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## Early prediction keys for COVID-19 cases progression: A meta-analysis

Mostafa M. Khodeir<sup>a,b,\*</sup>, Hassan A. Shabana<sup>c</sup>, Abdullah S. Alkhamiss<sup>b</sup>, Zafar Rasheed<sup>d,\*</sup>,  
Mansour Alsoghair<sup>e</sup>, Suliman A. Alsagaby<sup>f</sup>, Muhammad I. Khan<sup>g</sup>, Nelson Fernández<sup>h</sup>,  
Waleed Al Abdulmonem<sup>b</sup>



<sup>a</sup> Department of Pathology, Faculty of Medicine, Cairo University, Cairo, Egypt

<sup>b</sup> Department of Pathology, College of Medicine, Qassim University, Buraidah, Qassim, Saudi Arabia

<sup>c</sup> Chest Diseases Department, Faculty of Medicine, Cairo University, Cairo, Egypt

<sup>d</sup> Department of Medical Biochemistry, College of Medicine, Qassim University, Buraidah, Qassim, Saudi Arabia

<sup>e</sup> Department of Family and Community Medicine, College of Medicine, Qassim University, Buraidah, Qassim, Saudi Arabia

<sup>f</sup> Department of Medical Laboratories Sciences, College of Applied Medical Sciences, Majmaah University, Majmaah, Saudi Arabia

<sup>g</sup> Faculty of Medicine, School of Public Health, University of Queensland, Brisbane, Australia

<sup>h</sup> School of Life Sciences, University of Essex, Colchester, UK

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### ABSTRACT

**Background:** Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), within few months of being declared as a global pandemic by WHO, the number of confirmed cases has been over 75 million and over 1.6 million deaths since the start of the Pandemic and still counting, there is no consensus on factors that predict COVID-19 case progression despite the diversity of studies that reported sporadic laboratory predictive values predicting severe progression. We review different biomarkers to systematically analyzed these values to evaluate whether are they are correlated with the severity of COVID-19 disease and so their ability to be a predictor for progression. **Methods:** The current meta-analysis was carried out to identify relevant articles using eight different databases regarding the values of biomarkers and risk factors of significance that predict progression of mild or moderate cases into severe and critical cases. We defined the eligibility criteria using a PICO model.

**Results:** Twenty-two relevant articles were selected for meta-analysis the following biomarkers C-reactive protein, interleukin-6, LDH, neutrophil, %PD-1 expression, D-dimer, creatinine, AST and Cortisol all recorded high cut-off values linked to severe and critical cases while low lymphocyte count, and low Albumin level were recorded. Also, we meta-analyzed age and comorbidities as a risk factors of progression as hypertension, Diabetes and chronic obstructive lung diseases which significantly correlated with cases progression ( $p < 0.05$ ).

**Conclusions:** The current meta-analysis is the first step for analysing and getting cut-off references values of significance for prediction COVID-19 case progression. More studies are needed on patients infected with SARS-CoV-2 and on a larger scale to establish clearer threshold values that predict progression from mild to severe cases. In addition, more biomarkers testing also help in building a scoring system for the prediction and guiding for proper timely treatment.

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\* Corresponding authors at: College of Medicine, Qassim University, Buraidah, Qassim, Saudi Arabia.

E-mail addresses: [mm.khodeir@qu.edu.sa](mailto:mm.khodeir@qu.edu.sa) (M.M. Khodeir), [zrasheed@qu.edu.sa](mailto:zrasheed@qu.edu.sa), [zafarrasheed@qumed.edu.sa](mailto:zafarrasheed@qumed.edu.sa) (Z. Rasheed).

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## Introduction

Coronaviruses (CoV) are a group of viruses that lead to diseases variable from mild to many serious diseases such as Middle Eastern respiratory syndrome (MERS-CoV) and severe acute respiratory syndrome (SARS-CoV). Dec. 31, 2019, the Chinese Health Authority notified the World Health Organization (WHO) of numerous cases of pneumonia of unknown etiology in the city of Wuhan, in the area of Hubei, in central China [1]. On January 7, a new coronavirus, originally abbreviated as 2019-nCoV by WHO, was identified by a patient's throat swab sample, has not been recognized before in humans [2,3]. Subsequently, this pathogen was renamed as coronavirus 2 severe acute respiratory syndrome (SARS-CoV-2) and the coronavirus designated by WHO 2019 (COVID-19) [4] by January 30, in China 7736 cases recorded, 12,167 suspected and 82 cases had been perceived in 18 countries. Accordingly, WHO stated the SARS-CoV-2 epidemic as an international public health emergency [5]. On 11 March 2020, the World Health Organization (WHO) stated that COVID-19 as a pandemic [6]. While writing this review, worldwide cases over 75 million and over 1.6 million deaths which are increasing with the upward curve [7]. The dependence on CT scan findings to detect and diagnose cases of coronavirus affection although accurate, does not estimate or predict which patient will go for a severe or lethal course [8,9]. Therefore, it is mandatory to identify mild/moderate patients who can pass to severe/critical condition and give them efficient treatment to prevent deterioration as the early proper treatment of cases prone to severe/critical malignant progression are important ways to reduce mortality [10]. Unfortunately, most investigators focused on cross-sectional description and the comparison of clinical,

laboratory, and CT imaging results [11–14]. Some have focused on finding risks for death [15,16]. Few have presented their data and mentioned the prediction of progression of mild COVID-19 cases, but still, the work is separate and there is no review to gather and filter the information of significance. So our purpose is to fill the gap by doing meta-analysis of published researches based on criteria to obtain reference figures of statistically significant biomarkers levels ( $p < 0.05$ ) and getting mean number of all means of the analyzed papers to be easily consulted to detect cases that expected to deteriorate into severe/critical condition as a first step to start building a scoring system that can be objectively expect COVID-19 case progression which is best known to our knowledge this is the first time to be done. This will help doctors to begin efficient aggressive treatment without delay by adequately predicting severe/critical cases which will improve survival rates and reduce both illness and fatality in the COVID-19 pandemic.

## Methods

Using an online database, to conduct a meta-analysis on the early prediction of COVID-19 cases prone to deterioration. The main articles are mainly taken from PubMed, Google Scholar, MEDLINE, UpToDate, Medscape, Embase, Web of Science, and the preprint server medRxiv using the terms “COVID-19”, “SARS-CoV-2”, “prediction of severe/critical cases”, “Vulnerability Index”, “Risk factors mortality”, “prediction of survival”, “prediction of malignant progression”, “risk score” are the keywords for our search. Publications were left out if they had inappropriate data and were not appropriate to the specific purpose of our review. All relevant study reference lists have been selected to identify missing publica-

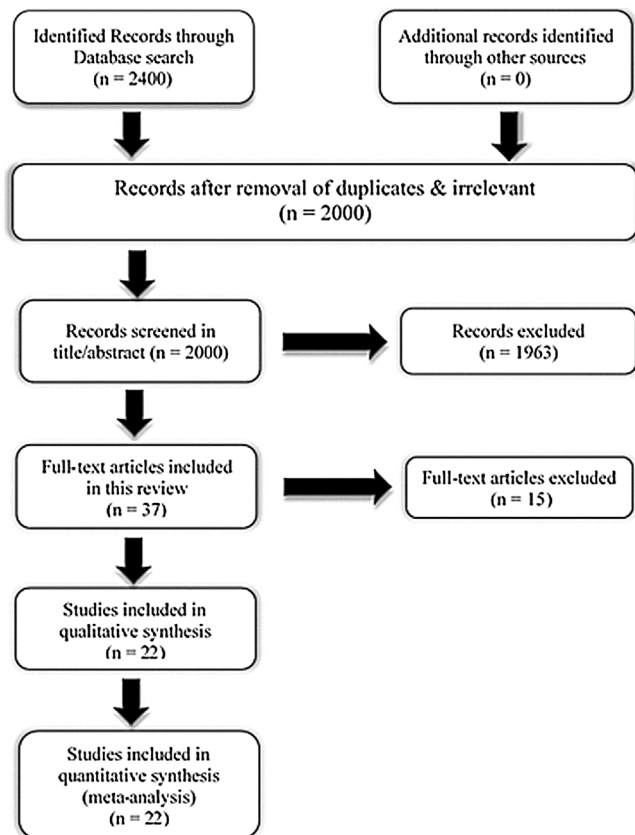


Fig. 1. Systematic review flow chart for literature refinement.

tions. After duplicates & irrelevant were removed, we identified 2000 papers. Search, of titles and abstracts were conducted by 6 independent working researchers by applying eligibility criteria and filter the relevant ones. Disagreements were resolved by discussion. We defined the eligibility criteria using a PICO model as follows. **Population:** no specific reference population. **Intervention:** Noninvasive lab investigations and biomarkers assay. **Comparison:** Imaging investigations, clinical symptoms progression or intra-individual pre-post comparison. **Outcome:** Patients with certain biomarkers levels progressed from mild/moderate to severe/critical. All eligible deemed articles have been retrieved for full-text review [Fig. 1]. We included studies for meta-analysis those show cohort, case-series case-control; studies on patients

with severe or mild illness, also those had death groups and survivors. We considered severity of the disease as “mild” for those patients described in the studies as mild or moderate cases, while considered ‘severe’ for described as having severe disease, ICU cases or required mechanical ventilation. Only studies of  $\geq 30$  patients were included. Only studies of score greater than 6 were considered of high quality of total score 9 according to Newcastle-Ottawa Scale (NOS) guidelines that was used by 4 independent reviewers, disagreement was resolved by additional reviewer [17].

### Statistical analysis

Meta-analyses were done using the metacount and metabin functions for continuous and binary variables respectively from the R package meta in R Studio [18]. For each study with more than one values of the biomarkers, a single value was calculated using the method described in Higgins and Green [19]. An overall weighted mean (SD) of the biomarkers was estimated within the mild and severe groups using standard weighted approach with built-in R functions. The overall difference in means or events between severe and mild patients were quantified by pooling the differences provided by the original studies using Random effect models, and the results represented as forest plots. Results for age and biomarkers were given as Mean Difference, MD (95%CI) while those of comorbidities as Relative Risks, RR (95%CI). Statistical heterogeneity between studies was assessed using  $I^2$ . For results with more than 2 studies, publication bias was assessed using the Egger regression [20].

## Results

### Literature screening and assessment

A total of 2400 records were identified from the databases. After a detailed assessment, 22 studies involving 4138 COVID-19 patients were included in the meta-analysis (Fig. 1).

### Characteristics of included studies

19 studies included in the meta-analysis were conducted in China examined Chinese patients, the remaining three were conducted in Iran, Italy and Cameron. All included studies were published in 2020. A large proportion of these studies ( $n = 20$ ) were single center data collected. All included studies received quality scores of 6–9, indicating high quality (Table 1).

Table 1  
Characteristics of the included studies in meta-analysis.

Author	Study design	Country	Cohort size	Biomarkers studied/comorbidity	Comments
Wang et al. [11]	Retrospective cohort, single center	China	138	Neutrophil cnt, Lymphocyte cnt, LDH	Higher Neutrophil count, LDH and lower lymphocyte count and significantly correlate this relation to severe critical cases
Yang et al. [12]	Retrospective cohort, multi center	China	149	Neutrophil cnt, Lymphocyte cnt, D-dimer, albumin, AST, creatinine, LDH, CRP	CT scan cannot exclude the diagnosis of COVID-19 as some patients with COVID-19 can present with normal chest finding however high biomarkers levels
Zhou et al. [15]	Retrospective cohort, multi center	China	191	Lymphocyte cnt, albumin, D-dimer, IL-6, creatinine, hypertension, Diabetes chronic obstructive lung disease	Considered D-dimer $> 1 \mu\text{g/mL}$ could help clinicians to identify patients with poor prognosis at an early stage.
Diao et al. [24]	Retrospective cohort, multi center	China	522	Lymphocyte cnt, IL-6	Recorded significant reduction in T cell counts in COVID-19 patients, and the surviving T cells appear functionally exhausted. Also, they negatively corrected T cells to IL-6. Considered Non-ICU patients with total T cells counts $< 800/\mu\text{L}$ still require urgent intervention, even in the immediate absence of more severe symptoms due to a high risk for further deterioration in condition.

Table 1 (Continued)

Author	Study design	Country	Cohort size	Biomarkers studied/comorbidity	Comments
Liu et al. [34]	Retrospective cohort, single center	China	40	Neutrophil cnt, Lymphocyte cnt, AST, LDH, creatinine, D-dimer, CRP, hypertension, Diabetes	Associated higher degree of lymphopenia and a proinflammatory cytokines with COVID-19 disease severity.
Feng et al. [36]	Retrospective cohort, single center	China	132	Lymphocyte cnt, Neutrophil cnt, CRP, IL-6, hypertension, Diabetes, chronic obstructive lung disease	Proposed CT scan as early screening could not satisfy every patient in COVID-19 outbreak and considered use of machine-learning algorithms to analyze clinical symptoms, biomarkers and other clinical information as a good tool for diagnosis and early prediction of cases prognosis before further CT examination
Qin et al. [37]	Retrospective cohort, single center	China	452	CRP, IL-6, Neutrophil cnt, Lymphocyte cnt	Compared different inflammatory biomarkers higher levels in severe and non-severe COVID-19 cases
Liu et al. [39]	Retrospective cohort, single center	China	140	IL-6, lymphocytes, neutrophils, AST, CRP, Creatinine, D-Dimer	They measured different biomarkers and correlated them with disease progression
Wu et al. [41]	Retrospective cohort, single center	China	201	IL-6	Significantly correlated higher IL-6 levels in severe cases
Chen et al. [43]	Retrospective cohort, single center	China	99	IL-6	Considered high IL-6 levels one of the measures that may detect COVID-19 severity.
Ji et al. [51]	Retrospective cohort, single center	China	33	CRP	Statistically significant increase in CRP with increase severity of the disease and considered it one of the measures can be used to judge severity
Etoga et al. [53]	Cross sectional single center	Cameroon	80	Cortisol	This study recorded higher levels of cortisol among COVID-19 cases who need further oxygen therapy than those of mild condition
Ramezani et al. [54]	Cross sectional single center	Iran	30	Cortisol	This study significantly correlated higher levels of cortisol in non-survived patients of Covid-19 in comparison with surviving patients.
Li et al. [55]	Retrospective cohort, single center	China	132	CRP	This study recorded noticeable difference of CRP between mild and severe critical cases
Tang et al. [56]	Retrospective cohort, single center	China	183	D-Dimer	Recorded higher levels of D-Dimer among non survivors COVID-19 cases
Zhang et al. [57]	Retrospective cohort, single center	China	343	D-Dimer	They study considered D-dimer level on admission > 2.0 µg/mL could effectively predict hospital mortality in patients with COVID-19
Huang et al. [58]	Prospective cohort, single center	China	41	IL-6, D-Dimer	Recorded higher levels of IL-6 and D-dimer among severe cases
Cheng et al. [60]	Prospective cohort, single center	China	701	Creatinine	They correlated high level of creatinine with severity and worse outcome in COVID-19 cases
Luo et al. [61]	Retrospective cohort, single center	China	35	LDH	Considered higher levels of LDH may indicate severity of the disease by their recorded levels of LDH in severe cases
Li et al. [62]	Retrospective cohort, single center	China	134	Lymphocyte cnt, Neutrophils cnt, D-dimer, albumin, AST, creatinine, IL-6, CRP, hypertension	Reached cut off value for decrease in albumin levels with the progression of the disease even they considered it as an independent predictor (cut-off point: 35.1 g/L) of the risk of non survivors among critical COVID-19 cases
Ferrari et al. [63]	Retrospective cohort, single center	Italy	207	LDH	LDH higher level among COVID-19 cases and considered it may help in diagnosis of such cases
Mo et al. [64]	Retrospective cohort, single center	China	155	LDH	Recorded higher levels among complicated cases and correlated LDH biomarker with the development of the disease.

**Table 2**

Egger's test of funnel plot asymmetry (publication bias).

Variable	Bias	Statistics	P value
Age	-1.5	-1.3	0.28
Lymphocytes	-0.3	-0.1	0.92
D-Dimer	3.1	3.1	0.05
IL-6	4.7	0.9	0.42
Neutrophils count	0.03	0.01	0.99
Creatinine	0.2	0.1	0.92
CRP	0.3	0.1	0.94
LDH	6	1.3	0.33
Hypertension	1.4	1.0	0.50
Diabetes	0.06	0.07	0.95

Bias: the intercept from the Egger's regression; p value of <0.05 signifies that the intercept is different from 0 and implying significant publication bias.

### Publication bias

The calculated p values of Egger's and the Begg's test for all analyzed studies outcomes showed no publication bias (Table 2). The recorded p values were >0.05 which indicates no publication bias.

### Age distribution

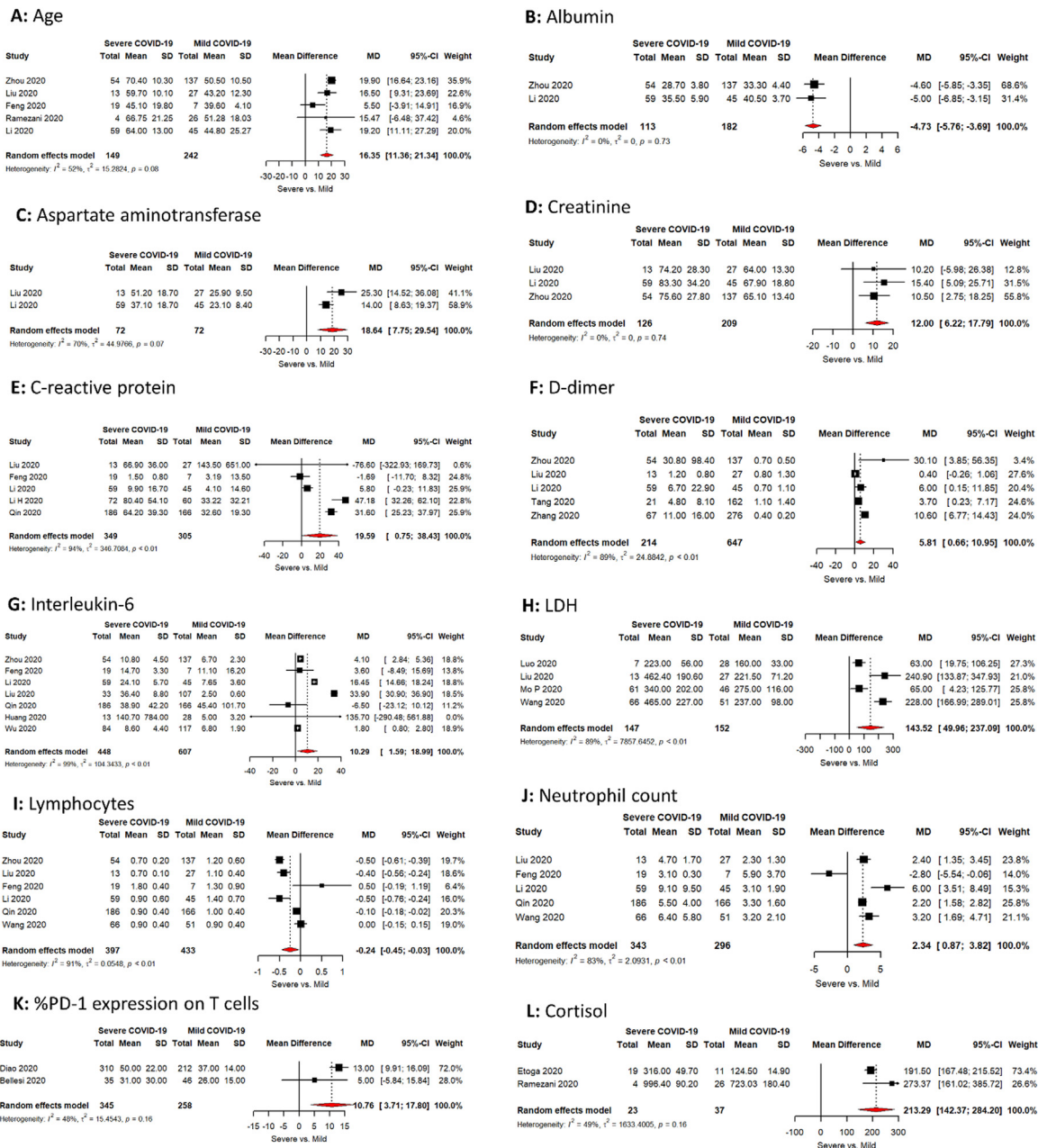
Severe cases were on average 16 years significantly older than those with Mild cases: Age difference 16.4 years (95%CI; 11.4, 21.3). There are no major differences in the study estimates and publication bias ( $I^2$  is <75%, Bias = -1.4, p value = 0.28). The mean age of severe group cases was 66.9 (STD 15.4) (Fig. 2A).

### Albumin

Albumin level was significantly lower in severe cases vs mild cases. The difference was of -4.7 g/L (95% CI; -5.8, -3.7). The mean Albumin level in severe group cases was 30.4 g/L (STD 6.1) (Fig. 2B).

### Aspartate aminotransferase

Severe cases recorded significantly higher level of AST vs mild cases with difference of 18.6 IU/L (95% CI; 7.8–29.5), with no major difference in the study estimates ( $I^2$  is <75%). The recorded mean AST level in severe group cases was 42.4 IU/L (STD 19.5) (Fig. 2C).



**Fig. 2.** (A–F): Meta-analysis of the difference between COVID-19 patients with severe vs mild disease in: (A) Mean age (B) Albumin level (C) Aspartate aminotransferase (D) Creatinine (E) C-reactive protein (F) D-Dimer. (G–L): Meta-analysis of the difference between COVID-19 patients with severe vs mild disease in: (G) Interleukin-6 (H) LDH (I) Lymphocytes (J) Neutrophil count (K) %PD-1 expression on T cells (L) Cortisol.

**Creatinine**

Creatinine level showed significantly higher levels in severe vs mild cases with difference of 12.00  $\mu\text{mol/L}$  (95% CI; 6.2; 17.8), with no major difference in the study estimates ( $I^2$  is <75%). Mean creatinine level in severe cases was 77.1  $\mu\text{mol/L}$  (STD 31.2) (Fig. 2D).

**C-reactive protein**

C-reactive protein level was higher in severe vs mild cases with difference of 19.6 mg/L (95% CI; 0.8; 38.4), however there was a major difference in the study estimates ( $I^2$  is >75%) with no significant publication bias (Bias = 0.3, p value = 0.9) Mean C-reactive recorded level in severe cases was 58.2 mg/L (STD 47) (Fig. 2E).

**D-dimer**

D-Dimer recorded higher levels in severe vs mild cases with mean difference of 5.8  $\mu\text{g/mL}$  (95% CI; 0.7; 10.9), however was a major difference in the study estimates ( $I^2$  is >75%). Publication bias was insignificant publication (Bias = -3.4, p value = 0.5). Mean D-Dimer level in severe cases was 12.9  $\mu\text{g/mL}$  (STD 52.7) (Fig. 2F).

**Interleukin-6**

IL-6 showed higher levels in severe vs mild cases with mean difference of 10.3 pg/mL (95% CI; 1.6; 19.0), there was a major difference in the study estimates ( $I^2$  is >75%). No significant publication bias (Bias = 4.7, p value = 0.4). Mean IL-6 level in severe cases was 29.6 pg/mL (STD 138) (Fig. 2G).

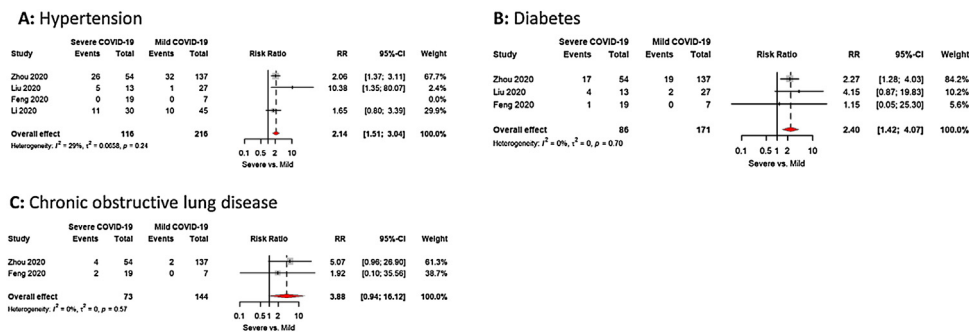


Fig. 3. (A–C): Meta-analysis of the difference between COVID-19 patients with severe vs mild disease in: (A) Hypertension (B) Diabetes (C) Chronic obstructive lung disease.

**LDH**

LDH level was higher in severe vs mild cases with mean difference of 143.52 U/L (95% CI; 50; 237.1), major difference was recorded in study estimates ( $I^2$  is >75%). No significant publication bias (Bias = 6, p value = 0.3). Mean LDH level in severe cases was 382 U/L (STD 221) (Fig. 2H).

**T-Lymphocytes count**

T-Lymphocytes count was lower in severe vs mild cases, the mean difference was  $-0.24 \times 10^9/L$  (95% CI;  $-0.45; -0.03$ ), the study estimate recorded major difference estimates ( $I^2$  is >75%). No significant publication bias (Bias =  $-0.3$ , p value = 0.9). Mean lymphocyte count in severe cases was  $0.8 \times 10^9/L$  (STD 0.46) (Fig. 2I).

**Neutrophil count**

Neutrophil count recorded higher levels in severe vs mild cases, the mean difference was  $2.3 \times 10^9/L$  (95% CI; 0.9; 3.8), the study estimate recorded major difference estimates ( $I^2$  is >75%). No significant publication bias (Bias = 0.03, p value = 0.9). Mean neutrophil count in severe cases was  $6.1 \times 10^9/L$  (STD 5.8) (Fig. 2J).

**%PD-1 expression on T cells**

%PD-1 expression on T-Lymphocytes was higher in severe vs mild cases, with mean difference of 10.8 (95% CI; 3.7; 17.8), there was no significant heterogeneity in the studies used ( $I^2$  is <75%). Mean of %PD-1 expression on T lymphocytes (the marker of T-cell exhaustion) in severe cases was 47 (STD 24) (Fig. 2K).

**Cortisol**

Although there are only two published studies about cortisol level among COVID-19 cases we included in our meta-analysis to check the significance of this biomarker and accordingly to recommend its importance for further studies. Cortisol recorded significant higher level in severe vs mild cases with mean difference of 213.3 nmol/L (95% CI; 142.4; 284.2). No significant heterogeneity was recorded in study estimates ( $I^2$  is >75%). Mean cortisol level in severe cases was 794 nmol/L (STD 264) (Fig. 2L).

**Hypertension**

Co-morbidity with hypertension was twice much more common in severe cases vs mild cases with RR 2.1(95% CI; 1.5; 3.0), No significant heterogeneity recorded in study estimates ( $I^2$  is < 75%) or publication bias (Bias = 1.4, p value = 0.5) (Fig. 3A).

**Diabetes**

Co-morbidity with diabetes was twice and half much more common in severe cases vs mild cases with RR 2.4 (95% CI; 1.4; 4.0), No

significant heterogeneity recorded in study estimates ( $I^2$  is <75%) or publication bias (Bias = 0.06, p value = 0.9) (Fig. 3B).

**Chronic obstructive lung disease**

Co-morbidity with chronic obstructive pulmonary disease was about four times much more common in severe cases vs mild cases with RR 3.9 (95% CI; 0.9; 16.1), No significant heterogeneity recorded in study estimates ( $I^2$  is <75%) (Fig. 3C).

**Study limitation**

Our meta-analysis included a large number of COVID-19 patients, but there are some limitations due to heterogeneity found in some studies, as well as most of the studies were from China and single center, so geographical and ethnic variations could not be studied well.

**Discussion**

**COVID-19 The disease**

COVID-19 is a respiratory infection with common signs including respiratory symptoms, fever, cough, and difficulty in breathing. In severe cases, the infection can cause pneumonia, severe acute respiratory syndrome, renal failure, and death [21,22]. Based on the staging of the infectious disease: The prodromal period is a phase in which the host begins to manifest general signs and symptoms. The openly symptomatic period is a phase in which the disease signs or symptoms are more evident, with positive laboratory results and chest imaging. For ICU patients, the ICU period is a phase in which the symptoms are more evident and severe. The period of decline is a phase in which clinical symptoms begin to decrease, laboratory results and chest imaging improve, and saturation of oxygen returns to normal [23,24]. The Chinese National Health Commission classified clinical types into mild/moderate/severe/critical [25].

**Factors that favor disease severity and worsen the prognosis**

Factors that favor disease severity and complications: Selecting cases with risk factors that could progress through a serious and complicated COVID-19 disease course is like selecting between death and life. Several researchers have investigated many risk factors, some findings were statistically significant (p < 0.05).

**Age and comorbidity**

Severe cases are those prone to serious complications and are at risk of death. The danger of serious complications from COVID-19 is greater for some vulnerable populations, particularly the elderly, the weak, or persons with multiple chronic diseases

[10,21,26–30]. Some studies reported advanced age and comorbidity with hypertension, as the most important risk factors for malignant progression [31]. The hazard of death was difficult to calculate, but some studies on COVID-19 patients in Wuhan reported that the risk of death rises with age and for those with diabetes, heart disease, clotting disorders. Since the fatality rate has changed from an average of 1%, to be 6% for persons with cancer, hypertension or chronic respiratory diseases, 7% for diabetes, and 10% for heart diseases. There was also a strong age gradient; the fatality rate for those over 80 was > 15% [15].

Our meta-analysis confirmed older age at more risk for case progression as we recorded age was higher by 16 years in COVID-19 severe cases than mild, with overall mean age of analyzed severe cases 66.9 (STD 15.4). Also, we recorded comorbidity of hypertension increase risk of progression from mild to severe twice, Diabetes twice and half, and Chronic obstructive lung disease showed four times which is the highest risk of progression among our analyzed studies.

### Biomarkers of prediction for case progression

#### Inflammatory markers

Lymphopenia is a common feature in COVID-19 patients and could be a critical factor associated with disease severity and mortality [24,32,33,35–37]. Even some studies considered low lymphocyte count is a biomarker is of >90% accuracy or of vital role for prediction of case progression that may aid as a possible therapeutic target [27]. Diao et al. studied lymphocytes function by measuring exhaustion markers and recorded increased expression of PD-1 and Tim-3 in T cells in cases proceeded from prodromal to symptomatic phases, further indicating T-cell depletion. The authors stated that these counts even in patients without intensive care may require aggressive intervention even in the absence of serious symptoms as liable to worsening of their condition [24]. Our meta-analysis on %PD-1 expression on T-Lymphocytes as one of exhaustion markers confirmed being higher in severe vs mild cases. The mean of %PD-1 expression in severe cases in studies analyzed was 47 (STD 24).

Many studies found a close and significant correlation between IL-6 high levels and case progression and even mortality. Some are negatively correlated it with low T-lymphocyte count and higher expression of PD-1 among severe cases [16,24,27,38,39]. Our meta-analysis confirmed higher levels of IL-6 in severe vs mild cases with overall mean level in severe cases 29.6 pg/mL (STD 138). Several studies recorded neutrophil count as an important biomarker that can predict progression of mild cases into severe/critical one either alone or compared to lymphocytes count. Some considered

it useful in surveillance and may predict critically ill patients early [11,16,37,40,41]. Our results revealed higher neutrophil count in severe vs mild cases, with the overall mean neutrophil count in analyzed studies is  $6.1 \times 10^9/L$  (STD 5.8). C-reactive protein was like a marker of common use several studies recorded higher levels in severe/critical than mild COVID-19 cases and some considered it to be of help for detection of case progression [10,27,35,39,41–51]. Our analysis confirmed higher levels of CRP among severe vs mild COVID-19 cases with overall mean level in severe cases 58.2 mg/L (STD 47).

#### Cortisol level

Three published studies on cortisol level in COVID-19 cases recorded higher level of cortisol among severe vs mild COVID-19 cases [52–54]. Our meta-analysis confirmed its higher levels in severe vs mild cases with over all mean of the studied severe cases is 794 nmol/L (STD 264).

#### Abnormal coagulation

Several studies recorded high levels of D-Dimer which reflect abnormal coagulation results among severe vs mild COVID-19 cases. Some considered certain level could effectively predict in-hospital mortality in patients although the recorded levels were different [11,15,27,39,55–57].

Our analysis confirmed D-Dimer higher levels in severe vs mild cases with overall mean level in severe cases is 12.9  $\mu\text{g/mL}$  (STD 52.7).

#### Multiorgan injury

COVID-19 severe cases not only related to respiratory tract infection but also progression into severe complicated cases and increased mortality could be due to multiorgan injury. Some studied worked on biomarkers those could reflect organs injury as AST, creatinine, LDH and Albumin on which they reported higher levels of the first three biomarkers and lower levels of the fourth one among severe/critical cases. Some strongly corrected decrease Albumin level with disease progression [11,16,27,39,41,46–49,58–64]. Our analysis confirmed higher levels of AST, creatinine and LDH among severe vs mild covid-19 cases with overall mean levels in severe cases 42.4 IU/L (STD 19.5), 77.1  $\mu\text{mol/L}$  (STD 31.2), and 382 U/L (STD 221) respectively. Albumin level was significantly lower among severe cases with overall mean level in severe cases is 30.4 g/L (STD 6.1).

**Table 3**

The collected biomarkers of all meta-analyzed studies of statistical significance with calculated mean of all recorded means in the studies of analysis to be a help key levels for prediction of progression from a mild/moderate case of COVID-19 into severe/critical case.

Positive COVID-19 patient			
Biomarkers of prediction progression of cases from mild/moderate to severe/critical			
Non-high-risk group <sup>a</sup>			
A-Indicators of COVID-19 progression into severe/critical condition		B-Indicators of multiorgan injury	
C-reactive protein	$\geq 58.2$ mg/L (STD 47)	LDH	$\geq 382$ U/L (STD 221)
Neutrophil count	$\geq 6.1 \times 10^9/L$ (STD 5.8).	Aspartate aminotransferase (AST), U/L	$\geq 42.4$ IU/L (STD 19.5)
T-Lymphocytes count	$\leq 0.8 \times 10^9/L$ (STD 0.46).	Albumin	$\leq 30.4$ g/L (STD 6.1)
D-Dimer	$\geq 12.9$ $\mu\text{g/mL}$ (STD 52.7)	Creatinine	$\geq 77.1$ $\mu\text{mol/L}$ (STD 31.2)
<b>T Cell Function:</b> % PD-1 expression on T cells	$\geq 47$ (STD 24)		
<b>% PD-1 On T-Cell</b>	$\geq 47$ (STD 24)		
<b>Cytokines:</b>			
IL-6	$\geq 29.6$ pg/mL (STD 138)		
<b>Cortisol level:</b>	$\geq 794$ nmol/L (STD 264)		

<sup>a</sup> Patient younger than 66.9 years (STD 15.4) with no comorbidity if show any indicator in this group considered a risk for progression into severe/ critical condition which necessitates aggressive treatment even if CT findings not clear yet and the patient condition still apparently mild.



**Table 4**

The collected risk factors of meta-analyzed studies of statistical significance to help as a key for prediction of progression from a mild/moderate case of COVID-19 into severe/critical case.

Positive COVID-19 patient	
Risk factors of prediction progression of cases from Mild/moderate to severe/critical	
High-risk group	
Risk factor	
A-Age $\geq$ 66.9 (STD 15.4)	
B-Any age with Comorbidity:	Risk degree for progression
1-Chronic obstructive lung disease	Four times
2-Hypertension	Twice
3-Diabetes	Twice and half

### Reference keys and prediction of severity

We collected the overall mean levels of our biomarkers of study those all included studies in our meta-analysis to seal the gap, best known to our knowledge not done before in any published meta-analysis on COVID-19, and reach a possible prediction references keys with their levels that can be used as a reference that can predict sunsets for mild or moderate COVID-19 cases who are vulnerable to progress into a severe course, entailing aggressive interventions in absence of severe symptoms which will be of great value to reduce the burden on intensive care and reduce complications and mortality (Tables 3 and 4). We considered it as the first step to start building a scoring system that can be used for the prediction that guides for proper timely treatment which will be of help to reduce mortality. We are working on another review article that will explain the immunopathogenesis of COVID-19 and explaining why these predictors are keys in predicting progression of the cases to severe/critical, we also propose the possible solutions for effective treatment.

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### Competing interests

None declared.

### Ethical approval

Not required.

### Authors' contributions

First two authors contributed equally to the manuscript and read and approved the final version of the manuscript. Other authors main work in reading and applying selection criteria final discussion and approval of final version of manuscript.

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### References

- [1] Harapan H, Itoh N, Yufika A, Winardi W, Keam S, Te H, et al. Coronavirus disease 2019 (COVID-19): a literature review. *J Infect Public Health* 2020;13(May (5)):667–73, <http://dx.doi.org/10.1016/j.jiph.2020.03.019>.
- [2] Hui DS, Azhar EI, Madani TA, Ntoumi F, Kock R, Dar O, et al. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health – the latest 2019 novel coronavirus outbreak in Wuhan, China. *Int J Infect Dis* 2020;91:264–6, <http://dx.doi.org/10.1016/j.ijid.2020.01.009>.
- [3] WHO | Novel Coronavirus – China [Internet]. World Health Organization [cited Jul 1, 2020]. Available from: <http://www.who.int/csr/don/12-january-2020-novel-coronavirus-china/en/>.
- [4] Gorbalenya Alexander E, Baker Susan C, Baric Ralph S, de Groot Raoul J, Drosten C, Gulyaeva Anastasia A, et al. The Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. *Nat Microbiol* 2020;5(April (4)):536–44, <http://dx.doi.org/10.1038/s41564-020-0695-z>.
- [5] Burki TK. Coronavirus in China. *Lancet Respir Med* 2020;8(March (3)):238, [http://dx.doi.org/10.1016/S2213-2600\(20\)30056-4](http://dx.doi.org/10.1016/S2213-2600(20)30056-4).
- [6] WHO Director-General's Opening Remarks at the Media Briefing on COVID-19. 1 May 2020. allAfrica.com (English). <https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19--11-march-2020>.
- [7] WHO. Coronavirus disease 2019 (COVID-19) “Weekly Epidemiological Update.” 2020 December 22. <https://www.who.int/publications/m/item/weekly-epidemiological-update--22-december-2020>.
- [8] Dangis A, Gieraerts C, Bruecker YD, Janssen L, Valgaeren H, Obbels D, et al. Accuracy and reproducibility of low-dose submillisievert chest CT for the diagnosis of COVID-19. *Radiol Cardiothorac Imaging* 2020;2(April (2)):e200196, <http://dx.doi.org/10.1148/rjct.2020200196>.
- [9] Pianura E, Di Stefano F, Cristofaro M, Petrone A, Albarello F, Fusco N, et al. COVID-19: a review of the literature and the experience of INMI Lazzaro Spallanzani two months after the epidemic outbreak. *J Radiol Rev* 2020;7:196–207, <http://dx.doi.org/10.23736/S2723-9284.20.00022-4>.
- [10] Bai X, Fang C, Zhou Y, Bai S, Liu Z, Xia L, et al. Predicting COVID-19 malignant progression with AI techniques. *medRxiv* 2020 <https://www.medrxiv.org/content/10.1101/2020.03.20.20037325v2.supplementary-material?versioned=true>.
- [11] 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 J Am Med Assoc* 2020;323(11):1061–9, <http://dx.doi.org/10.1001/jama.2020.1585>.
- [12] Yang W, Cao Q, Qin L, Wang X, Cheng Z, Pan A, et al. Clinical characteristics and imaging manifestations of the 2019 novel coronavirus disease (COVID-19): a multi-centre study in Wenzhou city, Zhejiang, China. *J Infect* 2020;80(April (4)):388–93, <http://dx.doi.org/10.1016/j.jinf.2020.02.016>.
- [13] Kim H. Outbreak of novel coronavirus (COVID-19): what is the role of radiologists? *Eur Radiol* 2020;30(June (6)):3266–7 <https://link.springer.com/article/10.1007/s00330-020-06748-2>.
- [14] Shi H, Han X, Jiang N, Cao Y, Alwalid O, Gu J, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. *Lancet Infect Dis* 2020;20(April (4)):425–34, [http://dx.doi.org/10.1016/S1473-3099\(20\)30086-4](http://dx.doi.org/10.1016/S1473-3099(20)30086-4).
- [15] 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. *Lancet* 2020;395(10229):1054–62, [http://dx.doi.org/10.1016/S0140-6736\(20\)30566-3](http://dx.doi.org/10.1016/S0140-6736(20)30566-3).
- [16] 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;46(May (5)):846–8, <http://dx.doi.org/10.1007/s00134-020-05991-x>.
- [17] Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010;25:603–5.
- [18] Team RC. R: a language and environment for statistical computing. Vienna: R Foundation for Statistical Computing; 2018 <https://www.R-project.org>.
- [19] Higgins PT, Green S. *Cochrane handbook for systematic reviews of interventions*: version 5.1.0. England: Wiley; 2008.
- [20] Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *Br Med J* 1997;315:629–34.
- [21] DeCaprio D, Gartner J, Burgess T, Kothari S, Sayed S, McCall CJ. Building a COVID-19 vulnerability index. *medRxiv* 2020, <http://dx.doi.org/10.1101/2020.03.16.20036723> <https://www.medrxiv.org/content/10.1101/2020.03.16.20036723v2>.
- [22] Tuttolomondo D, Frizzelli A, Aiello M, Bertorelli G, Majori M, Chetta A. Beyond the lung involvement in COVID-19 patients. A review. *Minerva Med* 2020, <http://dx.doi.org/10.23736/S0026-4806.20.06719-1>. In press.
- [23] Parker N, Schneegurt M, Thi Tu A-H, Lister P, Forster BM. Characteristics of infectious disease. In: *Microbiology*. Houston, Texas: OpenStax; 2016. Available from: <https://openstax.org/books/microbiology/pages/15-1-characteristics-of-infectious-disease>.
- [24] Diao B, Wang C, Tan Y, Chen X, Liu Y, Ning L, et al. Reduction and functional exhaustion of T cells in patients with coronavirus disease 2019 (COVID-19). *Front Immunol* 2020;11:827, <http://dx.doi.org/10.3389/fimmu.2020.00827>.
- [25] National Health Commission of the People's Republic of China. The notice of launching guideline on diagnosis and treatment of the novel coronavirus pneumonia (NCP); 2020. [Accessed 18 February 2020] [in Chinese] <http://www>.

- nhc.gov.cn/zyzygj/s7653p/202002/3b09b894ac9b4204a79db5b8912d4440/files/7260301a393845fc87fc6dd52965ecb.pdf.
- [26] Why is it so hard to calculate how many people will die from covid-19? [Internet]. [cited Jul 1, 2020]. Available from: <https://www.newscientist.com/article/mg24532733-700-why-is-it-so-hard-to-calculate-how-many-people-will-die-from-covid-19/>.
- [27] Yan L, Zhang H-T, Xiao Y, Wang M, Sun C, Liang J, et al. Prediction of criticality in patients with severe Covid-19 infection using three clinical features: a machine learning-based prognostic model with clinical data in Wuhan. medRxiv 2020, <http://dx.doi.org/10.1101/2020.02.27.20028027> <https://www.medrxiv.org/content/10.1101/2020.02.27.20028027v2>.
- [28] Song C-Y, Xu J, He J-Q, Lu Y-Q. COVID-19 early warning score: a multi-parameter screening tool to identify highly suspected patients. medRxiv 2020, <http://dx.doi.org/10.1101/2020.03.05.20031906> <https://www.medrxiv.org/content/10.1101/2020.03.05.20031906v1>.
- [29] 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. Crit Care 2020;24(1):108–12, <http://dx.doi.org/10.1186/s13054-020-2833-7>.
- [30] Velavan TP, Meyer CG. Estimation of risk factors for COVID-19 mortality - preliminary results. Trop Med Int Health 2020;25(March (3)):278–80, <http://dx.doi.org/10.1101/2020.02.24.20027268>.
- [31] Xie J, Tong Z, Guan X, Du B, Qiu H, Slutsky AS. Critical care crisis and some recommendations during the COVID-19 epidemic in China. Intensive Care Med 2020;46(May (5)):837–40 <https://link.springer.com/article/10.1007/s00134-020-05979-7>.
- [32] Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA J Am Med Assoc 2020;323(April (13)):1239–42, <http://dx.doi.org/10.1001/jama.2020.2648>.
- [33] Huang Y, Tu M, Wang S, Chen S, Zhou W, Chen D, et al. Clinical characteristics of laboratory confirmed positive cases of SARS-CoV-2 infection in Wuhan, China: a retrospective single center analysis. Travel Med Infect Dis 2020;36:101606, <http://dx.doi.org/10.1016/j.tmaid.2020.101606>.
- [34] Liu J, Li S, Liu J, Liang B, Wang X, Wang H, et al. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. EBioMedicine 2020;55(May):102763, <http://dx.doi.org/10.1016/j.ebiom.2020.102763>.
- [35] Tan L, Wang Q, Zhang D, Ding J, Huang Q, Tang Y-Q, et al. Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. Signal Transduct Target Ther 2020;5(March (1)).
- [36] Feng C, Huang Z, Wang L, Chen X, Zhai Y, Zhu F, et al. A novel triage tool of artificial intelligence assisted diagnosis aid system for suspected COVID-19 pneumonia in fever clinics. medRxiv 2020 <https://www.medrxiv.org/content/10.1101/2020.03.19.20039099v1>.
- [37] Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. Clin Infect Dis 2020;27(15):762–8, <http://dx.doi.org/10.1093/cid/ciaa248>.
- [38] Genevieve M, Crowther NJ, et al. Endothelial Dysfunction as a Primary Consequence of SARS-CoV-2 Infection. Adv Exp Med Biol 2021;1321:33–43, [http://dx.doi.org/10.1007/978-3-030-59261-5\\_3](http://dx.doi.org/10.1007/978-3-030-59261-5_3).
- [39] 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. J Clin Virol 2020;127(April):104370.
- [40] Liu T, Zhang J, Yang Y, Ma H, Li Z, Zhang J, et al. The potential role of IL-6 in monitoring severe case of coronavirus disease 2019. medRxiv 2020;(March) <https://www.medrxiv.org/content/10.1101/2020.03.01.20029769v2>.
- [41] 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 Intern Med 2020;180(7):934–43, <http://dx.doi.org/10.1001/jamainternmed.2020.0994>.
- [42] Gong J, Dong H, Xia SQ, Huang YZ, Wang D, Zhao Y, et al. Correlation analysis between disease severity and inflammation-related parameters in patients with COVID-19 pneumonia. medRxiv 2020;(February) <https://www.medrxiv.org/content/10.1101/2020.02.25.20025643v1>.
- [43] Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395(10223):507–13, [http://dx.doi.org/10.1016/S0140-6736\(20\)30211-7](http://dx.doi.org/10.1016/S0140-6736(20)30211-7).
- [44] Wong CK, Lam CWK, Wu AKL, Ip WK, Lee NLS, Chan IHS, et al. Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome. Clin Exp Immunol 2004;136(April (1)):95–103, <http://dx.doi.org/10.1111/j.1365-2249.2004.02415.x>.
- [45] Wu J, Wu X, Zeng W, Guo D, Fang Z, Chen L, et al. Chest CT findings in patients with coronavirus disease 2019 and its relationship with clinical features. Invest Radiol 2020;55(May (5)):257–61, <http://dx.doi.org/10.1097/RLI.0000000000000670>.
- [46] 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 2020;92(7):856–62, <http://dx.doi.org/10.1002/jmv.25871>.
- [47] Wang L. C-reactive protein levels in the early stage of COVID-19. Med Mal Infect 2020;50(4):332–4, <http://dx.doi.org/10.1016/j.medmal.2020.03.007>.
- [48] Liu W, Tao Z-W, Wang L, Yuan M-L, Liu K, Zhou L, et al. Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease. Chin Med J 2020;133(May (9)):1032–8.
- [49] 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. Lancet Respir Med 2020;8(February (5)):475–81.
- [50] Young BE, Ong SWX, Kalimuddin S, Low JG, Tan SY, Loh J, et al. Epidemiologic features and clinical course of patients infected with SARS-CoV-2 in Singapore. JAMA 2020;323(March (15)):1488–94.
- [51] Ji W, Bishnu G, Cai Z, Shen X. Analysis clinical features of COVID-19 infection in secondary epidemic area and report potential biomarkers in evaluation. medRxiv 2020;(March), 2020.03.10.20033613.
- [52] Tan T, Khoo B, Mills EG, Phylactou M, Patel B, Eng PC, et al. Association between high serum total cortisol concentrations and mortality from COVID-19. Lancet Diabetes Endocrinol 2020;8(8):659–60, [http://dx.doi.org/10.1016/S2213-8587\(20\)30216-3](http://dx.doi.org/10.1016/S2213-8587(20)30216-3).
- [53] Etoqa MCE, Inna AH, Guewo-Fokeng M, Dehayem M, Boli AO, Manga JAN, et al. <https://doi.org/10.21203/rs.3.rs-78801/v1>.
- [54] Ramezani M, Simani L, Karimialavijeh E, Rezaei O, Hajiesmaeili M, Pakdaman H. The role of anxiety and cortisol in outcomes of patients with Covid-19. BCN 2020;11(2):179–84 <http://bcn.iuims.ac.ir/article-1-1771-en.html>.
- [55] 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. J Infect 2020;80(6):646–55, <http://dx.doi.org/10.1016/j.jinf.2020.03.035>.
- [56] Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 2020;18(4):844–7.
- [57] 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. J Thromb Haemost [Internet]. [cited 2020 Apr 25];n/a(n/a). Available from: <https://onlinelibrary.wiley.com/doi/abs/10.1111/jth.14859>.
- [58] 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 2020;395(February (10223)):497–506.
- [59] Guan W-J, Ni Z-Y, Hu Y, Liang W-H, Ou C-Q, He J-X, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382(February (18)):1708–20.
- [60] Cheng Y, Luo R, Wang K, Zhang M, Wang Z, Dong L, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. Kidney Int 2020;97(May (5)):829–38.
- [61] Luo W, Lin Y, Yao X, Shi Y, Lu F, Wang Z, et al. Clinical findings of 35 cases with novel coronavirus pneumonia outside of Wuhan. Preprint from Research Square, 17 Apr 2020, PPR: PPR151913 <https://doi.org/10.21203/rs.3.rs-22554/v1>.
- [62] Li J, Li M, Zheng S, Li M, Zhang M, Sun M, et al. Plasma albumin levels predict risk for nonsurvivors in critically ill patients with COVID-19. Biomark Med 2020;14(July (10)):827–37, <http://dx.doi.org/10.2217/bmm-2020-0254>. Epub 2020 Jun 3. PMID: 32490680; PMCID: PMC7273900.
- [63] Ferrari D, Motta A, Strollo M, Banfi G, Locatelli M. Routine blood tests as a potential diagnostic tool for COVID-19. Clin Chem Lab Med (CCLM) 2020;58(7):1095–9, <http://dx.doi.org/10.1515/cclm-2020-0398>.
- [64] Mo P, Xing Y, Xiao Y, Deng L, Zhao Q, Wang H, et al. Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China. Clin Infect Dis 2020;(March), <http://dx.doi.org/10.1093/cid/ciaa270>. In press.