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Correlation analysis of coagulation dysfunction and liver damage in patients with novel coronavirus pneumonia: a single-center, retrospective, observational study

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ABSTRACT

Background: The novel coronavirus disease 2019 (COVID-19) is currently breaking out worldwide. COVID-19 patients may have different degrees of coagulopathy, but the mechanism is not yet clear. We aimed to analyse the relationship between coagulation dysfunction and liver damage in patients with COVID-19.

Methods: A retrospective analysis of 74 patients with COVID-19 admitted to the First People's Hospital of Yueyang from 1 January to 30 March 2020 was carried out. According to the coagulation function, 27 cases entered the coagulopathy group and 47 cases entered the control group. A case control study was conducted to analyse the correlation between the occurrence of coagulation dysfunction and liver damage in COVID-19 patients.

Results: Alanine aminotransferase (ALT) and aspartate aminotransferase (AST), markers of liver damage, were positively correlated with coagulopathy ($p = 0.039$, OR 2.960, 95% CI 1.055–8.304; and $p = 0.028$, OR 3.352, 95% CI 1.137–9.187). Alkaline phosphatase (ALP), γ-glutamyl transpeptidase (γ-GT), and total bilirubin (TBIL) were not statistically correlated with coagulopathy. According to the diagnosis and treatment plan, the included cases were classified into mild, moderate, severe, and critical. The results showed that the occurrence of coagulation dysfunction had no statistical correlation with the severity of COVID-19.

Conclusion: Coagulation dysfunction in patients with COVID-19 is closely related to liver damage. A longer course of the disease may cause a vicious circle of coagulopathy and liver damage. Clinicians need to closely monitor coagulation and liver function tests and to give prophylactic or supportive therapy when needed.

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Introduction

The novel coronavirus disease (COVID-19) is currently breaking out worldwide, threatening human health and quality of life seriously. Its main clinical manifestations are fever, dry cough, and fatigue. In some severe cases, acute respiratory distress, multiple organ failure, and even death may occur (1).

COVID-19 is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), belonging to the group of β-coronaviruses. It has the characteristics of a long incubation period (1–14 days, average 6.4 days), a long onset period, and strong infectivity. The S protein on the surface of SARS-CoV-2 binds to angiotensin-converting enzyme II (ACE2), which leads SARS-CoV-2 to enter the host cell (2,3). Some researchers (4–6) have reported that patients with COVID-19 have varying degrees of coagulopathy and liver damage as the disease progresses. The liver is closely related to the synthesis of coagulation factors, which means that when the liver is damaged, it will directly affect the coagulation function. The relationship between coagulation dysfunction induced by COVID-19 and liver damage is unclear. This study retrospectively analysed the clinical data of 74 confirmed cases of COVID-19 to explore the correlation between COVID-19 patients' coagulopathy and liver damage.

Methods

A total of 74 patients with COVID-19 admitted to the First People's Hospital of Yueyang, Hunan Province from 1 January to 30 March 2020 were enrolled. The hospital is the designated hospital for the treatment of COVID-19 patients. The Ethics Committee of the Third Xiangya Hospital of Central South University approved this study. Inclusion criteria were in line with the 'Novel Coronavirus Infection Pneumonia Diagnosis and Treatment Program (Trial Version 7)' (7) diagnosis requirements: (1) Have fever and/or respiratory symptoms; (2) Have lung-imaging features of new

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coronavirus pneumonia; (3) Real-time fluorescent RT-PCR detection of SARS-CoV-2 nucleic acid is positive. On this basis, according to coagulation function, patients with coagulation dysfunction were included in the coagulation dysfunction group, and those without coagulation dysfunction were included in the control group. Exclusion criteria: (1) history of coagulation disease or taking coagulation-related drugs; (2) liver and/or kidney dysfunction; (3) hepatobiliary diseases; (4) incomplete clinical data.

We collected clinical data from electronic medical records of all confirmed patients, including past history, gender, age, length of hospital stay, clinical symptoms and laboratory findings, mainly liver and coagulation function test results. Patients' first test results were selected for inclusion in the analysis.

Diagnostic criteria for coagulopathy

A fully automatic blood coagulation analyser (CS5100, Sysmex Corp., Japan) was used to detect the blood coagulation function. Prior to testing, all projects were subject to strict quality control testing. When one or more of the indicators listed in Table 1 were abnormal, it was defined as coagulation dysfunction.

Diagnostic criteria for liver damage

A fully automatic biochemical analyser (BS800, Mindray Corp., China) was used to detect liver function. Prior to testing, all projects were subject to strict quality control testing. When one or more of the following indicators exceeded the upper limit of normal value, it was defined as liver damage: serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST), total bilirubin (TBIL), γ-glutamyl transpeptidase (γ-GT), and alkaline phosphatase (ALP). The reference values were: ALT, 7–40 U/L; AST, 13–35 U/L; TBIL, 1.7–25 μmol/L; γ-GT, 7–45 U/L; and ALP, 50–135 U/L.

Statistical analysis

This study was conducted during the outbreak of COVID-19. Therefore, we did not estimate the sample size by formal hypotheses, and we have included the maximum number of patients who met the inclusion criteria.

Qualitative data were expressed in number of cases, percentage, or composition ratio. We used chi-square test to compare the qualitative data between the two groups. The quantitative data were tested for normality and homogeneity of variance. Normally distributed quantitative data were expressed as mean ± standard, and we used Student's *t* test for two independent samples to compare the qualitative data of the two groups. Tests were two-sided with significance set at $\alpha < 0.05$. SPSS 23.0 for Windows (SPSS Inc.) was applied for all analysis.

Table 1. Diagnostic criteria for coagulopathy.

Indicator	Reference values	Diagnostic criteria
PT	9.8–14.8 s	Extension > 3 s
TT	14–21 s	Extension > 3 s
INR	0.86–1.27	>1.3
APTT	23.3–32.5 s	Extension > 10 s
Fibrinogen content	2–4 g/L	<2 g/L
D-dimer	<500 μg/L	>500 μg / L
Platelet count	125–350 × 10^9/L	<125 × 10^9/L

APTT: activated partial thromboplastin time; INR: international normalised ratio; PT: prothrombin time; TT: thrombin time.

Results

Following the inclusion and exclusion criteria strictly, 74 patients (36 female and 38 male) with COVID-19 were included; 27 cases entered the coagulopathy group, and 47 cases entered the control group. General information between the two groups was compared (Table 2). There was no statistically significant difference.

According to the 'New Coronavirus Infected Pneumonia Diagnosis and Treatment Program (Trial Version 7)' (7), patients with different severity of pneumonia were classified into mild, moderate, severe, and critical. In the coagulation group, 4 cases were mild (14.8%), 12 were moderate (44.4%), and 11 were severe/critical (40.8%). In the control group, 14 cases (29.8%) were mild, 19 cases (40.4%) were moderate, and 14 cases (29.8%) were severe/critical. There was no significant correlation between coagulation dysfunction and COVID-19 severity (chi-square = 3.012, $p > 0.05$).

This study analysed the relationship between changes in liver damage markers and COVID-19 coagulation dysfunction. ALT and AST are markers that can reflect liver damage. COVID-19 coagulation dysfunction was associated with ALT and AST (Pearson chi-square test, both $p < 0.05$) (Table 3). However, ALP, γ-GT, and TBIL, reflecting the function of the bile duct system, showed no significant correlation with coagulopathy in the COVID-19 patients (Pearson chi-square test, all $p > 0.05$).

The above single factor analysis showed a statistically significant difference of ALT and AST levels between the coagulation dysfunction group and the control group. Therefore, a logistic regression analysis model of the influencing factors of coagulation dysfunction was constructed. Taking whether the patient has coagulation dysfunction as the dependent variable (normal = 0, abnormal = 1), and AST and ALT as the independent variable (normal = 0, abnormal = 1), a binary logistic regression analysis was performed. It was found that AST and ALT levels were the main risk factors affecting COVID-19 patients' coagulopathy ($p = 0.039$, OR 2.960, 95% CI 1.055–8.304; and $p = 0.028$, OR 3.352, 95% CI 1.137–9.187).

Table 2. General information on the two evenly matched groups.

Parameters	Coagulopathy group ($n = 27$)	Control group ($n = 47$)	*p*
Age (y)	52.5 ± 12.1	47.8 ± 17.1	>0.05
Gender			
Male	14 (51.9%)	24 (51.1%)	>0.05
Female	13 (48.1%)	23 (48.9%)	
Basic diseases			
Hypertension	5 (18.5%)	4 (8.5%)	>0.05
Diabetes	1 (3.7%)	1 (2.1%)	>0.05
COPD	1 (3.7%)	2 (4.3%)	>0.05
Other	7 (25.9%)	10 (21.3%)	>0.05

COPD: chronic obstructive pulmonary disease.

Table 3. The correlation between biochemical test index with coagulopathy in COVID-19.

Group	Abnormal[a] ALT	Abnormal[a] AST	Abnormal[a] TBIL	Abnormal[a] ALP	Abnormal[a] γ-GT
Coagulopathy group	12	11	7	3	6
Control group	10	8	5	2	14
Chi-square	4.406	5.056	1.932	0.423	0.498
p	0.036	0.025	0.165	0.516	0.481

[a]Abnormal means that the indicator exceeds the upper limit of normal value.

Discussion

At present, it has been observed that COVID-19 can lead to different degrees of coagulation dysfunction. Endothelial cells play a key role in the regulation of blood coagulation and fibrinolysis. The immune response *in vivo* of patients with COVID-19 implies the release of a variety of inflammatory mediators such as interleukin 6 (IL-6). There is damage of vascular endothelial cells, initiating endogenous coagulation pathways. The damaged endothelial cells increase the release of von Willebrand factor (vWF) and tissue factor (TF), and then subendothelial tissues become exposed. In the presence of calcium ions, FVII is activated to start the exogenous coagulation system and accelerates the production of thrombin, resulting in activation of the coagulation or fibrinolysis system (8,9). In addition, systemic inflammation may activate Nox2, and reactive oxygen species (ROS) derived from Nox2 will adversely affect blood coagulation.

Several studies have shown that, in addition to coagulation dysfunction, COVID-19 patients will have different degrees of liver damage as well. The pathogenesis of liver damage complicated by COVID-19 is not yet clear; however, current mainstream views on the mechanism of liver injury include: (1) Angiotensin-converting enzyme 2 (ACE2) mediates SARS-CoV-2 invasion of target cells. Bile duct epithelial cells highly express ACE2, and its expression level is similar to alveolar type II cells, which is the main target cell type of SARS-CoV-2 in the lung. But according to current clinical data, the levels of bile duct injury markers such as ALP and γ-GT in COVID-19 patients have not increased, so this mechanism needs further studies (10–12). (2) After infection with SARS-CoV-2, the immune cells are activated, and excessive accumulation of immune cells occurs. The excessively activated inflammatory cells infiltrating the tissue release many proinflammatory cytokines, oxygen free radicals, etc., which can cause damage. The cytokine storm triggered may be one of the mechanisms of liver injury (13,14). (3) Hypoxaemia and respiratory distress syndrome may occur in severe and critical pneumonia. When the tissue is hypoxic, an oxidative stress response may be triggered, resulting in liver function damage. At the same time, it promotes reactive oxygen species increasing continuously, which further initiates the release of various proinflammatory factors to induce liver damage. (4) Patients with COVID-19, especially those with severe and critical disease, usually receive different kinds of pharmacological therapy. A drug in itself or the interaction between different drugs may cause liver damage (15–18). Recent research has shown that the hypercoagulable state of COVID-19 patients alters intrahepatic vascular structures and causes a variable degree of luminal thrombosis. This may add to other mechanisms of liver damage in COVID-19 patients (19).

The synthesis of coagulation factors is closely related to the liver. Liver, as a production site for multiple clotting factors, might play a huge role in COVID-19 coagulopathy. Liver damage leads to reduced coagulation factors, plasma plasminogen activator inhibitors, and tissue-type plasminogen activator secretion, causing bleeding tendency. Fibrinogen (Fbg), one of the important proteins of the blood coagulation system, is synthesised by liver parenchymal cells. It is the final substrate for the successive activation of coagulation factors during coagulation. Because of its functions of hemostasis and mediating platelet aggregation, liver damage will cause a decrease in Fbg synthesis, which will affect blood coagulation.

It is worth mentioning that some studies have pointed out that the incidence of liver damage is related to the severity of COVID-19, and that patients with severe disease are more likely to have liver damage. In this study, however, it was found that there was no correlation between coagulopathy and the severity of COVID-19, which is inconsistent with a liver–COVID-19 relationship. Rather, it may suggest that the occurrence of coagulation dysfunction is not related to liver abnormalities. Moreover, we found that ALT and AST were positively correlated with COVID-19 coagulopathy, suggesting that after COVID-19 infection liver damage might be detrimental.

It might also be envisaged that the coagulation dysfunction in COVID-19 patients may cause liver damage due to thrombosis. A longer course of COVID-19 may cause a vicious circle of coagulation dysfunction and liver damage, which does not promote patient survival. Although there is yet no highly efficient specific therapy for SARS-CoV-2, it is important to prevent thrombosis and to identify coagulation and liver dysfunction by laboratory monitoring to enable supportive therapy.

In this study we found a correlation between coagulopathy and elevated liver transferases in COVID-19 patients. The coagulopathy was, in contrast to other studies, not related to the severity of the disease. The mechanism behind the association between coagulopathy and liver damage is still unclear and needs further investigation.

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Disclosure statement

The authors declare that they have no conflicts of interest.

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