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# Determinants of abnormal liver-related biomarkers in adult COVID-19 patients

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**Background:** Serum hepatic injury markers indexes are altered in COVID-19 patients. We aimed to explore the factors that could be associated with abnormal serum hepatic injury markers in adult COVID-19 patients.

**Methods:** Eight main hepatic injury markers were examined. Demographic and hematological information, mean CT values (MCTVs) of liver and pancreas, and abdominal subcutaneous fat thickness were recorded. Regression analysis was conducted to identify factors related to abnormal hepatic injury markers.

**Results:** 1,007 adult COVID-19 patients (444 males and 563 females) were included, among whom 697 patients (69.2%) had at least one abnormal hepatic injury markers marker. Females had lower risks of elevated Total Bilirubin (TBil), Direct Bilirubin (Dbil), ALT, AST, GGT and decreased albumin, with ORs of 0.61 (95%CI: 0.42-0.89), 0.36 (95%CI: 0.16-0.83), 0.20 (95%CI: 0.12-0.32), 0.42 (95%CI: 0.30-0.58), 0.36 (95%CI: 0.22-0.60) and 0.40 (95%CI: 0.30-0.54). Patients with greater ratios of subcutaneous fat thickness to abdominal diameters also had lower risks of abnormalities in these six markers. Older patients had higher serum levels of AST but lower levels of albumin and ALT. The risks of abnormal DBil and AST were 3.26 and 1.62 times higher in patients with a history of HBV infection. Patients with many abnormal hepatic injury markers indexes had significantly lower MCTVs of liver and pancreas and higher levels of fibrinogen and LDH in blood.

**Conclusions:** Sex, age, HBV infection, fibrinogen, LDH, liver and pancreas MCTVs, and ratio of abdominal subcutaneous fat thickness to the sum of the abdominal diameters were independently associated with many abnormal serum hepatic injury markers in adult COVID-19 patients.

## KEYWORDS

liver injury, COVID-19, abnormal hepatic injury markers, normal hepatic injury markers, adult patients

## 1 Background

Since cases of coronavirus disease 2019 (COVID-19) were first observed in 2019, the disease has spread globally (Gudbjartsson et al., 2020; Muttineni et al., 2021; Weinreich et al., 2021). To date, there have been more than 120 million COVID-19 cases, and over 2.6 million people have died of the disease worldwide (Tanne, 2020; Williamson et al., 2020; Marofi et al., 2021). The disease, caused by SARS-CoV-2, has created a major public health event threatening human life and health. In addition to causing lung damage, SARS-CoV-2 can invade multiple organs in humans, resulting in organ injury (Ackermann et al., 2020; Young et al., 2020). Nie and colleagues found that key factors associated with hypoxia, angiogenesis, blood coagulation, and fibrosis in multiple organs are dysregulated in COVID-19 patients (Nie et al., 2021). Shen's research has revealed that protein and metabolite changes occur in multiple organs in COVID-19 patients (Shen et al., 2020). Among the human organs attacked by SARS-CoV-2, the liver is especially vulnerable to virus-induced injury (Higuera-de la Tijera et al., 2021; Marjot et al., 2021). Studies have shown that liver dysfunction is closely related to hospital admission and mortality among COVID-19 patients (Li et al., 2020; Weber et al., 2021).

The liver is an important organ for metabolism and detoxification (Fuchs et al., 2017; Massafra et al., 2017; Berndt et al., 2021). SARS-CoV-2 can impair hepatocytes directly or indirectly via toxins, which can lead to liver injury and cause acute diffuse liver diseases (Li et al., 2020; Hofman et al., 2021; Nie et al., 2021; Weber et al., 2021). The proportion of COVID-19 patients with abnormal hepatic injury markers is extremely high (Dahiya et al., 2020; Marjot et al., 2021; Weber et al., 2021). However, some studies have focused only on a few common indicators of hepatic injury markers, such as bilirubin, albumin, alanine aminotransferase (ALT) and aspartate aminotransferase (AST). In addition to these common indicators, other indicators, such as alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), and total bile acid (TBA) in serum, can also reflect hepatic injury markers in humans. Exploration of the association of COVID-19 with abnormalities in only one or two serum hepatic injury markers indexes may bias the results (Roedl et al., 2021). The proportions of COVID-19 cases with abnormal hepatic injury markers have differed among various studies (Li et al., 2020; Pang et al., 2020; Marjot et al., 2021; Weber et al., 2021). In addition, the percentages of COVID-19 patients who have one, two or more abnormal hepatic injury markers indicators simultaneously are unknown. Some patients with SARS-CoV-2 infection have

normal serum hepatic injury markers indexes, and the differences between COVID-19 patients with abnormal hepatic injury markers indexes and those with normal hepatic injury markers indexes are unclear. Moreover, whether the abnormal hepatic injury markers in COVID-19 patients is related to factors other than liver damage caused by SARS-CoV-2 is ambiguous.

In this study, we focused on eight main serum hepatic injury markers in adult COVID-19 patients. We analyzed demographic data, blood test results and indicators on unenhanced CT scans in patients with abnormal or normal hepatic injury markers. We aimed to identify the potential factors associated with abnormalities in each hepatic injury markers marker in adult COVID-19 patients.

## 2 Methods

We retrospectively collected data for COVID-19 patients hospitalized in Wuhan Union Hospital from February 2020 to December 2022. A COVID-19 diagnosis is defined as a laboratory-confirmed infection with the SARS-CoV-2 virus, which is the virus that causes the disease COVID-19. This is usually done through a PCR test, which detects the genetic material of the virus. The general demographic characteristics and medical histories of the patients were recorded. We collected the hematological indexes of the COVID-19 patients within one week of hospitalization. Data on blood cell counts, immune cell percentages, indicators of coagulatory function, serum inflammatory indicators, hepatic injury markers, renal function indicators and other serum biochemical indexes were also collected. Patients younger than 18 year and patients without serological liver marker data were excluded.

Patients received unenhanced CT scans within one week after admission. The instrument was a Siemens SOMATOM Definition 64-slice spiral CT scanner. The CT data were based on the picture archiving and communication system (PACS) using the standard compression algorithm supported by DICOM 3.0. CT data collection was carried out by two researchers (XGQ and NXY) who were trained by a senior radiologist, and they were blinded to the patient information. Discrepancies in results between the two researchers were resolved by calculating the average values. We measured the mean CT value (MCTV) of the liver, the MCTV of the spleen, the MCTV of the pancreas, the abdominal subcutaneous fat thickness, abdominal transverse and anteroposterior diameters in the plane of the superior mesenteric artery originating from the abdominal aorta (Supplementary Figure 1) and other indicators for each individual using PACS software. We further assessed model performance to ensure robustness. Multicollinearity among independent variables was examined using the variance inflation factor (VIF), and no significant collinearity was detected. Model adequacy and goodness-of-fit were verified using the Hosmer–Lemeshow test, confirming satisfactory model stability.

IBM SPSS software (Version 22.0) was used to conduct data analysis. Independent t-tests and chi square tests were conducted to compare the variables between the normal and abnormal hepatic

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**Abbreviations:** ALP, Alkaline Phosphatase; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; BMI, Body Mass Index; CI, Confidence Interval; CK-MB, Creatine Kinase-MB; DBil, Direct Bilirubin; DICOM, Digital Imaging and Communications in Medicine; GGT, Gamma-glutamyl Transferase; HBV, Hepatitis B Virus; HCV, Hepatitis C Virus; HDL, High-density Lipoprotein; LDH, Lactate Dehydrogenase; LDL, Low-density Lipoprotein; LLN, Lower Limit of Normal; MCTV, Mean CT Value; OR, Odds Ratio; PACS, Picture Archiving and Communication Systems; ULN, Upper Limit of Normal; TBA, Total Bile Acid; TBil, Total Bilirubin.

injury markers groups. All variables with  $P$  values less than 0.2 were selected for binary logistic regression analysis to identify potential factors associated with each abnormal serum hepatic injury markers marker. A  $P$  value less than 0.05 was considered to indicate statistical significance.

### 3 Results

Ten patients were excluded from this study (1 was younger than 18 y, and 9 lacked hepatic injury markers results). A total of 1,007 adult COVID-19 patients were included. There were 444 males (44.1%) and 563 females (55.9%). The mean age of all patients was 59.9 y. Among the patients, 129 had a history of hepatitis B virus (HBV) infection. Unenhanced CT was performed on 983 patients (97.6%). The mean liver MCTV was 57.7 HU. Thirty-five patients (3.6%) had liver MCTVs less than 40 HU, and 33 (3.4%) had liver MCTVs greater than 70 HU. There were 109 patients (11.1%) with a liver MCTV/spleen MCTV ratio less than 1.0 and 93 (9.5%) with a ratio greater than 1.5 (Figure 1, Table 1).

Figure 2 displays the distribution of values for each serum hepatic injury markers index among all patients. A total of 697 patients (69.2%) had at least one abnormal serum hepatic injury markers marker. There were 269 patients (26.7%) with only one abnormal marker, 187 patients (18.6%) with two, 136 patients (13.5%) with three, 64 patients (6.4%) with four, 15 patients (1.5%) with five, 19 patients (1.9%) with six, 5 patients (0.5%) with seven, and 2 patients (0.2%) with eight abnormal hepatic injury markers indexes. Figure 3 shows the number of patients with abnormal values for each serum hepatic injury markers marker. The distributions of male and female COVID-19 patients with different levels of serum hepatic injury markers indicators are presented in Figure 4. Figure 5 displays the numbers and percentages of patients with various abnormal hepatic injury markers indexes grouped by age.

One hundred forty-four patients (14.3%) had abnormal serum total bilirubin (TBil). The proportion of males (82/362) with elevated TBil was higher than that of females (62/501) ( $P = 0.001$ ). Among patients less than sixty years old, 11.6% (48/414) had elevated TBil; among patients more than sixty years old, 16.2% (96/593) had elevated TBil. Table 2 shows that the values of 17 blood variables were significantly different between the abnormal and normal TBil groups. Table 3 demonstrates that the mean liver MCTV of patients with elevated TBil (55.9 HU) was lower than that of patients with normal TBil (58.0 HU) ( $P = 0.006$ ). The patients with elevated TBil had thinner abdominal subcutaneous fat layers and lower ratios of abdominal subcutaneous fat thickness to thoracic or abdominal diameters, with all  $P$  values less than 0.05 (Table 3). Table 1 shows the factors associated with elevated serum TBil, which included sex (odds ratio, OR: 0.61, 95% confidence interval, CI: 0.42-0.89), smoking (OR: 2.43, 95% CI: 1.09-5.42), liver MCTV (OR: 0.13, 95% CI: 0.03-0.58) and the ratio of abdominal subcutaneous fat thickness to the sum of abdominal anteroposterior and transverse diameters (OR: 0.06, 95% CI: 0.01-0.36).

Seventy-nine patients (7.85%) had elevated serum direct bilirubin (DBil). Males had a higher proportion (13.3%) of elevated DBil than females (5.0%). The mean age of patients with abnormal DBil was 64.0 y, which was greater than that of patients with normal DBil ( $P = 0.011$ ). Although univariate analysis showed that there were differences in 26 blood indicators between the two groups of patients (elevated vs. normal DBil) (Table 2), multivariate analysis indicated that only three serum markers (lactate dehydrogenase, LDH; total cholesterol; and low-density lipoprotein cholesterol) were independently related to abnormal DBil (Table 1). The liver MCTV, the liver MCTV/spleen MCTV ratio, the subcutaneous fat thickness and the ratio of subcutaneous fat thickness to the sum of the transverse and anteroposterior abdominal diameters were significantly reduced (Table 3). Table 1 indicates that females were less likely to develop elevated DBil than

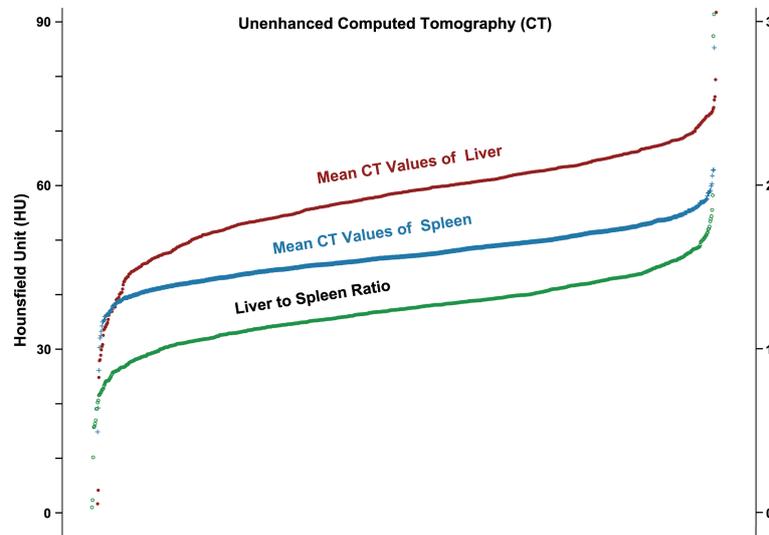


FIGURE 1

Scatter plot of the liver MCTVs, spleen MCTVs and liver MCTV/spleen MCTV ratios of adult COVID-19 patients.

TABLE 1 Comparison of the demographic characteristics of adult COVID-19 patients between the abnormal and normal serum hepatic injury markers index groups.

| Variables                |        | Total Bilirubin |                |       | Direct Bilirubin |                |        | Albumin      |                |        | ALT          |                |        | AST          |                |        | ALP         |             |                | GGT   |       |              | Total Bile Acid |        |              |                |        |
|--------------------------|--------|-----------------|----------------|-------|------------------|----------------|--------|--------------|----------------|--------|--------------|----------------|--------|--------------|----------------|--------|-------------|-------------|----------------|-------|-------|--------------|-----------------|--------|--------------|----------------|--------|
|                          |        | >ULN (n=144)    | Normal (n=863) | P     | >ULN (n=79)      | Normal (n=928) | P      | <LLN (n=296) | Normal (n=711) | P      | >ULN (n=350) | Normal (n=677) | P      | >ULN (n=177) | Normal (n=850) | P      | <LLN (n=38) | >ULN (n=20) | Normal (n=949) | P (L) | P (U) | >ULN (n=360) | Normal (n=647)  | P      | >ULN (n=103) | Normal (n=904) | P      |
| Gender                   | Male   | 82              | 362            | 0.001 | 52               | 392            | <0.001 | 177          | 267            | <0.001 | 220          | 224            | <0.001 | 110          | 334            | <0.001 | 14          | 12          | 418            | 0.38  | 0.155 | 225          | 219             | <0.001 | 49           | 395            | 0.453  |
|                          | Female | 62              | 501            |       | 27               | 536            |        | 119          | 444            |        | 110          | 453            |        | 67           | 496            |        | 24          | 8           | 531            |       |       | 135          | 428             |        | 54           | 509            |        |
| Mean Age (y)             |        | 61.6            | 59.7           | 0.192 | 64.0             | 59.6           | 0.011  | 68.2         | 56.5           | <0.001 | 58.0         | 60.9           | 0.004  | 63.7         | 59.2           | <0.001 | 53.7        | 59.1        | 60.2           | 0.008 | 0.733 | 61.1         | 59.3            | 0.061  | 65.3         | 59.3           | <0.001 |
| Age Groups-y             | 18-50  | 35              | 211            | 0.004 | 16               | 230            | <0.001 | 25           | 221            | <0.001 | 87           | 159            | 0.029  | 30           | 216            | 0.001  | 18          | 5           | 223            | 0.022 | 0.706 | 72           | 174             | 0.063  | 13           | 233            | 0.001  |
|                          | 50-60  | 13              | 155            |       | 7                | 161            |        | 32           | 136            |        | 69           | 99             |        | 28           | 140            |        | 5           | 5           | 158            |       |       | 73           | 95              |        | 13           | 155            |        |
|                          | 60-70  | 48              | 320            |       | 21               | 347            |        | 118          | 250            |        | 109          | 259            |        | 60           | 308            |        | 10          | 5           | 353            |       |       | 133          | 235             |        | 39           | 329            |        |
|                          | 70-80  | 31              | 117            |       | 24               | 124            |        | 75           | 73             |        | 47           | 101            |        | 35           | 113            |        | 3           | 4           | 141            |       |       | 54           | 94              |        | 25           | 123            |        |
|                          | >80    | 17              | 60             |       | 11               | 66             |        | 46           | 31             |        | 18           | 59             |        | 24           | 53             |        | 2           | 1           | 74             |       |       | 28           | 49              |        | 13           | 64             |        |
| Weight (kg)              |        | 63.1            | 62.3           | 0.687 | 64.5             | 62.2           | 0.277  | 62.9         | 62.3           | 0.674  | 65.9         | 60.6           | <0.001 | 62.6         | 62.4           | 0.936  | 59.4        | 61.2        | 62.6           | 0.35  | 0.729 | 66.2         | 60.8            | <0.001 | 59.9         | 62.7           | 0.206  |
| Height (cm)              |        | 164.8           | 163.5          | 0.223 | 166.2            | 163.4          | 0.034  | 164.1        | 163.5          | 0.459  | 166.2        | 162.4          | <0.001 | 164.7        | 163.5          | 0.232  | 162.8       | 162.8       | 163.7          | 0.633 | 0.687 | 165.5        | 162.9           | 0.002  | 164.2        | 163.6          | 0.675  |
| Mean BMI                 |        | 23.2            | 23.2           | 0.992 | 23.3             | 23.2           | 0.881  | 23.3         | 23.2           | 0.841  | 23.7         | 22.9           | 0.041  | 22.9         | 23.3           | 0.432  | 22.4        | 23.0        | 23.3           | 0.391 | 0.839 | 24.1         | 22.8            | 0.001  | 22.1         | 23.3           | 0.072  |
| BMI Groups               | <18    | 3               | 9              | 0.407 | 3                | 9              | 0.121  | 4            | 8              | 0.914  | 1            | 11             | 0.071  | 2            | 10             | 0.904  | 0           | 0           | 12             | 0.444 | 0.549 | 1            | 11              | 0.002  | 2            | 10             | 0.316  |
|                          | 18-24  | 26              | 193            |       | 16               | 203            |        | 58           | 161            |        | 71           | 148            |        | 36           | 183            |        | 10          | 5           | 204            |       |       | 55           | 164             |        | 20           | 199            |        |
|                          | 14-28  | 16              | 78             |       | 10               | 84             |        | 27           | 67             |        | 38           | 56             |        | 13           | 81             |        | 2           | 4           | 88             |       |       | 42           | 52              |        | 8            | 86             |        |
|                          | >28    | 3               | 23             |       | 4                | 22             |        | 8            | 18             |        | 12           | 14             |        | 5            | 21             |        | 0           | 0           | 26             |       |       | 10           | 16              |        | 0            | 26             |        |
| Hypertension             | No     | 74              | 489            | 0.238 | 39               | 524            | 0.223  | 145          | 418            | 0.004  | 176          | 387            | 0.25   | 90           | 473            | 0.135  | 21          | 13          | 529            | 0.953 | 0.409 | 175          | 388             | 0.001  | 50           | 513            | 0.112  |
|                          | Yes    |                 | 154            |       | 290              |                | 357    |              | 17             |        | 7            | 420            |        | 185          | 259            |        | 53          | 391         |                |       |       |              |                 |        |              |                |        |
| Coronary Atherosclerosis | No     | 130             | 805            | 0.196 | 69               | 866            | 0.048  | 264          | 671            | 0.004  | 301          | 634            | 0.159  | 155          | 780            | 0.003  | 36          | 19          | 880            | 0.639 | 0.698 | 331          | 604             | 0.405  | 96           | 839            | 0.883  |
|                          | Yes    |                 | 29             |       | 43               |                | 50     |              | 2              |        | 1            | 69             |        | 29           | 43             |        | 7           | 65          |                |       |       |              |                 |        |              |                |        |
| Type 2 Diabetes          | No     | 92              | 606            | 0.127 | 44               | 654            | 0.006  | 188          | 510            | 0.01   | 213          | 485            | 0.022  | 106          | 592            | 0.003  | 31          | 10          | 657            | 0.104 | 0.066 | 214          | 484             | <0.001 | 60           | 638            | 0.01   |
|                          | Yes    |                 | 117            |       | 192              |                | 238    |              | 7              |        | 10           | 292            |        | 146          | 163            |        | 43          | 266         |                |       |       |              |                 |        |              |                |        |
| Operation History        | No     | 111             | 594            | 0.045 | 63               | 642            | 0.049  | 210          | 495            | 0.676  | 239          | 466            | 0.243  | 130          | 575            | 0.272  | 27          | 13          | 665            | 0.897 | 0.624 | 251          | 454             | 0.882  | 76           | 629            | 0.377  |
|                          | Yes    |                 | 91             |       | 211              |                | 255    |              | 11             |        | 7            | 284            |        | 109          | 193            |        | 27          | 275         |                |       |       |              |                 |        |              |                |        |
| Allergic History         | No     | 128             | 783            | 0.486 | 74               | 837            | 0.312  | 276          | 635            | 0.053  | 302          | 609            | 0.429  | 164          | 747            | 0.275  | 36          | 19          | 856            | 0.352 | 0.473 | 326          | 585             | 0.943  | 94           | 817            | 0.772  |
|                          | Yes    |                 | 28             |       | 68               |                | 83     |              | 2              |        | 1            | 93             |        | 34           | 62             |        | 9           | 87          |                |       |       |              |                 |        |              |                |        |
| HBV Infection            | No     | 124             | 754            | 0.676 | 65               | 813            | 0.174  | 252          | 626            | 0.208  | 283          | 595            | 0.342  | 145          | 733            | 0.021  | 30          | 16          | 832            | 0.113 | 0.304 | 310          | 568             | 0.445  | 84           | 794            | 0.071  |
|                          | Yes    |                 | 47             |       | 82               |                | 97     |              | 8              |        | 4            | 117            |        | 50           | 79             |        | 19          | 110         |                |       |       |              |                 |        |              |                |        |
| Smoking                  | No     | 134             | 841            | 0.005 | 74               | 901            | 0.096  | 278          | 697            | 0.001  | 310          | 665            | <0.001 | 171          | 804            | 0.859  | 38          | 19          | 918            | 0.258 | 0.668 | 337          | 638             | <0.001 | 100          | 875            | 0.871  |
|                          | Yes    |                 | 20             |       | 12               |                | 26     |              | 0              |        | 1            | 31             |        | 23           | 9              |        | 3           | 29          |                |       |       |              |                 |        |              |                |        |
| Alcohol Drinking         | No     | 139             | 850            | 0.099 | 76               | 913            | 0.16   | 285          | 704            | 0.003  | 323          | 666            | 0.577  | 174          | 815            | 0.918  | 38          | 19          | 932            | 0.405 | 0.293 | 347          | 642             | 0.001  | 101          | 888            | 0.901  |
|                          | Yes    |                 | 7              |       | 11               |                | 15     |              | 0              |        | 1            | 17             |        | 13           | 5              |        | 2           | 16          |                |       |       |              |                 |        |              |                |        |

\* ULN, Upper Limit of Normal; LLN, Lower Limit of Normal; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; ALP, Alkaline Phosphatase; GGT, Gamma-glutamyl Transferase; BMI, Body Mass Index; HBV, Hepatitis B Virus.

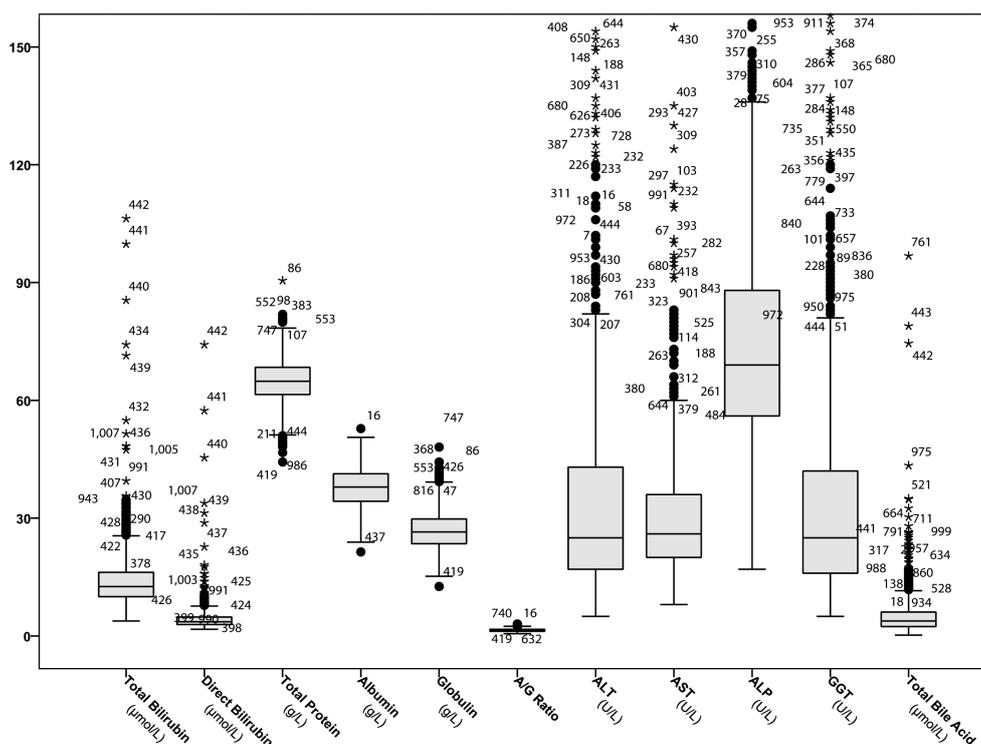


FIGURE 2 Boxplot of serum indicators of hepatic injury markers in adult COVID-19 patients.

males (OR: 0.36, 95% CI: 0.16-0.83). Adult COVID-19 patients who had a history of HBV infection had an elevated risk of abnormal DBil (OR: 3.26, 95% CI: 1.22-8.69).

There were 296 patients (29.4%) with decreased serum albumin. Albumin was below the lower limit of the normal range in more than one-third of males but in only approximately one-fifth of females. The mean age of the patients with reduced albumin was more than ten years older than that of the patients with normal albumin ( $P < 0.001$ ). The incidence of chronic diseases (such as hypertension and diabetes) was increased among COVID-19 patients with decreased serum albumin. Binary logistic regression analysis showed that twenty indicators were independently associated with reduced serum albumin in adult COVID-19 patients (Table 1).

Three hundred thirty patients (32.8%) had elevated serum ALT. One hundred and seventy-seven patients (17.6%) had elevated serum AST. The proportions of males were greater than the proportions of females in both the elevated ALT group and the elevated AST group, with  $P$  values less than 0.001. The patients with abnormal ALT were younger (mean age: 58.0 y) than the patients with normal ALT (mean age: 60.9 y), with a  $P$  value of 0.004. However, the mean age of the abnormal AST group (63.7 y) was greater than the mean age of the normal AST group (59.2 y), with a  $P$  value less than 0.001. Univariate analysis showed that the blood indexes and CT scan indicators that differed between the abnormal ALT and normal ALT groups were not the same as those that differed between the abnormal AST and normal AST groups (Tables 2, 3). The factors simultaneously independently associated

with abnormal ALT and AST were sex (OR: 0.20 and 0.42), age (OR: 0.98 and 1.02), the ratio of the sum of the abdominal diameters to the sum of the thoracic diameters (OR: 59.6 and 522.2), and the ratio of abdominal fat thickness to the sum of the abdominal diameters (OR: 0.12 and 0.15). Other indicators independently correlated with increased ALT or AST in adult COVID-19 patients are shown in Table 1.

Among all patients, only a small number had abnormal serum ALP (38 had decreased ALP, and 20 had increased ALP). Compared to the patients with normal ALP, the patients with low ALP were significantly younger ( $P = 0.008$ ); although patients with elevated ALP were also younger, the difference was not significant ( $P = 0.733$ ). In binary logistic regression analysis, there were few independent factors related to abnormal ALP (Table 1), perhaps because of the small number of abnormal ALP cases in our study or the lack of inclusion of other relevant factors.

Three hundred and sixty patients (35.8%) had elevated serum GGT. The proportion of males with abnormal GGT was significantly higher than that of females ( $P < 0.001$ ). Among adult COVID-19 patients, more patients with elevated GGT had chronic diseases (hypertension or type 2 diabetes) and unhealthy lifestyles (overweight, smoking or drinking) than patients with normal GGT, with all  $P$  values less than 0.05. Independent-sample t-test analysis revealed that 23 blood indexes were significantly different between the abnormal and normal GGT groups. As shown in Table 1, TNF- $\alpha$ , FDP, FIB, LDH, uric acid and triglycerides in blood were positively associated with elevated serum GGT. In addition, four CT scan indicators were independently associated with elevated

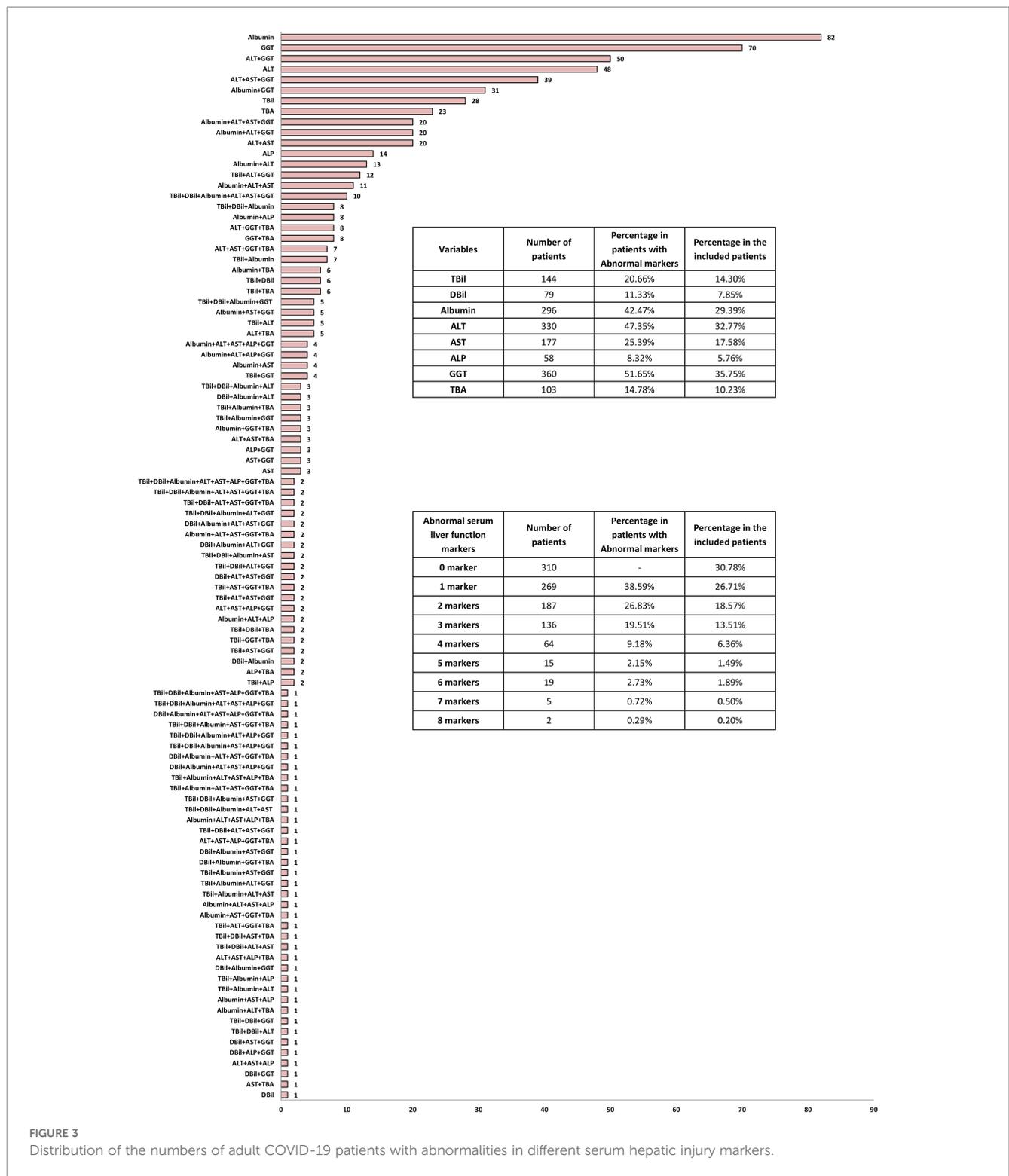


FIGURE 3 Distribution of the numbers of adult COVID-19 patients with abnormalities in different serum hepatic injury markers.

serum GGT, including the liver MCTV (OR: 0.97, 95% CI: 0.95-0.99), the anteroposterior abdominal diameter (OR: 0.82, 95% CI: 0.72-0.94), the anteroposterior abdominal diameter (OR: 1.39, 95% CI: 1.26-1.53) and the ratio of abdominal subcutaneous fat thickness to the sum of the abdominal anteroposterior and transverse diameters (OR: 0.04, 95% CI: 0.01-0.14).

There were 103 patients (10.2%) with elevated serum TBA. Patients with elevated TBA were older ( $P < 0.001$ ) and had a higher proportion of type 2 diabetes ( $P = 0.01$ ) than those without elevated TBA. The mean values of blood indicators such as red blood cells (RBCs), platelets, CD3+ T lymphocytes, CD4+ T lymphocytes, CD8 + T lymphocytes, B lymphocytes, IL-2, ATIII, CK-MB, and HDL cholesterol in the abnormal TBA group were different from those in

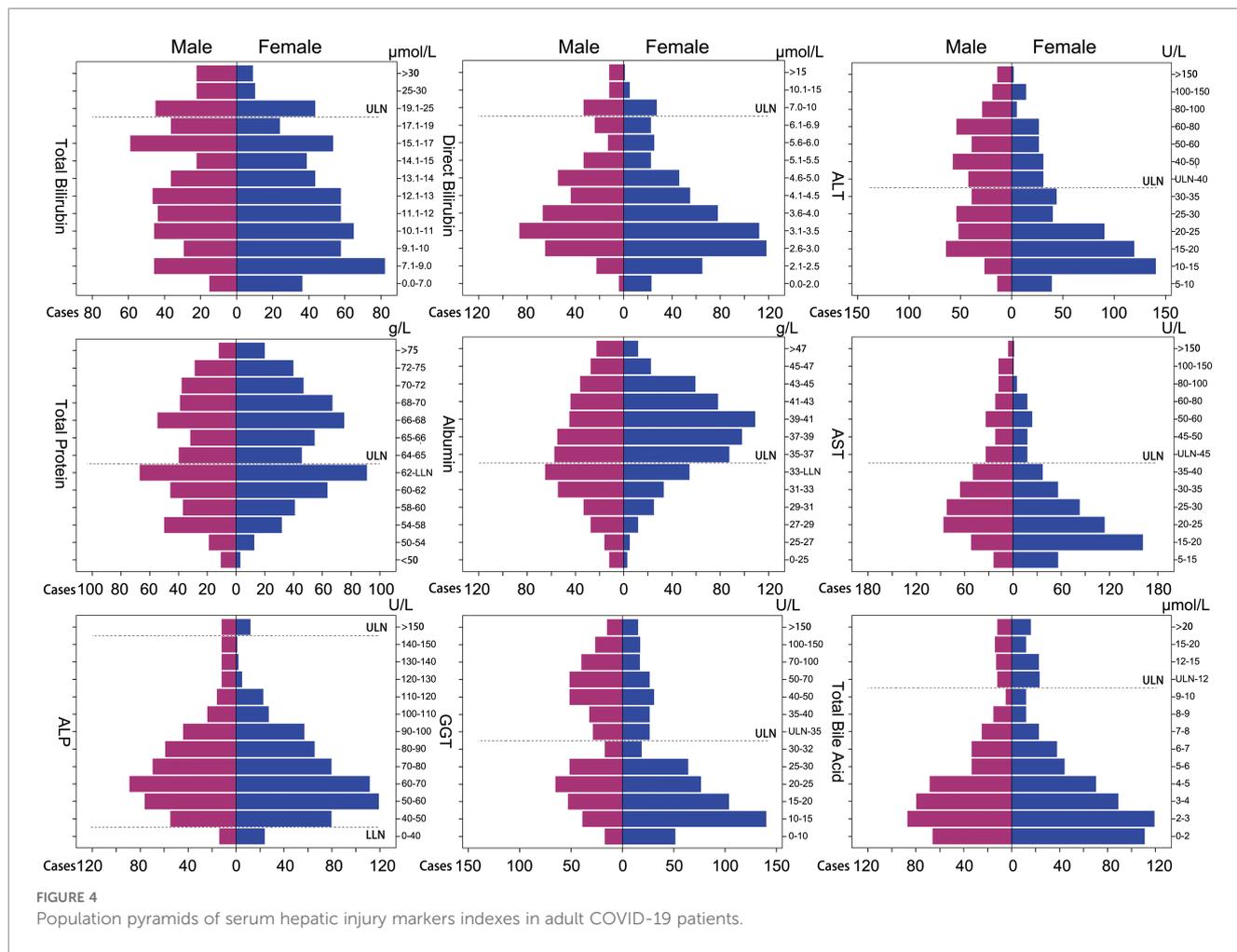


FIGURE 4 Population pyramids of serum hepatic injury markers indexes in adult COVID-19 patients.

the normal TBA group, but multivariate analysis showed no significant differences. Type 2 diabetes (OR: 2.78, 95% CI: 1.30-5.92), a ratio of liver MCTV to spleen MCTV less than 1.0 (OR: 0.24, 95% CI: 0.07-0.77) and a ratio of anteroposterior diameter to transverse diameter of the chest were independently correlated with elevated serum TBA (Table 1).

### 4 Discussion

Our study showed that approximately 69.2% of all adult COVID-19 patients had at least one abnormal serum hepatic injury markers marker. Univariate analysis and binary logistic regression analysis showed that the factors associated with each of the eight abnormal hepatic injury markers differed. However, our results suggested that the factors independently related to abnormalities in most of the eight hepatic injury markers indexes were sex, age, a history of HBV infection, blood FIB and LDH, the liver MCTV, the pancreas MCTV, and the ratio of abdominal subcutaneous fat thickness to the abdominal diameters.

We found that females accounted for a larger proportion of adult COVID-19 patients than males. However, the proportion of male patients with abnormal hepatic injury markers indicators was

higher than that of female patients with abnormal hepatic injury markers indicators. Our results showed that sex was independently associated with abnormalities in six of the eight hepatic injury markers (TBil, DBil, albumin, ALT, AST, and GGT) and that adult male COVID-19 patients were more likely to have abnormal hepatic injury markers than female patients. Other studies have similarly shown that among patients with other etiologies that cause hepatocyte damage (such as HBV infection and non-alcoholic liver disease), the proportion of males with abnormal hepatic injury markers is greater than the proportion of females with abnormal hepatic injury markers (Xiao et al., 2015; Xiao et al., 2017; Tobari and Hashimoto, 2020). We speculate that this result may be due in part to a more unhealthy lifestyle (smoking, alcohol drinking, etc.) among men than among women (Takenaka et al., 2020; Kezer et al., 2021). In addition, many experimental studies have indicated that the sex-biased hepatic expression of genes is correlated with sex differences in the incidence and progression of many liver diseases (Zhang et al., 2012; Luo et al., 2019; Lau-Corona et al., 2020).

Li's research showed that COVID-19-induced hepatic injury markers abnormalities are associated with age (Li et al., 2020). Our results indicated that COVID-19 patients with elevated ALT or decreased ALP tended to be younger, while patients with elevated AST or reduced albumin tended to be older. Other studies have

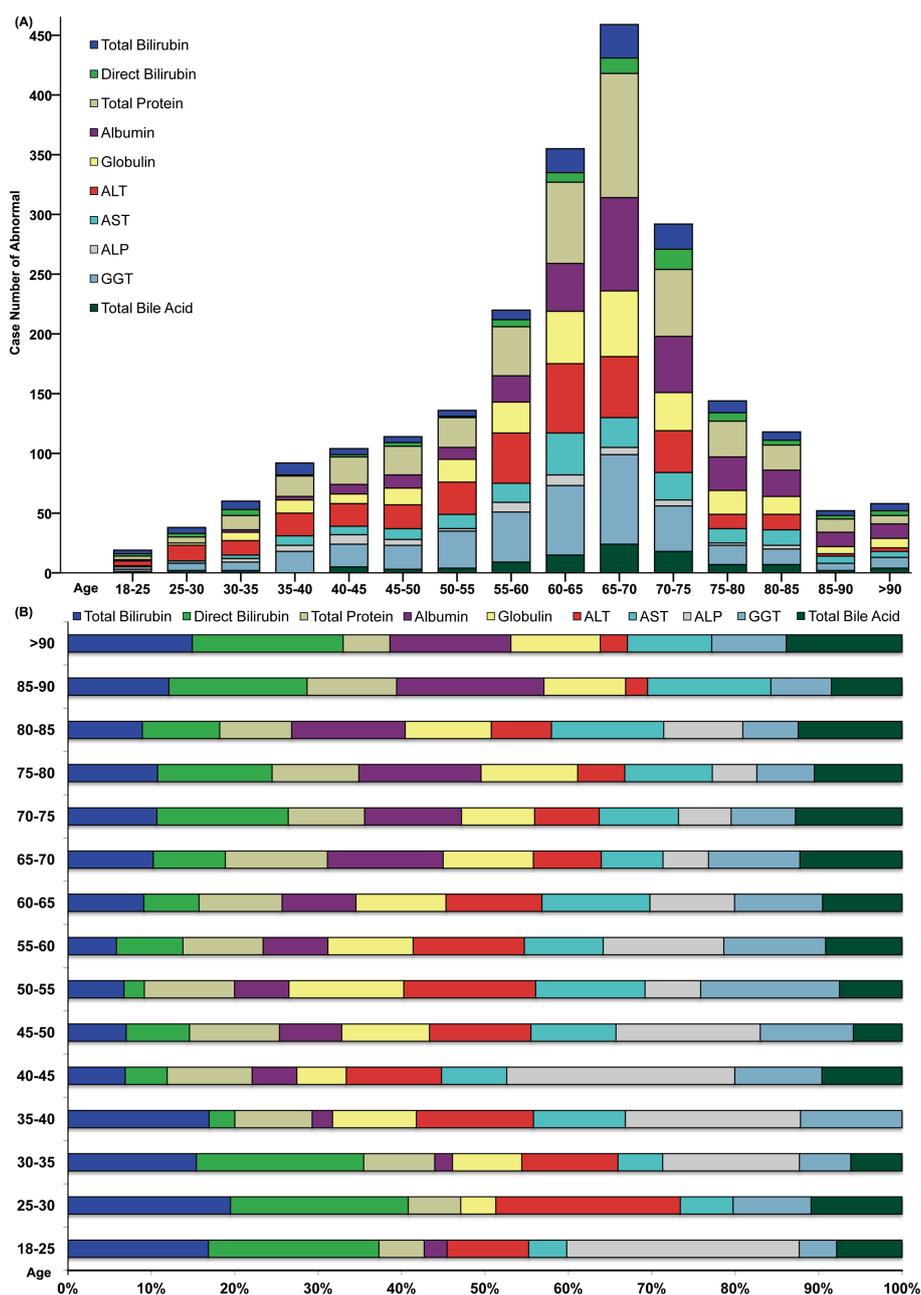


FIGURE 5 Case (A) and percentage (B) distributions of adult COVID-19 patients with abnormal serum hepatic injury markers indexes.

demonstrated that age-related chronic inflammation can promote hepatocyte senescence and chronic liver disease (Gómez-Santos et al., 2020; Bianchi et al., 2021). This mechanism may explain why age is related to abnormal hepatic injury markers to a certain extent. Ma and colleagues showed that hepatic deoxycholic acid levels vary with age in mice (Ma et al., 2020). Although the patients with abnormal TBil, DBil, GGT or TBA tended to be older, age was not an independent factor associated with abnormalities in these four hepatic injury markers.

Our results showed that adult COVID-19 patients with a history of HBV infection had elevated risks of increased DBil and AST.

However, HBV infection history was not independently correlated with abnormalities in the other six hepatic injury markers indicators. Lin and colleagues revealed that patients with inactive HBV and SARS-CoV-2 coinfection are at an increased risk of abnormal hepatic injury markers (Lin et al., 2020). In our study, 19 of 129 patients with HBV infection history were positive for hepatitis B surface antigen (HBsAg), while the others were positive only for hepatitis B core antibody (HBcAb) or both HBcAb and HBeAb. Previous research has shown that some people who are positive only for HBcAb may test positive for HBV DNA (El-Nabi et al., 2020; Khiangte et al., 2020). Because few people were tested

TABLE 2 Comparison of the laboratory test results of adult COVID-19 patients between the abnormal and normal serum hepatic injury markers index groups.

| Variables                        | Total Bilirubin |                |        | Direct Bilirubin |                |        | Albumin      |                |        | ALT          |                |        | AST          |                |        | ALP         |             |                | GGT   |       |              | Total Bile Acid |        |              |                |        |
|----------------------------------|-----------------|----------------|--------|------------------|----------------|--------|--------------|----------------|--------|--------------|----------------|--------|--------------|----------------|--------|-------------|-------------|----------------|-------|-------|--------------|-----------------|--------|--------------|----------------|--------|
|                                  | >ULN (n=144)    | Normal (n=863) | p      | >ULN (n=79)      | Normal (n=928) | p      | <LLN (n=296) | Normal (n=711) | p      | >ULN (n=330) | Normal (n=677) | p      | >ULN (n=177) | Normal (n=830) | p      | <LLN (n=58) | >ULN (n=20) | Normal (n=949) | P (L) | P (U) | >ULN (n=360) | Normal (n=647)  | p      | >ULN (n=103) | Normal (n=904) | p      |
| WBC (10 <sup>9</sup> /L)         | 6.8             | 5.7            | <0.001 | 7.6              | 5.7            | <0.001 | 6.6          | 5.5            | <0.001 | 6.2          | 5.6            | <0.001 | 6.5          | 5.7            | 0.009  | 4.9         | 7.4         | 5.8            | 0.024 | 0.176 | 6.3          | 5.5             | <0.001 | 5.9          | 5.8            | 0.824  |
| RBC (10 <sup>12</sup> /L)        | 3.9             | 3.9            | 0.644  | 3.8              | 3.9            | 0.300  | 3.7          | 4.0            | <0.001 | 4.0          | 3.8            | <0.001 | 3.9          | 3.9            | 0.679  | 3.7         | 3.5         | 3.9            | 0.022 | 0.071 | 3.9          | 3.9             | 0.897  | 3.8          | 3.9            | 0.042  |
| Hemoglobin (g/L)                 | 123.5           | 122.8          | 0.702  | 120.4            | 123.1          | 0.257  | 116.3        | 125.7          | <0.001 | 128.0        | 120.4          | <0.001 | 124.1        | 122.7          | 0.311  | 117.4       | 112.0       | 123.4          | 0.003 | 0.083 | 123.9        | 122.4           | 0.162  | 121.6        | 123.1          | 0.375  |
| Platelet (10 <sup>9</sup> /L)    | 202.8           | 236.0          | <0.001 | 203.6            | 233.6          | 0.004  | 241.8        | 226.9          | 0.024  | 245.6        | 224.3          | 0.001  | 235.1        | 230.4          | 0.585  | 231.4       | 244.8       | 231.0          | 0.977 | 0.674 | 243.7        | 224.4           | 0.002  | 212.4        | 233.4          | 0.023  |
| Neutrophils (10 <sup>9</sup> /L) | 4.9             | 3.7            | <0.001 | 6.0              | 3.7            | <0.001 | 4.9          | 3.4            | <0.001 | 4.2          | 3.6            | 0.001  | 4.8          | 3.6            | 0.001  | 3.0         | 5.9         | 3.8            | 0.048 | 0.087 | 4.3          | 3.6             | <0.001 | 3.9          | 3.8            | 0.933  |
| Lymphocytes (10 <sup>9</sup> /L) | 1.2             | 1.4            | 0.009  | 1.0              | 1.4            | <0.001 | 1.1          | 1.5            | <0.001 | 1.4          | 1.4            | 0.935  | 1.1          | 1.4            | <0.001 | 1.3         | 1.0         | 1.4            | 0.355 | 0.008 | 1.3          | 1.4             | 0.320  | 1.4          | 1.4            | 0.851  |
| Monocytes (10 <sup>9</sup> /L)   | 0.55            | 0.50           | 0.079  | 0.53             | 0.51           | 0.396  | 0.57         | 0.48           | <0.001 | 0.53         | 0.50           | 0.029  | 0.52         | 0.51           | 0.601  | 0.49        | 0.46        | 0.51           | 0.584 | 0.353 | 0.56         | 0.48            | <0.001 | 0.54         | 0.51           | 0.170  |
| Eosinophils (10 <sup>9</sup> /L) | 0.11            | 0.09           | 0.347  | 0.05             | 0.10           | 0.005  | 0.07         | 0.11           | <0.001 | 0.11         | 0.09           | 0.053  | 0.08         | 0.10           | 0.035  | 0.07        | 0.07        | 0.10           | 0.174 | 0.338 | 0.10         | 0.09            | 0.223  | 0.09         | 0.10           | 0.823  |
| Basophils (10 <sup>9</sup> /L)   | 0.02            | 0.02           | 0.902  | 0.02             | 0.02           | 0.581  | 0.02         | 0.02           | 0.922  | 0.02         | 0.02           | 0.652  | 0.02         | 0.02           | 0.098  | 0.02        | 0.01        | 0.02           | 0.894 | 0.271 | 0.02         | 0.02            | 0.905  | 0.02         | 0.02           | 0.909  |
| Neutrophil (%)                   | 67.8            | 62.7           | <0.001 | 73.7             | 62.5           | <0.001 | 69.7         | 60.8           | <0.001 | 64.9         | 62.7           | 0.004  | 68.0         | 62.4           | <0.001 | 60.4        | 71.1        | 63.4           | 0.113 | 0.103 | 65.3         | 62.4            | <0.001 | 63.7         | 63.4           | 0.821  |
| Lymphocyte (%)                   | 21.3            | 25.9           | <0.001 | 17.1             | 25.9           | <0.001 | 19.1         | 27.8           | <0.001 | 23.7         | 26.0           | 0.001  | 21.4         | 26.1           | <0.001 | 27.8        | 19.2        | 25.3           | 0.117 | 0.099 | 23.2         | 26.4            | <0.001 | 24.8         | 25.3           | 0.628  |
| Monocytes (%)                    | 8.78            | 9.32           | 0.098  | 7.96             | 9.35           | 0.001  | 9.59         | 9.10           | 0.100  | 9.15         | 9.29           | 0.578  | 9.02         | 9.29           | 0.369  | 9.89        | 8.19        | 9.24           | 0.271 | 0.405 | 9.47         | 9.11            | 0.179  | 9.53         | 9.21           | 0.392  |
| Eosinophils (%)                  | 1.80            | 1.67           | 0.655  | 0.84             | 1.76           | <0.001 | 1.19         | 1.90           | <0.001 | 1.79         | 1.64           | 0.268  | 1.28         | 1.78           | 0.003  | 1.45        | 1.30        | 1.71           | 0.441 | 0.379 | 1.71         | 1.68            | 0.849  | 1.63         | 1.70           | 0.756  |
| Basophils (%)                    | 0.38            | 0.43           | 0.382  | 0.32             | 0.43           | 0.127  | 0.40         | 0.43           | 0.417  | 0.39         | 0.44           | 0.155  | 0.34         | 0.44           | 0.032  | 0.47        | 0.24        | 0.43           | 0.644 | 0.168 | 0.39         | 0.44            | 0.231  | 0.40         | 0.43           | 0.675  |
| CD3+ T Lymphocytes (%)           | 72.2            | 74.4           | 0.067  | 69.9             | 74.4           | 0.001  | 71.5         | 75.2           | <0.001 | 74.2         | 74.0           | 0.856  | 70.8         | 74.8           | 0.001  | 75.8        | 72.9        | 74.0           | 0.343 | 0.683 | 73.9         | 74.2            | 0.732  | 69.3         | 74.6           | <0.001 |
| CD4+ T Lymphocytes (%)           | 44.8            | 46.6           | 0.055  | 43.1             | 46.6           | 0.018  | 45.8         | 46.5           | 0.286  | 46.8         | 46.1           | 0.290  | 44.7         | 46.6           | 0.028  | 48.7        | 45.5        | 46.2           | 0.046 | 0.773 | 46.2         | 46.4            | 0.818  | 44.2         | 46.5           | 0.044  |
| CD8+ T Lymphocytes (%)           | 24.1            | 24.3           | 0.844  | 24.0             | 24.3           | 0.804  | 22.9         | 24.9           | 0.003  | 24.0         | 24.4           | 0.485  | 23.0         | 24.6           | 0.047  | 23.8        | 23.9        | 24.3           | 0.722 | 0.870 | 24.3         | 24.3            | 0.984  | 22.2         | 24.5           | 0.023  |
| CD4+/CD8+ Ratio                  | 2.2             | 2.2            | 0.880  | 2.3              | 2.2            | 0.661  | 2.4          | 2.1            | <0.001 | 2.3          | 2.2            | 0.246  | 2.3          | 2.2            | 0.243  | 2.3         | 2.5         | 2.2            | 0.662 | 0.283 | 2.2          | 2.2             | 0.626  | 2.3          | 2.2            | 0.414  |
| B Lymphocytes (%)                | 14.5            | 12.4           | 0.189  | 14.0             | 12.4           | 0.269  | 12.8         | 12.6           | 0.845  | 13.7         | 12.2           | 0.204  | 14.1         | 12.4           | 0.435  | 7.5         | 17.7        | 12.6           | 0.115 | 0.488 | 13.1         | 12.5            | 0.542  | 9.5          | 13.0           | 0.049  |
| NK Cells (%)                     | 6.0             | 8.9            | 0.056  | 7.0              | 8.8            | 0.204  | 9.1          | 8.2            | 0.397  | 7.6          | 9.0            | 0.116  | 8.8          | 8.5            | 0.830  | 6.8         | 4.3         | 8.7            | 0.586 | 0.137 | 8.1          | 8.7             | 0.520  | 11.5         | 8.2            | 0.208  |
| IL-2 (pg/ml)                     | 3.2             | 3.0            | 0.068  | 3.1              | 3.0            | 0.552  | 2.9          | 3.1            | 0.016  | 3.2          | 3.0            | 0.010  | 3.1          | 3.0            | 0.223  | 2.7         | 3.5         | 3.0            | 0.003 | 0.122 | 3.1          | 3.0             | 0.053  | 3.2          | 3.0            | 0.046  |
| IL-4 (pg/ml)                     | 5.7             | 2.6            | 0.287  | 2.8              | 3.1            | 0.834  | 3.9          | 2.7            | 0.413  | 3.0          | 3.1            | 0.845  | 2.7          | 3.2            | 0.662  | 2.3         | 3.4         | 3.1            | 0.740 | 0.930 | 2.9          | 3.2             | 0.743  | 7.5          | 2.6            | 0.286  |
| IL-6 (pg/ml)                     | 56.2            | 40.0           | 0.367  | 73.4             | 39.7           | 0.303  | 57.5         | 35.9           | 0.046  | 43.2         | 42.0           | 0.875  | 60.5         | 38.6           | 0.184  | 28.7        | 20.8        | 43.3           | 0.460 | 0.457 | 42.4         | 42.3            | 0.991  | 43.4         | 42.3           | 0.932  |
| IL-10 (pg/ml)                    | 4.8             | 4.1            | 0.124  | 5.6              | 4.1            | 0.067  | 4.7          | 4.0            | 0.033  | 4.5          | 4.1            | 0.087  | 5.1          | 4.0            | 0.018  | 3.5         | 5.4         | 4.2            | 0.241 | 0.236 | 4.6          | 4.0             | 0.008  | 4.4          | 4.2            | 0.676  |
| TNF-α (pg/ml)                    | 4.7             | 5.1            | 0.510  | 4.7              | 5.1            | 0.640  | 5.2          | 5.0            | 0.784  | 5.7          | 4.8            | 0.066  | 4.5          | 5.2            | 0.207  | 3.8         | 3.9         | 5.1            | 0.219 | 0.472 | 5.6          | 4.8             | 0.090  | 5.7          | 5.0            | 0.352  |
| IFN-γ (pg/ml)                    | 2.6             | 2.7            | 0.812  | 3.1              | 2.6            | 0.490  | 2.6          | 2.7            | 0.858  | 2.8          | 2.5            | 0.063  | 2.7          | 2.6            | 0.948  | 2.7         | 3.1         | 2.6            | 0.968 | 0.425 | 2.6          | 2.7             | 0.844  | 2.8          | 2.6            | 0.393  |
| APTT (s)                         | 37.8            | 37.0           | 0.239  | 38.9             | 37.0           | 0.024  | 37.9         | 36.8           | 0.029  | 37.5         | 37.0           | 0.363  | 38.6         | 36.8           | 0.068  | 37.4        | 38.1        | 37.1           | 0.786 | 0.574 | 37.0         | 37.2            | 0.590  | 36.9         | 37.2           | 0.762  |
| PT (s)                           | 14.2            | 13.3           | <0.001 | 14.9             | 13.4           | <0.001 | 14.1         | 13.2           | <0.001 | 13.6         | 13.4           | 0.195  | 14.1         | 13.3           | 0.002  | 13.3        | 14.5        | 13.5           | 0.638 | 0.104 | 13.7         | 13.4            | 0.012  | 13.6         | 13.5           | 0.487  |

(Continued)

TABLE 2 Continued

| Variables              | Total Bilirubin |                   |        | Direct Bilirubin |                   |        | Albumin         |                   |        | ALT             |                   |        | AST             |                   |        | ALP            |                |                   |        |       | GGT             |                   |        | Total Bile Acid |                   |        |
|------------------------|-----------------|-------------------|--------|------------------|-------------------|--------|-----------------|-------------------|--------|-----------------|-------------------|--------|-----------------|-------------------|--------|----------------|----------------|-------------------|--------|-------|-----------------|-------------------|--------|-----------------|-------------------|--------|
|                        | >ULN<br>(n=144) | Normal<br>(n=863) | p      | >ULN<br>(n=79)   | Normal<br>(n=928) | p      | <LLN<br>(n=296) | Normal<br>(n=711) | p      | >ULN<br>(n=330) | Normal<br>(n=677) | p      | >ULN<br>(n=177) | Normal<br>(n=830) | p      | <LLN<br>(n=38) | >ULN<br>(n=20) | Normal<br>(n=949) | P (L)  | P (U) | >ULN<br>(n=360) | Normal<br>(n=647) | p      | >ULN<br>(n=103) | Normal<br>(n=904) | p      |
| D-dimer (mg/L)         | 2.8             | 1.3               | 0.006  | 5.8              | 1.1               | <0.001 | 3.1             | 0.9               | <0.001 | 1.9             | 1.3               | 0.059  | 3.0             | 1.2               | <0.001 | 0.8            | 5.4            | 1.5               | 0.005  | 0.074 | 2.3             | 1.1               | <0.001 | 1.5             | 1.5               | 0.972  |
| ATIII (%)              | 85.6            | 90.3              | 0.004  | 79.4             | 90.5              | <0.001 | 81.7            | 93.0              | <0.001 | 89.5            | 89.6              | 0.868  | 85.3            | 90.5              | <0.001 | 85.9           | 86.6           | 89.8              | 0.077  | 0.364 | 88.6            | 90.2              | 0.114  | 86.5            | 89.9              | 0.028  |
| FDP (ug/ml)            | 15.9            | 5.4               | 0.006  | 35.0             | 4.4               | <0.001 | 14.2            | 3.9               | <0.001 | 8.8             | 6.0               | 0.132  | 14.7            | 5.3               | 0.002  | 3.0            | 31.1           | 6.7               | 0.303  | 0.129 | 12.1            | 3.9               | <0.001 | 7.5             | 6.9               | 0.836  |
| INR                    | 1.1             | 1.0               | 0.001  | 1.2              | 1.0               | <0.001 | 1.1             | 1.0               | <0.001 | 1.1             | 1.0               | 0.171  | 1.1             | 1.0               | 0.002  | 1.0            | 1.2            | 1.0               | 0.648  | 0.103 | 1.1             | 1.0               | 0.014  | 1.1             | 1.0               | 0.425  |
| FIB (g/L)              | 4.1             | 4.1               | 0.626  | 4.4              | 4.1               | 0.164  | 4.8             | 3.8               | <0.001 | 4.4             | 4.0               | <0.001 | 4.8             | 4.0               | <0.001 | 4.2            | 4.9            | 4.1               | 0.727  | 0.143 | 4.5             | 3.9               | <0.001 | 4.0             | 4.1               | 0.400  |
| TT (s)                 | 17.4            | 17.3              | 0.449  | 18.2             | 17.2              | 0.003  | 17.9            | 17.1              | <0.001 | 17.5            | 17.2              | 0.006  | 17.9            | 17.2              | <0.001 | 17.3           | 17.2           | 17.3              | 0.923  | 0.739 | 17.5            | 17.2              | 0.007  | 17.5            | 17.3              | 0.369  |
| Cystatin C (mg/L)      | 1.3             | 1.2               | 0.132  | 1.4              | 1.2               | 0.007  | 1.4             | 1.1               | <0.001 | 1.2             | 1.2               | 0.965  | 1.4             | 1.1               | 0.004  | 1.0            | 1.7            | 1.2               | 0.061  | 0.189 | 1.3             | 1.1               | 0.001  | 1.2             | 1.2               | 0.271  |
| LDH (U/L)              | 253.2           | 213.8             | 0.004  | 344.3            | 208.9             | <0.001 | 276.4           | 195.6             | <0.001 | 253.3           | 202.9             | <0.001 | 308.6           | 200.5             | <0.001 | 222.5          | 394.4          | 215.8             | 0.654  | 0.006 | 246.9           | 204.3             | <0.001 | 215.1           | 219.9             | 0.638  |
| Creatine Kinase (U/L)  | 121.1           | 107.6             | 0.431  | 185.1            | 103.2             | 0.038  | 117.3           | 106.3             | 0.402  | 150.5           | 89.6              | <0.001 | 229.1           | 84.2              | <0.001 | 128.5          | 87.8           | 109.2             | 0.542  | 0.629 | 117.3           | 105.2             | 0.334  | 106.7           | 109.9             | 0.872  |
| Urea (mmol/L)          | 5.7             | 4.7               | 0.024  | 6.8              | 4.7               | 0.004  | 5.7             | 4.5               | 0.001  | 5.1             | 4.8               | 0.225  | 6.1             | 4.6               | 0.005  | 4.1            | 7.3            | 4.9               | 0.263  | 0.152 | 5.3             | 4.7               | 0.029  | 5.0             | 4.9               | 0.652  |
| Creatinine (μmol/L)    | 82.5            | 79.6              | 0.665  | 81.9             | 79.8              | 0.811  | 83.8            | 78.4              | 0.298  | 79.2            | 80.4              | 0.825  | 89.8            | 77.9              | 0.077  | 69.0           | 133.7          | 79.3              | 0.340  | 0.369 | 88.4            | 75.3              | 0.033  | 82.2            | 79.7              | 0.746  |
| Uric Acid (μmol/L)     | 287.9           | 276.1             | 0.225  | 271.8            | 278.3             | 0.671  | 269.2           | 281.3             | 0.104  | 296.4           | 268.6             | <0.001 | 285.3           | 276.2             | 0.363  | 229.9          | 269.8          | 279.9             | <0.001 | 0.748 | 295.1           | 268.2             | <0.001 | 266.7           | 279.1             | 0.214  |
| Blood Glucose (mmol/L) | 6.5             | 6.2               | 0.271  | 6.6              | 6.2               | 0.333  | 6.6             | 6.1               | 0.010  | 6.4             | 6.1               | 0.110  | 6.7             | 6.1               | 0.016  | 5.5            | 6.3            | 6.3               | <0.001 | 0.906 | 6.6             | 6.0               | 0.001  | 6.5             | 6.2               | 0.373  |
| Total Chol (mmol/L)    | 4.0             | 4.3               | 0.003  | 3.6              | 4.3               | <0.001 | 3.9             | 4.4               | <0.001 | 4.3             | 4.2               | 0.598  | 4.0             | 4.3               | <0.001 | 3.9            | 3.9            | 4.3               | 0.007  | 0.076 | 4.3             | 4.2               | 0.217  | 4.3             | 4.3               | 0.728  |
| Triglyceride (mmol/L)  | 1.3             | 1.5               | <0.001 | 1.2              | 1.5               | 0.016  | 1.4             | 1.6               | 0.005  | 1.6             | 1.4               | 0.003  | 1.5             | 1.5               | 0.562  | 1.3            | 1.5            | 1.5               | 0.196  | 0.870 | 1.7             | 1.4               | <0.001 | 1.5             | 1.5               | 0.883  |
| Troponin I (ng/L)      | 46.4            | 13.7              | 0.231  | 91.4             | 12.6              | 0.135  | 49.3            | 5.0               | 0.040  | 21.3            | 17.4              | 0.785  | 73.9            | 6.9               | 0.076  | 5.4            | 263.9          | 14.5              | 0.757  | 0.269 | 39.0            | 7.4               | 0.090  | 10.1            | 19.7              | 0.658  |
| CK-MB (ng/ml)          | 2.0             | 2.1               | 0.941  | 3.3              | 1.9               | 0.084  | 1.9             | 2.1               | 0.566  | 2.3             | 1.9               | 0.441  | 3.3             | 1.8               | 0.039  | 2.6            | 3.9            | 2.0               | 0.543  | 0.214 | 1.7             | 2.2               | 0.235  | 1.0             | 2.2               | <0.001 |
| Blood CO2 (mmol/L)     | 23.5            | 24.1              | 0.041  | 23.6             | 24.0              | 0.216  | 23.7            | 24.1              | 0.054  | 24.2            | 23.9              | 0.266  | 23.5            | 24.1              | 0.029  | 22.7           | 23.6           | 24.1              | 0.002  | 0.702 | 23.7            | 24.2              | 0.025  | 23.7            | 24.0              | 0.338  |
| LDL Chol (mmol/L)      | 2.2             | 2.3               | 0.015  | 2.1              | 2.3               | 0.005  | 2.2             | 2.3               | 0.002  | 2.3             | 2.3               | 0.136  | 2.1             | 2.3               | 0.001  | 2.0            | 2.0            | 2.3               | 0.001  | 0.100 | 2.4             | 2.2               | 0.004  | 2.2             | 2.3               | 0.486  |
| HDL Chol (mmol/L)      | 1.2             | 1.3               | 0.051  | 1.1              | 1.3               | <0.001 | 1.1             | 1.3               | <0.001 | 1.2             | 1.3               | <0.001 | 1.1             | 1.3               | <0.001 | 1.2            | 1.0            | 1.3               | 0.636  | 0.007 | 1.2             | 1.3               | <0.001 | 1.4             | 1.3               | 0.010  |

\* ULN, Upper Limit of Normal; LLN, Lower Limit of Normal; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; ALP, Alkaline Phosphatase; GGT, Gamma-glutamyl Transferase; LDH, Lactate Dehydrogenase; CK-MB, Creatine Kinase-MB; LDL, Low-density Lipoprotein; HDL, High-density Lipoprotein; WBC, White Blood Cell; RBC, Red Blood Cell; NK, Natural Killer; IL, Interleukin; Chol, Cholesterol.

TABLE 3 Comparison of the unenhanced CT features of multiple organs of adult COVID-19 patients between the abnormal and normal serum hepatic injury markers index groups.

| Variables              | Total Bilirubin |                |       | Direct Bilirubin |                |       | Albumin      |                |        | ALT          |                |        | AST          |                |        | ALP         |             |                | GGT    |       |              | Total Bile Acid |        |              |                |       |
|------------------------|-----------------|----------------|-------|------------------|----------------|-------|--------------|----------------|--------|--------------|----------------|--------|--------------|----------------|--------|-------------|-------------|----------------|--------|-------|--------------|-----------------|--------|--------------|----------------|-------|
|                        | >ULN (n=144)    | Normal (n=863) | P     | >ULN (n=79)      | Normal (n=928) | P     | <LLN (n=296) | Normal (n=711) | P      | >ULN (n=330) | Normal (n=677) | P      | >ULN (n=177) | Normal (n=830) | P      | <LLN (n=38) | >ULN (n=20) | Normal (n=949) | P (L)  | P (U) | >ULN (n=360) | Normal (n=647)  | P      | >ULN (n=103) | Normal (n=904) | P     |
| MCTV of Heart (HU)     | 42.4            | 42.7           | 0.652 | 41.3             | 42.7           | 0.039 | 41.8         | 42.9           | 0.003  | 43.3         | 42.3           | 0.014  | 42.1         | 42.7           | 0.207  | 42.1        | 40.7        | 42.7           | 0.554  | 0.143 | 42.6         | 42.6            | 0.949  | 42.0         | 42.7           | 0.215 |
| MCTV of Liver (HU)     | 55.9            | 58.0           | 0.006 | 54.4             | 58.0           | 0.001 | 56.9         | 58.0           | 0.034  | 55.8         | 58.7           | <0.001 | 54.6         | 58.3           | <0.001 | 60.3        | 54.7        | 57.7           | 0.063  | 0.156 | 55.2         | 59.1            | <0.001 | 57.8         | 57.7           | 0.904 |
| < 40 HU                | 4               | 31             | 0.57  | 5                | 30             | 0.093 | 7            | 28             | 0.001  | 17           | 18             | 0.018  | 9            | 26             | 0.001  | 1           | 1           | 33             | 0.974  | 0.817 | 18           | 17              | <0.001 | 2            | 33             | 0.432 |
| 40-65 HU               | 116             | 659            |       | 60               | 715            |       | 246          | 529            |        | 261          | 514            |        | 144          | 631            |        | 30          | 14          | 731            |        |       | 297          | 478             |        | 85           | 690            |       |
| 65-70 HU               | 15              | 125            |       | 7                | 133            |       | 25           | 115            |        | 35           | 105            |        | 11           | 129            |        | 6           | 2           | 132            |        |       | 30           | 110             |        | 10           | 130            |       |
| >70 HU                 | 5               | 28             |       | 0                | 33             |       | 4            | 29             |        | 7            | 26             |        | 1            | 32             |        | 1           | 0           | 32             |        |       | 3            | 30              |        | 3            | 30             |       |
| MCTV of Spleen (HU)    | 47.1            | 47.1           | 0.984 | 48.5             | 47.0           | 0.125 | 47.0         | 47.2           | 0.594  | 47.6         | 46.9           | 0.048  | 47.1         | 47.1           | 0.936  | 46.2        | 45.7        | 47.2           | 0.268  | 0.249 | 46.8         | 47.3            | 0.216  | 46.0         | 47.2           | 0.024 |
| Liver to Spleen Ratio  | 1.21            | 1.24           | 0.099 | 1.15             | 1.25           | 0.001 | 1.23         | 1.24           | 0.313  | 1.18         | 1.27           | <0.001 | 1.17         | 1.25           | <0.001 | 1.31        | 1.21        | 1.24           | 0.037  | 0.653 | 1.19         | 1.26            | <0.001 | 1.28         | 1.23           | 0.074 |
| < 1.0                  | 19              | 90             | 0.552 | 16               | 93             | 0.004 | 30           | 79             | 0.647  | 54           | 55             | <0.001 | 23           | 86             | 0.143  | 1           | 3           | 105            | 0.242  | 0.659 | 60           | 49              | <0.001 | 4            | 105            | 0.061 |
| 1.0-1.5                | 107             | 671            |       | 53               | 725            |       | 227          | 551            |        | 242          | 536            |        | 130          | 648            |        | 33          | 12          | 733            |        |       | 262          | 516             |        | 85           | 693            |       |
| > 1.5                  | 12              | 81             |       | 3                | 90             |       | 23           | 70             |        | 23           | 70             |        | 10           | 83             |        | 4           | 2           | 87             |        |       | 23           | 70              |        | 10           | 83             |       |
| MCTV of Abd Aorta(HU)  | 40.4            | 39.9           | 0.356 | 40.8             | 39.9           | 0.242 | 39.1         | 40.4           | 0.003  | 40.0         | 40.0           | 0.952  | 39.9         | 40.0           | 0.819  | 40.2        | 38.5        | 40.0           | 0.892  | 0.295 | 39.9         | 40.1            | 0.576  | 39.1         | 40.1           | 0.110 |
| MCTV of Pancreas (HU)  | 38.3            | 39.3           | 0.173 | 36.8             | 39.4           | 0.010 | 37.1         | 40.0           | <0.001 | 39.0         | 39.3           | 0.678  | 37.6         | 39.5           | 0.008  | 40.4        | 41.0        | 39.1           | 0.367  | 0.369 | 38.4         | 39.6            | 0.026  | 38.2         | 39.3           | 0.220 |
| MCTV of L-Kidney(HU)   | 28.4            | 28.9           | 0.191 | 28.3             | 28.8           | 0.437 | 28.2         | 29.0           | 0.008  | 28.8         | 28.8           | 0.794  | 28.3         | 28.9           | 0.097  | 29.7        | 27.5        | 28.8           | 0.164  | 0.231 | 28.6         | 28.9            | 0.174  | 28.7         | 28.8           | 0.747 |
| MCTV of R-Kidney(HU)   | 29.1            | 29.6           | 0.202 | 28.8             | 29.6           | 0.121 | 29.1         | 29.7           | 0.036  | 29.6         | 29.5           | 0.474  | 29.1         | 29.6           | 0.155  | 30.2        | 28.6        | 29.5           | 0.256  | 0.402 | 29.4         | 29.6            | 0.489  | 29.2         | 29.6           | 0.331 |
| Ant Tho Diameter (cm)  | 22.0            | 21.9           | 0.426 | 22.2             | 21.9           | 0.259 | 22.2         | 21.8           | 0.008  | 22.5         | 21.6           | <0.001 | 22.3         | 21.8           | 0.009  | 20.8        | 21.5        | 22.0           | <0.001 | 0.337 | 22.6         | 21.6            | <0.001 | 22.1         | 21.9           | 0.469 |
| Tra Tho Diameter (cm)  | 30.6            | 31.0           | 0.153 | 30.7             | 30.9           | 0.407 | 30.4         | 31.1           | <0.001 | 31.3         | 30.7           | 0.001  | 31.0         | 30.9           | 0.641  | 30.4        | 30.3        | 30.9           | 0.241  | 0.325 | 31.4         | 30.6            | <0.001 | 30.5         | 31.0           | 0.104 |
| Ant/Tra (Tho)          | 0.72            | 0.71           | 0.030 | 0.73             | 0.71           | 0.041 | 0.73         | 0.70           | <0.001 | 0.72         | 0.71           | <0.001 | 0.72         | 0.71           | 0.028  | 0.68        | 0.71        | 0.71           | 0.010  | 0.849 | 0.72         | 0.71            | 0.001  | 0.73         | 0.71           | 0.010 |
| Ant+Tra (Tho) (cm)     | 52.6            | 52.8           | 0.660 | 52.8             | 52.8           | 0.939 | 52.5         | 52.9           | 0.165  | 53.8         | 52.3           | <0.001 | 53.1         | 52.7           | 0.266  | 50.5        | 51.8        | 52.9           | <0.001 | 0.262 | 53.9         | 52.2            | <0.001 | 52.5         | 52.8           | 0.539 |
| Ant Abd Diameter (cm)  | 22.5            | 22.3           | 0.637 | 22.8             | 22.3           | 0.165 | 22.5         | 22.3           | 0.389  | 23.5         | 21.8           | <0.001 | 23.1         | 22.2           | <0.001 | 20.7        | 21.8        | 22.4           | <0.001 | 0.396 | 23.6         | 21.7            | <0.001 | 22.5         | 22.3           | 0.589 |
| Tra Abd Diameter (cm)  | 29.9            | 29.7           | 0.593 | 30.2             | 29.7           | 0.128 | 30.0         | 29.7           | 0.080  | 30.6         | 29.4           | <0.001 | 30.4         | 29.6           | 0.001  | 28.7        | 30.2        | 29.8           | 0.014  | 0.558 | 30.7         | 29.2            | <0.001 | 29.7         | 29.8           | 0.809 |
| Ant/Tra (Abd)          | 0.75            | 0.75           | 0.828 | 0.75             | 0.75           | 0.567 | 0.75         | 0.75           | 0.577  | 0.77         | 0.74           | <0.001 | 0.76         | 0.75           | 0.018  | 0.72        | 0.72        | 0.75           | 0.001  | 0.032 | 0.77         | 0.74            | <0.001 | 0.76         | 0.75           | 0.187 |
| Ant+Tra (Abd) (cm)     | 52.3            | 52.1           | 0.600 | 53.0             | 52.1           | 0.129 | 52.5         | 52.0           | 0.180  | 54.1         | 51.2           | <0.001 | 53.6         | 51.8           | <0.001 | 49.4        | 52.0        | 52.2           | 0.001  | 0.859 | 54.3         | 50.9            | <0.001 | 52.2         | 52.1           | 0.857 |
| Tho+Abd (Ant+Tra) (cm) | 105.0           | 104.9          | 0.918 | 105.9            | 104.8          | 0.360 | 105.0        | 104.9          | 0.889  | 107.9        | 103.5          | <0.001 | 106.7        | 104.6          | 0.007  | 99.9        | 103.8       | 105.2          | 0.001  | 0.542 | 108.2        | 103.1           | <0.001 | 104.8        | 104.9          | 0.859 |
| Abd/Tho (Ant+Tra)      | 0.99            | 0.99           | 0.236 | 1.00             | 0.99           | 0.026 | 1.00         | 0.98           | <0.001 | 1.01         | 0.98           | <0.001 | 1.01         | 0.98           | <0.001 | 1.00        | 1.00        | 0.99           | 0.770  | 0.160 | 1.01         | 0.98            | <0.001 | 0.99         | 0.99           | 0.329 |

(Continued)

TABLE 3 Continued

| Variables                               | Total Bilirubin |                |        | Direct Bilirubin |                |        | Albumin      |                |        | ALT          |                |       | AST          |                |        | ALP         |             |                | GGT   |       |              | Total Bile Acid |        |              |                |       |
|---|-----------------|----------------|--------|------------------|----------------|--------|--------------|----------------|--------|--------------|----------------|-------|--------------|----------------|--------|-------------|-------------|----------------|-------|-------|--------------|-----------------|--------|--------------|----------------|-------|
|   | >ULN (n=144)    | Normal (n=863) | P      | >ULN (n=79)      | Normal (n=928) | P      | <LLN (n=296) | Normal (n=711) | P      | >ULN (n=530) | Normal (n=677) | P     | >ULN (n=177) | Normal (n=830) | P      | <LLN (n=38) | >ULN (n=20) | Normal (n=949) | P (U) | P (L) | >ULN (n=360) | Normal (n=647)  | P      | >ULN (n=103) | Normal (n=904) | P     |
| Fat Thickness (mm)                      | 15.4            | 17.3           | 0.002  | 13.6             | 17.3           | <0.001 | 14.7         | 17.9           | <0.001 | 16.7         | 17.1           | 0.322 | 15.9         | 17.2           | 0.020  | 16.8        | 12.3        | 17.1           | 0.003 | 0.819 | 16.5         | 17.3            | 0.082  | 16.9         | 17.0           | 0.863 |
| Fat Thickness*10/Tho Diameter (Ant+Tra) | 0.29            | 0.32           | 0.001  | 0.25             | 0.32           | <0.001 | 0.28         | 0.34           | <0.001 | 0.31         | 0.32           | 0.054 | 0.30         | 0.32           | 0.005  | 0.33        | 0.24        | 0.32           | 0.003 | 0.546 | 0.30         | 0.33            | 0.001  | 0.32         | 0.32           | 0.893 |
| Fat Thickness*10/Abd Diameter (Ant+Tra) | 0.29            | 0.33           | <0.001 | 0.25             | 0.33           | <0.001 | 0.28         | 0.34           | <0.001 | 0.31         | 0.33           | 0.002 | 0.30         | 0.33           | <0.001 | 0.34        | 0.24        | 0.33           | 0.003 | 0.546 | 0.30         | 0.34            | <0.001 | 0.32         | 0.33           | 0.768 |
| Fat Thickness*10/Tho:Abd (Ant+Tra)      | 0.15            | 0.16           | 0.001  | 0.13             | 0.16           | <0.001 | 0.14         | 0.17           | <0.001 | 0.15         | 0.16           | 0.008 | 0.15         | 0.16           | 0.002  | 0.17        | 0.12        | 0.16           | 0.003 | 0.576 | 0.15         | 0.17            | <0.001 | 0.16         | 0.16           | 0.832 |

\* ULN, Upper Limit of Normal; LLN, Lower Limit of Normal; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; ALP, Alkaline Phosphatase; GGT, Gamma-glutamyl Transferase; MCTV, Mean CT Value; Abd, Abdominal; Tho, Thoracic; Ant, Anteroposterior; Tra, Transverse.

# Fat Thickness represents abdominal subcutaneous fat thickness (Measured on the slice of the superior mesenteric artery originated from the abdominal aorta and at the midline of the abdomen).

for HBV DNA in this study, the number of patients positive only for HBcAb who were in the active stage of HBV infection is unknown.

The univariate analysis showed that the mean values of multiple blood variables differed between the abnormal and normal hepatic injury markers index groups. However, binary regression analysis indicated that the main factors related to most of the abnormal serum hepatic injury markers indexes were FIB and LDH. Effenberger suggested that COVID-19 patients with elevated AST exhibit significantly elevated LDH and that systemic inflammation could drive hepatic injury in COVID-19 patients (Effenberger et al., 2021). Tsutsumi and colleagues proposed that an elevated D-dimer level is independently associated with ALT elevation and that liver dysfunction in COVID-19 patients might be induced by microvascular thrombosis (Tsutsumi et al., 2021). However, in a mouse model, intravascular fibrinogen was measured following acute liver injury (Poole et al., 2021).

We found that the MCTVs of the liver and pancreas were independently related to most of the abnormal serum hepatic injury markers in adult COVID-19 patients. The liver density and pancreas density were reduced (with reduced MCTVs of the liver and pancreas) in adult COVID-19 patients with abnormal hepatic injury markers in our study. Many other clinical or experimental studies have confirmed the correlation between fat deposition in the liver and fat deposition in the pancreas (Cohen et al., 2018; Taylor et al., 2018; Aliyari Ghasabeh et al., 2020; Chiyanika et al., 2020). It is unclear whether the liver dysfunction in COVID-19 is due to acute diffuse liver injury caused by SARS-CoV-2 or to acute diffuse liver injury caused by previous fatty infiltration. Research has shown that abdominal subcutaneous fat thickness is a reliable indicator of the severity of liver disease in obese nondiabetic individuals (Hegazy et al., 2019). Our study showed that although the subcutaneous fat thickness was reduced in adult COVID-19 patients with abnormal hepatic injury markers indexes, it was not an independent risk factor for abnormal hepatic injury markers indicators. This result may be attributable to the fact that few patients were obese in our study. Notably, researchers have shown that the mean body mass index of Chinese people is much lower than that of people in the Western world (Pang et al., 2020). However, our results demonstrated that the ratio of subcutaneous fat thickness to the sum of the transverse and anteroposterior abdominal diameters on the unenhanced CT scan was independently associated with most of the abnormal serum hepatic injury markers.

There were some limitations in this study. First, this was a retrospective study from a single center with a moderate number of subjects. Second, a portion of the included patients had a history of HBV infection, but very few patients tested positive for HBV DNA in the blood. In addition, the anti-HBV treatments were unknown. The results may be different from those of studies that have included patients with hepatitis C virus infection (Krist et al., 2020; Owens et al., 2020). Third, it was unclear whether any of the included patients had a history of alcoholic or non-alcoholic fatty liver disease. Fourth, due to the immune response caused by SARS-CoV-2 infection, immunoglobulin was produced in most patients, resulting in serum total protein levels in the normal range in most patients. Therefore, we

did not specifically analyze the characteristics of total protein and the ratio of albumin to globulin. Fifth, because most of the patients did not undergo scanning of the lower abdomen on CT examination, we measured the subcutaneous fat thickness and abdominal transverse and anteroposterior diameters in the plane of the superior mesenteric artery originating from the abdominal aorta using PACS software. Sixth, we did not record the patients' abdominal circumference data, and it is difficult to measure this variable with PACS software. The sum of the abdominal transverse and anteroposterior diameters may not adequately represent the abdominal circumference. Seventh, Given the observational nature of our study, the proposed relationships between abdominal fat distribution, organ density, and hepatic injury markers should be interpreted as associative rather than causal. Future prospective imaging–pathology correlation studies and mechanistic investigations are warranted to validate these hypotheses and clarify the biological pathways involved. Finally, the drugs and duration of anti-SARS-CoV-2 treatments before admission were not detailed. Antiviral drugs may cause damage to human hepatocytes, leading to abnormal serum hepatic injury markers; this possibility needs to be studied further.

## 5 Conclusions

In conclusion, sex, age, HBV infection, serum FIB content, blood LDH concentration, liver and pancreas MCTVs and the ratio of abdominal subcutaneous fat thickness to the sum of the transverse and anteroposterior abdominal diameters were independently correlated with abnormalities in many serum hepatic injury markers in adult COVID-19 patients. We look forward to prospective multicenter studies and experimental studies that will confirm the results.

## Data availability statement

The original contributions presented in the study are included in the article/[Supplementary Material](#). Further inquiries can be directed to the corresponding author.

## Ethics statement

Research protocols were approved by the ethics committee of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology. The present study was conducted following the Declaration of Helsinki. In this academic center, all patients or their legal guardians are initially explained that their information and possible samples will be anonymously collected and reviewed and reported in educational and research projects. The patients who give written consent to this issue will be included in the mentioned studies (like our study). Patients are allowed to freely choose whether or not their data be used in an anonymized database. This is also stated in the ethics committee approval. Informed consent was obtained from all the patients and/or their legal guardian(s) for this study.

## Author contributions

SZ: Conceptualization, Software, Writing – original draft, Investigation, Funding acquisition, Visualization, Resources, Writing – review & editing, Formal analysis, Methodology, Validation, Project administration, Data curation, Supervision. YH: Writing – review & editing, Visualization, Conceptualization, Supervision, Software, Investigation, Methodology, Resources, Funding acquisition, Project administration, Formal analysis, Writing – original draft, Data curation, Validation. LL: Validation, Visualization, Resources, Formal analysis, Data curation, Conceptualization, Project administration, Writing – review & editing, Methodology, Funding acquisition, Supervision, Investigation, Writing – original draft, Software. XN: Methodology, Data curation, Project administration, Visualization, Conceptualization, Software, Writing – original draft, Validation, Funding acquisition, Writing – review & editing, Investigation, Supervision, Formal analysis, Resources. QL: Supervision, Investigation, Writing – review & editing, Funding acquisition, Resources, Writing – original draft, Software, Project administration, Validation, Methodology, Visualization, Conceptualization, Formal analysis, Data curation. GX: Software, Funding acquisition, Conceptualization, Visualization, Writing – review & editing, Resources, Writing – original draft, Investigation, Formal analysis, Validation, Project administration, Supervision, Data curation, Methodology.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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