#### REVIEW



# The common risk factors for progression and mortality in COVID-19 patients: a meta-analysis

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# Abstract

Coronavirus disease 2019 (COVID-19), defined by the World Health Organization (WHO), has affected more than 50 million patients worldwide and caused a global public health emergency. Therefore, there is a recognized need to identify risk factors for COVID-19 severity and mortality. A systematic search of electronic databases (PubMed, Embase and Cochrane Library) for studies published before September 29, 2020, was performed. Studies that investigated risk factors for progression and mortality in COVID-19 patients were included. A total 344,431 participants from 34 studies were included in this meta-analysis. Regarding comorbidities, cerebrovascular disease (CVD), chronic kidney disease (CKD), coronary heart disease (CHD), and malignancy were associated with an increased risk of progression and mortality in COVID-19 patients. Regarding clinical manifestations, sputum production was associated with a dramatically increased risk of progression and mortality. Hemoptysis was a risk factor for death in COVID-19 patients. In laboratory examinations, increased neutrophil count, decreased lymphocyte count, decreased platelet count, increased C-reactive protein (CRP), coinfection with bacteria or fungi, increased alanine aminotransferase (ALT) and creatine kinase (CK), increased N-terminal pronatriuretic peptide (NT-proBNP), and bilateral pneumonia in CT/X-ray were significantly more frequent in the severe group compared with the non-severe group. Moreover, the proportion of patients with increased CRP and total bilirubin (TBIL) was also significantly higher in the deceased group than in the survival group. CVD, CKD, sputum production, increased neutrophil count, decreased lymphocyte count, decreased platelet count, increased CRP, coinfection with bacteria or fungi, increased ALT and CK, increased NT-proBNP, and bilateral pneumonia in CT/X-ray were associated with an increased risk of progression in COVID-19 patients. Moreover, the proportion of patients with increased sputum production, hemoptysis, CRP and TBIL was also significantly higher in the deceased group.

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# Introduction

Since December 2019, an outbreak of pneumonia caused by a novel coronavirus has affected China and spread all over the world [1, 2]. Coronavirus disease 2019 (COVID-19), defined by the World Health Organization (WHO), has infected more than 50 million patients worldwide and caused a global public health emergency [3]. Some patients develop adverse complications and exhibit poor prognosis, and deaths outside of China are increasing persistently. By November 17, 2020, there were 54,771,888 confirmed COVID-19 cases, including more than 1.32 million deaths, and the fatality rate was greater than 10% in some countries according to the WHO 2020 report [4, 5].

Therefore, there is a recognized need to identify risk factors for COVID-19 severity and mortality. Patients with risk factors might be identified earlier, and intensive surveillance or treatment could be administered in advance to improve prognosis [6]. Several studies have documented some clinical characteristics and laboratory test values as risk factors for severe and fatal COVID-19 [7–9]. However, various limitations were apparent in these articles, such as reliance on single-center studies and small sample sizes, which might lead to some bias and restrict the generality and applicability of their conclusions. Predictive factors for severe cases and fatal outcome continue to be debated [10]. A meta-analysis of populations from different studies with a larger sample size is needed.

In this article, the clinical characteristics and laboratory test values of COVID-19 patients with severe/fatal illness compared with those with mild/nonfatal illness were compared in 34 studies with 344,431 patients to identify risk factors for severe disease or death in COVID-19 patients. Based on these data, we can predict disease progression and provide intensive surveillance and rapid treatment to effectively improve the prognosis of COVID-19 patients.

# **Materials and methods**

This meta-analysis was registered in the International Prospective Register of Systematic Reviews (CRD42020179903). This meta-analysis was performed in accordance with the Cochrane Handbook for Systematic Reviews of Interventions guidelines [11].

#### Search strategy

The PubMed, EMBASE, and MEDLINE databases were systematically searched from December 1, 2019, to September 29, 2020, with English language limitations. We searched studies using Medical Subject Headings (MeSH) terms, and the main key words included "Covid-19", "Coronavirus Disease 2019", "Wuhan Pneumonia", "SARS-CoV-2", "New Coronavirus Pneumonia", "NCP", "progression", "severity", "bad outcome\*", "mortality", "death", and "risk factor\* or association\*". Additional records were identified manually through other sources.

## Inclusion and exclusion criteria

Inclusion criteria: (1) comparative studies: groups involving severity and non-severity, survival and death; (2) study type: randomized controlled trials, case-control studies, crosssectional studies and cohort studies; (3) study population: patients should be definitely infected with SARS-CoV2, and studies with more than 20 participants were included; (4) parameters: at least one result was reported among basic characteristics, laboratory examinations, comorbidities, and clinical manifestations in the study. Case reports and animal studies were excluded.

#### Data extraction and quality assessment

All the search results were imported into the EndNote reference management software (Clarivate Analytics) by L.Z. Duplicate records were removed by the software and hand-checked. Two reviewers (L.Z. and J.L.) independently screened the titles and abstracts of the remaining records for relevance against the protocol criteria and labeled these records as excluded, included, or uncertain. In cases of uncertainty, the full texts were retrieved to review the study in detail. Any disagreements were resolved by consulting a third reviewer. After confirming the included articles, data were extracted by two reviewers (L.Z. and S.X.) independently using a standardized form. Quality assessment of the included studies was conducted according to the Newcastle-Ottawa Scale [12] score by F.Z.M. and J.H. Any disagreements in the process of data extraction and quality assessment were discussed with other reviewers.

# **Statistical analysis**

We calculated the odds ratio (OR) with 95% confidence intervals (CIs) for dichotomous data and mean differences (MDs) with 95% CIs for continuous data. The I2 statistic was used to assess the heterogeneity test across studies, and P < 0.1 or  $I^2 > 50\%$  indicates statistical significance. If no statistical heterogeneity was noted, we used a fixed-effects model; otherwise, we chose a random-effects model. Publication bias was assessed using Egger's regression [13] and Begg's rank correlation analysis [14]. A significance of P <0.05 indicated the possibility of publication bias [15]. When the P-value was less than 0.05, we adopted a trim-and-fill method to confirm the result. After supplementing several possible missing studies, the meta-analysis was conducted again. If the estimated value of the combined-effect size did not change significantly, the impact of publication bias was not significant [16]. Moreover, we conducted sensitivity analysis to explore sources of heterogeneity. Sensitivity analysis was performed by excluding single studies one at a time to assess its influence on the pooled effects. All statistical analysis was performed using Stata/SE software 15.0 (StataCorp LP) and Review Manager (RevMan) 5.3 (Nordic Cochrane Centre).

# Results

## Literature search

We identified 3212 articles by searching EMBASE, PubMed, and MEDLINE, and four additional records were identified using other sources. After excluding 1520 duplicated records and reviewing the titles and abstracts, we had 132 eligible articles. Thirty-four studies were included after screening the full text [7, 9, 17–48]. The process of identification and selection is presented Figure 1.

## **Study characteristics**

analysis

A total of 344,431 participants were included in this metaanalysis. All of the articles were retrospective studies published in 2020. Eighteen studies were performed in Wuhan, 12 studies were conducted outside Wuhan in China, and four studies were done in other countries. The characteristics of the selected studies are presented in Table 1. Thirteen articles included survival and non-survival groups, and 24 included severe and non-severe groups. Subgroups analysis was performed based on severity or mortality. Three studies used the same or a similar population to investigate different aspects. Therefore, data from those studies were not included at the same time in the following comparisons.

COVID-19 severity was classified according to the Guidelines for the Diagnosis and Treatment of COVID-19 by the National Health Commission. In this meta-analysis, patients with mild or/and moderate disease were included in the non-severe group, and patients with severe or/and critical disease were included in the severe group. Moreover, patients in an intensive care unit (ICU) or with  $SpO_2 \leq$ 90% or progressive or refractory illness were included in the severe group in several studies.

## Study guality

A summary of the quality assessment of the included studies is presented in Figure S1. With the exception of two trials with a score of 6, the quality of the selected studies was generally high. All of the scores were greater than 5 and therefore could be included in this meta-analysis.

## **Basic characteristics**

We compared demographic characteristics between the two groups based on sex (male/total), age  $\geq 65$  years, and smoking. These results are shown in Figure 2. Twenty-eight studies reported a male/total ratio among 341,586 subjects. The

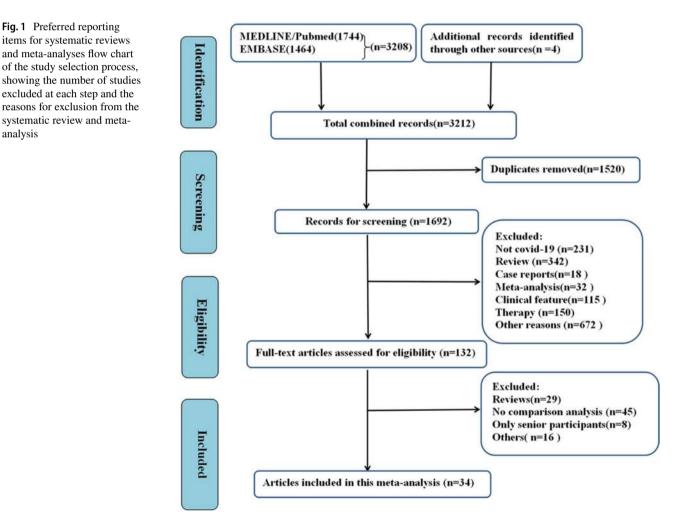


Table 1 Baseline characteristics of the included studies

Author	Region/country	No. of patients	Sex (male/total)	Mean age (SD)/mean (IQR)	NOS
Chen RC*	Throughout China	1590	904/1578	69 (51-86)	8
Chen XH	Wuhan, China	48	37/48	$64.6 \pm 18.1$	7
Cheng YC	Wuhan, China	701	367/701	63 (50-71)	7
Du RH	Wuhan, China	179	97/179	$57.6 \pm 13.7$	8
Feng Y	Wuhan,Shanghai and Anhui	476	271/476	53 (40-64)	8
Guan W*	Throughout China	1099	637/1096	47.0(35.0-58.0)	8
Guan WJ*	Throughout China	1590	904/1578	$48.9 \pm 16.3$	7
Huang CL	Wuhan, China	41	30/41	49.0 (41.0-58.0)	7
Ji D	Anhui,Beijing	208	117/208	$44.0 \pm 16.3$	8
Li KH	Chongqing,Jinan	83	44/83	45.5 (12.3)	7
Li XC	Wuhan, China	548	279/548	60 (48-69)	8
Li Y	Wuhan, China	25	12/25	N/A	8
Liu R	Wuhan, China	119	85/119	N/A	6
Liu W	Wuhan, China	78	39/78	38 (33-57)	7
Liu Y	Wuhan, China	383	162/383	46 (34-61)	7
Mo P	Wuhan, China	155	86/155	54 (42-66)	7
Qu R	Huizhou, China	30	16/30	50.5 (36-65)	7
Shi Y	Zhejiang,China	487	259/487	46 (19)	6
Tang N	Wuhan, China	183	98/183	$54.1 \pm 16.2$	7
Tian SJ	Beijing, China	262	127/262	47.5 (1-94)	7
Wang DW	Wuhan, China	138	75/138	56(42-68)	7
Wang RR	Fuyang	125	71/125	$38.76 \pm 13.799$	7
Wang ZL	Wuhan, China	69	32/69	42.0 (35.0-62.0)	7
Wu CM	Wuhan, China	201	128/201	51(43-60)	8
Wu J	Yancheng,Fuyang,Wuxi	280	151/280	$43.12 \pm 19.02$	8
Yang AP	Zhejiang,China	93	56/93	$46.4 \pm 17.6$	8
Yang XB	Wuhan, China	1476	776/1476	57 (47-67)	7
Yuan ML	Wuhan, China	27	12/27	60 (47–69)	7
Zhang J	Wuhan, China	663	321/663	55.6 (44-69)	8
Zhou F	Wuhan, China	191	119/191	56.0 (46.0-67.0)	8
Almazeedi	Kuwait	1096	888/1096	41 (25-57)	7
Cai QX	Guangdong,China	383	183/383	N/A	7
Chang MC	Daegu, South Korea	106	54/106	$67.6 \pm 15.3$	8
Parra-Bracamonte	Mexico	331,298	178,155/331,298	44 (33-56)	7

N/A, not applicable; SD, standard deviation; IQR, interquartile range; NOS, Newcastle-Ottawa Scale (score)

\*Three studies included the same or similar population but investigated different aspects. Therefore, their data were not included at the same time in one comparison.

proportion of males (65.09%) in the severe and deceased groups was significantly higher than in the non-severe and survival group (52.45%) (pooled OR = 1.72, 95% CI 1.68 to 1.75, P < 0.00001) without heterogeneity (I<sup>2</sup> = 21%) (Fig. 2A). Furthermore, 10 and 15 studies reported the proportion of patients older than 65 years and those who smoked, respectively, between the two groups (Fig. 2B and C). The proportion of patients in the severe or deceased group was significantly higher than in the non-severe or survival group (both P < 0.00001) (Fig. 2B and C). Smoking patients included current and former smokers.

**Fig.2** Association of general characteristics with progression and  $\blacktriangleright$  mortality in COVID-19. Forest plots are shown for the effects of (A) sex (male/total), (B) age  $\ge 65$  years, and (C) smoking.

	Severe/Dec		Non-severe/			Odds Ratio	Odds Ratio
Study or Subgroup 1.1.1 Severity	Events	Total	Events	Total	Weight	M-H. Fixed, 95% C	M-H. Fixed. 95% Cl
Almazeedi 2020	32	42	856	1054	0.1%	0.74 [0.36, 1.53]	
Cai QX 2020	58	91	125	292	0.2%	2.35 [1.44, 3.82]	
Chen XH 2020	24	27	13	21	0.0%	4.92 [1.11, 21.82]	
Ji D 2020	28	40	89	168	0.1%	2.07 [0.99, 4.35]	
LI KH 2020	15	25	29	58	0.1%	1.50 [0.58, 3.88]	
Li XC 2020	153	269	126	279	0.4%	1.60 [1.14, 2.24]	
Li Y 2020	6	9	6	16	0.0%	3.33 [0.60, 18.54]	
Liu R 2020	27	52	35	67	0.1%	0.99 [0.48, 2.04]	
Liu W 2020	7	11	32	67	0.0%	1.91 [0.51, 7.16]	
Mo P 2020	55	85	31	70	0.1%	2.31 [1.21, 4.41]	
Shi Y 2020	36	49	223	438	0.1%	2.67 [1.38, 5.17]	
Tian SJ 2020	26	46	101	216	0.1%	1.48 [0.78, 2.81]	
Wang DW 2020	22	36	53	102	0.1%	1.45 [0.67, 3.15]	
Wang RR 2020	16	25	55	100	0.1%	1.45 [0.59, 3.60]	
Wang ZL 2020	7	14	25	55	0.0%	1.20 [0.37, 3.88]	
Wu CM 2020	60	84	68	117	0.1%	1.80 [0.99, 3.28]	
Wu J 2020	45	83	106	197	0.2%	1.02 [0.61, 1.70]	
Yang AP 2020	18	24	38	69	0.0%	2.45 [0.87, 6.91]	
Zhang J 2020	205	409	116	254	0.6%	1.20 [0.87, 1.64]	
Subtotal (95% CI)	200	1421	110	3640	2.5%	1.55 [1.34, 1.78]	•
Total events	840		2127				
Heterogeneity: Chi <sup>2</sup> = 22.5		= 0 21)- H					
Test for overall effect: Z =			2070				
	0.0.1 (1	00017					
1.1.2 Mortality							
Almazeedi 2020	16	19	872	1077	0.0%	1.25 [0.36, 4.34]	
Chen BC 2020	39	50	865	1528	0.1%	2.72 [1.38, 5.35]	
Du RH 2020	10	21	87	158	0.1%	0.74 [0.30, 1.85]	
LI Y 2020	4	5	8	20	0.0%	6.00 [0.56, 63.98]	
Parra-Bracamonte 2020	25015	38310	153137	292988	96.6%	1.72 [1.68, 1.76]	
Tang N 2020	25015	21	82	292900	0.0%	3.12 [1.09, 8.92]	
Yang XB 2020	156	238	620	1238	0.5%	1.90 [1.42, 2.53]	
Yuan ML 2020	4	10	820	1230	0.0%	0.75 [0.15, 3.65]	
	15	25	306	638	0.0%		
Zhang J 2020 Subtotal (95% CI)	15	38699	306	297826	97.5%	1.63 [0.72, 3.68] 1.72 [1.68, 1.76]	
		29099		29/020	97.076	1.72 [1.00, 1.70]	
Total events	25275		155985				
Heterogeneity: Chi <sup>2</sup> = 9.09			12%				
Test for overall effect: Z =	47.98 (P < 0.	00001)					
Total (95% CI)		40120		301466	100.0%	1.72 [1.68, 1.75]	
Total events	26115	1001000	158112	10 M M M M M M M M	0.0000000000		201
Heterogeneity: Chi <sup>2</sup> = 34.0		= 0 17): 17					
	48.35 (P < 0.						0.05 0.2 1 5

#### B Age>=65years

	Severe/De		Non-severe/			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	M-H. Random, 95% CI
1.2.1 Severity							
Feng Y 2020	45	124	73	352	13.9%	2.18 [1.39, 3.41]	
Guan W 2020	44	163	109	848	14.4%	2.51 [1.68, 3.74]	
Li XC 2020	135	269	75	279	15.0%	2.74 [1.92, 3.91]	
LI Y 2020	7	9	5	16	3.1%	7.70 [1.16, 51.17]	
Tian SJ 2020	20	46	28	216	10.7%	5.16 [2.55, 10.46]	
Wu J 2020	49	83	20	197	11.5%	12.75 [6.75, 24.10]	
Zhang J 2020 Subtotal (95% CI)	246	409 1103	69	254 2162		4.05 [2.88, 5.69] 3.88 [2.58, 5.85]	
Total events	546		379				
Heterogeneity: Tau <sup>2</sup> = 0.2 Test for overall effect: Z =			(P = 0.0001); I <sup>3</sup>	<sup>a</sup> = 78%			
1.2.2 Mortality	522	20	2523 C				2
Du RH 2020	17	21	48	158		9.74 [3.11, 30.48]	
LI Y 2020	5	5	7	20		19.80 [0.96, 409.62]	
Parra-Bracamonte 2020	20673	0	40542	292988		Not estimable	
Zhang J 2020	19	25	296	638		3.66 [1.44, 9.28]	
Subtotal (95% Cl)		51		293804	16.3%	6.04 [2.70, 13.52]	
Total events	20714		40893	12121			
Heterogeneity: Tau <sup>#</sup> = 0.0 Test for overall effect: Z =			P = 0.31); I <sup>2</sup> = 1	6%			
Total (95% CI)		1154		295966	100.0%	4.20 [2.89, 6.08]	•
Total events	21260		41272				
Heterogeneity: Tau <sup>2</sup> = 0.2	21; Chi <sup>2</sup> = 31.5	8, df = 9	$(P = 0.0002); I^2$	<sup>2</sup> = 72%			0.02 0.1 1 10
Test for overall effect: Z =	= 7.57 (P < 0.0	0001)					Favours [experimental] Favours [control]
Test for subaroup differen	nces: Chi <sup>2</sup> = 0.	92. df = 1	(P = 0.34), I <sup>2</sup>	= 0%			Payou's texperimental Payou's teoritor
Smoking							
, shire hard	Severe/Dec	eased	Non-severe/S	Survival		Odds Ratio	Odds Ratio
tudy or Subaroup	Events	Total	Events		Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
.3.1 Severity	- ALL ALL ALL ALL ALL ALL ALL ALL ALL AL					ALL ALL AND ALL ALL ALL	
Imazeedi 2020	2	19	42	1077	0.0%	2.90 [0.65, 12.96]	
eng Y 2020	17	121	27	333	0.3%	1.85 [0.97, 3.54]	
iuan W 2020	38	172	120	913	0.6%	1.87 [1.25, 2.82]	
luang CL 2020	0	13	3	28	0.0%	0.27 [0.01, 5.62]	
i D 2020	6	40	13		0.1%		
		265	41	168		2.10 [0.75, 5.93]	
KH 2020	51	265		279	0.7%	1.38 [0.88, 2.17]	
i Y 2020	5		2	16 67	0.0%	8.75 [1.21, 63.43]	
iu W 2020	3	11	2		0.0%	12.19 [1.76, 84.31]	
10 P 2020		85	2	70	0.0%	1.68 [0.30, 9.45]	
hi Y 2020	6	49	34	438	0.1%	1.66 [0.66, 4.17]	
Vang RR 2020 ubtotal (95% CI)	7	25 809	9	100 3489	0.1% 2.0%	3.93 [1.30, 11.93] 1.82 [1.44, 2.31]	•
otal events	139		295				
leterogeneity: Chi <sup>2</sup> = 11.4	4, df = 10 (P =	= 0.32); I <sup>2</sup>	= 13%				
est for overall effect: Z =	4.94 (P < 0.00	0001)					
3.2 Mortality							

Total (95% CI) 39270 Total events 3372 21719 Heterogeneity: Chi<sup>2</sup> = 33.84, df = 15 (P = 0.004); l<sup>2</sup> = 56% Test for overall effect: Z = 8.81 (P < 0.00001) Test for subaroup differences: Chi<sup>2</sup> = 12.77, df = 1 (P = 0.0004). l<sup>2</sup> = 92.2%

 1.3.2 Mortality

 1.3.2 Mortality

 Almazeedi 2020
 5

 5
 50

 Chen RC 2020
 5

 5
 50

 Li Y 2020
 3

 5
 5

 2hou F 2020
 5

 5
 54

 Subtotal (95% Cl)
 38461

 Total events
 3233

 Heterogeneity: Chi<sup>2</sup> = 8.40, df = 4 (P = 0.08); I<sup>2</sup> = 52%

 Test for overall effect: Z = 8.12 (P < 0.00001)</td>

21424

299228 100.0%

0.1% 0.1% 0.0% 97.7% 0.1% 98.0%

3.52 [1.31, 9.44] 1.50 [0.58, 3.87] 6.00 [0.74, 48.90] 1.17 [1.13, 1.22] 2.23 [0.65, 7.63] 1.17 [1.13, 1.22]

1.19 [1.14, 1.23]

0.02 0.1 1 10 Favours [experimental] Favours [control]

50

A Diabetes	SeveralDeceased Non-servera	/Survival Odds	Ratia Oxi	te Ratio	F CKD Exversion Non-envertisivering Odds Ratio Odds Ratio
Elado er Sabarosan 21.1 Severity Almanesk 2020 Cel 02 2020 Felgi V 2020 Huang C. 2020 Li K 2020 Li K 2020 Li K 2020 Li K 2020 Li K 2020 Li V 2020 Mag 24. 3000 Wang 24. 3000 Wang 24. 3000 Yang AP 2020 Yang AP 2020	Frontia         Total         Number           10         42         117           112         91         100           12         91         100           12         126         322           46         2544         652           1         135         7           32         2669         214           1         1         0           2         11         30           12         14         200           2         11         30           12         14         20           14         0         0           15         60         22           7         60         22           8         30         20           6         16         10           15         64         10           15         64         10           15         138         10	Total         Weight         M-H. Bas           1054         0.8%         5.0           2502         4.9%         4.28           3662         7.0%         1.6           1252         4.9%         4.28           362         7.0%         1.6           1252         0.0%         4.74           10         0.4%         5.0           10         0.9%         4.74           60         1.2%         5.0           10         2.4%         5.0           10         2.4%         5.0           10         2.5%         4.74           63         3.5%         4.74           103         3.0%         4.74           103         3.0%         4.74           103         3.0%         4.74           103         3.0%         4.00           103         3.0%         4.00           103         3.0%         4.03           104         3.0%         4.03           105         3.0%         4.03           107         3.0%         4.03           108         3.2%         9.00	600m. 1055. C M 444. Bas (1) 7.8. (1) 2003 (1) 7.8. (1) 2003 (1) 7.8. (1) 2003 (1) 7.8. (1) 2004 (1) 7.		Biolog Schlagson         Enrarit         Total         Enrarit         Total         Total         North         Net/Link         Met/Link         M
Total evenis Heliarsgenets; Tav# = 0.2 Test five overall affect Z is Armazeet 3020 Chen RC 3020 Chen RC 3020 Dis HR 3020 Dis Helia (1955, CB) Total evenis Helecgenets; Tay* = 0.2	6 19 149 17 20 25 13 50 157 14 50 157 15 50 117 1 5 21 27 1 6 21 27 1 6 24 10 20 14252 33510 10 14253 3350 10 257 64, 45 17 17 50 25754 10 257 50 217 17 10 10 257 50 217 17 10 10 257 50 217 10 10 257 50 20 10 2	76 4.0% 2.6 1540 6.0% 4.2 156 3.5% 1.9 20 0.4% 13.67 292008 16.2% 3.8 17 0.5% 50.5612 137 5.0% 2.8 296013 41.2% 3.8	7 (1.06, 7.08) (7, 24, 6.34) (7, 24, 6.34) (6, 66, 5.36) - 5, 4.35 - 5, 4.35 - 5, 4.35 - 5, 5, 5, 5, 5, 5, 5, 5, 5, 5, 5, 5, 5,		2.8.1         monthly         3         10         1077         7.95         52.65         80.61         10.21<
Total (BS% CI) Total events Heterogeneity: Tau <sup>1</sup> = 0.1 Test for overall effect: Z = Test for subservue differe	38629 14578 42105 38: Chil* - 39:52, df = 22 (P = 0.01); i* 10:55 (P = 0.0007) 566: Chil* = 0.76 (df = 1.0° = 0.981; P	388348 188.8% 3.3 = 68% = 6%	(2.73, 4.23) 0.001 0,1 Favours (experimental	1 10 1000	Presspecies         0.01         0.1         10         00           Parts Invasid Head         2.7 BJ PF 4.000 PF 4.00 (FF - 10.07 FF - 25.06)         Feesan (spokrastic)         100           Fails Invasid Head         4.00 (FF - 4.00 (FF - 4.00 (FF - 10.07 FF - 25.06)         Feesan (spokrastic)         100           G         Additionaccy         Odds Autio         Odds Ratio         Odds Ratio         Odds Ratio           Staty at Subjects         Feesan (Social Control of Contr
Lore D     Los Alexano     Los Serverity     Las Serverity     Las Serverity     Las Serverity     Las X 2020     Cai GX 2020     Las V 2020     Subtract J055     Sch Total events     Neterogenetity     Ch <sup>o</sup> 2 M	BeyentDecented         Hurs-server           Dearts         Total         Eccols           2         42         3           15         81         19           1         27         1           16         127         1           16         254         9           1         15         254           1         13         0	CRUMMENT         Charlest           Tatlat         Watch         M.H. En           3864         0.0%         17.52 (2.4)           3862         0.9%         2.36 (1.2)           382         0.9%         5.2.36 (1.2)           382         0.9%         5.2.36 (1.2)           382         0.9%         6.7.6 (0.7)           383         0.0%         6.0.6 (1.2)           290         0.0%         6.0.6 (1.2)           270         0.0%         6.0.6 (1.2)           670         0.0%         6.0.6 (1.2)           70         0.1%         7.39 (1.2)           70         0.1%         7.39 (1.2)           70         0.1%         7.39 (1.2)           70         0.1%         7.39 (1.2)           710         0.1%         7.39 (1.2)           720         0.1%         7.38 (1.2)	ad. 93%. Cl M.H. Fia	Ratin et. 1924.CL	2 0 00 2000         CM00
Test for overall effect: 2 =		232260 91.0% 4.03 889 0.3% 8.221 137 0.1% 5.4910 294464 96.7% 4.051	9, 140.002 36, 45.560 3.87, 30.700,400 3.87, 4.273 108, 30.403 8.87, 4.200 1.88, 4.200	•	2.7.2 metally         0         16         107         1.4%         1.80         11.52.561           Oman 902 2020         4         0         5         70         87%         2.580         56.77           One R02 2020         4         0         5         70         87%         2.580         56.77           One R02 2020         3         60         15         1540         2.4%         6.691         2.23.380           Di RR 2020         1         21         3         58         1.5%         2.868         2.63.3804
Total events Heterogeneity: Chrl = 23. Teat Sir overall effect: 2 = Total for subsector differen C Hypertensio	1971 376.5 36. dl + 51.19 = 0.181.2 ≠ 2.2% 46.41 (2 + 0.60021) vest CoP = 0.65. dl + 1.49 + 0.471.4 Several/Decessed Frents Total Events	+ 0%. • Elsevival Odd Total Weight M-H, Ra	Basto Od	10 200 Farcurs (control) de Ratio sopre, 95% Cl	b Holinopandy, Ch <sup>2</sup> + 4.55, d1 × 6 p <sup>2</sup> + 3.69, p = 0%. Test for overal effect: Z × 2.09 + 0.605 Test (1991), Cl = 1.001 + 1
2.5.1 Severity Cas (22 502) Class (22 502) Class (22 502) Foung CL, 3020 L KH 2000 L KH 2000 L KH 2000 L KH 2000 More CL 2020 More CL	7 42 900 71 41 32 177 27 6 48 234 44 2 135 4 4 1 2 2 135 4 4 1 4 2 4 1 4 2 4 1 4 2 4 2 3 5 4 4 1 4 2 4 2 3 5 6 15 2 3 6 15	1024         4.3%         1.           280         6.4%         2.2%           1236         1.24%         4.22           1236         1.24%         1.6           28         1.2%         1.6           29         0.3%         2.2           116         0.5%         1.4           87         1.7%         1.5%           100         0.5%         1.4           80         1.2%         1.4           80         1.4%         1.7%           100         2.4%         1.2           438         6.2%         6.44           102         4.4%         5.00           86         1.7%         7.34           101         5.2%         7.34           102         4.4%         5.00           86         1.7%         7.34           107         5.2%         7.34           48602         82.3%         7.34	28         6.4         2.96           11         2.6         4.96           12         3.6         3.66           13         3.6         3.66           14         3.6         3.66           15         3.6         3.66           16         3.7         4.96           16         3.7         4.96           16         3.7         4.96           16         1.7         4.96           16         1.7         4.96           17         4.96         4.96		Newspaper, CP + 44.87, dr = 0 p - 0.74; p - 0.54;         - 0.54;         - 0.54;         - 0.55;           Tart for owned Head 2: 4 - 3.53 (r - 1.05 - 0.56;         Partial Forward Biological Private Biological P
2.3.2 mentaliky Almanaedi 2020 Chening NC 2000 Divi RH 2020 Divi RH 2020 U Y 2020 Planta-Bracumbete 2020 Yana ML 2020 Salmour F 2020 Salmour (2020) Salmour (2020)	8 19 160 20 30 39 28 50 241 13 21 46 1 5 1 16659 39310 46751 38 54 52 34469 52 34469 5228 55 504 4 30 41 1 1 9 0 2028	202080 1515 34 317 0.5% 3500 137 6.7% 3500 298813 37.7% 3.8 24%	1   1 50, 0.00] 0 (0 74, 4.50) 1 (1 56, 10.51) 1 (1 56, 10.51) 1 (0 20, 02.07) 6 (2 50, 2 76) 1 (2 50, 0.50) 1 (2 50, 4.66)		Heterography         CDF = 2.58, UF = 4 (P = 0.63); P = 0%;           Test for overall effect; Z = 2.13 (P = 0.03);         P = 0.03);           2.8.2 montality         19         5         1077         1.1%;         11.96 [1.32, 107.17];           Chen RC 2020         1         9         2.17         1440;         11.4%;         1.49 [1.52, 107.17];           Chen RC 2020         1         50         27         1540;         1.14%;         1.49 [1.52, 107.17];           Substrating (PS CL)         0         90         2.117;         1.25%;         2.11 [1.50, 16.32];           Toxis events         2         32         32         32         32         32         32         32         32         32         32         32         32         32         32         32         32         32         33         33         34         <
D CHD	39552 10867 50385 00; Chrl = 55.25, df = 22 (P = 0.0005) = 10.85 (P < 0.00001) most: Chrl = 1.05 df = 1 (P = 0.17). P Sevens/Deceased Non-sevens?	; 1° = 56% = 48.3%		Ratio	Test for overall effect: Z = 1.02 (P = 0.31)           → Test (9% C)         672         5419         980.0%         1.97 [1.12, 3.48]           Todi events         18         67
-Bady an Bubgenau 24.1 Seventy Amazandi 2029 Chen XH 2020 Chen XH 2020 Cuan WJ 2020 Guan WJ 2020 Guan WJ 2020 Guan WJ 2020 Guan WJ 2020 Guan WJ 2020 Guan WJ 2020 Mary 2020 Mary 2020 Wang 2L 2020 Wang	Events.         Total.         Events.           6         427         25           77         124         21           20         254         35           3         35         6           10         3         5           14         9         6           4         45         0           5         344         5           6         344         3           15         34         3           6         344         3           171         107         3           201         174         23           203         10         174           5         344         3           121         32         32           203         174         103           204         107         107	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	13, 16, 544] .04, 1, 111] .27, 4, 502] (6, 4, 608] (3, 14, 646] 	d. 93% C1	Image: Construction         Feasure (operministic)
2.4.2 montaility Amazonii 2020 Chen R.C. 2020 Li Y 2020 Yuan M. 2020 Zhang J 2020 Subtoati (16% Ct) Toat events Meteorets	5 18 36 8 50 51 1 5 3 3 10 0 16 25 146 13 54 2 160 45 240	1077         1.7%         10.39 [3]           1540         3.2%         5.56 [2]           20         1.2%         1.42 [0]           17         0.3%         16.33 [3]           620         4.3%         5.56 [2]           137         1.0%         21.40 [4]           1428         11.6%         7.43 [4.4]	11, 17,46]		Total (95%; CI)         234         728         100.0%         0.92 (0.48, 1.87)           Total events         12         39           Heterogeneity: ChF = 32 t; dF = 5 (P = 0.67); F = 0%         0.42         0.1         1         10         50           Test for overall effect; Z = 0.22 (P = 0.62)         Favours [experimental]         Favours [control]         Favours [control]
Total (95% CI) Total events Hattargeresity: CH* at Tarat for owned letter: 2 Tarat for owned letter: 2 Tarat for suberroup offler E CVD Bludy, as fullying and Annound State Annound State Annound State Chen SH 3020 Chen SH 3020	$\begin{array}{c} 32, dt \in S(t) = 0.05, t^{-2} $	1. <i>P</i> = 87.8%.	Ratia Oash ed. 35% GI M41 Pix 50.36.20]	10     100     100     100     100     100	2.13.1 Strending         4         1         1054         0.0%, 8.28 [0.33, 26.82]           Fing Y 1000         5         124         2         132         0.1%, 7.26 [1.4, 3.840]           Guar WJ 2020         1         2.44         2         132         0.1%, 7.26 [1.4, 3.840]           Guar WJ 2020         1         2.42         2         10.24         2.19.24         11.11           Total events         6         2742         0.2%         3.76 [1.6, 15.86]         1.11           Hetergoweicy CPF = 0.54, df = 2.P = 0.008]         2         2.742         0.2%         3.76 [1.6, 15.86]           2.13.2 minitipe         0         1.107         0.0%         1.40 [0.07, 146.00]         1.11           2.13.2 minitipe         0         9         3.1020         0.5%         4.29 [0.22, 48.21]
2.8.2 montaility Almaseed: 2000 Charp Mc 3020 Dar RK 2000 Yaam Mc 2000 Yaam Mc 2000 Subbotal (95% CB) Total avantal CHr <sup>2</sup> = 3 Teat for ownell effect: 2 Total events Hotesopenetry: CHr <sup>2</sup> = 9 Total events Hotesopenetry: CHr <sup>2</sup> = 9	0 10 7 6 30 6 6 50 24 1 10 0 1 30 5 25 5 26, df = 4 (P = 0.52) P = 05	17 1.3% 5.53 (23 2018 25,4% 6.47 [3 0095 100.0% 4.99 [	20. 49.39) .09, 8.01 .09, 8.01 .09, 10.00 .0, 10.00	Farcus [corror]	Person-Buscannote 2020 1001 30310 3105 290385 99.7% 2503 245,250 Substrat (975 C) 33379 25565 99.9% 254 [2.44, 2.63] Total works 1001 3139 Heatergosety: CP = 1.44, 41 = 2 (P = 0.42), 1 = 0%, Total (95% C) 3379 25637 100.0% 2.44 [2.46, 2.44] Total (95% C) 3379 3144 Heatergosety: CP = 3.45, 41 = 0, 42, 11 = 0%, Total works whethed, 2 = 3.71 (P = 0.0007) = 0.75 Heater governmented, 2 = 37.11 (P = 0.0007) = 0.75

◄Fig. 3 Comorbidity risk factors for progression and mortality in COVID-19. Forest plots are shown for the effects of (A) diabetes, (B) COPD, (C) hypertension, (D) CHD, (E) CVD, (F) CKD, (G) malignancy, (H) Hep B infection, (I) abnormal liver function, and (J) immunodeficiency.

#### Comorbidities

We compared 10 comorbidities – diabetes, chronic obstructive pulmonary disease (COPD), hypertension, coronary heart disease (CHD), cerebrovascular disease (CVD), chronic kidney disease (CKD), malignancy, hepatitis B virus infection (HepB), abnormal liver function, and immunodeficiency – between the two groups in this study. The outcomes are shown in Figure 3.

Eighteen studies with a total of 339,975 COVID-19 patients were included in the diabetes comorbidity comparison between the two groups. The proportion of patients with diabetes comorbidity was dramatically higher in the severe or deceased group then in the non-severe or survival group (OR = 3.39, 95% CI 2.73 to 4.22, pooled P < 0.00001) without heterogeneity ( $I^2 = 44\%$ ) (Fig. 3A). Patients with diabetes had a 3.55-fold higher risk of progression and 3.83-fold higher risk of mortality compared with those without diabetes among the SARS-CoV-2-infected population. Similarly, we identified an increased risk of progression and mortality in COVID-19 patients with COPD, hypertension, CHD, CVD, or CKD (all subgroups and total *P*-values < 0.00001) (Fig. 3B-F). Thus, these results confirmed that diabetes, COPD, hypertension, CHD, CVD, and CKD were all associated with an increased risk of progression and mortality in COVID-19 patients.

Moreover, subgroup analysis indicated that malignancy could increase the risk of progression (OR = 2.73, 95% CI 1.83 to 4.07, P < 0.00001) but did not increase the risk of mortality (OR = 2.13, 95% CI 1.02 to 4.47, P = 0.05) in COVID-19 patients without obvious heterogeneity (both I<sup>2</sup> = 0%) (Fig. 3G). Immunodeficiency was also correlated with an increased risk of severity (P = 0.0006) and mortality (P < 0.00001) without heterogeneity (Fig. 3J). Furthermore, we found that HepB infection and abnormal liver function were only correlated with severity in COVID-19 patients (Fig. 3H and I).

#### **Clinical manifestations**

We explored 14 common clinical manifestations of COVID-19 patients in this analysis (Fig. S1 and Table 2). Thirteen studies with a total of 5407 COVID-19 patients were included in the comparison of sputum production between the two groups. The incidence of sputum production was significantly higher in the severe or deceased group than in the non-severe or survival group (pooled OR = 2.08, 95% CI 1.55 to 2.80, pooled P < 0.00001). Sputum production was associated with dramatically increased risks of progression and mortality (Fig. S1G). Similarly, we found that the incidence of dyspnea was clearly elevated in the severe and deceased subgroup compared with the non-severe and survival subgroup (severity subgroup: OR = 5.33, 95% CI 3.36 to 8.45, P < 0.00001; mortality subgroup: OR = 8.55, 95% CI 2.70 to 27.72, P = 0.0003) with significant heterogeneity ( $I^2 = 62\%$  and  $I^2 = 77\%$ , respectively) (Fig. S1H).

We found the proportion of patients with anorexia, fatigue, or shortness of breath to be significantly higher in the severe group than in the non-severe group (P =0.0004, P = 0.04, and P < 0.00001, respectively). However, we did not identify similar evidence in the mortality subgroup (Fig. S1B, C, and J). The results also showed that the proportion of patients with hemoptysis was significantly higher in the survival group than in the nonsurvival group (P < 0.00001). Moreover, compared with the non-severe group, the proportion of patients with fever, pharyngalgia, cough, hemoptysis, dizziness, or nausea/ vomiting was higher, and the proportion with myalgia/ arthralgia, diarrhea, or headache was lower in the severe group; however, the differences were not statistically significant. Similarly, compared with the survival group, the proportion of patients with cough, myalgia/arthralgia, diarrhea, headache, or nausea/vomiting was higher, and the proportion of patients with fever was lower in the deceased group. However, these differences were not statistically significant (Fig. S1 and Table 2).

## Laboratory tests

We investigated 20 common laboratory examinations of COVID-19 patients in this analysis. Given that there were too many results to be presented, we divided laboratory results into four aspects as follows: Laboratory values greater than the upper limit of the locally defined reference range were regarded as elevated, and those lower than the lower limit were considered decreased.

#### **Routine blood tests**

In total, 13 studies with 5252 participants investigated the proportion of patients with elevated white blood cell (WBC) counts in each of the two groups of COVID-19 patients. The proportion of patients with elevated WBC counts was

Table 2 Results of meta-analysis of the clinical manifestation	ns
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Clinical manifestation	OR (95% CI)	P-value
Severity subgroup		
Fever	1.33 (0.83 to 2.12)	0.23
Anorexia	2.78 (1.58 to 4.89)	0.0004
Fatigue	1.22 (1.01 to 1.47)	0.04
Myalgia/arthralgia	0.77 (0.47 to 1.26)	0.30
Pharyngalgia	1.24 (0.82 to 1.88)	0.30
Cough	1.26 (0.88 to 1.80)	0.22
Sputum	2.11 (1.40 to 3.19)	0.0004
Dyspnea	5.33 (3.36 to 8.45)	< 0.00001
Hemoptysis	3.89 (0.95 to 15.91)	0.06
Shortness of breath	6.63 (3.05 to 14.41)	< 0.00001
Diarrhea	0.95 (0.75 to 1.22)	0.71
Nausea/vomiting	1.11 (0.76 to 1.62)	0.58
Headache	0.79 (0.56 to 1.12)	0.18
Dizziness	2.44 (0.83 to 7.14)	0.10
Mortality subgroup		
Fever	0.81 (0.47 to 1.38)	0.43
Fatigue	1.40 (0.98 to 2.00)	0.06
Myalgia /arthralgia	1.22 (0.77 to 1.95)	0.39
Cough	1.10 (0.56 to 2.17)	0.78
Sputum	1.98 (1.31 to 3.01)	0.001
Dyspnea	8.55 (2.70 to 27.12)	0.0003
Hemoptysis	165.82 (22.73 to 1209.81)	< 0.0001
Shortness of breath	4.65 (0.42 to 51.96)	0.21
Diarrhea	1.03 (0.54 to 1.95)	0.93
Nausea/vomiting	1.52 (0.74 to 3.11)	0.25
Headache	1.43 (0.81 to 2.53)	0.22
Dizziness	1.17 (0.15 to 9.02)	0.88

significantly higher in both the severe and mortality subgroups (OR = 3.22, 95% CI 2.03 to 5.11, P < 0.00001; OR = 6.87, 95% CI 4.59 to 10.29, P < 0.00001, respectively) without statistical heterogeneity (I<sup>2</sup> = 50% and I<sup>2</sup> = 5% respectively) (Fig. 4A). Moreover, the proportion of patients with a reduced WBC count was lower in the severe/ deceased group than in the non-severe/survival group, but the results were only statistically significant for the mortality subgroup (OR = 0.45, 95% CI 0.21 to 0.96, P = 0.04) (Fig. 4B). Similarly, the rates of increased neutrophil counts **Fig. 4** Routine blood test risk factors for progression and mortality  $\blacktriangleright$  in COVID-19. Forest plots are shown for the effects of (A) elevated WBC, (B) decreased WBC, (C) elevated neutrophils, (D) decreased neutrophils, (E) decreased platelets, and (F) decreased lymphocytes.

and reduced lymphocyte counts were significantly higher in both the severe and deceased groups than in the non-severe and survival groups (both pooled P < 0.00001, Fig. 4 C and F); however, some heterogeneity was noted in the subgroups (neutrophil increased: severity subgroup  $I^2 = 61\%$ ; lymphocyte decreased: mortality subgroup  $I^2 = 88\%$ ). Compared with the non-severe group, the proportion of patients with a reduced platelet count was significantly increased, and the proportion of patients with reduced neutrophil levels was lower in the severe group (P = 0.01, P = 0.04, and P = 0.03, respectively). However, we did not identify similar evidence in the mortality subgroup (Fig. 4D and E).

#### Infection-related results

Four infection-related factors – C-reactive protein (CRP), procalcitonin (PCT), IL-6, and coinfection with another pathogen – were investigated in this study (Fig. 5). The proportion patients with elevated CRP, elevated PCT, and coinfection with bacteria or fungi was significantly higher in the severe group than in the non-severe group (P < 0.00001, P < 0.00001, P = 0.03, and P = 0.01, respectively) without significant heterogeneity (Fig. 5A, B and D). The proportion of patients with elevated CRP or PCT was also significantly higher in deceased group than in the survival group (P =0.003 and P = 0.005, respectively), but heterogeneity was noted ( $I^2 = 73\%$  and  $I^2 = 80\%$ , respectively) (Fig. 5A and B). Sufficient evidence was not enough available to determine the effect of IL-6, a common inflammatory cytokine, on the risk of progression and mortality (Fig. 5C).

#### **Blood biochemistry**

Six common blood biochemistry results were studied in this meta-analysis (Fig. 6). The proportion of patients with increased aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatine kinase (CK), and serum creatinine (sCr), was significantly higher in the severe/deceased

A WBC elevated Study or Subgroup 4.1.1 Severity Feng Y 2020 Guan W 2020		Total	Events	Total	Weight	Odds Ratio M-H, Random, 95% Cl	Odds Ratio M-H. Random. 95% Cl
an annual f. T. T. Market Miller	26 19	124	23 39	351	11,4%	3.78 [2.07, 6.93] 2.54 [1.43, 4.52] 5.13 [1.19, 22.11]	
Huang CL 2020 Li KH 2020	7	13	55	27	4.9%	5.13 [1.19, 22.11] 2.02 [0.49, 8.26]	
J XC 2020 J Y 2020	65 4	267	8	275	9.8%	8.66 [4.04, 18.57] 0.62 [0.12, 3.22]	
Nang ZL 2020	1	1.4	0	53	1.3%	11.89 [0.46, 308.40]	
Zhang J 2020 Subtotal (95% CI)	62	409	18	254 1845	12.0% 60.4%	2.34 [1.35, 4.06] 3.22 [2.03, 5.11]	•
Fotal events Heterogeneity: Tau <sup>#</sup> = 0. Fest for overall effect: Z	178 .19; Chi <sup>2</sup> = 1- = 4.96 (P < 1	4.04, df = 1	7 $(P = 0.05); P$	- 50%			
L1.2 Mortality							
Cheng YC 2020 Du RH 2020	17 7	40 21	80 20	1281 158 20	10.8% 7.6% 2.3%	11.10 [5.70, 21.61] 3.45 [1.24, 9.58]	
LI Y 2020 Zhang J 2020 Zhou F 2020	4	5 25	9 70	638	9.1%	4.89 [0.46, 51.87] 5.41 [2.34, 12.50]	
Zhou F 2020 Subtotal (95% CI)	25	145	15	137 2234	9.9%	3.45 [1.24, 9.58] 4.89 [0.46, 51.87] 5.41 [2.34, 12.50] 7.01 [3.29, 14.95] 6.87 [4.59, 10.29]	•
Total events Heterogeneity: Tau <sup>#</sup> = 0. Test for overall effect: Z	63 01; Chi# = 4	20, df = 4	194 (P = 0.38); i* =	5%			C2.24
Fest for overall effect: Z Fotal (95% CI)	= 9.36 (P < 0	0.00001)			100.0%		
Total events Heterogeneity: Tau <sup>a</sup> = 0	241 25: Chi <sup>2</sup> = 2	11/3 8 03 df = 1	301 12 (P = 0.005)	1* = /57%		4.22 [2.65, 6.23]	· · · · · · · ·
Test for overall effect: Z	= 7.23 (P < 1	0.00001)	1 (P = 0.02).	* = 83.0%			0.01 0.1 1 10 10 Favours [experimental] Favours [control]
B WBC decreas	ed Severe/Deci	eased I Total	Non-severe/S Events	invivat	Weight	Odds Ratio M-H. Random. 95% Cl	Odds Ratio M-H. Random, 95% Cl
	24			351	12.0%	1 02 10 61 1 711	
Feng Y 2020 Guan W 2020 Huang CL 2020 Li KH 2020 Li XC 2020 Li XC 2020	102	124 167 13 25	228 9 6	811 27 58	13.2% 6.9% 9.9%	4.01 [2.84, 5.68] 0.17 [0.02, 1.49] 1.65 [0.42, 6.45]	
LI KH 2020 LI XC 2020	46	267	84	275		1.65 [0.42, 6.45] 0.47 [0.31, 0.71] 0.28 [0.03, 2.83]	the second se
LI Y 2020 Wang ZL 2020 Subtotal (95% CI) Fotal events	3	14 619	33	1591	0.6% 9.8% 72.3%	0.28 [0.03, 2.83] 0.17 [0.04, 0.67] 0.70 [0.26, 1.92]	
	181 42; Chi <sup>#</sup> = 70	0.71. df = 6	432 5 (P < 0.00001			otto format tranf	
Teat for overall effect: Z 4.2.2 mortality	= 0.69 (P = 6	0.49)					
4.2.2 mortality Du RH 2020 Li Y 2020	3	21	43	158	10.2%	0.45 (0.12, 1.69)	
Zhou F 2020 Subtotal (95% CI)	5	54 80	27	137 315	6.3% 11.2% 27.7%	0.45 [0.12, 1.59] 0.75 [0.07, 8.38] 0.42 [0.15, 1.14] 0.45 [0.21, 0.96]	
Fotal events Heterogeneity: Tau* = 0. Fest for overall effect: Z	00: ChP = 0		75 (P = 0.91); P =				
	= 2.07 (P = 0						
Fotal (95% CI) Fotal events Heterogeneity: Tau* = 1.	190 .30: Chir - **	699 6.45. df = 1	507 9 (P = 0.00001	1906 ); I" = 90"	100.0%	0.64 [0.28, 1.46]	dan da l
Test for overall effect: 2 Test for suboroup differe	= 1.06 (P = 6	0.29) 0.48. df =	1 (P = 0.49). I	P = 0%			0.02 0.1 1 10 1 Favours (experimental) Favours (control)
Tetal events Tetarogeneity: Tau" = 1. Teat for overall effect 2 Test for subaroup difference C Neutrophil e						Odds Ratio	Odds Ratio
Study or Subgroup 4.3.1 severity	Events	Total	Events	Total	Weight	M-H. Random, 95% CI	
LI KH 2020 LI XC 2020	7 96	25	10 22	58 276	10.2% 27.7%	1.87 [0.62, 5.65] 6.46 [3.91, 10.67]	
Zhang J 2020 Subtotal (95% CI)	154	409	35	254 587	32.5%	6.46 [3.91, 10.67] 3.78 [2.51, 5.69] 4.12 [2.38, 7.14]	
Fotal events teterogeneity: Tau <sup>#</sup> = 0. Fest for overall effect: 2	267 .14; Chi <sup>2</sup> = 5		67 (P = 0.08); I* =				
	= 5.06 (P < 0	0.00001)					
4.3.2 mortality Du RH 2020	12	21	39	158	13.2%	4.07 [1.59, 10.38]	
Zhang J 2020 Subtotal (95% CI)	12	25	177	638 796	16.4% 29.6%	2.40 [1.08, 5.37] 3.00 [1.63, 5.53]	
Total events Heterogeneity: Tau* = 0.	.00; Chi* = 0	.70, df = 1	216 (P = 0.40); I* =	- 0%		10000000000000000000000000000000000000	
l'est for overall effect: Z	= 3.54 (P = 0	0.0004)	and the second secon		ggenan	19 <u>11 - 19</u> 16 - 1920 - 1920 - 19300 - 19300 - 19300 - 19300 - 19300 - 19300 - 19300 - 19300 - 19300 - 19300 - 19300 - 19300 - 19	
Total (95% Cl) Total events	281	747	283		100.0%	3.82 [2.57, 5.69]	
Heterogeneity: Tau <sup>#</sup> = 0. Test for overall effect: Z	-6.62 (P < 0)	.95, df = 4 0.00001)	(P = 0.14); I* =	- 42%			0.1 0.2 0.5 1 2 5 10 Favours (experimental) Favours (control)
Test for overall effect: 2 DNeutrophil de	creased	0.57. df =	P = 0.45	· = 0%			
	Severally	eased	Non-severe	invition		Odds Patie	Odds Patio
study or subgroup	Severe/Dece Events	eased Total	Non-severe/S Events	urvival Total	Weight	Odds Ratio M-H. Random, 95% Cl	Odds Ratio M.H. Random, 95% Cl
4.4.1 severity Li KH 2020	2 17	25 267	3 50	58 275	14.4%	M-H, Random, 95% Cl	Odds Ratio M-H. Random, 95% Cl
4.4.1 severity Li KH 2020 Li XC 2020 Li Y 2020 Subtotal (95% CI)	2 17 2	25	3 50 24	58	14.4%	M-H, Random, 95% Cl	Odds Ratio M-H, Random. 95% CI
4.4.1 severity Li KH 2020 Li XC 2020 Li XC 2020 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0.	2 17 2 21 .27; Chi <sup>2</sup> = 3.	25 267 14 306 21, df = 2	3 50 24 77	58 275 53 386	14.4%	Odds Ratio M.H. Random, 95% Cl 1.59 [0.25, 10.18] 0.31 [0.17, 0.55] 0.20 [0.04, 0.99] 0.38 [0.15, 0.92]	Odds Ratio
A4.1 severity Li KH 2020 Li XC 2020 Li YZ 2020 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0. Test for overall effect: Z	2 17 2 21 .27; Chi <sup>2</sup> = 3.	25 267 14 306 21, df = 2	3 50 24 77	58 275 53 386	14.4%	M-H, Random, 95% Cl	Odds Ratio M:H. Random. 95% Cl
At.1 severity Li KH 2020 Li KH 2020 Li Y 2020 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>a</sup> = 0. Test for overall effect: Z 4.4.2 mortality Du RH 2020	2 17 2 21 .27; Chi <sup>2</sup> = 3.	25 267 14 306 .21, df = 2 0.03)	3 50 24 77	58 275 53 386 38%	14.4% 48.7% 18.1% 81.1%	M.H. Random, 95% Ci 1.59 [0.25, 10,18] 0.31 [0.17, 0.55] 0.20 [0.04, 0.99] 0.38 [0.15, 0.92]	Odds Ratio M.H. Random. 95% Of
Atudy of Subgroup 4.4.1 severity 1.1 K2 2020 1.1 K2 2020 Subtotal (85% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0. Test for overall effect: Z 4.4.2 mortality Du RH 2020 Subtotal (85% CI) Total events	2 17 2 27; Chi <sup>2</sup> = 3 = 2.14 (P = 1 2	25 267 14 306 .21. df = 2 0.03)	3 50 24 (P = 0.20); I <sup>2</sup> =	58 275 53 386 386	14,4% 48.7% 18,1% 81.1%	M-H, Random, 95% Cl	Odds Ratio M.H. Random. 95% Cl
all day of subgenoup all day of subgenoup Li KH 2020 Subtotal (85% CI) Total events: Tau <sup>2</sup> = 0. Test for overall effect: 2 4.4.2 mortality: Du RH 2020 (3) Total events Heterogeneity: Not appli	2 17 2 27; Chi <sup>2</sup> = 3 = 2,14 (P = 1 2 2 icable	25 267 14 306 .21, df = 2 0.03) 21 21	3 50 24 (P = 0.20); I <sup>2</sup> = 16	58 275 53 386 38%	14.4% 48.7% 18.1% 81.1%	M.H. Random, 95% Ci 1.59 [0.25, 10,18] 0.31 [0.17, 0.55] 0.20 [0.04, 0.99] 0.38 [0.15, 0.92]	Odds Ratio M-H, Random, 95% Cl
Istady coll subproup Li KH 2020 Li KH 2020 Li XC 2020 Total events Hotorogeneity: Tau <sup>2</sup> = 0. Test for overall effect: 2 Kubtotal (95% Cl) Test overall effect: 2 Test overall ef	2 17 2 27; Chi <sup>3</sup> = 3, 2 2,14 (P = 1 2 2 icable = 0.09 (P = 6	25 267 14 306 .21, df = 2 0.03) 21 21 21 0.93) 327	Events 3 24 (P = 0.20); P = 16 16	101a) 56 275 53 386 38% 158 158 544	14.4% 48.7% 18.1% 81.1%	M.H. Random, 95% Ci 1.59 [0.25, 10,18] 0.31 [0.17, 0.55] 0.20 [0.04, 0.99] 0.38 [0.15, 0.92]	Odds Ratio
Istudy of subgroup Li KH 2020 Li KH 2020 Li KC 2020 Li XC 2020 Li XC 2020 Li XC 2020 Li XC 2020 Li XC 2020 Subtotal (05% Cl) Total events featrogeneity: Not appli Test for overail effect. 2 Total (95% Cl) Total events Total events Total events Total events Total events Total events Total events Teatrogeneity: Tau" = 0	2 17 2 .27; Chl <sup>2</sup> = 3 = 2,14 (P = 1 2 icable = 0.09 (P = 1 .25; Chl <sup>2</sup> = 4 .25; Chl <sup>2</sup> = 4	25 267 14 306 21, df = 2 0.03) 21 21 0.93) 327 74, df = 3 0.05)	Events 3 50 24 (P = 0.20); P = 16 16 (P = 0.19); P =	158 275 53 386 38% 158 158 544 • 37%	14.4% 48.7% 18.1% 81.1% 18.9% 18.9%	M.H. Random 95% CI 1.59 [0.25, 101 ii) 0.31 [0.17, 0.55] 0.38 [0.16, 0.99] 0.38 [0.15, 0.92] 0.38 [0.15, 0.92] 0.93 [0.20, 4.38] 0.93 [0.20, 4.38]	M.H. Random. 95%. Ci
skudy of subproup Li KH 2020 Li XC 2020 Total events Hoterogeneity: Tau <sup>2</sup> = 0. Test for overall effect: 2 A.2: mortality Du RH 2020 Subtotal (26% CI) Test for overall effect: 2 Total (95% CI) Total events Hoterogeneity: Tau <sup>2</sup> = 0. Test for overall effect: 2 Test for overall effect: 2 Test for overall effect: 2 Note: 1 Note: 1	2 17 21 27; Chi <sup>2</sup> = 3, = 2,14 (P = ( 2 icable = 0.09 (P = ( 23 25; Chi <sup>2</sup> = 4, = 2,00 (P = ( - 20) (P = ( -	25 267 14 306 .21, df = 2 0.03) 21 21 0.93) 327 .74, df = 3 0.05) 1.00 df =	24 50 24 (P = 0.20); P = 16 16 (P = 0.10); P = 1 (P = 0.32), I	101a) 56 275 53 386 158 158 544 • 37% P = 0.1%	14.4% 48.7% 18.1% 81.1% 18.9% 18.9%	M.H. Random, 95%, GI 1.556 (0.75, 10, 16) 0.31 [0.17, 0.55] 0.20 [0.04, 0.99] 0.38 [0.15, 0.92] 0.38 [0.15, 0.92] 0.93 [0.20, 4.38] 0.93 [0.20, 4.38]	M.H. Random. 95%. Cl
Likely 201 Subdroub Li XH 2020 Li XC 2020 Total events Hoterogeneity: Tau" = 0. Fest for overall effect: 2 4.4.2 mortality Du RH 2020 Du RH 2020 Like CO Total events Heterogeneity: Tau" = 0. Fest for event effect Heterogeneity: Tau" = 0. Heterogeneity: Tau" = 0. Hetero	2 17 21 27; Chi <sup>2</sup> = 3, = 2,14 (P = ( 2 icable = 0.09 (P = ( 23 25; Chi <sup>2</sup> = 4, = 2,00 (P = ( - 20) (P = ( -	25 267 14 306 .21, df = 2 0.03) 21 21 0.93) 327 .74, df = 3 0.05) 1.00 df =	Events 3 50 24 (P = 0.20); P = 16 16 (P = 0.19); P =	101a) 56 275 53 386 158 158 544 • 37% P = 0.1%	14.4% 48.7% 18.1% 81.1% 18.9% 18.9%	M.H. Random 95% CI 1.59 [0.25, 101 ii) 0.31 [0.17, 0.55] 0.38 [0.16, 0.99] 0.38 [0.15, 0.92] 0.38 [0.15, 0.92] 0.93 [0.20, 4.38] 0.93 [0.20, 4.38]	M.H. Random. 95%. Ci
study of subgroup Li KH 2020 Li KH 2020 Li XC 2020 Tatal events Hoterogeneity: Tau <sup>2</sup> = 0. Test for overall effect: 2 Hoterogeneity: Tau <sup>2</sup> = 0. Test for overall effect: 2 Test for overall effect: 2 Effect effect decree Effect	2 17 21 27; Chi <sup>2</sup> = 3, = 2,14 (P = ( 2 icable = 0.09 (P = ( 25; Chi <sup>2</sup> = 4, = 2,20 (P = ( 23; Chi <sup>2</sup> = 4, = 2,20 (P = ( 25; Chi <sup>2</sup> = 4, = 2,20 (	21 25 267 14 306 .21, df = 2 0.03) 21 21 0.93) 327 74, df = 3 0.05) 100, df = eased 1 Total	(P = 0.20); P = (P = 0.20); P = 16 16 (P = 0.10); P = 1 (P = 0.32); I 1 (P = 0.32); I Non-severe/S	10131 56 275 53 386 = 38% 158 = 544 = 37% P = 0, 1% urvival Total 713	14.4% 48.7% 18.7% 81.1% 18.9% 18.9% 100.0% Weight 22.6%	M.H. Random, 95% CI 1.556 (275, 10, 16) 0.31 [0, 17, 0.55] 0.20 [0, 04, 0.99] 0.38 [0.15, 0.92] 0.38 [0.20, 4, 38] 0.93 [0.20, 4, 38] 0.44 [0.20, 0.98] Odde Ratio M.H. Random, 95% CI	M.H. Random. 95%. Ci
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Likely 201 Subgroup Likely 2020 Li XC 2020 Li XC 2020 Li XC 2020 Li XC 2020 Control (Control (Co	21 22 22 22 22 22 22 22 22 22 22 22 22 2	25 267 14 306 21, df = 2 0.03) 21 21 0.93) 327 .74, df = 3 0.05) 1.00 df = censed 1 13 3265 434	Events 3 50 24 (P = 0.20); P = 16 16 16 (P = 0.10); P = 1 (P = 0.32), I 1 (P = 0.32), I 1 (P = 0.32), I 225 65 294	1013) 56 275 53 386 38% 158 158 158 544 - 37% 744 - 37% 70 al Total 713 277	14.4% 48.7% 18.1% 81.1% 18.9% 18.9% 100.0% Weight 22.6% 4.8%	M.H. Random, 95% CI 1.556 (275, 10, 16) 0.31 [0, 17, 0.55] 0.20 [0, 04, 0.99] 0.38 [0.15, 0.92] 0.38 [0.20, 4, 38] 0.93 [0.20, 4, 38] 0.44 [0.20, 0.98] 0.44 [0.20, 0.98] Odde Ratio M.H. Random, 95% CI	M.H. Random. 95%. Ci
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Likely 2023 Likely 2020 Li XC 2020 Li X	Events 17 21 27 21 27 21 27 21 21 21 21 21 2 2 2 2 2 2 2 2 2 2 2 2 2	25 267 14 267 14 200 200 21 21 21 21 20 327 74, df = 3 0.03) 327 74, df = 3 0.03) 1.00 df = 0.030 1.100 df = 0.030 1.000 df = 0.000 1.000 df = 0.000 df = 0.0000 df = 0.00000 df = 0.00000000000000000000000000000000000	(P = 0.20); P = (P = 0.20); P = 16 (P = 0.10); P = 1 (P = 0.32); I 1 (P = 0.32); I Exents 225 1 (P = 0.04); P = 401 28 2 1 28 21 28 21 28 21 28 21 28 28 28 28 28 28 28 28 28 28	10181 2775 53 386 • 38% 158 158 544 • 37% * = 0, 1% 27 277 277 1014 • 08% 1016 334 137 1587	14,4% 48,7% 18,7% 18,9% 18,9% 100,0% Weight 22,6% 4,8% 49,9% 19,6% 19,6% 11,1%	M.H. Random, 95%, GI 1.556 (25, 10, 16) 0.31 [0, 17, 0.55] 0.30 [0, 04, 0.99] 0.38 [0, 15, 0.92] 0.38 [0, 20, 4, 36] 0.93 [0, 20, 4, 36] 0.93 [0, 20, 4, 36] 0.44 [0, 20, 0.98] 0.44 [0, 20, 0.98] 0.44 [0, 20, 0.98] 0.44 [0, 20, 0.98] 0.44 [0, 20, 0.98] 0.41 [0, 20, 3, 36] 0.41 [1, 20, 3, 79] 0.35 [0, 47, 1, 183] 0.35 [0, 47, 1, 183] 0.36 [0, 47, 1, 183] 17, 27 [0, 38, 80, 97]	M.H. Random. 95%. Ci
$\label{eq:constraints} \begin{array}{l} \mathbf{x}_{1} \mathbf{x}_{2} $	Events 17 21 27 21 27 21 27 21 21 21 21 21 2 2 2 2 2 2 2 2 2 2 2 2 2	25 267 14 267 14 2003) 21 21 21 21 21 21 21 21 21 21 21 21 21	(P = 0.20); P = (P = 0.20); P = 16 (P = 0.10); P = 1 (P = 0.32); I 1 (P = 0.32); I Exents 225 1 (P = 0.04); P = 401 28 2 1 28 21 28 21 28 21 28 21 28 28 28 28 28 28 28 28 28 28	568 275 5336 3365 3365 3365 3365 158 158 158 544 - 3756 t <sup>2</sup> = 0.15 27 274 1014 - 66% 1116 334 334 1637 1637 1637 1637 1637 1637 1637 1637	14.4% 48.7% 81.1% 18.9% 100.0% 40.0% 49.9% 10.6% 49.9%	M.H. Random, 95%, GI 1.556 (25, 10, 16) 0.31 [0, 17, 0.55] 0.20 [0,04, 0.99] 0.38 [0,15, 0.52] 0.93 [0,20, 4, 36] 0.93 [0,20, 4, 36] 0.93 [0,20, 4, 36] 0.44 [0.20, 0.98] 0.44 [0.20, 0.98] 0.44 [0.20, 0.98] 2.96 [0.27, 422] 2.96 [0.27, 422] 2.97 [0.12, 37, 54] 1.53 [1.05, 2.23] 2.14 [1.20, 3.79] 0.93 [0,47, 1,83] 8.20 [4,13, 16, 27] 17.27 [3,68, 80.97] 4.70 [0,80, 27,87]	M.H. Random. 95%. Ci
Statuty of subgroup $1 \times Krt 2020$ $1 \times C 2020$ $2 \times 10^{-1} C 2020$ $1 \times C 2020$ 1	EVents 17 21 27; Chil 2 21; Chil 2 2 12; Chil 2 2 2 14; Chil 2 2 2 2 2 2 2 2 2 2 2 2 2 2	25 267 144 24 267 146 21 21 21 21 0.03) 74.9(7 = 3 0.03) 74.9(7 = 3 0.03) 74.9(7 = 3 0.03) 74.9(7 = 3 0.03) 74.9(7 = 3 263 434 265 265 434 265 265 434 265 265 265 265 265 265 265 265 265 265	$E = 0.2015$ $\frac{3}{50}$ $\frac{3}{50}$ $\frac{3}{50}$ $\frac{1}{50}$ $\frac{1}{50}$ $\frac{1}{10}$ $\frac{9}{10}$ $\frac{9}{10}$ $\frac{9}{10}$ $\frac{9}{10}$ $\frac{9}{10}$ $\frac{9}{10}$ $\frac{9}{10}$ $\frac{9}{10}$ $\frac{229}{10}$ $\frac{2294}{20}$ $\frac{2294}{20}$ $\frac{2294}{20}$ $\frac{2294}{20}$ $\frac{2294}{20}$ $\frac{2294}{20}$ $\frac{2294}{20}$ $\frac{294}{20}$ $\frac{294}{20}$ $\frac{294}{20}$ $\frac{100}{20}$ $\frac{294}{20}$ $\frac{100}{20}$ $\frac{100}{20}$ $\frac{100}{20}$ $\frac{100}{20}$ $\frac{100}{20}$	568 275 5396 - 38% 158 158 544 - 37% 19 = 0.1% 014 715 727 1014 - 68% 1116 3397 1397 1397 1397 1397 1397 1397 1397	14.4% 48.7% 18.7% 81.1% 18.9% 100.0% Weight 22.6% 49.9% 19.6% 19.6% 19.6%	M.H. Random, 95%, GI 1.556 (25, 10, 16) 0.31 [0, 17, 0.55] 0.30 [0, 04, 0.99] 0.38 [0, 15, 0.92] 0.38 [0, 20, 4, 36] 0.93 [0, 20, 4, 36] 0.93 [0, 20, 4, 36] 0.44 [0, 20, 0.98] 0.44 [0, 20, 0.98] 0.44 [0, 20, 0.98] 0.44 [0, 20, 0.98] 0.44 [0, 20, 0.98] 0.41 [0, 20, 3, 36] 0.41 [1, 20, 3, 79] 0.35 [0, 47, 1, 183] 0.35 [0, 47, 1, 183] 0.36 [0, 47, 1, 183] 17, 27 [0, 38, 80, 97]	M.H. Random. 95%. Cl
Status of Suboroup Like 200 Li XC 2020 Li XC 2020 Suboral effect: 2 Li XC 2020 Suboral (89% CI) Fotal events Test for overall effect: 2 Li XC 2020 Suboral (89% CI) Fotal events Li XC 2020 Suboral (89% CI) Form for autoroup differe Li XC 2020 Suboral (89% CI) Fotal (99% CI) Fotal (95% CI) Fotal events Li XC 2020 Subotal (95% CI) Fotal events Test for overall effect: 2 Li XC 2020 Subotal (95% CI) Fotal events Test for overall effect: 2 Test for ov	Events 17 21 27; Chil 2 21; Chil 2 2 12; Chil 2 2 12; Chil 2 2 2 2 2 2 2 2 2 2 2 2 2 2	25 267 344 21 21 21 21 0.93) 327 74. 97 = 3 0.03) 327 74. 97 = 3 0.03) 195 326 434 265 434 265 434 265 434 49 49 49 49 49 49 49 49 49 49 49 49 49	$E = 0.2015$ $\frac{3}{50}$ $\frac{3}{50}$ $\frac{3}{50}$ $\frac{1}{50}$ $\frac{1}{50}$ $\frac{1}{10}$ $\frac{9}{10}$ $\frac{9}{10}$ $\frac{9}{10}$ $\frac{9}{10}$ $\frac{9}{10}$ $\frac{9}{10}$ $\frac{9}{10}$ $\frac{9}{10}$ $\frac{229}{10}$ $\frac{2294}{20}$ $\frac{2294}{20}$ $\frac{2294}{20}$ $\frac{2294}{20}$ $\frac{2294}{20}$ $\frac{2294}{20}$ $\frac{2294}{20}$ $\frac{294}{20}$ $\frac{294}{20}$ $\frac{294}{20}$ $\frac{100}{20}$ $\frac{294}{20}$ $\frac{100}{20}$ $\frac{100}{20}$ $\frac{100}{20}$ $\frac{100}{20}$ $\frac{100}{20}$	568 275 5396 - 38% 158 158 544 - 37% 19 = 0.1% 014 715 727 1014 - 68% 1116 3397 1397 1397 1397 1397 1397 1397 1397	14.4% 48.7% 18.7% 81.1% 18.9% 100.0% Weight 22.6% 49.9% 19.6% 19.6% 19.6%	M.H. Random, 95%, GI 1.556 (25, 10, 16) 0.31 [0, 17, 0.55] 0.20 [0,04, 0.99] 0.38 [0,15, 0.52] 0.93 [0,20, 4, 36] 0.93 [0,20, 4, 36] 0.93 [0,20, 4, 36] 0.44 [0.20, 0.98] 0.44 [0.20, 0.98] 0.44 [0.20, 0.98] 2.96 [0.27, 422] 2.96 [0.27, 422] 2.97 [0.12, 37, 54] 1.53 [1.05, 2.23] 2.14 [1.20, 3.79] 0.93 [0,47, 1,83] 8.20 [4,13, 16, 27] 17.27 [3,68, 80.97] 4.70 [0,80, 27,87]	M.H. Random. 95%. Cl
study of suboroup Li KH 2020 Li KH 2020 Li XC 2020 Li XC 2020 Li XC 2020 Li XC 2020 Li XC 2020 Suboral (2000) Total events Heterogeneity: Tau <sup>2</sup> = 0. Test for overall effect: 2 4.4.2 mortality Du RH 2020 Suboral (205% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0. Test for overall effect: 2 Test for overall effect: 2 Suboral (205% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0. Test for overall effect: 2 Case of the suboroup Li XD 2020 Nuany CL 2020 Suboral (205% CI) Total events Test for overall effect: 2 4.5.2 mortality Chen RC 2020 Li X 2020 Suboral (205% CI) Total events Test for overall effect: 2 Test for suboroup diffect <b>E</b> Lymphocyted	EVOID 2 17 2 21 27 21 2 2 2 2 2 2 2 2 2 2 2 2 2	25 267 144 21 21 21 21 21 327 327 327 327 327 327 327 327 327 327	E = 0.0015 $(P = 0.20); P = 0.20); P = 0.20); P = 0.20); P = 0.010); P = 0.010; P = 0.000; P = 0$	564 275 5386 - 38% 158 158 544 - 37% 7 = 0.1% 1014 7 37 7 274 1014 - 68% 1116 334 1014 - 334 1014 - 334 1014 - 334 1047 1047 - 344 -	14.4% 48.7% 18.7% 81.1% 18.0% 18.0% 100.0% 48% 48% 49.9% 19.6% 19.6% 19.6% 19.6% 6	M.H. Random, 95% CI 1.556 (25, 10, 16) 0.31 [0, 17, 0.55] 0.30 [0, 40, 0.99] 0.38 [0, 15, 0.92] 0.38 [0, 15, 0.92] 0.41 [0, 20, 4, 36] 0.44 [0, 20, 4, 36] 0.44 [0, 20, 0, 98] 0.44 [0, 20, 0, 98] 0.44 [0, 20, 0, 98] 2.96 [2.07, 4, 22] 2.17 [0, 12, 37, 64] 1.17 [0, 12, 37, 64] 1.29 [2.07, 4, 22] 2.14 [1, 26, 37, 9] 0.03 [0, 47, 1, 83] 8.20 [0, 47, 1, 83] 8.20 [0, 46, 27, 87] 2.97 [1, 48, 8, 98] 0.044 Ratio	M.H. Random. 95% Cl M.H. Random. 95% Cl 0.01 0.1 10 10 Favours [experimental] Favours [control] Odds Ratio 0.01 0.1
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Likely 2015 Subgroup Likely 2020 Likely 2020 Likely 2020 Likely 2020 Likely 2020 Total events Heterogeneity: Tau <sup>2</sup> = 0. Test for overall effect: 2 4.4.2 mortality Du RH 2020 Contail events Heterogeneity: Kot appli Test for overall effect: 2 Total events Heterogeneity: Kot appli Total events Heterogeneity: Kot appli Like 2020 Like 2020 Like 2020 Like 2020 Like 2020 Chour # 2020	Events 17 21 27; Chil = 2 21; Chil = 2 22; Chil = 2 23; Chil = 2 24 24 25; Chil = 2 25; Chil = 2 26; Chil = 2 20; Ch	25 267 366 21 21 21 21 21 21 21 21 21 21 21 21 21	$E = 0.2015 \\ 3 \\ 50 \\ 50 \\ 24 \\ (P = 0.20); P = 0.20); P = 0.20; P = 0.20; P = 0.10; P = 0.10; P = 0.10; P = 0.10; P = 0.20; P = 0.20;$	500 500 275 5300 544 544 544 544 544 544 544 5	14.4% 48.7% 18.7% 18.1% 18.9% 100.0% 100.0% 22.6% 49.9% 10.6% 100.0% 6 100.0% 6 100.0%	M.H. Random, 95% CI 1.55(2,5,10,16) 0.31(0,17,0.55) 0.30(0,40,0.99) 0.38(0,15,0.92] 0.38(0,15,0.92] 0.41(0,20,4,36) 0.93(0,20,4,36) 0.44(0,20,0.98] 0.44(0,20,0.98] 0.44(0,20,0.98] 0.44(0,20,0.98] 0.41(0,20,0.98] 0.41(0,20,0.98] 0.41(0,20,0.98] 0.41(0,20,0.98] 0.41(0,20,0.98] 0.41(0,20,0.98] 0.41(0,20,0.98] 0.41(0,20,0.98] 0.41(0,20,0.98] 0.41(0,20,0.98] 0.41(0,20,0.98] 0.41(0,20,0.98] 0.41(0,20,0.98] 0.41(0,20,0.98) 0.	M.H. Random. 95% Cl M.H. Random. 95% Cl 0.01 0.1 10 10 Favours [experimental] Favours [control] 0 dds Ratio 0 dds Ratio
skudy of subbroup Li KH 2020 Li KH 2020 Li KH 2020 Second Second Second Second Li XC 2020 Li XC 2020 Li XC 2020 Li XC 2020 Second Second Second Second Total events Heterogeneity: Tau" = 0. Test for overall effect: 2 A4.2: mortality Du RH 2020 Subtotal (95% CI) Total events Heterogeneity: Tau" = 0. Test for overall effect: 2 EPIAtelet decrea Subtotal (95% CI) Total events Heterogeneity: Tau" = 0. Test for overall effect: 2 Constant overall effect: 2 Subtotal (95% CI) Total events Heterogeneity: Tau" = 0. Test for overall effect: 2 Subtotal (95% CI) Total events Subtotal (95% CI) Total events Li XC 2020 Li XC 2020 Li XC 2020 Li XC 2020 Const for overall effect: 2 Test for overall effect: 2 Test for overall effect: 2 Test for subtoroup Total events Total events Total events Test for subtoroup Subtoroup 42020 Const for overall effect: 2 Test for subtoroup A5.1 sevently ELVMP Decyty 2020 Subtoroup 42020 Subtoroup 42	Events 2 17 2 21 27 21 2 2 2 2 2 2 2 2 2 2 2 2 2	25 267 144 24 267 146 21 21 21 21 327 74 df = 3 20 327 74 df = 3 20 327 100 df = 3 20 100 df = 3 20 100 df = 3 20 20 326 434 49 49 49 49 49 49 49 49 49 49 49 49 49	$E = 0.0005$ $\frac{3}{50}$ $\frac{3}{50}$ $\frac{3}{50}$ $\frac{3}{50}$ $\frac{3}{50}$ $\frac{1}{50}$ $\frac{1}{50}$ $\frac{1}{10}$ $\frac{1}{10$	10001           56           275           538%           158           158           158           158           158           158           158           158           158           158           158           158           158           158           158           158           158           158           158           159           1614           2635           1116           334 <td>14.7% 48.7% 18.0% 18.0% 18.0% 18.0% 100.0% 4.8% 22.6% 49.9% 19.6% 10.0% 6 100.0% 6 <b>Weight</b></td> <td>M.H. Random, 95% CI 1.556 (25, 10, 16) 0.31 [0, 17, 0.55] 0.30 [0, 20, 0, 4, 36] 0.33 [0, 20, 4, 36] 0.33 [0, 20, 4, 36] 0.33 [0, 20, 4, 36] 0.44 [0, 20, 0, 98] 0.44 [0, 20, 0, 98] 1.57 [0, 20, 20, 4, 36] 2.96 [2, 07, 4, 22] 2.17 [0, 12, 37, 64] 1.57 [0, 12, 37, 64] 1.57 [0, 12, 37, 64] 1.57 [0, 12, 37, 64] 1.57 [0, 16, 37, 76] 0.03 [0, 47, 1, 63] 8.20 [4, 13, 16, 27] 1.72 [3, 68, 60, 77] 2.97 [1, 48, 5, 98] 0.40 [2, 59, 6, 31] 6.99 [26, 98, 137 [3] 4.94 [2, 59, 6, 31] 6.99 [26, 98, 137 [3] 4.94 [2, 59, 6, 31] 5.99 [26, 98, 137 [3] 4.94 [25, 59, 137</td> <td>M.H. Random. 95% Cl M.H. Random. 95% Cl 0.01 0.1 10 10 Favours [experimental] Favours [control] 0 dds Ratio 0 dds Ratio</td>	14.7% 48.7% 18.0% 18.0% 18.0% 18.0% 100.0% 4.8% 22.6% 49.9% 19.6% 10.0% 6 100.0% 6 <b>Weight</b>	M.H. Random, 95% CI 1.556 (25, 10, 16) 0.31 [0, 17, 0.55] 0.30 [0, 20, 0, 4, 36] 0.33 [0, 20, 4, 36] 0.33 [0, 20, 4, 36] 0.33 [0, 20, 4, 36] 0.44 [0, 20, 0, 98] 0.44 [0, 20, 0, 98] 1.57 [0, 20, 20, 4, 36] 2.96 [2, 07, 4, 22] 2.17 [0, 12, 37, 64] 1.57 [0, 12, 37, 64] 1.57 [0, 12, 37, 64] 1.57 [0, 12, 37, 64] 1.57 [0, 16, 37, 76] 0.03 [0, 47, 1, 63] 8.20 [4, 13, 16, 27] 1.72 [3, 68, 60, 77] 2.97 [1, 48, 5, 98] 0.40 [2, 59, 6, 31] 6.99 [26, 98, 137 [3] 4.94 [2, 59, 6, 31] 6.99 [26, 98, 137 [3] 4.94 [2, 59, 6, 31] 5.99 [26, 98, 137 [3] 4.94 [25, 59, 137	M.H. Random. 95% Cl M.H. Random. 95% Cl 0.01 0.1 10 10 Favours [experimental] Favours [control] 0 dds Ratio 0 dds Ratio
statuty of subgroup Like 200 Like 200 Like 200 Like 200 Like 200 Second Second Second Second Second Second Feature General effect: 2 4.2 montained (85% CI) Fortal events -teterogeneity: Tau" = 0. Feat for overall effect: 2 Second Second Second Second Second Second Second Feature Second Se	Events 2 17 2 21 21 21 21 21 21 21 21 21	25 267 14 267 14 207 14 21 21 21 21 21 21 21 21 21 21 21 21 21	Events 3 50 24 (P = 0.20); P = 16 16 16 16 16 16 16 16 16 16	544 - 37% - 34 - 37% -	14.4% 48.7% 48.7% 48.7% 18.9% 18.9% 100.0% 49.9% 49.9% 49.9% 49.9% 49.9% 6 10.6% 10.0% 6 10.0% 6 10.0%	M.H. Random, 95%, Cl 1,556 (25, 10, 16) 0,31 [0, 17, 0, 55] 0,20 [0,04, 0,99] 0,38 [0,15, 0,22] 0,93 [0,20, 4, 36] 0,93 [0,20, 4, 36] 1,63 [1,16, 2,23] 2,17 [0,12, 37, 44] 1,63 [1,05, 2,23] 2,14 [1,26, 3,79] 0,93 [0,47, 1,83] 8,20 [4,13, 16, 27] 1,59 [1,36, 30,97] 4,79 [0,80, 27,57] 2,97 [1,46, 5,98] 0,04ds Ratio M-H. Random, 95%, Cl 4,04 [2,59, 6,31] 5,96 [2,56, 13,76] 4,04 [2,59, 6,31] 5,96 [2,57] 4,77 [0,80, 25,57] 1,20 [3,1, 44, 8]	M.H. Random. 95% Cl M.H. Random. 95% Cl 0.01 0.1 10 10 Favours [experimental] Favours [control] 0 dds Ratio 0 dds Ratio
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skidy, of subproup () KH 2020 () KH 2020 () KH 2020 () XC 2020	Events 17 21 27; Chil 2 27; Chil 2 2 27; Chil 2 2 2 2 2 2 2 2 2 2 2 2 2 2	25 267 366 267 366 21 21 21 21 21 21 21 21 21 21 21 21 21	E = 0.0015 $3 = 50$ $50$ $24$ $(P = 0.20); P = 0.20); P = 0.20; P = 0.20;$	10001           56           275           5300           5300           158           158           158           158           158           158           158           158           158           158           158           158           158           158           158           158           158           158           151           168           1713           274           132           132           132           132           133           133           134           135           136           131           132           1332           134           135           135           136           136           136           136           136           136           136           136           136 <td>14.4% 48.7% 81.1% 18.0% 18.0% 100.0% 100.0% 100.0% 10.6% 19.6% 19.6% 10.0% 6 Weight 19.6% 100.0% 6</td> <td>M.H. Random, 95%, GI 1.556 (25, 10, 16) 0.31 [0, 17, 0.55] 0.30 [0, 20, 0, 4, 36] 0.33 [0, 20, 4, 36] 0.93 [0, 20, 4, 36] 1.53 [1, 20, 2, 23] 2.17 [0, 12, 37, 64] 1.53 [1, 26, 2, 23] 2.17 [1, 26, 2, 23] 2.17 [1, 26, 30, 26] 1.53 [1, 26, 30, 27] 2.97 [1, 46, 5, 96] 1.97 [1, 46, 5, 96] 4.04 [2, 59, 6, 31] 5.96 [2, 41, 4, 40] 1.50 [3, 21, 44, 82] 3.72 [1, 91, 7, 26] 3.72 [1, 91, 7, 26] 3.7</td> <td>M.H. Random. 95% Cl M.H. Random. 95% Cl 0.01 0.1 10 10 Favours [experimental] Favours [control] 0 dds Ratio 0 dds Ratio</td>	14.4% 48.7% 81.1% 18.0% 18.0% 100.0% 100.0% 100.0% 10.6% 19.6% 19.6% 10.0% 6 Weight 19.6% 100.0% 6	M.H. Random, 95%, GI 1.556 (25, 10, 16) 0.31 [0, 17, 0.55] 0.30 [0, 20, 0, 4, 36] 0.33 [0, 20, 4, 36] 0.93 [0, 20, 4, 36] 1.53 [1, 20, 2, 23] 2.17 [0, 12, 37, 64] 1.53 [1, 26, 2, 23] 2.17 [1, 26, 2, 23] 2.17 [1, 26, 30, 26] 1.53 [1, 26, 30, 27] 2.97 [1, 46, 5, 96] 1.97 [1, 46, 5, 96] 4.04 [2, 59, 6, 31] 5.96 [2, 41, 4, 40] 1.50 [3, 21, 44, 82] 3.72 [1, 91, 7, 26] 3.72 [1, 91, 7, 26] 3.7	M.H. Random. 95% Cl M.H. Random. 95% Cl 0.01 0.1 10 10 Favours [experimental] Favours [control] 0 dds Ratio 0 dds Ratio
status voi suboroup Liki voi suboroup Liki voi suboroup Liki voi suboroup Liki voi voi voi voi voi voi voi voi voi voi voi voi voi voi voi voi voi	Events 2 17 2 21 21 21 21 21 21 21 21 21	25 267 144 267 144 207 21 21 21 21 21 21 21 21 21 21 21 21 21	Events 3 50 24 (P = 0.20); P = 16 16 16 16 16 16 16 16 16 16	10001           56           275           5386           1388           158           158           158           158           158           158           198           199           544           - 37%           1014           713           274           1014           68%           1116           324           1014           1057           2601           ): IP = 85%           2601           ): IP = 85%           2601           ): Z601           Total           326           726           726           726           726           726           726           726           726           726           726           726           726           726           726           726           726           726           726	14.4% 48.7% 18.1% 18.1% 18.9% 100.0% 100.0% 100.0% 10.6% 11.6% 19.6% 11.6% 19.6% 11.5% 50.7% 6 100.0% 6 100.0% 6	M.H. Random, 95%, GI 1.556 (25, 10, 16) 0.31 [0, 17, 0.55] 0.30 [0, 20, 0, 4, 36] 0.33 [0, 20, 4, 36] 0.93 [0, 20, 4, 36] 2.96 [2.07, 4, 22] 2.17 [0, 12, 37, 64] 1.29 [2, 0, 4, 22] 2.14 [1, 20, 3, 76] 2.91 [2, 0, 4, 30] 2.91 [2, 0, 4, 30] 2.95 [2, 0, 4, 30] 1.727 [3, 68, 60, 97] 4.70 [0, 56, 27, 57] 2.97 [1, 48, 5, 98] 0.91 [4, 25, 6, 61] 5.96 [2, 56, 13, 76] 4.97 [2, 56, 61, 37] 5.96 [2, 56, 13, 76] 4.77 [0, 50, 25, 57] 7.50 [3, 40, 16, 53] 12.00 [3, 21, 44, 82]	M.H. Random. 95% Cl M.H. Random. 95% Cl 0.01 0.1 10 10 Favours [experimental] Favours [control] Odds Ratio 0.01 0.1
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skidy, of subgroup Li KH 2020 Li KH 2020 Li XC 2020 Li XC 2020 Li XC 2020 Subgroup Status Total events Heterogeneity: Tau" = 0. Test for overall effect: Z 4.4.2: mortality Du RH 2020 Subtotal (95% CI) Total events Heterogeneity: Tau" = 0. Test for overall effect: Z Test for overall effect: Z taudy or Subgroup CL 2020 Chan W 2020 Chan For overall effect: Z Test for overall effect: Z tau S Test for overall effect: Z Test for overall	Events  2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	10101           25           267           146           21           21           21           21           2003)           327           74. df = 3           0.031           1000           326           25. df = 2           0.030)           38           49           49           49           124           0.030)           38           69           124           408           255           266           375           268           124           1254           1254           1263           163           163           163           163           163           163           164 <td><math display="block">E = 0.0015</math> <math display="block">\frac{3}{50}</math> <math display="block">\frac{3}{50}</math> <math display="block">\frac{3}{50}</math> <math display="block">\frac{3}{50}</math> <math display="block">\frac{3}{50}</math> <math display="block">\frac{3}{50}</math> <math display="block">\frac{1}{50}</math> <math display="block">\frac{1}{50}</math> <math display="block">\frac{1}{10}</math> <math display="block">\frac{1}{10} = 0.321</math> <math display="block">\frac{1}{10} = 0.321</math> <math display="block">\frac{1}{10} = 0.321</math> <math display="block">\frac{225}{10}</math> <math display="block">\frac{224}{101}</math> <math display="block">\frac{224}{20}</math> <math display="block">\frac{401}{28}</math> <math display="block">\frac{224}{21}</math> <math display="block">\frac{1}{10}</math> <math display="block">\frac{1}{17}</math> <math display="block">\frac{1}{77}</math> <math display="block">(P = 0.56); P = 0.49</math></td> <td>10131           56           275           5336           336           158           158           158           158           158           158           158           158           158           158           158           158           158           158           158           159           161           1334           334</td> <td>14.4% 4.8.7% 18.0% 18.0% 18.0% 100.0% Weight 19.6% 19.6% 19.6% 6 100.0% 6 Weight 19.6% 19.6% 6 0.3% 6 0.3%</td> <td>M.H. Random, 95% CI 1.556 (25, 10, 16) 0.31 [0, 17, 0.55] 0.30 [0, 20, 0, 4, 36] 0.33 [0, 20, 4, 36] 0.93 [0, 20, 4, 36] 2.96 [2.07, 4, 22] 2.17 [0, 12, 37, 64] 1.29 [2.07, 4, 22] 2.14 [1, 26, 37, 76] 1.29 [2.07, 4, 22] 2.97 [1, 46, 8, 98] 0.05 [0, 47, 1, 63] 1.29 [2.06, 13, 76] 4.70 [0, 50, 27, 57] 2.97 [1, 46, 8, 98] 0.05 [2.06, 13, 76] 4.70 [0, 90, 25, 57] 7.50 [3, 40, 16, 53] 1200 [3, 21, 44, 82] 0.23 [4, 43, 10, 00] 7.76 [1, 31, 56] 1.40 [2, 60, 6.7] 4.49 [3, 61, 5, 60] 8.94 [1, 22, 65, 36]</td> <td>M.H. Random. 95% Cl M.H. Random. 95% Cl 0.01 0.1 10 10 Favours [experimental] Favours [control] 0 dds Ratio 0 dds Ratio</td>	$E = 0.0015$ $\frac{3}{50}$ $\frac{3}{50}$ $\frac{3}{50}$ $\frac{3}{50}$ $\frac{3}{50}$ $\frac{3}{50}$ $\frac{1}{50}$ $\frac{1}{50}$ $\frac{1}{10}$ $\frac{1}{10} = 0.321$ $\frac{1}{10} = 0.321$ $\frac{1}{10} = 0.321$ $\frac{225}{10}$ $\frac{224}{101}$ $\frac{224}{20}$ $\frac{401}{28}$ $\frac{224}{21}$ $\frac{1}{10}$ $\frac{1}{17}$ $\frac{1}{77}$ $(P = 0.56); P = 0.49$	10131           56           275           5336           336           158           158           158           158           158           158           158           158           158           158           158           158           158           158           158           159           161           1334           334	14.4% 4.8.7% 18.0% 18.0% 18.0% 100.0% Weight 19.6% 19.6% 19.6% 6 100.0% 6 Weight 19.6% 19.6% 6 0.3% 6 0.3%	M.H. Random, 95% CI 1.556 (25, 10, 16) 0.31 [0, 17, 0.55] 0.30 [0, 20, 0, 4, 36] 0.33 [0, 20, 4, 36] 0.93 [0, 20, 4, 36] 2.96 [2.07, 4, 22] 2.17 [0, 12, 37, 64] 1.29 [2.07, 4, 22] 2.14 [1, 26, 37, 76] 1.29 [2.07, 4, 22] 2.97 [1, 46, 8, 98] 0.05 [0, 47, 1, 63] 1.29 [2.06, 13, 76] 4.70 [0, 50, 27, 57] 2.97 [1, 46, 8, 98] 0.05 [2.06, 13, 76] 4.70 [0, 90, 25, 57] 7.50 [3, 40, 16, 53] 1200 [3, 21, 44, 82] 0.23 [4, 43, 10, 00] 7.76 [1, 31, 56] 1.40 [2, 60, 6.7] 4.49 [3, 61, 5, 60] 8.94 [1, 22, 65, 36]	M.H. Random. 95% Cl M.H. Random. 95% Cl 0.01 0.1 10 10 Favours [experimental] Favours [control] 0 dds Ratio 0 dds Ratio
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status of suboroup $J_{k+1} = 2020$ $J_{k+1} = 2020$ $J_{k+2} $	Events 17 21 21 21 21 21 22 21 21 21 2 2 2 2 2 2 2 2 2 2 2 2 2	25 267 344 27 344 21 21 21 21 327 74 9(= 3 0.03) 327 74 9(= 3 0.03) 328 49 49 49 49 49 49 49 49 49 49 49 49 49	E vonts 3 3 50 24 (P = 0.20); P = 16 16 16 16 16 17 1 (P = 0.32); I P = 0.401; I P = 0.411; I	10001           56           275           5396           138           158           168	14.4% 18.7% 18.0% 18.0% 18.8% 100.0% 100.0% 22.6% 22.6% 49.0% 10.6% 100.0% 6 100.0% 6 100.0% 6 100.0% 6 100.0% 6 100.0% 6 100.0% 6 100.0% 6 100.0%	M.H. Random, 95%, GI 1.556 (0.25, 10, 16) 0.31 (0.17, 0.55) 0.20 (0.40, 0.99) 0.38 (0.15, 0.92) 0.38 (0.15, 0.92) 0.38 (0.15, 0.92) 0.41 (0.20, 4.38) 0.44 (0.20, 0.98) 0.44 (0.20, 0.98) 0.44 (0.20, 0.98) 0.44 (0.20, 0.98) 1.53 (1.05, 2.23) 2.14 (1.20, 3.79] 0.95 (0.47, 1.83) 8.20 (4.13, 16, 277) 1.53 (1.05, 2.23) 2.14 (1.20, 3.79] 0.95 (0.47, 1.83) 8.20 (4.13, 16, 277) 1.57 (0.80, 27, 57] 2.97 (1.48, 5.98] 0.44 (0.20, 6.31] 5.96 (2.58, 13, 75) 1.70 (0.92, 25, 63, 75) 1.40 (2.59, 6.31) 5.96 (2.58, 13, 75) 1.71 (0.20, 255, 61) 1.40 (2.59, 6.31) 5.96 (2.58, 13, 75) 1.71 (0.20, 255, 61) 1.40 (2.59, 6.31) 1.40 (2.59, 6.51) 1.40 (2.59, 6.51)	M.H. Random. 95% Cl M.H. Random. 95% Cl 0.01 0.1 10 10 Favours [experimental] Favours [control] Odds Ratio 0.01 0.1
the sty out study out of the style	Eventa 2 17 2 21 27 21 2 2 2 2 2 2 2 2 2 2 2 2 2	255 2677 366 2217 366 2217 327 74, df = 2 20,03) 21 21 21 21 21 21 21 21 21 21 21 21 21	Exercise Exercise $3 \\ 50 \\ 50 \\ 24 \\ 77 \\ (P = 0.20); P =$	10181 566 275 53368 544 • 3796 158 544 • 3796 1014 713 277 1014 1014 137 1014 137 1014 137 1014 137 1014 136 136 136 1016 136 136 105 105 105 105 105 105 105 105	14.4% 18.1% 18.1% 18.9% 100.0% 100.0% 100.0% 10.6% 10.	M.H. Random, 95%, GI 1.556 (0.55, 10.16) 0.31 (0.17, 0.55) 0.30 (0.40, 0.99) 0.38 (0.15, 0.42) 0.93 (0.20, 4.36) 0.93 (0.20, 4.36) 2.06 (2.07, 4.22) 2.17 (0.12, 37, 64) 2.14 (1.20, 3.76) 2.14 (1.20, 3.76) 2.14 (1.20, 3.76) 2.97 (1.48, 5.98] 0.053 (0.47, 1.83) 8.20 (4.13, 16.27) 17.27 (2.88, 80.97) 4.70 (0.66, 27, 67) 2.97 (1.48, 5.98] 0.91 (2.56, 5.175) 4.77 (0.98, 25, 57) 7.50 (3.40, 16.53) 1.37 (21, 91, 7.26) 1.37 (21, 91, 7.26) 1.37 (21, 91, 7.26) 1.37 (1.91, 3.151) 4.05 (3.60, 6.60) 8.94 (1.22, 65, 36) 3.97 (0.66, 36) 3.97 (0.67, 30, 3	M.H. Random. 95% Cl M.H. Random. 95% Cl 0.01 0.1 10 10 Favours [experimental] Favours [control] Odds Ratio 0.01 0.1
status voi suboroup i kri 200 i	Events 2 17 2 21 27 21 2 2 2 2 2 2 2 2 2 2 2 2 2	25 267 144 267 144 21 21 21 21 21 21 21 21 21 21	Exercise Exercise $3 \\ 50 \\ 50 \\ 24 \\ 77 \\ (P = 0.20); P =$	10181 566 275 53368 544 • 3796 158 544 • 3796 1014 713 277 1014 1014 137 1014 137 1014 137 1014 137 1014 136 136 136 1016 136 136 105 105 105 105 105 105 105 105	14.4% 18.1% 18.1% 18.9% 100.0% 100.0% 100.0% 10.6% 10.	M.H. Random, 95%, GI 1.556 (0.25, 10, 16) 0.31 (0.17, 0.55) 0.20 (0.40, 0.99) 0.38 (0.15, 0.92) 0.38 (0.15, 0.92) 0.38 (0.15, 0.92) 0.41 (0.20, 4.38) 0.44 (0.20, 0.98) 0.44 (0.20, 0.98) 0.44 (0.20, 0.98) 0.44 (0.20, 0.98) 1.53 (1.05, 2.23) 2.14 (1.20, 3.79] 0.95 (0.47, 1.83) 8.20 (4.13, 16, 277) 1.53 (1.05, 2.23) 2.14 (1.20, 3.79] 0.95 (0.47, 1.83) 8.20 (4.13, 16, 277) 1.57 (0.80, 27, 57] 2.97 (1.48, 5.98] 0.44 (0.20, 6.31] 5.96 (2.58, 13, 75) 1.70 (0.92, 25, 63, 75) 1.40 (2.59, 6.31) 5.96 (2.58, 13, 75) 1.71 (0.20, 255, 61) 1.40 (2.59, 6.31) 5.96 (2.58, 13, 75) 1.71 (0.20, 255, 61) 1.40 (2.59, 6.31) 1.40 (2.59, 6.51) 1.40 (2.59, 6.51)	M.H. Random. 95% Cl M.H. Random. 95% Cl 0.01 0.1 10 10 Favours [experimental] Favours [control] Odds Ratio 0.01 0.1
stat sty out student output i kit j 2020 i kit j 2020 kit j	Events 17 21 21 21 21 22 21 22 21 22 21 22 21 22 23 23 23 23 23 23 23 23 23	25 267 144 267 144 21 21 21 21 21 21 21 21 21 21	Exents 3 50 24 (P = 0.20); P = 16 16 16 16 16 16 16 225 Exents 225 225 (P = 0.32); P = 225 Exents 225 225 225 225 225 225 225 22	544 - 37% - 38% - 38% - 38% - 38% - 544 - 37% - 544 - 37% - 713 - 723 - 723 - 713 - 723 - 723 - 713 - 723 - 723 - 724 - 324 - 324 - 324 - 324 - 324 - 324 - 324 - 324 - 324 - 325 - 260 - 276 - 60% - 1161 - 158 - 66% - 66% - 726 - 66% - 726 - 727 - 726 -	14.4% 18.1% 18.1% 18.9% 100.0% 100.0% 100.0% 10.6% 10.	M.H. Random, 95%, GI 1.556 (0.25, 10, 16) 0.31 (0.17, 0.55) 0.20 (0.40, 0.99) 0.38 (0.15, 0.92) 0.38 (0.15, 0.92) 0.38 (0.15, 0.92) 0.41 (0.20, 4.38) 0.44 (0.20, 0.98) 0.44 (0.20, 0.98) 0.44 (0.20, 0.98) 0.44 (0.20, 0.98) 1.53 (1.05, 2.23) 2.14 (1.20, 3.79] 0.95 (0.47, 1.83) 8.20 (4.13, 16, 277) 1.53 (1.05, 2.23) 2.14 (1.20, 3.79] 0.95 (0.47, 1.83) 8.20 (4.13, 16, 277) 1.57 (0.80, 27, 57] 2.97 (1.48, 5.98] 0.44 (0.20, 6.31] 5.96 (2.58, 13, 75) 1.70 (0.92, 25, 63, 75) 1.40 (2.59, 6.31) 5.96 (2.58, 13, 75) 1.71 (0.20, 255, 61) 1.40 (2.59, 6.31) 5.96 (2.58, 13, 75) 1.71 (0.20, 255, 61) 1.40 (2.59, 6.31) 1.40 (2.59, 6.51) 1.40 (2.59, 6.51)	M.H. Random. 95% Cl M.H. Random. 95% Cl 0.01 0.1 10 10 Favours [experimental] Favours [control] 0 dds Ratio 0 dds Ratio
stat 47 2020 stat 47 2020 1 × K-1 2020 1 × K-2 2020 1 × C 202	Events 2 17 2 21 27 21 2 2 2 2 2 2 2 2 2 2 2 2 2	10131           25           267           144           21           21           21           21           2003)           327           74, df = 3           0.050           1000           327           74, df = 3           0.050           1000           327           74, df = 3           0.050           1000           326           250           0.000)           38           49           124           0.000)           38           49           1004           0.0000)           36           296           124           163           1054           1054           400           256           9           14           141           21           25           244           341, df =           20.00001           1438           354	Exents 3 3 50 24 (P = 0.20); P = 16 16 16 16 16 225 226 1 (P = 0.32); P = 225 226 1 (P = 0.32); P = 225 226 1 (P = 0.32); P = 401 28 22 2 (P < 0.00001 3 (P < 0.00001 177 (P = 0.56); P = 1147 152 36 5 (P < 0.00001 152 5 (P < 0.00001 152 152 152 152 152 152 152 15	10001           56           275           3360           156           158           158           158           158           158           158           158           158           1574           157           1614           1164           1163           137           137           137           137           137           137           137           137           137           137           137           137           137           1387           158           276           2801           128           1328           1320           200           13320           201           202           120           1312           12161           1220           13322           1312           1217	14.4% 18.7% 18.9% 100.0% Weight 22.8% 40.9% 10.6% 110.6% 111.7% 5 Weight 9.3% 7.7% 5.8% 5.8% 5.8% 5.8% 5.8% 6 100.0%	M.H. Random, 95%, GI 1,556 (25, 10, 16) 0,31 (0, 17, 0, 55) 0,20 (0, 64, 0, 99) 0,38 (0, 15, 0, 92] 0,38 (0, 15, 0, 92] 0,93 (0, 20, 4, 36) 0,93 (0, 20, 4, 36) 1,53 (1, 20, 2, 23) 2,17 (0, 12, 37, 64) 1,53 (1, 26, 27, 36) 1,53 (1, 26, 27, 36) 1,53 (1, 26, 37, 36) 1,72 (1, 36, 80, 97) 4,70 (0, 80, 27, 57) 4,70 (0, 80, 27, 57) 4,70 (0, 80, 27, 57) 4,70 (0, 80, 27, 57) 4,70 (0, 80, 27, 57) 4,04 (2, 59, 6, 31) 5,90 (1, 46, 5, 38) 12,20 (3, 21, 44, 82) 3,72 (1, 91, 7, 26) 1,14 (0, 56, 14) 1,50 (1, 22, 65, 36) 3,67 (0, 82, 10, 5, 67) 4,49 (3, 61, 5, 80) 1,74 (10, 76, 4, 01) 8,06 (1, 63, 15, 71) 8,06 (1, 63, 15, 71)	M.H. Random. 95% Cl M.H. Random. 95% Cl 0.01 0.1 10 10 Favours (experimental) Favours (control) 10 Odds Ratio 0.01 0.1 10 10 Favours (experimental) Favours (control) 10 0 dds Ratio 0 dds Ratio

		Deceas		Non-sev				Odds Ratio	Odds Ratio
tudy or Subgroup	Event	S	Total	Even	ts	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
.7.1 severity	1.000								
eng Y 2020	97		108	16		307	10.5%	7.20 [3.71, 13.97]	
iuan W 2020	110		135	37		658	27.3%	3.40 [2.15, 5.40]	
I KH 2020	23		25		7	58	1.5%	13.20 [2.85, 61.24]	
i XC 2020	255		268	20		272	11.5%	6.41 [3.44, 11.94]	
i Y 2020	1		9		9	16	1.7%	2.72 [0.43, 17.42]	
hang J 2020	324	4	409	Ş	14	254	28.1%	6.49 [4.58, 9.20]	
ubtotal (95% CI)			954			1565	80.6%	5.57 [4.41, 7.04]	· · · · · · · · · · · · · · · · · · ·
otal events	816			87	5				
leterogeneity: Chi <sup>2</sup> =	7.68, df = 5	5 (P = 0	0.17); P	2 = 35%					
est for overall effect;	Z = 14.37	(P < 0.0	00001)						
.7.2 mortality									
hen RC 2020	33		33	65		1039		39.30 [2.40, 643.22]	
u RH 2020	20		21	13		158	1.8%	2.90 [0.37, 22.80]	
i Y 2020		3	5		3	20	2.4%	0.81 [0.11, 6.04]	
hang J 2020	14	4	25	37	4	638	14.5%	0.90 [0.40, 2.01]	
ubtotal (95% CI)	122	2.7	84			1855	19.4%	2.48 [1.37, 4.50]	
otal events	70			118	0				
leterogeneity: Chi <sup>2</sup> =				12 = 73%					
est for overall effect:	Z = 2.99 (F	P = 0.00	03)						
otal (95% CI)			1038			3420	100.0%	4.97 [4.00, 6.19]	
otal events	886		00070423	205					
leterogeneity: Chi <sup>2</sup> =					%			č	0.01 0.1 1 10 1
est for overall effect:									Favours [experimental] Favours [control]
est for subaroup diffe		$hi^2 = 6.1$	15. df =	= 1 (P = 0)	.01). 12	= 83.7%			
Belevated PC	T.		-		500 <u>00</u> 000	200.2			
	Severe/D			Non-seve			A/-/-*	Odds Ratio	Odds Ratio
tudy or Subgroup 8.1 severity	Events	в Т	otal	Event	5	rotal	weight	M-H. Random, 95% Cl	M-H. Random. 95% Cl
a.1 seventy uan W 2020	16	1	117	1	9	516	17.0%	4.14 [2.06, 8.33]	
uang CL 2020	3		12		9	27	3.7%	20.26 [0.96, 429.41]	
KH 2020	21		25	2		58	12.4%	7.99 [2.43, 26.30]	
XC 2020	43		237		3	249	12.4%	18.18 [5.55, 59.47]	
/ang DW 2020	27	,	36	2	2	102	15.2%	10.91 [4.48, 26.56]	
/ang ZL 2020	0		12		4	50	3.9%	0.41 [0.02, 8.20]	
ubtotal (95% CI)	1.1.2.4		439	12		1002	64.6%	7.53 [3.66, 15.47]	-
otal events eterogeneity: Tau <sup>2</sup> =	110			7					
est for overall effect:				(1 - 0.00					
8.2 mortality									
hen RC 2020	14		34	3		838	16.4%	16.55 [7.71, 35.55]	
u RH 2020	4		21	1		158	12.3%	2.09 [0.63, 6.97]	
hou F 2020 ubtotal (95% CI)	13	1	51 106		1	113	6.7%	38.32 [4.85, 302.73]	
						1100	26 49%	0 0 2 14 00 40 221	
	31	ŕ	106	5	1	1109	35.4%	9.92 [1.99, 49.32]	
leterogeneity: Tau <sup>2</sup> =		= 9.79,	df = 2	5 (P = 0.00			35.4%	9.92 [1.99, 49.32]	
otal events leterogeneity: Tau <sup>2</sup> = 'est for overall effect:	1.54; Chi <sup>2</sup>	= 9.79, P = 0.00	df = 2 )5)			30%			
leterogeneity: Tau <sup>2</sup> = 'est for overall effect: 'otal (95% CI)	1.54; Chi <sup>2</sup> Z = 2.80 (F	= 9.79, P = 0.00	df = 2	(P = 0.00	7); I <sup>2</sup> = 1	30%	35.4%	9.92 [1.99, 49.32] 8.14 [4.25, 15.57]	•
feterogeneity: Tau <sup>2</sup> = 'est for overall effect: 'otal (95% CI) 'otal events	1.54; Chi <sup>2</sup> Z = 2.80 (F 141	= 9.79, P = 0.00	df = 2 )5) 545	(P = 0.00	7); I <sup>2</sup> = 1	30% 2111			•
leterogeneity: Tau <sup>2</sup> = 'est for overall effect: 'otal (95% CI) 'otal events leterogeneity: Tau <sup>2</sup> =	1.54; Chi <sup>2</sup> Z = 2.80 (F 141 0.52; Chi <sup>2</sup>	= 9.79, P = 0.00 = 20.34	df = 2 )5) 545 1, df = {	(P = 0.00	7); I <sup>2</sup> = 1	30% 2111			
leterogeneity: Tau <sup>2</sup> = 'est for overall effect: 'otal (95% CI) 'otal events	1.54; Chi <sup>2</sup> Z = 2.80 (F 141 0.52; Chi <sup>2</sup> Z = 6.33 (F	= 9.79, P = 0.00 = 20.34 P < 0.00	df = 2 )5) 545 4, df = { )001)	(P = 0.00 12 8 (P = 0.0	7); I <sup>2</sup> = 4 2 09); I <sup>2</sup> =	30% 2111 61%			0.002 0.1 1 10 5 Favours [experimental] Favours [control]
leterogeneity: Tau <sup>2</sup> = est for overall effect: total (95% CI) total events leterogeneity: Tau <sup>2</sup> = est for overall effect: test for suboroup diffe	1.54; Chi <sup>2</sup> Z = 2.80 (F 141 0.52; Chi <sup>2</sup> Z = 6.33 (F arences: Ch	= 9.79, P = 0.00 = 20.34 P < 0.00 $hi^2 = 0.0$	df = 2 )5) 545 4, df = 8 )001) 99, df =	(P = 0.00 12 8 (P = 0.0 1 (P = 0.	7); l <sup>2</sup> = 1 2 09); l <sup>2</sup> = 76). l <sup>2</sup> =	30% 2111 61% 0%		8.14 [4.25, 15.57]	Favours [experimental] Favours [control]
leterogeneity: Tau <sup>2</sup> = est for overall effect: otal (95% CI) otal events leterogeneity: Tau <sup>2</sup> = est for overall effect: est for suboroup diffe CIL-6	1.54; Chi <sup>2</sup> Z = 2.80 (F 141 0.52; Chi <sup>2</sup> Z = 6.33 (F arences: Ch Severe/E	= 9.79, P = 0.00 = 20.34 P < 0.00 hi <sup>2</sup> = 0.0 Decease	df = 2 (5) 545 (, df = 8 (001) (9), df = ed	(P = 0.00 12 8 (P = 0.0 1 (P = 0. Non-sev	7);   <sup>2</sup> = 1 2 09);   <sup>2</sup> = 76).   <sup>2</sup> = vere/Sui	30% 2111 61% 0% vival	100.0%	8.14 [4.25, 15.57] Std. Mean Difference	Favours [experimental] Favours [control] Std. Mean Difference
Ideorogeneity: Tau <sup>2</sup> = iest for overall effect: iotal (95% CI) iotal events leterogeneity: Tau <sup>2</sup> = iest for overall effect: iest for suboroup diffe CIL-6 itudy or Subgroup	1.54; Chi <sup>2</sup> Z = 2.80 (F 141 0.52; Chi <sup>2</sup> Z = 6.33 (F arences: Ch	= 9.79, P = 0.00 = 20.34 P < 0.00 $hi^2 = 0.0$	df = 2 (5) 545 (, df = 8 (001) (9), df = ed	(P = 0.00 12 8 (P = 0.0 1 (P = 0.	7);   <sup>2</sup> = 1 2 09);   <sup>2</sup> = 76).   <sup>2</sup> = vere/Sui	30% 2111 61% 0% vival		8.14 [4.25, 15.57] Std. Mean Difference	Favours [experimental] Favours [control] Std. Mean Difference
leterogeneity: Tau <sup>2</sup> = 'est for overall effect: 'otal (95% CI) 'otal events leterogeneity: Tau <sup>2</sup> = 'est for overall effect: 'est for overall effect: 'est for overall effect: <b>CIL-6</b> itudy or Subgroup .9.1 severity	1.54; Chi <sup>2</sup> Z = 2.80 (F 141 0.52; Chi <sup>2</sup> Z = 6.33 (F arences: Ch Severe/D Mean	= 9.79, P = 0.00 = 20.34 P < 0.00 ni <sup>2</sup> = 0.0 Decease SD	df = 2 )5) 545 4, df = 8 )001) 99. df = ed Total	(P = 0.00 12 8 (P = 0.0 1 (P = 0. Non-sev Mean	7); l <sup>2</sup> = 1 2 09); l <sup>2</sup> = 76). l <sup>2</sup> = vere/Sut SD	2111 61% 0% vival Total	100.0% Weight	8.14 [4.25, 15.57] Std. Mean Difference IV. Random, 95% C	Favours [experimental] Favours [control] Std. Mean Difference
leterogeneity: Tau <sup>2</sup> = est for overall effect: 'otal (95% CI) otal events leterogeneity: Tau <sup>2</sup> = est for overall effect: est for suberound iffe C IL-6 Ludy or Subgroup .9.1 severity .ben XH 2020	1.54; Chi <sup>2</sup> Z = 2.80 (F 141 0.52; Chi <sup>2</sup> Z = 6.33 (F severe/E Mean 42.44 5	= 9.79, = 0.00 = 20.34 > < 0.00 hi <sup>2</sup> = 0.0 Decease SD	df = 2 )5) 545 4, df = 8 )001) 99. df = ed Total 27	(P = 0.00 12 8 (P = 0.0 1 (P = 0. Non-sev Mean 10.4	7); 1 <sup>2</sup> = 1 2 09); 1 <sup>2</sup> = 76), 1 <sup>2</sup> = rere/Sur SD 20.15	30% 2111 61% 0% Vival Total 21	100.0% 	8.14 [4.25, 15.57] Std. Mean Difference IV. Random, 95% C 0.69 [0.10, 1.28]	Favours [experimental] Favours [control] Std. Mean Difference
leterogoneity: Tau <sup>2</sup> = est for overall effect: otal (95% CI) otal events leterogeneity: Tau <sup>2</sup> = est for overall offect: est for subaroup diffe C IL-6 tudy or Subgroup_ .9.1 severity han XH 2020	1.54; Chi <sup>2</sup> Z = 2.80 (F 141 0.52; Chi <sup>2</sup> Z = 6.33 (F severe/E Mean 42.44 5	= 9.79, P = 0.00 = 20.34 P < 0.00 ni <sup>2</sup> = 0.0 Decease SD	df = 2 )5) 545 4, df = 8 )001) 99. df = ed Total	(P = 0.00 12 8 (P = 0.0 1 (P = 0. Non-sev Mean	7); l <sup>2</sup> = 1 2 09); l <sup>2</sup> = 76). l <sup>2</sup> = vere/Sut SD	2111 61% 0% vival Total	Weight 24.3% 25.0% 25.4%	8.14 [4.25, 15.57] Std. Mean Difference IV. Random, 95% Gi 0.69 [0.10, 1.28] -0.84 [-1.29, -0.39] 1.83 [1.50, 2.17]	Favours [experimental] Favours [control] Std. Mean Difference
leterogeneity: Tau <sup>2</sup> = est for overall effect: otal (95% CI) cotal events leterogeneity: Tau <sup>2</sup> = est for subaroup diffe C IL-6 tudy or Subaroup .9.1 severity hen XH 2020 Ang RR 2020	1.54; Chi <sup>2</sup> Z = 2.80 (F 141 0.52; Chi <sup>2</sup> Z = 6.33 (F severe/E Mean 42.44 5 44.64	= 9.79, = 20.34 = 20.34 > < 0.00 $ni^2 = 0.0$ Oeceass SD = 8.06 27.3	df = 2 55 545 4, df = 8 0001) 99. df = ed Total 27 25	(P = 0.00 12 8 (P = 0.0 1 (P = 0. Non-sev Mean 10.4 61.61	7); 1 <sup>2</sup> = 1 2 09); 1 <sup>2</sup> = 76), 1 <sup>2</sup> = rere/Sut SD 20.15 17.89	30% 2111 61% 0% Vival Total 21 100	Weight 24.3% 25.0%	8.14 [4.25, 15.57] Std. Mean Difference IV. Random, 95% Gi 0.69 [0.10, 1.28] -0.84 [-1.29, -0.39] 1.83 [1.50, 2.17]	Favours [experimental] Favours [control] Std. Mean Difference
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◄Fig. 5 Infection-related risk factors for progression and mortality in COVID-19. Forest plots are shown for the effects of (A) elevated CRP, (B) elevated PCT, (C) elevated IL-6, (D) and co-infection.

group than in the non-severe/survival group (pooled results: AST: OR = 2.78, 95% CI 2.24 to 3.46, P < 0.00001; ALT: OR = 1.74, 95% CI 1.43 to 2.13, P < 0.00001; CK: OR = 2.03, 95% CI 1.40 to 2.96, P = 0.0002; sCr: OR = 3.80, 95% CI 2.32 to 6.20, P < 0.00001) (Fig. 6A, B, E, and F). In addition, lactate dehydrogenase (LDH) and total bilirubin (TBIL) levels were assessed. The results suggest that increased LDH is associated with a higher risk of progression (OR = 4.12, 95% CI 2.88 to 5.90, P < 0.00001) but not mortality; however, increased TBIL is associated with a higher risk of mortality (OR = 2.58, 95% CI 1.14 to 5.83, P < 0.00001) but not progression (Fig. 6C and D).

#### Other results

The proportion of elevated N-terminal pronatriuretic peptide (NT-proBNP) or D-dimer was significantly higher in the severe/deceased group than in the non-severe/survival group (pooled OR = 4.57, 95% CI 2.68 to 7.81, P < 0.00001; OR = 3.19, 95% CI 2.53 to 4.02, P < 0.00001, respectively) without significant heterogeneity ( $I^2 = 0\%$  and  $I^2 = 49\%$ , respectively) (Fig. 7B and C). We found that increased highsensitivity cardiac troponin I (Hs-cTnI) is associated with a higher risk of mortality (OR = 14.40, 95% CI 2.45 to 84.54, P = 0.003) but not severity (Fig. 7A); however, bilateral pneumonia in CT/X-ray is associated with a higher risk of severity (OR = 2.27, 95% CI 1.13 to 4.58, P = 0.02) but not mortality, with statistical significance despite some degree of heterogeneity ( $I^2 = 62\%$  and  $I^2 = 86\%$ , respectively) (Fig. 7D).

#### **Publication bias**

Egger's regression analysis and Begg's rank correlation analysis were performed to assess publication bias (Table S2). With the exception of dyspnea and smoking, the *P*-values for all factors were greater than 0.05, indicating the absence of publication bias. To confirm the publication bias for dyspnea, we adopted the trim-and-fill method (Fig. 8). After assessing five studies, the *P*-value was less than 0.0001, which is the same as the previous result; however, the OR (95% CI) changed from -1.809 (-2.251, -1.366) to 0.260 (0.160, 0.422), suggesting publication bias. Similarly, we did funnel plot analysis for smoking, showing asymmetry, indicating publication bias (Fig. 3).

#### Sensitivity analysis

Although subgroup analysis was used in this study, heterogeneity was still noted for some factors. We performed leaveone-out sensitivity analysis to identify possible explanations for heterogeneity (Table S3). High heterogeneity with an  $I^2$ > 50% and P < 0.05 was found in the analysis of some risk factors. Additionally, after the removal of each study from the analysis, similar results were obtained, and the heterogeneity of most risk factors changed significantly. The high heterogeneity was not reduced by sensitivity analysis in three comparisons (diabetes, decreased WBC, and LDH) in the severity or mortality group. However, after the removal of each study from the analysis of diabetes, decreased WBC, and LDH, the results were stable.

# Discussion

Within several months, COVID-19 spread across the world and became a serious health threat to all humans [3]. The number of critical patients and deaths increased substantially, although the majority of infected individuals survived [49]. Early diagnosis and treatment are essential in severe cases, which underscores the importance of identifying predictive factors of disease progression and death. Several studies have investigated risk factors for critical/fatal COVID-19 with a limited number of patients [7, 10]. However, these studies yielded conflicting results due to small sample sizes. To provide less-biased estimates on this specific topic, a meta-analysis, which is an objective, quantitative method, was employed.

Recently, a meta-analysis from China that included 13 studies from Jan 1, 2020, to Mar 20, 2020, was published [10]. Some risk factors for critical/fatal COVID-19 cases were identified. However, another 21 original studies on this topic were published subsequently within several months. An updated meta-analysis is needed to explore new risk factors for critical/fatal COVID-19. In addition to common risk factors, such as male sex, age over 65 years, smoking, hypertension, diabetes, cardiovascular disease, and respiratory diseases, shortness of breath or dyspnea, WBC, AST, Cr, PCT, LDH, hs-cTnI and D-dimer, we also identified some new factors in this study.

Regarding comorbidities, diabetes was one leading risk factor for progression in COVID-19 patients [50]. Zhu et al. also found that well-controlled blood glucose levels correlated with a reduced risk of detrimental complications and all-cause mortality in subjects with COVID-19 and pre-existing diabetes [51]. Uncontrolled glycemia and diabetes have been reported as important predictors

4.11.1 severity	Events	ased No Total	Events	urvival Total	Weight	M-H. Random, 95% C	Odds Ratio M-H. Random, 95% Cl
Guan W 2020 Huang CL 2020	56 8	142 13	112	615 28	23.2% 2.3%	2.92 [1.97, 4.34] 4.80 [1.18, 19.61]	
Li XC 2020	115	265	64	275	25.4%	2.53 [1.75, 3.66]	· · · · · · · · · · · · · · · · · · ·
Li Y 2020 Wang ZL 2020	57	14	12	16 55	1.7% 3.1%	1.25 [0.24, 6.44] 3.58 [1.05, 12.23]	
Zhang J 2020 Subtotal (95% CI)	131	409 852	40	254 1243	22.9% 78.6%	2.52 [1.70, 3.75] 2.67 [2.16, 3.32]	•
Total events Heterogeneity: Tau <sup>a</sup> = 0.0	322 00; Chi <sup>2</sup> = 2.0	08, df = 5 (P	243 = 0.84); l <sup>2</sup> =	= 0%			
Test for overall effect: Z = 4.11.2 mortality	8.97 (P < 0	.00001)					
Chen RC 2020 Du RH 2020	24 10	35 21	245 47	985 158	8.2% 5.3%	6.59 (3.18, 13.65) 2.15 (0.85, 5.40)	
LI Y 2020	2	5	10	20	1.2%	0.67 [0.09, 4.89]	
Zhang J 2020 Subtotal (95% CI) Total events	47	86	462	1801	21.4%	2.35 [1.04, 5.28] 2.76 [1.28, 5.97]	
Heterogeneity: Tau <sup>#</sup> = 0.3 Test for overall effect: Z =	35; Chi <sup>2</sup> = 7.4	45, df = 3 (P		= 60%			
Total (95% Cl)		938		3044	100.0%	2.78 [2.24, 3.46]	•
Total events Heterogeneity: Tau <sup>2</sup> = 0.0	369 01; Chi <sup>#</sup> = 10	.05, df = 9 (	705 P = 0.35); I <sup>a</sup>	= 10%			0.05 0.2 1 5
Test for overall effect: Z = Test for suboroup differen	9 20 (P < 0	00001)					Favours [experimental] Favours [control]
B elevated ALT <sub>s</sub>	Severe/Dec	eased N	on-severe/			Odds Ratio	Odds Ratio
Study or Subgroup 4.12.1 severity	Events	Total	Events		Weight	M-H, Fixed, 95% Cl	M-H. Fixed, 95% Cl
Guan W 2020 Li XC 2020	38 64	135 266	120 61	606 275	22.1% 32.1%	1.59 [1.04, 2.43] 1.11 [0.75, 1.66]	
Wang RR 2020 Zhang J 2020	6 110	14 409	17 41	55 264	2.8% 26.1%	1.68 [0.50, 5.58] 1.91 [1.28, 2.85]	
Subtotal (95% CI) Total events	218	824	239	1190	83.1%	1.51 [1.20, 1.90]	
Heterogeneity: Chi <sup>a</sup> = 3.6 Test for overall effect: Z =	37, df = 3 (P = 3.50 (P = f	= 0.30); l <sup>a</sup> - 0.0005)	- 18%				
4.12.2 mortality							
Chen RC 2020 Zhang J 2020	19 9	35 25	229 142	959 638	5.2% 4.8%	3.79 [1.92, 7.48] 1.96 [0.85, 4.54]	
Zhou F 2020 Subtotal (95% CI)	26	54 114	33	135 1732	6.9% 16.9%	2.87 [1.48, 5.57] 2.89 [1.92, 4.36]	-
Total events Heterogeneity: Chi <sup>a</sup> = 1.4	54 12, df = 2 (P	= 0.49); l <sup>a</sup>	404 = 0%				
Test for overall effect: Z =	= 5.07 (P < 0	0.00001)					
Total (95% CI) Total events	272	938	643	2922	100.0%	1.74 [1.43, 2.13]	-
Heterogeneity: Chi <sup>2</sup> = 12. Test for overall effect: Z =	.49, df = 6 (F = 5.42 (P < 6	P = 0.05); P 0.00001)	= 52%	20 22: 1997	291		0.2 0.5 1 2 5 Favours [experimental] Favours [control]
Test for overall effect: Z Test for subgroup different Celevated TBILs Study or Subgroup	nces: Chi <sup>2</sup> =	ased No	n-severe/S	). I <sup>2</sup> = 86.4 urvival	%	Odds Ratio	Odds Ratio
4,13.1 severity						M-H. Random, 95% C	M-H. Random, 95% Cl
Guan W 2020 Li XC 2020	17	128 266	59	594 275	36.9% 29.2%	1.39 [0.78, 2.47] 2.61 [1.07, 6.41]	
Subtotal (95% CI) Total events	34	394	66	869	66.1%	1.73 [0.96, 3.13]	
Heterogeneity: Tau <sup>a</sup> = 0.0 Test for overall effect: Z =	)5; ChP = 1.3 + 1.81 (P = 0	36, df = 1 (P 1.07)	= 0.24); f <sup>2</sup> =	= 26%			
4.13.2 mortality							
Chen RC 2020 Subtotal (95% CI)	14	36 36	106	939 939	33.9% 33.9%	5.00 [2.48, 10.07] 5.00 [2.48, 10.07]	
Total events Heterogeneity: Not applic	14		106				
Test for overall effect: Z =	= 4.51 (P < 0	.00001)		1000 (1000 L ).			
Study or Subgroup	Events	Total	Events	Total	Weight	Odds Ratio M-H. Random, 95% C	Odds Ratio M-H. Random. 95% Cl
4.14.1 severity Guan W 2020 Huang CL 2020	72 12	124	205	551 27	16.2%	2.34 [1.57, 3.47]	
JI D 2020 Li XC 2020	29	13 40 262	17 54 162	168 272	11.8%	2.34 [1.57, 3.47] 7.06 [0.79, 62.72] 5.57 [2.59, 11.97] 5.06 [3.24, 7.91]	
Li Y 2020 Wang ZL 2020	6 10	9	8	16	4.8%	2.00 [0.37, 10.92] 11.33 [2.21, 58.15]	
Zhang J 2020 Subtotal (95% CI)	263	409	67	254 1337	16.8%	4.53 [3.21, 6.38] 4.12 [2.88, 5.90]	-
Total events Heterogeneity: Tau <sup>a</sup> = 0.0	613 09: ChP = 11	.79, df = 6 (	528 P = 0.07); I <sup>2</sup>				5-04-0
Test for overall effect: Z =	7.72 (P < 0	.00001)					
4.14.2 mortality Chen RC 2020	32	35	411	884	7.7%	12.28 [3.73, 40.38]	
LI Y 2020		5	11		3.7%		
zhang J 2020	3 14	25	306	20 638	11.3%	1.23 [0.17, 9.02] 1.38 [0.62, 3.09]	
Zhou F 2020 Subtotal (95% CI)	14 53	25 54 119	70		11.3% 3.7% 26.5%	1.23 [0.17, 9.02] 1.38 [0.62, 3.09] 45.43 [6.10, 338.44] 5.23 [0.91, 30.06]	
Zhou F 2020 Subtotal (95% CI) Total events Nateroconstruct Tau2 = 2.6	14 53 102	54 119	70	638 130 1672	11.3%	1.38 [0.62, 3.09] 1.38 [0.62, 3.09] 45.43 [6.10, 338.44] 5.23 [0.91, 30.06]	
Zhou F 2020 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>z</sup> = 2.5 Test for overall effect: Z =	14 53 102	54 119 0.39, df = 3 ( 0.06)	70	638 130 1672 ; I <sup>z</sup> = 85%	11.3% 3.7% 26.5%	45.43 [0.10, 338.44] 5.23 [0.91, 30.06]	-
Zhou F 2020 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 2.5 Test for overall effect: Z = Total (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0.2	14 53 102 58: Chi <sup>2</sup> = 19 = 1.85 (P = 0 715 26: Chi <sup>2</sup> = 29	54 119 0.39, df = 3 ( 0.06) 988 0.45, df = 10	70 798 P = 0.0002) 1326 (P = 0.001)	638 130 1672 ; I <sup>x</sup> = 85% 3009 ; I <sup>2</sup> = 66%	11.3%	1.38 [0.62, 3.09] 45.43 [6.10, 338.44] 5.23 [0.91, 30.06] 4.24 [2.76, 6.53]	-
Zhou F 2020 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>3</sup> = 2.5 Test for overall effect: Z = Total (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0.2 Test for overall effect: Z = Test for subaroup different	14 53 102 58; Chi <sup>2</sup> = 19 1.85 (P = 0 715 26; Chi <sup>2</sup> = 29 6.56 (P < 0 nces; Chi <sup>2</sup> =	54 119 0.39, df = 3 ( 0.06) 988 0.45, df = 10 0.00001) 0.07, df = 1	70 798 P = 0.0002) 1326 (P = 0.001)	638 130 1672 ; I <sup>x</sup> = 85% 3009 ; I <sup>2</sup> = 66%	11.3% 3.7% 26.5%	45.43 [0.10, 338.44] 5.23 [0.91, 30.06]	0.01 0.1 10 1 Favours [experimental] Favours [control]
Zhou F 2020 Substail (95% CI) Total events Hoterogenoity: Tau <sup>s</sup> = 2.5 Tost (95% CI) Total (95% CI) Total events Heterogeneity: Tau <sup>s</sup> = 0.2 Test for autoroup different Test for autoroup different Eelevated CK s	14 53 102 58; Chi <sup>2</sup> = 19 1.85 (P = 0 715 26; Chi <sup>2</sup> = 29 6.56 (P < 0 nces; Chi <sup>2</sup> =	54 119 0.39, df = 3 ( 0.06) 988 0.45, df = 10 0.00001) 0.07, df = 1	70 798 P = 0.0002) 1326 (P = 0.001)	638 130 1672 ; I <sup>x</sup> = 85% 3009 ; I <sup>z</sup> = 66%	11.3% 3.7% 26.5%	45.43 [0.10, 338.44] 5.23 [0.91, 30.06]	0.01 0.1 1 10 1 Favours [experimental] Favours [control] Odds Ratio
Zhou F 2020 Substoal (95% CI) Total ovents Total (95% CI) Total (95% CI) Total (95% CI) Total events Total (95% CI) Total (95% CI) Tota	14 53 58; Chi <sup>2</sup> = 19 = 1.85 (P = 0 715 26; Chi <sup>2</sup> = 29 6.56 (P < 0 nces; Chi <sup>2</sup> = 8evers/Dece Events	54 119 0.39, df = 3 ( 0.68) 988 0.45, df = 10 0.000(1) 0.07, df = 1 eased N Total	70 798 P = 0.0002) (P = 0.001) (P = 0.79). [on-severe/ Events	638 130 1672 ; I <sup>2</sup> = 85% 3009 ; I <sup>2</sup> = 66% I <sup>2</sup> = 0% Survival Total	11.3% 3.7% 26.5% 100.0% Weight	45.43 [6.10, 338.44] 5.23 [0.91, 30.06] 4.24 [2.76, 6.53] Odds Ratio <u>M-H, Fixed, 95% CI</u>	Favours [experimental] Favours [control] Odds Ratio
Zhou F 2020 Substoal (85% CI) Total events Heterogeneity: Tau <sup>s</sup> = 2.5 Test for overall effect: Z = Total (85% CI) Total events Heterogeneity: Tau <sup>s</sup> = 0.2 Test for overall effect: Z = Test for suboroup differen Eelevated CK s Study or Suborous	14 53 102 58; Chi <sup>2</sup> = 19 1.85 (P = 0 715 26; Chi <sup>2</sup> = 29 6.56 (P < 0 nces; Chi <sup>2</sup> =	54 119 0.39, df = 3 ( 0.06) 988 0.45, df = 10 0.00001) 0.07, df = 1	70 798 P = 0.0002) 1326 (P = 0.001) (P = 0.79)	638 130 1672 ; I <sup>x</sup> = 85% 3009 ; I <sup>z</sup> = 66%	11.3% 3.7% 26.5%	45.43 [6.10, 338.44] 5.23 [0.91, 30.06] 4.24 [2.76, 6.53] Odds Ratio <u>M-H, Fixed, 95% CI</u>	Favours [experimental] Favours [control] Odds Ratio
Zhou F 2020 Substati (85% CI) Total events Hoterogeneity: Tau <sup>2</sup> = 2.5 Test for overall effect: Z = Total (95% CI) Total events Hoterogeneity: Tau <sup>2</sup> = 0.2 Test for aubornub offeren <b>E elevatted</b> CK $\pm$ Study or Substraug 4.15.1 severity Guan W 2020 Huang CL 2020	14 53 102 58; Chi <sup>2</sup> = 19 = 1.85 (P = 0 715 26; Chi <sup>2</sup> = 29 = 6.56 (P < 0 neces: Chi <sup>2</sup> = Severa/Decc Events 23 6 29	54 119 0.36, df = 3 ( 0.06) 988 0.45, df = 10 0.00001) 0.07, df = 1 eased N Total 13 134	70 798 P = 0.0002) 1326 (P = 0.001) (P = 0.79) (On-severe/ Events 67 7 74	638 130 1672 ; I <sup>2</sup> = 85% 3009 ; I <sup>2</sup> = 66% I <sup>2</sup> = 0% Survival Total 536 27	11.3% 3.7% 26.5% 100.0% Weight 58.8% 7.2%	45.43 [6.10, 338.44] 5.23 [0.91, 30.06] 4.24 [2.76, 6.53] Odds Ratio	Favours [experimental] Favours [control] Odds Ratio
Zhou F 2020 Subtotal (89% CI) Total events Teal (99% CI) Teal (99% CI) Total (99% CI) Total events Total (99% CI) Total events Teal for over Tau's 0.2 Teal for over Tau's 0.2 Teal for subtroum differen Elevented CK Subtotal (95% CI) Huang CL 2020 Subtotal (95% CI) Total events Heat rogenality: Chi <sup>2</sup> = 0.2	14 53 102 58: Chi <sup>3</sup> = 19 = 1.85 (P = 0 75 (P < 0 6.56 (P < 0 nces: Chi <sup>3</sup> = 29 8events Events 23 6 29 28, df = 1 (P	54 119 0.39, df = 3 ( 0.06) 988 0.45, df = 10 0.0001) 0.07, df = 1 eased N Total 121 13 134 = 0.60); l <sup>2</sup> =	70 798 P = 0.0002) 1326 (P = 0.001) (P = 0.79) (On-severe/ Events 67 7 74	638 130 1672 ; I <sup>2</sup> = 85% 3009 ; I <sup>2</sup> = 66% I <sup>2</sup> = 0% Survival Total 536 27	11.3% 3.7% 26.5% 100.0% Weight 58.8% 7.2%	45.43 [6.10, 338.44] 5.23 [0.91, 30.06] 4.24 [2.76, 6.53] Odds Ratio <u>M-H, Fixed, 95% CI</u>	Favours [experimental] Favours [control] Odds Ratio
Zhou F 2020 Subtotal (95% CI) Total events Total events Total coveral Total (95% CI) Total events Heterogeneity: Tau's 0.2 Test for overal effect: 2 = Test for subtroup differen <b>E elevated CK</b> 4.15.1 severity Guan W 2020 Huang CI 2000 Total events Heterogeneity: Ch' = 0.2 Test for overal effect: 2 = 4.15.2 mortality	14 53 102 58: Chi <sup>3</sup> = 19 = 1.85 (P = 0 75 (P < 0 6.56 (P < 0 nces: Chi <sup>3</sup> = 29 8events Events 23 6 29 28, df = 1 (P	54 119 0.39, df = 3 ( 0.06) 988 0.45, df = 10 0.0001) 0.07, df = 1 eased N Total 121 13 134 = 0.60); l <sup>2</sup> =	70 798 P = 0.0002) 1326 (P = 0.001) (P = 0.79) (On-severe/ Events 67 7 74	638 130 1672 ; I <sup>2</sup> = 85% 3009 ; I <sup>2</sup> = 66% I <sup>2</sup> = 0% Survival Total 536 27	11.3% 3.7% 26.5% 100.0% Weight 58.8% 7.2%	46.43 [6.10, 338.44] 5.23 [0.91, 30.06] 4.24 [2.76, 6.53] Odds Ratio MH, Fixed, 35% GI 1.64 [0.98, 2.77] 2.45 [0.61, 9.82] 1.73 [1.06, 2.81] 2.68 [1.24, 5.79]	Favours [experimental] Favours [control] Odds Ratio
Zhou F 2020 Subtotal (99% CI) Subtotal (99% CI) Test for overall effect: Z = Total (95% CI) Total events Heterogeneity: Tau's 0.2 Test for overall effect: Z = Test for subtoroup differen <b>Delevante</b> Study or Subbroup Huang CL 2020 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 0.2 Test for overall effect: Z = 4.15.2 sevents Heterogeneity: Chi <sup>2</sup> = 0.2 Test for overall effect: Z = 4.15.2 mortality Chen RC 2030 Subtotal (95% CI)	14 53 102 58: Chi <sup>2</sup> = 19 58: Chi <sup>2</sup> = 20 26: Chi <sup>2</sup> = 20 6.58 (P < 0 nces: Chi <sup>2</sup> = 2 8evers/Decc 23 6 28, df = 1 (P = ( 23 6 10 11	54 119 0.39, df = 3 ( 0.06) 988 0.45, df = 10 0.07, df = 1 easaed Total 121 13 134 = 0.060); l <sup>2</sup> =	70 = 798 = 0.0002 $P = 0.0002$ $(P = 0.001)$ $(P = 0.73)$ $P = 0.73$ $F = 0.73$ $7$ $7$ $7$ $7$ $74$ $126$ $11$	638 130 1672 ; I <sup>z</sup> = 85% 3009 ; I <sup>z</sup> = 86% I <sup>z</sup> = 86% I <sup>z</sup> = 86% <b>Survival</b> Total 536 27 563	11.3% 3.7% 26.5% 100.0% <u>Weight</u> 58.8% 66.1%	45.43 [6.10, 338.44] 5.23 [0.91, 30.06] 4.24 [2.76, 6.53] Odds Ratio <u>M-H, Fixed, 95% CI</u>	Favours [experimental] Favours [control] Odds Ratio
Zhou F 2020 Subtotal (99% CI) Total events Total events total events Total events Total events Heterogeneity: Tau's 0.2 Test for overal effect: 2 = Test for subtroub differen <b>E elevated CK</b> = Study or Subbroup 4.15.1 severity Guan W 2020 Subtotal (9% CI) Total events Heterogeneity: Ch <sup>2</sup> = 0.2 Test for overal effect: 2 = 4.15.2 mortality Chen RC 2020 Zhou F 2020 Subtotal (9% CI) Heterogeneity: Ch <sup>2</sup> = 0.0 Heterogeneity: Ch <sup>2</sup> = 0.0 Heterogeneity: Ch <sup>2</sup> = 0.0	14 53 102 58; Chi <sup>2</sup> = 19 = 1.85 (P = 0 26; Chi <sup>2</sup> = 29 = 6.56 (P < 0 reas: Chi <sup>2</sup> = 8 8 29 28, df = 1 (P = 2.21 (P = ( 10 11 21 11 21, df = 1 (P	54 119 988 1.45, df = 3 ( 0.06) 988 1.45, df = 10 0.0001) 0.07, df = 1 eased N Total 121 134 = 0.660); l* - 0.03) 32 82 84 = 0.94); l* -	70 798 P = 0.0002) 1326 ( $P = 0.001$ ) ( $P = 0.791$ ) 100-severe/ Events 67 74 = 0% 126 11 137	638 130 1672 ; I* = 85% 3009 ; I* = 66% i* = 0% Survival Total 536 257 563 868	11.3% 3.7% 26.5% 100.0% Weight 58.8% 66.1% 18.1% 55.8%	46.43 [6.10, 338.44] 5.23 [0.91, 30.06] 4.24 [2.76, 6.53] Odda Ratio M-H. Fixed, 95% CI 1.64 [0.98, 2.77] 2.45 [0.61, 9.82] 1.73 [1.06, 2.81] 2.68 [1.24, 5.79] 2.68 [1.24, 5.79]	Favours [experimental] Favours [control] Odds Ratio
Zhou F 2020 Subtotal (89% CI) Total events Total events Total (99% CI) Total events Total (99% CI) Total events Total (99% CI) Total events Total events Total events Total events Total events Total events Total events Elector auboroup differen Elector Constant Subtotal (95% CI) Subtotal (95% CI) Heterogeneity, Ch <sup>2</sup> = 0.2 Total events Chan RC 2020 Subtotal (95% CI) Subtotal (95% CI) Total events Heterogeneity, Ch <sup>2</sup> = 0.0 Total events Heterogeneity Ch <sup>2</sup> = 0.0 Total events Heterogeneity Ch <sup>2</sup> = 0.0	14 53 102 58; Chi <sup>2</sup> = 19 = 1.85 (P = 0 26; Chi <sup>2</sup> = 29 = 6.56 (P < 0 reas: Chi <sup>2</sup> = 8 8 29 28, df = 1 (P = 2.21 (P = ( 10 11 21 11 21, df = 1 (P	54 119 988 1.45, df = 3 ( 0.06) 988 1.45, df = 10 0.0001) 0.07, df = 1 eased N Total 121 134 = 0.660); l* - 0.03) 32 82 84 = 0.94); l* -	70 798 P = 0.0002) 1326 ( $P = 0.001$ ) ( $P = 0.791$ ) 100-severe/ Events 67 74 = 0% 126 11 137	638 130 1672 ; I <sup>2</sup> = 85% 3009 ; I <sup>2</sup> = 66% ; I <sup>2</sup> = 0% Survival 536 27 563 868 116 984	11.3% 3.7% 26.5% 100.0% Weight 568.8% 66.1% 18.1% 15.8% 33.9%	46.43 [6.10, 338.44] 5.23 [0.91, 30.06] 4.24 [2.76, 6.53] Odds Ratio <u>M:H. Fixed, 95% CI</u> 1.64 [0.96, 2.77] 2.45 [0.61, 9.82] 1.73 [1.06, 2.81] 2.68 [1.24, 5.79] 2.68 [1.24, 5.79] 2.66 [1.24, 5.79]	Favours [experimental] Favours [control] Odds Ratio
Zhou F 2020 Subtotal (05% CI) Total events Total (05% CI) Total events Total (05% CI) Total events Total events Total events Test for over all effect: z = Test for subtrave differen <b>Eelevated CK</b> Study or Subtrave Guan W 2020 Huang CL 2020 Subtotal (05% CI) Total events Subtra (05% CI) Total events Subtra (05% CI) Total events	14 53 102 15 5(ch) <sup>2</sup> = 10 715 25(ch) <sup>2</sup> = 0 715 25(ch) <sup>2</sup> = 20 6.56 (f = 0 0.000 Ch) <sup>2</sup> = 0 8everts 23 29 28, df = 1 (P 23 20 21 (D = 0 10 10 10 10 21 21 21 21 21 25 50	54 119 3.39, df = 3 ( 0.06) 988 1.45, df = 10 0.00001 0.07, df = 1 eased N 121 123 134 = 134 = 0.94); f* 0. 0.001) 218	70 70 71 P = 0.0002) (P = 0.001) (P = 0.79). (P = 0.79). (P = 0.79). (P = 0.79). (P = 0.79). (P = 0.001) (P = 0.001) (P = 0.001) (P = 0.0002) (P = 0.0002)	638 130 1672 ; I* = 85% 3009 ; I* = 66% i* = 0% Survival Total 536 257 563 868	11.3% 3.7% 26.5% 100.0% Weight 58.8% 66.1% 18.1% 55.8%	46.43 [6.10, 338.44] 5.23 [0.91, 30.06] 4.24 [2.76, 6.53] Odda Ratio M.H. Fixed, 95% CI 1.64 [0.98, 2.77] 2.45 [0.61, 9.82] 1.73 [1.06, 2.81] 2.68 [1.24, 5.79] 2.68 [1.24, 5.79]	Favours (experimental) Favours (control) Odds Ratio M.H. Fixed 90% Cl
Zhou F 2020 Subtotal (89% CI) Total events Test for overall effect: Z = Total (98% CI) Total events Total 98% CI) Total events Test for overall effect: Z = Test for subtraue differer <b>E elevated</b> CK $\pm$ Shudy or Subbroub Huang CL 2020 Subtotal (95% CI) Total events Chan RC 2020 Subtotal (95% CI) Total events Chan RC 2020 Subtotal (95% CI) Total events Total 98% CI) Total events Heterogeneity: Ch <sup>2</sup> = 0.0 Total events Heterogeneity: Ch <sup>2</sup> = 1.1 Total (95% CI) Total events Heterogeneity: Ch <sup>2</sup> = 1.2 Total (95% CI)	14 53 102 19 58 Chi <sup>2</sup> = 19 58 Chi <sup>2</sup> = 10 58 Chi <sup>2</sup> = 10 56 Chi <sup>2</sup> = 20 6.56 (Chi <sup>2</sup> = 20 6.56 (Ch <sup>2</sup> = 20 6.56 (Ch <sup>2</sup> = 20) 58 Chi <sup>2</sup> = 20 58 Chi <sup>2</sup> = 20 58 Chi <sup>2</sup> = 20 28 28 28 29 29 29 20 20 10 10 11 21 21 21 21 21 21 21 21 21 21 21 21	54 119 3.39, dt = 3 ( 0.00) 988 1.45, dt = 10 0.00001 0.07, dt = 1 eased 121 133 134 134 134 = 0.001) 252 84 = 0.001) 248 = 0.0001 / * 0.0001	70 P = 0.0002) (P = 0.001) (P = 0.001) (P = 0.001) (P = 0.001) P = 0.91 P = 0.91 67 74 126 126 11 126 127 126 127 126 127 127 126 127	638 130 1672 17 = 66% 17 = 66% 17 = 66% 17 = 66% 500 500 500 563 166 27 563 1667 1547	11.3% 3.7% 26.5% 100.0% Weight 58.8% 7.2% 66.1% 18.1% 33.9%	46.43 [6.10, 338.44] 5.23 [0.91, 30.06] 4.24 [2.76, 6.53] Odds Ratio <u>M:H. Fixed, 95% CI</u> 1.64 [0.96, 2.77] 2.45 [0.61, 9.82] 1.73 [1.06, 2.81] 2.68 [1.24, 5.79] 2.68 [1.24, 5.79] 2.66 [1.24, 5.79]	Favours (experimental) Favours (control) Odds Ratio M-H, Fixed, 90% Cl M-H, Fixed, 90% Cl
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Zhou F 2020 Subtotal (99% CI) Total events total events total events total events total events Heterogeneity: Tau' = 0.2 Total events Heterogeneity: Tau' = 0.2 Test for subtroub differen <b>E elevated CK</b> = 3 Study or Subbroub <b>E elevated CK</b> = 3 Study or Subbroub (415.1 severity Guan W 2020 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>o</sup> = 0.2 Test for overall effect. 2 = 4.4 1.5.2 mortality Chen RC 2020 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>o</sup> = 0.0 Total (95% CI) Total events Heterogeneity: Chi <sup>o</sup> = 0.0 Total (95% CI) Total events Heterogeneity: Chi <sup>o</sup> = 1.4 Test for overall effect. 2 = 1.4 Test for overall effect. 3 = 1.4Test for overall effect. 4 = 1.4Test for o	14 53 102 138 51 CH2 = 10 263 CH2 = 10 263 CH2 = 10 263 CH2 = 10 263 CH2 = 20 263 CH2 = 20 273 C	54 119 3.39, dr = 3 ( 0.06) 988 1.45, dr = 10 0.00001) 0.07, df = 1 eassed N 121 123 134 = 0.60); i <sup>p</sup> = 0.03) 32 52 52 52 52 52 52 52 52 52 52 52 52 52	70 788 P = 0.0002) (P = 0.001) (P = 0.001) (P = 0.01) (P = 0.94) Events 67 74 20% 74 1126 1137 = 0% 211 1 (P = 0.28) n=sever(8) Events	638 130 1985% 1985% 300% 1986% 19 = 66% 19 = 66% 1986 536 536 536 536 536 536 166 984 1547 1547 1547 1547	11.3% 3.7% 26.5% 100.0% Weight 18.1% 15.8% 100.0% 4.33.9% 100.0% 4.3%	46.43 [6.10, 338.44] 5.23 [0.91, 30.06] 4.24 [2.76, 6.53] Odda Ratio M.H. Elxed, 35% CI. 1.64 [0.96, 2.77] 2.45 [0.81, 9.82] 1.73 [1.06, 2.81] 2.66 [1.03, 6.36] 2.62 [1.45, 4.74] 2.03 [1.40, 2.96] 0dds Ratio M.H. Random 35% C 4.61 [1.46, 14.51] 2.96 [0.29, 18.97] 1.63 [1.11, 2.40]	Favours (experimental) Favours (control) Odds Ratio
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◄Fig. 6 Blood biochemistry test risk factors for progression and mortality in COVID-19. Forest plots are shown for the effects of (A) elevated AST, (B) elevated ALT, (C) elevated TBIL, (D) elevated LDH, (E) elevated CK, and (F) elevated sCr.

of severity and death in subjects infected with SARS-CoV, H1N1 influenza virus, and MERS-CoV [52-54]. In addition, CVD and CKD were associated with an increased risk of progression and mortality in COVID-19 patients. A growing body of evidence shows that SARS-CoV-2 attaches to the cell membrane and attacks host cells via the ACE2 receptor [55, 56]. ACE2 receptors, which are mainly distributed in the cardiovascular system, lung, kidneys, and colon, have also been detected in glial cells and neurons in the brain; thus, these sites are potential targets of SARS-CoV-2 [57, 58]. ACE2 expression in brain and kidney cells is downregulated by mechanisms such as internalization, shedding, and viral replication [59]. An inflammatory response and exudation of immune cells are induced via increased Ang II concentrations, resulting in a cytokine storm and target-organ damage [60, 61]. If patients with CVD are infected with SARS-CoV-2, bleeding from cerebral capillaries due to endothelial ruptures could have fatal consequences [62]. The prevalence of acute kidney injury among COVID-19 patients is approximately 0.5%. The available data suggest that cytokine damage, organ crosstalk, and systemic effects might represent potential mechanisms of kidney injury in COVID-19 [63, 64]. Kidneys from CKD patients can experience a second hit via viral infection, and these patients are more likely to develop to renal failure [63]. In addition, malignancy and immunodeficiency increase the risk of disease progression or mortality. Compared to a 2.3% fatality rate for all COVID-19 patients, the fatality rate for infected cancer patients in China is 28.6% [65]. Patients with cancers are at an increased risk of severe complications of respiratory viruses because they are frequently immunosuppressed as a result of their disease and treatment [66]. The immune response plays important role in virus elimination and disease progression. For patients with malignancy or immunodeficiency, COVID-19 more often results in critical/fatal cases [67, 68].

Regarding clinical manifestations, sputum production was associated with a dramatically increased risk of progression and mortality. Exudation is a clinical manifestation of inflammation [69], and the volume of exudate is positively correlated with the severity of inflammation. We also found that the incidence of anorexia, fatigue, and shortness of breath was significantly higher in the severe group than in the non-severe group. In an European investigation, that also identified infection-related pulmonary symptoms such as dyspnea, fever were more prevalent in patients with moderate-to-severe COVID-19 [70]. Notably, except for dyspnea, we found hemoptysis to be another important risk factor for mortality. Thus, patients with hemoptysis should be given particular attention.

Regarding laboratory examination, several test values are associated with severity and mortality of COVID-19. Increased neutrophil count, decreased lymphocyte count, decreased platelet count, increased CRP, coinfection with bacteria or fungi, increased ALT and CK, increased NT-proBNP, and bilateral pneumonia in CT/X-ray were significantly higher in the severe group than in the nonsevere group. Moreover, the proportion of patients with increased CRP and TBIL was also significantly higher in the deceased group than in the survival group. When the body is infected or the tissue is damaged, CRP plasma levels increase rapidly as an acute protein indicator [71]. These increased levels increase phagocytosis and activate the complement cascade [72]. Moreover, damaged, necrotic, and apoptotic tissues and cells, as well as the pathogen, are eliminated by CRP. The CRP concentration is a reflection of the body's response to infection [73]. Increased NT-proBNP and ALT indicate impaired cardiac function, and increased TBIL indicates impaired liver function. Coinfection with bacteria or fungi and bilateral pneumonia in CT/X-ray were associated with COVID-19 severity. This is consistent with the results of Li et al., showing that initial CT scores may be useful to stratify patients [74]. All of the risk factors are helpful for identifying possible severe cases and are potentially valuable for decisions regarding allocation of medical resources.

# Strengths and weaknesses

To the best of our knowledge, this is the first updated metaanalysis to assess all of the common risk factors for progression and mortality in COVID-19 patients using a large study sample. In this study, more confounding factors were adjusted, and more risk factors were found for the first time. High heterogeneity was found in the analysis of some risk factors, and the majority of factors were compensated by sensitivity analysis. Some results (decreased WBC and LDH in severe and fatal cases as well as dizziness) should be interpreted with caution given the limited number of included articles and high heterogeneity. Further high-quality studies are needed to verify these results.

This meta-analysis has some potential limitations. First, the source of heterogeneity for some risk factors was not identified by sensitivity analysis. Second, the small sample size of patients hindered the implementation of meta-regression analysis. Third, the nonrandomized and retrospective

tudy or Subgroup	evere/Dece Events	Total	on-severe/Si Events		Weight	Odds Ratio M-H, Random, 95% Cl	Odds R M-H, Randon	
.17.1 severity								
eng Y 2020	27	88	59	296	25.9%	1.78 [1.04, 3.04]		
uang CL 2020 i Y 2020	4 2	13	1	28 16	14.1% 10.0%	12.00 [1.18, 121.81] 11.00 [0.47, 258.41]		
ubtotal (95% CI)	2	110	0	340	50.0%	3.71 [0.90, 15.26]	-	
otal events	33		60			25 E E		
eterogeneity: Tau <sup>2</sup> = 0.78 est for overall effect: Z =			P = 0.16); l <sup>2</sup> =	45%				
17.2 mortality								
u RH 2020	13	21	28	158	23.4%	7.54 [2.86, 19.92]		
Y 2020	1	5	1	20	10.8%	4.75 [0.24, 92.97]	0	
nou F 2020	23	50	1	95	15.8%	80.07 [10.34, 620.36]		
ubtotal (95% CI) stal events	37	76	30	273	50.0%	14.40 [2.45, 84.54]		
eterogeneity: Tau <sup>2</sup> = 1.49	0.	25 df = 2 (		62%				
st for overall effect: Z =								
tal (95% CI)		186		613	100.0%	7.94 [2.26, 27.87]		
tal events	70	100	90	015	100.076	1.04 [2.20, 21.07]		-
eterogeneity: Tau <sup>2</sup> = 1.5	1; Chi <sup>2</sup> = 20	.08, df = 5	(P = 0.001); I	² = 75%			0.005 0.1 1	10 2
st for overall effect: Z =			5 III III III					avours [control]
st for subaroup different Belevated NT-p		1.38. df = 1	(P = 0.24).1	* = 27,3%				
-5	evere/Dece		lon-severe/5			Odds Ratio	Odds Ra	
udy or Subgroup 18.1 severity	Events	Total	Events	Total	Weight	M-H. Fixed, 95% CI	M-H, Fixed.	95% CI
XC 2020	75	199	17	136	84.0%	4.23 [2.36, 7.59]		
Y 2020	2	9	1	16	3.7%	4.29 [0.33, 55.59]		1
ubtotal (95% CI)	2014) 2014)	208	N2523	152	87.7%	4.24 [2.40, 7.48]		•
tal events	77 0 df = 1 /P	- 0.001.13	18					
est for overall effect: Z =			- 0%					
18.2 mortality	2503	231	122.22	2222	(22/212)		12.	
ARH 2020 Y 2020	20	21 5	107	158		9.53 [1.24, 73.01] 2.25 [0.16, 31.33]		
ubtotal (95% CI)		26	2	178		6.99 [1.46, 33.59]		
otal events	21		109					
eterogeneity: Chi <sup>2</sup> = 0.86			= 0%					
est for overall effect: Z =	2.43 (P = )	0.02)						
otal (95% CI)		234		330	100.0%	4.57 [2.68, 7.81]		•
otal events	98		127					1
eterogeneity: Chi <sup>2</sup> = 0.8 est for overall effect: Z =			= 0%				0.01 0.1 1	10
est for subaroup differen			1 (P = 0.56).	$1^2 = 0\%$			Favours [experimental] Fa	avours [control]
Celevated D-din	ner evere/Dece	based I	lon-severe/s	Invival		Odds Ratio	Odds Ra	die.
	Events	Total	Events		Weight		M-H, Fixed.	
19.1 severity		Total	Events	Total		M-H. Fixed, 95% CI		
19.1 severity uan W 2020	65	Total 109	Events 195	<u>Total</u> 451	36.5%	M-H. Fixed, 95% Cl 1.94 [1.27, 2.97]		
19.1 severity uan W 2020 D 2020	65 16	<u>Total</u> 109 40	Events 195 28	<u>Total</u> 451 168	36.5% 7.7%	M-H. Fixed. 95% Cl 1.94 [1.27, 2.97] 3.33 [1.57, 7.07]		
19.1 severity Juan W 2020 D 2020 I KH 2020 I Y 2020	65	<u>Total</u> 109 40 247 9	Events 195	Total 451 168 254 16	36.5% 7.7% 36.4% 2.3%	M-H, Fixed, 95% Cl 1.94 [1.27, 2.97] 3.33 [1.57, 7.07] 3.43 [2.37, 4.96] 2.08 [0.40, 10.95]		
19.1 severity Juan W 2020 I D 2020 I KH 2020 I KH 2020 I Y 2020 ubtotal (95% CI)	65 16 149 5	<u>Total</u> 109 40 247	Events 195 28 78 6	<u>Total</u> 451 168 254	36.5% 7.7% 36.4%	M-H. Fixed. 95% Cl 1.94 [1.27, 2.97] 3.33 [1.57, 7.07] 3.43 [2.37, 4.96]		
19.1 severity uan W 2020 D 2020 KH 2020 Y 2020 ubtotal (95% CI) otal events	65 16 149 5 235	Total 109 40 247 9 405	Events 195 28 78 6 307	Total 451 168 254 16	36.5% 7.7% 36.4% 2.3%	M-H, Fixed, 95% Cl 1.94 [1.27, 2.97] 3.33 [1.57, 7.07] 3.43 [2.37, 4.96] 2.08 [0.40, 10.95]		
.19.1 severity buan W 2020 D 2020 I KH 2020 I KH 2020 I V 2020 Ubtotal (95% CI) otal events leterogeneity: Chi <sup>2</sup> = 4.3: est for overall effect: Z =	65 16 149 5 235 3, df = 3 (P	Total 109 40 247 9 405 = 0.23); I <sup>2</sup>	Events 195 28 78 6 307	Total 451 168 254 16	36.5% 7.7% 36.4% 2.3%	M-H, Fixed, 95% Cl 1.94 [1.27, 2.97] 3.33 [1.57, 7.07] 3.43 [2.37, 4.96] 2.08 [0.40, 10.95]		
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19.1 severity uan W 2020 D 2020 KH 2020 Y 2020 ubtotal (95% CI) otal events eterogeneity: Chi <sup>2</sup> = 4.3: est for overall effect: Z = 19.2 mortality hen RC 2020	65 16 149 5 235 3, df = 3 (P 7.63 (P < 1 34	Total 109 40 247 9 405 = 0.23); l <sup>2</sup> 0.00001) 39	Events 195 28 78 6 307	Total 451 168 254 16 889 754	36.5% 7.7% 36.4% 2.3% 82.9%	M-H, Fixed, 95% Cl 1.94 [1.27, 2.97] 3.33 [1.57, 7.07] 3.43 [2.37, 4.96] 2.08 [0.40, 10.95]		
19.1 severity uan W 2020 D 2020 KH 2020 Y 2020 ubtotal (95% CI) otal events eterogeneity: Chi <sup>2</sup> = 4.3; est for overall effect: Z = 19.2 mortality hen RC 2020 u RH 2020	65 16 149 5 3, df = 3 (P 7.63 (P < 1 34 16	Total 109 40 247 9 405 = 0.23); l <sup>2</sup> 0.00001) 39 21	Events 195 28 78 6 307 = 31% 384 76	Total 451 168 254 16 889 754 158	36.5% 7.7% 36.4% 2.3% 82.9% 5.8% 5.1%	M-H. Fixed. 95% Cl 1.94 [1.27, 2.97] 3.33 [1.57, 7.07] 3.43 [2.37, 4.96] 2.08 [0.40, 10.95] 2.73 [2.11, 3.53] 6.55 [2.54, 16.93] 3.45 [1.21, 9.88]		
19.1 severity           uan W 2020           D 2020           KH 2020           Y 2020           ubtotal (95% CI)           otal events           eterogeneity: Chi² = 4.3:           est for overall effect: Z =           19.2 mortality           hen RC 2020           u RH 2020           v H 2020	65 16 149 5 235 3, df = 3 (P = 7.63 (P < 1 34 16 2	Total 109 40 247 9 405 = 0.23); l <sup>2</sup> 0.00001) 39 21 5	Events 195 28 78 6 307 = 31% 384 76 9	Total 451 168 254 16 889 754 158 20	36.5% 7.7% 2.3% 82.9% 5.8% 5.1% 2.6%	M-H, Fixed, 95% Cl 1.94 [1.27, 2.97] 3.33 [1.57, 7.07] 3.43 [2.37, 4.96] 2.08 [0.40, 10.95] 2.73 [2.11, 3.53] 6.55 [2.54, 16.93] 3.45 [1.21, 9.88] 0.81 [0.11, 5.99]		
19.1 severity         uan W 2020         D 2020         KH 2020         Y 2020         ubtotal (95% CI)         otal events         eterogeneity: Chi <sup>2</sup> = 4.3;         set for overall effect: Z =         19.2 mortality         hen RC 2020         u RH 2020         Y 2020         hou F 2020	65 16 149 5 3, df = 3 (P 7.63 (P < 1 34 16	Total 109 40 247 9 405 = 0.23); l <sup>2</sup> 0.00001) 39 21	Events 195 28 78 6 307 = 31% 384 76	Total 451 168 254 16 889 754 158	36.5% 7.7% 2.3% 82.9% 5.8% 5.8% 2.6% 3.7%	M-H. Fixed. 95% Cl 1.94 [1.27, 2.97] 3.33 [1.57, 7.07] 3.43 [2.37, 4.96] 2.08 [0.40, 10.95] 2.73 [2.11, 3.53] 6.55 [2.54, 16.93] 3.45 [1.21, 9.88]		
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19.1 severity ivan W 2020 D 2020 KH 2020 Y 2020 ubtotal (95% CI) otal events leterogeneity: Chi <sup>2</sup> = 4.3: est for overall effect: Z = .19.2 mortality hen RC 2020 u RH 2020 iv 2020 hou F 2020 ubtotal (95% CI) otal events leterogeneity: Chi <sup>2</sup> = 5.3: est for overall effect: Z = otal (95% CI)	65 16 149 235 3, df = 3 (P < 1 34 16 2 34 16 2 7, df = 3 (P < 1 102 7, df = 3 (P < 1	Total 109 40 247 9 405 = 0.23); l <sup>2</sup> 0.00001) 39 21 5 54 119 = 0.15); l <sup>2</sup>	Events 195 28 78 6 307 = 31% 384 76 9 67 536 = 44%	Total 451 168 254 166 889 754 158 200 118 1050	36.5% 7.7% 2.3% 82.9% 5.8% 5.8% 2.6% 3.7%	M-H. Fixed. 95% Cl 1.94 [1.27, 2.97] 3.33 [1.57, 7.07] 3.43 [2.37, 4.96] 2.08 [0.40, 10.95] 2.73 [2.11, 3.53] 6.55 [2.54, 16.93] 3.45 [1.21, 9.88] 0.81 [0.11, 5.99] 9.51 [3.23, 28.06]		
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19.1 severity ivan W 2020 D 2020 KH 2020 Y 2020 ubtotal (95% CI) otal events leterogeneity: Chi <sup>2</sup> = 4.3: est for overall effect: Z = .19.2 mortality hen RC 2020 u RH 2020 hou F 2020 hou F 2020 hou F 2020 hou F 2020 hou F 2020 ist for overall effect Z = otal (95% CI) otal events leterogeneity: Chi <sup>2</sup> = 5.3: est for overall effect Z = otal events leterogeneity: Chi <sup>2</sup> = 13.1: est for overall effect. Z =	65 16 149 5 235 3, df = 3 (P < 1 34 16 2 50 7, df = 3 (P < 1 50 7, df = 3 (P < 1 34 16 50 7, df = 3 (P < 1 34 16 50 7, df = 3 (P < 1 50 7, df = 3 (P < 1) 50 7, df = 3 (P < 1) 50	Total 109 40 247 9 405 = 0.23); l <sup>2</sup> 0.00001) 39 21 5 54 119 = 0.15); l <sup>2</sup> 0.00001) 524 P = 0.06); l 0.0000; l	Events 195 28 78 6 307 = 31% 384 76 9 67 536 = 44% ***********************************	Total 451 168 254 16 889 754 158 200 118 1050	36.5% 7.7% 36.4% 2.3% 82.9% 5.8% 5.1% 2.6% 3.7% 17.1%	M-H. Fixed. 95% Cl 1.94 [1.27, 2.97] 3.33 [1.57, 7.07] 3.43 [2.37, 4.96] 2.08 [0.40, 10.95] 2.73 [2.11, 3.53] 6.55 [2.54, 16.93] 3.45 [1.21, 9.88] 0.81 [0.11, 5.99] 9.51 [3.23, 28.06] 5.42 [3.14, 9.35]	M-H, Fixed.	95% Cl
19.1 severity ivan W 2020 D 2020 KH 2020 KH 2020 V 2020 ubtotal (95% CI) otal events set for overall effect: Z = .19.2 mortality then RC 2020 u RH 2020 i Y 2020 hou F 2020 Ubtotal (95% CI) otal events leterogeneity: Chi <sup>2</sup> = 5.3: set for overall effect: Z = otal (95% CI) otal events leterogeneity: Chi <sup>2</sup> = 13.1 set for subaroup differen	65 16 149 5 235 3, df = 3 (P < 1 34 16 2 50 102 7, df = 3 (P < 1 34 16 2 50 102 6.06 (P < 1 337 61, df = 7 (1 9.44 (P < 1) 9.44 (P < 1)	Total 109 40 247 9 405 = 0.23); l <sup>2</sup> 0.00001) 39 21 5 54 119 = 0.15); l <sup>2</sup> 0.00001) 524 P = 0.06); 0.0001 4.96. df =	Events 195 28 78 6 307 = 31% 384 76 9 67 536 e 44% z = 49% 1 (P = 0.03).	Total 451 168 254 16 889 754 158 200 118 1050	36.5% 7.7% 36.4% 2.3% 82.9% 5.8% 5.1% 2.6% 3.7% 17.1%	M-H. Fixed. 95% Cl 1.94 [1.27, 2.97] 3.33 [1.57, 7.07] 3.43 [2.37, 4.96] 2.08 [0.40, 10.95] 2.73 [2.11, 3.53] 6.55 [2.54, 16.93] 3.45 [1.21, 9.88] 0.81 [0.11, 5.99] 9.51 [3.23, 28.06] 5.42 [3.14, 9.35]	M-H, Fixed.	95% Cl
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19.1 severity uan W 2020 D 2020 KH 2020 Y 2020 Jabotal (95% CI) tal events eterogeneity: Chi <sup>2</sup> = 4.3: set for overall effect: Z = 19.2 mortality hen RC 2020 u RH 2020 Y 2020 hou F 2020 Jubtotal (95% CI) tal events eterogeneity: Chi <sup>2</sup> = 5.3: set for overall effect: Z = bal (95% CI) tal events eterogeneity: Chi <sup>2</sup> = 13.4 set for overall effect: Z = set for subaround efferem <b>Dilateral pneu</b> Set udy or Subgroup	65 16 149 5 235 3, df = 3 (P < 1 7, 63 (P < 1 34 16 2 50 102 7, df = 3 (P < 1 37 61, df = 7 (1 9.84 (P < 1 0.537 61, df = 7 (1) 9.84 (P < 1 0.537 102 102 102 102 102 102 102 102	Total 109 40 247 9 405 = 0.23); I <sup>2</sup> 0.00001) 39 21 5 54 119 = 0.15); I <sup>2</sup> 0.00001) 524 P = 0.06); I: 0.00001) 524 r = 0.06); I: 0.00001) 525 r = 0.05); I: 0.00001) 526 r = 0.05); I: 0.00001) 527 r = 0.05); I: 0.00001) 526 r = 0.05); I: 0.00001) 527 r = 0.0000]; I: 0.00001) 527 r = 0.0000]; I: 0.00001]; I: 0.0000001]; I: 0.00001]; I: 0.0000001]; I: 0.000	Events 195 28 78 6 307 = 31% 384 76 9 67 536 = 44% * = 49% 1 (P = 0.03). -ray	Total 451 168 254 16 889 754 158 20 118 1050 11939 1939 1 <sup>2</sup> = 79.8 <sup>4</sup>	36.5% 7.7% 36.4% 2.3% 82.9% 5.8% 5.1% 2.6% 3.7% 17.1%	<u>M-H. Fixed. 95% Cl</u> 1.94 [1.27, 2.97] 3.33 [1.57, 7.07] 3.43 [2.37, 4.96] 2.08 [0.40, 10.95] 2.73 [2.11, 3.53] 6.55 [2.54, 16.93] 3.45 [1.21, 9.88] 0.81 [0.11, 5.99] 9.51 [3.23, 28.06] 5.42 [3.14, 9.35] 3.19 [2.53, 4.02]	M-H, Fixed.	95% Cl
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◄Fig. 7 Other lab examination risk factors for progression and mortality in COVID-19. Forest plots are shown for the effects of (A) elevated hs-cTnl, (B) elevated NT-pro BNP, (C) elevated D-dimer, and (D) bilateral pneumonia in CT/X-ray.

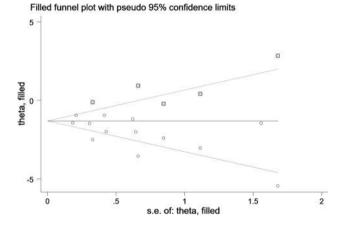


Fig. 8 Trim-and-fill analysis for the publication bias for dyspnea

nature of all studies should be taken into consideration as a source of bias. Randomized controlled trials are warranted in the future to provide high-quality evidence.

# Conclusions

Some new risk factors were identified in our updated metaanalysis. Regarding comorbidities, CVD, CKD, CHD, and malignancy were associated with an increased risk of progression and mortality in COVID-19 patients. Regarding clinical manifestations, sputum production was associated with a dramatically increased risk of progression and mortality. Hemoptysis was a risk factor for death in COVID-19 patients. In laboratory examinations, increased neutrophil count, decreased lymphocyte count, decreased platelet count, increased CRP, coinfection with bacteria or fungi, increased ALT and CK, increased NT-proBNP, and bilateral pneumonia in CT/X-ray were significantly higher in the severe group than in the non-severe group. Moreover, the proportion of patients with increased CRP and TBIL was also significantly higher in the deceased group than in the survival group.

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## Declarations

**Conflict of interest** The authors declare that they have no conflict of interest.

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