Research Article

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Lymphocyte-to-C-reactive protein ratio may serve as an effective biomarker to determine COVID-19 disease severity

Lenfosit-C-reaktif protein oranı COVID 19 hastalığının şiddetini belirlemede etkili bir biyobelirteç görevi görebilir

<https://doi.org/10.1515/tjb-2020-0410>Received August 21, 2020; accepted November 6, 2020;
published online December 2, 2020**Abstract****Objectives:** We aimed to evaluate the ability of lymphocyte-C-reactive protein ratio (LCR) to discriminate between different levels of severity of COVID-19 disease.**Methods:** This retrospective observational single-center study was performed on 61 confirmed (PCR positive) COVID-19 patients between March and June 2020. The study population was separated into three groups: mild/moderate (n=24), severe (n=25) and critically ill (n=12). The optimal cut-off values of the LCR and neutrophil-to-lymphocyte ratio (NLR) in discriminating between patients with different severity levels were calculated by applying the receiver operating curve (ROC) analysis.**Results:** At baseline, the LCR decreased significantly across the three severity groups (mild/moderate > severe > critically ill). ROC analysis showed that a mean LCR of 43.21 was the

cut-off value which best discriminated patients with the critically ill disease from severe patients (sensitivity: 84% and specificity: 69%). The discriminative performance of LCR (ROC AUC 0.820) was better than that of NLR (0.751) in this regard. LCR, unlike NLR was able to distinguish severe patients from mild/moderate patients, with a cut off value of 458.19 (sensitivity: 80% and specificity: 45%).

Conclusion: LCR was observed to be able to distinguish COVID-19 infected patients of different severity (mild/moderate, severe and critically ill) and was superior to NLR in this regard.**Keywords:** COVID-19; lymphocyte-C-reactive protein ratio; neutrophil-to-lymphocyte ratio; SARS-CoV-2; severity.**Öz****Amaç:** Lenfosit-C-reaktif protein oranının (LCR) COVID-19 hastalığının farklı şiddet düzeylerini ayırt etme yeteneğini değerlendirmeyi amaçladık.**Gereç ve Yöntem:** Bu retrospektif, gözlemsel, tek merkez çalışması Mart ve Haziran 2020 arasında 61 doğrulanmış (PCR pozitif) COVID-19 hastası üzerinde gerçekleştirildi. Çalışma popülasyonu üç gruba ayrıldı: hafif/orta (n=24), şiddetli (n=25) ve kritik hastalar (n=12). LCR ve nötrofil-lenfosit oranının (NLR) farklı şiddet düzeylerine sahip hastaları ayırt etmede optimal sınır değerleri, ROC analizi uygulanarak hesaplandı.**Bulgular:** Başlangıç LCR değerinin, hastalık ciddiyetinin artmasıyla (hafif/orta > şiddetli > kritik hasta) önemli ölçüde azaldığı görüldü. ROC analizi, 43.21'lik bir ortalama LCR değerinin, kritik hastalığı olan hastaları ağır hastalardan en iyi ayırt eden kesim değeri olduğunu gösterdi (duyarlılık:%84 ve özgüllük:%69). LCR'nin ayırt edici

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performansı (ROC AUC 0.820) bu açıdan NLR'den (0.751) daha iyiydi. NLR'den farklı olarak LCR, 458.19'luk bir kesim değeri (duyarlılık: %80 ve özgüllük: %45) ile şiddetli hastaları hafif/orta hastalardan ayırt edebildi.

Sonuç: LCR'nin COVID-19 ile enfekte farklı şiddette (hafif/orta, şiddetli ve kritik hasta) hastaları ayırt edebildiği ve bu açıdan NLR'den üstün olduğu gözlemlendi.

Anahtar kelimeler: COVID-19; lenfosit-C-reaktif protein; Oranı; nötrofil-lenfosit oranı; SARS-CoV-2; hastalık şiddeti.

Introduction

Coronavirus Disease 2019 (COVID-19) is a new infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with clinical symptoms ranging from asymptomatic forms to the life-threatening acute respiratory distress syndrome (ARDS) and sepsis [1, 2]. Since its first appearance in Wuhan, China in December 2019, SARS-CoV-2 virus has infected more than 13.8 million people worldwide and has caused more than 593,000 deaths as of July, 18, 2020 [3]. Most patients infected with COVID-19 experience a mild/moderate disease course (80%), while others experience a severe (15%) or a critical disease course (5%) generally requiring hospitalization and admission to an intensive care unit with a higher mortality rate [2].

Therefore, the early detection of severe cases will provide significant benefits in the management of supportive treatment, which is an opportunity to decrease morbidity, mortality, length of hospitalization and higher medical costs [4]. Several previous studies have shown that the level of viral load detected by using the technique of reverse transcription-polymerase chain reaction (RT-PCR) correlates well with the severity of COVID-19 disease [5, 6]. However, this test is not feasible in daily clinical practice, because of the high rate of false-positives and false-negatives, and because RT-PCR testing takes time, money and needs trained personnel to perform it, which are not available in every medical center [7]. Hence, there is an urgent need for inexpensive, more simple, rapid, easily accessible alternatives to viral load level, such as biomarker combination ratios, to assess the disease severity.

Since hyper inflammation in COVID-19 disease is known to be a major reason for poor prognosis of patients, biomarker combinations reflecting inflammation status may be a good alternative in this regard [8]. For example, lymphocyte-C-reactive protein ratio (LCR) is a newly developed biomarker for reflecting inflammation status in cancer cases, which takes into account lymphocyte counts and C-reactive protein (CRP) [9]. Since the SARS-CoV-2 viral load

has been highly correlated with lymphocyte count and CRP value, it was hypothesized that LCR could help predict of disease severity [5, 10]. To the best of our knowledge, to date, only one meta-analysis has been carried out to evaluate the feasibility of LCR to assess COVID-19 disease severity [11]. Therefore, this study aimed to determine whether or not LCR could be useful in the discrimination of COVID 19 cases with three different levels of severity.

Materials and methods

Patients and study design

This retrospective observational single-center study was conducted in the Infectious Disease Clinic of a tertiary referral hospital in Turkey. A total of 61 confirmed (had positive PCR result) COVID-19 patients were enrolled between March and June 2020.

The study population was separated into three groups: mild/moderate, severe and critically ill. The mild cases comprised symptomatic patients with no evidence of viral pneumonia or hypoxia, the moderate cases were defined as those with clinical signs of pneumonia (fever, cough, dyspnea, fast breathing), severe cases were those with the moderate symptoms plus $SpO_2 \leq 90\%$ and/or respiratory rate >30 breaths/min, and the critically ill cases were as previously defined plus ARDS and/or sepsis and/or septic shock [2].

Epidemiological and clinical characteristics and laboratory findings (including neutrophil and lymphocyte counts and C-reactive protein) were retrospectively obtained from the clinical records. Patients with a diagnosis of hematological disease were excluded.

Fasting venous blood samples were collected via venipuncture from COVID-19 patients into biochemistry tubes coated with gel for serum separation. The samples were centrifuged at $1,500 \times g$ for 10 min within 1 h after sampling. Whole blood samples were collected into ethylenediaminetetraacetic acid (EDTA) containing tubes and studied within 1 h.

The routine blood tests, including lymphocyte and neutrophil counts, were measured using a Mindray BC6800 device (Mindray Medical, Shenzhen, China). Serum CRP levels (cut off value 5.0 mg/L) were determined using a Siemens Dade Behring BN II Nephelometer (Siemens Healthcare Diagnostics Ltd, Erlangen, Germany).

The LCR was calculated by dividing the lymphocyte count (number/ μL) by the CRP level (mg/dL). The neutrophil-to-lymphocyte ratio (NLR) was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count.

The hematology laboratory test results (including neutrophil and lymphocyte counts) and inflammatory biomarkers (including CRP, LCR and NLR) on admission were compared between the three groups.

The mean values of NLR and LCR at five different time points after symptom(s) onset (day 1–4, day 5–7, day 8–10, day 11–14, day 15–and-over) and their trends during the disease course were recorded for the three different groups.

Statistics

All analyses were carried out using SPSS, version 23 software. The Shapiro Wilk test was applied to examine the distribution normality of

continuous data. Continuous variables were expressed as medians and interquartile range values, and categorical variables as the count (n) and percentages (%). The Kruskal-Wallis and Mann-Whitney U-tests were used for continuous variables, while the Chi-square or Fisher exact test was used for categorical variables in the comparisons between the different groups. The optimal cut-off values of the LCR and NLR for the differentiation of patients with different disease severity levels were calculated by applying the receiver operating curve (ROC) analysis. A value of $p < 0.05$ was considered statistically significant.

Results

The 61 patients included in the study comprised 36 (59%) males and 25 (41%) females with a mean age of 58.55 ± 15.94 years (range, 28–92 years). A total of 406 complete blood count (CBC) and CRP test results were available, taken from 24 mild/moderate patients, 25 severe patients and 12 critically ill patients. There was no statistical difference between the groups regarding days from onset to admission with a median time interval of three days ($p = 0.146$). The comparison of the baseline clinical and laboratory characteristics between the three groups is shown in Table 1. Compared with subjects in the mild/moderate group, those in the severe and critically ill group were older (Table 1). As shown in Table 1, the critically ill group was reported to have significantly lower lymphocyte counts and significantly higher neutrophil counts than the other two groups. The CRP level significantly increased from the mild/moderate group to the severe group, and from the severe group to the critically ill group ($p = 0.008$ and $p < 0.001$, respectively). The baseline LCR was significantly decreased across these three groups, and the NLR

value was significantly higher in the critically ill group than in the other two groups (Table 1).

As shown in Figure 1 only LCR showed a reasonable ability to distinguish severe patients from mild/moderate patients (AUC: 0.635, 95% CI: 0.531–0.740, $p = 0.015$). The NLR was not able to discriminate these two groups from each other ($p = 0.517$). The optimal cut off value for the LCR for the differentiation of mild/moderate patients from severe patients was 458.19 (sensitivity: 80% and specificity: 45%).

Both LCR and NLR showed a reasonable ability to distinguish critically ill patients from severe patients, while LCR had a higher ROC AUC than NLR (0.820, 95% CI: 0.749–0.883, $p < 0.001$ vs. 0.751, 95% CI: 0.675–0.828, $p = 0.001$) (Figure 1). The optimal cut-off values for the LCR and NLR to be able to differentiate critically ill patients from severe patients were 43.21 and 5.92, respectively (sensitivity: 84%, specificity: 69% vs. sensitivity: 55%, specificity: 89%).

The LCR on five different days decreased significantly across the three severity groups (mild/moderate > severe > critically ill, for all time points). After 8–10 days of symptom onset LCR levels in the mild/moderate and severe patients tended to increase, while the level started to decrease in critically ill patients until it reached the lowest value at days 11–14 and then increased again (Figure 2).

NLR levels in the mild/moderate and severe patients were lower than in the critically ill patients within 8–10 days of symptom onset. Then, NLR levels tended to decrease in the mild/moderate and severe patients, while the level started to increase in critically ill patients, reaching peak value at days 11–14 and then decreased (Figure 2).

Table 1: Comparison of baseline characteristics of COVID 19 patients according to the disease severity on admission.

Characteristics	Mild/moderate group (n=24)	Severe group (n=25)	Critically ill group (n=12)	p-Value		
				Overall	Mild/moderate vs. severe	Severe vs. critically ill
Age	43 (33–59)	64 (43–72)	64 (56–70)	<0.001	<0.001	0.659
Gender, male/female	14/10	16/9	8/4	0.659	0.324	0.494
Hematologic						
Lymphocyte ($\times 10^9/L$)	1.82 (1.46–2.17)	1.62 (1.22–2.15)	1.17 (0.73–1.61)	<0.001	0.349	<0.001
Neutrophil ($\times 10^9/L$)	4.78 (3.11–7.09)	4.32 (3.37–5.71)	7.45 (4.44–10.38)	<0.001	0.899	<0.001
Inflammatory biomarkers						
CRP, mg/L	9.30 (3.11–23.60)	15.10 (5.87–41.90)	103 (60.59–178.0)	<0.001	0.008	<0.001
LCR	218.40 (55.33–585.20)	108.27 (31.44–380.21)	13.19 (5.87–32.69)	<0.001	0.015	<0.001
NLR	2.40 (1.76–3.86)	2.49 (1.83–4.12)	7.10 (3.21–12.62)	<0.001	0.517	<0.001

Data expressed as median (interquartile range [IQR]) or n/n. CRP, C-reactive protein; LCR, lymphocyte-C-reactive protein ratio; NLR, neutrophil-to-lymphocyte ratio. Statistically significant values are indicated by bold font.

Figure 1: Receiver operating curve (ROC) curves for the abilities of lymphocyte-C-reactive protein ratio (LCR) and neutrophil-to-lymphocyte ratio (NLR) to distinguish COVID-19 infected patients of different severity. (A) The abilities to distinguish between severe and critically ill disease (0.820, 95% CI: 0.749–0.883, $p < 0.001$ vs. 0.751, 95% CI: 0.675–0.828, $p = 0.001$, respectively) (B) The abilities to distinguish between mild/moderate and severe disease (AUC: 0.635, 95% CI: 0.531–0.740, $p = 0.015$ for LCR).

Figure 2: Time-dependent changes in the levels of (A) lymphocyte-C-reactive protein ratio (LCR), and (B) neutrophil-to-lymphocyte ratio (NLR) during the disease course according to disease severity: Mild/moderate, severe and critically ill patients.

Discussion

Although the main target organ is the lungs, COVID-19 is now recognized as a multisystemic infection involving hematological and immunological systems [11, 12]. Since the prognosis of COVID-19 disease depends on the hematological system response, it is not surprising that changes can be seen in routine blood tests. Some may be used to discriminate disease severity [12]. The results of this study showed that the LCR is able to distinguish COVID-19 infected patients of different severity (mild/moderate, severe and critically ill) and it is superior to NLR in this regard. This can be especially useful for the early implementation of adequate supportive therapy, which will improve prognosis and reduce hospitalization and related costs.

LCR is a newly developed inflammatory score, which reflects the systemic inflammation status in cancer patients taking into account both lymphocyte counts and CRP [9]. Recently, a meta-analysis by Rangel demonstrated that the LCR was significantly decreased in severe cases, suggesting that this marker could reflect the severity of COVID-19

disease [11]. Supporting this hypothesis, data from several studies have revealed that the balance between host-immune response and hyperinflammatory response plays a key role in prognosis in COVID-19 disease [13, 14]. Therefore, lower LCR levels in severe patients could be the result of fewer lymphocytes leading to immune dysfunction and higher CRP levels reflecting the severe systemic inflammatory response of the patients [14, 15].

In the current study both NLR and LCR showed a reasonable ability to discriminate severe and critically ill patients, but LCR was superior to NLR. One explanation for this observation may be that the viral load of the SARS-CoV-2 virus, which correlates well with the severity of the disease, has also been shown to be highly correlated with CRP and lymphopenia in patients with COVID-19 pneumonia [5, 10]. However, it is not known whether the neutrophil count is directly related to the SARS-CoV-2 viral load. Taken together, there seems to be some evidence to indicate that LCR could be superior to NLR for the detection of COVID-19 disease severity, although further work is required to confirm this.

Lymphocytes are known to be responsible for eliminating virally infected cells but it is not clear whether

neutrophils play a role in anti-viral defense in viral pneumonia [16, 17]. Moreover, the presence of neutrophil infiltrations in the lungs seen only in pneumonia patients with ARDS, suggesting the presence of critical disease, but not those without it, supports the view that neutrophils play a role in antiviral defense in critically ill patients rather than in severe and mild/moderate patients [17].

NLR is a hematological index that is widely used to evaluate the severity of bacterial infections, taking into account neutrophil and lymphocyte counts [18]. Data from several studies suggest that NLR can help to predict the severity of COVID-19 disease [1, 15, 19]. However, it is not clear whether NLR is able to distinguish severe cases from mild/moderate cases. Sun et al. showed that the NLR could not discriminate these two groups from each other while Wang et al. reported that NLR could be a valuable parameter in this regard. However, this inconsistency in reported results may be due to Wang et al.'s findings having been somewhat limited by the small sample size, particularly in the severe group ($n=10$) [1, 15].

The differentiation of severe patients from mild/moderate patients is essential for adequate management of the disease which may prevent unnecessary hospitalization and decrease delayed treatment, which is associated with mortality risk because of silent hypoxia in severe cases [20, 21]. In the current study, it was observed that only LCR showed a reasonable ability to distinguish mild/moderate patients from severe patients, while the NLR was not able to discriminate these two groups from each other.

Consequently, in the present study, the NLR was not able to distinguish mild/moderate patients from severe patients, although it showed a reasonable ability to distinguish severe patients from critically ill patients. These results suggest that NLR may only be useful in identifying critically ill COVID-19 cases. These results also indicated that perhaps LCR could be used to triage patients with COVID-19 disease more effectively. However, further studies with larger patient series are warranted to confirm these results.

Finally, it was observed that patients with critically ill disease presented with a decreased LCR and an increased NLR both on admission and during the course of the disease compared with severe and mild/moderate patients. These results may be explained by the fact that critically ill patients have a significantly higher baseline viral load, which persists for a significantly longer time and may result in a more severe inflammatory process than patients with mild/moderate or severe disease [6, 22].

Moreover, the LCR found to be lower in severe patients than in mild/moderate patients on admission and at different time points with a similar trend of decreasing,

whereas the NLR of severe patients were similar to those of mild/moderate patients. One reason for this difference between LCR and NLR trends may be that the relatively higher level of viral load in severe patients could contribute to the lower levels of lymphocyte counts and higher levels of CRP, compared to mild/moderate patients [5, 6, 10, 23]. In contrast, patients with the severe disease did not significantly differ from patients with mild/moderate disease in terms of neutrophil counts [15].

A recent study by Zheng et al. demonstrated that patients with severe disease have a later viral load peak as compared to those with mild disease [22]. Other recent studies have also suggested a correlation between virus persistence and poor disease outcomes [24, 25]. Consistent with the reported trend of SARS-CoV-2 viral load, it was observed in the current study that LCR in the critically ill group remained low, while these values returned to normal more quickly in mild/moderate and severe patients [15]. Therefore it was speculated that dynamic observation of the LCR was relevant to SARS-CoV-2 viral load which could help to predict the disease severity in COVID-19 patients. Together, these results indicate that LCR may be a better alternative to viral load in determining disease severity than NLR.

This study was limited by the retrospective design and small sample size. Another source of uncertainty was the potential role of the patient comorbidities and treatments (such as antivirals) on blood routine parameters. Larger prospective studies with adjustment for these confounding factors warranted determining whether these results have any clinical implications.

Conclusion

LCR seems to be superior to NLR in determining the severity of COVID 19 disease. Moreover, the lower LCR levels and delay in increasing LCR could indicate the presence of critically ill disease in patients infected with COVID-19. These results also indicated that perhaps LCR-guided triage could be used to reduce hospitalization rates in patients with COVID-19 disease. Nevertheless, further studies are required.

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Informed consent: Informed consent was obtained from all individuals included in this study.

Ethical approval: This study was approved by the ethical committee of Mustafa Kemal University (date: 04/06/2020, number: 07/32).

References

1. 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. *J Am Med Assoc* 2020;323:1061–9.
2. World Health Organization. Clinical management of COVID-19: interim guidance, 27 May 2020 (No. WHO/2019-nCoV/clinical/2020.5). World Health Organization; 2020.
3. World Health Organization. reportWHO novel coronavirus (2019-nCoV) situation report-170; 2020. Available from: https://www.who.int/docs/default-source/coronaviruse/situationreports/20200121-sitrep-1-2019-ncov.pdf?sfvrsn=20a99c10_4 [Accessed 18 July 2020].
4. Tahmasebi S, Khosh E, Esmaeilzadeh A. The outlook for diagnostic purposes of the 2019-novel coronavirus disease. *J Cell Physiol* 2020. <https://doi.org/10.1002/jcp.29804> [Epub ahead of print].
5. Liu Y, Liao W, Wan L, Xiang T, Zhang W. Correlation between relative nasopharyngeal virus RNA load and lymphocyte count disease severity in patients with COVID-19. *Viral Immunol* 2020. <https://doi.org/10.1089/vim.2020.0062> [Epub ahead of print].
6. Liu Y, Yan LM, Wan L, Xiang TX, Le A, Liu JM, et al. Viral dynamics in mild and severe cases of COVID-19. *Lancet Infect Dis* 2020;20: 656–7.
7. Allam M, Cai S, Ganesh S, Venkatesan M, Doodhwala S, Song Z, et al. COVID-19 diagnostics, tools, and prevention. *Diagnostics* 2020;10:409.
8. Merad M, Martin JC. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. *Nat Rev Immunol* 2020;20:355–62.
9. Okugawa Y, Toiyama Y, Fujikawa H, Ide S, Yamamoto A, Omura Y, et al. Prognostic potential of lymphocyte-C-reactive protein ratio in patients with rectal cancer receiving preoperative chemoradiotherapy. *J Gastrointest Surg* 2020. <https://doi.org/10.1007/s11605-019-04495-4> [Epub ahead of print].
10. Shi F, Wu T, Zhu X, Ge Y, Zeng X, Chi Y, et al. Association of viral load with serum biomarkers among COVID-19 cases. *Virology* 2020;546:122–6.
11. Lagunas-Rangel FA. Neutrophil-to-lymphocyte ratio and lymphocyte-to-C-reactive protein ratio in patients with severe coronavirus disease 2019 (COVID-19): a meta-analysis. *J Med Virol* 2020. <https://doi.org/10.1002/jmv.25819> [published online ahead of print, 2020 Apr 3].
12. Terpos E, Ntanasis-Stathopoulos I, Elalamy I, Kastritis E, Sergentanis TN, Politou M, et al. Hematological findings and complications of COVID-19. *Am J Hematol* 2020;95:834–47.
13. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020;395:1033–4.
14. Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, et al. Dysregulation of immune response in patients with coronavirus 2019 (COVID-19) in Wuhan, China. *Clin Infect Dis* 2020;71:762–8.
15. Sun S, Cai X, Wang H, He G, Lin Y, Lu B, et al. Abnormalities of peripheral blood system in patients with COVID-19 in Wenzhou, China. *Clin Chim Acta* 2020;507:174–80.
16. Henry BM, de Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. *Clin Chem Lab Med* 2020;58:1021–8.
17. Camp JV, Jonsson CB. A role for neutrophils in viral respiratory disease. *Front Immunol* 2017;8:550.
18. Naess A, Nilssen SS, Mo R. Role of neutrophil to lymphocyte and monocyte to lymphocyte ratios in the diagnosis of bacterial infection in patients with fever. *Infection* 2017;45:299–307.
19. Fu J, Kong J, Wang W, Wu M, Yao L, Wang Z, et al. The clinical implication of dynamic neutrophil to lymphocyte ratio and D-dimer in COVID-19: a retrospective study in Suzhou China. *Thromb Res* 2020;192:3–8.
20. Tan L, Wang Q, Zhang D, Ding J, Huang Q, Tang YQ, et al. Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. *Signal Transduct Target Ther* 2020;5:33.
21. Teo J. Early detection of silent hypoxia in COVID-19 pneumonia using smartphone pulse oximetry. *J Med Syst* 2020;44:134.
22. Chen J, Qi T, Liu L, Ling Y, Qian Z, Li T, et al. Clinical progression of patients with COVID-19 in Shanghai, China. *J Infect* 2020;80: e1–6.
23. Zheng S, Fan J, Yu F, Feng B, Lou B, Zou Q, et al. Viral load dynamics and disease severity in patients infected with SARS-CoV-2 in Zhejiang province, China, January–March 2020: retrospective cohort study. *BMJ* 2020;369:m1443.
24. 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;395:1054–62.
25. Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. *Nat Rev Immunol* 2020;20:363–74.