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Impact of liver injury on the severity of COVID-19: Systematic Review with Meta-analysis

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ABSTRACT

Background and Aims

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

Methods

After a systematic review of the relevant studies, odds ratio, mean difference, sensitivity, specificity, and 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 the clinical utility. Heterogeneity was explored by sensitivity analysis and univariable meta-regression.

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Results

Twenty-six studies were included (22 studies and 5271 patients for AST, 20 studies and 5440 subjects for ALT, and 9 studies and 3542 patients for bilirubin). The outcomes of the studies were: survival (n=8), intensive care unit admission (n=4), and non-fatal severe complications (n=16). AST>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 78 %, 77 % and 94 % of specificity, 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 significantly higher risks of developing severe COVID-19 compared to those with normal liver function tests at admission. We should include the assessment of AST, ALT, and total bilirubin routinely in patients affected by SARS-CoV-2 in order to anticipate those at risk of developing COVID-19-related outcomes.

Keywords

COVID-19, SARS-CoV-2, coronavirus, liver, AST, ALT, bilirubin.

Abbreviations

AHT: Arterial hypertension; CI: Confidence interval; CRP: C-reactive protein; DM: Diabetes mellitus; ICU: Intensive care unit; LR: Likelihood ratio; OR: Odds ratio; TB: Total bilirubin; ULN: Upper limit of normal.

INTRODUCTION

The pandemic of SARS-CoV-2 as cause of COVID-19 comprises from asymptomatic forms to acute distress respiratory syndrome and systemic inflammatory response secondary to a cytokine storm(1). However, despite the fact that SARS-CoV-2 is primarily a respiratory virus, it has important and devastating systemic effects(2)(3)(4)(5)(6)(7)(8), determining 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 unspecific for this disease because they can be increased in many other conditions. Routine laboratory markers reflecting an organ failure (additionally to systemic inflammation) could help to improve the prediction of COVID-19 severity. In this setting, liver function tests have been found altered in these patients at baseline, primarily elevated AST and ALT, and slightly increased bilirubin(12). Thus, the liver has been proposed as a target of COVID-19 but also could play an additional role in expanding the hyperinflammatory and prothrombotic status. Besides, the impact of pre-existing liver disease on the prognosis of COVID-19 remains unknown, although some etiologies may negatively influence, such as NAFLD(13).

The identification of surrogate markers of severe COVID-19 is of great importance and could help clinicians to manage it quickly and accurately. Given the urgency required in the decision making of the COVID-19 outbreak, we aimed to put together all the available data and conduct a meta-analysis to explore how the liver injury markers impact on the COVID-19 management and prognosis. Particularly, the primary aim was to assess the impact of the baseline liver function (AST, ALT, and TB) on COVID-19-related outcomes, particularly on mortality, ICU admission, and non-fatal severe complications (use of mechanical ventilation, septic shock, kidney failure, myocardial injury). The secondary aims were to: a) measure, quantitatively, the mean difference of AST, ALT, and TB between patients with and without COVID-19 complications; b) calculate the sensitivity and specificity of AST > ULN, ALT > ULN, and TB > ULN at the time of the infection to use them as surrogate markers of the use of health care resources; c) 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 16 April 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 by using the appropriate Boolean logic. The 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 total bilirubin (TB) (at least, one of them); b) studies that assessed one of the following endpoints: COVID-19-related non-fatal severe complications, intensive care unit (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, total bilirubin, 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 (SaO2). When the same population was published in several journals, we retained only the most informative article or the most complete study, 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

We used STATA version 16 (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) of individual studies were determined from the available data.

The assumption of heterogeneity was tested for each planned analysis using the Cochran-Q heterogeneity and I2 statistics (significant heterogeneity according to I2 values >50 %)(16). The random-effects model was utilized in case of significant heterogeneity, and in the absence of it, the model of fixed effects was applied to pool results from studies. For the dichotomous variables (AST > ULN, ALT > ULN, TB > ULN, the effect denotes odds ratio (OR) and corresponding 95 % CIs, while we used the difference in means to specifically provide measures of the absolute difference between the mean values of the explored variables (AST U/L, ALT U/L, TB mg/dL). We identify COVID-19-related mortality, ICU admission, and severe complications as relevant outcomes. On the other hand, a bivariate regression was performed to estimate the overall sensitivity and specificity. Additionally, we calculated positive and negative likelihood ratios (LR) in order to generate Fagan nomograms. They were performed 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 of the virulence of SARS-CoV-2 (pretest probability of 20 % for hospitalization), which shows the relationship between the prior probability, the likelihood ratio, and the 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). Besides, potential heterogeneity was explored by univariable meta-regression and subgroup analyses(18).

The potential publication bias was assessed by 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 (Figure 1). Finally, twenty-six studies were included (twenty-two, twenty, and nine evaluating AST, ALT, and total bilirubin, respectively). All the studies included in the meta-analysis were from China, probably because the COVID-19 outbreak started in this country. The outcomes 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, 5271 patients were included in the group of studies on AST, 5440 subjects with an ALT assessment, and 3542 had a TB evaluation. The characteristics of the eligible studies are listed in Table 1. Seven of

the twenty-six 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 classified correctly 71.5 % (764/1069) of deaths, 73.8 % (739/1002) of ICU admission, and 65.1 % (1495/2297) of severe complications correctly. We found that baseline AST > ULN was associated with death (OR 3.82 (95 %CI 2.55-5.73)), the need for ICU admission (OR 2.98 (95 %CI 2.00-4.45)), and the 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, AST > ULN showed an overall OR 3.10 (95 %CI 2.61-3.68) for COVID-19-related outcomes, with a moderate heterogeneity (Q=33.77; I^2=46.7 %; p=0.01). (Figure 2a). Regarding the mean difference, we observed that AST values were higher in patients with adverse events (10.7 U/L (95 %CI 5.8-15.6)) (Figure 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+ 2.3 (95 %CI 1.8-2.9) and LR- 0.66 (95 %CI 0.60-0.73), for the use of any health care resource (Figure 2c).

Elevated or decreased ALT determined correctly the 65.6 % (852/1299) of the population who died, the 73.4 % (694/945) of those requiring ICU admission, 58.9 % (1261/2141) 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, the 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 2.15 (95 %CI 1.43-3.23) for COVID-19-related outcomes (Figure 3a). Besides, we found that ALT values were higher in patients with adverse events (8 U/L (95 %CI 1.0-15)) (Figure 3b). We found a high heterogeneity of 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+ 1.7 (95 %CI 1.3-2.3) and LR- 0.79 (95 %CI 0.69-0.92), for the use of health care resources (Figure 3c).

On the other hand, total bilirubin determined correctly the 73.8 % (1509/2046) 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)) (Figure 4a). Besides, we found that TB values were higher in patients with adverse events (0.3 mg/dL

(95 %CI 0.16-0.45)) (Figure 4b). We did not find a significant heterogeneity of 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+ 2.3 (95 %CI 1.6-3.4) and LR- 0.92 (95 %CI 0.87-0.97), for the use of any health care requirement (Figure 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, they were 17 % and 30 % for ALT > ULN, and 19 % and 37 % for TB > ULN.

Sensitivity analysis and univariable meta-regression

In order to explore the causes of heterogeneity, we performed a sensitivity analysis and a univariable meta-regression. Leaving out one study at a time from the meta-analysis, we did not find any individual study assessing AST, ALT or bilirubin that influenced the overall meta-analysis summary estimate.

The univariable meta-regression aimed to incorporate the effect of covarying factors on summary measures of AST, ALT, and total bilirubin. Lymphopenia was a possible source of heterogeneity of the combined studies on AST, while liver disease and albumin were for studies on ALT. By contrast, we did not find any variable causing heterogeneity in the studies assessing TB.

Publication bias

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

DISCUSSION

COVID-19 is characterized by a respiratory affectation that can result in death due to massive alveolar damage and progressive respiratory failure, achieving up to 25 % of mortality in patients admitted to 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 levels of ALT and AST, although a clinically significant liver injury was uncommon(22). Interestingly, patients with a severe infection have demonstrated to have higher rates of liver dysfunction(23). The following reasons can explain these findings: a) SARS-CoV2 could have a direct cytopathic effect on the liver because the virus bind to the ACE2 receptor, whose expression is enriched in cholangiocytes(24); b) immune-mediated damage due to the severe inflammatory response (e.g., cytokine storm)(25); c) hypoxic hepatitis, although the elevation of transaminases in COVID-19 is mild; d) a viral translocation to the portal system could not be excluded because the virus replicates actively on the enterocyte. 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 size are being published, we performed a meta-analysis including more than 5,000 patients from twenty-six 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 total bilirubin (ICU admission and non-fatal severe complications) increased the risk of poor COVID-19-related outcomes significantly when they were upper than the normal limit. However, we should not expect shocking alterations in the liver profile, because we observed that AST (11 U/L), ALT (8 U/L) and total bilirubin (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 the admission to anticipate the patients at risk of developing a poor prognosis.

The COVID-19 outbreak is collapsing many national health systems[27]. Thus, having prognostic factors of patients who could require ICU admission or develop severe complications (beyond mortality) is essential to manage the situation adequately. Few studies have been carried out to achieve this goal, being poorly reported, with a high risk of bias, and not including any parameter of liver disease(27). In our meta-analysis, the markers of liver injury were associated with COVID-19-related adverse outcomes (ranging from mortality to non-fatal severe complications). For instance, individuals with AST > ULN at baseline showed 40 % of post-test probability of suffering COVID-19 complications in the current scenario of virulence (prevalence 20 %). Besides, AST, ALT, and notably bilirubin showed high specificity (and reduced sensitivity) for COVID-19 outcomes, which means in clinical practice that patients with normal liver values have a low likelihood of poor prognosis. This approach

could result particularly relevant in areas like the Emergency Department, where many patients are attended and, sometimes, the decision of the hospitalization is not clear. The incorporation of the liver profile to other inflammatory markers, such as ferritin or D-dimer, could improve the decision-making process. Therefore, we believe that a panel of liver injury markers (including AST, ALT, and total bilirubin) must be routinely performed at baseline in patients suffering from an infection for SARS-CoV-2.

Our findings should be cautiously interpreted. First, all the studies included in this meta-analysis were from China that could limit the generalization of the results to other populations. However, no articles from Europe or America have been published evaluating the role of the liver dysfunction on the prognosis of COVID-19, 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 the 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, 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)(30)(31)(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 prediction of AST, ALT, or total bilirubin on the COVID-19 severity, probably modifying the cut-off of the upper limit of the normality. Finally, elevated levels of creatinine kinase or lactate dehydrogenase, together with transaminases elevation, 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 total bilirubin in our meta-analysis (and other studies demonstrating that albumin levels decrease(35)(36)) could represent, at least in part, the relevant role of the liver in the context of severe COVID-19.

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

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AUTHOR STATEMENT

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.

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Table 1. Characteristics of the included studies.

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	20	Chin	Single-	25	Survival	AST: Yes	2	10	3	10

Y(38)	20	a	center, retrospective, observational study			(N/A) ALT: No TB: No	N/A N/A	N/A N/A	N/A N/A	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	Multi-center, 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, observational study	118	Survival	AST: No ALT: Yes (40 U/L) TB: No	N/A 7 N/A	N/A 25 N/A	N/A 10 N/A	N/A 76 N/A
Zhang J(36)	2020	China	Single-center, retrospective, observational study	663	Survival	AST: Yes (N/A) ALT: Yes (N/A) TB: No	11 9 N/A	160 142 N/A	7 9 N/A	485 503 N/A
					COVID-19 complications	AST: Yes (N/A) ALT: Yes (N/A) TB: No	131 110 N/A	40 41 N/A	278 299 N/A	214 213 N/A
Guan W(42)	2020	China	Multi-center, retrospective, observational study	757	Survival / ICU Admission (composite endpoint)	AST: Yes (40 U/L) ALT: Yes (40 U/L) TB: Yes (1 mg/dL)	26 20 10	142 138 66	26 29 38	563 554 608
Huang C(43)	2020	China	Single-center, retrospective,	41	ICU Admission	AST: Yes (40 U/L) ALT: No TB: No	8 N/A N/A	7 N/A N/A	5 N/A N/A	21 N/A N/A

			observational study							
Zhang G(44)	2020	China	Single-center, retrospective, observational study	95	ICU Admission	AST: Yes (40 U/L) ALT: Yes (40 U/L) TB: No	19 21 N/A	26 31 N/A	6 4 N/A	44 39 N/A
Du R(45)	2020	China	Multi-center, retrospective, observational study	109	ICU Admission	AST: Yes (40 U/L) ALT: Yes (50 U/L) TB: No	25 10 N/A	25 8 N/A	26 41 N/A	33 50 N/A
Zhang Y(46)	2020	China	Single-center, retrospective, observational study	115	COVID-19 complications	AST: Yes (40 U/L) ALT: Yes (50 U/L) TB: Yes (1.2 mg/dL)	12 8 5	5 3 3	19 23 26	79 81 81
Wan S(47)	2020	China	Single-center, retrospective, observational study	135	COVID-19 complications	AST: Yes (40 U/L) ALT: No TB: No	15 N/A N/A	15 N/A N/A	25 N/A N/A	80 N/A N/A
Wang Z(48)	2020	China	Single-center, retrospective, observational study	69	COVID-19 complications	AST: Yes (40 U/L) ALT: Yes (35 U/L) TB: No	7 6 N/A	12 17 N/A	7 8 N/A	43 38 N/A
Shi H(49)	2020	China	Multi-center, retrospective, observational study	81	COVID-19 complications	AST: Yes (40 U/L) ALT: No TB: No	39 N/A N/A	4 N/A N/A	27 N/A N/A	11 N/A N/A
Cai Q(50)	2020	China	Single-center, retrospective, observat	298	COVID-19 complications	AST: Yes (N/A) ALT: Yes (N/A) TB: Yes	14 20 14	11 19 16	44 38 44	229 221 224

			ional study			(N/A)				
Ji D(13)	2020	China	Multi-center, retrospective, observational study	202	COVID-19 complications	AST: Yes (N/A) ALT: Yes (30 U/L) TB: Yes (N/A)	10 19 4	24 82 13	29 20 35	139 81 150
Zheng F(51)	2020	China	Single-center, retrospective, observational study	161	COVID-19 complications	AST: Yes (40 U/L) ALT: Yes (40 U/L) TB: Yes (1.2 mg/dL)	12 5 3	10 8 6	18 25 27	121 123 125
Li L(52)	2020	China	Single-center, retrospective, observational study	85	COVID-19 complications	AST: No ALT: Yes (N/A) TB: No	N/A 16 N/A	N/A 17 N/A	N/A 10 N/A	N/A 42 N/A
Li X(53)	2020	China	Single-center, retrospective, observational study	548	COVID-19 complications	AST: Yes (40 U/L) ALT: Yes (40 U/L) TB: Yes (1.2 mg/dL)	115 64 17	64 61 7	150 202 249	211 214 268
Author	**Year**	**Country**	**Study design**	**Patients**	**Outcome**	**Liver function assessment**	**Mean Endpoint**	**SD Endpoint**	**Mean Control**	**SD Control**
Yang X(37)	2020	China	Single-center, retrospective, observational study	52	Survival	AST: No ALT: No TB: Yes (mg/dL)	N/A N/A 1.14	N/A N/A 0.67	N/A N/A 0.77	N/A N/A 0.25
Ruan Q(54)	2020	China	Multi-center, retrospective, observational study	150	Survival	AST: No ALT: No TB: Yes (mg/dL)	N/A N/A 1.06	N/A N/A 0.63	N/A N/A 0.75	N/A N/A 0.40
Zhang Y(46)	2020	China	Single-center, retrospe	115	COVID-19 complica	AST: Yes (U(L) ALT: Yes	38.9 37.9 0.82	22.6 32.2 0.37	24.4 21.2 0.60	9.8 12.7 0.25

			ctive, observational study		tions	(U/L) Yes TB: Yes (mg/dL)				
Shi H(49)	2020	China	Multi-center, retrospective, observational study	81	COVID-19 complications	AST: Yes (U/L) ALT: Yes (U/L) TB: Yes (mg/dL)	43.2 49.7 0.75	18.5 31.5 0.24	30.2 30.8 0.54	8.7 8.9 0.04
Zhang X(55)	2020	China	Multi-center, retrospective, observational study	645	COVID-19 complications	AST: Yes (U/L) ALT: Yes (U/L) TB: Yes (mg/dL)	30.1 29.4 0.66	20.4 25.7 0.47	25.7 25.5 0.53	15.5 20 0.29
Cheng Y(56)	2020	China	Single-center, retrospective, observational study	701	COVID-19 complications	AST: Yes (U/L) ALT: Yes (U/L) TB: Yes (mg/dL)	47 32 1.23	33 29 0.33	41 36 0.64	43 40 0.41
Liu Y(57)	2020	China	Single-center, retrospective, observational study	245	COVID-19 complications	AST: Yes (U/L) ALT: Yes (U/L) TB: No	52.1 40.6 N/A	57.7 42.2 N/A	31.9 25.3 N/A	20.1 17.9 N/A
Meng H(58)	2020	China	Single-center, retrospective, observational study	58	COVID-19 complications	AST: Yes (U/L) ALT: Yes (U/L) TB: No	28.4 21.1 N/A	14.6 18.1 N/A	23.1 23.7 N/A	11 21.7 N/A
Zheng Y(59)	2020	China	Single-center, retrospective, observational study	69	COVID-19 complications	AST: Yes (U/L) ALT: Yes (U/L) TB: No	51.2 42.4 N/A	88.7 48.9 N/A	26.5 31.7 N/A	12.7 27.8 N/A

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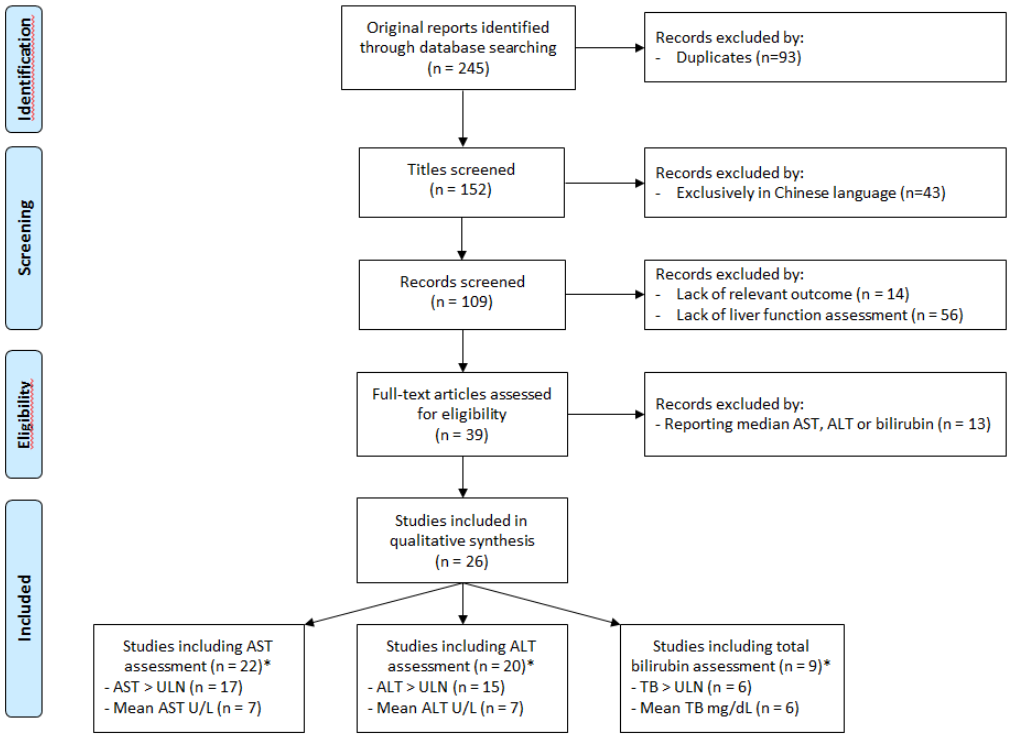

Figure 1. Flow-chart summarizing the selection of eligible studies. **** Individual studies, although some of them reported simultaneously dichotomous and continuous variables..***

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Figure 2a

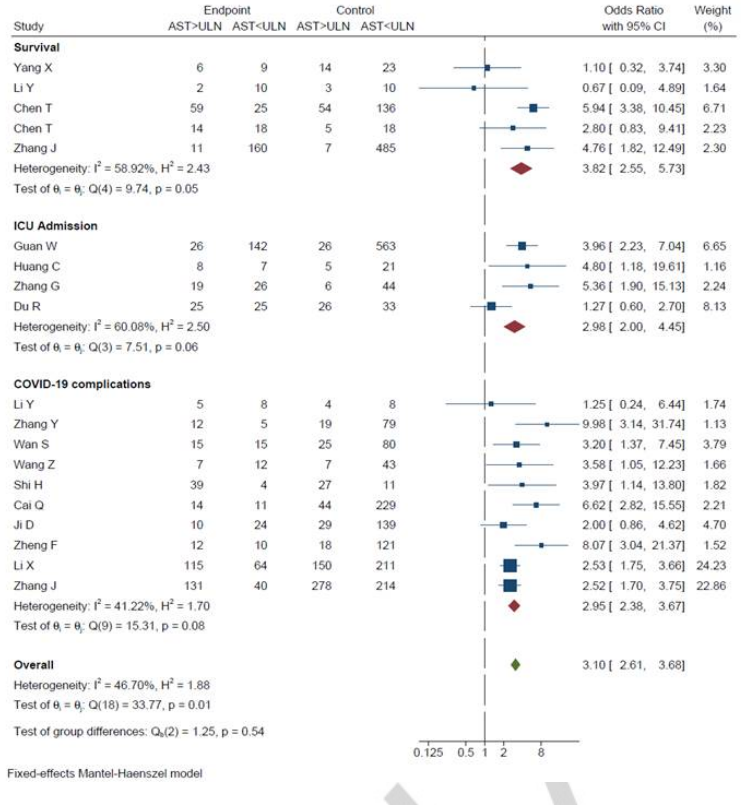

Figure 2b

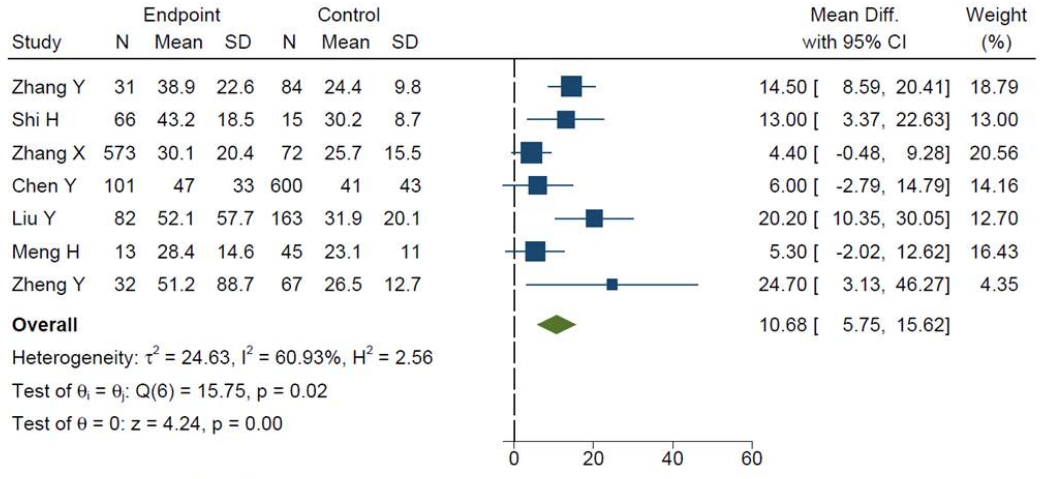

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Figure 2c

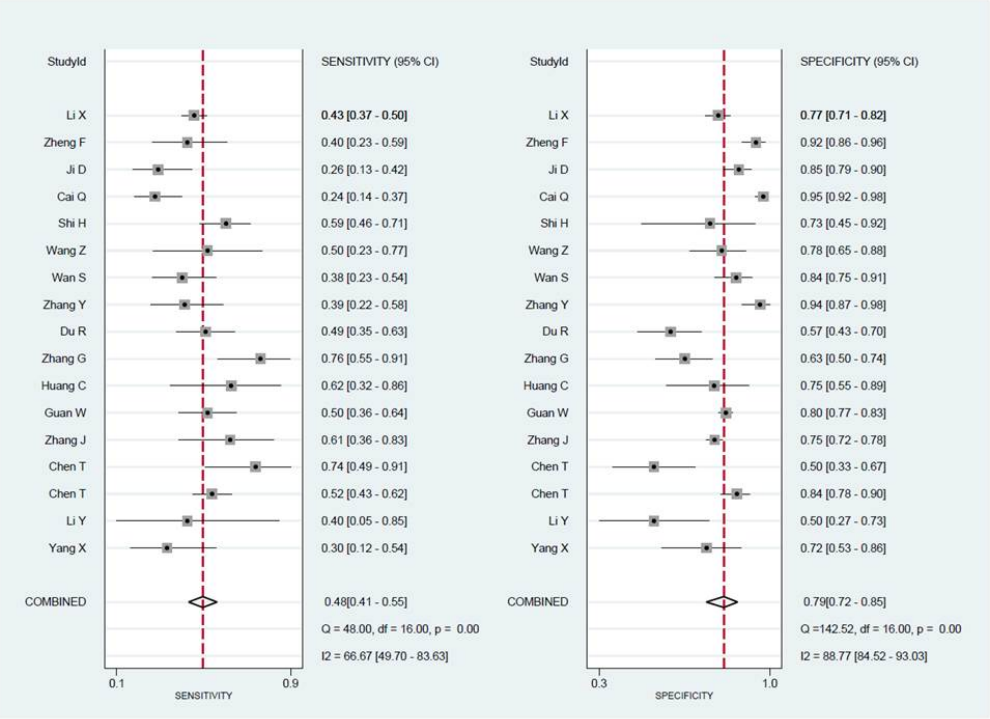

Figure 2. Forest plots of the studies assessing AST depending on the outcomes. A) Odds ratio. B) Mean difference. C) Sensitivity and Specificity.

Figure 3a

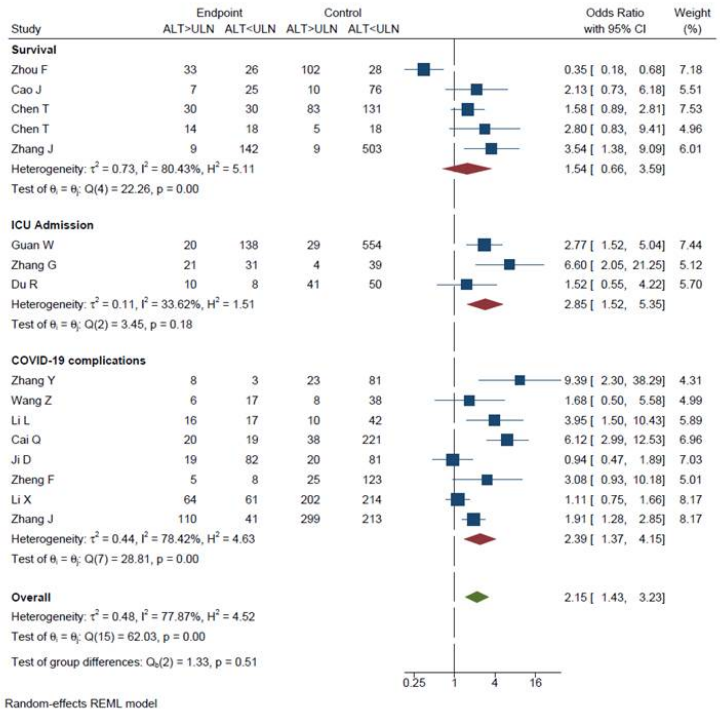

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Figure 3b

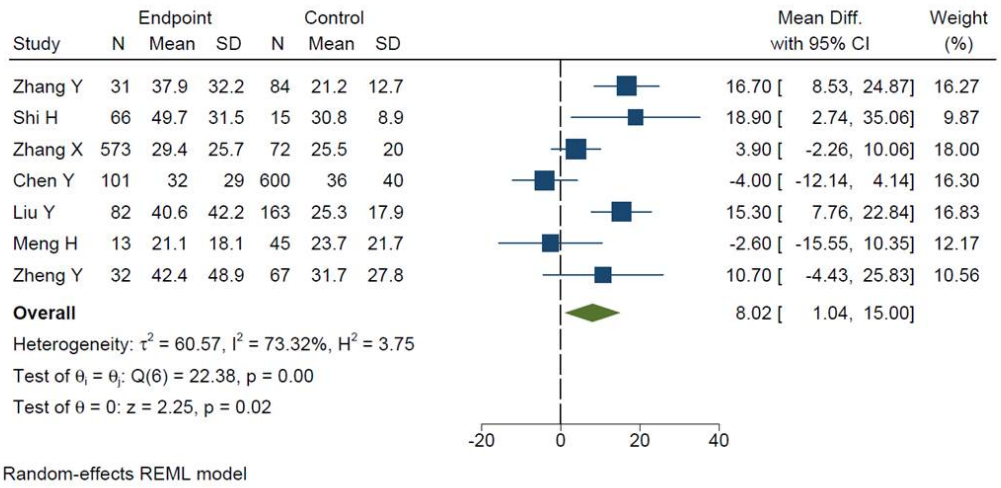

Figure 3c

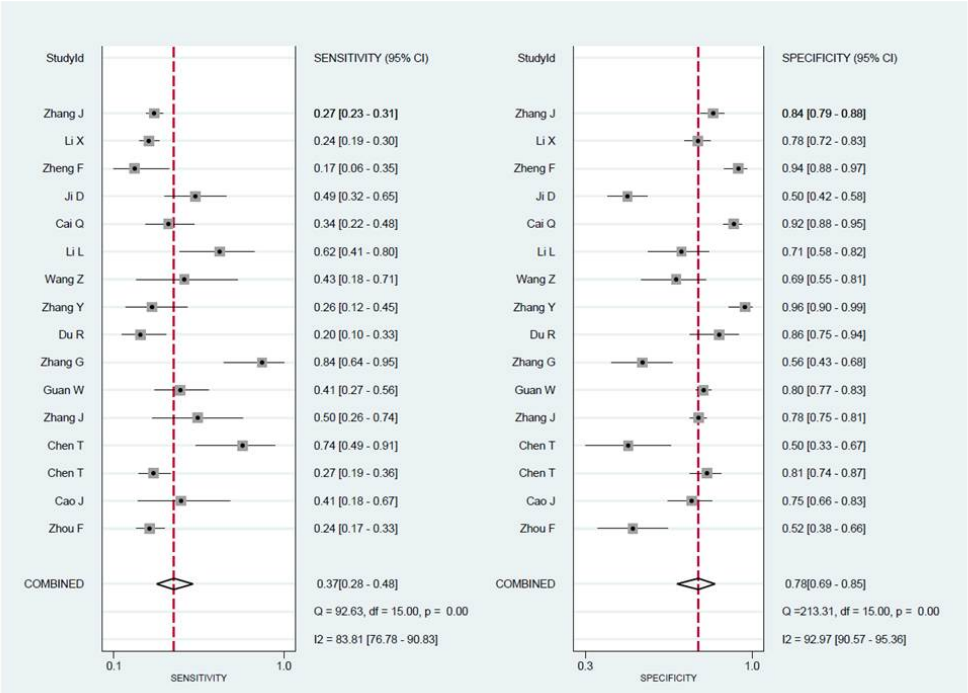

Figure 3. Forest plots of the studies assessing ALT depending on the outcomes. A) Odds ratio. B) Mean difference. C) Sensitivity and Specificity.

Figure 4a

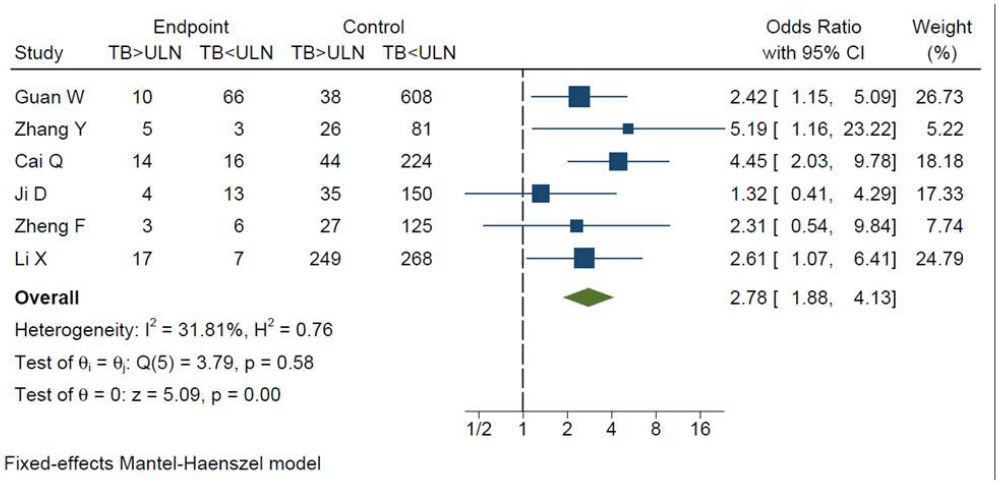

Figure 4b

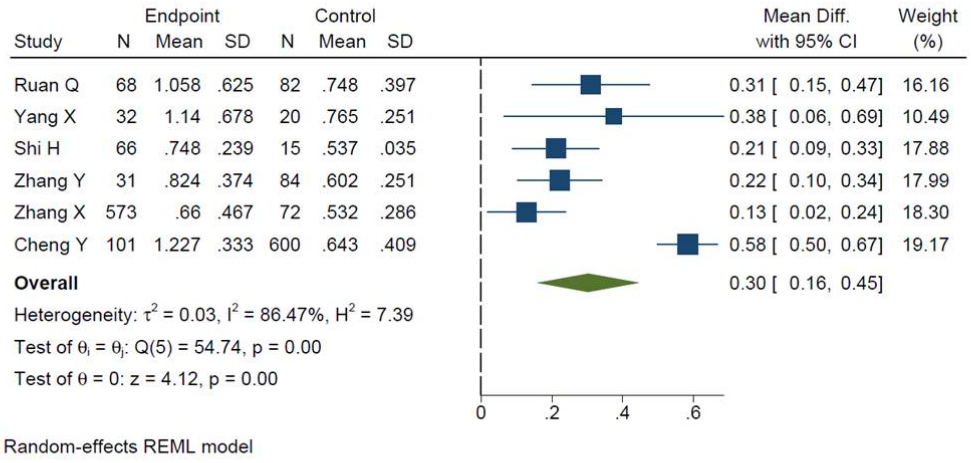

Figure 4.- Forest plots of the studies assessing total bilirubin. A) Odds ratio. B) Mean difference. C) Sensitivity and Specificity.