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Prevalence of chronic liver disease in patients with COVID-19 and their clinical outcomes: a systematic review and meta-analysis

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REVIEW ARTICLE

Prevalence of chronic liver disease in patients with COVID-19 and their clinical outcomes: a systematic review and meta-analysis

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Abstract

Abnormal liver enzymes are seen in 20% of hospitalized patients with COVID-19. The etiology of elevated liver enzymes is thought to be multifactorial including medications and underlying liver disease. The true prevalence and clinical significance of underlying chronic liver diseases (CLD) in COVID-19 remains poorly defined. In this systematic review and meta-analysis, we included 74 clinical studies that were identified after a thorough literature search across three databases. The prevalence of CLD patients (73 studies, 24,299 patients) was 3% among all COVID-19 patients. The prevalence of CLD patients was similar in COVID-19 positive and negative population (pooled OR 0.79 [95% CI 0.60, 1.05], $p=0.10$). The presence of CLD was significantly associated with more severe COVID-19 infection (pooled OR 1.48 [95% CI 1.17, 1.87], $p=0.001$) and overall mortality (pooled OR 1.78 [95% CI 1.09, 2.93], $p=0.02$). Additionally, there was a non-significant trend noted for increased ICU admissions and need for invasive mechanical ventilation among COVID-19 patients with CLD. To date, the clinical importance of chronic liver diseases among COVID-19 infection has remained undefined. In this novel systematic review and meta-analysis, the presence of underlying chronic liver disease was significantly associated with more severe COVID-19 infections and mortality.

Keywords Liver · Cirrhosis · Chronic liver disease · Coronavirus · COVID-19 · Severe · Critical · ICU · Mechanical ventilation · Mortality

Abbreviations

ALD	Alcoholic liver disease
CI	Confidence interval
CLD	Chronic liver disease
COVID-19	Novel coronavirus
FiO2	Inhaled oxygen concentration
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
ICU	Intensive care unit
NAFLD	Nonalcoholic fatty liver disease
OR	Odds ratio
PaO2	Partial pressure arterial oxygen concentration
SpO2	Oxygen saturation
WHO	World Health Organization

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Introduction

Abnormal liver enzymes (20%) and elevated bilirubin (16.7%) are common in hospitalized patients with COVID-19 [1–3]. The etiology of abnormal liver enzymes is thought to be multifactorial, and in majority of patients, it is thought to be due to medications or underlying liver diseases [3].

It is not known whether patients with chronic liver disease (CLD) are more likely to develop COVID-19 as there is a paucity of data on the prevalence of CLD among patients

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with COVID-19. It has been suggested that chronic liver disease is an established risk factor for severe COVID-19 [4]. Although it is intuitive to believe that patients with cirrhosis, especially those with decompensated cirrhosis, are likely to have more severe COVID-19, there is no firm evidence to support this. In one study, only 19 of 5700 (0.4%) of patients with COVID-19 hospitalized in NY hospitals had cirrhosis and only 11 (0.2%) patients had either HCV or HBV [5]. Similarly, only 28 of 1591 (2%) ICU admissions in Italy due to COVID-19 had chronic liver diseases. [6] The experience from Italy also suggests that COVID-19 is not disproportionately more common in liver transplant recipients, and 3 of 200 liver transplant recipients from one center who were tested positive did not develop pulmonary disease. [7] In another study from Milan, only 8 of 640 liver transplant recipients were diagnosed with COVID-19 during this pandemic, and of these only 5 were hospitalized and none required mechanical ventilation. [8] Moreover, there are only limited data on the clinical outcomes of patients with CLD including ICU admission, mechanical intubation rates, or mortality.

The primary aim of this systematic review and meta-analysis is to determine the prevalence of CLD in patients with COVID-19 and their clinical outcomes.

Methods

Literature search

Three major databases, including MEDLINE/PubMed, EMBASE, and medRxiv, were searched for clinical studies dated from January 1, 2019 to May 16, 2020. In an effort to broadly identify studies detailing CLD and COVID-19, the following search criteria were utilized: "(coronavirus OR Cov2 OR (Cov AND 2) OR ncov2 OR (ncov AND 2) OR (sars AND cov AND 2) OR (sars AND cov2) OR 'Sars Cov 2′ OR COVID OR (covid AND 19) OR 'COVID 19′) AND (chronic AND liver AND disease*) OR cirrhosis OR (hepatitis AND b) OR (hepatitis AND c) OR HBV OR HCV OR (alcohol AND liver AND disease) OR (alcoholic AND liver AND disease) OR ALD OR (nonalcoholic AND fatty AND liver) OR NAFLD OR (nonalcoholic AND steatohepatitis) OR (liver AND cancer) OR (hepatocellular AND carcinoma) OR HCC." This meta-analysis was conducted according to the Preferred Reporting Item for Systematic Reviews and Meta-Analyses [PRISMA] [9] and meta-analysis of observational studies and epidemiology [MOOSE] [10].

Inclusion criteria

Articles and clinical trials that met the following inclusion criteria were eligible for this meta-analysis: (1) studies performed in adult, human subjects; (2) studies reporting CLD among patients with COVID-19. No preference was given upon study design on the initial search strategy, and all types of studies including randomized controlled trials, non-randomized studies, cohort studies, and case–control studies were considered.

Exclusion criteria

Studies with the following characteristics were excluded from this meta-analysis: (1) studies performed among non-human subjects; (2) studies that were not a clinical trial, such as a review paper or letter; (3) studies that were out of scope of the study question detailed above; (4) studies that lacked proper controls; (5) studies that did not provide raw data in order to perform quantitative meta-analysis; (6) studies that were duplicates.

Study definitions

As mentioned above, CLD was defined by patients having any of the following diagnoses: cirrhosis, hepatitis B virus (HBV), hepatitis C virus (HCV), alcoholic liver disease (ALD), nonalcoholic fatty liver disease (NAFLD), or hepatocellular carcinoma (HCC).

Severe and critical COVID-19 infection was defined by criteria set forth in the WHO situation report and interim guidance [11]. Severe cases defined as any one of the following: respiratory distress with RR > 30 breaths per minute; mean oxygen saturation [SpO_2] < 93% on room air; or arterial blood oxygen [PaO_2]/oxygen concentration [FiO_2] ≤ 300 mmHg. Critical illness was defined by the presence of any one of the following: admission to ICU; respiratory failure requiring mechanical ventilation; shock; other multisystem organ failure requiring ICU level of care. Non-severe or mild cases of COVID-19 were defined as patients who tested positive for COVID-19, but did not meet criteria for severe or critical cases and were either asymptomatic or the symptoms from their infection were self-limiting.

Statistical analysis

This meta-analysis was performed using Review Manager [RevMan, software version 5.3, The Cochrane Collaboration, Denmark, 2014]. Odds Ratios [OR] were used as a summary measure for dichotomous data. 95% confidence intervals [CI] were reported for all measures. Data were considered statistically insignificant if OR includes 1.00 or $p > 0.05$. Statistical heterogeneity was assessed using the I^2 statistic. I^2 values of 0–25%, 25–50%, 50–75%, and > 75%

were awarded values of homogeneity, mild heterogeneity, moderate heterogeneity, and high heterogeneity, respectively. If significant heterogeneity was present [$I^2 \geq 50\%$], the random effects model was used to pool the effect sizes of included studies and subgroup analyses; if no significant heterogeneity was found [$I^2 < 50\%$], the fixed effects model was utilized. Publication bias was determined by visual inspection of funnel plots, which were calculated based on logarithmic ORs plotted against their standard errors [12]. Asymmetric funnel plots were deemed to represent studies with high risk of bias.

Results

Study selection

Overall, 437 clinical studies were identified for inclusion based upon the predefined search criteria. After a thorough literature appraisal and implementation of the exclusion criteria, 74 studies were finally included in this meta-analysis (Fig. 1 and Supplemental Table 2).

Prevalence of CLD among patients with COVID-19

Three studies (4221 patients) had compared the prevalence of CLD among COVID-19 positive patients and negative controls (Fig. 2). The prevalence of CLD patients was similar in COVID-19 positive and negative population with

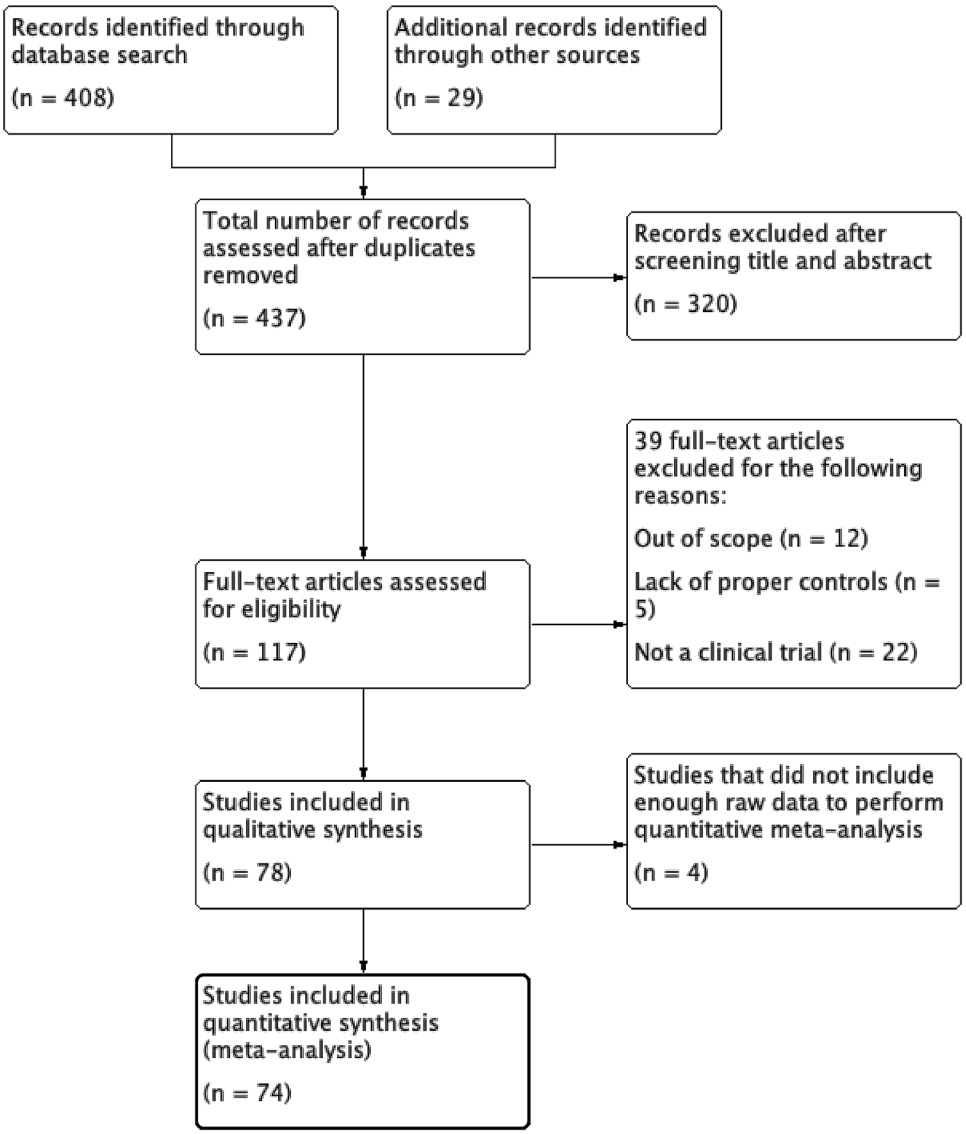

Fig. 1 Study flow diagram

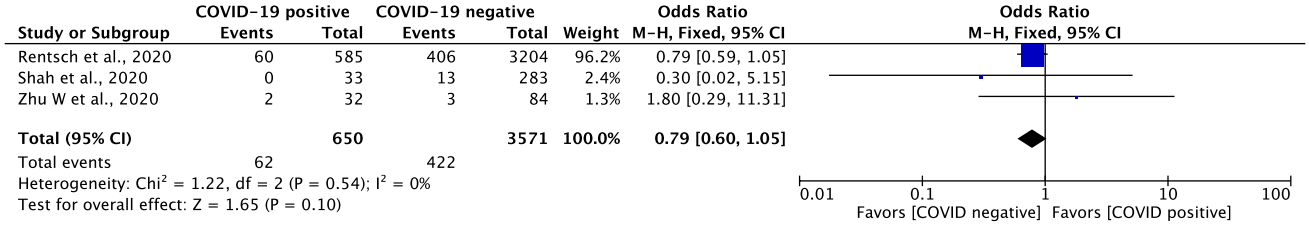

Fig. 2 Forest plot comparison of patients with underlying chronic liver disease among COVID-19 positive versus COVID-19 negative patients

pooled OR 0.79 [95% CI 0.60, 1.05; $p=0.10$; $I^2=0\%$]. In 73 studies (24,299 patients), the prevalence of CLD among patients positive for COVID-19 (regardless of the presence of negative controls) was 0.03 [95% CI 0.03, 0.04] (Table 1).

Clinical outcomes of patients with CLD and COVID-19

Significantly greater severe and/or critical illness events were present among COVID-19 patients with CLD when compared to those without CLD (pooled OR 1.48 [95% CI 1.17, 1.87]; $p=0.001$; $I^2=10\%$) (Fig. 3). There were no significant differences in ICU admissions in COVID-19 patients with CLD when compared to patients without CLD (pooled OR 1.38 [95% CI 0.88, 2.17]; $p=0.17$; $I^2=0\%$), but there was a trend, and not statistically significant, towards increased rate of invasive mechanical ventilation among COVID-19 patients with CLD (pooled OR 2.22 [95% CI 0.67, 7.42]; $p=0.19$; $I^2=36\%$) (Fig. 4). The overall mortality was significantly higher in COVID-19 patients with CLD when compared to COVID-19 patients without CLD (pooled OR 1.78 [95% CI 1.09, 2.93]; $p=0.02$; $I^2=0\%$) (Fig. 3).

Publication bias

Funnel plots were created for the outcomes of this meta-analysis and reported in Supplemental Figs. 1–3. No asymmetry was noted in the funnel plots to suggest a significant degree of publication bias.

Discussion

Our meta-analysis showed that there was no increased risk of COVID-19 in patients with CLD. However, patients with CLD were more likely to have severe or critical COVID-19 and they were also more likely to have a higher mortality when compared to those without CLD.

Recent recommendations made by the AASLD Expert Panel affirm an increased healthcare burden among COVID-19 positive patients with CLD [13]. Although it is intuitive to believe that patients with CLD are likely to have more severe COVID-19, the above assumptions were made in the absence of robust clinical data and were largely based on expert opinion.

Previous two large studies outside China also appear to suggest that the prevalence of CLD is not higher in hospitalized patients [5, 6]. Our meta-analysis supports those observations. Mild elevation of liver enzymes is common, especially in severe COVID-19, and it is thought to be multifactorial, and mostly medication related [1, 3]. Our study provides important epidemiological information on the comparative prevalence of CLD in patients with and without COVID-19. After meticulously identifying studies among the primary literature, no significant difference was identified among the studies comparing the prevalence of CLD among patients with or without COVID-19. The overall prevalence of CLD was only 3% across all studies characterizing COVID-19 positive patients, and this is similar to the reported prevalence of CLD in hospitalized patients in New York and ICU patients in Italy [5, 6] Some studies from China had reported a higher prevalence mostly because of chronic hepatitis B in that population. It is very true that retrospective nature of most studies and the general lack of predefined diagnoses for CLD among studies may have underestimated the true prevalence of CLD in COVID-19.

Our study, however, showed that those with CLD are more likely to have more severe or critical COVID-19 illness when compared to those without CLD, and moreover, those with CLD are more likely to have a higher mortality. An EMR based, propensity matched, study had recently reported higher mortality in 250 patients with CLD and our findings corroborate it [14]. Moreover, meta-analyses of early data, one based on 11 observational studies [15] and another one based on 22 studies [16], had also come to similar conclusions. We can only speculate that some of these observations could be related to decompensation precipitated by COVID-19 in those with advanced cirrhosis or perhaps related other comorbidities in the population with liver disease. We need more granular data to make any firm conclusions. Our data have also demonstrated a trend towards an increased frequency of ICU admissions and requirement for invasive mechanical ventilation. Previous studies had reported higher prevalence of liver injury in

Table 1 Prevalence of chronic liver diseases among COVID-19 positive patients

Study	Country	COVID-19 positive patients with CLD	Total COVID positive patients	CLD prevalence among COVID-19 positive patients [95% CI]
Ren et al. (2020)	China	1	5	0.20 [− 0.15, 0.55]
Kujawski et al. (2020)	USA	2	12	0.17 [− 0.04, 0.38]
Chen et al. (2020)	China	15	123	0.12 [0.06, 0.18]
Chen et al. (2020)	China	3	25	0.12 [− 0.01, 0.25]
Xu et al. (2020)	China	7	62	0.11 [0.03, 0.19]
Rentsch et al. (2020)	USA	60	585	0.10 [0.08, 0.13]
Yanover et al. (2020	Israel	404	4353	0.09 [0.09, 0.10]
Shi et al. (2020)	China	7	81	0.09 [0.03, 0.15]
Chen et al. (2020)	China	4	48	0.08 [0.00, 0.16]
Zhu et al. (2020)	China	21	325	0.07 [0.04, 0.09]
Li et al. (2020)	China	6	85	0.07 [0.02, 0.13]
Yu et al. (2020)	China	2	28	0.07 [− 0.03, 0.17]
Zha et al. (2020)	China	2	31	0.07 [− 0.02, 0.15]
Luo et al. (2020)	China	25	403	0.06 [0.04, 0.09]
Zhang et al. (2020)	China	8	140	0.06 [0.02, 0.10]
Du et al. (2020)	China	5	85	0.06 [0.01, 0.11]
Ji et al. (2020)	China	6	101	0.06 [0.01, 0.11]
Liu et al. (2020)	China	5	89	0.06 [0.01, 0.10]
Song et al. (2020)	China	4	73	0.06 [0.00, 0.11]
Li et al. (2020)	China	1	17	0.06 [− 0.05, 0.17]
Zhu et al. (2020)	China	2	32	0.06 [− 0.02, 0.15]
Sun et al. (2020)	China	3	55	0.06 [− 0.01, 0.12]
Chen et al. (2020)	China	15	291	0.05 [0.03, 0.08]
Wang et al. (2020)	China	12	242	0.05 [0.02, 0.08]
Zhao et al. (2020	China	4	75	0.05 [0.00, 0.10]
Arentz et al. (2020	USA	1	21	0.05 [− 0.04, 0.14]
Liu et al. (2020)	China	2	41	0.05 [− 0.02, 0.12]
Fu et al. (2020)	China	9	200	0.04 [0.02, 0.07]
Lian et al. (2020)	China	31	819	0.04 [0.02, 0.05]
Lu et al. (2020)	China	20	577	0.04 [0.02, 0.05]
Mo et al. (2020)	China	7	155	0.04 [0.01, 0.08]
Shi et al. (2020)	China	5	134	0.04 [0.01, 0.07]
Wu et al. (2020)	China	7	201	0.04 [0.01, 0.06]
Yan et al. (2020)	China	6	168	0.04 [0.01, 0.06]
Feng et al. (2020)	China	4	114	0.04 [0.00, 0.07]
Wang et al. (2020)	China	3	69	0.04 [− 0.01, 0.09]
Chen et al. (2020)	China	2	57	0.04 [− 0.01, 0.08]
Zhang et al. (2020)	China	7	221	0.03 [0.01, 0.06]
Cao et al. (2020)	China	6	198	0.03 [0.01, 0.05]
Huang et al. (2020	China	6	221	0.03 [0.01, 0.05]
Regina et al. (2020	Switzerland	6	200	0.03 [0.01, 0.05]
Zhang et al. (2020	China	9	315	0.03 [0.01, 0.05]
Cai et al. (2020	China	8	298	0.03 [0.01, 0.04]
Wang et al. (2020	China	4	138	0.03 [0.00, 0.06]
Liu et al. (2020	China	1	32	0.03 [− 0.03, 0.09]
Su et al. (2020)	China	2	73	0.03 [− 0.01, 0.06]
Guan et al. (2020)	China	23	1099	0.02 [0.01, 0.03]
Bai et al. (2020)	China	3	127	0.02 [0.00, 0.05]

Table 1 (continued)

Study	Country	COVID-19 positive patients with CLD	Total COVID positive patients	CLD prevalence among COVID-19 positive patients [95% CI]
Du et al. (2020)	China	4	179	0.02 [0.00, 0.04]
Xiao et al. (2020)	China	4	197	0.02 [0.00, 0.04]
Huang et al. (2020)	China	1	41	0.02 [− 0.02, 0.07]
Liu et al. (2020)	China	1	51	0.02 [− 0.02, 0.06]
Song et al. (2020)	China	1	51	0.02 [− 0.02, 0.06]
Yang et al. (2020)	China	1	55	0.02 [− 0.02, 0.05]
Cao et al. (2020)	China	2	102	0.02 [− 0.01, 0.05]
Duan et al. (2020)	China	2	116	0.02 [− 0.01, 0.04]
Liu et al. (2020)	China	2	112	0.02 [− 0.01, 0.04]
Yao et al. (2020)	China	2	108	0.02 [− 0.01, 0.04]
Wan et al. (2020)	China	2	135	0.01 [0.00, 0.03]
Qin et al. (2020)	China	6	452	0.01 [0.00, 0.02]
Almazeedi et al. (2020)	Kuwait	6	1099	0.01 [0.00, 0.01]
Liu et al. (2020)	China	3	620	0.01 [0.00, 0.01]
Richardson et al. (2020)	USA	30	5700	0.01 [0.00, 0.01]
Wang et al. (2020)	China	2	339	0.01 [0.00, 0.01]
Yan et al. (2020)	China	1	192	0.01 [0.00, 0.01]
Liu et al. (2020)	China	1	80	0.01 [− 0.01, 0.04]
Wang et al. (2020)	China	1	69	0.01 [− 0.01, 0.04]
Wu et al. (2020)	China	1	80	0.01 [− 0.01, 0.04]
Wang et al. (2020)	China	2	165	0.01 [− 0.01, 0.03]
Zhang et al. (2020)	China	1	111	0.01 [− 0.01, 0.03]
Guo et al. (2020)	China	1	118	0.01 [− 0.01, 0.02]
Shabrawishi et al. (2020)	Saudi Arabia	1	150	0.01 [− 0.01, 0.02]
Lu et al. (2020)	China	1	265	0.00 [0.00, 0.01]
Total		875	23,424	0.03 [0.03, 0.04]

those with severe COVID-19 and this could be major confounder of mortality in patients with CLD [2].

Despite the novel findings presented, in addition to minimal heterogeneity across studies, this systematic review and meta-analyses have some limitations. Most of the included studies were retrospective and based on hospitalized patients. These studies also may have under-reported CLD among comorbidities since CLD was not the primary focus of their studies and moreover, there was no predefined definition for CLD in these studies. In addition, the majority of studies did not stratify CLD patients based on the etiology of CLD, and most studies were from China, where chronic hepatitis B is more prevalent. In spite of the above limitations, this systematic review and meta-analysis provides useful information on the prevalence and complication of COVID-19 infection in those with CLD, and highlights the importance of prospective case-controlled studies that include both outpatients and hospitalized patients.

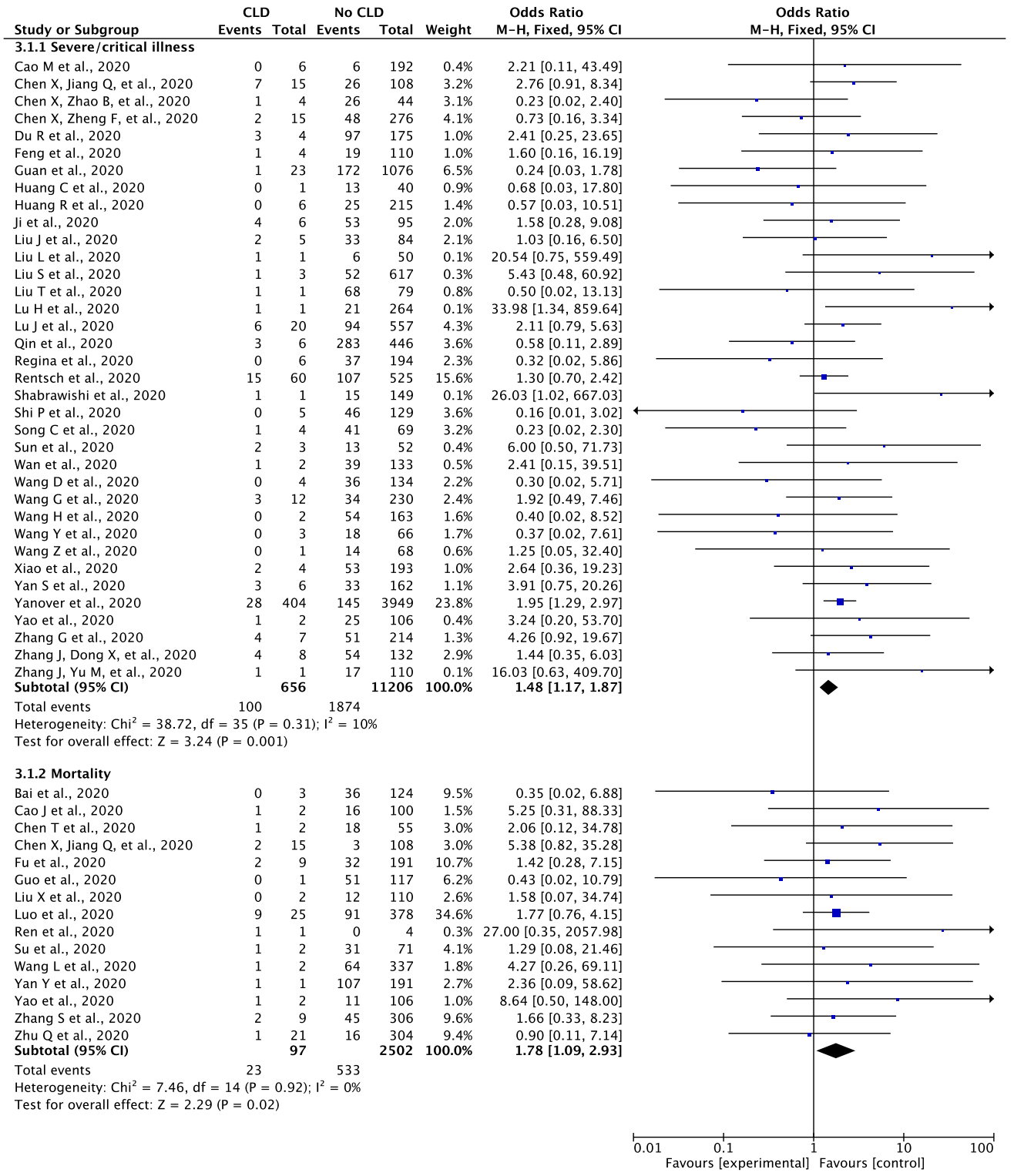

Fig. 3 Forest plot comparison of severity of illness [3.1.1] and mortality [3.1.2] among COVID-19 positive patients with versus without chronic liver diseases

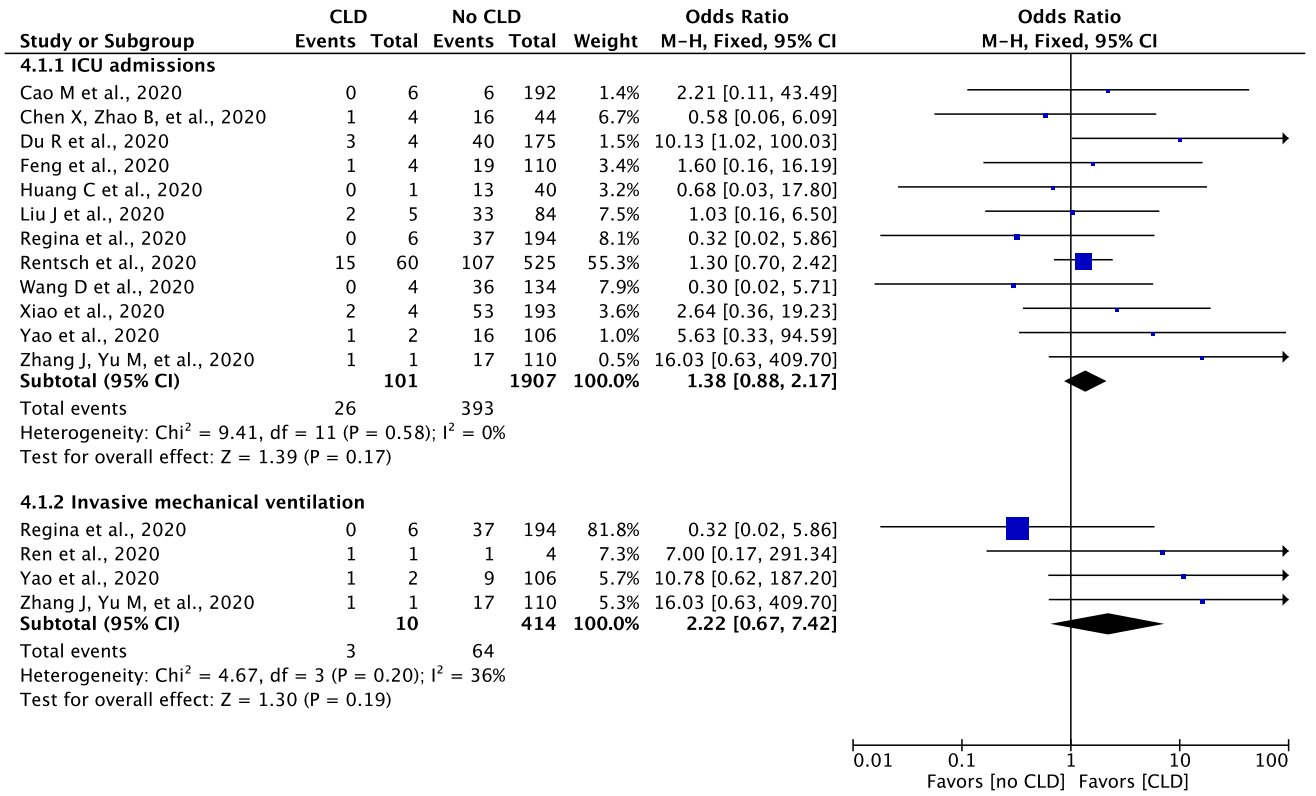

Fig. 4 Forest plot comparison of ICU admissions [4.1.1] and rates of invasive mechanical ventilation [4.1.2] among COVID-19 positive patients with versus without chronic liver diseases

Author contributions AK provided substantial contributions to conception and design of the study, acquisition of data/analysis and interpretation of data, drafting of the article, critical revisions of the article, and final approval of article. SS and PT provided substantial contributions to conception and design of the study, critical revisions of the article, and final approval of article

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Compliance with ethical standards

Conflict of interest Alexander J. Kovalic, Sanjaya K. Satapathy and Paul J. Thuluvath authors have no conflict of interest to disclose in the writing of this manuscript.

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