



REVIEW ARTICLE

What We Know of the Prognostic Value of Lymphopenia in SARS-CoV-2 Infection

Atieh Pourbagheri-Sigaroodi¹, Davood Bashash^{1*}, Meysam Olfatifar², Sina Salari³, Hassan Abolghasemi⁴

¹Department of Hematology and Blood Banking, School of Allied Medical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran

²Gastroenterology and Liver Diseases Research Center, Research Institute for Gastroenterology and Liver Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran

³Department of Medical Oncology, Hematology and Bone Marrow Transplantation, Taleghani Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

⁴Pediatric Congenital Hematologic Disorders Research Center, Mofid Children's Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

ARTICLE INFO

Article History:

Received: 26.04.2020

Accepted: 06.07.2020

Keywords:

SARS-CoV-2

COVID-19

Prognosis

Lymphocyte

Lymphopenia

Meta-analysis

*Corresponding author:

Davood Bashash, PhD;
Department of Hematology and Blood

banking, School of Allied Medical
Sciences, Shahid Beheshti University

of Medical Sciences, Tehran, Iran

Tel: +98-21-22717504

Fax: +98-21-22721150

Email: d.bashash@sbmu.ac.ir

ABSTRACT

Background: Although by comparing the number of deaths to the total number of cases one may conclude that most of the infected cases are recovering, taking a look at the increasing statistics of deaths shows that SARS-CoV-2 continues to take its toll. Since lymphocytes are the main immune cells battling with rapidly evolving viruses, it comes as no surprise to assume that a decreased number of these propitious soldiers may contribute to poor prognosis of the wide range of viral infections, including COVID-19.

Methods: To provide a better prospect representing the prognostic value of lymphopenia in COVID-19, we searched the national library of medicine Medline/PubMed and performed a meta-analysis of pertinent literature representing information on the lymphocyte count in COVID-19 patients.

Results: The results of our meta-analysis revealed that the number of lymphocytes retains a specific clinical and biological significance in this infection and lymphopenia is seemingly an important hematological abnormality that contributes to mirror the evolution toward an unfavorable outcome.

Conclusion: The rapidly evolving nature of COVID-19 together with relentless disclosure of novel findings denotes a major limitation to the current study, and further investigations in the field of prognostic biomarkers will definitively pave the way to better manage patients with severe COVID-19.

Please cite this article as: Pourbagheri-Sigaroodi A, Bashash D, Olfatifar M, Salari S, Abolghasemi H. What We Know of the Prognostic Value of Lymphopenia in SARS-CoV-2 Infection. IJBC 2020; 12(3): 75-79.

Introduction

COVID-19 has been issued as a public health emergency of international concern by world health organization (WHO). Due to the great rate of recombination as a consequence of transcription errors and RNA-dependent RNA polymerase (RdRP) jumps,¹ coronaviruses (CoV) are amongst multi-faces organisms infecting both humans and animals.² Most members of this family had been considered harmless microbes until 2002 when the first outbreak of viral pneumonia was reported by the emergence of the severe acute respiratory syndrome

(SARS) in the Guangdong state of China.³ During the past decade, highly contagious coronavirus outbreaks occurred again with the notion that the latter was the latest biological hazard to assume the relevance of an ominous global warning.⁴

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), formerly known as the 2019 nCoV, is a newly emerging virus that is presumably derived from a bat SARS-like coronavirus and is transmitted to humans after the emergence of mutations in protein S and nucleocapsid N protein.⁵ The virus was first described

during a pneumonia outbreak in Wuhan city (Hubei Province, China) at the end of 2019. It attracted great attention in a short period of time as death toll and the number of confirmed cases grew unexpectedly since the first case was reported. At the time of writing this article (April 26, 2020), over 2,990,000 cases were verified in 212 countries with more than 205,000 related deaths (Figure 1) (<https://www.who.int/>). Clinically, COVID-19 is a respiratory syndrome with a wide spectrum of symptoms; while some of the infected cases will present no or mild symptoms, others will develop more serious complications, entailing specialized management at intensive care units (ICUs).⁶ Early identification of the disease together with a timely prediction of its outcome are suggested as the most important steps in the management of the patients. Since lymphocytes are the main immune cells battling with the viruses,⁷ it comes as no surprise to assume that lymphopenic patients may probably face a more complicated condition in viral infections,^{8,9} and COVID-19 shall not be considered as an exception to this rule.¹⁰ In the current meta-analysis, we aimed to assess whether lymphocyte count could discriminate between severe and non-severe COVID-19 patients, and evaluate if there is a correlation between lymphopenia and disease severity.

Materials and Methods

To provide a better prospect representing the prognostic value of lymphopenia in COVID-19, we searched national library of medicine Medline/Pubmed using the keywords “laboratory” OR “lymphocytes” AND “COVID-19” OR “coronavirus 2019” OR “2019-nCoV” OR “SARS-CoV-2” between December, 2019 and the time of our analysis (i.e., April 15, 2020), without any restriction. The results of the initial search strategy were first screened by title and abstract, and then full texts of relevant articles representing information on lymphocyte count (either the value or the percentage of lymphopenia) in COVID-19 patients with a clinically validated definition of severe disease were finally selected. To strengthen our analysis, we also scrutinized the reference list of relevant documents.

To provide a better representation of data reported in the selected studies, we performed a meta-analysis with the calculation of mean difference (MD) and 95% confidence intervals (CIs) of lymphocyte counts in severe and non-severe patients. To do so, we estimated the standard deviation (SD) of selected studies based on mean and their related CIs. Since the mean and SD of lymphocyte counts were not reported in one study,¹¹ we calculated them from the sample size, median and interquartile range (IQR). The statistical analysis was implemented in the R “meta” package.¹² We also applied subgroup analysis by study definition of severity. Heterogeneity between studies was estimated using the I^2 method, where I^2 values of 25%, 50% and 75% were defined as low, moderate and high heterogeneity, respectively. Although when we wrote this article, some limitations such as low sample size and non-synchronized methods of representing the results may have adversely affected the ability to draw

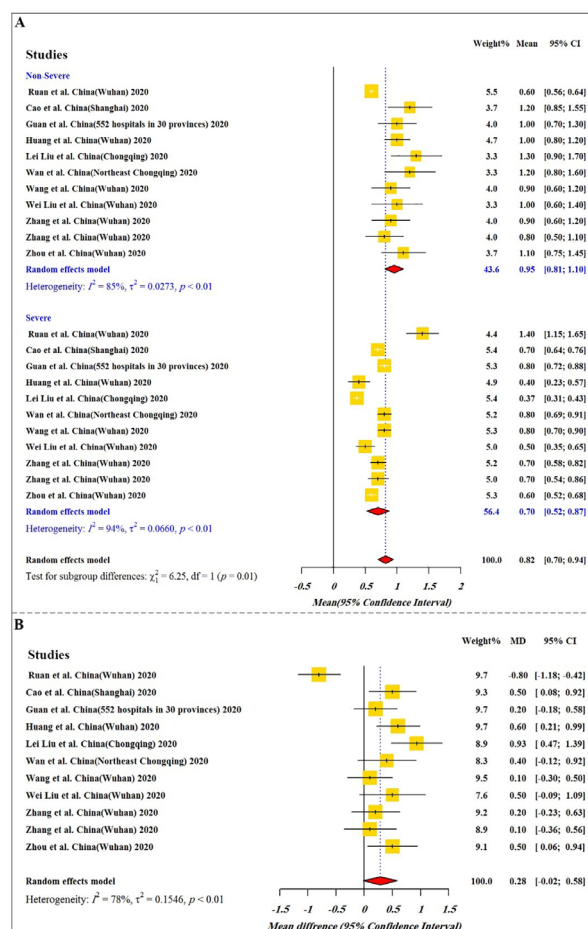


Figure 1: Forest plot of A) mean and B) mean difference in lymphocyte count between severe and non-severe COVID-19 patients.

a clear conclusion, the most important limitation was the variety in the cut-off defined for lymphopenia. As indicated in Table 1, lymphopenia was defined as the absolute lymphocyte counts <0.8 , <1.0 , <1.1 and $<1.5 \times 10^9/L$ in the selected studies (The relevant references are mentioned in the Table 1).

Results

Overall, 1892 articles were identified using the indicated criteria in our initial search and inspecting the reference lists, with a total excluding number of 1867 including 275 letters, 188 reviews, 141 editorials, 61 case reports, 53 comments, 6 guidelines, and 1 book as well as those articles that did not fulfill information on lymphocyte count and/or the percentage of lymphopenia. Studies reporting cases with incomplete information were excluded, as well. Out of 25 remaining articles, 11 studies were selected that represented lymphocyte count and the percentage of lymphopenia in both severe and non-severe COVID-19 cases. The main features of selected studies (totaling 2442 patients, 534 of whom (21.86%) with severe disease) were summarized in Table 1. In all these studies except one,¹³ infected men were more than women. The number of cases ranged between 41-1099, whilst severe cases, though with different definitions, varied between 7-173. While all 11 studies fulfilled information on the lymphocyte count, 3 studies did not

Table 1: Main features of the selected studies

	No. cases (Severe)	Age (year)	Female (%)	Severity definition	Lymphocytes ($\times 10^9/L$)			Lymphopenia (%)			Cut- off
					Total	Non- severe	Severe	Total	Non- severe	Severe	
Guan et al. ¹⁸	1099 (173)	47	41.9%	ICU admission Mech. ventilation Death	1.0 (0.7– 1.3)	1.0 (0.8– 1.4)	0.8 (0.6– 1.0)	83.2%	80.4%	96.1%	<1.5
Zhou et al. ¹⁹	191 (54)	56	38%	Death	1.0 (0.6– 1.3)	1.1 (0.8– 1.5)	0.6 (0.5– 0.8)	40%	26%	76%	<0.8
Cao et al. ²⁰	198 (19)	50	49%	ICU admission	1.1 (0.7– 1.1)	1.2 (0.8– 1.5)	0.7 (0.5– 0.9)	8.9%	0.6%	84.2%	<1.1
Zhang et al. ²¹	221 (55)	55	51%	WHO guideline ²²	0.8 (0.6– 1.1)	0.9 (0.6– 1.2)	0.7 (0.4– 0.9)	73.8%	69.3%	87.2%	<1.1
Wan et al. ²³	135 (40)	40	46.7%	ICU admission Mech. ventilation	1.1 (0.7– 1.5)	1.2 (0.8– 1.6)	0.8 (0.6– 1.0)	50%	38%	80%	<1.1
Wang et al. ²⁴	138 (36)	56	45.7%	ICU admission	0.8 (0.6– 1.1)	0.9 (0.6– 1.2)	0.8 (0.5– 0.9)	70.3%	NR	NR	<0.8
Liu et al. ²⁵	78 (11)	38	50%	ICU admission Mech. ventilation Death	0.98 (0.6–1.3)	1.0 (0.6– 1.4)	0.5 (0.3– 1.1)	NR	NR	NR	
Liu et al. ²⁶	51 (7)	45	37.3%	WHO guideline	1.1 (0.7– 1.6)	1.3 (0.9– 1.7)	0.37 (0.3–0.6)	51%	NR	NR	
Huang et al. ²⁷	41 (13)	49	27%	ICU admission	0.8 (0.6– 1.1)	1.0 (0.7– 1.1)	0.4 (0.2– 0.8)	63%	54%	85%	<1.0
Zhang et al. ²⁸	140 (58)	57	49%	CNHC guideline	0.8 (0.6– 1.1)	0.8 (0.6– 1.2)	0.7 (0.5– 1.0)	75%	70%	82%	<1.1
Ruan et al. ¹¹	150 (68)	58	32%	Death	1.10–3.20 (0.32)	0.6	1.4 (2.14)	NR	NR	NR	

NR: Not reported; CNHC: Chinese National Health Committee; Mech. Ventilation: Mechanical ventilation; ICU: Intensive care unit

present the percentage of lymphopenia. In addition, the cut-off defined for lymphopenia was different between these studies. As indicated in Table 1, lymphopenia was defined as the lymphocyte counts <0.8 , <1.0 , <1.1 and $<1.5 \times 10^9/L$ in the selected studies.

The results of our meta-analysis revealed that, in 10 out of 11 studies, non-severe COVID-19 cases displayed a higher number of lymphocyte as compared to patients with severe disease (mean difference ranging between 0.1 and $0.9 \times 10^9/L$) (Figure 1). Analysis of the pooled results of these 11 studies also confirmed that the number of lymphocytes was significantly lower in patients with severe disease (MD $0.28 \times 10^9/L$; 95% CI, -0.02 to $0.58 \times 10^9/L$). Concerning the severity of the disease, while the estimated pooled mean of lymphocytes in non-severe cases was 0.95 (95% CI, 0.81 – 1.10) with the heterogeneity of $I^2=85$ ($P<0.01$), it was 0.70 (95% CI, 0.52 – 0.87) in severe patients with the heterogeneity of $I^2=94$ ($P<0.01$) (Figure 1). Taking advantage of our data showing that the mean lymphocyte count in non-severe patients was significantly higher compared to severe patients ($X^2=6.25$, $P<0.01$), it is reasonable to propose that lymphopenia may effectively contribute to reflect the progression of the disease toward an unfavorable clinical picture. After removing the Ruan et al. study,¹¹ in which the number of lymphocytes was reported as the median and subsequently interquartile range (IQR), the pooled mean difference estimate was 0.4 (95% CI, 0.21 – 0.58) associating with a significant decrease in heterogeneity value ($I^2=27$; $P<0.19$). In this setting, the pooled mean estimate in non-severe and severe cases were 1.02 (95%

CI, 0.91 – 1.12 with the heterogeneity of $I^2=0$, $P<0.62$) and 0.64 (95% CI, 0.52 – 0.76 with the heterogeneity of $I^2=93$, $P<0.01$), respectively.

Discussion

In line with the increasing necessity to identify potent biomarkers as prognostic and predictive indicators of disease outcome, several lines of evidence prove that lymphocyte count may correlate with COVID-19 severity. Results of a recent study revealed a quite distinguishable difference in the lymphocyte number among patients with mild, moderate and severe conditions, reporting significant lymphopenia in the latter within the first week of hospitalization.¹⁴ In another interesting study using the Spearman correlation coefficient, Yingxia Liu and colleagues calculated the correlation between the 2019-nCoV virus cycle threshold (Ct) value (reciprocal to virus load) and disease severity. Not only they showed that the levels of viral load were significantly correlated with lymphocyte count also they reported that the area under the curve (AUC) of the receiver operating characteristics curve (ROC) for the infection and lymphocyte count was 1, thus may also predict disease severity.¹⁵ Although by comparing the number of the deaths to the total number of the cases, one may conclude that most of the infected cases are recovering, taking a look at the dreadful statistics of deaths increasing unceasingly reminds that the disease still continues to have a high mortality rate.¹⁶ The results of the recent studies declared that patients who died from COVID19 had experienced lymphopenia with a greater extent; further highlighting the fact that lymphocyte

count may predict disease severity in COVID19.^{11, 17}

Although, at the time of writing this article; some limitations such as low sample size, variable definition of disease severity as well as different cut-off for lymphopenia may adversely affect our interpretation, analysis of the current scientific literature would definitively shed light on the prognostic value of lymphopenia in COVID-19. Overall, the results of our study revealed that the number of lymphocytes retains a specific clinical and biological significance in this infection and lymphopenia is seemingly an important abnormality contribute to mirror the evolution toward an unfavorable outcome.

Conclusion

The rapidly evolving nature of COVID-19 together with its persistent novel findings denotes a major limitation to the current study, and further investigations in the field of biomarkers that can enable more precise and timely estimation of disease prognosis will pave the way to better manage patients with severe COVID-19.

Acknowledgments

The authors thank Shahid Beheshti University of Medical Sciences for supporting this study (Grant number: 23649).

Conflict of Interest: None declared.

References

- Drexler JF, Gloza-Rausch F, Glende J, Corman VM, Muth D, Goettsche M, et al. Genomic characterization of severe acute respiratory syndrome-related coronavirus in European bats and classification of coronaviruses based on partial RNA-dependent RNA polymerase gene sequences. *J Virol*. 2010;84(21):11336-49.doi: 10.1128/JVI.00650-10. PubMed PMID: 20686038. PubMed Central PMCID: PMC2953168.
- Coleman CM, Frieman MB. Coronaviruses: important emerging human pathogens. *J Virol*. 2014;88(10):5209-12.doi: 10.1128/JVI.03488-13. PubMed PMID: 24600003. PubMed Central PMCID: PMC4019136.
- Organization WH. *Consensus document on the epidemiology of severe acute respiratory syndrome (SARS)*. World Health Organization;2003.
- Li H, Liu SM, Yu XH, Tang SL, Tang CK. Coronavirus disease 2019 (COVID-19): current status and future perspective. *International Journal of Antimicrobial Agents*. 2020;105951.
- Benvenuto D, Giovanetti M, Ciccozzi A, Spoto S, Angeletti S, Ciccozzi M. The 2019-new coronavirus epidemic: Evidence for virus evolution. *J Med Virol*. 2020;92(4):455-9.doi: 10.1002/jmv.25688. PubMed PMID: 31994738. PubMed Central PMCID: PMC7166400.
- Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med*. 2020;8(4):420-2.doi: 10.1016/S2213-2600(20)30076-X. PubMed PMID: 32085846. PubMed Central PMCID: PMC7164771.
- Zimmer CL. Studies of innate and adaptive lymphocytes in human liver diseases and viral infections. 2019.
- Lalueza A, Folgueira D, Díaz-Pedroche C, Hernández-Jiménez P, Ayuso B, Castillo C, et al. Severe lymphopenia in hospitalized patients with influenza virus infection as a marker of a poor outcome. *Infectious Diseases*. 2019;51(7):543-6.
- Aung AK, Robinson J, Hey P, Lehmann M, Chow Y, Stark RJ, et al. Progressive multifocal leukoencephalopathy secondary to hepatitis C virus infection-related T-cell lymphopenia. *Intern Med J*. 2019;49(1):114-8.doi: 10.1111/imj.14174. PubMed PMID: 30680891.
- Henry BM. COVID-19, ECMO, and lymphopenia: a word of caution. *Lancet Respir Med*. 2020;8(4):e24. doi: 10.1016/S2213-2600(20)30119-3. PubMed PMID: 32178774. PubMed Central PMCID: PMC7118650.
- Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive care medicine*. 2020:1-3.
- Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. *Evidence-Based Mental Health*. 2019;22(4):153-60.
- Zhang G, Hu C, Luo L, Fang F, Chen Y, Li J, et al. Clinical features and short-term outcomes of 221 patients with COVID-19 in Wuhan, China. *J Clin Virol*. 2020;127:104364.doi: 10.1016/j.jcv.2020.104364. PubMed PMID: 32311650. PubMed Central PMCID: PMC7194884 conflicts of interest.
- Yuan J, Zou R, Zeng L, Kou S, Lan J, Li X, et al. The correlation between viral clearance and biochemical outcomes of 94 COVID-19 infected discharged patients. *Inflammation Research*. 2020:1-8.
- Liu Y, Yang Y, Zhang C, Huang F, Wang F, Yuan J, et al. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. *Sci China Life Sci*. 2020;63(3):364-74. doi: 10.1007/s11427-020-1643-8. PubMed PMID: 32048163. PubMed Central PMCID: PMC7088566.
- Baud D, Qi X, Nielsen-Saines K, Musso D, Pomar L, Favre G. Real estimates of mortality following COVID-19 infection. *Lancet Infect Dis*. 2020;20(7):773.doi: 10.1016/S1473-3099(20)30195-X. PubMed PMID: 32171390. PubMed Central PMCID: PMC7118515.
- Tan L, Wang Q, Zhang D, Ding J, Huang Q, Tang Y-Q, et al. Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. *Signal Transduct Target Ther*. 2020;5(1):1-3.doi: 10.1038/s41392-020-0148-4. PubMed PMID: 32296069.
- Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med*. 2020;382(18):1708-20.doi: 10.1056/NEJMoa2002032. PubMed PMID: 32109013. PubMed Central PMCID: PMC7092819.
- 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. *Lancet*. 2020;395(10229):1054-62.doi: 10.1016/S0140-6736(20)30566-3. PubMed PMID: 32171076. PubMed Central PMCID: PMC7270627.
20. Cao M, Zhang D, Wang Y, Lu Y, Zhu X, Li Y, et al. Clinical Features of Patients Infected with the 2019 Novel Coronavirus (COVID-19) in Shanghai, China. *medRxiv*. 2020.doi: 10.1101/2020.03.04.20030395. PubMed PMID: 32511465. PubMed Central PMCID: PMC7255784.
 21. Zhang G-q, Hu C, Luo L-j, Fang F, Chen Y-f, Li J-g, et al. Clinical features and treatment of 221 patients with COVID-19 in Wuhan, China. *China* (2/27/2020). 2020.
 22. Organization WH. Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected, Interim guidance, 13 March 2020. 2020.
 23. Wan S, Xiang Y, Fang W, Zheng Y, Li B, Hu Y, et al. Clinical features and treatment of COVID-19 patients in northeast Chongqing. *J Med Virol*. 2020;92(7):797-806.doi: 10.1002/jmv.25783. PubMed PMID: 32198776. PubMed Central PMCID: PMC7228368.
 24. 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.
 25. 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(9):1032-8.doi: 10.1097/CM9.0000000000000775. PubMed PMID: 32118640. PubMed Central PMCID: PMC7147279.
 26. Jian-ya G. Clinical characteristics of 51 patients discharged from hospital with COVID-19 in Chongqing, China. *medRxiv*. 2020.
 27. 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. *Lancet*. 2020;395(10223):497-506.doi: 10.1016/S0140-6736(20)30183-5. PubMed PMID: 31986264. PubMed Central PMCID: PMC7159299.
 28. Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. *Allergy*. 2020;75(7):1730-41.doi: 10.1111/all.14238. PubMed PMID: 32077115.