Review Article

Diagnosis and Treatment of Cytokine Storming as a Management of COVID-19 Infection

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Abstract

Background: COVID-19 is a global pandemic with 12% mortality rate. This pandemic has shattered health care sector of many developed countries across the globe. According to World Health Organization (WHO) India and Pakistan will be badly hit by the pandemic till end of June 2020. Both countries are densely populated and the fragile health sector of these countries is incapable to facilitate of large number of critically ill patients. Data analysis from different studies revealed that Cytokine Storming (CS) is main cause of COVID-19 related respiratory, renal, cardiac and neural complications in critically ill patients.

Objectives: The aim of this review is to highlight the significance of CS in management of COVID-19 infection.

Methods: Literature from previous studies was collected to suggest the possible diagnostic testing as well as strategies to manage these patients. Mesh terms such as Corona, Covid-19, Cytokine storming, Wuhan, Pandemic were applied on PUBMED as well as google to search for the latest published articles. Reports and newpapers were also considered as this is an ongoing pandemic and there is scarcity of knowledge and information in this regard.

Results: IL6 and TNFα blockers are helpful in regulating the uncontrolled immune response due to CS. Levels of different substances like ferritin, Cytokine Reactive Proteins and D-dimer can be helpful in early detection of these complications.

Conclusions: The early detection of CS can be used for selection of appropriate treatment, reduction in burden on Intensive Care Units (ICU) and ultimately saving many lives.

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Introduction

COVID-19 is a global pandemic with 61, 149,391 confirmed cases and 370,478 deaths till May 29, 2020. COVID-19 outbreak started in Wuhan, China and then spread to different countries of the world with an exponential increase in confirmed cases and number of deaths.[1] Data analysis indicated that mild cases of COVID-19 deteriorate rapidly causing sudden deaths. According to different studies there are clinical and laboratory evidences of cytokine storming in these patients.[2] As COVID-19 is a global pandemic with still 53036 critically ill patients, timely detection of cytokine storming can save many lives.[1] India and Pakistan are home to 1378million and 220 million people respectively.[3] According to World Health Organization (WHO) these counties are suspected to reach their COVID-19 outbreak peak by end of June2020.[1] These developing countries have poor health care facilities with insufficient number of hospitals, doctors and paramedical staff. Their fragile

health care sector cannot cater large number of critically ill patients which could lead to high mortality rates.[4] Cytokine storming can be used as an early indicator of deterioration of patients and can help in timely selection of appropriate treatment of COVID-19 patients. Neutralization of pro-inflammatory cytokine can play key role in severe cases.[2]

Cytokines

Cytokines are small soluble molecules mainly composed of protein and glycoprotein. They mainly serve as messenger for our immune system. They are produced by many types of white blood cells like neutrophils, basophils, eosinophil, dendritic cells, monocytes, macrophages, B-cells and T-cells. Cytokines act as inter-molecular mediators that bind with specific cytokines receptors on cells and trigger immune response Figure 1. They change the function of cell either by altering protein functions inside the cell or by changing the gene expression.[5] Moreover, cytokines have effect on growth, development, maturation and life span of immune cells. Cytokines have high affinity for cytokines receptors (CR) so they are effective in stimulating response even in low concentrations. High levels of cytokines are detected in critically ill COVID-19 patients.[6] There are four main groups of cytokines and each group has its own role in immune response during COVID-19 infection.

I. **Inter-leukins (IL):** This group includes 35 different types of cytokines ranging from IL1 to IL35. Among these IL6 is main pro-inflammatory cytokine and IL 10 is responsible for immune-paralysis. Studies showed that IL 6 and IL 10 expression is related to cytokine storming in COVID-19 patients.[7]

ii. Tumor Necrosis Factor (TNFs): Though mainly involved in mast cells and macrophage activation but are also responsible for immune cell activation, their growth, differentiation and death. TNFα is involved in potent activation of T-cells and has a prominent role in cytokine storming in Covid-19 patients.[2]

iii. **Interferons (IFN):** There are type I and type II interferons that are main antiviral protein produced by our body. As Covid-19 is a viral infection their role is very important in recovery of patient. As Retinoic acid-inducible gene I (RIG - I) showed an antiviral role against viral infections and was essential for activation of type I IFN signaling during infection.[8]

iv. **Colony Stimulating Factor (CSF):** They mainly act on stem cells in bone marrow and stimulate growth and differentiation of monocytes, dendrite cells and neutrophils. Hence, play a vital role in immune response.[2]

Cytokine Storm

Our immune system is our natural defense mechanisms against various infections. In normal circumstances infections stimulate our immune response and there is an increase in cytokine production which triggers pro-inflammatory response with production of large number of different types of white blood cells.[6] Clinical and laboratory evidence has indicated that in some COVID-19 patients this immune response is dis-regulated and kept on getting sever with production of large number of cytokines resulting cytokine storming in body.[9] This cytokine storming causes many adverse effects and causes multiple disorders[10] ranging from pneumonia, liver cirrhosis, kidney failure, cardiac arrest and neural dysfunction (Figure 1).

Progression

On contraction of COVID19, it travels down the respiratory tract and settles in alveoli and kept on multiplying in cells. This damage of cells release cytokines and when cell bursts it will release viral DNA which is received by antigen presenting (APCs) dendritic cells.[11,12] As a result IgM and IgG antibodies are produce. Our humoral and cellular immune response become active and release inflammatory cytokines.[6,13] Though it is a normal immune response by our body but in some COVID-19 patients it leads to a power full immune attack on body that begins in lungs and then spread to rest of the body. These immune responses cause production of large number of pro-inflammatory cytokines (IL6, TNFα and CSF) resulting in lung edema, acute respiratory distress syndrome and secondary bacterial infections. T-cells and natural killer cells are main contributors in cytokine storming.[14] It can result in many complication Figure 1. High levels of TNFα and IL6 will gradually cause multiple organ failure these cytokines are detected in blood of COVID-19 patients.[15]

Diagnosis

There are no specific tests for the prediction of cytokine storming but some of the following tests might be help full and can save many lives Table1.

Treatment

At present various drugs are being used in Randomized Clinical Trials (RCT) but results vary in different studies. One study revealed that treatment with lopinavir/ritonavir antivirals during early progression of disease can reduce risk of severity of disease.[24] chloroquine and hydroxychloroquine were also giving to patients during RCT as there effect as suppressor of TNFα and IL6 is well established but later studies did not support these early findings[25] Tocilizumab, is an already approved recombinant humanized anti-human IL6 receptors monoclonal

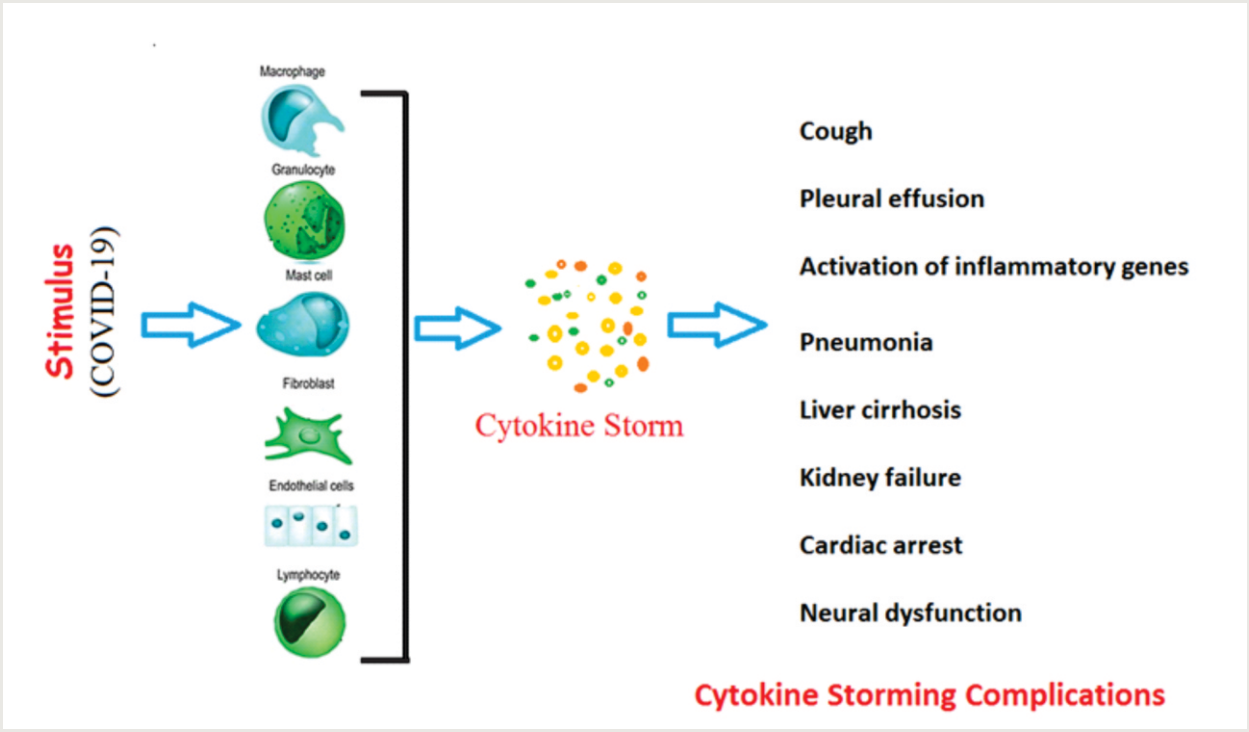

Figure 1: *Progression of Cytokine Storming in COVID-19 Patients and Medical Complications Associated with it*

antibody for treatment of rheumatoid arthritis. In RCT tocilizumab has shown positive results in suppressing pro-inflammatory response of body.[24,26] In another study human IgG monoclonal antibodies are also used as it effectively binds with soluble and membrane bound IL6.[27] All these treatments mainly work as immune suppressors. In countries like India and Pakistan hospital environment is not germ free and patients with low immunity will be highly vulnerable to catch other diseases.

Mortality

There are 6,047,501 confirmed cases of COVID-19 have been reported so far. Out of these cases, there are 30, 39,072 closed cases with a mortality rate of 12% with 367,149 deaths.[28] In India there are 169,114 confirmed cases out these 86422 are active cases and 82,692 are cured so far. 4971 patients had lost their lives in battle against COVID-19.[29] Similarly in Pakistan there are 66457 confirmed cases out of which 24131 have recovered and 1395 have lost their lives.[3,30] In both countries India and Pakistan a similar pattern is observed with low mortality rate of 6% and 5% respectively as compared to overall mortality rate of 12%.[3] This rate can be further lowered by using early biomarkers of cytokine storming and using appropriate treatment.

Conclusions

Fragile health care system of developing countries like India and Pakistan cannot bear the burden of critically ill patients. All studies across the globe indicated a link between COVID-19 related complications and CS. Government should invest to equip health sector for detection of early bio markers for CS. This early evaluation can reduce burden on Intensive Care Units in hospitals and save many lives.

Table 1: *Diagnostic tests as predictors of COVID-19 infection*

Sr. no	Test	Level normal (ng/ml)	Level In CS (ng/ml)	Cause	Reference
1.	Ferritin	10-300 male 10-150 female	1000s	Pro-inflammatory signals Early marker	16,17,18
2.	Cytokine Reactive Proteins	3	10	Response to IL6 by liver	19,20,21
3.	D-Dimer	-	3-4 times	Pro-inflammatory Signals	22,23

Conflict of Interest

Authors declare no conflict of interest.

References

1. World Health Organization: Coronavirus disease 2019 (COVID-19) Situation Report – 73[www.who.int] accessed on May 22, 2020.
2. Vaninov, N. In the eye of the COVID-19 cytokine storm. Nat Rev Immunol. 2020; 20, 277.
3. World Ometer: Population of South Asia [www.worldometers.info] accessed on May 22, 2020.
4. Pakistan Bureau of Statistic: [http:// www.pbs.gov.pk/] accessed on May 22, 2020.
5. Teijaro JR. Cytokine storms in infectious diseases. Seminars in immunopathology 2017; 39(5):501–3.
6. Mehta P, McAuley DF, Brown M. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020; 395(10229):1033-1034.
7. Hunter Christopher A, Jones Simon A. IL-6 as a keystone cytokine in health and disease. Nature immunology, 2015;16(5):448–57.
8. Montoya JG, Holmes TH, Anderson JN. Cytokine signature associated with disease severity in chronic fatigue syndrome patients. Proc Natl Acad Sci U S A. 2017; 114(34):7150-7158.
9. Pengfei Li, Xiangle Zhang, Weijun Cao, Fan Yang, Xiaoli Du, Zhengwang Shi. RIG-I is responsible for activation of type I interferon pathway in Seneca Valley virus-infected porcine cells to suppress viral replication. Virol J. 2018; 15: 162.
10. Brune K, Frank J, Schwingshackl A. Pulmonary epithelial barrier function: some new players and mechanisms. Am J Physiol Lung Cell Mol Physiol, 2015; 308(8):L731–45.
11. Kishimoto T, Kang S, Tanaka T. IL-6: A New Era for the Treatment of Autoimmune Inflammatory Diseases. In: Nakao K, Minato N, Uemoto S, eds. Innovative Medicine: Basic Research and Development. Tokyo: Springer; 2015:131-147.
12. Qian Liu, Rong-shuai Wang, Guo-qiang Qu, et al. Gross examination report of a COVID-19 death autopsy. Journal of Forensic Medicine, 2020; 36(1): 19–21.
13. Janeway CA Jr, Travers P, Walport M. Immunobiology: The Immune System in Health and Disease. 5th edition. New York: Garland Science. The distribution and functions of immunoglobulin isotypes. 2001, Available from: https://www.ncbi.nlm.nih.gov/ books/NBK27162/
14. Silk AW, Margolin K. Cytokine Therapy. Hematol Oncol Clin North Am. 2019;33(2):261-274.
15. Xu Zhe, Shi Lei, Wang Yijin, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. The Lancet Respiratory Medicine, 2020.
16. Medpage Today, cautions against ascribing too much influence to hyper-inflammation Ashish Kumar. Accessed on May 26, 2020. Available from: https://www.medpagetoday.com/infectiousdisease/covid19/86021.
17. MedicineNet: Ferritin blood test. Accessed on May 22, 2020. Available from: https://www.medicinenet.com/ferritin_blood_test/article.htm
18. Morikawa K, Oseko F, Morikawa S. A role for ferritin in hematopoiesis and the immune system. Leuk Lymphoma. 1995;18 (5-6):429-433.
19. Richter K, Sagawe S, Hecker A. C-Reactive Protein Stimulates Nicotinic Acetylcholine Receptors to Control ATP-Mediated Monocytic Inflammasome Activation. Front Immunol. 2018; 9:1604.
20. Laborada G, Rego M, Jain A. Diagnostic value of cytokines and C-reactive protein in the first 24 hours of neonatal sepsis. Am J Perinatol. 2003; 20(8): 491-501.
21. AIDIAN: CRP and COVID-19. Accessed on May 25, 2020. Available from: https://www.aidian.eu/latest-covid-19-updates-and-supportive-diagnostic-tools/crp-and-covid-19
22. Medscape: D-Dimer Reference Range. Accessed on May 26, 2020. Available from: https:// emedicine.medscape.com
23. Zhang L, Yan X, Fan Q. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. J Thromb Haemost. 2020;10:11
24. Cunningham AC, Goh HP, Koh D. Treatment of COVID-19: old tricks for new challenges. Crit Care. 2020; 24(1):91.
25. Golden EB, Cho HY, Hofman FM, Louie SG, Schonthal AH, Chen TC. Quinoline-based antimalarial drugs: a novel class of autophagy inhibitors. Neurosurg Focus.2015; 38(3):E12
26. Zhai P, Ding Y, Wu X, Long J, Zhong Y, Li Y. The epidemiology, diagnosis and treatment of COVID-19. Int J Antimicrob Agents. 2020; 55(5):105955.
27. Brudno JN, Kochenderfer JN. Recent advances in CAR T-cell toxicity: mechanisms, manifestations and management. Blood Rev. 2019; 34:45–55.
28. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the `Cytokine Storm' in COVID-19. J Infect. 2020; 80(6):607-613.
29. Ministry of Health and Family Welfare: COVID-19 India [https://www.mohfw.gov.in/] accessed on May 26, 2020.
30. Institute of Strategic Studies Islamabad: Issue Brief on "Impact of Covid-19 on Economy of Pakistan" [http://issi.org.pk/] Accessed on May 26, 2020.