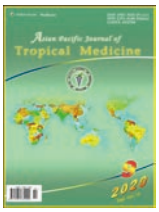

Letter to Editor

Asian Pacific Journal of Tropical Medicine

journal homepage: www.apjtm.org

doi: 10.4103/1995-7645.290588

Impact Factor: 1.94

Lymphopenia as a marker for disease severity in COVID-19 patients: A meta-analysis

Praveen Devanandan[1], Ranadheer Chowdary Puvvada[1], Vijey Aanandhi Muthukumar[2]✉

[1]*School of Pharmaceutical Sciences, Vels Institute of Science Technology and Advanced Studies, Chennai, India*

[2]*Department of Pharmaceutical Chemistry and Analysis, School of Pharmaceutical Sciences, Vels Institute of Science Technology and Advanced Studies, Chennai, India*

COVID-19 has become the global focus since December 2019[1]. Patients usually experience cough, fever and flu-like symptoms. Most patients also experience dyspnoea. Elevated procalcitonin, lymphopenia are observed in COVID-19 patients. Recently, a case series analysis has predicted that lymphopenia may be a very good prognostic marker for disease progression in COVID-19[2].

An extensive literature search is carried out in PubMed, Scopus and Google Scholar using the medical subject heading terminology (MeSH)-'novel coronavirus', 'ncov-2019', 'Wuhan', 'COVID-19' and 'SARS-CoV-2'. We included papers that reported the epidemiological aspects of COVID-19 such as retrospective studies, observational reports published between 1st January 2020 and 20th March 2020. Papers published in English that reported the biochemical data of these patients were included. Publications with emphasis on severity of the patients were included. Studies that did not report the absolute lymphocyte count, letters to the editor, reviews and opinions were excluded. A meta-analysis was then carried out with the selected studies and individual as well as pooled odds ratio was calculated to determine the statistical importance of lymphopenia on the severity of COVID-19 patients.

Overall 22 articles were identified using our selection criteria, out of which 16 were excluded after reviewing their abstract for full text reading. Six articles provided data of absolute lymphocyte count for all patients as well as for severely ill patients[3-8]. The summarised findings are reported in Table 1. Two of the articles did not provide data on number of patients who had lymphopenia. Hence 4 manuscripts were finally selected, their individual odds ratio as well as pooled odds ratio was calculated with 95% confidence interval[3,6-8]. The summarised findings are reported in Table 2 as well as Figure 1.

From the calculated data, baseline absolute lymphocyte count has a significant impact on the disease severity. A case report reported that patient had a fall in the absolute lymphocyte count even after the initiation of the therapy[9]. The calculated odds ratio suggested a four-fold increase in chance of disease severity (either for ICU care or death) in COVID-19 patients who had a low lymphocyte count at the baseline. In these selected studies, 90.58% (250/276) of the severely ill patients had lymphopenia. This may be a very essential factor in predicting the outcome of the treatment and the course of hospitalization of COVID-19 patients.

The common aetiology of lymphopenia is auto-immune disorders (such as rheumatoid arthritis, myasthenia gravis), carcinomas, infectious diseases like AIDS, tuberculosis and inherited conditions like ataxia-telangiectasia, and Wiskott-Aldrich syndrome. Chemotherapeutic agents may also cause lymphopenia. In the selected studies, totally 13 patients had carcinoma of various nature[3,6,8] 2 patients reported immunodeficiency[8] and 2 patients reported secondary pulmonary tuberculosis[7]. Among these only 3 cancer patients and 2 pulmonary tuberculosis patients reported for severe COVID-19 outcome[7,8]. Even if the data of these patients are not considered, the resulting odds ratio is 3.67 (95% *CI* 2.39 to 5.63).

Lymphopenia is commonly observed in severe acute respiratory syndrome (SARS) as well as Middle East respiratory syndrome (MERS) although the cause of lymphopenia in these diseases is

✉To whom correspondence may be addressed. E-mail: hodpchemistry@velsuniv.ac.in

How to cite this article: Devanandan P, Puvvada RC, Muthukumar VA. Lymphopenia as a marker for disease severity in COVID-19 patients: A meta-analysis. Asian Pac J Trop Med 2020; 13(9): 426-428.

Article history: Received 16 April 2020 Revision 13 July 2020
Accepted 14 July 2020 Available online 5 August 2020

Table 1. Absolute lymphocyte count in COVID-19 patients.

Study	Journal	Total No. of patients	Absolute lymphocyte Count ($\times10^9$ cells/L)	Severe outcome	No. of severely ill patients	Absolute lymphocyte count ($\times10^9$ cells/L) of severely ill patients
Huang *et al*[3]	*Lancet*	41	0.80 (0.6-1.1)	ICU Care	13	0.4 (0.2-0.8)
Wang *et al*[4]	*JAMA*	138	0.80 (0.6-1.1)	ICU Care	36	0.8 (0.5-0.9)
Yang *et al*[5]	*Lancet Resp Med*	20[#]	0.74 (0.40)[b]	Death	32	0.62 (0.37)[b]
Fei *et al*[6]	*Lancet*	191	1.00 (0.6-1.3)	Death	54	0.6 (0.5-0.8)
Zhang *et al*[7]	*Allergy* (Wiley)	138	0.80 (0.6-1.1)	Severe	56	0.7 (0.5-1.0)
Guan *et al*[8]	*JAMA*	1099[a]	1.00 (0.7-1.3)	Severe	153	0.8 (0.6-1.0)

Absolute lymphocyte count is denoted in median (inter-quartile range) unless otherwise mentioned. [#]Data available for Survivors instead of total population. [a]Lymphocyte count is available only for 879 patients out of 1 099. [b]Values are mentioned as mean (S.D). Table 1 denotes the selected studies along with the journals in which they are published. The total no.of patients included in each study and their absolute lymphocyte count is denoted. The nature of severe outcome as mentioned in each study is denoted followed by number of cases with such outcome and their absolute lymphocyte count is denoted.

Table 2. Meta–analysis of the available data.

Study	Total No.of patients	No. of patients with lymphopenia	No. of severe cases[a]	No. of severe cases with lymphopenia	*OR* (95% *CI*)	*P* value	Weight (%)
Huang *et al*[3]	41	26	13	11	4.77 (0.89-25.57)	0.068	3.28
Fei *et al*[6]	191	77	54	46	19.66 (0.40-46.04)	<0.001	15.29
Zhang *et al*[7]	138	104	56	46	1.90 (0.83-4.38)	0.130	11.05
Guan *et al*[8]	879	731	153	147	5.96 (2.58-13.75)	<0.001	70.38
Total	1 249	938	276	250	3.98 (2.60-6.10)	<0.001	100.00

[a]Severe cases refers to ICU care or death.

unknown. Studies reported that SARS CoV virus may lead to T cell depletion by directly infecting T cells; however, there are contraindicated studies which emphasized on the role of cytokine induced cell death as well as bone marrow hematopoietic progenitor cells suppression. It was observed from a study that delayed clearance of SARS coronavirus from the lung tissue was associated with reduced pulmonary recruitment of lymphocytes is seen in mice[10]. Additional studies are essentially needed to confirm whether lymphopenia could be a predictable marker for projecting the disease severity.

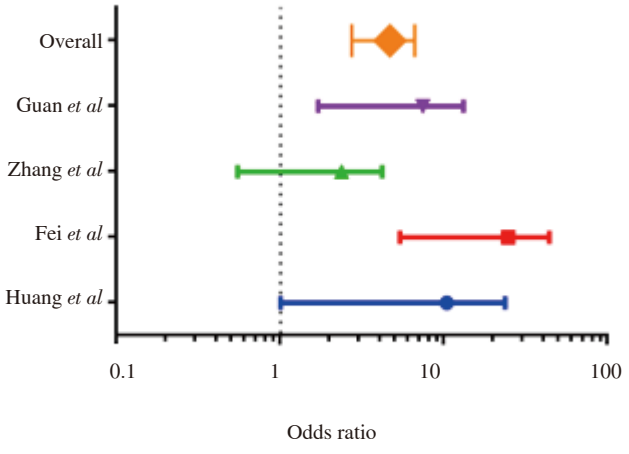

Figure 1. Forest plot of the available data: Odds ratio of the 4 selected studies along with cumulative odds ratio.

It could be observed that the absolute lymphocyte count is comparatively lesser in the severely ill patients as well as non-survivors. We sorted out 4 studies that reported on number of patients who had lymphopenia among all patients as well as severe cases[3,6-8].

The combined odds ratio calculated based on weight of each study is indicating extremely significant (P<0.001) outcome. The test for heterogeneity I^2=73%. An odds ratio above 1 is considered significant for the predicted outcome. The overall calculated odds ratio is 3.98 which indicates almost 4 times higher chance for the predicted outome (Disease Severity in COVID-19 patients).

In conclusion, there is a 4-fold higher risk of disease severity either ICU care or death in patients who have a low lymphocyte count at the baseline. Low lymphocyte count may affect drug selection. Hence, lymphopenia maybe a very essential factor in predicting the outcome of the treatment and the course of hospitalization of COVID-19 patients.

Conflict of interest statement

We declare that we have no conflict of interest.

Authors' contributions

P.D. developed the hypothesis, P.D., R.C.P conducted literature search. P.D, R.C.P., M.V.A carried out analytical calculations and writing of the manuscript. M.V.A is the superviser.

References

[1] Lu H, Stratton C, Tang, Y. Outbreak of pneumonia of unknown etiology in Wuhan China: the mystery and the miracle. *J Med Virol* 2020; **92**(4): 401-402.

[2] Tan L, Wang Q, Zhang D, Ding J, Huang Q, Tang Yi, et al. Lymphopenia predicts disease severity of COVID-19: A descriptive and predictive study. *Sig Transduct Target Ther* 2020; 33(5). doi:10.1038/s41392-020-0148-4.

[3] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet* 2020; **395**(10223): 497-506.

[4] Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA* 2020. doi:10.1001/jama.2020. 1585.

[5] Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: A single-centered, retrospective, observational study. *The Lancet* 2020. doi:10.1016/S2213-2600(20)30079-5.

[6] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. *The Lancet* 2020; **395**(10229): 1054-1062.

[7] Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, et al. Clinical characteristics of 140 patients infected by SARS-CoV-2 in Wuhan, China. *Allergy* 2020. doi:10.1111/all.14238.

[8] Guan WJ, Ni ZY, Hu Y, Liang W, Ou C, He J, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med* 2020. doi: 10.1056/NEJMoa2002032.

[9] Zhang Z, Li X, Zhang W, Shi Z, Zheng Z, Wang T. Clinical features and treatment of 2019-nCov pneumonia patients in Wuhan: Report of a couple cases. *Virol Sin* 2020; **35**(3): 330-336.

[10]Chen J, Lau YF, Lamirande EW, Paddock CD, Bartlett JH, Zaki SR, et al. Cellular immune responses to severe acute respiratory syndrome coronavirus (SARS-CoV) infection in senescent BALB/c mice: $CD4^+$ T cells are important in control of SARS-CoV infection. *J Virol* 2010; **84**: 1289–1301.