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COVID-19 Induced Hepatitis, Meta-analysis and Systematic Review

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Abstract

Background

The prevalence of elevated liver chemistries and the incidence of acute liver injury have been recently reported in COVID-19. We conducted a systematic review and meta-analysis to assessthe prevalence and degree of liver injury and impaired liver biochemistrybetween patients with severe and non-severe COVID-19.

Materials and methods

Electronicsearch was done for PubMed, Medline, Cochrane, Google scholarly and (Ovid) Embase databases for all the related literature published up toJanuary 30, 2021. The data were analyzed using RavMen 5.3 statistical software. The fixed-effects model was used for pooling the data. The risk of bias and quality of included studies was assessed using Cochrane Collaboration's tool for assessing risk of bias in randomized trials.

Results

We estimated the overall pooled data of these seventeen studies with 7132 COVID-19 infected patients (severe cases, n=2955; mild cases, *n*=4178), it was demonstrated that elevated serum levelsof AST (odds ratio (OR): 2.656% confidence interval (CI): 2.30, 2.035), with significantheterogeneity: Chi^2 = 34.67, df = 16 (p = 0.004); I^2 = 54%, Z = 13.53 (p = 0.001), ALT(odds ratio (OR): 3.0839% confidence interval (CI): 2.6347, 3.6097), with significant heterogeneity: Chi^2= 48.99, df = 16 (p = 0.001); I^2 = 65%, Z = 14.02 (p = 0.0001), and total bilirubin (odds ratio (OR): 1.8796% confidence interval (CI): 1.427, 2.4597),heterogeneity: Chi^2= 22.15, df = 9 (p = 0.0008); I^2 = 59%, Z = 4.48 (p = 0.0001), were associated with a significantincrease in the severity of COVID-19 infections. Additionally,collective data from the random effects modelpresented that lower serum levels of albumin (odds ratio (OR): 1.4062% confidence interval (CI): 1.0971, 1.8023),with slight heterogeneity: Chi^2= 11.58, df = 10 (p = 0.31); I^2 = 14%, Z = 2.69 (p = 0.007).

Conclusion

COVID-19 Induced Hepatitis is common in severe COVID-19 patients. Care givers must be responsive of potential development of severe disease in population with COVID- 19-associated liver injury.

Introduction

The corona virus disease 2019 (COVID-19) pandemic is still posing a serious public health threat worldwide and the global community continues to face high transmission rates of this unpredictable, fast spreading infectious disease that presents serious challenges to global health[1]. Mainly people with COVID-19 shows mild to moderate symptoms of characterized fever, dry cough and tiredness, and mostly do not require admissions to intensive care unit (ICU) [2]. However, in some patients, this infection may evolve to serious complications like pneumonia and respiratory failure. As of 4th April 2021, there were 132046206 confirmed cases and 2867242 confirmed deaths reported in 223 countries, areas or territories [3]. With consecutive rise in threat of COVID-19 crisis a global effort is ongoing to explore the severity of the disease and the complications it is creating on health conditions[4]. The group of patients who are older and have comorbidities like Hypertension (HT), Type 2 Diabetes Mellitus (T2DM), and Cardiovascular Disease (CVD) are much likely to develop severe form of COVID-19 which may need invasive mechanical ventilation or may require the need of hospitalization and Intensive Care Unit (ICU) admissions[5].

As the COVID-19 is a new disease, there is still need of much of information and new studies and researches are yet required it has become obvious that SAR-CoV-2 damages not only the respiratory system but also the cardiovascular, gastrointestinal, and hepatobiliary systems, subsequently resulting in Multi-Organ Failure (MOF) and death[6,7].Other than respiratory symptoms there are extra-pulmonary symptoms such as COVID-19 associated liver injury has been reported in literature [8]. The recent clinical reports showed that among COVID-19 patients tested during hospitalization had atypical liver test results had liver injury. The use of ritonavir/lopinavir also augmented the incidence of liver injury[9,10]. Nevertheless, this virus may not have an effect on all populations equally, and certain populations are particularly vulnerable, such as Chronic Liver Disease (CLD)

population with increasing burden worldwide. Additionally, patients with cirrhosis, and with compromised immune system, are probably more vulnerable and have worse outcomes in viral illness [11]. Numerous studies have reported the clinical characteristics and laboratory findings linked with various degrees of liver injury in patients with COVID-19 infection[12].

We executed this systematic review and meta-analysis of emerging studies reporting liver injury in patients with COVID-19 on the basis of GADOUR criteria; Gradual onset, elevated AST and ALT (AST and/or ALT >2x upper limit of normal), Dilated sinusoids with lymphocytic infiltration of liver parenchyma, non-Obstructive jaundice, and stable/absent Underlying liver disease and no new Radiological hepatobiliary changes[13]. We also analyzed Subgroup analysis of COVID-19 Associated Hepatitis including viral hepatitis A,B,C and E. and Subgroup of liver transplant patient including donors and recipient.

Methods

This systematic review was designed by following methods described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins, et al. 2019)[14] as well as guidelines presented in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher, et al. 2009) (Figure1-10) [15].

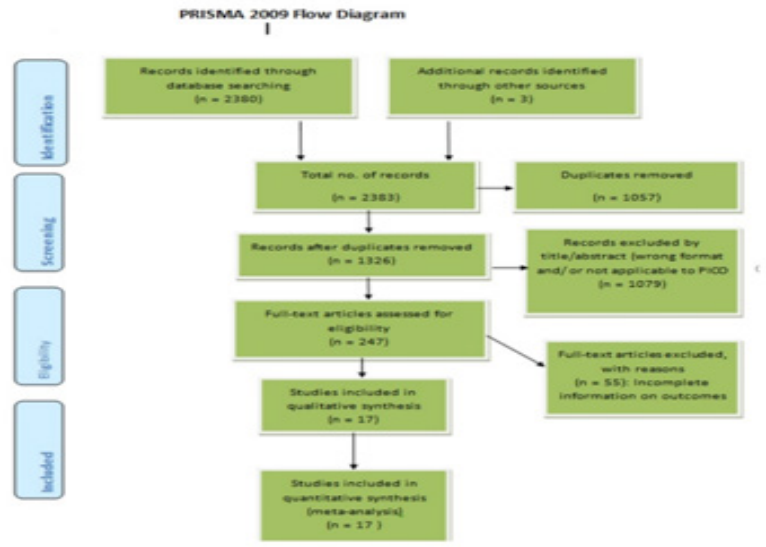

Figure 1: PRISMA

Search strategy

Detailed search strategies for each electronic database were developed. These were based on the one used for PubMed, Medline, Cochrane, Google scholarly and (Ovid) Embase but with appropriate database related search strategy modification such as the use of truncations, wildcards, and filters.Key search terms included “corona virus,” “COVID-19,” “SARS-CoV-2” or “severe acute respiratory syndrome,” OR “SARS-CoV-2” OR “novel coronavirus” OR “2019-nCoV”) AND (“alanine transaminase” OR “alanine aminotransferase” OR “SGPT” OR “aspartate aminotransferase” OR “SGOT” OR “bilirubin” OR “serum albumin” OR “liver”).

Searching other resources

We also conducted a grey literature search in DOAJ to identify not indexed studies in the databases listed above.The references were checked for all the included studies and use the citation alert to search for more up to date publications or new studies.

Search validation and data selection

Inclusion criteria for studies

- Design that included randomized controlled trials, nonrandomized controlled trials
- (Case control or controlled cohort), observational studies and case series,
- Study population that included adult patients’ above18 years old.
- Studies reporting reverse transcription-polymerase chain reaction (RT-PCR)-confirmed COVID-19 cases.
- Reported studies of liver biomarkers (albumin, bilirubin, ALT, AST) and their mean serum levels among severe and non-severe cases of COVID-19

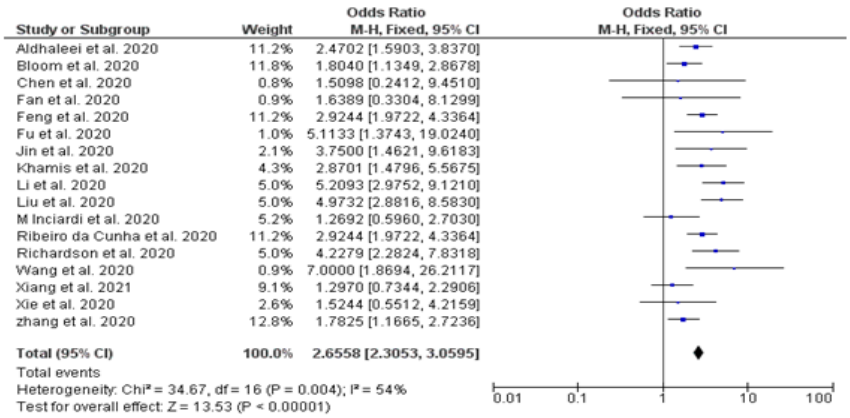

Figure 2: Forest plot for pooled analysis of serum AST levels using fixed effect model.

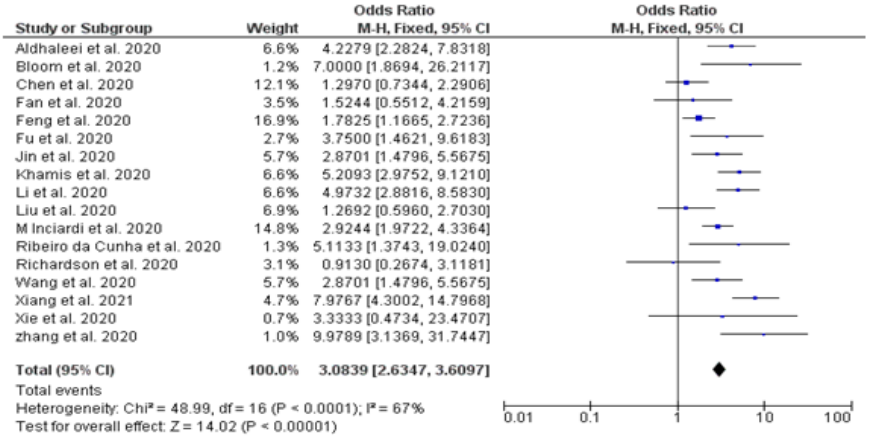

Figure 3: Forest plot for pooled analysis of serum ALT levels using fixed effect model.

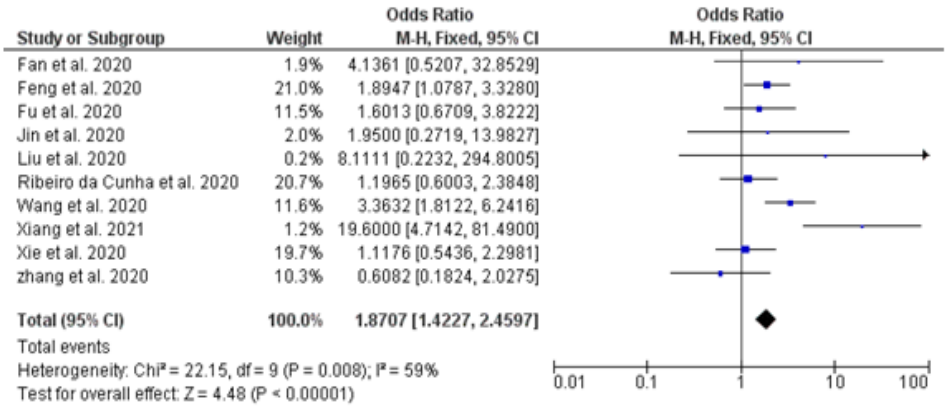

Figure 4: Forest plot for pooled analysis of serum Albumin levels using fixed effect model.

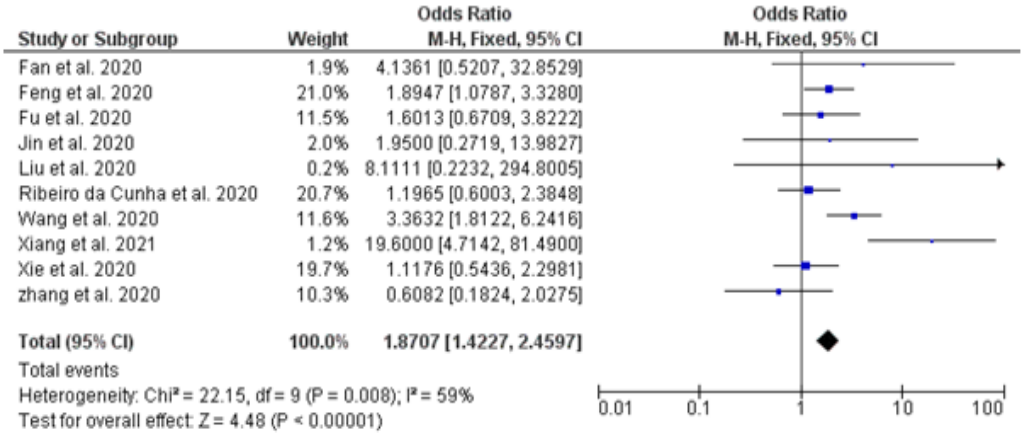

Figure 5: Forest plot for pooled analysis of serum bilirubin levels using fixed effect model.

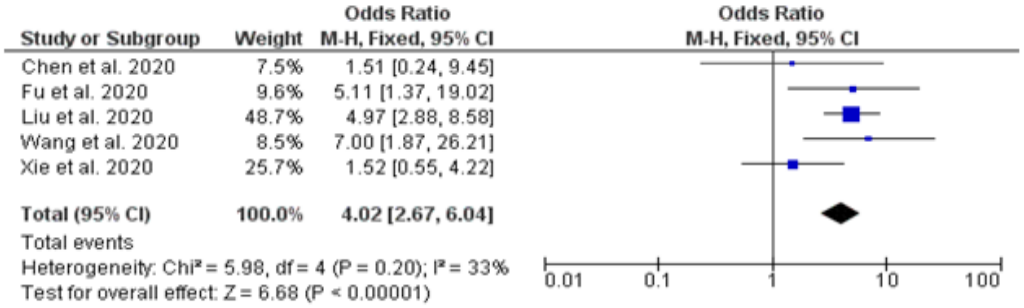

Figure 6: Forest plot for pooled analysis of serum GGT levels using fixed effect model.

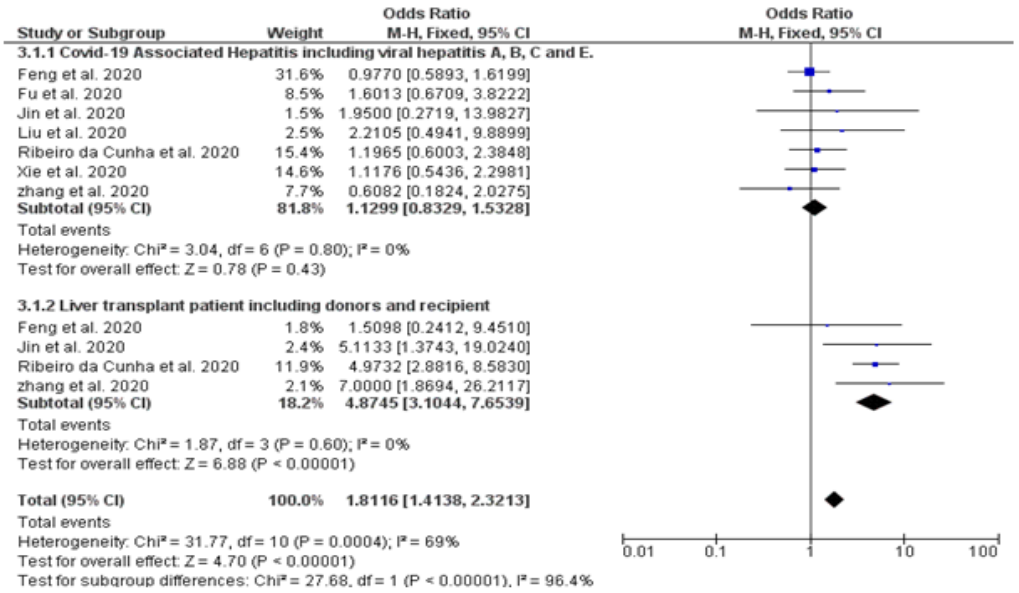

Figure 7: Subgroup analysis of Covid-19 Associated Hepatitis (A, B, C and E) and Liver transplantation.

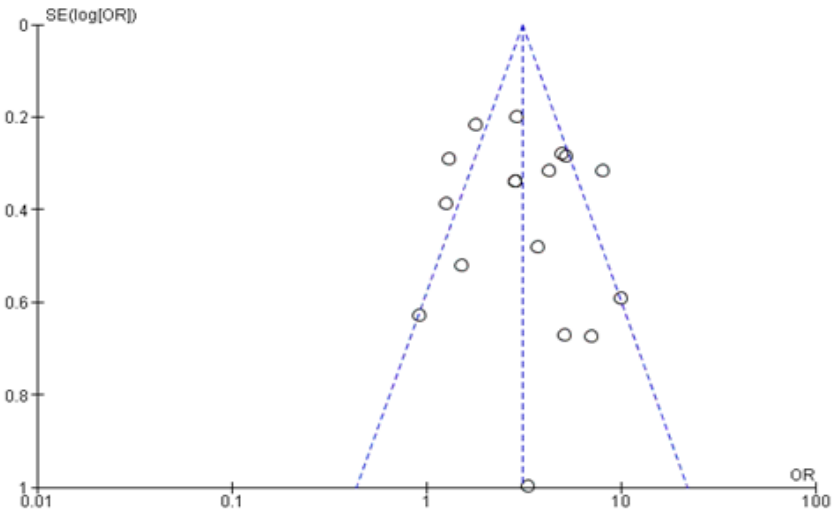

Figure 8: Funnel plot of included studies.

- Studies mentioning most of the laboratory data quantitatively, not qualitatively ;)
- Studies covering the characteristics and demographic information of the patients along with the year, country, number of patients, age, and sex.

GADOUR Criteria for liver injury and disease severity

Gradual onset,

Elevated AST and ALT (AST and/or ALT >2x upper limit of normal),

Dilated sinusoids with lymphocytic infiltration of liver parenchyma,

Non Obstructive jaundice and stable underlying liver disease.

No newRadiological hepatobiliary changes.

Moreover, severity was defined according to the need for Intensive Care Unit (ICU) admission, need for oxygen support, or death, or in parallel to the criteria explained in the studies.

Exclusion criteria for studies

- Review articles, opinion articles, case reports.
- Studies that did not define COVID-19 severity or did not include baseline physiologic data.
- studies reporting COVID-19 patients without laboratory diagnosis
- Retracted studies.
- Studies that reported probable COVID-19 only.
- Duplicate patient data (from the same source and capture period) with preference given to sample size and quality for inclusion.
- Papers that did not include primary information such as reviews, consensus, and guidelines.
- Studies published in a language other than English.

Data extraction and quality assessment

Primarily, titles and abstracts were assessed for inclusion criteria; the full text was examined in cases where the abstract was insufficient to evaluate whether the study met the inclusion criteria. For all eligible trials, data such as first author, year of publication, location, number of patients, age, sex, and serum levels of liver biomarkers (albumin, AST, ALT, and bilirubin) were extracted and recorded. The Microsoft Excel database (Microsoft Corporation, Redmond, Washington) was used to record all available laboratory data. Inconsistencies between the researchers were discussed to reach consensus.

All included studies were independently reviewed by 2 authors to assess for quality and risk of bias using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials:

1. Random sequence generation
2. Double-blinding.
3. Randomization.
4. Blinding of outcome assessment
5. Incomplete outcome data
6. Selective reporting
7. Other biases

The outcomes were evaluated as high risk, unclear, and low risk. Unclear was assigned if we could not find any descriptions of the item, low risk was assigned if the information were sufficient, and high risk was assigned if the information was inadequate. The summary and graph of risk of bias assessment are given in (figure 9,10).

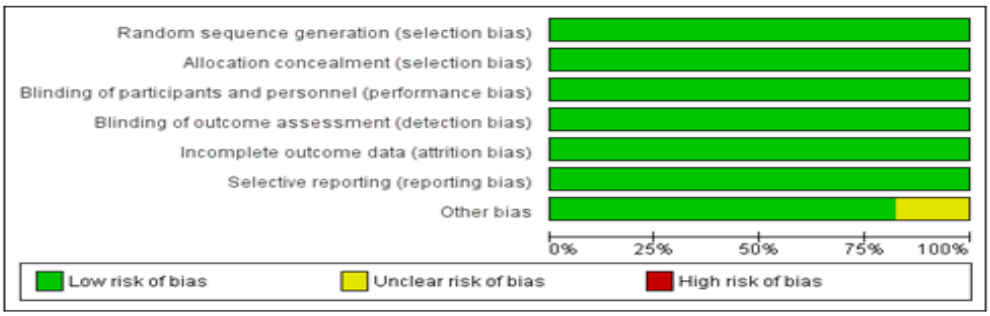

Figure 9: Risk of bias graph for included studies.

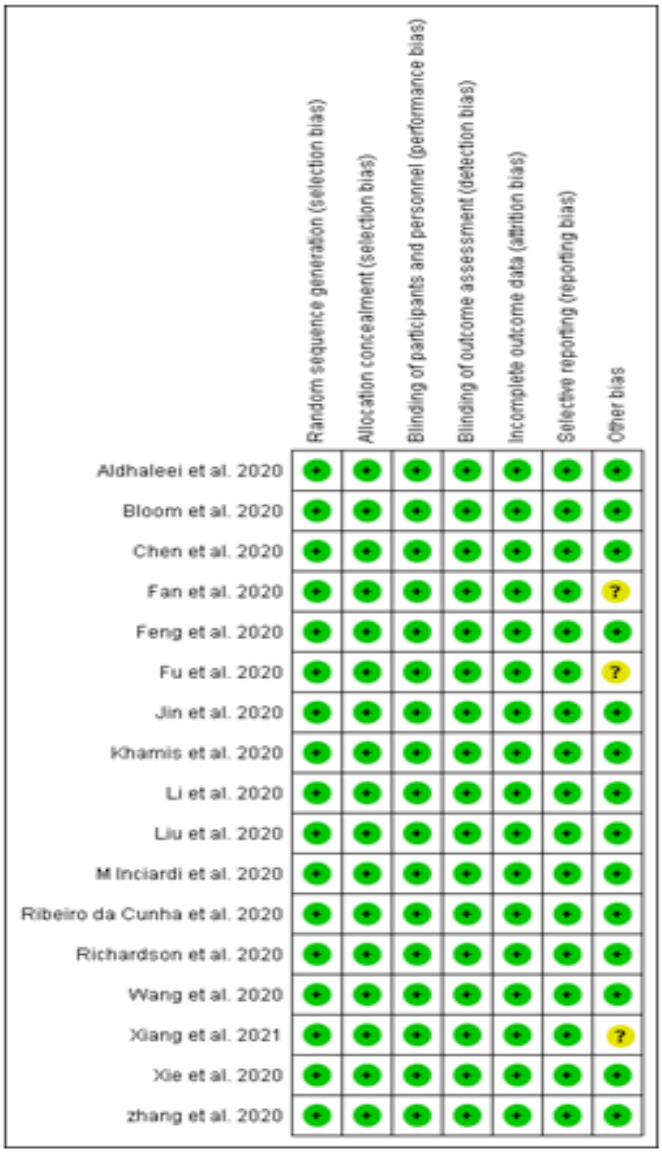

Figure 10: Risk of bias summary for included studies.

Statistical analysis

We used Review Manager Software version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) to perform our meta-analysis to estimate the pooled odds ratio (OR), Mean Difference (MD), and 95% confidence interval (95%CI). We used the random effects model and validated our results using sensitivity analysis and heterogeneity assessment across the included studies. A p-value of less than 0.05 was considered to be statistically significant to pool the results of the pertinent dichotomous and continuous data that were extracted from the included trials. Odds ratios (OR) were used to describe the ratio of the probability of events occurring in patients with severe versus non severeCOVID-19 for both, the corresponding 95%CI and forest plots were used. SD values were used when the data were in the same unit; and conversion should be made when different units were encountered in our meta-analysis. A pooled fixed-effect to measure the proportion ofCOVID-19 positive individuals with deranged Liver Function Tests (LFTs). A pooled random-effect RR of the probability of experiencing one or more colds while taking vitamin C was computed for 'incidence'.

Assessment of heterogeneity

We assessed heterogeneity using the chi2 test and the I2statistic(Higgins, etal.)[14]. A statistically significant result indicates heterogeneity; a non-significant result is not evidence of no heterogeneity. The I2statistic examines the percentage of total variation across studies that are due to heterogeneity rather than chance. A value of I2 about 50% indicates a moderate level of heterogeneity. As for our meta-analysis, when P< 0.05 or I2> 50%, the random-effects model (DerSimonian-Laird method) was used, and the comparison was made between high-quality studies and the whole otherwise, the fixedeffects model was preferred[15].

We performed subgroup analysis among subjects with critical COVID-19 associated hepatitis including viral hepatitis A,B,C and E with subgroup analysis of liver transplant patient including donors and recipient to minimize the impact of heterogeneity in the definition of severe COVID-19 on our results. As case control studies are generally considered to have a higher risk of bias and more susceptible to selection and recall bias we performed subgroup analysis based on study design (cohort study versus case-control study).

Results

Search results and patient's characteristics

Our search from different sources yielded a total of 2383 citations identified by using our predefined search strategy. Exclusion of duplicates brought down the number to 1326 studies. We further screened if they meet the inclusion criteria. This resulted in 1079 Records excluded by title/abstract, wrong format and/or not applicable to PICO. Further studies were screened for the following reasons and excluded: 119 studies presented no outcome data or were not providing any useful information regarding our review criteria, 22 comments or editorials, review article 37 and pediatric study 13. Thirty-eight more papers were excluded after scanning of the full body text of the 55 remaining studies a total of seventeen studies[18-34]met our inclusion criteria. The screening process of these included studies is demonstrated in a hierarchal flow diagram suggested by PRISMA in (figure 1) [14].

Characteristics and quality of the studies

The characteristics of all included studies are presented in (Table 1). Most studies were retrospective in nature except for two were cross sectional and prospective cohort study[19,27].Five studies reported multicenter data, while the remaining reported single-center data. Most of the studies were from China. The definition of severe COVID-19 was heterogeneous across all the included studies. The commonest definition of severe COVID-19 was based on clinical criteria followed by death and ICU admission all studies were published as a full manuscript. Overall, almost all studies were of high quality, while two studies were medium quality[21,22].The study sample size of all selected studies ranged between 10 and 5,700 patients with a mean age of 51.9 years (age range, 24-96 years). The results of the analysis confirmed a male-dominant pattern; 61.1% of all the patients were male while the remaining 39.9% were females. All seventeen studies were conducted in a hospital setting. The laboratory tests were obtained at the time of admission in each study included in the present meta-analysis.

Serum levels of AST, ALT, total bilirubin, and albumin and severity of COVID-19 infection

All our selected studies reported about serum levels of AST, ALT, total bilirubin, and albumin and severity of COVID-19 infection. The overall pooled data of these seventeen studies with 7132 COVID-19 infected patients (severe cases, n= 2955; mild cases, n= 4178), it was demonstrated that elevated serum levelsof AST (odds ratio (OR): 2.656% confidence interval (CI): 2.30, 2.035), with significant heterogeneity: Chi^2 = 34.67, df = 16 (p = 0.004); I^2 = 54%, Z = 13.53 (p = 0.001), (Figure 2), ALT(odds ratio (OR): 3.0839% confidence interval (CI): 2.6347, 3.6097), with significant heterogeneity: Chi^2= 48.99, df = 16 (p = 0.001); I^2= 65%, Z = 14.02 (p = 0.0001), (Figure 3), and total bilirubin (odds ratio (OR): 1.8796% confidence interval (CI): 1.427, 2.4597),heterogeneity: Chi^2= 22.15, df = 9 (p = 0.0008); I^2 = 59%, Z = 4.48 (p = 0.0001), (Figure 4) were associated with a significantincrease in the severity of COVID-19 infections. Additionally,collective data from the random-effects modelpresented that lower serum levels of albumin (odds ratio (OR): 1.4062% confidence interval (CI): 1.0971, 1.8023),with slight heterogeneity: Chi^2= 11.58, df = 10 (p = 0.31); I^2 = 14%, Z = 2.69 (p = 0.007) (Figure 5).

Serum Gamma-Glutamyl Transferase (GGT)

Five studies (973 subjects) reported outcome data on serum GGT. There is a tendency towards increased levels of GGT is higher in severe COVID-19 and critical COVID-19 (OR): 4.02% confidence interval (CI): 2.67, 6.04), with slight heterogeneity: Chi^2 = 5.98, df

Table 1:Study characteristics.

Study ID	Study type/ Center	No. of patients (n)	Median Age	Males, n (%)	Underlying liver disease	(n) of patients with elevated AST at baseline%	Percentage (n) of patients with elevated ALT at baseline unless specified	liver chemistries at baseline	liver chemistries during illness	Percentage of Mortality	Other reports
Cai Q HD, et al.2020 [18],	Retrospective observational/ Single center	21	70 (43-92)	11 (52%)	1 (cirrhosis)			38% (8/21)	3 patients (14·3%) developed acute hepatic injury	11 (52·4%)	Median (IQR) AST and ALT were 273(14-443)108 (11-1414)
Bloom P, et al. 2020 [19],	Crosssectional study	199	58 (49-68)	120 (60·3%)	None	20·5%	41%	41%		44 (22·1%) at day 28	(8/13) 62% had elevated AST at baseline in ICU vs 7/28 (25%) had elevated AST in non-ICU
Chen G, et al.2020 [20],	Retrospective observational/ Single center	99 (all severe cases)	55·5±13·1	67 (68%)	None	35%	28%	43·43%		11%	1 patient had severe liver function damage (ALT 7590 U/L, AST 1445 U/L). Hypoalbuminemia in 98% of severe COVID-19.
Fan Z,et al. 2020[21],	Retrospective observational/ Single center	148	50 (36-64)	75 (50·7%)	9 CLD patients. No difference in enzyme pattern between CLD and Non-CLDpatients	21·6% (32/148)	18·2% (27/148)	37·2% (55/148) of which 28 patients had used some medication.	48·4% (22 of 45) developed liver injury within 2 weeks.	0·006%	Baseline elevated liver chemistries was associated with prolonged hospital stay.6·1%, 4·1% and 17·6% had elevated bilirubin, ALP and GGT at baseline.
Feng Y,et al. 2020[22],	Retrospective observational/ Single center	476	47 (35-58)	637 (48·1%)	Hepatitis B in 23/1099 (2·1%)	22·2% (168/757) Non-Severe 112/615 (18·2) vs Severe-56/142 (39·4)	21·3% (158/741)	22·2% (out of 168/757)AST elevation in 112/615 (18·2%) in survivors vs 56/142 (39·4%) in non-survivors.		1·4%	10·5% (76 out of 722) had hyperbilirubinemia
Lin F,et al. 2020[23]	Retrospective/ Multi center	41	49 (41-58)	30 (73%)	1 (2%) liver cirrhosis	37%		37%		6 (15%)	Bilirubin and PT higher in ICU patients.
Jin Xi,et al. 2020[24],	Retrospective observational/ Single center	81	49·5 ±11	42 (52%) men	7 (9%) liver cirrhosis	53%		53%.		3 mortality at publication.	4/15 (27%) had elevated AST in subclinical cases compared to 39/66 (59·09%) in full-blown infected patients.

Khamis F, et al. 2020[25],	Retrospective/ Multi center	63	50 (36·5-57)	37 (40·5%)	None	9·89%	7·9%	~10%		None	47·25% had hypoalbuminemia
Li L,et al. 2020[26],	Retrospective/ Multi center	548 (269 were severe and 279 were non severe)	60 (48-69)	279 (50·9%)	5 patients Hepatitis B (0·9%)	179/540 (33·1%)	125/541 (23·1%)	33·1% (179/540)	19·3% (106/548)	16·5% (90/545)	320/541 (59·1%) had hypoalbuminemia at baseline [126/275 (45·8%) in non-severe vs 195/266(72·9%) in severe group].
Liu J,et al. 2020[27],	Retrospective observational/ Single center	61	35±8	10 (33·34%)	None			23·33% (7/30) abnormal liver function tests		None till publication	Severe patients had significant hypoalbuminemia and deranged liver function tests.
M Inciardi, et al. 2020[28],	Retrospective cohort	191 (Non-survivor-54 and s urvivor -137)	56 (46-67)	119 (62%)	None		31% (59/189)	31% (59/189)26/54 (48%) had elevated ALT in non-survivor vs 33/135 (24%) had elevated ALT in survivor		54/ 191 (28·27%)	On univariate analysis, high ALT and prolonged PT were predictors of in-hospital death. 6% had prolonged PT>16 s at baseline.
M Ribeiro C,et al.2020 [29],	Retrospective/ Multi center	10	42 (IQR-34-50)	4 males (40%)	1 CLD (Hepatitis B related)			Significant no. of patients developed hypoalbuminemia from day 9-12.	40% had a rise in serum bilirubin during the 2nd week of illness.		Duration of hospitalization was similar to other CLD patients. Leukopenia and lymphopenia were not noted in CLD patients.
Richardson S,et al. 2020 [30],	Retrospective/ Multi center	5700	63 (52-75)	3437 (60·3%)	Cirrhosis in 19 (0·4%), Chronic Hepatitis B in 8 (0·1%) and Chronic Hepatitis C in 3 (0·1%)	58·4% (3263/ 5586)	39% (2176/ 5587)	58·4% (of 5586)	2·1% (56/2626) developed acute hepatic injury during illness	21% (553/ 2634)	Acute hepatic injury was defined as >15 times ULN in enzymes.
Wang SL,et al. 2020 [31],	Retrospective observational/ Single center	138	66.0 (57.0-73.0) (Remdesivir) 64.0 (53.0-70.0) (Placebo	(59·32%)	None	75/233 (32·18%)	15·87% (37/233)	32·18%		14·09% (32/ 227)	Hyperbilirubinemia in 10% (15), AST elevation in 5% (7)-2 required drug discontinuation
Tian XZ,et al.2020 [32],	Retrospective observational/ Single center	10	56·5 years(±11·16)	6 (60%)	1 liver cirrhosis						PT prolonged in severe cases. Hypoalbuminemia significant in severe cases
Xie HX,et al. 2020 [33],	Retrospective observational/ Single center	32	41 (34-54)	16(50%)	2 (6·3%) liver disease						10·2% and 17% had elevated bilirubin and ALP at baseline

= 4 (p = 0.20); I^2 = 33%, Z = 6.68 (p = 0.0001) (Figure 6).

Subgroup analysis

We also performed a subgroup analysis of Covid-19 associated hepatitis including viral hepatitis A,B,C and E with (OR): 1.129% confidence interval (CI): 0.832, 1.532), with slight heterogeneity: Chi^2 = 3.04, df = 6 (p = 0.80); I^2 = 0%, Z = 0.78 (p = 0.043). (Figure 7) and subgroup analysis of liver transplant patient including donors and recipient (OR): 4.874% confidence interval (CI): 3.104, 7.653), with slight heterogeneity: Chi^2 = 1.87, df = 3 (p = 0.60); our subgroup analysis based on study data collection, by comparing we found that the effect size for the Covid-19 associated hepatitis including viral hepatitis A,B,C was bigger as compared to liver transplant patient including donors and recipient I^2 = 0%, Z = 6.88 (p = 0.0001),(Figure 7).

Publication bias

There was no evidence of publication bias based on visual inspection of the funnel plot (Figure 8).

Discussion

This present systematic review of ours studied the deranged liver function was associated with mortality and severity of COVID-19.The pathogenic mechanism of liver injury in COVID-19 infection is assumed to be multi factorial. Nonetheless, none of the available hypotheses provide a complete explanation, and further investigation is required not only to understand themechanism but also to formulate appropriate management plans. Severe systemic inflammatory response during severe COVID-19 can lead to immune-mediated damage or ischemic hepatitis from the severe systemic inflammatory response. Present treatment options of anti-viral drugs such as Lopinavir/ Ritonavir, Hydroxychloroquine and *Remdesivir* are potentially hepatotoxic and may cause Drug-Induced Liver Injury (DILI) [34]. Chai, et al. postulated in their study about direct viral invasion on the proposed receptor for the virus, Angiotensin Converting Enzyme 2 Receptor (ACE2R), has been found to only sparse in hepatocytes by ACE2 expression in 2.6% of hepatocytes, whereas up to 59.7% of cholangiocytes expressed ACE2R [36].Conversely, in their study Zhou, et al. did not agree with this postulated mechanism by enlightening that ACE2Rs on cholangiocytes are restricted to the apical surface, from where viral invasion is less likely. In addition, the hepatic pattern of serum level elevation fails to explain this possible ductal pathology. The furin protein are also express in hepatocytes, which might have a role in hepatic cell injury upon entry of the virus into the cells [37].

An inflammatory response to the virus may lead to constant leukocytic activation and the release of many mediators responsible for cellular damage. The association of a cytokine storm in liver injury has been supported by patients' elevated levels of interleukins 2,6, and 10, interferon-gamma, serum ferritin, and C-reactive protein [38].The patterns of liver injury in COVID-19 patients include both reversible dysfunction and irreversible injury as a component of multi-organ failure in terminally ill patients [39,40]. Nonetheless, hepatic dysfunction in COVID-19 cases is usually mild, and dysfunction in LFTs tend to improve within a few days after discharge [41]. Major increase in ALT and AST predicts hepato cellular injury [42]. Abnormal serum level of AST have been more severe compared with those of ALT [43,44].

The present met analysis showed that the laboratory findings reported a lower level of albumin and higher levels of ALT and AST in COVID-19 patients; moreover, we also noticed statistically insignificant elevated levels of total bilirubin. Our results are in agree with the previous researches on COVID-19, which also showed hypo-albuminemia associated by elevated serum levels of aminotransferases and bilirubin as main indicators of liver damage [45,46]. Reports in current literature proposed that severely ill COVID-19 positive patients have an increased proportion of abnormal liver biochemistries as compared to individuals with less severe disease [47].

In a previous systematic review by Arif, et al. reported in their limitation of study that, the majority of the included studies did not have any specific predefined clinical criteria for diagnosing liver injury in COVID-19. Furthermore, the included studies did not distinguish between a history of Liver Disease (eg, CLD) and liver injury secondary to COVID-19 [48]. This current meta-analysis is the first study to establish GADOUR criteria on the included studies falling in these criteria to evaluate the sensitivity and specificity in predicting the prognosis of severely ill COVID-19 patients with liver injury involvement with the disease progression. Our study analyzed deeply about the liver involvement in COVID-19, including increased liver chemistries during initial presentation, during illness and the impact of this on the outcome. We have also reported the elevation in each variable of liver function tests, that is, AST, ALT, bilirubin, albumin, ALP, GGT. We also reported the subgroup analysis of liver transplant patient including donors and recipient and Covid-19 associated hepatitis including viral hepatitis A, B, C and E from the available data. Higher level of liver chemistries at initial presentation or during illness is an important marker of disease severity. Serum albumin, a negative acute phase reactant, also indicates severe disease. Liver injury is more common in COVID-19 than non-COVID-19 infections [49]. The findings of this meta-analysis were in agreement with current literature that adult patients with severe COVID-19 have an increased risk of liver damage. Most hepatic injuries were not severe. So far, there is only one reported case of death from liver failure in COVID-19 patients without having any pre-existing liver disease. In a recently published international registry of COVID-19 among patients with chronic liver disease, only 12% of death was related to liver disease [48,50].

The most important patho-physiology includes hepatic congestion from right heart failure together with decreased blood flow to the liver or reperfusion injury following ischemia [51]. Reports suggests that sepsis in COVID-19 contributes to hypoxic liver damage, creating a surge in liver biomarkers, which

reasonably explains the elevated levels of serum ALT, AST, and total bilirubin in critically ill COVID-19 patients comparative to the non-severe group [52,53].

Patients aged above sixty five years have increase comorbidities, more severe symptoms, and are more prone to multiple organ involvement and death compared to the younger patients [54]. Factors contributing to poor health outcomes include physiological changes in aging and various age-related complications. Furthermore, older people's suspicion and detection thresholds for SARS-2 such as temperature, decreased function of cough, and shortness of breath are lower [3]. More concentration and attention should be given to COVID-19 patients with pre-existing liver disease especially elderly patients by frequently observing liver changes, and carefully ruling out the cause of hepatic abnormalities. Therefore COVID-19 involves a collection of problems that could result in hepatic injury could by directly infecting the liver or causing injury secondary to the association of other systems such as the pulmonary, cardiovascular, or neurological system. Nevertheless, there is still an insufficiency of literature reporting liver failure in COVID-19 patients with chronic liver diseases. Potential studies are necessary to investigate the mechanisms of hepatic dysfunction in patients with COVID-19.

Conclusion

This current meta-analysis, though, has a few limitations, to begin with, the majority of the studies included in the meta-analysis had a retrospective study design; therefore, there is a chance of bias in data collection. Furthermore, since all the studies reported only hospitalized patients, the incidence of liver injury among COVID-19 patients in our study may have been overestimated. Therefore, our results cannot be extrapolated to the entire population of COVID-19 patients. Third, numerous studies reported patients with pre-existing chronic liver disease, which renders them predisposed to developing an acute liver injury. Nevertheless, the present analysis did not monitor the possible effects of potential confounders, such as age, gender, and co morbidities; therefore, the conclusion must be interpreted with caution. Moreover, the greater part of the studies included is from China, and, therefore, may not correspond to variations between different populations. Regardless of, the reported limitations, this current systematic review and meta-analysis present helpful information on the prevalence and liver complications of COVID-19 infection.

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