Hematological and biochemical characteristics of COVID-19 non-survivors: a meta- and network analysis

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Abstract

Background: Understanding the most relevant hematological/biochemical characteristics, pre-existing health conditions and complications among survivors and non-survivor will help to predict the mortality in COVID-19 patients.

Methods: A literature review was conducted in PubMed, Scopus, and various preprint servers (bioRxiv, medRxiv and SSRN) for COVID-19 mortality, with more than 97 reported clinical studies and preprints, consisting of survivor and non-survivor sub-populations. A total of 19014 patients including 14359 survivors and 4655 non-survivors were included in this meta-analysis. Outcome data was extracted and compared between survivors and non-survivors. Meta and network analyses were performed using META-MAR V2.7.0 and PAST software.

Results: The finding showed higher concentrations of gamma-glutamyl transferase and creatinine and a higher number of neutrophils in non-survivors of COVID-19. A lower number of lymphocytes and platelets and a lower concentration of hemoglobin and albumin were observed in non-survivors. Data showed age, hypertension, and cerebrovascular disease as the most influential risk factors in non-survivors. Heart failure was the most common complication among non-survivors, accompanied by septic shock, and respiratory failure.

Conclusions: Increased number of neutrophils and decreased number of platelets and lymphocytes, along with higher GGT concentration and lower hemoglobin levels were the best mortality indicators for COVID-19 patients. In addition, age, hypertension, and cerebrovascular disease were prevalent risk factors among non-survivors of COVID-19. Heart failure and septic shock were the most common complications among non-survivors. Data indicated that cheap and quick biochemical and hematological tests can be used to predict the risk of mortality in COVID-19 patients.

Introduction

Healthcare staffs face difficulties in reducing the severity and mortality of COVID-19 worldwide. As a growing problem, many sub-populations of patients with moderate or non-severe COVID-19 encounter serious conditions or even death. It has been reported that approximately 19% of COVID-19 patients recorded serious illness and 61.5% died within 28 days of admission, on the other hand, 50% of hospitalized patients recorded no meaningful clinical and imaging remission after 10 days. Therefore, early diagnosis of patients with a potential severe infection with COVID-19 and a high risk of death will reduce pressure on medical services, as the treatment of a large number of patients is a major burden on medical resources. The position of risk prediction is dramatically changing and helps to effectively decide how protective protocols and the treatment of positive cases are being attempted. Therefore, early prognosis and care of this group of patients are crucial to reduce disease progression and death. In general, hematological predictors, risk factors, and possible complications of COVID-19 mortality need further understanding. Understanding the contribution of each risk factor to the progression of disease.
and mortality will help to define at-risk subpopulations and to assess the quality of health care. Efforts should also be made to take into account risk classes and to estimate the risk of fatality in order to better explain the real trends of mortality.

The aim of this systematic study and meta- and network analysis was to investigate which hematological/biochemical parameters, pre-existing conditions, and complications are more prevalent in COVID-19 non-survivors.

**Methods**

**Search strategy and selection criteria**

A literature review was conducted in PubMed, Scopus, and various preprint servers (bioRxiv, medRxiv and SSRN) for COVID-19, novel coronavirus, new coronavirus, coronavirus-2019, COVID-2019, SARS-COV-2, and 2019-nCOV with more than 170 published clinical studies and preprints (including 134046 patients) released between December 2019 and April 2020 (no language restrictions were applied). The systematic review resulted in 97 qualified retrospective observational studies (19014 patients), which including strictly sub-populations of survivors (n=14359) and non-survivors (n=4655). Reference lists for papers and other systematic reviews were also scrutinized. Studies without survivors or non-survivors and cases < 19 years of age were excluded. For each paper, an author reads the paper and extracts the necessary numerical data from the tables and the text in a standard format, and the hematological and biochemical indices were checked to be the same, unless otherwise converted to the same unit.

**Data extraction and analysis**

The results of the search strategy were initially evaluated using abstracts and titles. The full text of the relevant articles was then evaluated on the basis of the inclusion and exclusion criteria. Final lists of articles included were contrasted and the differences were resolved by a consensus discussion between the two contributors. Data including the type and date of publication, country, sample size, age, sex, blood indices and parameters, pre-existing health conditions, and complications were extracted independently by three researchers (SFK, EB, and AMR). Three authors (KS, AHM, and MS) tested the consistency of the data collected using a structured spreadsheet. For each parameter used, we selected those papers that reported hematological and biochemical parameters of survivors and non-survivors. This resulted in different sample sizes for different parameters between survivors and non-survivors. Outcome data were collected and the normality of the data was confirmed using the Anderson–Darling test. Meta-analysis and network analysis were performed using META-MAR V2.7.0 and PAST applications, respectively. The Standardized Mean Difference (SMD) was used to define the effect size of various hematological and biological indices, risk factors (pre-existing conditions), and complications in survivors and non-survivors of COVID-19. Due to heterogeneity within and across parameters, random-effect models were used to calculate the weighted mean prevalence and 95% confidence interval (CI) or the weighted mean and 95%
CI. The \( I^2 \) and \( \tau^2 \) statistics and the Cochran’s Q test were used to determine statistical heterogeneity. In addition, a meta-regression analysis was conducted to determine the effect of variables on the effect size. The Z-test and related P-values evaluated whether the observed prevalence varied from zero percent.

The risk of bias in the included studies was not evaluated because there was no agreement on the ideal method for prevalence studies\(^{103,104}\) and publications were pooled based on the presence of survivors or non-survivors. Furthermore, such tests will not alter the modeling or data presentation approach.\(^{104}\)

**Network analysis**

Network analysis was performed using the Pearson similarity index. The Circular and Fruchterman-Reingold algorithms were used as a force-directed layout algorithm using the PAST software (accessible at: [http://folk.uio.no/ohammer/past](http://folk.uio.no/ohammer/past)).

**Results**

**Characteristics of included studies**

As shown in Figure 1A, data from more than 200 published clinical studies and preprints was screened. After a comprehensive review of the data in figures and tables, 85 reports were excluded due to lack of survivor or non-survivor sup-groups, examining infants/children/pediatrics, or had no DOI, resulting in 97 eligible retrospective studies. These criteria resulted in a total of 19014 patients (>20 years of age) including 14359 survivors and 4655 non-survivors. The population considered in these studies originated from China, Italy, Scotland, the United States, UK, Japan, South Korea, Iceland, Chile, the Netherlands and Germany.

**Clinical outcomes**

Clinical outcomes are shown in Table 1. Based on the studies reported age, patients (n=9375) aged 25.3 to 80.0 years (49.8; CI\(_{95}\%\) [46.9, 52.7]). Of them, 5448 were survivors (age: 46.6; CI\(_{95}\%\) [44.2, 48.9]) and 3927 were non-survivors (age: 71.5; CI\(_{95}\%\) [66.4, 76.5]). In non-survivors, the proportion of males was higher than females (33.3 vs. 17.7%). The prevalence of any comorbidities (65.9%), hypertension (64.5%), diabetes (65.5%), cardiovascular disease (78.8%), chronic obstructive lung (74.1%), cancer (79.9%), and renal disease (88.6%) was higher among COVID-19 non-survivors than among survivors.

Mortality incidence in mild cases was zero compared to 89.8% of mortality in patients with severe COVID-19. The percentage of non-survivors among patients receiving antibiotics or antiviral drugs was 39.0% and 48.4%, respectively. Non-ICU patients were found to have survived; while, 56.8% of ICU (only)-
admitted patients died. Mortality in white or European ethnic groups (75.6%) was higher than in Asian (7.0%), African American (9.5%), and Hispanics-Latino ethnic groups (0.0%).

The number of neutrophils (NEUs) (3.52×10^9 L vs. 6.48×10^9 L found for survivors and non-survivors, respectively) and white blood cells (WBCs) (5.43×10^9 L vs. 8.55×10^9 L found for survivors and non-survivors, respectively) was higher in non-survivors than in survivors (P=0.0001). The number of lymphocytes (LYMs) (0.60×10^9 L vs. 1.23×10^9 L found for non-survivors and survivors, respectively) and PLTs (149.92×10^9 L vs. 187.76×10^9 L found for non-survivors and survivors, respectively) was lower in non-survivors than in survivors (P=0.0001).

Concentrations of aspartate transaminase (AST) (50.68 vs. 30.06 U/L, P=0.0003), creatinine (87.52 vs. 64.64 mol/L, P=0.0001), creatinine kinase (101.0 vs. 73.2 U/L, P=0.032), C-reactive protein (CRP) (96.39 vs. 22.32 mg/L, P=0.0001), and gamma-glutamyl transferase (GGT) (52.50 vs. 11.06 U/L, P=0.0001) were found to be higher in non-survivors compared to survivor. However, the concentrations of albumin (31.93 vs. 38.51 g/L, P=0.048) and hemoglobin (124.03 vs. 134.44 g/L, P=0.0001) were lower in non-survivors than in COVID-19 survivors.

Data showed that acute kidney injury (94.5%) was the most common complication among non-survivors, followed by respiratory failure (93.8%), septic shock (89.3%), heart failure (88.9%), acute cardiac injury (87.3%), coagulopathy (72.5%), acidosis (68.1%) and secondary infection (67.3%).

**Quantitative synthesis of data**

**Meta-regression analysis**

The multivariate meta-regression analysis showed that the risk factors (t, 4.77; CI_{95%} [0.64, 1.68]; P=0.000) were associated with the estimated intervention effects on COVID-19 mortality while biochemical/hematological indices (t, 1.85; CI_{95%} [-0.11, 1.60]; P=0.083) tended to be associated with this (Table 2). Moreover, complications were associated with the estimated intervention effects on COVID-19 mortality (t, 3.80; CI_{95%} [1.07, 4.36]; P=0.005).

**Meta-analysis of overall and individual hematological indices**

The individual Hedges’g for each parameter and the combined effect size with CI_{95%} are shown in Figure 1B. A random-effect model was used for the combined effect size as there was a significant statistical heterogeneity (P=0.000) between the parameters (Tau^2 as the between-group variance and I^2 as the proportion of total variation in the estimates of parameter effects). The overall increase in blood
parameters of COVID-19 non-survivors (0.74 [0.02, 1.46]; Z=2.02; P=0.044; \( \tau^2 = 100.0\% \); \( \tau^2 = 2.13 \)) was shown in the meta-analysis forest plot based on the random effect model (Figure 1B).

The number of NEUs (2.81 [2.70, 2.91]; Z=53.97; P=0.000) and WBCs (2.38 [2.29, 2.47]; Z=50.05; P=0.000) and the concentrations of GGT (4.10 [3.81, 4.39]; Z=27.40; P=0.000), creatinine (2.40 [2.30, 2.49]; Z=49.67; P=0.000), CRP (2.28 [2.19, 2.38]; Z=46.23; P=0.000), AST (1.44 [1.34, 1.54]; Z=29.11; P=0.000), creatinine kinase (1.14 [1.03, 1.25]; Z=19.58; P=0.000), IL-6 (0.95 [0.82, 1.08]; Z=14.04; P=0.000), blood urea nitrogen (BUN) (0.47 [0.38, 0.57]; Z=9.62; P=0.000), and bilirubin (0.20 [0.11, 0.29]; Z=4.46; P=0.000) were higher in non-survivor COVID-19.

The number of LYMs (-1.74 [-1.83, -1.66]; Z=41.36; P=0.000) and PLTs (-1.55 [-1.63, -1.47]; Z=36.89; P=0.000) and the concentration of hemoglobin (-1.26 [-1.35, -1.17]; Z=26.12; P=0.000), albumin (-0.80 [-0.90, -0.70]; Z=15.50; P=0.000) and procalcitonin (-0.12 [-0.20, -0.03]; Z=2.69; P=0.007) in non-survivors were lower than in survivors.

COVID-19 mortality increases with age, hypertension, cerebrovascular disease and diabetes

As shown in the meta-analysis forest plot based on the random effect model (Figure 2A), prevalence of pre-existing conditions increased COVID-19 mortality (1.16 [0.78, 1.55]; Z=5.87; P=0.000; \( \tau^2 = 100.0\% \); \( \tau^2 = 0.63 \)).

Prevalence of individual pre-existing conditions, such as age (3.11 [3.05, 3.17]; Z=100.70; P=0.000); hypertension (2.30 [2.26, 2.35]; Z=100.00; P=0.000), cerebrovascular disease (2.22 [2.13, 2.32]; Z=45.95; P=0.000), diabetes (2.11 [2.06, 2.15]; Z=96.66; P=0.000), any comorbidities (1.97 [1.99, 2.01]; Z=84.99; P=0.000), cardiovascular disease (1.55 [1.51, 1.59]; Z=76.90; P=0.000), COPD (1.16 [1.11, 1.20]; Z=56.68; P=0.000), renal disease (1.10 [1.06, 1.14]; Z=52.59; P=0.000), male sex (0.78 [0.75, 0.82]; Z=44.59; P=0.000), body mass index (BMI) (0.73 [0.46, 0.99]; Z=5.38; P=0.000), time from symptoms appearance to hospitalization (0.66 [0.61, 0.72]; Z=23.17; P=0.000), liver disease (0.52 [0.47, 0.56]; Z=22.42; P=0.000), cancer (0.45 [0.41, 0.48]; Z=23.13; P=0.000) and smoking history (0.13 [0.02, 0.24]; Z=2.41; P=0.016) was higher among non-survivors. The prevalence of current drinkers was lower among non-survivors (-0.62 [-0.82, -0.42]; Z=6.01; P=0.000), which could be product of a relatively small number of non-survivors (n=101) used for meta-analysis (Figure 2A).

Meta-analysis determines common complications among non-survivors of COVID-19

The prevalence of complications among COVID-19 non-survivors (2.71 [1.91, 3.51]; Z=6.66; P=0.000; \( \tau^2 = 100.0\% \); \( \tau^2 = 1.48 \)) increased as shown in the meta-analysis forest plot based on the random effect model (Figure 2B).
Heart failure (7.40 [7.15, 7.64]; Z=58.45; P=0.000) was the most common complication among non-survivors, followed by septic shock (4.49 [4.36, 4.63]; Z=65.90; P=0.000), acidosis (2.90 [2.64, 3.15]; Z=22.24; P=0.000), respiratory failure (2.80 [2.73, 2.87]; Z=78.36; P=0.000), acute cardiac injury (1.89 [1.83, 1.96]; Z=54.84; P=0.000), coagulopathy (1.79 [1.66, 1.93]; Z=25.32; P=0.000), acute kidney injury (1.64 [1.58, 1.69]; Z=58.91; P=0.000), secondary infection (1.31 [1.24, 1.37]; Z=39.24; P=0.000), and liver dysfunction (0.10 [0.01, 0.20]; Z=2.08; P=0.037) (Figure 2B).

**Network analysis supports the results of the meta-analysis**

The network correlation for blood indices (Figure 3A), risk factor (Figure 3B), and complication (Figure 3C) were shown at cutoff point of 50%. The number of PLTs and LYMs and the concentration of hemoglobin were associated with COVID-19 survivors at a maximum cutoff point of 72%, all parameters were disconnected after this cutoff point (Figure 3D). The number of NEUs, the concentration of GGT, and the incidence of COVID-19 mortality were associated together at a maximum cutoff point of 93% (Figure 3E).

Network analysis showed a relationship between COVID-19 mortality and age, hypertension, cerebrovascular disease, diabetes, any comorbidity, cardiovascular disease (at a maximum cutoff point of 79%, Figure 3F) and heart failure (at a maximum cutoff point of 97%, Figure 3G). These findings supported the results of the meta-analysis; however, the meta-analysis was able to rank the potent factors involved in COVID-19 mortality.

**Discussion**

This meta-analysis study identified 97 randomized trials that provided outcome data appropriate for three meta-analyses: blood parameters, pre-existing risk factors and complications. The results showed that NEU and WBC number and concentrations of GGT, creatinine and CRP were higher in COVID-19 non-survivors, whereas LYM and PLT count and hemoglobin concentration were lower. Moreover, age, hypertension, cerebrovascular disease, diabetes, heart failure, and septic shock were the most common risk factors and complications among non-survivors.

Our meta-analysis showed increased NEU and decreased LYM count in COVID-19 non-survivors. Qin et al.\textsuperscript{105} reported that lymphopenia (low counts of lymphocytes) and increased NEU–LYM ratio were frequently observed in patients with severe COVID-19, which was a more common feature of patients that died of disease.\textsuperscript{6} Serious cases of lymphopenia can be caused by inflammatory mediators, such as IL-2 and IL-6, and can contribute to LYM loss.\textsuperscript{105} Qin et al.\textsuperscript{105} indicated that infection with SARS-CoV-2 effects LYMs, leading to secondary bacterial infections and increased NEU count. Indeed, neutrophilia (NEU count > 7.5×10\textsuperscript{9}/L) is associated with bacterial inflammation, cytokine storm and hyper-inflammation\textsuperscript{106}, all of which have significant pathogenetic roles in COVID-19.\textsuperscript{105,107} Our findings support other studies that show a concomitant rise in WBC and NEU counts and a decline in LYM in COVID-19 non-survivors.\textsuperscript{26}
Therefore, changes in WBC, NEU, and LYM count may be considered for predicting the risk of death in COVID-19 patients.

Meta-analysis showed increased concentrations of GGT and AST in non-survivors. Concentrations of alanine aminotransferase (ALT), AST, and GGT have been reported to be markedly higher in deceased patients than in recovered patients\textsuperscript{26,108} Moreover, studies suggest that serum GGT levels can be used to predict organ injury in hypertension, diabetes, metabolic syndrome and coronary artery disease.\textsuperscript{109} In our study, 19.1\% of non-survivors were diagnosed with liver damage, while incidence of heart failure, septic shock, acute kidney injury, acute cardiac injury was 88.9\%, 89.3\%, 87.3\%, 94.5\%, and 87.3\%, respectively. With respect to severe conditions or death, GGT has been found to be involved in early stages of heart failure.\textsuperscript{108-110} Our meta-analysis showed that both hypertension and heart failure were respectively the most prevalent risk factor and complication in non-survivors. Our network-analysis also showed the relationship between GGT, heart failure and mortality in COVID-19 patients. Consequently, the results show that GGT is a promising predictor for predicting organ damage, heart failure and thus COVID-19 mortality.

The meta-analysis revealed higher concentrations of creatinine and BUN in non-survivors. It has also been stated that the occurrence of acute kidney failure of COVID-19 patients ranged from 0.5 to 29\%, a serious situation in which patients need to be admitted to the ICU.\textsuperscript{111} In our analysis, the prevalence of acute kidney injury in COVID-19 patients was 16.7\% and 94.5\% of these patients died. Angiotensin converting enzyme 2 (ACE2), which is the SARS-CoV-2 entry receptor, has been shown to be highly expressed in the brush border of proximal tubular cells.\textsuperscript{112} Moreover, SARS-CoV-2 was isolated from the patient’s urine sample and its antigens were accumulated in kidney tubules\textsuperscript{113-115}, indicting the clear effect of SARS-CoV-2 on human kidney\textsuperscript{111}. Higher creatinine and BUN in non-survivors would enable physicians to improve their understanding of impaired renal function in COVID-19 patients.

Current evidence indicates that complications in COVID-19 patients can be caused by the direct effect of the virus, immune-mediated inflammation or drug-induced toxicity, provided that the majority of patients received with high doses of antibiotics, antiviral drugs and steroids.\textsuperscript{108} Our analysis showed that non-survivors had high a proportion of respiratory failure (93.8\%), heart failure (88.9\%), septic shock (89.3\%), secondary infection (67.3\%), acute kidney injury (94.5\%), and acute cardiac injury (87.3\%). Zhou et al.\textsuperscript{6} reported that sepsis was the most frequent complication accompanied by respiratory failure, ARDS, heart failure, and septic shock. In our meta-analysis, the most common complications identified in deceased patients were heart failure and sepsis. Moreover, a high concentration of CRP was found in non-survivors. Li et al.\textsuperscript{116} indicated that direct viral disruption, hyper-inflammation, and hypoxemia may all contribute to cardiac injury. Serum CRP as an inflammatory marker has been reported to have been positively associated with disease severity,\textsuperscript{117} lung lesions,\textsuperscript{118} acute kidney damage,\textsuperscript{119} and cardiac injuries\textsuperscript{120} in COVID-19 patients. Sahu et al.\textsuperscript{121} observed stable high levels of CRP in COVID-19 patients that died from infection. Our results support these findings and indicate the significance of CRP as a potential biomarker for COVID-19 mortality, highlighting the importance of close monitoring of CRP changes.
The present meta-analysis revealed a decreased PLT count and concentration of hemoglobin and albumin in COVID-19 non-survivors. Our findings support the other reports that the number of PLTs in non-survivors decreased and increased in survivors.\textsuperscript{122} Zhao et al.\textsuperscript{122} suggested that PLT counts could drastically represent pathophysiological changes in COVID-19 patients and that early decrease in PLT counts was correlated with COVID-19 mortality. Viral infection appears to have caused lung tissue damages, resulting in PLT activation, aggregation and entrapment, leading to thrombosis, which enhances PLT consumption.\textsuperscript{122} PLTs have a short life cycle (8-10 days) and very few PLTs kept in the bone marrow;\textsuperscript{123} it may be responsive to the seriousness of the condition of the patient. Furthermore, viruses can cause a decrease in PLT production due to megakaryocyte infection, which may contribute to apoptosis of megakaryocytes.\textsuperscript{124} Therefore, repeated measurements of PLT count may be helpful for the care of COVID-19 patients, leading to a much earlier, more effective prognosis.

Liu et al.\textsuperscript{125} reported that hemoglobin decreased most frequently in COVID-19 patients. The first case of COVID-19 in the United States showed a small decrease in hemoglobin on day 6 of illness.\textsuperscript{24} Of note, it was more evident that patients with a composite endpoint (i.e., ICU admission, invasive ventilation, and death) had decreased hemoglobin levels.\textsuperscript{12} SARS-CoV-2-induced inflammation can interfere with erythropoiesis and reduce hemoglobin production. For example, IL-6 has been shown to be elevated in severe COVID-19 infection\textsuperscript{107} and disrupts the production of hemoglobin.\textsuperscript{126} The current meta-analysis showed an increased level of IL-6 in COVID-19 non-survivors. Our results indicate that decreased hemoglobin levels as a potential death marker for COVID-19, and that it would be more relevant to concentrate on the reduction of hemoglobin levels.

Our meta-analysis showed that age, hypertension, cerebrovascular disease, and diabetes are prevalent risk factors among non-survivors. In line with the other reports, we also found that non-survivors were older (46.6 vs. 76.5 years) and had a higher proportion of hypertension and diabetes than survivors.\textsuperscript{6} Expression of ACE2 has been shown to be significantly increased in patients with type-1 or type-2 diabetes and hypertension.\textsuperscript{127,128} Alternatively, diabetes and hypertension are treated with ACE inhibitors and angiotensin II type-I receptor blockers, resulting in an up-regulation of ACE2\textsuperscript{128,129}. As a result, increased expression of ACE2 will promote infection with COVID-19.\textsuperscript{128,129}

Importantly, a correlation between the existence of ACE insertion/deletion (I/D) polymorphism and COVID-19 severity and mortality has been reported.\textsuperscript{129} Li et al.\textsuperscript{130} reported that the frequency of the D allele is the highest in Europe and America while the lowest frequency is found in East Asia. Therefore, considering the spread of COVID-19 worldwide, European countries tend to have higher incidence and mortality rates.\textsuperscript{130} Similarly, we found a lower mortality rate for Asian ethnic groups (7.0%) than in White or European ethnic groups (75.6%).

In support of our findings, other studies have documented the association between cerebrovascular disease and the risk of death in COVID-19 patients.\textsuperscript{131} SARS-CoV-2 has been shown to have neuro-invasive abilities and may spread from the respiratory system to the central nervous system.\textsuperscript{132} COVID-19
can also cause cerebrovascular diseases due to inflammation, hypoxia, and diffuse intravascular coagulation.\textsuperscript{133} Thus, clinicians should strengthen the monitoring of COVID-19 patients with the cerebrovascular disease.

In conclusion, some hematological/biochemical indices, such as GGT, NEU and LYM, in combination with pre-existing conditions, such as age, hypertension, cerebrovascular disease and diabetes, have been identified as risk factors of mortality in patients with SARS-CoV-2 infection.

Declarations

Author contributions: SFK, EB, and AMR extracted data; RK and KS planned and drafted the manuscript; KS, AHM, and MS tested the data consistency; RK, AHM, and MS analyzed the data; RK, MS and AHM interpreted the data and reviewed the manuscript. All authors have read and approved the final version of the manuscript and agree with the order of presentation of the authors.

Declaration of Competing Interest

All authors report no conflicts of interest relevant to this article.

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Tables
Table 1. COVID-19 patient characteristics. Blood parameters, pre-existing conditions and complications.

| Characteristic          | All Patients       | Survivors         | Non-survivors      |
|-------------------------|--------------------|-------------------|--------------------|
| Age ± no, yr, mean (95% CI) | 9375, 49.8 (46.9, 52.7) | 5448, 46.6 (44.2, 48.9) | 3927, 71.5 (66.4, 76.5) |
| Gender                  |                    |                   |                    |
| Male ± no./total no. (%) | 9599/17778 (54.0)  | 6399/9599 (66.7)  | 3200/9599 (33.3)   |
| Female ± no./total no. (%) | 8179/17778 (46.0) | 6733/8179 (82.3) | 1446/8179 (17.7)   |
| Drinker                 |                    |                   |                    |
| Yes ± no./total no. (%) | 253/1606 (15.8)    | 243/253 (96.0)    | 10/253 (2.8)       |
| No ± no./total no. (%) | 1353/1606 (84.2)   | 1262/1353 (93.3)  | 91/1353 (6.7)      |
| Smoker                  |                    |                   |                    |
| Yes ± no./total no. (%) | 874/7583 (11.5)    | 843/874 (96.5)    | 31/874 (3.5%)      |
| No ± no./total no. (%) | 6709/7583 (88.5)   | 6377/6709 (95.1)  | 332/6709 (4.9)     |
| Day to Hospital ± no, mean (95% CI) | 5456, 5.9 (5.8, 6.0) | 2109, 5.7 (5.5, 5.8) | 3347, 8.0 (7.9, 8.1) |
| BMI ± no, mean (95% CI) | 383, 24.5 (24.3, 24.7) | 314, 24.1 (24.0, 24.3) | 69, 25.5 (24.7, 26.3) |
| Any comorbidities      |                    |                   |                    |
| Yes ± no./total no. (%) | 6321/11473 (55.1)  | 2156/6321 (34.1)  | 4165/6321 (65.9)   |
| No ± no./total no. (%) | 5152/11473 (44.9)  | 4873/5152 (94.6)  | 279/5152 (5.4)     |
| Hypertension           |                    |                   |                    |
| Yes ± no./total no. (%) | 4443/14080 (31.6)  | 1579/4443 (35.5)  | 2864/4443 (64.5)   |
| No ± no./total no. (%) | 9637/14080 (68.4)  | 8256/9637 (85.7)  | 1381/9637 (14.3)   |
| Diabetes               |                    |                   |                    |
| Yes ± no./total no. (%) | 2222/14423 (15.4)  | 766/2222 (34.5)   | 1456/2222 (65.5)   |
| No ± no./total no. (%) | 12201/14423 (84.6) | 9111/12201 (74.7) | 3090/12201 (25.3)  |
| Cardiovascular disease  |                    |                   |                    |
| Yes ± no./total no. (%) | 1679/14189 (11.8)  | 355/1679 (21.1)   | 1323/1679 (78.8)   |
| No ± no./total no. (%) | 12510/14189 (88.2) | 9202/12510 (73.6) | 3308/12510 (26.4)  |
| COPD                   |                    |                   |                    |
|                  | Yes  | No   | Total
|------------------|------|------|--------
| Yes  no./total no. (%) | 843/11925 (7.1) | 218/843 (25.9) | 625/843 (74.1) |
| No  no./total no. (%) | 11082/11925 (92.9) | 7408/11082 (66.8) | 3674/11082 (33.2) |
| **Cancer**        |      |      |        |
| Yes  no./total no. (%) | 952/11602 (8.2) | 191/952 (20.1) | 761/952 (79.9) |
| No  no./total no. (%) | 10650/11602 (91.8) | 6965/10650 (65.4) | 3685/10650 (34.6) |
| **Liver disease** |      |      |        |
| Yes  no./total no. (%) | 293/7783 (3.8) | 121/293 (41.3) | 172/293 (58.7) |
| No  no./total no. (%) | 7490/7783 (96.2) | 3806/7490 (50.8) | 3684/7490 (49.2) |
| **Cerebrovascular disease** |      |      |        |
| Yes  no./total no. (%) | 233/4172 (5.6) | 121/233 (51.9) | 112/233 (48.1) |
| No  no./total no. (%) | 3939/4172 (94.4) | 3368/3939 (85.5) | 571/3939 (14.5) |
| **Renal disease** |      |      |        |
| Yes  no./total no. (%) | 797/11551 (6.9) | 91/797 (11.4) | 706/797 (88.6) |
| No  no./total no. (%) | 10754/11551 (93.1) | 7546/10754 (70.2) | 3209/10754 (29.8) |
| **Other disease** |      |      |        |
| Yes  no./total no. (%) | 682/10562 (6.5) | 437/682 (64.1) | 245/690 (35.9) |
| **Severity**       |      |      |        |
| Mild  no./total no. (%) | 4041/19014 (21.2) | 4041/4041 (100.0) | 0/4041 (0.0) |
| Severe  no./total no. (%) | 4874/19014 (25.6) | 498/4874 (10.2) | 4376/4874, 89.8 |
| Unreported  no./total no. (%) | 10099/19014 (53.2) | 9800/10099 (97.0) | 299/10099 (3.0) |
| **Treatment**      |      |      |        |
| Antibiotics  no./total no. (%) | 9542/19042 (50.1) | 5817/9542 (61.0) | 3725/9542 (39.0) |
| Antiviral drugs  no./total no. (%) | 10371/19042 (54.5) | 5353/10371 (51.6) | 5018/10371 (48.4) |
| **ICU admission** |      |      |        |
| Non-ICU  no./total no. (%) | 4379/11420 (38.3) | 4379/4379 (100.0) | 0/4379 (0.0) |
| ICU-Endpoint  no./total no. (%) | 6754/11420 (59.2) | 6223/6754 (92.1) | 531/6754 (7.9) |
ICU-Only | no./total no. | 287/11420 (2.5) | 124/287 (43.2) | 163/287 (56.8)

| Ethnics |
|---------|
| White, European | no./total no. (%) | 4817/18442 (26.1) | 1176/4817 (24.4) | 3641/4817 (75.6) |
| African American | no./total no. (%) | 402/18442 (2.2) | 364/402 (90.5) | 38/402 (9.5) |
| Asian | no. (%) | 11632/18442 (63.1) | 10821/11632 (93.0) | 811/11632 (7.0) |
| Hispanic, Latino | no./total no. (%) | 922/18442 (5.0) | 922/922 (100.0) | 0/922 (0.0) |
| Multi-ethnicity | no./total no. (%) | 669/18442 (3.6) | 665/669 (99.4) | 4/669 (0.6) |

| Hematological indices | n, mean 10^9/L (CI95%) |
|----------------------|------------------------|
| WBC | 7174, 5.95 (5.52, 6.38) | 6591, 5.43 (5.17, 5.70) | 583, 8.55 (6.74, 10.36) |
| Lymphocyte | 7640, 1.11 (1.01, 1.22) | 6943, 1.23 (1.12, 1.34) | 697, 0.60 (0.52, 0.68) |
| Platelet | 7262, 179.49 (172.02, 186.95) | 6572, 187.76 (181.12, 194.41) | 690, 149.92 (131.13, 168.72) |
| Neutrophil | 4841, 4.19 (3.73, 4.65) | 4237, 3.52 (3.24, 3.81) | 604, 6.48 (5.39, 7.57) |

| Biochemical indices | n, mean 10^9/L (CI95%) |
|---------------------|------------------------|
| Hemoglobin | 6379, 132.58 (130.14, 135.01) | 5887, 134.44 (131.95, 136.92) | 492, 124.03(118.72, 129.34) |
| Albumin | 3491, 36.75 (33.71, 39.79) | 3040, 38.51 (3460, 42.41) | 451, 31.93 (30.15, 33.70) |
| Alanine aminotransferase | 5156, 29.41 (25.22, 33.60) | 4705, 29.27 (24.30, 34.23) | 548, 30.09 (23.38, 36.80) |
| Aspartate aminotransferase | 5020, 33.75 (29.17, 38.32) | 4526, 30.06 (26.48, 33.65) | 494, 50.68 (32.23, 69.13) |
| Gamma-glutamyl transferase | 1642, 19.35 (5.06, 33.65) | 1582, 11.06 (2.69, 19.43) | 60, 52.5 (36.88, 68.12) |
| Total bilirubin | 4758, 13.87 (10.94, 16.79) | 4206, 13.41 (9.74, 17.08) | 552, 15.47 (11.60, 19.34) |
| Blood urea nitrogen  mmol/L | 3801, 6.35 (4.30, 8.40) | 3326, 5.55 (2.82, 8.28) | 475, 8.55 (7.08, 10.02) |
|----------------------------|---------------------------|---------------------------|---------------------------|
| Creatinine  µmol/L         | 5306, 69.95 (65.86, 74.04) | 4670, 64.64 (61.74, 67.53) | 636, 87.52 (76.62, 98.41) |
| Creatine Kinase  U/L       | 4044, 79.46 (68.26, 90.69) | 3706, 73.20 (64.34, 82.06) | 338, 101.0 (56.75, 145.25) |
| C-reactive protein  mg/L   | 4895, 37.36 (26.03, 48.70) | 4297, 22.32 (14.63, 30.00) | 598, 96.39 (63.46, 129.31) |
| Interleukin-6  pg/mL       | 1827, 31.69 (7.44, 55.93) | 1557, 18.96 (-9.93, 47.86) | 270, 59.68 (8.27, 111.09) |
| Procalcitonin  ng/mL       | 4012, 0.68 (-0.30, 1.67)  | 3374, 0.78 (-0.58, 2.14)  | 638, 0.41 (0.19, 0.62)    |
| D-dimer  mg/L              | 4053, 6.78 (-0.13, 13.69) | 3390, 7.08 (-2.08, 16.25) | 663, 5.81 (3.00, 8.63)    |

**Complications**

| Liver dysfunction  no./total no. (%) | 602/3037 (19.8) | 487/602 (80.9) | 115/602 (19.1) |
|-------------------------------------|-----------------|----------------|----------------|
| Respiratory failure  no./total no. (%) | 3782/6313 (59.9) | 236/3782 (6.2) | 3546/3782 (93.8) |
| Heart failure  no./total no. (%)    | 189/2148 (8.8)  | 21/189 (11.1)  | 168/189 (88.9)  |
| Septic shock  no./total no. (%)     | 178/4567 (3.9)  | 19/178 (10.7)  | 159/178 (89.3)  |
| Coagulopathy  no./total no. (%)     | 51/1287 (4.0)   | 14/51 (27.5)   | 37/51 (72.5)    |
| Acute cardiac injury  no./total no. (%) | 732/5479 (13.4) | 93/732 (12.7)  | 639/732 (87.3)  |
| Acute kidney injury  no./total no. (%) | 1155/6936 (16.7) | 63/1155 (5.5)  | 1092/1155 (94.5) |
| Secondary infection  no./total no. (%) | 617/4993 (12.4) | 202/617 (32.7) | 415/617 (67.3)  |
| Acidosis  no./total no. (%)         | 47/515 (9.1)    | 15/47 (31.9)   | 32/47 (68.1)    |
Table 2. The multivariate meta-regression analysis.

| Variable     | t     | CI<sub>95%</sub>     | P value |
|--------------|-------|----------------------|---------|
| Blood indices| 1.85  | (-0.11, 1.60)       | 0.083   |
| Risk factors | 4.77  | (0.64, 1.68)        | 0.000   |
| Complications| 3.80  | (1.07, 4.36)       | 0.005   |

Figures

Figure 1

(A) Flow diagram of the number of records identified, included, and excluded from the search for systematic reviews, meta-analysis and network analysis of COVID-19 mortality interventions. (B) Forest plot of blood parameters in survivors and non-survivors of COVID-19. The Standardized Mean Difference (SMD) and the 95% confidence intervals were used to define the effect size of different blood indices in survivors and non-survivors. S, survivors; GGT, gamma-glutamyl transferase; NEU, neutrophil; WBC, white blood cell; CRP, C-reactive protein; AST, aspartate aminotransferase; CK, creatine kinase; IL-6, interleukin-6; BUN, blood urea nitrogen; ALT, alanine aminotransferase; PCT, procalcitonin; HBG, hemoglobin; PLT, platelet; LYM, lymphocyte.
Figure 2

Forest plot of pre-existing health conditions (A) and complications (B) in survivors and non-survivors of COVID-19. The Standardized Mean Difference (SMD) and the 95% confidence intervals (CIs) were used to define the prevalence of various risk factors and complications for survivors and non-survivors of COVID-19. Time to hospital, time from symptoms appearance to hospitalization; Cerebrovascular, cerebrovascular disease; Cardiovascular, cardiovascular disease; Renal, renal disease; Liver, liver disease;
BMI, body mass index; COPD, chronic obstructive pulmonary disease; ARDS, acute respiratory distress syndrome; S, survivors.

Figure 3

Correlation-based network analysis. The Pearson correlation threshold of 50% was used to show the network of all variables (A-C). More precisely, the Pearson correlation thresholds of 72% and 93% (D, E) were respectively selected to define the connection between survivors, non-survivors and blood parameters. The Pearson correlation thresholds of 79% and 97% were respectively chosen to assess the relationship between survivors, non-survivors and (F) risk factors or (G) complications. Circles of the network indicate the blood parameters (A, D, E), risk factors (B, F) and complications (C, G). The size of the node reflects the degree of connectivity of the node and the edges display the relationship between the two variables. The thicker edges reveal higher correlations between variables. Nodes with more links are close to each other. Network analysis and visualization was carried out using PAST and Fruchterman-Reingold algorithm or Circular algorithm as a force-directed layout algorithm. Abbreviations in panels A, D, and E: Alb, albumin; HBG, hemoglobin; NEU, neutrophil; PLT, platelet; LYM, lymphocyte; WBC, white blood cells, PCT, procalcitonin; GGT, gamma-glutamyl transferase; CRP, C-reactive protein, CK, creatine kinase; Creat: creatinine, BUN, blood urea nitrogen; Bili, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase. Abbreviations in panels B and F: BMI, body mass index; Time to H, Time From Symptoms Appearance to Hospitalization; Renal, renal disease; Cereb, Cerebrovascular Disease; Liver, liver disease; COPD, chronic obstructive pulmonary disease; Cardio, Cardiovascular Disease. Abbreviations in panels C and G: Fail, failure; Res, respiratory; Liver, liver dysfunction; Sec, secondary; Kidney, acute kidney injury; Cardiac, acute kidney injury.