The association of chronic liver disorders with exacerbation of symptoms and complications related to COVID-19: A systematic review and meta-analysis of cohort studies

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Funding information
No funding.

Abstract
Introduction: The aim of this review was to combine the results of published cohort studies to determine the exact association between chronic liver disorders, and the severe form of COVID-19, and its associated complications.

Methods: This meta-analysis employed a keyword search (COVID-19 and chronic liver disorders) using PubMed (Medline), Scopus, Web of Sciences, and Embase (Elsevier). All articles related from January 2019 to May 2022 were reviewed. The STATA software was used for analysis.

Results: The risk of death in COVID-19 patients with chronic liver disorders was higher than in ones without the chronic liver disease (RR: 1.52; CI 95%: 1.46–1.57; I²: 86.14%). Also, the risk of acute respiratory distress syndrome (ARDS) and hospitalization in COVID-19 patients with chronic liver disorders was higher than in ones without the chronic liver disease ([RR: 1.65; CI 95%: 1.09–2.50; I²: 0.00%] and [RR: 1.39; CI 95%: 1.23–1.58; I²: 0.20%]). Also, the meta-analysis showed cough, headache, myalgia, nausea, diarrhea, and fatigue were 1.37 (CI 95%: 1.20–1.55), 1.23 (CI 95%: 1.09–1.38), 1.25 (CI 95%: 1.04–1.50), 1.19 (CI 95%: 1.02–1.40), 1.89 (CI 95%: 1.30–2.75), 1.49 (CI 95%: 1.07–2.09), and 1.14 (CI 95%: 0.98–1.33), respectively, whereas the risk of all these symptoms was higher in COVID-19 patients with chronic liver diseases than ones without chronic liver disorders.

Conclusion: The mortality and complications due to COVID-19 were significantly different between patients with the chronic liver disease and the general population.

KEYWORDS
chronic liver disease, complications, COVID-19, meta-analysis, mortality
1 | INTRODUCTION

The chronic liver disease (CLD) is a progressive deterioration of liver function over 6 months, which slowly progresses, leaving the liver unable to synthesize coagulation factors, and proteins, detoxify harmful metabolic products, and excrete bile.\(^1,2\) It is a continuous process of inflammation, destruction, and regeneration of the liver parenchyma, which leads to fibrosis and cirrhosis.\(^3,4\) CLD is caused by a wide range of causes, including toxins, long-term alcohol abuse, infection, autoimmune diseases, genetic disorders, and metabolic disorders.\(^5,6\) Cirrhosis is the final stage of CLD, which leads to liver dysfunction, extensive nodule formation, vascular reorganization, neoangiogenesis, and extracellular matrix deposition.\(^7,8\) The underlying mechanism of fibrosis and cirrhosis at the cellular level is the uptake of stellate cells and fibroblasts, which leads to fibrosis while parenchymal regeneration relies on liver stem cells.\(^9\) The CLD is a very common clinical condition and the focus is more on its common causes, clinical manifestations and management.\(^1,8–11\) About 1.5 billion people worldwide have CLD, which causes more than 2 million deaths a year.\(^9,12\) With the rapid spread of COVID-19, there are considerable concerns that patients with CLD are a vulnerable population and at higher risks for the more severe form of COVID-19 and its associated complications.\(^13\) Early on, patients with underlying diseases such as diabetes, chronic lung diseases, cardiovascular diseases, hypertension, and cancer were labeled as those at high risks for severe COVID-19.\(^14\) Although the virus mainly affects the lungs, experiences of China and the United States suggest SARS-CoV-2 may affect extra-pulmonary systems, including the gastrointestinal and hepato-biliary systems.\(^15,16\)

However, it was not initially clear whether patients with the CLD were more susceptible to COVID-19. Data from some recent studies showed the CLD in the absence of immunosuppressive therapy was not associated with an increased risk of COVID-19,\(^17\) whereas results from other studies showed the CLD, including patients with cirrhosis and non-cirrhosis, was associated with higher rates of mortality because of COVID-19.\(^18–20\) Also, various reports from different countries showed more than half of the hospitalized adults due to COVID-19 had abnormal aminotransferase levels and 2% to 11% of them had underlying liver diseases.\(^17,21–25\) However, there are limited and conflicting reports on the liver disease nature among COVID-19 patients, and it is unclear how underlying CLD affects liver injuries and clinical outcomes in these patients.\(^26\) Due to the discrepancies in the results of previous studies and the importance of determining the association between various underlying diseases, especially liver disorders, and COVID-19 and its severe form, the authors in this meta-analysis decided to combine the results of published cohort studies to determine the exact association between chronic liver disorders, and the severe form of COVID-19, and its associated complications.

2 | METHODS

The guideline of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was used to review meta-analyses, and systematic reviews.\(^27\) Also, the study protocol was registered in PROSPER with the code CRD42022327806.

2.1 | Search strategy and screening

The search was performed without language restrictions. The search strategy consisted of the following main keywords extracted from Mesh:

- “COVID 19,”
- “Liver Disease,” and
- “Chronic Liver Dysfunction.”

Search databases included PubMed (Medline), Scopus, Web of Sciences, and Embase (Elsevier).

The search deadline was from January 1, 2019, to January 1, 2022. Duplicate published articles were removed considering their titles, authors, and publication years using Endnote software version 9. Then, the remaining studies were evaluated by reviewing their titles, abstracts, and full texts, considering the inclusion criteria. In addition to searching the mentioned databases, gray literature was searched by reviewing articles in the first 10 pages of Google scholar, and manual search was performed by reviewing references of related studies. Two authors (MA, MA) independently screened articles based on their titles, abstracts, and full texts, and disputes were resolved by the third one (YM). After screening, the studies were finally selected by evaluating their full texts.

2.2 | Inclusion and exclusion criteria

The inclusion criteria were defined based on the PECOT structure as follows:

Population included the whole population, whether people with the CLD or healthy ones, exposure was considered as the presence of chronic liver disorders, comparison included comparing healthy people with those with chronic liver disorders, and outcomes included the COVID-19 symptoms and its associated complications, such as hospitalization in the intensive care unit, death, and acute respiratory distress syndrome (ARDS). The
intended studies to conduct meta-analysis were cohort ones because this type of observational studies is much more important than others to examine the casual association.

Systematic reviews, case reports, case series, case controls, cross sectionals, clinical trials, and other interventional studies as well as letters to the editor were excluded from the present research. Also, studies that met the inclusion criteria but their full texts were not available, first by sending an email to their authors, the full texts were requested and if the authors did not respond, they were removed.

### 2.3 Data extraction

After three stages of evaluation of titles, abstracts, and full texts, the selected articles were retrieved for detailed analysis. Data were collected using a checklist included authors’ names, country, publication year, study type, study population, sample size, data source, age, number of patients with COVID-19, hospitalization and mortality due to COVID-19, ARDS, need for ventilation, ICU hospitalization, and evaluation of COVID-19 symptoms (fever, cough, weakness, chest pain, abdominal pain, CT scan, Chest X-ray, respiratory problems and shortness of breath, decreased sense of smell decreased sense of taste, fatigue, headache, dizziness, myalgia, diarrhea, nausea, and vomiting).

### 2.4 Risk of bias

Two of the authors (MA and PM) conducted a qualitative evaluation of the studies based on the Newcastle–Ottawa Quality Assessment Scale (NOS) checklist designed to evaluate the quality of observational studies. This tool examines each research with eight items in three groups, including how to select study samples, how to compare and analyze study groups, and how to measure and analyze the desired outcome. Each of these items is given a score of one if it is observed in the studies, and the maximum score for each study is 9 points. In case of discrepancies in the score assigned to the published articles, the discussion method and the third researcher were applied to reach an agreement.

### 2.5 Statistical analysis

To calculate the association, cumulative risk ratio (RR) with the 95% confidence interval and the meta set command were used considering logarithm and logarithm standard deviation of the RR. Heterogeneity was assessed between studies using the $I^2$ and Q Cochrane tests. Egger test was used to evaluate the publication bias. Statistical analysis was performed using STATA 16.0 and $P$-value < 0.05 was considered.

### 3 RESULTS

First, 2251 studies were collected by searching based on the search strategy in the desired databases, of which 491 studies were duplicated, and 1760 ones remained. After reviewing the remained articles based on their titles, abstracts and full texts, 17 studies were selected for analysis. All articles were conducted in 2020 and 2021 and were cohorts (Figure 1 and Tables 1 and 2).

The risk of death in COVID-19 patients with chronic liver disorders was compared with that in ones without the CLD in 15 studies.\(^{19,26,28–40}\) In all of these studies, the mortality rate in patients with COVID-19, and the CLD was higher than that in patients with COVID-19, and without the CLD.\(^{19,26,28,30,32–34,36–40}\) The cumulative RR after combining these studies was 1.52 (CI 95%: 1.46–1.57; $I^2$: 86.14%) (Figure 2).

The risk of ARDS in patients with COVID-19 who had chronic liver disorders was compared in three studies with those without chronic liver disorders.\(^{35,37,39}\) The cumulative RR after combining these studies was 1.65 (CI 95%: 1.09–2.50; $I^2$: 0.00%) (Table 3).

The risk of hospitalization of COVID-19 patients who had chronic liver disorders in the intensive care unit was compared with that of ones without the CLD in nine studies,\(^{26,29–31,34,35,37,39,42,43}\) in all of which the risk of hospitalization in the ICU was higher in the group of COVID-19 patients with the CLD.\(^{26,29–31,34,35,37,39}\) The cumulative RR after combining these studies was 1.39 (CI 95%: 1.23–1.58) with heterogeneity ($I^2$) of 0.2% (Figure 2).

The risk of need for ventilation in COVID-19 patients who had the CLD was evaluated in 11 studies compared with those who did not have chronic liver disorders.\(^{36,29,30,32–34,37–40,42}\) In all of these studies, the need for ventilation was higher in the group with the CLD\(^{36,29,30,32–34,37–40}\) The frequency of need for ventilation was higher in the group of patients with COVID-19 and liver disorders.\(^{42}\) The cumulative RR after combining these studies was 1.53 (CI 95%: 1.46–1.60) with heterogeneity ($I^2$) equal to 0.2% (Figure 3).

To determine the association between the COVID-19 symptoms and chronic liver disorders, patients with COVID-19 who had chronic liver disorders were compared with those who did not have the CLD, and the
results of the meta-analysis showed cough, headache, myalgia, nausea, diarrhea and fatigue were 1.37 (CI 95%: 1.20–1.55), 1.23 (CI 95%: 1.09–1.38), 1.25 (CI 95%: 1.04–1.50), 1.19 (CI 95%: 1.02–1.40), 1.89 (CI 95%: 1.30–2.75), 1.49 (CI 95%: 1.07–2.09), and 1.14 (CI 95%: 0.98–1.33), respectively, while the risk of all these symptoms was higher in COVID-19 patients with underlying liver diseases than ones without chronic liver disorders. Other symptoms have been reported in the table (Figure 3 and Table 3).

To examine the publication bias, the Eggers test was performed, which was not significant in all variables except myalgia and headache. That is, the publication bias has not occurred.

3.1 | Subgroups analysis

The results of subgroups analysis according to age and continents for symptoms and complications related to COVID-19 were reported in Table 4. The results show that complications related to COVID-19 are more significant and severe in patients with CLD with age <60 and live in Asia (Table 4).

3.2 | Discussion

The RR of complications and consequences of COVID-19 in patients with the CLD during the pandemic period was examined in this study and the results showed the need for ventilation and ARDS had higher risks than other outcomes related to COVID-19 in patients with chronic liver disorders. Exacerbation of alveolar epithelial damages, increased vascular permeability, and systemic inflammation are among the factors that predispose to increased ARDS in patients with the CLD. 44,45 Also, because these patients had a higher BMI and obesity was more prevalent in them, their need for ventilation was higher when they were infected with COVID-19. 46

Due to the direct and significant effect of SARS-CoV-2 virus on ACE-2 receptors in liver cells, patients with chronic liver disorders will have a more severe form of the disease if they develop COVID-19, which causes their hospitalization in the intensive care unit of hospitals due to COVID-19. According to the results of previous studies, patients with chronic liver disorders have a higher risk of being admitted to the intensive care unit than others in the community if they develop COVID-19. In the present meta-analysis, the same result was
**Table 1** Characteristics of included cohort studies (items related to COVID-19 complications)

| Ref. | Authors (years) country | Type of study | Study population | Sample size | Data sources | Age (male) |
|------|-------------------------|---------------|------------------|-------------|--------------|------------|
| 28   | Bahardoust, M. (2021) (Iran) | Cohort | Liver disease + Covid-19 Covid-19 | Liver disease = 81 Non-liver disease = 921 | Hospital | 62.2 |
| 29   | Bajaj, J. S. (2021) (use) | Cohort | Covid-19 alone Covid-19 + Cirrhosis Cirrhosis alone | COVID-19 alone = 108 COV + Cirrhosis = 37 Cirrhosis alone = 127 | Hospital | 61.3 |
| 30   | Davidov-Derevynko, Y. (2021) (Israel) | Cohort | COVID + Liver COVID + non-Liver | Covid-19 = 323 Covid-19 + Liver = 59 | hospital | 59.1 |
| 31   | Forlano, R. (2020) (England) | Cohort | NAFLD + Covid-19 Non-NAFLD + Covid-19 | NAFLD + Covid-19 = 61 Covid-19 = 132 | Hospital | 70.5 |
| 32   | Frager, S. Z. (2021) (USA) | Cohort | Covid-19 id Covid-19 + Liver | Covid-19 = 2895 Covid-19 + Liver = 457 | Hospital | 64.8 |
| 33   | Garrido, M. (2021) (Portugal) | Cohort | Covid-19 id Covid-19 + Liver | Covid-19 = 303 Covid-19 + Liver = 14 | Hospital | 70.5 |
| 34   | Guerra Veloz, M. F. (2021) (Spain) | Cohort | Covid-19 Covid-19 + Liver | Covid-19 = 419 Covid-19 + Liver = 28 | Hospital | 40.8 |
| 26   | Hashemi, N. (2020) (USA) | Cohort | Covid-19 Covid-19 + Liver | Covid-19 = 294 Covid-19 + Liver = 69 | Hospital | 64.8 |
| 35   | Huang, R. (2020) (China) | Cohort | Non-NAFLD + Covid-19 NAFLD + Covid-19 | Covid-19 = 194 Covid-19 + Liver = 86 | Hospital | 43.5 |
| 36   | Ji, D. (2020) (China) | Cohort | Covid-19 Covid-19 + Liver | Covid-19 = 118 Covid-19 + Liver = 22 | Hospital | 63.6 |
| 37   | Lee, Y. R. (2020) (South Korea) | Cohort | Covid-19 Covid-19 + Liver | COVID-19 + Liver = 47 COVID-19 = 958 | Hospital | 55.3 |
| 38   | Li, C. (2020) (China) | Cohort | Covid-19 Covid-19 + Liver | COVID-19 + Liver = 52 Covid-19 = 52 | Hospital | 58.2 |
**TABLE 1**  (Continued)

| Ref. | Authors (years) country | Type of study | Study population | Sample size | Data sources | Age (male) |
|------|-------------------------|---------------|------------------|-------------|--------------|------------|
| 39   | Liaquat, H. (2021) (USA)| Cohort        | COVID-19         | COVID-19 = 105 | Hospital     | 73.9       |
|      |                         |               | COVID-19 + Liver | COVID-19 + Liver = 34 |             |            |
| 40   | Mallet, V. (2020) (France)| Cohort       | COVID-19         | COVID-19 = 243 634 | Hospital     | 70         |
|      |                         |               | COVID-19 + Liver | COVID-19 + Liver = 15 476 |             |            |
| 41   | Ge, J. (2020) (USA)     | Cohort        | 1. Non-cirrhosis/negative | Healthy = 128 864 | Pop         | 53         |
|      |                         |               | 2. Non-cirrhosis/positive; | COVID-19 = 29 446 |             |            |
|      |                         |               | 3. Cirrhosis/negative; | Cirrhosis = 53 476 |             |            |
|      |                         |               | 4. Cirrhosis/positive | Cirrhosis + Covid-19 = 8941 |             |            |
| 19   | Singh, S. (2020) (USA)  | Cohort        | Covid-19 + Liver | All = 2780 | Pop         | 55.2       |
|      |                         |               | Covid-19         | Covid-19 + Liver = 250 |             |            |
|      |                         |               | Covid-19         | Covid-19 = 2530 |             |            |
| 42   | Younossi, Z. M. (2021) (USA)| Cohort   | NAFLD + Covid-19 | NAFLD = 553 | Hospital     | 54.7       |
|      |                         |               | Non-NAFLD + Covid-19 | Non-NAFLD = 2736 |             |            |

**TABLE 1** (Continued)

| Ref. | Number of COVID-19 | Admission to hospital (COVID-19) | Mortality (COVID-19) | ARDS | ICU | Ventilation |
|------|--------------------|----------------------------------|----------------------|------|-----|-------------|
| 28   | Liver disease = 81 | Liver disease = 81               | Liver disease = 10   | NR   | NR  | NR          |
|      | Non-liver disease = 921 | Non-liver disease = 921             | non-liver disease = 65 |      |     |             |
|      | Liver disease = 76 | non-liver disease = 598  >7 day |                      |      |     |             |
| 29   | COVID-19 alone = 108 | COVID-19 alone = 108 | Covid-19 = 15 | NR   |     |             |
|      | COVID-19 + cirrhosis = 37 | COVID-19 + cirrhosis = 37 | Covid-19 + Cirrhosis = 11 |     |     |             |
|      | Cirrhosis alone = 127 | Cirrhosis = 24 |                   |     |     |             |
| 30   | COVID-19 = 323 | COVID-19 = 323 | COVID-19 = 22 | NR   |     |             |
|      | COVID-19 + Liver = 59 | COVID-19 + Liver = 59 | COVID-19 + Liver = 10 |       |     |             |
|      | COVID-19 = 132 | Covid-19 = 132 | Covid-19 = 41 |     |     |             |
| 31   | NAFLD + Covid-19 = 61 | NAFLD + Covid-19 = 61 | NAFLD + Covid-19 = 18 | NR   |     |             |
|      | Covid-19 = 132 | Covid-19 = 41 | Covid-19 = 27 |     |     |             |
| 32   | Covid-19 = 2895 | Covid-19 = 2895 | Covid-19 = 769 | NR   |     |             |
|      | Covid-19 + Liver = 457 | Covid-19 + Liver = 457 | Covid-19 + Liver = 135 |     |     |             |
| 33   | Covid-19 = 303 | Covid-19 = 303 | Covid-19 = 67 | NR   |     |             |
|      | Covid-19 + Liver = 14 | Covid-19 + Liver = 14 | Covid-19 + Liver = 4 |     |     |             |
| 34   | Covid-19 = 419 | Covid-19 = 200 | Covid-19 = 39 | NR   |     |             |
|      | Covid-19 + Liver = 28 | Covid-19 + Liver = 26 | Covid-19 + Liver = 8 |     |     |             |
|      |                      |                      | Covid-19 = 28 |     |     |             |
|      |                      |                      | Covid-19 + Liver = 3 |     |     |             |
|      |                      |                      | Covid-19 + Liver = 2 |     |     |             |
| Ref. | Number of COVID-19 | Admission to hospital (COVID-19) | Mortality (COVID-19) | ARDS | ICU | Ventilation |
|------|---------------------|---------------------------------|---------------------|------|-----|-------------|
| 26   | Covid-19 = 294      | Covid-19 = 294                  | Covid-19 = 39       | NR   | Covid-19 = 103 | Covid-19 = 89 |
|      | Covid-19 + Liver = 69 | Covid-19 + Liver = 69           | Covid-19 + Liver = 16 |      | Covid-19 + Liver = 34 | Covid-19 + Liver = 33 |
| 35   | Covid-19 = 194      | Covid-19 = 194                  | Covid-19 = 0        | Covid-19 = 2 | Covid-19 = 13 | NR |
|      | Covid-19 + Liver = 86 | Covid-19 + Liver = 86           | Covid-19 + Liver = 0 | Covid-19 + Liver = 2 | Covid-19 + Liver = 5 | |
| 36   | Covid-19 = 118      | Covid-19 = 118                  | Covid-19 = 0        | NR   | NR   | NR          |
|      | Covid-19 + Liver = 22 | Covid-19 + Liver = 22           | Covid-19 + Liver = 1 |      |      |             |
| 37   | COVID-19 + Liver = 47 | COVID-19 + Liver = 47           | COVID-19 + Liver = 7 | COVID-19 + Liver = 8 | COVID-19 + Liver = 8 | Invasive mechanical ventilation |
|      | COVID-19 = 958      | COVID-19 = 958                  | COVID-19 = 70       | COVID-19 = 105 | COVID-19 = 89 | COVID-19 + Liver = 4 |
|      |                     |                                 |                     |      | COVID-19 = 66 | COVID-19 + Liver = 5 |
|      |                     |                                 |                     |      | Invasive mechanical ventilation | |
|      |                     |                                 |                     |      | COVID-19 + Liver = 1 | |
|      |                     |                                 |                     |      | COVID-19 = 17 | |
| 38   | COVID-19 + Liver = 52 | COVID-19 + Liver = 52           | COVID-19 + Liver = 9 | NR   | NR   | Non-invasive ventilation |
|      | COVID-19 = 52       | COVID-19 = 52                   | COVID-19 = 0        |      |      | COVID-19 = 2 |
|      |                     |                                 |                     |      | COVID-19 + Liver = 5 | |
|      |                     |                                 |                     |      | Invasive mechanical ventilation | |
|      |                     |                                 |                     |      | COVID-19 + Liver = 1 | |
|      |                     |                                 |                     |      | NO ventilation | |
|      |                     |                                 |                     |      | COVID-19 = 49 | |
|      |                     |                                 |                     |      | COVID-19 + Liver = 42 | |
| 39   | COVID-19 = 105      | COVID-19 = 105                  | COVID-19 = 29       | COVID-19 = 41 | COVID-19 = 25 | COVID-19 = 11 |
|      | COVID-19 + Liver = 34 | COVID-19 + Liver = 34           | COVID-19 + Liver = 9 | COVID-19 + Liver = 14 | COVID-19 + Liver = 7 | |
| 40   | COVID-19 = 243 634  | COVID-19 = 243 634              | COVID-19 = 35 262   | NR   | NR   | COVID-19 = 16 449 |
|      | COVID-19 + Liver = 15 476 | COVID-19 + Liver = 15 476     | COVID-19 + Liver = 2941 |      |      | COVID-19 + Liver = 1600 | |
| 41   | 2. COVID-19 = 29 446 | 4. Cirrhosis + Covid-19 = 8941 | NR                  | NR   | NR   | NR          |
| 19   | All = 2780          | Covid-19 + Liver = 130          | Covid-19 + Liver = 30 | NR   | NR   | NR          |
|      | Covid-19 + Liver = 250 | Covid-19 + Liver = 760         | Covid-19 + Liver = 110 |      |      |             |
|      | Covid-19 = 2530     |                                 |                     |      |      |             |
| 42   | NAFLD = 553         | NAFLD = 553                     | NAFLD = 60          | NR   | NAFLD = 196 | NAFLD = 76 |
|      | Non-NAFLD = 2736    | Non-NAFLD = 2736                | Non-NAFLD = 239    |      | Non-NAFLD = 726 | Non-NAFLD = 221 |
### Table 2
Characteristics of included cohort studies (items related to signs and symptoms of COVID-19)

| Fever | Cough | Chest pain | Dizziness | Headache | Myalgia |
|-------|-------|------------|-----------|----------|---------|
| Liver disease | Liver disease = 47 | Liver disease = 20 | Liver disease = 20 | Liver disease = 26 | Liver disease = 49 |
| ≥38.5 = 35 | Non-liver disease = 552 | Non-liver disease = 221 | Non-liver disease = 313 | Non-liver disease = 275 | Non-liver disease = 485 |
| <38.5 = 46 | Non-liver disease | ≥38.5 = 175 | <38.5 = 746 |

| Covid-19 | Covid-19 + Cirrhosis | Covid-19 + Liver = 8 | Covid-19 + Liver = 10 | COVID-19 + Liver = 23 | COVID-19 = 425 |
|-----------|----------------------|----------------------|----------------------|----------------------|------------------|
| Covid-19 = 75 | Covid-19 = 70 | Covid-19 = 19 | Covid-19 = 8 | Covid-19 = 15 | Covid-19 = 31 |
| Covid-19 + Cirrhosis = 20 | Covid-19 + Cirrhosis = 26 | Covid-19 + Cirrhosis = 3 | Covid-19 + Cirrhosis = 4 | Covid-19 + Cirrhosis = 2 | Covid-19 + Cirrhosis = 4 |
| COVID-19 + Liver = 55 | Covid-19 + Liver = 109 | Covid-19 + Liver = 47 | COVID-19 + Liver = 23 | COVID-19 = 245 | COVID-19 = 316 |
| COVID-19 = 425 | COVID-19 + Liver = 23 | COVID-19 + Liver = 23 | COVID-19 = 425 | COVID-19 + Liver = 23 | COVID-19 + Liver = 23 |

| COVID-19 + Liver = 55 | COVID-19 + Liver = 23 | COVID-19 = 425 | COVID-19 + Liver = 23 | COVID-19 + Liver = 23 |
| COVID-19 = 425 | COVID-19 + Liver = 23 | COVID-19 = 425 | COVID-19 + Liver = 23 | COVID-19 + Liver = 23 |

### Table 2 (Continued)

| Diarrhea | Vomiting | Test sense | Shortness of breath | Abdominal pain | Fatigue | Dyspnea |
|----------|----------|------------|---------------------|----------------|---------|---------|
| Liver disease | Liver disease = 37 | Liver disease = 13 | NR | NR | NR | NR |
| Liver disease = 230 | Non-liver disease = 276 | Non-liver disease = 166 | | | | |
| Covid-19 = 29 | Covid-19 = 29 | NR | Covid-19 = 74 | Covid-19 = 17 | Covid-19 = 44 | NR |
| Covid-19 + Cirrhosis = 3 | Covid-19 + Cirrhosis = 4 | | Covid-19 + Cirrhosis = 23 | Covid-19 = 17 | Covid-19 + Cirrhosis = 12 | |
| Covid-19 = 38 | Covid-19 = 23 | NR | Covid-19 = 17 | Covid-19 = 82 | Covid-19 = 108 | |
| Covid-19 + Liver = 2 | Covid-19 + Liver = 1 | | Covid-19 + Liver = 2 | Covid-19 + Liver = 3 | Covid-19 + Liver = 6 | |
| NR | NR | | Covid-19 = 42 | Covid-19 + Liver = 16 | NR | |
| NR | NR | | COVID-19 + Liver = 7 | COVID-19 + Liver = 15 | NR | |
| NR | NR | | COVID-19 = 232 | COVID-19 = 232 | NR | |

| NR | NR | NR | NR | NR | NR | NR |

| NR | NR | NR | NR | NR | NR | NR |

| NR | NR | NR | NR | NR | NR | NR |

| NR | NR | NR | NR | NR | NR | NR |

| NR | NR | NR | NR | NR | NR | NR |

| NR | NR | NR | NR | NR | NR | NR |

| NR | NR | NR | NR | NR | NR | NR |

| NR | NR | NR | NR | NR | NR | NR |
obtained, which was in line with the results of preliminary studies published in the world. However, the results of some studies in the world have not shown this association, for example, a study by Huang, R. et al. showed the risk of hospitalization in intensive care unit due to COVID-19 in patients with chronic liver disorders was not significantly different from other people in the community. The reason for this inconsistency can be attributed to differences in the study method, how to collect information, and the type of patients studied in these articles.

Also, the risk of death due to COVID-19 in the present meta-analysis was significantly higher in patients with chronic liver disorders than other individuals. The reason for this can be attributed to the increase in inflammatory cytokines such as IL-6, Ferritin and TNF-alpha. In patients with COVID-19, inflammatory cytokines increase, eventually leading to a cytokine storm in more severe forms of the disease. On the other hand, for patients with severe forms of COVID-19, drugs that aggravate cytokines and cause cytokine storms are prescribed, which may also exacerbate death in COVID-19 patients with chronic liver disorders. Coincidence of chronic liver disorders and the use of anti-COVID-19 drugs significantly increases the risk of mortality in COVID-19 patients with the CLD. Also, worsening liver

| Study                          | RR       | Weight (%) |
|-------------------------------|----------|------------|
| Bahardoust, M., 2021          | 1.74 [ 0.94, 3.23] | 0.34 |
| Bajaj, J. S., 2021             | 1.94 [ 1.10, 3.40] | 0.41 |
| Davidov-Derevyanko, Y., 2021  | 2.23 [ 1.26, 3.97] | 0.39 |
| Fontano, R., 2020              | 0.95 [ 0.60, 1.50] | 0.61 |
| Frager, S. Z., 2021            | 1.14 [ 0.94, 1.37] | 3.71 |
| Garrido, M., 2021              | 1.39 [ 0.45, 4.23] | 0.10 |
| Guerra Veloz, M. F., 2021      | 3.40 [ 1.59, 7.30] | 0.22 |
| Hashemi, N., 2020              | 1.69 [ 1.05, 2.73] | 0.56 |
| Ji, D., 2020                   | 6.62 [ 4.46, 9.82] | 0.83 |
| Lee, Y. R., 2020               | 2.11 [ 0.98, 4.55] | 0.22 |
| Li, C., 2020                   | 2.21 [ 1.77, 2.76] | 2.63 |
| Liaquat, H., 2021              | 0.96 [ 0.49, 1.86] | 0.29 |
| Mallet, V., 2020               | 1.49 [ 1.44, 1.55] | 86.38 |
| Singh, S., 2020                | 2.57 [ 1.83, 3.62] | 1.10 |
| Younossi, Z. M., 2021          | 1.22 [ 0.96, 1.55] | 2.23 |
| Overall                       | 1.52 [ 1.46, 1.57] |    |

Fixed-effects inverse-variance model
| Outcomes                     | No. of study (SS) | Sample size liver disease | Sample size non-liver disease | No. of Covid-19 | Pooled RR       | Heterogeneity assessment |
|------------------------------|-------------------|---------------------------|-------------------------------|-----------------|----------------|------------------------|
|                              |                   |                           |                               | A               | B              | C                      | D                  |
| Outcomes of Covid-19         |                   |                           |                               |                 |                |                        |                    |
| Mortality                   | 15 (272767)       | 17 240                    | 255 527                       | 3269            | 33 767         | 13 971                 | 221 760            | 1.52 (1.46–1.57)   | 86.14% | 0.00 | 100.97 |
| ARDS                        | 3 (1424)          | 167                       | 1257                          | 29               | 148            | 138                    | 1109               | 1.65 (1.09–2.50)   | 0.00% | 1.00 | 0.00  |
| ICU                         | 9 (6243)          | 974                       | 5269                          | 296             | 1088           | 678                    | 4181               | 1.39 (1.23–1.58)   | 0.00% | 0.31 | 0.64  |
| Ventilation                 | 11 (268653)       | 16 826                    | 251 827                       | 1864            | 17 474         | 14 962                 | 234 353            | 1.53 (1.46–1.60)   | 0.00% | 0.86 | 5.50  |
| Covid-19 symptoms           |                   |                           |                               |                 |                |                        |                    |
| Fever                       | 6 (6037)          | 818                       | 5219                          | 461             | 2264           | 357                    | 2955               | 1.37 (1.20–1.55)   | 81.32% | 0.00 | 26.77 |
| Cough                       | 8 (6280)          | 904                       | 5376                          | 536             | 2849           | 368                    | 2527               | 1.23 (1.09–1.38)   | 46.65% | 0.07 | 13.12 |
| Chest pain                  | 2 (1146)          | 118                       | 1028                          | 23              | 240            | 95                     | 788                | 0.92 (0.99–1.42)   | 32.41% | 0.22 | 1.48  |
| Dizziness                   | 3 (4435)          | 671                       | 3764                          | 47              | 393            | 624                    | 3371               | 1.12 (0.85–1.48)   | 70.49% | 0.03 | 6.78  |
| Headache                    | 5 (6037)          | 818                       | 5219                          | 113             | 837            | 705                    | 4382               | 1.25 (1.04–1.50)   | 64.72% | 0.02 | 11.34 |
| Myalgia                     | 6 (6037)          | 818                       | 5219                          | 172             | 1285           | 646                    | 3934               | 1.19 (1.02–1.40)   | 67.92% | 0.01 | 15.59 |
| Diarrhea                    | 3 (1463)          | 132                       | 1331                          | 44              | 297            | 88                     | 1034               | 1.89 (1.30–2.75)   | 83.88% | 0.00 | 12.41 |
| Vomiting                    | 3 (1463)          | 132                       | 1331                          | 42              | 328            | 90                     | 1003               | 1.44 (0.99–2.09)   | 75.22% | 0.02 | 8.07  |
| Test sense                  | 2 (4290)          | 634                       | 3656                          | 36              | 238            | 598                    | 3418               | 1.26 (0.93–1.71)   | 53.75% | 0.14 | 2.16  |
| Shortness of breath         | 4 (4719)          | 723                       | 3996                          | 361             | 1841           | 362                    | 2155               | 1.05 (0.92–1.21)   | 0.00% | 0.60 | 1.89  |
| Abdominal pain              | 2 (462)           | 51                        | 411                           | 11              | 34             | 40                     | 377                | 1.61 (0.91–2.85)   | 0.00% | 0.47 | 0.53  |
| Fatigue                     | 4 (4031)          | 690                       | 3341                          | 175             | 756            | 515                    | 2585               | 1.14 (0.98–1.33)   | 28.31% | 0.24 | 4.18  |
| Dyspnea                     | 3 (560)           | 100                       | 460                           | 49              | 198            | 51                     | 262                | 1.49 (1.07–2.09)   | 0.00% | 0.96 | 0.08  |

Note: A: COVID-19 individual with CLD; B: Healthy individual with CLD; C: COVID-19 individual without CLD; D: Healthy individual without CLD.
The pooled effect (risk ratio, RR) of chronic liver disorders on the ventilation needs, fever, and cough related to COVID-19.

### Ventilation Needs

| Study                  | RR with 95% CI | Weight (%) |
|------------------------|---------------|------------|
| Bahardoust, M., 2021   | 2.87 [1.90, 4.33] | 9.33       |
| Bajaj, J. S., 2021     | 0.62 [0.36, 0.70] | 5.28       |
| Garrido, M., 2021      | 0.99 [0.35, 2.78] | 1.48       |
| Huang, R., 2020        | 0.88 [0.61, 1.27] | 12.04      |
| Lee, Y. R., 2020       | 1.29 [0.74, 2.26] | 5.10       |
| Younossi, Z. M., 2021  | 1.44 [1.24, 1.67] | 66.77      |
| Overall                | 1.37 [1.20, 1.55] |            |

Heterogeneity: $I^2 = 81.32\%$, $H^2 = 5.35$

Test of $b = 0$: $Q(5) = 26.77$, $p = 0.00$

Test of $b = 0$: $z = 4.86$, $p = 0.00$

### Fever

| Study                  | RR with 95% CI | Weight (%) |
|------------------------|---------------|------------|
| Bahardoust, M., 2021   | 0.93 [0.61, 1.42] | 8.07       |
| Bajaj, J. S., 2021     | 1.21 [0.65, 2.23] | 3.01       |
| Garrido, M., 2021      | 1.58 [0.50, 4.88] | 1.12       |
| Huang, R., 2020        | 0.96 [0.67, 1.36] | 11.58      |
| Lee, Y. R., 2020       | 0.74 [0.42, 1.29] | 4.63       |
| Li, C., 2020           | 0.94 [0.58, 1.51] | 6.32       |
| Liaquat, H., 2021      | 0.94 [0.50, 1.74] | 3.73       |
| Younossi, Z. M., 2021  | 1.44 [1.24, 1.68] | 60.75      |
| Overall                | 1.23 [1.09, 1.38] |            |

Heterogeneity: $I^2 = 46.65\%$, $H^2 = 1.87$

Test of $b = 0$: $Q(7) = 13.12$, $p = 0.07$

Test of $b = 0$: $z = 3.33$, $p = 0.00$

### Cough
function reduces the number and disrupt the function of neutrophils, monocytes and innate immune proteins, and ultimately the number of both B and T lymphocytes involved in acquired immunity decreases and eventually immune dysfunction increases. In this study, in addition to the mentioned cases, the symptoms associated with COVID-19 including fever, cough, headache, myalgia, nausea, diarrhea, and fatigue were also evaluated in patients with the CLD. The results of this meta-analysis showed among these symptoms, nausea, diarrhea and abdominal pain were more common than other ones in patients with chronic liver disorders. Increased gastrointestinal symptoms may be due to liver dysfunction. In addition, other symptoms such as fever, cough, headache, myalgia, and fatigue were more common in patients with the underlying liver disease than in healthy individuals while cytokines were effective in worsening these symptoms. The severity of various symptoms in patients with chronic liver disorders can affect outcomes of COVID-19 and, as a result, increase the outcome and mortality in this group of patients.

Some studies on the effect of COVID-19 on the incidence of liver disorders published results, which suggested in the case of COVID-19 due to the widespread distribution of the main virus receptor called the angiotensin-converting enzyme 2 (ACE2), the virus could cause a widespread disease with more involvement of extra-pulmonary organs, especially the liver. ACE2 receptors are also expressed in the gastrointestinal tract, vascular endothelium, and hepatic cholangiocytes. Various studies showed elevated liver enzymes indicated liver damages and were common in COVID-19 patients with chronic and non-CLDs. On

| Outcomes of | Outcomes | Subgroups | No. of study (SS) | Sample size liver disease | Sample size non-liver disease | Pooled RR (95% CI) | Heterogeneity assessment |
|-------------|----------|-----------|------------------|---------------------------|-----------------------------|---------------------|------------------------|
| Mortality   | America  | 6(10068)  | 1400             | 8668                      | 1.35 (1.19–1.53)             | 76.39% 0.00 21.18  |
|             | Asia     | 5(2632)   | 261              | 2371                      | 2.66 (2.24–3.16)             | 84.49% 0.00 25.78  |
|             | Europe   | 4(260027) | 15 579           | 244 488                   | 1.49 (1.43–1.55)             | 63.62% 0.04 8.25   |
| ICU         | America  | 4(3936)   | 693              | 3243                      | 1.43 (1.25–1.65)             | 0.00% 0.71 1.38    |
|             | Asia     | 3(1668)   | 192              | 1475                      | 1.34 (0.89–2.02)             | 0.00% 0.37 1.97    |
|             | Europe   | 2(640)    | 89               | 551                       | 1.00 (0.61–1.64)             | 0.00% 0.37 0.82    |
| Ventilation | America  | 5(7288)   | 1150             | 6238                      | 1.47 (1.29–1.67)             | 11.55% 0.34 4.52   |
|             | Asia     | 3(1491)   | 158              | 1333                      | 1.55 (1.14–2.11)             | 0.00% 0.79 0.46    |
|             | Europe   | 3(259874) | 15 518           | 244 356                   | 1.54 (1.47–1.62)             | 0.00% 0.97 0.06    |

| Outcomes of Covid-19 symptoms | Outcomes | Subgroups | No. of study (SS) | Sample size | Sample size | Pooled RR (95% CI) | Heterogeneity assessment |
|------------------------------|----------|-----------|------------------|-------------|-------------|---------------------|------------------------|
| Fever                        | America  | 2(3434)   | 590              | 2644        | 1.35 (1.16–1.57) | 88.05% 0.00 8.37    |
|                             | Asia     | 3(2286)   | 214              | 2072        | 1.44 (1.13–1.84) | 88.78% 0.00 17.83   |
|                             | Europe   | 1(317)    | 14               | 303         | 0.99 (0.35–2.78) | - - -                |
| Cough                        | America  | 3(3573)   | 624              | 2949        | 1.40 (1.21–1.61) | 0.00% 0.37 1.98     |
|                             | Asia     | 4(2390)   | 266              | 2124        | 0.91 (0.73–1.13) | 0.00% 0.89 0.63     |
|                             | Europe   | 1(317)    | 14               | 303         | 1.56 (0.50–4.88) | - - -                |

| Outcomes of Covid-19 | Outcomes | Subgroups | No. of study (SS) | Sample size | Sample size | Pooled RR (95% CI) | Heterogeneity assessment |
|----------------------|----------|-----------|------------------|-------------|-------------|---------------------|------------------------|
| Mortality            | <60      | 6(8007)   | 989              | 7018        | 1.89 (1.64–2.16) | 75.76% 0.00 20.63   |
|                      | >60      | 9(264760) | 16 251           | 248 509     | 1.49 (1.44–1.55) | 88.57% 0.00 69.99   |
| ICU                  | <60      | 5(5403)   | 773              | 4630        | 1.40 (1.21–1.62) | 0.00% 0.72 2.08     |
|                      | >60      | 4(840)    | 201              | 639         | 1.35 (1.05–1.75) | 24.03% 0.27 3.95    |
| Ventilation          | <60      | 5(5237)   | 739              | 4488        | 1.59 (1.34–1.89) | 0.00% 0.97 0.49     |
|                      | >60      | 6(263426) | 16 087           | 247 339     | 1.53 (1.46–1.60) | 0.00% 0.44 4.82     |

| Outcomes of Covid-19 symptoms | Outcomes | Subgroups | No. of study (SS) | Sample size | Sample size | Pooled RR (95% CI) | Heterogeneity assessment |
|------------------------------|----------|-----------|------------------|-------------|-------------|---------------------|------------------------|
| Fever                        | <60      | 3(4574)   | 686              | 3888        | 1.33 (1.16–1.53) | 65.85% 0.05 5.86    |
|                             | >60      | 3(1436)   | 132              | 1331        | 1.57 (1.15–2.15) | 90.00% 0.00 20.00   |
| Cough                        | <60      | 4(4678)   | 738              | 3940        | 1.27 (1.12–1.45) | 70.74% 0.02 10.25   |
|                             | >60      | 4(1602)   | 166              | 1436        | 1.02 (0.76–1.37) | 0.00% 0.78 1.09     |
the other hand, initial clinical studies in this area also confirmed a significant increase in liver enzymes such as ALT, and AST due to SARS-CoV-2 infection.\textsuperscript{53–56} The results of a meta-analysis also showed the levels of ALP, and γ-GT enzymes were significant as a result of cholangiocellular damages.\textsuperscript{57–59} As the study results show, it is not yet clear how much an increase in liver enzyme levels can exacerbate the complications of COVID-19 or the disease progression. In patients with COVID-19 who have not had a chronic liver disorder or liver damage before infection, a slight liver disorder is found after recovery.\textsuperscript{60,61}

Abnormal results of liver tests were associated with more severe forms of COVID-19 and mortality. Although RNAs of SARS-CoV-2 have been detected in the liver of patients with COVID-19, it is not yet exactly clear how much SARS-CoV-2 infects the liver and multiplies in its cells.\textsuperscript{17,51} The range of liver damages in the COVID-19 disease may be direct infection by SARS-CoV-2, indirect involvement by systemic inflammation, and hypoxic changes. However, due to the major role of the liver in endobiotic and xenobiotic drug metabolism, coagulation, albumin, and production of acute phase reactants, liver dysfunction may affect the pathophysiology of the COVID-19 disease.\textsuperscript{62,63} The results of the present meta-analysis along with other published results can be useful in finding many of these answers. They are also useful in updating treatment and prevention guidelines. This study was the first meta-analysis to compare the complications and consequences associated with COVID-19 in two groups of patients with the CLD and healthy ones. On the other hand, the results of subgroup analyses and overall results had a high homogeneity, which indicated the homogeneous and correct selection of initial studies in order to perform this meta-analysis.

The heterogeneity in this meta-analysis only was higher at two outcomes (Fever and Mortality). For detecting sources of this heterogeneity, all primary cohort studies were reviewed, and extracted related variables that reported in selected cohort studies completely. Between reported variables, age and continents were extracted. Other variables like type of underlying diseases, such as diabetes, coronary heart disease (CHD), and cancers, type of study population, type of measures tools for outcomes measure were not reported in selected cohort studies. The results of subgroup analysis based on age and continents show that the heterogeneity was decreased in many of categories, but in fever and mortality not decreased. This heterogeneity rate confirms the difference between the combined studies. This difference may be due to differences in some section of studies such as the methods of measuring the outcomes and the tools used, the methods of sampling, presence of important underlying diseases (comorbidities) like diabetes, CHD, cancers, and chronic obstructive pulmonary disease (COPD). These variables and factors not reported in selected cohort studies in this meta-analysis, so authors could not subgroup analysis based on its.

The results of this research are also based on cohort studies, which are one of the most important observational studies in order to find a causal association, but the overall results of this study have not yet determined the exact association between SARS-CoV-2 infection and chronic liver disorders. In other words, according to the results of published studies, it can be claimed that there is a kind of causal association between these two factors, and in order to find it, studies based on genetics or molecular science such as Mendelian randomization are needed.

\section*{4 CONCLUSION}

The results of this study showed the mortality and consequences due to COVID-19 were significantly different between patients with the CLD and the general population. Also, the COVID-19 symptoms in people with liver disorders were significantly more severe than those in healthy people. So, taking measures is necessary to manage them. It is recommended to reduce the risk of mortality and other consequences of COVID-19 through screening and treating people with liver disorders in the lower stages of the CLD.

\section*{ACKNOWLEDGEMENTS}

We would like to thank all the authors whose articles have been used in this meta-analysis.

\section*{CONFLICT OF INTEREST}

The authors declare that they have no competing interests.

\section*{AUTHOR CONTRIBUTIONS}

YM: concept development (provided idea for the research). MA and PM: search strategy. MA, PM, and KZ: data extraction. YM: supervision. FM, SK, and MA: analysis/interpretation. All authors: writing (responsible for writing a substantive part of the manuscript).

\section*{DATA AVAILABILITY STATEMENT}

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.
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How to cite this article: Afraie M, Mohammadzadeh P, Azami M, et al. The association of chronic liver disorders with exacerbation of symptoms and complications related to COVID-19: A systematic review and meta-analysis of cohort studies. *Clin Respir J*. 2022;16(12):777-792. doi:10.1111/crj.13552