Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Clinica Chimica Acta 509 (2020) 180–194

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/cca

Comparative analysis of laboratory indexes of severe and non-severe patients infected with COVID-19

Jinfeng Bao[a,1], Chenxi Li[a,1], Kai Zhang[b,1], Haiquan Kang[c], Wensen Chen[d,e,*], Bing Gu[a,c,*]

[a] Medical Technology School of Xuzhou Medical University, Xuzhou Key Laboratory of Laboratory Diagnostics, Xuzhou, Jiangsu 221004, China
[b] Pancreas Center, The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu 210029, China
[c] Department of Laboratory Medicine, The Affiliated Hospital of Xuzhou Medical University, Xuzhou, Jiangsu 221006, China
[d] Department of Epidemiology and Biostatistics, School of Public Health, Xi'an Jiao tong University Health Science Center, Xi'an, Shaanxi 710061, China
[e] Department of Infection Management, The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu 210029, China

ARTICLE INFO

Keywords:
COVID-19
Laboratory findings
Meta-analysis
Prognosis

ABSTRACT

Background: The pandemic coronavirus disease 2019 (COVID-19) has threaten the global health. The characteristics of laboratory findings of coronavirus are of great significance for clinical diagnosis and treatment. We found indicators that may most effectively predict a non-severe COVID-19 patient develop into a severe patient.
Methods: We conducted a *meta*-analysis to compare the laboratory findings of severe patients with non-severe patients with COVID-19 from searched articles.
Results: Through the analysis of laboratory examination information of patients with COVID-19 from 35 articles (5912 patients), we demonstrated that severe cases possessed higher levels of leukocyte (1.20-fold), neutrophil (1.33-fold), CRP (3.04-fold), PCT (2.00-fold), ESR (1.44-fold), AST (1.40-fold), ALT (1.34-fold), LDH (1.54-fold), CK (1.44-fold), CK-MB (1.39-fold), total bilirubin (1.14-fold), urea (1.28-fold), creatine (1.09-fold), PT (1.03-fold) and D-dimer (2.74-fold), as well as lower levels of lymphocytes (1.44-fold), eosinophil (2.00-fold), monocyte (1.08-fold), Hemoglobin (1.53-fold), PLT (1.15-fold), albumin (1.15-fold), and APTT (1.02-fold). Lymphocyte subsets and series of inflammatory cytokines were also different in severe cases with the non-severe ones, including lower levels of CD4 T cells (2.10-fold) and CD8 T cells (2.00-fold), higher levels of IL-1β (1.02-fold), IL-6 (1.93-fold) and IL-10 (1.55-fold).
Conclusions: Some certain laboratory inspections could predict the progress of the COVID-19 changes, especially lymphocytes, CRP, PCT, ALT, AST, LDH, D-dimer, CD4 T cells and IL6, which provide valuable signals for preventing the deterioration of the disease.

1. Introduction

Since December 2019, the rapid propagation of a novel coronavirus (SARS-CoV-2) has broken out in China, and SARS-CoV-2 causes a novel pneumonia named COVID-19 [1]. SARS-CoV-2 is a β-coronavirus with a genome highly homologous to bats, which probably originated from wild animals [2]. Interpersonal transmission is the main cause of infection [3]. The World Health Organization (WHO) has declared it as a public health emergency of international concern [4]. As of May 3, 2020, a total of 3,405,914 cases were confirmed and 240,573 cases died globally [5]. The clinical features of severe COVID-19 are similar to those of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). It can cause acute respiratory distress syndrome (ARDS), acute heart injury, and even death. Its main clinical features are fever, cough and sore throat. According to the clinical classification method, the patients were divided into four types: ordinary type, mild type, severe type and critically ill type according to the severity of the disease [6,7]. In addition, the correlation between specific laboratory diagnosis and disease severity deserves attention. Several studies have reported different laboratory findings at the beginning of the outbreak of COVID-19 [8–10]. The purpose of this survey is to reveal the characteristics of laboratory findings of COVID-19 through the included articles, especially the changes of severe and critically ill patients, so as to provide more information for COVID-19 's diagnosis.

* Corresponding authors at: Department of Laboratory Medicine, The Affiliated Hospital of Xuzhou Medical University, Xuzhou, Jiangsu 221006, PR China (B. Gu). Department of Infection Management, The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu 210029, China (W. Chen).
E-mail addresses: wensenchen@njmu.edu.cn (W. Chen), binggu2015@xzhmu.edu.cn (B. Gu).
[1] these authors contributed equally to this work.

https://doi.org/10.1016/j.cca.2020.06.009
Received 4 April 2020; Received in revised form 11 May 2020; Accepted 3 June 2020
Available online 06 June 2020
0009-8981/ © 2020 Elsevier B.V. All rights reserved.

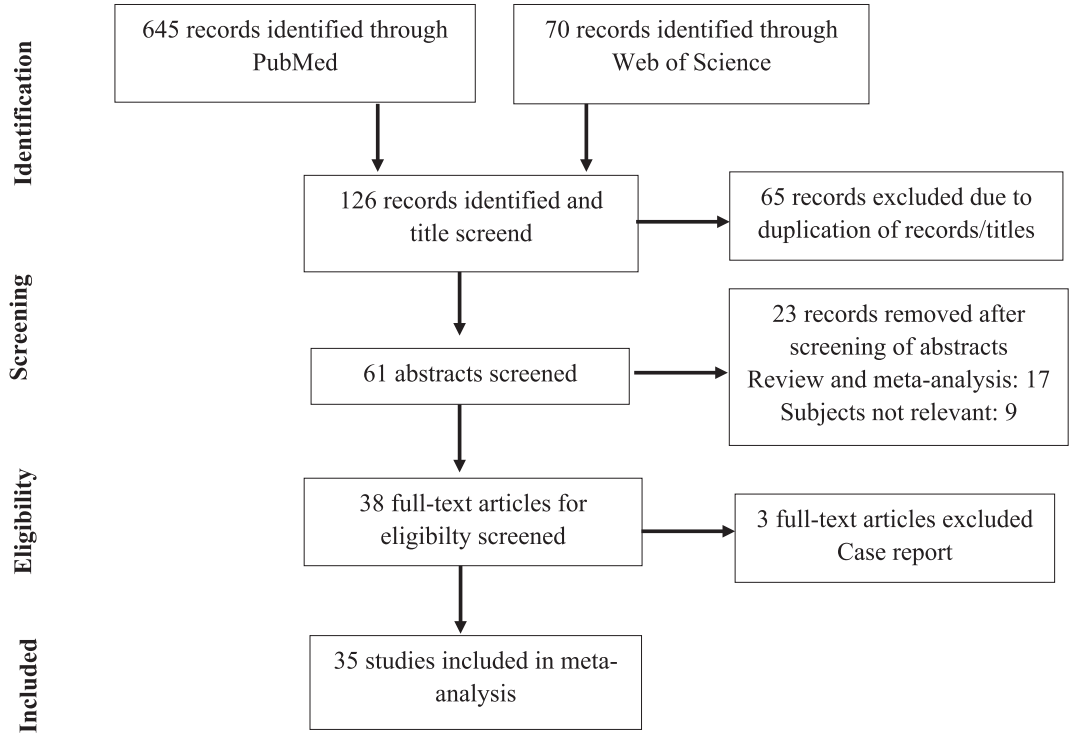

Fig. 1. Flow diagram for selection of studies.

Table 1
Summary the characteristics of 35 studies that described the risk factors with COVID-19 patients.

Author	Journal	Year	Country/ region	Number of total patients	Number of non-severe patients	Number of severe patients	Age, median (IQI) or mean (SD)
Qin C [13]	Clin. Infect. Dis.	2020	Shangha, China	452	166	286	58 (47–67)
Chen X [74]	Clin. Infect. Dis.	2020	Wuhan, China	48	21	27	64.6 ± 18.1
Wang R [75]	Int. J. Infect. Dis.	2020	Anhui, China	125	100	25	38.8 ± 13.8
Gao Y [68]	J. Med. Virol.	2020	Anhui, China	43	28	15	
Zheng YL [17]	J. Clin. Virol.	2020	Chengdu, China	99	67	32	49.4 ± 18.45
Ma J [15]	J. Infect.	2020	Wuhan, China	37	17	20	62 (59–70)
Wang DL [18]	Lancet	2020	Jiangsu, China	620	567	53	44.4 ± 17.2
Liu W [56]	Chin. Med. J.	2020	Wuhan, China	78	67	11	38 (33–57)
Yang AP [76]	Int. Immunopharmacol.	2020	China	93	69	24	46.4 ± 17.6
Li KH [77]	Invest Radiol	2020	Chongqing, China	83	58	25	45.5 ± 12.3
Zhang JJ [62]	Allergy	2020	Wuhan, China	140	82	58	57 (25–87)
Huang CL [10]	Lancet	2020	Wuhan, China	41	28	13	49 (41–58)
Wang DW [64]	JAMA	2020	Wuhan, China	138	102	36	56 (42–68)
Liu M [14]	Zhonghua Jie He He Hu Xi Za Zhi	2020	Wuhan, China	30	26	4	35 ± 8
Mo PZ [78]	Clin. Infect. Dis.	2020	Wuhan, China	155	70	85	54 (42–66)
Peng YD [79]	Zhonghua Xin Xue Guan Bing Za Zhi	2020	Shanghai, China	112	96	16	62 (55–67)
Feng Y [80]	Am. J. Respir. Crit. Care Med.	2020	China	476	352	124	53 (40–64)
Cai QX [81]	Allergy	2020	Shenzhen, China	298	240	58	47.5 (33–61)
Li H [82]	J. Infect.	2020	Wuhan, China	132	60	72	62 ± 12.7
Zheng F [83]	Eur Rev Med Pharmacol Sci	2020	Hunan, China	161	131	30	45 (33.5–57)
Wang KK [84]	Lancet	2020	Hong Kong, China	23	13	10	
Guan W [85]	New Engl J Med	2020	Wuhan, China	1099	926	173	47 (35–58)
Gong J [86]	Clin. Infect. Dis.	2020	Wuhan and Guangdong, China	189	161	28	49 (35–63)
Lei SQ [87]	E Clin Med	2020	China	34	19	15	55 (43–63)
Deng Q [88]	Int. J. Cardiol.	2020	Wuhan, China	112	45	67	65 (49–70)
Mao L [89]	JAMA Neurol.	2020	Wuhan, China	214	126	88	52.7 ± 15.5
Du RH [90]	Ann. Am. Thorac. Soc.	2020	Wuhan, China	109	58	51	70.7 ± 10.9
Xie HS [91]	Liver Int.	2020	Wuhan, China	79	51	28	60 (48–66)
Wu J [92]	J. Intern. Med.	2020	China	280	197	83	43 ± 19
Chen G [93]	J. Clin. Investig.	2020	Wuhan, China	21	10	11	56 (50–65)
Wan S [94]	J. Med. Virol.	2020	Chongqing, China	135	95	40	47 (36–55)
Pan HQ [42]	Lancet Infect. Dis.	2020	Wuhan, China	221	166	55	55 (39–66.5)
Bo XU [16]	J. Infect.	2020	Wuhan, China	187	80	107	62 (48.5–71)
GQQ [95]	Int. J. Med.	2020	Zhejiang, China	91	82	9	50 (36.5–57)
Lo LI [96]	Int. J. Biol. Sci.	2020	Macau, China	10	6	4	54 (27–64)

Table 2
The quality assessment of included studies.

Author	1	2	3	4	5	6	7	8	Score
Qin C [13]	2	2	2	2	2	0	2	2	14
Chen X [74]	2	2	2	2	2	0	1	1	12
Wang R [75]	2.	2	2	2	2	2	2	2	16
Gao Y [68]	2	2	2	2	2	0	2	1	13
Zheng YL [17]	2	2	2	2	2	2	2	1	15
Ma J [15]	2	2	2	2	2	0	2	1	13
Wang DL [18]	2	2	2	2	2	2	2	2	16
Liu W [56]	2	2	2	2	2	0	2	1	13
Yang AP [76]	2	2	2	2	2	1	1	1	13
Li KH [77]	2	2	2	2	2	0	2	1	13
Zhang JJ [62]	2	2	2	2	2	0	2	2	14
Huang CL [10]	2	2	2	2	2	0	2	1	13
Wang DW [64]	2	2	2	2	2	1	2	2	15
Liu M [14]	2	2	2	2	2	0	2	1	13
Mo PZ [78]	2	2	2	2	2	1	2	2	15
Peng YD [79]	2	2	2	2	2	2	2	1	15
Feng Y [80]	2	2	2	2	2	0	2	2	14
Cai QX [81]	2	2	2	2	2	2	2	2	16
Li H [82]	2	2	2	2	2	2	1	2	15
Zheng F [83]	2	2	2	2	2	0	2	2	14
Wang KK [84]	2	2	2	2	2	2	2	1	15
Guan W [85]	2	2	2	2	2	2	2	2	16
Gong J [86]	2	2	2	2	2	2	2	2	16
Lei SQ [87]	2	2	2	2	2	2	2	1	15
Deng Q [88]	2	2	2	2	2	2	1	2	15
Mao L [89]	2	2	2	2	2	0	1	2	13
Du RH [90]	2	2	2	2	2	2	2	2	16
Xie HS [91]	2	2	2	2	2	0	2	1	13
Wu J [92]	2	2	2	2	2	0	2	2	14
Chen G [93]	2	2	2	2	2	0	1	1	12
Wan S [94]	2	2	2	2	2	1	2	2	15
Pan HQ [42]	2	2	2	2	2	1	2	2	15
Bo XU [16]	2	2	2	2	2	2	2	2	16
GQQ [95]	2	2	2	2	2	0	2	1	13
Lo LI [96]	2	2	2	2	2	2	1	1	14

1. A clear purpose of the study; 2. Including continuous patients; 3. Expected collection of data; 4. The end point adapted to the research goal; 5. A fair assessment of the end point of the study; 6. A follow-up period commensurate with the objectives of the study; 7. Comprehensive laboratory indicators; 8. Sufficient numbers of patients.

2. Methods

2.1. Literature search and selection

PubMed and Web of Science were used to search for related articles. The key words are “2019-nCoV” “COVID-19” “SARS-CoV-2” “clinical characteristics” and “laboratory findings”. To ensure the comprehensiveness and accuracy of the study, we also consulted the references of the included literature. The searches were performed three times to identify articles published before April 27, 2020. Then we screen the articles according to the abstract, eliminate the articles that obviously do not meet the inclusion criteria, and then read the full text for re-screening. Articles that provided values of laboratory indicators for severe and non-severe patients, including blood routine, inflammatory factors, biochemical and immune-related indexes were included. Pre-printed articles are also included. Articles published repeatedly, translated articles, studies did not include the laboratory indicators needed for *meta*-analysis; research data were missing were excluded. In addition, conference summaries, reviews and *meta*-analysis were excluded.

2.2. Analysis content

Statistically analyzed the data related to laboratory indexes (blood routine, inflammatory markers, biochemical detection indexes, blood coagulation function and immune indexes) to compare the differences between severe and non-severe patients and summarize indicators with statistical significance and clinical value. These laboratory indicators were usually showed as the mean and standard deviation, but sometimes were median and interquartile range (IQR). The sample mean was estimated by Luo et al.'s method [11] and variance by Wan et al.'s [12] from the sample size, median and IQR. For these laboratory indexes, the inverse variance method for pooling was used to calculate the overall mean from studies reporting a single. The I^2 statistic is a test used to quantify heterogeneity and values of $I^2 > 50\%$ indicated that heterogeneity existed. When statistical heterogeneity was identified, the random effects model will be used. The meta package (ver 4.11–0; https://cran.r-project.org/) was used to conduct the overall mean. In addition, we analyzed the correlation and regularity of diverse laboratory indexes in patients with COVID-19 to find the considerable advantages of combined analysis in the diagnosis and treatment of patients' condition.

2.3. Risk of bias assessment

We will apply the following criteria to assess the risk of bias for each included study. 1. A clear purpose of the study; 2. Including continuous patients; 3. Expected collection of data; 4. The end point adapted to the research goal; 5. A fair assessment of the end point of the study; 6. A follow-up period commensurate with the objectives of the study; 7. Comprehensive laboratory indicators; 8. Sufficient numbers of patients. The project score is 0 (not reported), 1 (reported but insufficient), or 2 (reported and sufficient). The global ideal score for non-comparative studies is 16. In addition, we will draft funnel-plots for laboratory indicators with significant differences between severe and non-severe patients with COVID-19 if there are sufficient included studies (at least 10) and observe the symmetry of the funnel-plots to judge the publication bias.

3. Results

3.1. Characteristics of included studies

The process of study selection is displayed in Fig. 1. A total of 715 publications were retrieved, including 645 articles on PubMed, 70 articles on Web of Science. Among these studies, 65 records were excluded due to duplication of records/titles. 615 were removed because they did not meet the inclusion criteria based on title and/or abstract. Finally, we obtained the laboratory test results of 35 articles describing 5912 COVID-19 confirmed patients (up to May 2020). The basic characteristics of the articles included in the study are shown in Table 1.

Among these articles, 34 articles described the results of blood routine and infection-related biomarkers, 26 articles described the results of biochemical tests, 23 articles provided test results for blood coagulation and 5 articles described the results of immunoassay. A total of 5,912 patients (mean age:54.80; 95%CI (52.50–57.20)), including 4337 non-severe patients (mean age:48.50; 95%CI (45.70–51.30)) and 1663 severe patients (mean age:61.00; 95%CI (59.10–62.90)). More than half of them were male (3072/5912(51.96%)). 2531 of these patients with underlying disease, including hypertension, diabetes, cardiovascular disease, cerebrovascular disease, chronic obstructive pulmonary disease (COPD), chronic kidney disease and liver disease, Malignant tumors and patients with low immunity.

3.2. Analysis of laboratory indicators

Based on the comprehensive collation of the laboratory data provided in the selected 35 articles, the average value and variation range of various indexes of total patients, non-severe patients and severe patients were obtained and shown in Table 3. In addition, the Funnel plot of important laboratory indicators are shown in Figs. 2–10.

Table3
Results of Laboratory findings of severe and non-severe patients infected with COVID-19.

	Variables	Classification	Number of articles included	Number of patients included	Mean (95% CI)	P-value
Blood routine	WBC × 10^9 /l	Non-severe patients	34	4236	5.07 (4.90, 5.24)	< 0.01
		Severe patients		1703	6.06 (5.67, 6.46)	
		All patients		5939	5.39 (5.22, 5.55)	
	Neutrophils × 10^9 /l	Non-severe patients	29	3005	3.71 (3.36, 4.06)	< 0.01
		Severe patients		1368	4.94 (4.30, 5.58)	
		All patients		4373	4.22 (3.94, 4.51)	
	Lymphocytes × 10^9 /l	Non-severe patients	34	4228	1.15 (1.08, 1.22)	< 0.01
		Severe patients		1703	0.80 (0.75, 0.84)	
		All patients		5931	0.98 (0.92, 1.04)	
	Eosinophil × 10^9 /l	Non-severe patients	5	1035	0.04 (0.03, 0.05)	0.003
		Severe patients		451	0.02 (0.01, 0.02)	
		All patients		1486	0.03 (0.02, 0.04)	
	Monocyte × 10^9 /l	Non-severe patients	13	1397	0.41 (0.40, 0.42)	0.086
		Severe patients		700	0.38 (0.35, 0.41)	
		All patients		2097	0.40 (0.39, 0.42)	
	PLT × 10^9 /l	Non-severe patients	20	3068	184.19 (178.04, 190.33)	0.340
		Severe patients		1019	212.58 (154.63, 270.53)	
		All patients		4087	201.44 (175.75, 227.12)	
	Hb g/l	Non-severe patients	14	2652	131.36 (128.33, 134.39)	0.164
		Severe patients		711	126.73 (121.16, 132.30)	
		All patients		3363	128.98 (126.17, 131.78)	
Inflammation-related factors	ESR mm/60 min	Non-severe patients	8	1390	28.16 (20.13, 36.2)	0.111
		Severe patients		695	40.54 (27.61, 53.4)	
		All patients		2085	33.94 (28.10, 39.7)	
	CRP mg/l	Non-severe patients	26	2939	19.83 (16.67, 23.0)	< 0.01
		Severe patients		1415	60.91 (49.24, 72.5)	
		All patients		4354	36.99 (33.31, 40.67)	
	PCT ng/ml	Non-severe patients	22	2325	0.07 (0.05, 0.09)	< 0.01
		Severe patients		1222	0.14 (0.11, 0.17)	
		All patients		3547	0.10 (0.08, 0.12)	
Blood biochemistry	ALT U/l	Non-severe patients	26	2769	24.85 (22.69, 27.0)	< 0.01
		Severe patients		1027	33.78 (29.54, 38.0)	
		All patients		3796	28.31 (26.25, 30.3)	
	AST U/l	Non-severe patients	26	2731	26.24 (25.29, 28.18)	< 0.01
		Severe patients		1019	36.78 (33.69, 39.87)	
		All patients		3750	30.66 (29.19, 32.13)	
	LDH U/l	Non-severe patients	19	2306	224.20 (205.33, 243.07)	< 0.01
		Severe patients		811	344.48 (307.08, 381.88)	
		All patients		3117	271.82 (254.13, 289.52)	
	CK U/l	Non-severe patients	17	2241	77.69 (69.68, 85.70)	< 0.01
		Severe patients		849	111.92 (98.24, 125.61)	
		All patients		3090	90.92 (83.54, 98.29)	
	CK-MB U/l	Non-severe patients	9	1329	8.76 (4.74, 12.79)	0.246
		Severe patients		550	12.26 (7.93, 16.58)	
		All patients		1879	10.51 (8.33, 12.70)	
	Albumin g/l	Non-severe patients	10	985	39.41 (37.95, 40.87)	< 0.01
		Severe patients		431	34.29 (32.79, 35.80)	
		All patients		1416	36.75 (35.17, 38.32)	
	Creatinine μmol/l	Non-severe patients	25	2696	66.97 (64.65, 69.28)	< 0.01
		Severe patients		1000	72.94 (69.23, 76.66)	
		All patients		3696	69.61 (67.57, 71.65)	
	Urea mmol/l	Non-severe patients	16	1929	4.36 (4.12, 4.59)	< 0.01
		Severe patients		703	5.59 (5.39, 6.51)	
		All patients		2632	4.98 (4.72, 5.23)	
	Total bilirubin mmol/l	Non-severe patients	14	2065	10.38 (9.78, 10.99)	0.017
		Severe patients		564	11.86 (10.81, 12.91)	
		All patients		2629	10.92 (10.39, 11.45)	

(*continued on next page*)

Table3 (*continued*)

	Variables	Classification	Number of articles included	Number of patients included	Mean (95% CI)	P-value
Blood coagulation function	APTTs	Non-severe patients	12	1422	33.49 (31.17, 35.82)	0.724
		Severe patients		407	32.92 (30.78, 35.06)	
		All patients		1829	33.23 (31.59, 34.86)	
	PT s	Non-severe patients	12	1388	12.45 (11.98, 12.91)	0.319
		Severe patients		504	12.80 (12.29, 13.30)	
		All patients		1892	12.63 (12.31, 12.94)	
	D dimer mg/l	Non-severe patients	23	2503	0.47 (0.40, 0.53)	< 0.01
		Severe patients		1043	1.29 (0.03, 0.54)	
		All patients		3546	0.61 (0.54, 0.67)	
Lymphocyte subsets	CD4 T cells /μL	Non-severe patients	5	475	561.81 (485.46, 638.15)	< 0.01
		Severe patients		208	266.79 (204.51, 329.07)	
		All patients		683	407.03 (310.24, 503.83)	
	CD8 T cells /μL	Non-severe patients	5	475	349.01 (292.61, 405.40)	< 0.01
		Severe patients		208	174.61 (125.95, 223.27)	
		All patients		683	266.65 (198.49, 334.81)	
Cytokines	IL-1β pg/ml	Non-severe patients	2	246	5.01 (4.96, 5.06)	0.055
		Severe patients		393	5.11 (5.02, 5.20)	
		All patients		639	5.06 (4.98, 5.15)	
	IL-6 pg/ml	Non-severe patients	5	312	13.22 (6.88, 19.57)	0.027
		Severe patients		455	25.58 (16.69, 34.47)	
		All patients		767	19.66 (13.44, 25.89)	
	IL-10 pg/ml	Non-severe patients	2	246	5.71 (5.51, 5.90)	< 0.01
		Severe patients		393	8.87 (7.15, 10.59)	
		All patients		639	7.23 (6.18, 8.28)	

SPSS25 was used. Comparison between severe and non-severe patients with *t* test or Mann-Whitney *U* test.

3.2.1. Blood routine examination

Leukopenia was observed in 21.92% (363/1656) patients with lymphocytopenia in 29.02% (886/3053) patients. Elevated neutrophils were observed in 19.85% (81/408) patients. 14.73% (75/509) and 12.68% (78/615) patients were accompanied by a decrease in Hemoglobin and platelet count (PLT) respectively. Most importantly, there were several significant differences between severe patients and non-severe patients, including higher leukocyte (1.20-fold; 6.06 vs 5.07 $\times$ 10^9/l; P $<$ 0.01) and neutrophil (1.33-fold; 4.94 vs 3.71 $\times$ 10^9/l; P $<$ 0.01), lower lymphocyte (1.44-fold; 1.15 vs 0.80 $\times$ 10^9/l; P $<$ 0.01), eosinophils (2.00-fold; 0.04 vs 0.02 $\times$ 10^9/l; P = 0.03), monocytes (1.08-fold; 0.38 vs 0.41 $\times$ 10^9/l; P = 0.041), PLT (1.15-fold; 212.58 vs 184.19 $\times$ 10^9/l; P = 0.987) and hemoglobin (1.53-fold; 131.36vs 126.73 $\times$ 10^9 g/l; P = 0.163).

3.2.2. Inflammatory biomarkers examination

Increased C-reactive protein (CRP) concentration appeared in 57.40% (1494/2603) patients, procalcitonin (PCT) increased in 12.20% (256/2099) patients, and 39.26% (117/298) patients had an increase in erythrocyte sedimentation rate (ESR). Moreover, higher levels of CRP (3.04-fold; 60.91 vs 19.83 mg/l; P $<$ 0.01), PCT (2.00-fold; 0.14vs 0.07 ng/ml; P $<$ 0.01) and ESR (1.44-fold; 40.54 vs 28.16 mm/60 min; P = 0.096) were observed in severe patients in comparison with non-severe patients.

3.2.3. Blood biochemical examination

3.2.3.1. Cardiac markers examination. Our statistics showed that the related indexes of myocardial injury increased in different numbers of patients with COVID-19. (respectively creatine kinase (CK) (7.74% (157/2029)); aspartate aminotransferase (AST) (14.87% (388/2609)); lactate dehydrogenase (LDH) (24.50% (468/1910)). Several significant differences were noted between severe and non-severe patients, especially higher values of AST (1.40-fold; 36.78 vs 26.24 U/l; P $<$ 0.01), LDH (1.54-fold; 344.48 vs 224.20 U/l; P $<$ 0.01), CK (1.44-fold; 111.92 vs 77.69 U/l; P $<$ 0.01) and CK-MB (1.39-fold; 12.26 vs 8.76 U/l; P = 0.317).

3.2.3.2. Liver function. The increase of alanine aminotransferase (ALT) (12.27% (296/2412)) and AST (14.87% (388/2609)) with COVID-19 has been observed. Moreover, the decrease of albumin (143/221 (64.70%)) was more common while the increase of total bilirubin (TBIL) was relatively rare in the majority of patients (109/1558 (6.70%)). Comparing with non-severe patients, higher ALT (1.34-fold; 33.78 vs 24.85 U/l; P $<$ 0.01), AST (1.40-fold; 36.78 vs 26.24 U/l; P $<$ 0.01), TBIL (1.14-fold; 11.86 vs 10.38 U/l; P = 0.024) and lower albumin (1.15-fold; 39.41vs 34.29 g/l; P $<$ 0.01) of severe patients has been worked out.

3.2.3.3. Renal function. The increase of creatinine (2.41% (40/1659)) and urea (13.50% (47/348)) were observed among the included patients with COVID-19. Besides, albumin reduction (64.70% (143/221)) was very common. More importantly, higher levels of creatinine (1.09-fold;72.94 vs 66.97 μmol; P $<$ 0.01), urea (1.28-fold; 5.59 vs 4.36 mmol; P $<$ 0.01) and lower concentrations of albumin (1.15-fold; 39.41 vs 34.29 g/l; P $<$ 0.01) of severe patients were summed up in comparison with non-severe patients.

3.2.4. Blood coagulation function

Prothrombin time (PT) prolonged in 22.65% (53/234) patients and shortened in 10.68% (25/234) patients while activated partial thromboplastin time (APTT) prolonged in 21.79% (51/234) patients and shortened in 5.56% (13/234) patients. D dimer increased in 28.94% (534/1845) patients. Abnormal coagulation function is more obvious in severe patients, including shorter APTT (1.02-fold;33.49 vs 32.92 s; P = 0.804), increased D-dimer (2.74-fold; 1.29 vs 0.47 mg/l; P $<$ 0.01) and longer PT (1.03-fold; 12.80 vs 12.45 s; P = 0.407).

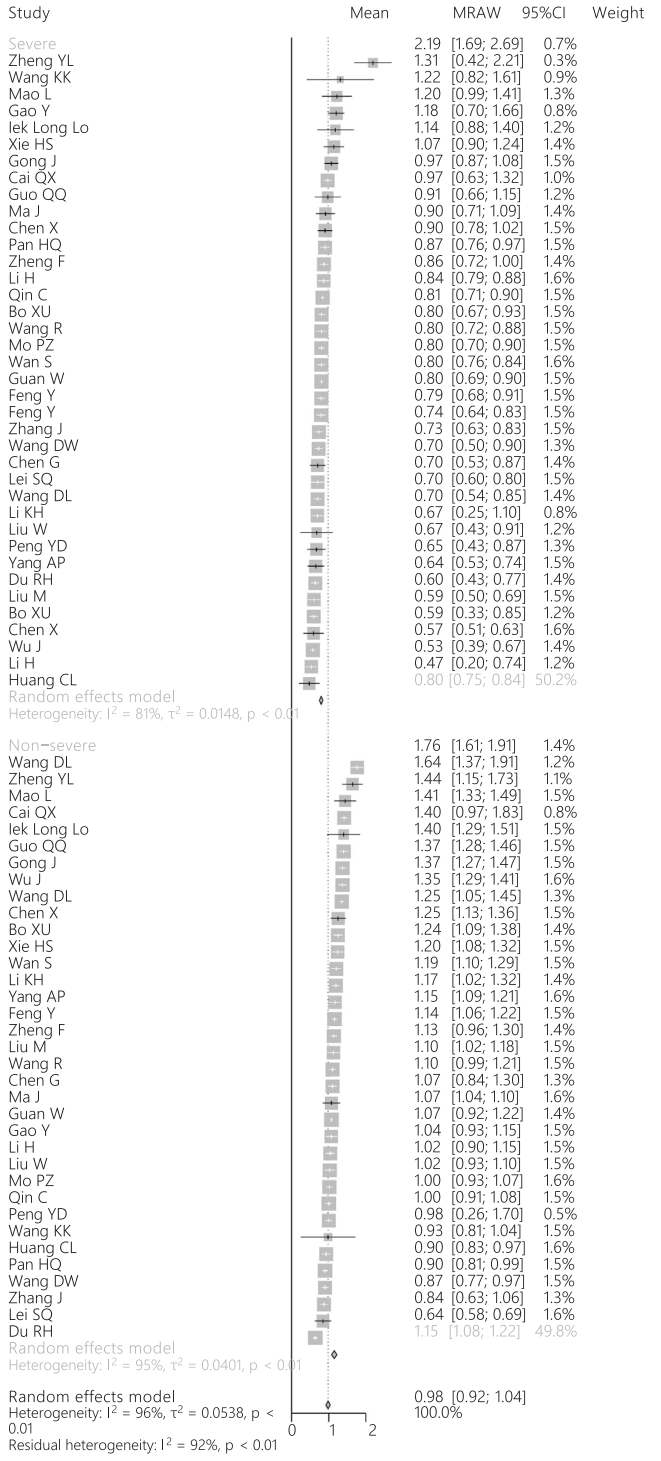

Fig. 2. Meta-analysis of lymphocytes.

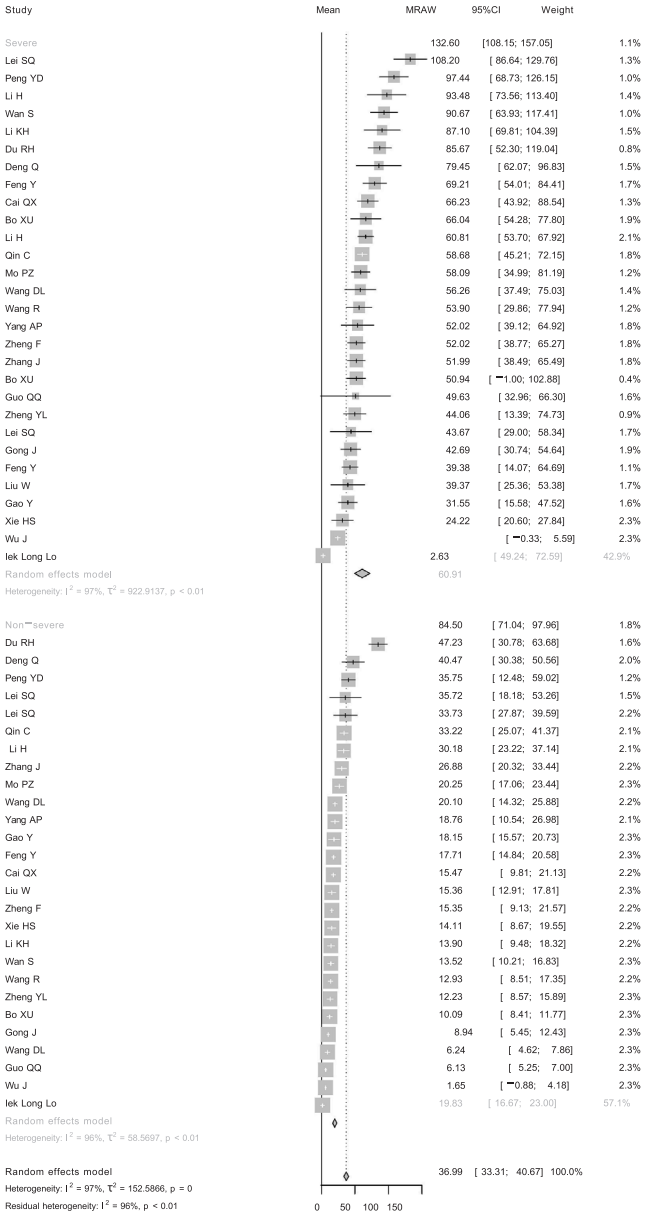

Fig. 3. Meta-analysis of CRP.

3.2.5. *Immunological examination*

3.2.5.1. Antibody detection. The values of antibodies and complements in blood serum in Qin's [13] study showed that immunoglobulins (IgA, IgG and IgM) and complement proteins (C3 and C4) of COVID-19 patients are within the normal range. Compared with the non-severe group, the IgM of the severe group was only slightly decreased, and there was no significant difference in other immunoglobulins and complement, which was consistent with the results of Feng's study [14].

3.2.5.2. Lymphocyte subsets. The total number of B cells, T cells and NK cells significantly decreased in patients with COVID-19 (852.9 /uL), and more evident in the severe cases (1.37-fold; 743.6 vs 1020.1 /uL; P = 0.032) compared to the non-severe group [13]. Lower levels of CD4 T cells (2.10-fold; 561.81 vs 266.79 cell/μl; P < 0.01), CD8 T cells (2.00-fold; 349.01 vs 174.61cell/μl; P < 0.01) were summarized in severe patients comparing with non-severe patients from 5 articles [14–18]. In addition, lower CD3 T cells (1.70-fold; 1070.23 vs 628.20 cell/μl; P < 0.01) in severe patients was noted in Liu et al. [18].

3.2.5.3. Cytokine. Series of inflammatory cytokines were also increaseted in severe cases than the non-severe ones, including interleukin (IL)-1β (1.02-fold; 5.11 vs 5.01 pg/ml; P = 0.098), IL-6 (1.93-fold; 25.58 vs 13.22 pg/ml; P = 0.043), IL-10 (1.55-fold; 8.87 vs 5.71 pg/ml; P < 0.01). In addition, Qin et al. found higher levels of IL-2R (1.14-fold; 757.0 vs 663.5 U/ml; P < 0.01), IL-8 (1.34-fold; 18.4 vs 13.7 pg/ml; P < 0.01) and TNF-α (1.04-fold; 8.7 vs 8.4 pg/ml; P = 0.037) in severe patients in comparison with non-severe patients [13]. Studies also reported that GSCF, IP-10, MCP1and MIP1A in severe patients were higher [10].

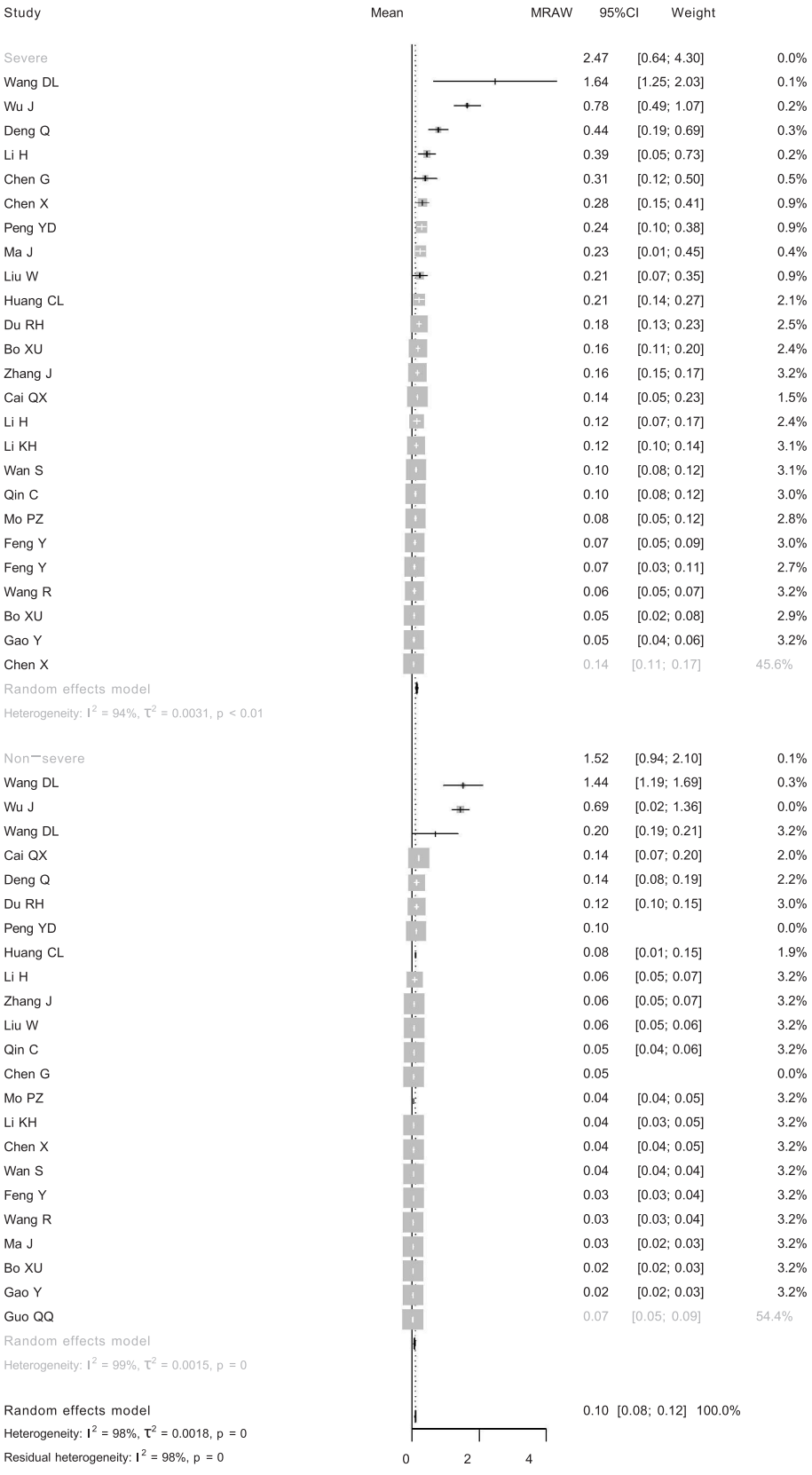

Fig. 4. Meta-analysis of PCT.

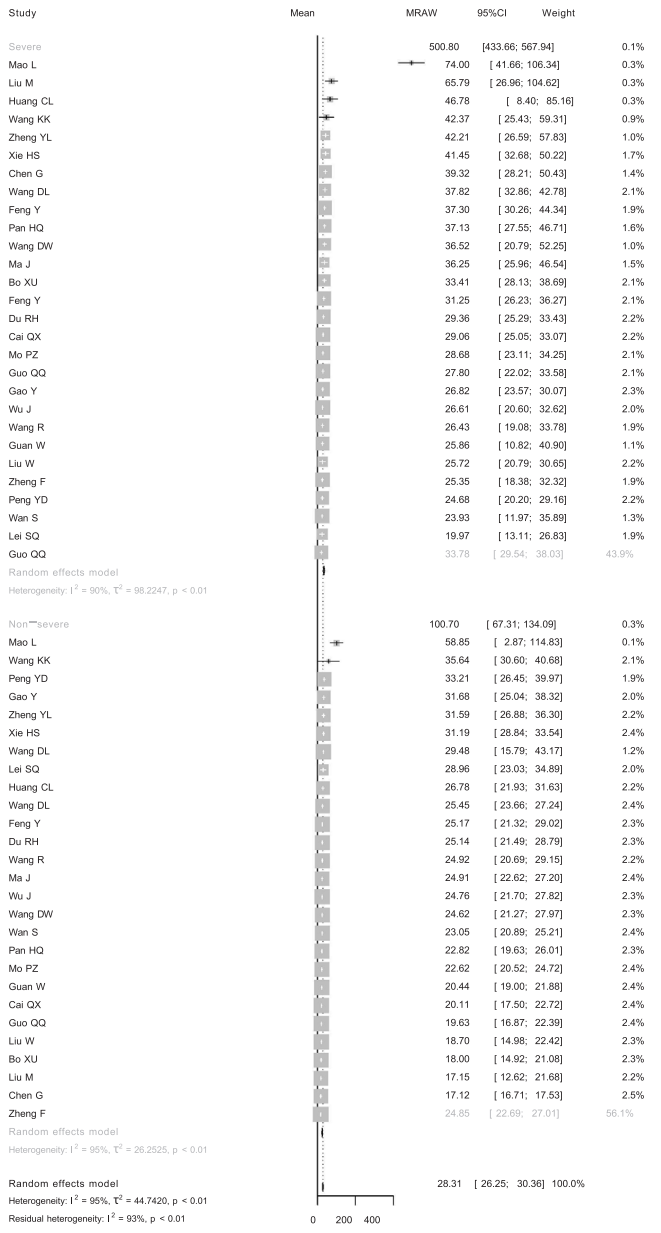

Fig. 5. Meta-analysis of ALT.

4. Quality assessment

Judging by the evaluation score, all of the included articles were classified as high quality and there was no considerable publication bias (Table 2). The quality assessment graph and the reporting bias of important laboratory indicators are exhibited in Supplementary materials.

5. Reports on laboratory indicators of COVID-19 patients worldwide except China

As the pandemic spreads to other countries and viral gene mutations, the characteristics of laboratory indicators of COVID-19 patients worldwide need to be grasped. Since only China has made a clear classification of the severity of patients with COVID-19, the definition of severe patients in countries expect China is simply summarized as staying in ICU. We decided to analyze the laboratory data of patients in representative articles about foreign countries to clarify the differences between foreign patients and Chinese patients with COVID-19.

In 21 critically ill patients with COVID-19 in Washington State, 67% and 38% of these patients had lymphopenia and abnormalities of liver function tests at admission respectively [19]. Higher concentrations of IL-6 and D-dimer at admission were independently associated with in-hospital mortality, which has been confirmed in 1150 patients in New York [20]. On a cohort of 300 COVID-19 patients from Italy, patients demonstrated lymphopenia in many cases [21]. In another group of Italian cases, the frequency of granulocyte morphological anomalies has been highlighted, especially in patients with severe ARDS at admission [22]. The values of leukocyte, IL-6, LDH, CK and D-dimer continued to increase in 50 COVID-19 patients with ARDS during hospitalization in a German report [23]. About Singapore, lymphopenia was present in 39% patients (7/16) and an elevated CRP in 38% patients (6/16), while kidney function remained normal [24]. Lower blood counts of leukocytes, platelets, neutrophils, lymphocytes, eosinophils, and basophils (all $P < 0.001$) in COVID-19 patients were significant predictors of SARS-CoV-2 positive test [25]. In addition, compared with less severe diseases, CRP is higher and the lymphocyte count is lower has been found in a study in Norway [26].

Overall, we found that foreign patients have similarities to the changes in laboratory indicators of Chinese patients, typically including a decrease in leukocytes and lymphocytes and an increase in inflammation-related factors. The abnormality of blood coagulation, liver and kidney function and immune function also appeared in foreign patients, especially in severe and critically ill patients. However, due to differences in viral gene variation and detection time, the diversity in the laboratory indicators of patients around the world is inevitable, and more data required to confirm.

6. Discussion

Facing the huge threat of COVID–19 to human health, laboratory evaluation and early prediction of patients' condition should be paid to more attention. At present, the characteristics of laboratory examination results of hospitalized patients were reported, but the discrepancies were observed between these reports due to the different proportions of severe patients in each study.

Among 5912 patients who underwent laboratory examinations on admission, lymphopenia was typical, which might be risk factors for disease progression of COVID-19 [27]. The PLT-to-lymphocyte ratio (PLR) and the neutrophil/lymphocyte ratio (NLR) may provide new indexes for the monitoring the changes of patients with COVID-19 [28-30]. The NLR was > 5 in severe patients critically ill patients, proving that severe patients are more likely to develop leukocytosis and lymphocytopenia [29]. Neutrophils and eosinophils may be used to predict the recovery probability [31,32]. The decrease of hemoglobin and PLT were significantly associated with the severity of the disease [33,34]. In addition, the combined parameter NLR&RDW-SD can help clinically to predict the severity of COVID-19 patients [35]. In conclusion, blood routine examination is of great value in the diagnosis and prognosis of COVID-19.

High infection-related biomarkers (i.e. PCT, ESR, and CRP) have been observed in our study. CRP is a good predictor of adverse consequences and related to inflammation of tissues and organs [36–38]. A simple death risk index (ACP) consisting of age and CRP was developed by Lu et al [39], by which the short-term mortality associated with COVID-19 can be predicted. Higher serum hypersensitive C-reactive protein (hs-CRP) is an important marker of poor prognosis in COVID-19 patients and can be used to predict the risk of death in severe patients, which reflects the persistent state of inflammation [40]. Increased PCT, SAA and ESR were identified as powerful factors to predict disease progression of patients with COVID-19 [41–44]. In addition, the combined detection of IL-6, ESR and CRP improve the efficiency of predicting the development of patients' condition [45]. On account of the common co-infection in children, the increase of PCT is more obvious than that in adults, so it should be used as an important index for the detection of children [46]. Thus, infection-related biomarkers are risk

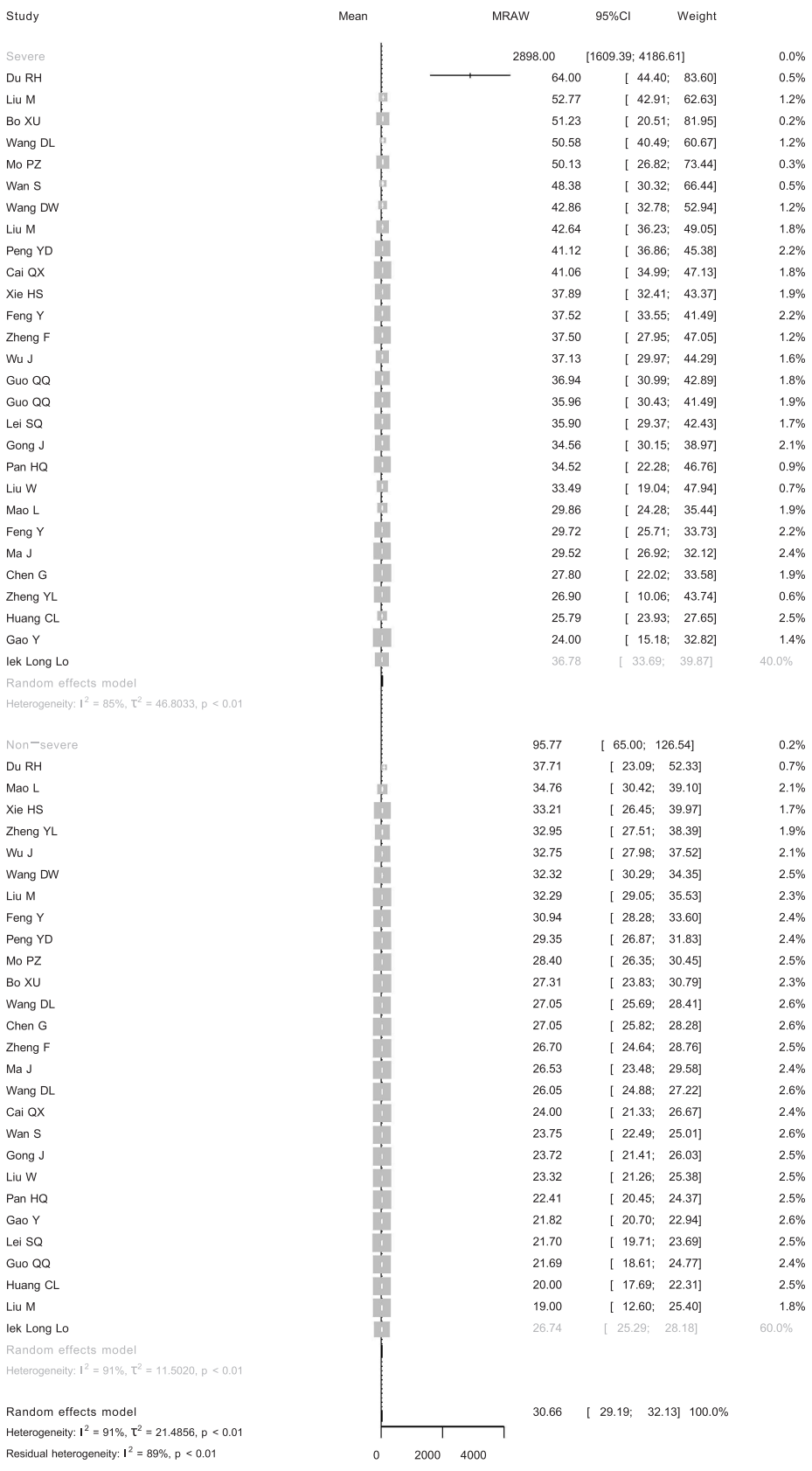

Fig. 6. Meta-analysis of AST.

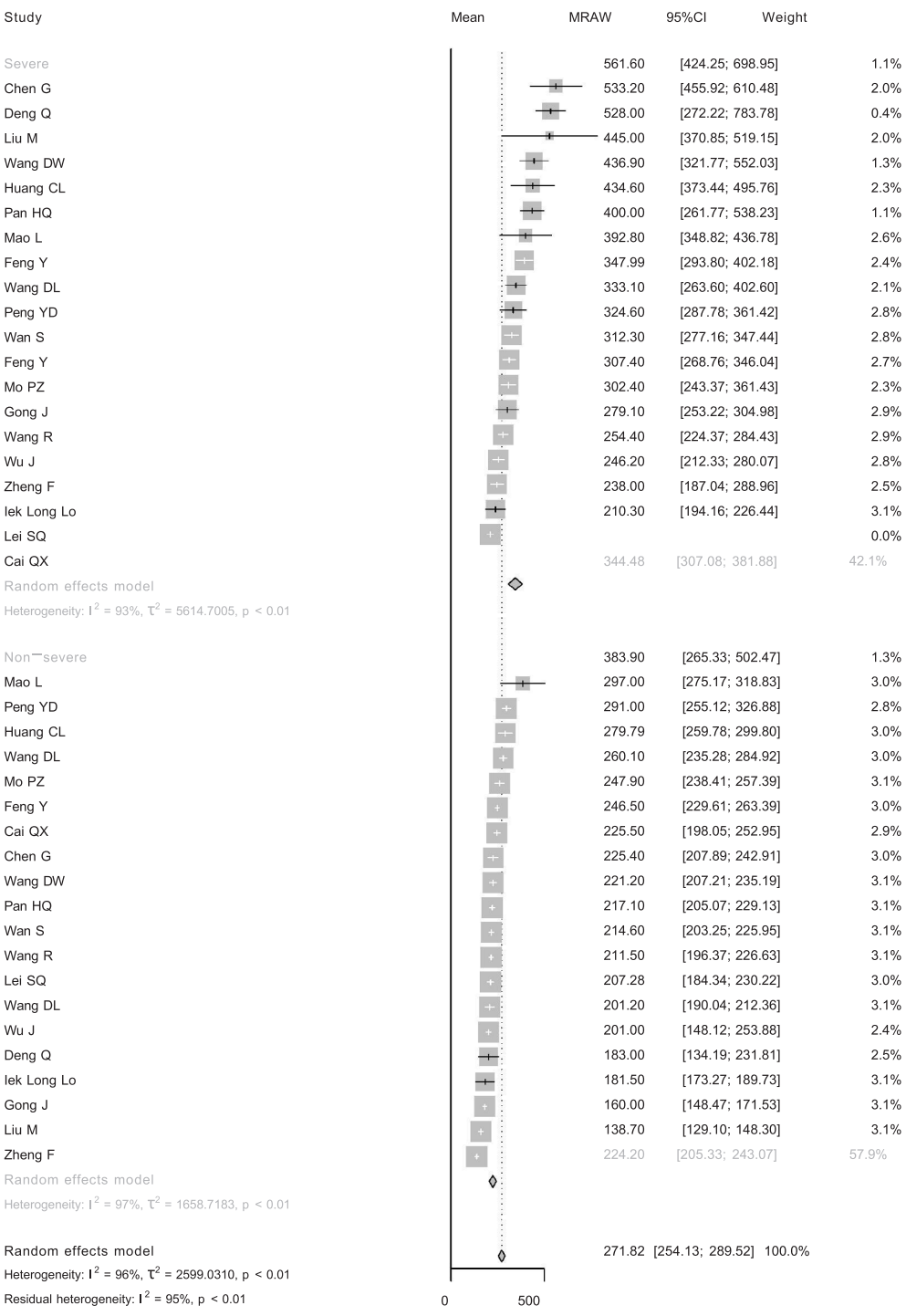

Fig. 7. Meta-analysis of LDH.

factors for disease progression.

In term of biochemical indicators, patients with organ dysfunction, (including ARDS, acute renal injury, heart injury, liver dysfunction, pneumothorax, etc.) are prone to exhibit abnormal results of blood biochemical examination [47]. Increased serum N-terminal proB-type natriuretic peptide (NT-proBNP), cardiac troponin-I (cTnI), myoglobin and creatinine were related factors of critical COVID-19 with heart damage [48,49]. Cardiac injury defined by the increase of hs-cTnI and D-dimer on admission and patients with high BNP is associated with a higher risk of mortality [50–52]. LDH, AST/ALT ratio, TBIL could be identified as powerful predictive factors for early recognition of liver injury and were positively correlated with death risk of COVID-19 patients [53–55]. Albumin, serum urea nitrogen and creatine were risk factor s for assessing kidney damage and disease progression [55,56]. Many patients have abnormal urine analysis on admission, including proteinuria or hematuria, which indicates that urine analysis can better reveal the potential kidney damage of COVID-19 patients to reflect and predict the severity of the disease [57,58]. In short, the cardiac biomarkers, liver and kidney function examination for severe and critically ill patients can evaluate the degree of extrapulmonary damage caused by complications.

Furthermore, the level of lactic acid, plasma angiotensin II, amylase and lipase can also be used as indicators to estimate the course of the disease [49,59]. Plasma angiotensin II level linearly correlated with

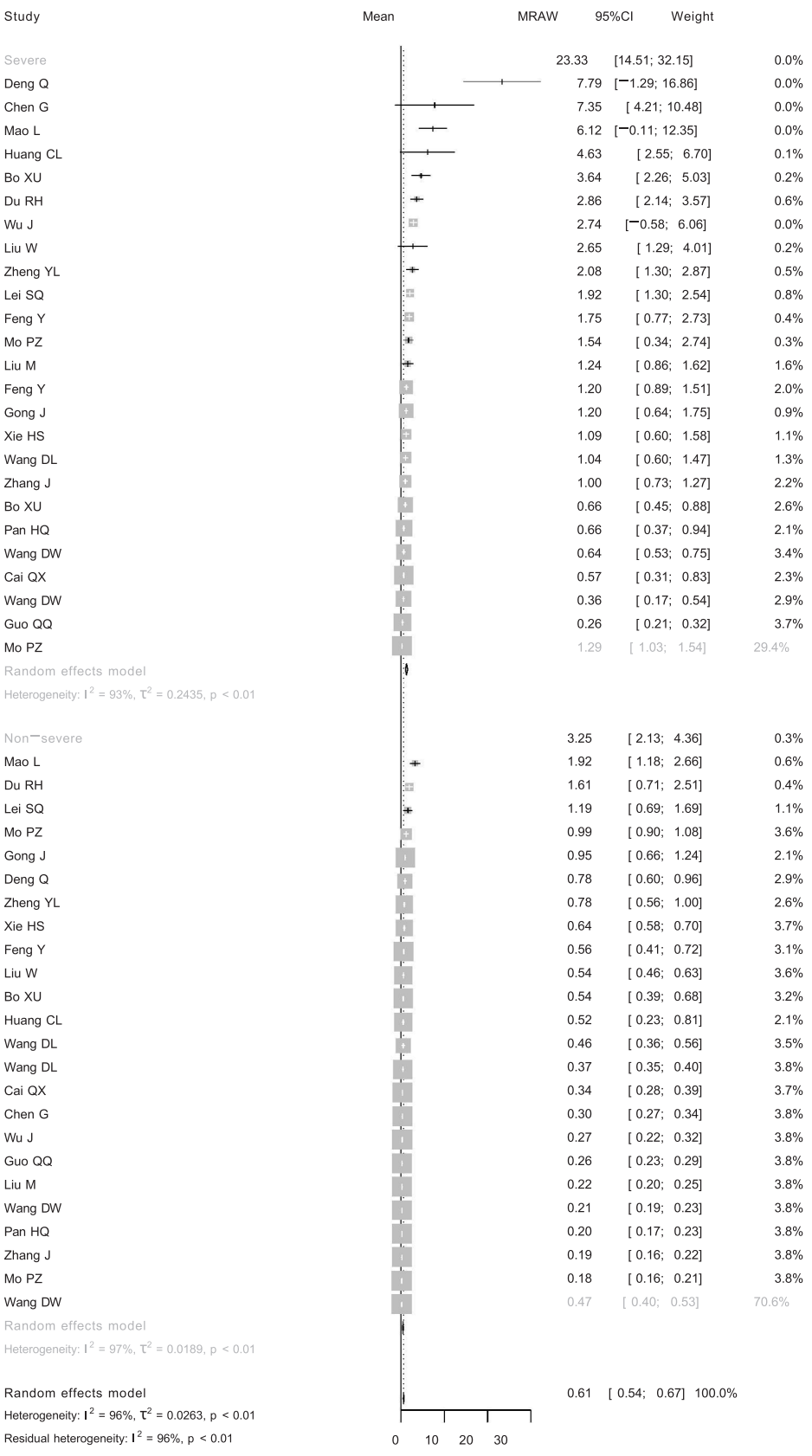

Fig. 8. Meta-analysis of D-dimer.

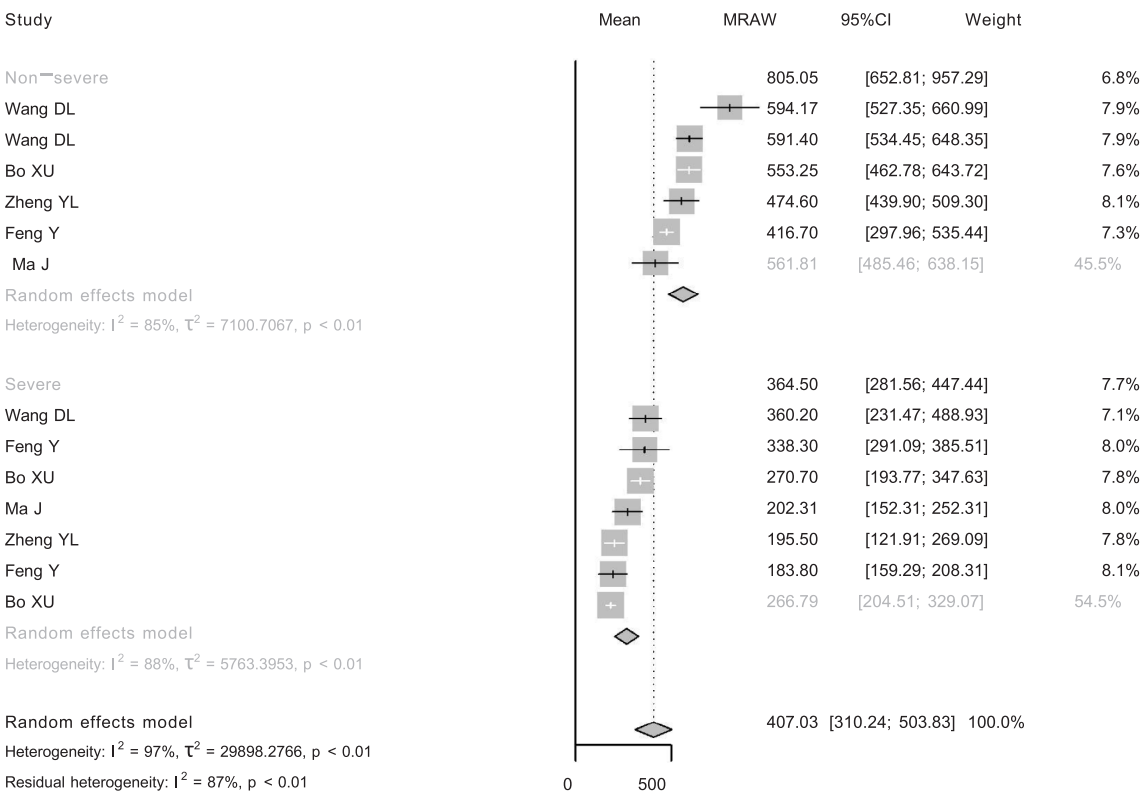

Fig. 9. Meta-analysis of CD4 T cells.

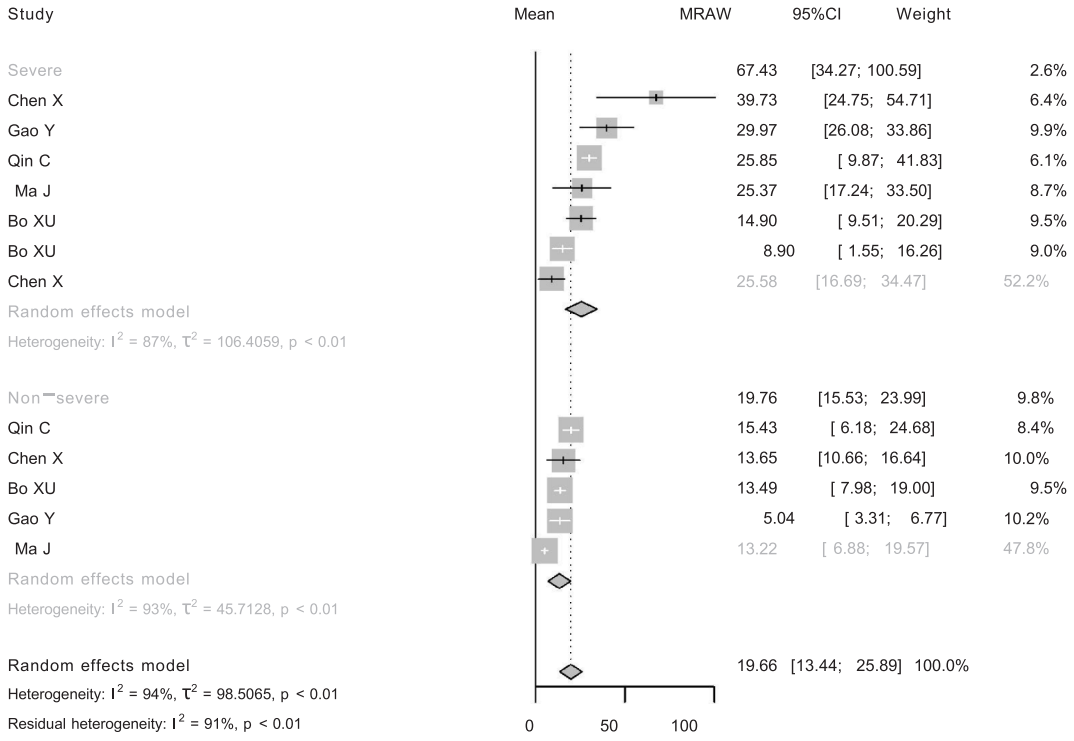

Fig. 10. Meta-analysis of IL-6.

virus titer and the degree of lung injury was increased in one study [49]. Other than the high expression of angiotensin-converting enzyme 2 (ACE2) in the pancreatic tissue of COVID-19 patients, the increase of serum amylase and lipase were found [60]. In addition, the detection of electrolyte and blood glucose indexes is of great significance for patients with underlying diseases of electrolyte balance disorder and glucose metabolism disorder.

The changes in blood coagulation, especially disseminated intravascular coagulation (DIC), which is common in critical diseases, should also been paid enough attention [61–64]. Severe patients may exhibit blood coagulation disorders, including increased D-dimer, prolonged PT and shortened APTT, which is consistent with reports

[62,63]. D-dimer is associated with the severity of COVID-19 [65]. Fibrinogen can be significantly increased in the early stages of severe patients, but notably decreased in the later stages, this may be the reason why serious people are more likely to suffer from cerebrovascular disease [66,67]. Bleeding and coagulation dysfunction and even DIC combined with COVID-19 is a process of dynamic change. Monitoring the blood coagulation function of patients is beneficial to the early diagnosis, prevention and treatment of the disease. In addition, The combined detection of IL-6 and D-dimer had important clinical value for early prediction of the severity of COVID-19 patients due to its high sensitivity and specificity [68].

Our analysis showed that lower levels of CD4 and CD8 and higher levels of inflammatory cytokines (IL-1β, IL-6, IL-10) in severe patients, which made important impacts in predicting the state of the illness changes from mild to severe. The decrease of CD4 and CD8 in peripheral blood and the increase of IL-6 are the high-risk factors of cytokine release syndrome-like (CRSL) [59,69,70]. CD3 + T cells, IP-10, MCP-3 and IL-1ra were also closely related to the severity and progression of COVID-19 [54,71]. Diao et al. [69] found that the number of T cells was negatively correlated with the concentration of serum IL-6, IL-10 and TNF-α. In addition, the immune response phenotype based on late IgG response can be used as a simple complementary tool to distinguish between severe and non-severe COVID-19 patients and to further predict their clinical outcomes [72]. Overall, close monitoring of the T lymphocyte subsets and cytokines might provide valuable information on the patient's condition change during the treatment process [73].

7. Limitations

Although our analysis showed the characteristics of laboratory findings of COVID-19 patients, relatively few patients were included in the analysis. In addition, the recruited participants in our study were hospitalized before April 27, 2020 and more laboratory tests of COVID-19 patients should be investigated.

8. Conclusion

Some certain laboratory inspections could predict the progress of the COVID-19 changes, especially, lymphocytes, CRP, PCT, ALT, AST, LDH, D-dimer, CD4 T cells and IL6, which provide valuable signals for preventing the deterioration of the disease.

CRediT authorship contribution statement

Jinfeng Bao: Conceptualization, Methodology, Software, Investigation, Writing - original draft. **Chenxi Li:** Validation, Formal analysis, Visualization, Software. **Kai Zhang:** Validation, Formal analysis, Visualization. **Haiquan Kang:** Resources, Writing - review & editing, Supervision, Data curation. **Wensen Chen:** Resources, Writing - review & editing, Supervision, Data curation. **Bing Gu:** .

Acknowledgement

This research was supported by Jiangsu Privincial Medical Talent (ZDRCA2016053), Six talent peaks project of Jiangsu Province (WSN-135), Advanced health talent of six-one project of Jiangsu Province (LGY2016042).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cca.2020.06.009.

References

[1] E. Mahase, Covid-19: WHO declares pandemic because of "alarming levels" of spread, severity, and inaction, BMJ (Clin. Res. Ed.) 368 (2020) m1036.
[2] P. Zhou, X.L. Yang, X.G. Wang, B. Hu, L. Zhang, W. Zhang, H.R. Si, Y. Zhu, B. Li, C.L. Huang, H.D. Chen, J. Chen, Y. Luo, H. Guo, R.D. Jiang, M.Q. Liu, Y. Chen, X.R. Shen, X. Wang, X.S. Zheng, K. Zhao, Q.J. Chen, F. Deng, L.L. Liu, B. Yan, F.X. Zhan, Y.Y. Wang, G.F. Xiao, Z.L. Shi, A pneumonia outbreak associated with a new coronavirus of probable bat origin, Nature 579 (7798) (2020) 270–273.
[3] Q. Li, X. Guan, P. Wu, X. Wang, L. Zhou, Y. Tong, R. Ren, K.S.M. Leung, E.H.Y. Lau, J.Y. Wong, X. Xing, N. Xiang, Y. Wu, C. Li, Q. Chen, D. Li, T. Liu, J. Zhao, M. Liu, W. Tu, C. Chen, L. Jin, R. Yang, Q. Wang, S. Zhou, R. Wang, H. Liu, Y. Luo, Y. Liu, G. Shao, H. Li, Z. Tao, Y. Yang, Z. Deng, B. Liu, Z. Ma, Y. Zhang, G. Shi, T.T.Y. Lam, J.T. Wu, G.F. Gao, B.J. Cowling, B. Yang, G.M. Leung, Z. Feng, Early Transmission Dynamics in Wuhan China, of Novel Coronavirus-Infected Pneumonia, Engl. J. Med. 382 (13) (2020) 1199–1207.
[4] World Health Organization.Statement on the second meeting of the International Health Regulations (2005) Emergency Committee regarding the outbreak of novel coronavirus (2019-nCoV).
[5] Coronavirus COVID-19 Global Cases. https://coronavirus.jhu.edu/map.html. (Accessed 3 May 2020).
[6] Guidelines for the diagnosis and treatment of novel coronavirus (SARS-CoV2) infection (trial version 7) 2020, (2020).
[7] World Health Organization, Clinical management of severe acute respiratory infection when Novel coronavirus (nCoV) infection is suspected, Interim Guidance (2020).
[8] H. Chen, J. Guo, C. Wang, F. Luo, X. Yu, W. Zhang, J. Li, D. Zhao, D. Xu, Q. Gong, J. Liao, H. Yang, W. Hou, Y. Zhang, Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records, Lancet 395 (10226) (2020) 809–815.
[9] K. Liu, Y.Y. Fang, Y. Deng, W. Liu, M.F. Wang, J.P. Ma, W. Xiao, Y.N. Wang, M.H. Zhong, C.H. Li, G.C. Li, H.G. Liu, Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province, Chin. Med. J. (Engl.) 133 (9) (2020) 1025–1031.
[10] C. Huang, Y. Wang, X. Li, L. Ren, J. Zhao, Y. Hu, L. Zhang, G. Fan, J. Xu, X. Gu, Z. Cheng, T. Yu, J. Xia, Y. Wei, W. Wu, X. Xie, W. Yin, H. Li, M. Liu, Y. Xiao, H. Gao, L. Guo, J. Xie, G. Wang, R. Jiang, Z. Gao, Q. Jin, J. Wang, B. Cao, Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, Lancet 395 (10223) (2020) 497–506.
[11] D. Luo, X. Wan, J. Liu, T. Tong, Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range, Stat. Methods Med. Res. 27 (6) (2018) 1785–1805.
[12] X. Wan, W. Wang, J. Liu, T. Tong, Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range, BMC Med. Res. Methodol. 14 (2014) 135.
[13] C. Qin, L. Zhou, Z. Hu, S. Zhang, S. Yang, Y. Tao, C. Xie, K. Ma, K. Shang, W. Wang, D.S. Tian, Dysregulation of immune response in patients with COVID-19 in Wuhan, China, Clin. Infect Dis. (2020).
[14] M. Liu, P. He, H.G. Liu, X.J. Wang, F.J. Li, S. Chen, J. Lin, P. Chen, J.H. Liu, C.H. Li, Clinical characteristics of 30 medical workers infected with new coronavirus pneumonia, Zhonghua Jie He He Hu Xi Za Zhi 43 (3) (2020) 209–214.
[15] J. Ma, J. Yin, Y. Qian, Y. Wu, Clinical characteristics and prognosis in cancer patients with COVID- 19: A single center's retrospective study, J. Infect. (2020).
[16] B. Xu, C.Y. Fan, A.L. Wang, Y.L. Zou, Y.H. Yu, C. He, W.G. Xia, J.X. Zhang, Q. Miao, Suppressed T cell-mediated immunity in patients with COVID-19: A clinical retrospective study in Wuhan, China, J. Infect. (2020).
[17] Y. Zheng, H. Xu, M. Yang, Y. Zeng, H. Chen, R. Liu, Q. Li, N. Zhang, D. Wang, Epidemiological characteristics and clinical features of 32 critical and 67 noncritical cases of COVID-19 in Chengdu, J. Clin. Virol. 127 (2020) 104–366.
[18] S.Q. Liu, H.Y. Luo, Y.C. Wang, D.L. Wang, S.H. Ju, Y. Yang, Characteristics and associations with severity in COVID-19 patients: a multicenter cohort study from Jiangsu province, Available at SSRN 3548753 (2020).
[19] M. Arentz, E. Yim, L. Klaff, S. Lokhandwala, F.X. Riedo, M. Chong, M. Lee, Characteristics and Outcomes of 21 Critically Ill Patients With COVID-19 in Washington State, JAMA (2020).
[20] M.J. Cummings, M.R. Baldwin, D. Abrams, S.D. Jacobson, B.J. Meyer, E.M. Balough, J.G. Aaron, J. Claassen, L.E. Rabbani, J. Hastie, B.R. Hochman, J. Salazar-Schicchi, N.H. Yip, D. Brodie, M.R. O'Donnell, Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study, The Lancet 395 (10239) (2020) 1763–1770, https://doi.org/10.1016/S0140-6736(20)31189-2.
[21] S. Buoro, M.F. Di, M. Rizzi, F. Fabretti, F.L. Lorini, S. Cesa, S. Fagiuoli, Papa Giovanni XXIII Bergamo Hospital at the time of the COVID-19 outbreak: letter from the warfront, Int. J. Lab. Hematol. (2020).
[22] F. Rotundo, S. Bellesi, G. D'onofrio, Morphological anomalies of circulating blood cells in COVID-19 infection, Am. J. Hematol. (2020).
[23] M. Dreher, A. Kersten, J. Bickenbach, P. Balfanz, B. Hartmann, C. Cornelissen, A. Daher, R. Stöhr, M. Kleines, S.W. Lemmen, J.C. Brokmann, T. Müller, D. Müller-Wieland, G. Marx, N. Marx, The characteristics of 50 hospitalized COVID-19 patients with and without ARDS, Deutsches Aerzteblatt Online (2020).
[24] B.E. Young, S.W.X. Ong, S. Kalimuddin, J.G. Low, S.Y. Tan, J. Loh, O.T. Ng, K. Marimuthu, L.W. Ang, T.M. Mak, S.K. Lau, D.E. Anderson, K.S. Chan, T.Y. Tan, T.Y. Ng, L. Cui, Z. Said, L. Kurupatham, M.I. Chen, M. Chan, S. Vasoo, L.F. Wang, B.H. Tan, R.T.P. Lin, V.J.M. Lee, Y.S. Leo, D.C. Lye, Epidemiologic Features and Clinical Course of Patients Infected With SARS-CoV-2 in Singapore, JAMA (2020).

[25] Y. Sun, V. Koh, K. Marimuthu, O. Ng, B. Young, S. Vasoo, M. Chan, V.J.M. Lee, P.P. De, T. Barkham, R.T.P. Lin, A.R. Cook, Y.S. Leo, Epidemiological and Clinical Predictors of COVID-19, Clin. Infect Dis. (2020).

[26] H. Ihle-Hansen, T. Berge, A. Tveita, E.J. Rønning, P.E. Ernø, E.L. Andersen, C.H. Wang, A. Tveit, M. Myrstad, Covid-19: Symptomer, forløp og bruk av kliniske skåringsverktøy hos de 42 første pasientene innlagt på et norsk lokalsykehus, Tidsskrift for Den Norske Legeforening (2020).

[27] S. Tabata, K. Imai, S. Kawano, M. Ikeda, T. Kodama, K. Miyoshi, H. Obinata, S. Mimura, T. Kodera, M. Kitagaki, M. Sato, S. Suzuki, T. Ito, Y. Uwabe, K. Tamura, The clinical characteristics of COVID- 19: a retrospective analysis of 104 patients from the outbreak on board the Diamond Princess cruise ship in Japan, medRxiv (2020).

[28] R. Qu, Y. Ling, Y.H. Zhang, L.Y. Wei, X. Li, X.Y. Liu, H.M. Liu, Z. Guo, H. Ren, Q. Wang, Platelet-to-lymphocyte ratio is associated with prognosis in patients with Corona Virus Disease-19, J. Med. Virol. (2020).

[29] J.Y. Liu, Y. Liu, P. Xiang, L. Pu, H.F. Xiong, C.S. Li, M. Zhang, J.B. Tan, Y.L. Xu, R. Song, Neutrophil-to-Lymphocyte Ratio Predicts Severe Illness Patients with 2019 Novel Coronavirus in the Early Stage, medRxiv (2020).

[30] Z.C. Feng, Q.Z. Yu, S.H. Yao, L. Luo, J. . Duan, Z.M. Yan, M. Yang, H.P. Tan, M.T. Ma, T. Li, D.L. Yi, Z. Mi, H.F. Zhao, Y. Jiang, Z.H. He, H.L. Li, W. Nie, Y. Liu, J. Zhao, M.Q. Luo, X.H. Liu, P.F. Rong, W. Wang, Early Prediction of Disease Progression in 2019 Novel Coronavirus Pneumonia Patients Outside Wuhan with CT and Clinical Characteristics, medRxiv (2020).

[31] S.Y. Tian, X.T. Zhu, X.J. Sun, J.M. Wang, Q. Zhou, C. Wang, L. Chen, J.C. Xu, Longitudinal analysis of laboratory findings during the process of recovery for patients with COVID-19, medRxiv (2020).

[32] R. Mardani, A.A. Vasmehjani, F. Zali, A. Gholami, S.D.M. Nasab, H. Kaghazian, M. Kaviani, N. Ahmadi, Laboratory Parameters in Detection of COVID-19 Patients with Positive RT-PCR; a Diagnostic Accuracy Study, Arch. Acad. Emerg. Med. 8 (1) (2020) e43.

[33] G. Lippi, C. Mattiuzzi, Hemoglobin value may be decreased in patients with severe coronavirus disease 2019, Hematol. Transfus. Cell Ther. (2020).

[34] H. Zhou, W.X. Chen, Z.P. Li, B.H. Yang, Q.Q. Zhou, P. Wang, J.H. Zhu, X.X. Chen, P. Yang, Delayed-Phase Thrombocytopenia in Patients of Coronavirus Disease 2019 (COVID-19), medRxiv (2020).

[35] C.Z. Wang, R.R. Deng, L.Y. Gou, Z.X. Fu, X.M. Zhang, F. Shao, G.Z. Wang, W.Y. Fu, J.P. Xiao, X. Ding, T. Li, X.L. Xiao, C.B. Li, Preliminary study to identify severe from moderate cases of COVID-19 using NLR&RDW-SD combination parameter, medRxiv (2020).

[36] X.M. Luo, W. Zhou, X.J. Yan, T.G. Guo, B.C. Wang, H. X Xia, Lye, J. Xiong, Z.P. Jiang, Y. Li, B.C. Zhang, W.Z. Yang, Prognostic value of C-reactive protein in patients with COVID-19, medRxiv (2020).

[37] T. Guo, Y. Fan, M. Chen, X. Wu, L. Zhang, T. He, H. Wang, J. Wan, X. Wang, Z. Lu, Cardiovascular Implications of Fatal Outcomes of Patients With Coronavirus Disease 2019 (COVID-19), JAMA Cardiol (2020).

[38] L. Li, S. Li, M.M. Xu, S.J. Zheng, Z.P. Duan, Y. Chen, J.F. Li, Risk factors related to hepatic injury in patients with corona virus disease 2019, medRxiv (2020).

[39] J.T. Lu, S.F. Hu, R. Fan, Z.H. Liu, X.R. Yin, Q.Y. Wang, Q.Q. Lv, Z.F. Cai, H.J. Li, Y.H. Hu, Y. Han, H.P. Hu, W.Y. Gao, S.B. Feng, Q.F. Liu, H. Li, J. Sun, J. Peng, X.F. Yi, Z.X. Zhou, Y.B. Guo, J.L. Hou, ACP risk grade: a simple mortality index for patients with confirmed or suspected severe acute respiratory syndrome coronavirus 2 disease (COVID-19) during the early stage of outbreak in Wuhan, China, medRxiv (2020).

[40] Y. Li, H.T. Zhang, Y. Xiao, M.L. Wang, Y.Q. Guo, C. Sun, X. Tang, L. Jing, S.S. Li, M.Y. Zhang, Y. Xiao, H.S. Cao, Y.Y. Chen, T.G. Ren, J.Y. Jin, F. Wang, Y.R. Xiao, S.F. Huang, X. Tan, N.N. Huang, B. Jiao, Y. Zhang, A.L. Luo, Z.G. Cao, H. Xu, Y. Yuan, Prediction of criticality in patients with severe Covid-19 infection using three clinical features: a machine learning-based prognostic model with clinical data in, Wuhan, medRxiv (2020).

[41] H.Z. Zhang, X.Y. Wang, Z.Q. Fu, M. Luo, Z. Zhang, K. Zhang, Y. He, D.D. Wan, L.W. Zhang, J. Wang, X.F. Yan, M. Han, Y.K. Chen, Potential Factors for Prediction of Disease Severity of COVID-19 Patients, medRxiv (2020).

[42] G. Zhang, C. Hu, L. Luo, F. Fang, Y.F. Chen, J.G. Li, Z.Y. Peng, H.Q. Pan, Clinical features and outcomes of 221 patients with COVID-19 in Wuhan, China, MedRxiv (2020).

[43] Z. Jun, Z.H. Liu, X.H. Luo, Y. Xi, Z.Q. Ren, Y.N. Li, W. Ren, H.Q. Wang, Clinical Hallmarks of 13 COVID-19 Patients, Revealing SAA Biomarker, The lancet preprint (2020).

[44] Y. Zhang, D.L. Wang, M.J. Lin, T. Sun, J.X. Chen, J.Q. Xu, H.G. Zhu, G.J. Zhu, R.Y. Lu, L.X. Hong, B. Shen, X.M. Wu, Y.F. Zheng, Serum Amyloid A Protein as a Potential Biomarker Useful in Monitoring the Course of COVID-19: A Retrospectively Studied, Res. Square Prep. (2020).

[45] F. Yi, Z.Y. Li, P. Li, S.L. Zhao, Y. Hu, Y.F. Chen, Z.Q. Zeng, Q.C. Xie, C.G. Deng, Z.X. Wang, X.B. Xie, Analysis of the clinical value of IL-6, ESR, CRP and routine biochemical tests for the diagnosis of COVID-19, Int. J. Lab. Med. (2020).

[46] W. Xia, J. Shao, Y. Guo, X. Peng, Z. Li, D. Hu, Clinical and CT features in pediatric patients with COVID-19 infection: Different points from adults, Pediatr. Pulmonol. 55 (5) (2020) 1169–1174.

[47] Cardiovascular complications of novel Wuhan Coronavirus (COVID-19) – A 2020 update.

[48] C. Chen, C. Chen, J.T. Yan, N. Zhou, J.P. Zhao, D.W. Wang, Analysis of myocardial injury in patients with COVID-19 and association between concomitant cardiovascular diseases and severity of COVID-19, Zhonghua Xin Xue Guan Bing Za Zhi 48 (2020) E008.

[49] Y.X. Liu, Y. Yang, C. Zhang, F.M. Huang, F.X. Wang, J. Yuan, Z.Q. Wang, J.X. Li, J.M. Li, C. Feng, Z. Zhang, L.F. Wang, L. Peng, L. Chen, Y.H. Qin, D.D. Zhao, S.G. Tan, L. Yin, J. Xu, C.Z. Zhou, C.Y. Jiang, L. Liu, Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury, Sci. China Life Sci. 63 (3) (2020) 364–374.

[50] S. Shi, M. Qin, B. Shen, Y. Cai, T. Liu, F. Yang, W. Gong, X. Liu, J. Liang, Q. Zhao, H. Huang, B. Yang, C. Huang, Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China, JAMA Cardiol. (2020).

[51] F. Zhang, D.Y. Yang, J. Li, P. Gao, T.B. Chen, Z.W. Cheng, K.G. Cheng, Q. Fang, W. Pan, C.F. Yi, H.R. Fan, Y.H. Wu, L.W. Li, Y. Fang, J. Liu, G.W. Tian, L.Q. He, Myocardial injury is associated with in-hospital mortality of confirmed or suspected COVID-19 in Wuhan, China: A single center retrospective cohort study, medRxiv (2020).

[52] Y.B. Liu, D.H. Liu, H.F. Song, C.L. Chen, M.F. Lv, X. Pei, Z.W. Hu, Z.H. Qin, J.L. Li, Clinical features and outcomes of 2019 novel coronavirus-infected patients with high plasma BNP levels, medRxiv (2020).

[53] D. Zhao, F. Yao, L. Wang, L. Zheng, Y. Gao, J. Ye, F. Guo, H. Zhao, R. Gao, A comparative study on the clinical features of COVID-19 pneumonia to other pneumonias, Clin. Infect Dis. (2020).

[54] Y. Han, H.D. Zhang, S.C. Mu, W. Wei, C.Y. Jin, Y. Xue, C.Y. Tong, Y.F. Zha, Z.J. Song, G.R. Gu, Lactate dehydrogenase, a Risk Factor of Severe COVID-19 Patients: A Retrospective and Observational Study, medRxiv (2020).

[55] L. Fu, J. Fei, H.X. Xiang, Y. Xiang, Z.X. Tan, M.D. Li, F.F. Liu, H.Y. Liu, L. Zheng, Y. Li, H. Zhao, D.X. Xu, Influence factors of death risk among COVID-19 patients in Wuhan, China: a hospital-based case-cohort study, medRxiv (2020).

[56] W. Liu, Z. Tao, L. Wang, M. Yuan, K. Liu, L. Zhou, S. Wei, Y. Deng, J. Liu, H. Liu, M. Yang, Y. Hu, Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease, Chin. Med. J. (Engl.) (2020).

[57] H.F. Zhou, Z.L. Zhang, H. Fan, J.Y. Li, M.Y. Li, Y.L. Dong, W.N. Guo, L. Lin, Z.Y. Kang, T. Yu, C.X. Tian, Y. Gui, R.J. Qin, H.J. Wang, S.S. Luo, D.S. Hu, Urinalysis, but not blood biochemistry, detects the early renal-impairment in patients with COVID-19, medRxiv (2020).

[58] Y. He, W. Gan, M. Zhang, X. Nie, H.L. Song, H. He, Y.H. Zhao, S.S. Liang, X.L. Li, G.X. Li, Evaluation of clinical biochemical results in the progression and treatment of COVID-19, Lab. Med. (2020).

[59] P.H. Yang, Y.B. Ding, Z. Xu, R. Pu, P. Li, J. Yan, J.L. Liu, F.P. Meng, L. Huang, L. Shi, T.J. Jiang, E.Q. Qin, M. Zhao, D.W. Zhang, P. Zhao, L.X. Yu, Z.H. Wang, Z.X. Hong, Z.H. Xiao, Q. Xi, D.X. Zhao, P. Yu, C.Z. Zhu, Z. Chen, S.G. Zhang, J.S. Ji, G.W. Cao, F.S. Wang, Epidemiological and clinical features of COVID-19 patients with and without pneumonia in Beijing, China, medRxiv (2020).

[60] F.R. Liu, X. Long, W.B. Zou, M.H. Fang, W.J. Wu, W. Li, B.X. Zhang, W.G. Zhang, X.P. Chen, Z.G. Zhang, Highly ACE2 Expression in Pancreas May Cause Pancreas Damage After SARS-CoV-2, InfectionmedRxiv (2020).

[61] Y.D. Wang, S.P. Zhang, Q.Z. Wei, M.M. Zhao, H. Mei, Z.L. Zhang, Y. Hu, COVID-19 complicated with DIC: 2 cases report and literatures review, Zhonghua xue ye xue za zhi 41 (2020) E001.

[62] J.J. Zhang, X. Dong, Y.Y. Cao, Y.D. Yuan, Y.B. Yang, Y.Q. Yan, C.A. Akdis, Y.D. Gao, Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China, Allergy (2020).

[63] D.R.J. Arachchillage, M. Laffan, Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia, J. Thromb. Haemost. 18 (5) (2020) 1233–1234.

[64] D.W. Wang, B. Hu, C. Hu, F.F. Zhu, X. Liu, J. Zhang, B.B. Wang, H. Xiang, Z.S. Cheng, Y. Xiong, Y. Zhao, Y.R. Li, X.H. Wang, Z.Y. Peng, Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China, JAMA 323 (11) (2020) 1061, https://doi.org/10.1001/jama.2020.1585.

[65] G. Lippi, E.J. Favaloro, D-dimer is Associated with Severity of Coronavirus Disease 2019: A Pooled Analysis, Thromb. Haemost. (2020).

[66] N Tang, D Wang, Z Sun, N Li, Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia, J. Thromb. Haemostasis 18 (4) (2020) 844–847.

[67] L. Mao, M.D. Wang, S. Chen, Q.W. He, J. Chang, C.D. Hong, Y.F. Zhou, D. Wang, Y.N. Li, H.J. Jin, B. Hu, Neurological Manifestations of Hospitalized Patients with COVID-19 in Wuhan, China: a retrospective case series study, medRxiv (2020).

[68] Y. Gao, T. Li, M. Han, X. Li, D. Wu, Y. Xu, Y. Zhu, Y. Liu, X. Wang, L. Wang, Diagnostic utility of clinical laboratory data determinations for patients with the severe COVID-19, J. Med. Virol. (2020).

[69] B. Diao, C.H. Wang, Y.J. Tan, X.W. Chen, Y. Liu, L.F. Ning, L. Chen, M. Li, Y.P. Liu, G. Wang, Reduction and Functional Exhaustion of T Cells in Patients with Coronavirus Disease 2019 (COVID-19), medRxiv (2020).

[70] W.J. Wang, J.X. He, P.Y. Lie, L.Y. Huang, S.P. Wu, Y.P. Lin, X.Q. Liu, The definition and risks of Cytokine Release Syndrome-Like in 11 COVID-19-Infected Pneumonia critically ill patients: Disease Characteristics and Retrospective Analysis, medRxiv (2020).

[71] Y. Yang, C.G. Shen, J.X. Li, J. Yuan, M.H. Yang, F.X. Wang, G.B. Li, Y.J. Li, L. Xing, L. Peng, J.L. Wei, M.L. Cao, H.X. Zheng, W.B. Wu, R.R. Zou, D.L. Li, Z.X. Xu, H.Y. Wang, M.X. Zhang, Z. Zhang, L. Liu, Y.X. Liu, Exuberant elevation of IP-10, MCP-3 and IL-1ra during SARS-CoV-2 infection is associated with disease severity and fatal outcome, medRxiv (2020).

[72] B.C. Zhang, X.Y. Zhou, J. Wang, Immune phenotyping based on neutrophil-to-lymphocyte ratio and IgG predicts disease severity and outcome for patients with COVID-19, medRxiv (2020).

[73] Q.B. Liu, X.M. Fang, S.C. Tokuno, U.G. Chung, X.X. Chen, X.Y. Dai, X.Y. Liu, F. Xu, B. Wang, P. Peng, Prediction of the clinical outcome of COVID-19 patients using T lymphocyte subsets with 340 cases from Wuhan, China: a retrospective cohort study and a web visualization tool, medRxiv (2020).

[74] X. Chen, B. Zhao, Y. Qu, Y. Chen, J. Xiong, Y. Feng, D. Men, Q. Huang, Y. Liu,

B. Yang, J. Ding, F. Li, 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).
[75] R. Wang, M. Pan, X. Zhang, X. Fan, M. Han, F. Zhao, M. Miao, J. Xu, M. Guan, X. Deng, X. Chen, L. Shen, Epidemiological and clinical features of 125 Hospitalized Patients with COVID-19 in Fuyang, Anhui, China, Int. J. Infect. Dis. (2020).
[76] A.P. Yang, J.P. Liu, W.Q. Tao, H.M. Li, The diagnostic and predictive role of NLR, d-NLR and PLR in COVID-19 patients, Int. Immunopharmacol. 84 (2020) 106504.
[77] K. Li, J. Wu, F. Wu, D. Guo, L. Chen, Z. Fang, C. Li, The Clinical and Chest CT Features Associated with Severe and Critical COVID-19 Pneumonia, Invest. Radiol. (2020).
[78] P. Mo, Y. Xing, Y. Xiao, L. Deng, Q. Zhao, H. Wang, Y. Xiong, Z. Cheng, S. Gao, K. Liang, M. Luo, T. Chen, S. Song, Z. Ma, X. Chen, R. Zheng, Q. Cao, F. Wang, Y. Zhang, Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China, Clin. Infect. Dis. (2020).
[79] Y.D. Peng, K. Meng, H.Q. Guan, L. Leng, R.R. Zhu, B.Y. Wang, M.A. He, L.X. Cheng, K. Huang, Q.T. Zeng, Clinical characteristics and outcomes of 112 cardiovascular disease patients infected by 2019-nCoV, Zhonghua xin xue guan bing za zhi 48 (2020) E004.
[80] Y. Feng, Y. Ling, T. Bai, Y. Xie, J. Huang, J. Li, W. Xiong, D. Yang, R. Chen, F. Lu, Y. Lu, X. Liu, Y. Chen, X. Li, Y. Li, H.D. Summah, H. Lin, J. Yan, M. Zhou, H. Lu, J. Qu, COVID-19 with Different Severity: A Multi-center Study of Clinical Features, Am. J. Respir. Crit Care Med. (2020).
[81] Q.X. Cai, D.L. Huang, P.C. Ou, H. Yu, Z.B. Zhu, Z. Xia, Y.N. Su, Z.H. Ma, Y.M. Zhang, Z.W. Li, Q. He, L. Liu, Y. Fu, J. Chen, COVID-19 in a designated infectious diseases hospital outside Hubei Province, China, Allergy (2020).
[82] H. Li, X. Xiang, H. Ren, L. Xu, L. Zhao, X. Chen, H. Long, Q. Wang, Q. Wu, Serum Amyloid A is a biomarker of severe Coronavirus Disease and poor prognosis, J. Infect. (2020).
[83] F. Heng, W. Tang, H. Li, Y.X. Huang, Y.L. Xie, Z.G. Zhou, Clinical characteristics of 161 cases of corona virus disease 2019 (COVID-19) in Changsha, Eur. Rev. Med. Pharmacol. Sci. 24 (6) (2020) 3404–3410.
[84] K.K. To, O. Tsang, W. Leung, A.R. Tam, T.C. Wu, D.C. Lung, C. Yip, J.P. Cai, J.M. Chan, T.S. Chik, D.P. Lau, C.Y. Choi, L.L. Chen, W.M. Chan, K.H. Chan, J.D. Ip, A.C. Ng, R.W. Poon, C.T. Luo, V.C. Cheng, J.F. Chan, I.F. Hung, Z. Chen, H. Chen, K.Y. Yuen, Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study, Lancet Infect. Dis. (2020).
[85] W.J. Guan, Z.Y. Ni, Y. Hu, W.H. Liang, C.Q. Ou, J.X. He, L. Liu, H. Shan, C.L. Lei, D.S.C. Hui, B. Du, L.J. Li, G. Zeng, K.Y. Yuen, R.C. Chen, C.L. Tang, T. Wang, P.Y. Chen, J. Xiang, S.Y. Li, J.L. Wang, Z.J. Liang, Y.X. Peng, L. Wei, Y. Liu, Y.H. Hu, P. Peng, J.M. Wang, J.Y. Liu, Z. Chen, G. Li, Z.J. Zheng, S.Q. Qiu, J. Luo, C.J. Ye, S.Y. Zhu, N.S. Zhong, Clinical Characteristics of Coronavirus Disease 2019 in China, N. Engl. J. Med. 382 (18) (2020) 1708–1720.
[86] J. Gong, J. Ou, X. Qiu, Y. Jie, Y. Chen, L. Yuan, J. Cao, M. Tan, W. Xu, F. Zheng, Y. Shi, B. Hu, A Tool to Early Predict Severe Corona Virus Disease 2019 (COVID-19): A Multicenter Study using the Risk Nomogram in Wuhan and Guangdong, China, Clin. Infect. Dis. (2020).
[87] S. Lei, F. Jiang, W. Su, C. Chen, J. Chen, W. Mei, L.Y. Zhan, Y. Jia, L. Zhang, D. Liu, Z.Y. Xia, Z. Xia, Clinical characteristics and outcomes of patients undergoing surgeries during the incubation period of COVID-19 infection, EClinicalMedicine (2020) 100331.
[88] Q. Deng, B. Hu, Y. Zhang, H. Wang, X. Zhou, W. Hu, Y. Cheng, J. Yan, H. Ping, Q. Zhou, Suspected myocardial injury in patients with COVID-19: Evidence from front-line clinical observation in Wuhan, China, Int. J. Cardiol. (2020).
[89] L. Mao, H. Jin, M. Wang, Y. Hu, S. Chen, Q. He, J. Chang, C. Hong, Y. Zhou, D. Wang, X. Miao, Y. Li, B. Hu, Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China, JAMA Neurol. (2020).
[90] R.H. Du, L.M. Liu, W. Yin, W. Wang, L.L. Guan, M.L. Yuan, Y.L. Li, Y. Hu, X.Y. Li, B. Sun, P. Peng, H.Z. Shi, Hospitalization and Critical Care of 109 Decedents with COVID-19 Pneumonia in Wuhan, China, Ann Am Thorac Soc. (2020).
[91] H. Xie, J. Zhao, N. Lian, S. Lin, Q. Xie, H. Zhuo, Clinical characteristics of non-ICU hospitalized patients with coronavirus disease 2019 and liver injury: A retrospective study, LiverInt (2020).
[92] J. Wu, W. Li, X. Shi, Z. Chen, B. Jiang, J. Liu, D. Wang, C. Liu, Y. Meng, L. Cui, J. Yu, H. Cao, L. Li, Early antiviral treatment contributes to alleviate the severity and improve the prognosis of patients with novel coronavirus disease (COVID-19), J. Intern. Med. (2020).
[93] G. Chen, D. Wu, W. Guo, Y. Cao, D. Huang, H. Wang, T. Wang, X. Zhang, H. Chen, H. Yu, X. Zhang, M. Zhang, S. Wu, J. Song, T. Chen, M. Han, S. Li, X. Luo, J. Zhao, Q. Ning, Clinical and immunological features of severe and moderate coronavirus disease 2019, J. Clin. Invest. 130 (5) (2020) 2620–2629.
[94] S. Wan, Y. Xiang, W. Fang, Y. Zheng, B. Li, Y. Hu, C. Lang, D. Huang, Q. Sun, Y. Xiong, X. Huang, J. Lv, Y. Luo, L. Shen, H. Yang, G. Huang, R. Yang, Clinical features and treatment of COVID-19 patients in northeast Chongqing, J. Med. Virol. (2020).
[95] G.Q. Qian, N.B. Yang, F. Ding, A.H.Y. Ma, Z.Y. Wang, Y.F. Shen, C.W. Shi, X. Lian, J.G. Chu, L. Chen, Z.Y. Wang, D.W. Ren, G.X. Li, X.Q. Chen, H.J. Shen, X.M. Chen, Epidemiologic and Clinical Characteristics of 91 Hospitalized Patients with COVID-19 in Zhejiang, China: A retrospective, multi-centre case series, QJM (2020).
[96] I.L. Lo, C.F. Lio, H.H. Cheong, C.I. Lei, T.H. Cheong, X. Zhong, Y. Tian, N.N. Sin, Evaluation of SARS-CoV-2 RNA shedding in clinical specimens and clinical characteristics of 10 patients with COVID-19 in Macau, Int. J. Biol. Sci. 16 (10) (2020) 1698–1707.