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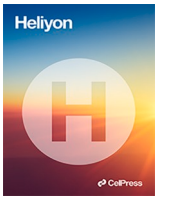

Research article

Liver function abnormality on admission predicts long COVID syndrome in digestive system

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ABSTRACT

Background: Clinical practice showed that many patients with SARS-CoV-2 infection presented with long COVID syndrome in digestive system. We sought to investigate the factor affecting the incidence of long COVID syndrome in digestive system.

Methods and results: Patients with SARS-CoV-2 infection diagnosed at two centers of Zhongshan Hospital and one center of Shanghai Pudong Hospital from March 01, 2022 to May 31, 2022 were enrolled, collected in the hospital database, and followed up until March 30, 2023. The primary outcome of the study was the occurrence of post-acute sequelae of COVID-19 in the digestive

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system (long COVID syndrome). Modified Poisson regression was used to calculate the relative risk (RR). This cohort study included 494 patients with SARS-CoV-2 infection, 144 (29.1 %) patients developed liver function abnormality on admission. During the follow-up period, the primary study outcome occurred in 30 (20.8 %) of the group presenting with liver function abnormality on admission and in 20 (5.7 %) of the group without liver function abnormality on admission (adjusted, RR = 3.550, 95%CI: 2.099–6.006, $P \leq 0.001$).

Conclusion: Our study suggests that patients with COVID-19 who experience liver function abnormality on admission have an increased risk of developing long COVID syndrome in the digestive system.

1. Introduction

The epidemic of SARS-CoV-2 infection has led to a growing concern about the post-acute sequelae it causes, also known as the long COVID syndrome. Long COVID syndrome is defined as symptoms that develop 3 months after infection with SARS-CoV-2, persist for at least 2 months, and cannot be explained by any other diagnosis [1]. Previous studies have shown that long COVID syndrome occurs in approximately 12.5%–20.0 % of people with SARS-CoV-2 infection and involves various systems [2–6]. Among them, post-acute sequelae in the digestive system have received little attention, because they are easy to ignore, such as nausea, vomiting, poor appetite, indigestion, etc [3,6]. However, once these symptoms persist for a long time, they may lead to nutritional deficiencies in patients, which not only affect the recovery process of SARS-CoV-2 infection, but may also cause dehydration, immunodeficiency and complications of other diseases such as anemia, infections of various systems, acute exacerbation of chronic diseases. These in turn can seriously threaten the life and health of patients [7–9]. Thus, better clinical identification of populations prone to post-acute sequelae (digestive system) is needed to protect them from serious nutritional and health threats.

In clinical practice, approximately 14%–53 % of patients with SARS-CoV-2 infection develop liver functional abnormalities at an early stage [10–13]. The mechanisms underlying early liver injury may involve in inflammation, immunity, cytokine storm, and organ hypoxia-ischemia-reperfusion caused by the virus [10,14–17]. To date, it is unclear whether there is an association between early liver injury and post-acute sequelae in the digestive system. Therefore, we designed an investigator-initiated, bi-center, prospective cohort study to investigate the association between liver function abnormality on admission and long COVID syndrome in the digestive system.

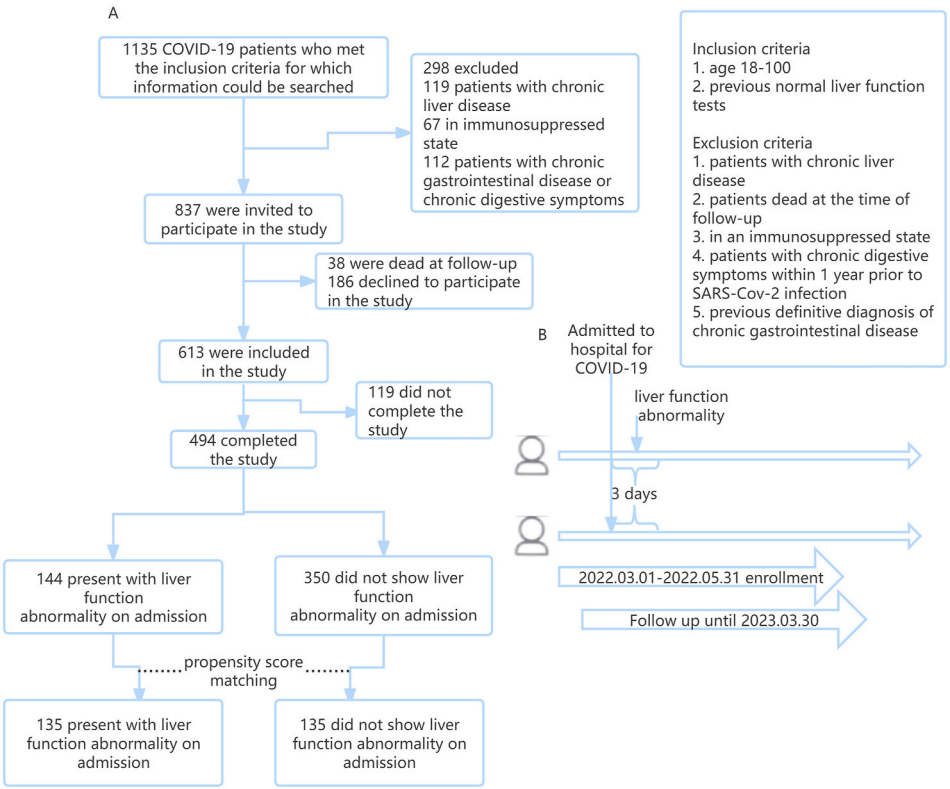

Fig. 1. A: Flowchart of the current study; B: Schematic diagram of the appearance of liver function abnormality on admission and follow-up.

2. Method

2.1. Study population

This bi-center, prospective cohort study was conducted by the investigators in accordance with the Declaration of Helsinki and was approved by the Medical Ethics Committee of Zhongshan Hospital of Fudan University (No.B2022-250R) and Shanghai Pudong Hospital (No.YJXG-22). Written informed consent was obtained from all the participants. The potential study population included COVID-19 cases confirmed at Zhongshan Hospital and Shanghai Pudong Hospital between March 1, 2022, and May 31, 2022. A confirmed case of SARS-CoV-2 infection refers to a suspected case with the following etiologic evidence: a positive nucleic acid test for SARS-CoV-2 [18,19]. Eligible patients met the following inclusion criteria: 1) older than 18 years and younger than 90 years; and 2) previous liver function tests were normal. Normal liver function tests were defined as the following laboratory indicators within the normal range: total bilirubin (TB $<$ 23.0 μmol/L), direct bilirubin (DB $<$ 8.0 μmol/L), alanine aminotransferase (ALT $<$40U/L), aspartate aminotransferase (AST $<$35U/L), alkaline phosphatase (ALP: 35–100 U/L), glutamyltransferase (GGT $<$45 U/L), lactate dehydrogenase (LDH: 120–250 U/L) within the last 3 months [20–22]. Patients were excluded if they met any of the following criteria: 1) patients with chronic liver disease (non-alcoholic fatty liver disease, viral hepatitis B, viral hepatitis C, autoimmune liver disease, liver transplantation, liver cancer); 2) patients who died during follow-up; 3) in an immunosuppressed state (HIV infection, tumor, organ transplantation, bone marrow transplantation, immunosuppressive application within 3 months) [23,24]; 4) patients with chronic digestive symptoms within 1 year prior to SARS-CoV-2 infection (general tiredness, fatigue, diarrhea, constipation, indigestion and bloating, sour regurgitation, nausea and vomiting, skipped meals, and anosmia); and 5) previous definitive diagnosis of chronic gastrointestinal disease (peptic ulcer, gastroesophageal reflux disease (GERD), inflammatory bowel disease (IBD) and functional gastrointestinal disease (FGD)).

Patients with liver function abnormality on admission for SARS-CoV-2 were included in the liver function abnormality on admission (LFA) group, and other patients were included in the no liver function abnormality on admission (no-LFA) group. Liver function abnormality on admission refers to patients with one of the following liver function indicators higher than the normal range within three days of admission: 1) TB, 2) DB, 3) ALT, 4) AST, 5) ALP, 6) GGT, 7) LDH [24,25]. Demographic data, medical history, and laboratory results were retrieved from the hospital electronic health records, updated, and confirmed with patients at follow-up. A flow chart is shown in Fig. 1. We sent invitations to all patients with COVID-19 hospitalized at our institution between March 1, 2022, and May 31, 2022, who met the inclusion criteria for this study. A total of 1135 individuals were invited to participate in this study and 494 finalized the study.

2.2. Follow up

The study population was followed up once a month from the date of discharge until March 30, 2023. At each follow-up, patients were asked if they had any of the following symptoms: general tiredness, fatigue, diarrhea, constipation, indigestion and bloating, sour regurgitation, nausea and vomiting, skipped meals, or anosmia [3,6]. The date of onset, the date of disappearance, and the severity of the symptoms were recorded.

At the same time, we collected the baseline information of the patients at the first follow-up visit, including: age, gender, height, weight, history of smoking and alcohol consumption, previous chronic diseases (hypertension, diabetes, coronary heart disease, cerebrovascular disease, etc.), COVID-19 severity, and whether they were vaccinated, when they were vaccinated and the number of doses. According to the ninth edition of the COVID-19 pneumonia prevention and control protocol and the COVID-19 pneumonia diagnosis and treatment protocol, the COVID-19 pneumonia is classified into asymptomatic patients, mild, normal, severe, and critical [19,26]. Considering the protective effect of the vaccine in patients with SARS-CoV-2 infection [27–29], we collected information on the vaccination status of the patients. The unvaccinated means that the patient has never received the inactivated whole-virion SARS-CoV-2 vaccines (CoronaVac, BBIBPCorV or WIBP-CorV)

2.3. Outcome

The primary outcome is the post-acute sequelae of COVID-19 in the digestive system, including general tiredness, fatigue, diarrhea, constipation, indigestion and bloating, sour regurgitation, nausea and vomiting, skipped meals, and anosmia [3,6]. Patients with any of the above symptoms within 3 months after infection and lasting longer than 2 months were considered to have a primary outcome [1]. The occurrence and date of the primary study outcome were obtained from the monthly telephone follow-up visit.

2.4. Statistical analysis

Directed acyclic plots (Supplementary Fig. 1) were drawn to aid in the analysis of confounding, and confounding variables were included in the regression model during statistical analysis to reduce the effect of confounding factors. The mediating variables were not included in the regression model because of their possible mediating role [30]. The directed acyclic diagram is available online at https://www.dagitty.net/dags.html (See **Appendix 1** for code).

Continuous data were summarized as median (interquartile range). Categorical variables were summarized as percentages. Baseline characteristics were compared between groups with liver function abnormality and those without liver function abnormality on admission using unpaired Student's *t*-test, Mann-Whitney *U* test, Chi-square test, or Fisher's exact test. All data were assessed for

normality (Kolmogorov-Smirnov test), and Bartlett's test was used to test the homogeneity of variances between groups.

To explore the relationship between liver function abnormality on admission and the occurrence of long COVID syndrome (digestive system) of COVID-19 in patients, we used univariable Poisson regression for analysis. The various post-acute sequelae in the digestive system, including general tiredness, fatigue, diarrhea, constipation, indigestion and bloating, sour regurgitation, nausea and vomiting, skipped meals, and anosmia, as well as the overall post-acute sequelae (digestive system), were analyzed separately in univariable Poisson regression models. We then adjusted using multivariable modified Poisson regression to minimize the effects of confounding factors. The confounding factors included age, gender, body mass index (BMI), habitual smoker, habitual drinker, comorbidities, COVID-19 severity, and vaccine status. A two-sided P value < 0.05 was considered statistically significant.

Propensity score matching (PSM) [31] was used to address a possible imbalance between patients with or without liver function abnormality on admission. The PS model was adjusted for the unbalanced baseline factors including gender, hypertension, COVID-19 severity, and vaccination status. We adopted a greedy nearest-neighbor matching algorithm with a matching ratio of 1: 1 and a caliper of 0.2 SDs of the logit of the propensity score calculated by multivariable logistic regression model [32,33]. Only those with a two-sided P value greater than 0.05 were considered adequately balanced.

We again used logistic regression for sensitivity analysis to minimize the possibility of bias and to assess the robustness of the results. In both unmatched and matched populations, we analyzed the association between early liver function abnormality and the occurrence of long COVID syndrome in the digestive system. Subsequently, adjustments were made using multivariable logistic regression to minimize the effects of confounding factors. A two-sided P value < 0.05 was considered statistically significant.

Results are expressed as relative risk (RR) and 95 % confidence interval (CI). SPSS27.0 statistical software was used to process the data.

3. Results

3.1. Patient characteristics

From March 1 to May 31, 2022, a total of 1135 patients were screened, of whom 494 were included in the final analysis (Fig. 1). Baseline characteristics of participants grouped according to the presence or absence of liver function abnormality on admission are shown in Table 1. All of these patients had improved liver function indices 3 months after hospital discharge. Of the study population, 144 (29.1 %) had liver function abnormalities on admission, and 350 (70.9 %) did not. The prevalence of liver function abnormality in the study population is shown in the Supplementary Fig. 2. The proportion of male patients was higher in the patients with liver function abnormality on admission than in the patients without liver function abnormality on admission (54.2 % vs. 37.7 %, $P <$ 0.001). The proportion of people with hypertension was higher in the patients with liver function abnormality on admission than in the patients without liver function abnormality on admission (55.6 % vs. 44.3 %, P = 0.023). At the same time, SARS-CoV-2 infection was more severe ($P = 0.014$) by clinical typing [19,26] in the patients with liver function abnormality on admission and patients with liver

Table 1
Characteristics of the patients with or without liver function abnormality on admission.

Characteristics	LFA	No-LFA	*P*
	N = 144	N = 350	
Demographics and history			
Age (years), M (IQR)	77 (68,86)	75 (67,85)	0.224
Male, n (%)	78 (54.2 %)	132 (37.7 %)	**<0.001**
BMI (kg/㎡), M (IQR)	21.49 (19.25,23.45)	21.64 (21.16,23.56)	0.488
Habitual smoker, n (%)	8 (5.6 %)	13 (3.7 %)	0.357
Habitual drinker, n (%)	9 (6.3 %)	12 (3.4 %)	0.157
Comorbidities			
All, n (%)	95 (66.0 %)	199 (56.9 %)	0.061
Hypertension, n (%)	80 (55.6 %)	155 (44.3 %)	**0.023**
Diabetes, n (%)	28 (19.4 %)	67 (19.1 %)	0.938
Coronary heart disease, n (%)	24 (16.7 %)	56 (16.0 %)	0.855
Cerebrovascular disease, n (%)	26 (18.1 %)	49 (14.0 %)	0.254
COVID-19 severity, n (%)			
Asymptomatic, n (%)	22 (15.3 %)	72 (20.6 %)	**0.014**
Mild, n (%)	84 (58.3 %)	221 (63.1 %)	
Normal, n (%)	33 (22.9 %)	55 (15.7 %)	
Severe or critical, n (%)	5 (3.5 %)	2 (0.6 %)	
Inactivated SARS-CoV-2 vaccination			
YES, n (%)	32 (22.2 %)	125 (35.7 %)	**0.003**
NO, n (%)	112 (77.8 %)	225 (64.3 %)	
Dose			
0 dose, n (%)	112 (77.8 %)	225 (64.3 %)	**0.002**
1 dose, n (%)	2 (1.4 %)	5 (1.4 %)	
2 doses, n (%)	20 (13.9 %)	50 (14.3 %)	
3 doses, n (%)	10 (6.9 %)	70 (20.0 %)	

LFA: patients with liver function abnormality on admission; No-LFA: patients without liver function abnormality on admission; BMI: Body Mass Index.

function abnormality on admission were less likely to receive inactivated SARS-CoV-2 vaccine (22.2 % vs. 35.7 %, $P = 0.003$).

3.2. Outcome

A total of 50 individuals (5.9 %) developed long COVID syndrome (digestive system) during the follow-up period. A total of 30 (20.8 %) patients in the liver function abnormality on admission group developed post-acute sequelae (digestive system), while 20 (5.7 %) in the no liver function abnormality on admission group developed post-acute sequelae (digestive system). The association between the presence of liver function abnormality on admission and the occurrence of the primary outcome was statistically significant with univariable Poisson regression (crude, RR = 3.646, 95%CI: 2.143–6.203, $P < 0.001$). The results were still statistically significant when age, sex, body mass index, smoking, alcohol consumption, chronic diseases, inactivated SARS-CoV-2 vaccination, and COVID-19 severity were included in the multivariable modified Poisson regression model for adjustment (adjusted, RR = 3.550, 95% CI: 2.099–6.006, $P < 0.001$). The results are presented in Table 2. Furthermore, patients with liver function abnormality on admission had an increased risk of developing symptoms of fatigue (6.9 % vs. 2.3 %, $P < 0.05$) and poor appetite (11.1 % vs. 2.6 %, $P < 0.05$), and the difference was statistically significant in the multifactorial regression model. The results are detailed in Table 2.

3.3. Sensitivity analysis

To exclude the effect of baseline differences on the primary study outcome, we applied propensity score matching to adjust for-unbalanced baseline factors between the liver function abnormality on admission group and the no liver function abnormality on admission group. After matching, there were 135 patients in each of the two groups and a total of 36 patients had a primary study outcome. In the liver function abnormality on admission group, 28 patients developed post-acute sequelae in the digestive system. In the no liver function abnormality on admission group, 8 patients developed post-acute sequelae in the digestive system (Table 3). For the primary study outcome, we analyzed it in the matched population with univariable Poisson regression. We then adjusted the results by including age, gender, body mass index, the presence of smoking and alcohol consumption, the presence of chronic underlying diseases, the presence of inactivated SARS-CoV-2 vaccination, and COVID-19 severity into the multivariable modified Poisson regression model (Supplementary Fig. 1.). The results were statistically significant, similar to those in the unmatched population: RR = 3.500 (crude, 95%CI: 1.656–7.399, $P = 0.001$) and RR = 3.473 (adjusted, 95%CI: 1.612–7.482, $P = 0.001$) (Table 3).

We again used logistic regression for sensitivity analysis to minimize the possibility of bias and to assess the robustness of the results. In both the unmatched and matched populations, we analyzed the association between liver function abnormality on admission and the occurrence of post-acute sequelae of COVID-19 in the digestive system. The OR values in the unmatched population were 4.342 (crude, 95%CI: 2.372–7.948, $P < 0.001$) and 4.391 (adjusted, 95%CI: 2.342–8.232, $P < 0.001$). The OR values in the matched population were 4.154 (crude, 95%CI: 1.817–9.496, $P < 0.001$) and 4.237 (adjusted, 95%CI: 1.829–9.815, $P < 0.001$) (Table 4). The results are similar to our main modeling analysis.

3.4. Other findings

We further analyzed the effects of gender, COVID-19 severity, presence or absence of vaccination, and presence or absence of hypertension on liver function abnormality on admission separately by univariable Poisson regression, and adjusted by multivariable modified Poisson regression. Our study found a statistical correlation between COVID-19 severity, inactivated SARS-CoV-2 vaccine,

Table 2
Proportion of different sequelae in the patients with COVID-19 who experience liver function abnormality on admission.

Long COVID	COVID-19 positive participants							
	N = 494							
	LFA	No-LFA	Poisson regression (univariate)			modified Poisson regression (multivariate)		
			RR	95%CI	*P*	RR	95%CI	*P*
Any [3,6]	30 (20.8 %)	20 (5.7 %)	3.646	2.143–6.203	<**0.001**	3.550	2.099–6.006	<**0.001**
General tiredness, n (%)	6 (4.2 %)	7 (2.0 %)	2.083	0.712–6.092	0.180	1.893	0.617–5.803	0.246
Fatigue, n (%)	10 (6.9 %)	8 (2.3 %)	3.038	1.224–7.542	**0.017**	3.203	1.278–8.025	**0.013**
Diarrhea, n (%)	3 (2.1 %)	1 (0.3 %)	7.292	0.765–69.517	0.084	5.638	0.446–71.246	0.191
Constipation, n (%)	1 (0.7 %)	2 (0.6 %)	1.215	0.111–13.297	0.873	1.614	0.108–24.228	0.729
Indigestion and bloating, n (%)	1 (0.7 %)	1 (0.3 %)	2.431	0.153–38.595	0.529	2.881	0.165–50.447	0.469
sour regurgitation, n (%)	0 (0.0 %)	0 (0.0 %)	–	–	–	–	–	–
Nausea and vomiting, n (%)	1 (0.7 %)	1 (0.3 %)	2.431	0.153–38.595	0.529	3.507	0.321–29.128	0.331
Skipped meals (poor appetite), n (%)	16 (11.1 %)	9 (2.6 %)	4.321	1.955–9.552	<**0.001**	4.113	1.942–8.714	<**0.001**
anosmia, n (%)	3 (2.1 %)	4 (1.1 %)	1.823	0.413–8.043	0.428	1.857	0.377–9.154	0.447

LFA: patients with liver function abnormality on admission; No-LFA: patients without liver function abnormality on admission; RR: relative risk; 95% CI: 95 % confidence interval.
When analyzing the association between the presence of liver function abnormality on admission and the occurrence of long COVID of digestive system, age, gender, body mass index, the presence of smoking and alcohol consumption, the presence of chronic underlying diseases, the presence of inactivated SARS-CoV-2 vaccination, and COVID-19 severity were included in a multifactorial regression model for adjustment.

Table 3
Characteristics and Long COVID syndrome (digestive system) in matched population.

Characteristics and main outcome	LFA	No-LFA	*P*
	N = 135	N = 135	
Demographics and history			
Age (years), M (IQR)	77 (68,86)	78 (70,87)	0.140
Male, n (%)	69 (51.1 %)	66 (48.9 %)	0.715
BMI (kg/m^2), M (IQR)	21.49 (19.22,23.45)	21.45 (19.46,23.16)	0.650
Habitual smoker, n (%)	8 (5.9 %)	7 (5.2 %)	0.790
Habitual drinker, n (%)	8 (5.9 %)	7 (5.2 %)	0.766
Comorbidities			
All, n (%)	87 (64.4 %)	84 (62.2 %)	0.705
Hypertension, n (%)	72 (53.3 %)	71 (52.6 %)	0.903
Diabetes, n (%)	26 (19.3 %)	31 (23.0 %)	0.456
Coronary heart disease, n (%)	21 (15.6 %)	28 (20.7 %)	0.269
Cerebrovascular disease, n (%)	21 (15.6 %)	19 (14.1 %)	0.732
COVID-19 severity, n (%)			
Asymptomatic, n (%)	22 (16.3 %)	19 (14.1 %)	0.766
Mild, n (%)	84 (62.2 %)	87 (64.4 %)	
Normal, n (%)	26 (19.3 %)	28 (20.7 %)	
Severe or critical, n (%)	3 (2.2 %)	1 (0.7 %)	
Inactivated SARS-CoV-2 vaccine			
YES, n (%)	32 (23.7 %)	29 (21.5 %)	0.662
NO, n (%)	103 (76.3 %)	106 (78.5 %)	
Main outcome			
Long COVID syndrome (digestive system)[a],[3,6]	28 (20.7 %)	8 (5.9 %)	**0.001 (crude)** **0.001 (adjusted)**

LFA: patients with liver function abnormality on admission; No-LFA: patients without liver function abnormality on admission; RR: relative risk; 95% CI: 95 % confidence interval.
When analyzing the association between the presence of liver function abnormality on admission and the occurrence of long COVID of digestive system, age, gender, body mass index, the presence of smoking and alcohol consumption, the presence of chronic underlying diseases, the presence of Inactivated SARS-CoV-2 vaccination, and COVID-19 severity were included in a multifactorial regression model for adjustment.
[a] Crude: RR = 3.500 (95%CI: 1.656–7.399); Adjusted: RR = 3.473 (95%CI: 1.612–7.482).

gander (male), hypertension and liver function abnormality on admission. The results are shown in Supplementary Table 1. The results showed a statistically significant relationship between these factors (gender, COVID-19 severity, vaccination, hypertension) and liver function abnormality on admission ($P < 0.05$).

Meantime, we analyzed the relationship between age, gender, COVID-19 severity, whether they had been vaccinated or not, and whether they had hypertension or not and our study outcome by univariable Poisson regression, adjusted by multivariable modified Poisson regression. Our data analysis showed no statistical correlation between gender, COVID-19 severity and the presence of hypertension and long COVID(digestive system) ($P > 0.05$). In contrast, there was a statistically significant correlation between the presence or absence of vaccination and long COVID (digestive system) (adjusted, RR = 0.380, 95%CI: 0.178–0.810, $P = 0.012$) (Supplementary Table 2).

4. Discussion

To the best of our knowledge, there are few cohort studies on the post-acute sequelae in the digestive system after SARS-CoV-2 infection. We investigated which populations are susceptible to liver function abnormality and the relationship between liver function abnormality on admission and long COVID syndrome (digestive system). Our study may provide a predictor of the risk of long COVID syndrome (digestive system).

In this bi-center, prospective cohort study, we found that (1)in the COVID-19 population, the risk of liver function abnormality on admission appears to be higher in males, those with hypertension, those who are not vaccinated, and those with more severe SARS-CoV-2 infections; (2)patients with liver function abnormality on admission have an increased risk of developing post-acute digestive sequelae (adjusted, RR = 3.550, 95%CI: 2.099–6.006, $P < 0.001$); (3)compared to patients without liver function abnormality on admission, patients with liver function abnormality on admission were more likely to experience various digestive symptoms for more than 2 months, especially fatigue (6.9 % vs. 2.3 %) and poor appetite (11.1 % vs. 2.6 %), with a statistically significant difference (adjusted, $P < 0.05$).

Previous studies on liver function abnormality in patients with COVID-19 mainly focused on its prognostic value, such as its impact on hospitalization rates, length of stay, readmission rates, and mortality [34–38]. In contrast, our study focused on the relationship between liver function abnormality and the long COVID syndrome (digestive system). To exclude the influence of pre-existing digestive symptoms on the results of the study, we excluded patients who had chronic digestive symptoms in the past year. Although the influence of pre-existing digestive disorders on the findings of this study could not be completely excluded, efforts were made to minimize their influence. Fatigue and poor appetite are the most common symptoms of long COVID syndrome. In support of our findings, the recent literature reports an increased probability of gastrointestinal diseases [39] after SARS-CoV-2 infections, as well

Table 4
Sensitive analyses ORs [95%CIs] for primary outcome.

outcome	Unmatched (n = 494)						Matched (n = 270)					
	crude			adjusted			crude			adjusted		
	OR	95%CI	P	OR	95%CI	P	OR	95%CI	*P*	OR	95%CI	P
Long COVID syndrome (digestive system) [3,6]	**4.342**	**2.372–7.948**	**<0.001**	**4.391**	**2.342–8.232**	**<0.001**	**4.154**	**1.817–9.496**	**<0.001**	**4.237**	**1.829–9.815**	**<0.001**

In unmatched as well as matched populations, we analyzed the correlation between liver function abnormality on admission and the occurrence of post-acute sequelae of COVID-19 in the digestive system by logistic regression.

When analyzing the association between the presence of liver function abnormality on admission and the occurrence of long COVID of digestive system, age, gender, body mass index, the presence of smoking and alcohol consumption, the presence of chronic underlying diseases, the presence of Inactivated SARS-CoV-2 vaccination, and COVID-19 severity were included in a multifactorial regression model for adjustment.

as autoimmune rheumatic diseases [40], which may present with symptoms such as fatigue and poor appetite. Although these symptoms are non-specific and are often overlooked, prolonged digestive symptoms can lead to reduced eating, lower energy levels, lowered immunity, dehydration, and other adverse effects. On the one hand, prolonged digestive symptoms could change the patient's daily lifestyle, reduce their quality of life, and even cause panic and anxiety, leading to psychological problems. On the other hand, these sequelae could not only delay the recovery process, but also make the patients vulnerable to other diseases (anemia, infections of various systems, acute exacerbation of chronic diseases, etc.) [7–9]. These malnutrition-induced diseases are potentially life-threatening when exacerbated, so it is important that we pay attention to the possibility of malnutrition in patients with SARS-CoV-2 infections. A predictor of post-acute sequelae (digestive system)can help clinicians identify patients at risk for malnutrition and provide early nutritional support. Our study demonstrated an increased risk of post-acute sequelae (digestive system) in patients with COVID-19 and liver function abnormality on admission. Therefore, laboratory indicators of liver function (liver function abnormality on admission) may serve as a predictor of long COVID syndrome (digestive system) and help to the timely protect patients with possible digestive sequelae from serious nutritional and health threats.

The proportion of liver function abnormality after SARS-CoV-2 infection ranges from 19 % to 76 % in various studies [13,41–45], and varies widely depending on the study population. In our study, when patients with chronic liver disease, previous liver function abnormality, and immunosuppression were excluded, the proportion of liver function abnormality on admission was 29.1 %. The proportion of patients with long COVID syndrome (digestive system) in our study was 10.1 %, which is the result of exclusion of previous chronic gastrointestinal diseases.

A meta-analysis of over 20,000 patients and other studies indicate that liver function issues are linked to COVID-19 severity, regardless of disease onset timing [11,46–48]. Additionally, the COVID-19 severity may contribute to long COVID syndrome, potentially explaining our study's findings [49]. The absence of repeat liver function tests for patients without initial abnormalities might have obscured the impact of liver function issues throughout the entire course of COVID-19 on long COVID syndrome (digestive system) in our study. Future research designs should be refined accordingly. Previous studies have reported that COVID-19 vaccination is effective in reducing the risk of severe COVID-19 and its associated complications [50–55]. Our study demonstrated that vaccinated patients had lower rates of liver function abnormality on admission and long COVID syndrome (digestive system). Currently, patients of advanced age and with underlying diseases are relatively unlikely to be vaccinated, and are more susceptible to COVID-19 [56,57]. Our results indicated that inactivated SARS-CoV-2 vaccine could be an effective approach to prevent liver function abnormality [58] and long COVID syndrome.

The mechanisms behind liver function abnormalities and long COVID in digestive system following SARS-CoV-2 infection remain unclear. The virus may cause liver injury by binding to hepatocyte receptors like ACE2 and ASGR1 [59,60]. Additionally, a cytokine storm, characterized by the release of pro-inflammatory cytokines such as IL-6 and TNF-α, can result in liver inflammation and dysfunction [61]. This immune response can lead to chronic cholestasis and microvascular damage [61], potentially causing post-acute sequelae like fatigue and poor appetite. However, further research is necessary to understand the full impact of COVID-19 on liver health and the development of long COVID syndrome.

The main manifestation of liver injury is cholestasis as well as hepatocyte destruction. AST, TB, and LDH do not specifically show liver function abnormality, but previous studies and clinical practice also use these three indicators to reflect the state of liver function [25,62–64]. The inclusion of these indicators in our subgroups may have had an adverse impact on our findings. In the future, a more rigorous inclusion of people with abnormal liver function is needed to further validate our study.

Taken together, we found that vaccination may have a protective effect on the development of early liver damage and the occurrence of post-acute sequelae of COVID-19 (digestive system). We also demonstrated an association between liver function abnormality on admission and long COVID syndrome in digestive system. Our study may provide insights into the prevention of liver function abnormality and the prediction of long COVID syndrome.

5. Advantages and disadvantages

The main strengths of this study are as follows: First, it is a bi-center, prospective cohort study, focusing on the relationship between liver function abnormality on admission and long COVID syndrome of the digestive system, an aspect that has received less attention previously. This study provides a possible predictor for long COVID syndrome in the digestive system. Second, this study excluded the patients with previous liver disease and other factors affecting liver function. In this way, our conclusions avoid the bias caused by the population with abnormal underlying liver function and are more applicable to the general population.

The main limitation of this study is that the sample size was small, which may need to be enlarged with a larger sample size and with data from more areas. The second limitation is that only hospitalized patients were included in this study, and the situation of non-hospitalized patients was not well observed and evaluated, which may have an adverse impact on the generalization of the results of our study. The third limitation is that the long COVID syndrome mainly studied the symptoms of the digestive tract while ignoring the symptoms of other systems.

6. Conclusion

Our study suggests that patients with COVID-19 who experience liver function abnormality on admission have an increased risk of developing long COVID syndrome (digestive system).

Data availability statement

The de-identified dataset for analysis will be made available to researchers upon request after publication. Requests for data should be directed to the corresponding authors.

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Statement of ethical approval

This observational, bi-center, cohort study was conducted by the investigators in accordance with the Declaration of Helsinki and approved by the Medical Ethics Committee of Zhongshan Hospital of Fudan University (No. B2022-536R) and Shanghai Pudong Hospital (NO.YJXG-22).

Patient consent statement

All patients included in this study have signed an informed consent form.

CRediT authorship contribution statement

Huibin Wu: Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation. **Yunjie Zhang:** Writing – review & editing, writing-revision. **Wenqing Tang:** Supervision, Resources, Investigation. **Minzhi Lv:** Visualization, Validation, Software, Methodology. **Zhixue Chen:** Writing – review & editing, Writing – original draft. **Fansheng Meng:** Investigation, Data curation. **Yitong Zhao:** Investigation, Data curation. **Huajie Xu:** Software, Methodology. **Yuxin Dai:** Investigation, Data curation. **Jindan Xue:** Investigation, Data curation. **Jingya Wang:** Investigation, Data curation. **Ling Dong:** Supervision, Methodology. **Dejun Wu:** Supervision, Methodology. **Si Zhang:** Writing – review & editing, Supervision, Methodology, Formal analysis. **Ruyi Xue:** Supervision, Project administration, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e37664.

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