

Original Article

Associations of pre-existing cardiovascular morbidity with severity and the fatality rate in COVID-19 patients: a systematic review and meta-analysis

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ABSTRACT

Objectives: The aim of this study was to evaluate the association of pre-existing cardiovascular comorbidities, including hypertension and coronary heart disease, with coronavirus disease 2019 (COVID-19) severity and mortality.

Methods: PubMed, ScienceDirect, and Scopus were searched between January 1, 2020, and July 18, 2020, to identify eligible studies. Random-effect models were used to estimate the pooled event rates of pre-existing cardiovascular disease comorbidities and odds ratio (OR) with 95% confidence intervals (95% CIs) of disease severity and mortality associated with the exposures of interest.

Results: A total of 34 studies involving 19,156 patients with COVID-19 infection met the inclusion criteria. The prevalence of pre-existing cardiovascular disease in the included studies was 14.0%. Pre-existing cardiovascular disease in COVID-19 patients was associated with severe outcomes (OR, 4.1; 95% CI, 2.9 to 5.7) and mortality (OR, 6.1; 95% CI, 2.9 to 12.7). Hypertension and coronary heart disease increased the risk of severe outcomes by 2.6 times (OR, 2.6; 95% CI, 1.9 to 3.6) and 2.5 times (OR, 2.5; 95% CI, 1.7 to 3.8), respectively. No significant publication bias was indicated.

Conclusion: COVID-19 patients with pre-existing cardiovascular comorbidities have a higher risk of severe outcomes and mortality. Awareness of pre-existing cardiovascular comorbidity is important for the early management of COVID-19.

Keywords: Coronary disease; COVID-19; Hypertension

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Introduction

The ongoing coronavirus disease 2019 (COVID-19) pandemic poses a significant public health threat to all nations worldwide [1,2]. As of August 23, 2021, COVID-19 has infected approximately 212,763,099 people, including roughly 4,447,912 patients who have died. Regrettably, these numbers have kept increasing worldwide, indicating that the peak is far from over and the global community remains on edge as the number of infected patients continues to escalate.

Several studies from different countries have reported that pre-existing cardiovascular comorbidities are prevalent among COVID-19 patients [3–6]. Understanding the association of cardiovascular comorbidities with the severity and outcomes of COVID-19 may highlight a cohort of patients who require more intensive monitoring during the early phase of infection [7,8]. Epidemiological studies have reported different mortality rates for COVID-19 patients with cardiac manifestations and pre-existing cardiovascular diseases, particularly hypertension and coronary artery disease [8].

Several studies have investigated the association between pre-existing cardiac disease and COVID-19 severity and fatality, and the pooled effects have been estimated in a number of meta-analyses. However, previous reviews varied in how COVID-19 severity was defined; did not report the country of the studies, and reported substantial heterogeneity. Therefore, the present meta-analysis was performed with the following aims: (1) to estimate the overall prevalence rate of pre-existing cardiovascular disease and cardiac manifestations in COVID-19 patients, and (2) to evaluate the association of pre-existing hypertension and coronary heart disease with the severity of COVID-19 and the mortality rate in COVID-19 patients using a randomeffect model that incorporates heterogeneity.

Materials and Methods

Data Search

Three databases (PubMed, Science Direct, and Scopus) were searched between January 1, 2020, and July 18, 2020. The following combined keywords were used for searching the databases: cardiovascular and COVID-19; cardiovascular and severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2); cardiovascular, and SARS-CoV-2; cardiovascular, hypertension, and COVID-19. Furthermore, the lists of references of all relevant studies were also manually checked to identify further studies. The protocol for this meta-analysis is registered at PROSPERO CRD42020191768. The meta-analysis was reported following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement [9].

Study Selection

The study selection was limited to articles in English and studies on adult humans. Case reports, review articles, and editorials were excluded from this analysis. Studies were selected if they provided adequate details on preexisting cardiovascular disease comorbidities, particularly in patients with positive diagnoses for COVID-19 and hypertension. Studies that did not provide enough details on the number of cases with severe or fatal outcomes were excluded.

Data Abstraction

For studies that met the inclusion criteria, the following data were extracted from each study using a standardized form: the surname of the first author; the design of the study; ratios of clinical characteristics of interest; sample size, country, data relevant to cardiovascular disease comorbidities factor; and pertinent data for arrhythmia and acute cardiac injury as outcomes, and the number of cases with severe and non-severe outcomes, and the number of survivors and non-survivors. As reported in the included studies, severe disease was identified if patients needed to be admitted to the intensive care unit, needed vital life support, or required mechanical ventilation. Non-survivors were defined as cases of death. Two investigators (FA and MA) extracted the relevant data.

Quality Assessment

We used the Joanna Briggs Institute (JBI) critical appraisal checklist for case series to assess the risk of bias [10]. The JBI includes 10 items dealing with confounding, selection, and information bias to assess the internal validity of the case series. The answers for each of the 10 items in the JBI checklist could be "yes," "no," "unclear," or "not applicable." A detailed description of how to use the JBI tool is provided by Munn et al. in 2020 [10]. It is advised that the results of the quality assessment of the included studies should not be shortened and reported as a score [10]. The quality assessment of the included studies in this meta-analysis was carried out by SA.

Quantitative Data Synthesis and Analysis

Data analysis was carried out using Comprehensive Meta-Analysis V2 (Biostat, Englewood, NJ, USA). A *p*-value of <0.05 was considered statistically significant. Randomeffect models were used to estimate the pooled event rates of pre-existing cardiovascular disease comorbidities as

well as the odds ratio (OR) with 95% confidence intervals (95% CIs) of disease severity and mortality associated with the exposures of interest. A random-effect model was used to incorporate heterogeneity among studies [11]. Heterogeneity in any analysis was tested by using the I² statistic (p < 0.1), which estimates the percentage of variation in study results that is explained by between-study heterogeneity rather than sampling error. Usually, an I² value >50% indicates considerable heterogeneity [11]. Funnel plots and Egger test were used to assess the presence of publication bias.

Results

Search Results and Study Characteristics

A total of 1,601 articles were identified from the 3 databases examined and other sources. After excluding duplicated or overlapping articles and removing reviews and editorials, 169 articles met the primary search criteria. For the quantitative part of our study, 34 studies that reported the event rate of pre-existing cardiovascular disease, arrhythmia, or acute cardiac injury as disease complications were included in the meta-analysis (Figure 1). Most studies



Figure 1. Flow chart of the literature search and study selection.

were conducted in China (n=21) and the United States of America (n=8), while 4 studies were conducted in Italy and 1 study reported results from different parts of the world. The setting for most of the included studies was the hospital (Table 1) [3-5,12-42].

Quantitative Analysis

The proportions of cardiovascular disease comorbidities and cardiac manifestations in COVID-19 patients

Relevant data regarding the event rate of pre-existing cardiovascular diseases, including hypertension and coronary heart disease, in 19,156 patients with COVID-19 were collected from 34 studies (Table 1) [3–5,12–42]. The pooled prevalence of pre-existing cardiovascular diseases or coronary heart disease among the included studies was 14% (95% CI, 11% to 18%), as is shown in Figure 2.

Pre-existing cardiovascular disease, hypertension, and coronary heart disease and the risk of severity outcomes and mortality in COVID-19

Table 2 summarizes the results of the current analysis. COVID-19 patients with pre-existing cardiovascular comorbidities were 4 times more likely to have severe outcomes (OR, 4.1; 95% CI, 2.9 to 5.7) (Figure 3) or not survive the disease (OR, 6.1; 95% CI; 2.9 to 12.7) (Figure 4), compared to patients with no pre-existing cardiovascular or coronary heart diseases. Severe disease was defined as patients needing to be admitted to the intensive care unit, needing vital life support, or requiring mechanical ventilation. Hypertension as a comorbid factor was associated with 2.6 times higher risk for severe outcomes (OR, 2.6; 95% CI, 1.9 to 3.6) and a 3 times higher fatality rate (OR, 3.2; 95% CI, 2.0 to 5.0) (Figures 5 and 6). However, coronary heart disease was associated with a 2.5 times higher risk for severe outcomes (OR, 2.5; 95% CI, 1.7 to 3.8) (Figure 7).

Quality of the Included Studies

Table S1 shows the quality assessment of the studies on cardiovascular disease as a comorbidity in COVID-19 patients using JBI's tool [3–5,12–42]. Most of the studies did not define participants' eligibility criteria. Moreover, most studies were unclear regarding whether they included consecutive participants and whether the inclusion was complete. The majority of the studies diagnosed COVID-19 and the outcomes of interest using valid and reliable methods. All included studies in this analysis reported the demographic and the clinical characteristics, as well as the outcomes of the participants. However, most of the multicenter studies did not present the demographic and the

tudy	Country	Condition	Setting	Comorbidities	Sample size (<i>n</i>)	Events (<i>n</i>)	Non- events (n)	Severe cases ratio	Non- severe cases ratio	Non- survivors	ivors
vang et al. [3]	China	CVD	Zhongnan Hospital of Wuhan, University in Wuhan, China	HP, CVD, DM, CLD, CRVD, COPD, CKD, Ca, HIV	138	20	115	9/36	11/102		
ioyal et al. [14]	USA	CAD	An 862-bed quaternary referral center and an affiliated 180-bed nonteaching community hospital in Manhattan	DM, obesity, HP, COPD, asthma, CAD	393	54	339	25/130	29/263		
hang et al. [15]	China	CVD	Zhongnan Hospital of Wuhan University, Wuhan, China	HP, CVD, DM, CLD, CRVD, COPD, CKD, Ca, immunosuppression	221	22	199	13/55	9/166		
lu et al. [16]	NSA	CVD	Tianyou Hospital, Wuhan University of Science and Technology, China	HP, CVD, DM, CLD, CRVD, COPD, CKD, Ca, cirrhosis	323	34	289	30/172	4/151		
tuo et al. [<mark>17</mark>]	China	CHD	The Seventh Hospital of Wuhan City, China	HP, CHD, DM, COPD, CKD, Ca, cardiomyopathy	187	29	158				
hang et al. [18]	China	CVD	The Seventh Hospital of Wuhan City, China	HP, DM, CHD, HL, CG, CVD, CKD, CRVD, COPD, arrhythmia cholelithiasis, fatty liver, thyroid diseases	140	15	125	10/58	5/82		
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Fable 1. Number of patients with CVD comorbidities among coronavirus disease 2019 patients

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Table

брг	Country	Condition	Setting	Comorbidities	Sample size (<i>n</i>)	Events (<i>n</i>)	Non- events (n)	Severe cases ratio	Non- severe cases ratio	Non- survivors	Survivors
et al. [19]	China	CHD	Hannan Hospital and Wuhan Union Hospital of Wuhan City, China	HP, DM, CHD, CRVD, CLD, COPD, CKD, Ca	85	10	75				
senberg et al. 20]	NSA	CVDs	25 hospitals in the New York City, metropolitan region	Obesity, cancer, CKD, COPD, DM, HP, CAD, CHD, dementia	1,438	468	1,000				
i et al. [21]	China	CVDs	Renmin Hospital, Zhongnan Hospital, Tongji Hospital, and Central Hospital in Wuhan	HP, Ca, DM, CVD, CRVD, COPD, CKD	34	2	27	6/15	1/19		
ercuro et al. 22]	NSA	CVDs	An academic tertiary care center in Boston, Massachusetts	HP, CHF, DM, CAD, AF, COPD, asthma	06	19	71				
ıleh et al. [23]	NSA	CVDs	14 hospitals of the New York State Northwell Health system	HP, HL, DM, AF, CAD, COPD, CKD, CHF	201	52	149				
ciardi et al. [24]	Italy	Cardiac disease	Civil Hospitals of Brescia, Lombardy, Italy	HP, HL, DM, HF, AF, CAD, COPD, CKD, Ca	66	53	46				
natla et al. [<mark>25</mark>]	NSA	CVDs	The Hospital of the University of Pennsylvania	CHD, HF, HP, AF, DM, COPD, CLD, CKD	700	203	497			48/79	155/621
ala et al. [26]	Italy	CAD	Seven COVID units at a third-level hub center, San Raffaele Hospital, Italy	CAD, COPD, HP, DM, Obesity, AF	132	6	123				
ızmann et al. [27]	NSA	CVD	Three hospitals in the Dakotas	Asthma, CHF, CVD, DM, RD, CKD, cirrhosis, Ca, immunosuppression	150	93	57				
uan et al. [4]	China	CHD	552 hospitals in 30 provinces, autonomous regions, and municipalities in mainland China	COPD, DM, HP, CHD, CRVD, HBV, CKD, immunosuppression	1,099	27	1,072	10/173	17/926		
in et al. [28]	China	CVD	Tongji Hospital	COPD, HP, CVD, CLD, DM, tuberculosis, Ca, CKD	452	27	425	24/286	3/166		
uang et al. [29]	China	CVD	2 hospitals in the Hubei provinces, China	HP, DM, CHD, Ca	223	13	210	86/6	4/125		
uang et al. [30]	China	CVD	Designated hospital in Wuhan	DM, HP, CVD, COPD, Ca, CLD	41	9	35	3/13	3/28		
'an et al. [31]	China	CVD	Chongqing University Three Gorges Hospital,	DM, CVD, HP, COPD, Ca, CLD	135	7	128	6/40	1/95		
ni et al. [<mark>32</mark>]	China	CVD	Renmin Hospital of Wuhan University	HP, DM, CAD, CRVD, CHF, CKD, COPD, Ca, HBV	416	61	355	36/82	25/334		
hou et al. [33]	China	CVD	Jinyintan Hospital and Wuhan Pulmonary Hospital	HP, DM, CHD, COPD, Ca, CKD	191	59	132			41/54	18/137
agi et al. [34]	Italy	CHD	University Hospital, Florence, Italy	DM, COPD, CHD, HP, HBV, CRVD, CKD	84	12	72	5/16	7/68		
ang et al. [35]	China	CVD	Zhongnan Hospital of Wuhan University in Wuhan and Xishui Hospital, Hubei Province, China	HP, CVD, DM, CLD, CVD, COPD, CKD	107	13	94			7/19	6/88
									(Cont	tinued to the	next page)

HP, DM, CVD, CHF, COPD, Ga, HBV, HN, CFWD, GKD, CG, Rable HW, IK, CFWD, GKD, CG, Rable HW, IK, CFWD, GKD, Buttommune disease 274 281 16/19 7/36 a HBV, HN, CFWD, GKD, CG, Rable HBV, HN, CFWD, GKD, Buttommune disease 52 5 47 3/32 2/20 a tutommune disease CVD, COPD, GRVD, DM, Ca, 52 5 47 3/32 2/20 frank HP, DM, CLD, Ca, CHD, CHP, COPD 510 966 4/734 3/32 2/20 MM, LD GOPD, Immune suppression 570 966 4/734 2/7108 4/85 MM, LD CAD, CHP, CAD, CHP, COPD, CLD 193 1 2/21 2/7108 4/85 MM, CDD, CAD, CHD 1590 59 1,531 20/55 2/41,531 4/85 MM, CDD, CAD, ML, CD	onditio	Setting	orbidities	Sample size (<i>n</i>)	Events (<i>n</i>)	Non- events (<i>n</i>)	Severe cases ratio	Non- severe cases ratio	Non- survivors	Survivors
Intersection CVD, COPD, CRVD, DM, Ca, Dementia 52 5 47 3/32 2/32 free permentia CVD, CRVD, Cac, CKD, CHD, CAC, CHT, COPD, Cac, CVD, CRVD, CKD, CAC, CPD, Cac, CVD, CRVD, CKD, CAC, CPD, Cac, CVD, CRVD, CRVD, CRVD, CAC, CPD, Cac, CVD 3/31 16/2 3/32 2/32 Sity, Long Cac, CVD, CRVD, CAC, CAPD, CBD, CLD 139 31 162 3/34 4/35 County, asthma CAC, CAPD, CRVD, CADD, CLD 139 31 162 3/41,531 4/35 Sevintial HP, CVD, CHF, CATMYLINIA, COPD 393 1,531 20/59 2341,531 4/35 Almotical HP, CVD, HL, DM, Ca, COPD, CG, CVD 303 1,368 2 2 2 an HP, CVD, HL, DM, Ca, COPD, CG 304 304 3	Wuhan Tongji Hospita	HP, DM, CVD, CI Ca, HBV, HIV, I CG, metabolic autoimmune c	CHF, COPD, , CRVD, CKD, ic arthritis, e disease	274	23	251			16/19	7/36
fCVD, CRVD, Ca9940594059gnatedCOPD, immunosuppression6515646	Wuhan Jin Yin-Tan Hosp	oital CVD, COPD, CR Dementia	RVD, DM, Ca,	52	ى ک	47			3/32	2/20
fHP, DM, CLD, Ca, CK0, CHD6515646gnatedCOPD, immunosuppression5,7009664,73420,1VDasthma27VD, HP, CAD, CHF, COPD15,909664,734County,asthma21,590591,53120/5927/108AmodalHP, DM, COPD, Ca, CVD1,590591,53120/594/85AmodalDM, CVD, CHF, Arrhythmia, COPD3057822727/1084/85AmodalDM, CVD, CHF, Arrhythmia, COPD3057822727/1084/85AmodalDM, CVD, CHF, Arrhythmia, COPD3057822727/1084/85AmodalDM, CVD, CHF, Arrhythmia, COPD3043062722/13318/211AmodalHP, DM, CD, COPD, CA, CVD, COPD3444030430621/10222/13318/211AmodalAmodal439521/3621/10222/13318/21122/13318/211AmodalCLDAmodal39319719670/130127/26328/1664/73AmodalHP, CVD, DM, CLD, CRVD, COPD32319519620/130127/26328/1664/73AmodalHP, CVD, DM, CLD, CRVD, COPD32319521/3621/10228/1664/73AmodalHP, CVD, DM, CLD, CRVD, COPD32319521/3621/1024/854/166AmodalHP, CVD, DM, CLD, CRVD, COPD32319521/3621/1024/16	Wuhan Jinyintan Hospit	al CVD, CRVD, Ca	u.	66	40	59				
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anHP, CVD, DM, CLD, CRVD, COPD, CKD, Ca, HIV138439521/102arrailDM, Obesity, HP, COPD, Asthma, S0-bed39319719670/130127/263anHP, CVD, DM, CLD, CRVD, COPD, CKD, Ca, immunosuppression2215516626/5528/166anHP, CVD, DM, CLD, CRVD, COPD, China2215516626/5528/166anHP, CVD, DM, CLD, CRVD, COPD, China32310521866/17239/151y, ChinaCKD, Ca, immunosuppression chole thy CVD, DM, CDD, CKD, CAD,18761126hanHP, CHD, DM, COPD, CKD, Ca, crutowpathy1876112626/5529/151JhanHP, CHD, DM, COPD, CKD, Ca1876112626/5620/82InanHP, DM, CHD, HL, CG, CVD, CKD, COPD, arrhythmia chole lithiasis, fatty liver, thyroid diseases140429822/5820/82	Tongji Hospital	HP, DM, CVD, C	COPD	344	40	304			22/133	18/211
erral DM, Obesity, HP, COPD, Asthma, 393 197 196 70/130 127/263 80-bed CAD hospital CAD an HP, CVD, DM, CLD, CRVD, COPD, 221 55 166 26/55 28/166 University HP, CVD, DM, CLD, CRVD, COPD, 323 105 218 66/172 39/151 gy, China CKD, Ca, immunosuppression Unhan HP, CHD, DM, CDD, CKD, Ca Uhan HP, CHD, ML, CG, CVD, 187 61 126 uhan HP, CHD, HL, CG, CVD, 140 42 98 22/58 20/82 uhan HP, DM, CHD, HL, CG, CVD, and the cardiomyopathy cholelithiasis, fatty liver, thyroid diseases	Zhongnan Hospital of Wuh University in Wuhan, Chir	ian HP, CVD, DM, Cl ia CKD, Ca, HIV	CLD, CRVD, COPD,	138	43	95 2	1/36	21/102		
Ian HP, CVD, DM, CLD, CRVD, COPD, CKD, Ca, immunosuppression 221 55 166 26/55 28/166 Iniversity HP, CVD, DM, CLD, CRVD, COPD, By, China 323 105 218 66/172 39/151 gy, China CKD, Ca, cirrhosis 105 218 66/172 39/151 uhan HP, CHD, DM, CDD, CKD, Ca, cardiomyopathy 187 61 126 uhan HP, DM, CHD, HL, CG, CVD, CKD, COPD, arrhythmia 140 42 98 22/58 20/82 uhan HP, DM, CHD, HL, CG, CVD, diseases 140 42 98 22/58 20/82	An 862-bed quaternary ref center and an affiliated nonteaching community in Manhattan	erral DM, Obesity, HF 180-bed CAD hospital	IP, COPD, Asthma,	393	197	196 7	0/130	127/263		
Jniversity HP, CVD, DM, CLD, CRVD, COPD, 323 105 218 66/172 39/151 gy, China CKD, Ca, cirrhosis 187 61 126 uhan HP, CHD, DM, COPD, CKD, Ca, 187 61 126 cardiomyopathy cardiomyopathy 140 42 98 22/58 20/82 CKD, CRVD, COPD, arrhythmia cholelithiasis, fatty liver, thyroid diseases	Zhongnan Hospital of Wu University, Wuhan, China	han HP, CVD, DM, Cl a CKD, Ca, imm	CLD, CRVD, COPD, nunosuppression	221	55	166 2	6/55	28/166		
 ^{(uhan} HP, CHD, DM, COPD, CKD, Ca, 187 61 126 ^{(uhan} HP, DM, CHD, HL, CG, CVD, 140 42 98 22/58 20/82 ^{(uhan} HP, DM, CHD, HL, CG, CVD, arrhythmia ^{(cholelithiasis, fatty liver, thyroid diseases} 	Tianyou Hospital, Wuhan of Science and Technol	University HP, CVD, DM, Cl ogy, China CKD, Ca, cirrh	CLD, CRVD, COPD, hosis	323	105	218 6	6/172	39/151		
uhan HP, DM, CHD, HL, CG, CVD, 140 42 98 22/58 20/82 CKD, CRVD, COPD, arrhythmia cholelithiasis, fatty liver, thyroid diseases	The Seventh Hospital of V City, China	Vuhan HP, CHD, DM, C cardiomyopat	COPD, CKD, Ca, athy	187	61	126				
	The Seventh Hospital of V City, China	Wuhan HP, DM, CHD, H CKD, CRVD, C cholelithiasis, diseases	HL, CG, CVD, COPD, arrhythmia s, fatty liver, thyroid	140	42	98	2/58	20/82		

Table 1. Continued

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Study	Country	Condition	Setting	Comorbidities	Sample size (<i>n</i>)	Events (n)	Non- events (n)	Severe cases ratio	Non- severe cases ratio	Non- survivors	Survivors
Du et al. [19]	China	ЧH	Hannan Hospital and Wuhan Union Hospital of Wuhan City, China	HP, DM, CHD, CRVD, CLD, COPD, CKD, Ca	85	32	53				
Rosenberg et al. [20]	NSA	ЧH	25 hospitals in the New York City, metropolitan region	Obesity, cancer, CKD, COPD, DM, HP, CAD, CHD, dementia	1,438	816	622				
Lei et al. [21]	China	Ч	Renmin Hospital, Zhongnan Hospital, Tongji Hospital, and Central Hospital in Wuhan	HP, Ca, DM, CVD,CRVD,COPD, CKD	34	13	21	9/15	4/19		
Mercuro et al. [22]	NSA	ЧH	An academic tertiary care center in Boston, Massachusetts	HP, CHF, DM, CAD, AF, COPD, asthma	06	48	42				
Saleh et al. [23]	NSA	НР	14 hospitals of the New York State Northwell Health system	HP, HL, DM, AF, CAD, COPD, CKD, CHF	201	121	80				
Inciardi et al. [24]	Italy	ЧH	Civil Hospitals of Brescia, Lombardy, Italy	HP, HL, DM, HF, AF, CAD, COPD, CKD, Ca	66	63	36				
Bhatla et al. [25]	NSA	ЧH	The Hospital of the University of Pennsylvania	CHD, HF, HP, AF, DM, COPD, CLD, CKD	700	347	353	62/79	285/621		
Sala et al. [26]	Italy	ЧH	Seven COVID units at a third-level hub center, San Raffaele Hospital, Italy	CAD, COPD, HP, DM, obesity, AF	132	60	72				
Guan et al. [4]	China	dН	552 hospitals in 30 provinces, autonomous regions, and municipalities in mainland China	COPD, DM, HP, CHD, CRVD, HBV, CKD, immunosuppression	1,099	165	934	41/173	124/926		
Qin et al. [28]	China	ЧH	Tongji Hospital	COPD, HP, CVD, CLD, DM, tuberculosis, Ca, CKD	452	135	317	105/286	30/166		
Huang et al. [29]	China	НР	2 hospitals in the Hubei provinces, China	HP, DM, CHD, Ca	223	40	180	38/98	12/125		
Huang et al. [30]	China	НР	Designated hospital in Wuhan	DM, HP, CVD, COPD, Ca, CLD	41	9	35	2/13	4/28		
Wan et al. [31]	China	ЧH	Chongqing University Three Gorges Hospital	DM, CVD, HP, COPD, Ca, CLD	135	13	122	4/40	9/95		
Shi et al. [32]	China	ЧH	Renmin Hospital of Wuhan University	HP, DM, CAD, CRVD, CHF, CKD, COPD, Ca, HBV	416	127	289	49/82	78/334		
Zhou et al. [33]	China	НР	Jinyintan Hospital and Wuhan Pulmonary Hospital	HP, DM, CHD, COPD, Ca, CKD	191	58	133			26/54	32/137
Lagi et al. [34]	Italy	ЧH	University Hospital, Florence, Italy	DM, COPD, CHD, HP, HBV, CRVD, CKD	84	31	53	5/16	26/68		
Wang et al. [35]	China	dН	Zhongnan Hospital of Wuhan University in Wuhan and Xishui Hospital, Hubei Province, China	HP, CVD, DM, CLD, CVD, COPD, CKD	107	26	81			10/19	16/88
Richardson et al. [13]	NSA	dН	12 hospitals in New York City, Long Island, and Westchester County, New York	ca, CVD, HP, CAD, CHF, COPD, asthma	5,700	3026	2674				
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s Surv	16,				72	hronic lure; AF	A
Non- survivor	57/108				69/133	;; CKD, cl heart fail	p C
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sever sever cases ratio						conges	n
Severe cases ratio						tive pulmo tritis; CHF,	D
Non- events (<i>n</i>)	120	1,321	66	1,082	203	c obstruc ironic gas	st C
Events (n)	73	269	206	509	141	D, chroni ia; CG, ch	a: fr
mple e (n)	33	290)5	591	14	e; COP	tł h
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/211 kidney clinical characteristics by site or clinic.

Assessment of Publication Bias

Publication bias was evaluated visually using a funnel plot. As shown in Figure 8 on the event rate of pre-existing cardiovascular comorbidity, a visual symmetry indicates the absence of publication bias. The Egger test also revealed no significant publication bias (Egger test, p = 0.09).

Discussion

n the present meta-analysis, we examined 36 independent tudies reporting clinical data on 19,156 patients with OVID-19 worldwide. The studies included in this metanalvsis include the latest research available on COVID-19 rom January to July 2020. Our pooled analyses indicated hat pre-existing cardiovascular diseases, in particular uppertension and coronary heart disease, are prevalent mong patients with COVID-19. Our pooled analyses lso clearly showed that the presence of pre-existing ardiovascular disease, including hypertension and coronary eart disease, is associated with COVID-19 severity and/or atality. This association can be confounded by older age, atients with poor outcomes may be older and have more ardiovascular events [43]. In this analysis meta-regression data are not shown) using the method of moments of the ffect of age, reported as mean or median, on association f pre-existing cardiovascular disease with COVID-19 utcomes revealed that age was significantly associated nly with estimated OR for severity in patients with prexisting cardiovascular disease.

In comparison, another meta-analysis of 6 published studies from China including 1,527 patients with COVID-19 that reported a 16.4% prevalence of cardio-cerebrovascular disease [44]. Another analysis of 7 Chinese studies showed that the prevalence of cardiovascular disease and that of hypertension were 21% and 8%, respectively [45]. Our meta-analysis on data from different countries reported a 14% prevalence of cardiovascular disease.

Pre-existing cardiovascular disease was associated with a 4-fold and 6-fold greater risk of disease severity and fatality, respectively. A previous study that analysed data of COVID-19 patients until March 20, 2020 found that cardiovascular disease increased the odds of combined critical/fatal cases of COVID-19 by 5 times [46] and in particular, hypertension was found to increase the odds of combined critical and fatal cases by 2.7 times. The main difference between our analysis and that by Zheng et al. [46] is that we analysed data separately for COVID-19 severity and mortality, while Zheng et al. [46] combined

Fable 1. Continued

Study name	Outcome	St	atistics	for eacl	n study		Event	rate and 9	5% CI		
		Event rate	Lower limit	Upper limit	p-value						Relative weight
Bhatla A	Cardiovascular diseases	0.29	0.26	0.32	0		1			k	3.04
Chen N	Cardiovascular diseases	0.40	0.31	0.50	0.057748027					>	2.87
Chen TL	Cardiovascular diseases	0.08	0.06	0.12	0						2.84
Du Y	Coronary heart disease	0.12	0.06	0.21	0					-	2.57
Enzmann MO	Cardiovascular disease	0.62	0.54	0.69	0.003611517				Т	>	2.93
Gold JAW	Cardiovascular diseases	0.26	0.21	0.31	0					\rightarrow	2.99
Goyal P	Coronary artery disease	0.14	0.11	0.18	0						2.97
Grasselli G	Cardiovascular diseases	0.14	0.12	0.16	0						3.05
Guan W	Coronary heart disease	0.02	0.02	0.04	0						2.89
Guan WJ	Cardiovascular diseases	0.04	0.03	0.05	0						2.99
Guo T	Coronary heart disease	0.16	0.11	0.21	0				∎	-	2.87
Hu L	Cardiovascular disease	0.11	0.08	0.14	0				-₩		2.91
Huang C	Cardiovascular disease	0.15	0.07	0.29	0.000065710					\longrightarrow	2.30
Huang Y	Cardiovascular disease	0.06	0.03	0.10	0			4			2.70
Inciardi R	Cardiac disease	0.54	0.44	0.63	0.482093989					>	2.87
Jin X	Cardiovascular disease	0.01	0.00	0.02	0						2.28
Lagi F	Coronary heart disease	0.14	0.08	0.23	0			Г			2.63
Lei S	Cardiovascular disease	0.21	0.10	0.37	0.001458868						2.35
Mercuro NJ	Cardiovascular diseases	0.21	0.14	0.31	0.00000333				— ·		2.76
Qin C	Cardiovascular disease	0.06	0.04	0.09	0			- 1 4	∎-		2.88
Richardson S	Cardiovascular diseases	0.17	0.16	0.18	0						3.07
Rosenberg E	Cardiovascular diseases	0.32	0.30	0.34	0					>	3.06
Sala S	Coronary heart disease	0.07	0.04	0.13	0						2.55
Saleh M	Cardiovascular disease	0.26	0.20	0.32	0				_	\rightarrow	2.94
Shi S	Cardiovascular disease	0.15	0.12	0.18	0						2.98
Wan S	Cardiovascular disease	0.05	0.02	0.10	0						2.44
Wang D2	Cardiovascular disease	0.12	0.07	0.20	0					-	2.67
Wang D1	Cardiovascular disease	0.14	0.10	0.21	0					-	2.79
Wang Y	Cardiovascular disease	0.12	0.09	0.15	0						2.93
Yan Y	Cardiovascular disease	0.16	0.12	0.22	0				╶╴╋╌╋	-	2.88
Yang X	Chronic cardiac disease	0.10	0.04	0.21	0.000001903			-	╶╴┫┫┤────	-	222
Zhang G	Cardiovascular disease	0.10	0.07	0.15	0				╶╋╋┼╌		2.83
Zhang J	Cardiovascular disease	0.11	0.07	0.17	0						2.72
Zhou F	Cardiovascular disease	0.31	0.25	0.38	0.000000272					>	2.95
		0.14	0.11	0.18	0						
						-0.25	-0.13	0	0.13	0.25	
							Favours A		Favours B		

Figure 2. Pooled event rate of pre-existing cardiovascular disease in patients with coronavirus disease 2019. Cl, confidence interval.

 Table 2. Effect of cardiovascular comorbidities on severity and mortality outcomes associated with coronavirus disease

 2019

Comoutidity	Sev	verity	Morta	lity
Comorbialty	No. of studies	OR (95% CI)	No. of studies	OR (95% CI)
Pre-existing cardiovascular diseases	14	4.1 (2.9 to 5.7)	7	6.1 (2.9 to 12.7)
Hypertension	14	2.6 (1.9 to 3.6)	4	3.2 (2.0 to 5.0)
Coronary heart disease	4	2.5 (1.7 to 3.8)	-	-

OR, odds ratio; CI, confidence interval; -, no data available to run analysis.

Odds ratio and 95% CI

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Study name	Outcome		Statis	tics for	each stu	ıdy
		Odds ratio	Lower limit	Upper limit	Z-value	p-value
Goyal P	Severe vs. nonsevere CVD	1.9	1.1	3.4	2.198	0.027979863
Guan W	Severe vs. nonsevere CHD	3.3	1.5	7.3	2.915	0.003554210
Guan WJ	Severe vs. nonsevere CVD	2.8	1.6	5.0	3.678	0.000235344
Hu L	Severe vs. nonsevere CVD	7.8	2.7	22.6	3.760	0.000170188
Huang C	Severe vs. nonsevere CVD	2.5	0.4	14.5	1.020	0.307632594
Huang Y	Severe vs. nonsevere CVD	3.1	0.9	10.2	1.812	0.069937583
Lagi F	Severe vs. nonsevere CVD	4.0	1.1	14.8	2.052	0.040207525
Lei S	Severe vs. nonsevere CVD	12.0	1.2	115.4	2.152	0.031397962
Qin C	Severe vs. nonsevere CVD	5.0	1.5	16.8	2.587	0.009692591
Shi S	Severe vs. nonsevere CVD	9.7	5.3	17.6	7.451	0
Wan S	Severe vs. nonsevere CVD	16.6	1.9	142.8	2.557	0.010563107
Wang D	Severe vs. nonsevere CVD	2.8	1.0	7.3	2.029	0.042507585
Zhang G	Severe vs. nonsevere CVD	5.4	2.2	13.5	3.610	0.000306320
Zhang JJ	Severe vs. nonsevere CVD	3.2	1.0	10.0	2.018	0.043625894
		4.1	2.9	5.7	8.043	0









data on COVID-19 critical conditions and mortality. Another previous meta-analysis [44] that included only studies from China reported that comorbid hypertension increased COVID-19 severity by 2-fold, suggesting the prognostic impact of this comorbidity. Our results clearly confirm previous findings and add to them. Li et al. [44] were not able to provide data on cardiovascular comorbidities and death from COVID-19 as data collection was incomplete, and most of the included studies in their analysis did not analyse comorbidities in death cases. Another analysis by Luo et al. [47] included a larger number of studies and found that hypertension was associated with 2.5 times higher odds of mortality; however, considerable heterogeneity was also reported. In this analysis, the relationship between hypertension comorbidity and COVID-19-induced death was pooled using data from China and other countries using a random-effect model to account for heterogeneity. Hypertension was associated with a 3-fold increased fatality rate. The American Heart Association and the American College of Cardiology define hypertension as systolic blood pressure (BP) \geq 130 or diastolic BP \geq 80 mmHg, and hypertension is a primary risk factor associated with atherosclerotic cardiovascular disease [48]. In line with our analysis, several studies identified high rates of hypertension among severely symptomatic COVID-19 patients [5,12,13]. Roughly half of United States patients

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Study name	Outcome		Statis	tics for	each stu	ıdy
		Odds ratio	Lower limit	Upper limit	Z-value	p-value
Bhatla A	Severe vs. nonsevere HP	4.3	2.5	7.5	5.111	0.00000320
Goyal P	Severe vs. nonsevere HP	1.2	0.8	1.9	1.036	0.300227066
Guan W	Severe vs. nonsevere HP	2.0	1.3	3.0	3.434	0.000595642
Hu L	Severe vs. nonsevere HP	1.8	1.1	2.9	2.389	0.016874520
Huang C	Severe vs. nonsevere HP	1.1	0.2	6.9	0.093	0.926206256
Huang Y	Severe vs. nonsevere HP	6.0	2.9	12.3	4.857	0.000001191
Lagi F	Severe vs. nonsevere HP	0.7	0.2	2.4	-0.520	0.603235194
Lei S	Severe vs. nonsevere HP	5.6	1.2	25.5	2.240	0.025076112
Qin C	Severe vs. nonsevere HP	2.6	1.7	4.2	4.096	0.000042091
Shi S	Severe vs. nonsevere HP	4.9	2.9	8.1	6.099	0
Wan S	Severe vs. nonsevere HP	1.1	0.3	3.7	0.095	0.924595887
Wang D 1	Severe vs. nonsevere HP	5.2	2.3	11.6	3.953	0.000077141
Zhang JJ	Severe vs. nonsevere HP	1.9	0.9	3.9	1.712	0.086987235
Zhang G	Severe vs. nonsevere HP	4.4	2.3	8.6	4.364	0.000012748
		2.6	1.9	3.6	5.769	0



Figure 5. Forest plot of the odds ratios of pre-existing hypertension (HP) in severe compared to non-severe coronavirus disease 2019 cases. CI, confidence interval.

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Study name	Outcome		Statis	tics for	each st	udy			Odds ratio	and 959	% CI		
		Odds ratio	Lower limit	Upper limit	Z-value	p-value							Relative weight
Wang Y	Nonsurvivors vs. survivors HP	2.1	1.3	3.2	3.240	0.001197214							36.23
Yan Y	Nonsurvivors vs. survivors HP	4.8	2.5	9.3	4.655	0.000003238				-			25.12
Zhou F	Nonsurvivors vs. survivors HP	3.0	1.6	5.9	3.286	0.001015958				-	H		25.03
Wang D 2	Nonsurvivors vs. survivors HP	5.0	1.7	14.3	3.002	0.002685497					■┼		13.62
		3.2	2.0	5.0	5.101	0.00000337							
							0.01	0.	1	1	10	100	
								Favou	irs A		Favours B		

Figure 6. Forest plot of the odds ratios of pre-existing hypertension (HP) non-survivor compared to survivor coronavirus disease 2019 patients. Cl, confidence interval.



Figure 7. Forest plot of the odds ratios of pre-existing coronary heart disease (CHD) in severe cases compared to non-severe coronavirus disease 2019 cases. CAD, coronary artery disease; CI, confidence interval.

Relative

weight 50.20

26.69

9.84

13.27



Figure 8. Funnel plot for publication bias based on cardiovascular comorbidity.

with hypertension are prescribed angiotensin-converting enzyme (ACE) inhibitors, aldosterone receptor blockers, and aldosterone antagonists, collectively called reninangiotensin-aldosterone system (RAAS) inhibitors [49]. The modulator of the RAAS is the ACE2 receptor, which is used by SARS-CoV-2 to bind via its spike (S) protein to allow entry into attached cells. The activation of the RAAS is suggested as a mechanism for severe lung injury, especially in COVID-19 patients [50]. Inhibition of the protective signaling pathways in cardiac myocytes may result in secondary the downregulation of ACE2 expression within the myocardium. Finally, COVID-19 infection induces profound changes in coagulation pathways that create a hypercoagulable state and risk of microvascular thrombosis [51].

A strength of our pooled analysis is that it included more studies than some of the previous ones, and thus a larger sample size from different countries compared to the previous meta-analyses. Hence, our pooled analysis is the most inclusive and up-to-date analysis. The mechanism by which pre-existing cardiovascular disease increases the risk of COVID-19 adverse outcomes is also thought to be through the way that drugs for this disease work [52]. However, studies did not report data on the type of medications prescribed for each comorbidity, and hence we were not able to perform subgroup analyses by medication type. Such analyses are needed in further research. Another strength of this analysis is that visual symmetry in the funnel plot indicates the absence of publication bias. A limitation of this analysis is that most studies did not report the eligibility criteria and whether participants were recruited consecutively. Therefore, selection bias is a likely concern in the included studies. Other biases in the included studies are less likely since all studies sufficiently addressed other points in the JBI tool. Another limitation of this analysis is the possible effect of confounding factors including age, sex, and presence of other comorbidities that contribute to heterogeneity of the included studies. However, we used a random-effect model that addresses heterogeneity.

Conclusion

In summary, the present evidence showed that pre-existing cardiovascular disease in general, as well as hypertension and coronary heart disease, are highly associated with the severity and the mortality rate of COVID-19. Awareness of pre-existing cardiovascular comorbidities is important for the early management of COVID-19.

Supplementary Material

Table S1. Quality assessment of the studies on cardiovascular disease as a comorbidity in coronavirus disease 2019 patients using the Joanna Briggs Institute's tool. Supplementary data are available at https://doi.org/10.24171/j.phrp.2021.0186.

Notes

Ethics Approval

Not applicable.

Conflicts of Interest

The authors have no conflicts of interest to declare.

Funding

None.

Availability of Data

The datasets are not publicly available but are available from the corresponding author upon reasonable request.

Authors' Contributions

Conceptualization: FA; Data curation: FA, SA, MA; Formal analysis: SA; Investigation: FA; Methodology: FA, SA; Project administration: FA; Software: SA; Supervision: FA; Validation: all authors; Visualization: FA, SA; Writing–original draft: FA, SA; Writing–review & editing: all authors.

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