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A meta-regression study of the clinical significance of serum aminotransferases in COVID-19

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Abstract. – OBJECTIVE: The aim of the study was to appraise the capacity of serum aminotransferases to discriminate between hepatic and other extra-pulmonary COVID-19-related manifestations and, potentially, to serve as predictors of poor clinical outcomes.

MATERIALS AND METHODS: Ninety-eight studies were identified (79% from China), including 43,554 patients (57% males), 9,983 (62% males) with poor outcomes and 33,571 (50% males) with favorable outcomes. After splitting studies depending on whether serum alanine aminotransferase (ALT) concentrations were statistically different between patients with poor vs. favorable outcomes, the 35 'hepatic involvement' articles ($p<0.05$) included 28,510 patients (51% males), 5,279 (66% males) and 23,231 subjects (48% males) with poor and favorable outcomes, respectively. The 63 'extra-hepatic involvement' studies ($p>0.05$) included 15,044 patients (54% males), 4,704 (60% males) with poor outcomes and 10,340 (51% males) with favorable outcomes.

RESULTS: The meta-analysis shows that serum aspartate aminotransferase (AST) concentrations were significantly higher in patients with poor outcomes than those with favorable outcomes (WMD 12.5 UI/L, 95% CI 10.9 to 14.1 p<0.001). Similarly, AST concentrations were significantly higher in the 'hepatic involvement' *studies* (WMD 16.3 UI/L, 95% CI 13.4 to 19.2 $p<0.001$) and in the 'extra-hepatic involvement' studies (WMD 10.3 UI/L, 95% CI 8.6 to 12.0 $p<0.001$).

CONCLUSIONS: The different association of serum AST concentrations with some clinical, demographic, and biochemical factors in the two clusters suggests that in COVID-19 patients, serum AST elevation is not necessarily linked to real liver damage.

Key Words:
COVID-19, Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Myositis, Liver damage.

Introduction

The SARS-CoV-2-related disease (COVID-19) rapidly spread throughout the world and the World Health Organization declared COVID-19 a pandemic on March 11, 2020[1]. Clinical manifestations range from asymptomatic infection or mild flu-like symptoms to severe and often fatal respiratory disease[2], e.g., acute respiratory distress syndrome (ARDS)[3], and multi-organ failure[4,5]. Abnormal hepatic function, typically associated with raised concentrations of the aminotransferases alanine aminotransferase (ALT) and aspartate aminotransferase (AST), as well as several inflammatory markers, is one of the most common extra-pulmonary manifestations of COVID-19[6]. Notably, liver dysfunction has been observed in more than half of COVID-19 patients[6,7], with severity proportional to that of the infection[8]. Aminotransferase elevations on admission have been reported in 35-46% of COVID-19 patients[9], with an absolute 14-53% increase compared to reference values[10]. A derived parameter, the AST/ALT ratio, known as the De Ritis ratio, on admission has also been associated with in-hospital mortality, with a superior predictive capacity to that of ALT and AST alone[11]. However, other studies[12-14] have reported an association between mortality and AST, but not ALT, or no association between aminotransferases on

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admission and mortality, which questions the clinical significance of these alterations. On the other hand, an increase in serum AST and ALT may also occur in several extra-hepatobiliary disorders[13]. Despite being found mainly in the liver, in fact, aminotransferases are also present in red blood cells, cardiomyocytes, muscle tissue, and other organs, such as the pancreas and kidneys[15]. Whilst an increase in ALT shows a greater specificity for liver damage[16], an increase in AST may also be indicative of myocardial infarction, acute pancreatitis, acute hemolytic anemia, acute kidney injury, and musculoskeletal diseases[17]. Thus, with a view to gain further insight into the capacity of aminotransferases to discriminate between hepatic and other extra-pulmonary COVID-19-related manifestations and, potentially, serve as predictors of poor clinical outcomes, we first conducted a systematic review and meta-analysis to explore the association between serum AST concentrations and clinical outcomes in COVID-19 patients. Then, after grouping studies depending on whether serum ALT concentrations were statistically different between patients with poor *vs.* favorable outcomes, a univariate random-effects meta-regression was performed to assess the potential association of the variations in AST concentrations with plausible clinical, demographic, and biochemical factors.

Materials and Methods

Search Strategy, Eligibility Criteria and Study Selection

A systematic literature search in the electronic databases PubMed, Web of Science, Google Scholar, and Scopus was performed from inception until December 2020 to find peer-reviewed studies reporting serum concentrations of AST and ALT, biomarkers of inflammation, cardiac damage, renal damage, tissue damage, sepsis, and pro-thrombotic tendency, and specific clinical endpoints such as severity of disease, survival status, occurrence of ARDS, admission to intensive care unit (ICU) and disease progression, need for mechanical ventilation and intubation, occurrence of pneumonia, need for hospitalization, poor prognosis, imaging findings, refractoriness of the disease, and general poor outcomes in COVID-19 patients. Without region restrictions, the identification of the articles was accomplished using a combination of the following keywords: "ALT", "AST", "COVID-19", "alanine aminotransferase", "aspartate aminotransferase", "aminotransferase", "transaminase", and "SARS-Cov-2". Additional studies that met the inclusion criteria were manually searched for in the reference list of the retrieved articles. Selection criteria included: (i) reporting continuous data on AST and ALT concentrations in COVID-19 patients, (ii) reporting information on serum concentration of other biomarkers and specific clinical outcomes, (iii) adult, non-pregnant, patients, (iv) ≥10 patients, (v) full-text available, and (vi) English language. Two reviewers, with a third involved in case of disagreement, independently screened the titles and abstracts for potential articles. Then, full texts were evaluated based on eligibility criteria. Data extraction was performed by one reviewer and relevant information was recorded in a standardized spreadsheet. The study was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline[18].

Statistical Analysis

Reported means and SDs were used to compute the pooled weighted mean differences (WMD) and 95% confidence intervals (CIs) for continuous variables using a random-effects model to account for interstudy variability. When means and SDs were not reported, these were derived from sample sizes, medians, interquartile range (IQR), or range values[19]. Heterogeneity across studies was assessed using the Cochran's Q statistic, with a significance level set at a p-value <0.10. Heterogeneity was expressed in terms of inconsistency and assessed by the I^2 statistic, with I^2 values of <25% indicating no heterogeneity, and 25-50%, 50-75%, and >75% indicating, respectively, moderate, large, and extreme levels of heterogeneity[20,21]. To assess the influence of covariates on the WMD value, a univariate random-effects meta-regression was performed for age, gender, index of illness severity (serum albumin), biomarkers of inflammation (C-reactive protein, CRP, white blood cell count, WBC, neutrophils count, NEU, lymphocytes count, LYM), liver damage (ALT, total bilirubin, TB), cardiac damage (troponin), renal damage (serum creatinine, blood urea nitrogen, BUN), tissue damage and sepsis (lactate dehydrogenase, LDH, procalcitonin, PCT, creatine kinase, CK), and pro-thrombotic and clotting tendency (D-dimer, prothrombin time, PT). A subgroup analysis was conducted after stratification by the difference in serum ALT concentrations between patients

with poor *vs.* favorable outcomes. If the reported differences in ALT concentrations were statistically significant, the articles were categorized as 'hepatic involvement', otherwise as 'extra-hepatic involvement'.

Results

A total of 2,715 articles were initially identified (Figure 1). After screening for duplicate or irrelevant articles, 2,571 were removed. When reviewing the remaining 144 articles, 46 were considered ineligible, mainly because of insufficient information (N = 40) or limited number of patients (N = 6), leaving 98 studies[7,11,22-118] (79% from China, 63 in the 'extra-hepatic involvement' group[11,22-83] and 35 in the 'hepatic involvement' group[7,84-117]) for analysis. Reported clinical endpoints included measures of disease severity (N = 53), survival (N =23), admission to ICU (N = 10), disease progression (N = 2), need for mechanical ventilation (N = 2), need for intubation (N = 1), presence of ARDS (N = 1), occurrence of pneumonia (N = 1), need for hospitalization (N = 1), poor prognosis (N = 2), normal imaging findings (N = 1), and refractoriness of the disease (N = 1). Overall, the identified 98 articles included 43,554 patients (57% males), 9,983 (62% males) with poor outcomes and 33,571 (50% males) with favorable outcomes. The 35 'hepatic involvement' articles included 28,510 patients (51% males), 5,279 (66% males) and 23,231 subjects (48% males) with poor and favorable outcomes, respectively. The 63 'extra-hepatic involvement' studies included 15,044 patients (54% males), 4,704 (60% males) with poor outcomes and 10,340 (51% males) with favorable outcomes. In the whole cohort, meta-analysis shows that AST concentrations were significantly higher in patients with poor outcomes than those with favorable outcomes (WMD 12.5 UI/L, 95% CI 10.9 to 14.1 $p<0.001$). Similarly, AST concentrations were significantly higher in patients with poor outcomes both in the 'hepatic involvement' studies (WMD 16.3 UI/L, 95% CI 13.4 to 19.2 $p<0.001$) and in the 'extra-hepatic involvement' studies (WMD 10.3 UI/L, 95% CI 8.6 to 12.0 $p<0.001$), with the former having significantly higher WMD values (t=2.83, $p=0.006$). Heterogeneity was extreme in the whole group ($I^2=88\%$, $p<0.001$) as well as the 'hepatic involvement' ($I^2=92\%$, $p<0.001$) and the 'extra-hepatic involvement' groups ($I^2=77\%$, $p<0.001$). In univariate meta-regression analysis, the pooled AST WMD in the whole group was significantly and positively associated with WBC (t=3.98, $p<0.001$), NEU (t=5.29, $p<0.001$), ALT (t=4.73, $p<0.001$), TB (t=2.49, $p=0.016$), LDH (t=5.77, $p<0.001$), CK (t=2.34, $p<0.026$), troponin (t=3.99, $p<0.001$), D-dimer (t=2.68, $p<0.009$), serum creatinine (t=2.77, $p<0.007$), and BUN (t=5.75, $p<0.001$). The association was significantly and negatively associated with LYM (t=-2.60, $p=0.011$) and albumin (t=-2.91, $p=0.005$). By contrast, no significant associations were observed between the pooled AST WMD and age (t=-1.24, $p=0.23$), gender (t=1.36, $p=0.18$), PCT (t=1.59, $p=0.12$), PT (t=2.27, $p=0.03$), or CRP (t=1.03, $p=0.31$). As shown in Table I, the pooled AST WMD in the 'hepatic involvement' group was significantly and positively associated with ALT (t=3.20, $p=0.03$), TB (t=2.20, $p=0.04$), NEU (t=2.37, $p=0.03$), PCT (t=2.36, $p=0.046$), LDH (t=2.65, $p=0.01$), serum creatinine (t=2.64, $p=0.015$), and BUN (t=3.46,

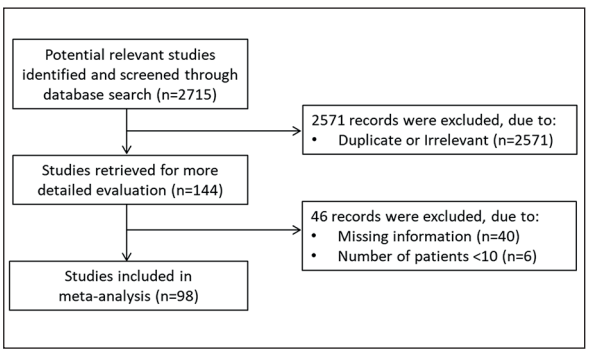

Figure 1. Flow chart of study selection.

Table I. Output of meta-regression analysis in studies included in the 'hepatic involvement' group.

	N	t	p
Age	33	-0.84	0.41
Gender	32	1.20	0.24
ALT	34	3.20	0.003
TB	20	2.20	0.04
WBC	24	2.07	0.051
NEU	24	2.37	0.03
LYM	27	-0.23	0.822
PCT	10	2.36	0.046
CRP	26	0.05	0.96
Albumin	26	-0.46	0.65
LDH	24	2.65	0.01
CK	14	0.44	0.67
Troponin	6	2.19	0.09
D-Dimer	23	0.95	0.35
PT	15	0.29	0.78
Creatinine	24	2.64	0.015
BUN	17	3.46	0.004

p=0.004). By contrast, no significant associations were observed with age (t=-0.84, p=0.41), gender (t=1.20, p=0.41), WBC (t=2.07, p=0.051), LYM (t=-0.23, p=0.82), CRP (t=0.05, p=0.96), albumin (t=-0.46, p=0.65), CK (t=0.44, p=0.67), troponin (t=2.19, p=0.09), PT (t=0.29, p=0.78), or D-dimer (t=0.95, p=0.35). As shown in Table II, the AST WMD in the 'extra-hepatic involvement' group was significantly and positively associated with WBC (t=3.03, p=0.004), NEU (t=4.33, p<0.001), PCT (t=2.95, p=0.006), CRP (t=2.13, p=0.04), LDH (t=5.87, p<0.001), CK (t=3.45, p<0.003), PT (t=2.27, p=0.03), D-dimer (t=3.26, p=0.002), BUN (t=5.50, p<0.001). The association was significantly and negatively associated with LYM (t=-3.07, p=0.003) and albumin (t=-3.52, p=0.001). Conversely, no significant associations were observed with age (t=-1.02, p=0.31), gender (t=-0.41, p=0.68), ALT (t=1.82, p=0.07), TB (t=1.32, p=0.2), troponin (t=1.79, p=0.09), or serum creatinine (t=1.26, p=0.22).

Discussion

Alterations in serum aminotransferases on admission are common in COVID-19 patients and antedate specific therapies. However, it is unclear whether their elevations result primarily from liver damage or, rather, extra-hepatic involvement. We sought to address this issue by conducting a systematic review and meta-analysis with meta-regression of studies reporting ALT, relatively liver-specific, and AST, relatively liver-nonspecific, concentrations in COVID-19 patients. Serum concentrations of AST, measured within 24-48 h from admission in virtually all studies, were significantly higher in patients with poor outcomes (WMD 12.5 UI/L, 95% CI 10.9-14.1, p<0.001). Although this group mainly included males (62%), and poor outcomes are more prevalent in men[117], meta-regression did not show any significant association between the pooled AST WMD and gender (t=1.36, p=0.18). Similarly, no association was observed with age (t=-1.24, p=0.22), although a correlation between disease severity and advanced age has been reported[117]. The extreme heterogeneity observed (I^2=88.1, p<0.001) might be related, at least partly, to the relatively wide range of clinical endpoints considered. On the other hand, it could also reveal the existence of different conditions, in addition to liver damage, underlying the increase of serum AST concentrations in COVID-19 patients. In support of this proposition, meta-regression analysis showed that the pooled AST WMD was associated with non-specific biomarkers of inflammation (WBC, NEU, and LYM) as well as liver damage (ALT, TB), cardiac damage (troponin), renal damage (serum creatinine, BUN), systemic tissue damage and sepsis (LDH, CK), and pro-thrombotic tendency (D-dimer). To investigate the possible influence of hepatic and extra-hepatic factors in serum AST elevations, articles were categorized according to serum ALT concentrations (Figure 2). Meta-analysis showed that 'hepatic involvement' studies, i.e., where serum ALT concentrations in patients with poor outcomes were significantly higher than those with favorable outcomes, AST concentrations were also higher in the former (WMD 16.3 UI/L, 95% CI 13.4 to 19.2 p<0.001). Furthermore, serum AST concen-

Table II. Output of meta-regression analysis in studies included in the 'non-hepatic involvement' group.

	N	t	p
Age	59	-1.02	0.31
Gender	59	-0.41	0.68
ALT	63	1.82	0.07
TB	30	1.32	0.2
WBC	57	3.03	0.004
NEU	45	4.33	< 0.001
LYM	52	-3.07	0.003
PCT	32	2.95	0.006
CRP	52	2.13	0.04
Albumin	45	-3.52	0.001
LDH	38	5.87	< 0.001
CK	19	3.45	0.003
Troponin	17	1.79	0.09
D-Dimer	40	3.26	0.002
PT	29	2.27	0.03
Creatinine	51	1.26	0.22
BUN	33	5.50	< 0.001

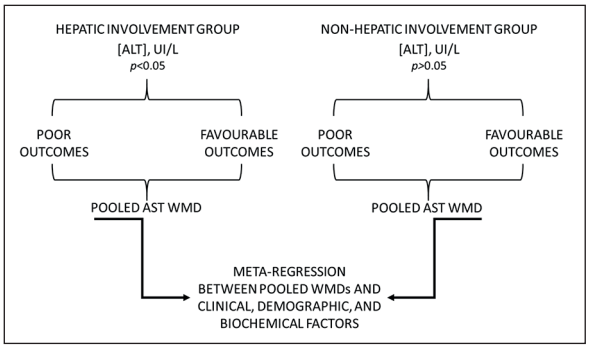

Figure 2. Criteria for grouping of studies for subgroup analysis.

trations were higher, albeit less so than what reported in the 'hepatic involvement' studies, in patients with poor outcomes in the 'extra-hepatic involvement' studies (WMD 10.3 UI/L, 95% CI 8.6 to 12.0 $p<0.001$), i.e., where no significant difference in serum ALT concentrations was present between patients with poor vs. favorable outcomes. This suggests that AST can discriminate between COVID-19 patients with different outcomes irrespective of the specific source(s) responsible for its elevation. The significant and negative association between the AST WMD and a general index of illness severity such as albumin (t=-2.91, $p=0.005$) would strengthen this interpretation. In the 'hepatic involvement' study subgroup, meta-regression analysis showed a significant and positive association between the AST WMD and ALT (t=3.20, $p=0.003$) and TB (t=2.20, $p=0.04$), thus supporting the notion of a primary liver involvement in such cluster. Moreover, the association between the AST WMD and LDH (t=2.65, $p=0.01$), a general marker of tissue and cellular damage, would provide additional evidence in favour of a viral cytopathogenic effect as a determinant of AST elevation. In addition, considering that immune dysregulation and coagulopathy often occur in advanced liver disease, the lack of association between the AST WMD and WBC (t=2.07, $p=0.051$), LYM (t=-0.23, $p=0.82$), PT (t=0.29, $p=0.78$), and D-dimer (t=0.95, $p=0.35$) would rule out pre-existing chronic liver disease as a contributor of serum AST elevations. Although COVID-19 patients with abnormal liver function often have concomitant alterations in inflammatory indexes and biomarkers of sepsis, e.g., CRP and PCT, in our meta-regression analysis only a weak association with PCT (t=2.36, $p=0.046$) was observed. However, the significant association between the AST WMD and NEU (t=2.37, $p=0.03$) still supports a link with sepsis and inflammation. Furthermore, considering that NEU are bacteria-responsive immune cells, it could also suggest a mediating role for superimposed infections. Depending on the specific liver enzymes involved and the magnitude of their elevation, liver disease in COVID-19 patients may be classified in parenchymal, cholestatic, and their combination[7]. This within-disease variability along with the wide range of endpoints analyzed, might explain the extreme heterogeneity observed among studies ($I^2=92.2\%$, $p<0.001$). On the other hand, conditions involving other organs might add further variability. While our meta-regression showed no associations between the AST WMD and markers of skeletal muscle breakdown or myocardial injury such as CK (t=0.44, $p=0.67$) and troponin (t=2.19, $p=0.09$), there was a significant and positive association with markers of renal disease such as creatinine (t=1.26, $p=0.015$) and BUN (t=3.46, $p=0.004$), suggesting that kidney disease might contribute to serum AST elevations in severe patients in this group. As expected, in the 'extra-hepatic involvement' study group, meta-regression analysis showed that the AST WMD was not significantly associated with either ALT (t=1.82, $p=0.07$) or TB (t=1.2, $p=0.2$), ruling out primary hepatic causes as determinant of serum AST elevation in severe patients in this cluster. Furthermore, unlike the 'hepatic involvement' study group, the association between the AST WMD with biomarkers of inflammation and sepsis such as CRP (t=2.13, $p=0.04$), PCT (t=2.95, $p=0.006$), and NEU (t=4.33, $p<0.001$) was significantly stronger. The association between the AST WMD and systemic inflammation is further supported by the significant and negative relation with LYM (t=-3.07, $p=0.003$). These associations were consistent with previous reports showing that a high neutrophil-to-lymphocyte ratio in COVID-19 patients is highly suggestive and predictive of clinical deterioration[51,118]. Inflammatory-based thromboembolic manifestations such as pulmonary embolism and disseminated intravascular coagulation (DIC), with elevation of D-dimer and prolongation of PT, are frequently detected in severe COVID-19 patients[119]. The significant relationship between the AST WMD and D-dimer (t=3.26, $p=0.002$) and PT (t=2.27, $p=0.03$) further support the link between systemic inflammation and COVID-19-associated coagulopathy. As in the 'hepatic involvement' study group, the presence of tissue/cell damage was signalled by the strong association between the AST WMD and LDH (t=5.87, $p<0.001$). This cytoplasmatic enzyme is not only recognized as an important prognostic biomarker of lung injury but can also reflect damage of other tissues, such as skeletal or cardiac muscle, kidney, and liver[120]. However, the lack of significant associations between the AST WMD and troponin (t=1.79, $p=0.09$), creatinine (t=1.26, $p=0.22$), TB (t=1.32, $p=0.2$), and ALT (t=1.82, $p=0.07$), suggests that these tissues do not significantly contribute to AST elevations in severe patients in the 'extra-hepatic involvement' study group.

Conversely, the significant positive relationship observed with CK (t=3.45, p=0.003) indicates a possible involvement of skeletal muscle, which is further supported by evidence of myositis in COVID-19 patients, similar to that documented in severe influenza[121]. The significant positive association between the AST WMD and BUN (t=5.50, p<0.001) further support this hypothesis as skeletal muscle wasting is accompanied by increased BUN production[122]. Interestingly, the increased levels of serum neutrophil extracellular traps (NETs) detectable in hospitalized COVID-19 patients and the evidence that their sera are potent stimulators of NETosis when added to neutrophils support a pro-NETotic effect of COVID-19[123]. Thus, the strong relationship between AST WMD and neutrophilia suggests that NETs may drive the muscle and extra muscular organ inflammation in this group.

The main limitation of this study is related to the relatively high representation of a single country, China, in the selected studies. On the other hand, the high number of articles included in the analysis, as well as the statistical approach used to summarize data, provide a robust estimate of the observed between-group differences in aminotransferases.

Conclusions

We observed that serum AST elevation in COVID-19 patients is significantly associated with poor outcomes. This association is retained after grouping the studies depending on whether serum ALT concentrations were statistically different between patients with poor *vs.* favorable outcomes. The association of AST elevation with ALT, TB, NEU, PCT, LDH, creatinine, and BUN in the group where ALT concentrations were significantly higher in patients with poor *vs.* favorable outcomes ('hepatic involvement' group), supports both the liver and kidney involvement as sources of AST in this cluster. The lack of association of AST with ALT and TB along with the relationship with WBC, NEU, LYM, PCT, CRP, albumin, LDH, CK, D-dimer, PT, and BUN in the group where ALT concentrations were not significantly higher in patients with poor vs. favorable outcomes ('non-hepatic involvement' group), suggests that skeletal muscle breakdown might be an important extra-hepatic cause of AST elevation in this group. Thus, serum AST elevation in COVID-19 patients does not necessarily indicate the presence of liver damage and may be useful to identify both extra-hepatic organ and tissue damage and co-existing hepatic and extra-hepatic involvement.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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