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

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Letter to the Editor

Factors associated with mortality in patients with COVID-19. A quantitative evidence synthesis of clinical and laboratory data

The COVID-19 pandemic caused by the severe acute respiratory coronavirus 2 (SARS-CoV-2) has become a serious challenge for health systems worldwide. Despite the favorable clinical course for most cases, a mortality rate of 30–70% is expected for COVID-19 patients treated on intensive care unit (ICU) [1]. Reports have shown an increased risk of death for older patients with existing comorbidities and potential biomarkers associated with severity for COVID-19 patients [2,3].

Because of the complexity and the limited evidence on the pathogenesis of COVID-19, the management of critically ill patients has been challenging. Multiple recent studies have provided valuable clinical and laboratory features of hospitalized patients with COVID-19, but in many of them the information is not complete and there is a potential for overlapping data. Therefore, findings from a comprehensive systematic review can help physicians to understand the disease and make decisions for critically ill patients. In this study, we performed a quantitative evidence synthesis of clinical and laboratory factors associated with mortality in patients with COVID-19.

We searched the peer-reviewed (PubMed, Web of Science, Scopus, Embase) and gray (Google Scholar, bioRxiv, medRxiv) literature to identify studies comparing clinical data, laboratory parameters (hematological, biochemical, inflammatory markers, coagulation factors, and blood gas analysis) and complications between non-survivors and survivors of COVID-19. We included only studies providing clinical data and at least one of the laboratory parameters previously mentioned. We excluded publications with potential overlapping reports, and studies from which data extraction was not possible. In case of potential overlapping data, we selected the study with most complete information.

Reports were screened in two stages: screening of titles and abstracts followed by the retrieval and screening of full-text articles. Searches were performed from January 1, 2020 up to April 06, 2020, without language restrictions. The reference lists of all eligible studies and reviews were also evaluated to identify additional studies for inclusion. The following search terms were used: “COVID-19″, "severe acute respiratory syndrome coronavirus 2″, "SARS-CoV-2″, "2019-nCoV", “coronavirus” and “coronaviruses”.

Data from publications were extracted by two authors and cross-checked for accuracy. Our outcome of interest was in-hospital death. Clinical data, laboratory parameters, and complications were considered predictor variables. Effect sizes were reported as mean difference (MD) or standardized mean difference (SMD) for continuous variables and risk ratio (RR) for dichotomous variables with 95% confidence intervals (CI). Not all studies reported data on all predictor variables, and the pooled analysis was estimated from the data available for each variable. A random-effects model was used to pool the results and a 2-tailed $p < 0.05$ was used to determine significance. Cohen's classification was used to interpret the magnitude of the effect size for the laboratory findings. SMD > 0.8 was considered a large effect size. Statistical heterogeneity was quantified by the I^2 index. Analyses were conducted using the Review Manager 5.3 (Cochrane IMS, Copenhagen, Denmark).

After screening 8692 titles and abstracts, 73 full-text articles were assessed for eligibility and 69 studies were excluded, 11 of which were due to potential overlapping data. Four retrospective Chinese studies were included. Data were collected from patients admitted to Tongji Hospital [4], Renmin Hospital [5], Number 1 Hospital [6], Jinyintan Hospital and Wuhan Pulmonary Hospital [7]. These studies provided data on 852 patients (489 male and 363 female) with confirmed SARS-CoV-2 infection by RT-PCR: 603 survivors and 249 non-survivors. We found an increased risk for in-hospital death in older patients (MD = 13.8, 95%CI 8.0 to 19.7), male gender (RR = 1.3, 95%CI 1.1 to 1.4), with comorbidities (RR = 1.6, 95%CI 1.4 to 2.0) and dyspnea (RR = 1.8, 95%CI 1.4 to 2.2). Non-survivor patients had increased levels of white blood cells (SMD = 1.1, 95%CI 0.9 to 1.4), neutrophils (SMD = 1.3, 95%CI 0.9 to 1.7), urea (SMD = 1.4, 95%CI 1.2 to 1.6), creatinine (SMD = 0.8, 95%CI 0.7 to 1.0), creatine kinase (SMD = 0.8, 95%CI 0.6 to 0.9), hypersensitive cardiac troponin I (SMD = 1.1, 95%CI 0.9 to 1.3), lactate dehydrogenase (SMD = 1.5, 95%CI 1.0 to 2.1), D-dimer (SMD = 1.1, 95%CI 0.9 to 1.2), and IL-6 (SMD = 1.5, 95%CI 1.1 to 1.7) compared to survivors of COVID-19. Decreased levels of albumin (SMD = −1.3, 95%CI −1.7 to −0.9), lymphocytes (SMD = −0.9, 95%CI −1.2 to −0.6), and gas exchange deficit (SMD PaO2/FiO2 = −1.8, 95%CI −2.1 to −1.5) were also associated with an increased risk for mortality. Complications of SARS-CoV-2 infection commonly seen in critically ill patients including ARDS (RR = 7.4, 95%CI 1.2 to 48.2), acute cardiac injury (RR = 6.9, 95%CI 3.2 to 15.0), acute kidney injury (RR = 22.6, 95CI% 3.1 to 165.1), disseminate intravascular coagulation (DIC) (RR = 27.1, 95%CI 3.7 to 199.3), and sepsis (RR = 2.4, 95%CI 2.1 to 2.7) were found to be risk factors for the COVID-19 related death. The Table 1 shows the detailed results of meta-analysis comparing clinical and laboratory data between non-survivors and survivors of COVID-19.

The results of this meta-analysis may provide insights into the pathogenesis and progression of COVID-19 and reinforces the evidence that age-associated immune alterations and sustained comorbidities are associated with poor prognosis of patients. In addition, our findings highlighted early markers for the risk of death in patients with COVID-19.

It has been shown that SARS-CoV-2 use the angiotensin-converting enzyme 2 (ACE2) receptor to invade host cells especially in kidney, lungs and heart leading to an enhanced release of cytokines and a hyperinflammatory state both implicated in the multi-organ damage in these patients [8]. Our meta-analysis showed important differences in biochemical markers of organ injury and infection-related indices between survivor and non-survivors of COVID-19. Therefore, SARS-CoV-2 infection may worsen pre-existing chronic inflammatory conditions as

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Table 1
Comparison of clinical, hematological, biochemical, infection-related indices and cellular immunity, coagulation function, blood gas, and complications data between non-survivors and survivors of COVID-19.

Parameter	MD (95% CI) between non-survivors and survivors	SMD (95% CI) between non-survivors and survivors	RR (95% CI)	p-value	I^2
Clinical					
Age	13.8 (8.0 to 19.7)	–	–	< 0.001	91%
Male	–	–	1.3 (1.1 to 1.4)	< 0.001	0%
Comorbidities	–	–	1.6 (1.4 to 2.0)	< 0.001	0%
Hypertension	–	–	1.5 (1.1 to 2.1)	0.006	66%
Diabetes	–	–	1.6 (1.1 to 2.2)	0.006	6%
Lung disease	–	–	3.5 (2.0 to 6.3)	< 0.001	0%
Cardiovascular disease	–	–	3.0 (1.2 to 7.6)	0.020	75%
Cerebrovascular disease	–	–	3.3 (1.8 to 6.2)	< 0.001	0%
Malignancy	–	–	1.5 (0.6 to 3.8)	0.420	0%
Chronic kidney disease	–	–	4.2 (1.4 to 12.8)	0.010	19%
Chronic liver disease	–	–	4.2 (0.3 to 66.5)	0.310	–
Clinical symptoms and signs					
Fever	–	–	1.0 (0.9 to 1.0)	0.780	0%
Cough	–	–	1.7 (0.6 to 5.1)	0.340	98%
Dyspnea	–	–	1.8 (1.4 to 2.2)	< 0.001	26%
Hemoptysis	–	–	1.9 (0.4 to 8.3)	0.390	–
Sputum production	–	–	1.0 (0.8 to 1.3)	0.780	0%
Vomiting	–	–	1.1 (0.5 to 2.5)	0.830	0%
Days from symptoms onset to admission	0.6 (−0.2 to 1.3)	–	–	0.120	0%
Hematological					
WBC	–	1.1 (0.9 to 1.4)	–	< 0.001	42%
Neutrophils	–	1.3 (0.9 to 1.7)	–	< 0.001	74%
Lymphocytes	–	−0.9 (−1.2 to −0.6)	–	< 0.001	61%
Platelet count	–	−0.6 (−0.8 to −0.4)	–	0.009	0%
Hemoglobin	–	−0.1 (−0.4 to 0.2)	–	0.380	70%
Biochemical					
ALT	–	0.3 (−0.1 to 0.6)	–	0.110	76%
AST	–	0.6 (−0.02 to 1.2)	–	0.060	90%
Albumin	–	−1.3 (−1.7 to −0.9)	–	< 0.001	72%
Blood urea nitrogen	–	1.4 (1.2 to 1.6)	–	< 0.001	0%
Creatinine	–	0.8 (0.7 to 1.0)	–	< 0.001	0%
Creatine kinase		0.8 (0.6 to 0.9)	–	< 0.001	0%
hs-cTnI	–	1.1 (0.9 to 1.3)	–	< 0.001	20%
LDH		1.5 (1.0 to 2.1)	–	< 0.001	87%
Infection-related indices and cellular immunity					
CRP	–	1.2 (0.7 to 1.7)	–	< 0.001	80%
ESR	–	0.4 (0.2 to 0.7)	–	< 0.001	–
IL-6	–	1.5 (1.1 to 1.7)	–	< 0.001	80%
Serum ferritin	–	1.3 (1.1 to 1.5)	–	< 0.001	0%
Procalcitonin	–	1.1 (0.6 to 1.5)	–	< 0.001	83%
CD4 cell count	–	−0.8 (−1.1 to −0.5)	–	< 0.001	–
CD8 cell count	–	−0.8 (−1.1 to −0.5)	–	< 0.001	–
Coagulation function					
PT	–	0.9 (0.5 to 1.3)	–	< 0.001	84%
APTT	–	0.1 (−0.04 to 0.3)	–	0.130	0%
D-dimer	–	1.1 (0.9 to 1.2)	–	< 0.001	28%
Blood gas analysis					
pH	–	0.0 (−0.2 to 0.2)	–	1.000	–
PaO_2	–	−1.4 (−1.7 to −1.2)	–	< 0.001	–
$PaCO_2$	–	−1.2 (−1.5 to −1.0)	–	< 0.001	–
SaO_2	–	−1.1 (−1.7 to −0.5)	–	< 0.001	70%
PaO_2/FiO_2	–	−1.8 (−2.1 to −1.5)	–	< 0.001	–
Complications					
ARDS	–	–	7.4 (1.2 to 48.2)	0.040	98%
Acute cardiac injury	–	–	6.9 (3.2 to 15.0)	< 0.001	79%
Acute kidney injury	–	–	22.6 (3.1 to 165.1)	0.002	80%
DIC	–	–	27.1 (3.7 to 199.3)	0.001	–
Sepsis	–	–	2.4 (2.1 to 2.7)	< 0.001	0%

WBC, white blood cells; ALT, alanine transaminase; AST, aspartate transaminase; LDH, lactate dehydrogenase; hs-cTnI, hypersensitive cardiac troponin I; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; PT, prothrombin time; APTT, activated partial thromboplastin time; PaO_2, partial pressure of oxygen; $PaCO_2$ partial pressure of carbon dioxide; SaO_2, oxygen saturation; ARDS, acute respiratory distress syndrome; DIC, disseminated intravascular coagulation; MD, mean difference; SMD, standardized mean difference; RR, risk ratio; CI, confidence interval. Negative results for SMD indicate decreased levels of laboratory parameters in non-survivor patients.

hypertension, diabetes and cardiovascular disease in older patients leading to death.

In the lungs, the inflammatory response due to SARS-CoV-2 infection increases the alveolar-capillary permeability resulting in alveolar edema, decreased gas exchange, hypoxemia, and progressive dyspnea. The impaired gas exchange found in severe and critically ill

patients with COVID-19 is commonly associated with ARDS which is a devastating condition that requires a complex ICU management focusing on lung protective ventilation, avoidance of fluid overload, and support of organ function. Interestingly, this meta-analysis showed that the early respiratory limitation is a prognostic marker of severity of disease. Although dyspnea has not been described as the predominant complaint for patients with COVID-19, the early recognition of respiratory distress can make difference in relation to the prognosis of patients.

The dysregulated immune response in severe and critically ill patients with COVID-19 seems to be associated with a cytokine storm. Increased amounts of cytokines, especially IL-6, have been associated lymphopenia with decreasing CD4+ and CD8+ cell counts, and severe lung injury in patients with COVID-19. It has been found that inflammatory cytokines may lead to apoptosis-induced lymphopenia and functional exhaustion cytotoxic lymphocytes leading to disease progression [9]. IL-6 receptor (IL-6R) antagonists have been investigated to control immune response and inflammation in severe COVID-19 disease.

Moreover, we found a large effect size for procalcitonin in non-survivor patients of COVID-19 which may be associated with the release of some cytokines, especially IL-6. It is well known that procalcitonin is a better marker to estimate the severity, prognosis, or further course of the sepsis and is helpful to guide antibiotic management. Therefore, the increased levels of procalcitonin in critical ill patients with COVID-19 can represent a bacterial coinfection and collected blood cultures for bacteria are needed to a prompt response. In the study by Wang et al. [5], 81.7% of patients who died with COVID-19 had associated bacterial infection. We found that sepsis was associated with a 2.5-fold increase in the risk of death in COVID.

The release of proinflammatory cytokines, endothelial dysfunction and increased oxidative stress may also lead to hypercoagulable state in patients with SARS-CoV-2 infection. In addition, sepsis has been commonly associated with artery and venous thrombosis along with microvascular embolism [6]. We found a prolonged PT, increased D-dimer and thrombocytopenia in non-survivor patients which is suggestive of DIC. Also, the presence of DIC was significantly associated with 27-fold increase in the risk of death in critical ill patients with COVID-19. It has been recommended the early initiation of IVIg and low molecular weight heparin (LMWH) therapy to alleviate the hypercoagulable state and improve the prognosis of critical type patients [10].

Although different scenarios should be considered when interpreting deaths from COVID-19 including environmental factors and therapeutic limitations, the results of the present study have important implications to make early clinical and laboratory indicators available in relation to the increased risk of death by COVID-19. From their understanding, physicians can make decision practices in critical care for patients with SARS-CoV-2 infection. Unfortunately, there is a high number of studies with potential overlapping data which compromise the strength of available evidence. The results of this meta-analysis are based on standard univariate model and further studies without overlapping reports should be published allowing to allow account for confounding factors.

In summary, this meta-analysis showed that older age, presence of chronic inflammatory states, dyspnea at disease onset, decreased gas exchange, increased IL-6 levels, lymphopenia, decreased CD4 and CD8 count cells, changes in biochemical indices, and coagulation abnormalities including prolonged PT, increased D-dimer and thrombocytopenia are important predictors for mortality in patients with COVID-19. Moreover, there is an increased risk of death for patients who develop ARDS, cardiac injury, acute kidney disease, DIC, and sepsis.

Authors contributions

Paulo Martins-Filho, Carolina Santos Souza Tavares and Victor Santos contributed equally to this manuscript.

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Declaration of Competing Interest

The authors declare that they have no conflicts of interest.

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