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RESEARCH ARTICLE

Factors associated with disease severity and mortality among patients with COVID-19: A systematic review and meta-analysis

Vignesh Chidambaram¹, Nyan Lynn Tun¹, Waqas Z. Haque¹, Marie Gilbert Majella², Ranjith Kumar Sivakumar³, Amudha Kumar⁴, Angela Ting-Wei Hsu¹, Izza A. Ishak¹, Aqsha A. Nur¹, Samuel K. Ayeh⁵, Emmanuella L. Salia⁶, Ahsan Zil-E-Ali¹, Muhammad A. Saeed⁷, Ayu P. B. Sarena⁸, Bhavna Seth⁹, Muzzammil Ahmadzada⁷, Eman F. Haque¹⁰, Pranita Neupane⁵, Kuang-Heng Wang¹, Tzu-Miao Pu¹, Syed M. H. Ali¹¹, Muhammad A. Arshad¹², Lin Wang¹, Sheriza Baksh¹, Petros C. Karakousis⁵, Panagis Galiatsatos⁹*

 Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, United States of America,
 Department of Preventive and Social Medicine, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India, 3 Department of Anaesthesia and Intensive Care, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, Hong Kong, China, 4 Department of Internal Medicine, University of Arkansas for Medical Sciences, Little Rock, Arkansas, United States of America, 5 Division of Infectious Diseases, Department of Medicine, Johns Hopkins School of Medicine, Baltimore, Maryland, United States of America, 6 Department of Pediatrics, Johns Hopkins School of Medicine, Baltimore, Maryland, United States of America, 7 Johns Hopkins University, Baltimore, Maryland, United States of America, 8 Bhayangkara Setukpa Hospital, Sukabumi, Indonesia, 9 Division of Pulmonary and Critical Care Medicine, Department of Medicine, Johns Hopkins School of Medicine, Baltimore, Maryland, United States of America, 10 Southern Methodist University, Dallas, Texas, United States of America, 11 Fatima Memorial Hospital, Lahore, Pakistan, 12 Nishtar Hospital, Multan, Pakistan

* pgaliat1@jhmi.edu

Abstract

Background

Understanding the factors associated with disease severity and mortality in Coronavirus disease (COVID-19) is imperative to effectively triage patients. We performed a systematic review to determine the demographic, clinical, laboratory and radiological factors associated with severity and mortality in COVID-19.

Methods

We searched PubMed, Embase and WHO database for English language articles from inception until May 8, 2020. We included Observational studies with direct comparison of clinical characteristics between a) patients who died and those who survived or b) patients with severe disease and those without severe disease. Data extraction and quality assessment were performed by two authors independently.

Results

Among 15680 articles from the literature search, 109 articles were included in the analysis. The risk of mortality was higher in patients with increasing age, male gender (RR 1.45, 95%

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CI 1.23–1.71), dyspnea (RR 2.55, 95%CI 1.88–2.46), diabetes (RR 1.59, 95%CI 1.41– 1.78), hypertension (RR 1.90, 95%CI 1.69–2.15). Congestive heart failure (OR 4.76, 95%CI 1.34–16.97), hilar lymphadenopathy (OR 8.34, 95%CI 2.57–27.08), bilateral lung involvement (OR 4.86, 95%CI 3.19–7.39) and reticular pattern (OR 5.54, 95%CI 1.24–24.67) were associated with severe disease. Clinically relevant cut-offs for leukocytosis(>10.0 x10⁹/L), lymphopenia(< 1.1 x10⁹/L), elevated C-reactive protein(>100mg/L), LDH(>250U/L) and Ddimer(>1mg/L) had higher odds of severe disease and greater risk of mortality.

Conclusion

Knowledge of the factors associated of disease severity and mortality identified in our study may assist in clinical decision-making and critical-care resource allocation for patients with COVID-19.

Introduction

Since the first documented reports of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, the virus has had a global impact, affecting millions, which led the World Health Organization (WHO) to declare the outbreak a pandemic [1, 2]. Patients who develop Coronavirus Disease 2019 (COVID-19) may require hospitalization and intensive care unit admission [3-5].

With variable access to critical care resources across countries, recent guidelines for the COVID-19 pandemic have called for allocating life sustaining treatments based on a patient's risk of mortality [6, 7]. Health systems preparedness requires a deeper understanding of how to effectively triage patients with COVID-19, in order to maximize the benefit of scarce intensive care unit resources while minimizing the potential harm of outpatient management of ill patients. While the guidelines warrant utilizing triage scores that have been previously validated for assessing organ failure/dysfunction and survival (e.g. sequential organ failure assessment, SOFA), these are non-specific in etiology [7, 8]. Thus, having an understanding of the predisposing conditions and disease-specific clinical, laboratory and radiological parameters, may lay the groundwork for developing a COVID-19 specific composite score at a later stage, which can predict unfavorable clinical outcomes.

With the massive influx of studies on COVID-19 in the recent months and their often conflicting or unclear findings, a systematic review of the factors associated with survival or disease severity in patients with COVID-19 that takes into consideration the inherent variability in study population, will be of great utility to clinicians, researchers and policy makers. In this systematic review and meta-analysis, we sought to better understand the clinical, laboratory and radiological parameters associated with mortality and disease severity among patients with COVID-19.

Methods

Search strategy and study selection

We followed the PRISMA guidelines for reporting in systematic reviews and meta-analyses [9]. We searched PubMed, Embase and the WHO COVID-19 database by using the search strategy included in the supplementary document in <u>S1 Appendix</u> (Section I). For PubMed and Embase, an initial search on March 26, 2020 was conducted, and updated multiple times

with the final update performed on May 7, 2020. The WHO database was initially downloaded on March 27, 2020 and the final update was performed on May 8, 2020. Only articles published in the English language were included. We only included article published in peer-reviewed academic journals; we did not include articles uploaded in the preprint servers, as they are not peer reviewed and the findings may not be reliable [10].

We included observational studies that included patients with microbiologically confirmed SARS-CoV-2 infection, irrespective of the age of the participants. The study designs of the included studies were assessed and recorded independently by two authors (VC and MM) acting as arbiters. The differentiation between case series and cohort studies was made based on the criteria outlined by Dekkers et al [11]. Case reports, case series, and randomized control trials were excluded from this review. We included all studies that reported a direct comparison of clinical, laboratory or radiologic characteristics between a) patients who died and those who survived or b) patients with severe disease and those without severe disease. Only those studies which defined "severe disease" based on the American Thoracic Society guidelines for the treatment of Community-acquired Pneumonia [12] or the Chinese National Health Commission guidelines for the Treatment of Novel Coronavirus infection [13], were included in our analysis. Studies which only described the characteristics of patients who died or patients with severe disease were excluded if there was no comparison group.

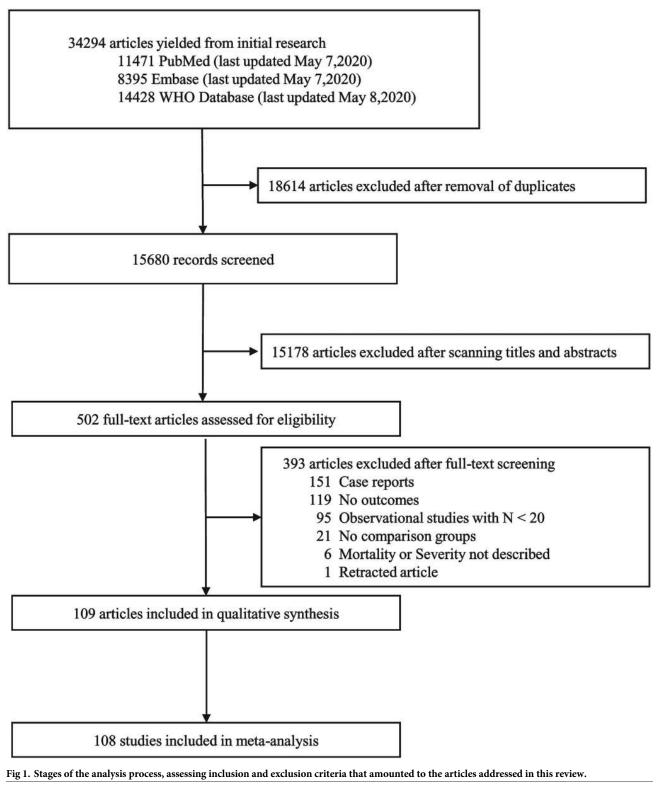
We only included studies reporting primary hospital data on patients, while studies with centralized data from national health agencies and databases were excluded from our review. Efforts were made, as feasible, to minimize overlap of patients across studies by collecting information on the name of the hospital, date of hospital admission of the participants and the names of the investigators.

Literature screening

The COVIDENCE platform was used for conducting this systematic review [14]. After deduplication, the titles and abstracts of the articles retrieved from the search strategy were screened independently by at least two of the following authors (VC, NT, WH, RS, AK, AH, II, AN, SA, ES, and MS) and conflicts were resolved by consensus between VC and NT. The full texts of the articles included after title and abstract screening were independently screened by at least two of the following authors (VC, NT, WH, RS, AK, AH, II, AN, SA, ES, and MS) and conflicts were resolved based on consensus between VC and NT. Specific reasons for study exclusion are listed in Fig 1.

Data extraction and quality assessment

Data extraction was performed independently by at least two of the authors (VC, NT, WH, MM, RS, AK, AH, II, AN, SA, ES, MS, AS, KW, and TP) and conflicts were resolved by a consensus between two authors (MM and VC). The data extraction form for this review was created using the Qualtrics platform [15]. The primary outcomes were a) death of the patient and b) the presence of severe disease in the patient. There were no secondary outcomes. Data on the study characteristics, source of funding, demographic characteristics, comorbidities, clinical symptoms, in-hospital complications, laboratory, and radiological features of the study participants were extracted. Data on sex of the patient, smoking status, presence of comorbidities, clinical symptoms, in-hospital complications, and radiological features were extracted as binary variables, while age was extracted as continuous data. For the laboratory parameters, data were extracted as both continuous and categorical variables. Binary data for the laboratory variables were collected using all the cut-offs described in the included studies. The time points for lab measurements, radiological evaluation and the disease severity assessment were



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extracted for the included studies. Continuous data for the age and laboratory variables were documented as mean. The median values reported in studies were transformed into mean [16].

The risk assessment for bias for all the studies included in this review was performed using the Newcastle-Ottawa quality assessment scale (NOS) for observational and cohort studies [17]. The three major domains of quality of a study covered by this tool were selection of participants, comparability of cohorts and outcome assessment against a total score of 9. This was performed independently by at least two of the following authors (RS, MM, ES, SA). When conflicts related to bias arose, the final decision was taken by a consensus between VC and NT.

Data synthesis and analysis

We performed a meta-analysis with random effects model to obtain pooled effect sizes for the outcomes of interest. The associations between binary parameters and mortality were reported using pooled risk ratios (with 95%CI). Due to the lack of consistency in the time point of assessment of disease severity, odds ratios (with 95%CI) were used to determine the association between the various factors and the presence of severe disease. When the laboratory parameters were reported using different cut-offs, we reported the effect sizes for each cut-off taken separately in addition to the pooled effect sizes for all the cut-offs taken together. Statistical heterogeneity across the studies was assessed by forest plots, I² and Tau² statistics. When the I^2 was more than 60%, we performed subgroup analyses based on the whether the studies included all patients with COVID-19 or only the patients who were critically ill. If the heterogeneity was still higher than 60%, we performed sensitivity analyses by excluding studies with a low quality (NOS < 5). Sensitivity analyses for the laboratory and radiological parameters were also performed by excluding studies which did not report the time points of assessment. Publication bias was assessed by visual inspection of the funnel plot, and Egger's test was performed for those exposures reported by at least 10 studies. For continuous variables, metaregression was performed to assess the percentage change in mortality or the presence of severe disease with unit increase in the mean of laboratory parameter reported in the studies. For the binary exposures, unadjusted effect sizes were calculated from the summary data. Adjusted effect sizes were not used due to the lack of consistency in the parameters that they are adjusted for, among the included studies. All analyses were carried out using the meta package in Stata (StataCorp, version 16) [18].

Role of the funding source

This study was not supported by any funding source.

Results

We identified 15680 studies from three databases after removing duplicates, of which the full text was retrieved for 502 articles. All the articles included were in the English language. The reasons for exclusion of studies are outlined in Fig 1. A total of 109 studies were included for this review, of which 42 studies assessed mortality risks [19–60]; 72 studies determined association with severe disease [24, 34, 39, 41, 56, 58, 61–126], out of which 5 studies reported both the outcomes [24, 34, 39, 56, 58]. Of the total 109 studies in the review, 101 were retrospective cohorts, seven were prospective cohorts, and one of them was an ambispective cohort study. There were no cross-sectional or case control studies that satisfied the inclusion criteria. Of the studies that determined the risk of mortality, an aggregate of 20296 participants were assessed, with 32 studies from China, six from the United States, two from Spain, one from the United Kingdom, one from Italy, one from Iran and a multi-country study. Five of these studies only

included patients who were critically ill or invasively ventilated [<u>19</u>, <u>23</u>, <u>32</u>, <u>35</u>, <u>48</u>]. Among the studies that assessed the association with severe disease, a total of 17992 participants were included with seventy-one studies from China and one study from Italy. The characteristics of the included studies, along with the time points for laboratory, radiological and disease severity assessment, are outlined in the S1 and S2 Tables (in <u>S1 Appendix</u> Section II).

Quality assessment was performed using the New-Castle Ottawa scale (NOS) as all of the studies used a cohort study design. This revealed that one of the studies (0.9%) had scored 9, 54 studies (49.5%) had scored 8, 39 studies (35.7%) scored 7, six studies (5.5%) scored 6. A total of nine studies were identified as low-quality studies (NOS \leq 5) with six studies (5.5%) scoring 5, and the remaining three studies (2.7%) scoring 4 (S3 and S4 Tables—in <u>S1 Appendix</u> section III).

<u>Table 1</u> and <u>Fig 2</u> show the list of exposures and their relationship with mortality. Males (RR 1.45, 95%CI 1.23–1.71) and ever-smokers (RR 1.43, 95%CI: 1.09–1.87) had higher risk of mortality. Patients with diabetes, hypertension, cardiovascular diseases, chronic renal disease, chronic liver disease and malignancy were associated with an increased risk of mortality; while hepatitis B and HIV infections did not result in higher risk of mortality. Section V of the supplementary document in <u>S1 Appendix</u> illustrates the forest and funnel plots of these associations.

Patients who had dyspnea (RR 2.55, 95%CI: 1.88-3.46) and hemoptysis (RR 1.62, 95%CI: 1.25–2.11) had a significantly higher risk of mortality while other clinical features like fever, sore throat, cough, expectoration, vomiting, diarrhea, nausea, myalgia, headache, anorexia, chest pain, abdominal pain, palpitations, and anosmia did not demonstrate any significant association with mortality. Acute respiratory distress syndrome (ARDS) was associated with an RR of 20.19 [95%CI: 10.87–37.52] with an I² of 79%. Cardiac complications such as acute cardiac injury and acute cardiac failure had higher risk of mortality with RR of 5.42 [95%CI: 3.79-7.77] and 3.10 [95%CI: 2.55-3.77] respectively. Other complications with higher risk of mortality were sepsis, bacteremia, shock, disseminated intravascular coagulation (DIC), acute kidney injury and acute liver dysfunction. Association of laboratory parameters (based on specific cut-offs) with the risk of mortality are mentioned in the Table 2. Among the laboratory parameters that were assessed using binary cut-offs, increased total leucocyte count, increased neutrophil count, decreased lymphocyte count and reduced platelet count were associated with increased risk of death. Inflammatory parameters such as C-reactive protein and procalcitonin were associated with increased risk of death with RRs of 5.49 [95%CI: 1.72-17.51] and 3.09 [95%CI: 2.35-4.07] respectively. Abnormal renal and liver parameters, hypernatremia and hyperkalemia also were associated with increased risk of mortality.

Presence of bilateral lung infiltrates (RR 1.35, 95%CI 1.07–1.69), consolidation (RR 2.07, 95%CI 1.35–3.16) and air-bronchogram (RR 3.56, 95%CI 1.37–9.29) on CT were associated with increased RR for mortality. The presence of unifocal involvement on CT had lower risk of death (RR 0.31, 95%CI 0.11–0.92). The presence of ground glass opacities or pleural effusion on CT demonstrated no association with mortality.

The odds ratios (OR) of severe disease in patients with various clinical characteristics are shown in <u>Table 1</u> and <u>Fig 3</u>. The odds of severe disease were high in patients with diabetes, hypertension, cardiovascular diseases, chronic kidney disease, chronic liver disease and chronic obstructive pulmonary disease. HIV and hepatitis B infections were not associated with severe disease. Odds ratios for severe disease were higher in patients with fever, cough, expectoration, anorexia, chest pain, dyspnea, and hemoptysis. The OR for severe disease in patients who had dyspnea was 4.72 [95% CI: 3.18–7.01] among 34 studies. Gastrointestinal symptoms nausea, vomiting and diarrhea did not show association with disease severity.

Clinical characteristics		Risk o	Risk of Mortality				Odds of	Odds of Severe disease		
	No. of Studies	No. of Patients	Pooled RR [95% CI]	Heterogeneity I ² T ²	geneity T ²	No. of Studies	No. of Patients	Pooled OR [95% CI]	Heterogeneity I ² T ²	eneity T ²
Baseline characteristics and co-morbidities										
Male sex	26	16422	*1.45 [1.23-1.71]	49%	0.07	59	17063	1.38 [1.24-1.53]	31%	0.04
Ever smoker	7	10419	1.43 [1.09–1.87]	0	0	10	4511	1.51 [1.06–2.14]	62%	0.33
Diabetes	27	16263	*1.59 [1.41-1.78]	23%	0.02	36	7552	2.09 [1.66-2.64]	40%	0.16
Hypertension	26	15947	*1.90 [1.69–2.15]	28%	0.02	33	7002	2.63 [2.08-3.33]	64%	0.25
Cardiovascular diseases	25	16576	2.27 [1.88–2.79]	71%	0.13	31	6932	2.83 [2.21-3.63]	23%	0.09
Congestive Heart Failure	5	9910	2.08 [1.54–2.80]	%0	0	.0	558	4.76 [1.34-16.97]	%0	0
Cerebrovascular Disease	15	2437	2.63 [1.97-3.51]	75%	0.20	13	4246	2.62 [1.76-3.90]	2%	0.04
COPD	15	9717	2.29 [1.90–2.75]	%0	0	19	4790	3.23 [1.97-5.31]	24%	0.27
Asthma	2	643	0.98 [0.42-2.32]	%0	0	:	:	:	:	Ľ
CKD	15	6556	2.24 [1.78-2.81]	39%	0.07	14	4442	2.62 [1.46-4.71]	27%	0.31
Chronic liver disease	9	3672	2.18 [1.40-3.40]	20%	0.07	17	8869	1.56 [1.12-2.17]	%0	0
Hepatitis B infection	2	822	1.14 [0.61–2.12]	%0	0	ŝ	1945	0.54 [0.17-1.71]	%0	0
HIV	1	274	1.21 [0.17-8.64]	:	:	2	397	4.86 [0.50-47.22]	%0	0
Cancer	18	7008	1.52 [1.21-1.90]	%0	0	20	6026	2.90 [1.99-4.24]	4%	0.04
Immunodeficiency	:	:	:	:	:	4	1838	2.51 [0.62-10.10]	16%	0.36
Endocrine diseases	:	:	:	:	:	4	1378	2.45 [1.49-4.04]	%0	0
Clinical features										
Fever	21	3551	0.82 [0.67-1.00]	28%	0.05	37	7501	1.75 [1.32–2.31]	56%	0.31
Sore throat	4	1256	0.79 [0.44-1.42]	%0	0	20	4721	0.79 [0.60-1.04]	%0	0
Cough	22	4098	1.00 [0.88-1.14]	16%	0.01	39	7746	1.22 [1.08-1.38]	5%	0.01
Expectoration	9	1977	1.19 [0.98-1.45]	55%	0.04	21	4960	1.55 [1.27-1.90]	32%	0.06
Vomiting	Ω	1644	0.86 [0.51-1.44]	%0	0	7	1919	1.02 [0.65-1.60]	%0	0
Diarrhea	14	3230	1.15 [0.85-1.57]	65%	0.17	33	6831	1.31 [1.00-1.71]	43%	0.19
Nausea	7	1725	1.00 [0.67-1.50]	1%	0	13	3809	1.01 [0.61–1.68]	49%	0.34
Myalgia	18	3270	0.91 [0.76-1.08]	8%	0.01	25	5831	1.22 [0.90-1.65]	62%	0.29
Headache	11	2645	0.95 [0.66-1.37]	21%	0.07	26	6340	1.44 [1.00-2.06]	53%	0.37
Anorexia	5	1119	1.04 [0.86-1.26]	%0	0	10	1157	2.72 [1.84-4.01]	%0	0
Chest pain	7	2026	1.16 [0.77-1.75]	43%	0.11	16	3558	2.70 [1.56-4.68]	75%	0.73
Dyspnea	20	3595	2.55 [1.88-3.46]	77%	0.30	34	7356	4.72 [3.18-7.01]	86%	06.0
Hemoptysis	6	1014	1.62 [1.25–2.11]	%0	0	5	2584	2.93 [1.47-5.83]	%0	0
Abdominal pain	5	1498	1.22[0.47-3.16]	7%	0.09	6	2506	2.86 [1.00-8.13]	%69	1.67
Palpitations	1	225	0.94 [0.59-1.49]	:	:	2	254	3.14 [0.88-11.19]	%0	0
Rhinorrhea	1	52	1.48 [0.96–2.29]	:	:	4	1096	0.94 [0.38-2.30]	%0	0
Anosmia	1	95	0.45 [0.03-6.40]	:	:	:	:	:	:	:
Complications										
ARDS	14	2795	*20.19 [10.87-37.52]	79%	06.0	:	:	:	:	:
Shock	6	1844	6.12 [3.59-10.45]	93%	0.54	:	:	:	:	:
Sepsis	3	573	47.95 [11.81–194.72]	%0	0	:	:	:	:	:
Bacteremia	6	1365	5.07 [2.02-12.69]	94%	1.18	:	:	:	:	:
Acute cardiac injury	14	2860	5.42 [3.79-7.77]	86%	0.36	:	:	:	:	:

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	No. of Studies	No. of Patients	Pooled RR [95% CI]	Ietero		No. of Studies	No. of Patients	Pooled OR [95% CI]	Heterogeneity	neity
				I^2 T^2					I^2	T^2
DIC	4	1394	3.41 [2.00–5.81]	95%	0.28	:	:	:	:	:
GI bleeding	4	1028	2.53 [1.42-4.49]	76%	0.26	:	:	:	:	:
Acute Kidney Injury	15	5331	*4.65 [3.25–6.65]	95%	0.42	:	:	:	:	:
Acute liver injury	10	4796	2.54 [1.77-3.66]	93%	0.28	:	:	:	:	:
Hepatic encephalopathy	1	109	3.99 [2.71–5.87]	:	:	:	:	:	:	:
V entilator associated pneumonia	1	52	0.51 [0.16–1.62]	:	:	:	:	:	:	:
CT features										
Peripheral distribution	1	27	0.32 [0.05–2.08]	:	:	4	313	1.40 [0.36-5.50]	28%	0.57
Bilateral involvement	11	2067	1.35[1.07-1.69]	0	0	19	3515	4.86 [3.19–7.39]	47%	0.28
Consolidation	3	243	2.07 [1.35–3.16]	0	0	6	1084	3.01 [1.32-6.88]	76%	1.09
GGO	υ	706	1.41 [0.87–2.28]	55%	0.15	14	2629	1.63 [1.22–2.17]	11%	0.03
Mixed GGO and consolidation	:	:	:	:	:	3	263	1.63 [0.69–3.85]	0	0
Air bronchogram	1	27	3.56[1.37–9.29]	:	:	4	333	4.79[1.11-20.61]	85%	1.85
Nodular infiltrates	1	27	0.41 [0.03-5.41]	:	0	4	356	1.03 [0.39–2.73]	46%	0.45
Hilar Lymphadenopathy	:	:	:	:	:	5	397	8.34 [2.57–27.08]	%0	0
Tree in bud appearance	:	:	:	:	:	1	120	4.30 [1.07–17.23]	·	0
Unifocal involvement	2	463	0.31 [0.11-0.92]	44%	0.27	3	1237	1.13 [0.46–2.81]	66%	0.38
Pleural effusion	2	78	1.06 [0.27-4.21]	:	:	8	642	5.30 [2.74-10.26]	%0	0
Pleural thickening	:	:	:	:	:	1	52	1.86[0.35-9.92]	:	0
Inter-lobular septal thickening	:	:	:	:	:	2	124	2.86 [1.06-7.72]	%0	0
Bronchiectasis	:	:	:	:	:	2	221	5.62 [2.22-14.24]	%0	0
Linear infiltrates	:	:	:	:	:	3	324	3.21[1.00-10.25]	72%	0.74
Crazy pavement sign	:	:	:	:	:	5	650	4.52 [2.08–9.81]	64%	0.50
Reticular pattern	:	:	:	:	:	4	425	5.54 [1.24-24.67]	72%	1.61
Abbreviations: ARDS = Acute Respiratory Distress Syndrome. CKD = Chronic Kidney Disease. COPD = Chronic Obstructive Pulmonary Disease. CT = Computed Tomography.	7 Distress Syndrome	. CKD = Chronic	Kidney Disease. COPD	= Chronic	Obstruct	ive Pulmonary	Disease. CT = Coi	mputed Tomography.		

DIC = Disseminated Intravascular Coagulation. GGO = Ground Glass Opacity. GI Bleeding = Gastrointestinal Bleeding. HIV = Human Immunodeficiency Virus. OR = Odds ratio. RR = Risk ratio. * denotes presence of publication bias by Egger's test (p–value < 0.05). AKUS ADDFevial

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Table 1. (Continued)

Study		Smokers		r smokers		Risk Ra	Fo	Weight	E				cardiac injury		Risk Ratio		Weight
Kun Wang	Died 1	Surviver 11	1 Died	Survived 266		with 95%		(%)	Study Qingchun Yao	Died 6	Survived 2	Died	Survived 94		12.50 [5.22, 2		(%) 6.00
Hernando Trujilio	0	2	18	5		0.22 [0.02,		1.12	Jia-Fu Wei	3	85	0	13		1.10 [0.06, 2		1.31
Yang-kai LI # Tao Chen #	3	4	2	16 151	<u>ti</u>	• 3.86 [0.81,		2.97	Xiaobo Yang S	9	3	23	17	-	1.30 [0.86,		8 23
Xiaoling Zou #	5	7	46	95		1.16 0.71,		18.07	Yang Wang #	107	4	26	207		8.64 [6.00, 1		8.48
Ke Wang #	18	74	56	396	-	1.58 [0.98.	2.56]	31,27	Tao Chen # Xiaojing Zou #	72	18 11	22 18	91 91		4.11 [2.78, 4.58 [2.91,		8.37
Fei Zhou \$	5	6	49	131	t	- \$,67 [0.84	2016	15.22	Yan Deng #	65	1	44	115		3.56 [2.76.		8.88
Overall Helerogeneity: 1 ⁸ =	0.00 1	= 0.00%	H ² = 1.0	n	1	1.43 [1.09,	1.87]		Ke Wang #	49	70	29	400		6.09[4.03,		8.28
Test of 8. = 8, Q(6			10 - 1.0						Fei Zhou S	32	1	22	136	-	6.96 [4.70, 1		8.36
Test of $\theta = 0$: $z = 2$	59.p≠0	0.01							Dawei Wang *	8	4	11	84		5.76 [2.90, 1		6.94
В					1.00				Rongrong Yang * Jianlei Cao *	12	16 3	19 5	171		2.73 [1.22,		6.34 5.93
2	Hyperte	nsion	No Hyper	tension		Risk Ratio	Weight		Wen-Jun Tu *	18	6	7	143	-	-16.07 [7.52. 3		6.56
Study	Died S	unvived	Died 5	iunvived	1.1.1.1.1	with 95% CI	(%)		Lang Wang @	39	31	26	243	-	5.76 [3.78,	8.78]	8.24
Kingli Yuan Kun Viang	5	0 33	5	17		3.63[1.78, 8.26] 5.44[2.35, 12.60]	2.14		Overall					+	5.42 [3.79.	7.77]	
Qingohun Yao	7		\$	87		-8.05[2.91. 22.27]	1.29		Heterogeneity: 1 Test of 8. = 8; Q								
Ming Ding Jerniter Tomine	0	6 24	3	23	•	0.55(0.03, 9.47]	0.18		Test of $\theta = 0$; z =			U					
Rono-Hul Du	11	45	9	51 113		2.10 [0.96, 4.55]	2.10		1001.01.0 - 0.2 -	over h	0.00			1.00			
Vikas Menta	47	100	14	57		1.62[0.96, 2.74]	3.98							1.00			
Gellym J Webb Mohamad N	4	12	5	16		0.93[0.29, 2.96] 1.71[0.88, 3.29]	1,02		F								
Hemando Trujilo	12	34	1	4.0/4	1.0	1.30[0.21, 8.04]	0.43		-	Acute K	idney injury	No Acute	Kidney injury		Risk Rat		Wei
Albeno Zangrilo	14	22	3	34		4.80 [1.50, 15.29]	1.01		Study	Died	Survived	Died	Survived		with 95%	CI	(%
Yang Wang # Yang-kai Li #	09	72	4	139		1.55[1.19, 2.02]	9.18		Qingchun Yao	7	9	5	87		8.05 [2.91,		
Tao Chén #	54	39	59	122		1.78[1.36, 2.34]	8.95		Xiaobo Yang S	12	3	20	17	•	1.48 [1.00,	2.19	
Xiaojing Zou #	21	26	31	75	1	1.54 [1.00, 2.38]	5.22		Safiya Richardson Yang Wang #	347	176	206 53	1,622		5.89 [5.11, 4.82 [3.78,	6.79	
Van Deng # Ke Wang #	40 38	128	69 40	98 342		1.67 [1.30, 2.14] 2.19 [1.46, 3.28]	9.61 5.74		Tao Chen #	28	1	53 85	209		4.82 [3.78, 2.78 [2.31,	3.35	
Yongi Yan #	57	16	\$1	69		1.84 [1.44, 2.34]	9.90		Xiaojing Zou #	24	1	28	101		4.42 [3.16.	6.20	
Glurong Ruan #	29	23	39 28	59 33		1.40[0.99, 1.98]			Yan Deng #	20	0	89	116		2.25 (1.90,	2.66	
Chaomin Wu S Fel Zhou S	18 26	7	28	33		1.82 [1.03, 2.22] 2.13 [1.36, 3.29]	6.15 5.21		Ke Wang #	30	63	48	407		3.06 [2.05,	4.55	7.1
TieLong Chien *		12	10	24		1.45[0.71, 2.90]	2.40		Qiurong Ruan #	21	2	47	80	a	2.47 [1.90,	3.20	
Davel Viang * Janiel Cao *	50 31	16	9	62 68		3.03 [1.39, 6.62] 4.85 [1.98, 11.86]	2.08		Fei Zhou S	27	1	27	136	-	5.82 [4.09,	8.28	 10.22
Wen Jut Tu *	12	25	13	124	4.4	3.42[1.70. 6.85]	2.53		Dawei Wang *	14	0	5	88		16.52 [7.30,	37.37	
Lang Wang 🖨	32	105	33	168	-	1.41 [0.91, 2.18]	5.21		Rongrong Yang * Jianlei Cao *	10	18	15	169		4.38 [2.19, 30.75 [7.64,	8.77	
Overall	12372		10.10			1.90 [1.69, 2.16]			Wen-Jun Tu *	19	8	6	141		17 24 1 7 59	39.18	
Hatarogenalty: 1 ⁴ = 0 Test of 8 = 9 : Q(25)			C=1.39		1				Lang Wang @	17	11	48	263		3.93 (2.65,	5.84	
Test of 8 = 0: z = 10.	50. p = 0.0	00							Overall					-	4.65 [3.25,	6.65	
~					1.00				Heterogeneity: 1 ² =	0.42, I [±] =	94.89%, H ^t	= 19.58					
C									Test of $\theta_i = \theta_j$: Q(14)	= 164.54	l, p = 0.00						
Study	Claseres Died	arrelitus durined	No Dister	es melitus Sunhad		Rick Ratio N with 95% Cl	(%)		Test of $\theta = 0$, $z = 8.4$	12, p = 0.0	10			1			
Mingil Yuan	6	D	4	17			1.88						1.	00			
KUN VIDIO	٠	24	13	253 -	·	4.09 [1.68, 9.97]	1.54										
	0	1.6	3		1 2 - 5	0.557 0.03 9.471	81.0		C								
Ming Dieg Jennifer Tomilitä	0 13	24	τ.	61		2.01 [1.25, 6.62]	1.79		G						Dist Date:	140-1-	
Ming Ding Jennifer Tombris Rong-Hui Du			7 15	81 131		2.91 [1.25, 6.62] 1.77 [0.74, 4.22]	1.79			Bilateral in Died	volvement A Survived	lo Bilataral i Died	nvolvement Survived		Risk Ratio with 95% CI	Weig (95)	
Ning Ding Jennifer Tomilitis Rong-mul Du Xiaobo Yang S Vikas Mensa		24 27 2 53	7 15 25 34	81 931 15 104		2.91 [1.25, 6.62] 1.77 [0.74, 4.22] 1.34 [0.87, 2.06] 1.37 [0.90, 2.09]	1.79 1.62 5.15 5.20									(95))
Ming Ding Jennifer Tomims Rong-Hul Du Xtacco Yang S Vicas Menta Gwilym J Webc	13 6 7 27 2	24 27 2 53	7 15 25 34 8	81 131 18 104 19		2.01[1.25, 6.82] 1.77[0.74, 4.22] 1.34[0.87, 2.06] 1.37[0.90, 2.09] 1.20[0.41, 4.02]	1.79 1.62 5.15 5.25 0.97		Study Hemando Trujilo Qingchun Yao	Died 6 12	Survived 10 86	Died 1 0	Survived 8 10		with 95% Cl 3.38 [0.48, 23.80 2.78 [0.18, 43.77	(95) (95) (95) (95) (95) (95) (95) (95)) 17 19
Ning Ding Jennifer Tombris Rong-Hul Du Xiaoco Yang S Vikas Mensa Gwitym J Webb Monamad N memando Thujiko	13 6 7	24 27 2 53 11 102 14	7 15 25 34 8 228 9	61 131 15 104 19 2,623 24		2.91 [125, 6.82] 1.77 [0.74, 4.22] 1.34 [0.87, 2.06] 1.37 [0.90, 2.09] 1.20 [0.41, 4.02] 1.22 [0.58, 2.16] 0.51 [0.29, 2.26]	1.79 1.62 5.15 5.28 0.97 3.31 1.16		Study Hernando Trujilo Qingchun Yao Mingli Yuan	Died 6 12 10	Survived 10 86 13	Died 1 0 0	Survived 8 10 4		with 95% Cl 3.38 [0.48, 23.80 2.78 [0.18, 43.77 4.38 [0.30, 63.07	(96) (95) (96) (96) (96) (96) (96) (96) (96) (96) 17 19 13
Ming Ding Jenniter Torditte Mong-Hui Du Xtaobo Yang S Vikas Menta Gwilym J Webb Monamad N	13 6 7 27 2	24 27 2 53 11 102	7 15 25 34 8 228	61 131 15 104 19 2,623		2.91 [1.25, 6.62] 1.77 [0.74, 4.22] 1.34 [0.87, 2.06] 1.37 [0.90, 2.09] 1.20 [0.41, 4.02] 1.22 [0.68, 2.16] 1.62 [0.54, 2.26] 1.52 [0.54, 4.26]	1.79 1.62 5.15 5.28 0.97 3.31		Study Hernando Trujilo Qingchun Yao Mingli Yuan Yang Wang #	Died 6 12 10 49	Survived 10 86 13 61	Died 1 0 84	Survived 8 10 4 150		with 95% Cl 3.38 [0.48, 23.80 2.78 [0.18, 43.77 4.38 [0.30, 63.07 1.24 [0.95, 1.63	(96) (§ 1.3 (] 0.6 (] 0.7 (] 0.7) 17 19 13 17
Ming Ding Jenntier Tomma Rong-Hui Du Xitacoo Yang S Vitas Menta Gwitym J Webb Monamad N memanso Trujiko Albeno Zangsilo Yang Vang # Yang-ka Li #	13 8 7 27 2 11 4 3 30 1	24 27 2 53 11 902 14 6 34 0	7 15 25 34 8 228 9 14 103 4	81 131 15 104 19 2,623 24 50 177 20	· · · · · · · · · · · · · · · · · · ·	2.01 [128, 8.62] 1.77 [0.74, 8.62] 1.34 [0.37, 2.06] 1.37 [0.90, 2.09] 1.32 [0.44, 8.62] 1.32 [0.44, 8.62] 1.34 [1.79 1.62 5.15 5.25 0.97 3.31 1.15 1.17 8.09 0.95		Study Hernando Trujilo Qingchun Yao Mingli Yuan	Died 6 12 10	Survived 10 86 13	Died 1 0 0	Survived 8 10 4		with 95% Cl 3.38 [0.48, 23.80 2.78 [0.18, 43.77 4.38 [0.30, 63.07	(%) (%) (%) (%) (%) (%) (%) (%) (%) (%)) 17 19 13 17 13
Ming Ding Jennier Tomana Rosp-tui Du Xiaceo Yang S Vikas Mensa Gwitym J Webo Monamad N memanoo Trujiko Albento Zangstio Yang Vang # Yang kai Li # Tao Chen #	13 6 7 27 2 11 4 30 30 1 24	24 27 2 53 11 02 14 6 34 0 23	7 15 25 24 8 228 9 14 103 4 89	81 131 15 104 19 2,623 24 50 117 26 138	· · · · · · · · · · · · · · · · · · ·	2.01 [126, 6.62] 1.77 [0.74, 4.62] 1.34 [0.87, 2.06] 1.35 [0.66, 2.09] 1.32 [0.68, 2.16] 1.32 [0.68, 2.16] 1.52 [0.64, 4.30] 1.52 [0.64, 4.30] 1.52 [0.64, 4.30] 1.52 [0.64, 1.728] 1.52 [0.54, 1.80]	1.79 1.62 5.15 5.28 0.97 3.31 1.16 1.17 8.09 0.95 7.50		Study Hernando Trujilio Qingchun Yao Mingi Yuan Yang Wang # Xiaojing Zou # Tao Chen # Fei Zhou 5	Died 6 12 10 49 52 113 45	Summed 10 86 13 65 96 152 98	Died 1 0 0 84 0	Survived 8 10 4 150 6 9 39		with 95% Cl 3.38 [0.48, 23.80 2.78 [0.18, 43.77 4.38 [0.30, 63.07 1.24 [0.95, 1.63 4.93 [0.34, 71.93 	(%) (%) (%) (%) (%) (%) (%) (%)) 57 59 73 77 73 73 71
Ming Ding Jennier torstein Kaspol vang S Visas Marta Gwitym J Webb Monantad N memanob Thujko Albeno Zangrito Vang Vang Jen Yang kat Li # Tao Chan # Xaojing 200 # Yan bang #	13 8 7 27 4 30 30 1 24 16 17	24 27 2 53 11 102 14 6 34 0 35 25 8	7 15 25 34 8 220 9 14 50 4 9 56 92	81 131 15 104 19 2,423 24 50 117 25 138 75 107		2.91 [125, 6.62] 1.77 [0.74, 6.22] 1.34 [0.27, 2.06] 1.35 [0.40, 2.09] 1.36 [0.41, 6.02] 1.32 [0.44, 6.02] 1.32 [0.44, 1.40] 1.32 [0.44, 1.72] 1.37 [0.54, 1.72] 1.37 [0.54, 1.72] 1.37 [0.54, 1.80]	1.79 1.62 5.15 5.25 0.97 3.31 1.16 1.17 8.09 0.95 7.50 4.50 7.67		Study Hernando Trujilo Qingchun Yao Mingi Yuan Yang Wang # Xiaojing Zou # Tao Chen # Fei Zhou 5 TieLong Chen *	Died 6 12 10 49 52 113 45 19	Summed 10 86 13 61 96 152 98 35	Died 1 0 84 0 9 9	Survived 8 10 4 150 6 9 30 30 1		with 95% Cl 3.38 [0.48, 23.80 2.78 [0.18, 43.77 4.36 [0.30, 63.07 1.24 [0.95, 163 4.93 [0.34, 7193 	(%) (%) 1.3 1.0.6 1.0.7 1.0.7 1.0.7 1.0.7 1.0.7 1.0.7 1.0.7 1.0.7 1.0.7 1.0.7 1.0.7 1.0.7 1.0.7 1.0.7 1.0.6 1.0.7 1.0.6 1.0.7 1.0.6 1.0.7 1.0.6 1.0.7 1.0.8 1.) 57 59 73 77 73 71 99 99
Ning Ding Jennine Tomera Roog-wul Du Xiaoo Yang S Vikas Menta Gwiym J Webo Monamad N Monamad N Monamad N Meena Zangstio Yang Wang # Yang Kau Li # Tao Chen # Xiaogng Zou # Yan Dang # Xia Yang #	13 6 7 27 4 30 1 24 16 17 19	24 27 2 23 11 02 14 6 34 0 23 24	7 15 25 3 8 220 9 14 39 36 32 89	81 131 15 104 19 2,023 24 50 177 25 138 75 107 406		201 1 28, 642 1.77 [0.74, 4.22] 1.34 [0.77, 2.03] 1.35 [0.64, 2.00] 1.32 [0.44, 4.02] 1.32 [0.44, 4.02] 1.32 [0.54, 4.20] 1.32 [0.54, 4.20] 1.32 [0.54, 1.12] 1.32 [0.54, 1.12] 1.32 [0.74, 1.03] 1.32 [0.74, 1.03] 1.32 [0.74, 1.03] 1.31 [0.34, 1.12] 1.32 [0.74, 2.04] 1.35 [1.14, 2.05]	1.79 1.62 5.15 5.28 0.97 3.31 1.18 1.17 8.09 0.95 7.50 4.50		Study Hemando Trujilo Qingchun Yao Mingti Yuan Yang Wang # Xiaojing Zou # Tao Chen # Fei Zhou 5 TieLong Chen * Dawei Wang *	Died 6 12 10 49 52 113 45 19 19	Survived 10 66 13 61 96 152 98 35 88	Died 1 0 84 0 9 0 0	Survived 8 10 4 150 6 9 30 1 - 2 -		with 95% Cl 3.38 [0.48, 23.80 2.78 [0.18, 43.77 4.38 [0.30, 63.07 1.24 [0.95, 1.63 4.93 [0.34, 71.93 8.53 [0.57, 127.64 1.68 [0.89, 3.17 1.42 [0.13, 16.06 1.10 [0.09, 14.30	(%) (%) (%) (%) (%) (%) (%) (%)) i7 i9 r3 r3 r1 i9 i9 i9 i9 i9 i0
Nang Ding Jennine Tomana Mang-Hui Du Xitaco Yang S Vitas Merza Gwiym J Vebo Monamad N memanos Trujklo Albens Zagistio Yang Wang # Xita Chen # Xita Signal Yang tau Li # Tao Chen # Xita Signal Xita Yang # Vongt Yan # Olurong Reuse #	13 6 7 27 4 11 4 30 1 24 16 17 19 30 12	24 27 2 53 11 10 14 6 4 0 33 24 8 64 9 13	7 15 25 34 8 228 9 14 103 4 89 36 22 89 49 58	81 131 164 19 2,823 24 80 177 20 188 107 406 78 69		201 [135, 4.42] 1,77 [674, 4.23] 1,37 [674, 4.23] 1,37 [600, 2.00] 1,32 [604, 2.63] 1,32 [604, 2.63] 1,32 [604, 2.63] 1,32 [604, 1.43] 1,37 [634, 1.43] 1,27 [634, 1.43] 1,27 [634, 1.43] 1,27 [634, 1.43] 1,27 [1,37, 2.43] 1,60 [1,4, 2.68] 1,77 [1,37, 2.43] 1,67 [0,56, 1.68] 1,67 [6,66, 1.68] 1,67 [6,7, 1.68] 1,67 [7, 1.68] 1,67 [7, 1.68] 1,67 [7, 1.68] 1,67	1.79 1.62 5.15 5.25 0.97 3.31 1.15 1.17 8.09 0.95 7.50 4.60 7.67 4.67 7.67 4.87		Study Hernando Trujilio Qingchun Yao Mingi Yuan Yang Wang # Xiaojing Zou # Tao Chen # Fei Zhou \$ TieLong Chen * Davrei Wang * Jiantei Cao *	Died 6 12 10 49 52 113 45 19 19 19 14	Survived 10 86 13 61 96 152 98 35 88 85 72	Died 1 0 84 0 9 0 0 3	Survived 8 10 4 150 6 9 30 1 - 2 - 30		with 95% Cl 3.38 [0.48, 23.80 2.78 [0.18, 43.77 4.38 [0.30, 63.07 1.24 [0.95, 1.61 4.93 [0.34, 71.93 - 8.53 [0.57, 127.64 1.68 [0.80, 317 1.42 [0.13, 16.06 1.10 [0.09, 14.20 1.79 [0.55, 5.83	(%) (%) (%) (%) (%) (%) (%) (%)) 77 199 17 17 19 19 19 19 19 19 19 19 19 19
Nang Ding Jennina Homana Mang-Hu Do Xiaoco Yang S Vitas Merca Galiym J Webo Monamao Tupilo Albeno Zangstio Yang Viang # Yang Yang # Yang Dau Lie Tao Chan # Xiaolog Zou # Yan Dang # Vang Bua # Yang Yan # Olurong Rua #	13 8 7 27 4 30 1 24 16 17 19 50 12 11	24 27 2 53 11 10 14 6 4 0 33 24 8 64 9 13 5	T 15 25 34 8 222 9 14 30 4 89 58 23	81 131 15 164 2,023 24 50 117 25 118 125 126 69 35		201 1 35, 642 177 1 57, 423 177 1 57, 423 137 1 57, 423 137 1 50, 200 137 1 50, 200 137 1 50, 200 132 1 50, 200 134 10	1.79 1.62 1.15 1.25 0.97 3.31 1.16 1.17 8.09 0.95 7.50 4.60 7.67 4.67 4.67 4.67 4.63 5.51		Study Hemando Trujilo Qingchun Yao Mingti Yuan Yang Wang # Xiaojing Zou # Tao Chen # Fei Zhou 5 TieLong Chen * Dawei Wang *	Died 6 12 10 49 52 113 45 19 19	Survived 10 66 13 61 96 152 98 35 88	Died 1 0 84 0 9 0 0	Survived 8 10 4 150 6 9 30 1 - 2 -		with 95% CI 3.38 [0.48, 2.386 2.78 [0.18, 43.77 4.38 [0.30, 63.07 1.24 [0.95, 163 4.93 [0.34, 71.93 	(%) (%) (%) (%) (%) (%) (%) (%)) 77 199 17 17 19 19 19 19 19 19 19 19 19 19
Neg Ding Jennim: Torrans Mag-Hui Du Xitaoo Yang S Waas Mersa Gwiym J Wabo Monamad N menanoo Tuglio Aberoo Zangrio Yang Vang Va Yang Yang H Yang Yang S Yang Yang P Yang Dang # Yang Dang # Yang Yang B Yang Yang B Yang Yang B Yang Dang # Yang Dang #	13 6 7 27 4 11 4 30 1 24 16 17 19 30 12	24 27 2 53 11 10 14 6 4 0 33 24 8 64 9 13	7 15 25 14 8 220 9 14 10 4 88 88 29 89 88 33 17 39	81 151 154 155 2,823 24 80 177 20 138 157 146 69 25 35 156		2001 135, 642 1771 674, 423 1771 674, 423 1371 600, 200 1371 600, 200 1371 600, 200 1371 600, 200 1371 604, 433 1371 634, 1373 1371 634, 1373 1371 634, 1373 1371 634, 1383 1371 634, 2333 1391 632, 2473 1391 632, 2475 1391 6	1.79 1.62 1.15 1.28 0.97 3.31 1.17 4.09 0.95 7.50 4.50 7.50 4.57 4		Study Hernando Trujillo Oingchun Yao Mingi Yuan Yang Wang # Xiaojing Zou # Tao Chen # Fei Zhou 5 TieLong Chen * Dawei Wang * Janiel Cao * J. Zhang @	Died 6 12 10 49 52 113 45 19 19 14 20	Survived 10 86 13 61 96 152 98 35 86 72 530	Died 1 0 84 6 9 0 0 0 3 5	Survived 8 10 4 150 6 9 30 1 - 2 - 30		with 95% CI 3.38 [0.48, 2.380 2.78 [0.18, 43.77 4.38 [0.30, 63.07 1.24 [0.95, 163 4.99 [0.34, 71.93 	(%) (%) (%) (%) (%) (%) (%) (%)) 77 199 17 17 19 19 19 19 19 19 19 19 19 19
Ming Ling Jennitier Torritins Mong-hul Du Xitoso Yang S Witos Merca Gwiym J Webo Abeno Zangrillo Abeno Zangrillo Abeno Zangrillo Abeno Zangrillo Yang Wang # Yang Kau Li# Tao Chan # Xito Yang Kuan # Chatom MJL S Chatom MJL S Autoro S Jogt U A Telcono S	13 8 7 27 4 11 3 30 1 28 16 17 9 9 12 11 17	24 27 2 53 11 25 4 6 34 0 55 4 8 48 9 13 5 19 59 7	7 15 25 14 8 22 9 14 30 4 88 36 12 89 68 55 37 39 14	81 331 15 16 19 2,003 24 20 00 177 20 0 105 107 406 16 9 25 115 109 29	***	200 [128, 642] 134 [037, 208] 137 [034, 462] 137 [034, 208] 137 [046, 209] 132 [046, 209] 132 [048, 209] 132 [044, 402] 132 [044, 404] 132 [046, 404] 132 [046] 132 [046]	1.79 1.62 1.15 1.28 0.97 3.31 1.16 1.17 8.09 0.95 7.50 4.60 7.87 4.67 4.67 4.87 4.87 4.87 1.92 5.31 5.31 4.89 5.31		Study Hernands Trujilo Qingchun Yao Mingi Yuan Yang Wang R Xiaojing Zou # Tao Chen # Fei Zhou 5 TieLong Chen * Juenic Cao * TieLong Chen * East of e. e. (c)(10)	Died 6 12 10 49 52 113 45 19 19 14 20 .00, 1 ² = 0 = 6.64, p	Survived 10 86 13 61 96 152 98 35 86 72 530 (00%, H [*] = 1 = 0.76	Died 1 0 84 6 9 0 0 0 3 5	Survived 8 10 4 150 6 9 30 1 - 2 - 30		with 95% CI 3.38 [0.48, 2.386 2.78 [0.18, 43.77 4.38 [0.30, 63.07 1.24 [0.95, 163 4.93 [0.34, 71.93 	(%) (%) (%) (%) (%) (%) (%) (%)) 17 19 13 17 13 17 19 19 19 10 19 10 15 15 15 15 15 15 15 15 15 15
Neg Ding Jennim: Torrans Mag-Hui Du Xitaoo Yang S Waas Mersa Gwiym J Wabo Monamad N menanoo Tuglio Aberoo Zangrio Yang Vang Va Yang Yang H Yang Yang S Yang Yang P Yang Dang # Yang Dang # Yang Yang B Yang Yang B Yang Yang B Yang Dang # Yang Dang #	13 8 7 27 4 11 3 30 1 22 18 17 19 19 19 11 11 17	24 27 2 53 11 00 4 6 34 0 53 24 8 6 9 13 5 19	7 15 25 14 8 220 9 14 10 4 88 88 29 89 88 33 17 39	81 151 154 155 2,823 24 80 177 20 138 157 146 69 25 35 156	***	200 [128, 642] 134 [027, 208] 137 [074, 442] 134 [027, 208] 137 [074, 402] 132 [041, 402] 132 [048, 208] 132 [054, 428] 132 [054, 428] 137 [137, 248] 146 [137, 248] 147 [054, 166] 147 [054, 248] 148 [054, 258] 148 [1.79 1.62 1.15 1.28 0.97 3.31 1.17 4.09 0.95 7.50 4.50 7.50 4.57 4		Study Hernando Trujilio Cingchun Yao Mingti Yuan Yang Wang # Xiaqing Zou # Tao Chen # Fei Zhou 5 TeLong Chen * Davei Wang * Janiel Cao * J. Zhang @ Overall	Died 6 12 10 49 52 113 45 19 19 14 20 .00, 1 ² = 0 = 6.64, p	Survived 10 86 13 61 96 152 98 35 86 72 530 (00%, H [*] = 1 = 0.76	Died 1 0 84 6 9 0 0 0 3 5	Survived 8 10 4 150 6 9 30 1 - 2 - 30		with 95% CI 3.38 [0.48, 2.386 2.78 [0.18, 43.77 4.38 [0.30, 63.07 1.24 [0.95, 163 4.93 [0.34, 71.93 	(%) (%) (%) (%) (%) (%) (%) (%)) 77 199 17 17 19 19 19 19 19 19 19 19 19 19
Hing Dirg Jampe Torses Mappinul Du Jaseo Tang S Vasa Mara Mana Mara Mana Mara Mana Mara Mana Mara Mana Mara Mana Mara Mana Mara Mang	13 8 7 7 4 11 4 3 30 1 24 16 17 19 13 13 11 17 35 5 8 6	24 27 2 33 11 02 14 6 3 0 33 24 8 64 9 13 5 19 59 7 6 5 19	7 15 25 14 5 22 9 14 33 4 89 36 22 89 49 48 35 77 39 14 14 11 11	51 151 151 151 151 152 152 152 152 152 1	***	2.00[1.03, 6.42] 1.34[0.47, 2.04] 1.34[0.47, 2.04] 1.34[0.47, 2.04] 1.34[0.44, 4.23] 1.32[0.44, 4.23] 1.32[0.44, 4.23] 1.32[0.44, 4.23] 1.32[0.44, 4.23] 1.32[0.44, 4.23] 1.32[0.44, 4.23] 1.32[0.44, 4.24] 1.32[0.44, 2.44] 1.32[0.44, 2	1.79 1.82 1.18 2.07 1.18 1.18 0.95 0.950 0.950 0.950 0.950 1.18 1.18 1.18 0.950 1.18 1.18 1.18 0.950 1.18 1.18 1.18 1.18 1.18 1.18 1.18 1.1		Study Hernands Trujilo Qingchun Yao Mingi Yuan Yang Wang R Xiaojing Zou # Tao Chen # Fei Zhou 5 TieLong Chen * Juenic Cao * TieLong Chen * East of e. e. (c)(10)	Died 6 12 10 49 52 113 45 19 19 14 20 .00, 1 ² = 0 = 6.64, p	Survived 10 86 13 61 96 152 98 35 86 72 530 (00%, H [*] = 1 = 0.76	Died 1 0 84 6 9 0 0 0 3 5	Survived 8 10 4 150 6 9 30 1 - 2 - 30		with 95% CI 3.38 [0.48, 2.386 2.78 [0.18, 43.77 4.38 [0.30, 63.07 1.24 [0.95, 163 4.93 [0.34, 71.93 	(%) (%) (%) (%) (%) (%) (%) (%)) 77 199 17 17 19 19 19 19 19 19 19 19 19 19
Anny Dirig Jammer Tomser Magyma Lou Xissee Tang St Vans Maras Annos Zaveyto Vang Vang Maras Manos Zaveyto Vang Vang Maras Vang Vang St Vang Vang Vang Vang Vang Vang Vang Vang	13 8 7 27 4 11 3 30 1 22 18 17 19 19 19 11 11 17	24 27 2 33 11 02 14 6 34 0 33 24 8 64 8 13 5 19 59 7 6 5	7 15 25 34 8 28 9 14 30 4 89 36 82 89 66 55 57 59 14 14 17	31 31 31 31 31 31 31 31 31 31 31 31 31 3	***	$\begin{array}{c} 2.91 \left[1.28, \ 6.42 \right] \\ 1.34 \left[0.67, \ 2.06 \right] \\ 3.37 \left[0.94, \ 4.62 \right] \\ 1.34 \left[0.68, \ 2.09 \right] \\ 1.32 \left[0.64, \ 4.62 \right] \\ 1.32 \left[0.64, \ 4.52 \right] \\ 1.32 \left[0.64, \ 1.52 \right] \\ 1.34 \left[1.36, \ 4.64 \right] \\ 1.32 \left[0.64, \ 1.52 \right] \\ 1.34 \left[1.36, \ 4.64 \right] \\ 1.32 \left[0.64, \ 1.52 \right] \\ 1.34 \left[0.64, \ 2.54 \right] \\ 1.32 \left[0.56, \ 2.54 \right] \\ 1.34 \left[0.64, \ 2.54 \right] \\ 1.32 \left[0.56, \ 0.54 \right] \\ 1.32 \left[0.56, \ 0.56 \right] \\ 1.32 \left[0.5$	1.79 1.82 1.15 1.20 7.31 1.17 8.09 0.95 7.450 7.457 4.80 1.18 1.80 1.18 1.10 1.10 1.10 1.10 1		Study Hernands Trujilo Qingchun Yao Mingi Yuan Yang Wang R Xiaojing Zou # Tao Chen # Fei Zhou 5 TieLong Chen * Juenic Cao * TieLong Chen * East of e. e. (c)(10)	Died 6 12 10 49 52 113 45 19 19 14 20 .00, 1 ² = 0 = 6.64, p	Survived 10 86 13 61 96 152 98 35 86 72 530 (00%, H [*] = 1 = 0.76	Died 1 0 84 6 9 0 0 0 3 5	Survived 8 10 4 150 6 9 30 1 - 2 - 30		with 95% CI 3.38 [0.48, 2.386 2.78 [0.18, 43.77 4.38 [0.30, 63.07 1.24 [0.95, 163 4.93 [0.34, 71.93 	(%) (%) (%) (%) (%) (%) (%) (%)) 77 199 17 17 199 199 199 199 1
sing Dré avente Torstein Kosp-un Du Xizaco Yang Yu Visa Marsa Kospen Ju Alano Zangsto Mano Zangsto Mano Zangsto Yang Wang Y Yang Yung Y Kasa Yang Y Yang Yung Y	13 8 7 27 2 11 4 3 300 1 24 16 17 9 39 12 11 13 5 5 8 6 11	24 27 2 33 11 10 4 4 6 34 0 35 24 8 4 8 4 3 5 19 19 7 6 5 5 10 10 4 4 5 35 10 10 4 4 5 5 5 10 10 4 4 5 5 5 5 10 10 4 5 5 5 5 10 10 4 5 5 5 5 10 10 4 5 5 5 5 10 10 4 5 5 5 5 5 10 10 4 5 5 5 5 10 10 10 10 10 10 10 10 10 10 10 10 10	下於 经延本额 单计码 牛胆酸酸 经经济部计计计计 计	51 151 151 151 151 152 152 152 152 152 1	***	2.00[1.03, 6.42] 1.34[0.47, 2.04] 1.34[0.47, 2.04] 1.34[0.47, 2.04] 1.34[0.44, 4.23] 1.32[0.44, 4.23] 1.32[0.44, 4.23] 1.32[0.44, 4.23] 1.32[0.44, 4.23] 1.32[0.44, 4.23] 1.32[0.44, 4.23] 1.32[0.44, 4.24] 1.32[0.44, 2.44] 1.32[0.44, 2	1.79 1.82 1.18 2.07 1.18 1.18 0.95 0.950 0.950 0.950 0.950 1.18 1.18 1.18 0.950 1.18 1.18 1.18 0.950 1.18 1.18 1.18 1.18 1.18 1.18 1.18 1.1		Study Hernando Trujilo Cingchun Yao Mingi Yuan Yaog Wang # Tao Chen # Fei Zhou 5 Tao Chen # Fei Zhou 5 Tao Chen # Davet Wang * Janiel Cao * J. Zhang @ Overall Heteroganally 1° = (Teat of 6: = 6: O(10) Teat of 6: = 0: z = 2.5	Died 6 12 10 49 52 113 45 19 19 14 20 .00, 1 ² = 0 = 6.64, p	Survived 10 86 13 61 96 152 98 35 86 72 530 (00%, H [*] = 1 = 0.76	Died 1 0 84 6 9 0 0 0 3 5	Survived 8 10 4 150 6 9 30 1 - 2 - 30		with 95% CI 3.38 [0.48, 2.386 2.78 [0.18, 43.77 4.38 [0.30, 63.07 1.24 [0.95, 163 4.93 [0.34, 71.93 	(%) (%) (%) (%) (%) (%) (%) (%)) 77 199 17 17 19 19 19 19 19 19 19 19 19 19
Mang Ding Jaynes Torosa Koop-Ju Cu Xisaoo Yang Si Yasa Marta G Koopin J Wasa Marta Kata Mang Mang Si Xisao Yang Si Xisao Xisao X	13 8 7 77 2 11 4 3 30 1 24 11 17 30 5 8 8 6 11	24 27 2 3 3 10 22 5 3 10 22 5 3 10 22 5 5 3 10 22 5 5 5 10 22 5 5 5 10 10 22 5 5 5 10 10 22 5 5 5 10 10 22 5 5 5 10 10 22 5 5 5 5 10 10 22 5 5 5 10 10 22 5 5 5 10 10 22 5 5 5 10 10 22 5 5 5 10 10 22 5 5 5 10 10 22 5 5 5 10 10 22 5 5 5 10 10 22 5 5 5 10 10 22 5 5 5 10 10 22 5 5 5 10 10 22 5 5 5 10 10 22 5 5 5 10 10 22 5 5 5 10 10 2 5 5 5 10 10 10 2 5 5 10 10 2 5 5 10 10 2 5 5 5 10 10 10 2 5 10 10 10 10 2 5 10 10 10 10 10 10 10 10 10 10 10 10 10	下於 经延本额 单计码 牛胆酸酸 经经济部计计计计 计	51 151 151 151 151 152 152 152 152 152 1	***	$\begin{array}{c} 2.91 \left[1.28, \ 6.42 \right] \\ 1.34 \left[0.67, \ 2.06 \right] \\ 3.37 \left[0.94, \ 4.62 \right] \\ 1.34 \left[0.68, \ 2.09 \right] \\ 1.32 \left[0.64, \ 4.62 \right] \\ 1.32 \left[0.64, \ 4.52 \right] \\ 1.32 \left[0.64, \ 1.52 \right] \\ 1.34 \left[1.36, \ 4.64 \right] \\ 1.32 \left[0.64, \ 1.52 \right] \\ 1.34 \left[1.36, \ 4.64 \right] \\ 1.32 \left[0.64, \ 1.52 \right] \\ 1.34 \left[0.64, \ 2.54 \right] \\ 1.32 \left[0.56, \ 2.54 \right] \\ 1.34 \left[0.64, \ 2.54 \right] \\ 1.32 \left[0.56, \ 0.54 \right] \\ 1.32 \left[0.56, \ 0.56 \right] \\ 1.32 \left[0.5$	1.79 1.82 1.18 2.07 1.18 1.18 0.95 0.950 0.950 0.950 0.950 1.18 1.18 1.18 0.950 1.18 1.18 1.18 0.950 1.18 1.18 1.18 1.18 1.18 1.18 1.18 1.1		Study Hernands Trujilo Qingchun Yao Mingi Yuan Yang Wang R Xiaojing Zou # Tao Chen # Fei Zhou 5 TieLong Chen * Juenic Cao * TieLong Chen * East of e. e. (c)(10)	Died 6 12 10 49 52 113 45 19 19 14 20 .00, 1 ² = 0 = 6.64, p	Survived 10 86 13 61 96 152 98 35 86 72 530 (00%, H [*] = 1 = 0.76	Died 1 0 84 6 9 0 0 0 3 5	Survived 8 10 4 150 6 9 30 1 - 2 - 30		vem 95% Cl 3.36 (0.48, 2.346) 2.78 (0.16, 43,77 4.36 (0.36, 8307) 4.93 (0.34, 71 s) -8.53 (0.57, 1274) -8.53 (0.57, 1274) -8.53 (0.57, 1274) -1.142 (0.13, 1600 1.101 (0.00, 14.302 1.791 (0.55, 5.61) 0.822 (0.32, 2.14) 1.355 (1.07, 1.66) 	(%) (%) (%) (%) (%) (%) (%) (%)) 17 19 13 17 13 19 19 19 19 19 19 10 15 18 10 15 18 10 15 10 15 15 15 15 15 15 15 15 15 15
Hing Dirg Jahren Torsen Kopp-un Du Xasen Yang Ya Wasa Marta Kopanya Li Wasa Marta Kasa Mano Zangsto Mano Zang Kang Qing Mano Zang Mano Zang Mano Mano Mano Zang Mano Zang Mano Mano Zang Mano Zang Mano Mano Zang Mano Zang Mano Mano Zang Mano Zang Mano Zang Mano Zang Mano Zang Mano Zang Mano Zang Mano Zang Mano	13 8 7 77 2 11 4 3 30 1 24 11 17 30 5 8 8 6 11	24 27 2 3 3 10 22 5 3 10 22 5 3 10 22 5 5 3 10 22 5 5 5 10 22 5 5 5 10 10 22 5 5 5 10 10 22 5 5 5 10 10 22 5 5 5 10 10 22 5 5 5 5 10 10 22 5 5 5 10 10 22 5 5 5 10 10 22 5 5 5 10 10 22 5 5 5 10 10 22 5 5 5 10 10 22 5 5 5 10 10 22 5 5 5 10 10 22 5 5 5 10 10 22 5 5 5 10 10 22 5 5 5 10 10 22 5 5 5 10 10 22 5 5 5 10 10 22 5 5 5 10 10 2 5 5 5 10 10 10 2 5 5 10 10 2 5 5 10 10 2 5 5 5 10 10 10 2 5 10 10 10 10 2 5 10 10 10 10 10 10 10 10 10 10 10 10 10	下於 经延本额 单计码 牛胆酸酸 经经济部计计计计 计	51 151 151 151 151 152 152 152 152 152 1	***	$\begin{array}{c} 2.91 \left[1.28, \ 6.42 \right] \\ 1.34 \left[0.67, \ 2.06 \right] \\ 3.37 \left[0.94, \ 4.62 \right] \\ 1.34 \left[0.68, \ 2.09 \right] \\ 1.32 \left[0.64, \ 4.62 \right] \\ 1.32 \left[0.64, \ 4.52 \right] \\ 1.32 \left[0.64, \ 1.52 \right] \\ 1.34 \left[1.36, \ 4.64 \right] \\ 1.32 \left[0.64, \ 1.52 \right] \\ 1.34 \left[0.64, \ 2.54 \right] \\ 1.32 \left[0.56, \ 2.54 \right] \\ 1.34 \left[0.64, \ 2.54 \right] \\ 1.32 \left[0.66, \ 0.54 \right] \\ 1.32 \left[0.6$	1.79 1.82 1.18 2.07 1.18 1.18 0.95 0.950 0.950 0.950 0.950 1.18 1.18 1.18 0.950 1.18 1.18 1.18 0.950 1.18 1.18 1.18 1.18 1.18 1.18 1.18 1.1		Study Hernandos Trujilio Gingchun Yao Mangi Yuan Yang Wang & Xiaoging Zoo # Talo Chen # Fei Zhou 5 TraLong Chen * Dawei Wang * Janiel Cao * J. Zhang @ Overail Historogenethy 1* < Hetarogenethy 1* < Text of 6; = 6; O(10) Text of 6; = 0; 2 : 2.5	Died 6 12 10 49 52 113 45 19 19 14 20 .000, 1 ² = 0 5, p = 0.0 ²	Survived 10 86 13 61 96 152 98 35 86 72 530 (00%, H [*] = 1 = 0.76	Died 1 0 84 0 9 0 0 3 5 5	Survived 8 10 4 150 6 9 30 1 - 2 - 30 108 -		with 95% CI 3.38 [0.48, 2.386 2.78 [0.18, 43.77 4.38 [0.30, 63.07 1.24 [0.95, 163 4.93 [0.34, 71.93 	(%) (%) (%) (%) (%) (%) (%) (%)) 17 19 13 17 13 19 19 19 19 19 10 15 18 10 15 18 10 15 10 15 10 15 15 15 15 15 15 15 15 15 15
Mang Ding Javanse Torsen Kosp-ku Du Xazao Yang Yang Wang Kasao Mang Mang Xang Yang Yang Yang Yang Yang Yang Yang Y	13 8 7 77 2 11 4 3 30 1 24 11 17 30 5 8 8 6 11	24 27 2 3 3 10 22 5 3 10 22 5 3 10 22 5 5 3 10 22 5 5 5 10 22 5 5 5 10 10 22 5 5 5 10 10 22 5 5 5 10 10 22 5 5 5 10 10 22 5 5 5 5 10 10 22 5 5 5 10 10 22 5 5 5 10 10 22 5 5 5 10 10 22 5 5 5 10 10 22 5 5 5 10 10 22 5 5 5 10 10 22 5 5 5 10 10 22 5 5 5 10 10 22 5 5 5 10 10 22 5 5 5 10 10 22 5 5 5 10 10 22 5 5 5 10 10 22 5 5 5 10 10 2 5 5 5 10 10 10 2 5 5 10 10 2 5 5 10 10 2 5 5 5 10 10 10 2 5 10 10 10 10 2 5 10 10 10 10 10 10 10 10 10 10 10 10 10	下於 经延本额 单计码 牛胆酸酸 经经济部计计计计 计	51 151 151 151 151 152 152 152 152 152 1	******	$\begin{array}{c} 2.91 \left[1.28, \ 6.42 \right] \\ 1.34 \left[0.67, \ 2.06 \right] \\ 3.37 \left[0.94, \ 4.62 \right] \\ 1.34 \left[0.68, \ 2.09 \right] \\ 1.32 \left[0.64, \ 4.62 \right] \\ 1.32 \left[0.64, \ 4.52 \right] \\ 1.32 \left[0.64, \ 1.52 \right] \\ 1.34 \left[1.36, \ 4.64 \right] \\ 1.32 \left[0.64, \ 1.52 \right] \\ 1.34 \left[0.64, \ 2.54 \right] \\ 1.32 \left[0.56, \ 2.54 \right] \\ 1.34 \left[0.64, \ 2.54 \right] \\ 1.32 \left[0.66, \ 0.54 \right] \\ 1.32 \left[0.6$	1.79 1.82 1.18 2.07 1.18 1.18 0.95 0.950 0.950 0.950 0.950 1.18 1.18 1.18 0.950 1.18 1.18 1.18 0.950 1.18 1.18 1.18 1.18 1.18 1.18 1.18 1.1		Study Hernando Trujilo Gingchun Yao Mingi Yuan Yang Wang # Xianjing Zou # Tao Chen # Fel Zhou S Tao Chen # Davet Wang * John Chen * Davet Wang * John Chen * Davet Wang * John Chen * Davet Wang * John Chen * Davet Wang * Hernogenetity * Test of # = 6: O(10) Test of # = 0: 2 = 2.5	Died 6 12 10 49 52 113 45 19 14 20 100,1° = 0.0° 100,1° = 0.0° 5, p = 0.0°	Survived 10 86 13 61 96 152 98 35 86 72 530 .00%, H ² = 1 .00%, H ² = 1	Died 1 0 84 0 9 0 0 0 3 5 1.00 Consolida Died	Survived 8 10 4 150 6 9 30 1 - 2 - 30 108 - - - - - - - - - - - - -		wenn 95% Cl 3.36 (0.48, 23.46) 2.78 (0.18, 43.77 4.36 (0.30, 53.07) 4.39 (0.34, 77.90) - 8.53 (0.34, 77.90) - 8.53 (0.34, 77.90) - 8.53 (0.35, 72.76 Å) - 1.36 (0.07, 127.64) 1.37 (0.55, 5.83) 0.42 (0.32, 2.14) 1.35 (1.07, 1.66) - - - - - - - - - - - - -	(%) (%) (%) (%) (%) (%) (%) (%)) 17 19 13 17 13 19 19 19 19 19 19 19 19 19 19
Mang Ding Jaynes Torosa Koop-Ju Cu Xisaoo Yang Si Yasa Marta G Koopin J Wasa Marta Kata Mang Mang Si Xisao Yang Si Xisao Xisao X	$\begin{array}{c} 13 \\ 6 \\ 7 \\ 27 \\ 4 \\ 30 \\ 1 \\ 24 \\ 10 \\ 10 \\ 10 \\ 10 \\ 10 \\ 10 \\ 10 \\ 1$	24 27 2 53 11 10 14 6 4 0 2 2 4 8 5 4 5 10 2 14 5 5 2 5 4 5 10 2 14 5 5 5 11 10 2 5 5 11 10 2 5 5 11 10 2 5 5 11 10 2 5 5 11 10 10 11 10 10 10 10 10 10 10 10 10	7 15 25 14 5 22 9 14 30 4 88 56 28 89 69 55 27 59 14 14 17 17 14 1.30	61 131 14 14 16 16 16 16 16 17 20 10 10 17 20 10 10 10 10 10 10 10 10 10 10 10 10 10	******	249 (124, 487) (124) (27, 246) (124) (27, 246) (127) (266, 207) (122) (266, 207) (122) (266, 207) (122) (266, 207) (122) (266, 207) (127) (268, 107) (127) (268, 107) (127) (27, 207) (127) (27, 207) (127) (28, 107) (127) (28,	1.79 1.82 1.12 0.97 1.10 0.93 1.10 0.93 1.10 0.95 1.10 0.95 1.10 0.95 1.10 1.10 0.95 1.10 1		Study Hernando Trujilio Gingchun Yao Mingi Yuan Yang Wang # Xiaoing Zou # Tao Chen # Fei Zhou \$ TieLong Chen * Dave Wang * Jannei Cao * J. Zhang @ Overall Heistorgenarity: 1 ⁺ = 6 Test of 6 = 6; Q(10) Test of 6 = 0; z = 2,5	Dead 6 12 10 49 52 113 45 19 19 14 20 100, 1° = 0 5, p = 0.0° Died 2	Survived 10 10 13 13 152 98 35 86 72 530 100%, H ² = 1 0.0%, H ² = 1 1 4tion present Survived 6	Died 1 0 84 0 9 0 0 3 5 1.00 Consolidé Died 5	Survived 8 10 4 150 6 9 30 10 30 108 		with 95% Cl 3.36 [0.46, 2.360] 2.78 [0.10, 43.77 4.36 [0.36, 83.07 4.38 [0.36, 87.09] 4.39 [0.34, 77.09] 4.39 [0.34, 77.09] 4.39 [0.34, 77.09] 4.31 [0.35, 71.27.04] 1.39 [0.09, 14.30] 1.79 [0.55, 5.81] 0.42 [0.32, 2.14] 1.35 [1.07, 1.66] 	(%) (%) (%) (%) (%) (%) (%) (%)) 17 19 13 17 19 19 19 19 19 10 15 18 10 10 10 10 10 10 10 10 10 10
Mang Dreg Jawner Torress Anner Torress Nosp-u Cu Xisteo Yang S Vasa Marta Kong-u Cu Xisteo Yang S Vasa Marta Atend Sargito Yang Vang Y Yang Yang Y Yang Yang Yang Yang Yang Yang Yang Yang Yang	13 6 7 27 27 21 4 30 1 24 15 24 15 29 12 15 15 26 6 11 26 19 19 10 11 26 10 12 26 10 12 26 10 12 26 10 12 26 10 12 10 12 10 10 10 10 10 10 10 10 10 10	24 27 2 53 11 10 14 6 4 0 2 2 4 8 5 4 5 10 2 14 5 5 10 2 14 5 5 5 10 10 14 5 5 5 10 10 14 5 5 5 10 14 5 5 5 10 14 15 5 5 10 14 14 15 5 15 15 15 15 15 15 15 15 15 15 15 1	7 15 23 4 8 8 9 14 28 9 14 28 9 14 28 9 14 28 29 14 28 29 20 20 20 20 20 20 20 20 20 20 20 20 20	51 131 14 15 15 2,833 40 177 18 406 40 107 18 40 40 40 40 40 40 53 105 105 105 105 105 105 105 105 105 105	******	249 (124, 647) (124, 647, 249) (127, 646, 249) (127, 646, 249) (127, 646, 249) (127, 646, 249) (127, 646, 249) (127, 646, 249) (127, 648, 249) (127, 648, 249) (127, 648, 249) (127, 648, 249) (127, 648, 149) (127, 127, 127, 127, 127) (127, 128, 149) (127, 129) (127, 129)	1.79 1.52 5.15		Study Hernando Trujilo Gingchun Yao Mingi Yuan Yang Wang # Xianjing Zou # Tao Chen # Fel Zhou S Tao Chen # Davet Wang * John Chen * Davet Wang * John Chen * Davet Wang * John Chen * Davet Wang * John Chen * Davet Wang * Hernogenetity * Test of # = 6: O(10) Test of # = 0: 2 = 2.5	Died 6 12 10 49 52 113 45 19 14 20 100,1° = 0.0° 100,1° = 0.0° 5, p = 0.0°	Survived 10 86 13 61 96 152 98 35 86 72 530 .00%, H ² = 1 .00%, H ² = 1	Died 1 0 84 0 9 0 0 0 3 5 1.00 Consolida Died	Survived 8 10 4 150 6 9 30 1 - 2 - 30 108 - - - - - - - - - - - - -		with 95% CI 3.36 [0.48, 23.40 2.78 [0.18, 43.77 4.36 [0.30, 53.07 4.37 [0.34, 77.30 4.39 [0.34, 77.30 8.31 [0.57, 127.64 1.36 [0.60, 3.17 1.42 [0.13, 15.06 1.30 [0.55, 54] 0.42 [0.32, 2.14 1.35 [1.07, 1.69 	(%) (%) (%) (%) (%) (%) (%) (%)) 17 19 13 17 19 19 19 19 19 19 10 15 16 16 16 16 16 16 16 16 16 16
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Mang Drig Anarher Tomas Mag-Pu Cu Xasao Yang S Vasa Marta Anarha Tomas Anarha Zangsto Yang Wang P Yang Kat Li e Tao Chan Anarha Zangsto Yang Kat Li e Tao Chan Anarha Sangsto Yang Kat Li e Tao Chan Anarha Sangsto Anarha Sangsto Yang Kat Li e Tao Chan Anarha Sangsto Yang Kat Li e Tao Chan Anarha Sangsto Yang Kat Sang Anarha Sangsto Yang Kat Sang Yang	13 6 7 27 27 21 24 30 17 24 19 19 12 11 24 19 19 12 11 25 6 6 11 10 10 10 10 10 10 10 10 10	24 27 25 31 10 6 4 0 25 24 8 8 4 9 10 5 5 5 8 8 4 3 5 9 7 7 8 8 9 7 7 8 9 9 7 8 9 9 7 8 9 9 7 8 9 9 7 2 5 3 10 9 10 9 10 9 10 10 10 10 10 10 10 10 10 10 10 10 10	7 15 23 4 8 8 9 14 28 9 14 28 9 14 28 9 14 28 29 14 28 29 20 20 20 20 20 20 20 20 20 20 20 20 20	51 131 14 15 15 2,833 40 177 18 406 40 107 18 40 40 40 40 40 40 53 105 105 105 105 105 105 105 105 105 105	******	2491 (124, 442) (134) (247, 249) (134) (247, 249) (134) (247, 249) (134) (247, 249) (132) (244, 432) (132) (244, 432) (132) (244, 432) (132) (244, 132) (132) (244, 1	1.79 1.52 5.15		Study Hernando Trujilo Cingchun Yao Mingi Yuan Yaog Wang # Xiaojing Zou # Talo Ohen * Dewei Wang * Johne Cao * J. Zhang @ Overall Heterogeneily: r ¹ = (Test of 6, = 6; O(10) Test of 6, = 6; O(10) Test of 6, = 0; 2, = 2,5 H Study Hernando Trujilo Mingi Yuan Fei Zhou S Overall Heterogeneily: r ¹	Died 6 6 12 10 10 49 52 113 45 19 19 19 52 0.00, 1 ² = 0 0.00 20 0.00, 1 ² = 0 Consolidat 2 4 40 0.00, 1 ² = 0 0.00, 1 ² = 0	Survived 10 86 13 13 13 14 152 96 95 95 95 95 95 95 95 95 95 95	Died 1 0 0 84 0 0 0 0 0 0 0 0 0 0 0 0 0	Survived 8 10 4 150 6 9 30 10 30 108 		wen 95% Cl 3.36 [0.46, 23.66] 2.78 [0.10, 43.77 4.36 [0.30, 83.07] 4.36 [0.30, 83.07] 4.37 [0.30, 87.08] 4.33 [0.30, 71.02] 4.33 [0.30, 71.02] 4.33 [0.30, 71.02] 4.33 [0.30, 71.02] 1.34 [0.10, 10.05] 1.35 [1.07] 1.66 1.35 [1.07] 1.66 1.35 [1.07] 1.66 	(%) (%) (%) (%) (%) (%) (%) (%)) 17 19 13 17 19 19 19 19 19 19 10 15 18 16 16 16 16
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Fig 2. Meta-analysis to assess risk of mortality for (A) smoking status. (B) hypertension. (C) diabetes mellitus. (D) COPD. (E) acute cardiac injury. (F) acute kidney injury. (G) bilateral lung involvement. (H) Lung consolidation. COPD = chronic obstructive pulmonary disease. !Shenzhen Third People's Hospital, Shenzhen, China. #Tongji Hospital, Wuhan, China. \$Wuhan Jinyintan Hospital, Wuhan, China. *Zhongnan Hospital of Wuhan University, Wuhan, China. %Tianyou Hospital, Wuhan, China. &Taizhou Public Health Medical Center, Zhejiang, China. +Chongqing Three Gorges Central Hospital, Chongqing, China. @Renmin Hospital of Wuhan University, Wuhan, China. ^General Hospital of Central Theater Command of People's Liberation Army, Wuhan, China.

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NA Decreased TLC Increased TLC Decreased Neutrophil		Pooled Ki	sk of Mortality			Lab Cut-offs		Risk of Mortal	Risk of Mortality (based on cut-offs)		
ecreased TLC creased TLC creased TLC ecreased Neutrophil	No. of Studies	No. of Patients	Pooled RR [95% CI]	Heterogeneity 1 ² T ²	neity T ²		No. of Studies	No. of Patients	Pooled OR [95% CI]	Heterogeneity 1 ² T ²	eity T ²
creased TLC ecreased Neutrophil	~	1534	0.43[0.31-0.59]	%0	0	$TLC < 3.5 \times 10^9 / L$		154	0.58[0.26-1.30]		
creased TLC ecreased Neutrophil						$TLC < 4.0 \text{ x} 10^9/L$				%0	0
ecreased Neutrophil	6	1708	3.85[2.56-5.78]	80.87%	0.06	$TLC > 9.5 \times 10^9/L$				31.88%	0.06
ecreased Neutrophil						$TLC > 10.0 \times 10^9/L$				90.80%	0.55
	2	727	0.33[0.03-3.15]	72.18%	1.93	$N < 1.8 \text{ x} 10^9/L$	1	179	0.94[0.24-3.72]	'	'
						$N < 2 \ x 10^9/L$	1	548	0.09[0.01-0.66]	'	'
Increased Neutrophil	3	1001	4.45 [3.20-6.18]	38.52%	0.03	$N > 6.3 \text{ x} 10^9 / L$	2	453	3.83 [2.90-5.07]	%0	0
						$N > 6.5 \text{ x} 10^9 / L$	1	548	5.95[3.93-8.99]	- 1	
Decreased Lymphocyte	8	1554	4.09 [1.69 - 9.91]	83.63%	1.24	$L < 0.8 \ x 10^9/L$	5	299	4.45[2.70-7.32]	%0	0
						$L < 1.0 \text{ x} 10^9/L$	2	329	2.20[0.35-14.07]	91.96%	1.65
						$L < 1.1 \text{ x} 10^9/L$	4	378	5.97[0.98-36.29]	79.77%	2.68
Decreased Platelet count	9	1439	2.42 [1.78-3.30]	51.04%	0.07	$Plt \ count < 100 \ x \ 10^9/L$	ε	354	2.45[1.30-4.62]	51.44%	0.16
						Plt count < $125 \times 10^9/L$	2	537	2.45[1.26-4.75]	74.92%	0.17
						Plt count $< 150 \text{ x } 10^9/\text{L}$	1	548	2.08 [1.39–3.13]	- 1	
Decreased Albumin	4	1031	3.30[2.61-4.18]	%0	0	Albumin < 32 g/L	1	274	3.52[2.61-4.74]	-	'
					_	Albumin < 35 g/L	2	702	3.27[2.19-4.88]	%0	0
					_	Albumin < 40 g/L	1	55	1.24[0.36-4.25]	'	'
Increased Globulin	2	603	1.65[1.15 - 2.37]	%0	0	Globulin >35 g/L	2	603	1.65[1.15-2.37]	%0	0
Increased T · Bilirubin	3	810	2.74[1.96-3.82]	%0	` 0	T. Bilirubin > 20 umol/L	3	810	2.74[1.96-3.82]	%0	0
Increased AST	5	1210	2.33[1.93-2.82]	%0	0	AST > 40 U/L	5	1210	2.33 [1.93-2.82]	%0	0
Increased ALT	9	1330	1.48[1.20 - 1.82]	8.88%	0.01	ALT > 40 U/L	ŝ	976	1.30[1.04 - 1.64]	%0	0
						ALT > 50 U/L	.0	354	2.00 [1.39–2.87]	%0	0
Increased GGT	:	:	:	:	:	:	:	:	:	:	:
Increased ALP	:	:	:	:	:	:	:	:	:	:	:
Increased INR	:	:	:	:	:	:	:	:	:	:	:
Increased PT	2	345	1.97[1.41–2.76]	%0	0	PT > 16s	2	345	1.97 [1.41–2.76]	%0	0
Elevated CK-total	4	508	1.96[1.43-2.70]	9.52%	0.01	CK-total > 171 U/L	2	209	1.87[0.88-3.97]	54.89%	0.18
					_	CK-total > 185 U/L	1	191	1.78[1.09-2.91]	:	:
					_	CK-total > 190 U/L	1	108	1.56[0.47-5.23]	:	:
Elevated CK-MB	1	108	5.75[2.12-15.62]	'	'	CK-MB > 25 U/L	1	108	5.75[2.12-15.62]	:	:
Increased BUN	2	702	4.42[2.99-6.55]	45.89%	0.04	BUN $\ge 7.6 \text{ mmol/L}$	1	548	5.34 [3.63-7.85]	:	:
					_	BUN $\ge 8.3 \text{ mmol/L}$	1	154	3.58 [2.32-5.51]	:	:
Increased Creatinine	9	1235	2.92[2.35-3.62]	%0	0	Creatinine > 85 umol/L	1	548	2.99[2.35-3.62]	:	:
					-	Creatinine > 104 umol/L	1	55	2.61[1.36-4.98]	:	:
					-	Creatinine > 115 umol/L	1	154	2.88[2.02-4.10]	:	:
						Creatinine > 133 umol/L	3	478	3.19 [1.62-6.31]	42.97%	0.15
Increased Na ⁺	2	428	2.70 [2.00-3.64]	63%	0.03	$Na^+ > 145 mmol/L$	2	428	2.70 [2.00-3.64]	63%	0.03
Increased K ⁺	3	536	2.34[1.87-2.94]	9.45%	0.00	$\rm K^+ > 5 \; mmol/L$	2	428	2.36[1.85-3.01]	24.03%	0.01
						$\rm K^+ > 5.4 \ mmol/L$	1	108	2.20[0.57-8.54]	9.45%	0.00
Decreased K ⁺	3	536	0.99[0.43–2.29]	60.38%	0.33	$\mathrm{K^+} < 3.5 \mathrm{~mmol/L}$	5	428	0.70[0.22-2.27]	67.68%	0.52
						${ m K}^+ < 3.8~{ m mmol/L}$	1	108		:	:
Elevated LDH	5	1222	5.37 [2.10-13.74]	80.61%	0.84	LDH > 245 U/L	3	345	4.19[0.85-20.66]	83.47%	1.59

Laboratory rarameters		Pooled R	tisk of Mortality			Lab Cut-offs		Risk of Mortal	Risk of Mortality (based on cut-offs)		
	No. of Studies	No. of Patients	Pooled RR [95% CI]	Heterogeneity 1 ² T ²	:neity T ²		No. of Studies	No. of Patients	Pooled OR [95% CI]	Heterogeneity I ² T ²	neity T ²
						LDH > 250 U/L	1	548	13.10[3.26-52.66]	:	
						LDH > 350 U/L	1	274	6.33[4.16–9.63]	:	
Elevated Myoglobin	1	179	5.30 [2.36-11.92]	:	0	Myoglobin> 100 μg/L	1	179	5.30 [2.36-11.92]	:	
Increased Uric acid	:		:	:	:	:	:	:	:	:	
Elevated Cystatin C	1	108	1.75[0.417.50]	:	:	Cystatin C >1.2mg/L	1	108	1.75[0.417.50]	:	
Elevated D-Dimer	6	2026	3.98[2.87-5.52]	65.13%	0.13	D-Dimer > 0.5mg/L	4	562	3.33[1.48-7.49]	63.45%	
						D-Dimer > 1mg/L	3	847	4.82[3.29-7.07]	%0	
						D-Dimer > 2mg/L	1	343	5.54[4.15-7.39]	:	
						D-Dimer > 21mg/L	1	274	3.06[2.44-3.85]	:	
Increased CRP	9	1338	5.49[1.72-17.51]	93.21%	1.59	CRP > 10 mg/L	1	108	6.22[0.83-46.36]	:	
						CRP > 100 mg/L	5	1175	5.72[1.40-23.41]	95.68%	2.12
Elevated ESR	2	603	0.96[0.64-1.44]	%0	0	ESR>15 mm/h	2	603	0.96[0.64-1.44]	%0	
Elevated Procalcitonin	8	1555	3.09[2.35-4.07]	53.89%	0.07	Procalcitonin $>0.05 \ \mu g/L$	3	810	4.45[3.19-6.21]	0%0	
						Procalcitonin $>0.5 \ \mu g/L$	4	069	2.21[1.13-4.33]	87.85%	0.35
						Procalcitonin >1 $\mu g/L$	1	55	2.67[1.45-4.90]	:	
Increased Serum ferritin	1	191	5.6 [1.47-21.6]	:	:	S. ferritin $> 300 \ \mu g/L$	1	191	5.6 [1.47–21.6]	:	
Increased SAA	:	:	:	:	:	:	:	:	:	:	
Increased IL–1β	1	274	0.84 [0.38-1.83]	:	:	$IL-1\beta > 5 ng/L$	1	274	0.84 [0.38-1.83]	:	
Increased IL–2	1	274	4.04 [2.18-7.49]	:	:	IL-2 > 710 U/L	1	274	4.04 [2.18-7.49]	:	
Increased IL–6	2	503	22.59[3.19-160.03]	%0	0	IL-6 > 2.9 ng/L	1	229	12.66[0.79-202.89]	:	
						IL-6 > 7 ng/L	1	274	40.13[2.53-636.24]	:	
Increased IL–8	1	274	2.29 [1.51-3.45]	:	:	IL-8 > 62 ng/L	1	274	2.29 [1.51-3.45]	:	
Increased IL–10	1	274	4.19 [2.56-6.84]	:	:	IL-10 > 9.2 ng/L	1	274	4.19 [2.56–6.84]	:	
Increased TNF–Alpha	1	274	2.57 [1.46-4.52]	:	:	TNF-Alpha >8.1 ng/L	1	274	2.57 [1.46-4.52]	:	
Increased NT–ProBNP	2	822	5.48 [3.78-7.34]	0%0	0	NT-ProBNP $> 285 \text{ ng/L}$	1	275	5.87[3.43-10.03]	:	
						NT-ProBNP > 500 ng/L	1	548	5.136[3.07-8.60]	:	
Elevated troponin	6	1006	4.49[3.74-5.38]	%0	0	hs Tn I > 15.6 ng/L	2	375	4.62[2.80-7.65]	52.63%	0.07
						hs Tn I > 26.2 ng/L	1	107	6.01[2.80-7.65]	:	
						hs Tn I > 28 ng/L	1	191	4.29[3.05-6.05]	:	
						${\rm Tn}~{\rm I} > 50~{\rm ng/L}$	1	179	5.47[2.44-12.28]	:	
						hs Tn I > 100 ng/L	1	154	4.28[2.91-6.29]	:	

Kinase. CRP = C-Reactive Protein. ESR = Erythrocyte Sedimentation Rate. GGT = Gamma–Glutamyl Transferase. IL = Interleukin. INR = International Normalized Ratio. K+ = Potassium. LDH = Lactate Dehydrogenase. N = Neutrophil count. Na+ = Sodium. NT-ProBNP = N-Terminal Fragment Brain Natriuretic Peptide. Plt count = Platelet count. OR = Odds ratio. PT = Prothrombin Time. RR = Risk ratio. T Bilirubin = Total Bilirubin. TLC = Total Leucocyte Count. TNF = Tumor Necrosis Factor. * denotes presence of publication bias by Egger's test (p-value < 0.05).

Table 2. (Continued)

A Study		Smokers Non-severe		smokers Non-severe		Odds R with 95%		Weight (%)	В							
Kiaochen Li	51	41	214	238		1.38 [0.88,		11.98	Study	Hype	ertensive Non-severe		Non-sevent		Odds Ratio with 55% CI	Weigh (%)
uirui Wang	7	9	18	91		3.93[1.30,			Zne Znu	8	23	8	88		3.83 [1.30, 11.29]	9] 2.61
in Feng	17	27	104	306	-	1.85 [0.97,	3.54		Xieochen Li	104	62	165	217		2.21 [1.52, 3.21]	
n-jin Zhang J Shi	6	3 34	52 43	79 391		3.04 [0.73, 1.60 [0.64,	12.69		Quyi Wang Xiugi Wei	49	22	11	171		3.53[1.12, 11.12]	
aoje Bi	5	34	17	88	1000	8.63 [1.88.			Gingchun Yao	9	7	16	75		6.11 (1.98, 18.82)	2 2.50
heng Yi	2	6	28	37		0.44 [0.08,	2.35		Yun Feng	40	73	84	275	-	1.82[1.15, 2.87]	
ng Zou	2	12	24	265		1.84 [0.39,	8.71		Marta Colaneri Jin-Jin Zhang	5 22	10	12	17		0.71[0.15, 2.61] 1.89[0.91, 3.94]	
ing-kai Li #	5	2	4	14		8,75 [1.21,			Fang Zheng	12	10	18	121		- 8.07 [3.04, 21.37]	
tuan Qin # ei-jie Guan S	3	4	283	162 793		0.43 [0.09, 1.87 [1.25,	1.94		Lijun Bun	6	2	9	38		12.67 (2.18, 73.44)	4] 1.37
ng Hu %	34	38	138	113		0.73 [0.43,	1.24		Shuts Zheng	31	4 +0	43	18		3.24[1.00, 10.53]	
ingging Chen &	3	12	40	90		0.56 [0.15,	2.10		Liong Shen Yu Shi	26	73	23	365		16.53 (5.35, 51.05) 5.65 (3.05, 10.45)	
uxin Wan +	1	8	39	87 —	-	0.28 [0.03,	2.31		Yong Geo	e	7	5	21		2.00 [0.52, 7.65]	5] 2.02
ui Zhang @	6	0	24	90		- 48.02 (2.61		1.81	Kunhus U	2	3	23	55		1.59 (0.25, 10.18)	
verall					*	1.60 [1.05,	2.43	8	Gingzian Call Jing Yuan 1	22	25	26	215		8.26 [2.68, 10.30] - 4.81 [1.01, 22.02]	
sterogeneity: 1" = st of 0, = 0,; D(14			= 2.68						Lu Huang #	6	5	21	95		4.52 [1.20, 17:05]	
est of $\theta = 0$: $z = 2$.									Gueng Chen ≠	4	1	7	9		5.14 [0.45, 56.90]	0.83
				-	1.00				Guangchang Pel a	· 70	37	118	107		1.72[1.07, 2.76]	
									Yang-kai Li # H Hou #	24	44	127	15			
2									Chuen Qin #	105	30	181	126	-	2.63 [1.66. 4.10]	
		es mellitus		etes mellitus		Odds Rat		Weight	Wellje Guan S	41	124	122	802	-	2.01 [1.35, 2.99]	
tudy	and the second second	Non-severe		Non-severe		with 95%	-	(99)	Hansheng Xie S Ling Hu %	4 66	10	24	41 112		0.68[0.19, 2.42]	
e Zhu aochen Li	52	10	16	101 248		0.29 (0.02,	5.24) 3.105	0.60	Ling Hu % Gingoing Chen &	66 5	13	106	112	-	1.79[1.11, 2.88]	
aochen Li zyl Wang	0	11	16	182		0.48 (0.03,	8.53]		Buxin War +	4		26	36		1.0610.31, 3.67	
uqi Wel	15	16	105	115	+	1.02 [0.48.		4.59	Rul Zhang 🚳	13	6	17	84		- 10.71 (3.67, 32.12)	
uan-Yuan Wel	7	4	23	133			37.36] 35.13]		Qing Deng @	24	12	43	22		1.53[0.67, 2.51]	
ingchun Yao un Feng	17	32	107	220		1.55 (0.87,		5.37	Luwen Wang G Xisohus Chen *	20	23 E	37	36		4.25[1.25, 14.50]	
arta Colaneri		6	16	21		0.22 [0.02,	2.00	0.98	Fang Liu A	22	41	11	66		3 22 [1.42, 7.32]	
n-jin Zhang	8 76	9	50 97	73		1.30 (0.47, 2.12 (1.37,		3.27	Overall					+	2.63 (2.08. 3.33)	3]
uyi Li ang Zheng	2	5	28	126		1.80 (0.33,		1.55	Heterogeneity: 1			-2.79				
(un Sun	2	3	13	37		1.90 [0.28,	12.65]	1.28	Test of 8 = 8; Q(2) Test of 8 = 0; z = 1							
n Ying Zheo hufe Zhena	1	2	25	59		1.02 (0.05,	11.89]				3 0			1.00		
nurs Zneng ano Rhen	10	1	64 15	21	20-4			1.05								
u 8n/	7	22	42	416	-	3.15 (1.27,	7.81	3.76	D							
unihua Li	7	۰	18	58		-47.43 (2.58, 3		0.59		co	PD	No C	OPD		Odds Ratio	Weight
heng YI Ingzien Cel I	3	10	27	42		4.67 (0.46)	47.21] 5.795	0.90	Study		on-severe \$				with 95% CI	(%)
Yuan (2	3	9	80			40.31]		Xiaochen Li	13	4	256	275		3.49 [1.12, 10.85]	10.66
Huang #	4	2	22	97		5.88 (1.22.		1.76	Yun Feng	14	8	110	344			13.49
uang Chen # uangchang Pel #	2	1 20	9	9	-	2.00 (0.15,	4.631	0.75	Marta Colaneri Jin-jin Zhang	0	2	17	25 - 82		0.29[0.01, 6.45] 7.30[0.34, 154.96]	2.32
ing-kal L(#	1	0	8	15				0.47	Juyi Li	8	10	165	179	-		12.73
Hau #	23	16	158	152		1.10 (0.56,		5.08	Fang Zheng	2	4	28	127			6.05
tuan Qin # ei-lie Guan \$	53	22	233	144		1.49 (0.87, 2.13 (1.95,	2.55) 5.150		Xin Ying Zhao Yong Gao	1	0	29 12	61 28	1.000		2.15
errje Guan a ansheng Xie ä	20	52	26	45	_	0.58 (0.11,	3.073		Peijie Lyu	3	0	36	12			2.40
ng Hu %	33	14	139	37	-	0.63 (0.30,	1.29]		Kunhua Li	4	1	21	57		10.86 [1.15, 102.77]	4.05
ngaing Chen &	7	7	26	55		2.64 (0.86.	8.05]		Lu Huang #	1	1	25	99			2.77
ul Zhang 🖸	9	3	31	92		8.90 (2.27, 		2,17	Yang-kai LI # H Hou #	4	1	5 218	15 168	1.000		3.59
ing Deng Q	14	5	53	40	-8-	2.11 (0.70.		2.56	Chuan Qin #	9	3	277	163	-	1.77 [0.47, 6.61]	8.89
wen Wang 🚳	10	8	47	51	-#-	1.36 [0.45,	3.73]		Wei-jie Guan \$	6	6	167	920			10.56
achus Chen ^	12	4	15	17		1.79 (0.46, 2.21 (0.94,	7.02) 5.17)		Ling Hu %	6	0	166 43	151			2.63
verall			0.50	**		2.09 (1.66.	2.64)		Qingqing Chen 8. Rui Zhang @	3	1	27	90			3.89
sterogeneity: 72 -	0.16,12	40.35%, H ³	+1.68			*144 5 - 144	***		Qing Deng @	3	1	64	44	-		3.91
st of 8, + 8; G(25									Overall					+	3.23 [1.97, 5.31]	
stofe=0:z=6	23.0=0.	00				-			Heterogeneity: 7 Test of 6 = 6: Q(1			- 1.33				
					1,00				Test of 8 = 0; z = 4							
Ξ													-	1.00		
		transverse		(involvement)		Odds Ratio		sight								
udy		Non-severe		Non-severe		with 95% CI		sight 56)	F							
lei Zhao	14	69	0	18		7.72 [0.44, 135	.53] 1	89								
ngchun Yao	25	73	0	10		7.29[0.41, 128		89			present C		n absent on-severe			eight %)
n Feng I-jin Zhang	107	266 68	8	61 10	ing in	3.07 [1.42, 6	63] 10 561 6		Wei Zhao		36	6	51		1.89[0.60, 5.91] 12.	and a second second
imivei Li	8	37	ō	33		15.19 [0.84, 273						96	259	-	0.75[0.43, 1.32] 15.	
si-Cai Liu	24	31	0	18	-	-28.78 [1.65, 501	60] 1.	90	Kai-Cai Liu	8	0	16	49		51.00 [2.79, 932.53] 5.	5.30
ung Zheng un Sun	26 15	63 29	4	68 11		7.02 [2.32, 21		63 86	Yu-Huan Xu Peijle Lyu	9 36	6	4	22 5		8.25 [1.87, 36.38] 10. 8.57 [1.66, 44.38] 9.	9.89
un Sun Iufa Zheng	15 68	29	6	10		9.44 (2.89, 30		09				3	27		6.39 [1.72, 23.72] 11.	
sije Lyu	37	4	2	8		37.00 [5.75, 238	.03] 3	87	Jiaojiao Chu #	4	2	37	9 —	-	0.49[0.08, 3.08] 8.	97
inhua Li	25 10	54	0	4		4.21 [0.22, 81		79	Ji Mengyao @	8 25	10	43	60 53		1.12 [0.41, 3.06] 13.	
uang Chen # aojiao Chu #	10 35	11	1	3		4.29[0.37, 50	1.10	47 80	Rui Zhang @ Overall	2	31	3	53		7.16[2.51, 20.43] 12. 3.01[1.32, 6.88]	
ei-jie Guan S	137	368	30	440		5.46 [3.59, 8	30] 14		Heterogeneity: 1 ² =	1.09, 12 = 75	62%, H ² = 4.	10			mail the wool	
ingging Chen &	40	75	3	27		4.80 [1.37, 16		64	Test of 0. = 0.: Q(8)	= 34.92, p =						
prin Wan +	40	95 195	0 54	0 - 59		0.42[0.01, 21			Test of $\theta = 0$: $z = 2.6$	52, p = 0.01			_		-	
"hann @		50	4	20		4.70 1.50, 14								1.00		
	47	30														
Mengyao @	47 28	40	2	50		17.50[3.93, 77		32								
Mengyao @ ii Zhang @ verall	28	40					93] 5	32								
Zhang @ Mengyao @ ui Zhang @ verall eterogeneity: τ ² = (sst of θ. = θ. O(18)	28 0.28,1 ² = -	40 47.07%, H ² =			•	17.50[3.93, 77	93] 5	32								

Fig 3. Meta-analysis to assess odds of severe disease for (A) smoking status (B) hypertension (C) diabetes mellitus (D) COPD E. bilateral lung involvement (F) Lung consolidation. COPD = chronic obstructive pulmonary disease. !Shenzhen Third People's Hospital, Shenzhen, China. # Tongji Hospital, Wuhan, China. \$Wuhan Jinyintan Hospital, Wuhan, China. *Zhongnan Hospital of Wuhan University, Wuhan, China. %Tianyou Hospital, Wuhan, China. &Central hospital of Wuhan, Wuhan. +Chongqing Three Gorges Central Hospital, Chongqing, China. @Renmin Hospital of Wuhan University, Wuhan, China. ^General Hospital of Central Theater Command of People's Liberation Army, Wuhan, China.

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1.00

Among the laboratory parameters that were assessed for association with severe disease using binary cut-offs (Table 3), decreased lymphocyte count (OR 2.64, 95%CI 1.12–6.23), decreased serum albumin (OR 5.63, 95%CI 1.45–21.87), increased aspartate transaminase (OR 4.33, 95%CI 2.17–8.63) demonstrated increased odds of severe disease. Inflammatory parameters namely, elevated CRP (OR 3.32, 95%CI 1.92–5.71), elevated procalcitonin (OR 5.50, 95% CI 3.38–8.93) and increased ESR (OR 1.68, 95%CI 1.13–2.49) had high ORs for severe disease. Bilateral lung involvement on CT was associated with an OR of 4.86[95%CI: 3.19–7.39] among 19 studies. Other radiological features on CT with higher odds of severe disease were lung consolidation, ground glass opacities, air bronchogram, hilar lymphadenopathy, pleural effusion, crazy-pavement pattern, reticular pattern, tree-in bud appearance, inter-lobar septal thickening, and bronchiectasis. However, the OR of severe disease were not increased with peripheral distribution of infiltrates, nodular infiltrates, linear infiltrates, unifocal involvement or pleural thickening.

Meta-regression of continuous variables (Table 4) revealed that with every ten-year increase in the mean age of the patients, there was a 7.6% and 11.2% increase in the mortality (pvalue = 0.02) and disease severity (p-value < 0.001) respectively. Increase in the mean total leukocyte count (p-value = 0.04) and a decrease in the mean lymphocyte count (p-value = 0.02) were significantly associated with higher mortality. Higher levels of mean C-reactive protein and mean D-dimer during admission were linked to higher proportion of both severe disease as well as mortality. Increasing mean lactate dehydrogenase and creatine kinase among the included studies were associated with higher mortality but not severe disease. Higher serum creatinine levels and lower serum albumin levels correlated with disease severity but was not significantly associated with mortality, though the direction of the relationship was consistent. Unit increase in the mean blood urea nitrogen resulted in 5.3% increase in the mortality (pvalue = 0.030). Our analysis did not reveal a significant association between mortality or disease severity and other laboratory parameters, such as platelet count, hemoglobin, prothrombin time, activated partial thromboplastin time (aPTT), procalcitonin, aspartate transaminase (AST), alanine transaminase (ALT), erythrocyte sedimentation rate, total bilirubin and interleukin-6 levels. Bubble plots assessing the linear relationship between the variables and the outcomes (proportion with severe disease and proportion who died) are shown in Figs 4 and 5and Supplementary Section VI in S1 Appendix.

Subgroup analyses based on the restriction of inclusion to critically ill participants are shown in S5 Table and in the Supplementary Figures in <u>S1 Appendix</u> Section IV. Subgroup analysis did not significantly reduce heterogeneity between studies except for the association of elevated procalcitonin levels and presence of diarrhea with mortality. The magnitude of the effect size changed significantly in the subgroups however the direction of the effect remained consistent for multiple parameters, including dyspnea, cardiovascular disease, cerebrovascular disease, diabetes mellitus, bacteremia, and gastrointestinal bleeding. In studies with critically ill patients, the direction of the effect was reversed for gender and elevated procalcitonin levels, but the association was not statistically significant in the subgroups. Sensitivity analysis by excluding low-quality studies (NOS<5) did not significantly reduce heterogeneity or alter the pooled effect sizes for the exposures with $I^2 > 50\%$ for mortality. Sensitivity analysis by excluding low-quality studies reporting COVID-19 severity yielded a decrease in the heterogeneity for various exposures, such as smoking, hypertension, myalgia, and air-bronchogram in CT. Nevertheless, heterogeneity was substantially high for exposures, such as dyspnea, chest pain, abdominal pain, unifocal involvement in CT and certain laboratory parameters. Sensitivity analysis for the laboratory and radiological variables by excluding studies with an unclear timepoint for the assessment of the parameters did not result in change in the direction or significance of the association. In our analysis, bias due to small study effect could not be ruled

Decreased TLC No. of Studies Decreased TLC 11 Increased TLC 11 Decreased TLC 11 Decreased TLC 11 Decreased Neutrophil 2 Decreased Neutrophil 3 Decreased Lymphocyte 7 Decreased Platelet count 9	No. of Patients		;							
		Pooled RR [95% CI]	Heterogeneity 1 ² T ²	ity	No. of Studies		No. of Patients	Pooled OR [95% CI]	Heterogeneity 1 ² T ²	eity T ²
	3074	0.84[0.52-1.37]	78.58%	46 TLC	< 3.5 x10 ⁹ /L	4	548	0.70[0.37-1.33]	29.06%	:
				TLC <	$TLC < 4.0 \text{ x}10^9/L$	6	2482	0.89[0.43-1.82]	88.86%	0.67
Intra la construction de la cons				TLC <	$TLC < 5.0 \text{ x}10^9/L$	1	44	1.21[0.36-4.08]	:	:
unt te te	3353	3.70[2.31-5.93]	49.71%	0.27 TLC >	$TLC > 9.5 \text{ x}10^9/L$	4	548	2.94[2.31-5.93]	47.12%	0.47
tte tunt				TLC >	TLC >10.0 x10 ⁹ /L	6	1706	4.65[2.17-9.98]	63.09%	0.49
te t				TLC >	TLC >11.0 x10 ⁹ /L		1099	2.54[1.43-4.52]	:	:
te te num	689	0.33[0.19-0.58]	%0	0	< 1.8 x10 ⁹ /L	-	141	0.95[0.10-8.97]	:	:
te te numt				Z	$N < 2 x 10^9/L$	1	548	0.31[0.17 - 0.55]	:	:
	554	2.00[0.93-4.31]	52.14%	0.25 N >	> 6.3 x10 ⁹ /L	1	141	4.95[1.67-14.68]	:	:
				X	> 6.5 x10 ⁹ /L	-	90	1.19[0.32-4.42]	:	:
				Z	$N > 7.5 x 10^9/L$	-	323	1.52[0.93-2.47]	:	:
	2922	2.64[1.12-6.23]	87.02%	1.04 L <	$L < 0.8 x 10^9/L$	2	342	3.10[0.49-19.69]	83.84%	1.49
				L	$L < 1.0 x 10^9/L$	-	476	4.04[2.59-6.31]	:	:
				r	$L < 1.1 x 10^9/L$	5	638	1.77[0.09–33.23]	94.51%	4.23
					$L < 1.5 x 10^9/L$	1	1143	8.56[0.44-165.38]	:	:
				L	$< 2.0 \text{ x}10^{9}/\text{L}$	1	323	1.84[1.12-6.23]	:	:
	2691	2.39[1.72-3.34]	34.31%	0.13 Plt count $< 100 \text{ x} 10^9/\text{L}$	$100 \ge 10^{9}/L$	3	592	2.27[1.08-4.78]	%0	0
				Plt count $< 125 \text{ x } 10^9/\text{L}$	125 x 10 ⁹ /L	Э	408	3.09[1.37-6.99]	45.21%	0.23
				Plt count $< 150 \text{ x } 10^9/\text{L}$	$150 \ge 10^9/L$	3	1691	2.22[1.32-3.73]	67.23%	0.13
Decreased Albumin 2	663	5.63[1.45-21.87]	77.32%	0.77 Album	Albumin < 35 g/L	-	548	3.19[2.22-4.57]	:	:
				Album	Albumin < 40 g/L	1	115	13.07[3.68-46.40]	:	:
Increased Globulin 2	663	1.98[1.44-2.72]	%0	0 Globu	Globulin >30 g/L	1	115	1.67[0.77-3.64]	%0	0
				Globu	Globulin >35 g/L	-	548	2.05[1.44-2.90]	%0	0
Increased T · Bilirubin 5	2031	2.23[1.34-3.71]	23.14%	0.08 T. Bilirubin > 20 umol/L	20 umol/L	5	2031	2.23[1.34-3.71]	23.14%	0.08
Increased AST 7	2624	4.85[2.52-9.34]	86.47%	0.62 AS	AST > 40 U/L	7	2624	4.85[2.52-9.34]	86.47%	0.62
Increased ALT 7	2920	2.40[1.09-5.29]	89.03%	0.97 AL	ALT > 40 U/L	4	2607	2.36[0.81-6.89]	97.33%	2.41
				AL	ALT > 50 U/L	Э	313	2.33[0.85-6.38]	%0	0
Increased GGT 1	115	1.42[0.44-4.55]	:	:	GGT > 57 U/L	1	115	1.42[0.44 - 4.55]	:	:
Increased ALP 1	115	6.07[1.05-35.03]	:	·· ALP	ALP > 120 U/L	1	115	6.07[1.05-35.03]	:	:
Increased INR 1	115	1.38[0.60-3.18]	:	:	INR > 1.15	1	115	1.38[0.60–3.18]	:	:
Increased PT 2	413	2.35[1.26 - 4.41]	%0	0	PT > 12.8s	1	90	1.65[0.58 - 4.67]	:	:
					PT > 14s	1	323	2.88[1.31-6.32]	:	:
Elevated CK-total 6	1733	3.11[1.74-5.55]	41.86%	0.21 CK-total	CK-total > 190 U/L	Э	359	3.73[1.97-7.07]	2.42%	0.01
				CK-total	CK-total > 190 U/L	3	1374	2.87[1.03-8.00]	49.25%	0.42
Elevated CK-MB 4	794	1.41[0.42-4.67]	72.23%	1.02 CK-N	CK-MB > 5 U/L	2	596	0.73[0.14-3.69]	77.79%	1.08
				CK-M	CK-MB > 25 U/L	2	198	2.83[1.03-7.82]	%0	0
Increased BUN 2	871	4.06[2.71-6.07]	%0	0 BUN \ge	$BUN \ge 7.6 \text{ mmol/L}$	1	548	4.77[2.75-8.29]	:	:
				BUN	BUN≥8 mmol/L	1	323	3.37[1.87-6.09]	:	:
Increased Creatinine 8	2508	2.49[1.41-4.41]	21.59%	0.14 Creatinine > 87 umol/L	87 umol/L	2	709	1.66[1.14-2.43]	%0	0
				Creatinine > 97 umol/L	97 umol/L	2	225	5.88[0.63-54.73]	47.51%	1.33
				Creatinine > 133 umol/L	133 umol/L	3	1251	3.81[1.4-10.11]	%0	0
				Creatinine > 144 umol/L	144 umol/L	1	323	2.18[0.42-11.41]	:	:

Laboratory Parameters		Pooled Odds	Pooled Odds of Disease Severity			Lab Cut-offs	Po	oled Odds of Disea	Pooled Odds of Disease Severity (based on cut-offs)	t-offs)	
	No. of Studies	No. of Patients	Pooled RR [95% CI]	Heterogeneity 1 ² T ²	neity T ²		No. of Studies	No. of Patients	Pooled OR [95% CI]	Heterogeneity 1 ² T ²	neity T ²
Increased Na ⁺	:	:	:	:	:	:	:	:	:	:	:
Increased K ⁺	1	108	0.94[0.18-4.86]	:	:	$K^+ > 5.1 mmol/L$	1	108	0.94[0.18-4.86]	:	:
Decreased K ⁺	1	108	7.59 [2.67–21.60]	:	:	$\rm K^+ < 3.8~mmol/L$	1	108	7.59 [2.67–21.60]	:	:
Elevated LDH	7	2425	3.77[1.95-7.30]	82.69%	0.61	LDH > 225 U/L	1	161	4.70[2.02-10.94]	:	:
						LDH > 243 U/L	1	115	5.90[2.33-14.95]	:	:
						LDH > 250 U/L	4	2105	2.92[0.95-8.93]	92.70%	1.18
						LDH > 300 U/L	1	44	6.29[1.60-24.73]	:	:
Elevated Myoglobin	1	273	4.57[2.05-10.17]	:	:	Myoglobin> 100 μg/L	1	273	4.57[2.05-10.17]	:	:
Increased Uric acid	1	06	3.28[0.52-20.77]	:	:	Uric acid >417 umol/L	1	60	3.28[0.52-20.77]	:	:
Increased Cystatin C	1	108	2.14[0.66-6.88]	:	:	Cystatin C > 1.2mg/L	1	108	2.14[0.66-6.88]	:	:
Elevated D-Dimer	5	1985	2.75[1.92-3.93]	32.40%	0.05	D-Dimer > 0.25mg/L	2	230	3.44[1.48-8.02]	%0	0
						D-Dimer > 0.5mg/L	1	1099	1.94[1.27-2.97]	:	:
						D-Dimer > 1mg/L	2	656	3.33[2.37-4.69]	%0	0
Increased CRP	12	3375	3.32[1.92-5.71]	73.74%	0.55	CRP > 30 mg/L	3	595	1.82[0.63-5.24]	50.77%	0.45
						CRP > 50 mg/L	1	108	9.25[2.05-41.80]]	:	:
						CRP > 80 mg/L	2	301	14.43[3.89-53.50]	0%0	0
						CRP > 100 mg/L	9	2371	2.92[1.55-5.51]	77.52%	0.43
Elevated ESR	1	548	1.68[1.13-2.49]	:	:	ESR>20 mm/h	1	548	1.68[1.13-2.49]	:	:
Elevated Procalcitonin	8	2392	5.50[3.38 - 8.93]	38.70%	0.18	Procalcitonin >0.05 μg/L	2	240	3.45[1.61-7.37]	%0	0
						Procalcitonin >0.1 μg/L	2	275	6.34[1.58-25.38]	78.13%	0.79
						Procalcitonin >0.5 μg/L	4	1877	6.97[3.12-15.58]	39.61%	0.26
Increased Serum ferritin	1	548	3.57 [2.12-6.01]	:	:	S. ferritin $> 500 \ \mu g/L$	1	548	3.57 [2.12-6.01]	:	:
Increased SAA	5	830	1.54[0.84 - 2.82]	19.73%	0.10	SAA > 1mg/L	1	121	0.92[0.43-2.01]	:	:
						SAA > 10mg/L	4	709	2.39[0.92-6.22]	27.08%	0.28
Increased IL–1β	1	548	0.62[0.37 - 1.02]	:	:	$IL-1\beta > 5 ng/L$	1	548	0.62[0.37-1.02]	:	:
Increased IL-2	1	548	2.60[1.63 - 4.14]	:	:	IL-2 receptor $> 710 \text{ U/L}$	1	548	2.60[1.63-4.14]	:	:
Increased IL–6	3	778	3.30[0.73-14.93]	82.0%	1.38	IL-6 > 7 ng/L	3	778	3.30[0.73-14.93]	82.0%	1.38
Increased IL-8	1	548	1.83[0.79 - 4.27]	:	:	IL-8 > 62 ng/L	1	548	1.83[0.79-4.27]	:	:
Increased IL-10	1	548	1.62[0.98-2.67]	:	:	$\rm IL-10 > 9.2 ~ng/L$	1	548	1.62[0.98-2.67]	:	:
Increased TNF–Alpha	1	548	1.90[1.20-3.03]	:	:	TNF-Alpha >8.1 ng/L	1	548	1.90[1.20-3.03]	:	:
Increased NT–Pro BNP	2	821	4.43[2.80-7.02]	%0	0	NT-Pro BNP > 500 ng/L	1	548	4.23[2.36-7.59]	:	:
						NT-Pro BNP > 900 ng/L	1	283	4.78[2.27-10.08]	:	:
Elevated troponin	2	596	3.04 [1.03-8.97]	77.67%	0.48	hs Tn I $> 40 \text{ ng/L}$	2	596	3.04 [1.03-8.97]	77.67%	0.48

> = Blood Urea Nitrogen. CK = CreatineKinase. CRP = C-Reactive Protein. ESR = Erythrocyte Sedimentation Rate. GGT = Gamma-Glutamyl Transferase. IL = Interleukin. INR = International Normalized Ratio. K+ = Potassium. LDH = Lactate Dehydrogenase. N = Neutrophil count. Na+ = Sodium. NT-ProBNP = N-Terminal Fragment Brain Natriuretic Peptide. Plt count = Platelet count. OR = Odds ratio. Abbreviations: ALP = Alkaline Phosphatase. ALT = Alanine Aminotransferase. AST = Aspartate Aminotransferase. BNP = Brain Natriuretic Peptide. BUN PT = Prothrombin Time. RR = Risk ratio. T Bilirubin = Total Bilirubin. TLC = Total Leucocyte Count. TNF = Tumor Necrosis Factor. *denotes presence of publication bias by Egger's test (p–value < 0.05).

Table 3. (Continued)

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Variable	Mean increase of the variable	No· of studies	No∙ of patients	Percentage change in mortality [95% CI]	p-value	No∙ of studies	No∙ of patients	Percentage change in severe disease [95% CI]	p-value
Age	10 years	41	20296	7.6 [1.0, 14.2]	0.02	70	17799	11.3 [6.5, 16.2]	< 0.001
Hb	lg/L	12	2519	1.1 [-1.4, 3.6]	0.41	13	3013	-1.1 [-1.6, -0.5]	0.002
TLC	1x10^9/L	20	9797	5.4 [0.2, 10.6]	0.04	28	5370	15.2 [6.23, 24.18]	< 0.001
Lymphocyte count	0·1x10^9/L	24	10097	-4.1 [-7.4, -0.8]	0.02	31	5696	-17.3 [- 35.9, 1.3]	0.07
Neutrophil count	1x10^9/L	14	8930	10.5 [0.5, 20.6]	0.04	22	3586	9.8 [0.5, 19.1]	0.04
Platelet count	50 x 10^9/L	14	3120	-18.8 [-41.6, 3.85]	0.10	15	3190	0.1 [-0.4, 0.51]	0.82
Prothrombin time	1 s	16	3277	3.3 [-4.2, 10.8]	0.39				
aPTT	1 s	12	2651	1.0 [-0.9, 3.0]	0.24				
CRP	100 mg/L	19	3974	6.1 [3.3, 8.9]	< 0.001	27	4517	5.0 [2.9, 7.0]	< 0.001
D-dimer	1mg/L	15	3621	21.6 [7.0, 36.4]	< 0.01	21	3387	2.9 [0.1, 5.8]	0.04
Pro-calcitonin	0.1 mg/L	10	2349	4.5 [-19.3, 28.5]	0.71	19	2725	8.5 [-1.5, 18.4]	0.09
Serum LDH	100 U/L	13	2682	9.1 [2.4, 15.8]	0.01	12	1666	-0.02 [-0.1, 0.1]	0.52
Serum creatinine	10 μmol/L	19	3817	0.2 [-0.4, 0.7]	0.51	18	3062	9 [0.7, 17.5]	0.03
BUN	1 mmol/L	14	2979	5.3 [0.5, 10.2]	0.03				
Total Bilirubin	1 μmol/L	12	2191	2.6 [-0.2, 5.5]	0.07	13	8040	-2.0 [-6.8, 2.7]	0.41
Albumin	10 g/L	12	1986	-4.1 [22.9, 14.6]	0.67	12	7789	-5.0 [-7.2, -2.8]	< 0.001
AST	10 U/L	15	8927	1.7 [-0.9, 4.4]	0.19	18	8395	-1.9 [-14.6, 10.8]	0.77
ALT	10 U/L	19	9664	2.6 [-1.2, 6.4]	0.18	20	8836	7.4 [- 7.6, 22.5]	0.33
CK-total	10 U/L	10	2051	1.6 [0.02, 3.1]	0.04	12	2331	-0.3 [-0.7, 0.2]	0.31
IL-6	10 ng/L					13	2404	1 [-0.2, 3]	0.09

Table 4. Association of clinical parameters expre	essed as continuous variables with mortality	v and disease severity in	patients with COVID-19 by meta-regression.

Abbreviations: ALT = Alanine Aminotransferase. aPTT = activated Partial Thromboplastin Time. AST = Aspartate Aminotransferase. BUN = Blood Urea Nitrogen. CK = Creatinine Kinase. CRP = C-Reactive Protein. Hb = Hemoglobin. IL = Interleukin. LDH = Lactate Dehydrogenase. TLC = Total Leucocyte Count.

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out while assessing risk of mortality for the following exposures, such as gender, diabetes mellitus, hypertension, ARDS and acute kidney injury and hence the results for these factors should be interpreted with caution.

Discussion

A total of 109 articles were deemed suitable for data synthesis and identification of variables associated with severe COVID-19 disease and mortality. Specific determinants were identified from a array of clinical parameters such as symptoms, co-morbidities, laboratory, and radio-logical data. Our findings have potential implications for clinical decision-making, as well as allocation of scarce critical care resources for patients with COVID-19.

The presence of various comorbidities was reported to be associated with severe disease and/or death in patients with COVID-19 in prior studies [127]. Although the direction of association was consistent with previous reports, the risks of death in patients with diabetes and hypertension were lower in our study with an RR of 1.59 [95% CI: 1.41–1.78] and 1.90 [95% CI: 1.69–2.15] respectively for mortality. The levels of control of diabetes and hypertension in these patients, as well as pharmacotherapy for these conditions were not taken into consideration in our review, which might account for the clinical heterogeneity. There was a significant association between pre-existing cardiovascular diseases and COVID-19 attributable mortality, with an RR of 2.27 [95%CI: 1.88–2.79]. This is similar to the association of cardiovascular

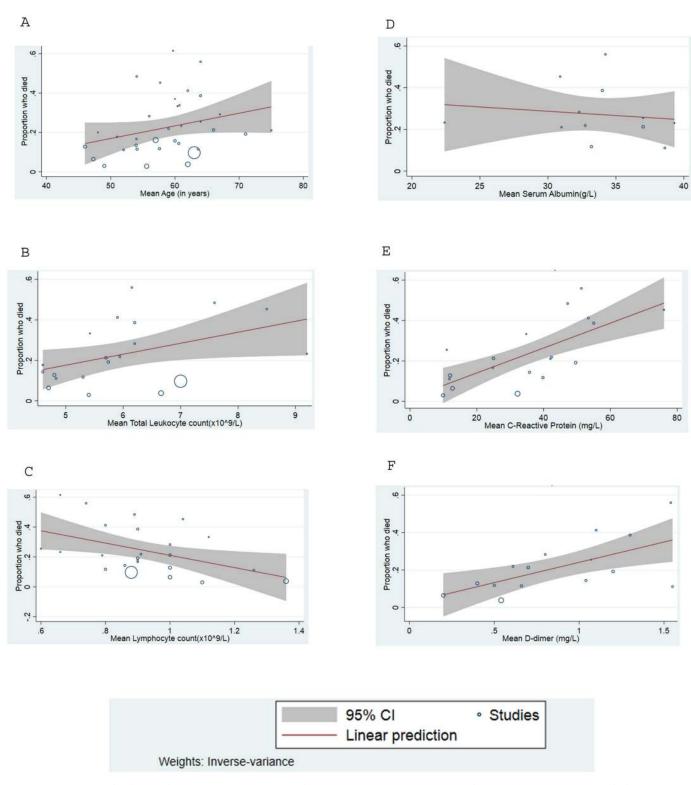


Fig 4. Meta-regression plot showing the proportion increase in mortality among COVID-19 patients regressed against (A) mean age. (B) mean leukocyte count. (C) mean lymphocyte count. (D) mean serum albumin. (E) mean C-reactive protein. (F) mean D-dimer.

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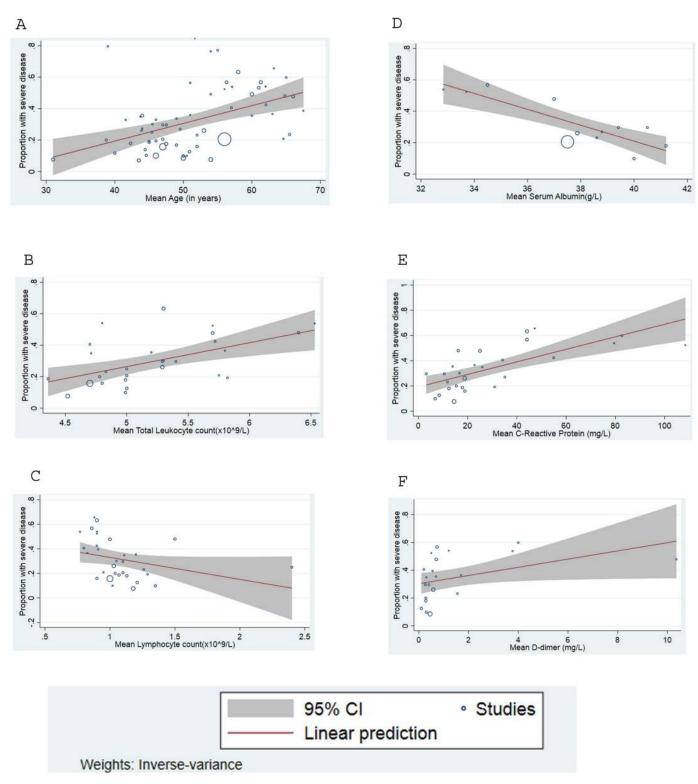


Fig 5. Meta-regression plot shows the proportion increase in severity among COVID-19 patients regressed against (A) mean age. (B) mean leukocyte count. (C) mean lymphocyte count. (D) mean serum albumin. (E) mean C-reactive protein. (F) mean D-dimer.

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diseases with mortality seen in patients with other viral infections [128, 129]. Chronic kidney disease and chronic liver disease were also associated with higher mortality, but because of the lack of data in the available studies, distinction could not be made with respect to the stage of the kidney and liver dysfunction. Pre-existing diseases of the lung were also associated with adverse outcomes in our study.

The identification of COVID-19-related symptoms associated with mortality and severe disease is especially important since this is among the most readily accessible information during the initial evaluation of patients. Our finding that dyspnea was associated with higher RR of mortality and higher OR for severe disease is consistent with data reported in other retrospective studies on ICU admission and the development of ARDS in patients with COVID-19 [23, 130]. Despite the common occurrence of gastrointestinal symptoms (nausea, vomiting and diarrhea) in patients with COVID-19, no association was found between the presence of these symptoms and the presence of severe disease or mortality in our study.

We found that ARDS had a RR of 20.19 [95%CI: 10.87–37.52] for mortality, which is consistent with a previous study reporting a 28-day survival of 50% among COVID-19 patients with severe ARDS [20]. In contrast to the relatively transient cardiac involvement in SARS-CoV infection [131], we found that cardiac complications such as acute heart failure and acute cardiac injury were associated with a high RR of death in COVID-19 in our study. While the presence of underlying cardiovascular disease increases the risk of developing cardiac complications, Chen *et al* reported that COVID-19 related cardiac complications were also frequent among those without pre-existing cardiovascular diseases [20]. A previous report from 2009 suggested direct cardiac muscle damage in patients with SARS-CoV infection [132]. The cardiac injury seen in patients with COVID-19, might be due to a similar mechanism. Elevated troponin levels were associated with an OR of 3.04 [95% CI: 1.03–8.97] for severe disease in our study. Consistent with our findings, patients with underlying cardiovascular diseases and non-elevated levels of troponin were shown to have lower death rates compared to those without cardiovascular disease but with elevated troponin [133].

Patients with leukocytosis and lymphopenia had higher OR for severe disease and greater RR for mortality. The occurrence of lymphopenia in severe disease may be due to apoptosis of lymphocytes as a result of increased levels of cytokines in the blood in patients with severe disease [134–136]. Hypoalbuminemia was associated with an increased RR of mortality (RR 3.30, 95%CI 2.61-4.18), and is likely related to the systemic inflammatory response in severe COVID-19 [74]. Increased levels of acute phase reactants, such as CRP and ferritin in patients with severe disease, also documented in our review, further supports the inflammatory nature of the disease [85]. Elevated levels of procalcitonin may indicate a secondary bacterial sepsis in patients with severe COVID-19, which was associated with a high RR of mortality in our meta-analysis [137]. COVID-19 has been hypothesized to be a prothrombotic state due to endothelial dysfunction and increased hypoxia-inducible transcription factor in patients with severe pneumonia, and plasminogen activation inhibition in patients who develop sepsis [138–140]. DIC, which is common in patients succumbing to COVID-19, is typically accompanied by elevated D-dimer levels [21]. The levels of D-dimer were found in our meta-analysis to be significantly associated with mortality (RR 3.98, 95%CI 2.87-5.52) and severe disease (OR 2.75, 95%CI 1.92–3.93). Although their association with mortality has not been fully investigated, thromboembolic complications, such as pulmonary embolism and acute stroke, have been noted with increasing frequency in patients with COVID-19 [141, 142].

COVID-19 can manifest in a variety of radiographic patterns on chest CT scan, most of which are consistent with viral pneumonia. We found that bilateral lung involvement and consolidation were associated with higher RR of mortality and higher OR of severe disease. Consistent with our findings, the occurrence of bilateral lung involvement was shown to increase with disease progression, and is more commonly observed in the late phases of COVID-19 [143]. The ground-glass opacities seen in a large proportion of COVID-19 patients may be due to the thickening of the alveolar septa following inflammation or the incomplete filling of the alveoli, as seen in Influenza A [144]. As noted for other respiratory viruses, our data revealed that consolidation was associated with a higher RR of mortality and OR of severe disease compared to ground glass opacities in patients with COVID-19 [145, 146]. Hilar lymphadenopathy, though rare in COVID-19 patients, could be due to infiltration of the hilar lymph nodes by lymphocytes and macrophages, and appears to be associated with severe disease in our meta-analysis [147–149].

Although this systematic review is able to delineate important parameters associated with disease severity and mortality in COVID-19, our study has a few limitations. First, we included current published articles related to the highly dynamic information available on COVID-19. As this pandemic has not impacted all regions within the same time frame, there is a potential timing bias, whereby the majority of patients described are from early-hit regions, which may not be representative of other patient populations, based on sociodemographic characteristics and preexisting conditions. Although a pooled analysis of effect sizes adjusted for potential confounders would have been desirable, most studies did not uniformly report estimates adjusted for the same parameters. Time points of evaluation of laboratory, radiological and disease severity assessment were not clearly defined in many of the studies, which precluded the calculation of risk ratio of severe disease. We did not take into account the critical care interventions and strategies that potentially impact the course of the disease and/or survival, as such interventions (e.g. mechanical ventilation, extracorporeal membrane oxygenation, convalescent plasma) vary across different regions. Further investigation is warranted to evaluate which interventions impact the morbidity and mortality of patients with COVID-19. Future studies may investigate if individual and contextual-level sociodemographic factors are associated with morbidity and survival.

In summary, this study comprehensively examined the effect of several demographic, clinical, laboratory and radiological risk factors associated with mortality and severe disease among patients with COVID-19. Knowledge of these risk factors may help health care professionals to develop improved clinical management plans based on risk stratification. Policy makers can utilize these findings to develop triage protocols and effectively allocate resources in resourcelimited settings.

Supporting information

S1 Appendix. (PDF)

S1 PRISMA Checklist. (DOC)

S1 File. (DOCX)

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Author Contributions

Conceptualization: Vignesh Chidambaram, Nyan Lynn Tun, Waqas Z. Haque, Petros C. Karakousis, Panagis Galiatsatos.

- Data curation: Vignesh Chidambaram, Nyan Lynn Tun, Waqas Z. Haque, Ranjith Kumar Sivakumar, Amudha Kumar, Angela Ting-Wei Hsu, Izza A. Ishak, Aqsha A. Nur, Samuel K. Ayeh, Emmanuella L. Salia, Ahsan Zil-E-Ali, Muhammad A. Saeed, Ayu P. B. Sarena, Bhavna Seth, Muzzammil Ahmadzada, Eman F. Haque, Pranita Neupane, Kuang-Heng Wang, Tzu-Miao Pu, Syed M. H. Ali, Muhammad A. Arshad, Lin Wang, Sheriza Baksh.
- Formal analysis: Vignesh Chidambaram, Marie Gilbert Majella, Sheriza Baksh.
- Investigation: Vignesh Chidambaram, Angela Ting-Wei Hsu.
- Methodology: Vignesh Chidambaram, Marie Gilbert Majella, Lin Wang, Sheriza Baksh, Panagis Galiatsatos.
- Supervision: Sheriza Baksh, Petros C. Karakousis, Panagis Galiatsatos.
- Visualization: Ranjith Kumar Sivakumar, Amudha Kumar.
- Writing original draft: Vignesh Chidambaram, Nyan Lynn Tun, Marie Gilbert Majella, Ranjith Kumar Sivakumar, Amudha Kumar, Izza A. Ishak, Emmanuella L. Salia, Bhavna Seth, Petros C. Karakousis, Panagis Galiatsatos.
- Writing review & editing: Vignesh Chidambaram, Marie Gilbert Majella, Amudha Kumar, Izza A. Ishak, Sheriza Baksh, Petros C. Karakousis, Panagis Galiatsatos.

References

- 1. WHO Director-General's opening remarks at the media briefing on COVID-19–11 March 2020 [Internet]. [cited 2020 May 23]. <u>https://www.who.int/dg/speeches/detail/who-director-general-s-opening-</u> remarks-at-the-media-briefing-on-covid-19—11-march-2020
- WHO Timeline—COVID-19 [Internet]. [cited 2020 May 23]. <u>https://www.who.int/news-room/detail/27-04-2020-who-timeline—covid-19</u>
- Grasselli G, Pesenti A, Cecconi M. Critical Care Utilization for the COVID-19 Outbreak in Lombardy, Italy: Early Experience and Forecast During an Emergency Response. JAMA. 2020 Apr 28; 323 (16):1545–6. <u>https://doi.org/10.1001/jama.2020.4031</u> PMID: <u>32167538</u>
- Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, et al. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. JAMA. 2020 Apr 28; 323(16):1574–81. <u>https://doi.org/10.1001/jama.2020.5394</u> PMID: <u>32250385</u>
- Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet [Internet]. 2020; Available from: <u>https://www.ncbi.nlm.nih.gov/pubmed/31986264</u>
- Rhodes A, Ferdinande P, Flaatten H, Guidet B, Metnitz PG, Moreno RP. The variability of critical care bed numbers in Europe. Intensive Care Med. 2012 Oct; 38(10):1647–53. <u>https://doi.org/10.1007/s00134-012-2627-8</u> PMID: <u>22777516</u>
- Maves RC, Downar J, Dichter JR, Hick JL, Devereaux A, Geiling JA, et al. Triage of Scarce Critical Care Resources in COVID-19 An Implementation Guide for Regional Allocation: An Expert Panel Report of the Task Force for Mass Critical Care and the American College of Chest Physicians. Chest. 2020 Apr 11;
- Pettilä V, Pettilä M, Sarna S, Voutilainen P, Takkunen O. Comparison of multiple organ dysfunction scores in the prediction of hospital mortality in the critically ill. Crit Care Med. 2002 Aug; 30(8):1705– 11. <u>https://doi.org/10.1097/00003246-200208000-00005</u> PMID: <u>12163780</u>
- Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic Reviews. 2015 Jan 1; 4(1):1. <u>https://doi.org/10.1186/2046-4053-4-1</u> PMID: <u>25554246</u>
- Glasziou PP, Sanders S, Hoffmann T. Waste in covid-19 research. BMJ [Internet]. 2020 May 12 [cited 2020 Jul 16]; 369. Available from: <u>https://www.bmj.com/content/369/bmj.m1847</u> PMID: <u>32398241</u>
- Dekkers OM, Egger M, Altman DG, Vandenbroucke JP. Distinguishing Case Series From Cohort Studies. Annals of Internal Medicine. 2012 Jan 3; 156(1_Part_1):37. <u>https://doi.org/10.7326/0003-4819-156-1-201201030-00006</u> PMID: <u>22213493</u>

- Metlay JP, Waterer GW, Long AC, Anzueto A, Brozek J, Crothers K, et al. Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med. 2019 Oct 1; 200(7):e45–67. https://doi.org/10.1164/rccm.201908-1581ST PMID: 31573350
- Lin L, Li TS. Interpretation of "Guidelines for the Diagnosis and Treatment of Novel Coronavirus (2019nCoV) Infection by the National Health Commission (Trial Version 5)". Zhonghua Yi Xue Za Zhi. 2020; 100(0):E001–E001. PMID: <u>32033513</u>
- 14. Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org.
- 15. Qualtrics (2020) Qualtrics.com. Available at: http://www.qualtrics.com/ (accessed 24 march 2020).
- Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Medical Research Methodology. 2005 Apr 20; 5(1):13.
- 17. Ottawa Hospital Research Institute [Internet]. [cited 2020 May 26]. <u>http://www.ohri.ca/programs/</u> clinical_epidemiology/oxford.asp
- 18. StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC.
- Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. The Lancet Respiratory Medicine [Internet]. 2020; Available from: <u>http://www.sciencedirect.com/science/ article/pii/S2213260020300795</u> PMID: 32105632
- Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ. 2020 Mar 26; m1091. <u>https://doi.org/10.1136/bmj.m1091</u> PMID: <u>32217556</u>
- Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. Journal of Thrombosis and Haemostasis. 2020 Apr; 18 (4):844–7. <u>https://doi.org/10.1111/jth.14768</u> PMID: <u>32073213</u>
- 22. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med. 2020.
- Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Internal Medicine [Internet]. 2020 Mar 13 [cited 2020 May 25]; Available from: https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2763184 PMID: 32167524
- Li Y, Peng S, Li L, Wang Q, Ping W, Zhang N, et al. Clinical and Transmission Characteristics of Covid-19—A Retrospective Study of 25 Cases from a Single Thoracic Surgery Department. Current Medical Science. 2020 Apr; 40(2):295–300. <u>https://doi.org/10.1007/s11596-020-2176-2</u> PMID: 32232652
- 25. Deng Y, Liu W, Liu K, Fang Y-Y, Shang J, zhou L, et al. Clinical characteristics of fatal and recovered cases of coronavirus disease 2019 (COVID-19) in Wuhan, China: a retrospective study. Chinese Medical Journal. 2020 Mar; 1. https://doi.org/10.1097/CM9.00000000000824 PMID: 32209890
- Yuan M, Yin W, Tao Z, Tan W, Hu Y. Association of radiologic findings with mortality of patients infected with 2019 novel coronavirus in Wuhan, China. PLOS ONE. 2019; 10.
- Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The Lancet. 2020 Mar; 395 (10229):1054–62. <u>https://doi.org/10.1016/S0140-6736(20)30566-3</u> PMID: <u>32171076</u>
- Cao J, Tu W-J, Cheng W, Yu L, Liu Y-K, Hu X, et al. Clinical Features and Short-term Outcomes of 102 Patients with Corona Virus Disease 2019 in Wuhan, China. Clinical Infectious Diseases [Internet]. 2020 Apr 2 [cited 2020 May 25]; Available from: <u>https://academic.oup.com/cid/advance-article/doi/10. 1093/cid/ciaa243/5814897</u>
- 29. Du R-H, Liang L-R, Yang C-Q, Wang W, Cao T-Z, Li M, et al. Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: a prospective cohort study. European Respiratory Journal. 2020 May; 55(5):2000524. <u>https://doi.org/10.1183/13993003.00524-2020</u> PMID: <u>32269088</u>
- Tu W-J, Cao J, Yu L, Hu X, Liu Q. Clinicolaboratory study of 25 fatal cases of COVID-19 in Wuhan. Intensive Care Medicine [Internet]. 2020 Apr 6 [cited 2020 May 25]; Available from: <u>http://link.springer.</u> <u>com/10.1007/s00134-020-06023-4</u> PMID: <u>32253448</u>
- Wang L, He W, Yu X, Hu D, Bao M, Liu H, et al. Coronavirus disease 2019 in elderly patients: Characteristics and prognostic factors based on 4-week follow-up. Journal of Infection. 2020 Jun; 80(6):639–45. https://doi.org/10.1016/j.jinf.2020.03.019 PMID: 32240670
- Wang Y, Lu X, Chen H, Chen T, Su N, Huang F, et al. Clinical Course and Outcomes of 344 Intensive Care Patients with COVID-19. American Journal of Respiratory and Critical Care Medicine [Internet].

2020 Apr 8 [cited 2020 May 25]; Available from: <u>https://www.atsjournals.org/doi/10.1164/rccm.</u> 202003-0736LE PMID: <u>32267160</u>

- Dai M, Liu D, Liu M, Zhou F, Li G, Chen Z, et al. Patients with cancer appear more vulnerable to SARS-COV-2: a multi-center study during the COVID-19 outbreak. Cancer Discovery. 2020 Apr 28; CD-20-0422.
- Ding M, Zhang Q, Li Q, Wu T, Huang Y. Correlation analysis of the severity and clinical prognosis of 32 cases of patients with COVID-19. Respiratory Medicine. 2020 Jun; 167:105981. <u>https://doi.org/10.1016/j.rmed.2020.105981</u> PMID: <u>32421546</u>
- 35. Barrasa H, Rello J, Tejada S, Martín A, Balziskueta G, Vinuesa C, et al. SARS-CoV-2 in Spanish Intensive Care Units: Early experience with 15-day survival in Vitoria. Anaesthesia Critical Care & Pain Medicine [Internet]. 2020 Apr [cited 2020 May 25]; Available from: <u>https://linkinghub.elsevier.com/retrieve/pii/S2352556820300643</u> PMID: <u>32278670</u>
- 36. Chen T, Dai Z, Mo P, Li X, Ma Z, Song S, et al. Clinical Characteristics and Outcomes of Older Patients with Coronavirus Disease 2019 (COVID-19) in Wuhan, China: A Single-Centered, Retrospective Study. Newman A, editor. The Journals of Gerontology: Series A [Internet]. 2020 Apr 11 [cited 2020 May 25]; Available from: <u>https://academic.oup.com/biomedgerontology/advance-article/doi/10.1093/gerona/glaa089/5819242</u> PMID: 32279081
- Trujillo H, Caravaca-Fontán F, Sevillano Á, Gutiérrez E, Caro J, Gutiérrez E, et al. SARS-CoV-2 Infection in Hospitalized Patients With Kidney Disease. Kidney International Reports [Internet]. 2020 May [cited 2020 May 25]; Available from: <u>https://linkinghub.elsevier.com/retrieve/pii/S2468024920312274</u> PMID: <u>32363253</u>
- Webb GJ, Moon AM, Barnes E, Barritt AS, Marjot T. Determining risk factors for mortality in liver transplant patients with COVID-19. The Lancet Gastroenterology & Hepatology [Internet]. 2020 Apr [cited 2020 May 25]; Available from: <u>https://linkinghub.elsevier.com/retrieve/pii/S2468125320301254</u> PMID: 32339474
- 39. Yao Q, Wang P, Wang X, Qie G, Meng M, Tong X, et al. Retrospective study of risk factors for severe SARS-Cov-2 infections in hospitalized adult patients. Polish Archives of Internal Medicine [Internet]. 2020 Apr 24 [cited 2020 May 25]; Available from: https://www.mp.pl/paim/issue/article/15312
- 40. Wei F, Wang H, Huang H, Luo C, Zhou X, Xu N, et al. Acute myocardial injury is common in patients with covid-19 and impairs their prognosis.: 6.
- Tomlins J, Hamilton F, Gunning S, Sheehy C, Moran E, MacGowan A. Clinical features of 95 sequential hospitalised patients with novel coronavirus 2019 disease (COVID-19), the first UK cohort. Journal of Infection [Internet]. 2020 Apr [cited 2020 May 25]; Available from: <u>https://linkinghub.elsevier.com/</u> retrieve/pii/S0163445320302322
- 42. Yang X, Yang Q, Wang Y, Wu Y, Xu J, Yu Y, et al. Thrombocytopenia and its association with mortality in patients with COVID-19. Journal of Thrombosis and Haemostasis [Internet]. 2020 May 4 [cited 2020 May 25]; Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/jth.14848 PMID: 32302435
- Yang R, Gui X, Zhang Y, Xiong Y. The role of essential organ-based comorbidities in the prognosis of COVID-19 infection patients. Expert Review of Respiratory Medicine. 2020 Apr 28;1–4. <u>https://doi.org/ 10.1080/17476348.2020.1761791</u> PMID: 32345072
- 44. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. JAMA [Internet]. 2020 Apr 22 [cited 2020 May 25]; Available from: <u>https://jamanetwork.com/journals/jama/fullarticle/2765184</u>
- 45. Gold JAW, Wong KK, Szablewski CM, Patel PR, Rossow J, da Silva J, et al. Characteristics and Clinical Outcomes of Adult Patients Hospitalized with COVID-19—Georgia, March 2020. MMWR Morbidity and Mortality Weekly Report. 2020 May 8; 69(18):545–50. <u>https://doi.org/10.15585/mmwr.mm6918e1</u> PMID: 32379729
- 46. Gao L, Jiang D, Wen X, Cheng X, Sun M, He B, et al. Prognostic value of NT-proBNP in patients with severe COVID-19. Respiratory Research [Internet]. 2020 Dec [cited 2020 May 25]; 21(1). Available from: https://respiratory-research.biomedcentral.com/articles/10.1186/s12931-020-01352-w PMID: 32293449
- Singh S, Khan A. Clinical Characteristics and Outcomes of COVID-19 Among Patients with Pre-Existing Liver Disease in United States: A Multi-Center Research Network Study. Gastroenterology [Internet]. 2020 May [cited 2020 May 25]; Available from: <u>https://linkinghub.elsevier.com/retrieve/pii/</u> S0016508520305850
- **48.** Zangrillo A, Beretta L, Scandroglio AM, Monti G, Fominskiy E, Colombo S, et al. Characteristics, treatment, outcomes and cause of death of invasively ventilated patients with COVID-19 ARDS in Milan, Italy. Critical Care and Resuscitation.: 12.

- 49. Yan Y, Yang Y, Wang F, Ren H, Zhang S, Shi X, et al. Clinical characteristics and outcomes of patients with severe covid-19 with diabetes. BMJ Open Diabetes Research & Care. 2020 Apr; 8(1):e001343.
- Wang K, Zuo P, Liu Y, Zhang M, Zhao X, Xie S, et al. Clinical and laboratory predictors of in-hospital mortality in patients with COVID-19: a cohort study in Wuhan, China. Clin Infect Dis. 2020 May 3;
- 51. Wang K, Zhang Z, Yu M, Tao Y, Xie M. 15-day mortality and associated risk factors for hospitalized patients with COVID-19 in Wuhan, China: an ambispective observational cohort study. Intensive Care Medicine [Internet]. 2020 Apr 23 [cited 2020 May 25]; Available from: <u>http://link.springer.com/10.1007/s00134-020-06047-w</u> PMID: <u>32328724</u>
- 52. Zhang L, Yan X, Fan Q, Liu H, Liu X, Liu Z, et al. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. Journal of Thrombosis and Haemostasis. 2020; 18(6):1324–9. <u>https:// doi.org/10.1111/jth.14859</u> PMID: <u>32306492</u>
- 53. Wang D, Yin Y, Hu C, Liu X, Zhang X, Zhou S, et al. Clinical course and outcome of 107 patients infected with the novel coronavirus, SARS-CoV-2, discharged from two hospitals in Wuhan, China. Critical Care [Internet]. 2020 Dec [cited 2020 May 25]; 24(1). Available from: <u>https://ccforum.biomedcentral.com/articles/10.1186/s13054-020-02895-6</u> PMID: 32354360
- Liu Y, Sun W, Guo Y, Chen L, Zhang L, Zhao S, et al. Association between platelet parameters and mortality in coronavirus disease 2019: Retrospective cohort study. Platelets. 2020 May 18; 31(4):490– 6. https://doi.org/10.1080/09537104.2020.1754383 PMID: <u>32297540</u>
- 55. Liu Y, Du X, Chen J, Jin Y, Peng L, Wang HHX, et al. Neutrophil-to-lymphocyte ratio as an independent risk factor for mortality in hospitalized patients with COVID-19. Journal of Infection [Internet]. 2020 Apr [cited 2020 May 25]; Available from: <u>https://linkinghub.elsevier.com/retrieve/pii/S0163445320302085</u> PMID: 32283162
- 56. Li J, Wang X, Chen J, Zhang H, Deng A. Association of Renin-Angiotensin System Inhibitors With Severity or Risk of Death in Patients With Hypertension Hospitalized for Coronavirus Disease 2019 (COVID-19) Infection in Wuhan, China. JAMA Cardiology [Internet]. 2020 Apr 23 [cited 2020 May 25]; Available from: <u>https://jamanetwork.com/journals/jamacardiology/fullarticle/2765049</u> PMID: 32324209
- Nikpouraghdam M, Jalali Farahani A, Alishiri G, Heydari S, Ebrahimnia M, Samadinia H, et al. Epidemiological characteristics of coronavirus disease 2019 (COVID-19) patients in IRAN: A single center study. Journal of Clinical Virology. 2020 Jun; 127:104378. <u>https://doi.org/10.1016/j.jcv.2020.104378</u> PMID: <u>32353762</u>
- Zhang J, Wang X, Jia X, Li J, Hu K, Chen G, et al. Risk factors for disease severity, unimprovement, and mortality in COVID-19 patients in Wuhan, China. Clinical Microbiology and Infection. 2020 Jun; 26 (6):767–72. <u>https://doi.org/10.1016/j.cmi.2020.04.012</u> PMID: <u>32304745</u>
- Mehta V, Goel S, Kabarriti R, Cole D, Goldfinger M, Acuna-Villaorduna A, et al. Case Fatality Rate of Cancer Patients with COVID-19 in a New York Hospital System. Cancer Discovery. 2020 May 1;CD-20-0516.
- Zou X, Li S, Fang M, Hu M, Bian Y, Ling J, et al. Acute Physiology and Chronic Health Evaluation II Score as a Predictor of Hospital Mortality in Patients of Coronavirus Disease 2019: Critical Care Medicine. 2020 May; 1.
- Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. New England Journal of Medicine [Internet]. 2020; Available from: <u>https://doi.org/10.1056/ NEJMoa2002032</u>
- Xu Y-H, Dong J-H, An W, Lv X-Y, Yin X-P, Zhang J-Z, et al. Clinical and computed tomographic imaging features of Novel Coronavirus Pneumonia caused by SARS-CoV-2. Journal of Infection [Internet]. 2020; Available from: <u>http://www.sciencedirect.com/science/article/pii/S0163445320301006</u>
- Tian S, Hu N, Lou J, Chen K, Kang X, Xiang Z, et al. Characteristics of COVID-19 infection in Beijing. Journal of Infection. 2020 Apr; 80(4):401–6. <u>https://doi.org/10.1016/j.jinf.2020.02.018</u> PMID: <u>32112886</u>
- 64. Li K, Wu J, Wu F, Guo D, Chen L, Fang Z, et al. The Clinical and Chest CT Features Associated With Severe and Critical COVID-19 Pneumonia. Investigative Radiology. 2020 Jun; 55(6):327–31. <u>https:// doi.org/10.1097/RLI.00000000000672</u> PMID: <u>32118615</u>
- Zhao W, Zhong Z, Xie X, Yu Q, Liu J. Relation Between Chest CT Findings and Clinical Conditions of Coronavirus Disease (COVID-19) Pneumonia: A Multicenter Study. AJR Am J Roentgenol. 2020;1–6. <u>https://doi.org/10.2214/AJR.20.22976</u> PMID: <u>32125873</u>
- 66. Han H, Yang L, Liu R, Liu F, Wu K, Li J, et al. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. Clinical Chemistry and Laboratory Medicine (CCLM) [Internet]. 2020 Mar 16 [cited 2020 May 25]; 0(0). Available from: <u>https://www.degruyter.com/view/journals/cclm/ahead-ofprint/article-10.1515-cclm-2020-0188/article-10.1515-cclm-2020-0188.xml</u> PMID: <u>32172226</u>

- Qian G-Q, Yang N-B, Ding F, Ma AHY, Wang Z-Y, Shen Y-F, et al. Epidemiologic and Clinical Characteristics of 91 Hospitalized Patients with COVID-19 in Zhejiang, China: A retrospective, multi-centre case series. QJM. 2020 Mar 17; https://doi.org/10.1093/gjmed/hcaa089 PMID: 32181807
- Qu R, Ling Y, Zhang Y, Wei L, Chen X, Li X, et al. Platelet-to-lymphocyte ratio is associated with prognosis in patients with Corona Virus Disease-19. Journal of Medical Virology [Internet]. 2020 Mar 17 [cited 2020 May 25]; Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/jmv.25767
- Gao Y, Li T, Han M, Li X, Wu D, Xu Y, et al. Diagnostic Utility of Clinical Laboratory Data Determinations for Patients with the Severe COVID-19. Journal of Medical Virology [Internet]. 2020 Mar 17 [cited 2020 May 25]; Available from: <u>https://onlinelibrary.wiley.com/doi/abs/10.1002/jmv.25770</u> PMID: <u>32181911</u>
- Liu K-C, Xu P, Lv W-F, Qiu X-H, Yao J-L, Gu J-F, et al. CT manifestations of coronavirus disease-2019: A retrospective analysis of 73 cases by disease severity. European Journal of Radiology. 2020 May; 126:108941. https://doi.org/10.1016/j.ejrad.2020.108941 PMID: 32193037
- Wan S, Xiang Y, Fang W, Zheng Y, Li B, Hu Y, et al. Clinical features and treatment of COVID-19 patients in northeast Chongqing. Journal of Medical Virology [Internet]. 2020 Apr 1 [cited 2020 May 25]; Available from: <u>http://doi.wiley.com/10.1002/jmv.25783</u> PMID: <u>32198776</u>
- Shi Y, Yu X, Zhao H, Wang H, Zhao R, Sheng J. Host susceptibility to severe COVID-19 and establishment of a host risk score: findings of 487 cases outside Wuhan. Critical Care [Internet]. 2020 Dec [cited 2020 May 25]; 24(1). Available from: <u>https://ccforum.biomedcentral.com/articles/10.1186/s13054-020-2833-7</u>
- 73. Li K, Fang Y, Li W, Pan C, Qin P, Zhong Y, et al. CT image visual quantitative evaluation and clinical classification of coronavirus disease (COVID-19). European Radiology [Internet]. 2020 Mar 25 [cited 2020 May 25]; Available from: http://ink.springer.com/10.1007/s00330-020-06817-6
- 74. Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, et al. Dysregulation of Immune Response in Patients With Coronavirus 2019 (COVID-19) in Wuhan, China. Clin Infect Dis [Internet]. [cited 2020 Jun 6]; Available from: <u>https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa248/ 5803306</u>
- Huang L, Han R, Ai T, Yu P, Kang H, Tao Q, et al. Serial Quantitative Chest CT Assessment of COVID-19: Deep-Learning Approach. Radiology: Cardiothoracic Imaging. 2020 Apr 1; 2(2):e200075.
- 76. Zhang J-J, Dong X, Cao Y-Y, Yuan Y-D, Yang Y-B, Yan Y-Q, et al. Clinical characteristics of 140 patients infected by SARS-CoV-2 in Wuhan, China. Allergy. 2020; <u>https://doi.org/10.1111/all.14238</u> PMID: <u>32077115</u>
- Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. Journal of Clinical Investigation. 2020 Apr 13; 130(5):2620– 9. https://doi.org/10.1172/JCI137244 PMID: 32217835
- 78. Chu J, Yang N, Wei Y, Yue H, Zhang F, Zhao J, et al. Clinical characteristics of 54 medical staff with COVID-19: A retrospective study in a single center in Wuhan, China. Journal of Medical Virology [Internet]. 2020 Apr 6 [cited 2020 May 25]; Available from: <u>https://onlinelibrary.wiley.com/doi/abs/10.1002/</u> jmv.25793
- Yuan J, Zou R, Zeng L, Kou S, Lan J, Li X, et al. The correlation between viral clearance and biochemical outcomes of 94 COVID-19 infected discharged patients. Inflammation Research. 2020 Jun; 69 (6):599–606. <u>https://doi.org/10.1007/s00011-020-01342-0</u> PMID: <u>32227274</u>
- Wang L, Li X, Chen H, Yan S, Li D, Li Y, et al. Coronavirus Disease 19 Infection Does Not Result in Acute Kidney Injury: An Analysis of 116 Hospitalized Patients from Wuhan, China. American Journal of Nephrology. 2020; 51(5):343–8. https://doi.org/10.1159/000507471 PMID: 32229732
- Han H, Xie L, Liu R, Yang J, Liu F, Wu K, et al. Analysis of heart injury laboratory parameters in 273 COVID-19 patients in one hospital in Wuhan, China. Journal of Medical Virology [Internet]. 2020 Apr 15 [cited 2020 May 25]; Available from: http://doi.wiley.com/10.1002/jmv.25809
- Xie H, Zhao J, Lian N, Lin S, Xie Q, Zhuo H. Clinical characteristics of non-ICU hospitalized patients with coronavirus disease 2019 and liver injury: A retrospective study. Liver International [Internet].
 2020 Apr 12 [cited 2020 May 25]; Available from: <u>http://doi.wiley.com/10.1111/liv.14449</u> PMID: 32239591
- Cai Q, Huang D, Ou P, Yu H, Zhu Z, Xia Z, et al. COVID-19 in a designated infectious diseases hospital outside Hubei Province, China. Allergy [Internet]. 2020 Apr 17 [cited 2020 May 25]; Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/all.14309
- Zhang Y, Zheng L, Liu L, Zhao M, Xiao J, Zhao Q. Liver impairment in COVID-19 patients: A retrospective analysis of 115 cases from a single centre in Wuhan city, China. Liver International [Internet]. 2020 Apr 28 [cited 2020 May 25]; Available from: <u>https://onlinelibrary.wiley.com/doi/abs/10.1111/liv.14455</u> PMID: <u>32239796</u>

- 85. Tan C, Huang Y, Shi F, Tan K, Ma Q, Chen Y, et al. C-reactive protein correlates with computed tomographic findings and predicts severe COVID-19 early. J Med Virol [Internet]. 2020 Apr 25 [cited 2020 Jun 5]; Available from: <u>https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7262341/</u> PMID: <u>32281668</u>
- 86. Chen X, Yang Y, Huang M, Liu L, Zhang X, Xu J, et al. Differences between COVID-19 and suspected then confirmed SARS-CoV-2-negative pneumonia: a retrospective study from a single center. Journal of Medical Virology [Internet]. 2020 Apr 1 [cited 2020 May 25]; Available from: <u>http://doi.wiley.com/10.</u> <u>1002/jmv.25810</u> PMID: <u>32237148</u>
- Zheng F, Tang W, Li H. Clinical characteristics of 161 cases of corona virus disease 2019 (COVID-19) in Changsha.: 7.
- Deng Q, Hu B, Zhang Y, Wang H, Zhou X, Hu W, et al. Suspected myocardial injury in patients with COVID-19: Evidence from front-line clinical observation in Wuhan, China. International Journal of Cardiology [Internet]. 2020 Apr [cited 2020 May 25]; Available from: <u>https://linkinghub.elsevier.com/</u> retrieve/pii/S0167527320311153 PMID: 32291207
- Li H, Xiang X, Ren H, Xu L, Zhao L, Chen X, et al. Serum Amyloid A is a biomarker of severe Coronavirus Disease and poor prognosis. Journal of Infection. 2020 Jun; 80(6):646–55. <u>https://doi.org/10.1016/j.jinf.2020.03.035</u> PMID: <u>32277967</u>
- 90. Zou Y, Guo H, Zhang Y, Zhang Z, Liu Y, Wang J, et al. Analysis of coagulation parameters in patients with COVID-19 in Shanghai, China. BioScience Trends [Internet]. 2020 [cited 2020 May 25]; Available from: <u>https://www.jstage.jst.go.jp/article/bst/advpub/0/advpub_2020.03086/_article_PMID: 32350161</u>
- Shi F, Wu T, Zhu X, Ge Y, Zeng X, Chi Y, et al. Association of viral load with serum biomakers among COVID-19 cases. Virology. 2020 Jul; 546:122–6. <u>https://doi.org/10.1016/j.virol.2020.04.011</u> PMID: 32452410
- Wang G, Wu C, Zhang Q, Wu F, Yu B, Lv J, et al. C-Reactive Protein Level May Predict the Risk of COVID-19 Aggravation. Open Forum Infectious Diseases [Internet]. 2020 May 1 [cited 2020 May 25]; 7(5). Available from: <u>https://academic.oup.com/ofid/article/doi/10.1093/ofid/ofaa153/5826961</u> PMID: <u>32455147</u>
- Ji M, Yuan L, Shen W, Lv J, Li Y, Li M, et al. Characteristics of disease progress in patients with coronavirus disease 2019 in Wuhan, China. Epidemiology and Infection [Internet]. 2020 [cited 2020 May 25]; 148. Available from: <u>https://www.cambridge.org/core/product/identifier/S0950268820000977/type/journal_article</u> PMID: <u>32374248</u>
- 94. Shen L, Li S, Zhu Y, Zhao J, Tang X, Li H, et al. Clinical and laboratory-derived parameters of 119 hospitalized patients with coronavirus disease 2019 in Xiangyang, Hubei Province, China. Journal of Infection [Internet]. 2020 Apr [cited 2020 May 25]; Available from: <u>https://linkinghub.elsevier.com/retrieve/pii/S0163445320301663</u> PMID: <u>32283164</u>
- 95. Yang F, Shi S, Zhu J, Shi J, Dai K, Chen X. Clinical characteristics and outcomes of cancer patients with COVID-19. Journal of Medical Virology [Internet]. 2020 May 5 [cited 2020 May 25]; Available from: <u>https://onlinelibrary.wiley.com/doi/abs/10.1002/jmv.25972</u>
- 96. Ma J, Yin J, Qian Y, Wu Y. Clinical characteristics and prognosis in cancer patients with COVID-19: A single center's retrospective study. Journal of Infection [Internet]. 2020 Apr [cited 2020 May 25]; Available from: <u>https://linkinghub.elsevier.com/retrieve/pii/S0163445320302140</u> PMID: <u>32298677</u>
- 97. Chen Q, Zheng Z, Zhang C, Zhang X, Wu H, Wang J, et al. Clinical characteristics of 145 patients with corona virus disease 2019 (COVID-19) in Taizhou, Zhejiang, China. Infection [Internet]. 2020 Apr 28 [cited 2020 May 25]; Available from: <u>http://link.springer.com/10.1007/s15010-020-01432-5</u> PMID: 32342479
- 98. Colaneri M, Sacchi P, Zuccaro V, Biscarini S, Sachs M, Roda S, et al. Clinical characteristics of coronavirus disease (COVID-19) early findings from a teaching hospital in Pavia, North Italy, 21 to 28 February 2020. Eurosurveillance [Internet]. 2020 Apr 23 [cited 2020 May 25]; 25(16). Available from: <u>https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2020.25.16.2000460</u> PMID: <u>32347201</u>
- 99. Zhao X-Y, Xu X-X, Yin H-S, Hu Q-M, Xiong T, Tang Y-Y, et al. Clinical characteristics of patients with 2019 coronavirus disease in a non-Wuhan area of Hubei Province, China: a retrospective study. BMC Infectious Diseases [Internet]. 2020 Dec [cited 2020 May 25]; 20(1). Available from: <u>https://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-020-05010-w</u>
- 100. Chen L, Li Q, Zheng D, Jiang H, Wei Y, Zou L, et al. Clinical Characteristics of Pregnant Women with Covid-19 in Wuhan, China. New England Journal of Medicine [Internet]. 2020 Apr 17 [cited 2020 May 25]; Available from: <u>http://www.nejm.org/doi/10.1056/NEJMc2009226</u>
- 101. Sun L, Shen L, Fan J, Gu F, Hu M, An Y, et al. Clinical Features of Patients with Coronavirus Disease 2019 (COVID-19) from a Designated Hospital in Beijing, China. Journal of Medical Virology [Internet]. 2020 May 5 [cited 2020 May 25]; Available from: <u>https://onlinelibrary.wiley.com/doi/abs/10.1002/jmv. 25966</u> PMID: <u>32369208</u>

- 102. Zhu Z, Cai T, Fan L, Lou K, Hua X, Huang Z, et al. Clinical value of immune-inflammatory parameters to assess the severity of coronavirus disease 2019. International Journal of Infectious Diseases. 2020 Jun; 95:332–9. <u>https://doi.org/10.1016/j.ijid.2020.04.041</u> PMID: <u>32334118</u>
- 103. Liu Y, Liao W, Wan L, Xiang T, Zhang W. Correlation Between Relative Nasopharyngeal Virus RNA Load and Lymphocyte Count Disease Severity in Patients with COVID-19. Viral Immunology [Internet]. 2020 Apr 10 [cited 2020 May 25]; Available from: <u>https://www.liebertpub.com/doi/10.1089/vim.2020.</u> 0062 PMID: 32297828
- 104. Feng Y, Ling Y, Bai T, Xie Y, Huang J, Li J, et al. COVID-19 with Different Severity: A Multi-center Study of Clinical Features. American Journal of Respiratory and Critical Care Medicine [Internet]. 2020 Apr 10 [cited 2020 May 25]; Available from: <u>https://www.atsjournals.org/doi/10.1164/rccm.202002-04450C</u>
- 105. Zhang R, Ouyang H, Fu L, Wang S, Han J, Huang K, et al. CT features of SARS-CoV-2 pneumonia according to clinical presentation: a retrospective analysis of 120 consecutive patients from Wuhan city. European Radiology [Internet]. 2020 Apr 11 [cited 2020 May 25]; Available from: <u>http://link.springer.com/10.1007/s00330-020-06854-1</u> PMID: <u>32279115</u>
- 106. Chen X, Zhao B, Qu Y, Chen Y, Xiong J, Feng Y, et al. Detectable serum SARS-CoV-2 viral load (RNAaemia) is closely correlated with drastically elevated interleukin 6 (IL-6) level in critically ill COVID-19 patients. Clinical Infectious Diseases [Internet]. 2020 Apr 17 [cited 2020 May 25]; Available from: https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa449/5821311
- 107. Wei X, Su J, Yang K, Wei J, Wan H, Cao X, et al. Elevations of serum cancer biomarkers correlate with severity of COVID-19. Journal of Medical Virology [Internet]. 2020 Apr 29 [cited 2020 May 25]; Available from: <u>https://onlinelibrary.wiley.com/doi/abs/10.1002/jmv.25957</u> PMID: 32347972
- 108. Zheng Y, Xiong C, Liu Y, Qian X, Tang Y, Liu L, et al. Epidemiological and clinical characteristics analysis of COVID-19 in the surrounding areas of Wuhan, Hubei Province in 2020. Pharmacol Res. 2020 Jul; 157:104821. https://doi.org/10.1016/j.phrs.2020.104821 PMID: 32360481
- 109. Wang R, Pan M, Zhang X, Han M, Fan X, Zhao F, et al. Epidemiological and clinical features of 125 Hospitalized Patients with COVID-19 in Fuyang, Anhui, China. International Journal of Infectious Diseases. 2020 Jun; 95:421–8. https://doi.org/10.1016/j.ijid.2020.03.070 PMID: 32289565
- 110. Yao Z, Zheng Z, Wu K, Junhua Z. Immune environment modulation in pneumonia patients caused by coronavirus: SARS-CoV, MERS-CoV and SARS-CoV-2. Aging. 2020 May 2; 12(9):7639–51. <u>https:// doi.org/10.18632/aging.103101</u> PMID: 32364527
- 111. Lei F, Liu Y, Zhou F, Qin J, Zhang P, Zhu L, et al. Longitudinal association between markers of liver injury and mortality in COVID-19 in China. Hepatology [Internet]. 2020 May 2 [cited 2020 May 25]; Available from: <u>https://onlinelibrary.wiley.com/doi/abs/10.1002/hep.31301</u> PMID: 32359177
- 112. Lu L, Xiong W, Liu D, Liu J, Yang D, Li N, et al. New onset acute symptomatic seizure and risk factors in coronavirus disease 2019: A retrospective multicenter study. Epilepsia [Internet]. 2020 May 2 [cited 2020 May 25]; Available from: <u>https://onlinelibrary.wiley.com/doi/abs/10.1111/epi.16524</u> PMID: 32304092
- 113. Yang Y, Shen C, Li J, Yuan J, Wei J, Huang F, et al. Plasma IP-10 and MCP-3 levels are highly associated with disease severity and predict the progression of COVID-19. Journal of Allergy and Clinical Immunology [Internet]. 2020 Apr [cited 2020 May 25]; Available from: <u>https://linkinghub.elsevier.com/retrieve/pii/S0091674920305765</u> PMID: <u>32360286</u>
- 114. Bi X, Su Z, Yan H, Du J, Wang J, Chen L, et al. Prediction of severe illness due to COVID-19 based on an analysis of initial Fibrinogen to Albumin Ratio and Platelet count. Platelets. 2020 May 5;1–6.
- 115. Liu F, Li L, Xu M, Wu J, Luo D, Zhu Y, et al. Prognostic value of interleukin-6, C-reactive protein, and procalcitonin in patients with COVID-19. Journal of Clinical Virology. 2020 Jun; 127:104370. <u>https:// doi.org/10.1016/j.jcv.2020.104370</u> PMID: <u>32344321</u>
- 116. Pei G, Zhang Z, Peng J, Liu L, Zhang C, Yu C, et al. Renal Involvement and Early Prognosis in Patients with COVID-19 Pneumonia. Journal of the American Society of Nephrology. 2020 Apr 28; ASN.2020030276. https://doi.org/10.1681/ASN.2020030276 PMID: 32345702
- 117. Hu L, Chen S, Fu Y, Gao Z, Long H, Wang J, et al. Risk Factors Associated with Clinical Outcomes in 323 COVID-19 Hospitalized Patients in Wuhan, China. Clinical Infectious Diseases [Internet]. 2020 May 3 [cited 2020 May 25]; Available from: <u>https://academic.oup.com/cid/advance-article/doi/10.1093/</u> cid/ciaa539/5828282 PMID: 32361738
- 118. Liu X, Zhou H, Zhou Y, Wu X, Zhao Y, Lu Y, et al. Risk factors associated with disease severity and length of hospital stay in COVID-19 patients. Journal of Infection [Internet]. 2020 Apr [cited 2020 May 25]; Available from: <u>https://linkinghub.elsevier.com/retrieve/pii/S0163445320302164</u> PMID: <u>32305490</u>
- 119. Wei Y-Y, Wang R-R, Zhang D-W, Tu Y-H, Chen C-S, Ji S, et al. Risk factors for severe COVID-19: Evidence from 167 hospitalized patients in Anhui, China. Journal of Infection [Internet]. 2020 Apr [cited

2020 May 25]; Available from: https://linkinghub.elsevier.com/retrieve/pii/S016344532030219X PMID: 32305487

- 120. Li X, Xu S, Yu M, Wang K, Tao Y, Zhou Y, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. Journal of Allergy and Clinical Immunology [Internet]. 2020 Apr [cited 2020 May 25]; Available from: https://linkinghub.elsevier.com/retrieve/pii/S0091674920304954 PMID: 32294485
- 121. Zheng Y, Zhang Y, Chi H, Chen S, Peng M, Luo L, et al. The hemocyte counts as a potential biomarker for predicting disease progression in COVID-19: a retrospective study. Clinical Chemistry and Laboratory Medicine (CCLM) [Internet]. 2020 Apr 29 [cited 2020 May 25]; 0(0). Available from: <u>https://www. degruyter.com/view/journals/cclm/ahead-of-print/article-10.1515-cclm-2020-0377/article-10.1515cclm-2020-0377.xml PMID: 32352397</u>
- 122. Wang F, Hou H, Luo Y, Tang G, Wu S, Huang M, et al. The laboratory tests and host immunity of COVID-19 patients with different severity of illness. JCI Insight [Internet]. 2020 May 21 [cited 2020 May 25]; 5(10). Available from: https://insight.jci.org/articles/view/137799 PMID: 32324595
- 123. Lyu P, Liu X, Zhang R, Shi L, Gao J. The performance of chest CT in evaluating the clinical severity of COVID-19 pneumonia: identifying critical cases based on CT characteristics. Investigative Radiology. 2020 Apr; 1. <u>https://doi.org/10.1097/RLI.00000000000689</u> PMID: <u>32304402</u>
- 124. Liu R, Ma Q, Han H, Su H, Liu F, Wu K, et al. The value of urine biochemical parameters in the prediction of the severity of coronavirus disease 2019. Clinical Chemistry and Laboratory Medicine (CCLM) [Internet]. 2020 Apr 14 [cited 2020 May 25]; 0(0). Available from: <u>https://www.degruyter.com/view/journals/cclm/ahead-of-print/article-10.1515-cclm-2020-0220/article-10.1515-cclm-2020-0220.xml</u> PMID: 32286242
- 125. Hou H, Zhang B, Huang H, Luo Y, Wu S, Tang G, et al. Using IL-2R/lymphocytes for predicting the clinical progression of patients with COVID-19. Clinical & Experimental Immunology [Internet]. 2020 May 15 [cited 2020 May 25]; Available from: <u>https://onlinelibrary.wiley.com/doi/abs/10.1111/cei.13450</u> PMID: <u>32365221</u>
- 126. Zheng S, Fan J, Yu F, Feng B, Lou B, Zou Q, et al. Viral load dynamics and disease severity in patients infected with SARS-CoV-2 in Zhejiang province, China, January-March 2020: retrospective cohort study. BMJ. 2020 Apr 21; m1443. https://doi.org/10.1136/bmj.m1443 PMID: 32317267
- 127. Huang I, Lim MA, Pranata R. Diabetes mellitus is associated with increased mortality and severity of disease in COVID-19 pneumonia—A systematic review, meta-analysis, and meta-regression. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2020 Jul 1; 14(4):395–403. <u>https://doi.org/</u> 10.1016/j.dsx.2020.04.018 PMID: 32334395
- 128. Pranata R, Huang I, Lim MA, Wahjoepramono EJ, July J. Impact of cerebrovascular and cardiovascular diseases on mortality and severity of COVID-19–systematic review, meta-analysis, and meta-regression. Journal of Stroke and Cerebrovascular Diseases. 2020 Aug 1; 29(8):104949.
- 129. Yeh J-J, Lin C-L, Kao C-H. Relationship between pneumonia and cardiovascular diseases: A retrospective cohort study of the general population. Eur J Intern Med. 2019; 59:39–45. <u>https://doi.org/10. 1016/j.ejim.2018.08.003</u> PMID: <u>30098854</u>
- Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA. 2020; <u>https://doi.org/10.1001/jama.2020.1585</u> PMID: <u>32031570</u>
- 131. Yu C-M. Cardiovascular complications of severe acute respiratory syndrome. Postgraduate Medical Journal. 2006 Feb 1; 82(964):140–4. <u>https://doi.org/10.1136/pgmj.2005.037515</u> PMID: <u>16461478</u>
- **132.** Oudit GY, Kassiri Z, Jiang C, Liu PP, Poutanen SM, Penninger JM, et al. SARS-coronavirus modulation of myocardial ACE2 expression and inflammation in patients with SARS. Eur J Clin Invest. 2009 Jul; 39(7):618–25. <u>https://doi.org/10.1111/j.1365-2362.2009.02153.x</u> PMID: <u>19453650</u>
- 133. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, et al. Cardiovascular Implications of Fatal Outcomes of Patients With Coronavirus Disease 2019 (COVID-19). JAMA Cardiol [Internet]. 2020 Mar 27 [cited 2020 Jun 5]; Available from: <u>https://jamanetwork.com/journals/jamacardiology/fullarticle/2763845</u>
- 134. Singh S, Sharma A, Arora SK. High Producer Haplotype (CAG) of -863C/A, -308G/A and -238G/A Polymorphisms in the Promoter Region of TNF-α Gene Associate with Enhanced Apoptosis of Lymphocytes in HIV-1 Subtype C Infected Individuals from North India. PLoS One [Internet]. 2014 May 16 [cited 2020 Jun 4]; 9(5). Available from: <u>https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4024031/</u>PMID: 24837009
- 135. Liao Y-C, Liang W-G, Chen F-W, Hsu J-H, Yang J-J, Chang M-S. IL-19 induces production of IL-6 and TNF-alpha and results in cell apoptosis through TNF-alpha. J Immunol. 2002 Oct 15; 169(8):4288–97. https://doi.org/10.4049/jimmunol.169.8.4288 PMID: 12370360
- 136. Aggarwal S, Gollapudi S, Gupta S. Increased TNF-alpha-induced apoptosis in lymphocytes from aged humans: changes in TNF-alpha receptor expression and activation of caspases. J Immunol. 1999 Feb 15; 162(4):2154–61. PMID: <u>9973490</u>

- 137. Simon L, Gauvin F, Amre DK, Saint-Louis P, Lacroix J. Serum procalcitonin and C-reactive protein levels as markers of bacterial infection: a systematic review and meta-analysis. Clin Infect Dis. 2004 Jul 15; 39(2):206–17. <u>https://doi.org/10.1086/421997</u> PMID: <u>15307030</u>
- 138. Levi M, van der Poll T. Coagulation and sepsis. Thrombosis Research. 2017 Jan; 149:38–44. <u>https://doi.org/10.1016/j.thromres.2016.11.007</u> PMID: 27886531
- 139. Schmitt FCF, Manolov V, Morgenstern J, Fleming T, Heitmeier S, Uhle F, et al. Acute fibrinolysis shutdown occurs early in septic shock and is associated with increased morbidity and mortality: results of an observational pilot study. Ann Intensive Care [Internet]. 2019 Jan 30 [cited 2020 Jun 6]; 9. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6353981/ PMID: 30701381
- 140. Gupta N, Zhao Y-Y, Evans CE. The stimulation of thrombosis by hypoxia. Thrombosis Research. 2019 Sep 1; 181:77–83. <u>https://doi.org/10.1016/j.thromres.2019.07.013</u> PMID: <u>31376606</u>
- 141. Grillet F, Behr J, Calame P, Aubry S, Delabrousse E. Acute Pulmonary Embolism Associated with COVID-19 Pneumonia Detected by Pulmonary CT Angiography. Radiology. 2020 Apr 23; 201544. https://doi.org/10.1148/radiol.2020201544 PMID: 32324103
- 142. Avula A, Nalleballe K, Narula N, Sapozhnikov S, Dandu V, Toom S, et al. COVID-19 presenting as stroke. Brain Behav Immun [Internet]. 2020 Apr 28 [cited 2020 Jun 17]; Available from: <u>https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7187846/</u> PMID: <u>32360439</u>
- 143. Bernheim A, Mei X, Huang M, Yang Y, Fayad ZA, Zhang N, et al. Chest CT Findings in Coronavirus Disease-19 (COVID-19): Relationship to Duration of Infection. Radiology. 2020;200463–200463. <u>https://doi.org/10.1148/radiol.2020200463</u> PMID: <u>32077789</u>
- 144. Marchiori E, Zanetti G, Fontes CAP, Santos MLO, Valiante PM, Mano CM, et al. Influenza A (H1N1) virus-associated pneumonia: High-resolution computed tomography–pathologic correlation. European Journal of Radiology. 2011 Dec 1; 80(3):e500–4. <u>https://doi.org/10.1016/j.ejrad.2010.10.003</u> PMID: 21035974
- 145. Grinblat L, Shulman H, Glickman A, Matukas L, Paul N. Severe Acute Respiratory Syndrome: Radiographic Review of 40 Probable Cases in Toronto, Canada1. Radiology [Internet]. 2003 Sep 1 [cited 2020 Jun 6]; Available from: https://pubs.rsna.org/doi/abs/10.1148/radiol.2283030671
- 146. Feng F, Jiang Y, Yuan M, Shen J, Yin H, Geng D, et al. Association of Radiologic Findings with Mortality in Patients with Avian Influenza H7N9 Pneumonia. PLOS ONE. 2014 Apr 4; 9(4):e93885. <u>https:// doi.org/10.1371/journal.pone.0093885</u> PMID: <u>24705783</u>
- 147. Song F, Shi N, Shan F, Zhang Z, Shen J, Lu H, et al. Emerging Coronavirus 2019-nCoV Pneumonia. Radiology. 2020;200274–200274. <u>https://doi.org/10.1148/radiol.2020200274</u> PMID: <u>32027573</u>
- 148. Jin Y-H, Cai L, Cheng Z-S, Cheng H, Deng T, Fan Y-P, et al. A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). Military Medical Research. 2020; 7(1):4. <u>https://doi.org/10.1186/s40779-020-0233-6</u> PMID: <u>32029004</u>
- 149. Chen Y, Feng Z, Diao B, Wang R, Wang G, Wang C, et al. The Novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Directly Decimates Human Spleens and Lymph Nodes. medRxiv. 2020 Mar 31;2020.03.27.20045427.