the HMCS team during the first wave of COVID-19 in Brazil and prior to the use of vaccination.

In summary, health professionals and military personnel with suspected COVID-19 were referred to the Oswaldo Cruz Polyclinic (OCP) in Porto Velho, capital of the state of Rondônia. They were submitted to a medical evaluation and diagnosis of SARS-CoV-2 infection by RT-PCR, via sample collection using an intranasal swab.[14] When participants received a diagnosis of SARS-CoV-2 infection by RT-PCR, they were treated by the HMCS team. Patients who presented signs of clinical severity, evidenced by a Glasgow score of ⩽14, respiratory rate above 24 respiratory incursions per minute, and O_2 saturation less than 90%, were referred for hospitalization to receive therapeutic and ventilatory support or admission to the ICU. All the patients who had no advanced symptoms or signs of clinical deterioration were followed up by HMCS team due to clinical signs and alterations in serological markers.

Clinical and laboratory monitoring of patients with COVID-19

From 2nd June 2020 to 31st December 2020, 218 patients with a positive diagnosis for COVID-19 were followed up by the HMCS team. The medical team of the HMCS carried out the telemonitoring and, when necessary, carried out face-to-face visits. The treatment was also personalized at home by a nursing team that checked the patient's vital signs and administered medication, when necessary. In case of fever, chills, cough, fatigue, muscle or body aches, and a headache for more than 3 days, patients received antibiotic therapy with 875 mg of amoxicillin +125 mg of clavulanate 3 times a day for 7 days. Of the 218 patients, in addition to common symptoms, 48 patients exhibited fever above 38°C, difficulty in breathing characterized by respiratory rate of over 20 respiratory incursions per minute (RIPM) and O_2 saturation of less than 95%. Chest tomography showed multiple ground-glass shadows and lung parenchymal condensations and air bronchogram compatible with a secondary bacterial infection. Lymphopenia and leukocytosis were major hematological parameters. All the hemocultures were negative. The treatment was individualized for patients but, in general, they received venous antibiotic therapy and subcutaneous anticoagulant for 7 days, or a maximum of 14 days until clinical and radiological improvement and improvement in laboratory parameters. Of these 48 patients, 33 evolved to improvements in clinical signs and laboratory results.

Around the sixth day of follow up, the remaining 15 patients presented low O_2 saturation accompanied by an increase in respiratory rate. Some of them required oxygen therapy. As telemonitoring was individualized and serological markers were continually determined, IL-6 levels increased earlier than those of CRP levels, and the peak of IL-6 in pg/mL was proportionally higher than the peak of CRP in mg/L (see below in Results). An increase in fibrinogen levels above 437 mg/dL was associated with an abrupt increase in IL-6. For these 15 patients, pulse therapy with 20 mg of dexamethasone was performed on the first day, which was followed by 3 days at 10 mg/day and 3 days at 5 mg/day. A broad-spectrum antibiotic was added to the treatment with an increase in enoxaparin to 2 mg/kg/day for 7 days. These 15 patients evolved to improvements in clinical signs and laboratory results after a few days.

Serological markers

The determination of laboratory parameters and 4 markers were performed at *Laboratório Estadual de Patologia e Análises Clínicas* (LEPAC) of Porto Velho, capital of the state of Rondônia state. Access to the serological data regarding IL-6, CRP, fibrinogen, D and dimer of these patients was made available. The fibrinogen was determined using the Clauss

method in a coagulation analyzer (IL ACL Top 300, Werfen, USA). CRP and D dimer were determined using immunoturbidimetry (GOD-PAP, Modular EVO, Roche®), and IL-6 using electrochemiluminescence (Roche®).

Ethical aspects

The study was approved by the Ethics Review Board of the Fundação de Medicina Tropical Dr. Heitor Vieira Dourado (CAAE: 51963021.9.0000.000). As it is secondary data obtained from the HMCS team and each electronic medical record was obtained anonymously, an informed consent form was not required for this research.

Results

The kinetics of markers for those who showed improvements in clinical signs after therapy

The Methods topic summarizes the clinical signs of 48 patients that exhibited with fever over 38°C, a respiratory rate of over 20 respiratory incursions per minute (RIPM) and O_2 saturation of less than 95%. Chest tomography showed multiple ground-glass shadows associated with lung parenchymal condensation and an air bronchogram compatible with secondary bacterial infection associated with leukocytosis. The patients showed an increase in the levels of CRP, IL-6 and fibrinogen and therefore received venous antibiotic therapy and a subcutaneous anticoagulant.

Of the 48 patients, 33 evolved to improvements in clinical signs and laboratory results. Figure 1A to D presents the kinetics of CRP, IL-6, fibrinogen and D-dimer, respectively. Increased fibrinogen was used within this protocol as the standard indicator for anticoagulant use (see red arrow) and patients were treated with one dose of 1 mg/kg/day of enoxaparin for 7 days. CRP started with higher levels and, when the patients were treated with venous antibiotic therapy, they had a progressive reduction in CRP (Figure 1A). The same is observed with IL-6 levels after antibiotic therapy. When CRP levels were below 25 mg/L, IL-6 reduced to normal levels (Figure 1B). After the increase in fibrinogen levels to over 437 mg/dL, the provision of a daily dose of 1 mg/kg/day of enoxaparin for 9 days was sufficient for the normalization of the results (Figure 1C). There was no substantial increase in D-dimer (Figure 1D).

The kinetics of markers for those who evolved to hypoxemia and needed supplementary therapy

Of the 48 patients, the remaining 15 presented with low O_2 saturation accompanied by an increase in respiratory rate around the sixth day of follow-up. Some of them required oxygen therapy. For all of them, the symptoms were accompanied by increases in IL-6, which was followed by increases in CRP levels (Figure 1E and F). For these patients, a broad-spectrum antibiotic was added to the treatment with an increase in enoxaparin to 2 mg/kg/day, and the introduction of pulse therapy with 20 mg dexamethasone on the first day followed by 3 days at 10 mg/day and 3 days at 5 mg/day.

The kinetic display of CRP levels started with high levels and, after the start of antibiotic therapy, there was a progressive drop (Figure 1E). IL-6 levels increased earlier than those of CRP levels, and the peak of IL-6 in pg/mL was proportionally higher than the peak of CRP in mg/L (see thick green arrow, Figure 1F). In Figure 1G, in the graph showing the fibrinogen levels, it is clearly demonstrated that when the patient was recruited by the service, the patient already presented increased levels of CRP, IL-6 and fibrinogen (see thin red arrow), which demonstrates that these patients had already had the disease for several days. Fibrinogen rose again after a few days, even when after returning to normal levels in the first days after antibiotic and enoxaparin therapy. For these patients, pulse therapy was prescribed with a broad-spectrum antibiotic and an increase in enoxaparin to 2 mg/kg/day. The pulse therapy was individualized with 20 mg dexamethasone on the first day, which was followed by 3 days at 10 mg/day and 3 days at 5 mg/day. The re-appearance of an elevation in fibrinogen levels was an indicator for an increase in anticoagulation therapy with enoxaparin at 2 mg/kg day (see blue and red thick arrows, Figure 1E and G). D-dimer has been considered one of the severity criteria for SARS; however, D-dimer levels increased late in relation to fibrinogen (Figure 1H).

Discussion

The COVID-19 pandemic has had a profound and far-reaching impact on a global scale and continues to represent a substantial public health concern. For this reason, the use of markers for early diagnosis can help healthcare providers to start interventions promptly.[11] Until now, there are no data in the literature that demonstrate a follow-up using markers in COVID-19 patients.[9,15,16] Our study is the first to show a clinical and laboratory follow-up of patients with COVID-19 since the first symptoms. At the time when HMCS was instituted, several randomized clinical trials had already demonstrated that corticosteroids and anticoagulants were effective in reducing hospitalizations, severity and mortality from COVID-19.[17-20] There have been studies based on series of autopsy warning as to whether hemophagocytic lymphohistiocytosis could be the core issue of severe COVID-19 cases.[21,22] As corticosteroid treatment was not routinely recommended for the treatment of pneumonia caused by SARS-CoV-2, at the beginning of the COVID pandemic, Xu et al[23] suggested that an appropriate use of corticosteroids together with ventilator support should have been considered for the severe patients in order to prevent the development of ARDS. Here, the prescription of a broad-spectrum antibiotic therapy, pulse therapy with dexamethasone and an increased dose of anticoagulant for those patients who required oxygen therapy prevented worsening of the infection. This prescription is in agreement with the study by López Zúñiga et al[20] that discusses high-dose corticosteroid pulse therapy as a way to increase the survival rate of COVID-19 patients at risk of hyper-inflammatory response.

Early diagnosis and inflammatory biomarker trends predict respiratory decline and for this reason their use can help

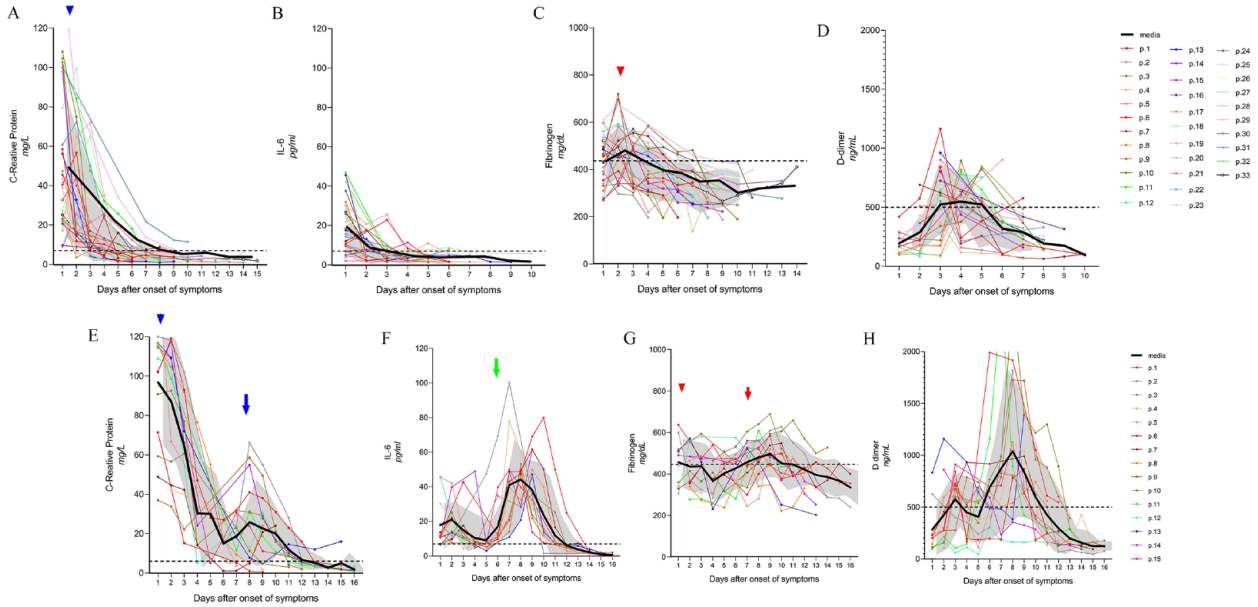

Figure 1. Kinetics of CRP, IL-6 and fibrinogen. (A-D) The kinetics of the markers in patients treated with antibiotics and an anticoagulant. (A) CRP levels during 16 days of follow-up. Dashed line - the reference value is 5 milligram per liter (mg/L); (B) IL-6. Dashed line - the reference value is 7 picograms per milliliter (pg/mL); (C) Fibrinogen. Dashed line - the reference value is 437 milligrams per milliliter (mg/mL); The red arrowheads indicate the beginning of anticoagulant therapy. The thick black line represents the mean of data and the gray area the standard deviation. (D) D-dimer. Dashed line - the reference value is 500 nanograms per deciliter (ng/dL); (E-H) The kinetics of the markers in patients treated with venous antibiotics, anticoagulant and corticoid. (E) CRP levels during 16 days of follow-up. Dashed line - 5 mg/L CRP, reference value; (F) IL-6, dashed line - 7 pg/mL IL-6, reference value; (G) Fibrinogen, dashed line - 437 mg/mL fibrinogen, reference value. (H) D-dimer, dashed line - 500 ng/dL D-dimer, reference value. The blue arrowheads indicate the beginning of antibiotic therapy. The blue arrow indicates the initiation of broad-spectrum antibiotic therapy in order to prevent superinfections; The red arrow indicates the increase in anticoagulation therapy with enoxaparin at 2 mg/kg day; The green arrow indicates the pulse therapy due to the inversion of IL-6 levels in relation to CRP, which is characterized by increases in IL-6 levels earlier than those of CRP levels, in which the peak of IL-6 in pg/mL was proportionally higher than the peak of CRP in mg/L.

healthcare providers to start interventions promptly.[9,11,24-26] In this context, it has been established that the cytokine storm plays an important role in the process of aggravation of the disease.[7-9,27] Several studies have demonstrated that a rapid rise in CRP and IL-6 levels precedes respiratory deterioration and the onset of severe disease.[9,24,28,29] Here, patients who needed oxygen showed alterations in CRP, IL-6 and fibrinogen, as seen in Figure 1D to F, which has already been demonstrated by several studies.[28-34] The computed tomography scans showed a high rate of lung involvement (CT images and personnel communications of clinicians from the HMCS team) and all the patients needed oxygen support. Effective suppression of the cytokine storm is an important way to prevent the deterioration of patients with severe COVID-19,[19] as has occurred with other epidemics involving SARS, MERS, and severe influenza.[35,36] In our study, the early and longitudinal monitoring of IL-6 and C-reactive protein helped to identify early on which patients would develop a worse clinical picture, with IL-6 proving to be the best marker for the cytokine storm in severe COVID-19.[9,12,13,15,37-39] Therefore, our study is the first to show a clinical and laboratory follow-up of patients with COVID-19 since the first symptoms, and IL-6 served as the best marker to identify who might evolve to SARS.

Lastly, some studies have already demonstrated that fibrinogen levels serve as a good predictor for the dose of anticoagulant needed in the treatment of COVID-19.[40,41] Herein, D-dimer increased late in relation to fibrinogen. The increase in fibrinogen, due to an even greater increase in CRP and IL-6, led to the use of antibiotic therapy and anticoagulant treatment that resolved the infection. Our findings call into question the use of fibrinogen as an early marker of this thrombotic stage, as seen in the H1N1 pandemic.[42] One study demonstrated via postmortem samples from people who died of influenza during 1918 to 1919 that they all exhibited severe changes that were indicative of bacterial pneumonia.[43] According to the authors, colonization of the nasopharynx with pathogenic bacteria in respiratory virus infections may predispose patients to a secondary bacterial infection due to impaired mucociliary clearance, thus allowing secondary bacterial invasion, formation of vasculitis zones, capillary thrombosis and necrosis around the areas of bronchiolar damage.[42] This finding in H1N1 infection seems to be in the same context as in COVID-19 patients since neutrophilia is common.[42,44] In this context, one study demonstrated a signature of immune-based biomarkers associated with mortality in COVID-19 patients. According to the authors, a leukocyte migration from the blood-stream to infected tissues and abnormal levels of biomarkers associated with endothelial integrity indicate an endothelial dysfunction as the underlying mechanism of thrombosis in COVID-19.[44] Taken together, the alterations in

fibrinogen observed here were resounding in exposing endothelial dysfunction and were indicative of the dose of anticoagulant needed in the treatment of COVID-19. Therefore, our findings reinforce that the pulse therapy would not be sufficient without an increased dose of cutaneous anticoagulant and a broad-spectrum antibiotic therapy as reported in several studies.[9,39,45-49]

Our study also had some significant limitations. The drawbacks of the study were that, for some patients, not all the daily data for the 4 markers were present, despite our efforts to perform the monitoring and dosing of the 4 markers every day. This was due to some patients not presenting at the LEPAC or they were not present at their home address. In addition, this study has all the limitations of retrospective studies, such as the lack of complete clinical information in medical records, etc.

Conclusion

The following up of the markers was important to show important changes in the kinetics of IL-6 and CRP as effective markers of severity, as well as the use of fibrinogen to monitor anticoagulant therapy. As the mortality and morbidity of COVID-19 is an ongoing concern, despite vaccine efficacy, the monitoring of IL-6 and CRP may improve the management of severe/critical cases of COVID-19 for precociously identifying worsening clinical signs.

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Author Contributions

SPMMF, FSM and RHM conceived the study and wrote the initial proposal.
SPMMF, FSM, RHM contributed intellectually to the development of the protocol.
PAN estimated the sample size and performed all statistical analysis.
SPMMF, FSM, RHM, ABS and DCOM were the leads for the logistics and data collection for the study.
RSP, FSM, ABS, DCOM, PJG, ELO, JAL, and YOC actively reviewed all the data from the patients treated by the multidisciplinary home medical care service team.
PJG and ELO did the laboratory work.
The initial draft of the article was written by PAN and SPMMF, who had full access to and verified all the data underlying the study.
All authors had access to the data, agreed to the submission of the manuscript for publication, and vouch for the integrity, accuracy, and completeness of the data and for the fidelity of the patients' laboratory data.
SPMMF, JPZ, RHM, and PAN contributed intellectually to the manuscript. All authors approved the final submitted version.

Data Sharing

Anonymized participant data can be made available upon request directed to the corresponding author. Proposals will be reviewed on the basis of scientific merit. After approval of a proposal, data can be shared via a secure online platform after signing a data access agreement.

Role of the Funder/Sponsor

Neither the funder/sponsor of the study (the Rondônia State Health Department) had any role in design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication. Neither the funder nor the sponsor had any right to veto publication or to control the decision regarding to which journal the manuscript was submitted. All drafts of the manuscript were prepared by the authors.

REFERENCES

1. WHO. Coronavirus (COVID-19) Dashboard. 2023. https://covid19.who.int/
2. Hadj Hassine I. Covid-19 vaccines and variants of concern: a review. *Rev Med Virol*. 2022;32:e2313.
3. Miao G, Chen Z, Cao H, et al. From immunogen to COVID-19 vaccines: prospects for the post-pandemic era. *Biomed Pharmacother*. 2023;158:114208.
4. Quiroga B, Ortiz A, Cabezas-Reina CJ, et al. Evolving spectrum but persistent high mortality of COVID-19 among patients on kidney replacement therapy in the vaccine era: the Spanish COVID-19 KRT Registry. *Clin Kidney J*. 2022;15:1685-1697.
5. Chinta S, Rodriguez-Guerra M, Shaban M, et al. COVID-19 therapy and vaccination: a clinical narrative review. *Drugs Context*. 2023;12:2022.
6. Fajgenbaum DC, June CH. Cytokine Storm. *New Engl J Med*. 2020;383: 2255-2273.
7. Haigh K, Syrimi ZJ, Irvine S, et al. Hyperinflammation with COVID-19: the key to patient deterioration? *Clin Infect Pr*. 2020;7:100033.
8. Henderson LA, Canna SW, Schulert GS, et al. On the alert for cytokine storm: immunopathology in COVID-19. *Arthritis Rheumatol*. 2020;72:1059-1063.
9. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the 'cytokine storm' in COVID-19. *J Infect*. 2020;80:607-613.
10. Arnold DT, Donald C, Lyon M, et al. Krebs von den Lungen 6 (KL-6) as a marker for disease severity and persistent radiological abnormalities following COVID-19 infection at 12 weeks. *PLoS One*. 2021;16(4):e0249607.
11. Semiz S. COVID19 biomarkers: What did we learn from systematic reviews? *Front Cell Infect Microbiol*. 2022;12:1038908.
12. Aliyu M, Zohora FT, Anka AU, et al. Interleukin-6 cytokine: an overview of the immune regulation, immune dysregulation, and therapeutic approach. *Int Immunopharmacol*. 2022;111:109130.
13. Majidpoor J, Mortezaee K. Interleukin-6 in SARS-CoV-2 induced disease: interactions and therapeutic applications. *Biomed Pharmacother*. 2022;145:112419.
14. Botelho-Souza LF, Nogueira-Lima FS, Roca TP, et al. SARS-CoV-2 genomic surveillance in Rondônia, Brazilian Western Amazon. *Sci Rep*. 2021;11:3770-3812.

15. Merad M, Martin JC. Author correction: pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. *Nat Rev Immunol*. 2020;20:448-362.
16. Gustine JN, Jones D. Immunopathology of hyperinflammation in COVID-19. *Am J Pathol*. 2021;191:4-17.
17. Ho JC, Ooi GC, Mok TY, et al. High-dose pulse versus nonpulse corticosteroid regimens in severe acute respiratory syndrome. *Am J Respir Crit Care Med*. 2003;168:1449-1456.
18. Horby P, Lim WS, Emberson JR, et al. Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med*. 2021;384:693-704.
19. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *Lancet*. 2020;395:473-475.
20. López Zúñiga MÁ, Moreno-Moral A, Ocaña-Granados A, et al. High-dose corticosteroid pulse therapy increases the survival rate in COVID-19 patients at risk of hyper-inflammatory response. *PLoS One*. 2021;16:e0243964.
21. Opoka-Winiarska V, Grywalska E, Roliński J. Could hemophagocytic lymphohistiocytosis be the core issue of severe COVID-19 cases? *BMC Med*. 2020;18:214-311.
22. Prilutskiy A, Kritselis M, Shevtsov A, et al. SARS-CoV-2 infection-associated hemophagocytic lymphohistiocytosis an autopsy series with clinical and laboratory correlation. *Am J Clin Pathol*. 2020;154:466-474.
23. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med*. 2020;8:420-422.
24. Mueller AA, Tamura T, Crowley CP, et al. Inflammatory biomarker trends predict respiratory decline in COVID-19 patients. *Cell Rep Med*. 2020;1:100144.
25. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395:1054-1062.
26. Chen G, Wu D, Guo W, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. *J Clin Investig*. 2020;130:2620-2629.
27. Hu B, Huang S, Yin L. The cytokine storm and COVID-19. *J Med Virol*. 2021;93:250-256.
28. Sharifpour M, Rangaraju S, Liu M, et al. C-reactive protein as a prognostic indicator in hospitalized patients with COVID-19. *PLoS One*. 2020;15: e0242400-e0242410.
29. Herold T, Jurinovic V, Arnreich C, et al. Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19. *J Allergy Clin Immunol*. 2020;146:128-136.e4.
30. Mosquera-Sulbaran JA, Pedreañez A, Carrero Y, Callejas D. C-reactive protein as an effector molecule in Covid-19 pathogenesis. *Rev Med Virol*. 2021;31(6):e2221.
31. Tan C, Huang Y, Shi F, et al. C-reactive protein correlates with computed tomographic findings and predicts severe COVID-19 early. *J Med Virol*. 2020;92:856-862.
32. Sheriff A, Kayser S, Brunner P, Vogt B. C-reactive protein triggers cell death in ischemic cells. *Front Immunol*. 2021;12:630430-630438.
33. Pepys MB. C-reactive protein predicts outcome in COVID-19: is it also a therapeutic target? *Eur Heart J*. 2021;42:2280-2283.
34. Nadeem R, Elhoufi AM, Iqbal NE, et al. Prediction of cytokine storm and mortality in patients with COVID-19 admitted to ICU: do markers tell the story? *Dubai Med J*. 2021;4:142-150.
35. Arabi YM, Mandourah Y, Al-Hameed F, et al. Corticosteroid therapy for critically ill patients with middle east respiratory syndrome. *Am J Respir Crit Care Med*. 2018;197:757-767.
36. Ni YN, Chen G, Sun J, Liang BM, Liang ZA. The effect of corticosteroids on mortality of patients with influenza pneumonia: a systematic review and meta-analysis. *Crit Care*. 2019;23:99.
37. Antunez Muiños PJ, López Otero D, Amat-Santos IJ, et al. The COVID-19 lab score: an accurate dynamic tool to predict in-hospital outcomes in COVID-19 patients. *Sci Rep*. 2021;11:9361.
38. McGonagle D, Ramanan AV, Bridgewood C. Immune cartography of macrophage activation syndrome in the COVID-19 era. *Nat Rev Rheumatol*. 2021;17:145-157.
39. Soy M, Keser G, Atagündüz P, et al. Cytokine storm in COVID-19: pathogenesis and overview of anti-inflammatory agents used in treatment. *Clin Rheumatol*. 2020;39:2085-2094.
40. Vinayagam S, Sattu K. SARS-CoV-2 and coagulation disorders in different organs. *Life Sci*. 2020;260:118431.
41. Ranucci M, Ballotta A, Di Dedda U, et al. The procoagulant pattern of patients with COVID-19 acute respiratory distress syndrome. *J Thromb Haemost*. 2020;18:1747-1751.
42. Chertow DS, Memoli MJ. Bacterial coinfection in influenza: a grand rounds review. *JAMA*. 2013;309:275-282.
43. Morens DM, Taubenberger JK, Fauci AS. Predominant role of bacterial pneumonia as a cause of death in pandemic influenza: implications for pandemic influenza preparedness. *J Infect Dis*. 2008;198:962-970.
44. Abers MS, Delmonte OM, Ricotta EE, et al. An immune-based biomarker signature is associated with mortality in COVID-19 patients. *JCI Insight*. 2021;6:20.
45. Histiocyte Society. Recommendations and Considerations from the Histiocyte Society During the Evaluation of Hospitalized COVID-19 Patients for Hyperinflammation. *J Chem Inform Model*. 2020. https://www.histiocytesociety.org/resources/Documents/HS%20COVID-19%20Statement%20-%20FINAL.pdf
46. Alunno A, Carubbi F, Rodríguez-Carrio J. Storm, typhoon, cyclone or hurricane in patients with COVID-19? Beware of the same storm that has a different origin. *RMD*. 2020;6:1-4.
47. Henter JI, Aricò M, Egeler RM, et al. HLH-94: a treatment protocol for hemophagocytic lymphohistiocytosis. HLH study Group of the Histiocyte Society. *Med Pediatr Oncol*. 1997;28:342-347.
48. Lehmberg K, Pink I, Eulenburg C, et al. Differentiating macrophage activation syndrome in systemic juvenile idiopathic arthritis from other forms of hemophagocytic lymphohistiocytosis. *J Pediatr*. 2013;162:1245-1251.
49. Moore C, Ormseth M, Fuchs H. Causes and significance of markedly elevated serum ferritin levels in an academic medical center. *J Clin Rheumatol*. 2013;19:324-328.