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Impact of liver injury on the severity of COVID-19: a systematic review with meta-analysis

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AUTHOR'S CONTRIBUTION

Guarantor of the article: JA, MRG

Study design: JA

Drafting the manuscript: JA, MRG

Statistical analyses and interpretation: JA

Data acquisition and critical review of the manuscript: JA, YS, MRGL, DM, MRG

All authors approved the final version of the article, including the authorship list.

ABSTRACT

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Background and aims: SARS-CoV-2 is mainly a respiratory virus that has relevant systemic effects. We assessed the impact of baseline liver function (aspartate aminotransferase [AST], alanine aminotransferase [ALT], bilirubin) on COVID-19-related outcomes, including mortality, intensive care unit (ICU) admissions, and non-fatal severe complications.

Methods: after a systematic review of the relevant studies the odds ratio (OR), mean difference, sensitivity, specificity, and both positive and negative likelihood ratios were calculated for the prediction of relevant COVID-19 outcomes by performing a meta-analysis using fixed and random effects models. A Fagan nomogram was used to assess clinical usefulness. Heterogeneity was explored by sensitivity analysis and univariate meta-regression.

Results: twenty-six studies were included (22 studies and 5,271 patients for AST, 20 studies and 5,440 subjects for ALT, and nine studies and 3,542 patients for bilirubin). The outcomes assessed by these studies were: survival (n = 8), ICU admission (n = 4), and non-fatal severe complications (n = 16). AST > upper limit of normal (ULN) (OR: 3.10 [95 % CI, 2.61-3.68]), ALT > ULN (OR: 2.15 [95 % CI, 1.43-3.23]), and bilirubin > ULN (OR: 2.78 [95 % CI, 1.88-4.13]) were associated with an increased prevalence of severe complications with a specificity of 78 %, 77 %, and 94 %, respectively. The mean difference between mild and severe COVID-19 was 10.7 U/l (95 % CI, 5.8-15.6) for AST, 8 U/l (95 % CI, 1.0-15) for ALT, and 0.3 mg/dl (95 % CI, 0.16-0.45) for bilirubin.

Conclusions: patients showing liver injury had a significantly higher risk of developing severe COVID-19 as compared to those with normal liver function tests at admission. We should include the assessment of AST, ALT, and total bilirubin (TB) routinely in the workup of patients affected by SARS-CoV-2 in order to predict those at risk of developing COVID-19-related outcomes.

Keywords: COVID-19. SARS-CoV-2. Coronavirus. Liver. AST. ALT. Bilirubin.

INTRODUCTION

The pandemic of SARS-CoV-2 as the cause of COVID-19 includes cases ranging from asymptomatic forms to acute distress respiratory syndrome and systemic inflammatory response secondary to cytokine storm (1). However, despite the fact that SARS-CoV-2 is primarily a respiratory virus, it has important and devastating systemic effects (2-8), which

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involve alterations in circulating lymphocytes and the immune system (9).

Inflammatory markers are usually elevated in COVID-19 patients, and they are being used as surrogate markers of severity (e.g., procalcitonin, ferritin, C-reactive protein, erythrocyte sedimentation rate, D-dimer) (10,11). However, they are nonspecific for this disease since they may be increased in many other conditions. Routine laboratory markers reflecting organ failure (in addition to systemic inflammation) may help improve the prediction of COVID-19 severity. In this setting, liver function tests have been found to be altered in these patients at baseline (primarily elevated aspartate aminotransferase [AST] and alanine aminotransferase [ALT], and slightly increased bilirubin levels) (12). Thus, the liver has been proposed as a target of COVID-19, but also may play an additional role in expanding the hyperinflammatory and prothrombotic status. Furthermore, the impact of pre-existing liver disease on the prognosis of COVID-19 remains unknown, although some conditions may exert a negative influence, including non-alcoholic fatty liver disease (NAFLD) (13).

Identification of surrogate markers of severe COVID-19 is of great importance, and could help clinicians manage the condition quickly and accurately. Given the urgency decision making requires in the setting of the COVID-19 outbreak, we aimed to put together all the available data and conduct a meta-analysis to explore how liver injury markers may impact COVID-19 management and prognosis. Particularly, our primary endpoint was to assess the impact of baseline liver function (AST, ALT, total bilirubin [TB]) on COVID-19-related outcomes, particularly on mortality, Intensive Care Unit (ICU) admission, and non-fatal severe complications (use of mechanical ventilation, septic shock, kidney failure, myocardial injury). Secondary endpoints included: a) to quantitatively measure the mean differences in AST, ALT, and TB between patients with and without COVID-19 complications; b) to calculate the sensitivity and specificity of AST > ULN, ALT > ULN, and TB > ULN at the time of infection for use as surrogate markers of the use of health care resources; and c) to determine their usefulness in the current clinical scenario according to the virulence of SARS-CoV-2.

METHODS

Study identification and selection

The search strategy was in accordance with the recommendations of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group (60). One of the reviewers (JA), with experience in database searches, designed the search strategy, which was subsequently revised by other three investigators (YS, MRGL, DM). They independently searched the Medline (using PubMed as the search engine), EMBASE, and Cochrane databases, and collected all results separately. Disagreements between them were resolved by a third investigator (MRG) or by consensus. Databases were used to identify suitable studies that were published up to April 16th, 2020. MeSH terms and keywords were used, and the search terms were as follows: SARS-CoV-2, COVID-19, coronavirus, mortality, survival, death, ICU, severe disease, infection, and a combination of those MeSH terms using the appropriate Boolean logic. Searches were limited to English-language publications with human subjects. A manual search was conducted by using the references listed in the original articles and review articles retrieved. Only fully published articles were considered, so oral presentations, abstracts, and posters were not considered. The inclusion criteria were: a) studies that reported dichotomized (upper limit of normal [ULN] or not) AST, ALT, or TB (at least, one of them); b) studies that assessed one of the following endpoints: COVID-19-related non-fatal severe complications, ICU admission, or mortality (at least, one of them); c) adults (≥ 18 years old). The exclusion criteria were as follows: a) duplicate reports; b) case reports, comments, and letters to the editors; and c) systematic reviews or meta-analyses. This study was performed according to the PRISMA statement (14).

Data extraction and quality assessment

The following data were extracted: author, country, year, population selection criteria, sample size, COVID-19-related endpoint, AST, ALT, TB, age, sex, liver disease, arterial hypertension (AHT), diabetes mellitus (DM), lymphocyte, LDH, C-reactive protein (CRP), D-dimer, ferritin, albumin, heart rate, respiratory rate, fever, X-ray, and oxygenation (SaO_2). When the same population was published in several journals, only the most informative article or the most complete study was retained in order to avoid duplication. We also asked the investigators for additional information, and if we received no answer, "unreported" items were treated as "unclear" or "not available". On the other hand, three investigators (SG, RM, MG) independently assessed the quality of the studies using the Quality in Prognostic Studies (QUIPS) tool (15).

Statistical analysis

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We used the STATA version 16 software (Stata Corp; College Station, TX) with the commands "Midas," "Metan," and "Metaninf." All statistical tests were two-sided, with p-values ≤ 0.05 denoting statistical significance. Confidence intervals (CIs) for individual studies were determined from the available data.

The assumption of heterogeneity was tested for each planned analysis using Cochran's Q-test for heterogeneity and I2 statistics (significant heterogeneity according to I2 values > 50 %) (16). A random-effects model was utilized in case of significant heterogeneity; in the absence of the latter, a fixed-effects model was applied to pool the results from the studies. For dichotomous variables (AST > ULN, ALT > ULN, TB > ULN) the effect was expressed as odds ratios (OR) and corresponding 95 % CIs, while mean differences were used to specifically provide measures of the absolute differences between the mean values of the explored variables (AST, U/L; ALT, U/L; TB, mg/dl). COVID-19-related mortality, ICU admission, and severe complications were identified as relevant outcomes. On the other hand, a bivariate regression was performed to estimate overall sensitivity and specificity. Additionally, we calculated the positive and negative likelihood ratios (LR) in order to generate Fagan nomograms. They were used to evaluate the clinical utility of AST > ULN, ALT > ULN, and TB > ULN for the use of health care resources, according to the current clinical scenario concerning the virulence of SARS-CoV-2 (pretest 20 % probability for hospitalization), which shows the relationship between prior probability, likelihood ratio, and posterior test probability.

In case of heterogeneity, a sensitivity analysis was performed to determine if there was any undue influence exerted by a single study on the results of the combined studies (17). Furthermore, potential heterogeneity was explored by univariate meta-regression and subgroup analyses (18).

The potential publication bias was assessed using Egger's test, and graphically by a funnel plot. A p-value < 0.10 indicated statistical significance.

RESULTS

Eligible study characteristics and quality assessment

The flow-chart diagram details the article selection process for this meta-analysis (Fig. 1). Finally, 26 studies were included (22, 20, and nine evaluating AST, ALT, and TB, respectively). All the studies included in the meta-analysis were from China, probably because the COVID-

19 outbreak started in that country. The endpoints of the studies were: survival (n = 8), ICU admission (n = 4), and non-fatal severe complications (n = 16) (two of them assessed both survival and severe complications). Overall, 5,271 patients were included in the group of studies on AST, 5,440 subjects in the ALT assessment group, and 3,542 had their TB assessed. The characteristics of the eligible studies are listed in table 1. Seven of the 26 studies showed a low risk of bias, while the rest of them showed a moderate risk according to the quality assessment by QUIPS.

Data analyses

The presence of increased or decreased AST correctly classified 71.5 % (764/1,069) of deaths, 73.8 % (739/1,002) of ICU admissions, and 65.1 % (1,495/2,297) of severe complications. We found that baseline AST > ULN was associated with death (OR: 3.82 [95 % CI, 2.55-5.73]), need for ICU admission (OR: 2.98 [95 % CI, 2.00-4.45]), and occurrence of non-fatal severe complications (OR: 2.95 [95 % CI, 2.38-3.67]), in comparison with patients showing decreased AST levels. Taking all the outcomes together, AST > ULN showed an overall OR of 3.10 (95 % CI, 2.61-3.68) for COVID-19-related outcomes, with moderate heterogeneity (Q = 33.77; I^2 = 46.7 %; p = 0.01) (Fig. 2A). Regarding mean differences, we observed that AST values were higher in patients with adverse events (10.7 U/l [95 % CI, 5.8-15.6]) (Fig. 2B). AST > ULN showed a sensitivity of 0.48 (95 % CI, 0.41-0.55) and a specificity of 0.79 (95 % CI, 0.72-0.85), with a LR+ of 2.3 (95 % CI, 1.8-2.9) and LR- of 0.66 (95 % CI, 0.60-0.73) for the use of any health care resource (Fig. 2C).

Elevated or decreased ALT correctly determined 65.6 % (852/1,299) of the population who died, 73.4 % (694/945) of those requiring ICU admission, and 58.9 % (1,261/2,141) of subjects suffering from any non-fatal severe complication. Regarding ALT > ULN, it was not associated with increased mortality (OR 1.54 [95 % CI, 0.66-3.59]). However, need for ICU admission (OR: 2.85 [95 % CI, 1.52-5.35]) and COVID-19-related severe complications (OR: 2.39 [95 % CI, 1.37-4.15]) were increased in patients with ALT > ULN. Taking all the outcomes, ALT > ULN showed an overall OR of 2.15 (95 % CI, 1.43-3.23) for COVID-19-related outcomes (Fig. 3A). We also found that ALT values were higher in patients with adverse events (8 U/l [95 % CI, 1.0-15]) (Fig. 3B). We found a high heterogeneity for the combined studies on ALT (Q = 62; I^2 = 77.8 %; p = 0.0001). ALT > ULN showed a sensitivity of 0.38 (95 % CI, 0.29-0.49) and a specificity of 0.77 (95 % CI, 0.68-0.85), with a LR+ of 1.7 (95 % CI, 1.3-2.3) and LR- of 0.79 (95 % CI, 0.69-0.92) for the use of health care resources (Fig. 3C).

On the other hand, TB correctly determined 73.8 % (1,509/2,046) of the population who showed non-fatal severe complications. Thus, TB > ULN was associated with an increased prevalence of severe complications (OR: 2.78 [95 % CI, 1.88-4.13]) (Fig. 4A). Furthermore, we found that TB values were higher in patients with adverse events (0.3 mg/dl [95 % CI, 0.16-0.45]) (Fig. 4B). We did not find any significant heterogeneity for the combined studies on TB (Q = 3.79; I^2 = 31.8 %; p = 0.580). Also, TB > ULN showed a sensitivity of 0.13 (95 % CI, 0.09-0.20) and a specificity of 0.94 (95 % CI, 0.91-0.96), with a LR+ of 2.3 (95 % CI, 1.6-3.4) and LR- of 0.92 (95 % CI, 0.87-0.97) for the use of any health care resources (Fig. 4C).

Fagan nomograms

In the current scenario of COVID-19 virulence (20 % of likelihood of hospitalization), the results of Fagan nomograms showed a negative posterior probability of 14 % and a positive posterior probability of 38 % for AST > ULN. In comparison, these values were 17 % and 30 % for ALT > ULN, and 19 % and 37 % for TB > ULN.

Sensitivity analysis and univariate meta-regression

In order to explore the causes of heterogeneity a sensitivity analysis and a univariate meta-regression were performed. Leaving out one study at a time from the meta-analysis, no individual study assessing AST, ALT, or bilirubin that influenced the overall meta-analysis summary estimate was found.

The univariate meta-regression aimed to incorporate the effect of co-varying factors on the summary measures of AST, ALT, and TB. Lymphopenia was a possible source of heterogeneity among the combined studies on AST, while liver disease and albumin were potential sources for studies on ALT. In contrast, we did not find any variable causing heterogeneity in the studies assessing TB.

Publication bias

Egger's test failed to identify any publication bias for AST (p = 0.712), ALT (p = 0.108), or TB (p = 0.804).

DISCUSSION

COVID-19 is characterized by a respiratory involvement that may result in death due to massive alveolar damage and progressive respiratory failure, with mortality reaching up to 25 % among patients admitted to the ICU (19). To date, COVID-19 has been related to other complications such as myocardial infarction or neurological disorders (20,21). However, the relationship between SARS-CoV-2 and the liver remains poorly understood. It has been published that about 14-53 % of COVID-19 cases showed abnormal ALT and AST levels, although clinically significant liver injury was uncommon (22). Interestingly, patients with severe infection have been shown to have higher rates of liver dysfunction (23). The following reasons can explain these findings: a) SARS-CoV-2 may have a direct cytopathic effect on the liver as the virus binds the ACE2 receptor, whose expression is enhanced in cholangiocytes (24); b) immune-mediated damage due to severe inflammatory response (e.g., cytokine storm) (25); c) hypoxic hepatitis, although transaminases are mildly elevated in COVID-19; and d) a viral translocation to the portal system cannot be excluded since the virus replicates actively in enterocytes. Hepatotoxicity secondary to antiviral drugs or hepatic congestion (by increasing right atrial pressure secondary to mechanical ventilation) are relevant once the patients have been hospitalized (26).

Given that cohorts with low-to-moderate sample sizes are being published, a meta-analysis was performed including more than 5,000 patients from 26 studies that assessed liver function. We found that AST (mortality, ICU admission, and non-fatal severe complications), ALT (ICU admission and non-fatal severe complications), and TB (ICU admission and non-fatal severe complications) increased the risk of poor COVID-19-related outcomes significantly when they were above the upper normal limit. However, we should not expect shocking alterations in the liver profile as we observed that AST (11 U/l), ALT (8 U/l) and TB (0.3 mg/dl) showed relatively, slightly higher levels in patients developing COVID-19 complications. Thus, we must pay close attention to the markers of liver injury at admission to predict which patients are at risk of developing a poor prognosis.

The COVID-19 outbreak is collapsing many national health systems (27). Thus, having prognostic factors for patients who could require ICU admission or develop severe complications (other than mortality) is essential to manage the situation adequately. Few studies have been carried out to achieve this goal, and they are poorly reported, with a high risk of bias, and not including any parameters of liver disease (27). In our meta-analysis, liver injury markers were associated with COVID-19-related adverse outcomes (ranging from

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mortality to non-fatal severe complications). For instance, individuals with AST > ULN at baseline showed a 40 % post-test probability of suffering COVID-19 complications in the current virulence scenario (prevalence 20 %). Furthermore, AST, ALT, and notably bilirubin showed high specificity (and reduced sensitivity) for COVID-19 outcomes, which in clinical practice means that patients with normal liver values have a low likelihood of having a poor prognosis. This approach could result particularly relevant in areas like the Emergency Room, where many patients are cared for and, sometimes, the decision of hospitalization is unclear. The incorporation of the liver profile to other inflammatory markers such as ferritin or D-dimer may improve the decision making process. Therefore, we believe that a panel of liver injury markers (including AST, ALT, and TB) must be routinely performed at baseline in patients suffering from infection with SARS-CoV-2.

Our findings should be cautiously interpreted. First, all the studies included in this meta-analysis were from China, which could limit the generalization of results to other populations. However, no articles from Europe or America have been published evaluating the role of liver dysfunction on COVID-19 prognosis, probably because the first wave of the infection started in Wuhan (China) months earlier (28). Second, some studies could not be included in this meta-analysis because liver function was not adequately assessed. In other studies, transaminases were reported as median and interquartile range, probably because they did not follow a normal distribution, thus precluding their inclusion in a meta-analysis. However, most of these studies showed high AST and ALT levels in patients with COVID-19-related outcomes (20,21,29-32). Third, the information about pre-existing liver diseases is suboptimal in the published studies. When this information was reported, the percentage of patients with liver disease was very low (33). This fact could influence the predictive value of AST, ALT, or TB for COVID-19 severity, probably modifying the cut-off point for the upper limit of normal. Finally, elevated levels of creatinine kinase or lactate dehydrogenase, together with elevated transaminases, have been reported and could support an additional extrahepatic origin of these alterations (beyond liver dysfunction) (34). However, the fact of observing similar findings about TB in our meta-analysis (and other studies demonstrating that albumin levels decrease [35,36]) could represent, at least in part, a relevant role of the liver in the context of severe COVID-19.

In summary, patients with markers of liver injury had a significantly higher risk of developing severe COVID-19 when compared to those with normal liver function tests at admission. Our findings make it essential to routinely include an assessment of AST, ALT, and TB for all patients affected by SARS-CoV-2 in order to anticipate those at risk of developing COVID-19 complications.

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Table 1. Characteristics of the studies included

Author	*Year*	*Country*	*Study design*	*Patients*	*Outcome*	*Liver function assessment*	*True positive*	*False positive*	*False negative*	*True negative*
Yang X (37)	2020	China	Single-center, retrospective, observational study	52	Survival	AST: Yes (N/A) ALT: No TB: No	6 N/A N/A	9 N/A N/A	14 N/A N/A	23 N/A N/A
Li Y (38)	2020	China	Single-center, retrospective, observational study	25	Survival	AST: Yes (N/A) ALT: No TB: No	2 N/A N/A	10 N/A N/A	3 N/A N/A	10 N/A N/A
					COVID-19 complications	AST: Yes (N/A) ALT: No TB: No	5 N/A N/A	8 N/A N/A	4 N/A N/A	8 N/A N/A
Chen T (39)	2020	China	Single-center, retrospective, observational study	274	Survival	AST: Yes (40 U/l) ALT: Yes (41 U/l) TB: No	59 30 N/A	25 30 N/A	54 83 N/A	136 131 N/A
Zhou F (40)	2020	China	Multicenter, retrospective, observational study	189	Survival	AST: No ALT: Yes (40 U/l) TB: No	N/A 33 N/A	N/A 26 N/A	N/A 102 N/A	N/A 28 N/A
Cao J (41)	2020	China	Single-center, retrospective,	118	Survival	AST: No ALT: Yes (40	N/A 7	N/A 25	N/A 10	N/A 76

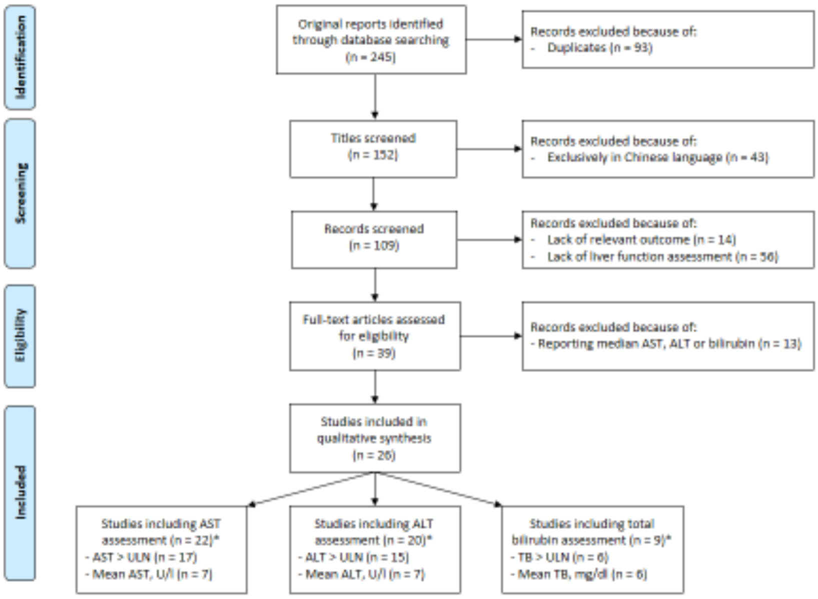


Fig. 1. Flow chart summarizing the selection of eligible studies. *Individual studies, although some of them reported simultaneously dichotomous and continuous variables.

Fig. 2A

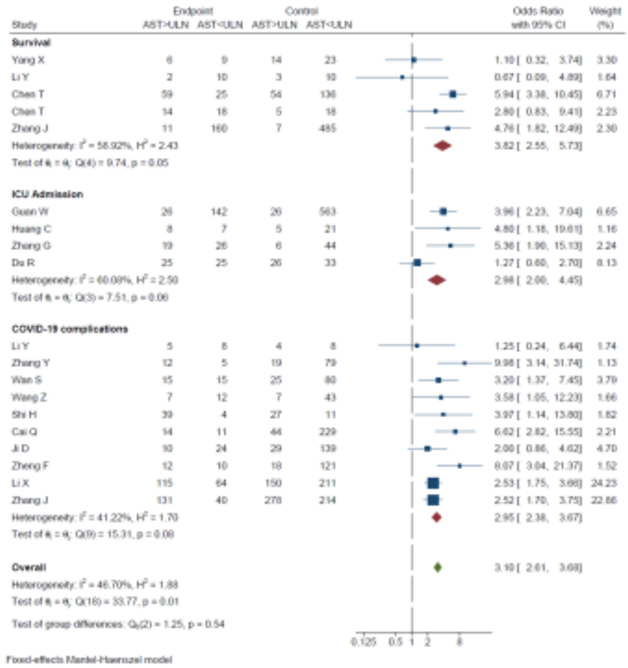

Endpoint
Control
Study
AST>ULN AST<ULN AST>ULN AST<ULN
Odds Ratio with 95% CI
Weight (%)
Survival
Yang X 6 9 14 23 1.10 [0.32, 3.74] 3.30
Li Y 2 10 3 10 0.67 [0.09, 4.89] 1.64
Chen T 59 25 54 136 5.94 [3.38, 10.45] 6.71
Chen T 14 18 5 18 2.80 [0.83, 9.41] 2.23
Zhang J 11 160 7 485 4.76 [1.82, 12.49] 2.30
Heterogeneity: I^2 = 58.92%, H^2 = 2.43 3.82 [2.55, 5.73]
Test of $\theta_i = \theta_j$: Q(4) = 9.74, p = 0.05
ICU Admission
Guan W 26 142 26 563 3.96 [2.23, 7.04] 6.65
Huang C 8 7 5 21 4.80 [1.18, 19.61] 1.16
Zhang G 19 26 6 44 5.36 [1.90, 15.13] 2.24
Du R 25 25 26 33 1.27 [0.60, 2.70] 8.13
Heterogeneity: I^2 = 60.08%, H^2 = 2.50 2.98 [2.00, 4.45]
Test of $\theta_i = \theta_j$: Q(3) = 7.51, p = 0.06
COVID-19 complications
Li Y 5 8 4 8 1.25 [0.24, 6.44] 1.74
Zhang Y 12 5 19 79 9.98 [3.14, 31.74] 1.13
Wan S 15 15 25 80 3.20 [1.37, 7.45] 3.79
Wang Z 7 12 7 43 3.58 [1.05, 12.23] 1.66
Shi H 39 4 27 11 3.97 [1.14, 13.80] 1.82
Cai Q 14 11 44 229 6.62 [2.82, 15.55] 2.21
Ji D 10 24 29 139 2.00 [0.86, 4.62] 4.70
Zheng F 12 10 18 121 8.07 [3.04, 21.37] 1.52
Li X 115 64 150 211 2.53 [1.75, 3.66] 24.23
Zhang J 131 40 278 214 2.52 [1.70, 3.75] 22.86
Heterogeneity: I^2 = 41.22%, H^2 = 1.70 2.95 [2.38, 3.67]
Test of $\theta_i = \theta_j$: Q(9) = 15.31, p = 0.08
Overall 3.10 [2.61, 3.68]
Heterogeneity: I^2 = 46.70%, H^2 = 1.88
Test of $\theta_i = \theta_j$: Q(18) = 33.77, p = 0.01
Test of group differences: $Q_b(2)$ = 1.25, p = 0.54
0.125 0.5 1 2 8
Fixed-effects Mantel-Haenszel model

Fig. 2B

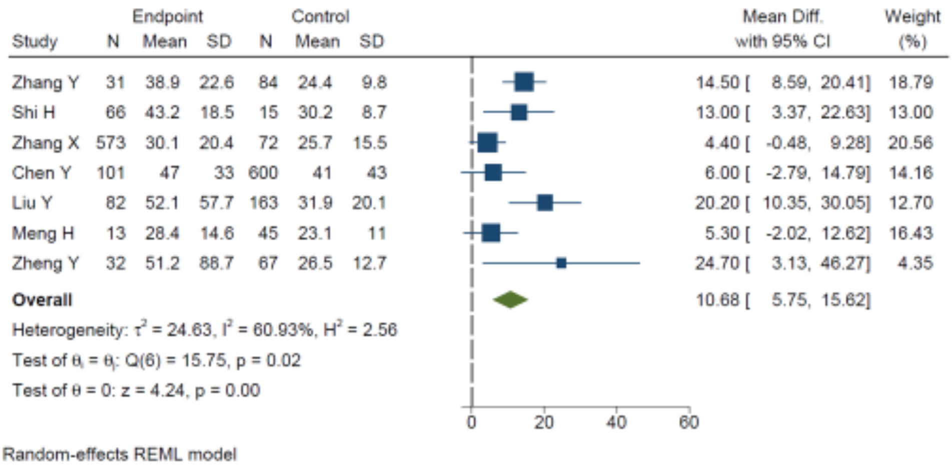

Endpoint
Control
Study N Mean SD N Mean SD
Mean Diff. with 95% CI
Weight (%)
Zhang Y 31 38.9 22.6 84 24.4 9.8 14.50 [8.59, 20.41] 18.79
Shi H 66 43.2 18.5 15 30.2 8.7 13.00 [3.37, 22.63] 13.00
Zhang X 573 30.1 20.4 72 25.7 15.5 4.40 [-0.48, 9.28] 20.56
Chen Y 101 47 33 600 41 43 6.00 [-2.79, 14.79] 14.16
Liu Y 82 52.1 57.7 163 31.9 20.1 20.20 [10.35, 30.05] 12.70
Meng H 13 28.4 14.6 45 23.1 11 5.30 [-2.02, 12.62] 16.43
Zheng Y 32 51.2 88.7 67 26.5 12.7 24.70 [3.13, 46.27] 4.35
Overall 10.68 [5.75, 15.62]
Heterogeneity: τ^2 = 24.63, I^2 = 60.93%, H^2 = 2.56
Test of $\theta_i = \theta_j$: Q(6) = 15.75, p = 0.02
Test of θ = 0: z = 4.24, p = 0.00
0 20 40 60
Random-effects REML model

Fig. 2C

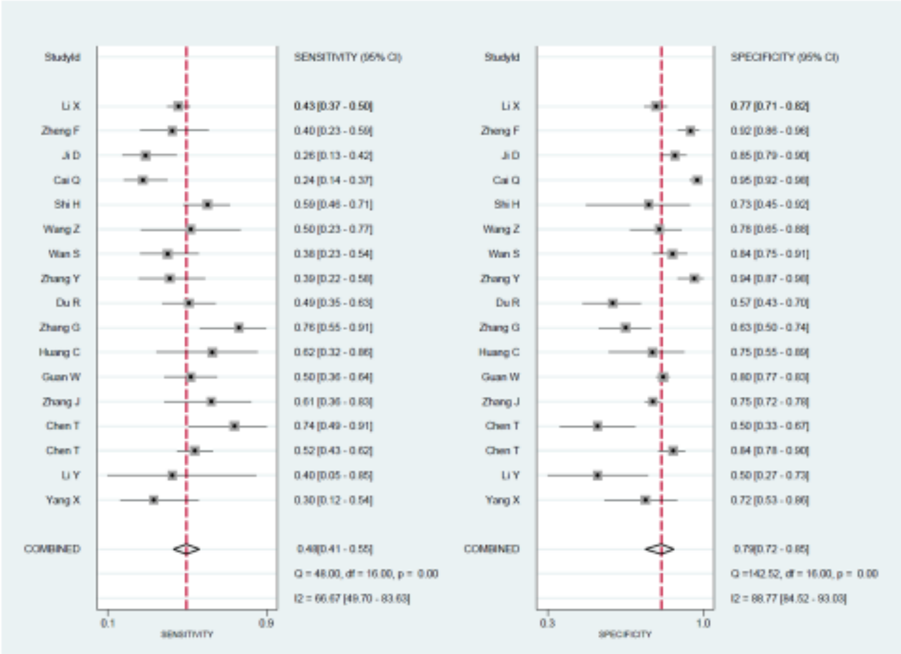
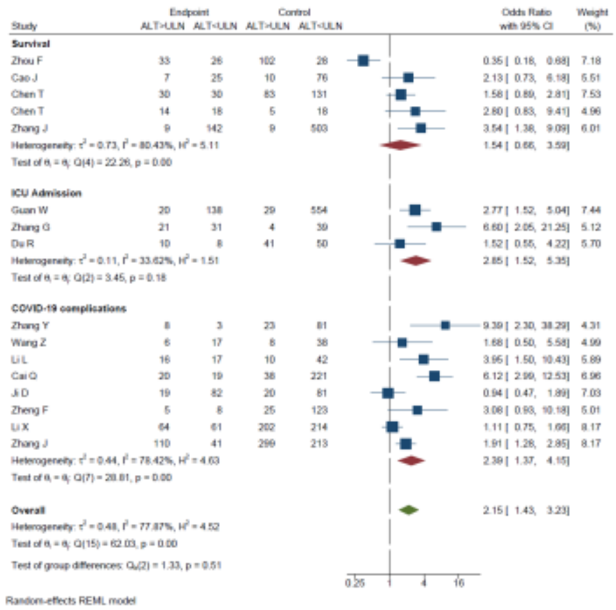


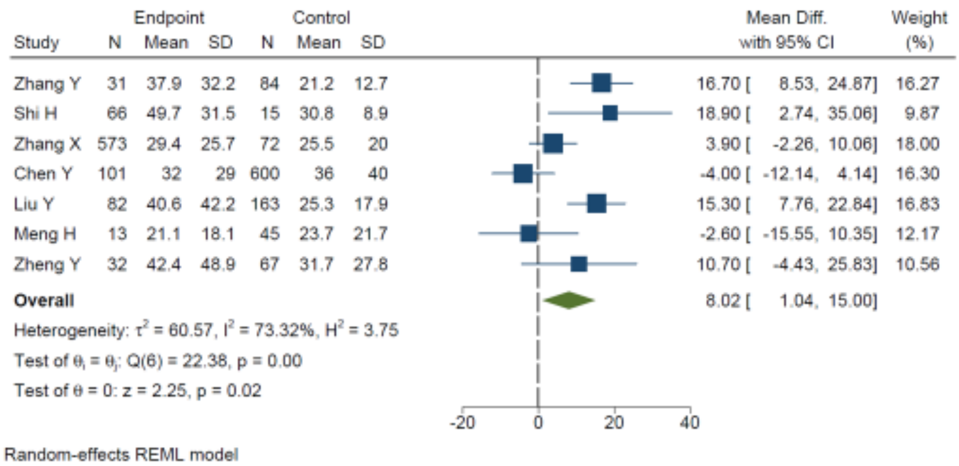
Fig. 2. Forest plots of the studies assessing AST depending on the outcomes. A. Odds ratio. B. Mean difference. C. Sensitivity and specificity.

Fig. 3A



Study
Endpoint
ALT>ULN ALT<ULN
Control
ALT>ULN ALT<ULN
Odds Ratio with 95% CI
Weight (%)
Survival
Zhou F 33 26 102 28 0.35 [0.18, 0.68] 7.18
Cao J 7 25 10 76 2.13 [0.73, 6.18] 5.51
Chen T 30 30 83 131 1.58 [0.89, 2.81] 7.53
Chen T 14 18 5 18 2.80 [0.83, 9.41] 4.96
Zhang J 9 142 9 503 3.54 [1.38, 9.09] 6.01
Heterogeneity: τ² = 0.73, I² = 80.43%, H² = 5.11 1.54 [0.66, 3.59]
Test of θi = θj: Q(4) = 22.26, p = 0.00
ICU Admission
Guan W 20 138 29 554 2.77 [1.52, 5.04] 7.44
Zhang G 21 31 4 39 6.60 [2.05, 21.25] 5.12
Du R 10 8 41 50 1.52 [0.55, 4.22] 5.70
Heterogeneity: τ² = 0.11, I² = 33.62%, H² = 1.51 2.85 [1.52, 5.35]
Test of θi = θj: Q(2) = 3.45, p = 0.18
COVID-19 complications
Zhang Y 8 3 23 81 9.39 [2.30, 38.29] 4.31
Wang Z 6 17 8 38 1.68 [0.50, 5.58] 4.99
Li L 16 17 10 42 3.95 [1.50, 10.43] 5.89
Cai Q 20 19 38 221 6.12 [2.99, 12.53] 6.96
Ji D 19 82 20 81 0.94 [0.47, 1.89] 7.03
Zheng F 5 8 25 123 3.08 [0.93, 10.18] 5.01
Li X 64 61 202 214 1.11 [0.75, 1.66] 8.17
Zhang J 110 41 299 213 1.91 [1.28, 2.85] 8.17
Heterogeneity: τ² = 0.44, I² = 78.42%, H² = 4.63 2.39 [1.37, 4.15]
Test of θi = θj: Q(7) = 28.81, p = 0.00
Overall 2.15 [1.43, 3.23]
Heterogeneity: τ² = 0.48, I² = 77.87%, H² = 4.52
Test of θi = θj: Q(15) = 62.03, p = 0.00
Test of group differences: Qb(2) = 1.33, p = 0.51
0.25 1 4 16
Random-effects REML model

Fig. 3B



Study
Endpoint
N Mean SD
Control
N Mean SD
Mean Diff. with 95% CI
Weight (%)
Zhang Y 31 37.9 32.2 84 21.2 12.7 16.70 [8.53, 24.87] 16.27
Shi H 66 49.7 31.5 15 30.8 8.9 18.90 [2.74, 35.06] 9.87
Zhang X 573 29.4 25.7 72 25.5 20 3.90 [-2.26, 10.06] 18.00
Chen Y 101 32 29 600 36 40 -4.00 [-12.14, 4.14] 16.30
Liu Y 82 40.6 42.2 163 25.3 17.9 15.30 [7.76, 22.84] 16.83
Meng H 13 21.1 18.1 45 23.7 21.7 -2.60 [-15.55, 10.35] 12.17
Zheng Y 32 42.4 48.9 67 31.7 27.8 10.70 [-4.43, 25.83] 10.56
Overall 8.02 [1.04, 15.00]
Heterogeneity: τ² = 60.57, I² = 73.32%, H² = 3.75
Test of θi = θj: Q(6) = 22.38, p = 0.00
Test of θ = 0: z = 2.25, p = 0.02
-20 0 20 40
Random-effects REML model

Fig. 3C

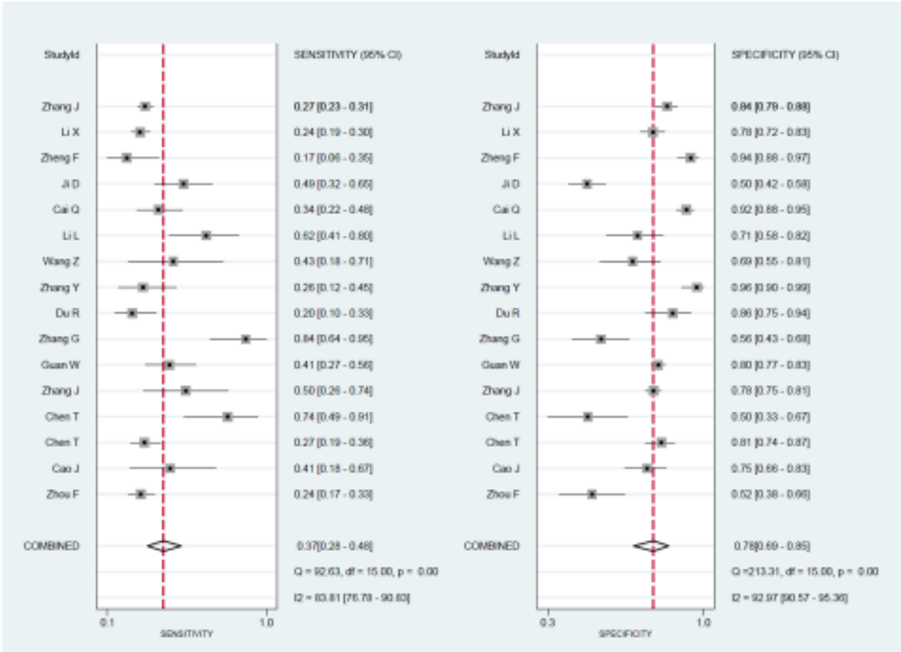


Fig. 3. Forest plots of the studies assessing ALT depending on the outcomes. A. Odds ratio. B. Mean difference. C. Sensitivity and specificity.

Fig. 4A

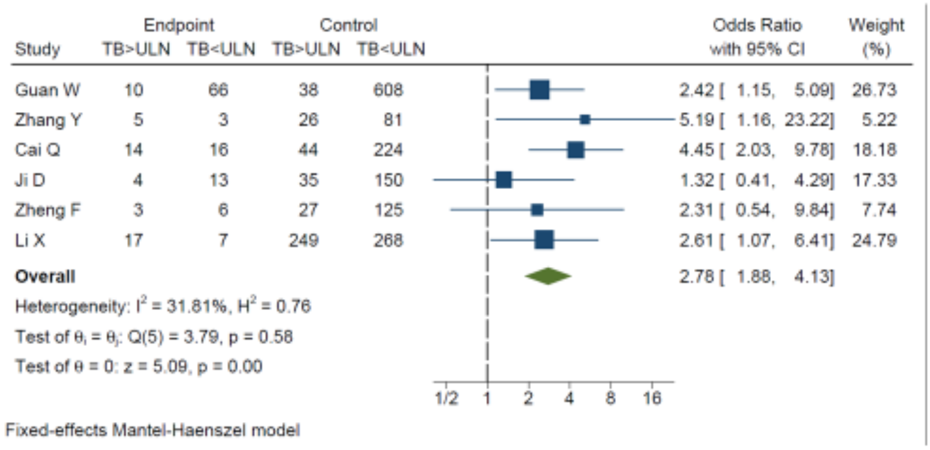
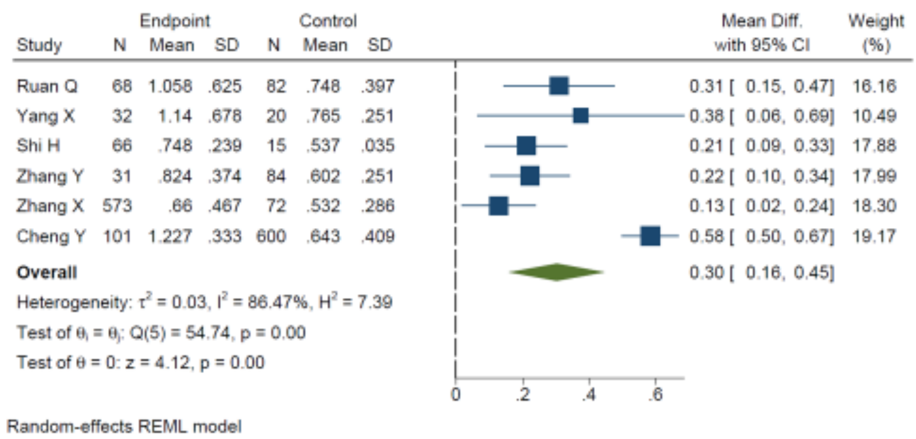

Study
Endpoint
TB>ULN TB<ULN
Control
TB>ULN TB<ULN
Odds Ratio with 95% CI
Weight (%)
Guan W 10 66 38 608 2.42 [1.15, 5.09] 26.73
Zhang Y 5 3 26 81 5.19 [1.16, 23.22] 5.22
Cai Q 14 16 44 224 4.45 [2.03, 9.78] 18.18
Ji D 4 13 35 150 1.32 [0.41, 4.29] 17.33
Zheng F 3 6 27 125 2.31 [0.54, 9.84] 7.74
Li X 17 7 249 268 2.61 [1.07, 6.41] 24.79
Overall 2.78 [1.88, 4.13]
Heterogeneity: I² = 31.81%, H² = 0.76
Test of θi = θj: Q(5) = 3.79, p = 0.58
Test of θ = 0: z = 5.09, p = 0.00
1/2 1 2 4 8 16
Fixed-effects Mantel-Haenszel model

Fig. 4B


Study
Endpoint
N Mean SD
Control
N Mean SD
Mean Diff. with 95% CI
Weight (%)
Ruan Q 68 1.058 .625 82 .748 .397 0.31 [0.15, 0.47] 16.16
Yang X 32 1.14 .678 20 .765 .251 0.38 [0.06, 0.69] 10.49
Shi H 66 .748 .239 15 .537 .035 0.21 [0.09, 0.33] 17.88
Zhang Y 31 .824 .374 84 .602 .251 0.22 [0.10, 0.34] 17.99
Zhang X 573 .66 .467 72 .532 .286 0.13 [0.02, 0.24] 18.30
Cheng Y 101 1.227 .333 600 .643 .409 0.58 [0.50, 0.67] 19.17
Overall 0.30 [0.16, 0.45]
Heterogeneity: τ² = 0.03, I² = 86.47%, H² = 7.39
Test of θi = θj: Q(5) = 54.74, p = 0.00
Test of θ = 0: z = 4.12, p = 0.00
0 .2 .4 .6
Random-effects REML model

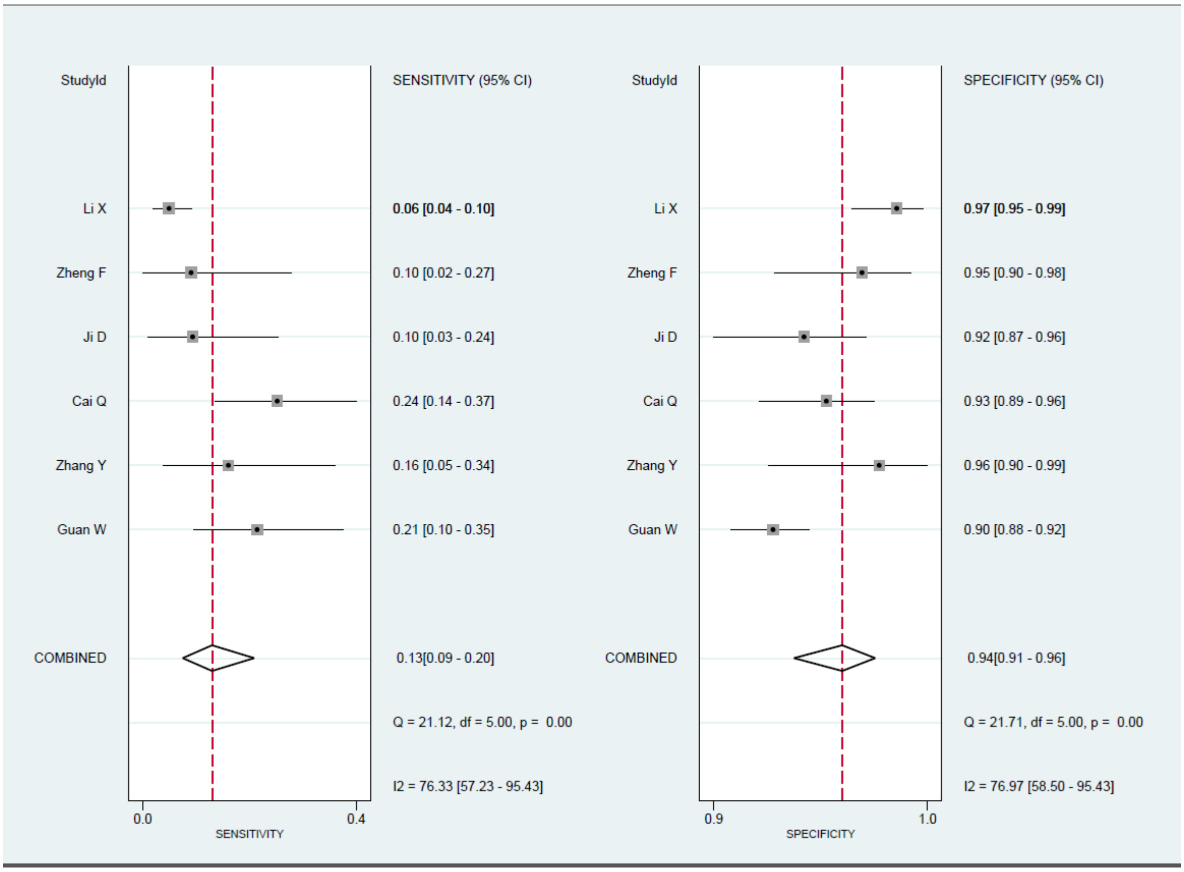


Fig. 4. Forest plots of the studies assessing total bilirubin. A. Odds ratio. B. Mean difference. C. Sensitivity and specificity.