The Pattern of Liver Dysfunction in Patients with COVID-19: A Retrospective Study

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Research Article

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Abstract

Background. Information about liver dysfunction in patients with COVID-19 is scarce. We aimed to explored the pattern and risk factors of liver dysfunction in patients with COVID-19.

Methods. In this retrospective study, we included all consecutive confirmed patients with COVID-19 in Fuyang Second People's Hospital between January 20 and February 25, 2020 and collected clinical characteristics until discharge. The pattern and risk factors of liver dysfunction, viral shedding and outcome were analyzed.

Results. Totally, 146 patients were analyzed. The median age was 44.9 years and 54.1% were men, 43.8% patients presented liver dysfunction (22.6% on admission, 21.2% during hospitalization). The percentage of elevated ALT (15.1% on admission and 24.7% during hospitalization) were significantly higher than ALP (2.1% on admission and 3.4% during hospitalization) ($P < 0.001$). Four clinical types were identified, type 1 (persistent normal liver function, 56.2%), type 2 (normal liver function on admission developed to liver dysfunction during hospitalization, 21.2%), type 3 (liver dysfunction on admission restored to normal on discharge, 13.0%) and type 4 (persistent liver dysfunction, 9.6%). The median duration of viral shedding was 12.0 (type 1), 15.0 (type 2), 14.0 (type 3) and 18.0 (type 4) days ($P < 0.001$). Prolonged viral shedding and severity were potential risk factors associated with liver dysfunction.

Conclusions. The incidence of liver dysfunction in patients with COVID-19 is common but not severe, which mainly due to SARS-CoV-2-mediated immune injury on hepatocyte rather than cholangiocyte, DILI and underlying chronic liver disease should not be neglect.

1. Background

The pandemic of corona virus disease 2019 (COVID-19) has negative impact on global social activity.[1-6] SARS-CoV-2 shares 82% genome sequence similarity to SARS-CoV-2 and 50% genome sequence homology to Middle East respiratory syndrome coronavirus (MERS-CoV),and all three coronaviruses can cause severe respiratory symptoms. Liver injury has been reported in patients with SARS or MERS-CoV.[7,8] Studies have confirmed that SARS-CoV-2 enters cells primarily through angiotensin converting enzyme2 (ACE2), the high expression of ACE2 in alveolar type II cells makes the lung become the main target organ.[9,10] A number of existing clinical studies showed that some patients with COVID-19 had different degrees of liver dysfunction [11-16] and the liver biopsy from a dead COVID-19 case showed moderate microvascular steatosis and mild lobular activity in addition to severe lung injury.[17] The objective of this retrospective study was to explored the pattern of liver dysfunction, risk factors and outcomes in patients with COVID-19, so as to provide reference for clinical decision-making.

2. Methods

2.1 Study design

All consecutive patients with COVID-19 admitted to the Fuyang Second People's Hospital (FYSPH) in Anhui Province of China between January 20, 2020 and February 25, 2020 were retrospective enrolled. The including criteria was SARS-CoV-2 positive using real-time reverse-transcriptase polymerase chain reaction (RT-PCR) assay by local municipal Center for Diseases Prevention and Control (CDC) as described previously. The excluding criteria was other primary pathogens infection, such as bacteria, fungi, other respiratory virus, mycoplasma, or chlamydia, and age below 18 years old. (Figure 1). Clinical outcomes were followed up until discharge. COVID-19 was diagnosed based on the guidance for corona virus disease 2019 issued by National Health Commission of China[18]. The criteria of discharge included all the following conditions: body temperatures remained normal over 3 days, the symptoms of respiratory improved obviously, pulmonary imaging shows remarkable absorption of inflammation, and repeated tests for SARS-CoV-2 at least 24 hours apart confirmed viral clearance. The study was approved by the Ethics Committees of FYSPH (20200303006). Written informed consent was waived in view of the designated hospital for new emerging infectious diseases.

2.2 Data collection

All the patients' information, such as epidemiological, demographic (age, sex, etc.), smoking and drinking history , chronic liver disease and comorbidity, laboratory findings, treatment and outcome data, were collected from electronic medical records. Thereafter, alanine aminotransferase (ALT), aspartate transaminase (AST), total bilirubin (TBIL), alkaline phosphatase (ALP) were collected until the last follow-up. All the data in source documents were confirmed independently by at least two researchers.

2.3 Definitions

Liver dysfunction was defined as ALT level over 50 U/L (the upper limit of normal, ULN) or AST level over 40 U/L (ULN) or TBIL level over 26μmol/L (ULN) or ALP level over 125 U/L (ULN), according to Fuyang Second People's Hospital laboratory department of the normal reference value. Comorbidity was defined as having at least one of the followings: hypertension, diabetes, cardiovascular disease, asthma, chronic lung disease and malignancy for over 6 months. We defined the degree of severity of COVID-19 on admission based on the guidance for corona virus disease 2019 issued by National Health Commission of China[18]. Viral shedding was calculated by date of SARS-CoV-2 negative minus date of illness onset.

2.4 Statistical analysis

Continuous variables were expressed as medians and interquartile ranges and were compared using the Mann–Whitney test. Categorical variables were presented as numbers (percentage) and compared by the chi-square test or the Fisher exact test. Correlation analyses were performed by Pearson's method. Comparisons among multiple groups were performed using one-way ANOVA and pairwise comparisons were performed using the LSD test. A P-value < 0.05 was considered as significant for all statistical tests. The statistical analyses were performed using SPSS (version 22.0; SPSS, Chicago, IL).

3. Results

3.1 Clinical characteristics of the patients on admission

A total of 153 hospitalized patients with confirmed COVID-19 was screened. After the exclusion of 7 patients (5 patients below 18 years old and 2 patients with incomplete clinical data), a cohort of 146 patients was enrolled (Figure 1). The median age (IQR) was 44.9 (35.2, 54.2) years and 79 (54.1%) were men, 18 (12.3%) had smoking history, 22 (15.1%) had drinking history, 7 (4.7%) combined with HBV infection (4 had detectable HBV DNA, 3 had undetectable HBV DNA), 9 (6.2%) were severe, 28 (19.2%) had one or more underlying comorbidity. Totally, 22.6% (33/146) patients presented liver dysfunction on admission, the percentage of elevated ALT (15.1%) or AST (15.1%) were significantly higher than ALP (2.1%) ($P < 0.001$). The median duration of viral shedding was 13.0 (IQR 10.0–17.3), which was significant longer in patients with liver dysfunction than normal liver function ($P < 0.05$). Male or severe patients were more likely to show liver dysfunction on admission ($P < 0.05$) (Table 1, Figure 2).

3.2 The dynamic change in four types of liver dysfunction

According to clinical course of liver dysfunction, four clinical types were identified, type 1 (persistent normal liver function, 56.2%), type 2 (normal liver function on admission developed to liver dysfunction during hospitalization, 21.2%), type 3 (liver dysfunction on admission restored to normal on discharge, 13.0%) and type 4 (persistent liver dysfunction, 9.6%) (Figure 1,Table 2).

As shown in Figure 3, the liver enzymes in type 1 remained normal until discharge. However, in type 2, 74.2% (23/31) patients presented liver dysfunction during hospitalization, the percentage of elevated ALT (45.2%,14/31) or AST (35.5%,11/31) was significantly higher than ALP (0%)($P < 0.001$), most of them showed slight elevation (less than 2ULN). The elevation of ALT or AST occurred from 5th day to10th day after admission and the highest level of ALT/AST was 360/170U/L. ALT was significantly correlated with AST [admission ($r = 0.547$, $P < 0.05$), peak ($r = 0.920$, $P < 0.001$), discharge ($r = 0.920$, $P < 0.001$)] (Figure 4 A,B,C). 22.6% (7/31) patients had slightly elevated TBIL (range, 28.5-32.6 μmol/L) and the elevation occurred from 3rd day to 6th day after admission (Table S1, Figure S1).

In type 3, 94.7% (18/19) patients presented liver dysfunction during hospitalization, the percentage of elevated ALT (63.2%,12/19) or AST (57.9%, 11/19) was significantly higher than ALP (10.5%, 2/19)($P < 0.05$), more than 80% patients showed slight elevation. The peak of ALT or AST was 183/107U/L. ALT was significantly correlated with AST [admission ($r = 0.500$, $P < 0.05$), peak ($r = 0.817$, $P < 0.05$)] (Figure 4 D,E,F). 21.1% (4/19) patients had slightly elevated TBIL (range,27.6-35.7 μmol/L). All patients' liver function restored to normal on discharge (Figure 3,Table S1, Figure S2).

In type 4, all patients showed liver dysfunction from admission until discharge, the percentage of elevated ALT or AST (71.4%,10/14) was significantly higher than ALP (14.3%, 3/14) ($P < 0.05$). 60% (ALT) or 30% (AST) patients showed >2ULN elevation which was higher than other three types. The peak of ALT or AST was 414/309 U/L. Correlation between ALT and AST was also observed in type 4 [admission ($r = 0.691$, P

< 0.05), peak (r = 0.673, *P* < 0.05), discharge (r = 0.699, *P* < 0.05)] (Figure 4 G,H,I), 21.4% (3/14) patients had elevated TBIL (range, 40.9-70.5 μmol/L) (Figure 3, Table S1, Figure S3).

3.3 Clinical outcome and risk factors of liver dysfunction

Totally, 26.7% (39/146) patients presented liver dysfunction, the percentage of elevated ALT (19.9%) or AST (11.0%) were significantly higher than ALP (0.7%) on discharge (*P* < 0.001) (Figure 1,Table S1).

To determine the potential risk factors of liver injury in patients with COVID-19, sex, drinking history, HBV infection, comorbidity, severity of illness, viral shedding and treatment were analyzed. The median duration of viral shedding were 12 (IQR 10–15) in type 1, 15 (IQR 12–19) in type 2, 14 (IQR 12–20) in type 3 and 18 (IQR 12–21) days in type 4 (*P* < 0.001), pairwise comparisons showed that viral shedding in type 1 was significant shorter than other types (*P* <0.05). Severe of illness was another risk factor among different types (*P* < 0.05), while the other variables were not risk factors (*P* > 0.05) (Table 2, Figure 2).

4. Discussion

COVID-19 has developed into a pandemic, although some literature had reported 14–53% patients with COVID-19 had elevated ALT and AST,[2,3,12,15] little data analyzed other liver enzymes (such as ALP) and the dynamic change of liver function from admission until discharge. In this retrospective study, we clarified four clinical types, and concluded that the liver injury was common but slight in non-critical patients. In 146 enrolled patients, 43.8% patients presented liver dysfunction (22.6% on admission, 21.2% during hospitalization). Briefly, the percentage of elevated ALT (15.1% on admission and 24.7% during hospitalization) were significantly higher than ALP (2.1% on admission and 3.4% during hospitalization) (*P* < 0.001).

Next, we analyzed the potential mechanisms associated with liver dysfunction in COVID-19 patients. First, SARS-CoV-2 directly damage the hepatocyte. Zhang et al consider the liver injury could have been caused by SARS-CoV-2 infection based on SARS-CoV-2 RNA has been detected in stool and blood samples,[19] Chai et al found that the specific expression of ACE2 in cholangiocytes was 20 times higher than hepatocyte, [20] while Xu et al analyzed the pathological of liver tissue from a patient who died from COVID-19 did not observed viral inclusions in the liver.[17] In our study, ALP, a diagnostic biomarker for cholangiocyte injury, was not observed significant elevated and the incidence was scarce. Therefore, liver injury in COVID-19 patients was not directly caused by SARS-CoV-2 infection. Second, SARS-CoV-2-mediated immune injury. Literature reported that "cytokine storm" may be one of the important causes of liver injury in COVID-19 patients.[21-23] In the present study, viral shedding was significant longer in patients with liver dysfunction than normal liver function which implied that prolonged viral shedding caused more intense cytokine storm, and further damage of multiple organs, including the liver. We speculate that liver dysfunction of type 3 might induced by this mechanism. Third, drug-induce liver injury. Some studied showed that about majority of COVID-19 patients had received nonsteroidal anti-inflammatory drugs, antibiotics and antiviral agents (e.g., acetaminophen, moxifloxacin, oseltamivir, arbidol,

lopinavir/ritonavir, etc), all of above drugs had explicit liver injury effect, such as type 2 and type 4, however, it is even difficult to evaluate exact liver damage particularly in combination therapy.[2,3,11,12,14,22] Fourth, underlying of chronic liver disease. Guan et al found that non-severe patients with COVID-19, even though they have basic liver diseases (such as viral hepatitis, etc.), seldom showed liver dysfunction which is consistent with our results.[13] Nevertheless, we should pay more attention to the potential liver injury in those with chronic hepatitis B, obesity, hyperlipidemia and metabolic syndrome.

This study has several limitations. First, the number of severe or critical patients was small, so the pattern of liver dysfunction in these kinds of patients was not obtained. Second, due to the limitations of local test condition, many cytokines (e.g., IL-6, TNF-α, ferritin, percentage of T lymphocytes) could not be detected. Last, this is a single-center study, and more patients are needed to further study.

5. Conclusion

our study summarized four clinical types of liver dysfunction in patients with COVID-19, and speculated that the mechanism of liver dysfunction might due to SARS-CoV-2-mediated immune injury on hepatocyte, besides DILI and underlying chronic liver disease. Further research should focus on the causes of liver dysfunction, treatment and outcome of COVID-19.

Abbreviations

COVID-19: corona virus disease 2019.

MERS-CoV: Middle East respiratory syndrome coronavirus.

ACE2: angiotensin converting enzyme2.

RT-PCR: reverse-transcriptase polymerase chain reaction.

CDC: Center for Diseases Prevention and Control.

ULN: the upper limit of normal.

ALT: alanine aminotransferase.

AST: aspartate transaminase.

TBIL: total bilirubin.

ALP: alkaline phosphatase.

IL-6: interleukin-6.

TNF-α: Tumor necrosis factor-α.

Declarations

Ethical Approval and Consent to participate

The study was approved by the Ethics Committees of Fuyang Second People's Hospital (20200303006). Written informed consent was waived in view of the designated hospital for new emerging infectious diseases. We confirmed that the identification information of all participants (including patient names, ID numbers, home addresses and telephone numbers) would not be included in recordings, written descriptions or publications.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Tables

Figures

Table 1 Baseline characteristics and liver function of the Study Patients with COVID-19 on admission

	All Patients (n = 146)	Normal liver function (n = 113)	Liver dysfunction (n = 33)	*P* value
Characteristic				
Male sex	79.0(54.1)	56.0(49.6)	23.0(69.7)	0.041 [a]
Age (years)[†]	44.9(35.2-54.2)	44.4(33.7-53.1)	46.0(35.2-57.3)	0.775 [b]
Smoking history	18.0(12.3)	14.0 (12.4)	4.0 (12.1)	1.000 [a]
Drinking history	22.0(15.1)	17.0 (15.0)	5.0(15.2)	1.000 [a]
Comorbidity	28.0(19.2)	24.0 (21.2)	4.0 (12.1)	0.242 [a]
HBV infection	7.0(4.7)	5.0 (4.4)	2.0 (6.1)	1.000 [a]
Severe	9.0 (6.2)	4.0 (3.5)	5.0 (15.2)	0.042 [a]
Fever	119.0(81.5)	91.0(80.5)	28.0(84.8)	0.574 [a]
Viral shedding(days)	13.0(10.0-17.3)	13.0(10.0-17.0)	15.0(12.0-20.5)	0.015 [b]
Liver function				
ALT(U/L)[†]	24.0(14.0-37.0)	21.0(13.0-30.0)	62.0(36.0-76.5)	0.000 [b]
>50 U/L	22.0(15.1)	0	22.0(60.5)	0.000 [c]
AST(U/L)[†]	25.0(19.0-33.0)	23.0(19.0-28.0)	46.0(35.0-58.5)	0.000 [b]
>40 U/L	22.0(15.1)	0	22.0(57.9)	0.000 [c]
TBIL(μmol/L)[†]	9.8(7.0-15.4)	9.6(6.9-15.1)	10.9(7.4-24.7)	0.158 [b]
>26 μmol/L	8.0(5.5)	0	8.0(21.1)	0.000 [c]
ALP(U/L)[†]*	62.0(50.0-70.0)	61.0(50.0-69.0)	65.0(52.5-80.5)	0.088 [b]
>125 U/L	3.0(2.1)	0	3.0(18.4)	0.011 [c]

All data are presented as n (%) or [†]median (IQR). Comparison between two groups was performed using a (Chi-square test) or b (Manm-Whitney U test) or c (Fisher's exact test) as appropriate. ALT, alanine aminotransferase; AST, aspartate transaminase; TBIL, total bilirubin; ALP, alkaline phosphatase.
* indicated significant difference between ALT or AST and ALP (P <0.001).

Table 2 Features and risk factors of four clinical types in patients with COVID-19

	Normal liver function		Liver dysfunction		*P* value
	Type 1 (n=82)	Type 2 (n=31)	Type 3 (n=19)	Type 4 (n=14)	
Male sex	39.0 (47.6)	17.0 (54.8)	12.0 (63.2)	11.0 (78.6)	0.143 [a]
Age (years)[†]	44.4(34.5-55.3)	44.3(37.7-50.4)	44.5(35.0-55.3)	46.8(31.9-63.3)	0.937 [b]
Smoking history	11.0 (13.4)	3.0 (9.7)	2.0 (10.5)	2.0 (14.3)	0.941 [a]
Drinking history	15.0 (18.3)	2.0 (6.5)	4.0 (21.1)	1.0(7.1)	0.298 [a]
Comorbidity	15.0 (18.3)	9.0 (29.0)	2.0 (10.5)	2.0 (14.3)	0.374 [a]
HBV infection	3.0 (3.7)	2.0 (6.5)	1.0 (5.3)	1.0 (7.1)	0.897 [a]
Fever	63.0(76.8)	28.0(90.3)	14.0(73.7)	13.0(92.9)	0.205 [a]
Severe	4.0 (4.9)	0 (0)	1.0 (5.3)	4.0 (28.6)	0.002 [a]
Viral shedding(days)	12.0 (10.0-15.0)	15.0 (12.0-19.0)	14.0 (12.0-20.0)	18.0 (12.0-21.0)	0.000 [b]
Hospitalization(days)	15.0 (12.0-20.0)	17.0 (13.0-23.0)	16.0 (13.0-23.0)	17.5(14.8-19.5)	0.709 [b]
Antibiotics	34.0 (41.5)	14.0 (45.2)	11.0 (57.9)	8.0 (57.1)	0.481 [a]

All data are presented as n (%) or [†]median (IQR). Comparison between four types was performed using a (Chi-square test) or b (ANOVA) as appropriate.

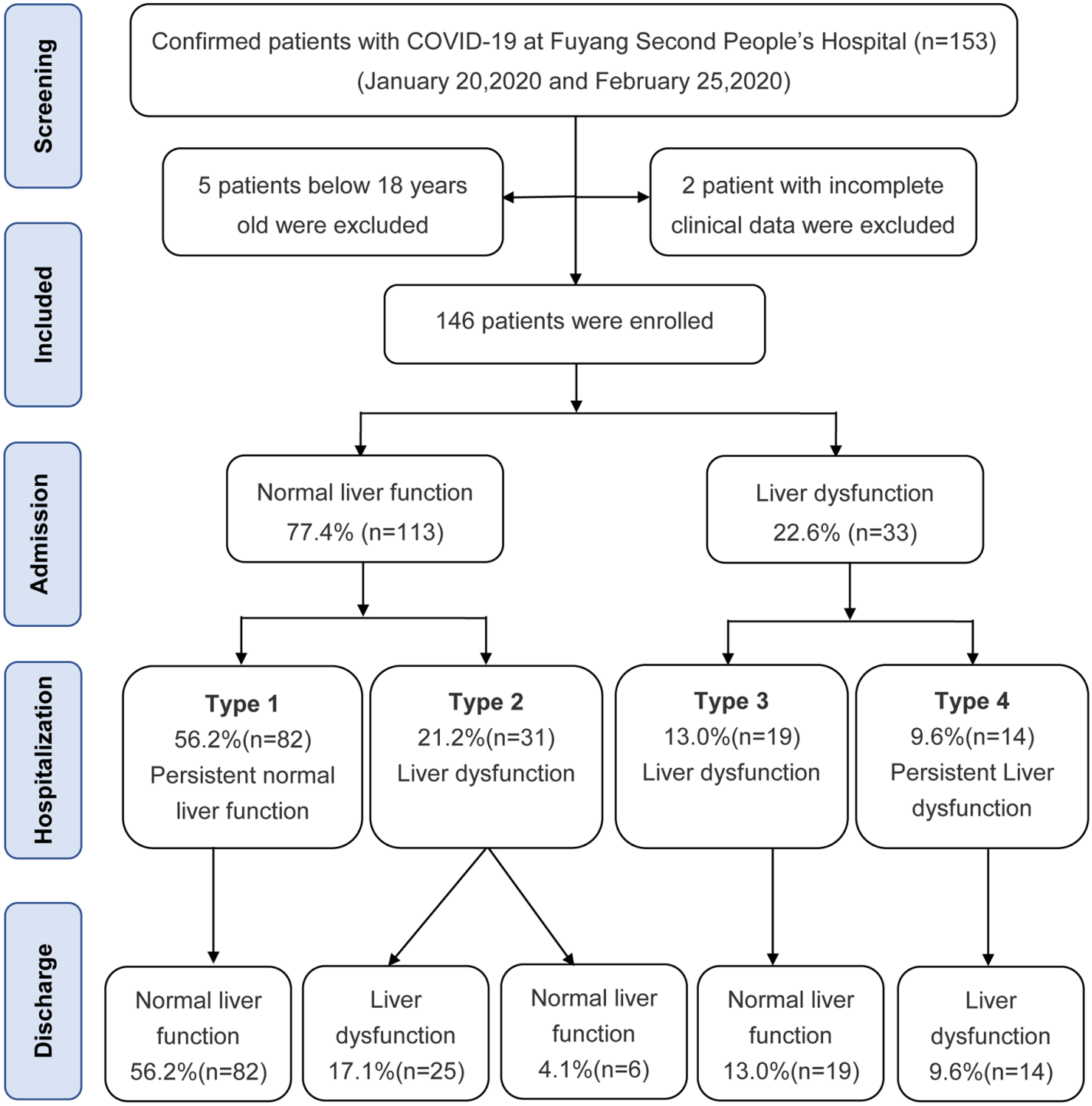

Figure 1

Flow diagram of patients' enrollment and study design.

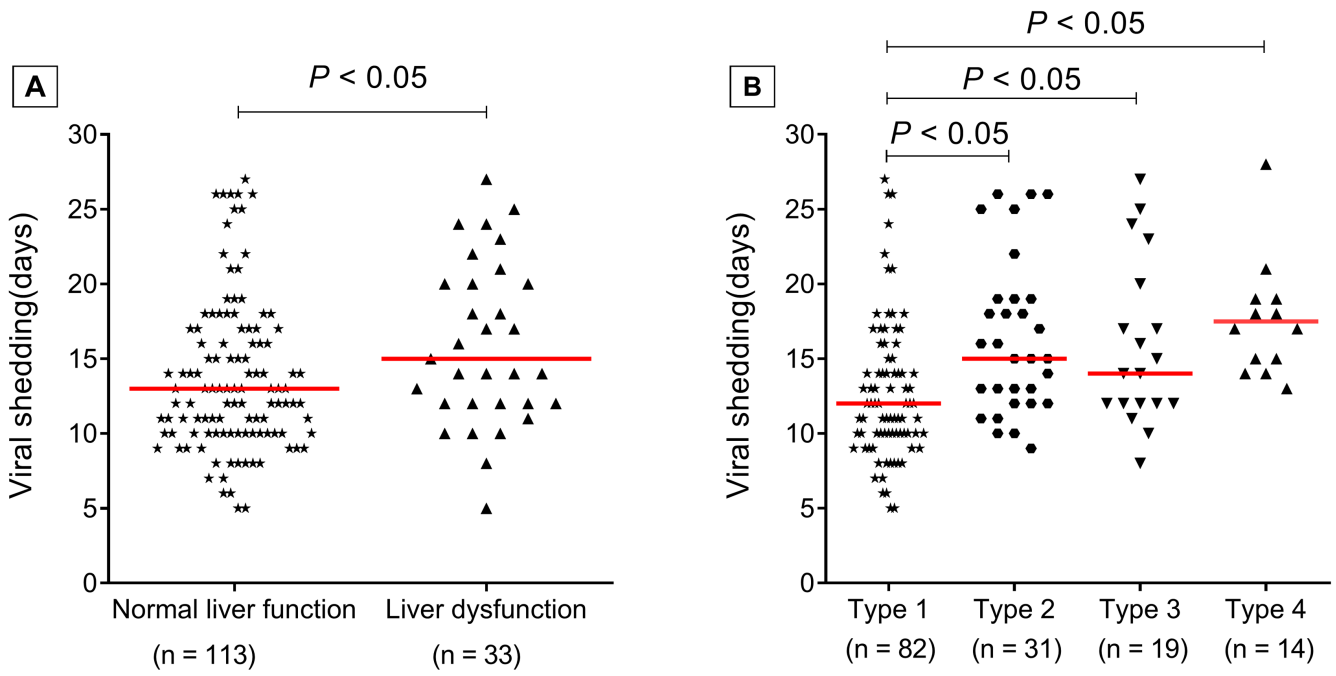

Figure 2

Viral shedding in normal liver function and liver dysfunction groups or four clinical types(A,B). The solid lines in red represent the median of viral shedding. Comparison between two groups was performed using Manm-Whitney U test. Comparison between different types was performed using one-way ANOVA and pairwise comparisons were performed using the LSD test.

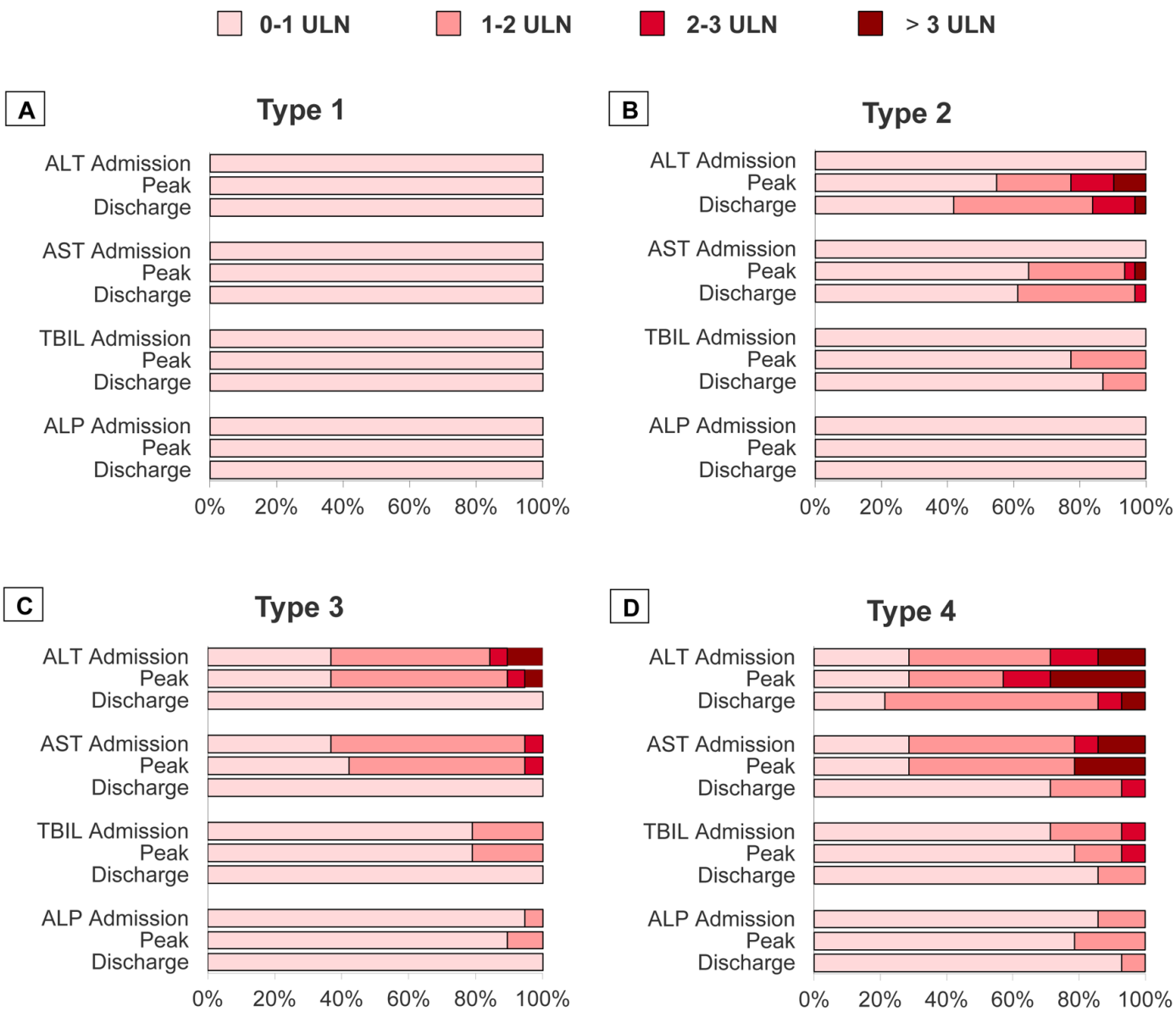

Figure 3

Dynamic change of liver function in patients with COVID-19.

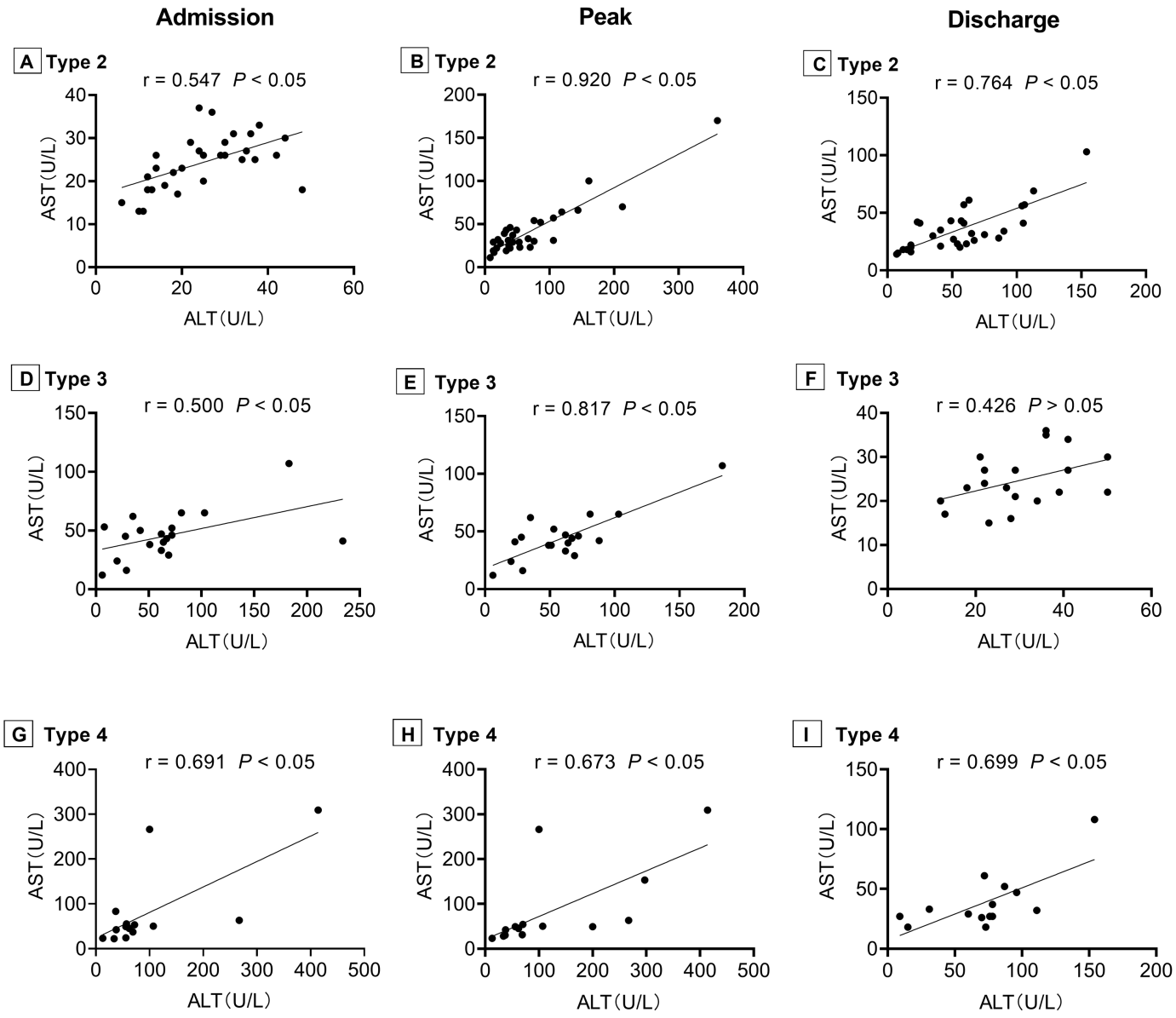

Figure 4

Correlation between ALT and AST in type2, type 3, type 4 patients with COVID-19. Correlation analyses were performed by Pearson's method.

Supplementary Files

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