Laboratory tests and outcome for patients with COVID-19: A systematic review and meta-analysis

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List of abbreviations:

ALT: alanine aminotransferase

AST: aspartate aminotransferase

CRP: C-reactive protein

COVID-19: severe acute respiratory syndrome coronavirus 2

ICU: intensive care unit

LDH: lactate dehydrogenase

MD: mean differences

PCT: procalcitonin

QUADAS-2: Quality Assessment of Diagnostic Accuracy Studies-2

SD: standard deviation

SMD: standardised mean differences

WBC: white blood cell

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Abstract

Background: Severe acute respiratory syndrome coronavirus 2 (COVID-19) poses substantial challenges for health care systems. With a vastly expanding amount of publications on COVID-19, clinicians need evidence synthesis to produce guidance for handling patients with COVID-19. In this systematic review and meta-analysis, we examine which routine laboratory tests are associated with severe COVID-19 disease.

Content: PubMed (Medline), Scopus, and Web of Science were searched until the 22nd of March 2020 for studies on COVID-19. Eligible studies were original articles reporting on laboratory tests and outcome of patients with COVID-19. Data were synthesised and we conducted random effects meta-analysis and estimated mean difference (MD) and standard mean difference at biomarker level for disease severity. Risk of bias and applicability concern was evaluated using the Quality Assessment of Diagnostic Accuracy Studies -2.

Summary: 45 studies were included, of which 21 publications were used for the meta-analysis. Studies were heterogeneous, but had low risk of bias and applicability concern in terms of patient selection and reference standard. Severe disease was associated with higher white blood cell count (MD 1.28 x10^9/L), neutrophil count (MD 1.49 x10^9/L), C-reactive protein (MD 49.2 mg/L), lactate dehydrogenase (MD 196 U/L), D-dimer (SMD 0.58), and aspartate aminotransferase (MD 8.5 U/L), all $p< 0.001$. Furthermore, low lymphocyte count (MD -0.32 x10^9/L), platelet count (MD -22.4 x10^9/L), and haemoglobin (MD -4.1 g/L), all $p < 0.001$, were also associated with severe disease. In conclusion, several routine laboratory tests are associated with disease severity in COVID-19.

Systematic review registration PROSPERO CRD42020176387

Impact statement: This study will benefit patients with COVID-19, as it reports on routine laboratory analysis evaluated at admission that are associated with disease severity. The study thus combines data on laboratory results and disease severity from multiple studies on the topic, raising the evidence level. We are able to provide estimates of the difference observed in specific laboratory analysis between patients with mild and severe COVID-19. The manuscript therefore contributes to an enhanced understanding of the use of laboratory analysis in the evaluation of patients with COVID-19.

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes coronavirus disease 2019 (COVID-19), which was declared a global pandemic by the World Health Organization (WHO) on the 11th of March 2020. As the number of infected cases and death tolls rise, health care systems around the world are facing a monumental challenge. COVID-19 affects the respiratory tract, but the course of the ensuing disease is highly individual, ranging from asymptomatic to severe or fatal disease (1). Laboratory data are eminent in the handling of viral infections and, including viral pneumonia (2, 3). Biomarkers are thus relevant for clinical decision-making. COVID-19 is, however, a novel disease, and even though an overview has addressed this topic (4), the amount of studies on COVID-19 soars, and the evidence is quickly expanding. Given the developing situation with coronavirus, clinicians urgently need evidence synthesis to produce guidance for handling patients with COVID-19. In this systematic review and meta-analysis, we investigate which laboratory tests are associated with severe disease in COVID-19 infection.

Methods

The review is registered at PROSPERO, (registration number CRD42020176387). A search was performed on PubMed (Medline), Scopus, and Web of Science on the 22nd of March 2020. The search criteria were "COVID-19" OR "2019 novel coronavirus" OR "SARS-CoV2" published after November 2019. There were no language limitations. We included all studies about patients admitted to hospital with COVID-19 infections. Studies on outpatients were thus not included. Two reviewers screened titles and abstracts independently using the Review Manager Covidence (www.covidence.org). A third reviewer resolved disagreements. All investigators screened full text publications and a minimum of two investigators screened each study. If disagreement persisted, a third investigator screened the study and the decision was reached by a majority vote. We excluded reviews, editorials, viewpoints, articles on prevention and surveillance, case reports containing less than three patients, studies where patients were not hospitalized or hospitalized due to other conditions than COVID-19, and studies with no full text available or if only the abstract was written in English. Further, we excluded studies that did not report any laboratory results, if the COVID-19 diagnosis was not confirmed with real time-polymerase chain reaction (RT-PCR), and if studies did not report on patient outcome. We reviewed the reference list of each article for identifying other potential eligible documents.

Data extraction

Two independent reviewers collected and evaluated data regarding patient demographics, laboratory data, and patient outcome (see supplementary table 1 for data extracted). A third reviewer solved disagreements. For studies reporting data for severe disease and non-severe disease, we extracted data of sample sizes, mean values and standard deviations (SD) of the biomarkers. We made an a priori list of routine laboratory tests: white blood cell count (WBC), neutrophil count, lymphocyte count, platelet count, haemoglobin, C-reactive protein (CRP), procalcitonin (PCT), aspartate

aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), and creatinine. All laboratory tests reported as frequently as the analyses on the a priori list were also included in the meta-analysis. For the qualitative synthesis, we extracted information about laboratory variables, clinical characteristics, and study design. Clinical outcomes of interest was disease severity and, for the meta-analysis, studies reporting on groups based on disease severity. Disease severity as defined in the publications was used. In the qualitative synthesis, outcome was disease severity, which comprised of one or more of the following: intensive care treatment, mechanical intervention, or death.

Quality assessment

All studies meeting the eligibility criteria were assessed for their methodological quality using the QUADAS-2 tool (5). Quality assessment was based on patient selection, reporting of laboratory tests, method of defining and applying outcome, and timing of laboratory tests (Supplementary text 1). Two investigators conducted the quality assessment independently. Disagreements were discussed and persisting disagreements settled by a third investigator. Each study was given a score, which was used in the sensitivity analysis of the meta-analysis. The score ranged from 0 - 14, where 14 was considered excellent.

Statistical analysis and meta-analysis

For the meta-analysis, the statistical analysis was performed with RevMan 5.3.5 software (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) and GrahPad Prism 7.0 (GraphPad Software, San Diego, CA, USA). We included all studies meeting the criteria, which reported data for calculation of mean differences (MDs) between groups based on severity of disease, if possible to adjust to same scale. Otherwise, standardised mean differences (SMDs) were determined. For all estimates, 95% confidence intervals (95% CIs) were determined. Graphically, we

displayed data using forest plots. Heterogeneity was identified using I^2. The I^2 in meta-analysis describes the percentage of variation across the included studies which is caused by heterogeneity rather than chance. Thus significant heterogeneity was defined I^2<50% (6). A Mantel-Haenszel method was used as random effect method.

We generated funnel plots to assess potential publication bias, and compared results from a fixed-effects meta-analysis against those from a random-effects meta-analysis. Sensitivity analyses were performed by 1) removing each trial in turn from a meta-analysis to establish the extent to which they contributed to heterogeneity and to the overall result; 2) by exclusion of studies with paediatric populations and 3) by exclusion of studies with a score on ≤5 in QUADAS-2.

Results

The search identified 1,699 studies; after removing duplicates, 1,382 title and abstracts were screened, and 250 full-text articles were assessed for eligibility. Screening and full-text assessment was based on the pre-defined exclusion criteria. Of the 250 studies, we included 45 studies (7-42), of which 21 (7-24) were eligible for meta-analysis (Figure 1). Out of the 45 studies, one was conducted in the USA (25), two in Singapore (7, 23); the remainder were from China (Supplementary Table 1). Studies comprised mainly cohort studies, but nine were either case series (11, 25, 32, 33), case-control studies (10, 22, 42), or intervention studies (27). The average sample size was 104, ranging from 4 to 1099 participants. Out of 4,438 patients in total, 208 were children (< 18 years). The age of participants ranged from 1 day to 95 years, with 19 studies including only adults (≥ 18 years) and seven studies including solely children (< 18 years). The percentage of male patients varied from 33% to 85%. Reporting of co-morbidities differed, and was either not disclosed or unclear in 11 studies. In the remainder, the percentage of patients with co-morbidities ranged from 0 - 86%. Radiological

abnormalities were observed in 33 - 100% of patients, but unclear or undisclosed in 14 studies (Supplementary Table 1).

Disease severity was reported as outcome in 20/45 studies, of which one had calculated odds ratios for severe disease (30). Two studies reported data that enabled establishment of groups based on severity and calculation of mean and SDs for laboratory variables. Definitions of disease severity varied between studies. Overall, 298 deaths were reported, which corresponds to 6.7% of the patients described, and 18 of the 45 studies reported on mortality (9-11, 16-22, 25, 27, 30, 31, 35, 37, 42). The mortality rate in children was 0.4% (1 child) (37). However, 30 studies ended follow-up whilst a varying part of patients (7-94%) were still admitted to hospital (Supplementary Table 1), which means that the overall mortality of the admitted patients with COVID-19 may have been higher.

Data synthesis

Details on all included studies are displayed in Supplementary table 1.

Meta-analysis

Biomarkers included in the meta-analysis were lymphocyte count (n = 18 studies), WBC (n = 17), platelet count (n = 14), neutrophil count (n = 12), LDH (n = 12), ALT (n = 12), creatinine (n = 12), CRP (n = 11), AST (n = 11), D-dimer (n = 11), PCT (n = 10), prothrombin time (n = 9), and haemoglobin (n = 9). For D-dimer, the units did not enable conversion for direct comparisons and SMDs were used for reporting. The effect size estimates were not significantly altered when changing from random effects to fixed effect estimates. Exclusion of single studies did not affect the effect size estimates significantly either. Estimates were unaffected by exclusion of the study from Sun et al. (13) comprising a paediatric population and by exclusion of studies that scored low in the QUADAS-

2 assessment (Supplementary Text 1 and Supplementary Table 3). Significant heterogeneity was observed for most studies for all parameters, which is illustrated in the forest plots (Supplementary Figure 1). Publication bias was present for some biomarkers, as indicated through asymmetrical funnel plots (Supplementary Figure 2). Removal of studies that fell outside of the funnel plot did not alter findings.

Association between laboratory variables and clinical outcome

WBC was higher in patients with severe disease by 1.28 x10^9/L (MD, 95% CI 0.37 - 2.20, p <0,0001, I^2 = 92%) (Figure 2 and Supplementary Figure 1). When addressing studies from the qualitative synthesis, Chen et al (30) reported that univariate odds ratio (OR) was 1.28 (95% CI 1.08-1.52, p = 0.004) for ICU (intensive care unit) admission per 1 x 10^9/L increase in WBC. Thirty-nine studies evaluated WBC. Whilst 18 studies found subsets of patients with high WBC, low WBC was also present, and 17 studies found WBC < 3.5-4 x10^9/L in 9-54% of patients (7, 9, 11, 13, 15, 18, 19, 24, 27, 31-33, 35, 39, 41, 42).

A lower lymphocyte count was of -0.32 x10^9/L (MD, 95% CI -0.42 - 0.21, p < 0.0001, I^2 = 77%) was associated with severe disease. Congruently, Chen et al (30) reported that for lymphocytes univariate OR was 0.24 x 10^9/L (95% CI 0.08-0.75, p = 0.01) for ICU admission. Lymphocyte count was determined in 37 studies. In all studies where the lymphocyte count was compared with reference intervals (n = 27), a subset of lymphopenic patients were found.

In severe cases, neutrophil count was 1.49 x10^9/L higher (MD, 95% CI 0.64 – 2.35, p < 0.0001, I^2 = 85 %) than in non-severe cases. There was large variation among studies. Eleven studies reported

high neutrophil count in more than 25% of the patients, albeit with varying cut-offs (≥5.8 to >7.5 $x10^9$/L) (11, 13, 21, 26, 28, 31-33, 39-41).

Lower platelet count -22.4 $x10^9$/L (MD, 95% CI -35.3 - -9.5), $p < 0.0001$, $I^2 = 59\%$) was associated with severe disease. Out of the 23 studies reporting on platelet count, nine studies stated that a platelet count < 150 x 10^9/L was observed in up to 36% of patients with COVID-19 infection (9, 11, 13, 18, 21, 27, 31, 41).

Patients with severe disease had lower haemoglobin, -4.1 g/L (MD, 95% CI -6.42 – (-1.78), p <0,0001, $I^2 = 8\%$). Six studies (13, 31, 33, 36, 39, 40) described low haemoglobin in patients with COVID-19, whilst four studies found that all patients had haemoglobin within the reference interval (25, 26, 28, 37). Comparison with reference intervals was, however, not possible in all studies.

Higher CRP, 49.2 mg/L (MD, 95 % CI 31.2 - 67.1, $p < 0.0001$, $I^2 = 85\%$), was associated with severe disease. In accordance, Chen et al (30) found that for CRP the OR was 1.04 (95% CI 1.02-1.05, p < 0.001) for ICU admission. CRP was reported in 30 studies, and all studies congruently reported that the majority of patients have increased CRP.

There was no association between procalcitonin and disease severity (MD 0.03 ng/mL, 95% CI 0.00-0.06, $p = 0.09$, $I^2 = 89\%$). Procalcitonin was determined in 22 studies. The results are, however, very heterogeneous with increased procalcitonin observed in < 1% to 80% of the patients.

High D-dimer was associated with severe disease (SMD 0.58, 95% CI 0.37 - 0.78, $p < 0.0001$, $I^2 = 56\%$). D-dimer was assessed in 21 studies. Fifteen studies reported that 14 - 50% of patients had elevated D-dimer (9, 11, 13, 18, 21, 24, 26, 28, 31, 32, 36, 37, 39-41).

Slightly higher prothrombin time, 0.77 seconds (MD, 95% CI 0.37-1.18, $p < 0.0001$, $I^2 = 81\%$), was observed among patients with severe disease compared to non-severe disease. Prothrombin was evaluated in 14 studies. Only four out of the nine studies with data acceptable for meta-analysis reported an increased prothrombin time among 2.1-14.1% of patients with COVID-19 infection (17, 21, 31, 41).

We found no significant correlation between creatinine and disease severity in COVID-19 (MD, 3.42 μM, 95% CI -0.87 – 7.72, $p = 0.12$, $I^2 = 34\%$). Twenty-one studies reported on creatinine. Nine studies described that up to 10% of patients had increased creatinine (9, 11, 18, 21, 27, 31, 39), and three studies reported that up to 40% of patients had levels above the reference interval (13, 28, 41). Six studies found a subgroup of patients with low creatinine (11, 13, 26, 31, 36, 41).

Patients with severe disease had high LDH, 196 U/L (MD, 95% CI 131 - 260, $p < 0.0001$, $I^2 = 77\%$). Chen et al (30) reported that for LDH, the OR was 1.02 (95% CI 1.00-1.02, $p < 0.05$) for ICU admission. With the exception of Lu et al. (37), studies (n = 21) reported high LDH levels in patients, and one study described 98% of patients with LDH levels above the reference interval (21).

A small difference was found in AST when comparing severe and non-severe patients, as AST was 8.5 U/L higher (MD, 95% CI 3.0 - 14.0, $p = 0.003$, $I^2 = 67\%$) in patients with severe disease. For ALT, no association with severe disease was found (MD 3.5 U/L, 95% CI -2.6 - 9.7, $p = 0.26$, $I^2 =$

72%). This persisted if excluding the study of Zhou et al (18), which only measured ALT. In Chen et al (30), neither AST, nor ALT were associated with ICU admission. Overall, several studies found increased AST (9-11, 18, 19, 21, 26, 27, 31, 36, 37, 39-42) and ALT (9, 11, 13, 18, 19, 21, 25-27, 31, 36, 37, 39-42) in a subset of patients, ranging from 3.8 – 80% of patients.

Several other laboratory tests were evaluated in patients with COVID-19 (see Supplementary Table 1 and 2 for details on all the parameters mentioned by the included studies). Thus, some patients with COVID-19 showed increased ferritin and erythrocyte sedimentation range, whilst most patients had bilirubin within the reference range. In accordance with impaired coagulation, as assessed with D-dimer and prothrombin time, the literature suggests that activated partial thromboplastin time is prolonged in patients with COVID-19 (21, 28, 31, 40, 41). Elevated fibrinogen was also observed in some publications (17, 28, 32). CK-MB was reported by seven studies (11, 13, 20, 21, 26, 31, 39), and one study found the cardiac biomarker elevated in up to 50% of patients with COVID-19 (26). Creatine kinase was elevated in a subset of patients from in 12 out of the 17 studies that investigated this parameter (9, 11, 13, 18, 24, 27, 31, 42). Five studies reported on findings regarding the acid-base balance, and found decreased PaO2 in a large part of patients with COVID-19 infection (12, 13, 27, 32, 41).

Quality assessment and publication bias

The 45 studies included were assessed using the QUADAS-2 tool; Figure 3 shows the summary of the QUADAS-2 evaluation of the 21 studies included in the meta-analysis (see Supplementary Table 3 for details on all studies). For patient selection, most studies (86%) consecutively included patients with COVID-19 infection, and both risk of bias and applicability concern generally was low. Regarding the risk of bias for laboratory tests, 33% of the studies either did not report reference

intervals, specified cut-offs for the laboratory parameters, or stated timing of the laboratory tests (i.e. if the laboratory test were analyses at hospital admission or during admission). As the index test results were interpreted without the knowledge of the reference standard in 95% of the included studies (i.e. blood samples were analysed at admission), the risk of bias was primarily due to lack of clearly stated reference intervals or cut-off. A high applicability concern was found in 24% of studies, as blinding status and threshold values used were not stated or defined. In terms of outcome evaluation, most studies stated outcome and/ or disease severity a priori, and risk of bias was overall low. For applicability concern, some studies did not clearly define outcome and/ or definitions of disease severity, and interpretations of outcome in terms of laboratory analysis was unclear in 9% and high in 14%. Risk of bias was highest in timing and flow (43%), due to missing data. Adjustments for other prognostic factors and survival analysis to obtain hazard ratios were not used in any of the studies.

Regarding publication bias, we found significant heterogeneity for WBC and CRP, but publication bias was low for the remaining analytes (see supplemental figure 2).

Discussion

This review summarizes the laboratory findings of patients with laboratory confirmed COVID-19 from 45 studies. Severe disease was associated with higher WBC, higher CRP, higher D-dimer, higher LDH, higher AST and lower lymphocyte count, lower platelet count, and lower haemoglobin at admission. We found no association between neither creatinine nor procalcitonin and disease severity. The findings are robust, as the associations were consistent in all sensitivity analysis. Thus, exclusion of studies that fell outside the funnel plots, studies with a poor QUADAS-2 assessment, or a study with a paediatric population (13) did not alter the conclusions.

Interpretation of the patient's clinical features and laboratory results at admission are essential for implementing and adjusting an appropriate treatment. In this aspect, the typical pattern of laboratory results may, in times of a pandemic, aid in faster patient management and risk stratification of the individual patient.

Moderately increased CRP, white blood cell count, and neutrophil count with normal or only slightly elevated procalcitonin were among the laboratory findings in hospitalized patients with COVID-19. This observation is in accordance with typical findings in viral infection and thus, it does not itself exclude other infective viral agents (44). A recent systematic review showed that in managing community-acquired pneumonia, procalcitonin does not enable clinicians to immediately determine whether the infection is bacterial or viral and thus if antibiotics should be administered or withheld (45). The current evidence in COVID-19 does not seem to alter this conclusion.

For patients with COVID-19, the exact cause of death is still somewhat unclear, but both hypoxia and multiorgan dysfunction are presumed causes (21). Organ dysfunction, including acute kidney injury, has been reported for a significant proportion of patients with critical COVID-19 disease (46). In the presented studies, we found no association between markers of kidney function (creatinine at admission) and disease severity during hospitalization, in spite of several studies describing some patients having creatinine above the reference interval. Similarly, there was only little association between markers of liver function (ALT, AST, and prothrombin time) at time of admission and severe disease course. While this may be due to erroneous classification of severe disease, it could also reflect that deterioration often occurs during disease exacerbation, which was illustrated by Zhou et al. (18), who found significantly increased D-dimer and LDH over time in non-survivors. Another interesting finding is that higher D-dimer at time of admission is present in patients developing severe

disease. Tang et al (17) thus found that 71% of non-survivors versus < 1% of survivors met the criteria of disseminated intravascular coagulation during their hospital stay, making disseminated intravascular coagulation a likely contributor to cause of death. Few studies described patients with high creatine kinase or elevated CK-MB. Thus, muscular affection is a possibly a part of the disease manifestation and might cause cardiac insufficiency (47). The four studies reporting on troponin (8, 11, 18, 20), found increased troponin to be associated with ICU admission and death, supporting cardiac insufficiency as a causality of death in some patients. Whilst several other biomarkers were evaluated in the included studies, the present findings do not allow for any conclusions as to their use in COVID-19.

A strength of the included studies is that patients had laboratory confirmed SARS-CoV-2, and most included patients consecutively. The majority of studies furthermore reported laboratory analysis from the patients at admission. Limitations are that several studies had a weak or unclear definition of disease severity and did not disclose time course from admission to end of follow up. The studies did not include prognostic effect estimates such as hazard ratios or risk ratios. Only the study be Chen et al. (30) evaluated odds ratios, and adjustments for confounders were lacking. The studies available at the time this review was conducted did thus not allow for longitudinal data to be included in the meta-analysis, as the studies were mainly descriptive and did not provide survival analyses. The studies do, however, provide essential information regarding the laboratory data at admission as a tool for risk stratification of patients with COVID-19. Another limitation is that most of the studies were published before an outcome was reached for all the patients included, which may induce classification bias. The study populations were heterogeneous in terms of age and comorbidities. As children generally have been found to be mildly affected by COVID-19 (48), and have reference intervals that differ from adults (49), studies with mixed populations may abrogate an association

between laboratory results and outcome as reported by the studies. However, exclusion of the paediatric study did not alter results.

The current data did not allow for molecular and serologic tests to be included. In depth analysis of both molecular and serologic findings regarding COVID-19 disease severity is, however, relevant, to ensure both an enhanced understanding of COVD-19 disease mechanisms, as well as determining the use of these tests as prognostic markers.

Conclusion

The current evidence indicates that there is a specific laboratory pattern at admission for patients with severe COVID-19 disease course, which can be applied both for triaging of and treatment decision for patients. Based on the present findings, patients with a severe COVID-19 disease course are likely to have a distinct pattern in terms of the results of routine laboratory tests. This favours a systematic approach with the use of multiple relevant routine tests, rather than a single specific biomarker. Further research regarding the use of laboratory tests as prognostic biomarkers of COVID-19 disease severity and outcome is needed. Such research needs to be consistent and homogeneous in terms of disease severity definition and evaluate adjusted prognostic effect estimates.

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A. Alnor, statistical analysis, administrative support, provision of study material or patients; P.J. Vinholt, statistical analysis.

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Figures

Figure 1

Flow diagram of study selection.

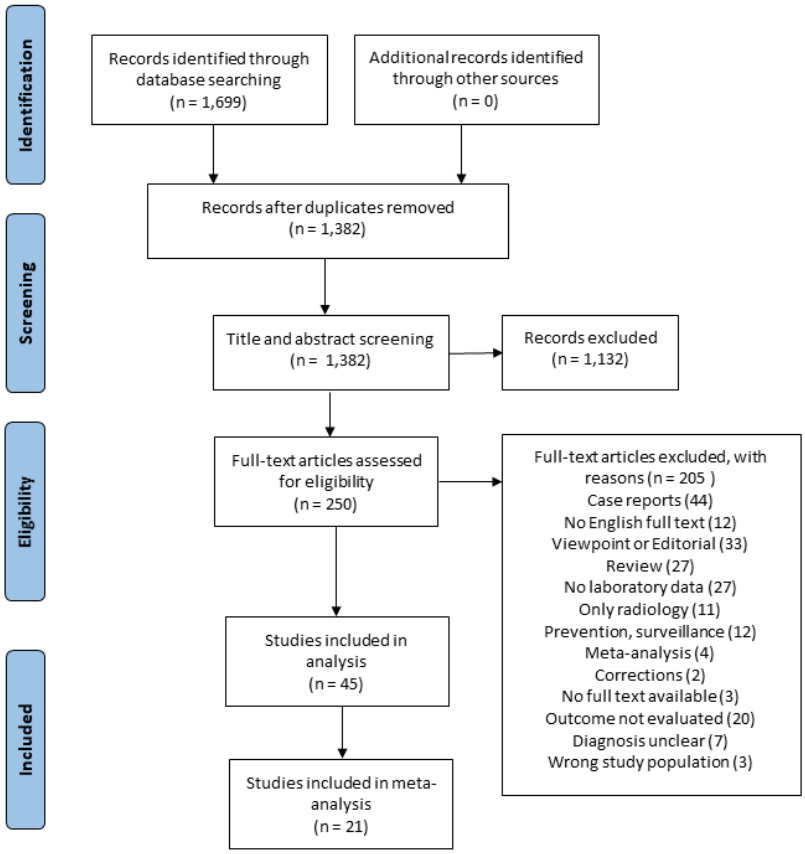
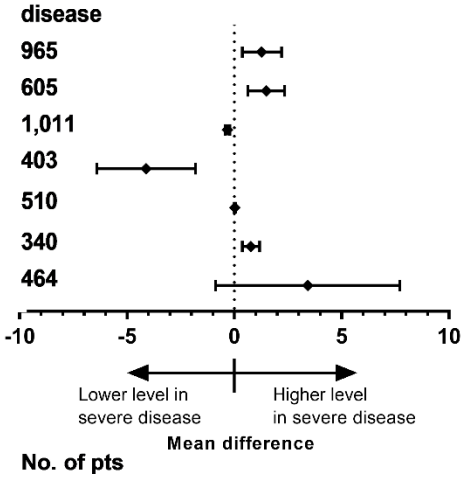


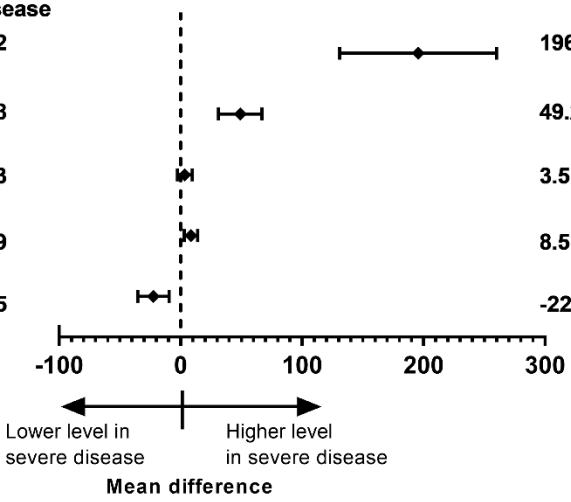
Figure 2

Pooled mean differences (MDs) and standard mean differences (SMDs) with 95% confidence intervals (CIs) for severe COVID-19 disease by biomarker. Studies included: Gao et al. (8), Guan et al. (9), Han et al. (10), Huang et al. (11), Li et al. (12), Liu W et al. (13), Liu Y et al. (11), Qin et al. (14), Qu et al. (15), Ruan et al. (16), Sun et al (13), Tang et al. (17), Wan et al. (18), Wang D et al. (20), Wang Z et al. (19), Wu et al. (21), Yang et al. (22), Young et al. (23), Zhang et al. (24), and Zhou et al. (18) (see Supplementary Figure 1 for details).

Biomarker	No. of studies	No. of pts	No. of pts with severe disease	Pooled MDs [95%CI]
WBC (x109/L)	17	2,921	965	1.28 [0.37, 2.20]
Neutrofil. (x109/L)	12	1,278	605	1.49 [0.64, 2.35]
Lymphocyte (x10 ^{9}/L)	18	2,968	1,011	-0.32 [-0.42,-0.21]
Haemoglobin (g/L)	9	1,763	403	-4.10 [-6.42, -1.78]
Procalcitonin (ng/mL)	10	1,209	510	0.03 [0.00, 0.06]
Prothrombin (Sec)	9	1,078	340	0.77 [0.37, 1.18]
Creatinine (μM)	12	1,097	464	3.42 [-0.87, 7.72]



Biomarker	No. of studies	No. of pts	No. of pts with severe disease	Pooled MDs [95%CI]
LDH (U/L)	12	938	362	196 [131, 260]
CRP (mg/L)	11	935	328	49.2 [31.2, 67.1]
ALT (U/L)	12	1,096	413	3.5 [-2.6,9.7]
AST (U/L)	11	905	359	8.5 [3.0, 14.0]
Platelet count (x109/L)	14	2,248	605	-22.4 [-35.3, -9.5]



Biomarker	No. of studies	No. of pts	No. of pts with severe disease	Pooled SMDs [95%CI]
D-dimer	11	1,250	378	0.58 [0.37, 0.78]

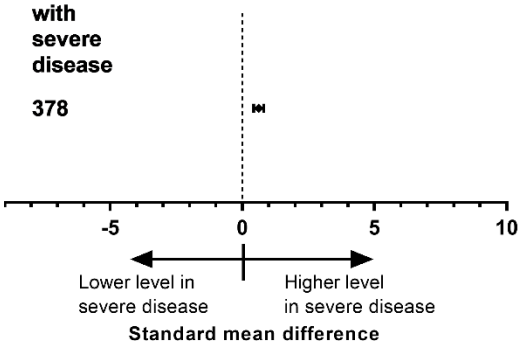


Figure 3

QUADAS-2 risk of bias and applicability assessment. QUADAS-2 risk of bias and applicability concern for the studies included in the meta-analysis (n = 21), showing the author's evaluation of each domain as percentages of included studies. Green, red and orange colour indicates low, unclear or high risk or applicability concern, respectively. Full QUADAS-2 for all studies is available in Supplementary Table 3.