2020

Elevated Liver Biochemistries in Hospitalized Chinese Patients with Severe COVID-19: Systematic Review and Meta-analysis.

A. J. Kovalic

G. Huang

P. J. Thuluvath

S. K. Satapathy
Zucker School of Medicine at Hofstra/Northwell

DR. ALEXANDER J. KOVALIC (Orcid ID : 0000-0002-5211-5200)
DR. SANJAYA SATAPATHY (Orcid ID : 0000-0003-0153-2829)

Article type : Original

Elevated Liver Biochemistries in Hospitalized Chinese Patients with Severe COVID-19: Systematic Review and Meta-analysis

Alexander J. Kovalic,[1] Glen Huang,[2] Paul J. Thuluvath,[3,4] and Sanjaya K. Satapathy[5,6]

From the [1]Department of Internal Medicine, Novant Forsyth Medical Center, Winston-Salem, NC; [2]Department of Internal Medicine, Division of Infectious Diseases, University of California, Los Angeles, CA; [3]Institute of Digestive Health & Liver Diseases, Mercy Medical Center, Baltimore, MD; [4]Department of Medicine, University of Maryland School of Medicine, Baltimore, MD; [5]Department of Internal Medicine, Division of Transplantation, Sandra Atlas Bass Center for Liver Diseases & Transplantation, Barbara and Zucker School of Medicine for Hofstra/Northwell Health, Manhasset, NY; [6]Department of Internal Medicine, Division of Hepatology, Sandra Atlas Bass Center for Liver Diseases & Transplantation, Barbara and Zucker School of Medicine for Hofstra/Northwell Health, Manhasset, NY.

Potential conflict of interest: Nothing to report.

Total word count (excluding references): 2786

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/HEP.31472

ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO:

Sanjaya K. Satapathy, M.B.B.S., M.D., D.M., M.S., FACG, FASGE, AGAF, FAASLD
Department of Internal Medicine, Division of Hepatology, Sandra Atlas Bass Center for Liver Diseases & Transplantation, Barbara and Zucker School of Medicine for Hofstra/Northwell Health
400 Community Drive, Manhasset, NY 11030
E-mail: ssatapat@northwell.edu
Tel.: +1-516-562-2096

Abbreviations: ACE2, angiotensin-converting enzyme 2; ACEI, angiotensin-converting enzyme inhibitor; ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; ARB, angiotensin receptor blocker; AST, aspartate aminotransferase; CAD, coronary artery disease; cells/L, cells per liter; CI, confidence interval; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; df, degrees of freedom; g/L, grams per liter; IV, inverse variance; LDH, lactate dehydrogenase; M-H, Mantel-Haenszel; MD, mean difference; mg/dL, milligrams per deciliter; OD, odds ratio; PT, prothrombin time; s, seconds; SARS, severe acute respiratory syndrome; U/L, units per liter; WBC, white blood count.

Abstract

Background & Aims: Several recent studies have reported an abnormal liver chemistry profile among patients with coronavirus disease 2019 (COVID-19), although its clinical significance remains unknown.

Approach & Results: This novel systematic review and meta-analysis identified six studies of 586 patients delineating liver chemistries among patients with severe/critical illness versus mild cases of COVID-19 infection. Patients with severe/critical illness with COVID-19 infection have increased prevalence of coronary artery disease (CAD), cerebrovascular disease, and chronic obstructive pulmonary disease (COPD) as compared to mild cases. A significant association between severe/critical COVID-19 infections with elevations in aspartate aminotransferase (AST) (pooled mean difference [MD], 11.70 U/L; 95% confidence interval [CI], 2.97, 20.43; *P* = 0.009), elevated total bilirubin (pooled MD, 0.14 mg/dL; 95% CI, 0.06, 0.22; *P* = 0.0005), and decreased albumin (pooled MD, –0.68 g/L; 95% CI, –0.81, –0.55; *P* < 0.00001) was noted. There was also a trend toward elevated alanine aminotransferase (ALT) levels among these severe cases (pooled MD, 8.84 U/L; 95% CI, –2.28, 19.97; *P* = 0.12); however, this did not reach statistical significance. More severe/critically ill cases were associated with leukocytosis, neutrophilia, lymphopenia, elevated creatinine kinase, elevated lactate dehydrogenase (LDH), and elevated prothrombin time (PT).

Conclusions: Comorbidities, including CAD, cerebrovascular disease, and COPD, are more prevalent in hospitalized Chinese patients with severe/critical illness from COVID-19, and these patients are more likely to manifest with abnormal liver chemistries. Further prospective studies are crucial to understand the pathophysiologic mechanisms underlying the hepatic manifestations of the novel COVID-19 infection and its clinical significance.

After recently being declared a global pandemic, the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), or coronavirus disease 2019 (COVID-19), has spread to more than 200 countries with close to 2 million confirmed cases in the United States alone.[1] Although this infection typically presents with an incubation period followed by pulmonary manifestations, the presence of concomitant liver injury among patients with COVID-19 has recently been described.[2] However, the significance of liver injury remains unknown.

It is still relatively early in the evolution of the COVID-19 pandemic. The exact pathophysiologic mechanism remains uncertain, especially regarding the hepatobiliary involvement of this disease. The primary aim of this novel systematic review and meta-analysis is to further characterize liver injury and other unique clinical characteristics across COVID-19 severity.

Materials and Methods

Literature Search

We searched three major databases—MEDLINE/PubMed, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL)—for clinical studies dated from inception to March 22, 2020. In an effort to broadly identify studies detailing liver chemistry testing among patients with COVID-19, the following search criteria were used: (coronavirus OR cov2 OR “cov 2” OR ncov OR (sars AND cov2)

OR “sars cov 2” OR covid) AND (liver OR ast OR “aspartate aminotransferase” OR alt OR “alanine aminotransferase”). This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[3] and Meta-Analyses of Observational Studies in Epidemiology (MOOSE).[4] Identification of studies reporting liver chemistries were prioritized in order to ascertain an association among patients who had severe or critical illness versus mild cases of COVID-19 infection. Severe cases were defined as significant respiratory distress from the COVID-19 infection based on work of breathing or degree of hypoxia (diagnosed by either pulse oximetry or arterial blood gas). Critical cases were defined as patients requiring admission to the intensive care unit (ICU) for either mechanical ventilation, shock, or multisystem organ failure. Mild cases 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.

Inclusion Criteria

Articles and clinical studies that met the following inclusion criteria were eligible for this meta-analysis: (1) studies performed in adult, human subjects; (2) studies written in English; (3) studies measuring liver chemistries among COVID-19 patients (aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin); (4) studies comparing patients with severe or critical illness versus mild cases.

Exclusion Criteria

Studies with the following characteristics were excluded from this meta-analysis: (1) studies in nonhuman subjects; (2) studies written in a language other than English; (3) studies that were not a clinical trial, such as a review paper or letter; (4) studies that were out of scope of the study question detailed above; (5) studies that lacked proper controls; (6) studies that did not provide raw data in order to perform quantitative meta-analysis; (7) studies conducted in pediatric subjects; (8) studies that did not have an available manuscript; (9) studies that were duplicates; (10) studies there were ongoing or not completed.

Outcomes and Endpoints

The primary outcomes for this meta-analysis were as follows: (1) liver chemistries (AST, ALT, total bilirubin, albumin); (2) demographic data (age, gender, comorbidities); (3) laboratory parameters from complete blood count (CBC), comprehensive metabolic panel (CMP), or coagulation testing (white blood count [WBC], neutrophils, lymphocytes, platelets, creatinine, creatinine kinase, lactate dehydrogenase [LDH], prothrombin time [PT], activated partial thromboplastin time [aPTT]); (4) mortality.

Data Extraction

The authors extracted data from the literature search, and any disagreements were resolved by consensus. Ambiguity in the reported data was attempted to be resolved by e-mailing the corresponding author of the study where appropriate. Author names, dates, study type, setting of study, number and characteristics of patients, and treatment outcomes were gathered for all included studies.

Risk of Bias

Nonrandomized studies were assessed by the Newcastle-Ottawa Scale (NOS).[5] The authors determined the quality of selection, comparability, and exposure/outcome in the NOS. Each form of bias was awarded either a low, high, or unclear risk of bias. A funnel plot was calculated to determine the presence of publication bias.

Statistical Analysis

This meta-analysis was performed using Review Manager (RevMan, version 5.3, The Cochrane Collaboration, Denmark). Odds ratios (ORs) were used as a summary measure of efficacy for dichotomous data, and mean differences (MDs) were used between groups for continuous variables; 95% confidence intervals (CIs) were reported for both measures. If medians and interquartile ranges (IQRs) were provided in the included studies instead of MDs and standard deviations, the MD and standard deviations were imputed as described in other studies[6-7, 8] as well as the *Cochrane*

Handbook for Systematic Reviews of Interventions.[9] Data were considered statistically insignificant if $P > 0.05$, OR includes 1.00, or MD includes 0. Statistical heterogeneity was assessed using the I^2 statistic. I^2 values of 0% to 25%, 25% to 50%, 50% to 75%, and more than 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-effect model was used.[10, 11] Publication bias was determined by Egger's regression asymmetry test.[12] Funnel plots were qualitatively assessed by visual inspection based on logarithmic ORs plotted versus their standard errors.[13] Asymmetric funnel plots represented studies with high risk of publication bias.

Results

Study Selection

The data search, literature review, and study selection are outlined in Fig. 1. Overall, 455 clinical studies were identified based on the predefined inclusion and exclusion criteria. Studies that did not have an appropriate clinical comparison between groups or present enough data to perform a quantitative meta-analysis were excluded. In the end, six studies with 586 patients were finalized that satisfied all of these criteria.[14-19] Also of note, all of these studies present data from COVID-19 positive patients from China. Five are from Wuhan and the province of Hubei. The final study details a patient cohort from the neighboring province of Chongqing.[16] All data were included from hospitalized patients with laboratory data collected and analyzed upon presentation. Quality assessment of the included studies is provided in Supporting Table S1.

Higher burden of increased age and comorbidities among patients with severe or critical COVID-19 infection

The characteristics of patients with severe/critical illness versus mild cases of COVID-19 are shown in Figs. 2 and Supporting Fig. S1. Comorbidities were not uniformly reported in all six studies. Overall,

severe/critical cases of COVID-19 infection were significantly associated with patients who had coronary artery disease (CAD) (pooled OR, 2.68; 95% CI, 1.43, 5.01; *P* = 0.002), cerebrovascular disease (pooled OR, 20.20; 95% CI, 2.34, 174.44; *P* = 0.006), and chronic obstructive pulmonary disease (COPD) (pooled OR, 12.22; 95% CI, 2.57, 58.09; *P* = 0.002) at baseline as compared to patients with mild cases. Increased age (pooled MD, 11.15; 95% CI, –1.75, 24.0; *P* < 0.09) and diabetes mellitus (pooled OR, 2.34; 95% CI, 0.66, 8.26; *P* = 0.19) demonstrated a trend toward association with severe/critical COVID-19 cases; however, these differences not reach statistical significance. These studies failed to show a significant link of severe cases with gender, hypertension, active smoking or tobacco use, chronic liver disease, chronic kidney disease, malignancy, or current treatment with angiotensin-converting enzyme inhibitor (ACEI)/angiotensin 2 receptor blocker (ARB). However, these studies did not delineate the definition of "chronic liver disease" into the underlying etiology, such as cirrhosis or viral hepatitis.

Elevated liver chemistries more pronounced among COVID-19 patients with severe or critical illness

The comparison of liver chemistries among patients with severe/critical illness versus mild COVID-19 cases is provided in Fig. 3. Overall, there was a significant correlation of severe or critical COVID-19 infections with elevations in AST (pooled MD, 11.70; 95% CI, 2.97, 20.43; *P* = 0.009), elevated total bilirubin (pooled MD, 0.14; 95% CI, 0.06, 0.22; *P* = 0.0005), and decreased albumin (pooled MD, –0.68; 95% CI, –0.81, –0.55; *P* < 0.00001) upon presentation. There was also a trend toward association of severe/critical cases with elevated ALT (pooled MD, 8.84; 95% CI, –2.28, 19.97; *P* = 0.12). However, this did not reach statistical significance.

Other laboratory aberrancies associated with severe or critical COVID-19 infection

A more comprehensive battery of laboratory testing provided among these studies is further detailed in Supporting Fig. 2. Overall, more severe or critical illness from COVID-19 was statistically associated with leukocytosis (pooled MD of WBC, 2.14; 95% CI, 0.20, 4.08; *P* = 0.03), neutrophilia (pooled MD, 1.68; 95% CI, 0.38, 2.97; *P* = 0.01), lymphopenia (pooled MD, –0.40; 95% CI, –0.58, –0.22; *P* < 0.001), elevated creatinine kinase (pooled MD, 39.95; 95% CI, 20.94, 58.95; *P* < 0.0001),

elevated LDH (pooled MD, 96.39; 95% CI, 65.92, 126.87; $P < 0.0001$), and elevated PT (pooled MD, 0.48; 95% CI, 0.25, 0.72; $P < 0.0001$). Platelet count appeared to be decreased among more severe infections; however, this did not achieve statistical significance (pooled MD, –18.36; 95% CI, –50.22, 13.51; $P = 0.26$). No significant relationship was established between serum creatinine or aPTT among patients with severe/critical illness versus mild cases.

Mortality data among severe or critical illness in patients with COVID-19 infection

Mortality data are presented in Fig. 4. Overall, only three studies reported mortality data. Although there was no outpatient analysis for these patients, the mortality data included follow-up throughout the duration of their inpatient stay. Unsurprisingly, there was a significantly increased rate of mortality (pooled OR, 21.70; 95% CI, 7.01, 67.24; $P < 0.00001$) in studies reporting survival among patients with severe versus mild COVID-19 infections.

Publication Bias

Funnel plots were generated for the outcomes of this meta-analysis and are demonstrated in Supporting Figs. S3-S7. Where appropriate, 95% CIs were included for fixed-effect model analysis. Overall, there was no asymmetry noted in the funnel plots to suggest a large degree of publication bias.

Discussion

As the current pandemic continues to sweep the globe, there will inevitably be an increasing amount of clinical data from Europe and North American regarding liver injury among patients with COVID-19, however at the time of this meta-analysis, the data have come exclusively from China. There remains a paucity of data on liver histopathology and limited autopsy case reports reveal microvesicular steatosis in addition to lobular and portal inflammation, although not as exaggerated as inflammation seen in the lungs.[20] Our study shows that abnormalities of liver chemistries are more common in severe COVID-19 disease and more likely to be seen in those with other serious

comorbidities. Based upon circumstantial evidence, the CDC and the AASLD Expert Panel has suggested that there will be a heightened health care burden among patients with chronic liver diseases, especially those requiring liver transplantation.[21,22] Our study appears to support the above statement since patients with NASH cirrhosis or those waiting liver transplant are likely to have significant comborbidities.

Several studies from Europe and North America have emerged recently.[23 24] Among 5700 hospitalized patients in New York, only 19 total patients (0.4%) had cirrhosis with only 11 patients (0.2%) described having either HBV or HCV.[23] Another Italian study reports chronic liver disease only among 28 out of 1591 patients admitted to the ICU.[24] Mildly increased liver chemistries is a common finding, particularly among severe COVID-19 infections, however has been previously demonstrated to lack significant, standalone impact on mortality.[25,26] One the other hand, a large propensity-matched study has reported that patients with chronic liver disease and COVID-19 have a three-fold higher mortality risk as compared to patients without liver disease.[27] Conversely, two other meta-analyses have recently failed to demonstrate a link between chronic liver disease and either mortality or severity of COVID-19 infection.[28, 29]

Mechanism of liver injury and its relationship with severity of COVID-19 infection is largely speculative. Similar to previous SARS-CoV infections, the binding and uptake by the angiotensin-converting enzyme 2 (ACE2) cholangiocyte receptor has been demonstrated to mediate liver damage among patients with COVID-19.[30] Not only does the degree of AST or ALT elevation appear to correlate with the severity of COVID-19 infection, but this mechanism for liver injury appears to be mediated by an up-regulation of ACE2 also among hepatocytes in a mouse model.[31] Other etiologies for liver injury include underlying liver disease, medications including experimental drugs, and in severe cases, the cytokine storm (through tumor necrosis factor α (TNF-α), interleukin [IL]-6, or IL-18) as well as the ischemic hypoxia-reperfusion that accompanies more severe COVID-19 infections.[32]

Although this manuscript reports novel findings in this area, it is not without limitations. First, our analysis is limited to hospitalized patients from China and hence cannot be generalizable to other geographical areas. Studies detailing liver chemistries and other clinical characteristics remain extremely limited for outpatient population. In our study, significant heterogeneity was found with respect to outcomes of age (I^2 = 95%), history of hypertension (I^2 = 82%), history of diabetes mellitus (I^2 = 68%), AST (I^2 = 78%), ALT (I^2 = 81%), WBC (I^2 = 86%), neutrophil count (I^2 = 70%), lymphocyte count (I^2 = 77%), platelet count (I^2 = 69%), and serum creatinine (I^2 = 63%). This phenomenon is most likely related to small sample size, limited study data, and skewed representation of patient populations. Another potential limitation is the definition used to stratify severe/critical COVID-19 disease. Some studies included only patients requiring ICU admission, whereas others included severe respiratory distress not requiring intubation in their severe patient cohort. Laboratory parameters were all collected from patients upon presentation for their inpatient admission to the hospital. A more comprehensive trend of liver chemistries may be a future focus in order to capture the peak of these laboratory parameters and compare them based on clinical outcomes. Furthermore, characterization of baseline "chronic liver disease" remains ill-defined among these studies and warrants further investigation. Many of these laboratory findings, such as aberrancies in liver chemistries, low platelet count, decreased albumin, or prolonged PT, could be explained by an acute COVID-19 infection but also may be influenced by underlying cirrhosis or viral hepatitis that is not clearly reported among these included studies.

The characterization of liver injury among COVID-19 infection remains paramount with respect to potential therapeutic options. Hydroxychloroquine (HCG) has been used in many countries as a potential therapeutic option against COVID-19,[33] and although hepatotoxicity is relatively uncommon, this drug is metabolized by the liver and has been reported to cause acute liver injury in select cases.[34] Furthermore, the use of antiviral therapies has undergone increased investigation. Remdesivir, a novel antiviral agent that acts as an RNA-chain terminator, has been demonstrated to be effective in vitro, and in early clinical trials in the US.[35] Recent published studies on remdesvir have shown infrequent liver test abnormalities among other side effects.[36-38] However, elevation of

AST or ALT greater than five times the upper limit of normal remains an exclusion criterion for initiation of remdesivir among COVID-19 patients, and this may exclude many patients with preexisting liver disease from receiving remdesvir. The true incidence of remdesvir hepatotoxicity is an area for further research. Preliminary studies of IL-6 inhibitor, tocilizumab in patients with COVID-19 also suggest that this drug also may be associated with uncommon hepatotoxicity.[39] Among preliminary data from a study reporting the first hospitalized cases of COVID-19 in the United States, all patients treated with remdesivir developed transaminitis during their clinical course.[40]

As demonstrated in this systematic review and meta-analysis, the patients suffering from more severe or critical COVID-19 infections have significantly increased liver chemistries. This clinical finding poses quite a dilemma for future patients infected with COVID-19 because many of the current investigational or ongoing randomized controlled trials are excluding patients with values of AST or ALT greater than five times the upper limit of normal.[41-43] Therefore, further characterization and recognition of liver injury is vital among patients harboring severe/critical COVID-19 infections, particularly if one of the few therapeutic options is predicated on the status of underlying liver chemistries.

As the COVID-19 pandemic continues to afflict more individuals across the globe, both the incidence and clinical significance of liver injury among this patient population will be important to analyze. In this novel systematic review and meta-analysis, the characterization of severe or critically ill patients as compared to individuals suffering from mild cases of COVID-19 is described in detail. There appears to be a significant correlation of aberrant liver chemistries, in addition to CAD, cerebrovascular disease, COPD, leukocytosis, neutrophilia, lymphopenia, elevated creatinine kinase, elevated LDH, and increased PT, among patients with severe or critical illness from COVID-19 as compared to mild cases. Current knowledge of contributing factors, such as underlying liver disease or use of concomitant medications, remains unknown. It is imperative for future prospective studies to continue to examine the role of multiple confounders in the pathogenesis of liver injury in COVID-19 infection.

Acknowledgment: We thank Alexander Kovalic for substantial contributions to conception and design of the study, acquisition of data/analysis and interpretation of data, and drafting, critical revisions, and final approval of the article; Glen Huang for substantial contributions to acquisition of data/analysis and interpretation of data and drafting, critical revisions, and final approval of the article; Muhammad Ali Khan and Fuad Zain for contributions with the finalization of figures and tables; and Paul Thuluvath and Sanjaya Satapathy for substantial contributions to conception and design of the study, interpretation of data, and critical revisions and final approval of the article.

REFERENCES

1. Sohrabi C, Alsafi Z, O'Neill N, et al. World Health Organization declares global emergency: A review of the 2019 novel coronavirus (COVID-19). Int J Surg 2020;76:71-76.
2. Zhang C, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. Lancet Gastroenterol Hepatol 2020.
3. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009;151:264-9, w64.
4. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. Jama 2000;283:2008-12.
5. Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale [NOS] for assessing the quality of nonrandomised studies in meta-analyses. 2013. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
6. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Medical Research Methodology 2005;5.
7. Luo D, Wan X, Liu J, et al. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. Stat Methods Med Res 2018;27:1785-1805.
8. Wan X, Wang W, Liu J, et al. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC medical research methodology 2014;14:135.
9. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions: The Cochrane Collaboration, 2011.
10. Borenstein M, Higgins JPT. Meta-Analysis and Subgroups. Prevention Science 2013;14:134-143.
11. Richardson M, Garner P, Donegan S. Interpretation of subgroup analyses in systematic reviews: A tutorial. Clinical Epidemiology and Global Health 2018.

12. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. Bmj 1997;315:629-34.
13. Easterbrook PJ, Berlin JA, Gopalan R, et al. Publication bias in clinical research. Lancet 1991;337:867-72.
14. Cao W. Clinical features and laboratory inspection of novel coronavirus pneumonia (COVID-19) in Xiangyang, Hubei. medRxiv 2020.
15. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506.
16. Liu C, Jiang ZC, Shao CX, et al. [Preliminary study of the relationship between novel coronavirus pneumonia and liver function damage: a multicenter study]. Zhonghua Gan Zang Bing Za Zhi 2020;28:148-152.
17. Peng YD, Meng K, Guan HQ, et al. [Clinical characteristics and outcomes of 112 cardiovascular disease patients infected by 2019-nCoV]. Zhonghua Xin Xue Guan Bing Za Zhi 2020;48:E004.
18. Wan S, Xiang Y, Fang W, et al. Clinical Features and Treatment of COVID-19 Patients in Northeast Chongqing. J Med Virol 2020.
19. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. Jama 2020.
20. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med 2020.
21. Fix OK, Hameed B, Fontana RJ, et al. Clinical Best Practice Advice for Hepatology and Liver Transplant Providers During the COVID-19 Pandemic: AASLD Expert Panel Consensus Statement. Hepatology 2020.
22. What to Know About Liver Disease and COVID-19. https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/liver-disease.html. Accessed on June 8, 2020.
23. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. Jama 2020;323:2052-9.

24. Grasselli G, Zangrillo A, Zanella A, et al. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. Jama 2020;323:1574-81.
25. Sultan S, Altayar O, Siddique SM, et al. AGA Institute Rapid Review of the Gastrointestinal and Liver Manifestations of COVID-19, Meta-Analysis of International Data, and Recommendations for the Consultative Management of Patients with COVID-19. Gastroenterology 2020.
26. Mao R, Liang J, Shen J, et al. Implications of COVID-19 for patients with pre-existing digestive diseases. Lancet Gastroenterol Hepatol 2020;5:425-427.
27. Singh S, Khan A, Clinical Characteristics and Outcomes of COVID-19 Among Patients with Pre-Existing Liver Disease in United States: A Multi-Center Research Network Study, Gastroenterology (2020), doi: https://doi.org/10.1053/j.gastro.2020.04.064.
28. Wang X, Fang X, Cai Z, et al. Comorbid Chronic Diseases and Acute Organ Injuries Are Strongly Correlated with Disease Severity and Mortality among COVID-19 Patients: A Systemic Review and Meta-Analysis. Research (Wash D C) 2020;2020:2402961.
29. Lippi G, de Oliveira MHS, Henry BM. Chronic liver disease is not associated with severity or mortality in Coronavirus disease 2019 (COVID-19): a pooled analysis. European Journal of Gastroenterology & Hepatology 9000;Publish Ahead of Print.
30. Chai X, Hu L, Zhang Y, et al. Specific ACE2 expression in cholangiocytes may cause liver damage after 2019-nCoV infection. bioRxiv 2020.
31. Guan GW, Gao L, Wang JW, et al. [Exploring the mechanism of liver enzyme abnormalities in patients with novel coronavirus-infected pneumonia]. Zhonghua Gan Zang Bing Za Zhi 2020;28:E002.
32. Hu LL, Wang WJ, Zhu QJ, et al. [Novel coronavirus pneumonia related liver injury: etiological analysis and treatment strategy]. Zhonghua Gan Zang Bing Za Zhi 2020;28:E001.
33. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 2020:105949.

34. Hydroxychloroquine. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases, 2012.
35. McCreary EK, Pogue JM. COVID-19 Treatment: A Review of Early and Emerging Options. Open Forum Infectious Diseases 2020.
36. Grein J, Ohmagari N, Shin D, et al. Compassionate Use of Remdesivir for Patients with Severe Covid-19. New England Journal of Medicine 2020.
37. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 — Preliminary Report. New England Journal of Medicine 2020.
38. Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. New England Journal of Medicine 2020.
39. Zhang S, Li L, Shen A, et al. Rational Use of Tocilizumab in the Treatment of Novel Coronavirus Pneumonia. Clin Drug Investig 2020;40:511-518.
40. Kujawski SA, Wong KK, Collins JP, et al. First 12 patients with coronavirus disease 2019 (COVID-19) in the United States. medRxiv 2020.
41. ClinicalTrails.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2020 March 6 - . Identifier NCT04292899. Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants With Severe Coronavirus Disease (COVID-19) [accessed 30 March 2020].
42. ClinicalTrails.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2020 March 15 - . Identifier NCT04292730. Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants With Moderate Coronavirus Disease (COVID-19) Compared to Standard of Care Treatment [accessed 30 March 2020].
43. ClinicalTrails.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2020 February 21 - . Identifier NCT04280705. Adaptive COVID-19 Treatment Trial (ACTT) [accessed 30 March 2020].

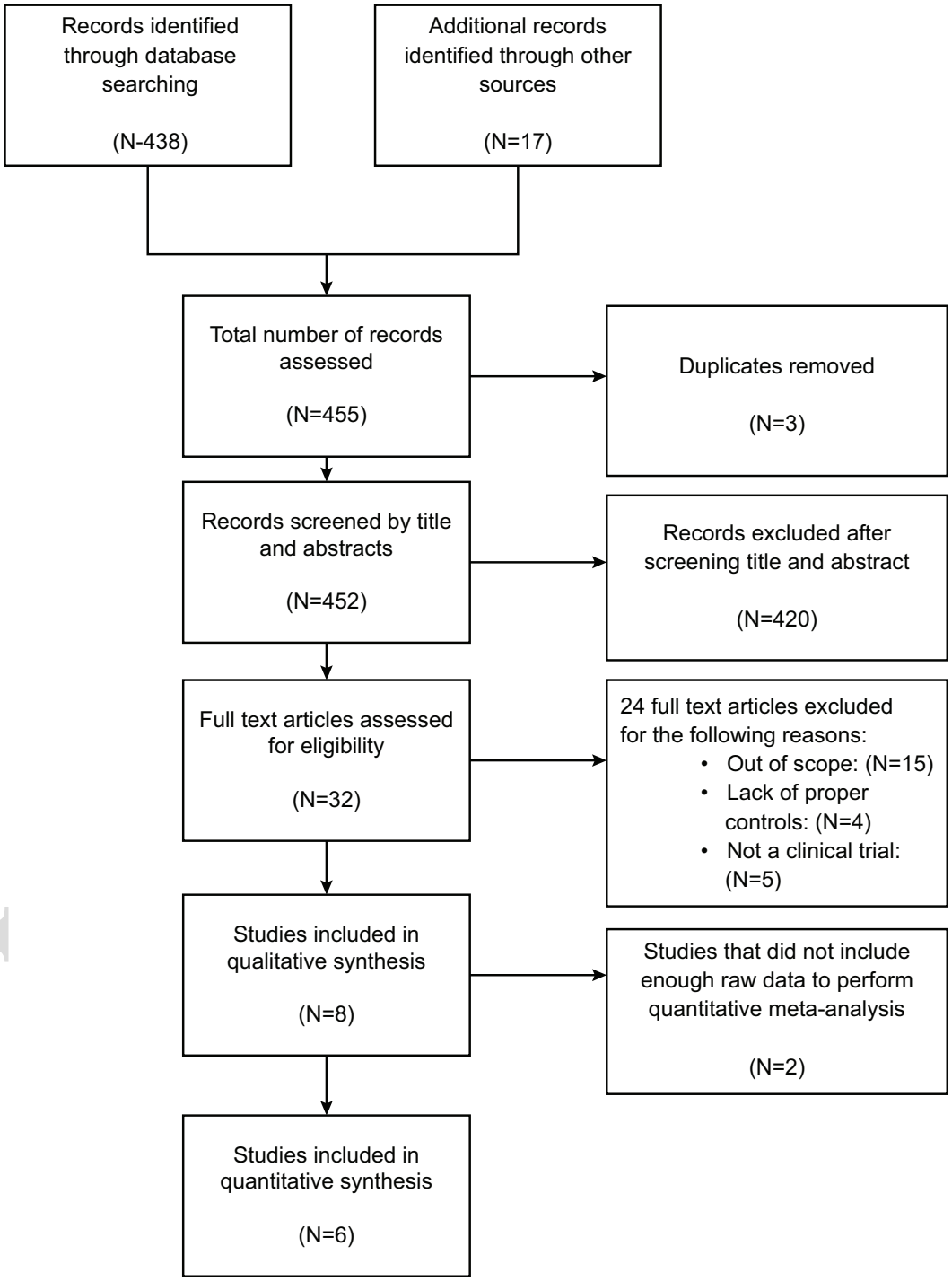
Figure Legends

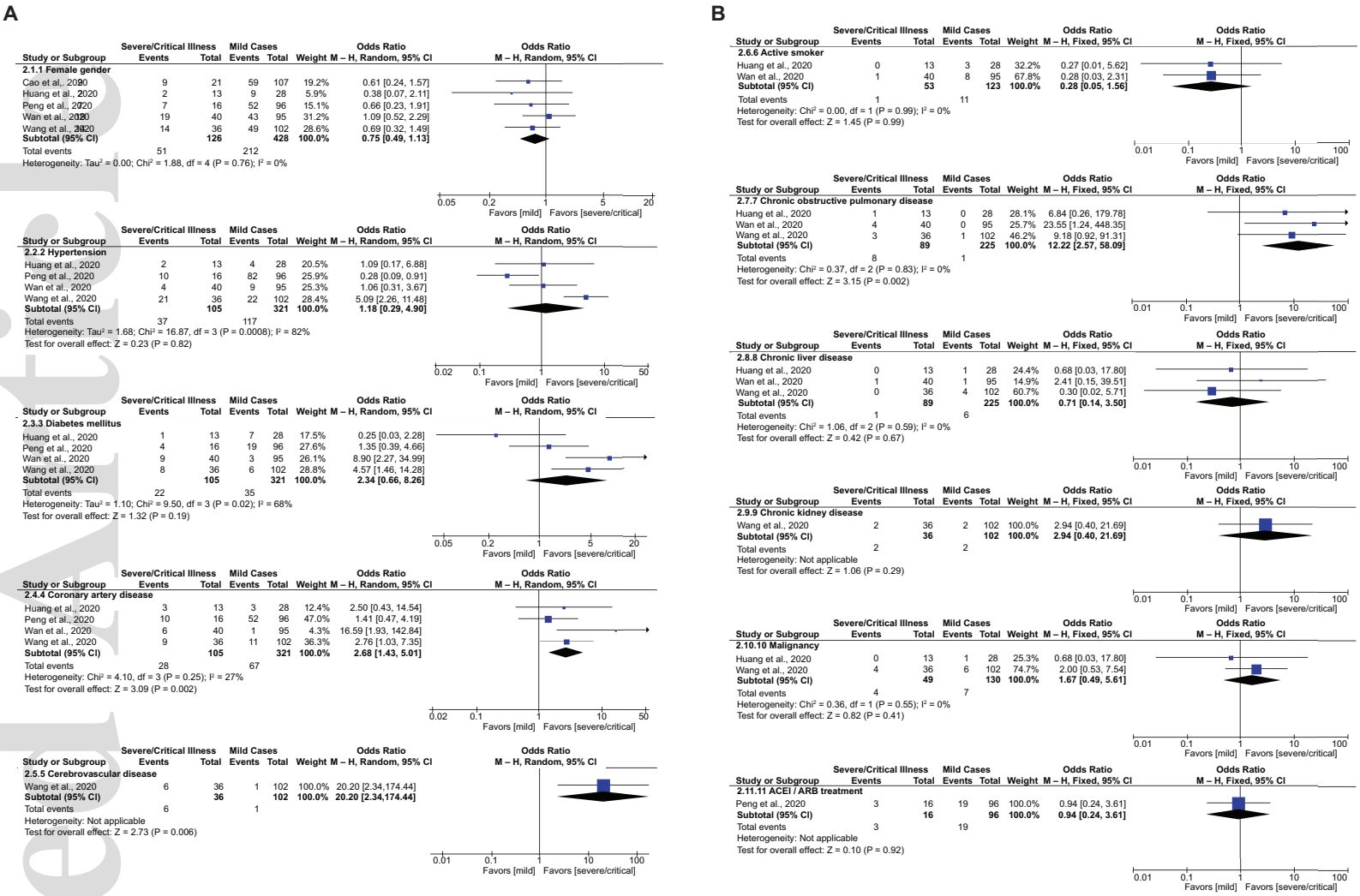
FIG. 1. Study flow diagram.

FIG. 2. Forest plot comparison of demographic data among patients with severe/critical illness versus mild COVID-19 infection.

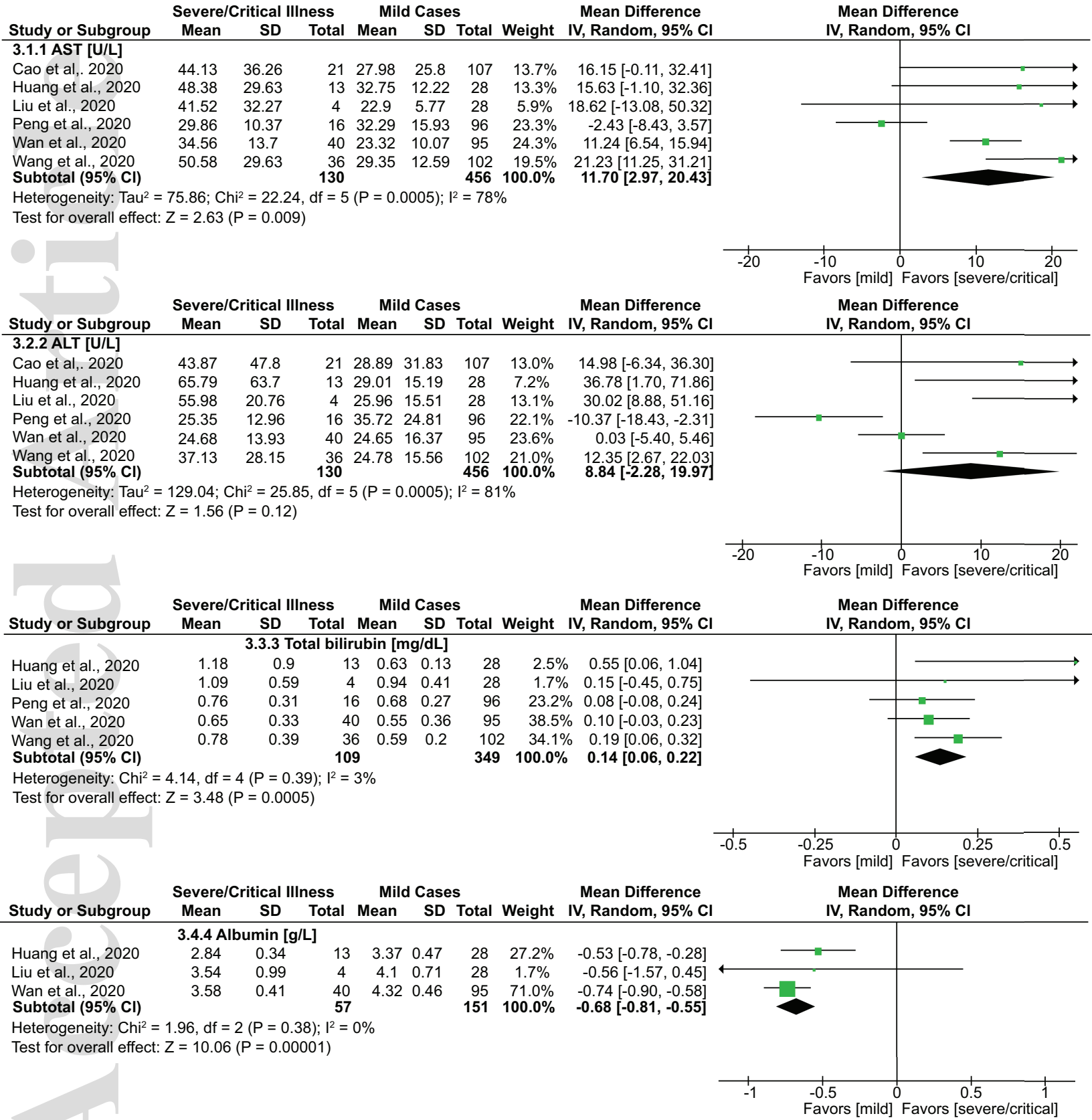
FIG. 3. Forest plot comparison of liver chemistries among patients with severe/critical illness versus mild COVID-19 infection.

FIG. 4. Forest plot comparison of mortality reported among patients with severe/critical illness versus mild COVID-19 infection.





hep_31472_f2.eps

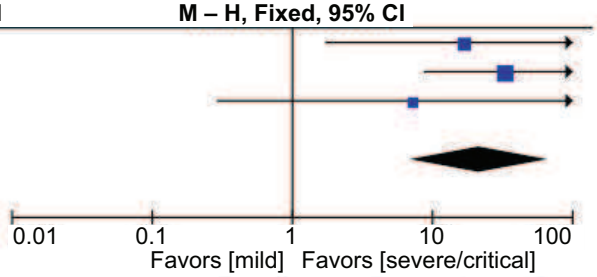


hep_31472_f3.eps

Study or Subgroup	Severe/Critical Illness Events	Total	Mild Cases Events	Total	Weight	Odds Ratio M – H, Fixed, 95% CI
Huang et al., 2020	5	13	1	28	32.1%	16.88 [1.71, 166.21]
Peng et al., 2020	11	16	6	96	44.1%	33.00 [8.63, 126.26]
Wan et al., 2020	1	40	0	95	23.7%	7.25 [0.29, 181.90]
Total (95% CI)		**69**		**219**	**100.0%**	**21.70 [7.01, 67.24]**
Total events	17		7			

Heterogeneity: $Chi^2 = 0.87$, df = 2 (P = 0.65); $I^2 = 0\%$

Test for overall effect: Z = 5.33 (P<0.00001)



hep_31472_f4.eps