Risk of mortality in COVID-19 patients: a meta- and network analysis

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Abstract

Introduction: Understanding the most relevant hematological/biochemical characteristics, pre-existing health conditions and complications in survivors and non-survivor will aid in predicting COVID-19 patient mortality.

Materials and Methods: A literature review was conducted for COVID-19 mortality in PubMed, Scopus, and various preprint servers (bioRxiv, medRxiv and SSRN), with 97 observational studies and preprints, consisting of survivor and non-survivor sub-populations. This meta/network analysis comprised 19014 COVID-19 patients, consisting of 14359 survivors and 4655 non-survivors. Meta and network analyses were performed using META-MAR V2.7.0 and PAST software.

Results: The study revealed that non-survivors of COVID-19 had elevated levels of gamma-glutamyl transferase and creatinine, as well as a higher number of neutrophils. Non-survivors had fewer lymphocytes and platelets, as well as lower hemoglobin and albumin concentrations. Age, hypertension, and cerebrovascular disease were shown to be the most influential risk factors among non-survivors. The most common complication among non-survivors was heart failure, followed by septic shock and respiratory failure.

Conclusion: This meta-analysis showed that inexpensive and fast biochemical and hematological tests, as well as pre-existing conditions and complications, can be used to estimate the risk of mortality in COVID-19 patients.

Introduction

Globally, healthcare workers encounter challenges in reducing coronavirus disease of 2019 (COVID-19) severity and mortality.[1] Many subpopulations of patients with mild to non-severe COVID-19 experience serious problems or even death, which is a growing concern.[1,2] According to reports, approximately 19% of COVID-19 patients experienced serious illness and 61.5% died within 28 days of admission, while 50% of hospitalized patients had no significant clinical and medical remission after 10 days.[3–5] Therefore, early diagnosis of patients with a possible serious COVID-19 infection and a high risk of mortality will relieve pressure on medical services, since treating a large number of patients places a significant burden on medical resources. The role of risk prediction is drastically shifting, and it helps to effectively determine if preventive protocols and treatment of positive cases are attempted. Therefore, early prognosis and care for this patient group are crucial to limiting disease progression and death.[1] In general, hematological predictors, risk factors, and potential complications of COVID-19 mortality need further investigation. Understanding the relevance of each risk factor to disease progression and mortality can assist in recognizing at-risk subpopulations and evaluating healthcare quality. Efforts should also be made to prepare for risk groups and estimate the risk of fatality in order to better understand the true patterns of mortality.[6] For example, age and gender have been identified as well-known risk factors for severe COVID19 outcomes: about 90% of COVID-19-related deaths in the UK have

occurred in people over the age of 60, with 60% occurring in men.[7] Pre-existing conditions (such as tobacco use, coronary disease, hypertension, diabetes, respiratory and renal disease, and cancer) have also been related to an elevated risk of death.[6] For example, the Chinese Center for Disease Control and Prevention reported in a survey of 44,672 people (1,023 deaths) that cardiovascular diseases, hypertension, diabetes, respiratory diseases, and cancers were associated with a high risk of death from COVID-19.[8]

The aim of this meta-analysis was to assess the relevance of hematological/biochemical indices, pre-existing conditions, and complications to COVID-19 mortality, assuming an association between these factors. Furthermore, the association between hematological/biochemical indices, pre-existing conditions, and complications in COVID-19 non-survivors was investigated. The primary outcomes of this study were COVID-19 mortality and survival, and exposures included pre-existing conditions (such as age, gender, smoking, alcohol consumption, and so on) and comorbidities (i.e., hypertension, cerebrovascular diseases, diabetes, any comorbidities, cardiovascular diseases, renal diseases, chronic obstructive pulmonary disease (COPD), cancer, and liver diseases).

A network analysis was also used to estimate complex patterns of interaction,[9] to assess the specific structure of interrelationships between various factors, and to classify the degree of centrality and connectivity of patient characteristics/prognostic features to COVID-19 mortality.

Methods

Assessment of multicollinearity and correlation in influencing factors

The variance inflation factor (VIF) was used to determine whether any comorbidities or hematological and biochemical indices contribute to complications in COVID-19 patients. VIF is used to calculate the amount of multicollinearity in variables, i.e., influencing factors. In addition, the bivariate Pearson correlation was used to assess the association between influencing factors (i.e., blood indices and comorbidities) and complications. Correlation is significant at the 0.05 level (Bonferroni-corrected P value). Since the Anderson–Darling test confirmed that the data were normal, the Pearson correlation was used for bivariate analysis.

Search strategy

A literature review was performed between December 2019 and April 2020 (no language restrictions were applied) in PubMed, Scopus, and various preprint servers (bioRxiv, medRxiv and SSRN) using MeSH keywords/terms, such as “COVID-19” AND “novel coronavirus” AND “new coronavirus” AND “coronavirus-2019” AND “COVID-2019” AND “SARS-COV-2” AND “2019-nCOV”.

Data extraction and analysis

The results of the search strategy were initially evaluated using abstracts and titles. Following that, the full text of the related articles was then checked using the inclusion and exclusion criteria. The final list of papers included was contrasted, and the disagreements were settled by a consensus discussion between authors. Three researchers (RK, AM, and AMR) independently extracted data such as the type and date of release, country, sample size, age, sex, blood indices and parameters, pre-existing health conditions, and complications. Using a structured spreadsheet, three authors (RK, AMR, and MS) tested the consistency of the data obtained. The Anderson–Darling test was used to determine if the resulting data was normal. For Meta-analysis and network analysis, META-MAR V2.7.0 and PAST were used, respectively. The effect size of various hematological/biochemical indices, risk factors (pre-existing conditions), and complications in COVID-19 survivors and non-survivors was defined using the Standardized Mean Difference (SMD). Due to heterogeneity, random-effect models were used to calculate the weighted mean effect sizes and 95% confidence interval (CI).

Inclusion criteria

Figure 1 shows the flow diagram of studies assessed for inclusion. We collected data from research that recorded, at least, one of the following criteria, such as hematological/biochemical indices, pre-existing conditions, demographic factors, complications, and clinical outcomes (i.e., mortality or survival).

Pre-existing health conditions were described as conditions that existed prior to the patient's arrival at the emergency department/hospital, and the decision was based on the medical record.[10] Complications (i.e., heart failure, septic shock, acidosis, respiratory failure, coagulopathy, acute renal injury, liver dysfunction, and secondary infection) were unanticipated events, diseases or symptoms triggered by the combination of a given disease[11] and pre-existing conditions. Importantly, complications can occur even though appropriate precautions are taken. COVID-19 has been found to cause serious medical complications and death, especially in elderly patients and people with pre-existing health conditions.

Exclusion criteria

Data from over 200 reported clinical studies and preprints were screened. Following a comprehensive review of the data in figures and tables, 105 reports were excluded due to a lack of survivor or non-survivor sup-groups, examining infants/children/pediatrics, or having no DOI. This resulted in 97 eligible observational studies (19014 patients)[4,12-107], with survivors (n = 14359) and non-survivors (n = 4655) as strict subpopulations.

The reference list of papers and other systematic reviews were also scrutinized. The hematological and biochemical indices were checked to ensure they were the same, unless otherwise converted to the same unit. In terms of inclusion and exclusion criteria, paper selection resulted in different sample sizes for different parameters between survivors and non-survivors. These studies included patients from China, Italy, Scotland, the United States, UK, Japan, Singapore, South Korea, Iceland, Chile, the Netherlands, and Germany. **Supplementary Table 1** describes the characteristics of the studies selected for meta-analysis.

Heterogeneity and risk of bias in individual studies

The I^2 and Tau^2 statistics were used to determine statistical heterogeneity.[108] According to the Cochrane's handbook for Systematic Reviews of Interventions, the I^2 expresses the proportion of variance due to heterogeneity (i.e., 30% to 60%, 50% to 90% and 75% to 100% correspond to moderate, substantial and considerable degrees of heterogeneity, respectively).[109] In addition, a meta-regression analysis was performed to assess the effect of variables on the effect size. The Z-test and its associated P-values determined whether the observed prevalence varied from zero percent.

Moreover, the Quality in Prognostic Studies (QUIPS) tool, a non-validated instrument with space for personal interpretation, was employed to assess the risk of bias in the studies.[110,111] The Cochrane Methods Prognosis group recommends the QUIPS tool for prognosis research because it tackles all common sources of bias.[110,111] Based on this, we concluded that the QUIPS method was sufficient for determining bias risk. Two team members (AM and RK) independently assessed the risk of bias in each study and classified it as low, moderate or high risk.[112] Any disagreements were resolved by consensus. The QUIPS tool includes domains on: study participation, study attrition, prognostic factor measurement, outcomes measurement, statistical analysis and reporting, and study confounding.[113]

Studies with a low risk of bias had thorough explanations of the population, design, and measures; as well as clear descriptions of how the measure was executed, equipments used, and how the data were interpreted. In studies with a medium risk of bias, there was some bias, but not enough to invalidate the data. These studies do not meet all of the requirements for a low risk of bias ranking, but no error is likely to result in significant bias. Studies with a high risk of bias had major flaws, indicating different forms of bias that might invalidate the findings. The high-risk study included one or more crucial or “fatal” flaws in its design, analysis, or reporting, as well as significant amounts of missing information.[112] The findings of the risk of bias assessment were identified in the narrative synthesis but were not included in the meta-analysis.

Network analysis

Data from variable, such as blood indices, pre-existing conditions (i.e., male, liver diseases, renal diseases, cerebrovascular diseases, diabetes, COPD, drinking, smoking, any comorbidities, cancer, cardiovascular diseases, hypertension), or complications (i.e., heart failure, respiratory failure, secondary infection, coagulopathy, acidosis, liver dysfunction, septic shock, acute cardiac injury, and acute kidney injury) were used for network analysis as the proportion of each parameter obtained from each study. In terms of parameters, such as age, time to hospital and BMI, the mean of each parameter obtained from each study was used for network analysis. Then data were classified in a binary manner for network analysis, with 0 and 1 representing mortality and survival, respectively. The PAST software (accessible at: http://folk.uio.no/ohammer/past) was used to implement the Circular and Fruchterman-Reingold algorithms as a force-directed layout algorithm. The Anderson–Darling test confirmed the normality of data, so the Pearson similarity index was used as a parametric index for network analysis. The Pearson

correlation threshold of 50% (as a basic level) was used to establish the network of all variables. To be more specific, Pearson correlation thresholds of 72% and 93% were respectively selected to characterize the relationship between blood indices and outcomes (i.e., survivors or non-survivors, Fig. 2 d, e). Pearson correlation thresholds of 79% and 97% were selected to determine the relationship between risk factors (pre-existing conditions) or complications and outcomes (i.e., survivors or non-survivors, Fig. 2 f, g). These cutoff points were selected because there was no subsequent interaction among the variables after these thresholds. The node's size represents its degree of connectivity, and the edges display the relationship between the two variables. The thicker edges indicate stronger correlations between variables. Nodes with more links are closer together. Small nodes and thin edges represent small values.

Results

Data characteristics and multicollinearity among the influencing factors

Table 1 presents the clinical outcomes, and **Appendix 1** describes the data collection process for Table 1. The patient's age (n = 9375) ranged from 25.3 to 80.0 years (49.8; $CI_{95\%}$ [46.9, 52.7]). There were 5448 survivors (age: 46.6; $CI_{95\%}$ [44.2, 48.9]) and 3927 non-survivors (age: 71.5; $CI_{95\%}$ [66.4, 76.5]). Males outnumbered females in the non-survivor population (33.3 vs. 17.7%).

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 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	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 ($CI_{95\%}$)			
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 (172.06, 187.08)	6572, 187.76 (181.22, 194.32)	690, 149.92 (132.87, 166.96)
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 ($CI_{95\%}$)			
Hemoglobin g/L	6379, 132.58 (130.14, 135.01)	5887, 134.44 (131.95, 136.92)	492, 124.03(118.72, 129.34)
Albumin g/L	3491, 36.75 (33.71, 39.79)	3040, 38.51 (3460, 42.41)	451, 31.93 (30.15, 33.70)
Alanine aminotransferase U/L	5156, 29.41 (25.22, 33.60)	4705, 29.27 (24.30, 34.23)	548, 30.09 (23.38, 36.80)
Aspartate aminotransferase U/L	5020, 33.75 (29.17, 38.32)	4526, 30.06 (26.48, 33.65)	494, 50.68 (32.23, 69.13)
Gamma-glutamyl transferase U/L	1642, 19.35 (5.06, 33.65)	1582, 11.06 (2.69, 19.43)	60, 52.5 (36.88, 68.12)
Total bilirubin μmol/L	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,	3706, 73.20 (64.34,	338, 101.0 (56.75,

	90.69)	82.06)	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)

The bivariate Pearson correlation (**Supplementary Table 2**) revealed that certain hematological and biochemical indices were associated with complications in COVID-19 patients. Higher gamma-glutamyl transferase (GGT) levels (r = 0.91) and lower platelets (PLT) numbers (r = -0.75) were significantly associated with respiratory failure. Heart failure was significantly associated with higher GGT levels (r = 0.88), higher white blood cells (WBC) counts (r = 0.77), higher blood urea nitrogen (BUN) levels (r = 0.89), and lower PLT counts (r = -0.83). Septic shock was significantly associated with higher creatinine (r = 0.75) and lower PLT counts (r = -0.76). Acute cardiac injury was significantly correlated with higher GGT level (r = 0.75), higher creatinine level (r = 0.70), and lower PLT counts (r = -0.85). Acute kidney injury was

significantly correlated with higher GGT levels (r = 0.77). Secondary infection was associated with higher neutrophil (NEU) counts (r = 0.76).

Moreover, we found relationships between certain pre-existing health conditions and complications in COVID-19 patients (**Supplementary Table 3**). According to the Pearson analysis, age (r = 0.80), comorbidities (r = 0.78), and cardiovascular disease (r = 0.79) were all significantly correlated with heart failure in COVID-19 patients. Furthermore, cerebrovascular diseases were significantly correlated with heart failure (r = 0.75) and septic shock (r = 0.73) in COVID-19 patients.

Furthermore, we found a very high VIF in blood indices as influencing variables for COVID-19 patient's complications (**Supplementary Table 4**). In addition, COPD and cerebrovascular disease were pre-existing health conditions that contributed to elevated collinearity (**Supplementary Table 5**). This suggested that complications in COVID-19 patients could be caused by pre-existing health conditions or changes in blood parameters.

Heterogeneity and publication bias

Clinical heterogeneity can lead to statistical heterogeneity, and can be observed using techniques like the I^2 index or meta-regression.[114] The I^2 index was high (100%) across all meta-analysis (Fig. 3–5). In an attempt to better explain heterogeneity, multivariate meta-regression analysis revealed substantial heterogeneity in the outcome of interest (i.e. mortality and survival), which may be attributed to heterogeneity in exposure sources, such as blood indices, pre-existing conditions, or complications (Table 2).

Table 2
The Multivariate meta-regression analysis.

Variable	t	$CI_{95\%}$	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

Supplementary Table 6 shows the risk of bias assessment using QUIPS tool for all the observational studies used in the meta-analysis (n = 97). The majority of these 97 studies scored well (low risk of bias) in three of the QUIPS tool's six domains: study attrition, prognostic factor measurement, and outcome measurement. The other three domains, namely study participation, study confounding and statistical analysis, were more problematic. According to the QUIPS tool, the majority of studies (74/97) used in this analysis had a moderate to high risk of bias.

Quantitative synthesis of data

As shown in Table 2 and **Appendix 2**, the multivariate meta-regression analysis revealed that the risk factors (exposures) (t, 4.77; $CI_{95\%}$ [0.64, 1.68]; P = 0.000) were associated with the estimated intervention effect on COVID-19 mortality (outcome). Biochemical/hematological indices (t, 1.85; $CI_{95\%}$ [-0.11, 1.60]; P = 0.083) tended to be associated with the estimated intervention effect on COVID-19 mortality. Moreover, complications were linked to the estimated intervention effect on COVID-19 mortality (t, 3.80; $CI_{95\%}$ [1.07, 4.36]; P = 0.005).

Meta-analysis of individual hematological indices

Figure 3 displays the individual Hedges'g for each blood parameter, along with the corresponding $CI_{95\%}$. Since there was substantial statistical heterogeneity (P = 0.000), a random-effect model was used to evaluate the effect sizes (**Appendix 2)**.

Non-survivor COVID-19 had higher number of NEU (2.81[2.70, 2.91]; Z = 53.97; P = 0.000) and WBC (2.38 [2.29, 2.47]; Z = 50.05; P = 0.000) counts, as well as higher 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), c-reactive protein (CRP) (2.28 [2.19, 2.38]; Z = 46.23; P = 0.000), aspartate aminotransferase (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), interleukin (IL-6) (0.95 [0.82, 1.08]; Z = 14.04; P = 0.000), 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) levels.

Compared to survivors, non-survivors had a smaller number of lymphocyte (LYM) (-1.74 [-1.83, -1.66]; Z = 41.36; P = 0.000) and PLT (-1.55 [-1.63, -1.47]; Z = 36.89; P = 0.000), as well as lower 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) levels.

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

Figure 4 shows the meta-analysis forest plot in terms of pre-existing conditions based on the random effect model (**Appendix 2**). Patient's 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 = 0.0001), 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.

Meta-analysis identifies common complications among COVID-19 non-survivors

The prevalence of current complications was higher in COVID-19 non-survivors (2.71 [1.91, 3.51]; Z = 6.66; P = 0.000; I^2 = 100.0%; Tau^2 = 1.48) than survivors (Fig. 5, **Appendix 2**). Heart failure was the most

common complication in COVID-19 non-survivors (7.40 [7.15, 7.64]; Z = 58.45; P = 0.000), 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).

Network analysis supports the results of the meta-analysis

At a cutoff point of 50%, the network correlation for blood indices (Fig. 2a), risk factors (Fig. 2b**)**, and complication (Fig. 2c**)** was demonstrated. The number of PLT and LYM, as well as hemoglobin concentration, was associated with COVID-19 survivors at a maximum cutoff point of 72% where all parameters were disconnected after this cutoff point (Fig. 2d). At a maximum cutoff point of 93%, the number of NEU, GGT concentration, and the incidence of COVID-19 mortality were all related (Fig. 2e).

COVID-19 mortality was discovered to be linked to patient's age, hypertension, cerebrovascular disease, diabetes, any comorbidities, cardiovascular disease (as pre-existing conditions, at a maximum cutoff point of 79%, Fig. 2f) and heart failure (as a complication, at a maximum cutoff point of 97%, Fig. 2g), according to the network analysis. These findings corroborated the results of the meta-analysis. The network analysis was able to map the association between all parameters, including mortality, blood indices, complications and pre-existing conditions, while the meta-analysis only ranked the potent factors involved in COVID-19 mortality.

Discussion

According to the findings of this study, certain hematological/biochemical markers, pre-existing conditions, and complications were associated with mortality in COVID-19 patients and should be taken into account for patient care. Furthermore, a multilevel approach based on network analysis and correlation analysis will aid in the deeper understanding of interactions within and between exposures and outcomes.

Our meta-analysis revealed that COVID-19 non- survivors had higher NEU and lower LYM counts. According to the study of Qin et al.[115], lymphopenia (low LYM counts) and an increased NEU–LYM ratio were frequently observed in patients with severe COVID-19. This was also a more common characteristic in COVID-19-related death.[12] Inflammatory mediators, such as IL-2 and IL-6, can cause serious lymphopenia, resulting in LYM loss.[115] Qin et al.[115] indicated that SARS-CoV-2 infection affects LYMs, resulting in secondary bacterial infections and an increased NEU count. Indeed, neutrophilia (NEU count > 7.5×10^9/L) has been linked to bacterial inflammation, cytokine storm, and hyper-inflammation[116], all of which play significant pathogenetic roles in COVID-19 infection.[115,117] In line with previous study, we found an increase in WBC and NEU counts, as well as a decrease in LYM in COVID-19 non-survivors.[32]

Therefore, changes in WBC, NEU, and LYM counts were associated with the risk of death in COVID-19 patients.

GGT and AST concentrations were found to be higher in non-survivors in this Meta-analysis. Concentrations of alanine aminotransferase (ALT), AST, and GGT have been found to be markedly greater in dead patients than in recovered patients.[32,118] In a previous study[119], GGT levels were shown to be elevated in COVID-19 patients. Higher GGT levels were associated with lower albumin and higher CRP, ALT, and ALP levels in the 82 COVID-19 patients who did not have chronic liver disease or an alcohol history. This elevation suggests that the liver is involved in COVID-19 patients.[120] Bernal-Monterde et al reported that increased levels of GGT and ALP, as well as decreased albumin levels, were associated with increased risk of death in COVID-19.[119] Indeed, viral infections that commonly affect the respiratory tract cause hypoxia.[119] In patients with pandemic H1N1 influenza infection, serum levels of ALT, AST, and GGT were found to be positively correlated with hypoxia.[121] These findings were consistent with our Pearson analysis, which found a strong relationship between GGT levels and respiratory failure (r = 0.91) or heart failure (r = 0.88), but not with liver failure (r = 0.14). As mentioned above, heart failure was found to be the most common complications in non-survivors. Increased ALT, AST, and GGT levels in COVID-19 patients, particularly in non-survivors, appeared to be caused by heart failure-induced hypoxia, although further research is required to understand the details.

Since meta-analysis cannot establish relationships between variables, Pearson correlation and VIF were used to determine relationships and multicollinearity among influencing factors (i.e., blood indices and pre-existing conditions). Data showed that some complications found in COVID-19 patients, such as heart failure, were correlated with pre-existing conditions (i.e., age), as well as lower PLT and LYM counts or higher GGT levels. Moreover, network analysis was used to visualize the structure of relationships between factors affecting the COVID-19 outcome. Indeed, this approach will help in explaining the relationships between variables like blood indices, pre-existing conditions and complications, as well as the relationships between these variables and the outcome, i.e., mortality and survival. Network analysis identified a link between heart failure and increased mortality in COVID-19 patients. Therefore, combining a multi-level analysis with meta-analysis would help to achieve a better understanding of the relationships between patient characteristics and outcome.

This meta-analysis found greater concentrations of GGT, BUN, and creatinine in non-survivors, indicating that SARS-CoV-2 has a clear effect on human kidneys.[122] A study of 701 patients revealed that elevated serum creatinine levels on admission were associated with severity due to severe coagulation pathway abnormalities.[123] Furthermore, increased urea levels had comparable, if not greater, impacts on hazard ratios. Another kidney failure marker is GGT[124], which is a cell-surface enzyme that metabolizes extracellular glutathione, the primary antioxidant in mammalian cells.[125] A high level of GGT is often regarded as an early and marker of oxidative stress[126] and it can be a source of reactive oxygen species in the presence of iron[126,127]. This, in turn, may result in renal vasoconstriction, salt retention, and subsequent kidney damage.[128] Abnormalities in the routine urine test performed on admission have been

linked to disease progression and an increased risk of in-hospital death.[129] As a result, renal abnormalities on admission revealed a greater risk of deterioration, requiring proper triaging[129]; further research is needed.

Current evidence indicates that complications in COVID-19 patients may be caused by the virus's direct effect, immune-mediated inflammation or drug-induced toxicity, assuming that the majority of patients were given high doses of antibiotics, antiviral drugs, and steroids.[118] The Pearson correlation revealed that some complications (e.g., heart failure) in COVID-19 patients were associated with both pre-existing conditions (such as age and cerebrovascular disease) and blood parameters (such as PLT and LYM numbers); however, it is unclear to what extent complications are exacerbated by COVID-19 infection. Zhou et al.[12] found that sepsis was the most common complication, followed by respiratory failure, ARDS, and heart failure. In our meta-analysis, heart failure and septic shock were the most common complications diagnosed in dead patients. Sahu et al.[130] found that COVID-19 patients who died from infection had a gradual increase in CRP levels. Li et al.[131] suggested that direct viral disruption, hyper-inflammation, and hypoxemia may all contribute to cardiac injury. Serum CRP, as an inflammatory marker, has been linked to disease severity[132], lung lesions[133], acute kidney damage[134], and cardiac injuries[135] in COVID-19 patients. Our findings suggested that CRP is a potential biomarker for COVID-19 mortality, highlighting the importance of closely monitoring CRP changes.

According to the current mea-analysis, COVID-19 non-survivors had a lower PLT count as well as lower hemoglobin and albumin concentrations. Our findings corroborated the previous study that showed a decrease in the number of PLTs in non-survivors but an increase in survivors.[136] Zhao et al.[136] found that PLT count may dramatically reflect pathophysiological changes in COVID-19 patients, and an early decrease in PLT was associated with COVID-19 mortality. Viral infection appears to have damaged lung tissue, resulting in PLT activation, aggregation, and entrapment, which lead to thrombosis and increased PLT consumption.[136] PLTs have a short life cycle (8–10 days) and very few PLTs are preserved in bone marrow;[137] it may be responsive to the severity of the patient's conditions. Furthermore, viruses may cause a decrease in PLT production as a result of megakaryocyte infection, which may contribute to megakaryocyte apoptosis.[138] Therefore, PLT measurement may be beneficial in the care of COVID-19 patients, leading to a much earlier and more effective prognosis.

Liu et al.[139] reported that COVID-19 patients had the most consistent decreases in hemoglobin levels. The first case of COVID-19 in the United States revealed a minor decrease in hemoglobin on day 6 of illness.[30] Notably, patients with a composite outcome (i.e., ICU admission, invasive ventilation, and death) had lower hemoglobin levels.[18] Inflammation caused by SARS-CoV-2 can disrupt erythropoiesis and decrease hemoglobin production. For example, IL-6 has been shown to be elevated in severe COVID-19 infection[117] and disrupts hemoglobin production.[140] The current meta-analysis revealed that COVID-19 non-survivors had higher levels of IL-6. Our findings suggested that lower hemoglobin levels may be attributed to higher levels of IL-6, which requires further study in COVID-19 patients.

Age, hypertension, cerebrovascular disease, and diabetes were found to be common risk factors among non-survivors in our meta-analysis. In accordance with the previous study[12], we found that non-survivors were older (46.6 vs. 76.5 years) and had a greater proportion of hypertension and diabetes than survivors. ACE2 has been shown to be over-expressed in diabetic or hypertensive patient.[141,142] Diabetes and hypertension are treated with ACE inhibitors and angiotensin II type-I receptor blockers, which causes an increase in ACE2 expression and infection with COVID-19.[142,143] Moreover, another study found a link between cerebrovascular disease and the risk of death in COVID-19 patients[144], which was consistent with our findings. SARS-CoV-2 has been shown to have neuro-invasive properties and the ability to spread from the respiratory system to the central nervous system.[145] COVID-19 can also cause cerebrovascular complications as a result of inflammation, hypoxia, and diffuse intravascular coagulation.[146] Therefore, pre-existing conditions, such as cerebrovascular disease, diabetes and hypertension, may contribute to a higher risk of death in COVID-19 patients. Thus, COVID-19 patients with these pre-existing conditions should be closely monitored.

We found that exposures, i.e., demographic factors (e.g., age, gender, smoking, and alcohol consumption), as well as pre-existing conditions or comorbidities, were the primary sources of heterogeneity in this study. This may be due to inconsistencies in study designs, large differences in sample size, and differences in study characteristics. In this study, we focused on a large particular subgroup (e.g., survivors or non-survivors, which included patients of various ages, genders, and pre-existing health conditions). This basically results in heterogeneity as confirmed by I^2 index and multivariate meta-regression analysis. Moreover, the high heterogeneity in this meta-analysis may be explained by studies that reported either individual patient data or the mean for a cohort of patients. Other factors such as heterogeneity in survival group (which included mild to severe cases) and non-survival groups (who had various treatments) can also lead to publication bias.[147] According to the QUIPS assessment, the majority of the studies used had a moderate risk of bias. The majority of the studies included in this meta-analysis lacked data on the impact of blood parameters and pre-existing conditions on comorbidities, as well as the relationship between such comorbidities and mortality. QUIPS assessment suggested that future research should consider experiments with adequate statistical power and appropriate statistical methods to address the potential interrelationships between all prognostic factors, complications, and outcomes in COVID-19 patients.

In this study, we used a multi-level approach, including meta-analysis, bivariate analysis, and network analysis, to establish potential associations between exposures (e.g., patient characteristics) and outcomes (e.g., mortality or survival). However, this meta-analysis has several limitations. We did not perform sensitivity and subgroup analyses, despite the inclusion of studies with patients at various stages of COVID-19. Moreover, the data were obtained from a variety of countries, including developed and developing nations, with varying levels of medical facilities, suggesting different management guidelines for related medical comorbidities.

In conclusion, some pre-existing conditions and biochemical/hematological indices were associated with a higher risk of death in COVID-19 patients. Also, the data showed that complications, such as heart failure and septic shock, were more common in COVID-19 non-survivors, which could be attributed to patient characteristics, emphasizing the importance of pre-screening at triage.[148]

Declarations

Authors' contributions

SFK, EB, and AMR extracted data; RK, AM, 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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Availability of data and material

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

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Figures

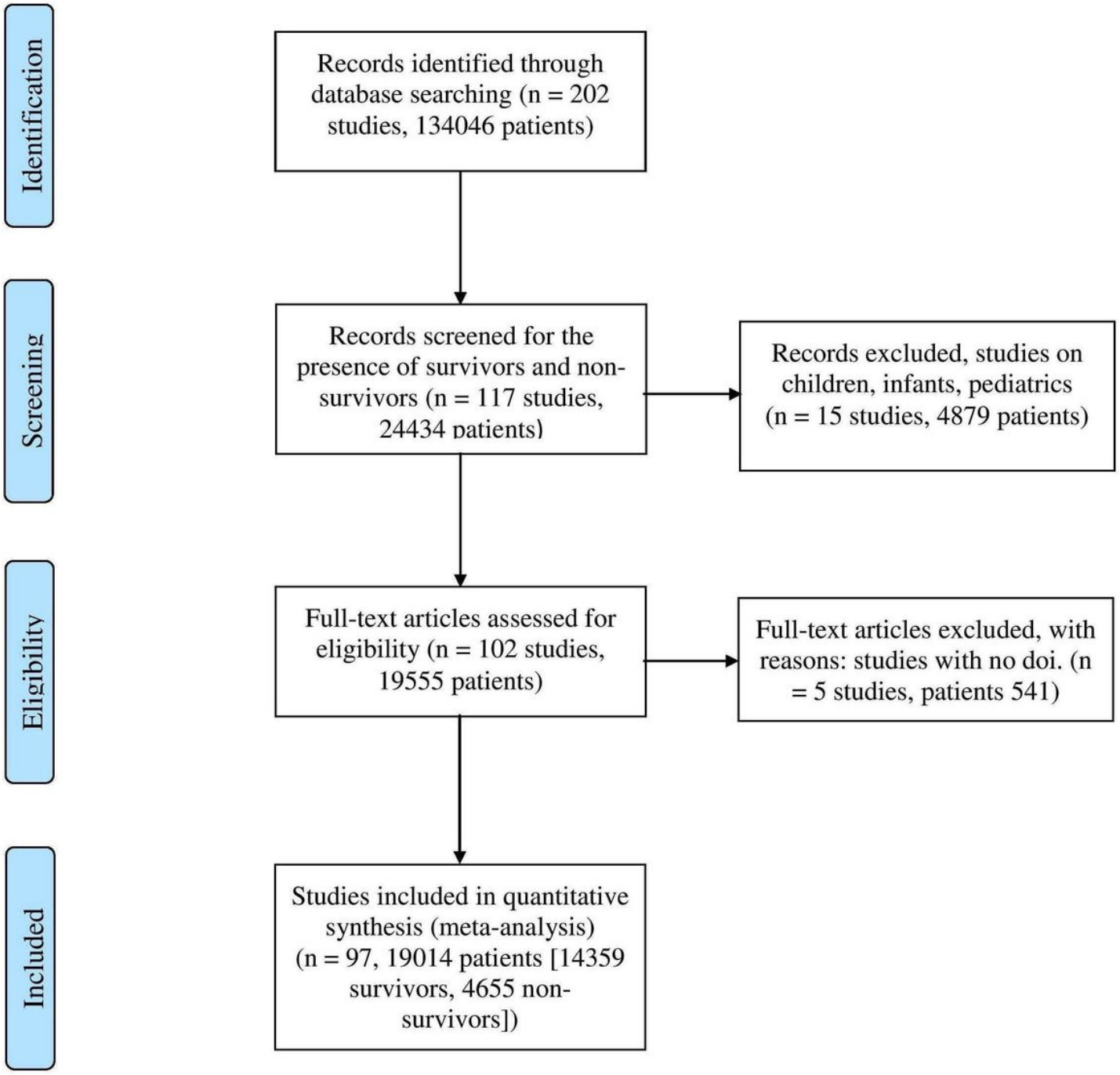

Figure 1

PRISMA flow diagram of the studies identified, screened, reviewed, and included in the meta-analysis.

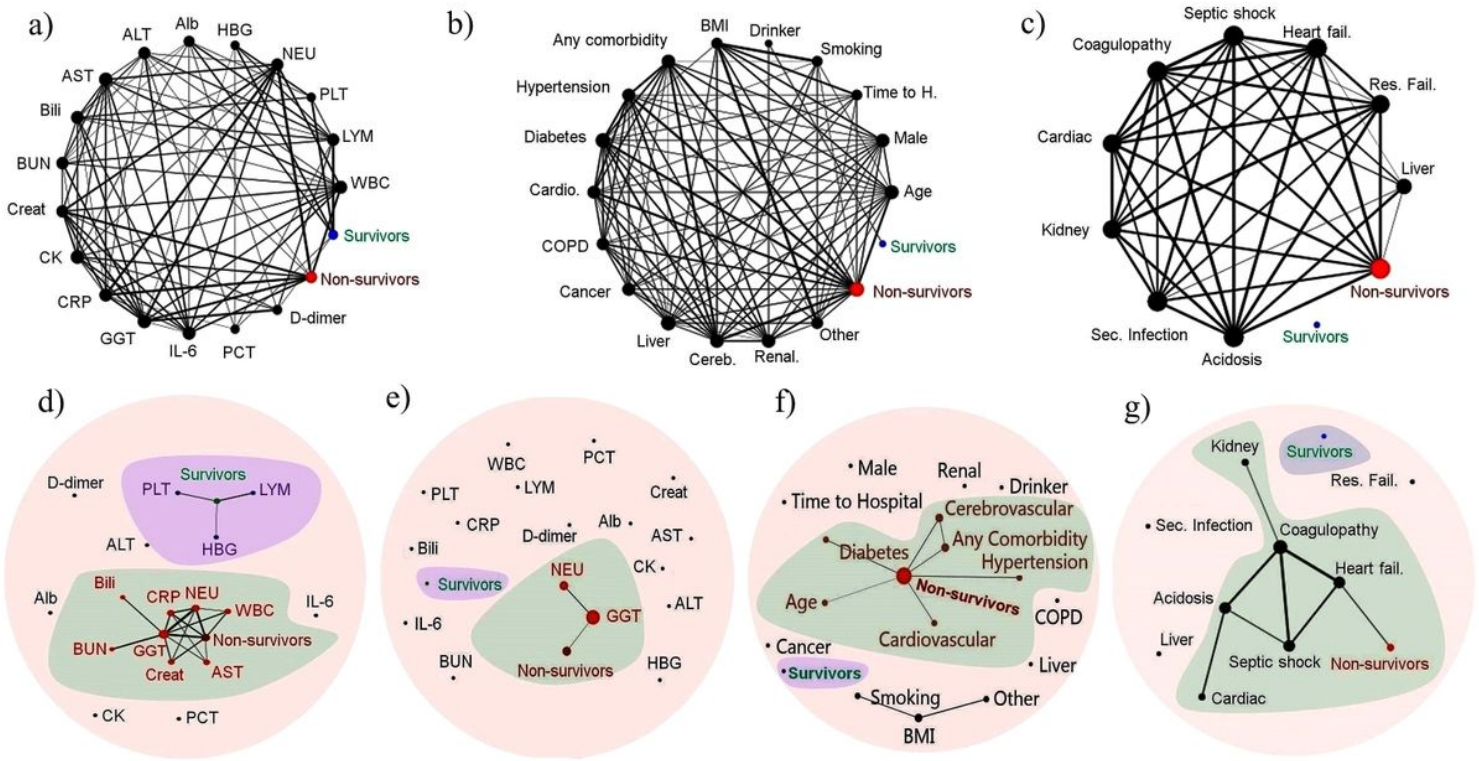

Figure 2

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.

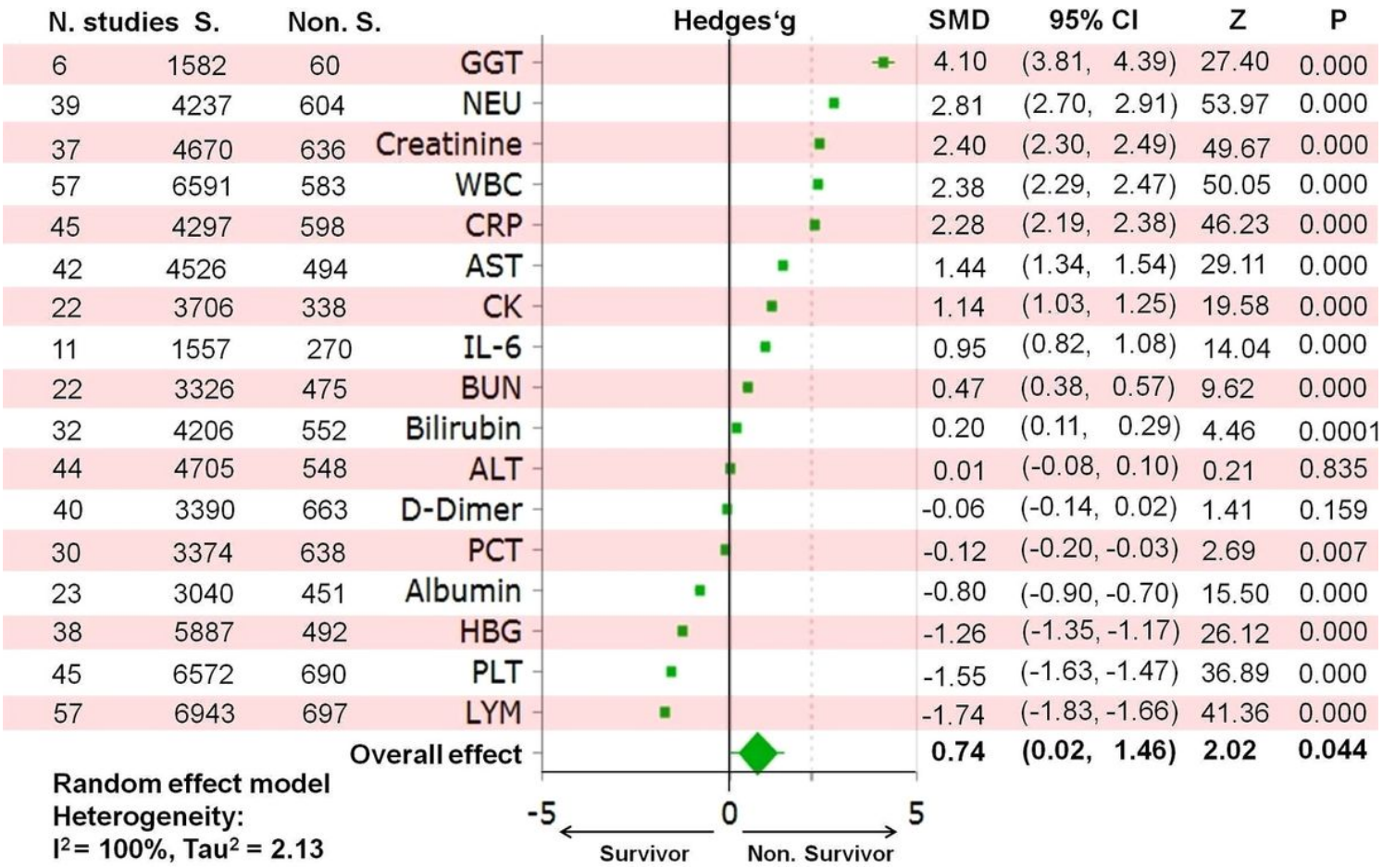

Figure 3

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.

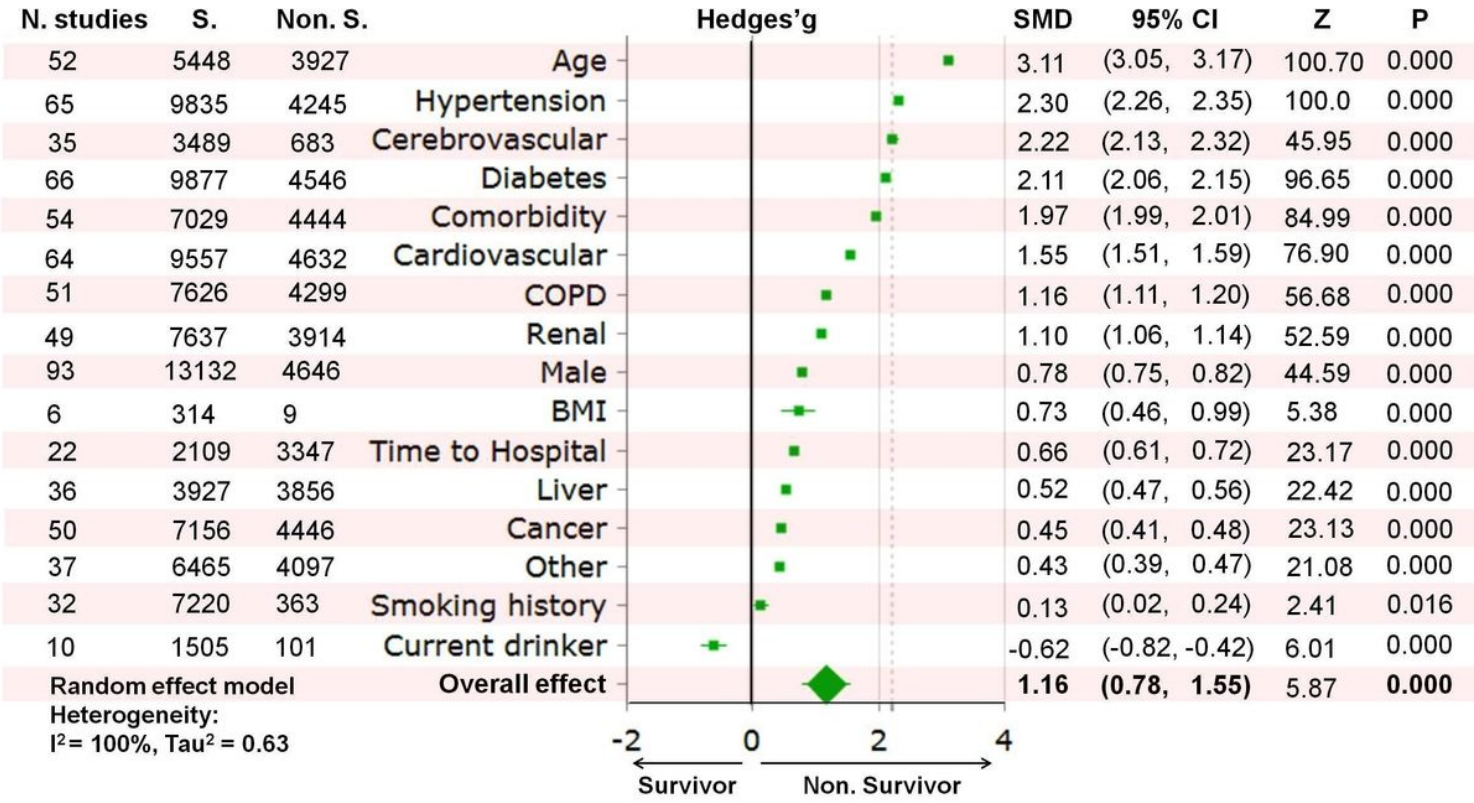

Figure 4

Forest plot of pre-existing health conditions 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; S, survivors.

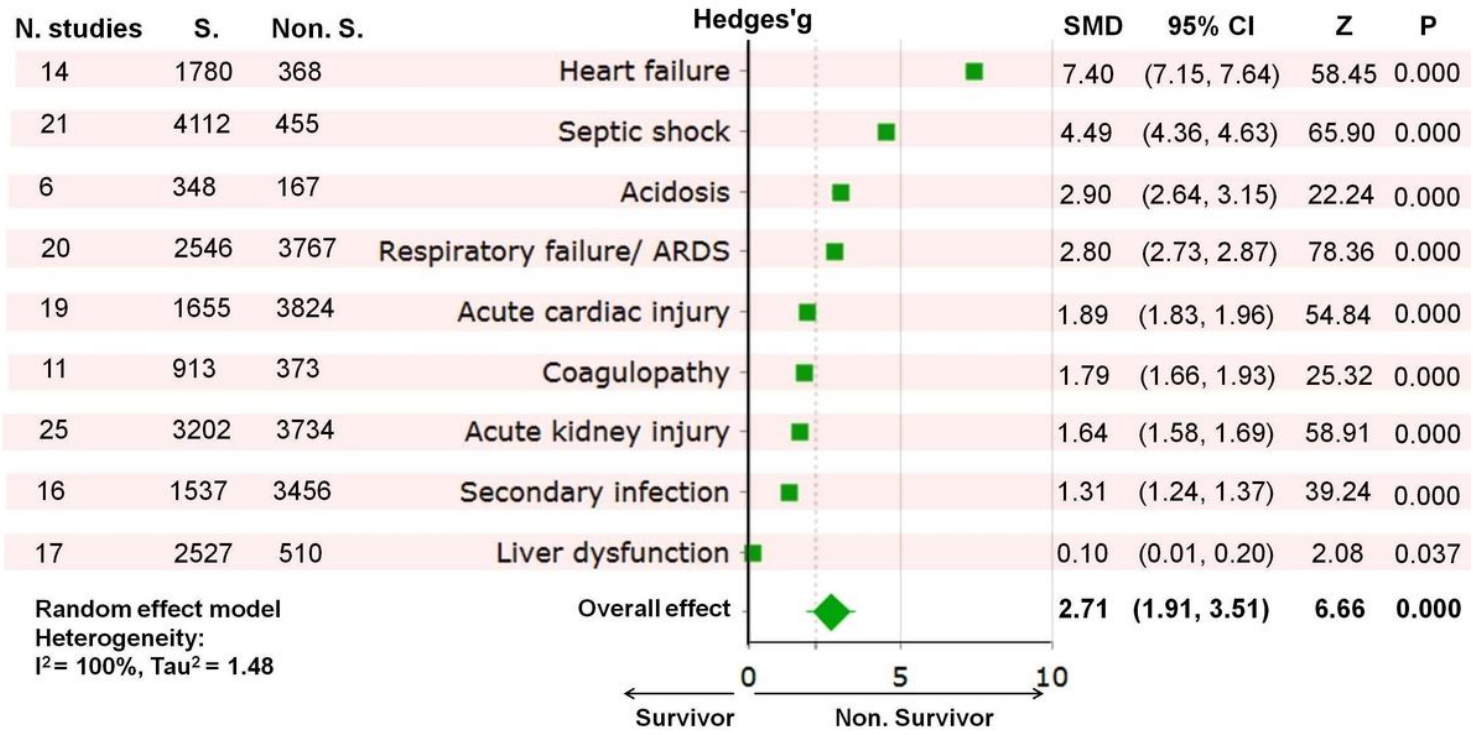

Figure 5

Forest plot of complications 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. ARDS, acute respiratory distress syndrome; S, survivors.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryInformation.RiskofmortalityinCOVID19patientsametaandnetworkanalysis.pdf