# Risk of acute liver injury following the mRNA (BNT162b2) and inactivated (CoronaVac) COVID-19 vaccines

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**Appendix 1. Acute liver injury severity according to the Drug-Induced Liver Injury Network**

The Drug-Induced Liver Injury Network (DILIN)(1) developed a 5 point scale for grading the severity of liver injury based upon the presence of jaundice, hospitalization, signs of hepatic or other organ failure, and ultimate outcome.

- **1+, Mild:** Raised serum aminotransferase or alkaline phosphatase levels or both, but total serum bilirubin <43 umol/L and no coagulopathy (INR <1.5)

- **2+, Moderate:** Raised serum aminotransferase or alkaline phosphatase levels or both <u>and</u> total serum bilirubin level ≥43 umol/L <u>or</u> coagulopathy (INR ≥1.5) without hyperbilirubinemia

- **3+, Moderate to Severe:** Raised serum aminotransferase or alkaline phosphatase levels and total serum bilirubin level ≥2.5 mg/dL <u>and</u> hospitalization (or pre-existing hospitalization is prolonged) because of the drug induced liver injury

- **4+, Severe:** Raised serum aminotransferase or alkaline phosphatase levels and serum bilirubin ≥43 umol/L <u>and</u> at least one of the following:

    o Prolonged jaundice and symptoms beyond 3 months, <u>or</u>

    o Signs of hepatic decompensation (INR ≥1.5, ascites, encephalopathy), <u>or</u>

    o Other organ failure believed to be related to drug induced liver injury

- **5+, Fatal:** Death or liver transplantation for drug induced liver injury

**Table S1. Cause of acute liver injury following the BNT162b2 and CoronaVac vaccination among those with a follow-up period of at least 28 days after acute liver injury onset**

|  | BNT162b2 (N=2,101) | CoronaVac (N=1,846) |
|---|---|---|
| Chronic liver disease | 8.0% | 10.5% |
|    Cirrhosis | 0.2% | 0.6% |
|    Fatty liver | 0.2% | 0.1% |
|    Hepatocellular carcinoma | 0.4% | 1.4% |
|    Viral hepatitis | 6.6% | 9.6% |
| Viral hepatitis B | 0.0% | 0.1% |
| Viral hepatitis C | 0.1% | 0.3% |
| Cancer | 1.9% | 3.7% |
| Solid organ/ blood cancer | 0.9% | 1.2% |
| Alcoholism/ harmful alcohol use/ alcoholic hepatitis | 0.6% | 0.4% |
| Cholestasis/ cholangitis/ cholecystitis/ cholelithiasis | 3.3% | 4.0% |
| Admission for chemotherapy | 0.4% | 0.6% |

**Table S2. Risks of acute liver injury among people in the modified self-controlled case series analysis**

|  | New events | Person-years | IRR | 95% CI | P-value |
|---|---|---|---|---|---|
| BNT162b2 (N=2,473)* |  |  |  |  |  |
| Non-exposure period | 1,645 | 721 |  | (reference) |  |
| Days 0-55 after first dose | 307 | 147 | 0.800 | (0.680, 0.942) | 0.007 |
| Days 0-55 after second dose | 521 | 225 | 0.949 | (0.816, 1.091) | 0.432 |
| CoronaVac (N=2,204)* |  |  |  |  |  |
| Non-exposure period | 1,426 | 629 |  | (reference) |  |
| Days 0-55 after first dose | 304 | 161 | 0.689 | (0.588, 0.807) | <0.001 |
| Days 0-55 after second dose | 474 | 197 | 0.905 | (0.781, 1.048) | 0.182 |

Notes: CI = Confidence interval; IRR = Incidence rate ratio

* The number of vaccinated people who had incident acute liver injury during the observation period

**Table S3. Sensitivity analyses of varying the risk windows, addition of pre-risk period, excluding patients who died during the observation period, excluding pre-vaccination period, and limiting patients who had liver panel results. Subgroup analyses of patients with and without underlying liver diseases.**

| Acute liver injury | New events | Person-years | IRR | 95% CI | P-value |
|---|---|---|---|---|---|
| **Limiting the exposure periods to 14 days** | | | | | |
| BNT162b2 (N=2,473)* | | | | | |
| Non-exposure period | 2,192 | 893 | | (reference) | |
| Days 0-13 after first dose | 140 | 91 | 0.728 | (0.604, 0.877) | <0.001 |
| Days 0-13 after second dose | 141 | 77 | 0.820 | (0.673, 0.998) | 0.047 |
| CoronaVac (N=2,204)* | | | | | |
| Non-exposure period | 1,961 | 800 | | (reference) | |
| Days 0-13 after first dose | 116 | 81 | 0.683 | (0.558, 0.835) | <0.001 |
| Days 0-13 after second dose | 127 | 65 | 0.862 | (0.707, 1.050) | 0.140 |
| **Limiting the exposure periods to 28 days** | | | | | |
| BNT162b2 (N=2,473)* | | | | | |
| Non-exposure period | 1,910 | 806 | | (reference) | |
| Days 0-27 after first dose | 282 | 142 | 0.887 | (0.761, 1.034) | 0.125 |
| Days 0-27 after second dose | 281 | 140 | 0.865 | (0.739, 1.014) | 0.074 |
| CoronaVac (N=2,204)* | | | | | |
| Non-exposure period | 1,705 | 699 | | (reference) | |
| Days 0-27 after first dose | 247 | 153 | 0.680 | (0.580, 0.798) | <0.001 |
| Days 0-27 after second dose | 252 | 120 | 0.862 | (0.732, 1.015) | 0.074 |
| **Limiting the exposure periods to 42 days** | | | | | |
| BNT162b2 (N=2,473)* | | | | | |
| Non-exposure period | 1,747 | 762 | | (reference) | |
| Days 0-41 after first dose | 303 | 145 | 0.892 | (0.766, 1.040) | 0.145 |
| Days 0-41 after second dose | 423 | 188 | 0.988 | (0.856, 1.141) | 0.874 |
| CoronaVac (N=2,204)* | | | | | |
| Non-exposure period | 1,528 | 666 | | (reference) | |
| Days 0-41 after first dose | 288 | 160 | 0.747 | (0.640, 0.871) | <0.001 |
| Days 0-41 after second dose | 388 | 163 | 0.990 | (0.853, 1.149) | 0.897 |
| **Including pre-risk period** | | | | | |
| BNT162b2 (N=2,473)* | | | | | |
| Non-exposure period | 1,286 | 530 | | (reference) | |
| Pre-risk period (Days -56 to -1) | 359 | 327 | 0.428 | (0.366, 0.500) | <0.001 |
| Days 0-55 after first dose | 307 | 147 | 0.778 | (0.659, 0.919) | 0.003 |
| Days 0-55 after second dose | 521 | 225 | 0.924 | (0.798, 1.071) | 0.294 |
| CoronaVac (N=2,204)* | | | | | |
| Non-exposure period | 1,172 | 475 | | (reference) | |
| Pre-risk period (Days -56 to -1) | 254 | 260 | 0.365 | (0.306, 0.434) | <0.001 |
| Days 0-55 after first dose | 304 | 161 | 0.679 | (0.578, 0.797) | <0.001 |
| Days 0-55 after second dose | 474 | 197 | 0.895 | (0.772, 1.038) | 0.142 |

**Excluding patients with history of COVID-19 infection prior to vaccination**

BNT162b2 (N=2,458)*

| | | | | | |
|---|---|---|---|---|---|
| Non-exposure period | 1,636 | 717 | | (reference) | |
| Days 0-55 after first dose | 302 | 146 | 0.792 | (0.672, 0.933) | 0.005 |
| Days 0-55 after second dose | 520 | 225 | 0.942 | (0.814, 1.089) | 0.418 |

CoronaVac (N=2,200)*

| | | | | | |
|---|---|---|---|---|---|
| Non-exposure period | 1,423 | 627 | | (reference) | |
| Days 0-55 after first dose | 303 | 161 | 0.690 | (0.589, 0.809) | <0.001 |
| Days 0-55 after second dose | 474 | 197 | 0.905 | (0.781, 1.048) | 0.183 |

**Excluding death cases during observation period**

BNT162b2 (N=2,405)*

| | | | | | |
|---|---|---|---|---|---|
| Non-exposure period | 1,616 | 698 | | (reference) | |
| Days 0-55 after first dose | 294 | 143 | 0.933 | (0.788, 1.105) | 0.423 |
| Days 0-55 after second dose | 495 | 219 | 1.032 | (0.887, 1.200) | 0.684 |

CoronaVac (N=2,098)*

| | | | | | |
|---|---|---|---|---|---|
| Non-exposure period | 1,387 | 592 | | (reference) | |
| Days 0-55 after first dose | 274 | 153 | 0.774 | (0.655, 0.915) | 0.003 |
| Days 0-55 after second dose | 437 | 189 | 0.957 | (0.819, 1.118) | 0.579 |

**Excluding pre-vaccination period**

BNT162b2 (N=1,228)*

| | | | | | |
|---|---|---|---|---|---|
| Non-exposure period | 400 | 131 | | (reference) | |
| Days 0-55 after first dose | 307 | 71 | 0.809 | (0.681, 0.961) | 0.016 |
| Days 0-55 after second dose | 521 | 123 | 0.952 | (0.818, 1.108) | 0.525 |

CoronaVac (N=1,257)*

| | | | | | |
|---|---|---|---|---|---|
| Non-exposure period | 479 | 167 | | (reference) | |
| Days 0-55 after first dose | 304 | 94 | 0.692 | (0.586, 0.817) | <0.001 |
| Days 0-55 after second dose | 474 | 128 | 0.909 | (0.780, 1.059) | 0.219 |

**Including patients who had results of liver panel**

BNT162b2 (N=2,470)*

| | | | | | |
|---|---|---|---|---|---|
| Non-exposure period | 1,643 | 720 | | (reference) | |
| Days 0-55 after first dose | 306 | 147 | 0.800 | (0.679, 0.941) | 0.007 |
| Days 0-55 after second dose | 521 | 225 | 0.947 | (0.819, 1.095) | 0.462 |

CoronaVac (N=2,203)*

| | | | | | |
|---|---|---|---|---|---|
| Non-exposure period | 1,426 | 629 | | (reference) | |
| Days 0-55 after first dose | 304 | 161 | 0.690 | (0.589, 0.808) | <0.001 |
| Days 0-55 after second dose | 473 | 197 | 0.904 | (0.781, 1.048) | 0.181 |

**Including patients with underlying liver diseases**

BNT162b2 (N=77)*

| | | | | | |
|---|---|---|---|---|---|
| Non-exposure period | 63 | 19 | | (reference) | |
| Days 0-55 after first dose | 5 | 5 | 0.147 | (0.032, 0.679) | 0.014 |
| Days 0-55 after second dose | 9 | 7 | 0.337 | (0.118, 0.960) | 0.042 |

CoronaVac (N=93)*

| | | | | | |
|---|---|---|---|---|---|
| Non-exposure period | 67 | 23 | | (reference) | |

| | | | | | |
|---|---|---|---|---|---|
| Days 0-55 after first dose | 8 | 7 | 0.587 | (0.239, 1.438) | 0.244 |
| Days 0-55 after second dose | 18 | 8 | 1.127 | (0.560, 2.266) | 0.738 |
| **Excluding patients with underlying liver diseases** | | | | | |
| BNT162b2 (N=2,396)* | | | | | |
| Non-exposure period | 1,582 | 702 | | (reference) | |
| Days 0-55 after first dose | 302 | 142 | 0.830 | (0.705, 0.978) | 0.026 |
| Days 0-55 after second dose | 512 | 218 | 0.968 | (0.836, 1.122) | 0.668 |
| CoronaVac (N=2,111)* | | | | | |
| Non-exposure period | 1,359 | 606 | | (reference) | |
| Days 0-55 after first dose | 296 | 155 | 0.695 | (0.592, 0.817) | <0.001 |
| Days 0-55 after second dose | 456 | 189 | 0.898 | (0.773, 1.044) | 0.162 |

Notes: CI = Confidence interval; IRR = Incidence rate ratio

* The number of vaccinated people who had incident acute liver injury during the observation period

**Table S4. Baseline characteristics of 6,353 adult COVID-19 patients who had SARS-CoV-2 PCR positive between 1st September 2020 and 30th September 2021, and had no prior of history ALI before SAR-S-CoV-2 PCR positive**

| Baseline characteristics | Patients with COVID-19 infection (N=6,353) | |
| --- | --- | --- |
| | N / Median | % / IQR |
| Age, years | 46 | 34-60 |
|   18-40 | 2,462 | 38.8% |
|   41-65 | 2,837 | 44.7% |
|   >65 | 1,054 | 16.6% |
| Sex | | |
|   Male | 2,942 | 46.3% |
|   Female | 3,411 | 53.7% |
| Pre-existing comorbidities | | |
|   Charlson's index | 1 | 0-3 |
|     0-1 | 3,602 | 56.7% |
|     2-4 | 2,417 | 38.1% |
|     ≥5 | 334 | 5.3% |
|   Chronic liver diseases | 168 | 2.6% |
|   Myocardial infraction | 26 | 0.4% |
|   Hypertension | 963 | 15.2% |
|   Peripheral vascular disease | 6 | 0.1% |
|   Cerebrovascular disease | 88 | 1.4% |
|   Chronic obstructive pulmonary disease | 71 | 1.1% |
|   Dementia | 8 | 0.1% |
|   Paralysis | 1 | 0.0% |
|   Diabetes without chronic complication | 523 | 8.2% |
|   Diabetes with chronic complication | 35 | 0.6% |
|   Malignancy | 58 | 0.9% |
|   Metastatic solid tumor | 9 | 0.1% |
| Medications used | | |
|   Renin-angiotensin-system agents | 590 | 9.3% |
|   Beta blockers | 355 | 5.6% |
|   Calcium channel blockers | 855 | 13.5% |
|   Diuretics | 113 | 1.8% |
|   Nitrates | 93 | 1.5% |
|   Lipid lowering agents | 766 | 12.1% |
|   Insulins | 144 | 2.3% |
|   Antidiabetic drugs | 535 | 8.4% |
|   NSAID | 286 | 4.5% |
|   Antivirals | 245 | 3.9% |
|   Antibiotics | 352 | 5.5% |
|   Immunosuppressants | 101 | 1.6% |

Note: IQR = interquartile range; NSAID = nonsteroidal anti-inflammatory drugs;

**Table S5. Baseline characteristics of adult COVID-19 patients who had SARS-CoV-2 PCR positive between 1st September 2020 and 30th September 2021, BNT162b2 recipients and CoronaVac recipients among those who had no prior of history of ALI, before and after propensity score weighting**

| | Before weighting | | | | | | | After weighting | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline characteristics | Patients with SARS-CoV-2 infection | | BNT162b2 | | CoronaVac | | ASMD | Patients with SARS-CoV-2 infection | | BNT162b2 | | CoronaVac | | ASMD |
| | N / Median | % / IQR | N / Median | % / IQR | N / Median | % / IQR | | Median | % / IQR | Median | % / IQR | Median | % / IQR | |
| Age, years | 46 | 34-60 | 45 | 32-58 | 56 | 46-65 | 0.63 | 49 | 37-61 | 51 | 37-62 | 51 | 38-62 | 0.02 |
| 18-40 | 2,462 | 38.8% | 568,050 | 42.2% | 161,934 | 16.3% | 0.62 | | 31.3% | | 31.2% | | 30.8% | 0.01 |
| 41-65 | 2,837 | 44.7% | 620,345 | 46.1% | 599,282 | 60.3% | | | 52.3% | | 52.2% | | 52.4% | |
| >65 | 1,054 | 16.6% | 156,702 | 11.7% | 232,629 | 23.4% | | | 16.4% | | 16.6% | | 16.8% | |
| Sex | | | | | | | 0.04 | | | | | | | 0.00 |
| Male | 2,942 | 46.3% | 597,227 | 44.4% | 454,353 | 45.7% | | | 45.0% | | 45.0% | | 45.2% | |
| Female | 3,411 | 53.7% | 747,870 | 55.6% | 539,492 | 54.3% | | | 55.0% | | 55.0% | | 54.8% | |
| Pre-existing comorbidities | | | | | | | | | | | | | | |
| Charlson's index | 1 | 0-3 | 1 | 0-2 | 2 | 1-3 | 0.55 | 1 | 0-3 | 2 | 0-3 | 2 | 0-3 | 0.01 |
| 0-1 | 3,602 | 56.7% | 797,237 | 59.3% | 342,772 | 34.5% | 0.52 | | 51.8% | | 48.4% | | 48.7% | 0.11 |
| 2-4 | 2,417 | 38.1% | 513,276 | 38.2% | 596,085 | 60.0% | | | 43.0% | | 47.9% | | 47.4% | |
| ≥5 | 334 | 5.3% | 34,584 | 2.6% | 54,988 | 5.5% | | | 5.1% | | 3.7% | | 4.0% | |
| Chronic Liver diseases | 168 | 2.6% | 12,896 | 1.0% | 12,950 | 1.3% | 0.13 | | 2.2% | | 1.1% | | 1% | 0.08 |
| Myocardial infarction | 26 | 0.4% | 1,644 | 0.1% | 2,270 | 0.2% | 0.06 | | 0.4% | | 0.2% | | 0.2% | 0.05 |
| Hypertension | 963 | 15.2% | 177,688 | 13.2% | 227,839 | 22.9% | 0.25 | | 16.1% | | 16.7% | | 18.0% | 0.05 |
| Peripheral vascular disease | 6 | 0.1% | 671 | 0.0% | 933 | 0.1% | 0.02 | | 0.1% | | 0.1% | | 0.1% | 0.01 |
| Cerebrovascular disease | 88 | 1.4% | 12,463 | 0.9% | 19,285 | 1.9% | 0.09 | | 1.4% | | 1.2% | | 1.5% | 0.02 |
| Chronic obstructive pulmonary disease | 71 | 1.1% | 12,366 | 0.9% | 12,183 | 1.2% | 0.03 | | 1.1% | | 1.0% | | 1.0% | 0.00 |
| Dementia | 8 | 0.1% | 272 | 0.0% | 736 | 0.1% | 0.04 | | 0.1% | | 0.0% | | 0.0% | 0.03 |
| Paralysis | 1 | 0.0% | 363 | 0.0% | 579 | 0.1% | 0.02 | | 0.0% | | 0.0% | | 0.0% | 0.02 |
| Diabetes without chronic complication | 523 | 8.2% | 76,713 | 5.7% | 101,303 | 10.2% | 0.17 | | 8.7% | | 7.1% | | 8.1% | 0.06 |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Diabetes with chronic complication | 35 | 0.6% | 2,713 | 0.2% | 3,588 | 0.4% | 0.06 | 0.6% | 0.2% | 0.3% | 0.05 |
| Malignancy | 61 | 1.0% | 14,328 | 1.1% | 13,919 | 1.4% | 0.04 | 0.9% | 1.2% | 1.2% | 0.04 |
| Metastatic solid tumor | 9 | 0.1% | 1,210 | 0.1% | 1,227 | 0.1% | 0.02 | 0.1% | 0.1% | 0.1% | 0.01 |
| Medications used | | | | | | | | | | | |
| Renin-angiotensin-system agents | 590 | 9.3% | 107,187 | 8.0% | 132,371 | 13.3% | 0.17 | 9.7% | 10.0% | 10.5% | 0.03 |
| Beta blockers | 355 | 5.6% | 63,188 | 4.7% | 77,880 | 7.8% | 0.13 | 5.7% | 5.9% | 6.2% | 0.02 |
| Calcium channel blockers | 855 | 13.5% | 158,427 | 11.8% | 204,272 | 20.6% | 0.24 | 14.1% | 15.0% | 16.1% | 0.06 |
| Diuretics | 113 | 1.8% | 15,196 | 1.1% | 20,078 | 2.0% | 0.07 | 1.6% | 1.5% | 1.6% | 0.01 |
| Nitrates | 93 | 1.5% | 11,505 | 0.9% | 15,652 | 1.6% | 0.07 | 1.4% | 1.2% | 1.2% | 0.02 |
| Lipid lowering agents | 766 | 12.1% | 156,620 | 11.6% | 193,983 | 19.5% | 0.22 | 12.7% | 15.0% | 15.1% | 0.07 |
| Insulins | 144 | 2.3% | 9,629 | 0.7% | 11,309 | 1.1% | 0.13 | 2.0% | 0.9% | 0.9% | 0.10 |
| Antidiabetic drugs | 535 | 8.4% | 80,450 | 6.0% | 104,087 | 10.5% | 0.16 | 8.8% | 7.5% | 8.3% | 0.05 |
| NSAID | 286 | 4.5% | 89,376 | 6.6% | 68,836 | 6.9% | 0.10 | 4.5% | 7.0% | 6.4% | 0.11 |
| Antivirals | 245 | 3.9% | 13,323 | 1.0% | 12,856 | 1.3% | 0.19 | 1.7% | 1.1% | 1.2% | 0.05 |
| Antibiotics | 352 | 5.5% | 42,481 | 3.2% | 32,531 | 3.3% | 0.12 | 3.3% | 3.2% | 3.2% | 0.01 |
| Immunosuppressants | 101 | 1.6% | 4,196 | 0.3% | 2,798 | 0.3% | 0.14 | 0.7% | 0.3% | 0.3% | 0.06 |

Note: ASMD = absolute standardized mean difference; IQR = interquartile range; NSAID = nonsteroidal anti-inflammatory drugs;

**Supplementary reference**

1.      National Institute of Diabetes and Digestive and Kidney Diseases. Severity Grading In Drug Induced Liver Injury Bethesda (MD)2012 [updated 2019 May 4. Available from: https://www.ncbi.nlm.nih.gov/books/NBK548241/.