Role of C - reactive protein, Serum Ferritin and D-Dimer in Covid Cases: Systematic Review & Meta Analysis

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ABSTRACT:
Introduction: Patients severely ill with coronavirus disease-2019 (COVID-19) showed hyperinflammation, and the associated biomarkers may be beneficial for risk stratification. We investigated the association between several biomarkers, including serum C-reactive protein (CRP), D-dimer, serum ferritin, and the COVID-19 severity.
Methods: We conducted an online search for the COVID patients with the included lab reports and severity. The outcome of interest for this study was the composite poor outcome, which comprises mortality, acute respiratory distress syndrome, need for care in an intensive care unit, and severe COVID-19.
Results: A total of 5351 patients were pooled from 25 studies. Elevated CRP, D-dimer, ferritin was associated with an increased composite poor outcome, with an association of the mortality and the severity at various levels.
Conclusion: CRP, D-dimer, and ferritin were associated with a poor outcome in COVID-19.
Keywords: C-reactive protein (CRP), D-dimer, and Serum ferritin, and COVID-19 severity.

INTRODUCTION

Coronavirus disease-2019 is a pandemic that has claimed multiple lives.1 In few they progress to severe pneumonia, acute respiratory distress syndrome (ARDS), multi-organ failure, and coma, death.2 The progress of the disease is unpredictable as to who will have mild and who will progress to severe illness. Comorbidities and laboratory markers have been suggested for risk stratification.3–6 There is enough evidence that in critically ill patients, there are features of hyperinflammation, which consist of incresed serum C-reactive protein (CRP), D-dimer, and hyperferritinemia. These observations suggest a possibly important role

of a cytokine storm in COVID-19 pathophysiology.7-10Laboratory biomarkers to foretell the severity of COVID-19 are vital in a pandemic, because resource allocation must be prudently planned, especially in the situation of respiratory support readiness. In the current study, we directed a systematic review and meta-analysis to investigate the association between various biomarkers, including serum CRP, D-dimer, and serum ferritin, and the severity of COVID-19.

MATERIALS AND METHODS

We conducted the search for the data from the online sources like the "EMBASE", "Pubmed", "Scopus" "Medline" and other sources. The study was conducted by two reviewers independently. The PRISMA guidelines were followed. The articles were collected from January 2020 to February 2021. The search words are COVID, COVID19, SARS, CoV2, PANDEMIC, CRP, D-dimer, and serum ferritin. The animal studies, population data, epidemiology, reviews were excluded along with the inconclusive diagnosis, other languages than can't be translated to English. We included those studies with adult patients with COVID-19 with data for serum CRP, D-dimer, and serum ferritin and reported the data based on the presence or absence of clinically validated definitions of mortality, severe COVID-19, ARDS, and intensive care unit (ICU) care.The heterogeneity of the analysis was studied using Cochran Q-statistic and I^2 statistic with $P<0.05$ for Q-statistic, $I^2 \geq 50\%$ as significant. Total participants, year of study, study type, clinical features, comorbidities, number of the patients were noted for all the studies. **Table 1** Based on the WHO criteria meta regression was performed for the factors that may impact the severity.[12-14] statistical analysis was done keeping the p value<0.05.

RESULTS

In the study 25 articles with 5350 patients were finalized from 313 records. **Figure 1**

Raised CRP and outcome

This meta-analysis of 13 studies showed that an elevated serum CRP was associated with an increased composite poor outcome [RR 1.84 (1.45, 2.33), p < 0.001; I2: 96%, p < 0.001] (Figure 2(a)).15–22,25–28,31 Subgroup analysis showed that an elevated CRP was associated with an increased risk of severe COVID-19 [RR 1.41 (1.14, 1.74), p = 0.002; I2: 93%, p < 0.001], need for ICU care [RR 1.96 (1.40, 2.74), p < 0.001], but not mortality [RR 2.95 (0.90, 9.68), p = 0.07; I2: 99%, p < 0.001].

Raised D-dimer and outcome

The meta-analysis of 11 studies showed that an elevated D-dimer was associated with an increase in composite poor outcome [RR 2.93 (2.14, 4.01), p < 0.001; I2: 77%, p < 0.001] (Figure 3(a)).16–23,25– 27,31 Subgroup analysis showed that an elevated D-dimer was associated with increased mortality [RR 4.15 (2.43, 7.08), p < 0.001; I2: 83%, p = 0.01], severe COVID-19 [RR 2.42 (1.72, 3.40), p < 0.001; I2: 58%, p = 0.05], but not the need for ICU care [RR 0.94 (0.43, 2.07), p = 0.88]. By removing the Hu et al. study, 18 sensitivity analysis reduced heterogeneity for severe COVID-19 [RR 2.77 (2.06, 3.73), p < 0.001; I2: 19%, p = 0.30].

Ferritin and poor outcome

Patients with a composite poor outcome had a higher ferritin level [SMD 0.90 (0.64,

1.15), p< 0.0001; I2: 76%] (Figure 4) in 10 stud- ies.10,23,24,27–33 Subgroup analysis results demon- strated that ferritin level was higher in non-survivors (mortality) [SMD 0.96 (0.78,1.13), p < 0.00001; I2: 0%, p = 0.41] and patients with severe COVID-19 [SMD 0.97 (0.43, 1.50), p < 0.004; I2: 82%, p = 0.001].

Meta-regression

Meta-regression analysis demonstrated that the association between an elevated CRP, D-dimer, serum ferritin level, and the composite poor outcome was not significantly affected by gender, age, hypertension, cardiovascular disease, diabetes, and COPD (p > 0.05).

Publication bias

The funnel-plot was qualitatively asymmetrical for D-dimer, PCT, CRP, and ferritin. Regression- based Egger's test depicted no indication of small- study effects for D-dimer (p = 0.073) and ferritin (p = 0.372) on the composite poor outcome. There was indication of small-study effects in the association between PCT (p = 0.003), CRP (p < 0.001), and a composite poor outcome.
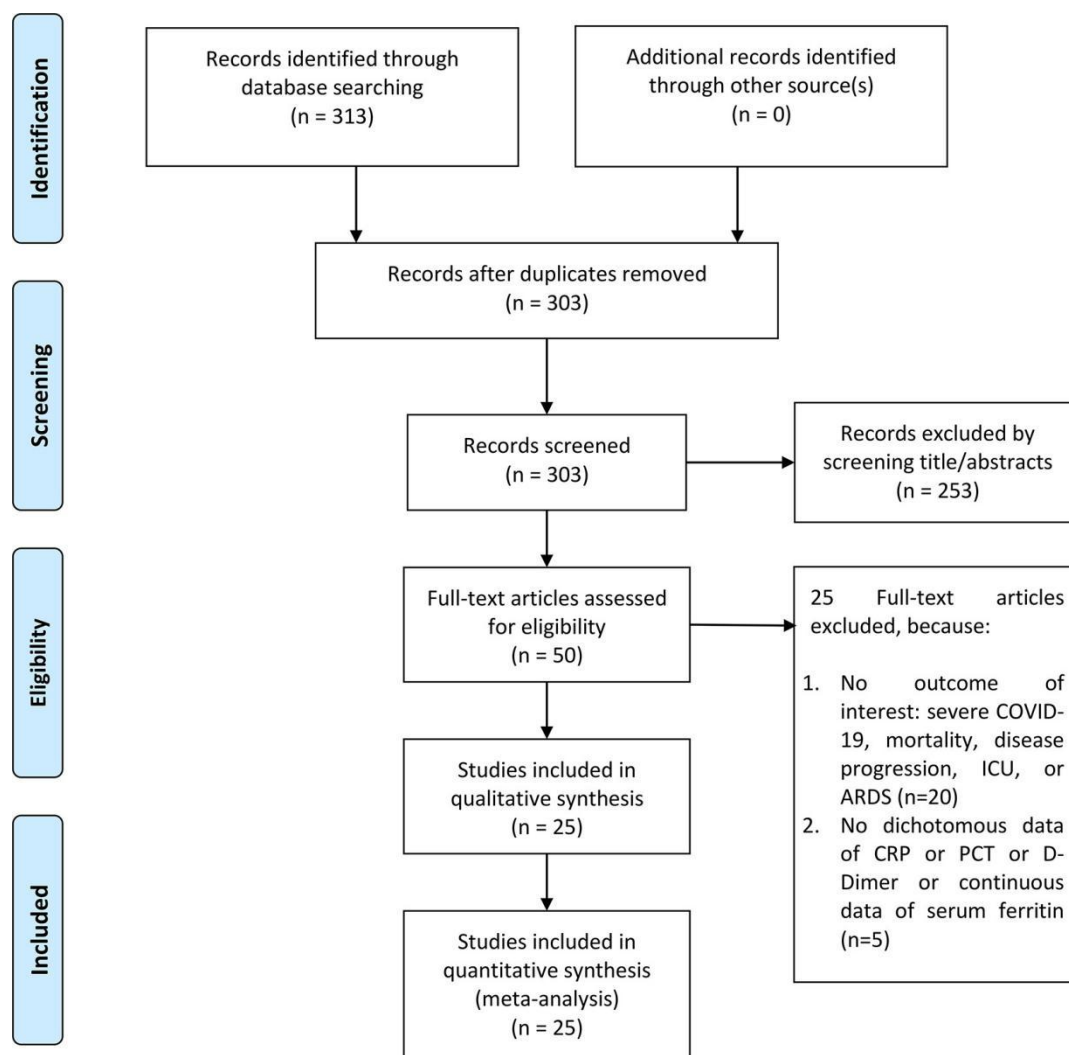
Figure 1. Study flow diagram.

TABLE 1- Comparison of the studies.

| Authors	Study design	Samples	Age (mean/median, years)	Male (%)	CRP	CRP cutoff	PCT cutoff	D-dimer cutoff	Ferritin mean/median (ng/ml)	DM (%)	HTN (%)	CAD/CVD (%)	COPD (%)	Outcome of interest
Chen et al.[27]	Retrospective Observational	274 (113/161)	68.0 versus 51.0	73 versus 55	hs-CRP	>100 mg/L	□0.5 ng/ml	>21 µg/ml	1418.3 versus 481.2	21.0 versus 14.0	48.0 versus 24.0	14.0 versus 4.0 (CVD)	10.0 versus 4.0 (CLD)	Mortality
Li et al.[26]	Retrospective Observational	102 (15/87)	69 versus 55	73 versus 55	hs-CRP	3 mg/L	□0.05 ng/ml	>1 µg/ml	N/A	13.0 versus 15.0	47.0 versus 28.0	13.0 versus 2.0	7.0 versus 1.0	Mortality
Luo et al.[25]	Retrospective Observational	403 (100/303)	71 versus 49	57 versus 44.9	CRP	□100 mg/L	>0.5 ng/ml	>5 mg/L	N/A	25.0 versus 10.6	60.0 versus 17.5	16.0 versus 6.6)	17.0 versus 3.6	Mortality
Ruan et al.[24]	Retrospective Observational	150 (68/82)	67 versus 50	72 versus 65	N/A	N/A	N/A	N/A	1297.6 versus 614	18.0 versus 16.0	43.0 versus 28.0	19.0 versus 0)	3.0 versus 1.0	Mortality
Zhou et al.[23]	Retrospective Observational	191 (54/137)	69.0 versus 52.0	70 versus 59	N/A	N/A	□0.5 ng/ml	>0.1 mg/L	1435.3 versus 503.2	31.0 versus 14.0	48.0 versus 23.0	24.0 versus 1.0	7.0 versus 1.0	Mortality
Cao et al.[21]	Retrospective Observational	102 (17/85)	72 versus 53	76.5 versus 47.1	CRP	□ 10 mg/L	□0.1 ng/ml	□500 mg/L	N/A	35.3 versus 5.9	64.7 versus 20.0	17.6 versus 2.4	23.5 versus 7.1	Mortality
Cai et al.[20]	Retrospective Observational	298 (58/240)	64 versus 40	56.9 versus 46.3	CRP	>8 U/L	N/A	>0.5 mg/L	N/A	6.4	12.8	3.7	N/A	Severe COVID-19
Guan et al.[19]	Retrospective Observational	1099 (173/926)	52.0 versus 45.0	57.8 versus 38.2	CRP	□10 mg/L	□0.5 ng/ml	□ 0.5 mg/L	N/A	16.2 versus 5.7	23.7 versus 13.4	5.8 versus 1.8	3.5 versus 0.6	Severe COVID-19
Hu et al.[18]	Retrospective Observational	323 (172/151)	65 versus 56	52.9 versus 49.7	CRP	□3 mg/L	>0.1 ng/ml	>0.5 mg/L	N/A	19.2 versus 9.3	38.3 versus 25.8	19.2 versus 5.3 (CVD)	3.5 versus 0	Severe COVID-19
Tabata et al.[17]	Retrospective Observational	104 (28/76)	68 (total)	45.2 (total)	CRP	>10 mg/L	N/A	N/A	N/A	6.7 (total)	N/A	29.8 (total)	6.7 (unspecified)	Severe COVID-19
Zhang et al.[16]	Retrospective Observational	140 (58/82)	<30 (1.7 versus 4.9), 30–49 (15.5 versus 34.1) 50–69 (48.3 versus 50), □70 (34.5 versus 11.0)	56.9 versus 46.3	CRP	>3 mg/L	>0.1 ng/ml	>0.243 mg/L	N/A	13.8 versus 11.0	37.9 versus 24.4	6.9 versus 3.7	3.4 versus 0	Severe COVID-19
Zhao et al.[15]	Retrospective Observational	77 (57/20)	69 versus 45	55 versus 40.4	CRP	□10 mg/L	N/A	N/A	N/A	10.0 versus 7.0	40.0 versus 14.0	30.0 versus 5.3	15.0 versus 5.3 (unspecified)	Severe COVID-19
Zhang et al.[14]	Retrospective Observational	221 (55/166)	62 versus 51	63.6 versus 44.0	N/A	N/A	□1 ng/ml	N/A	N/A	10 (12.7 versus 9.0)	47.3 versus 16.9	23.6 versus 5.4	7.3 versus 1.2	Severe COVID-19
Wan et al.[13]	Retrospective Observational	135 (40/135)	56 versus 44	52.5 versus 54.7	N/A	N/A	□0.25 ng/ml	N/A	N/A	22.5 versus 3.1	10 versus 9.4	15.0 versus 1.0 (CVD)	2.5 versus 0 (CLD)	Severe COVID-19
Li et al.[13]	Retrospective Observational	325 (26/299)	65 versus 49	76.9 versus 49.2	N/A	N/A	□0.5 ng/ml	N/A	N/A	19.2 versus 8.4	46.2 versus 22.1	19.2 versus 4.3	7.7 versus 0.6	Severe COVID-19
Wang et al.[34]	Retrospective Observational	143 (71/72)	65 versus 44	62 versus 40.3	N/A	N/A	□0.5 ng/ml	N/A	N/A	12.7 versus 5.6	43.7 versus 6.9	16.9 versus 5.6	9.9 versus 4.2	Severe COVID-19
Ji et al.[33]	Retrospective Observational	49 (15/34)	56.5 versus 37.9	66.7 versus 61.8	N/A	N/A	N/A	N/A	907.4 versus 318.1	N/A	N/A	N/A	N/A	Severe COVID-19
Liu et al.[44]	Retrospective Observational	40 (13/40)	59.7 versus 43.2	53.8 versus 29.6	N/A	N/A	N/A	N/A	835.5 versus 367.8	30.8 versus 7.4	38.5 versus 3.7	N/A	N/A	Severe COVID-19
Liu et al.[31]	Retrospective Observational	80 (69/11)	56 versus 31	47.8 versus 9.09	CRP	□10 mg/L	□0.5 ng/ml	□0.5 mg/L	827.2 versus 155.7	15.9 versus 0	20.3 versus 0	8.7 versus 0	N/A	Severe COVID-19
Ma et al.[30]	Retrospective Observational	84 (20/64)	58 versus 46.5	60 versus 56.3	N/A	N/A	N/A	N/A	1104 versus 368.5	35 versus 4.7	20.0 versus 12.5	10.0 versus 4.7	10.0 versus 4.7 (CLD)	Severe COVID-19
Qin et al.[29]	Retrospective Observational	452 (286/166)	61 versus 53	54.2 versus 48.2	N/A	N/A	N/A	N/A	800.4 versus 523.7	18.5 versus 13.3	36.7 versus 18.1	8.4 versus 1.8 (CVD)	3.1 versus 1.8	Severe COVID-19
Chen et al.[28]	Retrospective Observational	21 (11/10)	61 versus 52	90.9 versus 70	hs-CRP	>60 mg/L	□0.5 ng/ml	N/A	1598.2 versus 337.4	18.2 versus 10.2	36.4 versus 10.0	N/A	N/A	Severe COVID-19
Cao et al.[32]	Retrospective Observational	198 (19/176)	63.7 versus 48.6	89.5 versus 46.9	hs-CRP	□10 mg/L	>0.05 ng/ml	>0.5 mg/L	N/A	10.5 versus 7.3	31.6 versus 20.1	26.3 versus 3.9 (CVD)	N/A	ICU care
Wang et al.[11]	Retrospective Observational	138 (36/102)	66 versus 51	61.1 versus 52.0	N/A	N/A	□0.05 ng/ml	N/A	N/A	22.2 versus 5.9	58.3 versus 21.6	25.0 versus 10.8	8.3 versus 1.0	ICU care
Wu et al.[10]	Retrospective Observational	201 (84/117)	58.5 versus 48	71.4 versus 58.1	N/A	N/A	N/A	N/A	1029.3 versus 545.5	19 versus 5.1	27.4 versus 13.7	6.0 versus 2.6	2.5 (total) (CLD)	ARDS
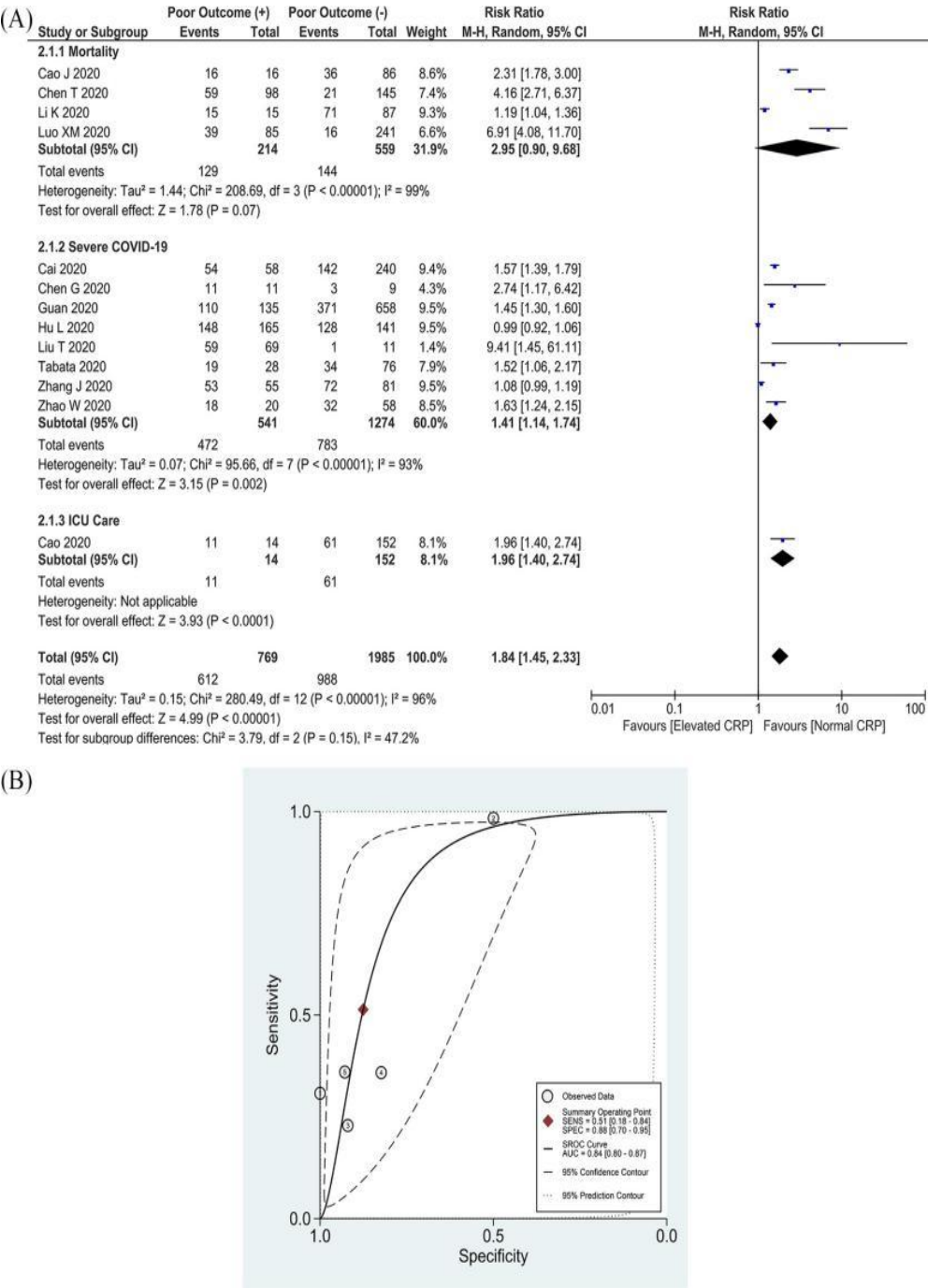
Figure 2. Elevated CRP and composite poor outcome. (a) Patients with a composite poor outcome comprising mortality, ARDS, need for ICU care, and severe COVID-19 have an elevated serum CRP. (b) SROC (summary receiver operating characteristic.)analysis (with prediction and confidence contours) of an elevated CRP and a composite poor outcome.
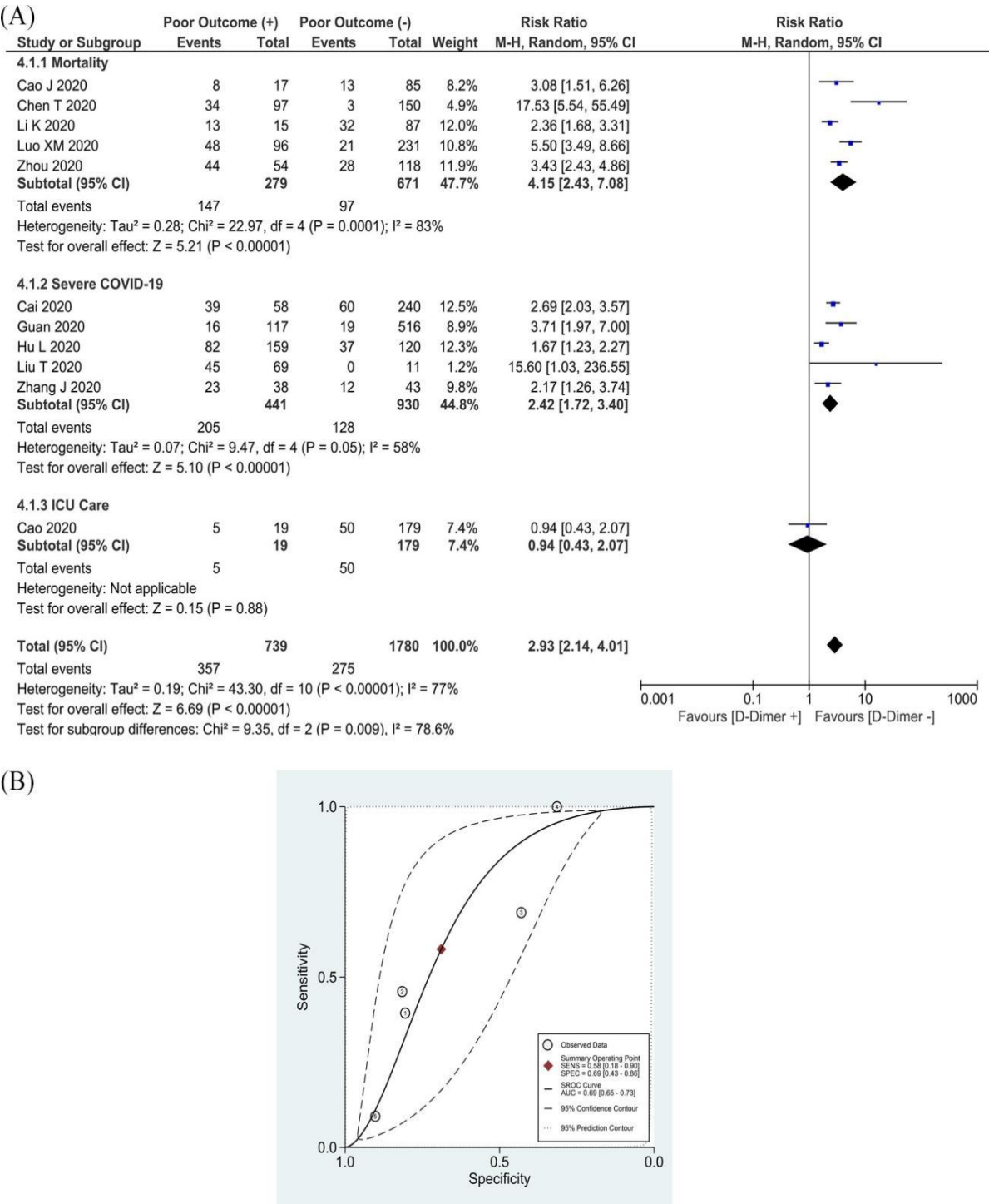
Figure 3. Elevated D-dimer and composite poor outcome. (a) Patients with a composite poor outcome comprising mortality, ARDS, need for ICU care, and severe COVID-19 have an elevated serum PCT. (b) SROC analysis (with prediction and confidence contours) of elevated D-dimer and a composite poor outcome.
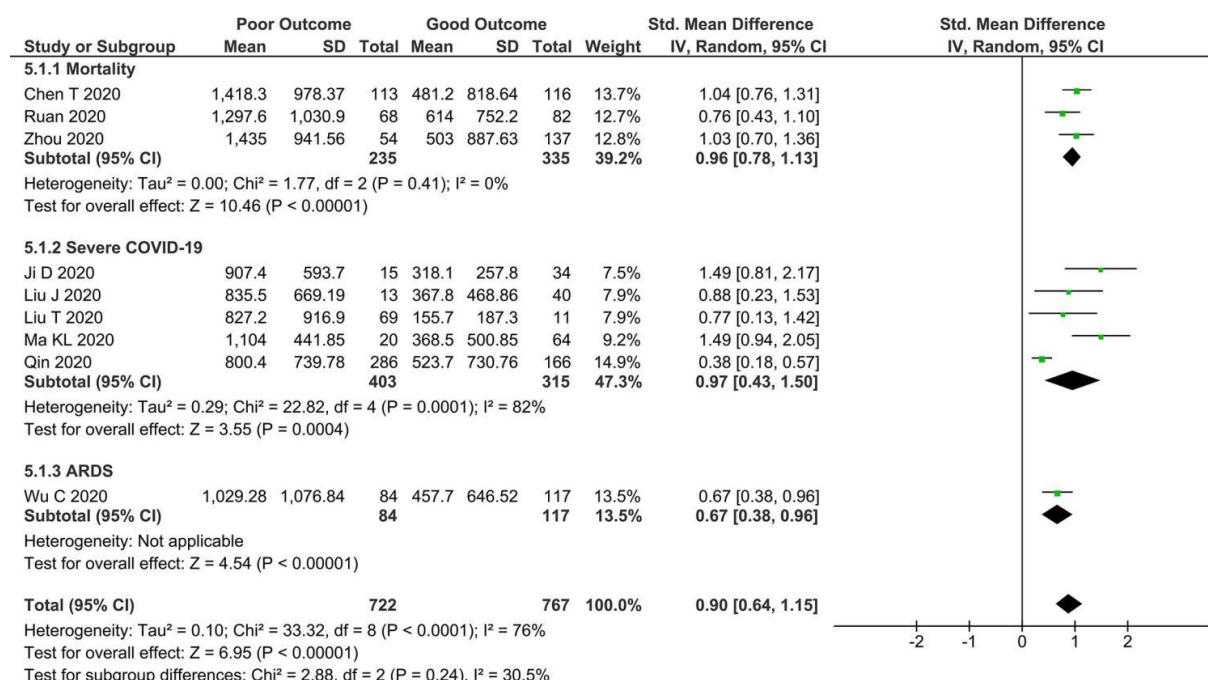
Figure 4. Higher serum ferritin and a composite poor outcome. Patients with a composite poor outcome comprising mortality, ARDS, need for ICU care, and severe COVID-19 have a higher serum ferritin level.

Discussion

This meta-analysis showed that elevated serum CRP, D-dimer, and serum ferritin levels were related with an augmented composite poor outcome that includes mortality, severe COVID-19, ARDS, and the need for ICU care in patients with COVID-19. The effect estimate was not significantly modified by age, gender, cardiovascular disease, diabetes, and COPD.

In the systemic hyperinflammation phase of COVID-19 projected by Siddiqi and Mehra,35 there is a significant elevation of inflammatory cytokines and biomarkers, such as interleukin (IL)-2, IL-6, IL-7, granulocyte-colony stimulating factor, tumor necrosis factorβ, CRP, ferritin, and D-dimer. This stage has the most severe manifestation of the cytokine storm, in which extreme hyperinflammation may cause to cardiopulmonary collapse and multi-organ failure.CRP is an acute phase inflammatory protein manufactured by the liver that may be raised in several conditions, such as inflammation, cardiovascular disease, and infection. In the present study of 13 articles, an elevated CRP was concomitant with severe COVID-19, the need for ICU care, but not with death. Though there is no general agreement on a cutoff point to determining the severity of COVID-19, the majority of the studies used a ⩾10 mg/L limit. In present study, the cutoff values of serum CRP varied widely, with the lowest and highest values being >3 mg/L and >100 mg/L. These findings mirrored the paramount need for pursuing the optimal serum CRP cutoff value for COVID-19 prediction. The time period for serum CRP measurement was critical in light of the timely manner of serum CRP increment, which culminates 72 h after the initial insults.37,41 Despite its value in predicting a poor outcome in COVID-19, it should be noted that various aspects could affect serum CRP levels, including age, gender, smoking status, weight, lipid levels, BP, and liver health.37 These factors should be taken into account while interpreting the serum CRP level. Also, current research has shown that serum CRP level could also be used in checking the

progression and improvement of patients with COVID-19.43In our study, we also found that an elevated D-dimer was linked with an increased composite poor outcome, particularly mortality and severe COVID-19. These findings support the hypothesis that SARS-CoV-2 may induce the dysfunction of the hemostatic system, leading to a hypercoagulable state, a condition which we commonly encounter in sepsis. In the absence of contraindications, a prophylactic dose of an anticoagulant is suggested for all hospitalized patients with COVID-19.Accompanied by other biomarkers included in this study, we also found that a higher serum ferritin level was independently associated with ARDS, mortality, and severe COVID-19. This suggests a presence of secondary hemophagocytic lymphohistiocytosis (sHLH) in COVID-19.7 sHLH is a condition of hyperinflammation described by a cytokine storm causing fatal multi-organ failure. This situation is most commonly triggered by viral infections, which might lead to a hypothesis of SARS-CoV-2 inducing this hyperinflammatory syndrome. The limitations of this systematic review and meta- analysis is the publication bias, non-peer-reviewed studies, and type of the retrospective studies.

Conclusion
This meta-analysis showed that an elevated serum CRP, PCT, D-dimer, and serum ferritin were associated with a composite poor outcome in patients with COVID-19.

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