Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
A linear relationship between De Ritis ratio and mortality in hospitalized patients with COVID-19: A secondary analysis based on a large retrospective cohort study

Yanling Fu, Shouwen Du, Xiaodi Liu, Lin Cao, Guilin Yang, Hongtao Chen*

Abstract

Background and aims: Although some studies have identified a possible link between the De Ritis ratio and the mortality of patients with COVID-19, the predictive value and the optimal cut-value remain unclear. This study aimed to explore the correlation between the De Ritis ratio and mortality in hospitalized COVID-19 patients.

Methods: The data for this cohort study came from a retrospective cohort study that was carried out in a medical system in New York City. The primary outcome was the in-hospital mortality of included patients. The researchers ran multivariate Cox regression analyses, curve fitting, and subgroup analysis to support our findings. Overall survival in different De Ritis ratio groups was plotted as Kaplan–Meier survival curves.

Results: The study enrolled 4371 participants with COVID-19 from March 1, 2020 to April 16, 2020. The overall mortality was 24.8% (1082/4371). The curve fitting analyses indicated that the De Ritis ratio has a positive linear connection with mortality in patients with COVID-19. After adjusting for all covariates, participants with a De Ritis ratio ≥ 2 exhibited 1.29 times the risk of in-hospital mortality compared with those with a De Ritis ratio < 1 (hazard ratio 1.29, 95% confidence interval 1.02–1.62, p = 0.031). The p for trend was < 0.05 for all models. Patients in the group with a De Ritis ratio ≥ 2 experienced the shortest survival time in the Kaplan–Meier survival analysis.

Conclusions: A higher baseline De Ritis ratio is correlated with a corresponding higher mortality among hospitalized people with COVID-19.

1. Introduction

The coronavirus disease 2019 (COVID-19) has generated unprecedented challenges worldwide. Although its clinical presentation is often mild or even asymptomatic, the studies have shown that up to 20%–30% or more of patients with COVID-19 in hospitals experience critical illness [1–3]. Numerous clinical prognostic factors, including race, age, cigarette smoking, underlying comorbidities, and laboratory tests, have been recognized as contributing to more severe disease [4–6]. An abnormal liver test is common in patients with COVID-19 and has been reported to be associated with a more severe outcome and overall mortality [9]. Some studies have reported a correlation between COVID-19 severity and any abnormal liver function tests, with no differentiation between alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels [7,8]. Other studies found that patients with severe COVID-19 showed a considerably greater rate of aberrant AST at admission but found no difference in ALT or total bilirubin at baseline between patients with severe and non-severe COVID-19 [9]. Additionally, Chew et al. showed that significant liver injury (AST ≥ 5 × ULN or ALT ≥ 5 × ULN) was not associated with death [10].

The De Ritis ratio (AST to ALT ratio) was first described in 1957 as a screening test for viral hepatitis, and it remains in use today to determine the severity of liver impairment. Some studies have found possible correlations between the De Ritis ratio and other diseases including cancer and acute myocardial infarction [11,12]. A prior study from Turkey that investigated 554 patients with COVID-19 reported that the De Ritis ratio

Abbreviations: ACE2, angiotensin-converting enzyme 2; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CI, confidence interval; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; HR, hazard ratio; INR, international normalized ratio; MAP, mean arterial blood pressure; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation; WBC, white blood cells.

* Corresponding author.

E-mail address: 843139770@qq.com (H. Chen).

https://doi.org/10.1016/j.iliver.2022.08.002
Received 22 June 2022; Received in revised form 31 July 2022; Accepted 7 August 2022
Available online 30 August 2022
2022 Published by Elsevier Ltd on behalf of Tsinghua University Press. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
was a good predictor of hospitalization in the intensive care unit but did not predict mortality [13]. Another study from Spain found a higher De Ritis ratio in non-survivors of COVID-19 than that in the survivors [14]. In addition, Harsh et al. found that De Ritis ratio at admission was a significant predictor of mortality [15]. A meta-analysis found that a higher De Ritis ratio was linked to poor outcomes from COVID-19, although previous published studies have been limited to small sample sizes [16]. This study therefore set out to assess the predictive value of the baseline De Ritis ratio in a large set of hospitalized patients with COVID-19.

2. Materials and methods

2.1. Database

The dataset from the Dryad Database was used in this retrospective observational cohort study, shared by Altschul and David [2] (https://datadryad.org/stash/dataset/10.5061/dryad.7d7wm37sz).

2.2. Study population

Patients diagnosed as COVID-19-positive by RT-PCR and admitted to four hospitals in the Montefiore Health System in New York City from March 1, 2020, to April 16, 2020 were included. Patients with COVID-19 over the age of 18 were included; for patients who were hospitalized multiple times, only the most recent admission was considered. Patients were excluded from this analysis if they were either not admitted or died before admission to the hospital or had insufficient or unavailable AST or ALT data to calculate the De Ritis ratio. This study included a total of 4371 patients. Follow-up lasted from 0 to 56 days, terminating on May 7, 2020.

2.3. Variables

The following variables that were available at the time of entry were included: (1) demographic information: age and race, with patients of two or more races being classified as "others"; (2) history of myocardial infarction, cerebrovascular disease, diabetes, congestive heart failure, central nervous system disease, chronic obstructive pulmonary disease, or renal dysfunction; (3) vital signs, including mean arterial blood pressure (MAP), oxygen saturation (SpO₂) and body temperature (T); (4) laboratory tests, including white blood cells, C-reactive protein (CRP), D-dimer, platelets, blood urea nitrogen (BUN), creatinine, blood sodium, blood glucose, international normalized ratio (INR), procalcitonin (PCT), troponins, AST, and ALT. The AST to ALT ratio was used to calculate the De Ritis ratio.

2.4. Outcomes

The outcome of the study was in-hospital mortality. The number of days from admission to in-hospital mortality was used as the time-to-event data. In-hospital mortality registration and the National Death Registry were used to gather this information.

2.5. Statistical analysis

Participants were divided into three groups (<1, 1–2, and ≥2) according to the De Ritis ratio. Patient characteristics were determined based on the De Ritis ratio. Continuous variables are represented by means and standard deviation, whereas categorical variables are expressed by numbers and percentages. To assess differences across the distinct groups of De Ritis ratios, the Chi-square test (categorical variables), one-way analysis of variance test (normal distribution), or Kruskal–Wallis H test (skewed distribution) were used.

Hazard ratios (HRs) and 95% confidence intervals (CIs) for mortality associated with the De Ritis ratio were estimated using Cox proportional-hazards models. We built four different models: (1) the unadjusted model; (2) the model adjusted for age and race; (3) the model adjusted for age, race, renal disease, central nervous system disease, oxygen saturation, temperature, and median arterial blood pressure; (4) the model adjusted for age, race, renal disease, central nervous system disease, oxygen saturation, temperature, median arterial blood pressure, D-dimer, platelets, INR, BUN, creatinine, sodium, ALT, AST, CRP, PCT, and troponins. The multivariate model included clinically relevant parameters and significant covariates from the univariate analysis (p < 0.05). Trend tests were used to investigate the statistical significance of trends.

Subsequently, the relationships between the De Ritis ratio and in-hospital mortality were assessed using cubic spline curves and smooth curve fitting on a continuous scale. Stratified Cox proportional-hazards models were used for the subgroup analyses. The likelihood ratio test was used evaluate how the subgroups interacted. We did an interaction test after converting continuous factors to categorical data according to
3. Results

3.1. Selection of participants

Of the 4711 adult participants who completed follow-up, 340 participants were excluded according to the exclusion criteria. The final analysis set comprised 4371 participants. The flow chart of the study is shown in Fig. 1.

3.2. Baseline data

The baseline data of all individuals, divided into three groups according to the De Ritis ratio, are presented in Table 1. The mean age of the participants was 63.7 ± 16.5 years. There were statistically significant differences in age, race, cerebral vascular disease, renal disease, central nervous system disease, SpO2, MAP, D-dimer, platelets, BUN, creatinine, sodium, AST, ALT, PCT, CRP, and troponins.

3.3. Outcomes

The overall mortality was 24.8% of hospitalized patients. In-hospital mortality was 14.8% in the De Ritis ratio <1 group, 22.2% in the 1–2 group, and 34.9% in the ≥2 group. Participants with a De Ritis ratio ≥2 had a higher incidence of mortality than the 1–2 group and the <1 group (p < 0.001) (Fig. 2).

3.4. Multivariate models of De Ritis ratio and in-hospital mortality

A univariate Cox regression analysis of covariates and in-hospital mortality demonstrated the potential confounders shown in Supplemental Table A.1 (Supplemental file). Age, race, renal disease, central nervous system disease, oxygen saturation, temperature, median arterial blood pressure, D-dimer, platelets, BUN, creatinine, sodium, AST, ALT,
CRP, PCT, and troponins were selected and adjusted for in the multivariable Cox regression analysis.

The De Ritis ratio was used as a continuous and categorical variable in a multivariable Cox regression to examine the associations between the De Ritis ratio and mortality (Table 2). In the crude analysis, the unadjusted HR was 1.11 (1.09–1.13). After adjusting for age and race (Model I), the adjusted HR was 1.08 (95% CI 1.06–1.1, p < 0.001). After adjusting for age, race, renal disease, central nervous system, oxygen saturation, temperature, and median arterial blood pressure (Model II), the adjusted HR was 1.06 (95% CI 1.03–1.08, p < 0.001). After controlling for all of the chosen factors (Model III), the adjusted HR was 1.04 (95% CI 1.01–1.07, p = 0.009).

When the De Ritis ratio was incorporated into the fully adjusted model (Model III) as a categorized variable, the changing trend of the practical value in different De Ritis ratio groups was non-equidistant. The ≤1 group had 1.02 times the risk of in-hospital mortality compared with the <1 group (HR 1.02, 95% CI 0.82–1.26, p = 0.868) and the ≥2 group had 1.29 times the risk compared with the <1 group (HR 1.29, 95% CI 1.02–1.62, p = 0.031). P for trend was 0.001 (Table 2).

3.5. Relationship between De Ritis ratio and mortality

The baseline De Ritis ratio and in-hospital mortality were discovered to have a linear relationship after the adjustment for age, race, renal disease, central nervous system, oxygen saturation, temperature, MAP, D-dimer, platelets, BUN, creatinine, sodium, AST, ALT, CRP, PCT, and troponins (Fig. 3).

3.6. Subgroup analysis

When analyzed by subgroups, the correlation between the De Ritis ratio and in-hospital mortality remained consistent. However, the De Ritis ratio-related risk of mortality varied by age, race, oxygen saturation, INR, and PCT. Among patients aged <60 years, white race, oxygen saturation ≥2.03 (1.64–2.51) had a significant correlation with in-hospital mortality (HR 2.03, 95% CI 1.64–2.51, p = 0.001). Among patients aged ≥60 years, white race, oxygen saturation ≥3.5, and INR had significant correlation with in-hospital mortality (HR 3.5, 95% CI 3.2–3.8, p = 0.001).

Table 2

| Variable | Non-adjusted Model HR (95%CI) | p-value | Model I HR (95%CI) | p-value | Model II HR (95%CI) | p-value | Model III HR (95%CI) | p-value |
|----------|-------------------------------|---------|-------------------|---------|-------------------|---------|---------------------|---------|
| De Ritis Ratio Subgroups | | | | | | | | |
| <1 | 1.11 (1.09–1.13) | <0.001 | 1.08 (1.06–1.11) | <0.001 | 1.06 (1.03–1.08) | <0.001 | 1.04 (1.01–1.07) | 0.009 |
| 1–2 | 1.28 (1.04–1.58) | 0.019 | 1.1 (0.89–1.35) | 0.382 | 1.02 (0.83–1.26) | 0.837 | 1.02 (0.82–1.26) | 0.868 |
| ≥2 | 2.03 (1.64–2.51) | <0.001 | 1.58 (1.28–1.96) | <0.001 | 1.36 (1.1–1.69) | 0.005 | 1.29 (1.02–1.62) | 0.031 |

Model I: Adjusted for age, race.
Model II: Adjusted for the variables in Model I plus renal disease, central nervous system, oxygen saturation, temperature and median arterial blood pressure.
Model III: Adjusted for the variables in Model II plus D-dimer, platelets, INR, BUN, creatinine, sodium, ALT, AST, CRP, procalcitonin and troponin.
saturation ≥94%, INR ≤1.2, and PCT ≤0.1, a higher De Ritis ratio was linked with a more significant elevation of mortality (p for interaction < 0.05) (Fig. 4).

4. Discussion

4.1. De Ritis ratio as a predictor of mortality

Hepatic dysfunction has been documented in previous studies in approximately 10%–60% of patients with COVID-19 and is considered to be associated with higher mortality [17]. Some studies found that non-survivors had a significantly higher incidence of any abnormal liver biochemical indicators, but others found that AST, rather than ALT, played the more critical function [9,16].

The De Ritis ratio has garnered considerable attention in predicting fulminant hepatitis and underlying fibrosis in viral hepatitis [18,19]. However, there is controversy about the predictive function of the De Ritis ratio in COVID-19, and the De Ritis ratio’s ideal predictive cut-off value remains unknown. According to Cheng Qin et al., a De Ritis ratio of ≥1.38 was related to poor prediction of patients with COVID-19 regardless of AST rise [20]. In 105 patients with COVID-19, Zinellu et al. reported that a De Ritis ratio of 1.63 was highly associated with mortality [21]. A study from the USA reported that a De Ritis ratio > 2 was seen in 34% (68/200) of patients and was associated with a need for intubation and vasopressors [22]. A meta-analysis revealed that the De Ritis ratio was a superior predictor for COVID-19 than ALT or AST alone [16], although the cut-off values differed in these studies.

This study set out to assess the importance of the De Ritis ratio in patients with COVID-19 in a large cohort. The results of this study clearly show that the De Ritis ratio is an independent predictor of prognosis among hospitalized patients with COVID-19. Patients with a De Ritis ratio of ≥2 had higher mortality, and this influence persisted after adjusting for many covariates, in concurrence with evidence from previous observations [9]. Surprisingly, the relationship between the De Ritis ratio and in-hospital COVID-19 mortality in the present study was linear, which was not detected in the earlier studies.

4.2. Subgroup analysis

In subgroup analysis, we found the De Ritis ratio and mortality had a consistent connection. However, we discovered that the De Ritis ratio had a more significant influence on mortality among patients younger than 60 years, those of white race, and those with oxygen saturation ≥94%, INR ≤1.2, and PCT ≤0.1. According to our findings, the De Ritis ratio and age have a considerable positive association (Table 1), which is in accordance with previous studies [14,20]. Surprisingly, the predictive function of the De Ritis ratio for mortality is more robust in patients younger than 60 years. Thus, we should pay particular attention to high De Ritis ratios in younger patients.

Another unanticipated finding was that white people with an elevated De Ritis ratio seem to experience higher mortality than other races. The reason for this finding is unclear; it is inconsistent with previous studies, which indicated that black and Hispanic/Latino populations had the highest death rates [23,24]. In our study, patients of white race were older than patients in other races (Supplemental Table A.2), which may be the reason for their higher mortality. Whether the De Ritis ratio plays a different role in ethnically diverse populations merits further investigation.
4.3. Underlying mechanisms

The exact mechanism of the predictive significance of a high De Ritis ratio in many diseases remains unknown. ALT is a more liver-specific measurement while AST is widely expressed in different tissues, mainly in the liver, skeletal muscle, and cardiac muscle and is also distributed in the kidney, pulmonary system, pancreas, and brain. As a result, ALT is a sensitive marker for liver disease, but AST is a marker indicating more severe illness, such as rhabdomyolysis, myocardial injury, or severe liver damage [16].

Angiotensin-converting enzyme 2 (ACE2) has been identified as a target of SARS-molecular CoV-2 [25]. Gene expression levels of ACE2 differ across the human body; ACE2 expression is high in the small intestine and terminal ileum, heart muscle, testis, kidney, and thyroid gland but is lower in the liver and lung [26]. Meanwhile, ACE2 activity is relatively higher in hepatic duct cells than in hepatocellular tissue [7,27]. Hence, the cytokine storm-mediated immune activation caused by the SARS-CoV-2 virus leads to multi-organ injury, especially in skeletal muscle and myocardium [25]. As a result, we hypothesize that the release of AST is mainly from a non-hepatocellular source. Additionally, the clearance of AST from the circulation by the liver sinusoids is thought to be diminished by injury to endothelial cells, which also contain ACE2 [18]. Therefore, patients with the more severe disease may have a higher AST level, but the difference is not apparent in ALT.

Our study has some limitations to note. Some potential confounders, such as sex and underlying liver disorders, were not available in the database. Additionally, this study does not contain information about therapeutic interventions. Despite its limitations, this large cohort study certainly adds to our understanding of the predictive role of the De Ritis ratio for mortality of in-hospital patients with COVID-19, with greater predictive power than ALT or AST alone. The De Ritis ratio is a simple, non-invasive, and cost-effective marker for identifying patients at a greater risk of death. We propose a new non-invasive prognostic model incorporating the De Ritis ratio for COVID-19 rather than the De Ritis ratio alone, especially in resource-limited areas.

5. Conclusions

The most prominent finding from this study is its demonstration of a linear relationship between the De Ritis ratio and mortality. These findings support the notion that monitoring the baseline De Ritis ratio in hospitalized patients with COVID-19 is necessary, and that a new non-invasive prognostic model for COVID-19 that incorporates the De Ritis ratio is needed.
Author contributions
Yanling FU conducted the data analysis and wrote the manuscript. Hongtao CHEN designed the study and reviewed the manuscript. Shou-wen DU conducted data analysis and reviewed the manuscript. Xiaodi LIU and Lin CAO conducted the data collection. Guilin YANG conducted the data collection and reviewed the manuscript.

Acknowledgments
The authors thank Dr. Liu Jie (People's Liberation Army of China General Hospital, Beijing, China) and Dr. Yang Qilin (The Second Affiliated Hospital of Guangzhou Medical University, Guangzhou, Guangdong, China) for assisting in this revision.

Declaration of competing interest
The authors declare that they have no competing interests.

Data available statement
The data that support the findings of this study are openly available in the Dryad Database at [https://datadryad.org/stash/dataset/10.5061/dryad.7d7w7m37sz].

Funding
This study was supported by the National Natural Science Foundation of China (No. 31972719) and the Shenzhen Municipal Health Commission project (No. SZXJ2018018).

Ethics statement
The new ethics approval was not applicable because the original author had obtained ethical approval when conducting this study.

Informed consent
Seeking additional permission to participate was not appropriate because our research was a retrospective study that re-used data, and all patients remained anonymous.

Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.jliver.2022.08.002.

References
[1] Cummings MJ, Baldwin MR, Abrams D, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. Lancet 2020;395(10239):1763-70.
[2] Eskandar EN, Altschul DJ, de la Garza Ramos R, et al. Neurologic syndromes predict higher in-hospital mortality in COVID-19. Neurology 2021;96(11):e1527–38.
[3] Agha SM, Ahmed AS, Maniford B, et al. Rate of Intensive Care Unit admission and outcomes among patients with coronavirus: a systematic review and Meta-analysis. PLoS One 2020;15(7):e235655.
[4] Brandt EB, Beck AF, Mersha TB. Air pollution, racial disparities, and COVID-19 mortality. J Allergy Clin Immunol 2020;146(1):61–3.
[5] Weiss P, Murdoch DR. Clinical course and mortality risk of severe COVID-19. Lancet 2020;395(10229):1014–5.
[6] Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in wuhan, China. JAMA Intern Med 2020;180(7):934–43.
[7] Saviano A, Wernsch F, Ghany MG, et al. Liver disease and coronavirus disease 2019: from pathogenesis to clinical care. Hepatology 2021;74(2):1088–100.
[8] Bloom PP, Meyerowitz EA, Reinus Z, et al. Liver biochemistry in hospitalized patients with COVID-19. Hepatology 2021;73(3):890–900.
[9] Wu Y, Li H, Guo X, et al. Incidence, risk factors, and prognosis of abnormal liver biochemical tests in COVID-19 patients: a systematic review and meta-analysis. Hepatol Int 2020;14(5):621–37.
[10] Chew M, Tang Z, Radcliffe C, et al. Significant liver injury during hospitalization for COVID-19 is not associated with liver insuficiency or death. Clin Gastroenterol Hepatol 2021;19(10):2182–91.
[11] Riedl JM, Posch F, Prager G, et al. The AST/ALT (De Ritis) ratio predicts clinical outcome in patients with pancreatic cancer treated with first-line nab-paclitaxel and gemcitabine: post hoc analysis of an Austrian multicenter, noninterventional study. Ther Adv Med Oncol 2020;12:432451384.
[12] Steininger M, Winter MP, Reiberger T, et al. De-Ritis ratio improves long-term risk prediction after acute myocardial infection. J Clin Med 2018;7(12).
[13] Meteatalibeyoglu A, Catma Y, Senkal N, et al. The effect of liver test abnormalities on the prognosis of COVID-19. Ann Hepatol 2020;19(6):614–21.
[14] Benede-Ubieto R, Estevze-Vazquez O, Flores-Perojo V, et al. Abnormal liver function test in patients infected with coronavirus (SARS-CoV-2): a retrospective single-center study from Spain. J Clin Med 2021;10(5).
[15] Goel H, Harmouch F, Garg K, et al. The liver in COVID-19: prevalence, patterns, predictors, and impact on outcomes of liver test abnormalities. Eur J Gastroenterol Hepatol 2021;33(15 Suppl 1):e274–81.
[16] Pranata R, Huang J, Lim MA, et al. Elevated de ritis ratio is associated with poor prognosis in COVID-19: a systematic review and meta-analysis. Front Med 2021;8:676581.
[17] Jothimani D, Venugopal R, Abedin MF, et al. COVID-19 and the liver. J Hepatol 2020;73(5):1231–40.
[18] Botros M, Sikaris KA. The de ritis ratio: the test of time. Clin Biochem Rev 2013;34(3):117–30.
[19] Giannini E, Rimo D, Botta F, et al. Validity and clinical utility of the aspartate aminotransferase-alanine aminotransferase ratio in assessing disease severity and prognosis in patients with hepatitis C virus-related chronic liver disease. Arch Intern Med 2003;163(2):218–24.
[20] Qin C, Wei Y, Lyu X, et al. High aspartate aminotransferase to alanine aminotransferase ratio on admission as risk factor for poor prognosis in COVID-19 patients. Sci Rep 2020;10(1):16496.
[21] Zinella A, Arru F, De Vito A, et al. The De Ritis ratio as prognostic biomarker of in-hospital mortality in COVID-19 patients. Eur J Clin Invest 2021;51(1):e13427.
[22] Yadlapati S, Lo KB, Dejoy R, et al. Prevailing patterns of liver enzymes in patients with COVID-19 infection and association with clinical outcomes. Ann Gastroenterol 2021;34(2):224-4.
[23] Thompson CN, Baumgartner J, Pichardo C, et al. COVID-19 outbreak - New York city, february 29-june 1, 2020. MMWR Morb Mortal Wkly Rep 2020;69(46):1725-9.
[24] Bhala N, Curry G, Martineau AR, et al. Sharpening the global focus on ethnicity and race in the time of COVID-19. Lancet 2020;395(10238):1673–6.
[25] Jackson CB, Farzan M, Chen B, et al. Mechanisms of SARS-CoV-2 entry into cells. Nat Rev Mol Cell Biol 2022;23(1):3–20.
[26] Pirola CJ, Sookoian S. COVID-19 and ACE2 in the liver and gastrointestinal tract: putative biological explanations of sexual dimorphism. Gastroenterology 2020;159(4):1620–1.
[27] Zhao W, Li H, Li J, et al. The mechanism of multiple organ dysfunction syndrome in patients with COVID-19. J Med Virol 2022;94(5):1886–92.