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Systematic Review

Critical complications of COVID-19: A descriptive meta-analysis study

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The coronavirus disease 2019 (COVID-19) is a novel coronavirus infection that has rapidly spread worldwide, causing a pandemic. The main objective of this meta-analysis was to evaluate the prevalence of the most common symptoms and complications of COVID-19. All relevant studies on the clinical complications of COVID-19 have been identified by searching two web databases (i.e., PubMed and Scopus). Afterward, the relevant data were extracted from the selected studies, and then analyzed by the STATA (Version 14) random-effects model. The 30 studies selected for our meta-analysis covered 6,389 infected patients. The prevalence rates of the most common symptoms were as follows: fever: 84.30% (95% CI: 77.13-90.37; I^2 = 97.74%), cough: 63.01% (95% CI: 57.63-68.23; I^2 = 93.73%), dyspnea: 37.16% (95% CI: 27.31-47.57%; I^2 = 98.32%), fatigue: 34.22% (95% CI: 26.29-42.62; I^2 = 97.29%), and diarrhea: 11.47% (95% CI: 6.96-16.87; I^2 = 95.58%). Moreover, the most prevalent complications were found to be acute respiratory distress syndrome (ARDS) with 33.15% (95% CI: 23.35-43.73; I^2 = 98.56%), arrhythmia with 16.64% (95% CI: 9.34-25.5; I^2 = 92.29%), acute cardiac injury with 15.68% (95% CI: 11.1-20.97; I^2 = 92.45%), heart failure with 11.50% (95% CI: 3.45-22.83; I^2 = 89.48%), and acute kidney injury (AKI) with 9.87% (95% CI: 6.18-14.25; I^2 = 95.64%). In this study, we assessed the prevalence of the main clinical complications of COVID-19, and found that following respiratory complications, cardiac and renal complications are the most common clinical complications of COVID-19.

Keywords

COVID-19; ARDS; acute cardiac injury; acute kidney injury (AKI)

1. Background

Since the emergence of a cluster of pneumonia cases in Wuhan, China in December 2019, the COVID-19 disease has attracted a lot of global attention. On 9 January 2020, the Chinese Center for Disease Control and Prevention stated that the cause of this newly-emerged disease was a novel virus from the coronavirideae family, which was later named the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), while the disease caused by this virus was then called coronavirus disease 2019 (COVID-19). Unfortunately, this epidemic was not just limited to China. On 11 March 2020, the World Health Organization (WHO) announced the COVID-19 outbreak as a pandemic (Kreutz et al., 2020; WHO, 2020b). According to WHO, as of writing this draft (8 August, 2020), about 20,000,000 individuals have been diagnosed with COVID-19, and unfortunately more than 700,000 of these patients have died (WHO, 2020a). Moreover, based on the latest reports, the most common symptoms of COVID-19 are fever, dry cough, fatigue, dyspnea, and diarrhea (Guan et al., 2020).

The main clinical complications of COVID-19 are related to the respiratory system, ranging from simple pneumonia in mild cases to acute respiratory distress syndrome (ARDS) and shock in severe patients. In this regard, the angiotensin-converting enzyme 2 (ACE2) was identified as the host cell receptor responsible for the entry of SARS-CoV-2 and the facilitation of infection. It should

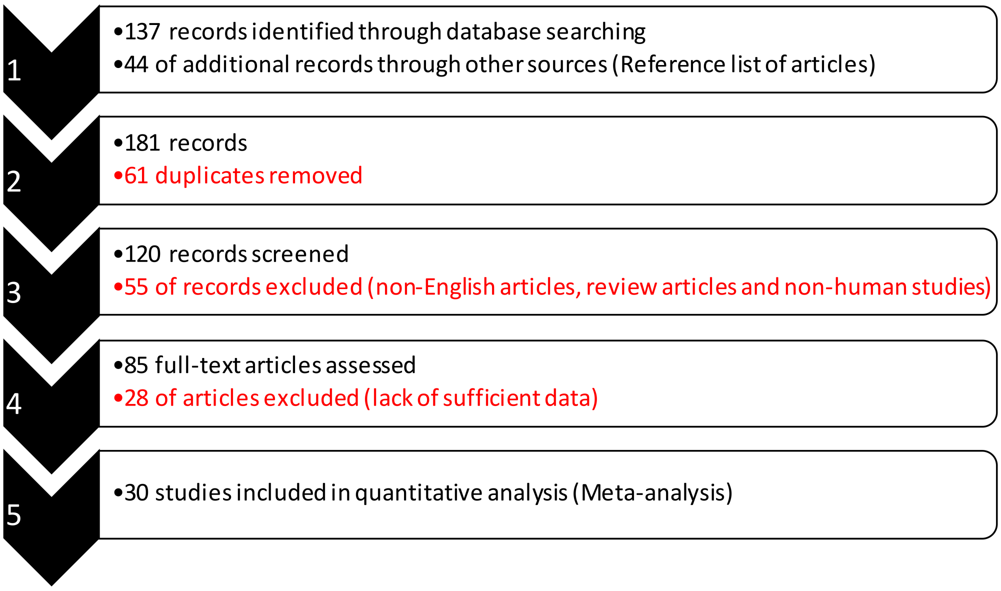

Fig. 1. Study flow diagram. To find eligible cross-sectional and case-control studies, a 5 step screening process was conducted (based on PRISMA checklist).

be noted that lung, heart, kidney, and intestine cells express ACE2.

As previously observed for SARS-CoV (Li et al., 2003), SARS-CoV2 (Hoffmann et al., 2020) can similarly use ACE2 as a receptor for viral cell entrance. In the Renin-Angiotensin-Aldosterone System (RAAS), ACE2 has a catalytic effect on the conversion of angiotensin II to angiotensin 1-7, which has a number of protective effects in the cardiovascular system, and can be considered as a vasodilator. In animal experiments, the increased activity and expression of ACE2 in different organs (e.g., the heart) were associated with the administration of ARB and ACE-I (Ferrario et al., 2005; Kuster et al., 2020). Human pathogenic coronaviruses (i.e., SARS-CoV2 and SARS-CoV) may bind to their target cells through ACE2, which is expressed by the epithelial cells of the kidney, the intestine, the blood vessels, and the lung (Fang et al., 2020; Y. Wan et al., 2020). In addition, severe lung inflammation caused by SARS-CoV-2 infection can lead to dysregulation of the renin-angiotensin system as well as further development of ARDS.

In addition to respiratory manifestations, cardiovascular and renal complications may also occur following COVID-19 infection. In practice, growing evidence confirms cardiovascular involvement in the COVID-19 disease, and its negative impact on prognosis (Shi et al., 2020a). There are also some studies confirming that acute and chronic renal injuries are expected due to the high expression of ACE2 in the renal tubular epithelium (South et al., 2020).

Since these complications are extremely life-threatening, their prevalence in the clinical outcomes of patients can act as determining factors in the morbidity and mortality rates of the disease. Therefore, this paper aimed to determine the prevalence of critical complications in patients with COVID-19 through a systematic review of a number of recent studies and analyzing the relevant data.

2. Methods

2.1 Selection of studies

In order to identify the eligible cross-sectional and case-control studies published on COVID-19 until May 1, 2020, we conducted a web search in the citations in PubMed. Accordingly, two authors have independently conducted the search process. In this regard, our search queries included 'ARDS AND COVID', '((Heart) OR Cardio-) AND COVID', '((Kidney) OR Renal) AND COVID', and 'Complications AND COVID'. Eligible studies were then selected based on the titles of the identified papers. In addition, the reference lists of all the related reviews (i.e., narrative and systematic) were searched to identify more related articles (Table 1 and Fig. 1).

2.2 Inclusion and exclusion criteria

At the first stage, all the studies analyzing the clinical complications of COVID-19 were examined. To be included in the final analysis, the screened studies must report data on the prevalence of each of the clinical complications in COVID-19 patients, including ARDS, acute heart damage, arrhythmia, heart failure, and AKI.

For all the included studies, related data, i.e., the name of the first author, date of publication, location of publication, sample size, sample age, sample gender, prevalence of symptoms (including fever, cough, dyspnea, fatigue, and diarrhea), critical complications (including ARDS, acute cardiac injury, arrhythmia, heart failure, and AKI), and clinical outcomes (e.g., mortality rate) were extracted. To avoid including conflicting results, the authors extracted data from each study separately, and then the results were compared (Table 1).

Table 1. Baseline characteristics of studies included in this meta-analysis

Study (ref)	Place	Patients (No.)			Age (Median)	Symptoms (P.)					Complications (P.)			Mortality (%)
		All	Male	Female		Fever	Cough	Fatigue	Diarrhea	Dyspnea	Acute Cardiac Injury	AKI	ARDS	
Zhou et al., 2020	China	191	119	72	56	94	79	23	5	29	17	15	54	28
Du et al., 2020	China	85	62	23		92	22	59	19	59	5		47	
L. Wang et al., 2020	China	339	166	173	69	92	53	40	13	41	21	8	21	19
X. Li et al., 2020	China	25	10	15	73					92			92	100
N. Chen et al., 2020	China	99	67	32		83	82	11	2	31		3	17	11
D. Wang et al., 2020	China	138	75	63		99	59	70	10	31	7	4	20	4
Guan et al., 2020	China	1099	637	459	47	44	68	38	4	19		0.5	3	1
X. Yang et al., 2020	China	52	35	17		98	77	12		64		30	67	62
Guo et al., 2020	China	187	91	96								15	25	23
Y. Liu et al., 2020	China	12	8	4		83	92	33	17				50	
W. Liu et al., 2020	China	78	39	39	38		44						26	
Z. Li et al., 2020	China	193	95	98	57	89	69	39	18	36	12	28	28	66
T. Chen et al., 2020	China	274	171	103	62	91	68	50	28	44	44	11	72	41
J. Zhang et al., 2020	China	82	54	28	72.5	78	65	46	12	63			100	
Shi et al., 2020a	China	416	205	211	64	80	35	13	4	28		2	23	14
L. Wang et al., 2020	China	116	67	49	54								10	
Arentz et al., 2020	USA	21	11			52	48			76		2		52
T. Chen et al., 2020	China	203	108	95	54	89	60	8		2				13
G. Zhang et al., 2020	China	221	108	113	55	91	61	71	11	29	8	5	22	5
Cao et al., 2020	China	102	53	49	54	81	49	55	11	34	15	20	20	17
Hu et al., 2020	China	323	166	157	61	84	51			4	7	5	4	
Huang et al., 2020	China	41	30	11	49	98	76	44	3	55	12	0.7	29	15
X. C. Li et al., 2020	China	548	279	269	60	95	76	47	33	57	22	17	38	17
Lian et al., 2020	China	136	58	78		85	63	18		13		2	17	0
Lian et al., 2020	China	652	349	303		80	65	18		3		2	5	0
S. Wan et al., 2020	China	135	72	63	47	89	77	33	13	13	7	4	16	0.7
Deng et al., 2020	China	112	57	55	65	88	71			56	13			0
Shao et al., 2020	China	136	90	46		38	52	49	20	75				0
Tu et al., 2020	China	25	19	6	70						72	76	92	100
Tu et al., 2020	China	149	60	89	51						5	5	5	0
F. Yang et al., 2020	China	91	49	43							34	17	80	100
Yao et al., 2020	China	108	43	65	52	74	78	26	8	14	7	15	42	11

*Abbreviations: No = Number; P = prevalence.

2.3 Statistical analysis

The prevalence of cardiovascular and renal complications was considered as the effect size in this study. Moreover, using the binomial distribution, its variance was assessed (with 95% confidence interval). Average weight was then applied to combine the prevalence rates from different studies. Afterward, an inverse relationship was found between the study weight and its variance. The Q statistic and the I^2 index with a significance level of less than 10% were employed to investigate the heterogeneity of the data. Once the studies were found to be heterogeneous, the meta-analysis (random effects model) was applied. For the data analysis, the STATA software (version 14) was used, and the Metaprop (meta-analysis for proportion) command was then used in STATA, when p was close to 0 or 1. To stabilize the variances, we applied the Freeman-Tukey Double Arcsine Transformation (Freeman and Tukey, 1950). It should be noted that in Metaprop, two variables in the format of P = n/N have to be declared. This study was carried out under the approval of the Ethics Committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.RETECH.REC.1399.083).

3. Results

3.1 Selection of studies

In order to perform the analysis, we used the PRISMA checklist (Liberati et al., 2009). Initially, 137 studies were identified through database searches, and 44 additional studies were also included through other sources (e.g., the reference list of review articles). Of these 181 studies, 61 studies were excluded due to duplication. After screening the abstracts, 55 other articles were excluded as well (based on exclusion criteria, listed in the Methods Section, e.g., non-English articles, review articles, and non-human studies). Therefore, the full-text of 85 remaining studies were evaluated, and 28 other studies were excluded due to various reasons (e.g., lack of sufficient data). After carefully reviewing the selected studies, 30 published articles carried out from February, 2020 to April, 2020 were included for further analyses (Fig. 1 and Table 1).

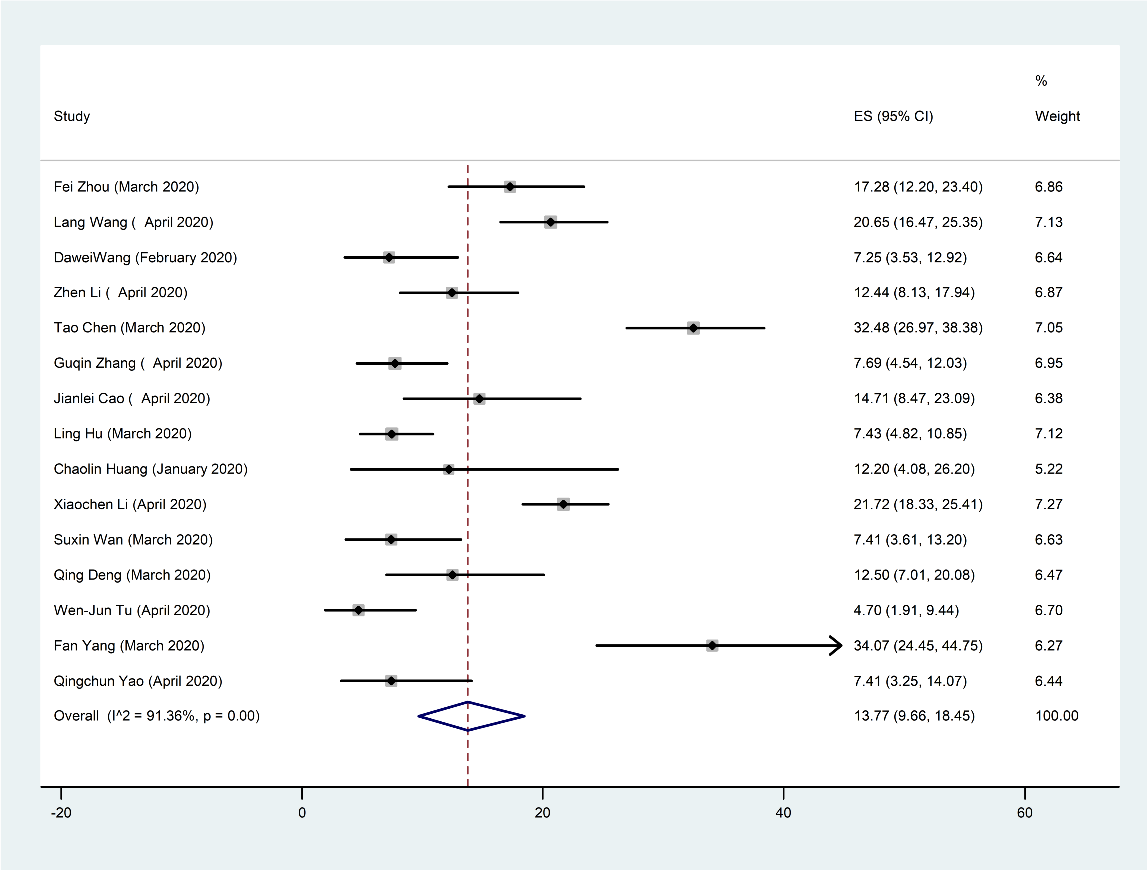

Fig. 2. Forest Plot of the prevalence of acute cardiac injury in COVID-19 patients. Each square shows effect estimate of individual studies with their 95% CI. Size of squares is proportional to the weight of each study in the meta-analysis. In this plot, studies are shown in the order of publication date and first author's names (based on a random effects model).

3.2 Demographic characteristics of the included studies

Pooling all the extracted data together, the total number of COVID-19 positive patients was 6,389, including 1,402 patients with ARDS, 494 patients with acute cardiac injury, and 418 patients with AKI. The selected studies have been primarily conducted in China, except for one, which was carried out in the United States. According to the average value calculated from the articles reporting the median age of the subjects, the mean age of the patients was 57.64 years, while 45.29% of the patients were female (95% CI: 42.61% to 47.99%; I^2 = 74.56%).

3.3 Clinical manifestations

Our meta-analysis revealed that the most common symptoms of COVID-19 were fever: 84.30% (95% CI: 77.13-90.37; I^2 = 97.74%), cough: 63.01% (95% CI: 57.63-68.23; I^2 = 93.73%), dyspnea: 37.16% (95% CI: 27.31-47.57%; I^2 = 98.32%), fatigue: 34.22% (95% CI: 26.29-42.62; I^2 = 97.29%), and diarrhea: 11.47% (95% CI: 6.96-16.87; I^2 = 95.58%).

3.4 Complications

Cardiac and renal complications were also assessed in these patients. In addition, the most common respiratory complication was ARDS with 33.15% (95% CI: 23.35-43.73; I^2 = 98.56%). The prevalence rates of arrhythmia, acute cardiac injury, and heart failure were16.64% (95% CI: 9.34-25.5; I^2 = 92.29%), 15.68% (95% CI: 11.1-20.97; I^2 = 92.45%), and 11.50% (95% CI: 3.45-22.83; I^2 = 89.48%), respectively. Unfortunately, few related studies were available that analyzed the prevalence rates of arrhythmia and heart failure. Furthermore, the primary analysis of AKI showed a prevalence rate of 9.87 % (95% CI: 6.18-14.25; I^2 = 95.64%) (Table 2).

3.5 Outcomes

Based on the primary analysis, the mortality rate was calculated as 21.70% (95% CI: 12.39-32.70; I^2 = 98.81%); however, after the elimination of three of the included studies, which were only conducted on deceased patients, the total mortality rate reduced to12.29% (95% CI: 6.20-19.99; I^2 = 98.29%). Moreover, we conducted a subgroup analysis to determine the mortality rate by location. As noted earlier, the included articles were mainly performed in China, with a mortality rate of 11.20% (95% CI: 5.36-18.75; I^2 = 98.34%), and only one was conducted in the USA, with a mortality rate of 52.38% (95% CI: 29.78-74.29).

3.6 Sensitivity analysis

According to the primary analysis, the prevalence of acute cardiac injury was 15.68% (95% CI: 11.1-20.97; I^2 = 92.45%); however, after the elimination of part of the data from the Wen-Jun Tu study, and conducting sensitivity analysis (eliminating outlier data), the prevalence rate reduced to 13.77% (95% CI: 9.66-18.45; I^2 = 91.36%) (Fig. 2). Furthermore, the primary analysis of AKI

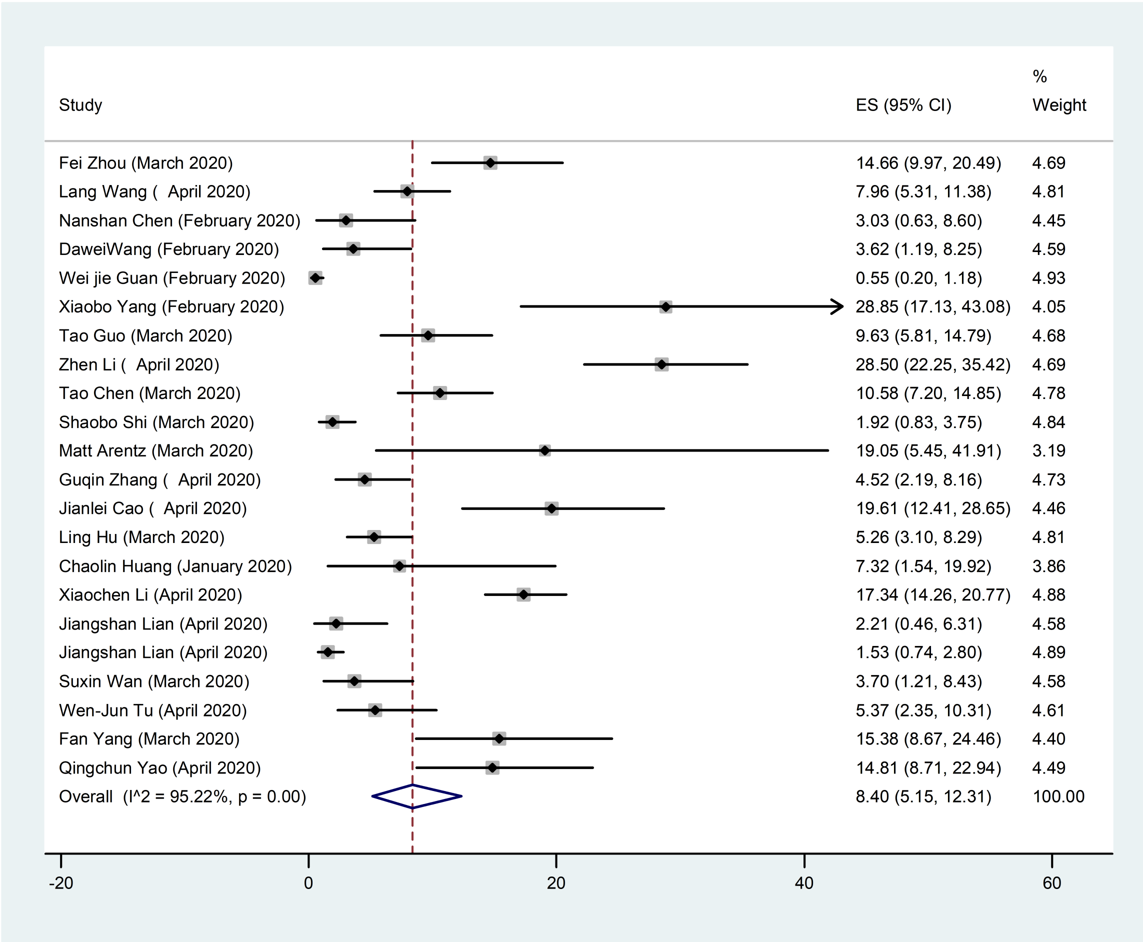

Fig. 3. Forest Plot of the prevalence of acute kidney injury (AKI) in COVID-19 patients. Each square shows effect estimate of individual studies with their 95% CI. Size of squares is proportional to the weight of each study in the meta-analysis. In this plot, studies are shown in the order of publication date and first author's names (based on a random effects model).

showed a prevalence rate of 9.87% (95% CI: 6.18-14.25; I^2 = 95.64%); however, after eliminating part of the data from Wen-Jun Tu study, and conducting the sensitivity analysis (eliminating outlier data), this prevalence rate decreased to 8.40% (95% CI: 5.15-12.31; I^2 = 95.22%) (Fig. 3).

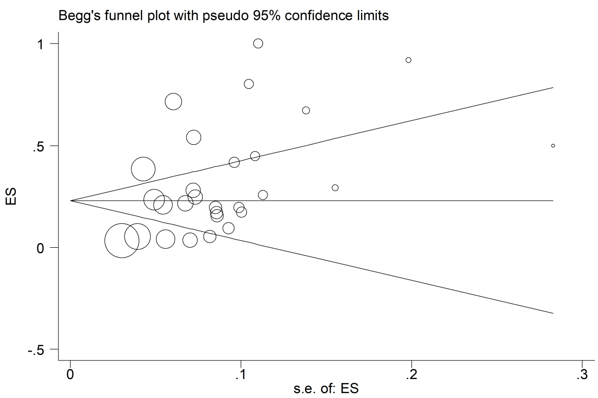

Fig. 4. Begg's funnel plot for publication bias.

3.7 Publication bias

Fig. 4. shows the Begg's funnel plot for the studies related to cardiac and renal injuries in COVID-19 patients. The interpretation of this plot showed no sign of publication bias in the included studies (P = 0.08). Accordingly, this result implies that reports have been published with both positive and negative results (Fig. 4).

4. Discussion

Since late 2019, a novel coronavirus outbreak, i.e., coronavirus disease 2019 (COVID-19), has emerged and spread around the world (Ghebreyesus, 2020). The city of Wuhan in China was the first infected area and the starting point of this pandemic (J. Li and Xu, 2020). It is noteworthy that COVID-19 is highly transmittable and has great ability to infect a cluster of cases (Chan et al., 2020).

Earlier in the pandemic, many patients did not have outpatient testing and diagnosis; therefore, they presented late and had the diagnosis made in the hospital (McCullough and Arunthamakun, 2020).

To date, no definite treatment has been discovered for COVID-19. The current recommendations regarding this disease include a number o reduce the risk of infection (N. Chen et al., 2020; W.

Table 2. Statistical analysis of reviewed studies

	Number of study	Prevalence (%)	95% CI	I^2 (%)	*P* Value for heterogeneity
Mortality	22	12.29	(6.20-19.99)	98.29	0.00
Mortality in China	21	11.20	(5.36-18.75)	98.34	0.00
Mortality in USA	1	52.38	(29.78-74.29)		
Gender					
Female	29	45.29	(42.61-47.99)	74.56	0.00
Male	29	54.72	(52.04-57.39)	74.33	0.00
Clinical Manifestations					
Fever	24	84.30	(77.13-90.37)	97.74	0.00
Cough	25	63.01	(57.63-68.23)	93.73	0.00
Dyspnea	23	37.16	(27.31-47.57)	98.32	0.00
Fatigue	21	34.22	(26.29-42.62)	97.29	0.00
Diarrhea	18	11.47	(6.96-16.87)	95.58	0.00
Complications					
Respiratory					
ARDS	27	33.15	(23.35-43.73)	98.56	0.00
Cardiovascular					
Acute Cardiac injury	15	15.68	(11.01-20.97)	91.36	0.00
Arrhythmia	5	16.64	(9.34-25.50)	92.29	0.00
Heart failure	4	11.50	(3.45-22.83)	89.48	0.00
Renal					
AKI	21	9.87	(6.18-14.25)	95.64	0.00

Liu et al., 2020).

It has been shown that home treatment for COVID-19 immediately following the onset of symptoms is likely to significantly reduce hospitalizations, critical complications, and death (McCullough et al., 2020). Unfortunately, in severe cases of COVID-19, the disease can cause acute respiratory distress syndrome (ARDS), which is one of the deadliest complications of COVID-19, and can consequently contribute to death. According to Tian et al. (Tian et al., 2020), the prevalence rate of severe and mild outcomes was 18% of severe cases, while the remaining 82% were common cases (i.e., mild cases (73.3%), non-pneumonia cases (4.2%), and asymptomatic cases (5.0%)).

Based on very recent evidence, SARS-CoV-2 reactivation is also possible. Many factors can affect this viral reactivation, including virologic factors and immunosuppressive therapies. Virologic factors include SARS-CoV-2 genotype and viral load. Viral load can also determine disease severity and treatment response (Zou et al., 2020). Immunosuppressive agents, as commonly used agents, can generally inhibit immune functions in different ways. For instance, steroids can suppress interleukin production and lead to impaired cell-mediated immunity (Löwenberg et al., 2007). Therefore, immunosuppressive agents can be considered as a potential predisposing factor for SARS-CoV-2 reactivation (Ye et al., 2020). However, as these findings are limited to a group of 3 patients, further studies are highly recommended on the mechanism of SARS-CoV-2.

Our meta-analysis was conducted on data extracted from 30 previously published studies. These studies collected data from laboratory-confirmed COVID-19 patients, and they were mainly conducted in hospitals in China. According to previous reports during SARS-CoV and MERS-CoV outbreaks, these coronaviruses have been shown to affect men in higher numbers than women (Badawi and Ryoo, 2016; Channappanavar et al., 2017). Moreover, regarding COVID-19, J. Yang et al. (2020) revealed that men were at a greater risk compared to women. The results of our study also confirm findings that indicate SARS-CoV-2 has a higher risk in men (54.72% (95% CI: 52.04-57.39; I^2 = 74.33%)) compared to women (45.29% (95% CI: 42.61-47.99; I^2 = 74.56%)). This difference could have resulted from stronger innate immune responses in women (Jaillon et al., 2019), and more harmful lifestyle habits (e.g., smoking) in men (Zheng et al., 2020), as well as a greater exposure to occupational hazards (e.g., Hunan wet market in China) (Huang et al., 2020). According to the age-based analysis, the mean age of subjects was 57.64 years, which is close to the number reported in previous studies (Rodriguez-Morales et al., 2020). Elderly patients have been shown to be at a greater risk of more serious complications and further death cases, which may be related to a higher prevalence of comorbidities in elderlies (J. J. Zhang et al., 2020) or their weakened immune system (Zheng et al., 2020).

We also extracted data on the most frequent symptoms of COVID-19. According to our analysis, fever with 84.30% (95% CI: 77.13-90.37; I^2 = 97.74%), cough with 63.01% (95% CI: 57.63-68.23; I^2 = 93.73%), dyspnea with 37.16% (95% CI: 27.31-47.57%; I^2 = 98.32%), fatigue with 34.22% (95% CI: 26.29-42.62; I^2 = 97.29%), and diarrhea with 11.47% (95% CI: 6.96-16.87; I^2 = 95.58%) are the most prevalent symptoms of COVID-19. These results are almost identical to those of the previous reports (Rodriguez-Morales et al., 2020; J. Yang et al., 2020).

As we looked at the included studies, we realized that the most reported complication was ARDS, which had a33.15% prevalence rate (95% CI: 23.35-43.73; I^2 = 98.56%). ARDS occurs as a result of the accumulation of fluids in alveoli, and these fluids prevent the lungs from receiving enough air. Accordingly, the cause of this phenomenon is the leakage of fluid from capillaries into the alveoli due to their damaged walls (MayoClinic, 2018). This high prevalence of ARDS is justifiable in terms of the pneumonia caused by this virus. Among the other non-respiratory outcomes, acute cardiac injury and AKI were the highest reported. Acute myocardial injury and its complications were observed in 9.5% of all terminally-ill COVID-19 patients in Italy (as of April 13, 2020) (Sanità, 2020). According to our analyses, the prevalence rate of acute cardiac injury was 13.77% (95% CI: 9.66% to 18.45%; I^2 = 91.36%). Moreover, this complication has signs and symptoms similar to COVID-19 respiratory complications, and it may develop at any stage of this disease.

As it has already been proved that respiratory tract infections are associated with a high risk of vascular diseases (e.g., artery and venous thrombosis), clotting changes and further thrombosis are also predictable in SARS-CoV-2. According to previous reports, 10% of patients with pneumonia may experience a myocardial infarction (MI) and ischemic stroke (less frequent) (Cangemi et al., 2014; Violi et al., 2020). In addition, several studies have reported that the elevation of troponin level in COVID-19 patients is associated with poor outcomes (Lippi et al., 2020). This elevated troponin level may have different meanings in COVID-19 patients (Zimmermann et al., 2015), including pulmonary embolism (PE), type 1 and 2 MI, myocarditis, non-specific myocardial injury, and impaired renal function (Thygesen et al., 2018). It seems that elevated natriuretic peptide level is a non-specific sign, and thrombosis must be considered in an appropriate clinical context (Bikdeli et al., 2020). On the other hand, deep vein thrombosis (DVT) has not been reported yet. In addition to pneumonia, sepsis can also lead to systemic coagulation abnormalities, e.g., clotting activation and anticoagulant inhibition (Violi et al., 2020). The pathogenesis of hypercoagulability in COVID-19 is not yet identified (Singhania et al., 2020).

Acute myocardial injuries in patients with COVID-19 include arrhythmias, heart failure, cardiac arrest, acute coronary syndromes, cardiomyopathy, myocarditis, cardiogenic shock, pericarditis, and pericardial effusion (NICE, 2020). In our analysis, the prevalence rate of arrhythmia was estimated at 16.64% (95% CI: 9.34-25.5; I^2 = 92.29%), while that of heart failure was 11.50% (95% CI: 3.45-22.83; I^2 = 89.48%); however, due to the insufficient number of included articles and lack of sufficient data, the real numbers may be overestimated. It should be noted that symptoms related to acute cardiac injury are dyspnea, severe fatigue, chest pain, and palpitation.

Markers that can be useful in the diagnosis of an acute myocardial injury include high sensitivity troponin I (hs-cTnI) or T (hs-cTnT), and NT-proBNP. In this regard, performing an electrocardiogram (ECG) can also be helpful as ECG changes show myocardial ischemia. Moreover, the troponin level has diagnostic value as inflammatory responses of the heart to severe illness can lead to elevated troponin levels (NICE, 2020). In addition, the prevalence rate of AKI was 8.40% (95% CI: 5.15-12.31; I^2 = 95.22%). AKI is described as a sudden failure in kidney function, which includes both structural damage (injury) and loss of function (failure). Markers that can help with AKI diagnosis include serum creatinine (sCr) and/or urine output (UO) (Makris and Spanou, 2016).

Acute cellular injury due to SARS-CoV-2 fibroblast, pericytes, or cardiomyocyte infection via ACE2-mediated entry, and thus viral replication is still a theory and has not been proven yet. Analyzing histological samples has shown the direct viral infection of the conductive heart cells and myocardium with SARS-CoV-1 (Clerkin et al., 2020; Zhao et al., 2001; Zhou et al., 1982). Previous experiences of acute myocarditis with the substitute viruses indicate that direct cell damage is associated with the combination of cardiotropic viral entry into the myocytes and delayed innate immune responses which may cause diffused or focal myocardial necrosis (Cooper Jr, 2009). A few days into this direct cellular damage, necrosis and edema may cause clinical symptoms and contractile dysfunction (Cooper Jr, 2009). If correct in COVID-19, these secondary damages can suddenly manifest as clinical symptoms after a few days of persistence (Hendren et al., 2020).

Cardiovascular comorbidities are often seen among hospitalized patients, and they are related to an increase in cardiovascular outcomes and mortality rates. Recent clinical studies on COVID-19 demonstrate that about 33% of the hospitalized COVID-19 patients have at least one comorbidity, e.g., diabetes (20%), hypertension (15%), or cardiovascular disease (15%). All these underlying diseases had an association with an increase in the mortality rate (7.3%, 6%, and 10.5%, respectively) (N. Chen et al., 2020; Madjid et al., 2020). Common cardiac outcomes reported in COVID-19 patients due to treatment side-effects or myocardial injury include arrhythmias, myocarditis, and acute coronary syndromes. Patients with cardiovascular injury, i.e., those with an increased troponin level, have a higher mortality rate and prevalence of ARDS (Monsuez, 2020; Shi et al., 2020b).

As noted earlier, the main focus of this study was to determine the most frequent respiratory and non-respiratory complications in COVID-19 patients, which can help in identifying the causes of the worst outcomes and death in these patients. On March 3, 2020, the mortality rate of COVID-19 was reported as 3.4% by World Health Organization (WHO) (WHO, 2020c), while according to our analysis, the mortality rate was 12.29% (95% CI: 6.20-19.99; I^2 = 98.29%); this number was calculated after eliminating the studies that only included deceased patients. It should be noted that the majority of the included articles were conducted on severe cases; therefore, this higher mortality rate is reasonable. We also performed a subgroup analysis to determine the mortality rate based on the location in which the results were obtained, indicating 11.20% (95% CI: 5.36-18.75; I^2 = 98.34%) in China and 52.38% (95% CI: 29.78-74.29) in the USA. These results overestimate the mortality rate of patients with COVID-19 both due to the inclusion of predominantly severe cases and the lack of sufficient studies with useful data. Since no systematic review and meta-analysis has so far been published on the non-respiratory outcomes of COVID-19, we anticipate that the current study have useful results for the medical community.

5. Conclusions

COVID-19 infection has a high morbidity rate, especially in elderly patients. These severely-ill patients require supportive medical care, which can place a huge burden on the healthcare system in different countries. There are several complications that can put these patients in critical conditions. The most frequent clinical outcome of COVID-19 involves respiratory complications, in particular ARDS. There are also a number of non-respiratory outcomes in COVID-19 patients. Accordingly, while these outcomes are less common compared to respiratory outcomes, they can have fatal effects on patients. Two of the most frequent non-respiratory complications in COVID-19 patients are acute cardiac injury and AKI. This information gives clinicians a better insight into what they are fighting. Since these data are being updated on a daily basis, further evaluation of these clinical outcomes is recommended.

Authors' contributions

K.V. and M.F. conceived of the presented idea, searched electronic databases and collected the data. K.V. wrote the manuscript. F.S. performed the computation and analytical methods. M.H. and M.R supervised the findings of this work. F.S., A.M., M.H. and A.P. critically revised the manuscript. All authors discussed the results and contributed to the final manuscript.

Ethics approval and consent to participate

This study was carried out under the approval of ethics committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.RETECH.REC.1399.083).

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Availability of Data and Materials

All data generated or analyzed during this study are included in published articles available in Table 1.

Competing Interests

The authors declare that they have no competing interests.

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