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**Supplementary Data**

**Inactivated SARS-CoV-2 booster vaccine enhanced immune responses in patients with chronic liver diseases**

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**Supplementary methodology**

For total anti-SARS-CoV-2 antibodies, specific total antibodies (including IgM, IgG and IgA) targeted the receptor binding domain (RBD) region of S1 subunit (antigen) were detected. The RBD constitutes about 33% of the S1 subunit and no epitopes could be recognized by cross-reactivity outside this domain. When performing total anti-SARS-CoV-2 detection, three wells of negative control, two wells of positive control and one well of blank control on each plate were set up. According to the manufacturer’s instruction, the coincidence rate of the positive reference materials was 5/5, and negative reference materials was 20/20, coefficient of variation (CV) ≤ 15%. An evaluation of nine commercial SARS-CoV-2 immunoassays from Denmark has suggested that the Wantai total antibody kit (Beijing Wantai Biological Pharmacy Enterprise Co.,Ltd., China) had the best detection performance with the area under curve (AUC) of 0.973 (95% CI: 0.921–1.000), sensitivity of 93% (28/30), specificity of 100% (82/82), positive predictive value (PPV) of 100% (28/28) and negative predictive value (NPV) of 98% (82/84). This study also identified the Wantai total antibodies test had a sensitivity of 71% in the early phase that plateaued at 100% after 10 days of illness duration (Lassaunière et al., 2020). According to the manufacturer’s instruction, this kit exhibited a sensitivity of 69.91% (79/113) within 7 days of SARS-CoV-2 infection, 93.67% (148/158) in the second week (8–14 days), and 99.49% (196/197) after two weeks (≥ 15 days) of disease duration. In addition, there were no cross-reactivity between the RBD of SARS-CoV-2 and other β-coronaviruses (hCoV-OC43 and hCoV-HKU1). During the experimental operation, the optical density (OD) value of the negative control and positive control well was less than 0.10 and greater than 0.19, respectively, otherwise the test was invalid. If the OD value of one negative control well is greater than 0.10, it was discarded. If the OD value of two or more negative control wells were greater than 0.10, the experiment would be repeated.

For neutralizing antibody (NAb), the surrogate neutralization test (sVNT) in detecting NAb against SARS-CoV-2 prototype and Omicron BA.4/5 is similar, which could detect circulating NAbs against SARS-CoV-2 that block the interactions between the RBD of viral spike glycoprotein with the angiotensin-converting enzyme 2 (ACE2) cell surface receptor. The SARS-CoV-2 sVNT Kit (GenScript cPass™ SARS-CoV-2 Neutralization Antibody Detection Kit, USA) is a blocking ELISA detection tool, which mimics the virus neutralization process. The kit contains two key components: the horseradish peroxidase (HRP) conjugated recombinant SARS-CoV-2 RBD fragment (HRP-RBD) and the human ACE2 receptor protein (hACE2). The protein-protein interaction between HRP-RBD and hACE2 can be blocked by neutralizing antibodies against SARS-CoV-2 RBD. For kit design, the ELISA coat was coated with invariable hACE2 protein, the only difference in detecting NAbs targeting SARS-CoV-2 prototype and Omicron sublineage BA.4/5 is the sequence of RBD conjugated with HRP.

When performing detection, two wells of negative control and two wells of positive control on each plate were set up. To assure the validity of the results, the OD450 values of positive (> 1.0) and negative controls (< 0.3) must fall within the ranges. The inhibition rate of NAb was calculated according to the formula: inhibition rate = (1 − OD value of sample/OD value of negative control) × 100%. Samples with inhibition rates above or equal to 30% were considered positive. The cutoff value is based on validation with manufacture’s panel of confirmed COVID-19 patient serum and healthy control serum. According to the manufacture’s instruction, the intra-assay variation of this kit is ≤ 10%, while the inter-assay variation is ≤ 15%; as for clinical performance, this kit showed a sensitivity of 100% (26/26) and specificity of 100% (88/88) when comparing with the comparator plaque reduction neutralization test. A study from Switzerland (Meyer et al., 2020) had reported a high specificity of 99.2% and an overall sensitivity of 80.3% (cut off: inhibition rate of 20%) for the sVNT in determining 269 PCR-confirmed COVID-19 patients and 259 pre-pandemic samples when comparing with cell-based neutralization assays. Another study from Singapore (Tan et al., 2020) has also identified a sensitivity (95%−100%) and specificity (99.93%) (cut off: inhibition rate of 30%), which both showed the outstanding validity in measuring the neutralization capacity of anti-SARS-CoV-2 antibodies directed against RBD.

**Supplementary Table S1** The statistical analysis for comparison between different groups in demographic and clinical characteristics.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Characteristics | *P* valuea | *P* valueb | *P* valuec | *P* valued | *P* valuee | *P* valuef |
| Age (year) | 0.060 | 0.750 | 0.948 | 0.129 | 0.011 | 0.647 |
| Male/female | 0.547 | 0.781 | > 0.999 | 0.263 | 0.356 | 0.567 |
| Type of CLD, n (%) |  |  |  |  |  |  |
| Hepatitis B | 0.768 | 0.302 | 0.114 | 0.787 | 0.480 | 0.710 |
| Hepatitis C | > 0.999 | > 0.999 | > 0.999 | > 0.999 | > 0.999 | > 0.999 |
| Cirrhosis | > 0.999 | 0.764 | > 0.999 | > 0.999 | > 0.999 | 0.522 |
| Other | 0.497 | 0.089 | 0.015 | 0.449 | 0.267 | > 0.999 |
| Treatments, n (%) | > 0.999 | > 0.999 | 0.581 | 0.766 | 0.394 | 0.503 |
| Antiviral treatmentd, n (%) | > 0.999 | 0.781 | 0.815 | 0.577 | 0.627 | > 0.999 |
| Chinese patent medicinese, n (%) | 0.217 | > 0.999 | 0.402 | 0.161 | 0.009 | 0.253 |
| Hepatitis B parameters, n (%) | | | | | | |
| HBsAg (IU/mL) | 0.707 | 0.530 | 0.415 | 0.983 | 0.430 | 0.563 |
| HBsAg (+), n (%) | 0.075 | 0.192 | 0.131 | 0.433 | 0.263 | 0.857 |
| HBsAg (mIU/mL) | 0.269 | 0.037 | 0.052 | 0.229 | 0.528 | 0.288 |
| HBsAb (+), n (%) | 0.223 | > 0.999 | > 0.999 | 0.548 | 0.265 | > 0.999 |
| HBeAg (+), n (%) | 0.276 | 0.339 | 0.771 | 0.766 | 0.379 | 0.486 |
| HBeAb (+), n (%) | 0.755 | > 0.999 | 0.622 | 0.577 | 0.300 | 0.679 |
| HBcAb (+), n (%) | 0.139 | 0.794 | 0.659 | 0.180 | 0.112 | 0.856 |
| HBV DNA (+), n (%) | 0.066 | 0.462 | 0.257 | 0.343 | 0.261 | 0.577 |
| Liver function parameters |  |  |  |  |  |  |
| Alanine aminotransferase (U/L) | 0.296 | 0.663 | 0.649 | 0.320 | 0.189 | 0.931 |
| Aspartate aminotransferase (U/L) | 0.791 | 0.573 | 0.695 | 0.166 | 0.265 | 0.671 |
| γ-glutamyl transferas (U/L) | 0.890 | 0.045 | 0.303 | 0.057 | 0.342 | 0.090 |
| Alkaline phosphatase (U/L) | 0.521 | 0.412 | 0.969 | 0.050 | 0.446 | 0.087 |
| Total bilirubin (μmol/L) | 0.870 | 0.228 | 0.979 | 0.466 | 0.722 | 0.181 |
| Direct bilirubin (μmol/L) | 0.696 | 0.467 | 0.728 | 0.724 | 0.363 | 0.121 |
| Total biliary acid (μmol/L) | 0.491 | 0.320 | 0.541 | 0.672 | 0.914 | 0.406 |
| Total protein (g/L) | 0.054 | 0.238 | 0.022 | 0.136 | 0.533 | 0.183 |
| Albumin (g/L) | 0.080 | 0.209 | 0.032 | 0.564 | 0.926 | 0.383 |
| Prealbumin (mg/L) | 0.735 | 0.761 | 0.451 | 0.950 | 0.185 | 0.160 |
| Lactate dehydrogenase (U/L) | 0.616 | 0.814 | 0.462 | 0.636 | 0.878 | 0.531 |
| Cholinesterase (U/L) | 0.426 | 0.851 | 0.669 | 0.341 | 0.362 | 0.655 |
| Blood cell counts |  |  |  |  |  |  |
| White blood cells (×109/L) | 0.239 | 0.138 | 0.284 | 0.849 | 0.622 | 0.376 |
| Lymphocytes (×109/L) | 0.464 | 0.219 | 0.383 | 0.405 | 0.844 | 0.391 |

Statistical analysis was performed by *t*-test, Wilcoxon rank sum test, or χ2 test.

aThe comparison between 2nd dose after > 180 days group and 3rd dose after < 120 days group.

bThe comparison between 2nd dose after > 180 days group and 3rd dose after 121–180 days group.

cThe comparison between 2nd dose after > 180 days group and 3rd dose after > 180 days group.

dThe comparison between 3rd dose after < 120 days group and 3rd dose after 121–180 days group.

eThe comparison between 3rd dose after < 120 days group and 3rd dose after > 180 days group.

fThe comparison between 2nd dose after 121–180 days group and 3rd dose after > 180 days group.

CLD, chronic liver disease; HBsAg, hepatitis B surface antigen; HBsAb, hepatitis B surface antibody; HBeAg, hepatitis B envelope antigen; HBeAb, hepatitis B envelope antibody; HBcAb, hepatitis B core antibody.

**Supplementary Table S2** Demographic characteristics of patients with CLD and HCs.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Total participants | Above 180 days after the second dose | Below 120 days after booster dose | 121–180 days after booster dose | Above 180 days after booster dose |
| Number, n | | | | | |
| CLD | 237 | 24 | 22 | 38 | 153 |
| HC | 170 | 17 | 22 | 34 | 97 |
| Age (years) | | | | | |
| CLD | 48.00 (38.00, 56.00) | 47.00 (40.00, 61.75) | 41.32 (10.81) | 46.84 (14.64) | 49.00 (39.50, 56.00) |
| HC | 44.00 (36.00, 61.00) | 37.00 (30.50, 51.50) | 41.23 (10.35) | 48.09 (13.64) | 48.00 (36.00, 63.00) |
| *P* value | 0.789 | 0.108 | 0.977 | 0.711 | 0.384 |
| Male/female | | | | | |
| CLD | 154/83 | 16/8 | 12/10 | 27/11 | 99/45 |
| HC | 94/76 | 10/7 | 13/9 | 22/12 | 49/48 |
| *P* value | 0.048\* | 0.608 | 0.761 | 0.564 | 0.026\* |
| Days after vaccination | | | | | |
| CLD | 176.50 (219.00, 244.00) | 370.70 (53.47) | 97.50 (58.25, 107.30) | 152.2 (14.41) | 213.00 (223.00, 245.50) |
| HC | 146.00 (210.00, 266.00) | 382.10 (82.46) | 51.25 (105.00, 117.00) | 149.4 (17.16) | 210.80 (230.00, 269.30) |
| *P* value | 0.318 | 0.860 | 0.291 | 0.454 | 0.113 |

Statistical analysis was performed by *t*-test, Wilcoxon rank sum test, or χ2 test.

\**P* < 0.05.

Normally distributed data are shown as mean (standard deviation), non-normally distributed data are shown as median (Q1, Q3).

CLD, chronic liver disease; HCs, healthy controls.

**Supplementary Table S3** The levels of four anti-SARS-CoV-2 antibodies between CLD patients and HCs.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Total participants | Above 180 days after the second dose | Below 120 days after booster dose | 121–180 days after booster dose | Above 180 days after booster dose |
| Total anti-SARS-CoV-2 antibodies, (OD/450nm) | | | | | |
| CLD | 3.13 (3.00, 3.19) | 1.00 (0.47, 2.91) | 3.11 (3.05, 3,19) | 3.11 (3.05, 3.14) | 3.16 (3.06, 3.21) |
| HC | 3.21 (3.07, 3.28) | 2.99 (1.70, 3.19) | 3.11 (3.05, 3.17) | 3.19 (3.05, 3.23) | 3.24 (3.16, 3.33) |
| *P* value | < 0.001\*\*\* | 0.060 | 0.830 | 0.007\*\* | < 0.001\*\*\* |
| The positive rate of total anti-SARS-CoV-2 antibodies, n (%) | | | | | |
| CLD | 226 (95.36) | 19 (79.17) | 20 (90.91) | 36 (94.74) | 151(98.69) |
| HC | 164 (96.47) | 15 (88.24) | 22 (100.00) | 32 (94.12) | 95 (97.94) |
| *P* value | 0.580 | 0.488 | > 0.999 | 0.643 | 0.619 |
| Anti-RBD IgG antibodies, (BAU/mL) | | | | | |
| CLD | 104.30 (28.05, 305.50) | 0.00 (0.00, 28.65) | 321.6 (136.5, 595.5) | 119.30 (56.67, 463.70) | 107.10 (34.97, 242.10) |
| HC | 299.40 (111.80, 597.50) | 58.08 (0.00, 118.60) | 431 (181.9, 602.8) | 452.30 (206.80, 601.70) | 266.20 (106.40, 554.50) |
| *P* value | < 0.001\*\*\* | 0.011\* | 0.012\* | 0.028\* | < 0.001\*\*\* |
| The positive rate of anti-RBD IgG antibodies, n (%) | | | | | |
| CLD | 200 (87.34) | 10 (43.48) | 20 (90.91) | 33 (91.67) | 137 (92.57) |
| HC | 165 (93.75) | 12 (70.59) | 22 (100.00) | 33 (97.06) | 92 (94.85) |
| *P* value | 0.032\* | 0.088 | 0.488 | 0.615 | 0.480 |
| Neutralizing antibody against SARS-CoV-2 prototype, (inhibition rate, %) | | | | | |
| CLD | 23.42 (8.00, 52.48) | 5.89 (0.00, 10.77) | 49.37 (14.99, 89.46) | 26.32 (4.17, 57.45) | 25.17 (9.04, 48.80) |
| HC | 52.98 (20.68, 87.84) | 4.53 (1.70, 11.71) | 90.23 (59.00, 97.22) | 68.48 (37.04, 89.54) | 49.17 (21.23, 84.30) |
| *P* value | <0.001\*\*\* | 0.797 | 0.009\*\* | 0.006\*\* | <0.001\*\*\* |
| The positive rate of neutralizing antibody against SARS-CoV-2 prototype, n (%) | | | | | |
| CLD | 98 (41.35) | 1 (4.17) | 16 (72.73) | 17 (44.74) | 64 (41.83) |
| HC | 113 (66.47) | 0 (0.00) | 22 (100.00) | 27 (79.41) | 64 (65.98) |
| *P* value | < 0.001\*\*\* | > 0.999 | 0.021\* | 0.003\*\* | < 0.001\*\*\* |
| Neutralizing antibody against SARS-CoV-2 BA.4/5, (inhibition rate, %) | | | | | |
| CLD | 3.15 (0.00, 10.84) | 0.00 (0.00, 0.05) | 11.08 (3.44, 29.63) | 6.01 (0.53, 6.01) | 3.63 (0.00, 10.42) |
| HC | 9.96 (4.22, 22.01) | 3.82 (1.61, 5.35) | 23.84 (15.70, 47.91) | 14.11 (5.98, 23.04) | 8.82 (4.19, 20.03) |
| *P* value | < 0.001\*\*\* | < 0.001\*\*\* | 0.033\* | 0.035\* | < 0.001\*\*\* |
| The positive rate of neutralizing antibody against SARS-CoV-2 BA.4/5, n (%) | | | | | |
| CLD | 11 (4.64) | 0 (0.00) | 5 (22.73) | 3 (7.89 ) | 3 (1.96) |
| HC | 24 (14.12) | 0 (0.00) | 7 (31.82) | 2 (5.88) | 15 (15.46) |
| *P* value | < 0.001\*\*\* | > 0.999 | 0.736 | > 0.999 | < 0.001\*\*\* |

Statistical analysis was performed by Wilcoxon rank sum test and χ2 test.

\*\*\**P* < 0.001, \*\**P* < 0.01, \**P* < 0.05.

Normally distributed data are shown as mean (standard deviation), non-normally distributed data are shown as median (Q1, Q3).

CLD, chronic liver disease; HCs, healthy controls; NAbs-prototype, neutralizing antibodies against SARS-CoV-2 prototype; NAbs-BA.4/5, neutralizing antibodies against SARS-CoV-2 BA.4/5; RBD, receptor binding domain.

**Supplementary Table S4** Differences in the inhibition and positive rates of NAbs-prototype and NAbs-BA.4/5 in CLD subgroups.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Total participants | Above 180 days after the second dose | Below120 days after booster dose | 121–180 days after booster dose | Above 180 days after booster dose |
| The inhibition rate of NAbs in patients with CLD, (%) | | | | | |
| NAbs-prototype | 23.42 (8.00, 52.48) | 5.89 (0.00, 10.77) | 49.37 (14.99, 89.46) | 26.32 (4.17, 57.45) | 25.17 (9.04, 48.80) |
| NAbs-BA.4/5 | 3.15 (0.00, 10.84) | 0.00 (0.00, 0.05) | 11.08 (3.44, 29.63) | 6.01 (0.53, 6.01) | 3.63 (0.00, 10.42) |
| *P* value | < 0.001\*\*\* | < 0.001\*\*\* | 0.001\*\* | 0.001\*\* | < 0.001\*\*\* |
| The positive rate of NAbs in patients with CLD, n (%) | | | | | |
| NAbs-prototype | 98 (41.35 ) | 1 (4.17 ) | 16 (72.73) | 17 (44.74) | 64 (41.83) |
| NAbs-BA.4/5 | 11 (4.64) | 0 (0.00) | 5 (22.73) | 3 (7.89) | 3 (1.96) |
| *P* value | < 0.001\*\*\* | > 0.999 | 0.001\*\* | 0.001\*\* | < 0.001\*\*\* |
| The inhibition rate of NAbs in HCs, (%) | | | | | |
| NAbs-prototype | 52.98 (20.68, 87.84) | 4.53 (1.70, 11.71) | 90.23 (59.00, 97.22) | 68.48 (37.04, 89.54) | 49.17 (21.23, 84.30) |
| NAbs-BA.4/5 | 9.96 (4.22, 22.01) | 3.82 (1.61, 5.35) | 23.84 (15.70, 47.91) | 14.11 (5.98, 23.04) | 8.82 (4.19, 20.03) |
| *P* value | < 0.001\*\*\* | 0.228 | < 0.001\*\*\* | < 0.001\*\*\* | < 0.001\*\*\* |
| The positive rate of NAbs in patients with HCs, n (%) | | | | | |
| NAbs-prototype | 113 (66.47) | 0 (0.00) | 22 (100.00) | 27 (79.41) | 64 (65.98) |
| NAbs-BA.4/5 | 24 (14.12) | 0 (0.00) | 7 (31.82) | 2 (5.88) | 15 (15.46) |
| *P* value | < 0.001\*\*\* | > 0.999 | < 0.001\*\*\* | < 0.001\*\*\* | < 0.001\*\*\* |

Statistical analysis was performed by Wilcoxon rank sum test and χ2 test.

\*\*\**P* < 0.001, \*\**P* < 0.01.

Normally distributed data are shown as mean (standard deviation), non-normally distributed data are shown as median (Q1, Q3).

CLD, chronic liver disease; HCs, healthy controls; NAbs-prototype, neutralizing antibodies against SARS-CoV-2 prototype; NAbs-BA.4/5, neutralizing antibodies against SARS-CoV-2 BA.4/5.

**Supplementary Table S5** Factors related to antibody levels after booster vaccination.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | NAbs-prototype | | NAbs-BA.4/5 | | Anti-RBD IgG | | Total antibodies | |
|  | r | *P* | r | *P* | r | *P* | r | *P* |
| NAbs-prototype (inhibition rate, %) | 1.00 | **<0.001** | 0.66 | **<0.001** | 0.83 | **<0.001** | 0.38 | **<0.001** |
| NAbs-BA.4/5 (inhibition rate, %) | 0.66 | **<0.001** | 1.00 | **<0.001** | 0.69 | **<0.001** | 0.33 | **<0.001** |
| Total antibodies (OD450nm) | 0.38 | **<0.001** | 0.33 | **<0.001** | 0.34 | **<0.001** | 1.00 | **<0.001** |
| Anti-RBD IgG (BAU/mL) | 0.83 | **<0.001** | 0.69 | **<0.001** | 1.00 | **<0.001** | 0.34 | **<0.001** |
| Age (years) | -0.17 | **0.014** | -0.22 | **0.001** | -0.21 | **0.002** | -0.06 | 0.364 |
| HBsAg (IU/mL) | 0.29 | **0.001** | 0.27 | **0.003** | 0.28 | **0.002** | -0.01 | 0.941 |
| HBsAb (mIU/mL) | -0.08 | 0.420 | -0.02 | 0.827 | -0.12 | 0.227 | 0.20 | **0.040** |
| HBcAb (S/CO) | 0.21 | 0.062 | 0.16 | 0.151 | 0.32 | **0.004** | -0.03 | 0.769 |
| Total bilirubin (μmol/L) | -0.12 | 0.090 | -0.16 | **0.024** | -0.06 | 0.422 | -0.05 | 0.494 |
| Total bilirubin (μmol/L) | -0.15 | **0.033** | -0.16 | **0.019** | -0.07 | 0.283 | -0.12 | 0.079 |
| γ-glutamyl transferas (U/L) | -0.13 | 0.072 | -0.14 | **0.041** | -0.08 | 0.268 | -0.08 | 0.280 |

Statistical analysis was performed by Spearman’s correlation.

NAbs-prototype, neutralizing antibodies against SARS-CoV-2 prototype; NAbs-BA.4/5, neutralizing antibodies against SARS-CoV-2 BA.4/5; RBD, receptor binding domain; HBsAg, hepatitis B surface antigen; HBsAb, hepatitis B surface antibody; HBcAb, hepatitis B core antibody.

**Supplementary Table S6** Factors related to antibodies seroconversion after booster vaccination.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Positive NAbs-prototype | | Positive NAbs-BA.4/5 | | Positive anti-RBD IgG | | Positive total antibodies | |
|  | r | *P* | r | *P* | r | *P* | r | *P* |
| NAbs-prototype (inhibition rate, %) | 1.00 | **<0.001** | 0.66 | **<0.001** | 0.40 | **<0.001** | 0.25 | **<0.001** |
| Positive rate of NAbs-prototype | 0.86 | **<0.001** | 0.53 | **<0.001** | 0.29 | **<0.001** | 0.16 | **0.023** |
| NAbs-BA.4/5 (inhibition rate, %) | 0.66 | **<0.001** | 1.00 | **<0.001** | 0.32 | **<0.001** | 0.16 | **0.019** |
| Positive rate of NAbs-BA.4/5 | 0.36 | **<0.001** | 0.39 | **<0.001** | 0.08 | 0.238 | 0.04 | 0.564 |
| Total antibodies (OD450nm) | 0.38 | **<0.001** | 0.33 | 0.550 | 0.48 | **<0.001** | 0.30 | **<0.001** |
| Positive rate of total antibodies | 0.25 | **0.023** | 0.16 | 0.564 | 0.49 | **<0.001** | 1.00 | **<0.001** |
| Anti-RBD IgG (BAU/mL) | 0.83 | **<0.001** | 0.69 | **<0.001** | 0.54 | **<0.001** | 0.27 | **<0.001** |
| Positive rate of anti-RBD IgG | 0.40 | **<0.001** | 0.32 | 0.238 | 1.00 | **<0.001** | 0.49 | **<0.001** |
| Age (years) | -0.17 | 0.313 | -0.22 | **0.002** | -0.07 | 0.301 | -0.07 | 0.328 |
| HBsAg (IU/mL) | 0.29 | **0.006** | 0.27 | 0.669 | 0.10 | 0.300 | 0.08 | 0.379 |
| HBcAb (S/CO) | 0.21 | **0.016** | 0.16 | 0.698 | 0.14 | 0.228 | 0.27 | **0.018** |
| Severe liver disease | -0.06 | 0.458 | -0.05 | 0.491 | 0.04 | 0.533 | -0.15 | **0.028** |

Statistical analysis was performed by Spearman’s correlation.

NAbs-prototype, neutralizing antibodies against SARS-CoV-2 prototype; NAbs-BA.4/5, neutralizing antibodies against SARS-CoV-2 BA.4/5; RBD, receptor binding domain; HBsAg, hepatitis B surface antigen; HBcAb, hepatitis B core antibody.

**Supplementary Table S7** Univariate logistic regression analysis for factors associated with negative SARS-CoV-2 antibodies in CLD patients with booster vaccination.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Categories | Risk factors | OR | 95% CI | *P* value |
| Negative NAbs against prototype | Age (years) | 1.014 | 0.991–1.037 | 0.243 |
| HBsAg (IU/mL) | 1 | 1–1 | 0.727 |
| Direct bilirubin (μmol/L) | 0.988 | 0.958–1.018 | 0.427 |
| Total biliary acid (μmol/L) | 0.993 | 0.981–1.005 | 0.25 |
| HBcAb (S/CO) | 1.008 | 0.969–1.049 | 0.7 |
| Negative NAbs against BA.4/5 | HBsAg (IU/mL) | 1 | 1–1 | 0.538 |
| Total bilirubin (μmol/L) | 0.996 | 0.957–1.038 | 0.863 |
| Direct bilirubin (μmol/L) | 0.99 | 0.944–1.039 | 0.682 |
| γ-glutamyl transferas (U/L) | 1.017 | 0.982–1.054 | 0.338 |
| Negative anti-RBD IgG antibodies | Age (years) | 1.023 | 0.986–1.061 | 0.222 |
| HBsAg (IU/mL) | 1 | 1–1 | 0.383 |
| HBcAb (S/CO) | 0.841 | 0.655–1.08 | 0.175 |
| Negative total anti-SARS-CoV-2 antibodies | HBsAb (mIU/mL) | 0.825 | 0.411–1.656 | 0.588 |

Statistical analysis was performed by binary logistic regression analyses.

NAbs, neutralizing antibodies; RBD, receptor binding domain; HBsAg, hepatitis B surface antigen; HBcAb, hepatitis B core antibody; HBsAb, hepatitis B surface antibody.

**Supplementary Table S8** Changes of lymphocyte subset after booster vaccination.

|  |  |  |  |
| --- | --- | --- | --- |
|  | Vaccinated CLD  (n = 90) | Vaccinated HC  (n = 113) | *P* value |
| Lymphocytes (×109/L) | 1.70 (1.22, 2.08) | 1.62 (1.39, 1.94) | 0.833 |
| CD3+ T cells (/uL) | 1162 (850.20, 1494.00) | 1129 (922, 1341) | 0.915 |
| CD3+ T cells (%) | 73.25 (63.50, 78.00) | 70.72 (64.51, 76.10) | 0.186 |
| CD4+ T cells (/uL) | 579 (443.10, 791.50) | 590.3 (496.80, 775.00) | 0.310 |
| CD4+ T cells (%) | 38.1 (8.15) | 38.1 (8.16) | 0.997 |
| CD8+ T cells (/uL) | 427.3 (292.20, 597.20) | 408.1 (317.00, 544.60) | 0.625 |
| CD8+ T cells (%) | 26.5 (21.98, 34.38) | 24.97 (20.58, 32.49) | 0.128 |
| B cells (/uL) | 144.4 (74.90, 228.30) | 171.8 (128.50, 231.80) | 0.013\* |
| B cells (%) | 9.15 (5.68, 13.30) | 10.64 (8.39, 12.89) | 0.062 |
| NK cells (/uL) | 184.3 (122.10, 337.50) | 250.2 (189.30, 351.00) | 0.015\* |
| NK cells (%) | 13.3 (9.75, 20.45) | 15.12 (11.03, 20.80) | 0.097 |

Statistical analysis was performed by Wilcoxon rank sum test or *t*-test.

\**P* < 0.05.

Normally distributed data are shown as mean (standard deviation), non-normally distributed data are shown as median (Q1, Q3).

CLD, chronic liver disease; HCs, healthy controls; NK cells, natural killer cells.

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**Supplementary Fig. S1.** The differences of anti-SARS-CoV-2 antibodies and lymphocyte subsets between compensated and decompensated cirrhosis patients after booster vaccination. **A–D**.The levels oftotal anti-SARS-CoV-2 antibodies (**A**), anti-RBD IgG antibodies (**B**), and neutralizing antibodies toward prototype (**C**) and Omicron BA.4/5 (**D**) in patients with compensated (n = 28) and decompensated (n = 20) cirrhosis. **E, F** The lymphocyte counts (**E**) and lymphocyte subset counts (**F**) of compensated (n = 11) and decompensated (n = 12) cirrhosis patients. Statistical analysis was performed by Wilcoxon rank sum test. Data were shown as median. CLD, chronic liver disease; NAbs-prototype, neutralizing antibodies against SARS-CoV-2 prototype; NAbs-BA.4/5, neutralizing antibodies against SARS-CoV-2 BA.4/5; RBD, receptor binding domain; NK cell: natural killer cell.

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**Supplementary Fig. S2** Changes of lymphocyte subsets after booster shots in CLD patients. **A** The lymphocyte counts of CLD patients (n = 90) and HC (n = 113). **B, C** The count (**B**) and percentage (**C**) of B cells and NK cells of CLD patients (n = 90) and HC (n = 113). **D, E** The count (**D**) and percentage (**E**) of T cell subsets (including CD3+ T cells, CD4+ T cells, and CD8+ T cells) cells of CLD patients (n = 90) and HC (n = 113). Statistical analysis was performed by Wilcoxon rank sum test. Data were shown as median with interquartile range. CLD, chronic liver disease; HC, healthy controls; NK cell, natural killer cell.

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**Supplementary Fig. S3.** Changes of lymphocyte subsets after booster shots in patients with or without SLD.The lymphocyte counts (**A**) and T cell subsets, B cells and NK cells (**B**) in SLD (n = 37) and NSLD patients (n = 29). Statistical analysis was performed by Wilcoxon rank sum test. Data were shown as median. SLD, severe liver disease; NSLD, non-severe liver disease; NK cell, natural killer cell.

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