Title: No increase in risk of acute liver injury following the mRNA (BNT162b2) and inactivated (CoronaVac) COVID-19 vaccines: A self-controlled case series study

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Abstract (Word count 275)

Background

Case reports of severe acute liver injury (ALI) following COVID-19 vaccination are recently described. We evaluated the risks of ALI following COVID-19 vaccines (BNT162b2 or CoronaVac).

Methods

We conducted a modified self-controlled case series analysis using the vaccination records in Hong Kong with data linkage to electronic medical records from territory-wide healthcare database. Incidence rate ratios (IRRs) for ALI outcome in the 56-day period following first and second doses of COVID-19 vaccines in comparison to the non-exposure period were estimated, and compared to the ALI risk in patients with SARS-CoV-2 infection.

Results

Among 2,343,288 COVID-19 vaccine recipients who were at risk, 4,677 patients had the first incident ALI from 23rd February 2021 to 30th September 2021. Number of ALI within 56 days after the first and second dose of vaccination were 307 and 521 (335 and 334 per 100,000 person-years) for BNT162b2, and 304 and 474 (358 and 403 per 100,000 person-years) for CoronaVac, respectively, compared to 32,997 ALI cases per 100,000 person-years among patients within 56 days of SARS-CoV-2 infection. Compared to the non-exposure period, no increased risk was observed in the 56-day risk period for first (IRR=0.800, 95%CI: 0.680–0.942) and second (IRR=0.944, 95%CI: 0.816–1.091) dose of BNT162b2; first (IRR=0.689, 95%CI: 0.588–0.807) and second (IRR=0.905, 95%CI: 0.781–1.048) dose of CoronaVac. Of all ALI cases following COVID-19 vaccination, there were no severe or fatal cases.

Conclusion

There was no evidence of an increased risk of ALI associated with BNT162b2 or CoronaVac vaccination. Based on all current available evidence from previous studies and our study, the benefit of mass vaccination far outweighs the ALI risk from vaccination and SARS-CoV-2 infection.

Lay summary

Our study did not find an increased risk of acute liver injury following COVID-19 vaccination. Among the very few observed cases of acute liver injury, they were mostly mild and self-limiting. As acute liver injury is far more common after SARS-CoV-2 infection than following COVID-19 vaccination, benefits of mass vaccination outweigh the risks during this pandemic.

Background

Introduction

Since the global outbreak in early 2020 of coronavirus disease (COVID-19), an infection caused by the acute respiratory syndrome coronavirus 2 (SARS-CoV-2), tremendous efforts have been placed on preventive vaccination. Within a very short time, several types of vaccines were approved for emergency use for immunization against the SARS-CoV-2 virus and population-based vaccination campaign was promoted across the globe following the World Health Organization's declaration of the pandemic. Acute liver injury (ALI) was not reported in clinical trials for COVID-19 registration as the sample size had been insufficient to detect rare adverse events following vaccination. Since the widespread rollout of COVID-19 vaccination programs across the globe, cases of adverse events including rare complications affecting the liver in the form of ALI mimicking autoimmune hepatitis (AIH) have been described (1-6). The hepatotoxicity was evidenced by elevated liver enzymes levels (either hepatocellular or cholestatic pattern) as well as bilirubin level which clinically presented as jaundice(1-5). The seropositivity rate for anti-nuclear antibody and anti-smooth muscle antibody were variable among different reports. Individual liver biopsies revealed heterogenous patterns including histopathological features typical of AIH such as interface hepatitis, portal inflammation or non-specific changes of centrilobular necrosis (2). There were also reports of severe venous thrombosis of unusual sites such as the portal and splenic vein and immune thrombocytopenic purpura associated with the ALI (7, 8). Incidents were reported from recipients of various vaccines including the adenovirus-based vaccine of Oxford-AstraZeneca and the mRNA vaccine of Pfizer-BioNTech (also known as BNT162b2 mRNA) and the Moderna, suggesting that these adverse events may be independent of the vaccine mechanisms(2, 4). The concern over autoimmune disease was raised from the

interferon pathway of immunization with molecular mimicry and bystander activation being the possible mechanisms(1, 2).

Although new variants of SARS-CoV-2 are emerging, vaccination remains an effective and reliable way to reduce disease severity, hospitalization requirement and more importantly, mortality (9). BNT162b2 mRNA vaccine and CoronaVac inactivated vaccine are the only two vaccines currently available in Hong Kong. Both vaccines trigger a robust adaptive immune response and the production of neutralizing antibodies (10, 11). In response to the safety signal of ALI generated from the published case reports, this pharmacovigilance was conducted to investigate the risk and severity of ALI following COVID-19 vaccination.

Methods

Data source

Anonymized, population-wide COVID-19 vaccination records in the Hong Kong Special Administrative Region, China were obtained from the Department of Health. These records included date of vaccination, and brand of vaccine. Electronic medical records were retrieved from the Hong Kong Hospital Authority (the statutory body managing public healthcare services in the region). These records included demographics, date of registered death, drug dispensing records, diagnoses, procedures and laboratory tests. Records were linked using a unique de-identified mapping key. These two linked sources of data have been extensively used for COVID-19 vaccine pharmacovigilance research (12-25) and drug-induced liver injury research (26).

Study design and study population

A self-controlled case series (SCCS) design was used to investigate the risk of ALI following BNT162b2 and CoronaVac. The SCCS was originally developed for vaccine safety(27-29) , and has recently been used to investigate COVID-19 vaccine-associated thromboembolic events (30, 31) and hematological disorders including leukopenia, neutropenia and thrombocytopenia(18, 30, 32). Such hematological disorders are diagnosed based on laboratory parameters. It is appropriate to apply the SCCS design on the ALI outcome, a laboratory-based diagnosis, using the electronic medical record database of the Hong Kong Hospital Authority. Laboratory results are automatically updated and transferred to the research database daily.

The population of interest was described as those adults had received at least one dose of COVID-19 vaccine between 23rd February 2021 and 30th September 2021. A schematic presentation of the SCCS design is shown in Figure 1. As SCCS analysis only requires individuals with first incident of ALI; we only included those whose first incident of ALI was diagnosed between 23rd February 2021 and 30th September 2021 and had been identified by liver function test results extracted from the electronic medical records. ALI was defined by the levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and total bilirubin according to the criteria listed in Asia Pacific Association of Study of Liver consensus guidelines (33) and the drug-induced liver injury clinical practice guidelines of the European Association for the Study of Liver Disease (34). Briefly, ALI is diagnosed when one of the following thresholds is met: 1) ≥5 x upper limit of normal (ULN) elevation in ALT, 2) ≥2 x ULN elevation in AST, or 3) ≥3 x ULN elevation in ALT and simultaneous elevation of total bilirubin ≥2 x ULN, with the absence of other etiologies, where the ULN of ALT, AST, and total bilirubin are 40U/L, 40U/L and 19μmol/L, respectively.

A review of published case reports showed ALI following COVID-19 vaccination could present from several days up to 46 days post-vaccination(35, 36). Hence, a risk window of 56 days post-vaccination was chosen to define the exposure period. Two risk periods which covered 0-55 days after first and second doses were included. For individuals who received the second dose before day 56 was reached post-first dose, the period was considered as post-second dose exposure. For instance, when the second dose of vaccine was received on day 21, day 0-20 was regarded as post-first dose risk period, whereas day 21-77 was regarded as post-second dose risk period (Figure 1). The remaining periods during the observation period were identified as non-exposure periods.

In addition, adult patients who had SARS-CoV-2 polymerase chain reaction (PCR) positive results between 1st September 2020 and 30th September 2021, with no prior history of ALI before the positive result, were selected to compare the risk of ALI following SARS-CoV-2 infection and following COVID-19 vaccination. Governmental statutory policy during the study period required every person with confirmed diagnosis of SARS-CoV-2 infection to undergo mandatory hospitalization or quarantine in medical facilities, regardless of the severity of symptoms from the infection. Therefore, our study captured the data from all patients with SARS-CoV-2 infection during the specified period.

Statistical analyses

The crude incidence rate of ALI following COVID-19 vaccination (cases per 100,000 person-years) and that of ALI following SARS-CoV-2 infection (cases per 100,000 person-years) were estimated. A propensity score model (PSM) in which the dependent variable was the receipt of the first dose of BNT162b2, the first dose of CoronaVac, or the diagnosis of SARS-CoV-2 infection was constructed by a logistic regression. Inverse probability of

treatment weights (IPTW) was used to equilibrate the baseline characteristics such as age, sex, pre-existing comorbidities and medication used across the three groups. Conditional Poisson regression models weighted by IPTW were fitted to estimate the incidence rate ratio (IRR) and 95% confidence interval (CI) of ALI risks for BNT162b2 or CoronaVac recipients relative to patients with SARS-CoV-2 infection.

The severity of ALI following vaccination and SARS-CoV-2 infection was assessed by the following parameters: peak ALT level, peak AST level, Drug-Induced Liver Injury Network (DILIN) scale(37), the De Ritis ratio (i.e., AST: ALT ratio which has been associated with poor prognosis in SARS-CoV-2 infection (38, 39), proportion of patients requiring hospitalization, and intensive care unit (ICU) admission. Follow-up information about the ALI such as the proportion of patients who would had a delayed second dose (>42 days after the first dose of BNT162b2 or >56 days after the first dose of CoronaVac)(24), incident AIH and liver diseases among those with a follow-up period of at least 28 days after their ALI was explored. Differences in ALI severity and follow-up information between the two vaccines were compared using ordered or binary logistic regressions adjusting for baseline characteristics.

The SCCS study design has been used in pharmacovigilance studies to investigate vaccine safety, including COVID-19 vaccines(40-42). Three assumptions should be satisfied to ensure the appropriate use of SCCS(27). Firstly, the event should be independently recurrent such that each occurrence does not affect subsequent events. However, events could occur repeatedly and may increase the probability of future episodes. Therefore, only the first episode was treated as the outcome of interest in this study. Secondly, the event of interest should be independent of the exposure. Patients with events might be less likely to receive

the vaccines and hence this assumption might not be supported when applying the standard SCCS model, especially for the second dose vaccination. Therefore, we applied a modified SCCS model, which was designed for investigating outcomes that are associated with exposure(43). Lastly, the event should not censor the observation period. The modified SCCS for event dependent exposure analysis was applied using the R function "eventdepenexp" in the R-package "SCCS"(28). IRRs and their corresponding 95% Cis were estimated using conditional Poisson regression, with non-exposure period as the reference period and length of risk period as offset variable. Unlike the classical SCCS, the modified SCCS requires unvaccinated patients with ALI during the observation period (e.g. no scheduled vaccination appointment, or cancellation of vaccination appointment if the ALI events occurred before receiving the vaccine) to inform timing of the events by adjusting for the monthly seasonal effects. It is important to note that these unvaccinated patients did not act as controls. A comprehensive discussion on use of the modified SCCS for COVID-19 vaccine research can be found in a recent publication(44).

To ensure the robustness of the main results, sensitivity analyses were conducted by 1) varying the duration of risk window from 14 to 42 days; 2) excluding the pre-vaccination period due to potential increased liver function abnormalities detected during the pre-vaccination interval when people might have had health check-up prior to vaccination; 3) adding pre-risk periods of days -56 to -1 prior to two doses as people who had events onset at pre-risk period might decrease the likelihood of vaccination, 4) excluding patients with SARS-CoV-2 infection after the rollout of the vaccination program in Hong Kong as they would have had exposure to both the vaccination and natural infection which might trigger a greater immune response and increase the ALI risk; and 5) excluding patients who had no liver panel results during the observation period. Subgroup analyses of patients with and

without chronic liver diseases were conducted, where chronic liver disease is defined as patients with cirrhosis, fatty liver disease, hepatitis, hepatocellular carcinoma, and use of viral hepatitis drugs.

All statistical analyses were performed with R version 4.1.1 and Stata MP v17.0 (StataCorp LLC). A two-sided significance level of 5% was used in all statistical analyses. Two investigators (ICHA and FWTC) independently conducted the statistical analyses for quality assurance.

Ethics approval

Ethical approval for this study was granted by the Institutional Review Board of the University of HK/HA HK West Cluster (UW21-149 and UW21-138) and the Department of Health Ethics Committee (LM 21/2021).

Results

Baseline characteristics

A study population of 4,029,257 people was identified from the database after excluding 132,329 people aged below 18 years. Of the 3,981,696 people without a history of ALI, 2,343,288 COVID-19 had been vaccine recipients (BNT162b2: 1,348,411; CoronaVac: 994,877) in the period between 23rd February 2021 and 30th September 2021. These include 1,267,318 (94.0%) and 915,690 (92.0%) people who had received the second dose of BNT162b2 or CoronaVac, respectively. Figure 2 summarizes the patient deposition of the study. Table 1 shows the baseline characteristics of 4,677 patients who had the first incident ALI and had been vaccinated from 23rd February 2021 to 30th September 2021. The median

(interquartile age range [IQR]) of ALI patients who received BNT162b2 or CoronaVac were 52 (IQR: 38-63) and 60 (IQR: 49-68) years, respectively. Female ALI cases following BNT162b2 and CoronaVac vaccination accounted for 41.4% and 40.5%, respectively.

Clinical presentation and severity of ALI among subjects with ALI during risk periods

The median duration from vaccination to onset of ALI was 20 (IQR: 11-33) days. There were 307 ALI events which occurred within 56 days after the first dose of BNT162b2, and 304 ALI events which occurred within 56 days after the first dose of CoronaVac vaccination. The crude incidence rate of 56-day ALI was 335 cases per 100,000 person-years (307 cases/ 91,722 person-years) for the first dose BNT162b2 recipients, and 358 cases per 100,000 person-years (304 cases/ 84,993 person-years) for first dose CoronaVac recipients within 56 days. A total of 521 and 474 ALI events occurred within 56 days after the second dose of BNT162b2 and CoronaVac vaccination, respectively. The crude incidence rate of 56-day ALI was 334 cases per 100,000 person-years (521 cases/ 156,161 person-years) for second dose BNT162b2 recipients, and 403 cases per 100,000 person-years (474 cases/ 117,607 person-years) for second dose CoronaVac recipients within 56 days.

Of the 1,606 vaccinated individuals who had an incident ALI during the exposure periods (i.e. within 56 days after first or second dose of COVID-19 vaccination), 676 (42.1%) patients required hospitalization (median length of stay: 4, IQR: 2-7 days) and 19 (1.2%) stayed in the ICU during the hospitalization. In total, 2.9% of BNT162b2 recipients and 3.5% of CoronaVac recipients were hospitalized because of a primary diagnosis of ALI. The median duration of ALI was 4 days (IQR 2-7); most cases (99.2%) had resolved by day 42. No patients developed severe or fatal ALI (i.e., DILIN scale 4 or 5) in either vaccinated group. Most ALI patients had a peak ALT <20 x ULN or AST <10 x ULN, while a peak

ALT >20x ULN and a peak AST >10x ULN were observed in 3.8% and 25.5% of BNT162b2 recipients, and 3.6% and 26.5% of CoronaVac recipients, respectively. There were no significant differences in the ALI severity defined by the DILIN scale (P=0.405), peak ALT (P=0.908), peak AST (P=0.329), the De Ritis ratio (P=0.221), hospitalization rate (P=0.237), and ICU admission (P=0.193) between the two vaccine recipient groups (Figure 3). Of those patients who were followed-up for at least 28 days after ALI onset, there were no significant differences in the proportion of recipients delaying the second dose of vaccine (P=0.260), risks of incident AIH (0% for both groups) and new-onset liver diseases (P=0.269). Chronic liver disease was the leading potential cause of post-vaccination ALI (BNT162b2: 8.0%; CoronaVac: 10.5%), followed by cholestasis/ cholangitis/ cholecystitis/ cholelithiasis (BNT162b2: 3.3%; CoronaVac: 4.0%), and cancer (BNT162b2: 1.9%; CoronaVac: 3.7%). (Supplementary Table 1).

Modified SCCS analysis

The total number of ALI events during the observation period in both vaccinated subject groups was 4,677 (2,473 from BNT162b2 and 2,204 from CoronaVac) (Figure 2). The proportion of individuals who received both doses of vaccines were 87.3% and 83.5% for BNT162b2 and CoronaVac, respectively.

Figure 4 and Supplementary Table 2 show the IRRs of ALI following COVID-19 vaccination and a comparison by event-dependent exposure SCCS. Compared with the non-exposure period, no increased risk was observed in the 56-day risk period for the first dose of BNT162b2 (IRR=0.800, 95%CI: 0.680–0.942), first dose of CoronaVac (IRR=0.689, 95%CI: 0.588–0.807), the second dose of BNT162b2 (IRR=0.949, 95%CI: 0.816–1.091), or the second dose of CoronaVac (IRR=0.905, 95%CI: 0.781–1.048). We compared the peak liver

enzymes of the non-exposure vs the exposure period using linear regression. The peak ALT and peak AST for BNT162b2 recipients was 288 vs 268 U/L (p=0.204) and 216 vs 224 U/L (p=0.716), respectively. Similarly, the peak ALT and peak AST for CoronaVac recipients was 288 vs 250 U/L (p=0.030) and 245 vs 215 U/L (p=0.458), respectively.

Sensitivity analyses with various risk periods, adding pre-risk periods, excluding patients who died during the observation period, excluding the pre-vaccination period including patients who had liver panel results, and subgroup analyses of patients with and without chronic liver diseases, demonstrated consistent findings (Supplementary Table 3) in both vaccines.

ALI risk in comparison with patients with SARS-CoV-2 infection

Of the 6,353 adult patients with SARS-CoV-2 infection without prior ALI (Supplementary Table 4), the number of ALI cases within a 56-day period of SARS-CoV-2 infection was 309. Crude incidence rate was 32,997 cases per 100,000 person-years.

After propensity score weighting (Supplementary Table 5), vaccinated individuals had lower 56-day ALI risks than patients with SARS-CoV-2 infection (BNT162b2: IRR=0.052 95%CI 0.045-0.059 p<0.001; CoronaVac: IRR=0.051 95%CI 0.045-0.058 p<0.001). The median time from SARS-CoV-2 infection to ALI onset was 9 days (IQR: 4–14). The median length of hospitalization was 13 (IQR: 6 to 21) days and 62 (19.1%) required ICU admission. The mean peak ALT and peak AST were 254 and 185 U/L, respectively. The proportion of patients with SARS-CoV-2 infection who developed moderate ALI (i.e., DILIN scale 2) was 3.02%, peak ALT >20x ULN was 10.87%, and peak AST >10x ULN was 1.63%.

Discussion

To the best of our knowledge, this is the first SCCS study using population-based data to examine the risk of ALI after COVID-19 vaccinations. The current study did not identify any increased risk of ALI after BNT162b2 or CoronaVac vaccination. Our findings suggested that the absolute risk of ALI is very low following COVID-19 vaccination, and lower than ALI following SARS-CoV-2 infection. Over 90% of the ALI cases following COVID-19 vaccination were mild cases, while none of the ALI cases were severe or fatal.

ALI following COVID-19 vaccination was reported in cases which presented with a variety of clinical signs and laboratory results. The majority of liver injury cases in mRNA vaccine recipients showed hepatocellular injury along with high titers of autoantibodies, elevated IgG and response to corticosteroid therapy (35, 36). Only association, but not causality, were suggested between COVID-19 vaccination and ALI due to the presence of other confounding factors in these case reports (4, 5). Although most studies did not suggest direct vaccine-induced liver injury and AIH, vaccine-induced immune-mediated hepatitis was postulated as one of the possible mechanisms (35, 36, 45). Theoretically, mRNA vaccines are more immunogenic than inactivated whole-virus vaccines as observed from the superior seroconversion rates of anti-spike receptor binding domain IgG after vaccination(46). mRNA vaccines are known to be “self-adjuvanted” due to the capacity of the mRNA to stimulate innate responses via the endosomal toll-like receptors 3,7,8 and 9, as well as stimulation of type I interferon from RIG-I sensing. In comparison, inactivated whole-virus vaccines are not sufficiently immunogenic on their own and require the addition of an adjuvants, which in the case of CoronaVac is aluminium hydroxide (47). Detailed analyses with head-to-head comparison of the T cell response following mRNA vaccine or inactivated whole-virus

vaccines are however lacking. One study reported a different spectrum of T cell responses (in terms of epitopes and IFN-γ-positive T cell response) between BNT162b2 and BBIBP-CorV (inactivated virus) but it was concluded that both vaccines were immunologically effective(48). A recent case report has shed some light on deciphering the potential immunopathogenesis of mRNA vaccine associated AIH(49). In a 52-year-old man with clinically robust AIH which was steroid-responsive, SARS-CoV-2-specific CD8+ T cells were enriched and demonstrated activated phenotype both peripherally and intra-hepatically, in comparison with vaccinated subjects who did not develop hepatitis. In addition, CD38 expression level corresponding to T cell activation mirrored transaminase levels and response to systemic corticosteroid therapy. These findings strongly support the hypothesis that mRNA COVID-19 vaccine is capable of causing AIH. However, considering 760 million doses of mRNA COVID-19 vaccine have been administrated worldwide(50), if there was a causal association, the risk is extremely small.

Taking a broader view, not all cases of ALI following COVID-19 vaccination can be accounted for by AIH. The exact mechanisms for the majority of ALI cases following COVID-19 vaccination remain unknown. Previous population-based studies have shown that drug-induced hepatoxicity occurred in 19 cases per 100,000 recipient while hepatoxicity with autoimmune features was seen in fewer than 1 per million cases(35, 51). In the reported cases of suspected vaccine-induced immune hepatitis, the subjects had good previous health with no history of autoimmune disease, or exposure to hepatotoxic agents or other AIH-related risk factors. The response to immunosuppressive treatment in those reports and the presence of autoimmune comorbidities (e.g. Hashimoto thyroiditis)(52, 53) would speak for immune-mediated events, yet a definite causality between COVID-19 vaccine and AIH could not be established (1-4). Although elevated IgG level, interface hepatitis and lymphoplasmacytic

infiltrate were typical features in autoimmune hepatitis, such features were not consistently observed in some cases associated with COVID-19 vaccine(4, 5). Previous studies found 10% to 34% of these patients were asymptomatic and had significantly lower or normal aminotransferase and immunoglobulin levels but similar liver histopathological features as symptomatic patients; this suggests poor correlation between clinical features and liver histology (54, 55). Therefore, we cannot exclude the possibility that the number of injurious cases has been underestimated in the literature to date, as well as in our population-based data. Indeed, access to care and patients' hesitancy to comply with medical follow-ups during the pandemic likely masked some cases of ALI as shown in a single-center study in Germany(56). The same group reported no increased risk of AIH after COVID-19 vaccination and 25 patients with "newly diagnosed AIH" that was temporally related to the vaccine displayed features of definite pre-existing chronic liver disease(56). Therefore, the true incidence of ALI (and possibly AIH) following COVID-19 vaccination is compounded by many confounding factors such as case identification, alternative causes of ALI, and pre-existing liver disease.

In addition, cases of immune thrombocytopenic purpura with or without coincidental liver injury were reported following COVID-19 vaccines, further supporting the possible mechanism of immune-mediated injury(5, 7, 57). However, this hypothesis was challenged by the lack of interaction between anti-PF-4 antibody and spike protein, and the absence of relapse(58). Because cases of AIH and immune thrombocytopenic purpura were rarely reported despite the overwhelming number of COVID-19 vaccine doses administered daily and globally, direct causation between vaccines and liver injury was difficult to establish (35). Nevertheless, the vast majority of subjects with ALI following COVID-19 vaccination in our cohort presented with mild severity, low rates of hospitalization and ICU admission,

and spontaneous recovery without the need of immunosuppressive therapy, thereby speaking against the phenomenon of vaccine-induced chronic AIH or immune-mediated DILI, which typically requires corticosteroid therapy to induce remission. In our cohort, the mean platelet count among vaccinated subjects with ALI was not significantly lower during the ALI period in comparison with pre-ALI onset (ALI onset: 241.8±121.3 10^9/L vs. pre-ALI onset 242.8±110.2 10^9/L, p=0.617; data not shown), findings not supportive of immune phenomenon. Our analysis showed that the risk of ALI following COVID-19 vaccination was not higher than in the non-exposure period. Vaccinated individuals in Hong Kong might have had a health check-up prior to the vaccination and therefore have higher chance of ALI being detected in the pre-vaccination period. Nevertheless, the results remained the same after the discounting the pre-vaccination period (Supplementary Table 3). Overall, the risk of severe liver injury or liver failure was extremely low after COVID-19 vaccination. The incidence rate of ALI following COVID-19 vaccination was much less than that following SARS-CoV-2 infection. Since presentation of severe SARS-CoV-2 infection is associated with ALI (59, 60), vaccination is recommended for protection against ALI associated with severe COVID-19.

Although vaccination should be considered a pharmaceutical product for the prevention of different diseases, there are no registries like DILIN to comprehensively track and investigate into the events of ALI(61). Most ALI following administration of drug, also known as drug-induced liver injury (DILI), occurs in the first few weeks in both intrinsic or idiosyncratic events. Intrinsic DILI typically presents with a dose-related pattern and occurs in a large proportion of individuals exposed to the drug within a short time span (hours to days). In idiosyncratic DILI, cases are not dose-related and exhibit a variable latency to onset of days to weeks (34). Therefore, defining the exposure period as the first 55 days after vaccination in

our cohort can reasonably account for the majority of ALI cases potentially associated with COVID-19 vaccination. Moreover, we performed additional sensitivity analysis considering different lengths of exposure period, which yielded similar findings of no increase in the risk of ALI in the exposure period compared to the non-exposure period (Supplementary Table 3).

There are several limitations in the current study. Firstly, our study reported a low rate of chronic liver disease among vaccinated individuals with incident ALI so it is possible that some underlying liver diseases may have been underdiagnosed. However, our previous publications have shown that vaccine recipients in Hong Kong were younger, healthier, and on fewer medications than unvaccinated people during the observation period (12, 15, 16). Hence, our findings may not be fully applicable to people in poor health. Nevertheless, a "healthy vaccine recipient effect" is unlikely to affect our results because of the within-person comparison nature of the SCCS. Furthermore, our study yielded negative results. This confirms that its study design does not suffer from detection bias i.e. better surveillance of ALI post vaccination to cause an apparent association. Consequently, it does not affect the interpretation of our results. Secondly, results of liver biopsy and ductal enzymes like alkaline phosphatase were not available in our data source; and only laboratory data of ALT, AST, and total bilirubin were used for outcome definition. Supportive data on autoantibodies and immunoglobulin pattern will be helpful in future studies to improve characterization of ALI and identify immune-mediated hepatitis following COVID-19 vaccination. However, severe autoimmune conditions following COVID-19 vaccination are rare(25). It is worth considering that the current literature is potentially influenced by publication bias, where cases with features of AIH following vaccination are preferentially reported. Currently, the relative number of COVID-19 vaccines administered significantly outweighs the number of

SARS-CoV-2 infections on a global level(50, 62). This could also contribute to the numerous case reports of post-vaccination ALI in the literature compared to ALI associated with natural infection, the latter being mediated by non-immunological mechanisms(63), Diagnosis of pre-existing cases unmasked, and under-diagnosis of asymptomatic cases cannot be completely ruled out. However, severe cases which required emergency services and hospitalization are likely to have been captured in our study. Lastly, with the assumption used in SCCS analysis meant that only new-onset ALI but not recurrent events were included in our analysis. Future studies are needed to explore the risk of ALI following COVID-19 vaccination in patients with underlying liver diseases or previous episode of ALI.

Conclusion

Although case reports of severe ALI following COVID-19 vaccination have been recently described, our analytical study found no increased risk of ALI after BNT162b2 or CoronaVac COVID-19 vaccination. Our findings showed that the absolute risk of ALI is very low following COVID-19 vaccination in our cohort of over 2 million vaccine recipients. Based on all current available evidence from previous studies and our study, the potential benefit of mass vaccination far outweighs the potential ALI risk from vaccination and SARS-CoV-2 infection.

Abbreviations

AIH – Autoimmune hepatitis

ALI – Acute liver injury

ALT – Alanine aminotransferase

AST – Aspartate aminotransferase

CI – Confidence interval

COVID-19 – Coronavirus disease 2019

DILI – Drug-induced liver injury

DILIN - Drug-Induced Liver Injury Network

ICU – Intensive care unit

IQR – Interquartile range

IRR – Incidence rate ratio

IPTW - Inverse probability of treatment weights

PCR – Polymerase chain reaction

SARS-CoV-2 – Severe acute respiratory syndrome coronavirus 2

SCCS – Self-controlled case series

ULN – Upper limit of normal

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Author names in bold designate shared co-first authorship

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Table 1. Baseline characteristics of people who had the first incident acute liver injury from 23rd February 2021 to 30th September 2021 in BNT162b2 or CoronaVac in the self-controlled case series study

Baseline characteristics	Acute liver injury (N=4,677)			
	BNT162b2 (N=2,473)		CoronaVac (N=2,204)	
	N / Median	% / IQR	N / Median	% / IQR
Age, years	52	38-63	60	49-68
18-40	699	28.3%	233	10.6%
41-65	1,281	51.8%	1,266	57.4%
>65	493	19.9%	705	32.0%
Sex				
Male	1,449	58.6%	1,311	59.5%
Female	1,024	41.4%	893	40.5%
Pre-existing comorbidities				
Charlson's index	2	0-3	3	2-4
0-1	1,088	44.0%	550	25.0%
2-4	1,179	47.7%	1,361	61.8%
≥5	206	8.3%	293	13.3%
Chronic Liver diseases	77	3.1%	93	4.2%
Myocardial infarction	26	1.1%	23	1.0%
Hypertension	508	20.5%	622	28.2%
Peripheral vascular disease	13	0.5%	8	0.4%
Cerebrovascular disease	55	2.2%	72	3.3%
Chronic obstructive pulmonary disease	44	1.8%	46	2.1%
Dementia	4	0.2%	6	0.3%
Paralysis	3	0.1%	4	0.2%
Diabetes without chronic complication	223	9.0%	315	14.3%
Diabetes with chronic complication	15	0.6%	18	0.8%
Malignancy	112	4.5%	122	5.5%
Metastatic solid tumor	19	0.8%	24	1.1%
Medications used				
Renin-angiotensin-system agents	394	15.9%	427	19.4%
Beta blockers	278	11.2%	314	14.2%
Calcium channel blockers	525	21.2%	656	29.8%
Diuretics	134	5.4%	124	5.6%
Nitrates	85	3.4%	77	3.5%
Lipid lowering agents	486	19.7%	552	25.0%
Insulins	76	3.1%	70	3.2%
Antidiabetic drugs	278	11.2%	341	15.5%
NSAID	269	10.9%	201	9.1%
Antivirals	148	6.0%	183	8.3%

Antibiotics	499	20.2%	411	18.6%
Immunosuppressants	32	1.3%	18	0.8%
COVID-19 survivor	15	0.6%	4	0.2%
Received second dose	2,158	87.3%	1,840	83.5%

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

Figure 1. Observation timeline of patients in the modified self-controlled case series

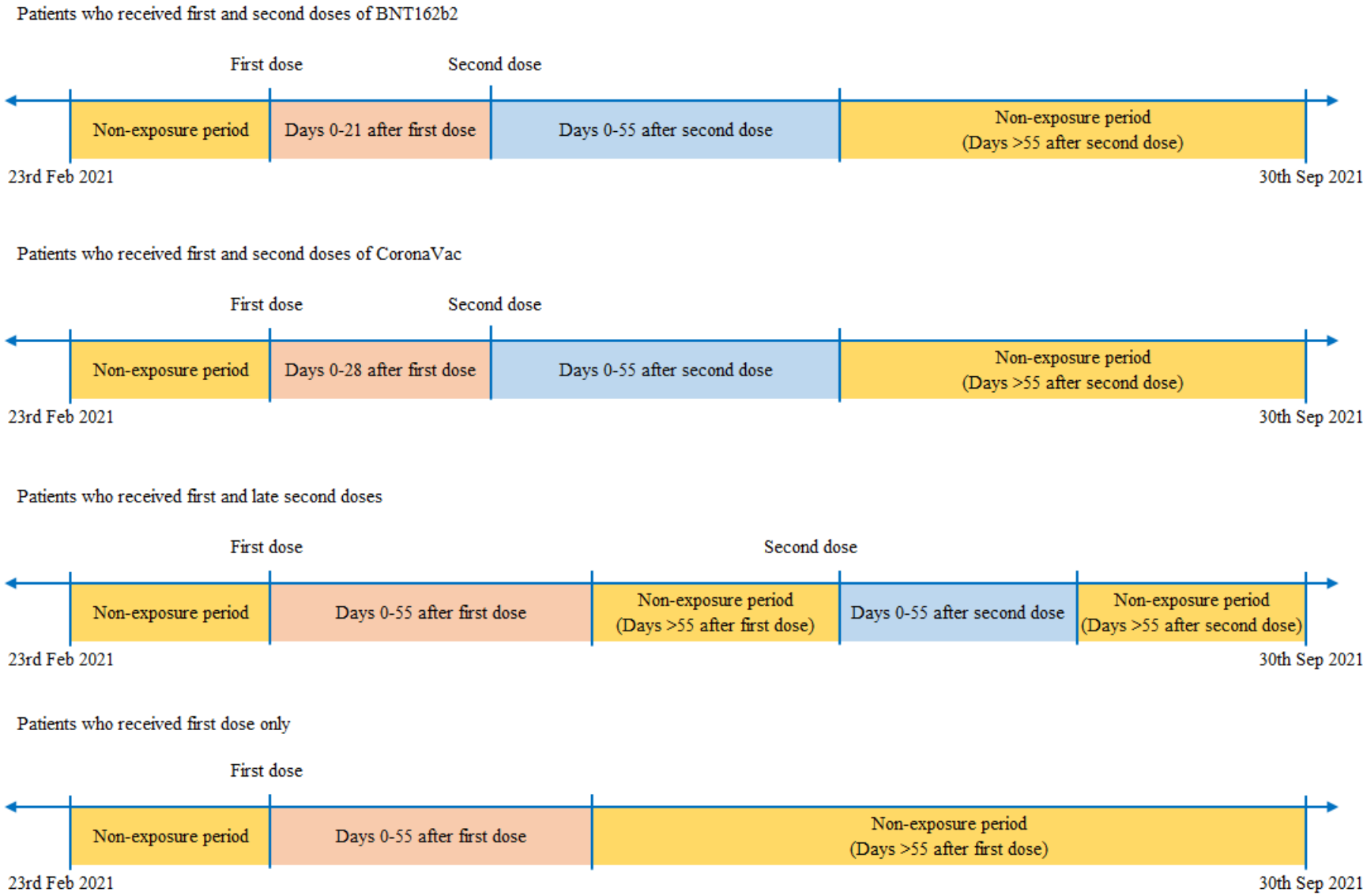
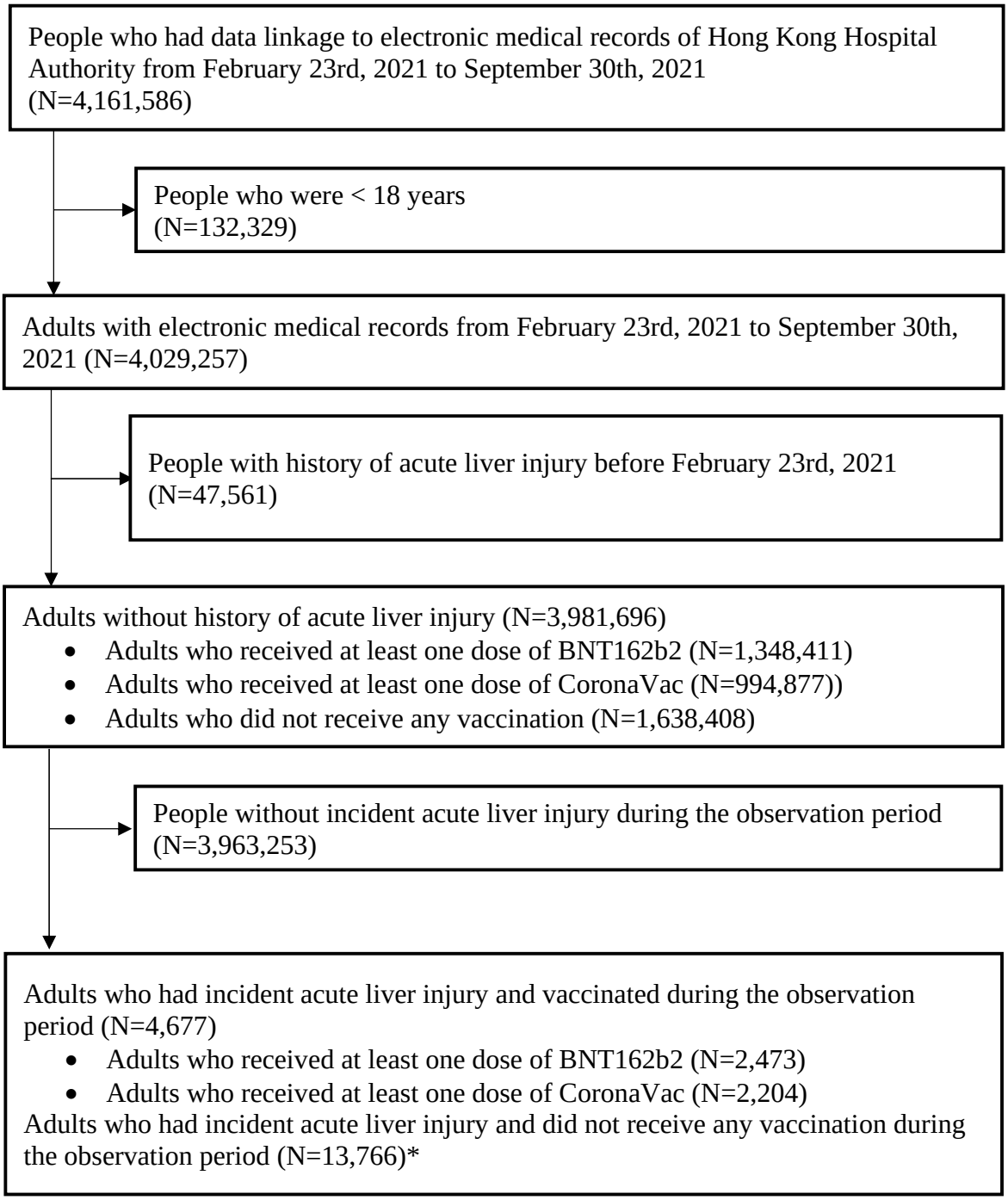
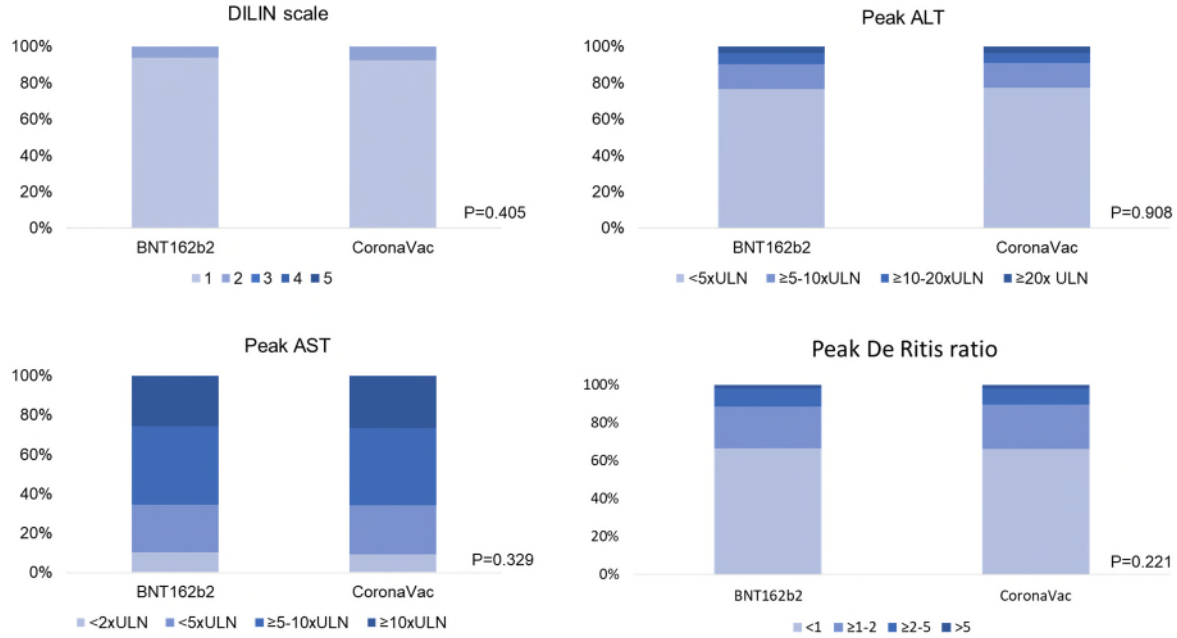


Figure 2. Inclusion and exclusion criteria for modified self-controlled case series analysis of people from February 23rd, 2021 to September 30th, 2021 in Hong Kong SAR, China.



* Unvaccinated patients with ALI during the observation period (e.g. no scheduled vaccination appointment, or cancellation of vaccination appointment if the ALI events occurred before the scheduled appointment) was included to inform the timing of events by adjusting for the monthly seasonal effects (44). These unvaccinated patients did not act as controls.

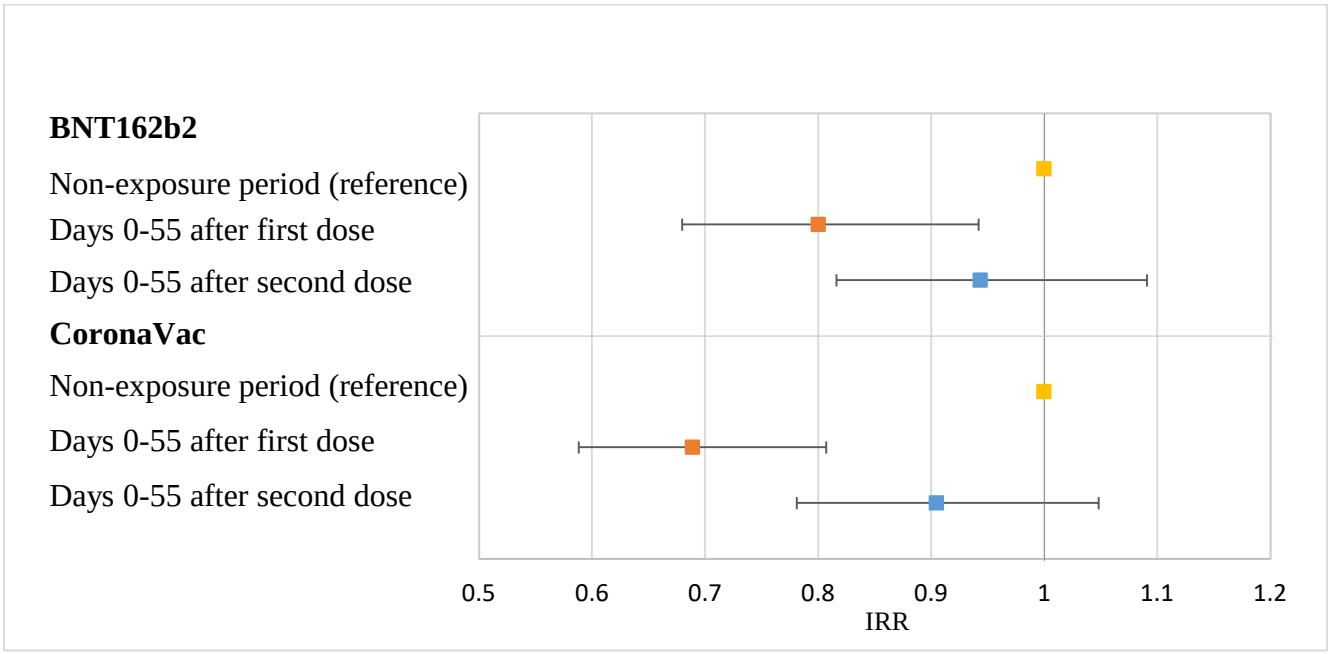
Figure 3. Severity of ALI in people who received BNT162b2 and CoronaVac vaccination.



ALI: acute liver injury, ALT: alanine aminotransferase, AST: aspartate aminotransferase, DILIN: Drug Induced Liver Injury Network, ULN: upper limit of normal

P-value of differences in ALI severity between people who received BNT162b2 and CoronaVac vaccination using ordered logistic regression adjusting for baseline characteristics

Figure 4. Risks of acute liver injury among people who received BNT162b2 and CoronaVac vaccination in the modified self-controlled case series analysis



Notes: CI = Confidence interval; IRR = Incidence rate ratio
Error bar is a 95% confidence interval of the incidence rate ratio

Title: No increase in risk of acute liver injury following the mRNA (BNT162b2) and inactivated (CoronaVac) COVID-19 vaccines: A self-controlled case series study

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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 and total serum bilirubin level ≥43 umol/L or 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 and 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 and at least one of the following:
    - Prolonged jaundice and symptoms beyond 3 months, or
    - Signs of hepatic decompensation (INR ≥1.5, ascites, encephalopathy), or
    - Other organ failure believed to be related to drug induced liver injury
- **5+, Fatal:** Death or liver transplantation for drug induced liver injury

Supplementary Table 1. 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%

Supplementary Table 2. 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

Supplementary Table 3. 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

Supplementary Table 4. 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;

Supplementary Table 5. 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

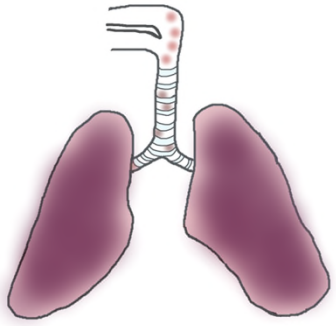
Baseline characteristics	Before weighting							After weighting						
	Patients with SARS-CoV-2 infection		BNT162b2		CoronaVac		ASMD	Patients with SARS-CoV-2 infection		BNT162b2		CoronaVac		ASMD
	N / Median	% / IQR	N / Median	% / IQR	N / Median	% / IQR		Median	% / IQR	Median	% / IQR	Median	% / IQR	
Age, 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

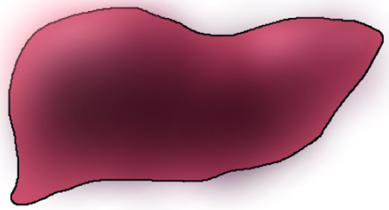
Note: ASMD = absolute standardized mean difference; IQR = interquartile range; NSAID = nonsteroidal anti-inflammatory drugs;

References

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/.



SARS-CoV-2 infection



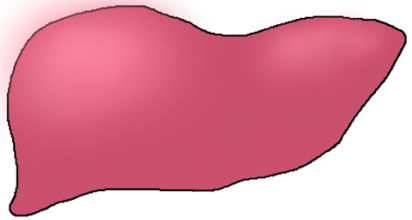
Risk of ALI

Crude incidence rate of 56-day ALI (per 100,000 person years): 32,997

COVID-19 vaccination

Self-controlled case series analysis

N=4,677 cases of first episode incident ALI
out of 2,343,288 vaccine recipients



No increased risk of ALI during exposure period* compared to non-exposure period

**Crude incidence rate of 56-day ALI (per 100,000 person years):*
Following 1st dose – BNT162b2: 335, CoronaVac: 358
Following 2nd dose – BNT162b2: 334, CoronaVac: 403

Severity of ALI among vaccinated subjects during exposure period (i.e. 56-days after 1st or 2nd dose of vaccine)