STUDY PROTOCOLS

Health Science Reports *Open Access* WILEY

A systematic review and meta-analysis of abnormalities in hematological and biochemical markers among Bangladeshi COVID-19 cases

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Abstract

Background and Aims: Abnormalities in hematological and biochemical markers are assumed to be associated with the progression of COVID-19 disease. This meta-analysis was performed to assess the consequences of abnormalities of biomarkers (D-dimers, C-reactive protein [CRP], serum ferritin, lactate dehydrogenase [LDH], random blood sugar [RBS], absolute neutrophil count [ANC], neutrophil to lymphocyte ratio (NLR), serum creatinine, and hemoglobin) in the Bangladeshi COVID-19 patients.

Methods: The data of biomarker levels in Bangladeshi COVID-19 patients were gathered from five databases: PubMed, ScienceDirect, Web of Science, Google Scholar and Bangladesh Journals Online between January 2020 to March 2022. Review Manager 5.4 was used for the meta-analysis, and Egger's test and Begg-Mazumdar's rank correlation were used to investigate publication bias.

Results: This study included 1542 patients with 567 severe and 975 nonsevere statuses. Based on the accumulated data synthesis, there is a strong correlation between disease severity and different biomarkers, including D-dimer, CRP, ferritin, LDH, RBS, NLR, and serum creatinine (MD = 1.16, $p = 0.0004$; MD = 22.97, $p = 0.003$; MD = 419.26, $p < 0.00001$; MD = 118.37, $p = 0.004$; MD = 1.96, $p = 0.02$; MD = 1.26, $p = 0.02$; and MD = 0.31, $p = 0.008$, respectively). A significantly decreased correlation was observed for hemoglobin levels in severe COVID-19 patients (MD = −0.73, $p = 0.10$).

Conclusion: The elevated biomarkers level was noticed in severe cases compared to nonsevere patients, revealing that D-dimer, CRP, ferritin, LDH, RBS, NLR, and serum creatinine are significantly correlated to COVID-19 severity. Only lower hemoglobin level was found to be associated with COVID-19 severity.

KEYWORDS
COVID-19, creatinine, CRP, D-dimer, meta-analysis

1 | INTRODUCTION

The novel coronavirus (2019-nCoV) or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) first appeared in Wuhan, Hubei Province, China, at the end of 2019. Because of its pervasive perspective and virulent impacts, the World Health Organization (WHO) announced a global virus outbreak on March 11, 2020.[1] An estimated 486,974,361 COVID-19 cases and 6,166,935 deaths have been reported by March 30, 2022, throughout the globe.[2] In Bangladesh, about 1,951,504 cases have been identified, and 29,122 patients have died due to COVID-19 infection till March 30, 2022.[2] By attaching to the angiotensin-converting enzyme 2 receptor, this virus is hypothesized to enter the respiratory system via contaminated droplets or mucosal contact.[3] Even though most COVID-19 sufferers are asymptomatic, some individuals die from severe pneumonia, acute respiratory distress syndrome (ARDS), and multiorgan failure due to COVID-19 infection.[4,5] According to existing research, SARS-CoV-2 predominantly infects the upper respiratory system before progressing to the lower airways.[6] The severity of COVID-19 has been reported to be correlated with older age, being male and comorbidities such as diabetes, abnormally high blood pressure, adiposity, chronic respiratory illnesses, cardiovascular disease, and cancer.[7]

Coronavirus is an RNA virus that undergoes rapid mutation and forms new varieties.[8,9] Moreover, WHO enlist delta and omicron as currently circulating variants of concern.[10,11] However, the vaccination rate has a direct and significant impact on the status of the COVID-19 epidemic and the ability of health systems to confine it.[12–14] Even though the licensed COVID-19 vaccine has been demonstrated to be safe and effective, mass vaccination in Bangladesh remains a problem due to the awareness, emotions, and beliefs of the population about the COVID-19 vaccine and vaccination implementation.[12–14]

When evaluating an individual with COVID-19 infection, biomarkers may aid in the initiation of treatment and continuous surveillance. While biomarkers can improve prediction and outcomes, high diversity in their concentration across individuals may impact the study findings.[15] Several studies have linked higher levels of proinflammatory cytokines in serum with pulmonary inflammation and significant lung damage in SARS and MERS coronavirus infections.[16–18] Numerous research revealed that inflammatory biomarkers such as C-reactive protein (CRP) and D- dimer levels are comparatively predominant in intensive care unit patients than in mild and moderate individuals infected with COVID-19.[15,19,20]

The flu-like symptoms of COVID-19 infection are often followed by changes in the hemogram and inflammatory markers.[21] The level of the inflammatory marker CRP can be utilized to make an early diagnosis of pneumonia.[22] Patients who presented with severe pneumonia had high levels of CRP.[23] D-dimer levels have been linked to the severity of community-acquired pneumonia as well as the patient's prognosis.[24] Hemogram-derived NLR is an emerging inflammatory marker that has been linked to a variety of diseases, including thyroid inflammation,[25] Hashimoto's disease,[26] Irritable Bowel Syndrome,[27] and even COVID-19 infection.[28] Ferritin as a

molecule of signaling and immune system mediator. Several medical disorders, as well as a poorer prognosis for critically ill individuals, are linked to hyperferritinemia. Autopsy results and the clinical progression of some COVID-19 patients have shown a possible link between COVID-19 and "Hyperferritinemic Syndrome."[29] High levels of ferritin have been linked to both an increased risk of developing ARDS and an increased mortality risk.[30] Hemoglobin and red blood cell distribution width were found to be good indicators of recurrent hospitalizations during outbreaks, according to a recent.[31] In the COVID-19 era, hemogram markers are considered indicative of frail patients.[32] Moreover, CRP is an independent risk factor for comorbid disease like metabolic and autoimmune disorders including autoimmune thyroiditis,[33] stroke,[34,35] rheumatoid arthritis,[36] type 2 diabetes,[37] sensory impairments,[38] and cerebrovascular disease.[39] D-dimer is associated with stroke,[34,35] diabetic kidney disease,[40] lung disease,[41,42] and neurological deficits.[43] High level of ferritin is also associated with diabetes,[44–46] coronary heart disease,[47] cerebrovascular disease.[48,49]

The purpose of this meta-analysis is to highlight the correlation of numerous biomarkers, including D-dimers, CRP, serum ferritin, lactate dehydrogenase (LDH), random blood sugar (RBS), absolute neutrophil count (ANC), neutrophil to lymphocyte ratio (NLR), serum creatinine, and hemoglobin with the severity of COVID-19 patients in Bangladesh and how their values change based on the intensity of the illness.

2 | METHODS

2.1 | Literature search strategy and screening

The current meta-analysis adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses principles.[50] To find relevant published research, we carefully searched four worldwide databases (PubMed, Google Scholar, ScienceDirect, and Web of Science) and one national database (Bangladesh Journals Online) up to March 30, 2022. For excluding identical research, EndNote X 7.0 software was used. During the search, the following keywords were used alone or in combination: "COVID-19," "Bangladesh," "Bangladeshi," "biological marker," "CRP," "D-Dimer," "Ferritin," "LDS," "RBH," "ANS," "NLR," "serum creatinine," "hemoglobin level," "biomarker," "hematological abnormalities," "hematological biomarker," "biochemical markers," and "Hematological findings." This meta-analysis included only Bangladeshi studies. To identify missing research, we evaluated the reference lists of the included publications.

2.2 | Eligibility criteria

To be eligible for inclusion, publications must comply with the following requirements:

(1) Research articles published in English peer-reviewed journal;
(2) Studies containing only confirmed COVID-19 infection in

Bangladesh; (3) Cohort and case-control investigations; (4) Using human research subjects; (5) Data sufficient to compute the MD and 95% confidence interval (CI).

The following are the exclusion criteria:

(1) Research published in languages other than English; (2) Studies published in other populations than Bangladesh; (3) Commentary from experts, editorials, conference abstracts, reviews, and letters; (4) Irrelevant to extracting data; (5) Investigations based on animal data; (6) Overlapping or same publications.

2.3 | Data extraction

Three researchers (KKB, MAB, and MAA) independently used eligibility requirements to retrieve data. Independently, they searched for publications, appraised them, and extracted data into an excel file. Another researcher (MSI) resolved any study disagreements that emerged throughout the process. The studies used Rayyan QCRI, a systematic review online software.[51] The authors' names, year of production, number of participants, gender, age, biomarker level, and hematological results of severe and nonsevere cases were retrieved from the related articles.

2.4 | Methodological quality assessment

The Newcastle-Ottawa Scale (NOS) was used to evaluate the qualitative characteristics of prospective observational studies.[52] Any dissension among the investigators was resolved through conversation.

2.5 | Statistical analysis

The analysis was conducted using Review Manager 5.4 (The Cochrane Collaboration, Oxford, United Kingdom). Review Manager 5.3 was also used to examine the heterogeneity (χ^2 and I^2). Statistically, significant heterogeneity was defined as $p < 0.1$ or $I^2 > 50\%$. High heterogeneity was characterized by an I^2 value of 75% and low heterogeneity by 25%. In addition, Egger's regression test and Begg-Mazumdar's rank correlation were utilized to examine publication biases. The significance level was set at $p \leq 0.05$, and while the findings were bigger than predicted, there was no evidence of publication bias.

3 | RESULTS

3.1 | Study selection, characteristics, and quality assessment

During the first retrieval, 583 publications were detected from five databases (PubMed, Google Scholar, ScienceDirect, Web of Science and Bangladesh Journals Online); however, 213 entries were discarded due to the repetition. After scanning the title and abstract,

257 articles were deleted, and 85 were rejected from the remainder of 113 articles on a different basis. The rigorous assessment and inclusion criteria included eight full-text papers[53–60] encompassing 1542 COVID-19 cases (567 severe and 975 nonsevere) in this meta-analysis. The smallest sample size was 99, while the highest was 350. Figure 1 depicts the procedure of conducting the literature review, screening, and determining the acceptability of papers for study. All of the listed studies were performed on Bangladeshi COVID-19 patients between 2020 and 2022, and details are described in Table 1. Based on the NOS, the majority of the included literature was of high quality (scores between 6 and 8), as shown in Table S1.

3.2 | Presence of D-dimer (mg/L) level on disease severity

Among the 1542 patients, 567 were severe or critical cases and 975 were nonsevere cases. There was a significant heterogeneity when the D-dimer level was evaluated between the severe and nonsevere COVID-19 patients ($I^2 = 96\%$, $p < 0.00001$). In the meta-analysis, the random-effect model was employed, and the findings revealed that severe COVID-19 patients D-dimer is significantly higher than nonsevere patients (severe and nonsevere = 36.77% and 63.23%, MD = 1.16, 95% CI = 0.52–1.80, $p = 0.0004$) (Figure 2).

3.3 | Effect of CRP (mg/L) level on severity

Figure 3 illustrates the ratio of severe and nonsevere patients (0.61:1), and a considerable heterogeneity is found ($I^2 = 93\%$, $p < 0.00001$). COVID-19 patients who were in a critical state showed 22.97 mg/L higher CRP level compared to those who were not in critical condition (severe and nonsevere = 37.80% and 62.2%, MD = 22.97, 95% CI = 8.04–37.90, $p = 0.003$).

3.4 | The influence of ferritin (ng/ml) on severity

Among the five studies, the percentages of critical and noncritical cases were 34.84% and 65.16%, respectively, and showed remarkable heterogenicity compared with ferritin levels ($I^2 = 79\%$, $p = 0.0002$). Moreover, 419.26 ng/ml elevated association was observed for ferritin levels in the individuals with the severe condition than in the nonsevere state (severe vs. nonsevere 34.84% vs. 65.16%, MD= 419.26, 95% CI = 283.46–555.05, $p < 0.00001$) (Figure 4).

3.5 | Impact of LDH (U/L) and RBS (mmol/L) level on severity

Figures 5 and 6 depict the LDH (U/L) and RBS (mmol/L) levels in severe and nonsevere patients infected with SARS-CoV-2. The number of severe and nonsevere patients is 276 and 533 for LDH
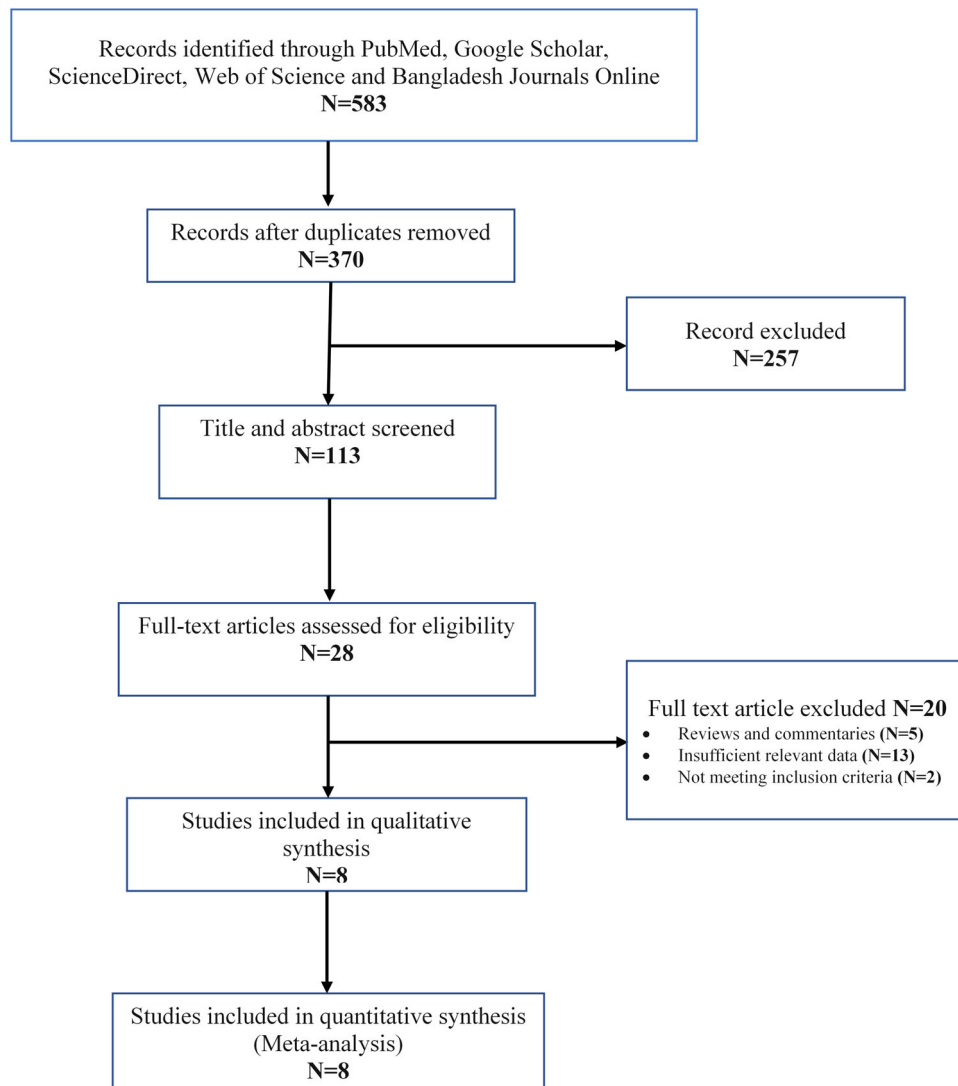
FIGURE 1 Flow diagram of the study selection process based on the PRISMA guideline. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

(U/L) whereas 62 and 138 for RBS (mmol/L), respectively. However, it is translucent that there was a significant heterogeneity compared with LDH (U/L) in the severe and nonsevere group (I^2 = 92%, p < 0.00001), whereas RBS (mmol/L) did not show significant heterogeneity when compared to the severe and nonsevere group (I^2 = 0%, p = 0.43). LDH level was 118.37 U/L higher in severe patients than in nonsevere patients (severe vs. nonsevere 34.12% vs. 65.88%, MD = 118.37, 95% CI = 38.60–198.14, p = 0.004), whereas RBS level was observed higher in severe cases as compared to nonsevere cases and the result was statistically significant (severe vs. nonsevere 31% vs. 69%, MD = 1.96, 95% CI = 0.36–3.57, p = 0.02).

3.6 | Effect of ANC (×10⁹/L) level on severity

The percentages of severe hand nonsevere patients in the three studies were 27.13% and 72.87%, respectively, as seen in Figure 7

and demonstrated considerable heterogeneity compared to ANC levels (I^2 = 93%, p < 0.00001). Furthermore, SARS-CoV-2-infected individuals with the severe condition had 1.42×10^9/L higher ANC levels than nonsevere individuals (severe vs. nonsevere 27.13% vs. 72.87%, MD = 1.42, 95% CI = −1.77–4.62, p = 0.38).

3.7 | Effect of NLR level on severity

There was considerable heterogeneity when the NLR level was compared between the severe and nonsevere COVID-19 patients (I^2 = 90%, p < 0.00001). Using the random-effect model, the meta-analysis found that NLR levels were considerably higher in the severe patients than in the nonsevere patients. A greater NLR level was seen in individuals with severe COVID-19 disease compared to those without severe illness (severe vs. nonsevere: 33.04% vs. 66.96%, MD = 1.26, 95% CI = 0.24–2.27, p = 0.02) (Figure 8).

TABLE 1 Hematological and biochemical parameters of COVID-19 patients

Parameters	Akter et al. (2022)[55]	Bhuiyan et al. (2021)	Islam et al. (2020)	Layla et al. (2021)[54]	Nasir et al. (2021)[58]	Rahman et al. (2021)[59]	Saha et al. (2021)	Sultana et al. (2021)[60]
Total cases	100	100	259	100	99	306	350	228
Severe	25	22	81	37	39	108	133	122
Nonsevere	75	78	178	63	60	198	217	106
Male								
Severe	17	18	–	23	23	30	92	99
Nonsevere	43	53	–	44	42	95	156	79
Female								
Severe	8	4	–	14	9	16	34	33
Nonsevere	32	25	–	19	18	103	61	27
Age (mean± SD)								
Severe	50.50 ± 7.70	46.67 ± 15.85	–	–	65.02	54.07 ± 9.82	54.19 ± 15.23	62.35 ± 10.49
Nonsevere	42.82 ± 8.07	32.33 ± 8.31	–	–	57.28	45.55 ± 6.34	43.03 ± 13.68	60.63 ± 16.90
D-dimer (mg/L)								
Severe	1.04 ± 1.17	0.92 ± 0.97	0.61 ± 0.83	4.78 ± 3.42	1.57 ± 2.01	0.76 ± 0.60	2.77 ± 1.92	5.87 ± 2.61
Nonsevere	0.34 ± 0.25	0.51 ± 0.10	0.47 ± 0.7	1.09 ± 1.82	1.36 ± 2.12	0.24 ± 0.99	2.04 ± 1.33	2.27 ± 1.15
CRP (mg/L)								
Severe	90.49 ± 73.31	–	63.46 ± 58.07	23.24 ± 20.81	32.13 ± 27.4	65.5 ± 72.5	47.15 ± 22.71	52.38 ± 59.89
Nonsevere	31.79 ± 47.81	–	27.15 ± 29.59	10.73 ± 7.08	36.14 ± 24.62	1.90 ± 1.10	39.35 ± 23.22	50.98 ± 51.76
Ferritin (ng/ml)								
Severe	838.95 ± 957.95	–	823.58 ± 468.60	1003.36 ± 555.50	954.19 ± 704.17	651.86 ± 793.30	1118.05 ± 265.81	–
Nonsevere	358.88 ± 417.51	–	562.21 ± 518.81	301.92 ± 220.47	841.71 ± 612.28	86.41 ± 34.78	739.86 ± 142.93	–
LDH (U/L)								
Severe	441.9 ± 157.51	–	410.42 ± 128.04	655.70 ± 223.25	–	–	379.94 ± 101.91	–
Nonsevere	266.57 ± 118.85	–	370.24 ± 188.53	390.93 ± 223.67	–	–	344.16 ± 97.55	–
RBS (mmol/L)								
Severe	11.79 ± 5.11	–	–	11.42 ± 5.75	–	–	–	–
Nonsevere	9.13 ± 5.58	–	–	10.05 ± 4.66	–	–	–	–

(Continues)

TABLE 1 (Continued)

Parameters	Akter et al. (2022)[55]	Bhuiyan et al. (2021)	Islam et al. (2020)	Layla et al. (2021)[54]	Nasir et al. (2021)[58]	Rahman et al. (2021)[59]	Saha et al. (2021)	Sultana et al. (2021)[60]
ANC (×10⁹/L)								
Severe	6.39 ± 2.16	11.57 ± 3.57	–	–	7.81 ± 3.99	–	–	–
Nonsevere	4.86 ± 2.87	6.81 ± 6.33	–	–	9.64 ± 3.49	–	–	–
NLR								
Severe	8.90 ± 5.23	14.98 ± 39.56	4.51 ± 1.63	–	9.76 ± 6.68	–	2.8 ± 0.32	–
Nonsevere	6.17 ± 7.29	8.35 ± 4.60	3.39 ± 1.19	–	5.99 ± 3.99	–	2.7 ± 0.28	–
Serum creatinine (mg/dl)								
Severe	0.94 ± 0.26	–	–	1.45 ± 1.25	2.30 ± 2.57	1.15 ± 0.93	1.9 ± 0.8	–
Nonsevere	0.93 ± 0.32	–	–	1.00 ± 0.27	1.39 ± 1.08	0.83 ± 0.27	1.5 ± 0.9	–
Hemoglobin (g/dL)								
Severe		12.57 ± 1.98	11.95 ± 1.94		–	12.61 ± 5.98		
Nonsevere	–	14.23 ± 1.28	12.38 ± 1.86		–	12.68 ± 1.36	–	

Abbreviations: ANC, absolute neutrophil count; CRP, C-reactive protein; LDH, lactate dehydrogenase; NLR, absolute neutrophil/absolute lymphocyte or %neutrophil/%lymphocyte; RBS, random blood sugar.
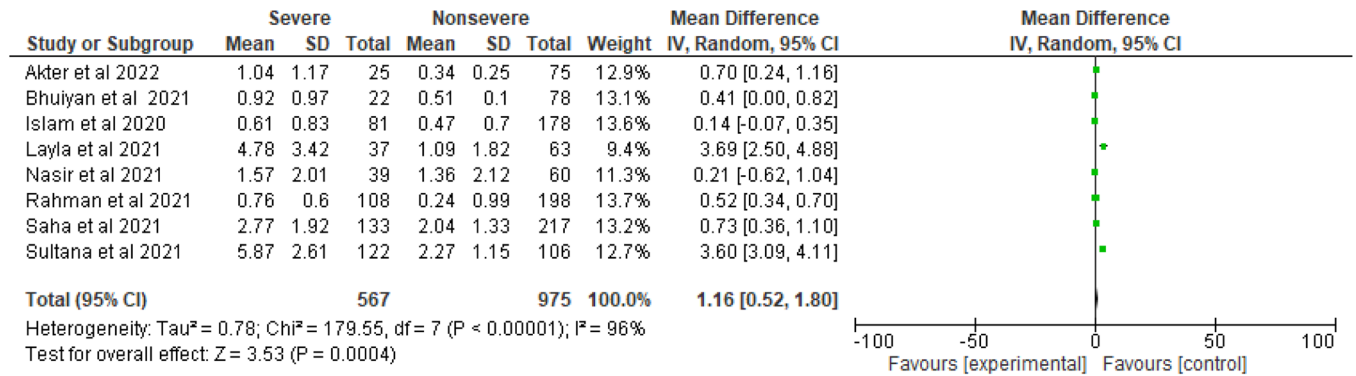
Study or Subgroup	Severe Mean	SD	Total	Nonsevere Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Akter et al 2022	1.04	1.17	25	0.34	0.25	75	12.9%	0.70 [0.24, 1.16]
Bhuiyan et al 2021	0.92	0.97	22	0.51	0.1	78	13.1%	0.41 [0.00, 0.82]
Islam et al 2020	0.61	0.83	81	0.47	0.7	178	13.6%	0.14 [-0.07, 0.35]
Layla et al 2021	4.78	3.42	37	1.09	1.82	63	9.4%	3.69 [2.50, 4.88]
Nasir et al 2021	1.57	2.01	39	1.36	2.12	60	11.3%	0.21 [-0.62, 1.04]
Rahman et al 2021	0.76	0.6	108	0.24	0.99	198	13.7%	0.52 [0.34, 0.70]
Saha et al 2021	2.77	1.92	133	2.04	1.33	217	13.2%	0.73 [0.36, 1.10]
Sultana et al 2021	5.87	2.61	122	2.27	1.15	106	12.7%	3.60 [3.09, 4.11]
Total (95% CI)			**567**			**975**	**100.0%**	**1.16 [0.52, 1.80]**

Heterogeneity: Tau² = 0.78; Chi² = 179.55, df = 7 (P < 0.00001); I² = 96%
Test for overall effect: Z = 3.53 (P = 0.0004)

FIGURE 2 Pooled effects of the linkage of D-dimer (mg/L) with COVID-19 patients

Study or Subgroup	Severe Mean	SD	Total	Nonsevere Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Akter et al 2022	90.49	73.31	25	31.79	47.81	75	9.7%	58.70 [27.99, 89.41]
Islam et al 2020	63.46	58.07	81	27.15	29.59	178	14.5%	36.31 [22.94, 49.68]
Layla et al 2021	23.24	20.81	37	10.73	7.08	63	15.9%	12.51 [5.58, 19.44]
Nasir et al 2021	32.13	27.4	39	36.14	24.62	60	15.2%	-4.01 [-14.63, 6.61]
Rahman et al 2021	65.5	72.5	108	1.9	1.1	198	14.4%	63.60 [49.93, 77.27]
Saha et al 2021	47.15	22.71	133	39.35	23.22	217	16.1%	7.80 [2.86, 12.74]
Sultana et al 2021	52.38	59.89	122	50.98	51.76	106	14.2%	1.40 [-13.09, 15.89]
Total (95% CI)			**545**			**897**	**100.0%**	**22.97 [8.04, 37.90]**

Heterogeneity: Tau² = 353.45; Chi² = 89.35, df = 6 (P < 0.00001); I² = 93%
Test for overall effect: Z = 3.01 (P = 0.003)

FIGURE 3 Pooled effects of the linkage of CRP (mg/L) with COVID-19 patients. CRP, C-reactive protein.

Study or Subgroup	Severe Mean	SD	Total	Nonsevere Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Akter et al 2022	838.95	957.95	25	358.88	417.51	75	8.2%	480.07 [92.85, 867.29]
Islam et al 2020	823.58	468.6	81	562.21	518.81	178	20.1%	261.37 [134.00, 388.74]
Layla et al 2021	1,003.36	555.5	37	301.92	220.47	63	16.7%	701.44 [514.35, 888.53]
Nasir et al 2021	954.19	704.17	39	841.71	612.28	60	12.4%	112.48 [-157.41, 382.37]
Rahman et al 2021	651.86	793.3	108	86.41	34.78	198	18.9%	565.45 [415.76, 715.14]
Saha et al 2021	1,118.05	265.81	133	739.86	142.93	217	23.7%	378.19 [329.18, 427.20]
Total (95% CI)			**423**			**791**	**100.0%**	**419.26 [283.46, 555.05]**

Heterogeneity: Tau² = 19630.05; Chi² = 24.33, df = 5 (P = 0.0002); I² = 79%
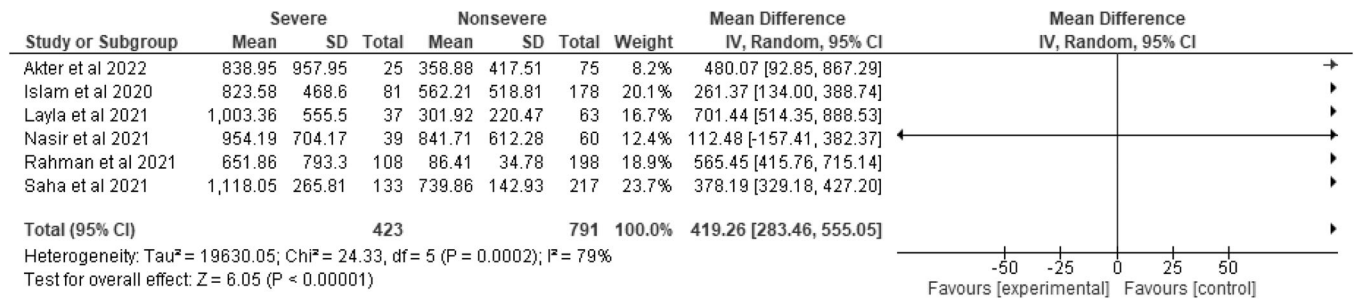Test for overall effect: Z = 6.05 (P < 0.00001)

FIGURE 4 Pooled effects of the linkage of ferritin (ng/ml) with COVID-19 patients

Study or Subgroup	Severe Mean	SD	Total	Nonsevere Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Akter et al 2022	441.9	157.51	25	266.57	118.85	75	23.9%	175.33 [107.98, 242.68]
Islam et al 2020	410.42	128.04	81	370.24	188.53	178	26.9%	40.18 [0.88, 79.48]
Layla et al 2021	655.7	223.25	37	390.93	223.67	63	21.0%	264.77 [174.08, 355.46]
Saha et al 2021	379.94	101.91	133	344.16	97.55	217	28.2%	35.78 [14.14, 57.42]
Total (95% CI)			**276**			**533**	**100.0%**	**118.37 [38.60, 198.14]**

Heterogeneity: Tau² = 5751.60; Chi² = 36.39, df = 3 (P < 0.00001); I² = 92%
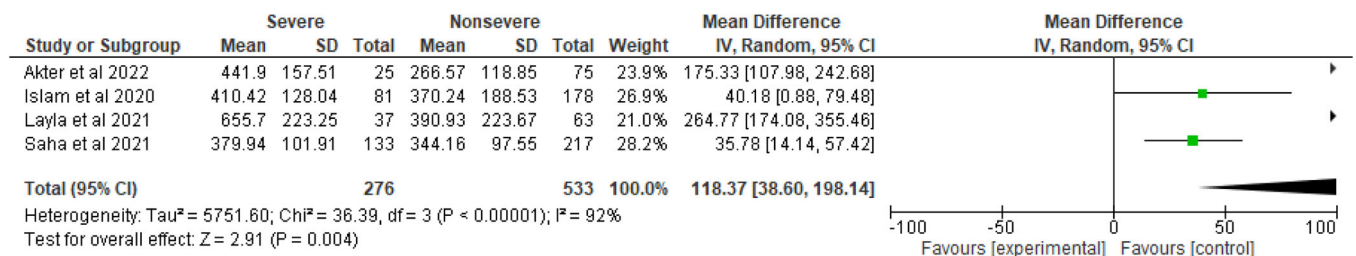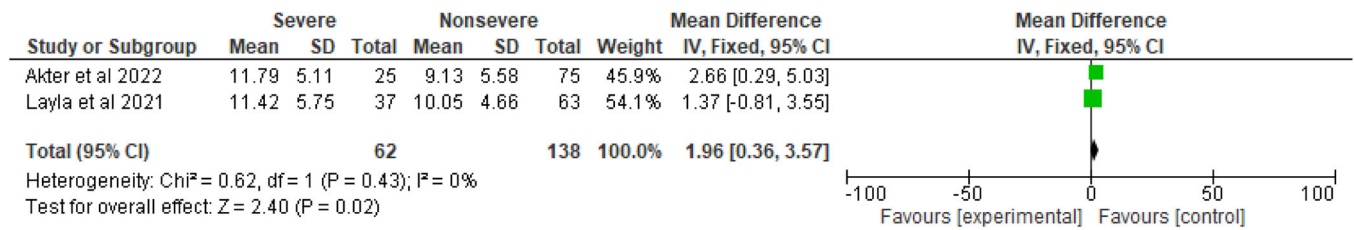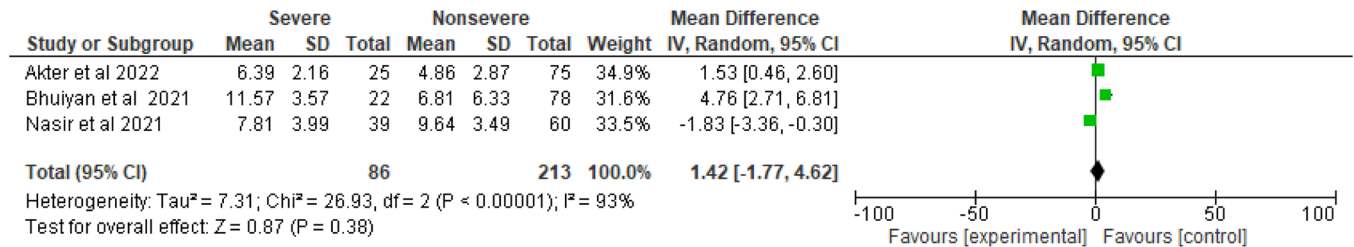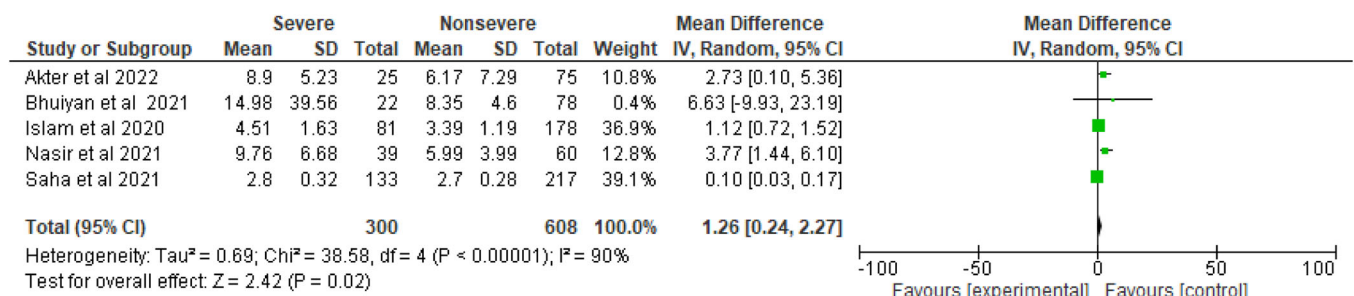Test for overall effect: Z = 2.91 (P = 0.004)

FIGURE 5 Pooled effects of the linkage of LDH (U/L) with COVID-19 patients. LDH, lactate dehydrogenase.
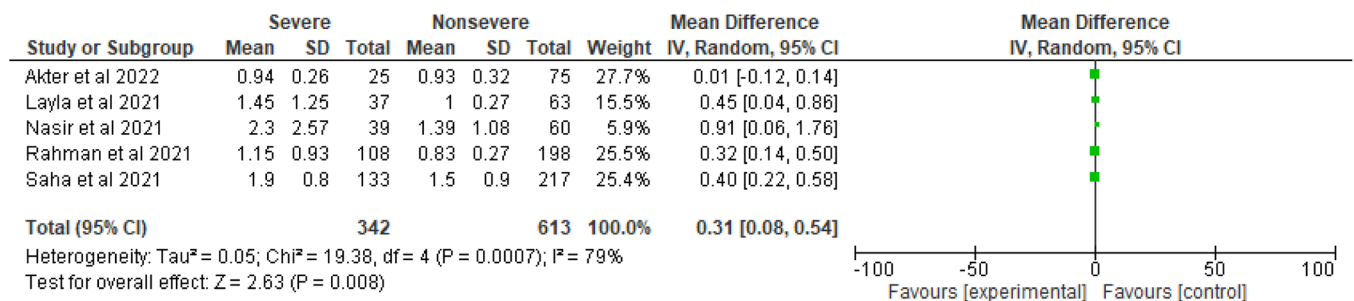
FIGURE 6 Pooled effects of the linkage of RBS (mmol/L) with COVID-19 patients. RBS, random blood sugar.

FIGURE 7 Pooled effects of the linkage of ANC (×10^9/L) with COVID-19 patients. ANC, absolute neutrophil count

FIGURE 8 Pooled effects of the linkage of NLR with COVID-19 patients. NLR, neutrophil to lymphocyte ratio.

FIGURE 9 Pooled effects of the linkage of serum creatinine (mg/dl) with COVID-19 patients.
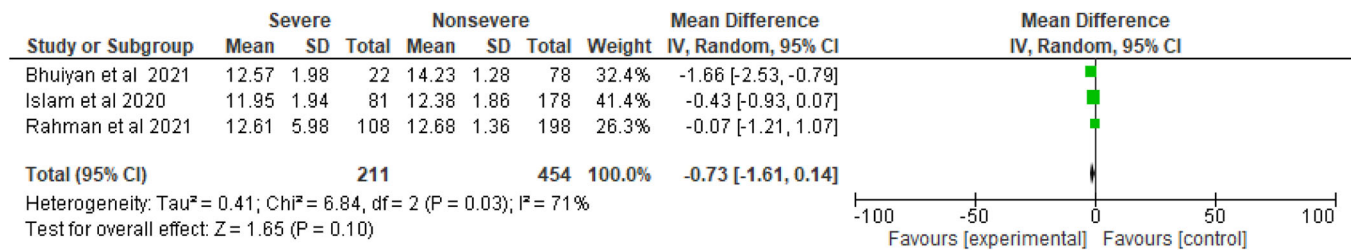
3.8 | Effect of serum creatinine (mg/dl) level on severity

There was a significant heterogeneity when the serum creatinine level was compared across COVID-19 individuals (severe and nonsevere) (I^2 = 79%, p = 0.0007). The results showed that serum creatinine levels are elevated in the severe group compared to the nonsevere cohort (severe vs. nonsevere, 34.03% vs. 65.97%, MD = 0.31, 95% CI = 0.08–0.54, p = 0.008) (Figure 9).

3.9 | Effect of hemoglobin (g/dl) level on severity

Of the eight studies, three studies included hemoglobin in their studies. The percentages of severe and nonsevere cases were 37.73% and 68.27%. Figure 10 elucidates significant heterogeneity between the severe and nonsevere groups in terms of hemoglobin levels (I^2 = 71%, p = 0.03). However, severe patients had a lower haemoglobin level than nonsevere individuals (severe vs. nonsevere, 37.73% vs. 68.27%, MD = −0.73, 95% CI = −1.61–0.14, p = 0.10).

Study or Subgroup	Severe			Nonsevere			Weight	Mean Difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total		
Bhuiyan et al 2021	12.57	1.98	22	14.23	1.28	78	32.4%	-1.66 [-2.53, -0.79]
Islam et al 2020	11.95	1.94	81	12.38	1.86	178	41.4%	-0.43 [-0.93, 0.07]
Rahman et al 2021	12.61	5.98	108	12.68	1.36	198	26.3%	-0.07 [-1.21, 1.07]
Total (95% CI)			**211**			**454**	**100.0%**	**-0.73 [-1.61, 0.14]**

Heterogeneity: Tau² = 0.41; Chi² = 6.84, df = 2 (P = 0.03); I² = 71%
Test for overall effect: Z = 1.65 (P = 0.10)

Mean Difference
IV, Random, 95% CI

Favours [experimental]　Favours [control]

FIGURE 10　Pooled effects of the linkage of hemoglobin (g/dl) with COVID-19 patients

3.10 | Publication bias

Our meta-analysis investigated the publication bias using Begg-Mazumdar's and Egger's assessment. Both analyses yielded no significant publication bias (Table S2).

4 | DISCUSSION

COVID-19 has brought worldwide public health disaster, and the sickness it produced has a widely varied clinical appearance. Moreover, its consequences are disseminated worldwide and are claiming millions of lives. Bangladesh is analogous to the rest of the world in that age, gender, and comorbidities are related to COVID-19 infections. Nevertheless, in comparison to other nations, the likelihood of dying from COVID-19 in Bangladesh is low, presumably because of the demographic features of our population, with just 10–15% of the population aged over 50 years.[7,55,61,62] To our knowledge, this is the first meta-analysis to look at numerous biochemical and hematological indicators in SARS-CoV-2 infected people in Bangladesh. We collected eight independent studies from January 2020 to March 2022 that reported severity, inflammatory biomarkers, hematological markers, and varied outcomes on 1542 COVID-19 patients from Bangladesh.

In our study, we observed that critical patients have higher D-dimer (MD = 1.16, p = 0.0004) levels compared to nonsevere patients. An equivalent conclusion was also noted earlier in some other studies.[7,63–65] The elevated D-dimer level in COVID-19 is due to excessive clotting and hypoxia. As a result of D-dimer being a consequence of fibrin breakdown, its presence in severe stages may also signify blood clots and deep venous thrombosis (DVT). COVID-19 patients who have venous thromboembolism episodes (both DVT and pulmonary embolism) had elevated D-dimer levels in their blood.[66]

It is also discernible that CRP, a commonly measured inflammatory marker, is elevated in most COVID-19 patients and is connected to the degree of severity (MD = 22.97, p = 0.003). CRP levels can rise quickly due to inflammation (reaction to inflammatory cytokines such as IL-6, IL-1, or TNF), cell damage, or tissue injury. As a result, significantly high serum CRP levels in severe conditions insinuate an inflated inflammatory response, consistent with elevated serum proinflammatory cytokines in COVID-19 patients.[67]

In our study, the value of serum ferritin was shown to be statistically significant (MD = 419.26, p < 0.00001) compared with critical and noncritical cases. Several other studies concluded that serum ferritin is significantly increased in patients with a severe course of the disease than in those who are not critically ill, documenting its position as the most potential biomarker in foreseeing COVID-19 severity.[68,69]

The forest plot described that the LDH, an enzyme that transforms lactate to pyruvate, was considerably higher in severe cases than that in less severe patients (MD = 118.37, p = 0.004), and our result is consistent with other findings.[70,71] Khalid et al.[72] also found a link between a high level of LDH and a severe COVID-19 infection. Besides, RBS was shown to have a substantial relationship with disease severity and was statistically noteworthy (MD = 1.96, p = 0.02). On the contrary, research demonstrates that hyperglycemia is a risk factor that leads to the severity and death of COVID-19 victims.[73] This research revealed no significant difference in the ANC label between people with moderate and severe COVID-19 cases (MD = 1.42, p = 0.38). NLR was a helpful biomarker primarily used in tumor-related disorders, autoimmune disorders, infectious bacterial pneumonia, and tuberculosis.[74–77] Our study found that the NLR for individuals with severe illnesses was much higher than for those with less severe illness (MD = 1.26, p = 0.02). Besides, our study is analogous to some different studies.[78,79]

The level of creatinine indicates the health of the kidneys. Our findings demonstrate that higher creatinine levels are significantly related to severe COVID-19 (MD = 0.31, p = 0.008), suggesting that SARS-CoV-2 infection may cause acute inflammation. Previous meta-analyses have produced conclusions that are congruent with ours.[80–82] Our meta-analysis found decreased hemoglobin levels in the Bangladeshi population infected with COVID-19 (MD = −0.73, p = 0.10), and these findings are similar to other meta-analyses.[82,83]

There are several strengths of this meta-analysis. Numerous meta-analyses have already been published on the correlation of biochemical and hematological irregularities with the intensity of COVID-19 patients from various countries. However, no meta-analysis has been published on the relationship between hematological and biochemical malformations with the severity of COVID-19 infected Bangladeshi patient inhabitants. This is the first comprehensive systematic review and meta-analysis. The literature covered in this study is of excellent quality, the methodology is meticulous, and the study's outcomes are very plausible. All relevant cohort and case-control investigations are included in this meta-analysis and the number of participants is quite good for performing a meta-analysis. We employed a heterogeneity investigation and publication bias assessment during our meta-analysis.

The information presented in this meta-analysis must be considered along with several limitations. First, the meta-analysis cases are retrospective investigations and were not randomized clinical studies. Second, the total number of studies in the analysis is low (eight studies) if we compare with other meta-analyses with large number of articles. Thirdly, just the combination of nine markers was mentioned to foreshadow the severity of COVID-19 patients, and coming research may investigate amalgamating more additional biomarkers in the same way. Other concomitant conditions such as diabetes, heart disease, lung disease, kidney disease were not considered in this meta-analysis. Fourth, all indicators and measures have only been examined once upon admission; thus, variations within these parameters could not be assessed. Despite these drawbacks, the results of our meta-analysis are more consistent and comprehensive, allowing us to monitor patients' conditions and detect severe patients earlier.

5 | CONCLUSION

The most promising indicators in determining the severity of COVID-19 infections are biochemical and hematological indicators. Our meta-analysis found that hematological and biochemical biomarkers- D-dimer, CRP, ferritin, LDH, RBS, NLR, and serum creatinine are significantly linked with the severity of COVID-19 cases. At the same time, the hemoglobin levels of patients with severe sickness are lower than those with less severe COVID-19 infestations. This analysis aids in identifying individuals at high risk for COVID-19-related complications and assists in appropriate medication and care to be given quickly and effectively. This research also pays particular attention to these risk variables and aids in developing individualized therapy regimens for COVID-19 patients in Bangladesh. Nevertheless, this aspect has to be analyzed further to expedite the commencement and optimization of COVID-19 therapy.

AUTHOR CONTRIBUTIONS

Khokon Kanti Bhowmik: data curation; methodology; software; writing—original draft. **Md. Abdul Barek**: data curation; methodology; software; validation; writing—original draft. **Md. Abdul Aziz**: data curation; methodology; project administration; resources; validation; writing—review and editing. **Mohammad Safiqul Islam**: conceptualization; formal analysis; methodology; software; supervision; validation; writing—review and editing. Mohammad Safiqul Islam affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted; and any discrepancies from the study as planned (and, if relevant, registered) have been explained.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article and/or its supplementary materials.

TRANSPARENCY STATEMENT

Mohammad Safiqul Islam affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted; and any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.