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# Real-world effectiveness of COVID-19 vaccination in liver cirrhosis: a systematic review with meta-analysis of 51,834 patients

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## ABSTRACT

SARS-CoV-2 vaccinations were found to be highly effective in phase 3 clinical trials. However, these trials have not reported data regarding the subgroup of liver disease or excluded patients with liver disease. The effectiveness of COVID-19 vaccines among liver cirrhosis (LC) patients is unclear. We conducted this meta-analysis to assess the effectiveness of SARS-CoV-2 vaccination in LC patients. A comprehensive literature search was conducted to include all the relevant studies that compared the outcomes of LC patients who received SARS-CoV-2 vaccines vs. unvaccinated patients. Pooled risk ratios (RRs) with 95% confidence intervals (CIs) were calculated by the Mantel-Haenszel method within a random-effect model. Four studies with 51,834 LC patients (20,689 patients received at least one dose vs 31,145 were unvaccinated) were included. COVID-19–related complications, including hospitalization (RR 0.73, 95% CI 0.59–0.91, $P = 0.004$), mortality (RR 0.29, 95% CI 0.16–0.55, $P = 0.0001$), and need for invasive mechanical ventilation (RR 0.29, 95% CI 0.11–0.77, $P = 0.01$), were significantly lower in the vaccinated group compared to the unvaccinated group. SARS-CoV-2 vaccination in LC patients reduced COVID-19–related mortality, intubation, and hospitalization. SARS-CoV-2 vaccination is highly effective in LC. Further prospective studies, preferably randomized controlled trials, are necessary to validate our findings and determine which vaccine is superior in patients with LC.

**KEYWORDS** Chronic liver disease; COVID-19 vaccine; liver cirrhosis; SARS-CoV-2 vaccine

Coronavirus disease 2019 (COVID-19), which is caused by an infection with SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), has become a global pandemic and led to significant morbidity and mortality.[1] However, development of mRNA SARS-CoV-2 vaccines led to a significant reduction in the risk of breakthrough infections, COVID-19–related hospitalization, and disease progression to death or mechanical ventilation among the vaccinated group compared to the unvaccinated group among the general population.[2] However, patients with chronic liver disease, especially liver cirrhosis (LC), are at greater risk of hospitalization, need for mechanical ventilation, and mortality from COVID-19 in comparison to the general population.[3]

Although phase 3 clinical trials showed that the COVID-19 vaccinations were highly effective in providing protection against infection, they have not reported data regarding the subgroup of LC due to stringent exclusion criteria used in these trials.[4–6] In the Pfizer trial, 217 (0.6%) of 37,706 participants had liver disease, and only three (<0.1%) had moderate to severe liver disease.[5] In the Moderna trial as well, only 196 (0.6%) of 30,351 participants had liver disease.[4]

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The AstraZeneca vaccine trial explicitly excluded patients with liver disease.[6] The efficacy of COVID-19 vaccines in patients with chronic liver disease (CLD), especially LC, is still not well studied.[7] It is known that cirrhotic patients demonstrated hyporesponsiveness to vaccinations due to immunological dysregulation.[8,9] Few observational studies have reported the clinical outcomes after COVID-19 vaccination in this selected subgroup of LC.[10–12] However, the real-world effectiveness of COVID-19 vaccines in LC patients remains unclear. Therefore, we performed a systematic review and meta-analysis to evaluate the real-world effectiveness of COVID-19 vaccination in patients with LC.

## METHODS

We included studies that met the following eligibility criteria: 1) cohort studies or randomized controlled trials (RCTs), 2) that compared the COVID-19 vaccinated group to an unvaccinated group, 3) in patients with LC, and 4) reported the outcomes of interest. We excluded conference abstracts. Outcomes of interest included COVID-19–related hospitalization, mortality, and need for invasive mechanical ventilation (IMV).

We performed a systematic search for published studies indexed in PubMed, Embase, Web of Science, and preprint servers (medRxiv and bioRxiv) from inception to July 30, 2022. We also performed a manual search for additional relevant studies using references of the included articles. The following search terms were used: ("COVID-19 vaccine") and ("liver cirrhosis"). The search was not limited by language, study design, or country of origin. Supplementary Table S1 describes the full search terms used in each database searched. Two investigators (AB and OS) independently performed the search and screened and shortlisted the studies for final review. The bibliographic software EndNote was used. Any discrepancies were resolved by a third reviewer (MM). We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement guidelines to select the final studies.[13]

The following data were extracted from the studies: first author name, publication year, country of origin, study design, sample size, gender and age of patients, electronic Child-Turcotte-Pugh and MELD-Na scores, types of COVID-19 vaccines used, and follow-up duration. Outcome measures were retrieved, including COVID-19–related hospitalizations, mortality, and need for IMV. Two investigators (AB and OS) independently extracted the data from the included studies. Microsoft Excel was used for data extraction. Any discrepancies were resolved by consensus.

The primary outcomes of our study were COVID-19–related hospitalization and COVID-19–related mortality in vaccinated LC patients compared to unvaccinated patients. The need for IMV was a secondary outcome.

We performed a meta-analysis of the included studies using Review Manager 5.3 (Cochrane Collaboration, Copenhagen, Nordic Cochrane Centre). The median and interquartile range were converted to mean and SD where applicable.[14] Pooled risk ratio (RR) with the corresponding 95% confidence intervals (CIs) were obtained by the Mantel-Haenszel method within a random-effect model.[15] A $P$ value $< 0.05$ was considered statistically significant. A fixed-effects model was used alternatively as a sensitivity tool. The heterogeneity of the effect size estimates across the studies was quantified using the Q statistic and $I^2$ ($P < 0.10$ was considered significant). A value of $I^2$ of 0% to 25% indicates insignificant heterogeneity; 26% to 50%, low heterogeneity; 51% to 75%, moderate heterogeneity; and 76% to 100%, high heterogeneity.[16]

The Newcastle Ottawa Quality Assessment Scale was used to assess the quality of the included studies based on the selection of the study groups, comparability of study groups, and ascertainment of exposure/outcome.[17] Studies with total scores of $\geq 6$ were considered to have a low risk of bias. Two authors (AB and MM) independently assessed each study for bias. Discrepancies were resolved by a third reviewer (ZA). We could not assess for publication bias due to limited number of included studies ($<10$ studies).

## RESULTS

Our search strategy retrieved a total of 1022 studies. Among these, 12 studies were eligible for systematic review. Subsequently, we excluded eight studies because of lack of appropriate outcome or population (liver transplant patients) or lack of control group. Eventually, four studies[10–12,18] met our inclusion criteria and were included in the meta-analysis. *Figure 1* shows the PRISMA flow chart that illustrates how the final studies were selected.

*Table 1* shows the study and patient characteristics of the studies included in the meta-analysis. All the included studies were published between October 2021 and February 2022 and reported the desired outcomes in patients with LC. Three studies[10,11,18] originated from the USA, and one study[12] was multinational. All the included studies were retrospective cohort studies. A total of 51,834 patients with LC (with 20,689 patients who received at least one dose and 31,145 who were unvaccinated) were included. The follow-up duration ranged from 30 to 60 days. The most used types of COVID-19 vaccine were mRNA-1273 (Moderna, 51%) and BNT162b2 mRNA (Pfizer, 49.2%). Three studies[10,11,18] reported the median MELD-Na score for the comparison groups (vaccinated vs. unvaccinated). Median MEDL-Na scores were comparable between the vaccinated and unvaccinated groups in those studies.[10,11,18]

*Table 1* summarizes the outcomes of the individual studies included in the meta-analysis. All four studies,[10–12,18] which included 51,834 patients with LC, reported COVID-19–related hospitalization (0.83% in the vaccinated group and 12.2% in the unvaccinated group). The overall COVID-19–related hospitalization rate was significantly lower in the vaccinated group compared to the unvaccinated

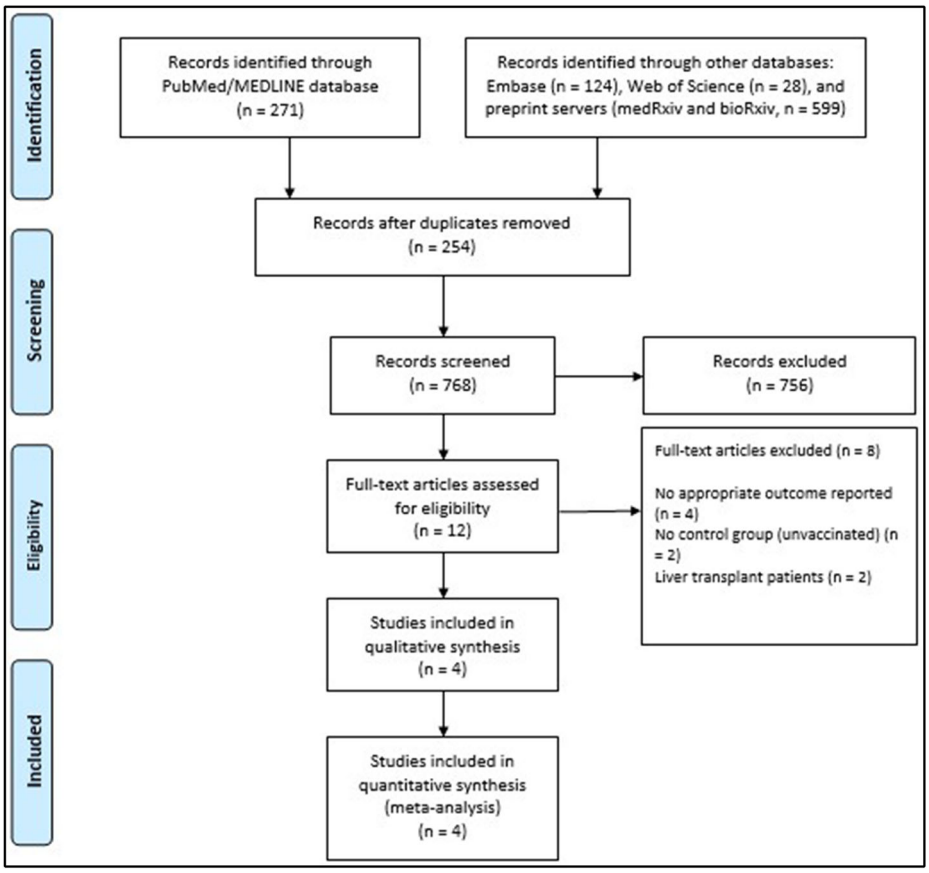


**Figure 1.** PRISMA flow diagram for the selection of studies.

group (RR 0.73, 95% CI 0.59–0.91, $P = 0.004$, $I^2 = 34\%$, *Figure 2a*).

Three studies,[10–12] which included 41,014 patients with LC, reported the incidence of COVID-19–related mortality (0.05% in the vaccinated group and 0.39% in the unvaccinated group). The vaccinated group had significantly lower COVID-19–related mortality compared to the unvaccinated group (RR 0.29, 95% CI 0.16–0.55, $P = 0.0001$, $I^2 = 0\%$, *Figure 2b*). Two studies,[11,12] which included 940 patients with LC, reported the need for IMV. The vaccinated group had significantly lower need for IMV than the unvaccinated group (RR 0.29, 95% CI 0.11–0.77, $P = 0.01$, $I^2 = 0\%$, *Figure 2c*). Our results remained consistent on the alternative fixed-effects model.

Quality assessment scores of the studies are summarized in Supplementary Table S2. There was a low risk of bias for all four studies.

## DISCUSSION

In this meta-analysis of four observational studies that included 51,834 patients with LC, we found significant reductions in COVID-19–related hospitalization, mortality, and need for IMV in cirrhotic patients who received COVID-19 vaccination compared to those who did not.

A robust immune response and a significant reduction in the acquisition of COVID-19 infection and amelioration of its complications have been observed in the general population after vaccination against SARS-CoV-2.[19] Patients with LC, especially decompensated ones, are at higher risk of COVID-19–related complications such as hospitalization, intensive care unit admission, mortality, and need for IMV.[3,20] Therefore, guidelines of the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) recommend all patients with CLD, including LC, receive COVID-19 vaccination as early as possible to reduce the risk of COVID-19 acquisition and COVID-19–related morbidity and mortality.[21,22] SARS-CoV-2 vaccination is proven to be safe in patients with CLD, including LC.[23]

On the other hand, given the underlying immunological dysfunction seen in patients with CLD and notably LC, there are rising concerns regarding the risk of reduced vaccination immunogenicity in these patients.[24] Patients with LC have well-known deficits in both their innate immunity and their humoral immunity, which is referred to as cirrhosis-associated immune dysfunction.[24] Willuweit et al[25] revealed that 96% of patients with LC developed antibodies against SARS-CoV-2, compared to 99% in the control group ($P = 0.400$). However, the median SARS-CoV-2 IgG titer was significantly lower in patients with LC in comparison to the control group ($P = 0.0001$).[25] Furthermore, there was a rapid and significant decline in the antibody titers in patients with LC compared to the control group.[25] The main three

**Table 1. Characteristics and outcomes of the studies included in the meta-analysis**

| Study, year | | Ge, 2022 | John, 2021 | John, 2022 | Moon, 2021 |
|---|---|---|---|---|---|
| Study design | | Retrospective cohort | Retrospective cohort | Retrospective cohort | Retrospective cohort |
| Country | | USA | USA | USA | Multinational |
| Total patients, n (VG/UVG) | | 10,820 (379/10,441) | 40,074 (20,037/20,037) | 762 (254/508) | 178 (19/159) |
| Age (VG/UVG), median (IQR) | | 59 (49-67) / 62 (53-70) | 69.1 (8.4) / 69 (8.8) | 63.8 (10.4) / 64.2 (10.0) | NR |
| Males, n (%) | | 5966 (55.1) | 38930 (97.1) | 732 (96.1) | NR |
| eCTP class, n (VG/UVG) | A | NR | 16,895/16,895 | 195/394 | NR |
| | B | | 3028/3028 | 55/105 | |
| | C | | 114/114 | 4/9 | |
| MELD-Na score, median (IQR) (VG/UVG) | | 17 (11-24) / 14 (10-18) | 8 (5) / 8 (5) | 9 (7) / 8 (6) | NR |
| Type of COVID-19 vaccine used (%) | | BNT162b2 mRNA (67), mRNA-1273 (28), and JNJ-784336725 (<5) vaccines | BNT162b2 mRNA (48.9) and mRNA-1273 (51.5) vaccines | Ad.26.COV2.S (2.8), BNT162b2 mRNA (47.6), and mRNA-1273 (47.6) vaccines | AstraZeneca (63.2), BNT162b2 mRNA (10.5), Bharat Biotech (10.5), CanSino (5.3), mRNA-1273 (5.3), and Sinovac (5.3) vaccines |
| Mortality, n (VG/UVG) | | NR | 4/9 | 7/57 | 0/15 |
| Hospitalization, n (VG/UVG) | | 86/3529 | 28/29 | 50/117 | 7/118 |
| Need for IMV, n (VG/UVG) | | NR | NR | 4/29 | 0/9 |
| Follow-up duration | | 30 days | 42 days | 60 days | NR |

eCTP indicates electronic Child-Turcotte-Pugh; IMV, invasive mechanical ventilation; IQR, interquartile range; NOS, Newcastle Ottawa Scale; NR, not reported; UVG, unvaccinated group; VG, vaccinated group.

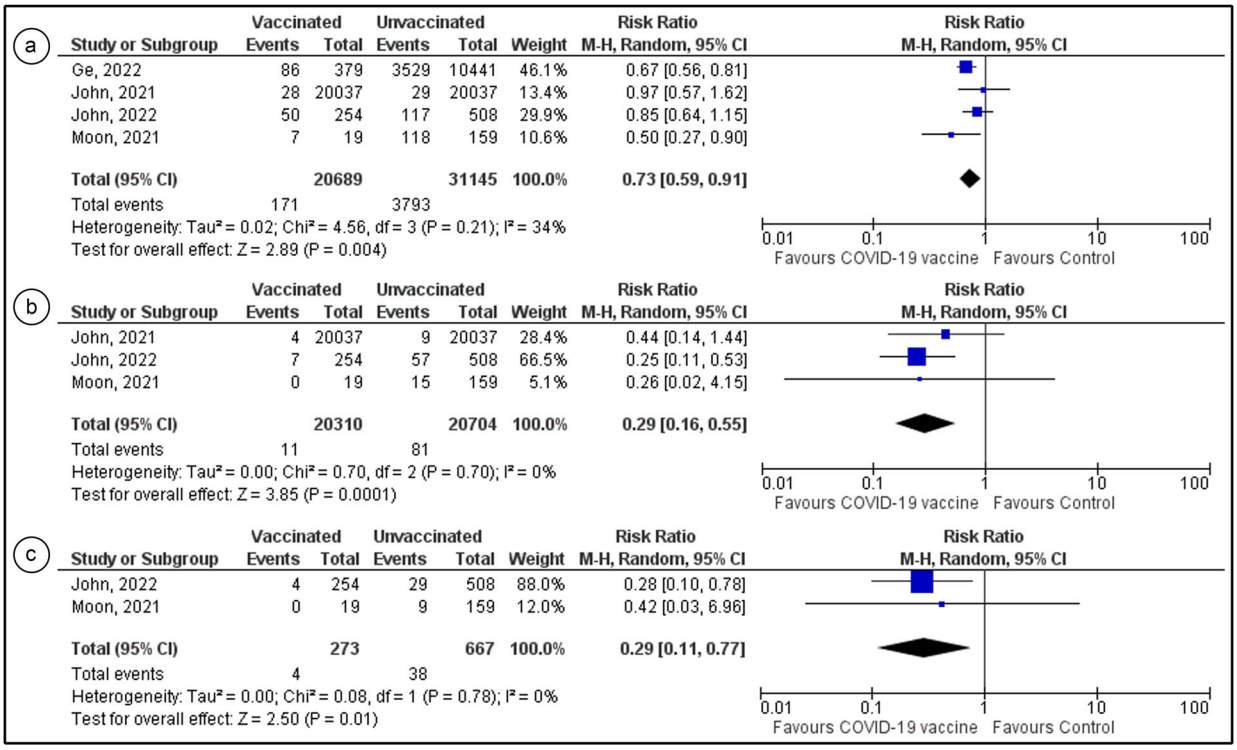


**Figure 2.** Forest plots comparing vaccinated and unvaccinated groups of patients with liver cirrhosis regarding **(a)** hospitalization, **(b)** mortality, and **(c)** need for invasive mechanical ventilation.

COVID-19 trials lacked the effectiveness data of the LC cohort due to stringent exclusion criteria.[4–6] Few postmarketing studies have reported significant improvement in the clinical outcomes post-COVID-19 vaccination in this selected subgroup of LC. Therefore, we conducted this meta-analysis to provide a quantitative assessment of the real-world effectiveness of COVID-19 vaccination in this selected cohort.

Our study findings support the recent recommendations from AASLD and EASL guidelines, which strongly encouraged the administration of SARS-CoV-2 vaccination to patients with CLD and LC despite the low vaccination immunogenicity in these patients.[21,22] Our study demonstrated a significant reduction in COVID-19–related hospitalization, mortality, and need for IMV among vaccinated patients with LC compared to those who did not get vaccinated. This is consistent with the findings of Moon et al,[12] which showed that the COVID-19–related hospitalization rate was significantly lower (37% vs. 74%) in patients who received at least one dose of COVID-19 vaccine compared to those who did not. On the other hand, a recently published retrospective cohort study showed no significant difference in COVID-19–related hospitalization between the vaccinated and unvaccinated groups of patients with LC at day 60 of follow-up (19.7% vs. 23%, respectively, $P = 0.29$).[11] This discrepancy is likely due to a lack of standardized criteria for hospitalization between healthcare facilities, and patients were hospitalized for different reasons such as isolation in the absence of caretakers or for close monitoring in cases of advanced LC.[11] John et al[10] demonstrated similar rates of hospitalization (28/20,037 [0.14%] vs. 29/20,037 [0.14%]) between the vaccinated and unvaccinated groups of patients with LC. However, all 28 patients who required hospitalization in the vaccinated group were admitted to the hospital within the first 28 days of their first dose, before the vaccine had fully taken effect.[10] None of the vaccinated patients required hospitalization after 28 days of COVID-19 vaccination.[10] This demonstrates the importance of full immunization with COVID-19 vaccines and receiving the booster dosages in patients with CLD, especially LC.

We observed a significantly lower COVID-19–related mortality among the vaccinated group compared to the unvaccinated group in our analysis. This is consistent with previously published studies, which showed lower mortality among the vaccinated group of patients with LC compared to the unvaccinated group.[11,12] The cohort study by John et al[11] showed that patients with LC who received COVID-19 vaccination had significantly lower mortality compared to the unvaccinated group (2.8% vs. 11.2%). Our findings are important to reassure patients with LC regarding the effectiveness of SARS-CoV-2 vaccinations and to encourage them to receive or complete the SARS-CoV-2 vaccination series to reduce the risk of COVID-19 infection and disease progression. Results from this study are a valuable addition to the literature for better care of patients with LC during this pandemic.

Our study has limitations. First, this meta-analysis was limited by the low number of studies. In addition, our study was based on observational studies only. RCTs are needed to evaluate the effects of SARS-CoV-2 vaccinations on the clinical outcomes of patients with LC. Currently, there are many ongoing RCTs, such as the COVISHIELD trial (NCT04794946), which will shed light on the effectiveness of COVID-19 vaccine in patients with LC. Second, two of the included studies were veteran cohorts, limiting the proportion of women. Third, there was some low heterogeneity in the measurement of COVID-19–related hospitalization, which could be attributed to variable follow-up periods, and differences in the type and dosages of the vaccine. Fourth, we could not assess the infection rate post-vaccination in LC patients due to limited reported data. Furthermore, even though the median MELD-Na scores reported by three studies were comparable between the vaccinated and unvaccinated groups, we were unable to perform meta-regression to assess the effect of MELD-Na score on our study outcomes due to the small number of included studies ($<10$). Lastly, publication bias assessment was not feasible due to the limited number of included studies, limiting assessment of the certainty of the evidence.

Despite the limitations, our meta-analysis has several strengths. First, we included a robust number of patients with LC ($n = 51,834$). To our knowledge, this is the first systematic review and meta-analysis to assess the real-world effectiveness of SARS-CoV-2 vaccination among patients with LC. Second, our results remained consistent on the alternative fixed-effects model. Lastly, all the included studies were of high quality based on quality assessment.

In conclusion, SARS-CoV-2 vaccination in patients with LC reduced COVID-19–related hospitalization, mortality, and the need for IMV. SARS-CoV-2 vaccination is highly effective in LC. Further prospective studies, preferably RCTs, are necessary to validate our findings and determine which vaccine is superior in patients with LC.

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