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A meta-analysis on the risk factors adjusted association between cardiovascular disease and COVID-19 severity

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Abstract

Background: Cardiovascular disease (CVD), one of the most common comorbidities of coronavirus disease 2019 (COVID-19), has been suspected to be associated with adverse outcomes in COVID-19 patients, but their correlation remains controversial.

Method: This is a quantitative meta-analysis on the basis of adjusted effect estimates. PubMed, Web of Science, MedRxiv, Scopus, Elsevier ScienceDirect, Cochrane Library and EMBASE were searched comprehensively to obtain a complete data source up to January 7, 2021. Pooled effects (hazard ratio (HR), odds ratio (OR)) and the 95% confidence intervals (CIs) were estimated to evaluate the risk of the adverse outcomes in COVID-19 patients with CVD. Heterogeneity was assessed by Cochran's Q-statistic, I^2test, and meta-regression. In addition, we also provided the prediction interval, which was helpful for assessing whether the variation across studies was clinically significant. The robustness of the results was evaluated by sensitivity analysis. Publication bias was assessed by Begg's test, Egger's test, and trim-and-fill method.

Result: Our results revealed that COVID-19 patients with pre-existing CVD tended more to adverse outcomes on the basis of 203 eligible studies with 24,032,712 cases (pooled ORs = 1.41, 95% CIs: 1.32-1.51, prediction interval: 0.84-2.39; pooled HRs = 1.34, 95% CIs: 1.23-1.46, prediction interval: 0.82-2.21). Further subgroup analyses stratified by age, the proportion of males, study design, disease types, sample size, region and disease outcomes also showed that pre-existing CVD was significantly associated with adverse outcomes among COVID-19 patients.

Conclusion: Our findings demonstrated that pre-existing CVD was an independent risk factor associated with adverse outcomes among COVID-19 patients.

Keywords: Coronavirus disease 2019, cardiovascular disease, adverse outcome, adjusted effect estimate

Introduction

Since December 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a global outbreak of coronavirus disease 2019 (COVID-19). Currently, the pandemic has affected more than 127,319,002 people in more than 200 countries and killed more than 2,785,838 people (https://www.who.int/emergencies/diseases/novel-coronavirus-2019). Previous studies have reported that several pre-existing medical conditions, such as hypertension, diabetes and so on, might accelerate disease progression of COVID-19 [1–3]. Cardiovascular disease (CVD), one of the most common comorbidities of COVID-19, has been observed to be associated with adverse outcomes among COVID-19 patients by Li et al. in a meta-analysis study [4]. Nevertheless, it is worth noting that the results of Li et al.'s study were based on the

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unadjusted effect estimates [4]. It is reported that age, sex, and co-existing diseases are known to affect the outcomes of COVID-19 patients [5–7], which may modulate the association between CVD and adverse outcomes in COVID-19 patients. Moreover, Zhou et al. observed that coronary heart disease (CHD), one of CVD, was strongly correlated with an increased risk of in-hospital mortality among COVID-19 patients in univariable analysis (odds ratio (OR) = 21.4, 95% confidence interval (CI): 4.64-98.76), but no significant correlation was observed in multivariable analysis (OR = 2.14, 95% CI: 0.26-17.79) [8]. The similar results were also observed by Robilotti et al. [9] and Louapre et al. [10]. Therefore, it is necessary to clarify whether pre-existing CVD was an independent risk factor associated with adverse outcomes in COVID-19 patients. In this study, we performed a quantitative meta-analysis on the basis of adjusted effect estimates.

Methods

This is a quantitative meta-analysis on the basis of adjusted effect estimates. Admittedly, our study was not registered, but our meta-analysis was made in strict accordance with the process of systematic evaluation (Fig. 1). Moreover, our study is less likely to be biased by artificial bias because this study was carried out rigorously in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines (Online supplemental Table A1) [11].

Literature search strategy

The databases of PubMed, Web of Science, MedRxiv, Scopus, Elsevier ScienceDirect, Cochrane Library and Embase were searched to obtain a complete data source up to January 7, 2021. The search strategies were as follows: ("COVID-19" OR "coronavirus disease 2019" OR "SARS-CoV-2" OR "2019-nCoV") AND ("cardiovascular disease" OR "coronary heart disease" OR "cardiac disease" OR "heart disease" OR "heart failure" OR "coronary artery disease") AND ("outcome" OR "severe" OR "critical" OR "severity" OR "fatality" OR "mortality" OR "death" OR "adverse outcome" OR "poor outcome" OR "clinical characteristics"). All the terms matched the MesH browser. Beyond that, the relevant references of preceding studies were also taken into account.

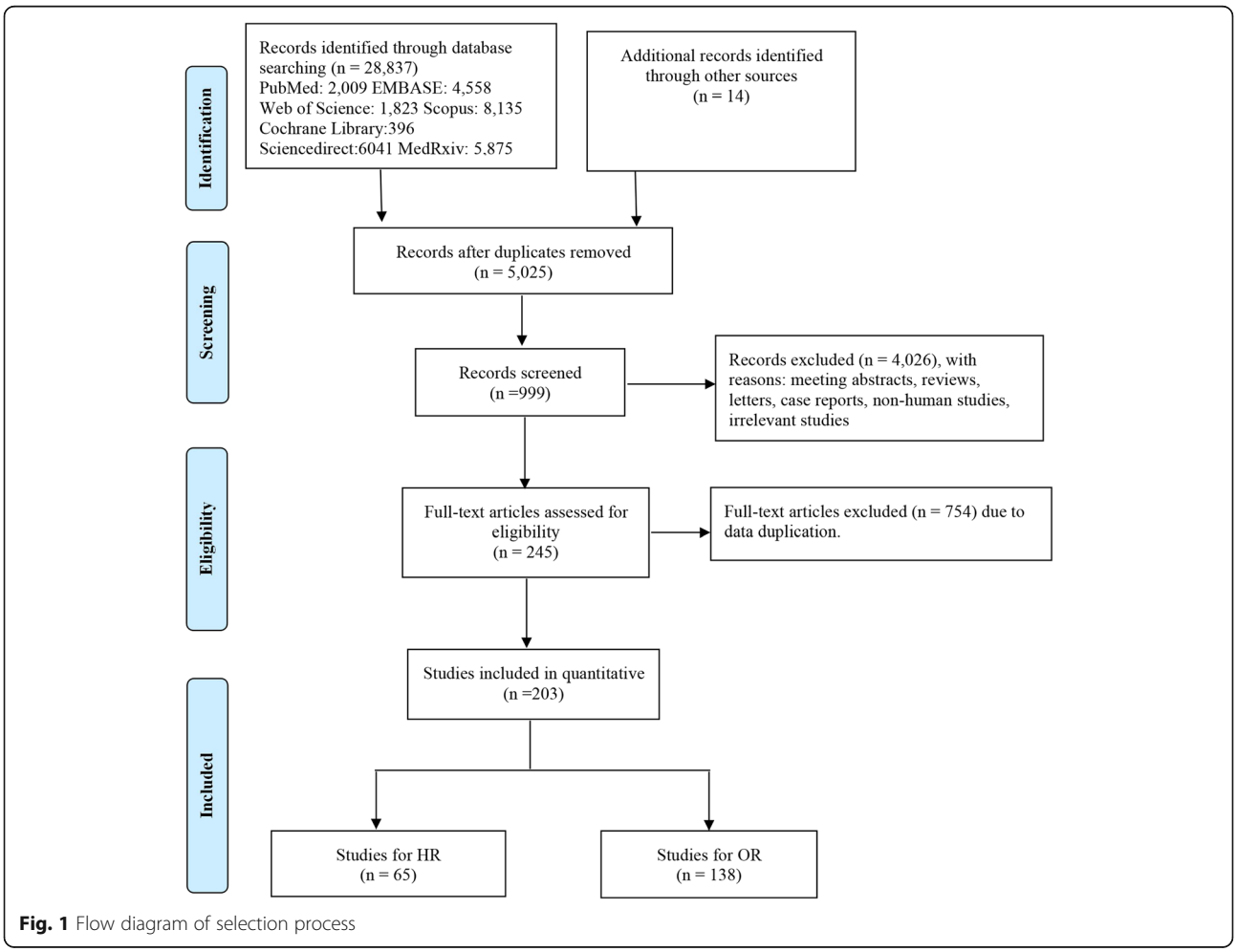

Fig. 1 Flow diagram of selection process

Table 1 Main characteristics of the included studies

Author (Year)	Country	Patients(n)	Mean/ Median Age(years)	Male (%)	Study design	Kinds of diseases	CVD (%)	Adjusted effect estimate (95%CI)	Outcome	Confounders	NOS Score
Zhou et al. (2020) [8]	China	191	56·0 (46·0–67·0)	119 (62)	Retrospective cohort study	Coronary heart disease	18 (8)	OR 2.14 (0.26-17.79)	In-hospital death	Age, SOFA score	7
Yu et al. (2020) [19]	China	333	50(35-63)	172 (51.7)	Descriptive study	Heart disease	24 (7.2)	OR 4.2 (1.2-14.2)	Severity	Age, sex, diabetes, HTN, respiratory disease	8
Cummings et al. (2020) [3]	USA	257	62 (51–72)	171 (67)	Prospective observational cohort study t	Chronic cardiac disease	49 (19)	HR 1.76 (1.08-2.86)	In-hospital mortality	Age, gender, symptom duration before hospital, presentation, COPD or interstitial lung disease, diabetes, IL-6, D-dimer	8
Zhao et al. (2020) [20]	China	1000	61 (46-70)	466 (46.6)	Retrospective study	Coronary heart disease	60 (6)	HR 0.972 (0.547-1.726)	Death	Age	8
Sabri et al. (2020) [21]	Iran	60	54.1±15.5	NR	Retrospective cohort study	Heart Disease	10 (15.9)	OR 1.12 (1.08-1.14)	ICU admission	Pericardial effusion, blood oxygen saturation	7
Lala et al. (2020) [22]	USA	2736	66.4	1630 (59.6)	NR	Coronary Artery Disease	453 (16.6)	OR 1.08 (0.85-1.37)	Mortality	age, sex, BMI, race, ethnicity, history of CAD, history of AF, history of HF, history of HTN, history of CKD, history of DM, statin use, angiotensin converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) use, and CURB-65 score at hospital admission	7
Cen et al. (2020) [2]	China	1007	61(49-68)	493(49.0)	Multi-center observational study	Coronary artery disease	65 (6.5)	HR 1.828 (1.256-2.660)	Disease progression was defined as progression to the severe or critical disease stage, or death	Age, sex, smoking history, HTN, diabetes, chronic obstructive lung disease, CAD, CRD, CVA, hepatitis B infection, anti-viral drug, aeration of anti-viral therapy	7
Ciceri et al. (2020) [23]	Italy	410	65 (56-75)	299 (72.9)	NR	Coronary artery disease	51 (12.6)	HR 2.93 (1.77-4.86)	Death	Age, gender, cancer, radiographic assessment of lung edema score, WBC count, lymphocyte count, hemoglobin, platelets.	7
Barman et al. (2020) [24]	Turkey	607	59.5±14.8	334 (55.02)	Multi-center retrospective study	Coronary artery disease	116 (19.1)	OR 1.26 (1.06-1.50)	Mortality	Age, gender, HTN, diabetes, CAD, COPD, smoking, creatinine, uric acid, glucose	7
Bravi et al. (2020) [25]	Italy	1603	58.0±20.9	758 (47.36)	Case-control, retrospective study	Major cardiovascular diseases	258 (16.1)	OR 1.88 (1.32-2.70)	Severe or very severe/lethal	Age, gender, HTN, diabetes, cancer, COPD, renal disease	7

Table 1 Main characteristics of the included studies *(Continued)*

Author (Year)	Country	Patients(n)	Mean/ Median Age(years)	Male (%)	Study design	Kinds of diseases	CVD (%)	Adjusted effect estimate (95%CI)	Outcome	Confounders	NOS Score
Deiana et al. (2020) [26]	Italy	1223	80.4±10.6	499 (40.8)	Matched case-control study	CVD	63 (64.9)	OR 4.0 (1.7-9.7)	Severity	Active tumors, diabetes, HIV, CLD, CRD, metabolic diseases, obesity, chronic neurological diseases, other pathologies	7
Zhang et al. (2020) [27]	China	80	51.16± 17.476	33 (41.25)	Retrospective cohort	Cardiac disease	9 (11.25)	HR 0.21 (0-22.09)	Severity	Age, respiratory diseases, HTN, more than 2 kinds of diseases, WBC, neutrophil, LYM%, NEU%, NLR, FIB, CRP, TBIL, ALB, GFR, CK-MB, myoglobin, troponin	7
Nie et al. (2020) [28]	China	671	43±15.09	377 (56.2)	NR	CVD	70 (10.4)	OR 0.809 (0.306–2.142)	Severity	Age, gender, coexisting disorder (HTN, diabetes, respiratory diseases, diabetes, respiratory diseases), Animal/ human transmission source contact, Contact with confirmed cases, Contact with confirmed cases, Contact with individuals who had been to Wuhan, Close to cluster outbreak, Visited hospital, Visited wet market, No contact, Days from illness onset to diagnosis, X-ray with pneumonia features, CT with pneumonia features, Blood routine test Leucocyte count, Lymphocyte count, Lymphocyte percentage, Neutrophil percentage	7
Robilotti et al. (2020) [9]	USA	423	60.2	212 (50)	NR	Cardiac disorder	84 (20)	HR 1.44 (0.88-2.37)	Severe respiratory illness,	Age, gender, race, BMI, smoking, asthma/COPD, cancer, major surgery, diabetes, HTN/CKI, Systemic chemotherapy, Chronic lymphopenia or corticosteroids, ICI	8
Hashemi et al. (2020) [29]	USA	363	63.2±13.2	201 (55.37)	Multi-center retrospective study	Cardiac diseases	39 (10.7)	OR 0.98 (0.46-2.09)	Death	CLD, age, obesity, gender, HTN, diabetes, hyperlipidemia, pulmonary disorders	7
Lanza et al. (2020) [30]	Italy	222	66.4 (53.8–75.8)	163 (73)	Observational retrospective study,	Heart disease	27 (12.16)	OR 1.19 (0.58-2.44)	In-hospital death	Age, gender, smoke habit, CRP, Lung disease, cancer, diabetes, CKD, CURB-65a 1, CURB-65a 2, diabetes, BMI	8

Table 1 Main characteristics of the included studies *(Continued)*

Author (Year)	Country	Patients(n)	Mean/ Median Age(years)	Male (%)	Study design	Kinds of diseases	CVD (%)	Adjusted effect estimate (95%CI)	Outcome	Confounders	NOS Score
Zeng et al. (2020) [31]	China	461	45.00 (34.50-57.00)	239 (51.84)	Multicenter retrospective study	CVD	25 (5.42)	HR 2.30 (0.99-5.38)	Severity	Age, gender, HTN, diabetes, hematology, biochemistry, infection-related indices, co-agulation function	8
Petrilli et al. (2020) [32]	USA	5279	54 (38-66)	2615 (49.5)	Prospective cohort study	Coronary artery disease	704 (13.3)	OR 1.08 (0.81-1.44)	Mortality	Age, gender, BMI, race, COPD and asthma, diabetes, HTN, cirrhosis, CKD, CAD, immuno-suppression, cancer, tobacco smoking	8
Arshad et al. (2020) [33]	USA	2541	63.7±16.5	1298 (51.1)	Retrospective cohort study	Cardiovascular Comorbidity	222 (8.7)	HR 1.062 (0.8-1.410)	Death	HCQ alone (vs. neither medication), azithromycin alone (vs. neither medication), HCQ+AZM (vs. neither medication), age, gender, ethic, BMI,lung comorbidity, CKI comorbidity,COPD, HTN, asthma, COPD,cancer,diabetes, percent O2 saturation < 95, admission to ICU, ventilator, given steroid, given tocilizumab	7
San Román et al. (2020) [34]	Spain	522	68±15	294 (56)	NR	Heart disease	68 (13.02)	OR 2.017 (1.050-3.876)	Severity	Age, SatO2 <90%, creatinine > 1.5 mg/dL, c-reactive protein> 10 mg/L	7
Cheng et al. (2020) [35]	China	456	54.97± 18.59	211 (46.27)	Retrospective cohort study	CVD	52 (11.4)	OR 1.204 (0.554-2.619)	Any in-hospital disease progression	Age, gender, HTN, diabetes, CKD, neural system diseases, pulmonary disease, cancer, laboratory findings(leucocytes count, neutrophil count, lymphocyte count, NLR, platelet count, albumin, APTT, prothrombin time, INR, D-dimer, aspartate aminotrans-ferase, creatinine, potassium, creatine kinase, lactate de-hydrogenase, procalcitonin, C-reactive protein, erythrocyte sedimentation rate, IL-6	8
Oussalah et al. (2020) [36]	France	149	65 (54–77)	91 (61.1)	Retrospective, longitudinal cohort study	CVD	38 (25.5)	OR 2.35 (0.35-15.68)	Death	Age, COPD, gender, creatinine >10.1 mg/L, HTN	8
Kim et al. (2020)[37]	Korea	9148	51*	3556 (38.9)	Observational Study	Heart failure	124 (1.4)	OR 3.17 (1.88–5.34)	Mortality	Gender, age, type of distiricts, high epidemic region and socio-economic status	8

Table 1 Main characteristics of the included studies *(Continued)*

Author (Year)	Country	Patients(n)	Mean/ Median Age(years)	Male (%)	Study design	Kinds of diseases	CVD (%)	Adjusted effect estimate (95%CI)	Outcome	Confounders	NOS Score
Chen et al. (2020) [38]	China	3309	62(49-69)	1642 (49.6)	Retrospective	CVD	242 (7.3)	OR 1.41 (0.94-2.13)	Death	Age, gender, HTN, diabetes, cerebrovascular disease, malignancy, CKI, COPD, days from onset to clinics (vs ≤5d), days from onset to admission (vs ≤12d)	9
Ferrante et al. (2020) [39]	Italy	332	66.9 (55.4-75.5)	237 (71.4)	Single-center cohort study	CAD	49 (14.5)	OR 2.14 (0.99-4.63)	Death	Age, HTN, CVA, Cancer, eGFR, PaO/FiO2 ratio, PA diameter, baseline ACEI/ARB use	7
Rastad et al. (2020) [40]	Iran	2597	54.8±16.9	1589 (53.7)	Retrospective cohort study	CVD	314 (10.6)	OR 0.61 (0.30, 1.24)	In-hospital mortality	WBC, neutrophils, lymphocytes, serum concentrations, creatinine, LDH, AST, ALT, Hb, ESR, CRP, age	8
Hwang et al. (2020) [41]	South Korea	103	67.62± 15.32	52 (50)	Retrospective cohort study	CVD	12 (12)	HR 2.556 (0.535–12.207))	Mortality	Age, diabetes, CLD, Alzheimer's dementia, stroke	7
Grasselli ei al. (2020) [42]	Italy	3988	63 (56-69)	3188 (79.9)	Retrospective, observational cohort study	Heart disease	533 (13.4)	HR 1.08 (0.91-1.29)	Death	Age, gender, respiratory support, HTN, hypercholesterolemia, type 2 diabetes, Malignancy, COPD, ACE inhibitor therapy, ARB therapy, statin, diuretic, PEEP at admission, FiO2 at admission, PaO2/FiO2 at admission	8
Deng et al. (2020) [43]	China	264	64.5 (53.3-74.0)	130 (49.2)	Retrospective study	Coronary heart disease	32 (12.1)	HR 1.855 (1.006-3.421)	Death	Age, gender, HTN, cTnI-ultra, CK-MB, MYO, NT-proBNP, Cr	7
Al-Salameh et al. (2020) [44]	France	433	72±14.3	226 (52.1)	Observational cohort	CVD	99 (31.2)	HR 1.84 (1.1-3.08)	Death	Age, diabetes, gender, abnormal LFTs	7
Atkins et al. (2020) [45]	UK	507	74.3±4.5	311 (61.3)	NR	CHD	108 (21.5)	OR 0.86 (0.55-1.36)	Death	Age, gender, race, education, atrial fibrillation, stroke, HTN, diabetes (type 2), CKD, depression, dementia, asthma, COPD, osteoporosis, osteoarthritis, delirium, pneumonia, falls/fragility fractures	8
Yao et al. (2020) [46]	USA	242	66.1±18.3	104 (42.98)	Single-institution retrospective	Heart Disease	39 (13.6)	HR 0.94 (0.43-2.07)	Mortality	Zinc sulfate (yes vs no), age, gender, COPD, clinical severity, lopinavir/ritonavir, steroids, IL-	8

Table 1 Main characteristics of the included studies *(Continued)*

Author (Year)	Country	Patients(n)	Mean/ Median Age(years)	Male (%)	Study design	Kinds of diseases	CVD (%)	Adjusted effect estimate (95%CI)	Outcome	Confounders	NOS Score
					study					6 receptor inhibitors,	
Pinto et al. (2020) [47]	Italy	1226	71.7±14.5	733 (59.8)	Observational cohort Study	CVD	NR (NR)	OR 1.58 (0.68–3.68)	Death	Age, sex, presence of metastatic disease, time since cancer diagnosis	7
Chilimuri et al. (2020) [48]	USA	375	63.0 (52.0-72.0)	236 (63)	Retrospective cohort study	CVD	62 (17)	OR 1.56 (0.78-3.11)	Mortality	Age, gender, HTN, lymphocyte, creative protein, alanine aminotransferase, aspartate aminotransferase, creatine kinase	8
Lian et al. (2020) [49]	China	232	NR	108 (46.5)	Retrospective study	Heart disease	31 (13.36)	HR 2.587 (1.156-5.787)	Severity	Age, NLR, multiple mottling and ground-glass opacity	8
Zhao et al. (2020) [50]	USA	641	58.9±17.5	358 (55.85)	Retrospective study	Heart failure	20 (3.12)	OR 33.48 (4.99-224.45)	Mortality	LDH, procalcitonin, smoking history, SpO2, lymphocyte count, procalcitonin, LDH, COPD, SpO2, heart rate, age	8
Wang et al. (2020) [51]	USA	1827	52.7±21.1	500 (32.6)	NR	CVD	589 (32.2)	OR 2.21 (1.21-4.04)	Severity	Gender, race, marital status, Insurance type, smoking history, BMI, comorbidities (diabetes, COPD, CKD, CLD, HTN, allergic rhinitis), SABA, combination	7
Garcia-Azoin et al. (2020) [52]	Spain	576	67.18± 14.75	326 (56.6)	Retrospective cohort study	Cardiac disease	154 (26.7)	OR 1.20 (0.730-1.999)	Mortality	mRS≥3, age, gender, HTN, diabetes, smoking, pulmonary disorders, cancer, chronic neurological disorders, immunosuppression	7
Alkhatib et al. (2020) [53]	USA	158	57±15.1	61 (38.6)	Retrospective cross-sectional analysis	Heart Failure	21 (13.3)	OR 2.4 (0.734-7.845)	Severity	Age, gender, diabetes, HTN, lung disease, CKD, BMI	7
Hernández-Galdamez et al. (2020) [54]	Mexico	211003	45.7±16.3	115442 (54.71)	Cross-sectional study	CVD	4949 (2.35)	OR 0.93 (0.87-1.00)	Death	At least one comorbidity/risk, CKD, immunosuppression, diabetes, COPD, HTN, asthma, obesity, smoking	8
Bellmann-Weiler et al. (2020) [55]	Australia	259	66.8±14.3	157 (60.62)	Retrospective	CVD	152 (58.62)	OR 2.127 (0.309–14.647)	Death	Age, CKD, COPD, eGFR, leukocytes, PCT, anemia,	8
Berenguer et al. (2020) [56]	Spain	4035	70 (56 – 80)	2433 (61)	Retrospective nationwide cohort study	Chronic heart disease	932 (23.3)	HR 1.58 (1.38-1.81)	Death	Gender, age, HTN, diabetes, COPD, obesity, CKI stage 4, liver cirrhosis, chronic neurological disorder, cancer, dementia, headache, myalgia/	7

Table 1 Main characteristics of the included studies *(Continued)*

Author (Year)	Country	Patients(n)	Mean/ Median Age(years)	Male (%)	Study design	Kinds of diseases	CVD (%)	Adjusted effect estimate (95%CI)	Outcome	Confounders	NOS Score
										arthralgia, anosmia, cough, sputum production, dyspnea, chest pain, vomiting/nausea, altered consciousness, low SaO2, WBC count, neutrophil-to-lymphocyte ratio, platelets, prolonged APTT, eGFR, ALT, CRP	
Gottlieb et al. (2020) [57]	USA	8673	41 (29 – 54)	4045 (46.6)	Retrospective case-control study t	Congestive Heart Failure	218 (14.7)	OR 1.45 (1.00-2.12)	Critical Illness	Age, gender, race, COPD, HTN, hyperlipidemia, diabetes, prior CVA, CKD, current ESRD, obstructive sleep apnea, bloodborne cancer, symptoms (anosmia, cough, headache, myalgias), labs(WBC, ALC,ANC/ ALC, total Bilirubin, albumin, AST, ALT, LDH, lactate, D-Dimer, CRP, ferritin, troponin)	8
Agarwal et al. (2020) [58]	USA	1126	67.9±13.7	630 (49.3)	Retrospective	CVD	754 (59)	OR 1.18 (0.88-1.57)	Mortality	Treatment regimen (noninsulin only, insulin 1 noninsulin, insulin only), HTN, CKD, COPD	7
Shang et al. (2020) [59]	China	2529	66	73 (64.6)	Retrospective	CHD	28 (24.8)	OR 5.611 (1.392-22.623)	Death	Age, D-dimer, PCT, LYM, diabetes, CRP, BUN	8
Shi et al. (2020)[60]	Iran	386	59.46± 15.82	236 (61.1)	Prospective, single-center study	CVD	97(25.1)	HR 1.121 (0.565-2.226)	Death	Age, diabetes, malignancy, CKD, CVA/TIA, previous ACEI/ ARB use, ARDs, AKI	7
Posso et al. (2020) [62]	Spain	834	60	400 (46.5)	Retrospective	Heart Failure	37 (37.4)	OR 1.6 (1.01-2.55)	Death	Age, gender	7
Shu et al. (2020) [63]	China	571	50.0 (38.0-59.0)	278 (48.7)	Single-center, retrospective cohort study	Coronary heart disease	12 (2.1)	OR 6.75 (0.629-72.61)	Severity	Smoke, HTN, diabetes, dyspnea, consolidation, interstitial abnormalities, lymphocyte counting	8
Parra-Bracamonte et al. (2020) [64]	Mexico	142690	45 (34.0-57.0)	79280 (56)	NR	Cardiopathy	3521 (2.0)	OR 1.012 (0.92-1.112)	Mortality	Age, gender, smoking, hospitalized, pneumonia, comorbidity (HTN, obesity, diabetes, COPD, asthma, immunosuppressed, CKD, other complication)	8
Pablos et al. (2020) [65]	Spain	456	65±17.9	182 (41)	Retrospective observational matched	Heart failure	106 (23.2)	OR 1.57 (0.93-2.66)	Composite severe COVID-19 outcome	CTD, age, gender, obesity, diabetes, glucocorticoids (any dose), antivirals	8

Table 1 Main characteristics of the included studies *(Continued)*

Author (Year)	Country	Patients(n)	Mean/ Median Age(years)	Male (%)	Study design	Kinds of diseases	CVD (%)	Adjusted effect estimate (95%CI)	Outcome	Confounders	NOS Score
					cohort study						
Zhang et al. (2020) [66]	China	461	51 (38-64)	264 (57.3)	Multicenter study	Coronary heart disease	25 (5.4)	OR 0.382 (0.096-1.526)	Critical illness	Age, gender, comorbidities (HTN, diabetes, CLD), types of previous surgery (gastrointestinal surgery, urogenital surgery, skeletal surgery, cardiovascular surgery, others), WBC, neutrophil, lymphocyte, LDH, hemoglobin, platelet, albumin, AST, ALT, DBIL, IBIL, TBIL, APTT, PT, D-dimer, creatinine, hs-CRP, procalcitonin, urea nitrogen, FBG, CT score)	8
Fox et al. (2020) [67]	USA	389	66.2±14.2	208 (46.5)	Single-center retrospective analysis	CAD	77 (19.79)	OR 1.579 (0.562–4.436)	In-hospital mortality	Age, BMI, gender, ethnic, Hispanic, others, COPD, asthma, CAD, HTN, atrial fibrillation, CKD	7
Vena et al. (2020) [68]	Italy	317	71 (60-82)	213 (67.2)	Retrospective study	CVD	63 (19.9)	OR 2.58 (1.07-6.25)	All-cause in-hospital mortality	AKI, age, CRP, IL-6	7
Ng et al. (2020) [69]	USA	10482	66	6239 (59.5)	Retrospective study	Heart Failure	920 (8.78)	OR 1.32 (1.14-1.53)	Death	Age, sex, race/ethnicity, BMI, diabetes mellitus, HTN, cancer, mechanical ventilation, use of vasoactive medication, hemoglobin, lymphocyte, blood urea nitrogen, albumin, C-reactive protein and ferritin	8
He et al. (2020) [70]	China	288	48.5 (34.3-62)	131(45.5)	Single-center, retrospective cohort study	CVD	85 (29.5)	OR 0.986 (0.052-18.588)	Death	Age, CKD, exposure history in Wuhan >2 weeks, diarrhea, WBC count, lymphocyte count, creatinine, PCT,	8
Gupta et al. (2020) [71]	USA	2626	63.99± 16.49	1497(57.00)	Retrospective study	CAD	516 (19.6)	OR 1.179 (0.844-1.647)	In-hospital mortality	Age, gender, CKD, exposure history in Wuhan >2 weeks, diarrhea, white blood cell count, lymphocyte count, creatinine	6
Czernichow et al. (2020) [72]	Europe	5795	59.8±13.6	3791 (65.4)	Prospective cohort study	HF	264 (4.55)	OR 1.15 (0.82-1.59)		Body mass index, age, diabetes, hypertension, dyslipidemia, sleep apnea, CKD, malignancies, history of smoking, gender	8
Sisó-Almirall et al. (2020)	Spain	322	56.7±17.8	161 (50.0)	Multicenter, observational	HF	25(7.8)	OR 1.92 [0.74–	Death or ICU admission	Age, gender	7

Table 1 Main characteristics of the included studies *(Continued)*

Author (Year)	Country	Patients(n)	Mean/ Median Age(years)	Male (%)	Study design	Kinds of diseases	CVD (%)	Adjusted effect estimate (95%CI)	Outcome	Confounders	NOS Score
[73]					descriptive study			4.84]			
Brenner et al*. (2020) [74]	Germany	9548	62.1	4182 (43.8)	Ongoing statewide cohort study	CVD	4186 (43.8)	HR 1.285 (0.936–1.763)	Mortality	Any cause, age, gender, cancer, respiratory disease, Season	8
De Rossi et al. (2020) [75]	Italy	158	66.38± 13.44	113 (71.52)	Retrospective cohort study	Heart disease	33 (20.89)	HR 3.001 (1.422-6.332)	Mortality	GROUP, age, gender, diabetes, HTN, CRP at admission, time to hospitalization, Time to hospitalization	7
Nimkar et al. (2020) [76]	USA	327	71 (59–82)	182 (55.7)	Retrospective case series	Cardiac Disease	98 (29.9)	OR 1.7 (0.7–3.9)	Mortality	AKI, ARDS, demographics (age, gender, race), HTN, diabetes mellitus, overweight (25 - 29.9), obese (>= 30), underweight < 18.5	7
Klang et al. (2020) [77]	USA	1320	74.48± 12.88	772 (58.48)	Multicenter observational retrospective study	CHD	258 (19.55)	OR 1.00 (0.8–1.4)	Death	Age, CAD, HTN, diabetes, CKD, COPD, cancer, obesity, smoking	7
Emami et al. (2021) [78]	Iran	1239	51.48± 19.54	692 (55.9)	NR	CVD	132 (10.7)	HR 3.52 (1.23–11.15)	Mortality	Age, diabetes, chronic liver disease, cancer, HIV, smoking, asthma, immunodeficiency disease	5
Liu et al. (2020) [79]	China	2044	62.0 (51.0-70.0)	1000 (48.92)	Mini-national multicenter, retrospective, cohort study	CHD	199 (9.76)	OR 1.65 (1.02-2.66)	Critical disease (vs. moderate and severe disease)	Factors with effect modification, HTN, COPD, age, diabetes, tumor, CKD, cough	6
Giorgi et al. (2020) [61]	Italy	2653	63.2	1328 (50.1)	Population-based prospective cohort	CHD	168 (7.1)	HR 1.7 (1.2–2.5)	Death	Age, gender	7
Feng et al. (2020) [81]	China	114	63.96± 13.41	71 (62.3)	Single-center, prospective study	CVD	31 (27.2)	HR 1.062 (0.380–2.970)	Poor outcome	Age, gender	7
Li et al. (2020) [82]	China	199	67 (61-78)	89 (44.7)	Retrospective study	CVD	NR (NR)	OR 0.250 (0.020-3.155)	Death	Age, CKD, HTN, Diabetes, d-dimer at admission, lymphocyte count at admission, fasting plasma glucose at admission, treatment with low molecular weight heparin, Antidiabetic drugs	7
Seiglie et al. (2020) [83]	USA	450	63.32± 17.13	259 (57.5)	Observational study	CHF	52 (11.56)	OR 1.94 (0.78-4.85)	Death	Diabetes, BMI category (overweight, Obese), age,	7

Table 1 Main characteristics of the included studies *(Continued)*

Author (Year)	Country	Patients(n)	Mean/ Median Age(years)	Male (%)	Study design	Kinds of diseases	CVD (%)	Adjusted effect estimate (95%CI)	Outcome	Confounders	NOS Score
										male, race/ethnicity (Hispanic, African American, other, unknown/missing), HTN, COPD/asthma, cancer (active), liver disease, renal disease	
Tural Onur et al. (2020) [84]	Turkey	301	57±18	206 (68.4)	Retrospectively	CVD	19 (6.3)	OR 15.331 (3.394-69.272)	Death	Age, length of stay, lung cancer	7
Anzola et al. (2020) [85]	Italy	431	65±16	263 (61)	Prospective study	CVD	77 (18)	OR 0.618 (0.297-1.285)	Death	Age, lymphocyte count, creatinine, AST, CRP, diabetes, HTN, gender (male),	7
Ioannou et al. (2020) [86]	USA	10131	61.6±15.9	9221 (91.0)	Longitudinal cohort study	CAD	2203 (21.7)	HR 1.02 (0.88-1.18)	Death	Diabetes, cancer, HTN, congestive heart failure, cerebrovascular disease, dialysis, chronic kidney disease, cirrhosis, asthma, COPD, obstructive sleep apnea, obesity, hypoventilation, alcohol dependence, smoking, Charlson comorbidity body index score	9
Bahl et al. (2020) [87]	USA	1461	62.0 (50.0–74.0)	770 (52.7)	Multicentered cohort study	CVD	163 (11.2)	HR 1.32 (0.95–1.83)	Mortality	Age, gender, race (Black/ African American, White/ Caucasian, other), diabetes mellitus, HTN, respiratory rate, blood oxygen saturation White blood cell count, hemoglobin, ALT, creatinine, d-dimer, procalcitonin, lactic acid	6
Kabarriti et al. (2020) [88]	USA	5902	58 (44-71)	2768 (46.9)	Cohort study	CVD	1306 (22.1)	HR 1.20 (1.03-1.41)	Death	Age, gender, socioeconomic status (Lowest quartile, Second quartile, third quartile, highest quartile)	8
Jackson et al. (2020) [89]	USA	51	60 (45–69)	29 (56.9)	Retrospective observational cohort	CAD	10 (19.6)	OR 2.37 (1.08–5.23)	Death	End-stage renal disease, neurologic disorders,	6
Desai et al. (2020) [90]	Italy	575	64.8 (27-93)	380 (66.09)	Single-center, retrospective, observational study	CVD	155 (27.1)	HR 1.78 (1.21–2.61)	Death	Age, ACEi, therapy: LMWH	8
Wang et al.	China	663	58 (44-69)	321 (48.4)	Retrospective	CVD	164	OR 1.66	Poor therapeutic effect	Age, gender, respiratory	8

Table 1 Main characteristics of the included studies *(Continued)*

Author (Year)	Country	Patients(n)	Mean/ Median Age(years)	Male (%)	Study design	Kinds of diseases	CVD (%)	Adjusted effect estimate (95%CI)	Outcome	Confounders	NOS Score
(2021) [91]							(24.7)	(0.82-3.47)		diseases, urinary diseases, T2DM, severe and critical condition, Fever, Expectoration, dyspnea, chest tightness, muscle aches, dizziness, neutrophil count >6.3 × 10 per L, Lymphocyte count <1.1 × 10 per L, Hemoglobin <115 g/L, ALT >40 U/L, ALT >40 U/L, Cr >73 mmol/L, Cr >73 mmol/L, albumin <35 g/L, LDH >300 U/L, CRP >10 mg/L	
Solerte et al. (2020) [92]	Italy	169	69±1.0	115 (68)	Multicenter, case-control, retrospective, observational study	CVD	53 (38)	OR 2.5 (1.30–4.81)	Mortality	Treatment with sitagliptin, age, gender, cancer, chronic kidney disease, use of hydroxychloroquine use of antiviral agents	8
Hayek et al. (2020) [93]	USA	5019	60.42± 14.86	3165 (63.06)	Multicenter cohort study	CAD	676 (13.47)	OR 1.13 (0.87-1.47)	In-hospital cardiac arrest	Number of intensive care unit beds (≥100 (reference), 50-99, <50), age, gender, Black compared with non-Hispanic white, Hispanic compared with non-Hispanic white, body mass index per 5 kg/m2, current or former tobacco use, diabetes mellitus, HTN, coronary artery disease, congestive heart failure, kidney disease (chronic or end stage), COPD, active malignancy, mSOFA score per 2 units	8
Chen et al. (2020) [94]	China	2828	60.0 (50.0-68.0)	1442 (51.0)	single-center Retrospective cohort study	CHD	181 (6.4)	OR 3.09 (1.69-5.64)	Adverse outcomes (death, ARDS, respiratory failure and septic shock during hospitalization, mechanical ventilation, ICU admission, as well as clinical cure and discharges)	Age, COPD, AKI, Hs-CRP, neutrophil, lymphocyte, blood pressure	5
Lee et al. (2020) [95]	South Korea	5061	45.44± 17.92	2,229 (44%)	Retrospective cohort study	CVD	49 (0.97)	HR 2.316 (1.053-5.094)	Mortality	Age, gender, cerebrovascular disease, HTN, diabetes, pulmonary disease, malignancy, CKD	8
Nachega et al. (2020) [96]	South Africa	766	46 (34–58)	500 (65.6)	Retrospective cohort study	Heart disease	30 (3.9)	HR 1.40 (0.68–	Death	Age, gender, clinical stage at admission (mild or moderate,	8

Table 1 Main characteristics of the included studies *(Continued)*

Author (Year)	Country	Patients(n)	Mean/ Median Age(years)	Male (%)	Study design	Kinds of diseases	CVD (%)	Adjusted effect estimate (95%CI)	Outcome	Confounders	NOS Score
								2.88)		Severe or critical, HTN, diabetes, obesity, asthma/ chronic obstructive pulmonary, chronic kidney disease, cancer, HIV, current tuberculosis, chloroquine/ azithromycin–based, received oxygen	
Rozaliyani et al. (2020) [97]	India	4052	45.8±16.3	2169 (53.5)	Retrospective cohort study	Heart disease	148 (6.9)	OR 1.43 (0.85-2.41)	Death	Age, gender, registered address (West Jakarta, Central Jakarta, South Jakarta, East Jakarta, North Jakarta, outside Jakarta, citizenship, foreigner), Symptoms (cough, fever, malaise, dyspnea, headache, nausea/emesis, Sore throat, cold/runny nose, myalgia, chills, abdominal pain, diarrhea, pneumonia), temperature, comorbidity (HTN, COPD, diabetes, renal disease, malignancy, immunological disorder, liver failure, Obesity)	7
Wang et al. (2020) [98]	China	293	59.2 (42.8-73.1)	138 (47.1)	Retrospective study	Coronary heart disease	21 (7.2)	HR 1.771 (1.013-3.097)	Mortality	Age, gender, fever, cough, expectoration, dyspnea, catarrhal symptoms, neuromuscular symptoms, digestive symptoms, comorbidity, Hypertension, diabetes, cerebrovascular disease, COPD, chronic renal disease, chronic liver disease, malignancy, only one comorbidity, ≥2 comorbidities, complications, shock, acute cardiac injury, acute renal injury, acute liver injury, Only one complication, ≥2 complications	8
Liu et al. (2020) [99]	China	77	63.6±3.6	48 (62)	Retrospective study	CVD	15 (20)	HR 2.533 (1.108-6.306)	In-hospital death	HbA1C, age, gender, CRD	8
Al Kuwari et al. (2020)	Qatar	5685	35.8±12.0	5052 (88.9)	Case series	CVD	250 (4.4)	OR 0.54 (0.24-1.22)	Severe or critical illness	Age, gender, Qatari nationality, HTN, diabetes	8

Table 1 Main characteristics of the included studies *(Continued)*

Author (Year)	Country	Patients(n)	Mean/ Median Age(years)	Male (%)	Study design	Kinds of diseases	CVD (%)	Adjusted effect estimate (95%CI)	Outcome	Confounders	NOS Score
[100]										mellitus, chronic lung disease, chronic kidney disease, cancer	
Balbi et al. (2020) [101]	Italy	340	68 (57–76)	252 (74)	Retrospective observational study	CVD	86 (25)	OR 3.21 (1.28–8.39)	Death	Age, SpO2, PaO2/FiO2 ratio, Brixia score	6
Calmes et al. (2021) [102]	Belgium	493	58 ± 19	244 (49.49)	NR	Cardiopathy	88 (18)	OR 0.94 (0.53-1.7)	Intensive care unit stay	Age, gender	8
Talavera et al. (2020) [103]	Spain	576	67.18± 14.75	325 (56.6)	Retrospective cohort study	Cardiological disorders	154 (26.7)	OR 1.201 (0.716-2.016)	Mortality	Age, sex, hypertension, diabetes, smoking habit, cardiological disorders, pulmonary disorders, cancer, and chronic neurological disorders	6
Zinellu et al. (2020) [104]	Italy	105	72.0 (59.5-80.0)	70 (66.67)	Retrospective	CVD	59 (56.19)	HR 2.53 (0.80-7.99)	In-hospital mortality	Age, gender, smoking status, intensity of care, respiratory disease, kidney disease, diabetes, cancer, De Ritis index ≥ 1.63	7
Mallow et al. (2020) [105]	USA	21676	64.9±17.2	11442 (52.8)	Retrospective cohort study	Severe heart disease	12000 (55.4)	OR 1.27 (1.16-1.40)	Mortality	Age, gender, insurance (Medicaid as any payer), teaching status (nonteaching hospital vs teaching hospital), hospital bed Size, chronic lung disease, moderate to severe asthma, immunocompromised, obesity, diabetes, CKD with dialysis, liver disease, HTN, DNR, statin use in hospital	8
Abbasi et al. (2020) [106]	Iran	262	58 (43–67)	172 (65.6)	Retrospective cohort study	CAD	78 (29.8)	OR 6.7 (1.08–42.2)	Mortality	Age, HTN, diabetes, chronic renal failure, hypoxia at admission, WBC, LYM count, LYM% less than 20%, Hb, Plt, AST, ALT, LDH, CRP, ESR, Cr, CT severity score	6
Craig-Schapiro et al. (2021) [107]	USA	136	56.24± 35.04	93 (68.38)	NR	CVD	52 (38.23)	OR 0.76 (0.26-2.23)	Mortality	Waitlist status, age, gender, BMI, black, diabetes, pulmonary disease, history of stroke, smoking history, ACE / ARB use	7
Ryan et al. (2020) [108]	USA	556	57±17	296 (53)	Retrospective case-control study	CVD	71 (13)	OR 1.41 (0.77–2.58)	Composite of ICU Admission, Mechanical Ventilation, and Death	Age, immunocompromised status, dyspnea, vomiting, chronic kidney disease, COPD,	6

Table 1 Main characteristics of the included studies *(Continued)*

Author (Year)	Country	Patients(n)	Mean/ Median Age(years)	Male (%)	Study design	Kinds of diseases	CVD (%)	Adjusted effect estimate (95%CI)	Outcome	Confounders	NOS Score
										diabetes mellitus, ACE inhibitor, gender, obesity, current or former smoker, obstructive sleep apnea, HTN, hyperlipidemia	
Serin et al. (2020) [109]	Turkey	2217	47.66± 17.23	1175 (53)	NR	CAD	165 (7.4)	HR 1.726 (0.645 −4.618)	Mortality	COPD, chronic heart failure, HTN, diabetes mellitus, chronic renal failure, malignancy, without Involvement in CT, unilaterally, bilaterally, WBC, neutrophil, hemoglobin, C-Reactive Protein, D-Dimer, urea, aspartate aminotransferase, Lactate Dehydrogenase/Lymphocyte	5
Cao et al. (2020) [110]	China	101	56.6±15.1	67 (66.3)	Retrospective, two-center study	CVD	21 (20.8)	OR 0.439 (0.081–2.387)	Mortality	Age, respiratory rate, dyspnea, acute respiratory distress syndrome, diabetes, HTN, chronic pulmonary disease, bacterial infection	7
Gupta et al. (2020) [111]	USA	3099	62 (51–71)	2003 (64.6)	Multicenter cohort study	CAD	390 (12.6)	OR 1.17 (0.65-2.13)	28-day mortality	Age, gender, Non–white race, HTN, diabetes mellitus, BMI, chronic kidney disease, congestive heart failure, active malignancy, ≤3 days from hospital to ICU admission, lymphocyte count <1,000 mm3, PaO2:FiO2, altered mental status, ICU Day 1, secondary Infection, ICU Day 1, vasopressors, coagulation Component of SOFA Score, Liver component of SOFA Score, urine output (ml/day), initial RRT modality initial RRT modality, hospital size (no. pre-COVID ICU beds), regional density of COVID-19 (quartiles)	7
Raparelli et al. (2021) [112]	Italy	3517	77.64± 11.51	2346 (66.7)	Retrospective analysis	Congestive Heart Failure	539 (15.7)	OR 0.75 (0.56-1.00)	Death	AGE, IHD, T2DM, dementia, COPD, CLD, CKD, AD, fever, SOB, cough, admission in ICU, AKI, acute cardiac injury, shock, antivirals, tocilizumab, length of stay	6
Chinnadurai	UK	215	74 (60–82)	133 (61.9)	Single-center	CVD	93	OR 1.20	Mortality	Age, care home resident,	6

Table 1 Main characteristics of the included studies *(Continued)*

Author (Year)	Country	Patients(n)	Mean/ Median Age(years)	Male (%)	Study design	Kinds of diseases	CVD (%)	Adjusted effect estimate (95%CI)	Outcome	Confounders	NOS Score
et al. (2020) [113]					observational study		(43.3)	(0.61–2.40)		frailty, smoking, respiratory diseases	
Rajter et al. (2020) [114]	USA	280	59.6±15.9	153 (64.6)	NR	Cardiac Disease	43 (15.4)	OR 1.51 (0.43-5.22)	Mortality	Treatment group (Ivermectin VS Control), age, gender, current or former smoker, Race (Black, Hispanic, Other, White), comorbidities (diabetes, pulmonary, HTBN, No comorbidities), BMI, severe presentation, Intubated at study entry, MAP < 70 mm Hg, corticosteroid treatment, peripheral white cell count, lymphocyte count	7
Naaraayan ey al. (2020) [115]	USA	362	71 (59–82)	200 (55.3)	Retrospective case series	Cardiac diseases	119 (32.9)	OR 0.9 (0.5–1.4)	In-hospital mortality	age, sex, hypertension, diabetes, race, chronic obstructive pulmonary disease, renal disease and obesity	6
Cherri et al. (2020) [116]	Italy	53	75 (68–83)	32 (60.4)	Retrospective study	Cardiopathy	20 (37.7)	OR 1.15 (0.187-7.13)	Mortality	Age, BMI, diabetes, active oncological disease	7
Rodríguez-Molinero et al. (2020) [117]	Spain	418	65.4±16.6	238 (56.9)	Observational cohort study	Heart failure	26 (6.22)	OR 1.16 (0.44–3.06)	Case fatality	Age, gender, diabetes mellitus, obesity, chronic kidney disease, HTN, atrial fibrillation, dementia, OSAS, Auto-immune disease	6
Clift et al. (2020) [118]	UK	8256158	44.33± 27.42	4111197 (49.8)	Cohort study	Heart failure	96225 (1.17)	HR 1.14 (1.08–1.20)	Death	No learning disability, learning disability apart from down syndrome, down syndrome, males vs. females, Townsend material deprivation score (5-unit increase), White, Indian British, Pakistani British, Bangladeshi British, Other Asian British, Caribbean British, Black British, Chinese British, other ethnic group, not in care home or homeless, lives in residential or nursing home, Homeless according to GP records, No kidney failure, chronic kidney disease stage, chemotherapy grad, blood cancer, bone marrow or stem	9

Table 1 Main characteristics of the included studies *(Continued)*

Author (Year)	Country	Patients(n)	Mean/ Median Age(years)	Male (%)	Study design	Kinds of diseases	CVD (%)	Adjusted effect estimate (95%CI)	Outcome	Confounders	NOS Score
										cell transplant in past 6 month, respiratory tract cancer, Radiotherapy in past 6 month, Solid organ transplant (excluding kidney and bone marrow), immunosuppressant drug, ≥4 scripts from GP in past 6 mo, Leukotriene or LABA, ≥4 scripts in past 6 month, Oral steroids, ≥4 scripts in past 6 month, Sickle cell disease or severe immunodeficiency, type 1 diabetes, type 2 diabetes, COPD, asthma, rare lung conditions (bronchiectasis, CF, or alveolitis), pulmonary hypertension or pulmonary fibrosis, coronary heart disease, stroke, atrial fibrillation, congestive heart failure, thromboembolism, peripheral vascular disease, congenital heart disease, dementia, Parkinson disease, Epilepsy MND, MS, myasthenia gravis, or Huntington disease, Cerebral palsy, severe mental illness, osteoporotic fracture (hip, spine, wrist, or humerus), rheumatoid arthritis or SLECirrhosis	
Clift et al. (2020) [119]	UK	6083102	48.21± 18.57	3035409 (49.90)	Population based cohort study	Coronary heart disease	215069 (3.54)	HR 1.24 (1.10-1.40)	Death	No learning disability, learning disability apart from down syndrome, down syndrome, males vs. females, Townsend material deprivation score (5-unit increase), White, Indian British, Pakistani British, Bangladeshi British, Other Asian British, Caribbean British, Black British, Chinese British, Other ethnic group, not in care home or homeless, lives in residential or nursing home, homeless according to GP records, No kidney failure,	9

Table 1 Main characteristics of the included studies *(Continued)*

Author (Year)	Country	Patients(n)	Mean/ Median Age(years)	Male (%)	Study design	Kinds of diseases	CVD (%)	Adjusted effect estimate (95%CI)	Outcome	Confounders	NOS Score
										chronic kidney disease stage, chemotherapy grad, blood cancer, bone marrow or stem cell transplant in past 6 month, respiratory tract cancer, radiotherapy in past 6 month, solid organ transplant (excluding kidney and bone marrow), immunosuppressant drug, ≥4 scripts from GP in past 6 month, Leukotriene or LABA, ≥4 scripts in past 6 month, Oral steroids, ≥4 scripts in past 6 month, sickle cell disease or severe immunodeficiency, type 1 diabetes, type 2 diabetes, COPD, asthma, rare lung conditions (bronchiectasis, CF, or alveolitis), pulmonary hypertension or pulmonary fibrosis, coronary heart disease, stroke, atrial fibrillation, congestive heart failure, thromboembolism, peripheral vascular disease, congenital heart disease, dementia, Parkinson disease, epilepsy MND, MS, myasthenia gravis, or Huntington disease, cerebral palsy, severe mental illness, osteoporotic fracture (hip, spine, wrist, or humerus), rheumatoid arthritis or SLEcirrhosis	
Gamberini et al. (2020) [120]	Italy	2540	66 (59–72)	300 (76.7)	Multicenter prospective observational study	Chronic ischemic heart disease	35 (9)	HR 0.277 (0.181–0.423)	Mechanical ventilation	Age, SOFA score at ICU admission, renal replacement therapy during ICU stays, lowest PaO2/FiO2 within 5 days, CRS < 40 mL/cmH2O within 5 days, neurologic complications	7
Omrani et al. (2020) [121]	Qatar	1409	39.82±14.2	1167 (82.8)	Retrospective cohort study	Coronary artery disease	31 (2.4)	OR 1.090 (0.449–2.643)	Admission to ICU	Age, gender, diabetes mellitus, HTN, chronic liver disease, chronic kidney disease, BMI	6
Yahyavi et al.	Iran	2553	58.1±17.9	1498 (58.7)	Retrospective	CVD	942	OR 1.1	Mortality	angiotensin-converting	7

Table 1 Main characteristics of the included studies *(Continued)*

Author (Year)	Country	Patients(n)	Mean/ Median Age(years)	Male (%)	Study design	Kinds of diseases	CVD (%)	Adjusted effect estimate (95%CI)	Outcome	Confounders	NOS Score
(2020) [122]					cohort study		(36.9)	(0.8-1.5)		enzyme inhibitors, angiotensin receptor blockers, chronic kidney disease, chronic pulmonary disease, diabetes mellitus, intensive care unit, diuretics, beta-blockers, and calcium channel blockers	
Guisado-Vasco et al. (2020) [135]	Spain	607	69±22.0	394 (65.02)	Retrospective, observational, longitudinal study	Chronic cardiac disease	133 (22.62)	OR 1.956 (0.778-4.922)	In-hospital death	Age, gender, Chest X-ray score, hydroxychloroquine, tocilizumab, lopinavir/ritonavir, cyclosporine A, Glucocorti-coids, Lymphocyte count at admission, Ferritin at admis-sion, C-reactive protein at ad-mission, lactate dehydrogenase (LDH) at ad-mission, d-dimer at admission, Creatinine at admission, arter-ial hypertension, diabetes mel-litus, chronic respiratory disease, PaO2/FiO2	7
Izzy et al.* (2020) [124]	USA	5190	52 (36–66)	2378 (46)	NR	Coronary artery disease	257 (5)	OR 0.52 (0.323–0.835)	ICU Admission	Age, gender, smoking status, last BMI, comorbidities (diabetes mellitus, hyperlipidemia, HTN, obstructive lung disease, interstitial lung disease, cerebrovascular disease, obstructive sleep apnea, CKD, transplantation, auto-immune diseases, malignancy), total comorbidities (0, 1–2, >2)	8
Chow et al. (2020) [125]	USA	412	55 (41-66)	244(52.9)	Retrospective, observational cohort study	CAD	52 (12.62)	HR 1.91 (1.06-3.42)	In-hospital death	Age, gender, BMI, Ethnicity (African American, Asian, Hispanic/Latino), HTN, DM, renal disease, aspirin use	6
Raines et al. (2020) [126]	USA	440	60.8±14.07	393 (89.32)	Retrospective	CVD	364 (82.73)	OR 0.9 (0.47-1.73)	Mortality	Age, gender, race, BMI, immunodeficiency syndromes, pulmonary diseases, oncologic diseases, gastrointestinal diseases, renal diseases, hematologic diseases, endocrine diseases, neurologic problems, lifetime tobacco user	7

Table 1 Main characteristics of the included studies *(Continued)*

Author (Year)	Country	Patients(n)	Mean/ Median Age(years)	Male (%)	Study design	Kinds of diseases	CVD (%)	Adjusted effect estimate (95%CI)	Outcome	Confounders	NOS Score
Ramos-Rincon et al. (2020) [123]	Spain	2772	86.3 (83.2-89.6)	1367 (49.4)	Nationwide, multicenter, retrospective, observational study	CVD	855 (30.8)	OR 1.22 (0.96-1.54)	Mortality	Age, gender, degree of dependence (independent or mild, moderate, Severe), comorbidities (Charlson comorbidity Index, non-atherosclerotic cardiovascular disease, atherosclerotic cardio-vascular diseases, dementia, obesity, moderate-severe renal disease), symptoms (shortness of breath, anorexia, diarrhea), physical exam (Oxygen satur-ation < 90% (pulsi oximetry), temperature 37.8 ºC, HTN (sys-tolic blood pressure<100 mmHg), tachycardia (>100 beats per minute), Tachyp-noea (20 breaths per minute), confusion, pulmonary rales, qSOFA score 2 (high risk)), chest X-ray (normal, unilateral infiltrates, bilateral infiltrates), laboratory findings (leukocytes 10.0 x103/L, neutrophils 7.5 x103/L, Lymphocytes<0.800 x103/L, monocytes<0.500 x103/L, pH<7.40, PO2, PO2/ FiO2 ratio < 200, glucose > 126 mg/dL, eGFR < 45ml/ min/1.73m2, lactate dehydro-genase 500 U/L, AST,ALT, CRP, venous lactate, procalcitonin, interleukin-6, d-dimer, serum ferritin)	6
Zhang et al. (2021) [127]	China	222	51.5 (34.0-65.3)	90(40.54)	NR	Chronic cardiovascular disease	44 (19.82)	HR 3.616 (1.111-11.776)	Mortality	Dyspnea, pharyngalgia, COPD, elevated myocardial enzymes, acute liver dysfunction, acute kidney injury	6
de Souza et al. (2020) [128]	Brazil	9807	70.21±8.37	4662 (47.5)	Retrospective population-based study	CVD	1192 (12.2)	OR 1.15 (0.95–1.39)	Mortality	Age, gender, initial symptoms reported (initial symptoms reported, fever, fatigue, headache, myalgia, odynophagia, dyspnea, diarrhea), comorbidities (diabetes, HTN, chronic lung disease, chronic kidney	8

Table 1 Main characteristics of the included studies *(Continued)*

Author (Year)	Country	Patients(n)	Mean/ Median Age(years)	Male (%)	Study design	Kinds of diseases	CVD (%)	Adjusted effect estimate (95%CI)	Outcome	Confounders	NOS Score
										disease, obesity)	
Kolhe et al. (2020) [129]	UK	1161	72.1±16.0	657 (56.59)	Retrospective cohort study	Congestive cardiac failure	207 (17.83)	OR 1.38 (0.95-1.99)	Mortality	Age, gender, ethnicity (White, Asian, Black, mixed, others, not stated), cerebrovascular disease, Dementia, chronic lung disease, connective tissue disorder, Diabetes with complication, paraplegia, chronic kidney disease, chronic liver disease, Cancer, treatment (ACEI or ARB use, ACEI or ARB use), AKI	8
Kim et al. (2021) [130]	USA	10861	65 (54-77)	6468(59.6)	NR	CAD	1447 (13.3)	OR 1.02 (0.90-1.17)	Death	Age, gender, race/ethnicity, BMI, HTN, DM,CKD, end stage renal disease, cancer, asthma, COPD, smoking status, hospital type	6
Giustino et al. (2020) [131]	New York City & Milan	305	63 (53–73)	205 (67.2)	International, multicenter cohort study	Heart failure	24 (7.9)	OR 5.38 (1.65-17.54)	In-Hospital Death	Age, Hispanic ethnicity, history of heart failure, cardiocirculatory shock, acute respiratory distress syndrome, acute kidney injury stage II or III, no cardiac injury (No cardiac injury vs cardiac injury with echocardiographic abnormalities)	7
An et al. (2020) [132]	Korea	228	44.97± 19.79	107 (46.9)	Cohort study	CVD	70 (30.7)	HR 1.23 (0.89-1.70)	Mortality	Age, gender, income level, residence, household type, disability, symptom, infection route, underlying medical condition (none, HTN, diabetes mellitus, hyperlipidemia, cerebrovascular disease, cancer, chronic lung disease or asthma, chronic renal disease, mental illness, chronic liver disease)	6
Piazza et al. (2020) [133]	USA	1114	50.6±18.3	511 (45.9)	Retrospective observational cohort analysis	CAD	90 (8.1)	OR 1.09 (0.38–3.16)	Death	Major arterial or venous thromboembolic event (Age, gender, VTE prophylaxis, ARDS, d-dimer (decile))	7
Rao et al. (2020) [134]	China	240	48 (23–87)	111 (46.250	Retrospective cohort study	CVD	43 (17.9)	OR 3.326 (0.721-	Severe pneumonia	Age	7

Table 1 Main characteristics of the included studies *(Continued)*

Author (Year)	Country	Patients(n)	Mean/ Median Age(years)	Male (%)	Study design	Kinds of diseases	CVD (%)	Adjusted effect estimate (95%CI)	Outcome	Confounders	NOS Score
								15.336)			
Tehrani et al. (2021) [136]	Sweden.	255	66±17	150 (59)	Retrospective analysis	Chronic heart failure	34 (13)	OR 1.01 (0.42-2.42)	Death	Age, HTN, chronic kidney disease, previous stroke	8
Hyman et al. (2020) [137]	USA	755	63±13	483 (64.0)	Retrospective cohort study	Congestive heart failure or valve disorder	30 (4.3)	HR 1.39 (0.87–2.23)	Mortality	Hospital site, baseline demography, preexisting comorbidities, laboratory findings at admission, maximum vital sign values	7
Hamilton et al. (2020) [138]	UK	1032	71 (56–83)	569 (55.1)	Retrospective review	Congestive Heart Failure	129 (12.5)	HR 2.01 (1.51-2.67)	Mortality	AKI, cancer, other ethnicity, diabetes, gender, RAASi, race, dementia, myocardial infarction, age	6
Liu et al. (2020) [139]	China	774	64 (54–73)	452 (58.4)	Multicenter retrospective observational study	Chronic cardiac disease	91 (11.8)	HR 1.12 (0.68–1.84)	Mortality	Time-varying exposure, age, gender, APACHE II score, COPD, diabetes, HTN, chronic kidney disease, chronic liver disease, stroke, malignancy, immunosuppression, fever at admission, systolic pressure at admission, leukocytes, hemoglobin, platelets, lymphocytes, d-dimer, total bilirubin, serum creatinine, procalcitonin, corticosteroids, corticosteroids, human immunoglobulin	8
Ganatra et al. (2020) [140]	USA	2467	59 (18–101)	1032 (42)	Retrospective study	CAD	184 (7.0)	OR 0.92 (0.66–1.27)	Severe disease	Age, prior/current smoker, β-blockers, history of cancer, gender, diabetes mellitus, ACEi or ARB, HTN, COPD, CKD	4
Rubio-Rivas et al. (2020) [141]	Spain	12066	68 (56–79)	7052 (58.5)	Cohort study	Chronic heart failure	809 (6.7)	OR 1.16 (1.02–1.32)	In-hospital mortality	Age, gender, BMI, clusters, comorbidity (Arterial hypertension, diabetes mellitus, hyperlipidemia, hyperlipidemia, chronic kidney disease, chronic hepatopathy, active cancer), Charlson's index, heart rate upon admission, respiratory rate upon admission > 20 bpm, PaO2/FiO2 upon admission, lab test upon admission (CRP mg/L, LDH U/L), treatments during admission (Redeliver,	9

Table 1 Main characteristics of the included studies *(Continued)*

Author (Year)	Country	Patients(n)	Mean/ Median Age(years)	Male (%)	Study design	Kinds of diseases	CVD (%)	Adjusted effect estimate (95%CI)	Outcome	Confounders	NOS Score
										tocilizumab, corticosteroids)	
Mendes et al. (2020) [142]	Switzerland	235	86.3±6.5	102 (43.4)	Retrospective monocentric cohort study	Heart failure	66 (28.1)	OR 1.51 (0.95-2.40)	Mortality	Gender	6
Nemer et al. (2020) [143]	USA	350	64±16	194 (55)	Prospective	Congestive heart failure	42 (12)	OR 0.76 (0.17-3.39)	Primary composite outcome was defined as death, ICU transfer, or increased oxygen requirement.	Age, BMI, COPD, peripheral oxygen saturation on room air, CRP, lactate dehydrogenase level, abnormal troponin T level, abnormal d-dimer level, Abnormal chest x-ray findings	8
Guo et al. (2020) [144]	China	350	43(32–56)	173(49.4)	Retrospective, multicenter study	CVD	15 (4.3)	OR 1.81 (0.42–7.84)	Severe COVID-19	Age, gender, Wuhan exposure, family cluster case, smoking, comorbidity (HTN, diabetes, chronic kidney disease, chronic liver disease, cerebral infarction)	6
Hilbrands et al. (2020) [145]	Netherlands	305	60±13	189(62)	Observational study	Heart failure	64 (21)	OR 1.39 (1.02–1.89)	28-day case-fatality	Age, gender	5
Wang et al. (2020) [146]	China	7283	64 (53–71)	3732 (51.2)	Retrospective observational study	CVD	161 (2.2)	HR 1.83 (1.33-2.51)	Death	Age, gender, location (central area in Wuhan, Other areas), occupation (medical workers, retirees, others), diabetes, HTN, respiratory disease, number of symptoms at admission, date of onset (Dec 2019–9 Jan 2020, 10–22 Jan 2020, 23 Jan–1 Feb 2020, 2–25 Feb 2020)	9
Tang et al. (2020) [147]	USA	752	73.9 (21.9-105.4)	323 (43)	Cohort study	Coronary heart disease	240 (31.91)	HR 0.83 (0.58-1.19)	Death	Age, gender, race, and facility	8
Annweiler et al. (2020) [173]	France	77	88 (85–92)	39 (50.6)	Retrospective quasi-experimental study	Cardiomyopathy	42 (54.5)	HR 4.04 (0.81-20.30)	14-day mortality	Age, gender, Iso resource groups score, severe undernutrition, history of cancer, history of HTN, glycated hemoglobin, number of acute health issue, use antibiotics, use of systemic corticosteroids, use treatments of respiratory disorder	5
Huang et al. (2020) [148]	China	676	56.0 (39.0–68.0)	314 (46.4)	Retrospective study	Heart Disease	71 (10.5)	HR 1.40 (0.76–2.47)	Hospital mortality	Age, gender, HTN, Diabetes, cancer, d-dimer, CRP, PCT, LDH	6

Table 1 Main characteristics of the included studies *(Continued)*

Author (Year)	Country	Patients(n)	Mean/ Median Age(years)	Male (%)	Study design	Kinds of diseases	CVD (%)	Adjusted effect estimate (95%CI)	Outcome	Confounders	NOS Score
Poterucha et al. (2021) [149]	USA	887	64.1	513 (58)	Retrospective study	CAD	104 (12.0)	HR 1.56 (1.04-2.33)	Mortality	AF/AFL, QRS abnormality, ST-T wave abnormality, Initial hs-cTnT ≥ 20 ng/L, age, gender, Hypertension, Diabetes, CKD, primary lung disease, Obesity, HFrEF, HFpEF, active cancer, history of cancer	6
Li et al. (2020) [150]	China	100	62.0 (51.0–70.8)	56 (56.0)	NR	CVD	15 (15.0)	HR 3.73 (0.41–33.84)	Cardiac damage	Age, gender, Hypertension, diabetes, hyperlipidemia, white blood count, prothrombin time, d-dimer, creatinine interleukin-6, procal-citonin, hs-CRP	6
Prado-Galbarro et al. (2020) [151]	Mexico	9487	31.37 (41.13-51.18)	5050 (53.2)	Observational study	CVD	171(1.8)	HR 0.85 (0.67-1.06)	Mortality	Age, gender, indigenous ethnicity, pneumonia, COPD, diseases associated with immunosuppression, additional comorbidity (Chronic diseases interaction, HTN, diabetes, obesity, chronic kidney disease, intensive care unit), region, density, mode of transport (driving, public transport, walking)	8
Shah et al. (2020) [152]	USA	487	68.53± 16.66	273 (56.06)	Retrospective review	Cardiomyopathy	16 (3.28)	OR 3.33 (1.07-10.41)	Mortality	Age, gender, patient admitted from home, PMH HTN, PMH hyperlipidemia, PMH A. fib, , PMH CVA, PMH diabetes, PMH dementia, PMH active cancer, AKI, Dyspnea in ED noted as positive, initial CXR/CT findings	7
Botta et al. (2021) [153]	Netherlands	553	67.0 (59.0–73.0)	417 (75)	National, multicenter, observational cohort study	Heart failure	25 (5.0)	OR 0.73 (0.26-2.08)	28-day mortality	Ventilatory variables on day 0 (positive end-expiratory pressure, tidal volume, respiratory system compliance), PaO2/FiO2, laboratory tests on day 0* pH, Lactate, Creatinine), vital signs on day 0 (Heart rate, mean arterial pressure), organ support on day 0 (use of vasopressor, fluid balance), demographic characteristics (age, gender, BMI, HTN, diabetes, chronic kidney disease,	6

Table 1 Main characteristics of the included studies *(Continued)*

Author (Year)	Country	Patients(n)	Mean/ Median Age(years)	Male (%)	Study design	Kinds of diseases	CVD (%)	Adjusted effect estimate (95%CI)	Outcome	Confounders	NOS Score
										COPD, use of angiotensin-converting enzyme inhibitor, use of angiotensin II receptor blocker)	
Di Domenico et al. (2020) [154]	France	310	64 (52–76)	200 (64.5)	Single-center retrospective study	Heart disease	50 (16.2)	HR 1.921 (0.893-4.135)	Death	Age, diabetes, HTN, CKD, obesity, vascular disease, ever been a smoker	7
Ayaz et al. (2020) [155]	Pakistan	66	50.6±19.1	40 (61)	Retrospective cohort study	Ischemic heart disease	10 (15)	OR 26.5 (4.7–147.8)	Mortality	Age, diabetes, HTN, ICU admission, mechanical ventilation, bilateral infiltrates on chest radiography, neutrophil to lymphocyte ratio ≥3.3, INR ≥1.2	6
Hippisley-Cox et al. (2020) [156]	UK	8275949	48.47± 18.41	4115973 (49.73)	Prospective cohort study	CVD	433631 (5.24)	HR 0.85 (0.66-1.10)	Admission to ICU	ACE inhibitor, angiobrnsin enzyme blocker, gender, material deprivation, ethnicity, geographical region, smoking status, BMI, chronic renal disease, atrial fibrillation, type 1 diabetes, type 2 diabetes, hypertension, asthma, COPD, Beta-blockers, calcium channel blockers, other diabetes drugs, sulfonylureas, biguanides, anti-coagulants, antiplatelets, sta-tins, statins, potassium-sparing diuretics	9
Tomasoni et al. (2020) [157]	Italy	692	66.5±13.3	415 (68.9)	Multicenter study	CAD	148 (21.4)	HR 1.20 (0.67-2.14)	In-hospital mortality	Age, gender, smoker, HTN, hyper dyslipidemia, Diabetes, atrial fibrillation, COPD, CKD, Treatment before hospitalization (ACE-i/ARBs/ ARNI, mineralocorticoids, Beta-blockers, direct oral anticoagu-lants, warfarin, Statins), base-line findings (heart rate, Oxygen saturation), laboratory measurements (PaO2/FiO2, red blood cell count, hemoglobin, hematocrit, lym-phocytes count, platelets count, creatinine, eGFR (CKD-EPI), CRP on admission, procal-citonin, troponin, NT-proBNP, d-dimer, aspartate	7

Table 1 Main characteristics of the included studies *(Continued)*

Author (Year)	Country	Patients(n)	Mean/ Median Age(years)	Male (%)	Study design	Kinds of diseases	CVD (%)	Adjusted effect estimate (95%CI)	Outcome	Confounders	NOS Score
										transaminase, albumin, international normalized Ratio)	
Elmunzer et al. (2020) [158]	North American	1846	59.9±16.4	1044 (56.6)	Large-scale retrospective cohort study	Congestive Heart Failure	284 (15.4)	OR 1.60 (1.12-2.28)	Death	H2RA Use, PPI Use, age, gender, race, dementia, number of comorbidities, WBC at admission, platelets at admission, AST at admission, albumin at admission	6
Polverino et al. (2020) [159]	Italy	3179		2171 (68.3)	Nationwide observational study	Coronary artery disease	359 (11.3)	OR 1.11 (0.83-1.49)	Death	Age, gender, atrial fibrillation, blood cancer, COPD chronic renal failure, diabetes, HTN, obesity, organ cancer, stroke	5
Sharp et al. (2020) [160]	USA	21280	50 (34-66)	9053 (42.5)	Retrospective cohort study	Congestive Heart Failure	NA (NA)	OR 1.45 (1.18–1.77)	Adverse outcomes (death, ARDS, respiratory failure and septic shock during hospitalization, mechanical ventilation, ICU admission, as well as clinical cure and discharges)	Age, gender, BMI, coagulopathy, diabetes, fluid and electrolyte disorders, other neurological disorders, weight Loss, heart rate, systolic BP, oxygen saturation, respiratory rate	8
Stebbing et al. (2020) [161]	Italy&Spain	166	74.05± 13.06	85 (51.2)	Observational studies	CVD	48 (28.9)	HR 1.41 (0.68-2.92)	Death & admission to ICU	Age, gender, HTN, diabetes, chronic Obstructive Lung disease, cronic kidney disease, Solid cancer, Charlson Comorbidity Index, baseline PaO2/FiO2, lymphocyte count (/mcL), alanine aminotransferase, hydroxychloroquine, lopinavir/ ritonavir, glucocorticoids, low molecular weight heparin, antibiotics	6
Fu et al. (2020) [162]	China	355	43.5*	193 (54.37)	Hospital-Based Retrospective Cohort Study	Heart disease	20 (6.2)	OR 0.454 (0.102-2.010)	Myocardial injury	Age, gender, HTN, diabetes	7
Sheshah et al. (2020) [163]	Saudi Arabia	300	49.7±13.2	259 (86.3)	Single-center, retrospective study	Coronary Artery Disease	10 (3.3)	OR 19.4 (1.5-260)	Mortality	Age, gender, HTN, type 2 diabetes mellitus, chronic kidney disease, acute kidney injury, stroke, methylprednisolone, dexamethasone, hydroxychloroquine, azithromycin	6
Bowe et al. (2020) [164]	USA	5216	70 (61–76)	4908 (94)	Cohort study	CVD	1588 (30.0)	OR 0.87 (0.76-1.01)	Severe AKI	Age, gender, race, Smoking status, HTN, diabetes mellitus	8

Table 1 Main characteristics of the included studies *(Continued)*

Author (Year)	Country	Patients(n)	Mean/ Median Age(years)	Male (%)	Study design	Kinds of diseases	CVD (%)	Adjusted effect estimate (95%CI)	Outcome	Confounders	NOS Score
										type 2, ACEI/ARB, diuretics, anticoagulant, immunosuppressants, b-blocker, aspirin, eGFR category	
Cheng et al. (2020) [165]	China	220	59.5 (48.3-70.0)	106 (48.2)	Retrospective, observational study	CAD	22 (10.0)	HR 0.97 (0.35-2.68)	In-hospital death	Hypertension, history of cerebrovascular disease, History of diabetes mellitus, history of diabetes mellitus	4
Neumann-Podczaska et al. (2020) [166]	Poland	50	74.8±9.4	35 (70.0)	Retrospective	Heart disease	26 (52.0)	HR 2.61 (0.92–7.39)	60-day mortality	Age, functional Capacity, Diabetes	6
Ken-Dror et al. (2020) [167]	UK	429	70±18	242 (56.4)	Prospective cohort study	Chronic cardiac disease/ congenital heart disease	103 (31.3)	OR 3.43 (2.1-5.63)	Mortality	Self-reported feverishness 38°C, cough self-report, oxygen saturation, history of fever, cough, sore throat, chest pain, muscle aches myalgia, altered consciousness confusion, obesity as defined by clinical staff, diabetes with complications, dementia, malnutrition, current admission to ICU/IMC/HDU, non-invasive ventilation BIPAP/CPAP, invasive ventilation, high flow nasal canula oxygen therapy, clinical pneumonia, inotropes vasopressors, viral pneumonia, bacterial pneumonia, anemia	7
Iannelli et al. (2020) [168]	France	8286	59.1±12.6	4296 (51.8)	Retrospective	Cardiac failure	569 (6.9)	OR 1.53 (1.24–1.89)	Death	Age, gender, cancer, diabetes, bariatric surgery	9
Sharifpour et al. (2020) [169]	USA	268	63±15	149 (55.6)	Cohort analysis	CAD	36 (13.4)	OR 1.381 (0.498–3.826)	Mortality	Age, CRP Slope d1to7, CRP tests (count d1 to 7), CRRT, CRP Max d1to7, obesity (BMI>= 30kg/m2), intubation, SOFA score, HTN	6
Martins-Filho et al. (2020) [170]	Northeast Brazil	1207	60 (46–73)	724 (60)	Retrospective cohort study	Heart failure	102 (8.45)	OR 2.00 (1.31–3.04)	Mortality	Infectious disease, kidney disease, age	6
Lee et al. (2020) [171]	Korea	7339	47.1±19.0	2970 (40.1)	Nationwide Population-Based Retrospective Study	CVD	455 (6.1)	OR 0.95 (0.64–1.40)	Death	Influenza, tuberculosis, COPD, pneumonia, asthma, DM, CKD, Chronic liver disease, HTN, malignancies, HIV infection,	8

Table 1 Main characteristics of the included studies *(Continued)*

Author (Year)	Country	Patients(n)	Mean/ Median Age(years)	Male (%)	Study design	Kinds of diseases	CVD (%)	Adjusted effect estimate (95%CI)	Outcome	Confounders	NOS Score
										lopinavir/ritonavir, Hydroxychloroquine, ribavirin, type I interferon, Human immunoglobulin G, Oseltamivir, antibiotics, age, gender	
Loffi et al. (2020) [172]	Italy	1252	64.7±15.5	798 (63.74)	Retrospective, observational, single-center study	CAD	124 (9.9)	HR 1.14 (0.79-1.63)	Death	Age, gender, LVEF<35%, CVA, atrial fibrillation, diabetes mellitus, hypertension, smoking, CKD	5
Grodecki et al. (2021) [175]	USA	109	63.74± 15.11	68 (62.39)	Prospective	Heart failure	16 (14.68)	OR 3.5 (1.1-8.2)	Death	Age, gender, diabetes mellitus, hypertension, smoking history, chronic lung disease, history of coronary artery disease, epicardial adipose tissue volume (mL), epicardial adipose tissue attenuation, total pneumonia burden	7
Rossi et al. (2020) [80]	Italy	590	76.2 (68.2–82.6)	399 (67.6)	Retrospective observational study	CVD	95 (16.1)	HR 1.180 (0.855–1.628)	Mortality	Age, gender, vital signs at admission (temperature, PaO2/FiO2, PaO2/FiO2<300), laboratory parameters (LDH, CRP, white blood cell count, lymphocyte's rate), chronic diseases (hyperlipidemia, diabetes, atrial fibrillation, COPD, CKD, stroke, malignancy, 3 or more comorbidities), chronical drugs intake (ACEi, ARBs, CCBs, Alpha blockers, Diuretics, Beta blockers)	6
Khan et al. (2020) [177]	Saudi Arabia	648	34±19	342 (52.8)	Retrospective cohort study	Cardiac diseases	23 (3.5)	OR 3.05 (1.16-8.02)	ICU admission	Age, gender, smoker, comorbidities (one or more comorbidity, two or more comorbidity, diabetes mellitus, HTN, CRD, chronic kidney diseases, cancer/ immunodeficiency), symptoms (fever, cough, sore throat, runny nose, headache, GI symptoms, myalgia), vital signs (temperature (≥38), heart rate ≥100, respiratory rate, respiratory rate,	7

Table 1 Main characteristics of the included studies *(Continued)*

Author (Year)	Country	Patients(n)	Mean/ Median Age(years)	Male (%)	Study design	Kinds of diseases	CVD (%)	Adjusted effect estimate (95%CI)	Outcome	Confounders	NOS Score
										respiratory rate, DBP, oxygen saturation, oxygen saturation)	
Rutten et al. (2020) [178]	Netherlands	1538	84±8.7	554 (36.02)	Prospective cohort study	CVD	53 (3.47)	HR 1.15 (0.97-1.35)	Mortality	Age, gender, comorbidity (Dementia, cerebrovascular disease, diabetes mellitus, chronic respiratory disease, reduced kidney function, Parkinson's disease)	6
Schuelter-Trevisol et al. (2020) [179]	Brazil	211	51.2*	113 (53.6)	Cohort study	Chronic heart disease	27 (12.9)	OR 0.98 (0.31-3.10)	Death	Age, gender, comorbidities (arterial hypertension, diabetes mellitus, obesity, neurologic/ psychiatric diseases, chronic lung diseases, dyslipidemia, smoking habits, cancer, chronic kidney diseases, vascular diseases)	6
FAI2R /SFR/ SNFMI/ SOFREMIP/ CRI/IMIDIATE (2020) [174]	France	694	56.1±16.4	232 (33.4)	Observational, multicenter, French national cohort study	Coronary heart diseases	68 (9.8)	OR 1.86 (0.97–3.56)	Severity	Age, gender	8
Nyaberaet al. (2020) [181]	USA	290	77.6±8.3	150 (51.7)	Single-center retrospective cohort study	CAD	80 (27.6)	OR 0.91 (0.52-1.62)	Mortality	BMI, age, COPD, asthma, DM, HTN, end-stage renal disease	4
Ozturk et al. (2021) [182]	Turkey	1160	60.5 (47–71)	627 (54.1)	Multicenter, retrospective, observational study	CVD	NR (NR)	HR 1.242 (0.850–1.815)	Death	Age, gender, diabetes mellitus, HTN, COPD, albumin, hemoglobin, lymphocyte count, platelet count, CRP increase, clinic presentation, COVID-19 diagnosis by RT-PCR, patient group, control group (HD group, RT group, CKD group)	5
Druyan et al. (2021) [183]	Israel	181	62.71*	107(59.1)	Single center study	Heart failure	10 (5.52)	OR 2.35 (0.24-18.64)	Severe, critical or fatal COVID19	Gender, AID, HTN, dyslipidemia, diabetes, malignancy, IHD, arrhythmia, obesity, pulmonary disease, smoking, CVA, renal failure, older age	5
Alguwaihes et al. (2020) [184]	Saudi Arabia	439	55 (19–101)	300 (68.3)	Single-center retrospective study	CVD	44 (10.0)	HR 1.8 (0.7–4.4)	Death	Age, gender, comorbidities (obesity, HTN, diabetes mellitus, chronic kidney disease, congestive heart failure, stroke, smoking),	7

Table 1 Main characteristics of the included studies *(Continued)*

Author (Year)	Country	Patients(n)	Mean/ Median Age(years)	Male (%)	Study design	Kinds of diseases	CVD (%)	Adjusted effect estimate (95%CI)	Outcome	Confounders	NOS Score
										medications (β-Blocker use, ACE inhibitor use, ARB Use), laboratory investigations (RBG, FPG, HbA1c>9.0%, bilateral lung infiltrates, neutrophil count>7.5, creatinine>90 μmol/l, ALT>65 U/l, 25(OH)D< 12.5 nmol/l)	
Özdemir et al. (2021) [185]	Turkey	101	49.60±18	55 (54.4)	Retrospective study	Chronic heart failure	10 (9.9)	HR 1.02 (0.98 – 1.10)	QTc prolongation	Baseline QTc, HCQ alone, HCQ + AZM	6
Gue et al. (2020) [186]	UK	316	73.42± 15.97	192 (61.1)	Single-center retrospective cohort	CAD	48 (15.19)	OR 1.62 (0.76– 4.07)	30-day mortality	Age, gender, HTN, atrial fibrillation, oral anticoagulants, modified sepsis-induced coagulopathy score	7
Galiero et al. (2020) [187]	Italy	618	65±15.2	379 (61.3)	Multicenter retrospective observational cohort study	Chronic Cardiac Disease	166 (26.9)	OR 0.96 (0.53-1.76)	Mortality	Age, gender, Glasgow Coma Score/15, respiratory severity Scale, CKD, CLD, chronic respiratory disease, malignancies	6
Rosenthal et al. (2020) [188]	USA	64781	56.1±19.9	31968 (49.3)	Retrospective cohort study	Myocardial infarction	3717 (5.7)	OR 1.47 (1.34-1.62)	In-Hospital Mortality	Age, gender, race, payer type, admission point of origin, hospital region, hospital beds, hospital teaching status, hospital teaching status, Sepsis, acute kidney failure, hypokalemia, acidosis, acute liver damage, neurological disorder, baseline comorbidities (Cerebrovascular disease, COPD, dementia, diabetes, any malignant neoplasm, metastatic solid tumor, hemiplegia, AIDS, HTN, Hyperlipidemia)	9
Rethemiotaki et al. (2020) [189]	the World Health Organization dataset and Chi nese Center for Disease Control and Preventio	44672	71*	22981 (51.44)	NR	CVD	92 (15.9)	OR 13.6 (10.3– 17.9)	Death	Age, gender, occupation (service industry, farmer/ laborer, health worker, retiree, other/none), province: (Hubei, Other), Wuhan-related exposure, comorbid condition (HTN, diabetes, chronic respiratory disease, cancer (any), none)	8

Table 1 Main characteristics of the included studies *(Continued)*

Author (Year)	Country	Patients(n)	Mean/ Median Age(years)	Male (%)	Study design	Kinds of diseases	CVD (%)	Adjusted effect estimate (95%CI)	Outcome	Confounders	NOS Score
Pantea Stoian et al. (2020) [176]	China	432	NR	NR	Multiple-case, multiple-center	Heart failure	30 (6.94)	OR 2.990 (1.612–5.546)	Death	Age, gender, HTN, obesity, diabetes type 2, dialysis, chronic kidney disease, COPD, supraventricular tachyarrhythmia, respiratory failure, Intercept	7
Zhou et al. (2020) [191]	China	134	62.08± 14.38*	85 (63.4)	Retrospective	Coronary heart disease	16 (11.94)	OR 1.098 (0.202–5.959)	Death	Gender, age, HTN, coronary heart disease, neutrophil, lymphocyte, ALT, IL-2, IL-6, TNF-α, D-dimer, and total CT score	6
Stefan et al. (2021) [192]	Romania	37	64 (55–71)	19 (51)	Retrospective, observational, single-center study	Coronary heart disease	19 (51.0)	HR 0.98 (0.05–17.54)	In-hospital death	Age, hemodialysis vintage, obesity, current smoker, diabetes mellitus, Charlson comorbidity index, basal oxygen saturation, hemoglobin, lymphocytes, CRP, serum albumin, LDH, Lopinavir–ritonavir, Tocilizumab, hydroxychloroquine, glucocorticoids	7
Ahnach et al. (2021) [180]	Morocco	101	50 (32–63)	75 (51.72)	Retrospective study	CVD	16 (11.03)	OR 3.74 (0.76–18.29	Disease severity	Age, gender, HTN, diabetes, other disease, respiratory symptom, neutrophil, lymphocyte, eosinophil, CRP	6
Eshrati et al. (2020) [193]	Iran	3188	55.05 ± 0.31	1925 (60.4)	Retrospective cohort study	CVD	401 (12.6)	HR 0.60 (0.83-1.13)	death	Age, gender, immune disease, diabetes, liver disease, kidney disease, ,COPD, cancer, chronic nervous disease, type of treatment	8
Özyılmaz et al. (2020) [194]	Turkey	105	45 (20–87)	76 (72.3)	Single-center, retrospective, observational study	CAD	14 (13.3)	OR 0.024 (0.000–1.207)	Mortality	Troponin I, C-Reactive protein, lymphocyte count, shortness of breath, HTN, hyperlipid-emia, diabetes mellitus	7
Tan et al. (2020) [195]	China	163	69.0 (62.0-78.0)	109 (66.9)	Retrospective study	Chronic cardiac injury	25 (15.3)	OR 2.660 (1.034-6.843)	Mortality	Age, gender, HTN, diabetes	5
Ling et al. (2020) [196]	UK	444	74 (63-83)	245 (55.2)	Cross-Sectional Multi-Centre Observational Study	Heart failure	54 (12.2)	OR 1.61 (0.87–2.99)	Mortality	Age, gender, diabetes, non-Caucasian ethnicity, baseline serum 25(OH)D levels, vitamin D deficiency, treatment with cholecalciferol booster ther-apy, admission SpO2 < 96%,	5

Table 1 Main characteristics of the included studies *(Continued)*

Author (Year)	Country	Patients(n)	Mean/ Median Age(years)	Male (%)	Study design	Kinds of diseases	CVD (%)	Adjusted effect estimate (95%CI)	Outcome	Confounders	NOS Score
										admission CRP > 73 mg/L, admission creatinine > 83 μmol/L, received CPAP, length of stay >11 days, diabetes (types 1 and 2 combined), admission glucose > 6·9 mmol/L, COPD, asthma, IHD, current or previous ACS, HTN, current or previous TIA or stroke, dementia, obesity, malignancy of solid organ, malignancy of skin, hematological malignancy, solid organ transplant, inflammatory arthritis, inflammatory bowel disease	
Zhong et al. (2020) [197]	China	126	66.3±10.6	56 (44.4)	Retrospective observational study	CVA	21 (16.7)	OR 2.03 (0.45-9.08)	Death	Age, gender, ACEI/ARB, stains	5
Izurieta et al. (2020) [198]	USA	12613	80.5*	6496 (51.5)	Retrospective cohort study	Congestive Heart Failure	3557 (28.2)	OR 1.30 (1.23, 1.36))	Death	Age, gender, reason for entering medicare, ADI national rank, logged COVID-19 circulation rate by 100,000, logged population density by county, vaccination, presence of medical conditions (HTN, obesity, diabetes, hospitalized stroke/TIA, coronary revascularization, atrial fibrillation, hospitalized AMI, other cerebrovascular disease, COPD, asthma without COPD, interstitial lung disease, hypersensitivity pneumonitis, bronchiectasis, chronic liver disease, neurological/neurodevelopmental conditions), frailty conditions, immunocompromised status, estimated overall, interaction effects of age, dual-eligibility, and race, 80 years old vs. 65 years old, dual-eligible vs. non-dual-eligible, dual-eligible vs. non-dual-eligible, effects of being dual-eligible, by race, non-whites vs. whites, non-dual-	8

Table 1 Main characteristics of the included studies *(Continued)*

Author (Year)	Country	Patients(n)	Mean/ Median Age(years)	Male (%)	Study design	Kinds of diseases	CVD (%)	Adjusted effect estimate (95%CI)	Outcome	Confounders	NOS Score
										eligible, non-whites vs. whites, dual-eligible	
Burrell et al. (2021) [199]	Australia	304	63.5 (53–72)	140 (69%)	Prospective, observational cohort study	Chronic cardiac disease	40 (20)	HR 3.38 (1.46–7.83)	Mortality	Age, gender, APACHE-II score on ICU day 1, comorbid conditions (comorbid conditions),	5
Li et al. (2020) [190]	China	123	64.43± 14.02	62 (50.41)	Retrospective study	CVD	26 (21.14)	OR 0.686 (0.227–2.076)	Unfavorable clinical outcomes	Age, gender, diabetes, HTN, COPD, CT severity score, GGO volume, GGO volume percentage, consolidation volume, consolidation volume percentage	4
Caliskan et al. (2020) [200]	Turkey	56	48±19.664	NR	Retrospective observational study	CAD	42 (7.4)	OR 6.252 (2.171-18.004)	Mortality	Former smoker, current smoker, age, COPD, diabetes, dementia, HTN, chronic renal failure, arrhythmia	5
Vafadar et al. (2021) [201]	Iran	219	57.8±16.5	137 (62.6)	Retrospective cohort	Ischemic heart disease	46 (22.37)	HR 1.98 (0.94–4.17)	Mortality	Respiratory rate, SpO2 ≤ 90%, WBC count, NLR, age	6
Working group for the surveillance and control of COVID-19 in Spain et al. (2020) [202]	Spain	2612	83 (75–89)	14680 (56.2)	NR	CVD	11444 (59.9)	OR 1.32 (1.23-1.42)	Death	Gender, age, pneumonia, acute respiratory distress syndrome, acute renal failure, Diabetes, HTN, chronic lung disease, chronic renal disease, healthcare worker	6
Rashidi et al. (2021) [203]	Iran, Germany, USA	1529	56 (32–80)	832 (54.4)	Multi-center prospective study	Cardiac disease	149 (9.7)	OR 0.80 (0.36–1.76)	Death	Age, gender, recent cancer, COPD, CKD, smoking, diabetes mellitus, HTN	5
Chaudhri et al. (2020) [204]	USA	317	59.16±17.5	166 (52.37)	Single-center cohort study	Coronary artery disease	27 (12)	OR 0.92 (0.39-2.17)	Key outcomes	Age, gender, history of ARB use,history of ACEI use, HTN, diabetes, CKD	5
Huh et al. (2021) [205]	South Korea	219961	49.4 (18–116)	104331 (47.4)	Retrospective case-control study	Chronic heart disease	32457 (14.76)	OR 1.31 (1.04-1.65)	The requirement of any one of the following or death: supplementary oxygen, high-flow nasal cannula, non-invasive ventilation, mechanical ventilation, and extracorporeal membrane oxygenation	Drugs commonly used for chronic conditions (angiotensin receptor blockers, angiotensin converting enzyme inhibitors, metformin, thiazolidinedione, Statins, NSAIDs), drugs with potential therapeutic effect, drugs with potential therapeutic effect, comorbidities (Charlson comorbidity index, mean (SD),	8

Table 1 Main characteristics of the included studies *(Continued)*

Author (Year)	Country	Patients(n)	Mean/ Median Age(years)	Male (%)	Study design	Kinds of diseases	CVD (%)	Adjusted effect estimate (95%CI)	Outcome	Confounders	NOS Score
										Diabetes, HTN, chronic lung disease, asthma and allergic rhinitis, chronic liver disease, Chronic kidney disease, Malignancy, RA, SLE, GCA, and JIA, other connective tissue disease, chronic neurologic disease, Pancreatitis), healthcare utilization	
Orioli et al. (2021) [206]	Belgium	73	69±14	48 (66.67)	Retrospective study	CVD	32 (43.8)	HR 3.54 (1.60-7.82)	In-hospital death	Diabetes, cognitive impairment, area of lung injury >50%	6
Gude-Sampedro et al. (2021) [207]	Spain	10454	58.0±20.0	4172 (39.9)	Retrospective cohort study	Ischemic heart disease		OR 1.61 (1.20-2.33)	Death	Age, gender, lymphoma/ leukemia, dementia, COPD, diabetes, chronic kidney disease	9
Monteiro et al. (2020) [208]	USA	112	61 (45–74)	74 (66)	Retrospective, observational cohort study	CAD	17 (15)	OR 0.48 (0.08–3.08)	Requiring mechanical ventilation	Age, gender, past medical history (obesity, diabetes, HTN, CKD), Tobacco exposure history	4
Lano et al. (2020) [209]	France	122	73.5 (64.2–81.2)	79 (65)	Observational cohort multicenter study	Congestive heart failure	13 (11)	OR 1.222 (0.309–4.649)	Mortality	Age, atrial fibrillation, ARBs (current medication)	8
Lanini et al. (2020) [210]	Italy	379	61.67± 15.60	273 (72.03)	Longitudinal cohort study	CVD	19 (5.01)	OR 2.79 (1.29-6.03)	Death	Age, gender, diabetes, neoplasm, obesity, chronic renal failure, COPD	4
Schwartz et al. (2020) [212]	Canada	56606	31*	29205 (51.59)	Cross-sectional study	CVD	4465 (7.89)	OR 1.10 (0.99–1.22)	Death	Healthcare worker, age, comorbidities (asthma, COPD, renal conditions, diabetes, immune compromise or cancer, obesity, other medical conditions None), exposed to long-term care home, symptoms (fever and/or cough, other symptoms, missing, asymptomatic)	9
Sun et al. (2021) [213]	China	3400	61 (50-68)	1649 (48.5)	Retrospective cohort study	CVD	343 (10.1)	OR 2.85 (1.65-4.94)	Death	Comorbid conditions (Neither HTN nor T2DM, Hypertension alone, T2DM alone, HTN and T2DM), age, gender, cerebrovascular disease, chronic kidney disease, chronic liver disease, chronic	6

Table 1 Main characteristics of the included studies *(Continued)*

Author (Year)	Country	Patients(n)	Mean/ Median Age(years)	Male (%)	Study design	Kinds of diseases	CVD (%)	Adjusted effect estimate (95%CI)	Outcome	Confounders	NOS Score
										lung disease, endocrine/ Immune system disease, tumor, ACEIs/ARBs treatment	
McGurnaghan et al. (2021) [214]	Scotland	319349	79.9 (71.4–85.7)	180486 (56.5)	Cohort study	Any heart disease	696 (64.3)	OR 2.425 (2.135–2.754)	Fatal or critical care unit-treated COVID-19	Sociodemographic (age, gender, diabetes type, diabetes duration, care home resident, any hypoglycemia admission in past 5 years, deprivation index, ethnicity, comorbidities (any diabetic ketoacidosis admission in past 5 years, any hypoglycemia admission in past 5 years, ever admitted to hospital in past 5 years, asthma or chronic lower airway disease, neurological and dementia (excluding epilepsy),liver disease, immune disease or on immunosuppressants, any listed condition), other clinical measures (insulin pump use, flash glucose monitor use, HbA1c, BMI, systolic blood pressure, diastolic blood pressure, total cholesterol, Estimated glomerular filtration rate, albuminuria grade, retinopathy grading, tobacco smoking), drug exposures (any lipid lowering, any proton pump inhibitor, any non-steroidal anti-inflammatory drugs, any anticoagulants, Any antihypertensive, number of ATC level 3 drug classes (excluding for diabetes), number of diabetes drug classes prescribed)	8
Cetinkal et al. (2020) [215]	Turkey	349	68.3±13.3	176 (50.43)	Retrospective single-center study	Heart failure	38 (10.89)	OR 2.40 (0.82-7.01)	In-hospital mortality	Neutrophil to lymphocyte ratio, gender, age, diabetes mellitus, Use of RAAS blockers, chronic kidney disease, Smoking, COPD, d-dimer, LDH, procalcitonin, Ferritin	6
Xu et al.	China	61	63.62±	33 (54.1)	Retrospective	Heart diseases	7 (11.5)	OR 2.94	Severity	Age, gender, diabetes, HTN,	4

Table 1 Main characteristics of the included studies *(Continued)*

Author (Year)	Country	Patients(n)	Mean/ Median Age(years)	Male (%)	Study design	Kinds of diseases	CVD (%)	Adjusted effect estimate (95%CI)	Outcome	Confounders	NOS Score
(2020) [216]			10.78					(0.42-21.78)		hepatic dysfunction, mild-nonlung involvement	
Lv et al. (2021) [217]	China	409	50.47± 12.43	188 (46)	Retrospective cohort Study	Heart disease	51 (12.5)	HR 2.650 (1.079–6.510)	Death	Age, gender, fever, cough, sputum, tiredness, body aches, diarrhea, number of symptoms, HTN, diabetes, pulmonary disease, other comorbidities, CT ground-glass, opacity, CT bilateral pulmonary infiltration	5
Guerra et al. (2021) [218]	Spain	447	55.0±22.5	190 (46.4)	Retrospective single center study	Coronary artery disease		OR 4.95 (1.51-16.27)	Mortality	Gender, HTN, COPD, cancer, diabetes, obesity, CLD, age	6

*, studies included 2 two different cohort samples; *HTN* Hypertension, *SOFA* sequential organ failure assessment, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *ARDS* acute respiratory distress syndrome, *INR* international normalized ratio, *ICU* intensive care unit, *HF* heart failure, *IL-8* interleukin-8, *AKI* acute cardiac injury, *CLD* chronic lung diseases, *CRD* chronic renal disease, *CKD* chronic kidney disease, *IL-6* interleukin-6, *WBC* white blood cell, *NR* not reported, *HTN* hypertension, *HR* hazard ratio, *OR* odds ratio, *CI* confidence interval, *CHD*, coronary heart disease, *CVD* cardiovascular disease, *CAD* coronary artery disease, *CKD* chronic kidney diseases, *CLD* chronic liver diseases, *COPD* chronic obstructive pulmonary disease, *CRP* C-reactive protein, *hs-CRP* high-sensitivity C-reactive protein, *BMI* body mass index, *LYM%* lymphocyte percentage, *NEU%* neutrophil percentage, *NLR* ratio of neutrophil to lymphocyte, *FIB* fibrinogen content, *TBIL* total bilirubin, *ALB* albumin, *Cr* creatinine, *GFR* glomerular filtration rate, *CK-MB* creatine kinase isoenzyme-MB, *CT* computerized tomography, *PCT* procalcitonin, *GGO* ground-glass opacity, *ICI* immune check point inhibitors, *HCQ* hydroxychloroquine, *AZM* azithromycin, *APTT* activated partial thromboplastin time, *ACE* angiotensin converting enzyme inhibitors, *ARB* angiotensin II receptor blockers, *eGFR* estimated glomerular filtration rate, *PAD* peripheral arterial disease, *Hb* hemoglobin, *LDH* lactate dehydrogenase, *ESR* erythrocyte sedimentation rate, *MYO* myoglobin, *LFTs* liver function tests, *SABA* short acting beta agonists, *ESRD* end-stage renal disease (on dialysis), *ALC* absolute lymphocyte count, *ANC* absolute neutrophil count, *MV* mechanical ventilation, *APACHE II* acute physiology and chronic health evaluation II, *BUN* blood urea nitrogen, *CVA* cerebrovascular accident, *TIA* transient ischemic attack, *DBIL* direct bilirubin, *IBIL* indirect bilirubin, *PT* prothrombin time, *FBG* fasting blood glucose.

Table 2 The results of subgroup analysis

Variables	Effects	NO. Of studies	Subgroup analysis		Prediction interval
			Pooled ES (95% CI)	I^2,Tau^2, *P* value	
Sample size					
>=1000	HR	24	1.16 (1.03-1.32)	$I^2 = 88\%, \tau^2 = 0.0697, P < 0.01$	0.66-2.04
	OR	53	1.41 (1.32-1.51)	$I^2 = 84\%, \tau^2 = 0.0694, P < 0.01$	0.84-2.39
<1000	HR	41	1.63 (1.41-1.88)	$I^2 = 64\%, \tau^2 = 0.0957, P < 0.01$	0.86-3.10
	OR	83	1.57 (1.40-1.77)	$I^2 = 57\%, \tau^2 = 0.0967, P < 0.01$	0.84-2.95
Age					
>=60	HR	41	1.42 (1.25-1.61)	$I^2 = 73\%, \tau^2 = 0.0914, P < 0.01$	0.76-2.65
	OR	78	1.49 (1.34-1.65)	$I^2 = 86\%, \tau^2 = 0.1144, P < 0.01$	0.75-2.95
<60	HR	23	1.18 (1.04-1.33)	$I^2 = 81\%, \tau^2 = 0.0181, P < 0.01$	0.77-1.80
	OR	58	1.30 (1.19-1.42)	$I^2 = 76\%, \tau^2 = 0.0379, P < 0.01$	0.87-1.94
NR	HR	1	2.59 (1.16-5.79)	-	-
	OR	2	1.75 (0.67-4.61)	$I^2 = 88\%, \tau^2 = 0.4301, P < 0.01$	-
Male (%)					
>=50	HR	44	1.41 (1.23-1.60)	$I^2 = 83\%, \tau^2 = 0.1123, P < 0.01$	0.71-2.80
	OR	94	1.33 (1.23-1.44)	$I^2 = 78\%, \tau^2 = 0.0558, P < 0.01$	0.83-2.14
<50	HR	21	1.25 (1.13-1.38)	$I^2 = 55\%, \tau^2 = 0.0179, P < 0.01$	0.92-1.69
	OR	36	1.42 (1.27-1.58)	$I^2 = 56\%, \tau^2 = 0.0431, P < 0.01$	0.92-2.20
NA	HR	0	-	-	-
	OR	8	2.25 (0.87-5.79)	$I^2 = 98\%, \tau^2 = 1.6735, P < 0.01$	0.08-65.97
Study design					
Retrospective/case series	HR	38	1.50 (1.30-1.73)	$I^2 = 81\%, \tau^2 = 0.1067, P < 0.01$	0.76-2.96
	OR	88	1.37 (1.28-1.47)	$I^2 = 65\%, \tau^2 = 0.0269, P < 0.01$	0.98-1.91
Prospective study	HR	9	1.11 (0.74-1.67)	$I^2 = 88\%, \tau^2 = 0.2724, P < 0.01$	0.28-4.39
	OR	7	1.31 (0.84-2.06)	$I^2 = 77\%, \tau^2 = 0.2451, P < 0.01$	0.32-5.34
Others	HR	19	1.25 (1.12-1.39)	$I^2 = 63\%, \tau^2 = 0.0214, P < 0.01$	0.90-1.74
	OR	43	1.45 (1.24-1.70)	$I^2 = 93\%, \tau^2 = 0.1725, P < 0.01$	0.62-3.42
Region					
Europe	HR	27	1.31 (1.17-1.47)	$I^2 = 83\%, \tau^2 = 0.0462, P < 0.01$	0.83-2.08
	OR	54	1.47 (1.33-1.64)	$I^2 = 75\%, \tau^2 = 0.0725, P < 0.01$	0.85-2.56
North America	HR	12	1.16 (1.02-1.33)	$I^2 = 52\%, \tau^2 = 0.0234, P = 0.02$	0.80-1.69
	OR	42	1.18 (1.08-1.29)	$I^2 = 77\%, \tau^2 = 0.0333, P < 0.01$	0.81-1.72
Asia	HR	24	1.64 (1.24-2.16)	$I^2 = 81\%, \tau^2 = 0.3015, P < 0.01$	0.51-5.30
	OR	37	1.55 (1.29-1.87)	$I^2 = 68\%, \tau^2 = 0.1272, P < 0.01$	0.73-3.29
Others	HR	2	2.12 (0.89-5.01)	$I^2 = 59\%, \tau^2 = 0.2289, P = 0.12$	-
	OR	5	3.54(0.86-14.60)	$I^2 = 92\%, \tau^2 = 2.2249, P < 0.01$	0.02-691.66
Disease					
CVD	HR	27	1.36 (1.15-1.61)	$I^2 = 79\%, \tau^2 = 0.1154, P < 0.01$	0.66-2.80
	OR	41	1.48 (1.24-1.76)	$I^2 = 91\%, \tau^2 = 0.1984, P < 0.01$	0.59-3.70
Cardiac disease	HR	25	1.40 (1.17-1.69)	$I^2 = 77\%, \tau^2 = 0.1141, P < 0.01$	0.68-2.90
	OR	38	1.43 (1.25-1.64)	$I^2 = 84\%, \tau^2 = 0.0762, P < 0.01$	0.80-2.55
HF	HR	4	1.23 (1.05-1.44)	$I^2 = 89\%, \tau^2 = 0.0173, P < 0.01$	0.63-2.39
	OR	31	1.46 (1.31-1.62)	$I^2 = 59\%, \tau^2 = 0.0290, P < 0.01$	1.01-2.10
CAD	HR	9	1.48 (1.14-1.93)	$I^2 = 70\%, \tau^2 = 0.0957, P < 0.01$	0.67-3.29

Table 2 The results of subgroup analysis *(Continued)*

Variables	Effects	NO. Of studies	Subgroup analysis		Prediction interval
			Pooled ES (95% CI)	I^2,Tau^2, *P* value	
	OR	26	1.17 (1.02-1.35)	$I^2 = 52\%, \tau^2 = 0.0416, P < 0.01$	*0.75-1.83*
Others	HR	-	-	-	
	OR	2	1.63 (1.05-2.53)	$I^2 = 33\%, \tau^2 = 0.0585, P = 0.22$	-
Outcomes					
Mortality	HR	55	1.39 (1.27-1.53)	$I^2 = 76\%, \tau^2 = 0.0597, P < 0.01$	*0.85-2.30*
	OR	98	1.44 (1.32-1.56)	$I^2 = 84\%, \tau^2 = 0.0840, P < 0.01$	*0.80-2.57*
Severity	HR	7	1.06 (0.70-1.60)	$I^2 = 88\%, \tau^2 = 0.2418, P < 0.01$	*0.30-3.68*
	OR	25	1.22 (1.03-1.43)	$I^2 = 66\%, \tau^2 = 0.0575, P < 0.01$	*0.72-2.06*
Disease progression	HR	3	1.65 (1.20-2.27)	$I^2 = 0\%, \tau^2 = 0.000, P = 0.56$	*0.21-12.92*
	OR	15	1.63 (1.31-2.04)	$I^2 = 68\%, \tau^2 = 0.0858, P < 0.01$	*0.84-2.39*

Note: ES, effect sizes; CI, confidence interval; OR, odds ratio; HR, hazards ratio.

Eligibility criteria

The criteria for including studies were: (1) Subjects should be laboratory-confirmed COVID-19 patients; (2) Studies should report the correlation between CVD and COVID-19 patients and the data are available; (3) Studies should be published in English; (4) Studies should include the multivariate analysis. The studies with the largest sample size were selected for inclusion when studies were conducted in the same hospital and the overlapping period. There was no restriction for region of study. The exclusion criteria included case reports, review papers, comments, errata, repeated studies, studies only reporting the characteristics of COVID-19 patients with CVD, and studies without available full text.

Data extraction and quality assessment

Data were extracted independently by two investigators (J.X. and W.X.), including the following information: the first author, source of data, country, date of data collection, number of patients, mean/median age, the percent of males, study design, the percent of COVID-19 patients with CVD, adjusted effect estimates (hazard ratio (HR) or OR) and adjusted risk factors. When both OR and HR existed in the same article, it was preferred to include HR because cox regression took time into account. Two researchers negotiated to resolve it in case of any issues not covered by the criteria and Y.W. acted as arbiter. The quality of the included studies was evaluated by investigators according to the Newcastle-Ottawa Scale [12]. High-quality studies referred to studies with a score above 7.

Data synthesis

The major information such as study design and effect estimates were directly extracted from original articles. The research type of some articles was not clear and some articles provided both OR and HR. Besides, the calculation methods of HR and OR are different. The calculation of HR takes into account the concept of time, and OR is the approximate value of risk ratio. Therefore, pooled HR, OR and 95% confidence intervals (CIs) were separately calculated to address the risk of adverse outcomes in COVID-19 patients with a history of CVD. Heterogeneity was assessed by Cochran's Q-statistic and I^2 test, if no significant heterogeneity was observed ($I^2 \leq 50\%$, $P > 0.1$), a fixed-effects model was adopted; otherwise, a random-effects model was applied [13]. In addition, we also provided the prediction interval, which was helpful for assessing whether the variation across studies was clinically significant [14, 15]. The robustness of the results was evaluated by sensitivity analysis which omitted one study at a time. Publication bias was assessed by Begg's test [16], Egger's test [17] and trim-and-fill method [18]. Subgroup analysis and meta-regression were conducted to determine the source of heterogeneity. Data analyses were conducted using Stata, version 12.0 (meta-program) and R, version 3.6.1 (netmeta package). A two-tailed P-value < 0.05 was regarded as significant.

Results

The flow chart of selection process is shown in Fig. 1. 5, 025 records were retrieved after removing 23,826 duplicates, of which 245 studies were full-text assessed. Eventually, a total of 203 eligible studies with 24,032, 712 patients were enrolled in our meta-analysis [2, 3, 8, 9, 19–210, 212–218]. 81 studies originated from Europe, 54 studies came from North America, 61 from Asia, 2 from Australia, and the remained 5 were not just from one country (Table 1). Among these studies, cardiac disease was mentioned in 63 studies, HF was involved in 35 studies, and CAD was involved in 35 studies (Table 2). Adjusted HR was reported in 65 studies and adjusted OR was reported in 138 studies (Table 2). The main

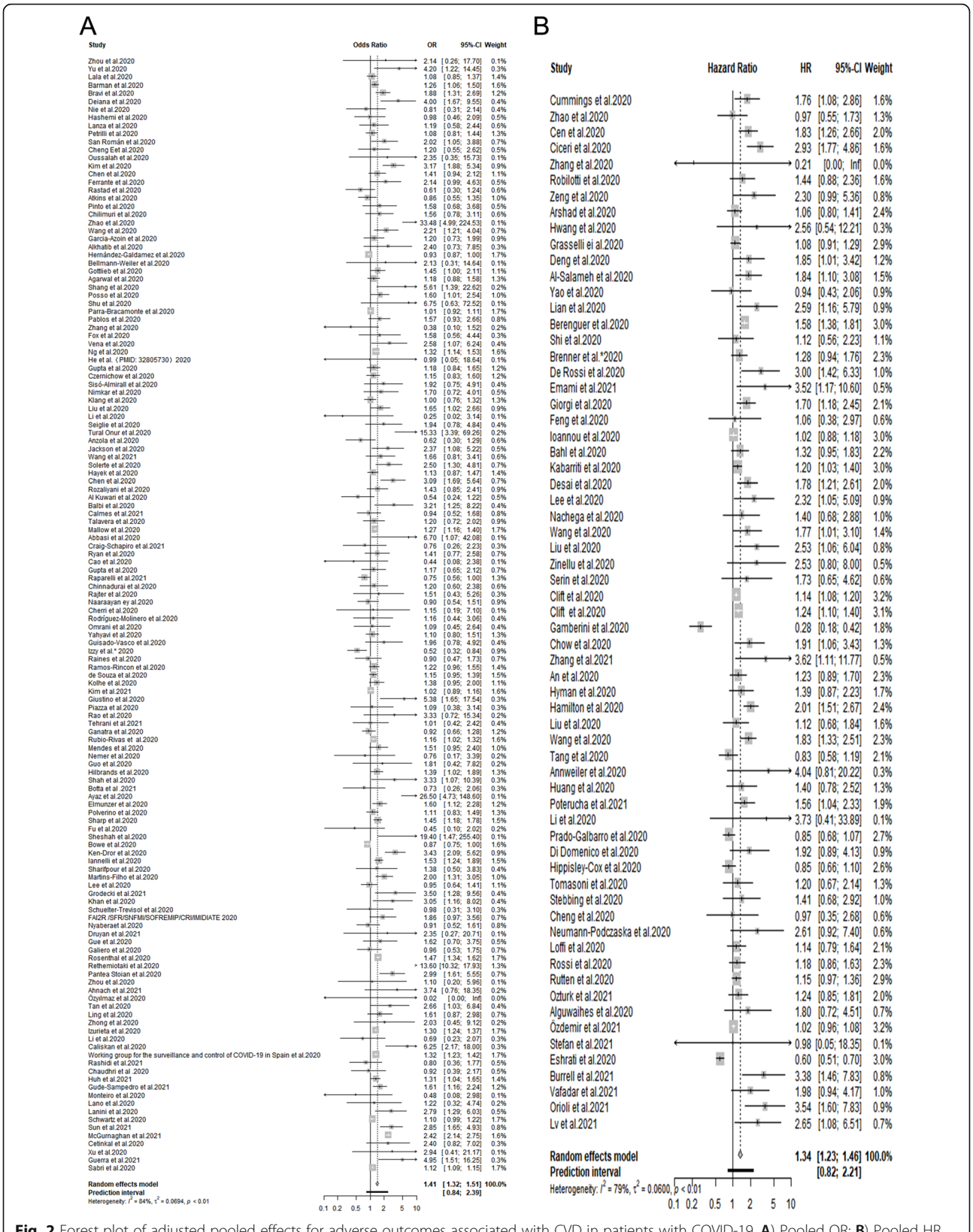

Fig. 2 Forest plot of adjusted pooled effects for adverse outcomes associated with CVD in patients with COVID-19. **A**) Pooled OR; **B**) Pooled HR

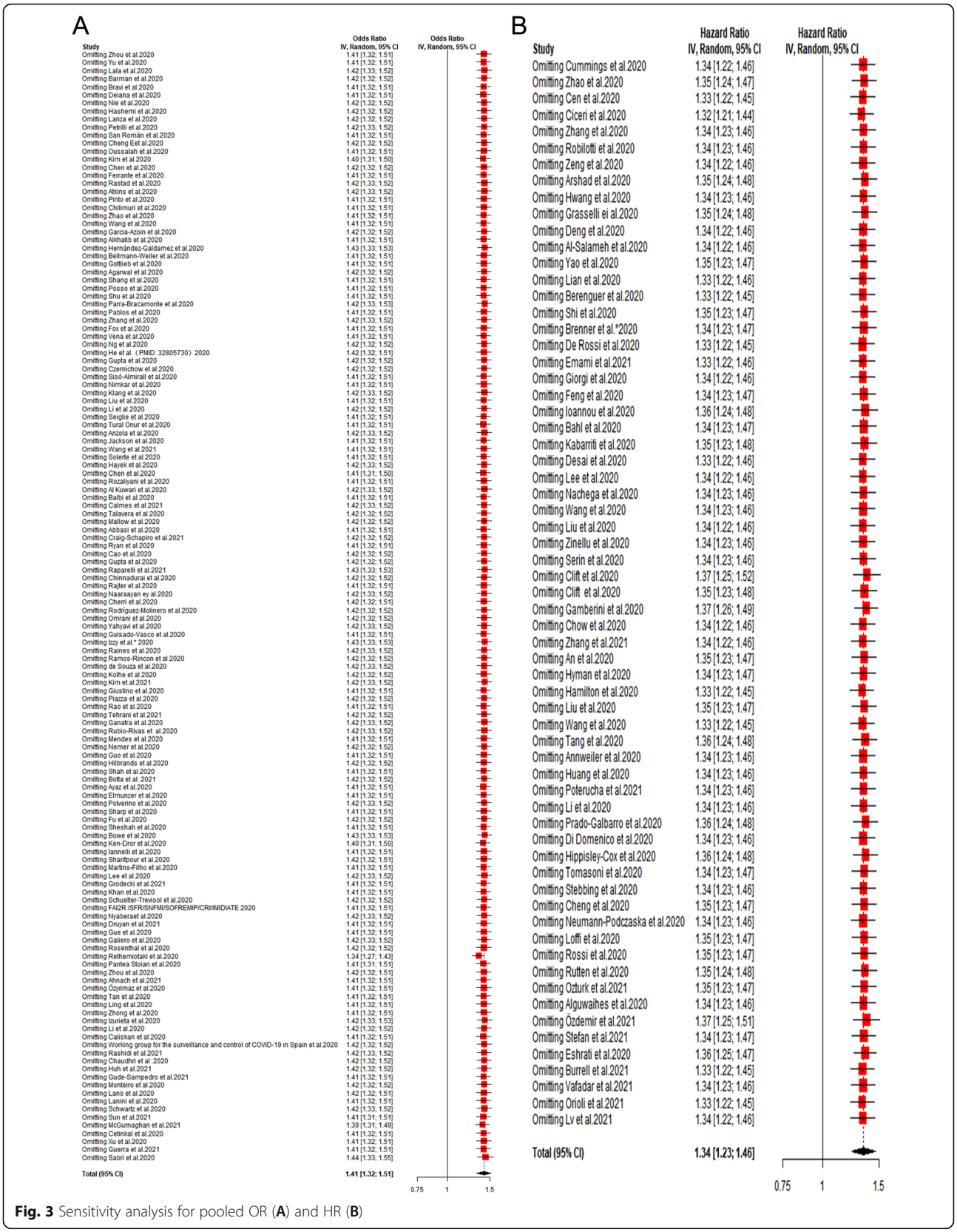

Fig. 3 Sensitivity analysis for pooled OR (**A**) and HR (**B**)

characteristics of the selected studies are summarized in Table 1.

Totally, our results revealed that COVID-19 patients who suffered from CVD tended more to adverse outcomes (pooled ORs = 1.41, 95% CIs: 1.32-1.51, prediction interval: 0.84-2.39; pooled HRs = 1.34, 95% CIs: 1.23-1.46, prediction interval: 0.82-2.21 Fig. 2). Subgroup analysis by sample size showed consistent results (pooled HRs = 1.16, 95% CIs: 1.03-1.32, prediction interval: 0.66-2.04; pooled ORs = 1.41, 95% CIs: 1.32-1.51, prediction interval: 0.84-2.39 for sample size >= 1000; pooled HRs = 1.63, 95% CIs: 1.41-1.88, prediction interval: 0.86-3.10; pooled ORs: 1.57, 95% CIs: 1.40-1.77, prediction interval: 0.84-2.95 for sample size < 1000; Table 2 and Fig. A1). The positive association between pre-existing CVD and adverse outcomes in COVID-19 patients was also observed in subgroup analysis by disease types (Table 2 and Fig. A2): cardiac disease (pooled HRs = 1.40, 95% CIs: 1.17-1.69, prediction interval: 0.68-2.90; pooled ORs = 1.43, 95% CIs: 1.25-1.64, prediction interval: 0.80-2.55), HF (pooled HRs = 1.23, 95% CIs: 1.05-1.44, prediction interval: 0.63-2.39; pooled ORs = 1.46, 95% CIs: 1.31-1.62, prediction interval: 1.01-2.10), and CAD (pooled HRs = 1.48, 95% CIs: 1.14-1.93, prediction interval: 0.67-3.29; pooled ORs = 1.17, 95% CIs:1.02-1.35, prediction interval: 0.75-1.83). In addition, subgroup analyses stratified by age, the proportion of males, region, disease outcomes and study design supported the above positive associations (Table 2 and Fig. A3-7). Sensitivity analysis indicated that our result was robust (Fig. 3A and B). There was no publication bias was detected by Begg's test (OR: P = 0.233, HR: P = 0.054; Fig. 4A and B), while significant publication bias was found by Egger's test (OR: P = 0.000, HR: P = 0.000; Fig. 4C and D). Therefore, the trim-and-fill method was adopted for further analysis. The results for HR showed that with the addition of 21 more studies, the results of the meta-analysis would be more robust but not reversed (pooled HRs = 1.11, 95% CIs: 1.01-1.14, fixed-effects model; pooled HRs = 1.16, 95% CIs: 1.06-1.26, random-effects model), and the OR results (pooled ORs: 1.18, 95% CIs: 1.16-1.20, fixed-effects model; pooled ORs: 1.21, 95% CIs: 1.12-1.30, random-effects model) showed that the results would be equally robust after adding 29 studies. However, there was high heterogeneity in our study. To find sources of heterogeneity, we conducted a meta-

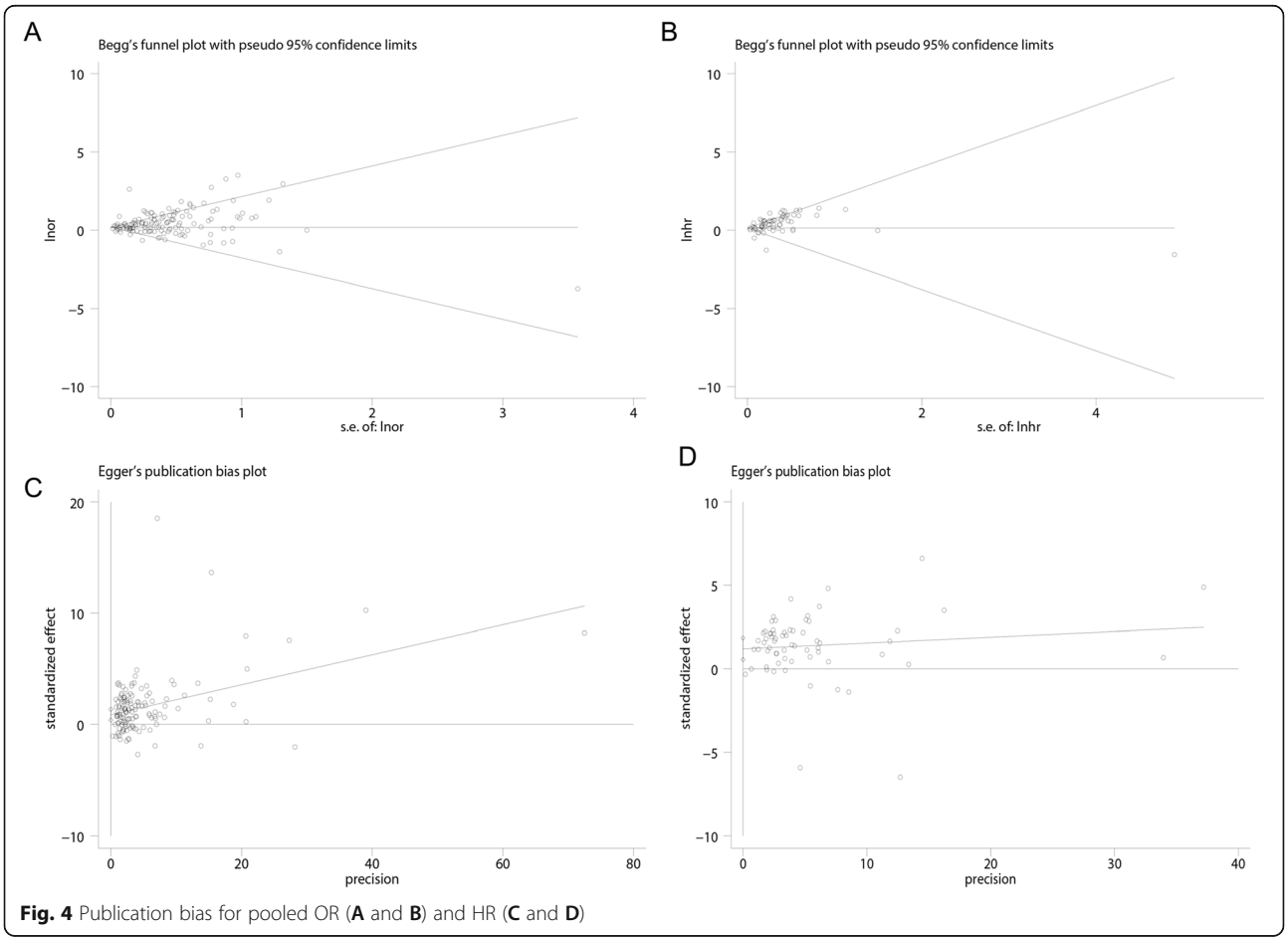

Fig. 4 Publication bias for pooled OR (**A** and **B**) and HR (**C** and **D**)

regression. However, adjustments for multivariate regression coefficients for sample size, age, proportion of males, study design, region, disease types, disease outcomes were not statistically significant (Table 3), suggesting that these were not sources of heterogeneity identified.

Discussion

Many countries have been hit by the pandemic caused by SARS-CoV-2, numerous people lost their lives because of this. Meanwhile, health systems in every country were under so unprecedented strain that it was very important to find an effective marker to help implement bed grading management. What called for special attention was that earlier studies have shown COVID-19 patients with at least one underlying conditions, such as chronic kidney disease, HIV, diabetes and other comorbidities, have a poor disease course [2, 29, 211, 219, 220], which means that those patients with underlying diseases should be monitored more carefully in case of disease getting worse. Furthermore, it was reported that the risk of primary respiratory syndrome severity and adverse outcomes was increased in Middle East respiratory syndrome (MERS) patients with pre-existing CVD. The research by Li et al. [8] with unadjusted effect estimates showed that there was a positive association between CVD and adverse outcomes in patients with

Table 3 The result of meta-regression

Variables	HR			OR		
	Tau^2	t-value	P-value	Tau^2	t-value	P-value
Sample size	0.0753	-0.3248	0.0007	0.0931	-0.1552	0.0449
>=1000						
<1000						
Age	0.0552	-	0.1123	0.0746	-	0.3495
>=60		0.1404	0.1206		0.1006	0.1674
<60						
NR		0.7562	0.1143		0.1713	0.5027
Male (%)	0.0734	0.0351	0.7253	0.0997	-	0.0086
>=50					-0.0678	0.4355
<50						
NR					0.4272	0.0119
Study design	0.0774	-	0.0828	0.0796	-	0.8863
Retrospective/case series		0.1064	0.3152		-0.0034	0.9647
Prospective study		0.1064	0.1628		-0.0823	0.6301
Others						
Region	0.0651	-	0.1800	0.0601	-	<0.0001
Europe		-0.1169	0.2910		-0.0307	0.7439
North America		-0.2287	0.0746		-0.2362	0.0132
Asia						
Others		0.3260	0.3447		1.3471	<0.0001
Disease	0.0702	-	0.8655	0.1005	-	0.4005
CVD		-0.1123	0.4286		0.1737	0.1365
Cardiac disease		-0.0681	0.6418		0.1620	0.1741
HF		-0.1221	0.5212		0.2230	0.0640
CAD						
Others					0.82	0.413
Outcomes	0.0694	-	0.0375	0.0810	-	0.1400
Mortality		-0.0990	0.6880		-0.1298	0.2733
Severity		-0.4713	0.0915		-0.2786	0.0528
Disease progression						

COVID-19, but the association might be confounded by other factors such as age, gender and comorbidities. Thus, we performed a quantitative meta-analysis on the basis of adjusted effect estimates to clarify whether pre-existing CVD was an independent risk factor associated with adverse outcomes in COVID-19 patients.

Our results based on adjusted effect estimates revealed that pre-existing CVD was significantly related to adverse outcomes in COVID-19 patients on the basis of 203 eligible studies with 24,032,712 cases. The significant association between pre-existing CVD and adverse outcomes in COVID-19 patients was still existent in further subgroup analyses stratified by the proportion of males, study design, disease types, sample size, region and disease outcomes, which suggests that our findings are relatively stable.

Similar to other meta-analyses, several limitations should be acknowledged in this present study. Firstly, data on drug and supportive treatments are not clear in the selected studies presently, thus, we could not evaluate the effects of treatments on the association between co-existing CVD and adverse outcomes in COVID-19 patients. Secondly, statistically significant results were more likely to be accepted and published than non-statistically significant results in similar studies, but in fact, the data of the meta-analysis mainly derived from the studies which have been published, which may lead to publication bias. Thirdly, the causal relationship of CVD and adverse outcomes in patients with COVID-19 cannot be confirmed on account of the inherent limitation of the observational study. Therefore, well-designed studies with larger sample sizes are needed for further verification.

Conclusions

In conclusion, our findings indicated that pre-existing CVD was an independent risk factor associated with adverse outcomes among COVID-19 patients. COVID-19 patients with a history of CVD might need more attention.

Abbreviations

CVD: Cardiovascular disease; COVID-19: Coronavirus disease 2019; CI: Confidence interval; OR: Odds ratio; HR: Hazard ratio; CHD: Coronary heart disease; CAD: Coronary artery disease; HIV: Human immunodeficiency virus; MesH: Medical Subject Headings; HF: Heart failure; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analysis

Supplementary Information

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Additional file 1: Table A1. Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines. **Fig. A1.** Subgroup analysis stratified by sample size. **Fig. A2.** Subgroup analysis stratified by type of disease. **Fig. A3.** Subgroup analysis stratified by age. **Fig. A4.** Subgroup analysis stratified by the proportion of male. **Fig. A5.** Subgroup analysis stratified by study design. **Fig. A6.** Subgroup analysis stratified by region. **Fig. A7.** Subgroup analysis stratified by outcome of disease.

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Authors' contributions

H.Y. and Y.W. designed the study; J.X., W.X., X.L. and P.Z. searched literature and extracted the data; J.X., L.S. and Y.W. contributed to the statistical analyses and interpretation; J.X. drafted the manuscript. All the authors have read and approved the final manuscript.

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Availability of data and materials

All data relevant to the study are included in the article or uploaded as supplementary information.

Declarations

Ethics approval and consent to participate

Not required.

Consent for Publication

Not applicable

Competing interests

The authors declare not any potential conflict of interest.

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