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Impact of hepatic steatosis on risk of acute liver injury in people with chronic hepatitis B and SARS-CoV-2 infection

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Abstract

Background: SARS-CoV-2 infection was known to be associated with higher risk of liver impairment in people with chronic hepatitis B infection (CHB). However, evidence regarding the impact of concomitant hepatic steatosis (HS) on the risk of liver disease among people with CHB and SARS-CoV-2 infection is lacking. We investigated the impact of concomitant HS on people with CHB suffering from SARS-CoV-2 infection.

Methods: This retrospective cohort study was performed using an electronic health database for people in Hong Kong with CHB and confirmed SARS-CoV-2 infection between 21 January 2020 and 31 January 2023. People with HS diagnosis (HS + CHB + COVID-19) were identified and matched 1:1 by propensity score with those without (CHB + COVID-19). Each person was followed up until death, outcome

Abbreviations: ALI, Acute liver injury; ALT, Alanine aminotransferase; CCI, Charlson Comorbidity Index; CHB, Chronic hepatitis B; CIs, Confidence intervals; CLD, Chronic liver disease; COVID-19, Coronavirus disease 2019; DH, Department of Health; DILIN, Drug-Induced Liver Injury Network; FIB-4, Fibrosis-4 index; HA, Hospital Authority; HBsAg, Hepatitis B surface antigen; HCC, Hepatocellular carcinoma; HS, Hepatic steatosis; ICD-9-CM, International Classification of Disease, 9th Revision, Clinical Modification; IRRs, Incidence rate ratios; MASLD, Metabolic dysfunction-associated steatotic liver disease; NAFLD, Non-alcoholic fatty liver disease; PASC, Post-acute sequelae of SARS-CoV-2 infection; RAT, Rapid antigen test; RT-PCR, Reverse transcription polymerase chain reaction; SLD, Steatotic liver disease; SMDs, Standardized mean differences.

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event, or 31st January 2023. Study outcome was incidence of acute liver injury (ALI) within first 28 days since COVID-19 diagnosis. Severity of ALI and comparison of ALI risk stratified by the presence of CHB infection and HS were also analysed. Incidence rate ratios (IRRs) were estimated by Poisson regression models.

Results: Of 52 259 COVID-19 patients with CHB infection in the cohort, 15 391 people with HS + CHB + COVID-19 and 15 391 people with CHB + COVID-19 were included after matching. HS + CHB + COVID-19 was associated with increased risk of ALI (IRR: 1.41, 95% CI:1.05–1.90, $p = 0.023$), compared to CHB + COVID-19. Over 99% ALI cases were mild to moderate severity, and there were no differences in the severity of ALI between HS + CHB + COVID-19 and CHB + COVID-19 ($p = 0.127$).

Conclusions: Concomitant HS was associated with increased risk of ALI among people with CHB infection suffering from SARS-CoV-2 infection.

KEYWORDS
acute liver injury, ALI, chronic hepatitis B, hepatic steatosis, long COVID, SARS-CoV-2 infection

1 | INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic, caused by SARS-CoV-2 infection, has affected more than 771 million people and caused more than 69 million deaths worldwide.[1] Chronic hepatitis B (CHB) is a common chronic liver disease (CLD), which affects over 350 million individuals globally and an estimated 1.5 million new infections each year.[2–4] Globally, CHB has caused 820 000 deaths, mostly from cirrhosis and hepatocellular carcinoma (HCC).[3,5] COVID-19 and hepatitis B are considered as major public health threats across the world and not to mention that coinfection of both diseases was associated with a higher risk of liver impairment.[6]

In addition, approximately 25%–40% of people with CHB infection also suffer from steatotic liver disease (SLD), which is another common CLD with constantly increasing prevalence.[7–9] Hepatic steatosis (HS) potentially leads to severe liver-related complications such as cirrhosis, liver cancer, and mortality.[10,11] CHB and SLD are two of the most prevalent liver-related diseases worldwide.[12] Hence, it is important to understand the impact of concomitant HS on the risk of liver disease among people with CHB and SARS-CoV-2 infection. Several studies had indicated that the co-infection of HS and CHB was associated with worsening of liver fibrosis and increased risks of HCC and cirrhosis.[13–16] Meanwhile, it was also suggested that the presence of HS was associated with lower viral load[14] and earlier age of hepatitis B surface antigen (HBsAg) seroclearance,[17] which is regarded as functional cure in CHB. In fact, the association of increasing chance of functional cure from hepatitis B virus among people with co-existing HS and CHB infection was reported previously.[13–15] Therefore, the debate on the diverse effects of HS on the natural history of CHB infection is ongoing and the relationship between HS and CHB still remains complicated and unclear.

Although it is well known that COVID-19 increases the risk of adverse liver outcomes in CHB, there is no data on how concomitant HS modifies the prognosis in this context. To address this knowledge gap, we carried out this population-based cohort study to investigate the impact of concomitant HS on people with CHB and SARS-CoV-2 infection.

Lay summary

Our study showed that either CHB or HS was associated with increased risk of ALI in COVID-19 infection and provided new evidence that additive effects of dual etiologies from CHB and HS in contributing to incidence of ALI following SARS-CoV-2 infection. Furthermore, our results showed that although the majority of ALI was mild in severity, CHB patients suffering from ALI after SARS-CoV-2 infection tended to have more severe ALI than patients with HS or overall population. These findings have important implications for optimization of treatment for underlying chronic liver disease is warranted to prevent risk of ALI following acute illness.

2 | MATERIALS AND METHODS

2.1 | Data source and study population

This study was conducted based on data of a territory-wide cohort of people with anonymized electronic health records provided by the Hospital Authority (HA), and COVID-19 vaccination records were available from the Department of Health (DH), The Government of Hong Kong Special Administrative Region, Hong Kong. Electronic medical records were retrieved from the HA. These

records included demographics, disease diagnoses, drug prescriptions, laboratory tests, hospital admissions, emergency department, and inpatient procedures. The HA data were linked to the COVID-19 vaccination records provided by the DH using the unique identification numbers. This linked database has been used extensively for studies on COVID-19 vaccine safety[18–20] and post-acute sequelae of SARS-CoV-2 infection (PASC).[21]

The study protocol was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (UW 20-556, UW 21-149 and UW 21-138); and the Department of Health Ethics Committee (LM 21/2021 and LM 175/2022). Informed patient consent was not required as the data used in this study were anonymized.

This study included people in Hong Kong with CHB and confirmed SARS-CoV-2 infection between 21st January 2020 and 31st January 2023. CHB was identified by International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis code, prescription of hepatitis antivirals, or positive HBsAg test (Table S1). SARS-CoV-2 infection was confirmed by a positive reverse transcription polymerase chain reaction test or rapid antigen test result. The index date was set at the first date of SARS-CoV-2 infection (i.e. only the first infection was eligible for the analysis). People who were identified with HS or non-alcoholic fatty liver disease (NAFLD), prior or within the first 6 months since the index date were classified into the HS + CHB + COVID-19 group, while people without HS or NAFLD were classified into the CHB + COVID-19 group. NAFLD ridge scores of COVID-19 patients were calculated and those with NAFLD ridge score higher than 0.44 were identified as HS or NAFLD.[22] Each person was observed from the index date to the occurrence of outcomes, death, or the end of observational period (i.e. 31st January 2023), whichever the earliest occurred.

We excluded people with CHB and SARS-CoV-2 infection who (i) died on or before the index date, and (ii) aged <18 or >80 years.

2.2 | Definition of covariates

Baseline characteristics including age, sex, date of SARS-CoV-2 infection, severe COVID-19 cases (classified by WHO clinical progression scale ≥6),[23] status of inpatient COVID-19 diagnosis, pre-existing comorbidities (Charlson Comorbidity Index [CCI], cirrhosis, HCC, liver decompensation, and baseline significant liver disease), receipt of antiviral treatment for hepatitis B and COVID-19, and COVID-19 vaccination status were captured based on ICD-9-CM diagnosis, procedure codes, treatment records and clinical parameters (Table S1). The fibrosis-4 index[24] was also used to identify cirrhosis and baseline significant liver disease. Baseline significant liver disease was defined as people with fibrosis-4 index higher than 3.25 (i.e., those who had a high probability of advanced fibrosis[25]) or the level of alanine aminotransferase (ALT) higher than 80 U/L. Fully vaccinated was defined as people with at least two doses of BNT162b2 (Comirnaty) or three doses of COVID-19 Vaccine (Vero Cell), Inactivated (CoronaVac).[26]

2.3 | Outcome definition

The study outcome was acute liver injury (ALI) within the first 28 days since the index date.

ALI was defined by ICD-9-CM diagnosis codes and the levels of ALT and total bilirubin according to the criteria listed in Asia Pacific Association of Study of Liver consensus guidelines[27] and the drug-induced liver injury clinical practice guidelines of the European Association for the Study of Liver Disease.[28] ALI was defined when satisfying at least one of the following conditions: (i) ICD-9-CM codes 570.X, 572.2 or 573.3, (ii) ≥5 x upper limit of normal (ULN) elevation in ALT, (iii) ≥3 × ULN elevation in ALT and simultaneous elevation of total bilirubin ≥2 × ULN, where the ULN of ALT and total bilirubin are 40 U/L and 19 μmol/L, respectively (Table S1).

2.4 | Severity of ALI

The severity of ALI was assessed based on the Drug-Induced Liver Injury Network (DILIN) scale,[29] The severity of ALI was presented by the following groups: (i) Overall population with COVID-19; (ii) People with HS and SARS-CoV-2 infection who did not have CHB infection (i.e. HS + COVID-19); (iii) People with CHB and SARS-CoV-2 infection who did not have HS (i.e. CHB + COVID-19); and (iv) People with CHB and SARS-CoV-2 infection who had HS (i.e. HS + CHB + COVID-19).

2.5 | Risk of ALI among people with SARS-CoV-2 infection, stratified by the presence of CHB infection and HS

Risk of study outcome among people with SARS-CoV-2 infection were also analysed between the following groups (i) HS + COVID-19 versus Overall population with COVID-19; (ii) CHB + COVID-19 versus Overall population with COVID-19; (iii) HS + CHB + COVID-19 versus Overall population with COVID-19; (iv) CHB + COVID-19 versus HS + COVID-19; and (v) HS + CHB + COVID-19 versus HS + COVID-19.

2.6 | Statistical analysis

Descriptive statistics of baseline characteristics between the HS + CHB + COVID-19 and CHB + COVID-19 groups were shown as mean and standard deviation for continuous variables, and numbers with percentages for categorical variables.

To balance the baseline covariates and reduce selection bias, we performed 1:1 propensity-score matching with a calliper width of 0.05 between groups of HS + CHB + COVID-19 and CHB + COVID-19. We constructed a propensity-score model conditional on baseline covariates including age, sex, CCI, year of SARS-CoV-2 infection (year 2020, 2021, 2022 and 2023), COVID-19 severity (severe COVID-19 case or mild or moderate COVID-19 case), status of inpatient COVID-19 diagnosis, and COVID-19 vaccination status (fully or not fully vaccinated) in a logistic regression model. The 1–1 nearest neighbour method was used to match the patients between the two groups (i.e., 1 patient from HS + CHB + COVID-19 was matched to 1 patient in CHB + COVID-19 with a similar propensity score). Standardised mean differences (SMDs) of each covariate between the groups after propensity-score matching were calculated, which was interpreted as balanced when the SMD was below the threshold of 0.1.[30] The incidence rate ratio (IRR) and corresponding 95% confidence intervals (CIs) were estimated using the Poisson regression model.

Subgroup analyses were performed on several patient groups, including the presence of cirrhosis, receipt of antiviral treatment for hepatitis B, severity of COVID-19 (mild or moderate vs severe cases), the presence of baseline significant liver disease, and receipt of antiviral treatment for COVID-19. Each subgroup analysis was re-constructed with a new propensity-score model, and rematched the pairs of people in HS + CHB + COVID-19 and CHB + COVID-19 groups.

All statistical analyses were performed using Stata, version 17 (StataCorp LLC). The analyses were conducted by MSHC and analysed independently by XX and LL for quality assurance. All significance tests were two-tailed, where p-value <0.05 was considered statistically significant.

3 | RESULTS

3.1 | Baseline characteristics

A total of 52 259 people with CHB and confirmed SARS-CoV-2 infection between 21st January 2020 and 31st January 2023 in Hong Kong were identified. Among this study cohort, 18 548 were diagnosed with HS and 33 711 were not diagnosed with HS (Figure 1). After applying exclusion criteria followed by 1:1 propensity-score matching, 15 391 people with CHB and COVID-19 who had HS (HS + CHB + COVID-19) and 15 391 matched controls (CHB + COVID-19) were included in the present study. The baseline characteristics are presented in Table 1. Baseline age (60.7 vs 61.1 years), sex (male: 61.8% vs 63.3%), medical comorbidities (CCI: 3.7 vs 3.5), and COVID-19 vaccination status (fully vaccinated: 62.2% vs 62.2%) were balanced between the two groups. In addition, underlying cirrhosis (10.9% vs 11.7%), HCC (3.2% vs 3.6%), decompensated liver disease (2.9% vs 3.5%), receipt of antiviral treatment for hepatitis B (67.9% vs 63.6%), and receipt of antiviral treatment for COVID-19 (1.1% vs 1.0%) were matched between HS + CHB + COVID-19 and CHB + COVID-19 groups (all SMDs ≤0.1). Of note, the majority (99.0%) of included subjects came from years 2022 and 2023 when the omicron strain of SARS-CoV-2 was ubiquitous.

3.2 | Risk of ALI between HS + CHB + COVID-19 and CHB + COVID-19 groups

Over 28 days of follow-up, 105 and 75 events of ALI were observed for HS + CHB + COVID-19 and CHB + COVID-19 groups, respectively. The crude incidence rates of ALI were 134.7 (95% CI: 110.2–163.0) events per 10 000 person-years (105 events/7796 person-years) for HS + CHB + COVID-19 group, and 95.3 (95% CI: 75.0–119.5) events per 10 000 person-years (75 events/7867 person-years) for CHB + COVID-19 group. HS + CHB + COVID-19 group was associated with a significantly higher risk of ALI (IRR: 1.41, 95% CI: 1.05–1.90, $p = 0.023$), compared to the CHB + COVID-19 group (Table 2). In addition, both HS + CHB + COVID-19 and CHB + COVID-19 groups had higher risk of ALI compared to the overall population with COVID-19 (Figure 2).

3.3 | Subgroup analyses

Results of ALI outcome among subgroups of people with mild or moderate COVID-19 cases, without baseline significant liver disease, and without antiviral treatment for COVID-19 were consistent with the main results. Besides, no significant differences of ALI risk were observed in the subgroups of people with and without cirrhosis, with and without antiviral treatment for hepatitis B, with severe COVID-19 cases, with baseline significant liver disease, and with antiviral treatment for COVID-19 (Table S2).

3.4 | Severity of ALI

Among people with SARS-CoV-2 infection who had ALI events, the majority of them developed mild ALI (i.e. DILIN scale 1) (Overall population with COVID-19: 76.4%; HS + COVID-19: 79.2%; CHB + COVID-19: 66.4%; HS + CHB + COVID-19: 78.2%), followed by moderate ALI (i.e. DILIN scale 2) (Overall population with COVID-19: 23.3%; HS + COVID-19: 20.8%; CHB + COVID-19: 32.7%; HS + CHB + COVID-19: 21.0%). Only a small proportion of people with COVID-19 developed fatal ALI (i.e. DILIN scale 5) (Overall population with COVID-19: 0.3%; HS + COVID-19: 0.0%; CHB + COVID-19: 0.9%; HS + CHB + COVID-19: 0.8%) and none of the patients developed moderate-to-severe or severe ALI (i.e. DILIN scale 3 or 4) (Figure S1). Notably, grade 2 and grade 5 ALI were significantly more prevalent among patients with CHB + COVID-19

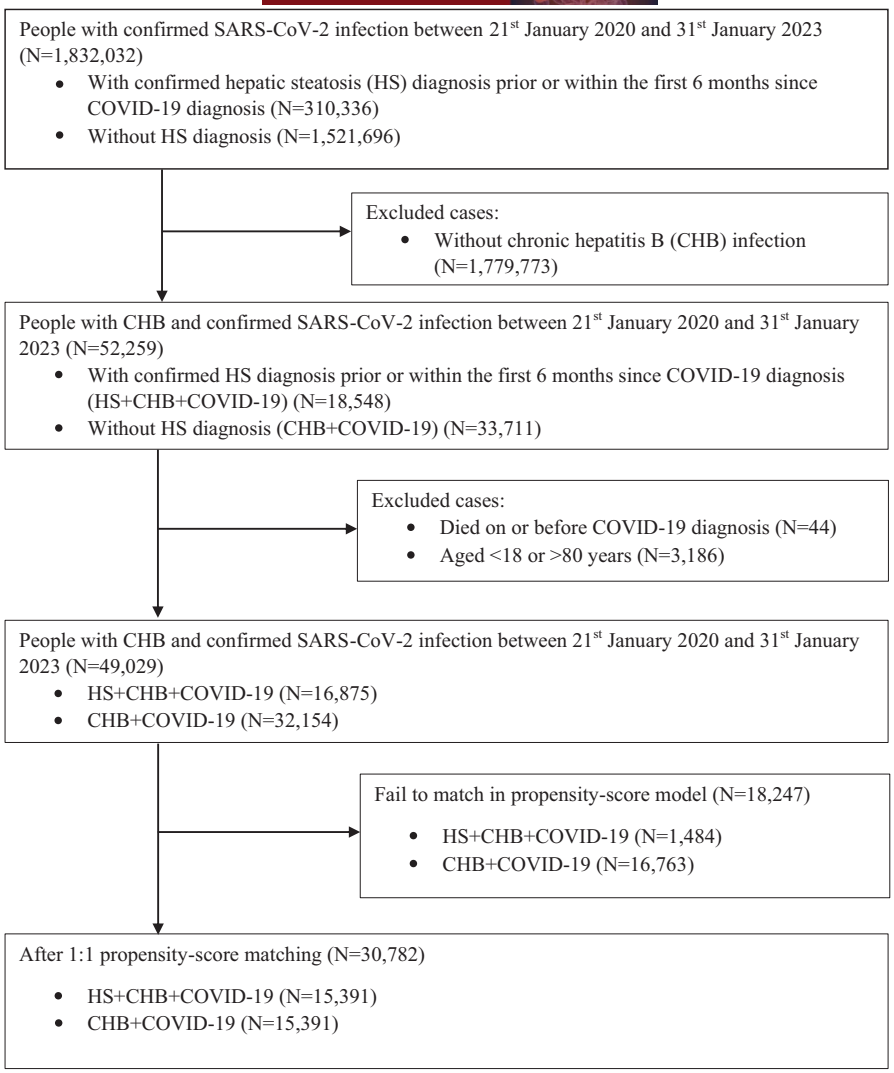

FIGURE 1 Study flowchart of eligible people with chronic hepatitis B and SARS-CoV-2 infection who were and were not diagnosed with hepatic steatosis for analysis.

compared to the overall population with COVID-19 ($p=0.027$) or patients with HS + COVID-19 ($p<0.001$).

3.5 | Risk of ALI among people with SARS-CoV-2 infection, stratified by the presence of CHB infection and HS

All HS + COVID-19, CHB + COVID-19, and HS + CHB + COVID-19 groups were associated with significantly higher risks of ALI (HS + COVID-19: IRR: 1.53, 95% CI: 1.37–1.72, $p<0.001$; CHB + COVID-19: IRR: 2.03, 95% CI: 1.46–2.83, $p<0.001$; HS + CHB + COVID-19: IRR: 2.14, 95% CI: 1.57–2.93, $p<0.001$), compared to the overall population with COVID-19 (Figure S2; Table S3).

Furthermore, HS + CHB + COVID-19 group was also associated with increasing risk of ALI (IRR: 1.65, 95% CI: 1.23–2.19, $p<0.001$), compared to the HS + COVID-19 group. However, no significant difference of the risk of ALI was observed for the CHB + COVID-19 group (IRR: 0.84, 95% CI: 0.65–1.10, $p=0.208$), compared to the HS + COVID-19 group (Figure S2; Table S3).

4 | DISCUSSION

HS and CHB infection are the top 2 leading causes of CLD in Hong Kong (population of 7.5 million), with an estimated 3 million (42% prevalence) and 0.6 million (7.8% prevalence) people suffering from HS and CHB, respectively.[31,32] COVID-19 pandemic swept every region in the world between year 2020 and 2023, with almost 3 million people in Hong Kong ever diagnosed with SARS-CoV-2 infection.[33,34] As ALI is independently associated with worse prognosis in terms of overall mortality and intensive care unit admission in SARS-CoV-2 infection,[35,36] it is important to understand how CLD, and the specific type of CLD, impacts the risk of ALI among people who were infected by SARS-CoV-2 infection. Leveraging the comprehensive territory-wide population-based database, our study was able to differentiate such risk with respect to the specific type of CLD in COVID-19. We confirmed that either CHB alone (IRR: 2.03, 95% CI: 1.46–2.83, $p<0.001$) or HS alone (IRR: 1.53, 95% CI: 1.37–1.72, $p<0.001$) was associated with ALI, and for the first time we demonstrated additive effects of dual etiologies from CHB and HS in contributing to incidence of ALI following SARS-CoV-2 infection (IRR: 2.14, 95% CI: 1.57–2.93,

TABLE 1 Baseline characteristics after 1:1 propensity score matching.

Baseline characteristics	HS + CHB + COVID-19 (*N* = 15391)		CHB + COVID-19 (*N* = 15391)		SMD
	N/Mean	%/SD	*N*/Mean	%/SD	
Age, years[a]	60.7	10.5	61.1	10.4	0.04
≤50	2772	(18.0%)	2520	(16.4%)	0.04
>50	12619	(82.0%)	12871	(83.6%)	
Sex					0.03
Male	9518	(61.8%)	9750	(63.3%)	
Female	5873	(38.2%)	5641	(36.7%)	
Date of SARS-CoV-2 infection					0.00
Year of 2020	122	(0.8%)	129	(0.8%)	
Year of 2021	27	(0.2%)	28	(0.2%)	
Year of 2022	14417	(93.7%)	14445	(93.9%)	
Year of 2023	825	(5.4%)	789	(5.1%)	
Severe COVID-19 case (WHO clinical progression scale ≥6)	956	(6.2%)	794	(5.2%)	0.05
Inpatient COVID-19 diagnosis	1076	(7.0%)	981	(6.4%)	0.02
Fully vaccinated	9580	(62.2%)	9568	(62.2%)	0.00
Pre-existing comorbidities					
Charlson Comorbidity Index[a,b]	3.7	2.1	3.5	2.2	0.06
Cirrhosis	1683	(10.9%)	1796	(11.7%)	0.02
Hepatocellular carcinoma	493	(3.2%)	554	(3.6%)	0.02
Liver decompensation	449	(2.9%)	532	(3.5%)	0.03
Antiviral treatment for hepatitis B	10453	(67.9%)	9786	(63.6%)	0.09
Antiviral treatment for COVID-19[c]	168	(1.1%)	154	(1.0%)	0.01

Abbreviations: ALI, acute liver injury; NA, not applicable; SMD, standardised mean difference.

[a]Age, and Charlson Comorbidity index are presented in mean ± SD.

[b]The calculation of Charlson Comorbidity Index does not include Acquired Immune Deficiency Syndrome.

[c]Antiviral treatment for COVID-19 includes the following antiviral medications: (i) molnupiravir, (ii) nirmatrelvir/ritonavir, and (iii) remdesivir.

$p < 0.001$) (Table S3). The evidence suggests a unanimous heightened risk of ALI after SARS-CoV-2 infection was universally observed in patients with either type of CLD. Interestingly, no significant difference of ALI risk was observed between patients with CHB and patients with HS, following SARS-CoV-2 infection (IRR: 0.84, 95% CI: 0.65–1.10, $p = 0.208$). Besides, the risk of ALI was magnified if the patient suffered from dual etiologies of CLD (Table S3).

There is ongoing controversy regarding the impact of concomitant HS on the natural history of CHB. HS, or more well-known as NAFLD or metabolic dysfunction-associated steatotic liver disease (MASLD),[37] increases adverse hepatic outcomes such as liver fibrosis progression and HCC.[13,15,16] On the other hand, a growing body of evidence, including previous work from our group, suggests that it might not be as straightforward, since HS appears to be associated with lower viral burden and higher likelihood of achieving functional cure.[13–15] The mechanisms are unknown but it was proposed that HS alters the cytoplasmic distribution of HBV viral antigens, leading to altered lipid metabolism in the lipid-laden HBV-infected hepatocytes and induced apoptosis that helps with viral clearance.[38] In the current study, the presence of HS in CHB patients further accentuated the risk of ALI after SARS-CoV-2 infection (IRR: 1.41, 95% CI: 1.05–1.90, $p = 0.023$) (Figure 2; Table 2). In the setting of SARS-CoV-2 infection, the onset of ALI was related to direct cytotoxicity, cytokine storm syndrome, hypoxemia, and drug-induced mechanisms.[39] Therefore, the underlying hepatic reserve would be the main determining factor for how the liver copes with the acute stress brought about by the various pathways of liver injury in SARS-CoV-2 infection. Our findings suggest that in the context of acute illness, as the overall mass of healthy and functional hepatocytes was lower in HS + CHB compared to patients with CHB alone, patients having dual etiologies of CLD (i.e. HS + CHB) were more susceptible to ALI. Although COVID-19 pandemic has come to an end, the findings of the current study offer an implication on the ALI risk in acute illnesses due to other causes. These highlight the importance of optimising each type of CLD by antiviral treatment in CHB and minimising metabolic dysfunction—the central pathogenesis of MASLD—to prevent the risk of ALI in patients with CLD when they come across acute illnesses that can set in any time.

TABLE 2 Comparison of study outcome after 1:1 propensity score matching.

Outcomes	HS + CHB + COVID-19 (N = 15391)					CHB + COVID-19 (N = 15391)					HS + CHB + COVID-19 vs CHB + COVID-19		
	Cumulative incidence		Crude incidence rate (Events/10000 person-years)			Cumulative incidence		Crude incidence rate (Events/10000 person-years)					
	New events	Rate	Estimate	95% CI	Person-years	New events	Rate	Estimate	95% CI	Person-years	IRR[a]	95% CI	*p*-value
ALI	105	0.77%	134.7	(110.2, 163.0)	7796	75	0.55%	95.3	(75.0, 119.5)	7867	1.41	(1.05, 1.90)	0.023

Abbreviations: ALI, acute liver injury; CI, confidence interval; IRR, incidence rate ratio.

[a]IRR >1 (or <1) indicates HS + CHB + COVID-19 group had higher (lower) risk of clinical outcome compared to the CHB + COVID-19 group.

Our subgroup analysis demonstrated that the heightened risk of ALI remained significant in several patient subgroups, including patients who did not require antiviral treatment for SARS-CoV-2, without baseline significant liver disease, and those with milder COVID-19. The role of concomitant HS in contributing to ALI among CHB patients diminished when patients were diagnosed with a severe phenotype of COVID-19 infection (Table S2). In particular, the IRR value for ALI was <1.0 for severe COVID-19 (IRR: 0.72, 95% CI: 0.41–1.25, $p = 0.244$). The effects of competing risk from death following diagnosis of COVID-19 infection could not be excluded. Additionally, our study showed that there was no significant difference of drug-induced liver injury by antiviral treatment of COVID-19 (IRR: 2.17, 95% CI: 0.19–24.98, $p = 0.532$) between HS + CHB + COVID-19 and CHB + COVID-19 groups. However, this might be contributed to the small sample size of COVID-19 antiviral users.

Fortunately, >99% ALI cases were of mild to moderate severity (DILIN scale 1–2), with <1% fatal cases overall (Figure S1). Patients with CHB suffering from ALI had a significantly higher proportion of grade 2 (i.e. moderate) severity (32.7%) and grade 5 (i.e. fatal) severity (0.9%) compared to the overall population (moderate ALI: 23.3% & fatal ALI: 0.3%; $p = 0.027$) or patients with HS (moderate ALI: 20.8% & fatal ALI: 0.0%; $p < 0.001$), respectively. Furthermore, no significant difference of ALI severity was observed between patients with CHB and patients with dual etiologies with ALI (moderate ALI: 21.0% & fatal ALI: 0.8%; $p = 0.127$). The reasons for the observed discrepancies in ALI severity are unclear. CHB is characterised by the presence of bystander non-HBV-specific cytotoxic T cells that are responsible for non-specific hepatocyte killing and the observed liver damage.[40,41] In the setting of ALI, the presence of these bystander lymphocytes might contribute to perpetuation of hepatocyte killing by cytokine production as induced by SARS-CoV-2 infection, such as interleukin 2 and interferon gamma, systemically and in the local micro-environment.[42] However, our current study design could not address this hypothesis.

Our study has several limitations. Firstly, HS or NAFLD diagnosis was based on NAFLD ridge score which detect HS or NAFLD by a dual cut-off, so it might have detected less patients than expected since those with NAFLD ridge score >0.24 and <0.44 were undetermined. Secondly, we could not address whether ALI in patients with CLD was associated with worse disease prognosis following SARS-CoV-2 infection. Thirdly, granular details of each disease aetiology, such as viral load for CHB and the presence/absence of metabolic dysfunction for HS, were not available.

In conclusion, either CHB or HS was associated with increased risk of ALI in COVID-19 infection. Concomitant HS further increased such risk among CHB patients. Although the majority of ALI was mild in severity, CHB patients suffering from ALI after SARS-CoV-2 infection tended to have more severe ALI than patients with HS or overall population. Optimization of treatment for underlying CLD is warranted to prevent risk of ALI following acute illness.

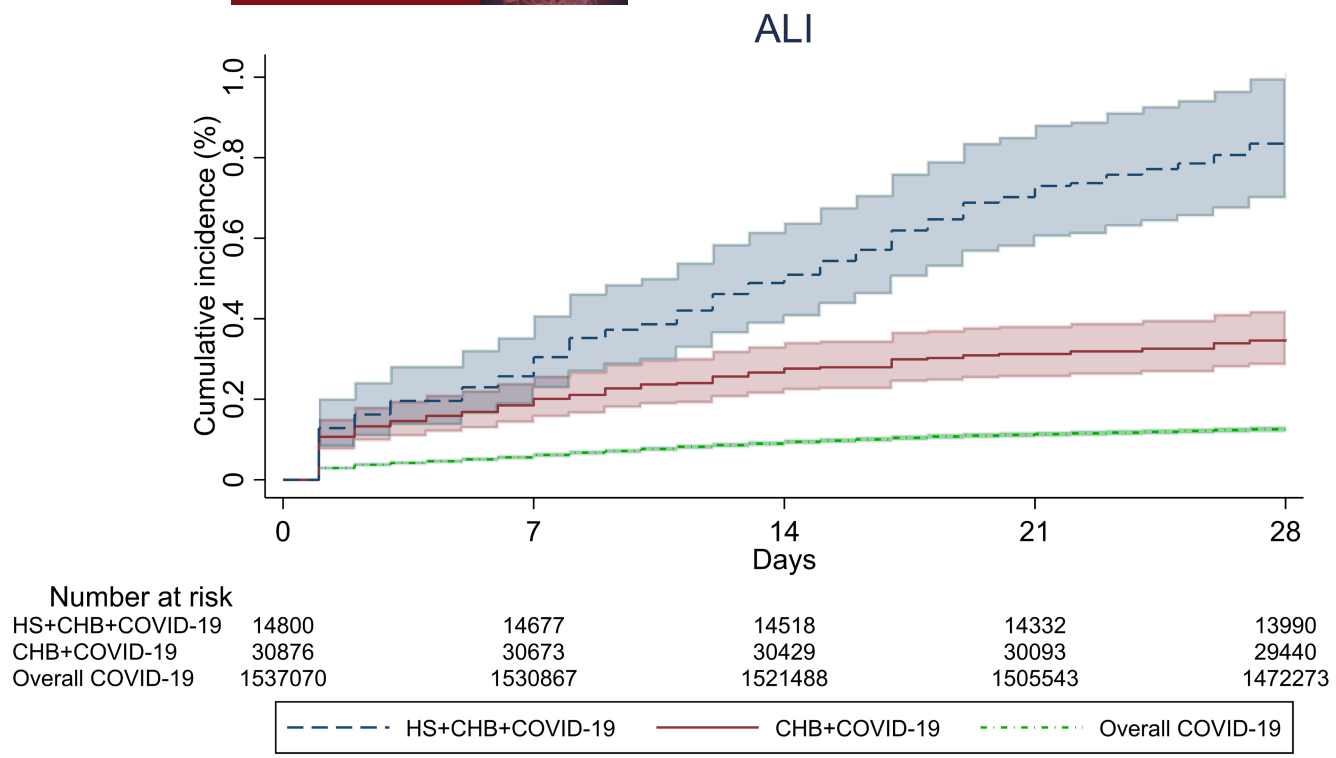

FIGURE 2 Cumulative incidence plots of ALI of HS + CHB + COVID-19, CHB + COVID-19 and overall population with COVID-19. ALI, acute liver injury.

AUTHOR CONTRIBUTIONS

MSHC, CKHW, and LYM reviewed the literature, conducted analyses, contributed to the interpretation of the analysis, and wrote the manuscript; CKHW and LYM reviewed the literature, designed the study and statistical analysis. MSHC, XX, and LL conducted analyses. XL, FTTL, EYFW, CSLC, FWTC, EWC, CLC, XX, LL, WKS, MFY, and ICKW contributed to the interpretation of the analysis. CKHW, LYM, and ICKW were responsible for the study concept. All authors contributed to the interpretation of the analysis, critically reviewed and revised the manuscript, and approved the final manuscript as submitted. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study were provided by the Hong Kong Hospital Authority. Restrictions apply to the availability of these data, which were used under licence for this study.

ETHICS APPROVAL AND PATIENT CONSENT STATEMENT

The study protocol was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (UW 20-556, UW 21-149, and UW 21-138); and the Department of Health Ethics Committee (LM 21/2021 and LM 175/2022). Informed patient consent was not required as the data used in this study were anonymised.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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