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Laboratory Markers and Mortality in Novel Coronavirus Disease 2019 (COVID-19): A Systematic Review and Meta-Analysis

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Abstract

Background: Novel coronavirus disease 2019 (COVID-19) is associated with high mortality. Many laboratory values have been suggested to predict patients at risk for a poor outcome in COVID-19.The objective of this project was to systematically review and meta-analyze all laboratory markers associated with prognosis of mortality in patients with COVID-19.

Methods: We searched OVID Medline, SCOPUS, MedRxIv, preprints.org, and Centers for Disease Control databases from November 2019 to April 10, 2020 for articles on laboratory values and mortality in COVID-19 and updated the search July 20, 2020. Teams of 2 independent reviewers reviewed titles and abstracts for studies that reported mortality and laboratory values and subsequently abstracted relevant data.

Results: Our initial search identified 6,973 articles and a total of 96 articles (30 articles from first search and 66 from updated search) on 72 laboratory values were included. Many laboratory values were associated with mortality, but those most associated with mortality included lymphopenia (OR 0.30, 95% CI 0.24-0.36), thrombocytopenia (OR 0.46, 95% CI 0.35-0.60), elevated lactate dehydrogenase (OR 7.32, 95% CI 5.19-10.33), and ferritinemia (OR 5.19, 95% CI 3.07-8.62). All cardiac markers were associated with mortality, with troponin being the least associated. A low PaO2:FiO2 ratio was also associated with mortality (OR 0.13, 95% CI -0.06-0.28). Heterogeneity was high and risk of bias was moderate.

Conclusions: This meta-analysis identified many laboratory abnormalities associated with mortality in COVID-19, though was limited by heterogeneity. Laboratory markers previously identified as associated with a poor prognosis in COVID-19 were confirmed to be those most associated with mortality in this large meta-analysis.

Keywords

Coronavirus, SARS, COVID-19, Mortality, Systematic Review, Laboratory

Introduction

Novel coronavirus disease 2019 (COVID-19) has caused over a million international deaths and overwhelmed health-care systems internationally: Wuhan, China; Lombardy, Italy; and New York City, New York. This disease has led to overall mortality rates from 1-6%, [1-3] with the subset of patients who require critical care or intubation having mortality as high as 50-80% [4,5].

The vast majority of patients will be asymptomatic or minimally symptomatic [6] and can be treated at home. However, a small percentage of patients will require hospitalization for aggressive supportive care - supplemental oxygen, intubation, and sometimes cardiac support [7]. Those at most risk for severe outcomes appear to be the obese, [8] the elderly, [3] and those with prior heart or lung disease [9]. Given the stretch on limited resources, predicting those at risk of de-

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terioration or mortality would be helpful to clinicians when making disposition or treatment decisions.

Several laboratory values have been proposed to predict severe illness. These include nonspecific inflammatory markers (C-reactive protein and ferritin), [10] liver enzymes (AST, ALT, LDH), [11] and blood cell counts (platelets, white blood cells, and lymphocytes) [10]. D-Dimer has been highly associated with mortality, with the newest theories recognizing that this may be due to risk of thrombotic complications, and not just inflammation alone [12,13]. As with many other diseases, troponin elevations, too, have been associated with mortality [14,15].

Given the reports of associations of these laboratory values and prognosis, we sought to do a systematic review and meta-analysis of laboratory values associated with mortality in adult patients with COVID-19.

Methods

This study was conducted in accordance with Preferred Reporting in Systematic Review and Meta-Analysis Guidelines (PRISMA) [16]. The PRISMA Checklist is available in Supplement 1 and the research protocol is available from the authors upon request. This study had no human subjects and was, therefore, exempt from Institutional Review Board Review.

Search strategy and study selection

We searched OVID Medline, SCOPUS, MedRxIV, preprints.org, and Centers for Disease Control (CDC) databases from November 2019 to April 10, 2020. The search used keyword terms for "COVID-19", "SARS", or "coronavirus". The CDC database was already compiled and was only filtered for English articles. Per PRISMA guidelines, 1 sample search strategy, in detail, is available in the Supplement 2. A complete search strategy is available from the authors upon reasonable request. The search was updated on July 20, 2020 with a focused search in PubMed and MedRxIV, using the laboratory values found in the initial search. These 2 sources were chosen because they could conduct a focused search that was also date limited to the month level and included one published and one unpublished source. An example of the updated search strategy is also available in Supplement 2. We reviewed citations from included articles, review articles, and suggestions from select content experts to find relevant articles that may have been missed. We also contacted authors of studies that appeared to have underlying data that would answer the research question to ask for additional data. Titles and abstracts from these search methods were screened independently by 3 trained reviewers (CT, SG, GH). If any reviewer thought an article was potentially relevant, a full text copy of the article was ordered and again reviewed for inclusion by these 3 authors.

Inclusion criteria were any research study type that evaluated human adult patients with COVID-19 and any laboratory value associated with mortality. Exclusion criteria included opinions (i.e. editorials, letters without data, etc.), abstracts, non-English papers, studies only on children, studies with < 10 participants, or studies with not enough data to address the research question. We did include preprint articles that are not yet peer reviewed. We planned to contact authors for updated data if data was incomplete. After full text review for inclusion, all authors independently identified articles for exclusion and any discrepancies were resolved with a consensus meeting among all 4 authors (JD, CT, SG, GH).

Data extraction and data synthesis

After title and abstract selection, a standardized abstraction form was developed by all of the authors. Two of three authors (CT, SG, GH) abstracted data from the studies and compared their results for discrepancies. These were resolved by consensus among all authors. Data included authors, publication year, population, setting, intervention, mortality, and other outcomes.

Risk of bias

Risk of bias within a study was assessed using the Quality in Prognostic Studies (QUIPS) tool. This was assessed by one author (JD) and verified by one other un-blinded author. Funnel plot analyses for each laboratory value was conducted for publication bias and heterogeneity was assessed using I^2.

Statistical analysis

Statistical analysis was conducted in RevMansoftware, version 5 (Review Manager (RevMan) [Computer program]. Version 5.4, The Cochrane Collaboration, 2020). A random effects model and inverse variance weighting was used in all analyses. All laboratory values with more than 2 studies were included in the meta-analysis. All of these were included in a standardized mean difference analysis. Studies who reported averages (either mean or median) were also included in an absolute mean difference analysis for laboratory values that were conducted on the same scale. Laboratory values were transformed to International System units when able, but laboratory values on different scales (e.g., C-reactive protein), where different assays may affect results (e.g., D-Dimer), or similar lab tests with different implications and measures (troponin I and troponin T) were not combined for absolute mean difference analysis and only included in a standardized mean difference analysis. Authors of studies that did not report averages were contacted to request this data. Studies that reported median data were transformed using the method recommended by Cochrane [18] and modified for low sample sizes when applicable using the method described by Wan, et al. [19] or Hozo, et al. [20] as applicable based on available data. Data for odds ratios (ORs), hazard ratios, and relative risk were transformed to standardized mean differences and associated standard errors using the method described by Chinn, et al. [21]. Unadjusted/unweighted ratios were preferred when available. In studies with a group with no patients, a dummy variable of 0.5 was used in calculation of odds ratio/standardized mean difference, and in studies with a group with no variance, the average of the standard deviations from all other studies on that laboratory test or the average value itself was used, whichever was lower. If there was no difference and no variance reported, a standard error of 0.01 was used. Studies that reported multiple

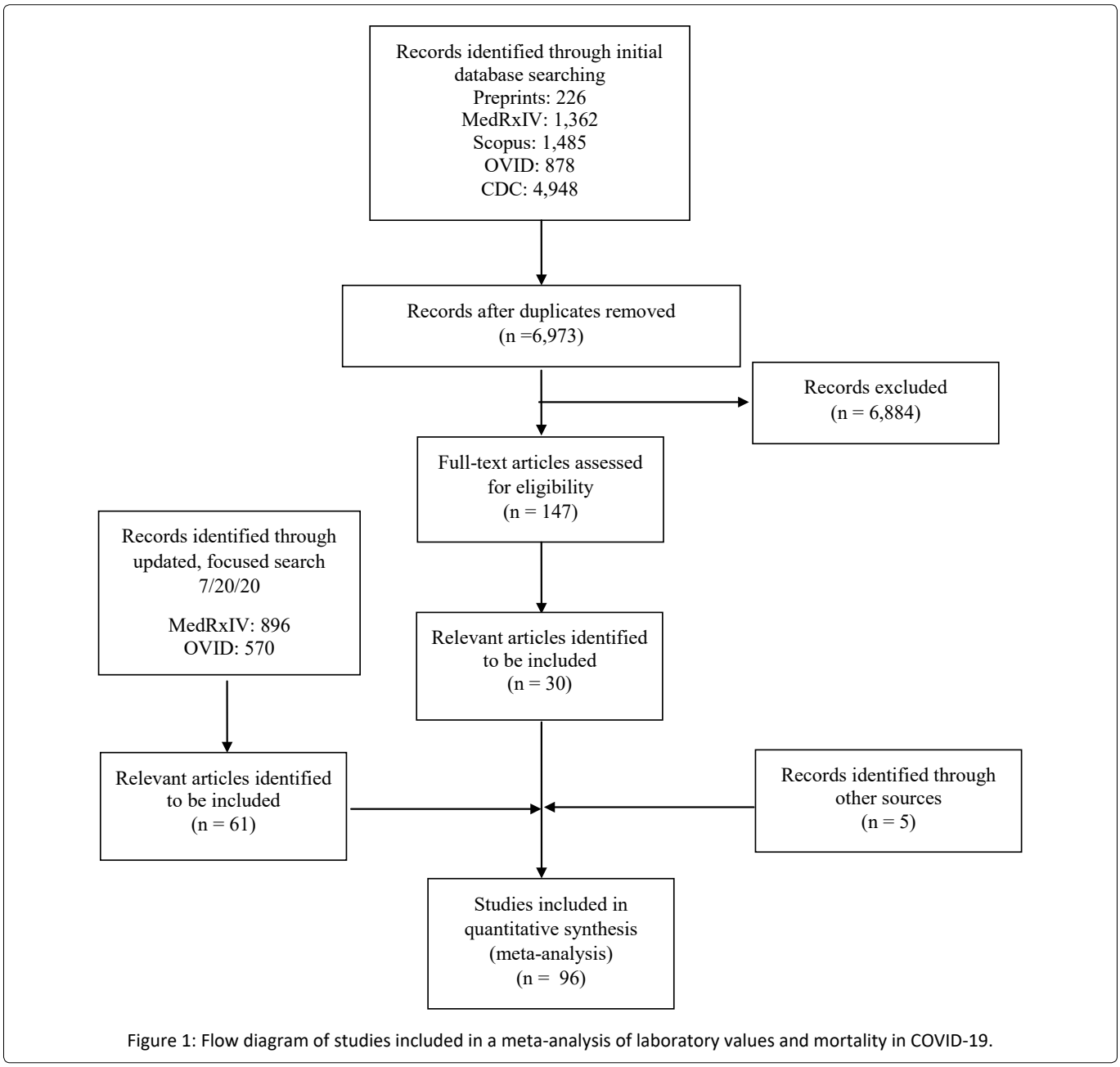

Figure 1: Flow diagram of studies included in a meta-analysis of laboratory values and mortality in COVID-19.

Table 1: Summary of characteristics of 91 studies included in a meta-analysis of laboratory values and mortality in COVID-19.

	N	%
Year		
2020	96	100%
Country		
China	67	70%
United States	10	10%
Italy	8	8%
Spain	3	3%
United Kingdom	3	3%
Iran	1	1%
Canada	1	1%
International	1	1%
Mexico	1	1%
Belgium	1	1%
Study type		
Retrospective cohort	59	61%
Case control	22	23%
Prospective cohort	14	15%
Ambispective cohort	1	1%
Patient type		
Inpatient	69	72%
ICU	12	13%
Inpatient/ICU	9	9%
Inpatient/Outpatient	1	1%
Unclear	3	3%

COVID-19: Novel coronavirus disease 2019; ICU: Intensive care unit.

different patient cohorts were included in separate analyses, but studies that had one cohort but separated "control" outcomes (i.e. severe vs. non-severe illness) were combined into one control group (survived). Studies that reported different analyses of the same outcome were only included once, with the preference for average (mean/median) data. Preprint articles that were subsequently published were only included once. Statistical significance was set at an alpha of 0.001 to account for multiple analyses.

Results

Our initial search identified 6,973 unique articles. 147 of these were identified for full text review, and 30 were deemed to meet all inclusion and no exclusion criteria (Figure 1). In the updated search, 61 new articles were identified (896 from medRxIV and 570 from PubMed), and 52 were included (18 from medRxIV and 34 from PubMed). Two studies in the initial search had since been published from a preprint form and these published versions were used. A total of 105 authors were contacted (90 for primary data and 15 for clarification of printed data). Thirteen of these authors responded (12.9%) and 10 (9.9%) of those provided new data. A total of 96 unique studies [11,12,14,15,22-113] with 30,985 patients and 72 different laboratory values were included. A summary of the characteristics of the included studies is in Table 1 and details of each study are available in Supplement 3.

The summary of the standardized mean difference analysis is available in Table 2. A summary of the results for the absolute mean difference analysis is available in Table 3. A forest plot and funnel plot for each laboratory value is available in Supplement 4, Supplement 5 and Supplement 6.

Hematologic

The most predictive complete blood cell count test was neutrophil percent (OR 26.47, 95% CI 5.68-121.09), though this was limited by a small number of studies and a wide confidence interval. Nonetheless, absolute neutrophil count (OR 4.66, 95% CI 3.30-6.45) and neutrophil to lymphocyte ratio (OR 3.36, 95% CI 1.60-6.57) were also the next most significant positive associations with mortality, and a low absolute lymphocyte count (OR 0.30, 95% CI 0.24-0.36) and lymphocyte percent (OR 0.05, 95% CI 0.02-0.11) were the most significant negative correlations, as was thrombocytopenia (OR 0.46, 95% CI 0.35-0.60). There was a moderate association with leukocytosis and mortality, as well (OR 3.68, 95% CI 2.91-4.74).

The absolute differences for white blood cell count (2.38 10^9/L, 95% CI 1.97-2.79), absolute neutrophil count (2.61 10^9/L, 95% CI 2.04-3.18), and absolute lymphocyte count (-0.34 10^9/L, 95% CI -0.28- -0.4) were modest. The absolute difference in neutrophil to lymphocyte ratio (4.04, 95% CI 1.59-6.48) and neutrophil (19.28%, 95% CI 12.33-26.22) and lymphocyte percent (-15.21%, 95% CI -12.33- -18.08) were more apparent. Thrombocytopenia also seemed to have a significant absolute difference (-39.85 10^9/L, 95% CI -27.65- -52.06).

Almost all lymphocyte subsets were negatively correlated

Table 2: Standardized mean difference of laboratory values associated with mortality in COVID-19 in a meta-analysis.

Laboratory value	Number of Studies	Odds Ratio	95% Lower Limit	95% Upper Limit	Standardized Mean Difference (SMD)	95% Lower Limit	95% Upper Limit	P (for SMD)	I^2 (for SMD)
Hematologic									
White Blood Cell Count	57	3.68	2.91	4.74	0.72	0.59	0.86	< 0.001	93%
Absolute Neutrophil Count	41	4.66	3.30	6.45	0.85	0.66	1.03	< 0.001	93%
Percent Neutrophil	6	26.47	5.68	121.09	1.81	0.96	2.65	< 0.001	96%
Absolute Lymphocyte Count	69	0.30	0.24	0.36	-0.67	-0.78	-0.57	< 0.001	80%
Percent Lymphocyte	8	0.05	0.02	0.11	-1.71	-2.2	-1.23	< 0.001	91%
Absolute Basophil Count	4	1.00	0.72	1.39	0	-0.18	0.18	1	0%
Absolute Eosinophil Count	5	0.91	0.87	0.96	-0.05	-0.08	-0.02	0.001	96%
Absolute Monocyte Count	10	0.76	0.60	0.98	-0.15	-0.28	-0.02	0.49	0%
Hemoglobin	37	0.82	0.75	0.90	-0.11	-0.16	-0.06	< 0.001	75%
Hematocrit	3	0.71	0.38	1.34	-0.19	-0.54	0.16	0.28	52%
Red Blood Cell Count	6	0.67	0.43	1.08	-0.22	-0.47	0.04	0.02	63%

Red Cell Distribution Width	3	2.34	1.88	2.96	0.47	0.35	0.6	< 0.001	0%
Platelet Count	49	0.46	0.35	0.60	-0.43	-0.58	-0.28	< 0.001	87%
Neutrophil To Lymphocyte Ratio	12	3.36	1.60	6.57	0.67	0.26	1.04	< 0.001	96%
Lymphocyte Subsets									
Total CD3+/T Cells	7	0.17	0.09	0.34	-0.97	-1.35	-0.59	< 0.001	76%
Total Cd4+/T Helper Cells	7	0.18	0.10	0.31	-0.96	-1.27	-0.65	< 0.001	70%
Percent Cd4+ Cells	3	0.31	0.12	0.80	-0.64	-1.15	-0.12	0.02	86%
Total Cd8+/Suppressor/Cytotoxic T Cells	7	0.13	0.05	0.36	-1.12	-1.68	-0.56	< 0.001	91%
Percent Cd8+ Cells	3	0.21	0.07	0.65	-0.86	-1.47	-0.24	0.006	90%
Total Natural Killer Cells	3	0.18	0.04	0.90	-0.95	-1.84	-0.06	0.04	86%
Total CD19+/B Cells	3	0.70	0.40	1.22	-0.2	-0.51	0.11	0.21	15%
Cd4+/Cd8+ Ratio	3	1.54	0.52	4.66	0.24	-0.36	0.85	0.43	79%
Electrolytes/Renal									
Sodium	12	0.90	0.64	1.24	-0.06	-0.25	0.12	0.48	68%
Potassium	10	1.29	0.85	1.95	0.14	-0.09	0.37	0.22	73%
Chloride	4	0.64	0.37	0.93	-0.25	-0.55	-0.04	0.09	71%
Calcium	5	0.21	0.04	1.22	-0.86	-1.83	0.11	0.08	95%
Glucose	21	2.66	1.75	4.03	0.54	0.31	0.77	< 0.001	93%
Blood Urea Nitrogen	37	7.06	4.33	11.51	1.08	0.81	1.35	< 0.001	97%
Creatinine	64	2.43	2.22	2.66	0.49	0.44	0.54	< 0.001	94%
Glomerular Filtration Rate	7	0.27	0.11	0.62	-0.73	-1.2	-0.26	0.003	97%
Cystatin C	3	1.63	0.28	9.43	0.27	-0.7	1.24	0.59	94%
Liver									
Aspartate Aminotransferase	40	2.61	1.92	3.55	0.53	0.36	0.7	< 0.001	89%
Alanine Aminotransferase	51	1.22	1.14	1.29	0.11	0.07	0.14	< 0.001	73%
Alkaline Phosphatase	5	2.10	1.57	2.76	0.41	0.25	0.56	< 0.001	0%
Gamma Glutamyl Transpeptidase	10	1.63	1.24	2.18	0.27	0.12	0.43	< 0.001	41%
Globulin	3	1.63	0.85	3.13	0.27	-0.09	0.63	0.14	70%
Albumin	30	0.24	0.17	0.33	-0.8	-0.98	-0.61	< 0.001	86%
Total Bilirubin	36	1.82	1.39	2.38	0.33	0.18	0.48	< 0.001	91%

Direct Bilirubin	8	2.14	0.87	5.38	0.42	-0.08	0.93	0.1	91%
Coagulation									
Activated Partial Thromboplastin Time	21	1.18	0.80	1.72	0.09	-0.12	0.3	0.4	81%
Prothrombin Time/International Normalized	38	2.86	2.10	3.89	0.58	0.41	0.75	< 0.001	86%
D-Dimer	57	3.30	2.76	3.96	0.66	0.56	0.76	< 0.001	94%
Fibrinogen	18	1.69	1.14	2.56	0.29	0.07	0.52	0.009	85%
Inflammatory									
C-Reactive Protein	56	4.03	3.68	4.41	0.77	0.72	0.82	< 0.001	97%
Erythrocyte Sedimentation Rate	13	1.82	1.34	2.47	0.33	0.16	0.5	0.002	60%
Interleukin 1 Beta	5	0.80	0.53	1.22	-0.12	-0.35	0.11	0.29	0%
Interleukin 2 Receptor	6	6.45	4.10	10.14	1.03	0.78	1.28	< 0.001	62%
Interleukin 6	28	5.01	2.71	9.43	0.89	0.55	1.24	< 0.001	97%
Interleukin 8	9	3.96	2.52	6.11	0.76	0.51	1	< 0.001	73%
Interleukin 10	7	5.29	2.96	9.27	0.92	0.6	1.23	< 0.001	81%
Tumor Necrosis Factor Alpha	10	2.71	1.39	5.19	0.55	0.18	0.91	0.004	89%
Cardiac									
Myoglobin	13	5.01	2.10	12.16	0.89	0.41	1.38	< 0.001	98%
Creatine Kinase Isoenzyme/Myocardial Band	14	2.71	1.75	4.18	0.55	0.31	0.79	< 0.001	66%
Alpha Hydroxybutyrate Dehydrogenase	4	9.27	5.01	17.14	1.23	0.89	1.57	< 0.001	29%
Troponin (T And I)	36	3.55	2.38	5.29	0.7	0.48	0.92	< 0.001	92%
Brain Natriuretic Peptide (And Pro-BNP)	17	5.48	3.07	9.78	0.94	0.62	1.26	< 0.001	95%
Blood Gas									
Ph	3	1.63	0.48	5.48	0.27	-0.4	0.94	0.43	94%
Partial Pressure Of Carbon Dioxide	7	0.74	0.30	1.85	-0.17	-0.67	0.34	0.52	93%
Partial Pressure Of Oxygen	7	0.49	0.19	1.29	-0.39	-0.91	0.14	0.15	93%
Bicarbonate	5	0.55	0.32	0.95	-0.33	-0.63	-0.03	0.03	75%
Pao2:Fio2 Ratio	9	0.13	0.06	0.28	-1.14	-1.57	-0.71	< 0.001	89%
Other									
Lactic Acid	11	2.30	1.27	4.18	0.46	0.13	0.79	0.006	91%
Ferritin	20	5.19	3.07	8.62	0.91	0.62	1.19	< 0.001	88%

Total Cholesterol	6	0.32	0.19	0.55	-0.63	-0.92	-0.33	< 0.001	68%
Triglycerides	5	1.99	0.79	5.10	0.38	-0.13	0.9	0.15	90%
High Density Lipoprotein	5	0.47	0.34	0.64	-0.42	-0.6	-0.25	< 0.001	0%
Low Density Lipoprotein	5	0.33	0.18	0.60	-0.61	-0.94	-0.28	< 0.001	63%
Hemoglobin A1c	5	1.34	0.88	1.99	0.16	-0.07	0.38	0.17	53%
Uric Acid	6	2.26	1.06	4.83	0.45	0.03	0.87	0.04	82%
Creatine Kinase	28	2.71	2.03	3.62	0.55	0.39	0.71	< 0.001	79%
Lactate Dehydrogenase	47	7.32	5.19	10.33	1.10	0.91	1.29	< 0.001	89%
Procalcitonin	38	4.18	2.96	5.89	0.79	0.6	0.98	< 0.001	93%

COVID-19: Novel coronavirus disease 2019; CD: Cluster of differentiation.

Table 3: Absolute mean difference of laboratory values associated with mortality in COVID-19 in a meta-analysis.

Laboratory Value	Units	Number of Studies	Number of Patients	Absolute Mean Difference	95% Lower Limit	95% Upper Limit	p	I^2
Hematologic								
White Blood Cell Count	10^9/L	48	10769	2.38	1.97	2.79	< 0.001	72%
Absolute Neutrophil Count	10^9/L	36	7687	2.61	2.04	3.18	< 0.001	85%
Percent Neutrophil Count	%	6	1468	19.28	12.33	26.22	< 0.001	96%
Absolute Lymphocyte Count	10^9/L	57	12201	-0.34	-0.4	-0.28	< 0.001	88%
Percent Lymphocyte Count	%	8	1884	-15.21	-18.08	-12.33	< 0.001	91%
Absolute Basophil Count	10^9/L	4	1196	0	0	0	1	0%
Absolute Eosinophil Count	10^9/L	5	1362	-0.05	-0.08	0.02	0.001	96%
Absolute Monocyte Count	10^9/L	9	1397	-0.04	-0.07	-0.01	0.01	0%
Hemoglobin	g/L	34	8266	-2.8	-4.9	-0.7	0.01	67%
Hematocrit	%	3	1636	-1.21	-3.3	0.88	0.26	48%
Red Blood Cell Count	10^9/L	5	2414	-0.17	-0.38	0.04	0.11	83%
Platelet Count	10^9/L	43	10727	-39.85	-52.06	-27.65	< 0.001	90%
Neutrophil to Lymphocyte Ratio	-	9	2560	4.04	1.59	6.48	0.001	91%
Lymphocyte Subsets								
Total CD3+/T cells	cells/µL	6	987	-412.56	-560.04	-265.08	< 0.001	93%
Total CD4+/T Helper Cells	cells/µL	7	1049	-216.47	-315.47	-117.47	< 0.001	95%
Percent CD4+ Cells	%	3	1095	-13.71	-53.08	5.67	0.17	98%

Total CD8+/Supressor/Cytotoxic T Cells	cells/µL	7	1166	-125.01	-177.54	-72.49	< 0.001	94%
Percent CD8+ Cells	%	3	1095	-9.96	-20.12	0.016	0.05	97%
Total Natural Killer Cells	cells/µL	3	301	-110.12	-226.16	5.92	0.06	94%
Total CD19+/B cells	cells/µL	3	301	-22.1	-55.7	11.5	0.2	51%
CD4+/CD8+ Ratio	-	3	866	-0.01	-0.43	0.4	0.94	53%
Electrolytes/Renal								
Sodium	mmol/L	12	2505	-0.29	-1.07	0.48	0.46	62%
Potassium	mmol/L	8	1580	0.08	-0.07	0.22	0.29	60%
Chloride	mmol/L	4	987	-0.85	-2.06	0.36	0.17	64%
Calcium	mmol/L	4	826	-0.1	-0.25	0.04	0.16	97%
Glucose	mmol/L	16	3577	1.35	0.88	1.81	< 0.001	74%
Blood Urea Nitrogen	mmol/L	34	6596	3.07	2.55	3.6	< 0.001	80%
Creatinine	µmol/L	48	9695	17.83	13.89	21.77	< 0.001	78%
Glomerular Filtration Rate	ml/min/1.7m^2	5	1840	-24.3	-33.64	-14.97	< 0.001	86%
Cystatin C	mg/L	3	44	80.1	-0.12	0.31	0.39	82%
Liver								
Aspartate Aminotransferase	U/L	37	7510	9.44	5.98	12.91	< 0.001	86%
Alanine Aminotransferase	U/L	47	9018	3.99	2.25	5.74	< 0.001	60%
Alkaline Phosphatase	U/L	5	928	9.35	5.04	13.65	< 0.001	0%
Gamma Glutamyl Transpeptidase	U/L	10	2299	6.93	1.44	12.42	0.01	55%
Globulin	g/L	3	786	1.74	0.13	3.36	< 0.001	95%
Albumin	g/L	28	5527	-3.93	-4.93	-2.92	0.03	49%
Total Bilirubin	µmol/L	32	6870	2.06	1.06	3.06	< 0.001	87%
Direct Bilirubin	µmol/L	8	1748	0.72	-0.41	1.86	0.21	90%
Coagulation								
Activated Partial Thromboplastin Time	sec	19	3097	0.08	-0.14	0.3	0.47	82%
Fibrinogen	g/L	16	4076	0.32	0.09	0.55	0.006	82%
Inflammatory								
Erythrocyte Sedimentation Rate	mm/hr	11	2223	8.17	4.33	12	< 0.001	40%
Interleukin 1 Beta	pg/mL	4	478	-0.3	-0.62	0.02	0.07	0%
Interleukin 2 Receptor	U/mL	6	1046	506.43	392.25	620.61	< 0.001	54%
Interleukin 6	pg/mL	24	4578	26.6	21.65	31.56	< 0.001	97%
Interleukin 8	pg/mL	8	1215	16.57	12.99	20.14	< 0.001	15%

Interleukin 10	pg/mL	7	1234	5.09	2.86	7.33	< 0.001	85%
Tumor Necrosis Factor Alpha	pg/mL	9	1422	3.74	1.07	6.41	0.006	93%
Cardiac								
Myoglobin	ng/mL	9	2226	93.88	47.52	140.25	< 0.001	92%
Creatine Kinase Isoenzyme/Myocardial Band	µmol/L	11	2462	2.63	1.74	3.52	< 0.001	52%
Blood Gas								
pH	-	3	624	0.01	-0.02	0.03	0.46	86%
Partial Pressure of Carbon Dioxide	mmHg	7	1450	-0.69	-4.53	3.15	0.73	90%
Partial Pressure of Oxygen	mmHg	7	1445	-15.39	-31.2	0.42	0.06	96%
Bicarbonate	mmol/L	5	920	-1.05	-1.9	-0.21	0.01	64%
PaO2:FiO2 Ratio	-	7	1580	-117.78	-196.72	-38.85	0.003	99%
Other								
Lactic Acid	mmol/L	10	2496	0.42	0.12	0.71	0.005	95%
Ferritin	ng/mL	19	3108	696.78	488.42	905.15	< 0.001	90%
Total Cholesterol	mmol/L	6	1421	-0.55	-0.84	-0.25	< 0.001	82%
Triglycerides	mmol/L	5	1430	0.26	-0.1	0.62	0.15	96%
High Density Lipoprotein	mmol/L	4	1129	-0.13	-0.17	-0.08	< 0.001	0%
Low Density Lipoprotein	mmol/L	5	1213	-0.47	-0.69	-0.25	< 0.001	72%
Hemoglobin A1c	%	5	1855	0.22	-0.14	0.58	0.23	82%
Uric Acid	µmol/L	6	854	46.48	2.41	90.55	0.04	75%
Creatine Kinase	U/L	24	5217	60.62	39.73	81.5	< 0.001	75%
Lactate Dehydrogenase	U/L	41	7883	164.89	128.87	200.9	< 0.001	92%
Procalcitonin	ng/mL	31	6792	0.21	0.14	0.29	< 0.001	92%

COVID-19: Novel coronavirus disease 2019; CD: Cluster of differentiation.

with mortality, except there was no significant association between CD19+/B cells and CD4+ to CD8+ ratio.

Electrolytes, renal, and liver function

Among electrolytes and renal function, only glucose (OR 2.66, 95% CI 1.75-4.03), blood urea nitrogen (BUN, OR 7.06, 95% CI 4.33-11.51), creatinine (OR 2.43, 95% CI 2.22-2.66) and low glomerular filtration rate (GFR, OR 0.27, 95% CI 0.11-0.62) were significant. Nearly all liver function tests (aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma glutamyl transpeptidase (GGT), total bilirubin) were significantly associated with mortality, with AST being most significant (OR 2.61, 95% CI 1.92-3.55) and more significant than ALT (OR 1.22, 95% CI 1.14-1.29). A low albumin was also significantly associated with mortality (OR 0.24, 95% CI 0.17-0.33). Globulin and direct bilirubin had no significant association with morality, but both were limited by a small number of studies.

The absolute difference in creatinine (17.83 µmol/L, 95% CI 13.89-21.77) and GFR (-24.3 ml/min/1.7m^2, 95% CI -14.97--33.64) were most significant. AST (9.44 U/L, 95% CI 5.98-12.91) and ALP (9.35 U/L, 95% CI 5.04-13.65) were the most significant absolute liver functions.

Coagulation

D-Dimer is the most significant coagulation parameter associated with mortality (OR 3.30, 95% CI 2.76-3.96), followed by prothrombin time/International Normalized Ratio (PT/INR, OR 2.86, 95% CI 2.10-3.89). Because these parameters are laboratory specific, an absolute mean difference was not calculated for them.

Inflammatory

Aside from interleukin measures, C-reactive protein (CRP) is the most significant inflammatory marker associated with morality (OR 4.03, 95% CI 3.68-4.41), and much more so than erythrocyte sedimentation rate (ESR, OR 1.82, 95% CI 1.34-2.47). All of the interleukin tests studied except interleukin 1 beta were significantly associated with mortality. Among the interleukin tests, interleukin 2 receptor (OR 6.45, 95% CI 4.10-10.14), interleukin 10 (OR 5.39, 95% CI 2.96-9.27), and interleukin 6 (OR 5.01, 95% CI 2.71-9.43) were most significant.

An absolute mean difference of CRP was not calculated due to its dependence on lab variability. The absolute mean difference in interleukin 2 receptor was most apparent (506.43 U/mL, 95% CI 392.25-620.61).

Cardiac

All cardiac markers (myoglobin, creatine kinase-myocardial band (CK-MB), alpha hydroxybutyrate dehydrogenase, troponin, and brain natriuretic peptide (BNP and pro-BNP)) were significantly associated with mortality, with alpha hydroxybutyrate dehydrogenase (OR 9.27, 95% CI 5.01-17.14), BNP (OR 5.48, 95% CI 3.07-9.78), and myoglobin (OR 5.01, 95% CI 2.10-12.16) the most significantly associated. Troponin and BNP were not analyzed for absolute mean difference due to their various laboratory tests (i.e. troponin I and troponin T or BNP and pro-BNP) and different cutoffs and interpretation. Myoglobin (93.88 ng/mL, 95% CI 47.52-140.25) and CK-MB (2.63 µmol/L, 95% CI 1.74-3.52) were both significantly associated with mortality in the absolute mean difference analysis as well.

Blood Gas

In the analysis of blood gas level, only PaO2:FiO2 ration (P/F ratio) was significant (OR 0.13, 95% CI -0.06-0.28) with an absolute mean difference of -117.78 (95% CI -38.85 - -196.72).

Other

Among the other tests studied, lactate dehydrogenase (OR 7.32, 95% CI 5.19-10.33) and ferritin (OR 5.19, 95% CI 3.07-8.62) were most significant. Lactic acid, triglycerides, hemoglobin A1c, and uric acid were not significant. Lower levels of total cholesterol (OR 0.32, 95% CI 0.19-0.55), high density lipoprotein (OR 0.47, 95% CI 0.34-0.64), and low density lipoprotein (OR 0.33, 95% CI 0.18-0.60) were associated with increased mortality. Elevated creatine kinase (CK, OR 2.71, 95% CI 2.03-3.62) and procalcitonin (OR 4.18, 95% CI 2.96-5.89) were also significantly associated with mortality, but less so.

Absolute mean differences in ferritin (696.78 ng/mL, 95% CI 488.42-905.15), LDH (164.89 U/L, 95% CI 128.87-200.9), and CK (60.62 U/L, 95% CI 39.73-81.5) were the largest. Other values were statistically significant but much smaller.

Risk of bias

The risk of bias within studies was low in 27% (n = 26), moderate in 63% (n = 60), and high in 11% (n = 10) of studies. The most common reason for high risk of bias was selective patient population. The most common reason for moderate risk of bias was either not accounting for patients still hospitalized or unclear reporting of the timing of either the laboratory value or the outcome (mortality). Overall heterogeneity was moderate to high with 58% (38/65) of laboratory values in the absolute mean difference analysis and 60% (43/72) in the standardized mean difference with I^2 values > 80%. Funnel plot analyses showed most values with a low risk of publication bias.

Discussion

This systematic review and meta-analysis identified many laboratory abnormalities associated with mortality in COVID-19, but was limited by heterogeneity and risk of bias. Laboratory tests that have been previously identified to have prognostic and diagnostic accuracy seem to be the most associated with mortality. This includes lymphopenia, thrombocytopenia, leukocytosis, elevated liver enzymes, elevated LDH, elevated cardiac enzymes, and elevated ferritin [10-15,114].

In light of the pandemic nature of COVID-19, the ability to accurately identify patients at risk for poor outcome is paramount. Most patients with COVID-19 do not die from it. Given that this disease has placed a strain on healthcare resources in many locations and will continue to potentially do so, identification of patients who need some of these precious resources, like hospitalization or ICU care, will help in fair al-

location. When effective targeted treatments are identified, these prognostic values may also help identify patients who are most likely to benefit from these therapies.

In regards to specific laboratory values, the combination of neutrophilia and lymphopenia has been combined into a relatively new value called the neutrophil to lymphocyte ratio (NLR). This has been studied in several infectious and inflammatory processes, like bacteremia, [115] pancreatitis, [116,117] and pulmonary embolism [118], and has shown some diagnostic and prognostic value. It appears to be significantly associated with mortality in our meta-analysis.

All cardiac biomarkers studied were significantly associated with mortality. This is not surprising, as the risk of cardiac involvement in COVID-19 has been well studied and has been previously associated with mortality [119]. COVID-19, too, has been reported to be associated with fatal myocarditis [120]. Interestingly, troponin, which is one of the more common cardiac biomarkers evaluated, is one of the least significant markers compared to other values like myoglobin and alpha hydroxybutyrate dehydrogenase.

Only the P/F ratio was significant when examining blood gas levels. One of the hallmarks of COVID-19 is a ARDS-like illness. P/F has been well studied in ARDS and has been shown to be associated with mortality, so its association with mortality in COVID-19 should be no surprise. More interesting, though, pH and pO_2 have no significance and lactic acid, interestingly, has only minimal significance.

When examining liver enzymes, AST, ALT, ALP, and GGT all have significant association with mortality. However, AST appears to be much more associated than ALT. This, in addition to the GGT elevation, has been described in the prior SARS outbreak [121], but is not typical of other viral hepatitis entities [122], like hepatitis B or C. It is more commonly seen in ischemic or congestive hepatopathy [123]. Therefore, direct viral injury may not be the only pathophysiology of liver injury in COVID-19 [124,125].

Nearly all markers of inflammation appear to be significantly associated with mortality in COVID-19, including tumor necrosis factor alpha and several interleukin levels. CRP appears to be the most significant inflammatory marker that is commonly available in clinical practice. Several other markers that have significant association with inflammation are also elevated, like D-Dimer, ferritin, and LDH. The pathophysiology of these values is poorly understood. D-Dimer has been hypothesized to be elevated not only due to inflammation but also due to a hypercoagulable state. However, recent research has shown that COVID-19 may not, in fact, be a hypercoagulable state [126] despite initial anecdotal reports and observations of this [127].

Our meta-analysis involved a very large number of studies so even small differences, which may not be clinically significant, were rendered statistically significant. For example, the absolute difference in white blood cell count associated with mortality was 2.38, which would not cause alarm to most clinicians. Also, several laboratory values, although significant, are not routinely available in clinical practice (e.g. lymphocyte subsets or interleukin values).

Limitations

Our meta-analysis has some limitations. There is always a risk of missing potentially germane articles, but we attempted to combat this by using a pre-specified protocol, searching multiple databases, using two independent reviewers, and searching other systematic reviews for references. There was also a very high rate of no response to email inquiries of authors for data, which could introduce bias. All of the included studies were observational, and there was, in general, a moderate risk of bias within the studies. Our process of assessing quality with two authors was not blinded, so there, again, could be bias in the assessment of quality. There also was a significant amount of heterogeneity, which can be expected when such a large number of studies is analyzed but also raises questions as to whether there are subsets of patients in whom specific laboratory values might be more or less accurate.

Conclusion

Our meta-analysis identified multiple laboratory values associated with mortality in COVID-19, but was limited by heterogeneity. Many of these have been described previously: Lymphopenia, thrombocytopenia, leukocytosis, elevated D-Dimer, ferritinemia, elevated LDH, elevated liver enzymes, and cardiac injury. Clinicians can use this information to help predict which patients are most at risk for adverse outcomes with COVID-19 and how best to allocate limited healthcare resources.

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Conflict of Interest

To the best of our knowledge, the authors have no conflicts of interest, financial or other, to declare regarding this manuscript.

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