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Review Article

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

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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.

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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

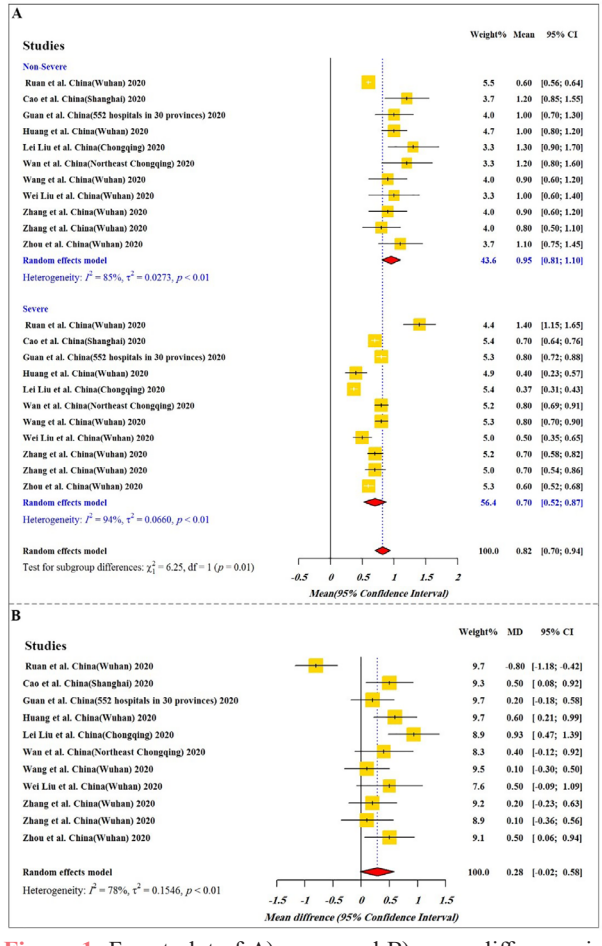

Figure 1: Forest plot of A) mean and B) mean difference in lymphocyte count between severe and non-severe COVID-19 patients.

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 × 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 (×10⁹/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	0.6 (0.32)	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 × 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 × 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 × 10^9/L; 95% CI, -0.02 to 0.58 × 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 sever 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 COIVD-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.

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Conflict of Interest: None declared.

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