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Clinical outcomes in COVID-19 and cirrhosis: a systematic review and meta-analysis of observational studies

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ABSTRACT

Background COVID-19 continues to pose a significant healthcare challenge throughout the world. Comorbidities including diabetes and hypertension are associated with a significantly higher mortality risk. However, the effect of cirrhosis on COVID-19 outcomes has yet to be systematically assessed.

Objectives To assess the reported clinical outcomes of patients with cirrhosis who develop COVID-19 infection.

Design/Method PubMed and EMBASE databases were searched for studies included up to 3 February 2021. All English language primary research articles that reported clinical outcomes in patients with cirrhosis and COVID-19 were included. The study was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The risk of bias was assessed using the Quality In Prognostic Score (QUIPS) risk-of-bias assessment instrument for prognostic factor studies template. Meta-analysis was performed using Cochrane RevMan V.5.4 software using a random effects model.

Results 63 studies were identified reporting clinical outcomes in patients with cirrhosis and concomitant COVID-19. Meta-analysis of cohort studies which report a non-cirrhotic comparator yielded a pooled mortality OR of 2.48 (95% CI: 2.02 to 3.04). Analysis of a subgroup of studies reporting OR for mortality in hospitalised patients adjusted for significant confounders found a pooled adjusted OR 1.81 (CI: 1.36 to 2.42).

Conclusion Cirrhosis is associated with an increased risk of all-cause mortality in COVID-19 infection compared to non-cirrhotic patients. Patients with cirrhosis should be considered for targeted public health interventions to prevent COVID-19 infection, such as shielding and prioritisation of vaccination.

BACKGROUND

COVID-19 first came to global attention in December 2019, when the Wuhan Municipal Health Commission in China reported cases of a novel 'viral pneumonia'. Since then, the virus has spread with alarming rapidity across the globe, leading to the WHO declaring a global pandemic on 11 March 2020.[1] As of 14 March 2021, the WHO reports 119 million global cumulative confirmed cases of COVID-19, with 2.6 million attributed deaths.[2]

Observational studies have identified several risk factors associated with COVID-19 mortality. A meta-analysis including 38 906 patients showed the summary relative risk of death was 1.8 (95% CI: 1.6 to 2.0) for hypertension, 1.5 (95% CI: 1.4 to 1.7) for diabetes and 1.6 (95% CI: 1.9 to 3.8) for chronic liver disease (CLD).[3] Another meta-analysis including 51 225 patients reported pooled OR of 1.09 for obesity (95% CI: 0.84 to 1.41), 2.98 for cardiovascular disease (95% CI: 2.51 to 3.53), 2.61 for hypertension (95% CI: 2.19 to 3.17), 2.12 for diabetes (95% CI: 1.79 to 2.52) and 1.80 for CLD (95% CI: 1.35 to 2.39).[4]

Many studies have examined the impact of CLD on the prognosis of COVID-19; however, CLD encompasses a heterogeneous group of patients with a variety of aetiologies as well as a spectrum of severity of liver fibrosis and dysfunction. Aetiologies, such as non-alcoholic fatty liver disease (NAFLD), have a high coprevalence with obesity and diabetes, two other conditions associated with increased mortality in COVID-19.[5] Cirrhosis represents the end stage of CLD. Development of infections in patients with cirrhosis is a well-established poor prognostic factor. Meta-analysis of studies examining the clinical outcome of patients with cirrhosis and any infection reported a mortality of 38%.[6] Factors proposed to contribute to this include cirrhosis-associated immune dysfunction as well as altered gut microbiome.[7 8]

Understanding the impact of concomitant cirrhosis in patients with COVID-19 is clinically important for several reasons. From a clinical perspective, it would inform decision-making on day-to-day treatment decisions, escalation and resuscitation status as well as on how to direct resources effectively. From a public health perspective, it would help shape healthcare policy-making regarding targeting of interventions such as vaccination prioritisation and shielding. This is particularly important in resource limited settings. On a lesser note, the

pandemic has resulted in a drastic reduction in hepatology outpatient face-to-face consultations. The risk of contracting COVID-19 while in hospital for routine bloods or surveillance imaging should be balanced appropriately against the risks of delaying access to these services.

To address this need, we performed a systematic literature review and meta-analysis to examine all primary studies reporting mortality of COVID-19 in patients with established cirrhosis.

METHODS

A systematic search of PubMed and EMBASE databases was performed for papers available on 3 February 2021. The study was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Search terms "cirrhosis", "chronic liver disease" and "liver disease" were combined with terms "COVID-19", "coronavirus", "SARS-CoV-2" and "ncov-19" in all possible permutations. After duplicates were excluded, all titles and abstracts were screened independently by two authors (PM and CH) for relevance and consideration of further review. Full texts were assessed by both authors (PM and CH) for consideration of inclusion. ML's review was performed in instances of disagreement in author inclusion. Eligible studies included any English language primary research study reporting adult patients with cirrhosis with concomitant acute SARS-CoV-2 infection and reported any clinical outcome including mortality, hospitalisation or mechanical ventilation. No exclusion criteria were applied regarding the definition of cirrhosis within the paper, and all manuscripts which reported patients being cirrhotic were considered. Review articles and systematic reviews were excluded. Reported cases in patients who had undergone liver transplantation were also excluded. A prepublished protocol was not created.

Data were extracted using a defined spreadsheet and included study design, inclusion criteria, definition of cirrhosis, definition of COVID-19, length of follow-up, reported mortality, adjusted mortality, hospitalisation rate, intubation/ventilation rate, cirrhotic decompensation, reporting of cirrhosis aetiology and reporting of cirrhosis severity including Child–Turcotte–Pugh Score, the Model of End-Stage Liver Disease (MELD) Score or compensation/decompensation status. Decompensation of cirrhosis included reported new or worsening hepatic encephalopathy, ascites, jaundice, coagulopathy, spontaneous bacterial peritonitis or variceal bleeding.

Studies that reported cirrhosis mortality alongside a non-cirrhotic comparator group were considered for meta-analysis assessment of all-cause mortality. These papers were assessed independently by two authors for risk of bias using the Quality In Prognostic Score (QUIPS) risk-of-bias assessment instrument for prognostic factor studies template.[9] Studies were assessed for consideration of risk of bias under six domains including study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding and statistical analysis and reporting. Studies were scored as low, medium or high risk of bias within each domain. Disagreement between authors was resolved by consensus. Within the 'study-confounding' domain, we assessed for the reporting and adjustment for known prognostic factors including age, gender, diabetes, obesity, cardiovascular disease, hypertension and lung disease.[3] We accepted statistical adjustment through cohort matching as well as multivariate regression analysis. We stipulated inclusion of a minimum of 10 patients with cirrhosis for a study to be deemed low risk of bias within the 'prognostic factor' domain. This is concordant with the previous systematic review and meta-analysis of clinical outcome in patients with cirrhosis and infections.[6] The primary outcome examined was all-cause mortality.

Meta-analysis to assess the pooled OR for mortality was conducted using RevMan V.5.4.[10] In cases where papers reported from the same cohort, only the paper reporting the largest cirrhotic cohort was included to prevent multiple reporting of the same patient cases. In cases where published abstracts and full articles of the same study were identified in our search, results from the complete paper were included. Crude OR was calculated from absolute values of total patients and patient deaths reported. RevMan calculator was used to derive absolute values from available data where it was not reported. Adjusted OR was input as reported. Interstudy heterogeneity was reported using the τ^2, χ^2 and I^2 statistical tests. A random effects model was used to perform meta-analysis, given the inherent variability of observational studies.

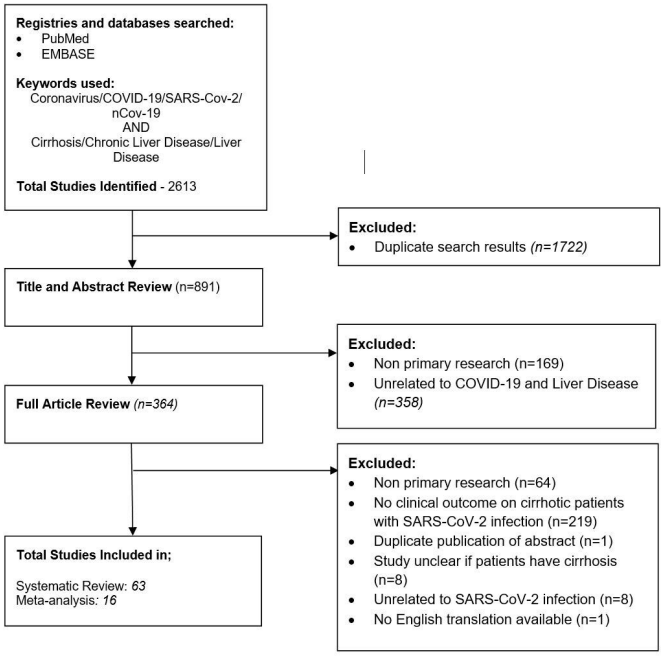

Figure 1 Flow diagram of study selection process.

Table 1 Characteristics of accepted studies

Studies	Country	Number of cirrhotic patients	Aetiology	Child–Turotte–Pugh (A/B/C)	Hospitalised	Decompensation of cirrhosis during admission	Mechanical ventilation	All-cause mortality (%)
Published abstracts								
Neppala *et al*[17]	USA	1	ARLD (1/1)	NR	1/1	1/1	1/1	1/1 (100%)
Rozenshteyn *et al*[18]	USA	1	ARLD (1/1)	NR	1/1	1/1	NR	NR
Garrido *et al*[19]	Portugal	3	NR	NR	3/3	NR	NR	2/3 (66.7%)
Joshi *et al*[20]	USA	3	ARLD (1/3) NASH (1/3) HCV (1/3)	B (1/3) C (2/3)	3/3	3/3	1/3	1/3 (33.3%)
Mangia *et al*[21]	Italy	10	Viral (3/10) Other (7/10)	NR	10/10	NR	NR	7/10 (70%)
Mandour *et al*[22]	UK	10	NR	NR	10/10	NR	NR	3/10 (30%)
Suresh *et al*[23]	USA	21	NR	NR	21/21	NR	NR	10/21 (47.6%)
Mendizabal *et al*[24]	Latin America	24	NR	NR	24/24	NR	NR	6/24 (25%)
Satapathy *et al*[25]	USA	84	NR	NR	84/84	NR	NR	NR
Choudhury *et al*[26]	Asia	121	NR	NR	NR	NR	NR	29/121 (24%)
Case reports								
Airoldi *et al*[27]	Italy	1	HCV (1/1)	B (1/1)	1/1	1/1	0/1	0/1 (0%)
Artru *et al*[28]	Switzerland	1	ARLD/NASH (1/1)	C (1/1)	1/1	0/1	0/1	0/1 (0%)
Culver *et al*[29]	France	1	ARLD (1/1)	B (1/1)	1/1	1/1	1/1	NR
El Kassas *et al*[30]	Egypt	1	HCV (1/1)	NR	1/1	1/1	1/1	0/1 (0%)
Gerstein *et al*[31]	USA	1	ARLD (1/1)	NR	1/1	1/1	0/1	0/1 (0%)
Glynn *et al*[32]	Ireland	1	ARLD (1/1)	B (1/1)	1/1	0/1	0/1	0/1 (0%)
Grosse *et al*[33]	Germany	1	NASH (1/1)	NR	1/1	1/1	0/1	0/1 (0%)
Umair *et al*[34]	Qatar	1	Cryptogenic (1/1)	B (1/1)	1/1	1/1	1/1	1/1 (100%)
Kreivenaite *et al*[35]	Lithuania	1	HCV (1/1)	B (1/1)	1/1	0/1	0/1	0/1 (0%)
Mangiameli *et al*[36]	France	1	RHF (1/1)	NR	1/1	0/1	0/1	0/1 (0%)
Martini *et al*[37]	Italy	1	AILD (1/1)	NR	1/1	1/1	0/1	0/1 (0%)
Passarelli *et al*[38]	Brazil	1	NR	NR	1/1	1/1	1/1	1/1 (100%)
Qiu *et al*[39]	China	1	ARLD (1/1)	NR	1/1	1/1	0/1	0/1 (0%)
Rhee *et al*[40]	USA	1	NASH (1/1)	NR	1/1	1/1	1/1	1/1 (100%)
Zelman *et al*[41]	USA	1	ARLD (1/1)	NR	1/1	1/1	0/1	0/1 (0%)
Case series								
Rela *et al*[42]	India	2	NASH (1/2) Crypotgenic (1/2)	C (2/2)	2/2	2/2	2/2	2/2 (100%)
Eisa *et al*[43]	USA	2	ARLD (2/2)	NR	2/2	2/2	1/2	2/2 (100%)

Continued

Table 1 Continued

Studies	Country	Number of cirrhotic patients	Aetiology	Child–Turotte–Pugh (A/B/C)	Hospitalised	Decompensation of cirrhosis during admission	Mechanical ventilation	All-cause mortality (%)
Kapuria *et al*[44]	USA	3	ARLD (3/3)	C (3/3)	3/3	3/3	3/3	3/3 (100%)
Qi *et al*[45]	China	3	HBV (1/3), ARLD (1/3) Schistosomiasis (1/3)	B (1/3) C (2/3)	3/3	3/3	1/3	2/3 (66.7%)
Kulkarni *et al*[46]	India	9	ARLD (5/9), AILD (2/9), cryptogenic (1/9), NASH (1/9)	NR	NR	7/9	4/9	4/9 (44.4%)
Liu *et al*[47]	China	17	HBV (12/17), HCV (2/17) Other (3/17)	A (15/17), B (1/17) C (1/17)	NR	NR	2/17	3/17 (17.6%)
Shalimar *et al*[48]	India	22	ARLD (8/22) Cryptogenic (6/22) Viral (4/22) AILD (2/22) Other (2/22)	A (8/22) B (8/22) C (6/22)	22/22	NR	N/A	3/22 (13.6%)
Kumar *et al*[49]	India	57	ARLD (25/57), NASH (13/57), cryptogenic (9/57) Viral (7/57), AILD (3/57)	A (11/57), B (20/57) C (26/57)	38/57	29 - 38/57	8/57	8/57 (14%)
Single-centre cohort								
Di Giorgio *et al*[11]	Italy	1	AILD (1/1)	NR	1/1	1/1	0/1	0/1 (0%)
Rigamonti *et al*[12]	Italy	1	AILD (1/1)	NR	1/1	NR	0/1	0/1 (0%)
Kroemer *et al*[50]	USA	3	ARLD (2/3) AILD (1/3)	NR	3/3	NR	1/3	1/3 (33.3%)
Forlano *et al*[51]	UK	6	NAFLD (6/6)	A (3/6) B (2/6) C (1/6)	6/6	NR	NR	3/6 (50%)
Guerra Veloz *et al*[52]	Spain	7	HCV (4/7) Other (3/7)	A (5/7) B (2/7)	7/7	NR	NR	3/7 (42.9%)
Shalimar *et al*[53]	India	26	ARLD (9/26), NAFLD (2/26) HBV (3/26), HCV (2/26), AILD (4/26), cryptogenic (6/26)	A (1/26)	NR	18/26	1/26	11/26 (42.3%)
Torres-Macho *et al*[54]	Spain	31	NR	NR	31/31	NR	NR	9/31 (29%)
Multicentre cohort								
Li *et al*[55]	China	2	HBV (2/2)	NR	2/2	0/2	0/2	0/2 (0%)
Ji *et al*[56]	China	3	NR	NR	3/3	0/3	NR	1/3 (33.3%)
Gerussi *et al*[57]	Italy	4	AILD (4/4)	A (3/4) B (1/4)	3/4	NR	NR	1/4 (25%)
Marjot *et al*[58]	UK	6†	NR	NR	NR	NR	NR	6/6 (100%)

Continued

Table 1 Continued

Studies	Country	Number of cirrhotic patients	Aetiology	Child–Turotte–Pugh (A/B/C)	Hospitalised	Decompensation of cirrhosis during admission	Mechanical ventilation	All-cause mortality (%)
Hashemi *et al*[59]	USA	9	ARLD (3/9) NAFLD (1/9) HCV (4/9) HBV (1/9)	NR	2/2	NR	NR	5/9 (55.6%)
Mangia *et al*[60]	Italy	10	Metabolic (7/10) HCV (3/10)	NR	10/10	NR	NR	7/10 (70%)
Lee *et al*[61]	South Korea	14	HBV (5/14) ARLD (5/14) HCV (2/14) AILD (1/14) Cryptogenic (1/14)	A (9/14) B (5/14)	14/14	0/14	3/14	4/14 (28.6%)
Nathwani *et al*[62]	UK	21	ARLD (10/27) Other (17/27)	A (8/21) B/C (13/21)	21/21	6/21	1/27	8/21 (38.1%)
Qi *et al*[63]	China	21	HBV (9/21) HCV (2/21) ARLD (2/21) Schistosomiasis (1/21) AILD (1/21) Other (6/21)	A (16/21) B (3/21) C (2/21)	21/21	NR	3/21	5/21 (23.8%)
Bajaj *et al*[64]	USA	37	HCV (9/37) ARLD (9/37) NASH (9/37) HCV+ARLD (4/37) Others (6/37)	NR	37/37	NR	14/37	11/37* (29.7%)
Iavarone *et al*[65]	Italy	50	HCV (14/50) HBV (5/50) ARLD (12/50) NAFLD (3/50) Other/Multiple (16/50)	A (26/50) B (18/50) C (6/50)	48/50	12/50	2/50	17/50 (34%)
Singh *et al*[66]	USA	50	NR	NR	NR	NR	NR	10/50 (20%)
Berenguer *et al*[67]	Spain	54	NR	NR	54/54	NR	NR	26/54 (48.1%)
Mendizabal *et al*[68]	Latin America	55	NR	NR	55/55	NR	NR	21/55 (38.2%)
Frager *et al*[69]	USA	83	NR	NR	83/83	NR	22/83	30/83 (36.1%)
Butt *et al*[13]	USA	93	HCV (79/93) Other (14/93)	NR	23/79	NR	NR	7/93 (7.5%)
Gottlieb *et al*[70]	USA	207	NR	NR	100/207	NR	NR	NR
Kim *et al*[71]	USA	227	NR	NR	NR	NR	NR	57/227 (25.1%)
Ioannou *et al*[72]	USA	305	HCV-related (144/305) Other (161/305)	NR	163/305	NR	40/305	52/305 (17%)
Multinational registry								

Continued

Table 1 Continued

Studies	Country	Number of cirrhotic patients	Aetiology	Child–Turotte–Pugh (A/B/C)	Hospitalised	Decompensation of cirrhosis during admission	Mechanical ventilation	All-cause mortality (%)
Sarin *et al*[73]	Asia	43	Metabolic (14/43) Viral (26/43) ARLD (2/43) Other (1/43)	NR	43/43	14/43	NR	7/43 (16.3%)
Moon *et al*[74]	International	103	NR	A (46/103) B (30/103) C (27/103)	98/103	39/103	18/103	41/103 (39.8%)
Marjot *et al*[75]	International	386	NAFLD (102/386) ARLD (158/386) HBV (37/386) HCV (72/386)	A (171/386) B (124/386) C (91/386)	345/386	179/386	71/386	123/386 (31.9%)
Marjot *et al*[76]	International	509	NR	A (231/509) B 163/509) C (115/509)	NR	NR	NR	161/509 (31.6%)

**Death/hospice.
†Cirrhotic patients from UK multicentre comparator cohort.
AILD, autoimmune liver disease; ARLD, alcohol-related liver disease; HBV, hepatitis B virus; HCV, hepatitis C virus; MAFLD, metabolic associated fatty liver disease; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NR, not reported for cirrhotic patients; RFH, right heart failure.

RESULTS

Search and study characteristics

After removal of duplicates, 891 study titles and abstracts were reviewed. Three hundred and sixty-four studies progressed to full article review (figure 1). Sixty-three studies were included in the final cohort (table 1). Ten studies were published in conference abstracts, with the remaining fifty-three papers comprising full articles and letters. Three studies were published as both full articles and abstracts. Country of origin included 22 studies from Europe, 14 studies from Asia, 19 studies from North American, 3 studies from South America, 1 study from Africa, 1 study from the Middle East and 3 international studies incorporating patients from different continents.

Study design was varied and included 17 case reports, 9 case series, 10 single-centre cohort studies, 22 multicentre cohort studies and 5 registry studies. The majority of cohort studies had a retrospective design, with only seven studies reporting a prospective or ambispective data collection. Two studies included a prospective telephone-based survey of their autoimmune liver disease patient cohort to screen for COVID-19 symptoms.[11 12] COVID-19 was defined by reverse transcription PCR testing/laboratory confirmed SARS-CoV-2 infection or in accordance with WHO criteria in 60/63 studies. Cirrhosis definition was varied, with the majority of studies presenting patients as having a premorbid diagnosis of cirrhosis. Nine studies stipulated additional histological, clinical, endoscopic or imaging features of cirrhosis. Three studies incorporated non-invasive serological screening tools, with one study using Fibrosis-4 Index as its primary determinator of cirrhosis.[13] Follow-up was defined as reaching a clinical endpoint such as death, discharge or liver transplant in 29 studies. Thirteen studies employed minimum follow-up period or a censoring date. Twenty studies did not provide a clear follow-up period.

Twenty-seven studies reported further decompensation of cirrhosis associated with COVID-19 infection. Twenty-five studies reported patients receiving intubation and mechanical ventilation.

Risk-of-bias assessment

Overall, 10/63 papers were found to be at low risk of bias across all domains. Common areas for potential bias included low number of cirrhotic patients, lack of confounder reporting and lack of adjustment for confounders.

Meta-analysis of cohort studies

All studies that reported all-cause mortality in a cohort of 10 or more patients with cirrhosis and COVID-19 alongside a non-cirrhotic COVID-19 comparator group were incorporated into the meta-analysis. Overall, 26 studies included 10 or more cirrhotic patients with COVID-19. Two published abstracts were excluded as they were already included as published full articles. Five studies were excluded as they did not report a non-cirrhotic COVID-19 comparator or did not report a mortality

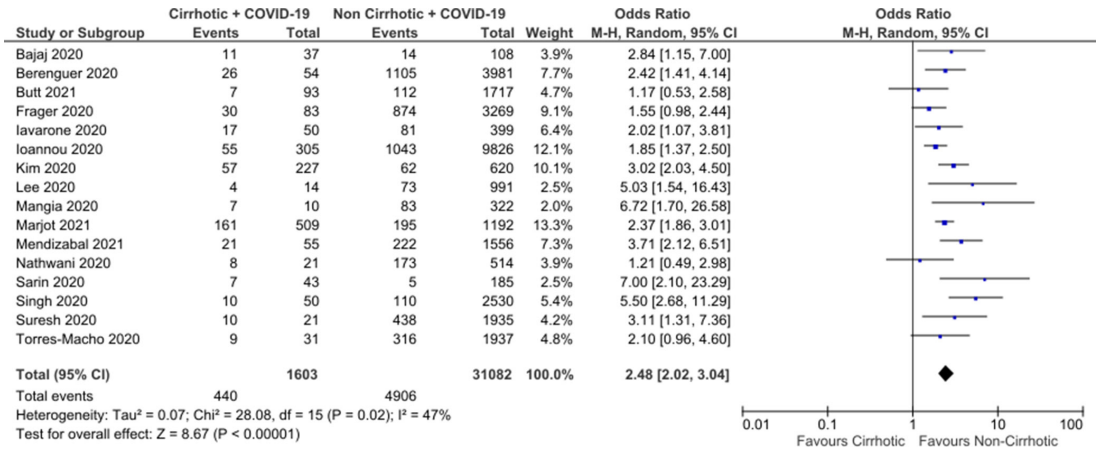

Figure 2 Meta-analysis of crude mortality OR comparing cirrhotic patients with COVID-19 with non-cirrhotic patients with COVID-19.

outcome. One abstract was excluded as it contained insufficient information to extract an OR. Two studies were excluded as they reported from the same registry as a larger third study which was included.

In total, 16 studies were included in the meta-analysis, producing a total of 1603 cirrhotic patients with COVID-19 compared with 31 082 non-cirrhotic patients with COVID-19 (figure 2). In the majority of studies (14/16), this included all other patients with COVID-19 including a proportion of patients with CLD without cirrhosis. Overall, 2/16 studies only reported patients with CLD without cirrhosis to provide a comparator group. A funnel plot showed a degree of publication bias towards studies reporting greater associated risk; however, this was within the smaller studies (figure 3). Using a random-effect model, a pooled crude OR for all-cause mortality for patients with cirrhosis was calculated as 2.48 (95% CI: 2.02 to 3.04). Moderate interstudy heterogeneity was found. Sensitivity analysis removing studies which only had a CLD comparator showed minimal change to the associated mortality OR to 2.64 (95% CI: 2.08 to 3.36).

Inclusion of only eligible studies with a low risk of bias yielded an OR 2.44 (95% CI: 2.05 to 2.91) without significant interstudy variability (figure 4). Five low risk-of-bias studies reported adjusted ORs for mortality between all cirrhotic patients and non-cirrhotic comparators. One study adjusted based on cohort matching for age and gender alone. Four studies reported adjusted ORs based on multivariate regression analysis incorporating age, gender as well as significant comorbidities including diabetes and cardiovascular disease in hospitalised patients. Pooled analysis of these four studies produced an adjusted OR of 1.81 (CI: 1.36 to 2.42) (figure 5). Two eligible low-risk studies reported adjusted ORs for mortality by disease severity, suggesting worsening mortality with more advanced cirrhosis (table 2).

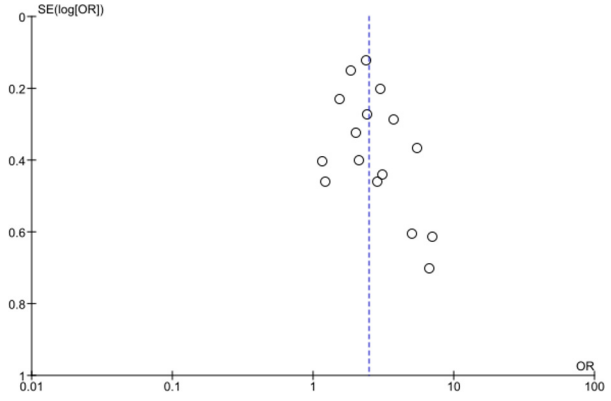

Figure 3 Funnel plot of studies included in the meta-analysis of crude mortality OR.

DISCUSSION

To the best of our knowledge, this study is the first to systematically examine and analyse the literature to describe the clinical outcome of patients with cirrhosis who have concomitant COVID-19. Pooled crude OR for mortality of 2.48 (95% CI: 2.02 to 3.04) is comparable to other established significant prognostic factors such as diabetes, hypertension and cardiovascular disease.[4] This additional mortality risk persisted on analysis of adjusted ORs in hospitalised cirrhotic patients, suggesting cirrhosis poses an additional risk independent of its association with other comorbidities, such as diabetes and cardiovascular disease in patients with NAFLD. Mortality risk is potentially higher in patients with more advanced cirrhosis. Further studies with subgroup outcome reporting based on severity of cirrhosis are required to fully evaluate this; however, to assess this appropriately large patient numbers will be required, likely only achievable by large multinational or registry-based studies.

This study provides evidence to support targeted interventions aimed at protecting patients with cirrhosis from COVID-19, such as prioritisation for vaccination, shielding and limitation of hospital attendance with support from telemedical interventions where appropriate. Healthcare professionals should be aware of the associated heightened COVID-19 mortality in patients with cirrhosis and the potential risk of associated cirrhotic

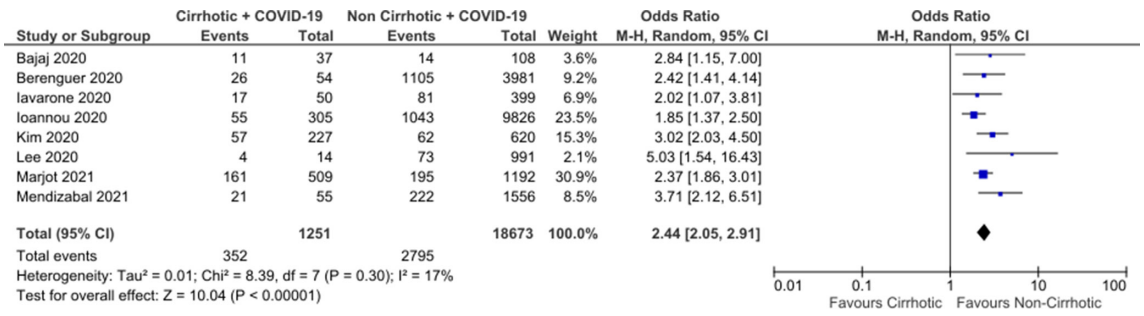

Figure 4 Meta-analysis of studies at lower risk of bias.

decompensation. However, the associated mortality risk in cirrhosis is not out-keeping with other common comorbidities such as cardiovascular disease or diabetes. Therefore, all cirrhotic patients should still be considered for mechanical ventilation or escalation to intensive care unit on an individual basis.

Following the date of censoring, further studies have been published which may have been suitable for inclusion and it is important to consider these. Ge *et al* have reported data from the N3C Consortium in the USA which uses electronic healthcare record data to identify patients who underwent SARS-CoV-2 testing or had related symptoms.[14] In total, 8941 patients with cirrhosis and COVID-19 were identified. When compared with SARS-COV-2 patients with non-cirrhotic CLD, they report an adjusted 30-day mortality HR of 3.31.[14] This risk is higher than adjusted risks for hospitalised patients identified in our systematic review, likely due to the high proportion of non-hospitalised patients in this study and the difference in risk of hospitalisation between groups (CLD 22.9% vs cirrhosis 50.1%).[14] Observational studies within our meta-analysis include predominantly patients who were hospitalised or presented to hospitals. This is likely due to changes in the availability and ease of access to SARS-CoV-2 testing in the community over time as the response to the pandemic has progressed.

Mallet *et al* have reported the outcomes of hospitalised COVID-19 from the French National Hospital Discharge database including 3207 patients with concomitant cirrhosis.[15] Comparing cirrhotic patients to all non-cirrhotic patients produced a mortality OR of 1.73 (1.59–1.88) which is in line with our findings. Adjusted OR for 30-day mortality in compensated cirrhosis (0.71; 0.63–0.80) and decompensated cirrhosis (2.21; 1.94–2.51) were provided, highlighting the importance of delineating cirrhosis severity when prognosticating outcome.[15] Mendizabal *et al* have published an update from their prospective study on hospitalised patients with COVID-19, which was already included in this systematic review.[16] This update provided an adjusted OR 3.1 (1.9–4.8) for patients with cirrhosis.[16] This represents an increase in reported mortality compared with their prior publication. However, they also report an increase in overall mortality for both cirrhotic patients (46.9% from 38.2%) and all non-cirrhotic patients (19.5% from 14.3%). As the pandemic progresses, regional variations in SARS-CoV-2 variant predominance, pressure on healthcare resources, public health policy and access and uptake of vaccination are likely to become more significant when predicting patient outcomes than in the first phase of the global pandemic with potentially increasing heterogeneity in reported outcomes.

The study has several limitations including the heterogeneity of study design and characteristics, the heterogeneity of the comparator group and the relatively small sample size with 34 out of 63 studies reporting fewer than 10 patients with cirrhosis. Although steps were taken to prevent multiple reporting of patient cases during meta-analysis, it is possible that cases reported are also included in registry-based studies and may be reported concurrently.

CONCLUSION

Systematic review and meta-analysis of observational studies of reporting COVID-19 in patients with cirrhosis supports an increased mortality rate compared with non-cirrhotic patients. Mortality is likely higher in those with more advanced cirrhosis. Patients with cirrhosis should be considered for targeted measures to prevent COVID-19, such as prioritisation of vaccination and shielding.

Contributors PM—authorship of manuscript, data collection, quality assessment and data analyses. CH—data collection, quality assessment and review of manuscript. ML—data collection, quality assessment and review of manuscript. All

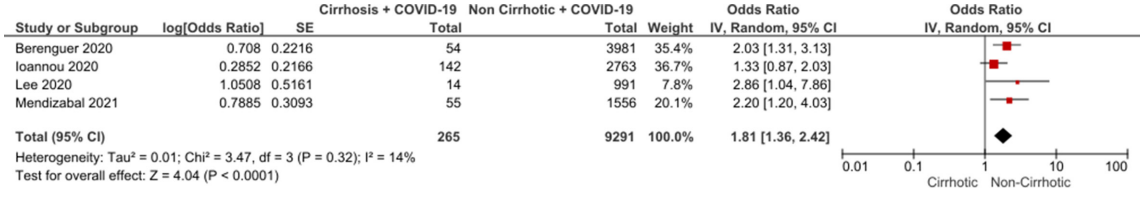

Figure 5 Meta-analysis of adjusted mortality OR in studies comparing cirrhotic inpatients with COVID-19 and non-cirrhotic inpatients with COVID-19.

Table 2 Studies reporting adjusted ORs for severity subgroups of cirrhosis compared with non-cirrhotic chronic liver disease comparator

Studies	Severity	Adjusted OR (CI 95%)
Marjot *et al*[76]	CP A	2.18 (1.24 to 3.84)
	CP B	4.79 (2.72 to 8.45)
	CP C	12.41 (6.73 to 22.88)
Kim *et al*[71]	Compensated	0.83 (0.46 to 1.49)
	Decompensated	2.91 (1.7 to 5.00)

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