REVIEW

Clinical characteristics, laboratory outcome characteristics, comorbidities, and complications of related COVID-19 deceased: a systematic review and meta-analysis

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Abstract

Background At present, novel coronavirus disease 2019 (COVID-19) has become a serious global public health problem. The current meta-analysis aimed to find risk factors for the COVID-19-related death, helping to enhance the efficacy and reduce the mortality of COVID-19.

Methods We searched PubMed, Embase, medRxiv, and Cochrane Library for articles published between January 1, 2020, and April 13, 2020. We statistically analyzed the risk factors of the COVID-19 deceased with meta-analysis.

Results A total of 2401 patients in 15 articles were included in this study. Meta-analysis showed that 66.6% of COVID-19 deceased were male, with a median age of 69.9 years. Common symptoms of deceased included fever (70.6–100%), dyspnea (38.89–85.7%), cough (22.4–78%), and fatigue (22–61.9%). The incidence of hypertension, chronic cardiovascular disease, diabetes, and chronic cerebrovascular disease among the COVID-19 deceased were 38.56% (95% confidence interval (CI) 25.84 ~ 52.12%), 17.54% (95% CI 13.38 ~ 21.69%), 22.2% (95% CI 19.30 ~ 25.10%), and 15.58% (95% CI 10.05 ~ 21.12%), respectively. Compared with the surviving COVID-19 patients, the deceased had lower platelet levels (mean difference (MD) = − 39.35, 95% CI − 55.78 ~ − 22.93) and higher C-reactive protein (CRP) (MD = 80.85, 95% CI 62.53 ~ 99.18) and lactate dehydrogenase (LDH) (MD = 246.65, 95% CI 157.43 ~ 335.88) at admission. The most common complications of the deceased were acute respiratory distress syndrome (ARDS) (OR = 100.36, 95% CI 64.44 ~ 156.32) and shock (OR = 96.60, 95% CI 23.80 ~ 392.14).

Conclusion Most of the COVID-19 deceased were elderly males. Fever, dyspnea, dry cough, fatigue, hypertension, chronic cardiovascular and cerebrovascular disease, diabetes, and laboratory examinations showed low levels of platelet content, increased CRP and LDH were associated with the risk of dying. ARDS and shock were risk factors for death in COVID-19 patients.

Keywords Death · COVID-19 · Severe acute respiratory syndrome coronavirus 2 · Meta-analysis

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Introduction

Since the outbreak of the new coronavirus (severe respiratory syndrome coronavirus 2 [SARS-CoV-2], formerly known as 2019-nCoV) in December 2019 in Wuhan, Hubei Province, China [1–3], confirmed cases have appeared in countries around the world. Genome sequencing and phylogenetic analysis show that SARS-CoV-2 is a new type of human-infected β-coronavirus. Bats are presumed to be the original host of this zoonotic virus, but there is no evidence that there is an intermediate host that promotes human infection with the virus [4]. According to the Coronavirus disease 2019 (COVID-19) Situation Report–84 [5] released by

the World Health Organization (WHO) on April 13, there were 1,773,084 confirmed cases of COVID-19 and 111,652 deaths worldwide. Patients infected with SARS-CoV-2 were prone to death when they develop severe pneumonia, pulmonary edema, ARDS, or multiple organ failure (such as shock, acute heart injury, and acute kidney injury) [6]. The increasing number of deaths forces us to find out the clinical characteristics of patients at risk of dying, so that clinical workers can take corresponding rescue measures in the early stage to reduce the occurrence of death.

At present, more and more retrospective studies have reported the clinical information of COVID-19 dead patients. Here we will provide systematic assessment and details, not only to assess the disease coexistence of all dead patients, the results of laboratory examinations, but also to compare the potential disease risks between survival and death patients. These results may assist management in developing prevention policies to address COVID-19 and its key results.

Methods

Search strategy and selection criteria

Literature search in the PubMed, Embase, medRxiv (https://www.medrxiv.org/), and Cochrane Library from January 1, 2020 to April 13, 2020, using a combination of the following keywords: "SARS-CoV-2" or "2019-nCoV" or "COVID-19" or "new coronavirus" or "Wuhan Coronavirus" and "die" or "death" or "fatality" or "mortality" or "decease" or "survive" or "survivors". Restrict publication language to English. In addition, to ensure the comprehensiveness and accuracy of the research, we also consulted the references of the included literature. This work was independently completed by two authors (Peishan Qiu and Yunjiao Zhou). Disagreements were resolved by the third investigator (Fan Wang). All the search results were evaluated according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement.

Inclusion and exclusion criteria

The inclusion criteria of the meta-analysis were as follows: (1) the cases in each study were patients diagnosed with COVID-19, (2) involving the death group or non-survivor group and the survivor group, (3) at least one outcome reported among demographic characteristics, comorbidities, and clinical manifestations of COVID-19 deceased. Studies such as (a) repetitive publications, (b) reviews, editorials, case reports, letters, and family-based studies, and (c) studies with fewer than five cases were excluded.

Data extraction and paper quality evaluation

Data extraction and literature quality evaluation were completed by two investigators (Peishan Qiu and Yunjiao Zhou) independently. Disagreements were resolved with a third investigator (Fan Wang) or by consensus. All included papers were evaluated using the Newcastle–Ottawa scale [7]. The following variables were extracted: the authors, the baseline details, clinical manifestations, laboratory examinations, and clinical outcomes.

Statistical analysis

Single-arm meta-analysis was performed using R 3.6.3 software. Review Manager 5.3 (RevMan version 5.3) software was used to compare the clinical characteristics and laboratory results of COVID-19 deceased and surviving patients. The odds ratio (OR, 95% confidence intervals (CI)) was used to describe the ratio of the probability of the complications occurring in dead patients vs. survivor. Mean difference (MD, 95%CI) was used to describe the differences in the mean of laboratory examinations between dead and surviving COVID-19 patients. Heterogeneity among the studies was assessed by the Cochran Chi-square and I^2 test. When $I^2 < 50\%$, a fixed-effect model was used, otherwise a random-effect model was selected. When there was statistical heterogeneity among the results, a further sensitivity analysis was performed to determine the source of heterogeneity. The publication bias was assessed using a funnel plot and quantified using Egger's linear regression test. $P < 0.05$ was statistically significant (two sided).

Results

Characteristics of included studies

As shown in Fig. 1, the total number of records initially determined based on the search strategy was 2679. After deleting 462 duplicates, we deleted another 2134 articles by reading the title and abstract of the article. We eliminated 68 articles by reading the full-text articles of the remaining 83 studies, 35 of which had no clinical data of death, 30 of which did not provide clinical data related to our study, and 3 of which included less than 5 cases. Finally, there were 15 articles included in our meta-analysis [8–22].

## Clinical manifestation of dead patients with COVID-19

The clinical data study included 15 studies [8–22] with a total of 2401 cases, including 904 deceased. The epidemiology, baseline characteristics, and clinical symptoms of all deaths included are summarized in Table 1. The median age of COVID19 deaths was 69.9 years, with 66.6% males. The main clinical symptoms of COVID19 dead patients on admission were fever (70.6–100%), dyspnea (38.89–85.7%), cough (22.4–78%), fatigue (22–61.9%), expectoration (22.2–57.1%), myalgia (2.78–33.3%), diarrhea (4–38.1%), anorexia (23.4–56.5%). Other rare symptoms included chest urgency (2.4–49%), headache (4.7–23.8%), sore throat (2.4–4.7%), hemoptysis (4–5.56%), nausea and vomiting (4–4.7%), abdominal pain (3.5–5%), and dizziness (9%).

Prevalence of underlying diseases in COVID-19 deaths

Through the current meta-analysis, we found that the prevalence rate of underlying diseases among COVID-19 dead patients was 72.21% (95% CI 62.85 ~ 79.96%).

Fig. 1 Flow diagram of the number of studies screened and included in the meta-analysis
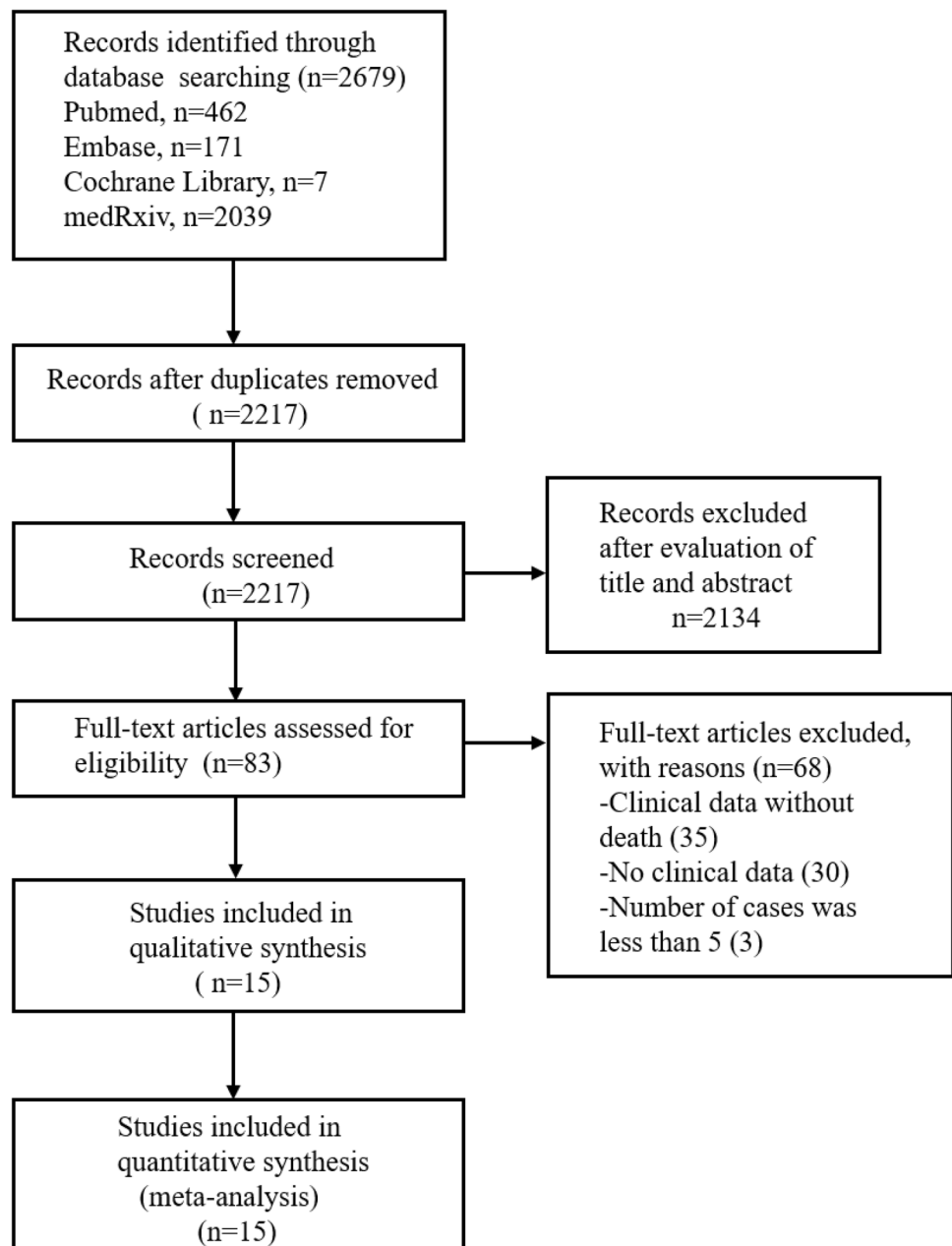
Hypertension

In a comprehensive analysis of 14 studies [8–17, 19–22], the pooled prevalence of hypertension in the COVID-19 deceased was estimated as 38.56% (95% CI 25.84~52.12%) (Fig. 2a). According to the results of the I^2 index (93%) and the Chi-square test, there was high and significant heterogeneity between the studies ($P < 0.01$), also no publication bias was present according to Eggers's test ($t = 0.083162$, $P = 0.9351$).

Chronic cardiovascular disease

To estimate the pooled prevalence of the cardiovascular disease in COVID-19 deceased, 14 studies were evaluated [8–17, 19–22]. The incidence was 23.48% (95% CI 16.75~30.20%), with high and significant heterogeneity ($I^2 = 83$%). There was publication bias by Eggers's test ($t = 3.2692$, $P = 0.006713$). Through sensitivity analysis, it was found that the heterogeneity significantly decreased ($I^2 = 52$%) after the exclusion of data from the "Korean" group [14] and the "Du RH" group [11]. The prevalence of meta-analysis after excluding studies affecting heterogeneity was 17.54% (95% CI 13.38~21.69%) (Fig. 2b), and there was no publication bias according to Eggers's test ($t = 3.1061$, $P = 0.01113$).

Diabetes

The pooled prevalence of diabetes in COVID-19 death patients was estimated to be 22.2% (95% CI 19.30~25.10%). The heterogeneity of the study was low ($I^2 = 28.4$%, $P = 0.1519$) (Fig. 2c). A fixed model was used to perform a meta-analysis of data from 14 studies [8–17, 19–22].

Chronic cerebrovascular disease

After the combination of 12 studies [8, 9, 11–17, 19–21], the random-effects model was used to calculate the prevalence of the cerebrovascular disease in COVID-19 deceased was 15.58% (95% CI 10.05~21.12%, $I^2 = 77.7$%, $P < 0.01$) (Fig. 2d). The heterogeneity of the study was high, using a random-effects model. The sensitivity analysis was relatively stable.

Other comorbidities

The results of the meta-analysis showed that the incidence of chronic lung disease in COVID-19 deceased was 14.2% (95% CI 11.27~17.21%). The prevalence of tumors (4.28%, 95% CI 2.21~6.99%), chronic kidney disease (4.17%, 95% CI 2.6~5.74%), and chronic liver disease (2.86%, 95% CI

1.6~4.48%) were slightly increased in COVID-19 deaths. There was no publication bias by Egger's test.

Characteristics of laboratory examinations of COVID-19 death patients

The purpose of this study was to explore the changes in laboratory indexes related to the poor prognosis of COVID-19 by comparing the laboratory examinations of the final dead patients with COVID-19 and the surviving patients (Table 2).

Through meta-analysis, we found that compared with patients who were also infected with SARS-CoV-2 but whose final outcome was alive, laboratory examinations showed a slightly higher leucocytes count (MD = 3.77, 95% CI 2.90~4.64), neutrophil count increased slightly (MD = 4.57, 95% CI 2.92~6.23), lymphocyte count decreased (MD = -0.37, 95% CI − 0.47~− 0.26), platelets count decreased significantly (MD = − 39.35, 95% CI − 55.78~− 22.93), D-dimer slightly increased (MD = 2.96, 95% CI 1.93~3.98), CRP increased significantly (MD = 80.85, 95% CI 62.53~99.18), alanine transaminase (ALT) slightly increased (MD = 5.07, 95% CI 0.26~9.88), aspartate transaminase (AST) significantly increased (MD = 14.26, 95% CI 11.70~16.81), blood urea nitrogen (BUN) slightly increased (MD = 4.00, 95% CI 3.33~4.67), serum creatinine (Scr) was significantly increased (MD = 21.20, 95% CI 16.79–25.61), and LDH was abnormally increased (MD = 246.65, 95% CI 157.43~335.88), creatine kinase (CK) increased (MD = 48.98, 95% CI 3.53~94.43), plasma albumin decreased (MD = − 4.00, 95% CI − 5.17~− 2.83), total bilirubin (Tbil) slightly increased (MD = 3.92, 95% CI 1.94~5.91), interleukin-6 (IL-6) significantly increased (MD = 27.57, 95% CI 17.45~37.69), prothrombin time (PT) slightly increased (MD = 1.13, 95% CI 0.67~1.60). However, there was no significant difference in hemoglobin, procalcitonin (PCT), and activated partial thromboplastin time (APTT) between the two groups.

Occurrence of complications of COVID-19 death patients

We compared the incidence of complications between dead and surviving patients after the SARS-CoV-2 infection. A total of eight studies [8–10, 17, 19–22] were included in the meta-analysis.

Acute respiratory distress syndrome (ARDS)

A total of eight studies were included [8–10, 17, 19–22]. The results showed that compared with the patients who survived COVID-19, the most common complication of the patients who eventually died was ARDS (OR = 75.05, 95%

Table 1 Demographics, baseline characteristics, and clinical symptoms of COVID-19 deceased included in the meta-analysis

Study	Author	Cao JL [8]	Chen T [9]	Deng Y [10]	Du RH [11]	Du YZ [12]	Hang Y [13]	Korean [14]	Li Xu [15]	NERC [16]	Ruan QR [17]	Tang N [18]	Tu WJ [19]	Wang L [20]	Yang XB [21]	Zhou F [22]
Dead	Number of patients	17	113	109	21	85	36	54	25	66	68	134	25	65	32	54
Age	median (IQR), y	72 (63–81)	68 (62–77)	69 (62–74)	70.2 (65–75.4)	65.8 (56.3–75.3)	69.22 (62.74–75.71)	75.5 (66–80)	71.83 (63.34–80.32)	77 (35–93)	67 (15–81)	68.7 (61–76.4)	70 (64–80)	76 (70–83)	64.6 (57–72.15)	69 (63–76)
Sex	Female	4 (23.5)	30 (27)	36 (33)	11 (52.4)	23 (27.1)	11 (30.56)	21 (38.89)	15 (60)	29 (43.9)	19 (28)	44 (32.8)	6 (24)	26 (40)	11 (34)	16 (30)
	Male	13 (76.5)	83 (73)	73 (67)	10 (47.6)	62 (72.9)	25 (69.44)	33 (61.1)	10 (40)	37 (56.1)	49 (72)	90 (67.2)	19 (76)	39 (60)	21 (66)	38 (70)
Signs and symptoms	Fever	12 (70.6)	104 (92)	95 (87.2)	21 (100)	78 (91.8)	34 (94.44)	–	–	–	59 (87)	–	–	56 (87.5)	31 (97)	51 (94)
	Cough	8 (47.1)	79 (70)	47 (43.1)	14 (66.7)	19 (22.4)	28 (77.78)	–	–	–	51 (75)	–	–	30 (46.9)	25 (78)	39 (72)
	Fatigue	9 (52.9)	64 (57)	30 (27.5)	13 (61.9)	50 (58.8)	17 (47.22)	–	–	–	15 (22)	–	–	26 (40.6)	–	15 (28)
	Anorexia	–	31 (27)	–	–	48 (56.5)	–	–	–	–	–	–	–	15 (23.4)	–	–
	Myalgia	5 (29.4)	21 (19)	30 (27.5)	7 (33.3)	14 (16.5)	1 (2.78)	–	–	–	9 (13)	–	–	1 (1.6)	4 (12.5)	8 (15)
	Dyspnoea	–	70 (62)	77 (70.6)	18 (85.7)	60 (70.6)	14 (38.89)	–	–	–	59 (87)	–	–	38 (59.4)	21 (66)	–
	Chest tightness	–	55 (49)	–	–	2 (2.4)	–	–	–	–	–	–	–	15 (23.4)	–	–
	Expectoration	–	35 (31)	35 (32.1)	12 (57.1)	32 (37.6)	8 (22.22)	–	–	–	29 (43)	–	–	17 (26.6)	–	14 (26)
	Pharyngalgia	–	4 (4)	–	–	2 (2.4)	–	–	–	–	–	–	–	3 (4.7)	–	–
	Haemoptysis	–	4 (4)	5 (4.6)	–	–	2 (5.56)	–	–	–	3 (4)	–	–	–	–	–
	Diarrhoea	3 (17.6)	27 (24)	19 (17.4)	8 (38.1)	16 (18.8)	3 (8.33)	–	–	–	–	–	–	8 (12.5)	–	2 (4)
	Nausea	–	8 (7)	–	–	–	–	–	–	–	–	–	–	1 (1.6)	–	3 (6)
	Vomiting	–	6 (5)	–	–	4 (4.7)	–	–	–	–	–	–	–	–	1 (3)	3 (6)
	Abdominal pain	–	6 (5)	–	–	3 (3.5)	–	–	–	–	–	–	–	–	–	-
	Headache	–	11 (10)	6 (5.5)	5 (23.8)	4 (4.7)	–	–	–	–	–	–	–	–	2 (6)	–
	Dizziness	–	10 (9)	–	–	–	–	–	–	–	–	–	–	2 (3.1)	–	–
NOS	score	8	9	6	8	9	6	6	7	6	9	7	9	7	9	9

Data are median (IQR) and *n* (%)

COVID-19 coronavirus disease 2019

CI 33.35 ~ 168.86, $P < 0.00001$). The heterogeneity of the study was high ($I^2 = 70\%$), and Egger's test showed publication bias ($P = 0.001$). The sensitivity analysis showed that the heterogeneity of the study was significantly reduced ($I^2 = 0\%$) after excluding the data of the "Yang XB" group [21]. Meta-analysis showed that ARDS was a risk factor for death in COVID-19 patients (OR = 100.36, 95% CI 64.44 ~ 156.32, $P < 0.00001$) (Fig. 3a). The Egger's test showed that there was no publication bias ($P = 0.61$).

Shock

A total of six studies were included [8–10, 19, 20, 22]. We found that dead patients were more likely to develop shock (OR = 51.55, 95% CI 8.32 ~ 319.28, $P < 0.0001$, $I^2 = 80\%$, $P = 0.001$) than COVID-19 survivors, but the heterogeneity of the study was high. The sensitivity analysis showed that the heterogeneity of this study decreased ($I^2 = 52\%$, $P = 0.08$) after excluding the "Wang L" group [20]. Therefore, the shock was a risk factor for death in patients COVID-19 (OR = 96.60, 95% CI 23.80 ~ 392.14, $P < 0.00001$) (Fig. 3b).

Other complications

Compared with the surviving patients, the incidence of infection (OR = 30.25, 95% CI 6.86 ~ 133.39, $P < 0.00001$, $I^2 = 82\%$, $P < 0.0001$), acute renal failure (AKI) (OR = 28.11, 95% CI 10.73 ~ 73.66, $P < 0.00001$, $I^2 = 69\%$, $P = 0.002$), acute heart injury (OR = 27.73, 95% CI 11.00 ~ 69.89, $P < 0.00001$, $I^2 = 78\%$, $P = 0.0002$) and acute liver injury (OR = 3.15, 95% CI 1.29 ~ 7.70, $P = 0.01$, $I^2 = 75\%$, $P = 0.003$) increased in patients with COVID-19 death.

Discussion

This meta-analysis included data from 15 laboratory-confirmed COVID-19 studies. Through our analysis, we found that 66.6% (602/904) of the dead patients were male, and the median age was 69.9 years old, in line with Huang et al. [3]. Common symptoms of COVID-19 deaths include fever, dyspnea, cough, and fatigue. Hypertension, chronic cardiovascular disease, diabetes, and chronic cerebrovascular disease are common comorbidities among COVID-19 deceased. COVID-19 patients with complications such as ARDS and shock are more likely to die. Laboratory examinations showed low levels of platelet content, increased CRP and LDH were associated with death in patients with COVID-19.

The elderly and men were the susceptible factors of COVID-19. For the high mortality rate of COVID-19 among the elderly, we believe that it may be related to the high prevalence of comorbidities among the elderly. Studies of

the Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV also found more infections in men than women [23, 24]. On the one hand, it is generally believed that women have stronger innate and adaptive immune responses than men [25], which may be due to the protection of X chromosomes and sex hormones [26]. For this reason, women are less likely to affect a variety of bacteria and viruses than men. On the other hand, men tend to have more bad habits than women (such as smoking, drinking, more underlying diseases), which may also be the reason why men with COVID-19 are more likely to die.

Chronic diseases have become a global economic burden [27]. Our study revealed that the prevalence of chronic underlying diseases in dead patients with COVID-19 was 72.21% (95% CI 62.85–79.96%). Compared to subjects with no comorbidities, severe pandemic influenza cases were significantly increased in patients with obesity, cardiovascular diseases, and hypertension [28]. The study of the data extracted from the severe MERS-CoV cases suggested that diabetes and hypertension were equally prevalent in approximately 50% of the patients [23]. The state of hyperglycemia and insulin resistance in diabetic patients would weaken the synthesis of pro-inflammatory cytokines such as interferon-γ and interleukin and their downstream acute phase reactants [29], which makes diabetic patients more susceptible to SARS-CoV-2. Simultaneously, viral infection may cause sharp fluctuations in blood glucose levels in patients with diabetes, which will adversely affect the rehabilitation of patients. The angiotensin-converting enzyme 2 (ACE2) has been proved to be the receptor for SARS-CoV-2 to enter the host cells [6]. A study analyzed the lung transcriptome samples of more than 700 patients with comorbidities associated with severe COVID-19 and found that ACE2 was highly expressed in these patients compared to the control individuals [30]. Hence, patients with comorbidities may have higher chances of developing severe COVID-19. Lippi et al. believed that hypertension was a clinical predictor of COVID-19 severity in elderly patients [31]. Our research showed that the incidence of hypertension in patients with COVID-19 death was 38.56% (95% CI 25.84 ~ 52.12%). Tikellis et al. found that the expression of ACE2 in patients with hypertension might be decreased [32], increasing the level of angiotensin II, which would promote the development of ARDS [33].

In a study of the pathophysiology of ARDS, increased inflammation, and lung injury in rat models were associated with increased age, which was caused by an imbalance in the lung renin-angiotensin system (RAS) [34]. We observed that patients who died were more likely to have ARDS than those who survived with COVID-19 (OR = 75.05, 95% CI 33.35–168.86). And as mentioned earlier, the elderly were the majority of the dead. ACE2 can antagonize the activation of the classical RAS and mediate vasodilation,
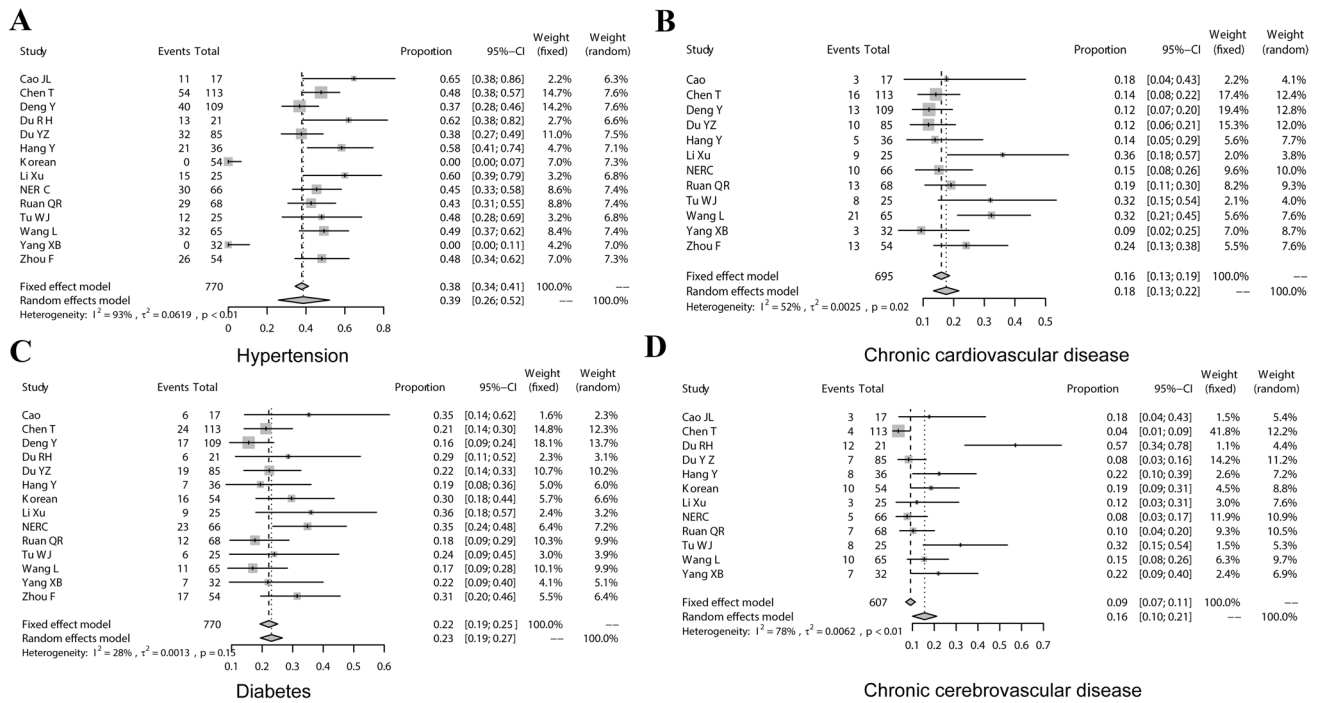
Fig. 2 Meta-analysis of the prevalence of comorbidities in COVID-19 deaths. **a** Hypertension; **b** chronic cardiovascular disease; **c** diabetes; **d** chronic cerebrovascular disease

Table 2 Comparison of laboratory results between COVID-19 deceased and surviving patients

	No. of studies	MD (95%CI)	P value	Heterogeneity		Model used
				I^2	P_h	
White blood cell count, $\times 10^9$/L	7	3.77 (2.90, 4.64)	< 0.00001	60%	0.02	Random
Neutrophil count, $\times 10^9$/L	3	4.57 (2.92, 6.23)	< 0.00001	71%	0.03	Random
Lymphocyte count, $\times 10^9$/L	8	− 0.37 (− 0.47, − 0.26)	< 0.00001	80%	< 0.0001	Random
Haemoglobin, g/L	5	− 0.30 (− 2.84, 2.24)	0.82	0	0.93	Fixed
Platelets, $\times 10^9$/L	6	− 39.35 (− 55.78, − 22.93)	< 0.00001	65%	0.01	Random
D-dimer, mg/L	6	2.96 (1.93, 3.98)	< 0.00001	0%	0.61	Fixed
CRP, mg/L	6	80.85 (62.53, 99.18)	< 0.00001	73%	0.002	Random
PCT, ng/mL	4	0.15 (− 0.04, 0.34)	0.12	86%	0.0008	Random
ALT, U/L	6	5.07 (0.26, 9.88)	0.04	74%	0.002	Random
AST, U/L	5	14.26 (11.70, 16.81)	< 0.00001	48%	0.11	Fixed
BUN, mmol/L	3	4.00 (3.33, 4.67)	< 0.00001	0%	0.52	Fixed
Scr, μmol/L	6	21.20 (16.79, 25.61)	< 0.00001	13%	0.33	Fixed
LDH, U/L	4	246.65 (157.43, 335.88)	< 0.00001	85%	0.0002	Random
CK, U/L	4	48.98 (3.53, 94.43)	0.03	78%	0.004	Random
Alb, g/L	4	− 4.00 (− 5.17, − 2.83)	< 0.00001	0%	0.77	Fixed
Tbil, mmol/L	4	3.92 (1.94, 5.91)	0.0001	59%	0.06	Random
IL-6, pg/mL	5	27.57 (17.45, 37.69)	< 0.00001	96%	< 0.00001	Random
PT, seconds	6	1.13 (0.67, 1.60)	< 0.00001	60%	0.03	Random
APTT, seconds	3	0.64 (− 0.17, 1.44)	0.12	22%	0.28	Fixed

COVID-19 Coronavirus disease 2019, *MD* mean difference, *CI* confidence interval, *CRP* C-reactive protein, *PCT* procalcitonin, *ALT* alanine transaminase, *AST* aspartate transaminase, *BUN* blood urea nitrogen, *Scr* serum creatinine, *LDH* lactate dehydrogenase, *CK* creatine kinase, *Alb* albumin, *Tbil* total bilirubin, *IL-6* interleukin-6, *PT* prothrombin time, *APTT* activated partial thromboplastin time

$P \leq 0.05$ was considered to be statistically significant

Fig. 3 Meta-analysis of the comparison of complications between COVID-19 dead patients and surviving patients. **a** Acute respiratory distress syndrome (ARDS); **b** shock

Acute respiratory distress syndrome(ARDS)

Shock
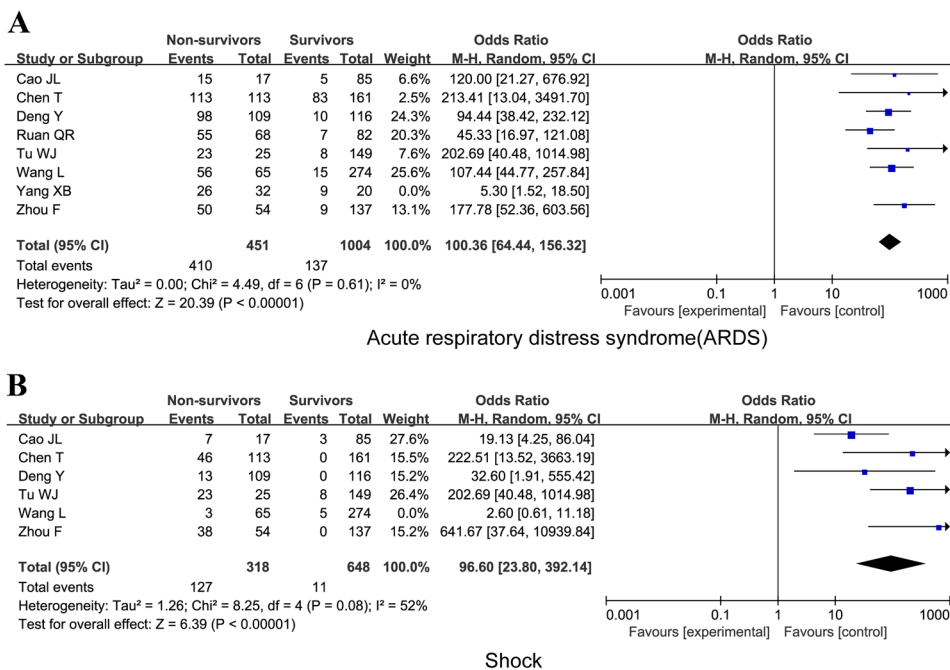
anti-inflammatory, and anti-proliferation [35]. Therefore, ACE2 has a protective effect on chronic underlying diseases and ARDS [33]. But when SARS-COV-2 binds to the ACE2 receptor and enters alveolar epithelial cells through membrane fusion, the expression of ACE2 in alveolar epithelial cells is down-regulated by mechanisms such as internalization, shedding, and viral replication [36, 37]. Moreover, the COVID-19 deceased were also more likely to have a shock. The electrolyte disorder and the decrease of systemic circulation blood volume during the shock would lead to the injury of various organs in the whole body and accelerate the death of the patients [38]. We found that patients with dyspnea were more likely to develop death. Dyspnea is a sign of decreased lung function and hypoxia. Therefore, when patients have symptoms of dyspnea, clinicians must be vigilant to prevent further deterioration of the condition. Interestingly, studies had shown that high fever (≥ 39 ℃) was positively related to the occurrence of ARDS, but negatively related to death [39, 40]. Although our study also showed that the most common symptom of COVID-19 deceased was fever. Unfortunately, we could not clarify the inevitable relationship between the death of COVID-19 patients and the degree of fever based on the available data.

Our analysis of the biochemical results showed that some indices were abnormally elevated in the blood of COVID-19 deceased, including LDH, AST, and Scr, which indicated the injury of the myocardium, liver, and kidney. This result is consistent with the extensive distribution of SARS-CoV-2 receptors ACE2, and can also partially explain why some patients died from multiple organ failure [6]. SARS-CoV-2 can cause tissues and organs injury by direct and/or indirect action [41]. The direct injury is to infect corresponding cells by identifying the ACE2 receptor. Another important cause for multiple organ failure and even death in critical patients is the release of cytokines from the inflammatory storm, causing systemic immune injury [42]. During the early stage of the inflammatory storm, the D-dimer increases significantly, which is the result of inflammation activating plasmin. The inflammation progresses and the presence of hypoxia will result in an overall hypercoagulable state or even disseminated intravascular coagulation. The inflammatory storm is also the main cause of eventual death in many patients with advanced SARS-CoV and MERS-CoV infection [43, 44]. In our study, we also observed a significant increase in IL-6 among COVID-19 deceased. IL-6 is a good predictor of disease severity and prognosis because it is expressed longer than other cytokines (such as TNF and IL-1) [45].

There are several limitations to our analysis and review. First, most of the included studies were cross-sectional studies with insufficient demonstration ability and lack of randomized controlled trials with optimized design. Second, our evidence was mostly from China. It would be better to include as many studies with a broad geographic scope and multiple races, to get a more comprehensive understanding of COVID-19 deceased. Third, the clinical data of patients provided by some studies were not comprehensive enough. Fourth, the actual cause of COVID-19 deceased might be obscured by unmeasured or unknown confounders. Despite our relatively large sample size, well-designed trials of high quality are needed to overcome inherent statistical bias and confirming the relationship between death and COVID-19.

Conclusion

According to the results of the current study, the majority of COVID-19 deaths have occurred in elderly men. Typical symptoms (fever, dyspnea, dry cough, and fatigue), chronic underlying diseases (hypertension, cardiovascular disease, diabetes, and cerebrovascular disease), associated laboratory abnormalities (low platelet count, increased CRP, and LDH), and complications (ARDS and shock) are risk factors for death in COVID-19 patients. Pay close attention to these risk factors and identify critical patients early. Personalized treatment regimens are needed to enhance the efficacy and reduce the risk of COVID-19 related death.

Availability for data and material The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical approval This is a review article and no human or animal participants were recruited to this study.

Human and animal rights This is a review article. All data used were from published articles, which were following the ethical standards of the institutional review board/international ethics committee for each center and with the 1964 Helsinki Declaration and its later amendments.

Informed consent All data used in this article were from studies that had obtained the informed consent of all individual participants.

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