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LYMPHOPENIA AND SEVERITY OF COVID-19 DISEASE A RETROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

Objective: To study lymphopenia as a marker in severity of COVID-19 disease
Materials & methods: It is a retrospectiove observational study of the 64 COVID-19 cases admitted at a dedicated tertiary COVID hospital in Mumbai. We reported 64 COVID-19 cases presenting to our center with variable presentations. All the patients were evaluated with blood investigations, inflammatory markers and computed tomography of thorax on admission
Results: The mean age of the study population was 54.93 years. Lymphopenia was noted in 34 number of cases and 45 patients had severe disease requiring oxygenation and intensive care. Total 8 patients died during the course of illness in the hospital. Out of the 8 patients died, 6 had absolute lymphopenia of less than 1000 cells/mm^3 and out of that 6,4 cases had lymphopenia of less than 500 cells/mm^3
Conclusion: Our study showed that lymphopeniawas associated with increased mortality, ARDS, need for ICU care, and severe COVID-19.Thus, lymphopenia can be useful to associate with the severity of the COVID-19 disease.

INTRODUCTION

The novel Coronavirus 2019 is an enveloped, positive-sense, single-stranded RNA beta-coronavirus. The spread of COVID-19 is known to occur via human to human transmission through respiratory tract or can be fomite borne as well.Because of a large number of patients being asymptomatic there is a great risk of transmission and they also possess a greater threat for this spread and outbreak[1].

The 2019-nCoV genome encodes non-structural proteins and has an incubation period of 3-7 days, which indicates long transmission[2].

The most common symptoms at the onset of illness which were considered as mild symptoms are fever, cough, and myalgia or fatigue along with stuffiness of nose, pharyngalgia or diarrhoea[3].

Severe symptoms or patients who were considered critical may have symptoms like dyspnea, hypoxemia one week after onset and may progressed into ARDS acute respiratory distress syndrome. For patients to meet the diagnostic criteria, laboratory confirmation of the samples taken from thenasopharynx, theoropharyngeal swab and if possible from lower respiratory tract e.g. sputum, bronchoalveolar lavage etc. is necessary[4].

Along with this, altered laboratory findings are also seen like lymphopenia, prolonged prothrombin time, and elevated lactate dehydrogenase, elevated aspartate aminotransferase, creatine kinase, creatinine, and C-reactive protein is seen[5,6,7,8]. This retrospective study was planned with an aim to report the demographic parameters as well as the clinical presentation and outcome of the patients suffering from COVID 19.

The data presented in this study was obtained from the patients admitted in hospital after screening and laboratory confirmation of COVID 19 infection.

MATERIALS & METHODS

It is a retrospectiove observational study of the 64 COVID-19 cases admitted at a dedicated tertiary COVID hospital in Mumbai. The oropharyngeal swabs reports were available from the local Viral Research & Diagnostic Laboratory (VRDL) or the private labs which used the quantitative polymerase chain reaction for confirmation. All the cases were hospitalized for the isolation facility and further management. The isolation facility at our hospital was assessed for preparedness according to a checklist standardized by Ministry

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of Health and Family Welfare (MoHFW)[9]. All the health-care workers caring for infected patients received comprehensive training and demonstrated competence in implementing infection control practices and procedures. All laboratory-confirmed cases irrespective of the mild, moderate and severe illness were eligible for inclusion in this study and the demographic, clinical, and laboratory data along with radiology investigations and outcome were recorded. The study includes all the adult patients between the age group of 25-80 years of age. The laboratory data includes complete hemogram profile along with inflammatory markers like Interleukin-6,D-dimer,ferrtitin.The radiological investigations done either Chest X-ray or the computed tomography of thorax.In the complete hemogram profile of the patients lymphocyte counts were noted and it has been co-realted with the severity of the patients. We defined severe disease as those patients who required oxygenation with the help of various oxygen delivery devices and admission to the ICU; non-severe disease was classified as those admitted to the hospital, but did not require ICU admission. Admission to the ICU was determined by clinical factors, namely respiratory failure and hemodynamic instability. Lymphocytopenia was not part of these criteria. All the patients received standard treatment as per the Indian council of Medical Research (ICMR) guidelines and were monitored during their stay at the hospital. The outcomes were noted as died, discharged or transferred to step down COVID care Center as per hospital policy.

Our study reported that lymphopenia has been associated with the severity of the COVID-19 infection and it can be used as a useful marker for predicting severity of the disease.

RESULTS

Total 64 cases included in the study which were admitted at tertiary care hospital. The mean age of the study population was 54.93 years (Range 26-77 years).

Out of the 64 patients 38 had associated co-morbidities (59.37%). The most common co-morbidity noted was Diabetes mellitus seen in 28 cases (43.75%) and second most common co-morbidity was hypertension seen in 14 cases (21.87%).The other common co-morbidities noted were chronic kidney disease, retro-viral disease, hypothyroidism, bronchial asthma. Many of the cases showed overlapping co-morbidities.

All the cases evaluated with blood investigations were analyzed for the absolute lymphocyte counts on admission. Out of the total 64 study population,34 cases (53.12%) had lymphopenia less than 1000 cells/mm^3.Out of the 34 cases,22 cases had lymphocyte count less than 500 cell/mm^3 and 12 cases had lymphocyte count between 500-1000 cells/mm^3.21 cases had lymphocyte count between 1000-2000 cells/mm^3.

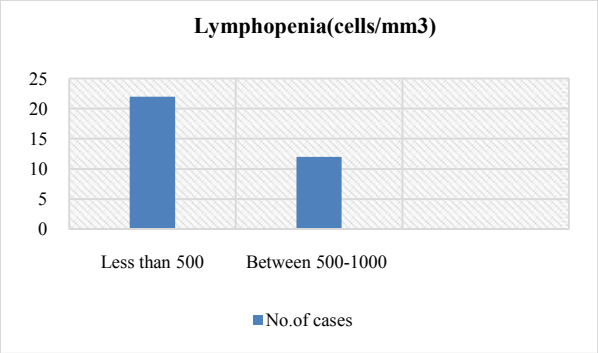

Chart 1

Total 45 cases were unstable and requiring oxygenation out of 64 cases(70.31%).16 cases needed nasal cannula while 29 cases managed with non rebreather breathing mask while 3 cases needed non-invasive ventilation. Out of the 45 unstable cases,32 cases had associated co-morbidities.

Table 1

Mean Age (in years)	54.93 years
No. of co-morbidities	38 out of 64 cases (59.37%)
Unstable cases	45 out of 64 cases (70.31%)
No.of patients who died	8 out of 64 cases (12.5%)

Total 8 patients died during the course of illness in the hospital. All the 8 cases were unstable and was requiring oxygenation and all the 8 cases had significant lung involvement on high resolution computed tomography of thorax ranging from 25% to maximum of 75-100%.The mean age of the patients who died was 61.62 years.

Out of the 8 patients died,6 had absolute lymphopenia of less than 1000 cells/mm3 and out of that 6,4 cases had lymphopenia of less than 500 cells/mm3.

DISCUSSION

The COVID-19 pandemic has affected more than 180 nations over a brief period of time and has caused global health crisis. The COVID-19 has variable presentation from asymptomatic presentation or upper respiratory tract infection to pneumonias and respiratory failure.

About 20 to 40 percent of all white blood cells are lymphocytes. A normal lymphocyte count for adults usually is between 1,000 and 4,800 lymphocytes per microliter of blood. For children, a normal lymphocyte count usually is between 3,000 and 9,500 lymphocytes per microliter of blood. The term "lymphocytopenia" refers to a count of less than 1,000 lymphocytes per microliter of blood in adults, or less than 3,000 lymphocytes per microliter of blood in children.

The Lymphopenia pathogenesis in COVID-19 can be described by studies of other similar beta-CoV infection, including severe acute respiratory syndrome (SARS)-CoV and Middle East respiratory syndrome (MERS)-CoV[10]. Peripheral T lymphocytes like CD4+ and CD8+, are rapidly reduced in acute SARS-CoV infection hypothetically due to lymphocyte sequestration in specific target organs [11]. Though MERS-CoV and SARS-CoV have structural similarity, they bind to different receptors for the entry into the cells. SARS-CoV attaches to angiotensinconverting enzyme 2 (ACE2) to enter the host cells, while MERS-CoV attaches to a different receptor, nameddipeptidyl peptidase 4 (DPP4) [12]. Although the mechanism of lymphopenia in severe COVID-19 remains unclear, there are hypothesis other than lymphocyte infiltration and sequestration in the lungs, gastrointestinal tracts, and or lymphoid tissues:

Lymphocytes play a decisive role in maintaining immune homeostasis and inflammatory response throughout the body..Some studies described four potential mechanisms leading to lymphocyte deficiency.

1. The virus might directly infect lymphocytes, resulting in lymphocyte death. Lymphocytes express the coronavirus receptor ACE2 and may be a direct target of viruses [13].
2. The virus might directly destroy lymphatic organs. Acute lymphocyte decline might be related to

lymphocytic dysfunction, and the direct damage of novel coronavirus virus to organs such as thymus and spleen cannot be ruled out. This hypothesis needs to be confirmed by pathological dissection in the future.

3. Inflammatory cytokines continued to be disordered, perhaps leading to lymphocyte apoptosis. Basic researches confirmed that TNFα, IL-6 and other pro-inflammatory cytokines could induce lymphocyte deficiency[14].
4. Inhibition of lymphocytes by metabolic molecules produced by metabolic disorders, such as hyperlacticacidemia. The severe type of COVID-19 patients had elevated blood lactic acid levels, which might suppress the proliferation of lymphocytes[15]. Multiple mechanisms mentioned above or beyond might work together to cause lymphopenia, and further research is needed.

Our study found out that 53.12% had lymphopenia less than 1000 cells/mm^3.Out of those cases 64.70% had lymphocyte count less than 500 cell/mm^3 and 35.29%cases had lymphocyte count between 500-1000 cells/mm^3.In our study 8 patients who died had lymphopenia out of 64 cases accounting to 12.5% of death rate.

The study by M.Zheng *et al* showed that the NK cells and Cytotoxic T lymphocytes were significantly reduced in patients with COVID-19[16].

Another study showed that the total number of CD8+and CD4+ T cells was adequately decreased in patients with SARSCoV2 infection, particularly in elderly patients more than 60 years old and patients needing intensive care unit[17].Lymphopenia as a major immunological abnormality is observed in up to 96.1% of severe COVID-19 patients, and its degrees correlate with disease outcome[18].

The proportion of blood lymphocyte has demonstrated the most significant and reliable correlation with disease progression in patients who died due to COVID-19[19]. According to meta-analysis study of 3099 patients from 24 studies by Huang *et al*[20] showed that lymphopenia on admission was associated with poor outcome in patients with COVID-19 disease and sub group analysis showed lower lymphocyte count less than 500 in patients who either died, experienced ARDS, received ICU care and had severe COVID-19 disease

CONCLUSION

Our study showed that lower lymphocyte count was associated with increased mortality, ARDS, need for ICU care, and severe COVID-19.The limitations of this study include small sample size and focus on one hospital. Along with that, other leukocyte subtypes such as eosinophil and neutrophil counts were not examined in this study. The strengths of this study include the use of an easily obtained laboratory value that is associated with clinical outcomes and a focus on a predominantly minority population of patients who seem to be heavily impacted by Covid-19. Thus, it appears likely that lymphocytopenia is related to disease severity and clinical outcomes in Covid-19.

References

1. Chan J. F.W., Yuan S., Kok K.H, *et al*. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. The Lancet. 2020. DOI: 10.1016/S0140-6736(20)30154-9
2. National Administration of Traditional Chinese Medicine. Diagnosis and treatment of novel coronavirus infected pneumonia (The fifth edition). [Accessed 9 Feb. 2020]. Available from: http://www.satcm.gov.cn
3. Chen N.S, Zhou M, Dong X, *et al*. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. The Lancet. 2020; DOI: 10.1016/S0140-6736(20)30211-7
4. Patel A JD: Initial Public Health Response and Interim Clinical Guidance for the 2019 Novel Coronavirus Outbreak-United States, December 31, 2019–February 4, 2020. MMWR Morb Mortal Wkly Rep 2020, 69:140.
5. Huang C, Wang Y, Li X, *et al*. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The lancet. 2020. DOI: 10.1016/S0140-6736(20)30183-5
6. WangD,HuB,HuC,ZhuF,LiuX,ZhangJ,WangB,XiangH, ChengZ, Xiong Y *et al*: Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA 2020
7. Gupta N, Agrawal S, Ish P, Mishra S, Gaind R, Usha G, Singh B, Sen MK, Safdarjung Hospital COVID 2019 working group. Clinical and epidemiologic profile of the initial COVID-19 patients at a tertiary care centre in India. Monaldi Archives for Chest Disease. 2020 Apr 10;90(1).
8. Lin L, Lu L, Cao W, Li T. Hypothesis for potential pathogenesis of SARS-CoV2 infection--a review of immune changes in patients with viral pneumonia. Emerg Microbes Infect Taylor & Francis. 2020;0:1 –14.
9. Li T, Qiu Z, Zhang L, Han Y, He W, Liu Z, *et al*. Significant changes of peripheral T lymphocyte subsets in patients with severe acute respiratory syndrome. *J Infect Dis*. 2004;189:648 –51.
10. Raj VS, Mou H, Smits SL, Dekkers DHW, Müller MA, Dijkman R, *et al*. Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC. Nature. 2013; 495:251 –4.
11. Xu H, Zhong L, Deng J, Peng J, Dan H, Zeng X, *et al*. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. *Int J Oral Sci Springer* US. 2020;12:1 –5
12. Liao YC, Liang WG, Chen FW, Hsu JH, Yang JJ, Chang MS. IL-19 induces production of IL-6 and TNF-alpha and results in cell apoptosis through TNF-alpha. *J Immunol* 2002; 169(8): 4288-97.
13. Fischer K, Hoffmann P, Voelkl S, *et al*. Inhibitory effect of tumor cell-derived lactic acid on human T cells. Blood 2007; 109(9): 3812-9.
14. Zheng M, Gao Y, Wang G, Song G, Liu S, Sun D, Xu Y, Tian Z. Functional exhaustion of antiviral lymphocytes in COVID-19 patients. Cellular & molecular immunology. 2020 May;17(5):533-5.
15. Diao B, Wang C, Tan Y, Chen X, Liu Y, Ning L, Chen L, Li M, Liu Y, Wang G, Yuan Z. Reduction and functional exhaustion of T cells in patients with coronavirus disease 2019 (COVID-19). Frontiers in Immunology. 2020 May 1;11:827.
16. Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, Xie C, Ma K, Shang K, Wang W, Tian DS. Dysregulation of

immune response in patients with COVID-19 in Wuhan, China. Clinical Infectious Diseases. 2020 Mar 12.

17. Tan L, Wang Q, Zhang D, Ding J, Huang Q, Tang YQ, Wang Q, Miao H. Lymphopeniapredicts disease severity of COVID-19: a descriptive and predictive study. Signal transduction and targeted therapy. 2020 Mar 27;5(1):1-3.
18. Huang I, Pranata R. Lymphopenia in severe coronavirus disease-2019 (COVID-19): systematic review and meta-analysis. *Journal of Intensive Care*. 2020 Dec;8(1):1-0.

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