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Prognosis of COVID-19 in Patients with Liver and Kidney diseases: An Early Systematic Review and Meta-analysis

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Abstract

Background: The mortality and severity in COVID-19 is increased in patients with comorbidities. The aim of this study was to evaluate the unknown risk of severity and mortality in COVID-19 patients with underlying kidney and liver diseases.

Method: We retrieved data on the clinical features and primary composite end point of COVID-19 patients released from inception till 16th of April 2020 from Medline and Embase. The data on two comorbidities, liver diseases and chronic kidney disease, present in COVID-19 were pooled and statistically analysed to explain the associated severity and mortality rate.

Results: 142 abstracts were screened, and 41 full articles were then read. In total, 22 studies including 5595 COVID-19 patients were included in this study with case fatality rate of 16%. The prevalence of liver diseases and CKD were 3% (95%CI; 2%-3%) and 1% (95%CI; 1%-2%) respectively. In patients with COVID-19 and underlying liver diseases, 57.33% (43/75) cases were severe with 17.65% mortality. While in CKD patients with COVID-19, 83.93% (47/56) severity and 53.33% (8/15) mortality were reported.

Conclusion: This study found an increased risk of severity and mortality in COVID-19 patients with liver diseases and CKD. This will allow for better clinical management and inform more stringent preventative measures for this group of patients.

Introduction

The 2010 Global Burden of Disease reported that liver diseases were responsible for about 2 million deaths annually and 50% of this associated with complications due to liver cirrhosis and the other half linked to hepatocellular carcinoma and viral hepatitis [1]. Cirrhosis is an end-stage decompensation of chronic liver disease often preceded by hepatocellular necrosis and progressive fibrosis triggered by various agents including viral infections and chronic alcohol use [2]. Alcohol-related liver disease, non-alcoholic steatohepatitis and hepatitis B and C have been reported to be the main aetiologies of liver cirrhosis with up to 80% mortality rate recorded 1-year after decompensation [3, 4]. Aside mortality, the economic impact of liver-associated morbidity is also high with associated disease-adjusted life years loss over 41 million globally. According to the World Health Organization (WHO) global health estimate of 2015 , chronic liver disease ranks as the 16th highest cause of morbidity globally [5, 6]. Despite the availability of vaccines for hepatitis C and B and the advances in clinical understanding and management of chronic liver diseases, the number of new cases is projected to go up due majorly to ageing and increasing global population [4].

According to Kidney Disease Improving Global Outcome (KDIGO), chronic kidney disease (CKD) is a dysfunction of the kidney characterised by established histological damage or sub-optimal (< 60 mL/min/1.73 m^2) glomerular filtration rate (GFR) persisting for at least 3 months [7]. Although, majority of CKD cases were linked to diabetes and hypertension [8], other risk factors including genetics [9], recreational drugs and alcohol consumption [10], obesity [11], gender [12, 13], age [12], lower birth weight [14], smoking status [15, 16], ethnicity [17], family history of CKD [18], acute kidney injury have been studied [19, 20]. In 2017, the number of deaths associated with CKD or CDK-related complications was estimated as 1.2 million,

accounting for 4.6% of global death [21]. Between 1990 and 2017, CKD rose as a cause of global mortality from 17th to 12th leading cause of death with a 46% increase in total number of death caused directly or indirectly via cardiovascular disease linked to kidney dysfunction [22]. While the relationship between COVID-19-induced acute kidney injury has been investigated previously [23], to the best of our knowledge, no studies have looked at the risk of COVID-19 in patients with all-form renal disease.

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a viral pathogen responsible for the corona virus disease 2019 (COVID-19) [24]. Symptoms of COVID-19 include fever, fatigue, dry cough, dyspnoea and sore throat with patients presenting with abnormal chest CT scans in the form of pulmonary ground glass opacity changes [25, 26]. The COVID-19 was first reported in December 2019 with possible origin linked to Wuhan seafood market in China [27]. Since first reported, SARS-CoV-19 have infected as of 2nd of April 2020, 896,450 people and caused 45,525 deaths worldwide, with this number rising daily [28]. So far, risk factors associated with poor clinical outcomes (Death and admission to ICU) have been reported to be old age and several comorbidities associated with compromised immune system to help patient fight the infection. The most common of these comorbidities are hypertension, diabetes, cardiovascular diseases and malignancy. These comorbidities individually or in combination with age were reported to be linked with poor prognosis [29]. Several studies have looked at the risk posed to patients with various chronic diseases by COVID-19. For instance, Alqahtani et al. 2020 looked at the risk of smoking status and chronic obstructive pulmonary disease (COPD) in COVID-19 patients, establishing an increased risk of death or admission to ICU for patients with COPD or smoking history infected with SARS-CoV-19 [30].

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While COVID-19-induced liver and kidney injuries have been documented, to the best of our knowledge there have been no report of the risk posed by COVID-19 infection in patients with history of liver or renal disease. Understanding the risk to this subpopulation of patients will allow for effective prevention decision and clinical management. We aim here to understand this risk by looking at reported cases since the outbreak of the COVID-19.

Methods

Preferred Reporting in Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed during the drafting of this review. The completed review was submitted to Prospero.

We searched Medline and Embase from November 2019 to April 10, 2020 and later the 14th of April 2020, an updated search was performed. The search strategy was designed to include all papers on COVID 19 published from November 21, 2019 when the first case of the disease was reported to right before this review was submitted (see supplementary Table S1). Search results was uploaded to Endnotes and duplicates removed. The duplicate-free studies were uploaded to Rayyan review software for screening based on title, abstract and then full text by two independent reviewers.

- **Inclusion and Exclusion Criteria**

Studies considered were those reporting clinical characteristics of diagnosed COVID-19 patients with underlying kidney and/or liver diseases. To be eligible studies must also report clinical outcome in the form of disease severity (defined as need for ICU care or need for respirators or intubation) as well as death. Excluded studies were those including COVID-19 patients clinical features but not liver or kidney diseases comorbidity, SARS, MERS and other

coronavirus infections, non-English manuscripts, reviews, qualitative studies, editorials and letters of correspondence.

- **Data Collection**

Potential studies were initially screened by two of the authors (TO and AJ) scrutinizing the title and abstract and coming to a final decision on which studies should be included. Included studies were then fully read by the authors to identify which of the included studies satisfy the inclusion criteria stated above. The finally selected studies were then screened for eligible studies listed in the reference. A third author was consulted all through the selection period to resolve conflicts between the two authors.

- **Quality Assessment**

The quality of the included studies was independently assessed by two authors using a modified version of the Newcastle-Ottawa Scale (NOS) [31]. Accordingly, the modified NOS included three domains and six questions scored with a star if satisfied and no star if otherwise. The domains cover the assessments of the quality of "Selection", "Ascertainment" and "Outcome" (Table S1).

- **Data Extraction and Analysis**

All analysis was performed using the Stata/SE15 software. The pooled prevalence of patients with CKD and liver diseases was analysed using the Metaprop procedure in Stata, utilising the random effect model due to the observed heterogeneity between the included studies. Forest plots was generated presenting the effect sizes (95% CI), percentage weights and the between-studies heterogeneity (I^2 Statistic, P-value, Figures 2 and 3). The prevalence and clinical outcomes of COVID-19 patients with CKD and liver diseases were synthesised from all

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studies included. Primary composite end points were disease severity and mortality. Disease severity was defined as extended hospital stay, admission to Intensive Care Unit (ICU) or need for mechanical ventilation.

Results

The initial databases search generated 142 paper from which 26 duplicates were removed. After the title and abstract were screened, 75 papers were excluded and 41 included based on the inclusion criteria. We performed a full-text review, another 22 studies were excluded resulting in 19 studies with the desired criteria. All the references of the 19 included studies were then screened for studies relevant to the review and three more studies were included from the references making a total of 22 studies (Figure). The modified NOS assessment performed showed a low risk of bias in the included studies (Table S1).

- **Description of included Studies**

The total number of confirmed COVID-19 cases included in this study is 5595 of which 2310 (41.29%) were females. In total, 147 (3%) and 78 (2%) have comorbidities of liver diseases and CKD respectively. The mean ± SD (range) of the sample sizes of all included studies is 253.53 ± 411.99 (29-1591). One each of the studies were conducted in Italy and the rest conducted in China. 15 of the 22 included studies including 5595 patients reported mortality. Where reported, the mortality was 656 (11.72%) in this review. The mean (±SD) follow-up time was 30.55 ± 13.24 days. The clinical characteristics of the liver diseases and CKD, including the stages and aetiology were not provided in all the studies (Table 1).

- **Prevalence of Renal Diseases in confirmed COVID-19 cases**

The prevalence of CKDs in patients diagnosed with COVID-19 was 2% (95%CI; 1%-2%). The level of heterogeneity is also moderate (I^2 = 40.36%, p=0.07).

- **Disease outcome for renal diseases patients with COVID-19**

In all, 5 studies including 3123 COVID-19 patients 56 of which have CKD, reported severity. Where reported, the severity of COVID-19 was 83.93% (47/56) in patients with underlying CKD. Only 3 studies, including 15 COVID-19 patients with CKD, reported mortality. The mortality in patients with CKD diagnosed with COVID-19 was 53.33% (8/15) (Table 1).

- **Prevalence of Liver Diseases in confirmed COVID-19 cases**

The prevalence of liver diseases in patients diagnosed with COVID-19 is 3% (95%CI; 2%-3%). The forest plot shows moderate level of heterogeneity (I^2 = 46.62%, p=0.01).

- **Disease outcome for Liver Diseases patients with COVID-19**

Six of the 22 included studies reported severity in COVID-19 patients with different forms of liver disease. The 6 studies including 3182 COVID-19 patients, 75 of which have underlying liver diseases reported in 57.33% (43/75) severe cases. Two of the 22 studies reported mortality in COVID-19 patients with liver diseases. These studies included 1373 COVID-19 cases which 34 of which had liver diseases on diagnosis. In all 6 deaths (17.65%) was recorded.

Discussion

We report here for the first time the prevalence, severity and mortality of patients diagnosed with COVID-19 with underlying chronic kidney disease and liver diseases. Our outcome shows that the overall prevalence of CKD and Liver Diseases in COVID-19 are 1% and 3% respectively. We also report COVID-19 severity of 83.93% (47/56) in patients with CKD and 57.33% (43/75)

in patients with liver diseases. The rate of mortality in COVID-19 patients with CKD and Liver diseases was found to be 53.33% (8/15) and 17.65% (6/34) respectively.

The presence of comorbidities is associated with poor prognosis in patients with COVID-19, with higher mortality rate and severity. The most common comorbidities reported so far in severe cases have been hypertension, diabetes, cardiovascular diseases, cerebrovascular diseases and COPD [32]. However, how these diseases contribute to the COVID-19 outcome remains unclear.

Biomarkers of liver injuries have been reported to increase in patients with COVID-19 [25, 33, 34], although, no virus was found in the liver tissue of patients who died from the disease [35]. This is expected as angiotensin II-converting enzyme (ACE2) receptor, a key player in the "docking" and replication of the SARS-CoV-19 virus is not expressed in hepatocytes. However, ACE2 expression have been reported in cholangiocytes [36] leading to suggestion that the binding of SARS-CoV-19 to the epithelial cells of the biliary tree may cause biliary dysfunction [36]. Zhang et al. 2020, also suggested that the transient liver injuries observed in COVID-19 patients may be associated with drug toxicity, cytokine storm or hypoxia [37]. While many studies have reported liver dysfunction in COVID-19 [25, 33, 34], the mechanistic link between the two remains to be established.

Furthermore, CKD have been associated with inflammation and dysregulation of the immune system [38]. This dysregulation of immune function which may exist in patients with underlying CKD may explain the increased severity and mortality due to COVID-19. The level of ACE2 receptor in the kidney have been previously reported to be altered in human kidney diseases [39]. In a recent study by Fan et al., it was reported that ACE2 receptor is overexpressed in the tubular cells of patients with CKD. Alteration in kidney functions

characterised by increased serum creatinine and urea nitrogen was also reported in patients with COVID-19 [40]. Taken together, the alterations in ACE2 receptor expression may explain the observed kidney dysfunction in COVID-19 and provide the answer to why patients with CKD are vulnerable to SARS-CoV-19 virus.

The power of this study is limited by several factors. Firstly, some included studies did not report comorbidities. Where comorbidities were specified, the criteria for defining severity is not uniform. Some studies included only patients with primary composite outcome while some did not report mortality. Lastly, the aetiology and pathophysiological characteristics of the comorbidities were not documented.

Indeed, this review involved an in-depth literature search followed by systematic analysis of data involving a total of 5595 patients with confirmed COVID-19. For the first time we have established the risk of COVID-19 in liver diseases and CKD patients which indicates an increased vulnerability of this sub-population.

The most important clinical implication of this study is that Liver diseases and CKD patients are highly vulnerable to COVID-19 and should be considered for remote consultation and most stringent social isolation to prevent infection. Future studies should investigate how liver diseases and CKD contribute to poor prognosis in COVID-19.

Conclusion

We report an increased risk of severity and mortality in COVID-19 patients with liver diseases and CKD. This study will allow for better clinical management and inform more stringent preventative measures for this group of patients.

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Tables and Figures : Table 1 – Characteristics of the studies included.

Authors	Country	Study Type	Sample Size	Female	Mortality	Follow-up Time (Days)	Liver Patients	Renal Patients	Liver Deaths	Liver Severity	Renal Death	Renal Severity
Chen J et al [41]	China-Shanghai	Retrospective Analysis	249	123	2	16	2	.	.	.	.	.
Chen L et al [42]	China-Wuhan	Retrospective Analysis	29	8	26	15	2	.	.	.	.	.
Chen N et al [33]	China-Wuhan	Descriptive Analysis	99	32	11	20	.	3	.	.	.	.
Chen T et al [43]	China-Wuhan	Retrospective Analysis	274	103	113	30	11	5	5	.	4	.
Grasselli et al [44]	Italy-Mullticentre	Retrospective Analysis	1591	287	405	34	28	36	.	28	.	36
Guan W et al [45]	China-Multicentre	Retrospective Analysis	1099	459	15	49	23	8	1	1	2	3
Huang C et al [25]	China-Wuhan	Prospective Analysis	41	11	.	32	1	.	.	.	.	.
Huang Y et al [46]	China-Wuhan	Retrospective Analysis	34	20	.	39	1	.	.	.	.	.
Lian J et al [47]	China-Zhejiang	Retrospective Analysis	788	381	.	26	31	7	.	.	.	.
Liu K et al [48]	China-Hainan	Retrospective Analysis	56	25	3	46	1	1	.	.	.	.
Mo P et al [49]	China-Wuhan	Retrospective Analysis	155	69	22	36	7	6	.	5	.	4
Shi H et al [50]	China-Wuhan	Descriptive Analysis	81	39	3	47	7	3	.	.	.	.
Wan S et al [51]	China-Chongqing	Retrospective Analysis	135	63	1	16	2	.	.	1	.	.
Wang D et al [34]	China-Wuhan	Retrospective Analysis	138	63	6	34	4	4	.	0	.	2
Wang Z et al [52]	China-Wuhan	Retrospective Analysis	69	37	5	19	1	.	.	.	.	.
Wu C et al [53]	China-Wuhan	Retrospective Analysis	201	73	44	63	7	2	.	.	.	.
Wu J et al [54]	China-Jiangsu	Retrospective Analysis	80	41	.	23	1	1	.	.	.	.
Xu T et al [55]	China-Changzhou	Retrospective Analysis	51	26	.	35	1	1	.	.	.	.
Xu X et al [56]	China-Zhejiang	Retrospective Analysis	62	27	.	16	7	1	.	4	.	.
Zhang J et al [57]	China-Wuhan	Retrospective Analysis	140	69	.	34	8	2	.	4	.	2
Zhou et al [58]	China-Wuhan	Retrospective Analysis	191	72	54	15	.	2	.	.	2	.
Zhu W et al [59]	China-Anhui	Retrospective Analysis	32	17	.	27	2	1	.	.	.	.

Figure 1 - Risk of COVID-19 in patients with chronic liver and kidney diseases, systematic review according to the Preferred Reporting Items for Systematic Reviews and Metanalyses diagram.

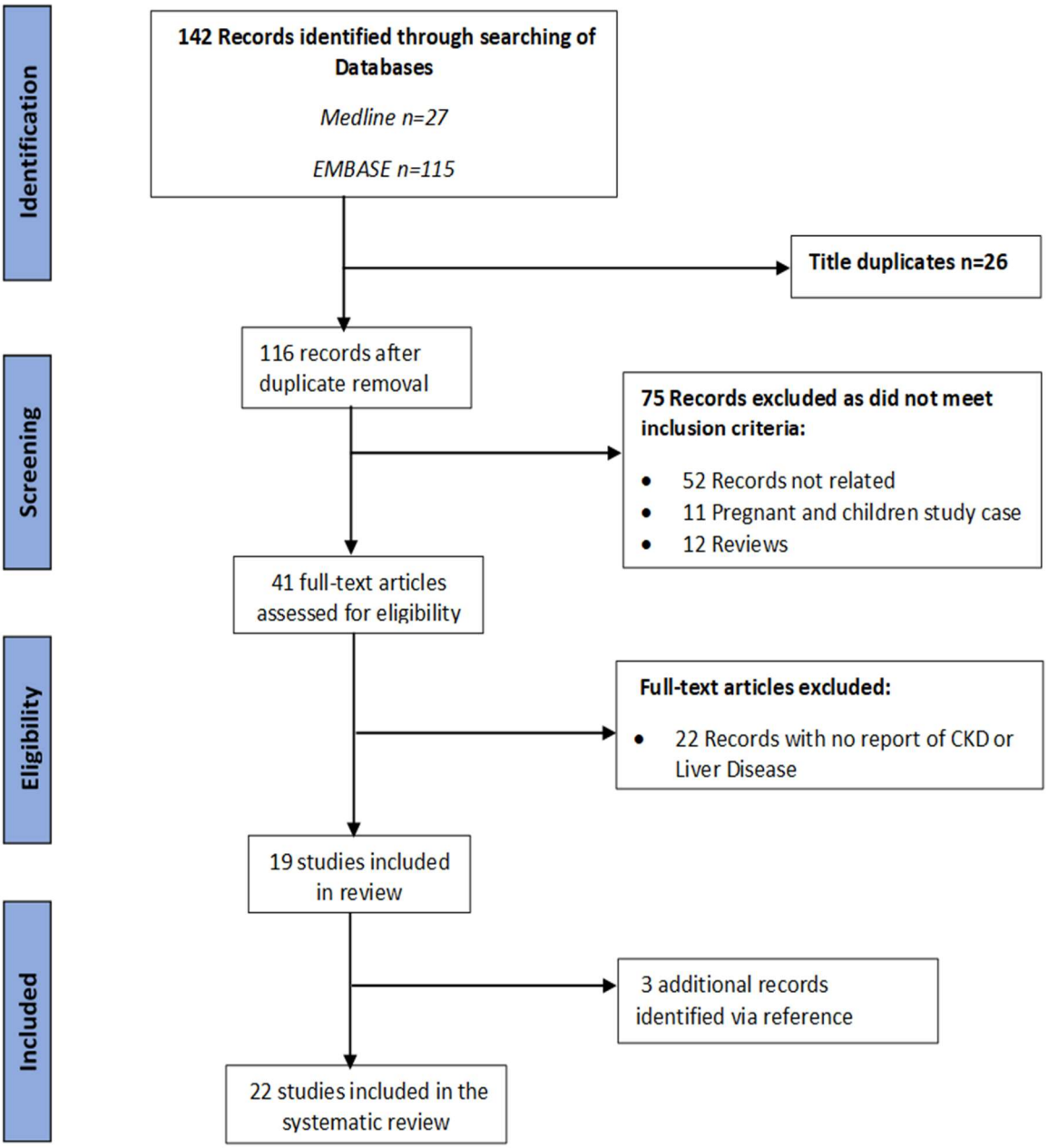

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Figure 2 – Pooled prevalence of patient with chronic renal diseases diagnosed with COVID-19.

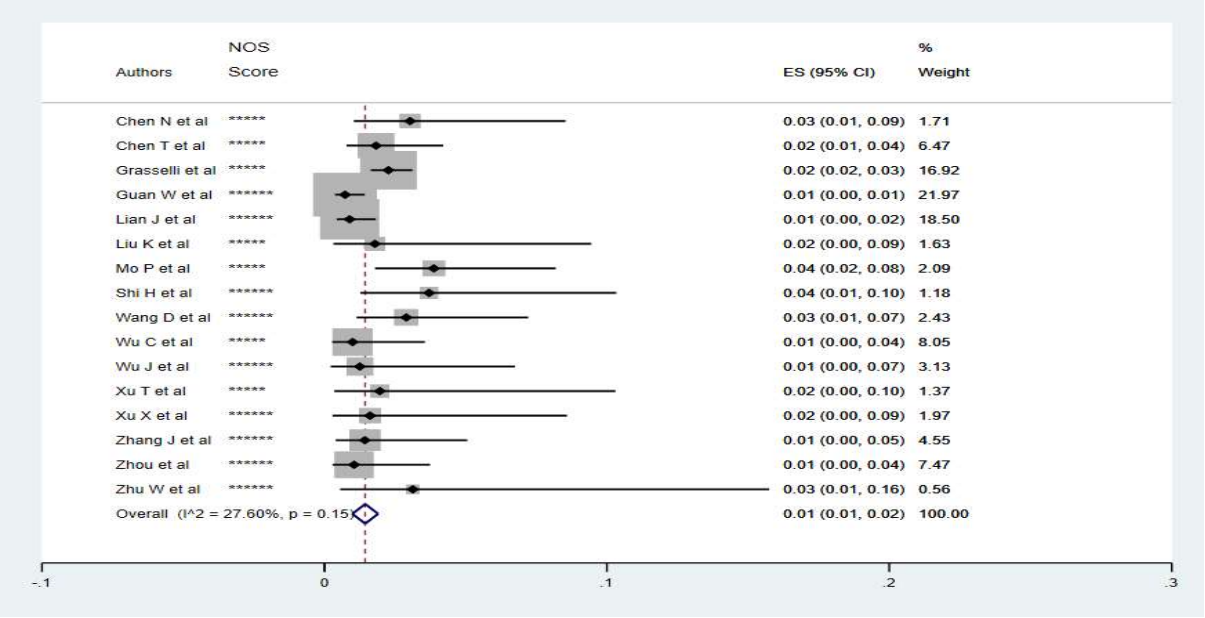
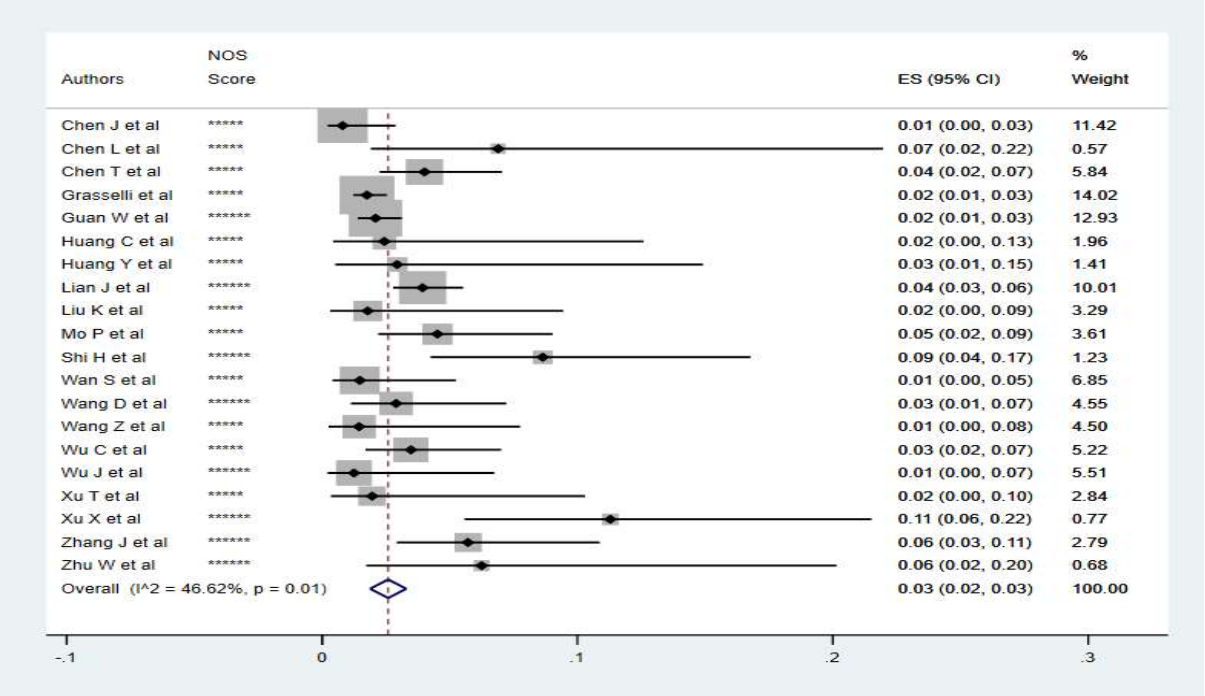


Figure 3 - Pooled prevalence of patient with liver diseases (Chronic Liver Diseases, Hepatitis B/C infections) diagnosed with COVID-19.



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Appendix:

Table S1 – Quality Assessment:

	SELECTION		ASCERTAINMENT		OUTCOME		OVERALL
First author	Sample Size Adequate	Population Representative (Multicentre)	Test Adequate	Comorbidity Confirmation Adequate (EMR)	Outcome Reported Adequately (Clinical Staff)	Follow-up Long Enough (≥2 weeks)	OVERALL (≥ 4 Stars = lower risk of bias)
Chen J et al	*		*	*	*	*	*****
Chen L et al	*		*	*	*	*	*****
Chen N et al	*		*	*	*	*	*****
Chen T et al	*		*	*	*	*	*****
Grasselli et al	*	*	*		*	*	*****
Guan W et al	*	*	*	*	*	*	******
Huang C et al	*		*	*	*	*	*****
Huang Y et al	*		*	*	*	*	*****
Lian J et al	*	*	*	*	*	*	******
Liu K et al	*		*	*	*	*	*****
Mo P et al	*		*	*	*	*	*****
Shi H et al	*	*	*	*	*	*	******
Wan S et al	*		*	*	*	*	*****
Wang D et al	*	*	*	*	*	*	******
Wang Z et al	*		*	*	*	*	*****
Wu C et al	*		*	*	*	*	*****
Wu J et al	*	*	*	*	*	*	******
Xu T et al	*		*	*	*	*	*****
Xu X et al	*	*	*	*	*	*	******
Zhang J et al	*		*	*	*	*	*****
Zhou et al	*	*	*	*	*	*	******
Zhu W et al	*	*	*	*	*	*	******

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Peer-reviewed version available at *Tropical Medicine and Infectious Disease* **2020**, *5*; doi:10.3390/tropicalmed5020080

Table S2 - Medline Search Strategy

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to April 10, 2020>
Search Strategy:
---
1 COVID-19.mp. (3190)
2 2019 novel coronavirus.mp. (363)
3 2019 coronavirus.mp. (46)
4 2019-nCoV.mp. (460)
5 SARS-CoV-2.mp. (1009)
6 Wuhan Coronavirus.mp. (14)
7 1 or 2 or 3 or 4 or 5 or 6 (3655)
8 clinical characteristic*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (67298)
9 clinical Characteristics.mp. (66591)
10 clinical features.mp. (100583)
11 clinical feature*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (104280)
12 8 or 9 or 10 or 11 (166495)
13 7 and 12 (181)
14 limit 13 to english language (159)
15 limit 14 to humans (27)

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Table S3 - Embase Search Strategy

Database: Embase <1980 to 2020 Week 15>
Search Strategy:
---
1 COVID-19.mp. (1687)
2 2019 novel coronavirus.mp. (450)
3 2019 coronavirus.mp. (34)
4 2019-nCoV.mp. (374)
5 SARS-CoV-2.mp. (561)
6 Wuhan Coronavirus.mp. (12)
7 1 or 2 or 3 or 4 or 5 or 6 (2218)
8 clinical characteristic*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (111691)
9 clinical Characteristics.mp. or exp clinical feature/ (742652)
10 clinical feature*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (721829)
11 8 or 9 or 10 (798804)
12 7 and 11 (139)
13 limit 12 to english language (127)
14 limit 13 to human (115)

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