Section: Biochemistry

Systematic Review and Meta Analysis

CRITICAL ROLE OF INFLAMMATORY BIOCHEMICAL MARKERS DURING CORONAVIRUS DISEASE 2019:- A SYSTEMATIC REVIEW AND META-ANALYSIS

Sangeeta Singh[1], Mamta Gupta[2], Basant Joshi[3], Kratika Singhal[4]

[1]Professor & Head, Department of Biochemistry, VCSGGIMSR, Srinagar, India.
[2]Assistant Professor, Department of Biochemistry, RMCH, Bareilly, India.
[3]Assistant Professor, Department of Biochemistry, RMCH, Bareilly, India
[4]SRF, Department of Biochemistry, Santosh Medical College, Ghaziabad, India.

Received : 19/03/2023
Received in revised form : 15/04/2023
Accepted : 28/04/2023

Keywords:
systematic literature review; meta-analysis; coronavirus; inflammatory biomarkers.

Corresponding Author:
Dr. Basant Joshi,
Email: bjoshi86@gmail.com

DOI: 10.47009/jamp.2023.5.3.143

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2023; 5 (3); 688-696

Abstract

Background: Biomarkers play an important role in clinical decision making in infectious diseases. The covid 19 pandemic caused by SARS-CoV-2 virus has impacted the whole world. The objective of this study is to conduct a systematic review and meta analysis to evaluate the association between select inflammatory biomarkers and outcome in covid 19 patients. This study seeks to inform subsequent research by statistically summarizing the levels of these biomarkers, in patients of covid 19 with varied severity. **Materials and Methods:** A meta-analysis and systematic literature review were carried out. The search focused on research papers that reported the laboratory results of COVID-19-positive patients and included the names of routine UK NHS laboratory tests. For each biomarker, a random effects meta-analysis of the standard deviation between the COVID-19-positive and -negative groups was carried out. Interleukin-6, ferritin, C-Reactive Protein, procalcitonin and D-dimer were taken from the studies as laboratory parameters. **Result:** Using the laboratory data, mean differences were estimated using meta-analyses with associated confidence intervals of 95 percent. Increased levels of interleukin-6, ferritin, C-Reactive Protein, procalcitonin and D-dimer were directly corelated to severe and fatal COVID-19 cases. **Conclusion:** Interleukin-6, ferritin, C-Reactive Protein, procalcitonin and D-dimer are important laboratory parameters in diagnosing coronavirus cases. Further exploration is expected to distinguish whether routine lab biomarkers can be utilized in the improvement of a clinical scoring framework to help with emergency of patients.

INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread rapidly across the globe, resulting in significant morbidity and mortality.[1] Without effective contact tracing, social distancing, lockdowns, or vaccination, the number of cases worldwide continues to rise and is likely to continue rising further. Fever, cough, sore throat, headache, fatigue, myalgia, breathlessness, anosmia, and ageusia are all common signs of the disease.[2]

It has been difficult for patients with COVID-19 to be identified in the laboratory. Additionally, a second or third infection peak is currently occurring in a number of nations,[3] putting a significant strain on testing facilities in numerous locations. On nasal samples, reverse transcription polymerase chain reaction (RT-PCR),[4] is the primary test used to support the diagnosis. Impediments of RT-PCR are the somewhat lengthy time required to circle back as well as defective awareness.[5]

Routine research facility biomarkers can give a general image of the wellbeing status of a patient in intense clinical settings. However, there are no routine laboratory biomarkers that can be used as a standalone diagnostic test or to assist physicians in determining which patients should receive treatment first.[6] To aid in the diagnosis of COVID-19, some attempts have been made to combine a number of biomarkers and other parameters into a clinical scoring algorithm.[7] However, these models are frequently poorly reported, have a high risk of bias due to poor reporting, poor methodological conduct, and lack robust validation. Involving these models by and by may bring about execution qualities that are lower than those announced in the writing.[8]

This study sought to inform subsequent research by statistically summarizing routine laboratory biomarker measurements in COVID-19-positive and

ISSN (O): 2687-5365; ISSN (P): 2753-6556

-negative patients. Clinical scoring algorithms that are likely to be important for use in clinical settings that do not readily have access to COVID-19 point-of-care (POC) or laboratory testing could benefit from this research.

MATERIALS AND METHODS

Protocol

We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) and Cochrane Collaboration Handbook recommendations.[9,10]

Search Strategy

Adapting the search to the specifics of each database, we used relevant descriptors and synonyms to search MEDLINE, EMBASE, LILACS, IBECS, and the Cochrane Central Register of Controlled Trials (CEN- TRAL). To find published, ongoing, and unpublished studies, we also searched the Open Grey database, the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP), and ClinicalTrials.gov. Finally, we searched the references lists of the included studies using the snowballing method.

Eligibility Criteria and Study Selection

We Included in the electronic search were all studies published in 2020 with no language restrictions. According to the National Health Commission of China (NHCC) Guidelines for Diagnosis and Management of COVID-19 or World Health Organization Interim Guidance for COVID-19,[11,12] studies were included if they presented laboratory data, such as serum IL-6 levels, from mild-to-moderate, severe, or critical COVID-19 patients. Rejection standards consisted of studies that evaluated pregnant ladies, pediatric patients, people co-tainted with different microorganisms, or populaces solely connected with oncological, rheumatological, transfers, or persistent renal infection.

Data Extraction and Quality Appraisal

To collect data from the included studies, we used a form that was already set up. We specifically extracted the following characteristics from the studies and participants: age, gender, the severity of the condition, the diagnostic criteria, the number of participants who were screened, randomized, analyzed, excluded, lost to follow-up, and dropped out, the setting, the length of the study, laboratory biomarkers, outcome measures, and time points that were reported are all important factors. The modified Newcastle-Ottawa Scale (NOS) was then used to evaluate each study's inherent bias risk.[13] When any study data or other details were missing, we attempted to get in touch with the studies' authors.

Summary Measures and Synthesis of Results

Concentrate on selection, information extraction, and evaluation of the selected studies were performed independently by two survey creators. Discussion or, if necessary, consulting a third author was used to resolve disagreements. For the purpose of analysis, the studies were divided into two distinct groups: mortality and severity groups. IL-6, ferritin, CRP, procalcitonin, and D-dimer were analyzed in the laboratory. Between studies, the assays for detecting laboratory tests were comparable.

Statistical analysis

We performed the meta-analysis by utilizing the R software's "meta" package (version 3.4.1) following the extraction of the data.[14] Following Hozo SP et al.'s method, we estimated the means and standard deviations for studies with continuous data presented as medians and interquartile ranges.[15] The mean difference (MD) and 95% confidence interval (CI) for each of the laboratory parameters related to patients with confirmed COVID-19, whether they had severe disease or not, non-survivors, and survivors were calculated in a meta-analysis. The I2 statistic and the chi-square (2) test were used to evaluate heterogeneity among the included studies. Pooled results were calculated using a random effects model. When I2 was greater than 50%, a sensitivity analysis was conducted to investigate the causes of heterogeneity. By excluding studies with unclear timepoints of collection and those that collected blood parameters seven days after hospital admission, we investigated the causes of heterogeneity. Egger's test was used to look for publication bias in meta-analyses that included at least ten studies (S2A and S2B Table).

RESULTS

Literature Retrieval

The search identified 1250 articles. After duplicate removal, title, abstract and full-text screening, 40 studies were included in this systematic review and meta-analysis.

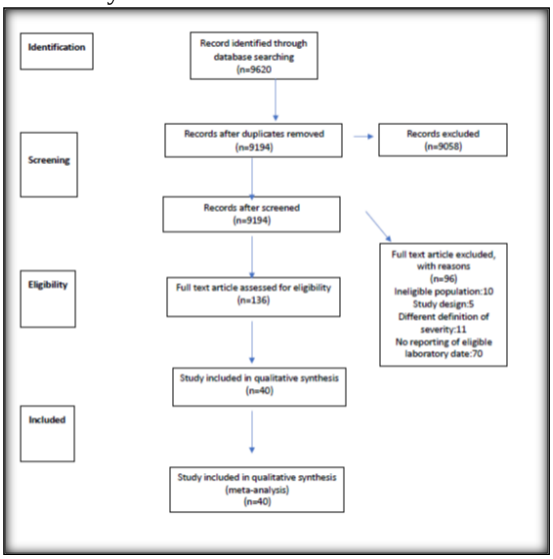

Figure 1: Study selection process flow chart based on Prisma

ISSN (O): 2687-5365; ISSN (P): 2753-6556

Characteristics of Included Studies

Most of the research (sixty percent) was carried out in China. Till January 2021, 20 % of the articles were still in pre-print, despite being published articles. Articles were either distributed or submitted between February 2020 to September 2020, and generally announced information were gathered between December 2019 to June 2020. The sample size was 340 patients on average (SD = 609.1), and 45% of those patients were found to be COVID-19 positive (SD = 22.48%). However, different definitions of COVID-19-positive patients were used in different studies. The official guidelines that were in place at the time of testing in the nation where the data were collected served as the foundation for the COVID-19 diagnoses. Instead of a composite reference standard, RT-PCR was typically used as the COVID-19 reference standard.

Table 1: Baseline and demographic characteristics of the included studies. Assessed outcome: Severity

Study ID	Severity criteria	Total enrolled patients	Severe group				Non-Severe group			
			No. (%)	Age*ω*	Male (%)	Comorbidity (%)	No. (%)	Age*ω*	Male (%)	Comorbidity (%)
Guang Chen, 2020.[16]	Severe vs Moderate cases according to NHCC COVID-19 Guideline (6th Edition) a	21	11 (52.38)	61.0 (56.5–66.0)	10 (90.9)	5 (45.5)	10 (47.62)	52.0 (42.8–56.0)	7 (70.0)	2 (20.0)
Yong Gao, 2020,[17]	Severe vs Mild cases according to WHO Interim Guidance for COVID-19c	43	15 (53.88)	45.20 (± 7.68)	9 (60)	*ωω*	28 (46.12)	42.96 (± 14.00)	17 (60.71)	*ωω*
Zhongliang Wang, 2020,[18]	Patients with SpO2<90% (Severe) vs Patients with SpO2>90% (Non- severe) according to NHCC COVID-19 Guidelines (3rd edition)a	69	14 (20.29)	70.5 (62.0–77.0)	7 (50)	*ωω*	55 (79.71)	37.0 (32.0–51.0)	25 (45)	*ωω*
Chuan Qin, 2020,[19]	Severe vs Moderate cases according to NHCC COVID-19 Guidelines (5th Edition)a	452	286 (63.27)	61 (51–69)	155 (54.2)	146 (51)	166 (36.73)	53 (41.25–62)	80 (48.2)	55 (33.1)
Chen Lei, 2020,[20]	Severe/Critical vs Mild cases according to NHCC COVID-19 Guidelines (4th Edition)a	29	14 (48.28)	NR	NR	*ωω*	15 (51.72)	NR	NR	*ωω*
Ruirui Wang, 2020,[21]	Critical (Severe or critical cases) vs Non-critical (mild or moderate) cases according to NHCC COVID-19 Guidelines (5thEdition)a	125	25 (20)	49.40 (±13.64)	16 (64)	12 (48)	100 (80)	39.47 (±14.84)	55 (55)	22 (22)
Zhe Zhu, 2020,[22]	Severe vs Non-severe cases according to NHCC COVID-19 Guidelines (6th Edition)a	127	16 (12.6)	57.50 (±11.70)	9 (56.25)	12 (75)	111 (87.4)	49.95 (±15.52)	73 (65.77)	40 (36.04)
Xiaohua Chen, 2020,[23]	Moderate vs Severe vs Critically ill cases according to NHCC COVID-19 Guidelines (6th Edition)a	48	Severe: 10 (20.83) Critically ill: 17 (35.42)	Severe: 63.9 (±15.2) Critically ill: 79.6 (±12.6)	Severe: 9 (90) Critically ill: 15 (88.2)	*ωω*	21 (43.75)	52.8 (±14.2)	13 (61.9)	*ωω*
Ming Ding, 2020,[24]	Mild vs Severe vs Critical cases according to NHCC COVID-19 Guidelines (7th Edition)a	32	Severe: 10 (31.25) Critical: 11 (34.37)	Severe:61.3 (±17.9) Critical: 73.5 (±12.3)	Severe: 5 (50) Critical: 7 (63.63)	Severe: 3 (30) Critical: 4 (36.36)	11 (34.37)	54.9 (±11.3)	1 (9.09)	3 of 5 (60)
Chen LD, 2020,[25]	Mild (without pneumonia) vs Moderate cases with pneumonia (Non- severe) vs Severe cases with pneumonia according to NHCC COVID-19	106	25 (23.6)	60.68 (± 15.23)	15 (60)	11 (44.0)	Mild: 12 (11.3) Moderate: 69 (65.1)	Mild: 43.92 (± 13.73) Moderate: 51.41 (± 15.77)	Mild: 4 (33.3) Moderate: 34 (49.3)	Mild: 0 (0.0) Moderate: 14 (20.3)

ISSN (O): 2687-5365; ISSN (P): 2753-6556

	Guidelines (7th Edition)a									
Chen R, 2020,[26]	Mild/Moderate cases vs Severe cases vs Critical cases according to NHCC COVID-19 Guidelines (7th Edition)a	548	Severe: 155 (28.3) Critical: 48 (8.8)	Severe: 60.9 (± 13.8) Critical: 61.4 (±13.6)	Severe: 93 (60) Critical: 38 (79.2)	ωω	345 (62.9)	67.3 (±12.1)	182 (52.75)	ωω
Chi Y, 2020,[27]	Mild vs Moderate vs Severe cases according to NHCC COVID-19 Guidelines (5th Edition)a	66	8 (12.1)	54.0 (± 12.38)	5 (62.5)	4 (50)	Mild: 22 (33.4) Moderate: 36 (54.5)	Mild: 43.32 (± 18.38) Moderate: 40.81 (± 11.8)	Mild: 13 (59.1) Moderate: 19 (53)	Mild: 6 (27) Moderate: 8 (22)
Hu ZJ, 2020,[28]	Severe vs Non-severe cases according to NHCC COVID-19 Guidelines (7th Edition)a	76	13 (17.2)	61.5 (57.1–65.9)	8 (61.5)	ωω	63 (82.8)	48.2 (46.0–50.4)	26 (41.3)	ωω
Huang Z, 2020,[29]	Moderate (Non-severe) vs Severe vs Critical cases according to NHCC COVID-19 Guidelines (7th Edition)a	83	Severe: 29 (35) Critical: 33 (39.7)	Severe: 67 (60–79) Critical: 58 (49–62)	Severe: 16 (55.2) Critical: 26 (78.8)	Severe: 20 (69) Critical: 21 (63.6)	21 (25.3)	68 (57–69)	12 (57.14)	9 (42.86)
Li X, 2020,[30]	Severe (Severe pneumonia/ ARDS) vs Non-severe cases (Mild/ Common pneumonia) according to NHCC COVID-19 Guidelines (7thEdition)a and WHO Interim Guidance for COVID-19c	215	56 (26.1)	56.5 (20–72)	36 (64.3)	ωω	159 (73.9)	44 (32–52)	91 (57.2)	ωω
Liu D, 2020,[31]	Moderate vs Severe vs Critical cases according to NHCC COVID-19 Guidelines (7th Edition)a	2044	Severe: 689 (33.7) Critical: 268 (13.1)	Severe: 64.0 (54.0–71.0) Critical: 69.0 (62.0–77.0)	Severe: 349 (50.65) Critical: 176 (65.67)	Severe: 423/687 (61.57) Critical: 212/266 (79.7)	1087 (53)	59 (46–67)	475 (43.7)	540/1086 (49.72)
Ozsurekci Y, 2020,[32]	Mild vs Moderate vs Severe/ Critical cases according to WHO Interim Guidance for COVID-19c	30	11 (36.7)	NR	NR	ωω	Mild: 4 (13.4) Moderate: 15 (50)	NR	NR	ωω
Xu X, 2020,[33]	Moderate (non-severe) vs Severe vs Critically ill cases according to NHCC COVID-19 Guidelines (7th Edition)a	88	Severe: 32 (36.4) Critically ill: 9 (10.2)	Severe: 59.94 (±13.96) Critically ill: 74.78 (±10.06)	Severe: 8 (25) Critically ill: 7 (77.78)	Severe: 17 (53.13) Critically ill: 7 (77.78)	47 (53.4)	52.49 (±14.62)	21 (44.68)	17 (36.17)
Zeng YL, 2020,[34]	Ordinary (Non-severe) vs Severe vs Critical cases according to NHCC COVID-19 Guidelines (6th Edition)a	49	Severe: 16 (32.7) Critical: 5 (10.2)	Severe: 60 (±16) Critical: 68 (±20)	Severe: 8 (50) Critical: 3 (60)	ωω	28 (57.1)	46 (±19)	15 (53.6)	ωω
Zeng Z, 2020,[35]	Moderate (Non-severe) vs Severe / Critical cases according to NHCC COVID-19 Guidelines (6th Edition)a	317	Severe: 167 (52.68) Critical: 57 (17.98)	Severe: 62.0 (51.0–69.0) Critical: 68.0 (57.0–77.0)	Severe: 90 (53.9) Critical: 31 (54.4)	ωω	93 (29.34)	59.0 (46.0–68.5)	41 (44.1)	ωω
Zhao C, 2020,[36]	Mild (Non-severe) vs Severe cases according to WHO Interim Guidance for COVID-19c	172	60 (34.8)	70.6 (±11.6)	37 (61.7)	38 (63.3)	112 (65.2)	64 (50–67)	45 (40.2)	57 (50.9)
Zou L, 2020,[37]	Severe vs Non-severe cases according to NHCC COVID-19	121	52 (42.98)	69.5 (61.5–79.75)	32 (61.5)	52 (88.5)	69 (57.02)	60.0 (52.0–68.0)	34 (49.3)	39 (56.5)

ISSN (O): 2687-5365; ISSN (P): 2753-6556

	Guidelines (3rd-6th Edition)									

*ω*Values expressed in Median (interquartile range) or Mean ± SD (standard deviation).
ωω study does not describe the exact prevalence of overall comorbidities in each group.

Quality Assessment

Out of 40 studies, 32 were deemed to have a low risk of bias. A high proportion of studies reporting data from Chinese hospitals at an early stage of the pandemic, which may have limited applicability to NHS hospitals in the UK, a change in the diagnostic criteria during the pandemic as knowledge of the disease increased, and papers that were still in pre-print long after submission were additional factors that may have introduced bias.

Meta-Analysis

The pursuit system included chosen biomarkers that are promptly accessible across Emergency Departments in the UK NHS. The included studies did not all provide data for all of the biomarkers.

Table 2: Results of meta-analysis comparing laboratory parameters in COVID-19 patients.[38]

	SEVERE versus NON-SEVERE					FATAL versus NON-FATAL				
Parameter	**Number of studies**	**MD**	**Random; 95% CI**	**I2**	**Number of participants**	**Number of studies**	**MD**	**Random; 95% CI**	**I2**	**Number of participants**
C-Reactive Protein	14	53.54	39.79; 67.29	0.97	4,138	15	58.48	43.35; 73.61	0.99	3,755
Procalcitonin	11	0.08	0.03; 0.14	0.99	3,480	11	0.24	0.13; 0.36	0.96	2,845
Creatinine	10	8.07	4.28; 11.87	0.85	3,036	9	17.93	11.89; 23.98	0.91	2,174
D-Dimer	9	2.15	0.68; 3.63	0.99	3,181	14	4.64	3.03; 6.24	0.97	3,965
Ferritin	6	654.4	383.48; 925.33	0.96	3,470	9	853.43	601.20; 1105.67	0.94	2,088
IL-6	22	28.93	18.18; 39.69	0.99	4,861	19	70.82	45.24; 96.41	0.96	5,229

Research facility boundaries in extreme versus non-serious patients and non-enduring versus surviving patients with Coronavirus are portrayed in Table 3. There was a correlation between severe and fatal cases of COVID-19 and elevated levels of IL-6, ferritin, D-dimer, CRP, procalcitonin, tnf alpha. Nineteen investigations evaluated deadly and non-lethal gatherings of patients with Coronavirus and revealed IL-6. Patients who died had higher levels of IL-6 than those who survived, according to the combined findings of these studies [MD 75.80; 95% CI]. Patients with severe COVID-19 had higher levels of Il-6 than patients with mild COVID-19, according to pooled results from twenty-two studies of both severe and non-severe cases [MD 32.09; 95% CI]. The pooled investigation of nine examinations showed that patients with Coronavirus who didn't endure likewise had more elevated levels of ferritin [MD 89.40; 95% CI]. Six studies reported ferritin levels.[16,20,21] A meta-analysis of severe and non-severe patients revealed that ferritin levels were higher in patients with severe COVID-19 [MD 54.64; 95% CI]. The IL-6 parameters were subjected to a sensitivity assessment. Five examinations were viewed as anomalies in the mortality bunch,[14,29,32,33,43] and three examinations in the seriousness bunch.[20-22] Their exclusion from this calculation [MD 75.15;] had no effect on the direction of the meta-analysis's effect.

Table 3: Results of meta-analysis comparing laboratory parameters in mild, moderate and severe COVID-19 patients.

Parameters	Mild COVID-19	Moderate COVID-19	Severe COVID-19
IL-6	Normal range	Slightly raised	Highly raised
ferritin	Normal range	Slightly raised	Highly raised
D-dimer	Normal range	Slightly raised	Highly raised
CRP	Normal range	Slightly raised	Highly raised
procalcitonin	Normal range	Slightly raised	Highly raised
tnf alpha	Normal range	Slightly raised	Highly raised

We assessed publication bias with the Egger's test, which found publication bias in the meta-analysis of the relationship between IL-6 and severity (p0.001).

Sensitivity Analysis

Two sensitivity analyses were conducted by us. One that only included studies with a low risk of bias and another that only included studies that were already published. The level of heterogeneity decreased when we removed the studies with a high risk of bias (five out of thirty studies), but it remained high across all studies (>60% I2 statistic). For instance, COVID-19-positive patients had significantly higher values of interleukin-6, ferritin, C-reactive protein, procalcitonin, and D-dimer compared to COVID-19-negative patients.

The level of heterogeneity remained above 70% across all studies when we removed pre-prints but not peer-reviewed papers. COVID-19-positive patients had raised values of biomarkers like interleukin-6, ferritin, C-Reactive Protein, procalcitonin and D-dimer that were statistically

ISSN (O): 2687-5365; ISSN (P): 2753-6556

significantly higher than those of COVID-19-negative patients.

DISCUSSION

Severe COVID-19 infection is associated with a cytokine profile resembling secondary hemophagocytic lymphohistiocytosis.[39] A distinct pattern of hematological, biochemical, inflammatory, and immune biomarker abnormalities could be distinguished between patients with and without severe disease in this living systematic review with meta-analysis.

As high irritation is an essential driver of pathology in Coronavirus, designated enemy of inflammatory medicines are being assessed to lessen aggravation prompted harm to the respiratory system and to moderate the cytokine storm.[40,41] COVID-19 progression has now been divided into three clinical phases based on observational studies,[42,43] the viremia stage, the pneumonia stage, and the recovery stage. According to Lin L et al., as the phases move through each other,[43] cells T and B lessen, while fiery cytokines and D-Dimer expansion in serious patients. Because of this progression, some authors have proposed starting anti-inflammatory treatment in the acute phase to stop the inflammatory storms.[44] The early identification of individuals who will progress into more severe forms of the disease and who require specific interventions or treatments is one of the primary obstacles in defining initial treatment for COVID-19 patients.

A response to many acute infections and cytokines, including viral infections, is increased monocyte and neutrophil production (myelopoiesis) and mobilization from the bone marrow.[45] These cells, which are typically regarded as proinflammatory, are recruited to the sites of inflammation where they can produce interleukin-1, interleukin-6, interleukin-12, and tumour necrosis factor (TNF) in response to pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs).[46] According to our findings, elevated neutrophils are associated with an increase in white blood cells. This finding may indicate clinical deterioration and an increased likelihood of a poor outcome.

Numerous provocative variables can cause foundational harm and multi-organ disappointment. Patients with COVID-19 who have elevated serum levels of CRP, AST, LDH, and ferritin may have liver dysfunctions, necessitating prompt treatment in order to avoid irreversible organ damage and an increased mortality risk.[47] The viral infection of liver cells may directly result in liver damage in these patients. Indeed, pathological investigations have demonstrated that liver tissues contain the SARS-CoV.[48,49]

In healthy individuals, procalcitonin levels are typically undetectable, and in those with a virus infection or systemic inflammatory conditions, they either remain the same or moderately rise. Be that as it may, its levels increment altogether in instances of summed up disease, predominantly bacterial or contagious.[50] Procalcitonin levels increased significantly in non-survivors, according to this systematic review, but there was only a small effect size in studies comparing severe patients to non-severe patients. A significant increase in procalcitonin levels was linked to bacterial co-infection, progression to severe forms of COVID-19, and death in the meta-analysis conducted by Lippi G. and Plebani M.[51]

Disseminated intravascular coagulation, which is life-threatening and requires prompt intervention, frequently leads to fatal cases.[52] Ongoing clinical encounters with anticoagulants recommend that these substances are related with a lower chance of thromboembolic illness and extreme ischemic signs in certain patients. As a result, it is critical to identify COVID-19 patients at high risk for early anticoagulation. N. Tang et al,[53] reported that at admission, non-surviving COVID-19 patients had higher levels of fibrin-related markers (D-dimer and fibrin degradation product) than survivors. Low molecular weight heparin was found to significantly increase survival in severe SARS-CoV-2-infected patients with elevated D-dimer or sepsis-induced disseminated intravascular coagulation, according to the same authors. In the present precise survey, expanded degrees of D-dimer at emergency clinic confirmation could be a decent indicator of extreme and lethal instances of Coronavirus. D-dimer's ability to differentiate between patients with and without severe forms of COVID-19 was found to be similar in another meta-analysis,[54] but mortality data were not provided.

Ferritin is an intense protein that expansions because of a wide spec-trum of incendiary states, including contaminations, threat, iron over-burden, and liver or youngster ney illness.[55,56] The relationship between adult COVID-19 patients with hyperferritinemia and high levels of IL-6 can be explained by the findings of our meta-analysis, which shed light on the role that ferritin plays in assessing systemic hyper-inflammation. In terms of immunological biomarkers, we believe that both parameters can be used as warning signs during hospital admission for severe and fatal COVID-19 infections. In addition, ferritin and C-reactive protein appear to be screening tools for the early diagnosis of a systemic inflammatory response syndrome (SIRS) in patients with a severe form of COVID-19 (referred to as CSS), and they are less expensive than IL-6 and more readily available in frontline clinical practice.

Regardless of these thorough endeavors to direct clinicians in diagnosing CSS, segregating this pathology from different circumstances, especially sepsis or spread intravascular coagulation, stays testing because of the huge level of cross-over in clinical show.[57] As a result, biomarkers that can

ISSN (O): 2687-5365; ISSN (P): 2753-6556

predict which patients will develop the severe forms of COVID-19 have significant clinical potential. Our audit showed that more seasoned age, male orientation, and comorbidities imply potential danger factors for extreme and lethal cases, as has previously been accounted for in the logical writing. This audit likewise affirms that specific research center tests that are essential for routine consideration have additionally been dependably connected with extreme and deadly instances of Coronavirus, and including serum IL-6 could be applicable for anticipation however could likewise further develop remedial direction.

Limitations

The nature of the included studies is the main limitation of this review; Because they were published amid the inherent urgency of a global pandemic, most of the included studies were observational. Any meta-analysis's interpretation relies heavily on assessing the statistical heterogeneity of the included studies. The meta-analysis of the majority of the results in this study revealed a great deal of heterogeneity, necessitating a more in-depth examination of the studies to identify possible causes for this issue. By conducting sensitivity analysis and thoroughly analyzing the clinical and methodological heterogeneity among the studies, we attempted to identify the sources of statistical heterogeneity. In the meta-analyses, we looked into the causes of heterogeneity, but we couldn't find any differences that could explain the causes of heterogeneity between studies. In our meta-analyses, we also looked for signs of publication bias, and a meta-analysis of the relationship between IL-6 and severity raised the possibility of non-reporting bias. As we found significant heterogeneity in this meta-examination and tests for adapting to channel plot deviation, for example, the trim and fill strategy are known to perform ineffectively when there is enormous between-concentrate on heterogeneity,[58] we didn't perform trim and fill test.

CONCLUSION

As indicators of severe and fatal cases of COVID-19, this review points to elevated levels of IL-6, ferritin, D-dimer, tnf alpha, procalcitonin, and CRP. Increases in ferritin and IL-6, two important biomarkers of covid stress scale (CSS), may indicate systemic inflammation and a poor prognosis in COVID-19 patients, particularly the elderly and those with comorbid conditions. We suggest further exploration to distinguish whether routine lab biomarkers can be utilized in the improvement of a clinical scoring framework to help with severity assessment of covid 19 patients and empower health care providers.

REFERENCES

1. Zhou, F.; Yu, T.; Du, R.; Fan, G.; Liu, Y.; Liu, Z.; Xiang, J.; Wang, Y.; Song, B.; Gu, X.; et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. Lancet 2020, doi:10.1016/S0140- mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. Lancet 2020. 6736(20)30566-3.
2. Singhal, T. A review of coronavirus disease-2019 (COVID-19). Indian J. Pediatr. 2020. [CrossRef]
3. WHO. Timeline: WHO's COVID-19 Response. Available online: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/interactive-timeline#event-14 (accessed on 23 September 2020). coronavirus-2019/interactive-timeline#event-14 (accessed on 23 September 2020.
4. PHE, COVID-19: Guidance for Sampling and for Diagnostic Laboratories. Available online: https://www.gov.uk/government/ publications/wuhan-novel-coronavirus-guidance-for-clinical-diagnostic-laboratories (accessed on 29 July 2020).
5. Axell-House, D.B.; Lavingia, R.; Rafferty, M.; Clark, E.; Amirian, E.S.; Chiao, E.Y. The estimation of diagnostic accuracy of tests for COVID-19: A scoping review. J. Infect. 2020. [CrossRef] [PubMed]
6. Stegeman, I.; Ochodo, E.A.; Guleid, F.; Holtman, G.A.; Yang, B.; Davenport, C.; Deeks, J.J.; Dinnes, J.; Dittrich, S.; Emperador, D. Routine laboratory testing to determine if a patient has COVID-19. Cochrane Database Syst. Rev. 2020. [CrossRef]
7. Assandri, R.; Montanelli, A. Modified Corona Score can easily identify Covid-19 patients with gastrointestinal symptoms: An Italian proposal. Gastroenterol. Hepatol. Bed Bench 2020, 13, 393–395. [PubMed]
8. Wynants, L.; Van Calster, B.; Collins, G.S.; Riley, R.D.; Heinze, G.; Schuit, E.; Bonten, M.M.J.; Dahly, D.L.; Damen, J.A.; Debray, T.P.A.; et al. Prediction models for diagnosis and prognosis of covid-19: Systematic review and critical appraisal. BMJ 2020, 369, m1328. [CrossRef] [PubMed]
9. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta- analyses: the PRISMA Statement. Open Med. 2009; 3(3):e123–30. Epub 2009/01/01. PMID: 21603045; PubMed Central PMCID: PMC3090117.
10. Higgins JPT TJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). 2021.
11. Commission CNH. Chinese Clinical Guidance For COVID-19 Pneumonia Diagnosis and Treatment 2020.
12. Patel A, Jernigan DB. Initial Public Health Response and Interim Clinical Guidance for the 2019 Novel Coronavirus Outbreak—United States, December 31, 2019-February 4, 2020. MMWR Morb Mortal Wkly Rep. 2020; 69(5):140–6. Epub 2020/02/07. https://doi.org/10.15585/mmwr.mm6905e1 PMID: 32027631; PubMed Central PMCID: PMC7004396 Journal Editors form for disclosure of potential con- flicts of interest. No potential conflicts of interest were disclosed.
13. Bazerbachi F, Haffar S, Hussain MT, Vargas EJ, Watt KD, Murad MH, et al. Systematic review of acute pancreatitis associated with interferon-α or pegylated interferon-α: Possible or definitive causation? Pancreatology. 2018; 18(7):691–9. Epub 2018/08/01. https://doi.org/10.1016/j.pan.2017.08.012 PMID: 30061072.
14. R software. Available from: (https://cran.r-project.org/bin/windows/base/old/3.4.1/)
15. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol. 2005; 5:13. Epub 2005/04/21. https://doi.org/10.1186/1471- 2288-5-13 PMID: 15840177; PubMed Central PMCID: PMC1097734.
16. Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. J Clin Invest. 2020; 130(5):2620–9. Epub 2020/03/29. https://doi.org/10.1172/JCI137244

ISSN (O): 2687-5365; ISSN (P): 2753-6556

PMID: 32217835; PubMed Central PMCID: PMC7190990.

17. Gao Y, Li T, Han M, Li X, Wu D, Xu Y, et al. Diagnostic utility of clinical laboratory data determinations for patients with the severe COVID-19. J Med Virol. 2020; 92(7):791–6. Epub 2020/03/18. https://doi.org/10.1002/jmv.25770 PMID: 32181911; PubMed Central PMCID: PMC7228247.
18. Wang Z, Yang B, Li Q, Wen L, Zhang R. Clinical Features of 69 Cases With Coronavirus Disease 2019 in Wuhan, China. Clin Infect Dis. 2020; 71(15):769–77. Epub 2020/03/17. https://doi.org/10.1093/cid/ciaa272 PMID: 32176772; PubMed Central PMCID: PMC7184452.
19. Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, et al. Dysregulation of Immune Response in Patients With Coronavirus 2019 (COVID-19) in Wuhan, China. Clin Infect Dis. 2020; 71(15):762–8. Epub 2020/ 03/13. https://doi.org/10.1093/cid/ciaa248 PMID: 32161940; PubMed Central PMCID: PMC7108125.
20. Chen L, Liu HG, Liu W, Liu J, Liu K, Shang J, et al. [Analysis of clinical features of 29 patients with 2019 novel coronavirus pneumonia]. Zhonghua Jie He He Hu Xi Za Zhi. 2020; 43(0):E005. Epub 2020/02/07. https://doi.org/10.3760/cma.j.issn.1001-0939.2020.0005 PMID: 32026671.
21. Wang R, Pan M, Zhang X, Han M, Fan X, Zhao F, et al. Epidemiological and clinical features of 125 Hospitalized Patients with COVID-19 in Fuyang, Anhui, China. Int J Infect Dis. 2020; 95:421–8. Epub 2020/04/15. https://doi.org/10.1016/j.ijid.2020.03.070 PMID: 32289565; PubMed Central PMCID: PMC7151431.
22. Zhu Z, Cai T, Fan L, Lou K, Hua X, Huang Z, et al. Clinical value of immune-inflammatory parameters to assess the severity of coronavirus disease 2019. Int J Infect Dis. 2020; 95:332–9. Epub 2020/04/26. https://doi.org/10.1016/j.ijid.2020.04.041 PMID: 32334118; PubMed Central PMCID: PMC7195003.
23. Chen X, Zhao B, Qu Y, Chen Y, Xiong J, Feng Y, et al. Detectable serum SARS-CoV-2 viral load (RNAaemia) is closely correlated with drastically elevated interleukin 6 (IL-6) level in critically ill COVID- 19 patients. Clin Infect Dis. 2020. Epub 2020/04/18. https://doi.org/10.1093/cid/ciaa449 PMID: 32301997; PubMed Central PMCID: PMC7184354.
24. Ding M, Zhang Q, Li Q, Wu T, Huang YZ. Correlation analysis of the severity and clinical prognosis of 32 cases of patients with COVID-19. Respir Med. 2020; 167:105981. Epub 2020/05/19. https://doi.org/10.1016/j.rmed.2020.105981 PMID: 32421546; PubMed Central PMCID: PMC7167578 of interest.
25. Chen LD, Zhang ZY, Wei XJ, Cai YQ, Yao WZ, Wang MH, et al. Association between cytokine profiles and lung injury in COVID-19 pneumonia. Respir Res. 2020; 21(1):201. Epub 2020/07/31. https://doi.org/10.1186/s12931-020-01465-2 PMID: 32727465; PubMed Central PMCID: PMC7389162.
26. Chen R, Sang L, Jiang M, Yang Z, Jia N, Fu W, et al. Longitudinal hematologic and immunologic varia- tions associated with the progression of COVID-19 patients in China. J Allergy Clin Immunol. 2020; 146 (1):89–100. Epub 2020/05/15. https://doi.org/10.1016/j.jaci.2020.05.003 PMID: 32407836; PubMed Central PMCID: PMC7212968.
27. Chi Y, Ge Y, Wu B, Zhang W, Wu T, Wen T, et al. Serum Cytokine and Chemokine Profile in Relation to the Severity of Coronavirus Disease 2019 in China. J Infect Dis. 2020; 222(5):746–54. Epub 2020/06/21. https://doi.org/10.1093/infdis/jiaa363 PMID: 32563194; PubMed Central PMCID: PMC7337752.
28. Hu ZJ, Xu J, Yin JM, Li L, Hou W, Zhang LL, et al. Lower Circulating Interferon-Gamma Is a Risk Factor for Lung Fibrosis in COVID-19 Patients. Front Immunol. 2020; 11:585647. Epub 2020/11/03. https://doi.org/10.3389/fimmu.2020.585647 PMID: 33133104; PubMed Central PMCID: PMC7550399.
29. Huang Z, Xu S, Chen J, Wei Q, Lin L, Ye X, et al. Predictive value of laboratory tests on severity of newly hospitalized patients with COVID-19. 新型冠状病毒肺炎患者入院时检验指标在病情严重程度中的预测价值. 2020; 43(10):973–7. rayyan-111796663.
30. Li X, Liu Y, Li J, Sun L, Yang J, Xu F, et al. Immune characteristics distinguish patients with severe dis- ease associated with SARS-CoV-2. Immunol Res. 2020; 68(6):398–404. Epub 2020/09/30. https://doi.org/10.1007/s12026-020-09156-2 PMID: 32989677; PubMed Central PMCID: PMC7521864.
31. Liu D, Cui P, Zeng S, Wang S, Feng X, Xu S, et al. Risk factors for developing into critical COVID-19 patients in Wuhan, China: A multicenter, retrospective, cohort study. EClinicalMedicine. 2020; 25:100471. Epub 2020/08/26. https://doi.org/10.1016/j.eclinm.2020.100471 PMID: 32840491; PubMed Central PMCID: PMC7391125.
32. Ozsurekci Y, Aykac K, Er AG, Halacli B, Arasli M, Oygar PD, et al. Predictive value of cytokine/chemo- kine responses for the disease severity and management in children and adult cases with COVID-19. J Med Virol. 2020. Epub 2020/11/24. https://doi.org/10.1002/jmv.26683 PMID: 33225509; PubMed Cen- tral PMCID: PMC7753701.
33. Xu X, Yu MQ, Shen Q, Wang LZ, Yan RD, Zhang MY, et al. Analysis of inflammatory parameters and disease severity for 88 hospitalized COVID-19 patients in Wuhan, China. Int J Med Sci. 2020; 17 (13):2052–62. Epub 2020/08/14. https://doi.org/10.7150/ijms.47935 PMID: 32788884; PubMed Central PMCID: PMC7415392.
34. Zeng YL, Zhang C, Gao F, Ma L, Ding GG, Guo EE, et al. [Analysis of clinical characteristics of 49 cases of COVID-19]. Zhonghua Jie He He Hu Xi Za Zhi. 2020; 43(8):654–8. Epub 2020/07/31. https://doi.org/10.3760/cma.j.cn112147-20200225-00184 PMID: 32727176.
35. Zeng Z, Yu H, Chen H, Qi W, Chen L, Chen G, et al. Longitudinal changes of inflammatory parameters and their correlation with disease severity and outcomes in patients with COVID-19 from Wuhan, China. Crit Care. 2020; 24(1):525. Epub 2020/08/29. https://doi.org/10.1186/s13054-020-03255-0 PMID: 32854750; PubMed Central PMCID: PMC7450961.
36. Zhao C, Bai Y, Wang C, Zhong Y, Lu N, Tian L, et al. Risk factors related to the severity of COVID-19 in Wuhan. Int J Med Sci. 2021; 18(1):120–7. Epub 2021/01/05. https://doi.org/10.7150/ijms.47193 PMID: 33390780; PubMed Central PMCID: PMC7738952.
37. Zou L, Dai L, Zhang Y, Fu W, Gao Y, Zhang Z, et al. Clinical Characteristics and Risk Factors for Dis- ease Severity and Death in Patients With Coronavirus Disease 2019 in Wuhan, China. Front Med (Lau- sanne). 2020; 7:532. Epub 2020/09/10. https://doi.org/10.3389/fmed.2020.00532 PMID: 32903644; PubMed Central PMCID: PMC7438719.
38. Melo AKG, Milby KM, Caparroz ALMA, Pinto ACPN, Santos RRP, Rocha AP, et al. (2021) Biomarkers of cytokine storm as red flags for severe and fatal COVID-19 cases: A living systematic review and meta-analysis. PLoS ONE 16(6): e0253894. https://doi.org/10.1371/journal.pone.0253894
39. Sinha P, Matthay MA, Calfee CS. Is a "Cytokine Storm" Relevant to COVID-19? JAMA Intern Med. 2020. Epub 2020/07/01. https://doi.org/10.1001/jamainternmed.2020.3313 PMID: 32602883.
40. Schijns V, Lavelle EC. Prevention and treatment of COVID-19 disease by controlled modulation of innate immunity. Eur J Immunol. 2020. Epub 2020/05/22. https://doi.org/10.1002/eji.202048693 PMID: 32438473; PubMed Central PMCID: PMC7280664.
41. Buckley LF, Wohlford GF, Ting C, Alahmed A, Van Tassell BW, Abbate A, et al. Role for Anti-Cytokine Therapies in Severe Coronavirus Disease 2019. Critical Care Explorations. 2020; 2(8):e0178. https://doi.org/10.1097/CCE.0000000000000178 02107256-202008000-00011. PMID: 32832913
42. Livingston E, Bucher K. Coronavirus Disease 2019 (COVID-19) in Italy. Jama. 2020. Epub 2020/03/18. https://doi.org/10.1001/jama.2020.4344 PMID: 32181795.

ISSN (O): 2687-5365; ISSN (P): 2753-6556

43. Lin L, Lu L, Cao W, Li T. Hypothesis for potential pathogenesis of SARS-CoV-2 infection-a review of immune changes in patients with viral pneumonia. Emerg Microbes Infect. 2020; 9(1):727–32. Epub 2020/03/21. https://doi.org/10.1080/22221751.2020.1746199 PMID: 32196410; PubMed Central PMCID: PMC7170333.
44. Zheng Z, Peng F, Xu B, Zhao J, Liu H, Peng J, et al. Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis. J Infect. 2020. Epub 2020/04/27. https://doi.org/10. 1016/j.jinf.2020.04.021 PMID: 32335169; PubMed Central PMCID: PMC7177098.
45. McGonagle D, Sharif K, O'Regan A, Bridgewood C. The Role of Cytokines including Interleukin-6 in COVID-19 induced Pneumonia and Macrophage Activation Syndrome-Like Disease. Autoimmun Rev. 2020; 19(6):102537. Epub 2020/04/07. https://doi.org/10.1016/j.autrev.2020.102537 PMID: 32251717; PubMed Central PMCID: PMC7195002.
46. Mangalmurti N, Hunter CA. Cytokine Storms: Understanding COVID-19. Immunity. 2020; 53(1):19–25. Epub 2020/07/02. https://doi.org/10.1016/j.immuni.2020.06.017 PMID: 32610079; PubMed Central PMCID: PMC7321048.
47. Zhang Y, Zheng L, Liu L, Zhao M, Xiao J, Zhao Q. Liver impairment in COVID-19 patients: A retrospec- tive analysis of 115 cases from a single centre in Wuhan city, China. Liver Int. 2020. Epub 2020/04/03. https://doi.org/10.1111/liv.14455 PMID: 32239796.
48. Ridruejo E, Soza A. The liver in times of COVID-19: What hepatologists should know. Ann Hepatol. 2020. Epub 2020/05/20. https://doi.org/10.1016/j.aohep.2020.05.001 PMID: 32425991; PubMed Cen- tral PMCID: PMC7233236.
49. Garrido I, Liberal R, Macedo G. Review article: COVID-19 and liver disease-what we know on 1st May 2020. Aliment PharmacolTher. 2020; 52(2):267–75. Epub2020/05/14. https://doi.org/10.1111/apt. 15813 PMID: 32402090; PubMed Central PMCID: PMC7272838.
50. Delèvaux I, Andre' M, Colombier M, Albuisson E, Meylheuc F, Bègue RJ, et al. Can procalcitonin mea- surement help in differentiating between bacterial infection and other kinds of inflammatory processes? Ann Rheum Dis. 2003; 62(4):337–40. Epub 2003/03/14. https://doi.org/10.1136/ard.62.4.337 PMID: 12634233; PubMed Central PMCID: PMC1754509.
51. Lippi G, Plebani M. Procalcitonin in patients with severe coronavirus disease 2019 (COVID-19): A meta-analysis. Clin Chim Acta. 2020; 505:190–1. Epub 2020/03/08. https://doi.org/10.1016/j.cca.2020. 03.004 PMID: 32145275; PubMed Central PMCID: PMC7094472.
52. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J ThrombHaemost. 2020; 18(4):844–7. Epub 2020/02/20. https://doi.org/10.1111/jth.14768 PMID: 32073213; PubMed Central PMCID: PMC7166509.
53. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mor- tality in severe coronavirus disease 2019 patients with coagulopathy. J ThrombHaemost. 2020; 18 (5):1094–9. Epub 2020/03/29. https://doi.org/10.1111/jth.14817 PMID: 32220112.
54. Henry BM, de Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune bio- marker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID- 19): a meta-analysis. Clin Chem Lab Med. 2020; 58(7):1021–8. Epub 2020/04/15. https://doi.org/10. 1515/cclm-2020-0369 PMID: 32286245.
55. Gualdoni GA, Hofmann GA, Wohlfarth P, Winkler HM, Winkler S, Haslacher H, et al. Prevalence and Outcome of Secondary Hemophagocytic Lymphohistiocytosis Among SIRS Patients: Results from a Prospective Cohort Study. J Clin Med. 2019; 8(4). Epub 2019/04/24. https://doi.org/10.3390/ jcm8040541 PMID: 31010216; PubMed Central PMCID: PMC6518152.
56. Meyron-Holtz EG, Moshe-Belizowski S, Cohen LA. A possible role for secreted ferritin in tissue iron dis- tribution. J Neural Transm (Vienna). 2011; 118(3):337–47. Epub 2011/02/08. https://doi.org/10.1007/ s00702-011-0582-0 PMID: 21298454.
57. Zheng Z, Peng F, Xu B, Zhao J, Liu H, Peng J, et al. Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis. J Infect. 2020; 81(2):e16–25. Epub 2020/04/27. https:// doi.org/10.1016/j.jinf.2020.04.021 PMID: 32335169; PubMed Central PMCID: PMC7177098.
58. Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Performance of the trim and fill method in the presence of publication bias and between-study heterogeneity. Statistics in Medicine. 2007; 26 (25):4544–62. https://doi.org/10.1002/sim.2889 PMID: 17476644

ISSN (O): 2687-5365; ISSN (P): 2753-6556