



Malnutrition Contributes to Low Lymphocyte Count in Early-Stage Coronavirus Disease-2019

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Background and Aim: Lymphocytes play an important role in fighting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections. Low total lymphocyte count (TLC), which contributes to poor clinical outcomes, is common in persons with coronavirus disease 2019 (COVID-19). The current explanation for the cause of low TLC is that it is directly related to the invasiveness of SARS-CoV-2, which attacks lymphocytes. We hypothesized that malnutrition contributes to the development of low TLC in early-stage COVID-19.

Methods: We prospectively enrolled 101 patients with confirmed COVID-19. On their first day of hospitalization, we collected baseline and laboratory data, including clinical symptoms; the Sequential Organ Failure Assessment, Nutrition Risk Screening 2002 and Subjective Global Assessment were used to assess the malnutrition status of the patients. Multivariable logistic regression was used to identify independent risk factors for low TLC and severe COVID-19.

Results: Malnutrition was associated with lower TLC in COVID-19. Fifty-nine (58.4%) of the patients showed low TLC, 41 (40.6%) were at risk for malnutrition, and 18 of them were malnourished. Low TLC was an independent risk factor for severe COVID-19. Compared to patients with normal TLC, those with low TLC more often presented with anorexia, malnutrition, higher SOFA scores ($P < 0.05$) and comorbidities (diabetes and malignancies). Malnutrition (OR: 3.05, 95% CI: 1.5–6.19, $P = 0.006$) and SOFA scores

(OR: 1.51, 95% CI: 1.04-2.43, $P = 0.042$) were identified as independent risk factors for low TLC.

Conclusions: Malnutrition was common among our patients with early-stage COVID-19, and it contributed to the occurrence of low TLC.

Keywords: malnutrition, COVID-19, lymphocyte, SARS-CoV-2, lymphopenia

INTRODUCTION

Coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), continues its rapid spread globally. A lymphocyte is a type of immune cell that plays an important role in fighting SARS-CoV-2 infection, and low total lymphocyte count (TLC) is common in COVID-19, ranging from 35 to 82% of patients (1, 2). Low TLC also contributes to poor clinical outcomes (2). Non-survivors showed severe lymphopenia over time (3). Increasing the TLC level may be a key therapeutic target for these infections, but until now, the cause of low TLC has been thought to be directly related to the invasive nature of SARS-CoV-2, which attacks immune cells (1, 4).

However, the cause of lymphopenia could be multifactorial, and malnutrition is a main contributor (5). Intensive care unit (ICU) stay, polymorbidity, and older age are associated with high risk for malnutrition, representing a relevant risk factor for higher morbidity in COVID-19 (6). The high incidence of gastrointestinal symptoms in COVID-19 may further increase malnutrition risk (7, 8). A recent study reported that 52.7% of elderly patients with COVID-19 are malnourished, and that 27.5% is at risk for malnutrition (9). Lymphopenia may occur when there is lack of protein and other nutrients that are necessary to produce enough lymphocytes. Significant decrease in TLC has been observed in elderly patients who are malnourished (9), indicating a possible correlation between TLC and malnutrition in persons with COVID-19. In this study, we aimed to establish a multivariable model and determine whether malnutrition is an independent risk factor for low TLC in COVID-19. Another goal of this study was to produce evidence for the pathogenesis of lymphopenia in early-stage COVID-19 and demonstrate the feasibility of elevating TLC levels through nutrition management as a treatment for affected patients.

MATERIALS AND METHODS

We prospectively enrolled adult patients admitted to the COVID-19 infection ward of a designated hospital in Wuhan who have confirmed COVID-19 from February 6 to March 20, 2020. On the first day of hospitalization, baseline data, clinical symptoms from disease onset to hospitalization, and laboratory data of the patients were collected. The Sequential Organ Failure Assessment (SOFA)¹, which measures the degree of dysfunction of six organ systems (respiratory, liver, cardiovascular, renal, coagulation, and

central nervous system), was conducted. The Nutrition Risk Screening 2002 (NRS-2002) was performed to identify patients at risk for malnutrition. Patients with an NRS-2002 score ≥ 3 were further assessed using the Subjective Global Assessment (SGA) (6). Malnutrition status was divided into three categories: (1) no risk for malnutrition (NRS-2002 score < 3), (2) risk for malnutrition (NRS-2002 score ≥ 3 with Subjective Global Assessment [SGA] A classification) and (3) malnourished (NRS-2002 score ≥ 3 and SGA B or C classification). Hospitalized patients were excluded from the study if they (1) were lost to follow-up or had insufficient information; or (2) history of cardiac arrest, death within 24 h or length of stay of less than 72 h, or with do-not-resuscitate orders. To verify the correlation between malnutrition and low TLC in non-hospitalized patients, the non-hospitalized patients with sufficient clinical information (such as NRS-2002 scores and results of routine blood tests) were enrolled at the same time. Their malnutrition status was classified as no risk for malnutrition (NRS-2002 score < 3) and risk for malnutrition (NRS-2002 score ≥ 3).

Data on the use of lymphopenia-inducing drugs (corticosteroids, cytotoxic drugs, thymic hormones, and interferons) (10) within 2 weeks and coexisting comorbidities related to lymphopenia (5) were also collected as confounding factors. The study was approved by the ethics committee of Qilu Hospital. Clinical outcomes of the hospitalized patients consisted of acute respiratory distress syndrome (ARDS), severe COVID-19, ICU care, and mortality. The outcomes of ARDS and severe COVID-19 were defined according to criteria from the World Health Organization (WHO) (11, 12). Mortality was defined as death, and ICU care was defined as the day of admittance to the ICU during the in-hospital care of a patient.

SPSS 16.0 (SPSS Inc, Chicago, IL, United States) was used for data analysis. Multivariable logistic regression analysis was performed to identify independent risk factors associated with low TLC and severe COVID-19, and odds ratios (ORs) and 95% confidence intervals (CIs) were estimated. Variables with $P \leq 0.2$ on the univariate analyses were included in the multivariable model. $P < 0.05$ was considered statistically significant. Univariate logistic regression was used to assess the consistency of the relationships between the categories of malnutrition status and low TLC with clinical outcomes.

RESULTS

A total of 101 cases were enrolled. As shown in **Table 1**, the mean age of the enrolled participants is 65.3 ± 13 years, and 59.4% are male. The mean SOFA score on the first day of hospitalization was 2.4 ± 1.3 , and 59 (58.4%) of the patients

¹<https://www.mdcalc.com/sequential-organ-failure-assessment-sofa-score#pearls-pitfalls>

TABLE 1 | Univariate analysis of the risk factors for low TLC in hospitalized patients with early-stage COVID-19.

Characteristics	Total (N = 101)	Low TLC(N = 59)	Normal TLC (N = 42)	P value
Age, years	65.3 ± 13.0	66.6 ± 14.3	63.6 ± 10.8	0.256
Sex				
Male	60 (59.4)	35 (59.3)	25 (59.5)	
Female	41 (40.6)	24 (40.7)	17 (40.5)	0.984
Lymphocyte count, × 10 ⁹ /L	1.12 ± 0.59	0.75 ± 0.22	1.64 ± 0.54	-
Comorbidities				
Hypertension	26 (25.7)	16 (27.1)	10 (23.8)	0.708
Cardiovascular disease	13 (12.9)	7 (11.9)	6 (14.3)	0.955
Diabetes	13 (12.9)	10 (16.9)	3 (7.1)	0.147
Cerebrovascular disease	4 (4.0)	3 (5.1)	1 (2.4)	0.866
Chronic obstructive pulmonary disease	3 (3.0)	2 (3.4)	1 (2.4)	0.764
Chronic liver disease	2 (2.0)	2 (3.4)	0 (0.0)	0.631
Chronic kidney disease	4 (4.0)	4 (6.8)	0 (0.0)	0.228
Comorbidities related to lymphopenia				
Malignancy	11 (10.9)	9 (15.3)	2 (4.8)	0.095
Lupus	1 (1.0)	1 (1.7)	0 (0.0)	0.864
Rheumatoid arthritis	2 (2.0)	1 (1.7)	1 (2.4)	0.631
Others ^a	0 (0.0)	0 (0.0)	0 (0.0)	-
Clinical symptoms				
Fever	93 (92.1)	55 (93.2)	38 (90.5)	0.615
Cough	66 (65.3)	40 (67.8)	26 (61.9)	0.540
Dyspnea	33 (32.7)	21 (35.6)	11 (26.2)	0.317
Anorexia	38 (37.6)	27 (45.8)	11 (26.2)	0.045
Diarrhea	14 (13.8)	10 (16.9)	4 (9.5)	0.287
Vomiting	9 (9.0)	6 (10.2)	3 (7.1)	0.864
Use of drug that may induce lymphopenia within 2 weeks before hospitalization				
Corticosteroid	9 (8.9)	6 (10.2)	3 (7.1)	0.864
Thymic hormones	5 (5.0)	3 (5.1)	2 (4.8)	0.941
Cytotoxic drugs	3 (3.0)	2 (3.4)	1 (2.4)	0.764
Interferon	2 (2.0)	1 (1.7)	1 (2.4)	0.631
Others ^b	0 (0.0)	0 (0.0)	0 (0.0)	-
Malnutrition status				
1 No risk for malnutrition	60 (59.4)	26 (44.1)	34 (81.0)	<0.001
2 Risk for malnutrition	23 (22.7)	17 (28.8)	6 (14.2)	0.086
3Malnourished	18 (17.8)	16 (27.1)	2 (4.8)	0.004
SOFA score	2.4 ± 1.3	2.7 ± 1.5	2.0 ± 0.8	0.012
Outcomes				
Severe COVID-19	54 (53.4)	37(62.7)	17 (42.5)	0.027
ARDS	38 (37.6)	27 (45.8)	11 (26.2)	0.045
ICU care	17 (16.8)	13 (22.0)	4 (9.5)	0.098
Death	5 (4.9)	4 (6.8)	1 (2.4)	0.315

Data are reported as n (%) or mean ± standard deviation (SD). TLC, total lymphocyte count; COVID-19, coronavirus disease 2019; SOFA, Sequential Organ Failure Assessment; ARDS, acute respiratory distress syndrome; ICU, intensive care unit. The cut-off point for low TLC and normal TLC is $1.1 \times 10^9/l$. a. including aplastic anemia, human immunodeficiency virus (HIV), hypersplenism, myelodysplastic syndrome, and tuberculosis. b. including monoclonal antibodies, cimetidine, and opioids. Bold values are $p < 0.05$, which are considered statistically significant.

showed low TLC on admission. The most common comorbidities were hypertension ($n = 26$, 25.7%), cardiovascular disease ($n = 13$, 12.9%), and diabetes ($n = 13$, 12.9%). A total of 41 (40.6%) patients were at risk for malnutrition (NRS-2002 score ≥ 3); 18 of them were malnourished, and 23 were at risk for malnutrition but were not malnourished. As shown in **Supplementary Figure 1**, low TLC and malnourishment are

associated with most worst clinical outcomes. Low TLC, instead of malnourishment, was identified as an independent risk factor for severe COVID-19 (**Supplementary Tables 1, 2**) using the multivariate logistic model.

Compared to patients with normal TLC, those with low TLC more often presented with anorexia from the onset of the disease. They were more often malnourished and had higher SOFA score

TABLE 2 | Multivariate logistic regression analysis of the risk factors for low TLC in hospitalized patients with early-stage COVID-19.

Characteristics	Univariate analysis		Multivariable analysis	
	OR (95%CI)	P value	OR (95%CI)	P value
Diabetes	2.65 (0.68–10.31)	1.159		
Malignancy	3.60 (0.74–17.61)	0.114		
Anorexia symptom	2.38 (1.01–5.61)	0.048		
SOFA score	1.65 (1.09–2.50)	0.018	1.51 (1.04–2.43)	0.042
Malnutrition status				
1 No risk for malnutrition	Reference	-	Reference	-
2 Risk for malnutrition	3.71 (1.28–10.71)	0.016	3.67 (1.24–10.82)	0.019
3 Malnourished	10.46 (2.21–49.59)	0.003	7.63 (1.55–35.58)	0.012
P value for trend	3.39 (1.71–6.71)	0.002	3.05 (1.50–6.19)	0.006

TLC, total lymphocyte count; OR, odds ratio; CI, confidence interval; SOFA, Sequential Organ Failure Assessment.

but less often well-nourished ($P < 0.05$, **Table 1**). The univariate analysis of the risk factors for TLC identified five indicators (i.e., comorbid diabetes and malignancy, anorexia, higher SOFA score, and malnutrition), which were included in the multivariate analysis. A similar trend in malnutrition was found among the cases that were not hospitalized (**Supplementary Table 3**).

The multivariate logistic regression identified the SOFA score (OR: 1.51, 95% CI: 1.04–2.43, $P = 0.042$) and a trend toward malnutrition (OR: 3.05, 95% CI: 1.5–6.19, $P = 0.006$) as independent risk factors for low TLC (**Table 2**). Compared to patients who were not at risk for malnutrition (set as a reference), the risk for low TLC increased 3.67- and 7.63-fold in patients who were at risk for malnutrition and those who were malnourished.

DISCUSSION

Our study found that malnutrition was common among our patients with early-stage COVID-19, and that it contributed to their low TLC. The data suggest that malnutrition is another important cause of lymphopenia, in addition to the invasive nature of SARS-CoV-2, which attacks immune cells.

Previous studies have identified lymphopenia as a significant prognostic marker for COVID-19 and TLC as a variable associated with disease severity and mortality (4, 13, 14). Appropriate functions of lymphocytes, such as cytotoxicity, antibody production, and immune response regulation, play critical roles in restricting SARS-CoV-2 infection. Lymphopenia is a hallmark of predisposition to severe disease, with incidence of about 85% in patients with severe COVID-19 (15). In this study, low TLC was also verified to be an independent risk factor for severe COVID-19 in hospitalized patients. An understanding of the pathogenesis of low TLC may facilitate the development and testing of therapeutic targets for COVID-19 management.

Malnutrition has been observed frequently in persons with infectious diseases such as COVID-19 (9, 16, 17). Thus, nutritional support is probably a reasonable approach to improve their prognosis (18, 19). The causes of malnutrition in COVID-19 are multifactorial. Polymorbidity, older age (6), gastrointestinal symptoms (7, 8), and catabolism stress

induced by infection, which are commonly found in COVID-19, may contribute to patients' deteriorated nutritional status in COVID-19. Sufficient protein and nutrients are necessary to produce lymphocytes, as protein–energy malnutrition leads to reduced production of lymphocytes (20). TLC is also a popular serum marker, which may be useful for determining nutritional status. Levels of TLC have been found to vary with the degree of malnutrition; for example, TLV levels $< 1,500/\text{mm}^3$ show a strong correlation with malnutrition, and levels $< 900/\text{mm}^3$ reflected severe malnutrition (21, 22). Consequently, immune function is affected, thereby increasing the risk of infection due to impaired cell-mediated immunity and cytokine, complement, and phagocyte function (23). Ensuring adequate nutrition in early-stage COVID-19 might increase the level of TLC and improve immune function and prognosis, but it needs to be verified by further intervention studies. Previous studies have found that malnutrition is associated with worse clinical outcomes (9, 16, 17), and nutritional support probably improves the prognosis (18, 19) of infectious diseases (including COVID-19). In this study, we also found that malnourishment was associated with the worse clinical outcomes in the univariate model (**Supplementary Figure 1**). However, malnutrition was not found to be an independent risk factor for severe COVID-19 in the multivariate analysis. Considering the significant correlation between malnutrition and low TLC, the prognostic value of malnutrition, with respect to COVID-19, may be partly attributable to its contribution to lymphopenia.

In this study, SOFA score was identified as an independent risk factor for low TLC, and the reason was probably related to the invasiveness of SARS-CoV-2. Infection with SARS-CoV-2 can damage multiple organ systems, including the respiratory (24), liver (25), cardiovascular (26), renal (27), coagulation (28), and central nervous systems (29). Given that SOFA score is calculated based on the degree of dysfunction of the above organ systems, higher SOFA score may indicate higher level of invasiveness of SARS-CoV-2 and damage to organ systems. Furthermore, SOFA score has been found to be associated with poor prognosis for COVID-19 (30).

Our study had some limitations. First, it was limited by the observational nature of the data. Further intervention research is needed regarding the effectiveness of nutrition support on lymphocyte count in patients with COVID-19. Second, because of the small sample size of this study, a multivariate model was not established to determine the association of lymphopenia and malnutrition with all clinical outcomes. Further study with a large sample size is warranted.

Our study indicated that malnutrition was common among our patients with early-stage COVID-19, and that it is an important but generally unrecognized cause of lymphopenia. Ensuring adequate nutrition in early-stage COVID-19 may prevent low TLC; therefore, this hypothesis needs to be verified through further intervention studies.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Qilu Hospital. The patients/participants provided their written informed consent to participate in this study.

REFERENCES

- Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. (2020) 395:507–13. doi: 10.1016/S0140-6736(20)30211-7
- Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of 2019 novel coronavirus infection in China. *medRxiv*. (2020). doi: 10.1056/NEJMoa2002032
- 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) 323:1061–9. doi: 10.1001/jama.2020.1585
- Liu J, Li S, Liu J, Liang B, Wang X, Wang H, et al. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. *medRxiv*. (2020). doi: 10.1016/j.ebiom.2020.102763
- Naeim F, Rao PN, Grody WW. *Atlas of Hematopathology: Morphology, Immunophenotype, Cytogenetics, and Molecular Approaches*. London, UK: Elsevier Health Science. (2013).
- Barazzoni R, Bischoff SC, Breda J, Wickramasinghe K, Krznaric Z, Nitzan D, et al. ESPEN expert statements and practical guidance for nutritional management of individuals with SARS-CoV-2 infection. *Clin Nutr*. (2020) 142:75–84. doi: 10.26800/LV-142-3-4-13
- Luo S, Zhang X, Xu H. Don't overlook digestive symptoms in patients with 2019 novel coronavirus disease (COVID-19). *Clin Gastroenterol Hepatol*. (2020) 18:1636. doi: 10.1016/j.cgh.2020.03.043
- Zhou Z, Zhao N, Shu Y, Han S, Chen B, Shu X. Effect of gastrointestinal symptoms on patients infected with COVID-19. *Gastroenterology*. (2020) 158:2294–7. doi: 10.1053/j.gastro.2020.03.020
- Li T, Zhang Y, Gong C, Wang J, Liu B, Shi L, et al. Prevalence of malnutrition and analysis of related factors in elderly patients with COVID-19 in Wuhan, China. *Eur J Clin Nutr*. (2020) 74:871–5. doi: 10.1038/s41430-020-0642-3
- Gergely P. Drug-induced lymphopenia: focus on CD4+ and CD8+ cells. *Drug Saf*. (1999) 21:91–100. doi: 10.2165/00002018-199921020-00003
- World Health Organization. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected 2020;1–21. Available online at: <https://www.who.int/publications/i/item/10665-332299> (accessed December 20, 2021).
- World Health Organization. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19) [Internet]. Available online at: <https://www.mdcalc.com/sequential-organfailure-assessment-sofa-score#pearls-pitfalls>
- Huang I, Pranata R. Lymphopenia in severe coronavirus disease-2019 (COVID-19): systematic review and meta-analysis. *J Intensive Care*. (2020) 8:36. doi: 10.1186/s40560-020-00453-4
- Lee J, Park SS, Kim TY, Lee DG, Kim DW. Lymphopenia as a Biological Predictor of Outcomes in COVID-19 Patients: A Nationwide Cohort Study. *Cancers (Basel)*. (2021) 13:471. doi: 10.3390/cancers13030471
- 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. *Lancet Respir Med*. (2020) 8:475–81. doi: 10.1016/S2213-2600(20)30079-5
- Li Y, Tong S, Hu X, Wang Y, Lv R, Ai S, et al. The relationship between nutritional status and the prognosis of COVID-19: A retrospective analysis of 63 patients. *Medicine (Baltimore)*. (2021) 100:e25287. doi: 10.1097/MD.00000000000025287
- Beck MA, Handy J, Levander OA. Host nutritional status: the neglected virulence factor. *Trends Microbiol*. (2004) 12:417–23. doi: 10.1016/j.tim.2004.07.007
- Barazzoni R, Bischoff SC, Breda J, Wickramasinghe K, Krznaric Z, Nitzan D, et al. ESPEN expert statements and practical guidance for nutritional management of individuals with SARS-CoV-2 infection. *Clin Nutr*. (2020) 39:1631–8. doi: 10.1016/j.clnu.2020.03.022
- Caccialanza R, Laviano A, Lobascio F, Montagna E, Bruno R, Ludovisi S, et al. Early nutritional supplementation in non-critically ill patients

AUTHOR CONTRIBUTIONS

HW, YC, and YL concept and design. All authors: acquisition, analysis, or interpretation of the data. HW and NZ drafting of the manuscript. HW and JF statistical analysis. HW and YC obtained funding. XH and ZH contributed to the collection of additional data and analysis in the revision. All authors approved the final version of the manuscript and are responsible for the content.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fnut.2021.739216/full#supplementary-material>

- hospitalized for the 2019 novel coronavirus disease (COVID-19): Rationale and feasibility of a shared pragmatic protocol. *Nutrition*. (2020) 74:110835. doi: 10.1016/j.nut.2020.110835
20. Saito H, Nomura K, Hotta M, Takano K. Malnutrition induces dissociated changes in lymphocyte count and subset proportion in patients with anorexia nervosa. *Int J Eat Disord*. (2007) 40:575–9. doi: 10.1002/eat.20417
 21. Omran ML, Morley JE. Assessment of protein energy malnutrition in older persons, Part II: Laboratory evaluation. *Nutrition*. (2000) 16:131–40. doi: 10.1016/S0899-9007(99)00251-8
 22. Seiler WO. Clinical pictures of malnutrition in ill elderly subjects. *Nutrition*. (2001) 17:496–8. doi: 10.1016/S0899-9007(01)00558-5
 23. Saunders J, Smith T. Malnutrition: causes and consequences. *Clin Med (Lond)*. (2010) 10:624–7. doi: 10.7861/clinmedicine.10-6-624
 24. 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) 395:497–506. doi: 10.1016/S0140-6736(20)30183-5
 25. Xu L, Liu J, Lu M, Yang D, Zheng X. Liver injury during highly pathogenic human coronavirus infections. *Liver Int*. (2020) 40:998–1004. doi: 10.1111/liv.14435
 26. Zheng YY, Ma YT, Zhang JY, Xie X. COVID-19 and the cardiovascular system. *Nat Rev Cardiol*. (2020) 17:259–60. doi: 10.1038/s41569-020-0360-5
 27. Fanelli V, Fiorentino M, Cantaluppi V, Gesualdo L, Stallone G, Ronco C, et al. Acute kidney injury in SARS-CoV-2 infected patients. *Crit Care*. (2020) 24:155. doi: 10.1186/s13054-020-02872-z
 28. Violi F, Pastori D, Cangemi R, Pignatelli P, Loffredo L. Hypercoagulation and Antithrombotic Treatment in Coronavirus 2019: A New Challenge. *Thromb Haemost*. (2020) 120:949–56. doi: 10.1055/s-0040-1710317
 29. Paniz-Mondolfi A, Bryce C, Grimes Z, Gordon RE, Reidy J, Lednický J, et al. Central Nervous System Involvement by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). *J Med Virol*. (2020) 92:699–702. doi: 10.1002/jmv.25915
 30. 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. doi: 10.1016/S0140-6736(20)30566-3

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