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 I² statistic with P<0.05 for Q-statistic, I² \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, Ddimer, 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.

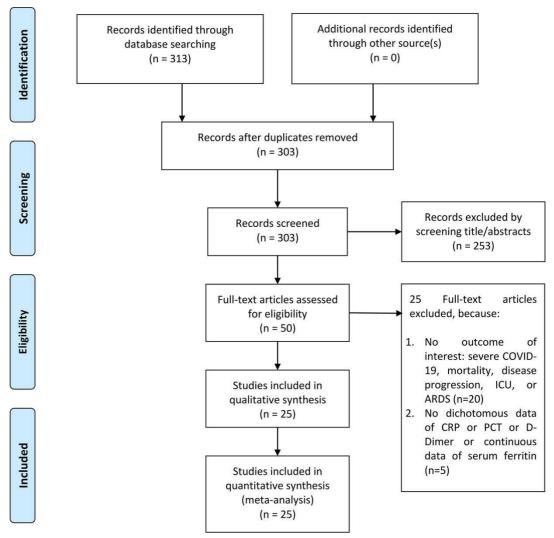


TABLE 1- Comparison of the studies.

rd = 1/2 Observational (113/14) 51.0 55 55 55 55 55 55 55 55 55 55 55 55 55 50 50 50 50 55 50 50 50 50 55 50	uthors	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 interes
Observational SS						hs-CRP	>100 mq/L	00.5 og /ml	>21 µq/ml					10.0 versus 4.0 (CLD)	Mortality
12111 Observational (100/303) 44.9 10.6 17.5 6.6 106 107.6 67 verse 107.6 <td></td> <td></td> <td>102 (15/87)</td> <td>69 versus 55</td> <td></td> <td>hs-CRP</td> <td>3 mg/L</td> <td>00.05 og/ml</td> <td>>1 µq/ml</td> <td>N/A</td> <td></td> <td></td> <td></td> <td>7.0 versus 1.0</td> <td>Mortality</td>			102 (15/87)	69 versus 55		hs-CRP	3 mg/L	00.05 og/ml	>1 µq/ml	N/A				7.0 versus 1.0	Mortality
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L ²² Observational (19/176) 48.6 46.9 7.3 20.1 3.9 (CVD) ng Retrospective 138 66 versus 51 61.1 versus: N/A N/A D0.05 pg/ml N/A N/A 22.2 versus 58.3 versus 25.0 versus L ¹¹ Observational (36/102) 52.0 5.9 21.6 10.8 Retrospective 201 58.5 versus 71.4 versus: N/A N/A N/A 1029.3 versus 19 versus 5.1 27.4 versus 6.0 versus			21 (11/10)	61 versus 52		hs-CRP	>60 mq/L	00.5 og/ml	N/A				N/A	N/A	Severe COVID-1
Observational (36/102) 52.0 5.9 21.6 10.8 Retrospective 201 58.5 versus 71.4 versus N/A N/A 1029.3 versus 19 versus 51.27.4 versus 6.0 versus						bs-CRP	□10 mq/L	>0.05 <mark>og</mark> /ml	>0.5 mg/L	N/A			26.3 versus 3.9 (CVD)	N/A	ICU car
Retrospective 201 58,5 versus 71.4 versus N/A N/A N/A N/A 1029,3 versus 19 versus 5.1 27.4 versus 6.0 versus ^{1.111} Observational (84/117) 48 58.1 3.7 2.6				66 versus 51		N/A	N/A	00.05 <mark>og</mark> /ml	N/A	N/A				8.3 versus 1.0	ICU car
	1 2L **	Retrospective Observational	201 (84/117)			N/A	N/A	N/A	N/A		19 versus 5.1		6.0 versus 2.6	2.5 (total) (CLD)	ARDS

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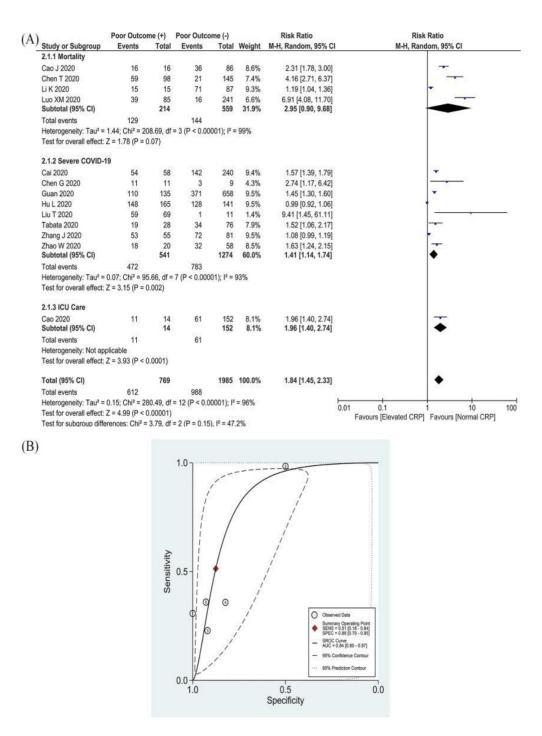


Figure 2. Elevated CRP and composite poor outcome. (a) Patients with a composite poor outcome comprising mortality, ARDS, need for ICU care, and severe COVID-19 have an elevated serum CRP. (b) SROC (summary receiver operating characteristic.)analysis (with prediction and confidence contours) of an elevated CRP and a composite poor outcome.

A)	Poor Outco	me (+)	Poor Outco	me (-)		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
4.1.1 Mortality							
Cao J 2020	8	17	13	85	8.2%	3.08 [1.51, 6.26]	
Chen T 2020	34	97	3	150	4.9%	17.53 [5.54, 55.49]	
Li K 2020	13	15	32	87	12.0%	2.36 [1.68, 3.31]	-
_uo XM 2020	48	96	21	231	10.8%	5.50 [3.49, 8.66]	-
Zhou 2020 Subtotal (95% CI)	44	54 279	28	118 671	11.9% 47.7%	3.43 [2.43, 4.86] 4.15 [2.43, 7.08]	→
Total events	147		97				
Heterogeneity: Tau ² =	0.28; Chi ² = 22	2.97, df =	4 (P = 0.000	1); l ² = 8	3%		
Test for overall effect:	Z = 5.21 (P < 0	0.00001)					
4.1.2 Severe COVID-	19						
Cai 2020	39	58	60	240	12.5%	2.69 [2.03, 3.57]	.
Guan 2020	16	117	19	516	8.9%	3.71 [1.97, 7.00]	-
Hu L 2020	82	159	37	120	12.3%	1.67 [1.23, 2.27]	+
iu T 2020	45	69	0	11	1.2%	15.60 [1.03, 236.55]	
Zhang J 2020	23	38	12	43	9.8%	2.17 [1.26, 3.74]	-
Subtotal (95% CI)		441		930	44.8%	2.42 [1.72, 3.40]	•
Total events	205		128				
Heterogeneity: Tau ² =	0.07; Chi ² = 9.	47, df = 4	(P = 0.05); I	² = 58%			
Test for overall effect:	Z = 5.10 (P < 0	0.00001)					
4.1.3 ICU Care							
Cao 2020	5	19	50	179	7.4%	0.94 [0.43, 2.07]	+
Subtotal (95% CI)		19		179	7.4%	0.94 [0.43, 2.07]	•
Fotal events	5		50				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 0.15 (P = 0	0.88)					
Total (95% CI)		739		1780	100.0%	2.93 [2.14, 4.01]	•
Total events	357		275			a o 853	
Heterogeneity: Tau ² =	0.19; Chi ² = 43	3.30, df =	10 (P < 0.00	001); l² =	: 77%		
lest for overall effect:	Z = 6.69 (P < 0)	0.00001)		1999 - 1999 - 1 999 - 1999 -			0.001 0.1 1 10 10
est for subgroup diff			= 2 (P = 0.00)	9) $l^2 = 7$	8 6%		Favours [D-Dimer +] Favours [D-Dimer -]

(B)

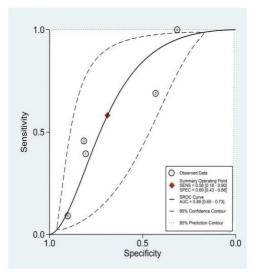


Figure 3. Elevated D-dimer and composite poor outcome. (a) Patients with a composite poor outcome comprising mortality, ARDS, need for ICU care, and severe COVID-19 have an elevated serum PCT. (b) SROC analysis (with prediction and confidence contours) of elevated D-dimer and a composite poor outcome.

	Poor	Outcome		Goo	d Outco	me		Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
5.1.1 Mortality									
Chen T 2020	1,418.3	978.37	113	481.2	818.64	116	13.7%	1.04 [0.76, 1.31]	+
Ruan 2020	1,297.6	1,030.9	68	614	752.2	82	12.7%	0.76 [0.43, 1.10]	
Zhou 2020	1,435	941.56	54	503	887.63	137	12.8%	1.03 [0.70, 1.36]	-
Subtotal (95% CI)			235			335	39.2%	0.96 [0.78, 1.13]	•
Heterogeneity: Tau ² =	0.00; Chi ² =	= 1.77, df =	2 (P =	0.41);	² = 0%				
Test for overall effect:	Z = 10.46 (P < 0.0000	1)						
5.1.2 Severe COVID-1	9								
Ji D 2020	907.4	593.7	15	318.1	257.8	34	7.5%	1.49 [0.81, 2.17]	
Liu J 2020	835.5	669.19	13	367.8	468.86	40	7.9%	0.88 [0.23, 1.53]	
Liu T 2020	827.2	916.9	69	155.7	187.3	11	7.9%	0.77 [0.13, 1.42]	
Ma KL 2020	1,104	441.85	20	368.5	500.85	64	9.2%	1.49 [0.94, 2.05]	
Qin 2020	800.4	739.78	286	523.7	730.76	166	14.9%	0.38 [0.18, 0.57]	-
Subtotal (95% CI)			403			315	47.3%	0.97 [0.43, 1.50]	•
Heterogeneity: Tau ² =	0.29; Chi ² =	= 22.82, df	= 4 (P	= 0.000	1); l ² = 82	2%			
Test for overall effect:	Z = 3.55 (P	= 0.0004)							
5.1.3 ARDS									
Wu C 2020	1,029.28	1,076.84	84	457.7	646.52	117	13.5%	0.67 [0.38, 0.96]	
Subtotal (95% CI)			84			117	13.5%	0.67 [0.38, 0.96]	•
Heterogeneity: Not app	licable								
Test for overall effect:	Z = 4.54 (P	< 0.00001)						
Total (95% CI)			722			767	100.0%	0.90 [0.64, 1.15]	•
Heterogeneity: Tau ² =	0.10; Chi ² =	= 33.32, df	= 8 (P	< 0.000	1); $ ^2 = 70$	6%			
Test for overall effect:			•						-2 -1 0 1 2
Test for subaroup diffe			·	P = 0.24), $ ^2 = 30$.	5%			

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 $\ge 10 \text{ mg/L}$ 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.

References

- 1. World Health Organization. World Health Organization. Coronavirus disease 2019 (COVID- 19) Situation Report 106, https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports (2020).
- 2. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020; 395: 507–513.
- 3. Pranata R, Huang I, Lukito AA, et al. Elevated N-terminal pro-brain natriuretic peptide associated with increased mortality in patients with COVID-19: systematic review and meta-analysis. Postgrad Med J 2020; postgradmedj-2020-137884.
- 4. Huang I, Lim MA and Pranata R. Diabetes mellitus is associated with increased mortality and severity of disease in COVID-19 pneumonia- a systematic review, meta-analysis, and meta- regression: diabetes and COVID-19. Diabetes Metab Syndr Clin Res Rev 2020; 14: 395–403.
- 5. Pranata R, Huang I, Lim MA, et al. Impact of cerebrovascular and cardiovascular diseases on mortality and severity of COVID-19 systematic review, meta-analysis, and meta-regression. J Stroke Cerebrovasc Dis 2020; 29: 104949.
- 6. Huang I and Pranata R. Lymphopenia in severe coronavirus disease-2019 (COVID-19): systematic review and meta-analysis. J Intensive Care 2020; 8: 36.
- 7. Mehta P, McAuley DF, Brown M, et al. COVID- 19: consider cytokine storm syndromes and immunosuppression. Lancet 2020; 395: 1033–1034.
- 8. World Health Organization. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected: interim guidance. 2020; 1–21.
- 9. World Health Organization. Report of the WHO- China joint mission on coronavirus disease 2019 (COVID-19), https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on- covid-19-final-report.pdf.
- 10. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan,

China. JAMA Intern Med 2020; 1–10.

- 11. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020; 1–9.
- 12. Li Q, Ling Y, Zhang J, et al. Clinical characteristics of SARS-CoV-2 infections involving 325 hospitalized patients outside Wuhan. Res Sq 2020; 1–15.
- 13. Wan S, Xiang Y, Fang W, et al. Clinical features and treatment of COVID-19 patients in Northeast Chongqing. J Med Virol 2020; 0–1.
- 14. Zhang G, Hu C, Luo L, et al. Clinical features and outcomes of 221 patients with COVID-19 in Wuhan, China. medRxiv 2020; 2020.03.02.20030452.
- 15. Zhao W, Yu S, Zha X, et al. Clinical characteristics and durations of hospitalized patients with COVID-19 in Beijing: a retrospective cohort study. medR 2020; 21: 1–9.
- 16. Zhang J-J, Dong X, Cao Y-Y, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy Eur J Allergy Clin Immunol 2020; 1–12.
- 17. Tabata S, Imai K, Kawano S, et al. Non-severe vs severe symptomatic COVID-19: 104 cases from the outbreak on the cruise ship "Diamond Princess" in Japan. medRxiv. Epub ahead of print 2020. DOI: 10.1101/2020.03.18.20038125.
- 18. Hu L, Chen S, Fu Y, et al. Risk factors associated with clinical outcomes in 323 COVID-19 patients in Wuhan, China. medRxiv. Epub ahead of print 2020. DOI: 10.1101/2020.03.25.20037721.
- 19. Guan W-J, Ni Z-Y, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020; 382: 1708–1720.
- 20. Cai Q, Huang D, Ou P, et al. COVID-19 in a designated infectious diseases hospital
- 21. outside Hubei Province, China. medRxiv 2020; 2020.02.17.20024018.
- 22. Cao J, Tu W, Cheng W, et al. Clinical features and short-term outcomes of 102 patients with corona virus disease 2019 in Wuhan, China. Clin Infect Dis. Epub ahead of print 13 March 2020. DOI: 10.1093/cid/ciaa243.
- 23. Cao M, Zhang D, Wang Y, et al. Clinical features of patients infected with the 2019 novel coronavirus (COVID-19) in Shanghai, China. medRxiv 2020; 2020.03.04.20030395.
- 24. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020; 395: 1054–1062.
- 25. Ruan Q, Yang K, Wang W, et al. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med 2020; 46: 846–848.
- 26. Luo X, Xia H, Yang W, et al. Characteristics of patients with COVID-19 during epidemic ongoing outbreak in Wuhan, China. medRxiv. Epub ahead of print 23 March 2020. DOI: 10.1101/2020.03.19.20033175.
- 27. Li K, Chen D, Chen S, et al. Radiographic findings and other predictors in adults with COVID-19. medRxiv; 2. Epubahead of print 27 March 2020. DOI: 10.1101/2020.03.23.20041673.
- 28. Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ 2020; 1091: m1091.
- 29. Chen G, Wu D, Guo W, et al. Clinical and immunologic features in severe and moderate coronavirus disease 2019. J Clin Invest 2020; 130: 2620–2629.
- 30. Qin C, Zhou L, Hu Z, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. Clin Infect Dis 2020; 53: 1689–1699.

- 31. Ma K-L, Liu Z-H, Cao F-C, et al. COVID-19 Myocarditis and severity factors: an adult cohort study. medRxiv. Epub ahead of print 23 March 2020. DOI: 10.1101/2020.03.19.20034124.
- Liu T, Zhang J, Yang Y, et al. The potential role of IL-6 in monitoring coronavirus disease 2019. SSRN Electron J. Epub ahead of print 10 March 2020. DOI: 10.2139/ssrn.3548761.
- 33. Liu J, Li S, Liu J, et al. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. medRxiv 2020; 2020.02.16.20023671.
- Ji D, Zhang D, Chen Z, et al. Clinical characteristics predicting progression of COVID-19. SSRN Electron J. Epub ahead of print 20 February 2020. DOI: 10.2139/ssrn.3539674.
- 35. Wang D, Li R, Wang J, et al. Correlation analysis between disease severity and clinical and biochemical characteristics of 143 cases of COVID-19 in Wuhan, China: a descriptive study. Res Sq; 1–17.
- 36. Siddiqi HK and Mehra MR. COVID-19 illness in native and immunosuppressed states: a clinical- therapeutic staging proposal. J Heart Lung Transplant 2020; 39: 405–407.
- 37. Zhang W, Zhao Y, Zhang F, et al. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID- 19): the experience of clinical immunologists from China. Clin Immunol 2020; 214: 108393.
- 38. Sproston NR and Ashworth JJ. Role of C-reactive protein at sites of inflammation and infection. Front Immunol 2018; 9: 1–11.