Blood biochemical parameters as predictors of disease severity and mortality in COVID-19 patients- an updated systematic review and meta-analysis

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Summary: Our manuscript discusses the various blood biochemical markers as potential predictors of disease severity and mortality in COVID-19 patients. The timely detection of these parameters can help in providing appropriate course of treatment and reducing the mortality rate in the patients. We have found an association between the blood biochemical markers and disease severity and mortality in COVID-19 patients. Serum albumin, alanine aminotransferase (ALT), Erythrocyte Sedimentation Rate (ESR), lymphopenia, hemoglobin, and leukocytosis can reflect the severity of the disease, while the LDH, leukocytosis and albumin can be considered as risk factor to higher mortality.

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ABSTRACT

Background: The outbreak of coronavirus disease 2019 (COVID-19) has been rapidly spreading across the globe and poses a great risk to human health. Patients with abnormalities in laboratory parameters are more susceptible to COVID-19. Therefore, we explored the association of blood biochemical parameters with severity and mortality of COVID-19 amongst 3695 patients across seventeen studies.

Methods: We searched PubMed, Cochrane library and LitCOVID database until February 28, 2021. Seventeen studies were included in the meta-analysis with 3695 COVID-19 patients.

Results: The pooled analysis showed that compared to non-severe group, severe group was characterised by significantly elevated alanine aminotransferase (ALT) (standardised mean difference [SMD]: 0.65, 95% confidence interval [CI]: 0.23 to 1.06; p<0.001, erythrocyte sedimentation rate (ESR) (SMD: 0.55, 95%CI: 0.02 to 1.07 p=0.004) and lymphopenia (SMD: -1.22, 95% CI: -2.15 to -0.30; p<0.01), decreased serum albumin (SMD: -1.60, 95% CI: -2.96 to -0.22 ; p<0.001), creatinine (SMD: 0.54, 95% CI: 0.17 to 0.90; p<0.001), lactate dehydrogenase (LDH)(SMD: -1.54, 95% CI: -2.27 to -0.80; p=0.002) and haemoglobin (SMD:-0.89, 95% CI: ; p<0.001). Additionally, in the non-survivor group, elevated lactate dehydrogenase (LDH) (SMD: 1.54 95% CI: -2.27 to 0.80; p=0.002), decreased serum albumin (SMD: 1.08, 95% CI: 0.75 to 1.42; p<0.001) were reported. There was no comorbidity which was found to be significant in the severe group.

Conclusion: Serum albumin, ALT, ESR, lymphopenia, haemoglobin, and leucocytosis can reflect the severity of COVID-19, while the LDH, leucocytosis and albumin can be considered as risk factor to higher mortality.

Keywords: COVID-19, laboratory parameters, SARS-CoV-2, disease severity, mortality

1.Introduction

Coronavirus disease 2019 (COVID-19) is a global pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The first case was reported in Wuhan (China), in December 2019. The number of cases and the associated mortality has increased dramatically (1). SARS-CoV-2 causes respiratory infections and is like Severe Acute Respiratory Syndrome Virus (SARS-CoV) (genome sequence-80 –90 per cent similar) and Middle East Respiratory Syndrome Virus (MERS-CoV) in terms of clinical symptoms. As per WHO (World Health Organisation) Coronavirus Update Report of February 14, 2021, there have been 108, 153, 741 confirmed cases of COVID-19 and 2, 381, 295 deaths worldwide (2).

The clinical spectrum of COVID-19 ranges from mild to severe form of the disease (3). Mild symptoms include fever, cough followed by sputum production, and fatigue; while severe symptoms include acute respiratory distress (ARDS) syndrome, and acute cardiac injury along with multiple organ failure (4).

There are various laboratory parameters such as lymphocytes, leukocytes, haemoglobin, liver enzymes, albumin, inflammatory markers and procalcitonin that are found to be

deranged during the SARS-CoV-2 infection (5,6). As per previous literature, liver enzymes such as ALT, AST and bilirubin are found to be elevated in severe form of the illness due to possible liver dysfunction by the virus (1,4,7). Albumin levels have been found to decrease in severe illness (8–10). The inflammatory markers such as C-reactive protein were also found to be elevated in cases of severe infection (11). Procalcitonin, which is found to be elevated in bacterial infections (12) was found to be in the normal range in SARS-CoV-2 infection. As the production of procalcitonin increases during bacterial infection (13), there is simultaneous increased levels of IL-1β, tumour necrosis factor (TNF) and IL-6, but in case of viral infections these are inhibited by interferon-γ release. Thus, it can be postulated that procalcitonin will only increase if there is a bacterial co-infection in the patient along with COVID -19 otherwise it will be within the range (12). Creatinine is primarily excreted by the kidneys and abnormally high levels of creatinine is an indication of renal insufficiency which is a common complication in COVID-19 patients (14).

Several comorbidities such as hypertension, diabetes, chronic heart disease (CHD), chronic kidney disease (CKD) and chronic obstructive pulmonary disorder (COPD) are known to be prevalent in the severe group (15–17). However, more evidence needs to be gathered about their individual prevalence. There are various complications such as ARDS, pneumonia, kidney injury, septic shock as well as secondary infections which are also known to be related to the severe form of the illness and also related to the mortality of the COVID-19 patients (18,19). As the cases of COVID-19 infection are rapidly increasing, conduct of a comprehensive and detailed research providing better insights in this domain has become essential. Not only it will help in the early diagnosis

of the severe form of the disease but also it will help in formulating better treatment modalities and risk stratification in COVID-19 patients.

Although, similar systematic reviews have been published previously (20,21). However, our systematic review has several merits including: a) most updated database search b) broader research question and, c) included additional parameters and outcomes in our meta-analysis which gives a detailed insight into the association of these parameters with disease severity and mortality in COVID-19 patients.

Therefore, in the present meta-analysis, we aimed to understand the association between laboratory parameters and disease severity and mortality of COVID-19 patients. This will not only help broaden the horizon but also lead to the optimisation of the use of resources for the population at risk.

2.Materials and Methods

"Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines for systematic reviews (22) and meta-analysis of observational studies in epidemiology (MOOSE) guidelines (23) were followed for designing, conduct and reporting this systematic literature review." The protocol of this review has been registered with PROSPERO (registration number CRD42020206741).

2.1 Data sources and searches:

We searched PubMed/Medline, Cochrane Central Register of Controlled Trials and Clinical Trial Registry- India until February 28, 2021 using the keywords “laboratory” OR “clinical”, OR “lab parameters”, “comorbidities”, “clinical outcome” AND

"coronavirus 2019" OR "COVID-19" OR "2019nCoV-2", OR "SARS CoV-2". We also searched grey literature using Google Scholar and reference list of eligible articles with the aim of identifying additional potential eligible studies.

2.2 Inclusion and exclusion criteria

Eligible studies were cross-sectional, case-control, cohort and case series reporting defined groups and extractable data on laboratory findings in confirmed COVID-19 patients were included. The editorials, reviews, letters, meta-analysis, consensus and case reports, studies not reported in English language were excluded from the study. First author (AM) searched data and screened article for eligibility. Senior author (PM) double checked all the included articles and any dispute was resolved by consensus.

2.3 Quality assessment

Two reviewers (AM and PM) assessed the quality of data in the included studies using the National Institute of Health (NIH) quality assessment tools (24). We preferred the NIH tool because it is comprehensive and widely accepted for an exhaustive assessment of data quality. We rated the overall quality of included studies as good, fair and poor, and incorporated them in the meta-analysis results.

2.4 Data extraction

Data were inputted into a standardized data extraction table (Excel) and independently checked by a second reviewer (PM) for accuracy. The following variables were extracted: name of the first author, year of publication, study design, gender, age, number of patients in severe and non-severe groups, days of hospitalization along with

comorbidities of all the patients and clinical outcomes in terms of death and discharge. If not mentioned, the mean and standard deviation were extrapolated by median, sample size and interquartile range (IQR) (25). The severity of disease was defined according to Diagnosis and Treatment Plan of COVID-19 issued by National Health Commission, China (7^{th} edition) as mild, common, severe, and critical based on the clinical symptoms (26).

2.5 Data synthesis

We performed an exploratory meta-analysis to understand the magnitude and direction of effect estimate. Continuous outcomes are presented using standardised mean difference (SMD) due to substantial variability in study designs and 95% confidence intervals (CIs). We interpreted the effect size using Cohen rule of thumb with SMD greater than or equal to 0.2 representing a small effect, SMD greater than or equal to 0.5 a moderate effect, and SMD greater than or equal to 0.8 a large

Effect (27) For dichotomous outcomes, risk ratios (RRs) were calculated and presented with respective 95% CIs. Mantel-Haenszel random-effects meta-analysis using DerSimonian and Laird method was used to pool ORs (28). Heterogeneity between studies was assessed using the χ^2-based Cochran's Q statistic ($p<0.1$ considered as the presence of heterogeneity) and I-squared (I^2) statistics (>50% representing moderate heterogeneity) (28). If any cell value was zero, then we added 0.5 to each cell to calculate risk ratio (29). Publication bias was not assessed as a total number of studies were less than ten in primary lab outcomes (28).

3. Results

Search results

The systematic search yielded a total of 792 publications. Out of 792 articles, 225 were found using search terms "laboratory findings and COVID-19", 108 articles were found using the keywords "laboratory parameters and COVID -19", 120 studies were found using the keywords "comorbidities and COVID-19". After removing duplicates, out of 453 studies, 110 articles were excluded because they were review articles (n=30), did not report data on COVID-19 disease (n=36), did not provide laboratory data on COVID-19 patients with or without severe or without the proper categorization of the patients (n=34), or were editorial material (n=6) and 4 articles were excluded as they were in Chinese full text and could not be translated into English. Five additional studies were identified from the reference list of selected articles. All studies reported laboratory values measured at admission or earliest time point on hospitalization. Except for one study in which the classification of disease severity was unclear and hence it was not included in the meta-analysis. Thus, the meta- analysis included 17 studies meeting the inclusion criteria (Figure 1).

3.1 Study Characteristics

All the included studies were found to be conducted in China. Out of 17 included studies, 11 studies reported data in severe and non-severe groups, 6 studies reported data in terms of patient's survival with survivor and non-survivor groups. Among the seventeen included studies, five were cross-sectional studies (4,30–33), four were cohort studies (34) while two were case-series. The included studies enrolled a total of 3695 patients, including 1884 males and 1811 females. The baseline characteristics of the subjects included in these studies are provided in Table-1.

The laboratory parameters of patients were taken into consideration along with the major comorbidities such as hypertension, diabetes, CHD, CRD. Complications in the patient's post-treatment such as shock, acute respiratory distress syndrome (ARDS), kidney disease as well as secondary infections were also assessed.

3.2 Quality Assessment

We assessed the quality of data included in the studies using the NIH quality assessment tools. The quality assessment indicated that most included studies were of acceptable quality. All the studies clearly stated the research question or objective, the study population was clearly defined, and all subjects were selected from the same or similar population. The detailed result of the quality assessment is provided in *Supplementary File.*

3.3 Laboratory Findings

Regarding the laboratory findings, the parameters that were significantly elevated in the severe group were ALT ($p<0.001$) and ESR ($p<0.001$), while the albumin ($p<0.001$), haemoglobin ($p<0.001$) and leukocyte count (leucopoenia) ($p<0.001$) were found significantly decreased in the severe group as compared to the non-severe group. However, no significant difference was found in other parameters such as creatinine, procalcitonin, AST, C-reactive protein, lymphocyte count and LDH. Levels of LDH, albumin and leucocyte count were found associated with the survival of the patient (Table 2).

3.4 Comorbidities

The prevalence of Hypertension (p=0.005) and Chronic Heart Disease (CHD) (p=0.001) and Chronic Obstructive Pulmonary Syndrome (COPD) (p=0.001) was found significantly higher in the severe group while there was no significant difference in the prevalence of Diabetes, Chronic Renal Disease (CRD) in the two groups. None of the above-mentioned comorbidities was related to the mortality of the patient (Table 3).

3.5 Complications

Out of the several complications studied, pneumonia (p=0.02) was the only significant complication in the severe group while there was no significant difference found in complications such as shock, ARDS, kidney injury and secondary infection between the two groups. None of the above-mentioned complications was associated with mortality of the patient (Table 3).

3.6 Clinical Outcome

The rate of hospitalisation (p=0.022) was more in the severe group while there was no significant difference in the death and discharge rates among the two groups (Table 3).

4. Discussion

Over the last one year, more than 111,762,965 cases of COVID-19 have been confirmed in China and other countries in Asia, Pacific, Europe, Africa, and the America. Clinical and laboratory, and factors associated with evolution of the disease and outcomes, constitute critical knowledge that should be cautiously studied when a new infectious disease arises. COVID-19 has a wide spectrum of disease severity ranging from asymptomatic to symptomatic, mild to severe and critical nature of the illness (35). In

this meta-analysis, we aimed to assess the association between the laboratory parameters along with comorbidities and complications with disease severity and mortality in 3695 COVID-19 patients. (36). The laboratory parameters that were observed in this meta-analysis were the elevated ALT and ESR while decreased levels of albumin and haemoglobin were noted. However, the levels of other parameters such as bilirubin, LDH, CRP, AST, lymphocyte count, leucocyte count and procalcitonin were not found significantly different in the two groups. Data from the 2002-2003 outbreak indicate that SARS may be associated with lymphopenia, leukopenia, and, elevated levels of Lactate Dehydrogenase (LDH), Alanine transaminase (ALT), Amino Aspartate Transaminase (AST), and creatine kinase (37,38) but they are not significantly seen, nor consistently reported, in COVID-19 studies and cases. The mortality was found to be associated with the LDH, albumin, leukopenia and leucocytosis across two studies (32,39).

As per previous studies, hypertension and diabetes have been reported to be the most prevalent comorbidities found in COVID-19 patients. In a study in China, out of 13 patients, hypertension was found in 5 (27.8%) and diabetes was found in 3 (16.7%) (16,40,41). In contrary to this, hypertension was the most prevalent comorbidity observed in the severe group while there was no significant difference in the prevalence of diabetes, CHD, CRD, and COPD between the two groups. None of the above-mentioned comorbidity had an association with the mortality of the patient.

Complications that were commonly observed in the severe group was pneumonia while the occurrence of shock, kidney injury, ARDS and secondary infections were similar in the two groups and only ARDS and kidney injury were related to the mortality of the

patients. The rate of hospitalisation was more in the severe group while there was no significant difference found in the rates of death and discharge between the two groups. Our results showed a deviation from the usual findings due to heterogeneity between the individual studies and small number of studies included in the meta-analysis. Thus, a more comprehensive analysis with a larger sample size needs to be done so that we can have a clear picture of the correlation of laboratory abnormalities and clinical parameters with the severity of the disease. More such studies are required to elucidate the risk factors for disease severity and death.

There are several limitations that needs to be mentioned. There was heterogeneity amongst individual studies because of which there was a deviation of some of our results from usual findings. Additionally, case-series were included in the present meta-analysis. Although we did an extensive search, we may have inadvertently missed relevant studies. Exclusion of studies in languages other than English (ie. Chinese) may have resulted in missing of relevant studies. Certain parameters such as IL-6 ad IL-10 which are strong indicators of cytokine storm were not included in this meta-analysis due to lack of available data as not all parameters were reported in each patient. As most of the articles were published in Chinese, findings should interpret with caution, thereby ensuring the generalizability of the results. Also, not all studies included all the desired parameters.

5. Conclusion

COVID-19 has a wide spectrum of severity. The detection of these laboratory as well as clinical parameters can assist in the timely diagnosis of such patients. They can be associated with disease severity and mortality along with deciding the course of action

for COVID-19 positive patients and reducing the mortality rates in the patients. The patients of liver dysfunction with abnormal levels of liver enzymes and comorbidities such as hypertension are more prone to severe form of COVID-19 infection and therefore, special attention should be given to such patients. However, more such studies with a greater sample size needs to be conducted to get a better insight into the role of liver enzymes in the prognosis of COVID-19.

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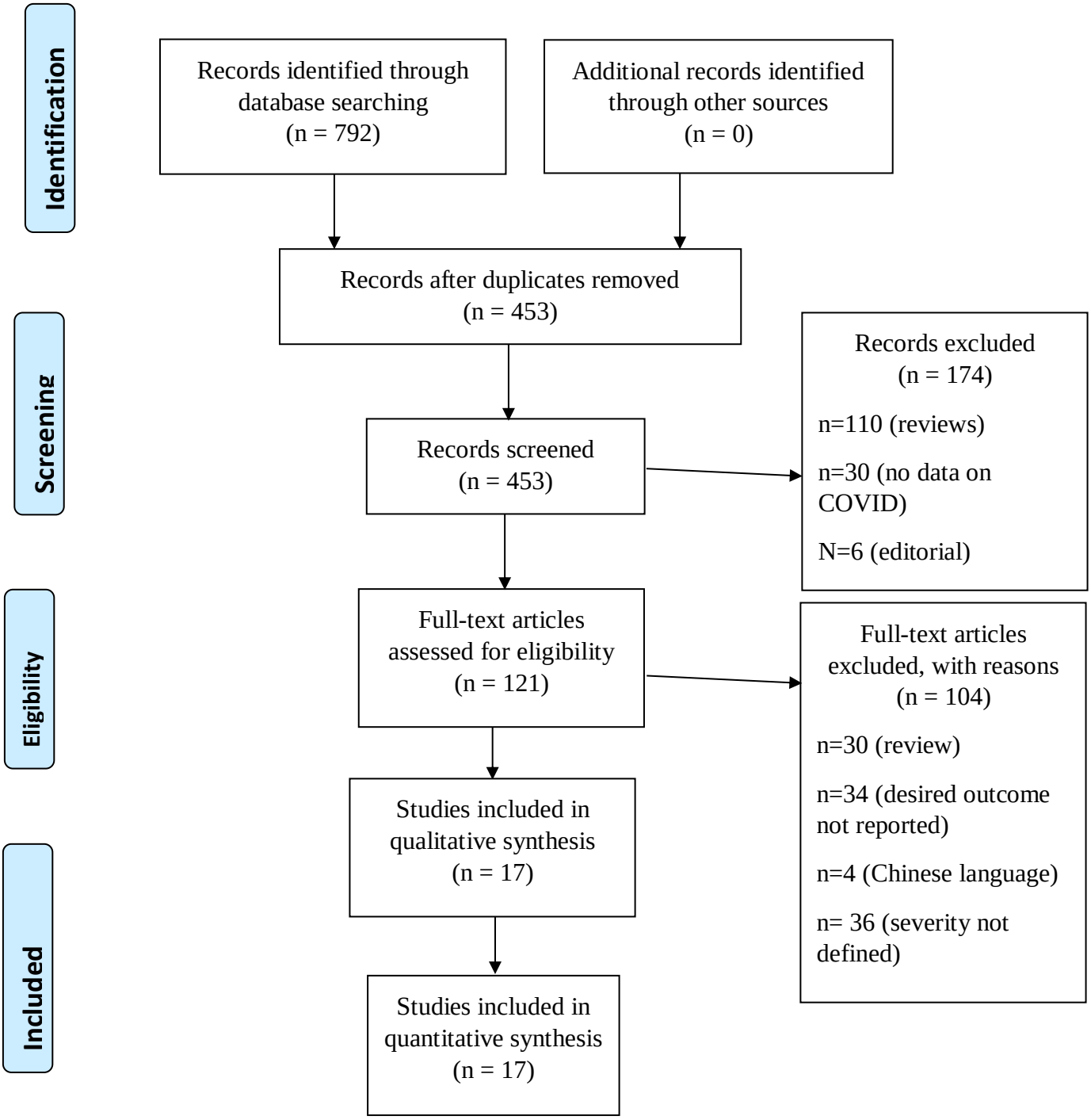

Fig.1 Flow diagram of the number of studies screened and included in the meta-analysis.

Table 1: Baseline characteristics of the subjects

Author	Year	Study Design	Groups	Number (n)	Gender	Age (mean)	Comorbidities (n%)	Hypertension n (%)	Diabetes n (%)	CHD n (%)	CRD n (%)	COPD n (%)
					Male							
Chen et al	2020	Retrospective Study	Total	21	17	56	7	5	3	NA	NA	NA
			Severe	11	10	61	5	4	2	NA	NA	NA
			Non- severe	10	7	52	2	1	1	NA	NA	NA
Guan et al	2020	Retrospective Study	Total	1099	640	47	261	165	81	27	8	12
			Severe	173	100	52	67	41	28	10	3	6
			Non- severe	926	537	45	194	124	53	17	5	6
Lang et al	2020	Retrospective Study	Total	339	166	69	60.7	138	54	53	13	21
			Survivors	274	127	68	NA	106	43	32	9	10
			Non- Survivors	65	39	76	NA	32	11	21	4	11
Huang et al	2020	Retrospective Study	Total	41	30	49	13	6	8	6	NA	1
			Severe	13	11	49	5	2	1	3	NA	1
			Non-severe	28	19	49	8	4	7	3	NA	0 (0)
Wang et al	2020	Case Series	Total	138	75	56	64	43	14	20	4	4
			Severe	36	22	66	26	21	8	9	2	3
			Non-severe	102	53	51	38	22	6	11	2	1
Qin et al	2020	Cohort Study	Total	452	235	58	201	135	75	27	10	12
			Severe	286	155	53	NA	105	53	24	6	9
			Non -Severe	166	80	61	NA	30	22	3	4	3
Rong et al	2020	Case Series	Total	30	16	50.5	NA	NA	NA	NA	NA	NA
			Severe	3	NA	60	NA	NA	NA	NA	NA	NA

			Non-Severe	27	NA	49.44	NA	NA	NA	NA	NA	NA
Jin-Jin et al	2020	Retrospective Study	Total	140	71	57	90	42	17	7	NA	2
			Severe	58	25	64	46	22	8	4	NA	2
			Non-Severe	82	44	51.5	44	20	9	3	NA	0
Zhou et al	2020	Cohort Study	Total	191	119	56	91	58	36	15	2	6
			Survivors	137	81	52	55	32	19	2	0	2
			Non-Survivors	54	38	69	36	26	17	13	2	4
Hongmei et al	2020	Cohort Study	Total	86	38	41	16.3	7	4.7	NA	1.2	1.2
			Severe	44	23	42.5	18.2	11.4	6.8	NA	0	0
			Non-Severe	42	15	40.5	14.3	2.4	2.4	NA	2.4	2.4
Yohung et al	2020	Retrospective Study	Total	51	27	58.9	33	41.2	21.6	12	2	8
			Severe	20	8	60.0	17	65	20	9	0	4
			Non-severe	31	19	58.3	16	25.8	22.6	3	2	4
Hao et al	2020	Retrospective Study	Total	59	29	64		42	9	26	NA	2
			ICU	44	23	66.5		20	6	23	NA	1
			Non-ICU	15	6	56		5	3	3	NA	1
Jiqian et al	2020	Retrospective Study	Total	113	71	62.5	43.9	43.9	18.4	35	NA	12
			Survivors	11	7	57.5	41	44.6	19.6	14	NA	3
			Non-survivors	102	64	65.7	64	43.5	17.7	21	NA	9
Buckner et al	2020	Retrospective Study	Total	105	53	69	NA	59	33	38	26	10
			Severe	51	30	70	NA	59	35	35	29	14
			Non-severe	54	23	67	NA	59	31	42	22	7

Cao et al	2020	Cohort Study	Total	80	38	53	NA	20	6	10	NA	5
			Severe	27	16	71	NA	4	0	5	NA	0
			Non-Severe	53	22	44	NA	16	6	5	NA	5
Li et al	2020	Retrospective Study	Total	312	187	69.2	NA	57.1	38.8	29.8	3.21	NA
			Severe	105	67	71.3	NA	82.9	46.7	43.8	3.81	NA
			Non-Severe	207	120	67.1	NA	44	34.8	22.7	2.9	NA
Wan et al	2020	Retrospective Study	Total	135	72	47	31.9	9.6	8.9	5.2	NA	0
			Severe	40	21	56	70	10	22.5	15	NA	4
			Non-Severe	95	52	44	16.3	9.4	3.1	1	NA	0

Data is presented as Median (IQR) or number (%).
No.-number. NA-not available. IQR-inter quartile range. COPD-Chronic Obstructive Pulmonary Syndrome. CHD-Chronic Heart Disease. CRD-Chronic Renal Disease. M-Male. F-Female.

Table 2: Results of meta-analysis comparing laboratory abnormalities in COVID-19 patients with and without severe illness and mortality.

Laboratory parameter	**Severe vs Non-severe**				**Survivors vs Non- survivors**			
	No. of Studies (patients)	***Effect size (95% CI)***	***p - value***	***I^2***	***No. of Studies (patients)***	***Effect size (95% CI)***	***p - value***	***I^2***
		SMD (95%CI)				***SMD (95%CI)***		
ALT	7 (240)	0.65 (0.23 to 1.06)	p<0.001	87.0 %	3 (643)	-0.38 (-2.66 to 1.88)	p<0.001	98.9%
AST	10 (494)	1.19 (0.40 to 1.98)	p<0.001	96.0 %	2 (452)	-1.84 (-3.91 to 0.23)	p<0.001	97.0%
LDH	7 (240)	1.48 (0.48 to 2.49)	p<0.001	97.1%	2 (530)	-1.54 (-2.27 to -0.80)	0.002	89.9%
Albumin	5 (279)	-1.59 (-2.96 to -0.22)	p<0.001	95.5%	1 (191)	1.08 (0.75 to 1.42)	p<0.001	“-“%
Bilirubin	9 (969)	0.47 (0.09 to 0.85)	p<0.001	85.4%	1 (113)	-0.80 (-1.43 to -0.17)	p<0.001	“-“%
C- reactive Protein	8 (944)	1.02 (-0.95 to 2.983)	p<0.001	96.5%	1 (339)	-0.92 (-1.20 to -0.64)	p<0.001	“-“%
Creatinine	10 (494)	0.53 (0.17 to 0.90)	p<0.001	84.9 %	2 (530)	-0.35 (-0.56 to -0.15)	0.973	0.0 %
Hemoglobin	8 (944)	-0.90 (-1.43 to -0.34)	p<0.001	94.0 %	2 (452)	-0.20 (-0.45 to 0.04)	0.489	0.0 %
Leucopenia	12 (2668)	1.10 (0.46 to 1.74)	p<0.001	97.5 %	3 (643)	-1.02 (-1.33 to -0.72)	0.154	46.6 %

Lymphopenia	13 (2698)	-1.22 (-2.14 to -0.30)	p<0.001	98.7 %	3 (643)	1.72 (-0.61 to 4.07)	p<0.001	98.7 %
Procalcitonin	8 (944)	0.66 (0.13 to 1.19)	p<0.001	98.6 %	1 (339)	-0.46 (-0.74 to -0.19)	-	-
ESR	3 (589)	0.54 (0.02 to 1.07)	0.004	82.0 %	-	-	-	-

SMD-Standard mean difference as follows: Severe vs. Non-severe; Non-survivors vs. survivor patients. CI-Confidence Interval. CRP-C-reactive protein. ALT-Alanine aminotransferase. AST-Aspartate aminotransferase. LDH-Lactate Dehydrogenase. ESR-Erythrocyte Sedimentation Rate.

Table 3: Results of meta-analysis comparing co-morbidities, complications, and clinical outcome in COVID-19 patients with and without severe illness and mortality.

Comorbidity				
	No. of Studies (subjects)	***RR (95%CI)***	***p - value***	I^2
Hypertension	13 (2660)	1.28 (1.08 to 1.53)	0.005	52.0 %
Diabetes	16 (2828)	1.25 (1.04 to 1.52)	0.018	64.2 %
CHD	11 (2612)	1.43 (1.16 to 1.77)	0.001	57.5 %
CRD	7 (2243)	1.26 (0.97 to 1.65)	0.083	0.0%
COPD	11 (2612)	1.85 (1.30 to 2.61)	0.001	68.6 %
Shock	3 (1278)	1.12 (0.91 to 1.38)	0.297	0.0%
ARDS	3 (1278)	2.02 (0.91 to 4.48)	0.082	74.7%
Kidney Injury	3 (1278)	1.04 (0.85 to 1.29)	0.675	0.0%
Pneumonia	1 (1099)	23.54 (3.27 to 169.54)	0.002	.%
Secondary Infection	1 (41)	1.44 (0.53 to 3.92)	0.470	.%
Discharge	2 (1140)	0.96 (0.76 to 1.201)	0.699	0.0%

Death	2 (1140)	1.11 (0.88 to 1.390)	0.384	0.0%
Hospitalization	2 (1140)	0.57 (0.35 to 0.92)	0.022	0.0%

RR-Relative Risk: Severe vs Non-severe; Non-survivor vs survivor patients. NA-Not Applicable. CI-Confidence interval. NA-not available. CHD-Chronic Heart Disease. CRD-Chronic Renal Disease. COPD-Chronic Obstructive Pulmonary Syndrome. ARDS-Acute respiratory distress syndrome

Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	1
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	4-5
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	5-6
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	-
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	7
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	7
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	6
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	7
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	8
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	-

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	8
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	9
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	9
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	-
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	10
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	11
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	12-13
Limitations	20	Discuss the limitations of the scoping review process.	14
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	14
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	2

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.

† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).

‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.

§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMAScR): Checklist and Explanation. Ann Intern Med. 2018;169:467–473. doi: 10.7326/M18-0850.