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, I² test, 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 24,033,838 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 male, 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.

Background

Since December 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a global outbreak of 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 coronavirus disease 2019 (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 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.

Method

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" "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.

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 male, study design, the percent of COVID-19 patients with CVD, adjusted effect estimates (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% 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 24,033,838 patients were enrolled in our meta-analysis [2, 3, 8, 9, 19-218]. 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. Among these studies, cardiac disease was mentioned in 63 studies, HF was involved in 35 studies, and CAD was involved in 35 studies. Adjusted HR was reported in 65 studies and adjusted OR was reported in 138 studies. The main 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 male, 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-regression. However, adjustments for multivariate regression coefficients for sample size, age, proportion of male, study design, region, disease, outcomes were not statistically significant (Table 2), 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, 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 [221]. 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 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 24,033,838 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 male, 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

Declarations

Ethics approval and consent to participate

Not required.

Consent for Publication

Not applicable

Availability of data and material

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

Competing interests

The authors declare not any potential conflict of interest.

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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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Tables

Table 1 Main characteristics of the included studies

Author (Year)	Country	Patients(n)	Mean/Median Age(years)	Male (%)	Study design	Kinds of diseases	CVD (%)
Zhou et al. (2020)	China	191	56.0 (46.0–67.0)	119 (62)	Retrospective cohort study	Coronary heart disease	18 (8)
Yu et al. (2020)	China	333	50.35-63.0	172 (51.7)	Descriptive study	heart disease	24 (7.2)
Cummings et al. (2020)	USA	257	62 (51–72)	171 (67.0)	Prospective observational cohort study	Chronic cardiac disease	49 (19)
Zhao et al. (2020)	China	1000	61 (46-70)	466 (46.6%)	Retrospective study	Coronary heart disease	60 (6)
Sabri et al. (2020)	Iran	60	54.1±15.5	NR	Retrospective cohort study	Heart Disease	10 (15.9)
Lala et al. (2020)	USA	2736	66.4	1630 (59.6)	NR	Coronary Artery Disease	453 (16.6)
Cen et al. (2020)	China	1007	61(49-68)	493(49.0)	Multi-center observational study	Coronary artery disease	65 (6.5)
Ciceri et al. (2020)	Italy	410	65 (56-75)	299 (72.9)	NR	Coronary artery disease	51 (12.6)
Barman et al. (2020)	Turkey	607	59.5±14.8	334 (55.02)	Multi-center retrospective study	Coronary artery disease	116 (19.1)
Bravi et al. (2020)	Italy	1603	58.0±20.9	758 (47.3)	Case-control, retrospective study	Major cardiovascular diseases	258 (16.1)
Deiana et al. (2020)	Italy	1223	80.4±10.6	499 (40.8)	Matched case-control study	CVD	63 (64.9)
Zhang et al. (2020)	China	80	51.16±17.476	33 (41.25)	Retrospective cohort	Cardiac disease	9 (11.25)
Nie et al. (2020)	China	671	43±15.09	377 (56.2)	NR	CVD	70 (10.4)
Robilotti et al.	USA	423	60.2	212 (50)	NR	Cardiac disorder	84 (20)

(2020)							
Hashemi et al. (2020)	USA	363	63.2±13.2	201 (55.37)	Multi-center retrospective study	Cardiac diseases	39 (10.7)
Lanza et al. (2020)	Italy	222	66.4 (53.8–75.8)	163 (73)	Observational retrospective study,	Heart disease	27 (12.16)
Zeng et al. (2020)	China	461	45.00 (34.50-57.00)	239 (51.84)	Multicenter retrospective study	CVD	25 (5.42)
Petrilli et al. (2020)	USA	5279	54 (38-66)	2615 (49.5)	Prospective cohort study	Coronary artery disease	704 (13.3)
Arshad et al. (2020)	USA	2541	63.7±16.5	1298 (51.1)	Retrospective cohort study	Cardiovascular Comorbidity	222 (8.7)
San Román et al. (2020)	Spain	522	68±15	294 (56%)	NR	Heart disease	68 (13.02)
Cheng et al. (2020)	China	456	54.97±18.59	211 (46.27)	Retrospective cohort study	CVD	52 (11.4)
Oussalah et al. (2020)	France	149	65 (54–77)	91 (61.1)	Retrospective, longitudinal cohort study	CVD	38 (25.5)
Kim et al. (2020)	Korea	9148	51*	3556 (38.9)	Observational Study	Heart failure	124 (1.4)
Chen et al. (2020)	China	3309	62(49-69)	1642 (49.6)	Retrospective	CVD	242 (7.3)
Ferrante et al. (2020)	Italy	332	66.9 (55.4-75.5)	237 (71.4)	Single-center cohort study	CAD	49 (14.5)
Rastad et al. (2020)	Iran	2597	54.8±16.9	1589 (53.7%)	Retrospective cohort study	CVD	314 (10.6)
Hwang et al. (2020)	South Korea	103	67.62±15.32	52 (50)	Retrospective cohort study	CVD	12 (12)
Grasselli ei al. (2020)	Italy	3988	63 (56-69)	3188 (79.9)	Retrospective, observational cohort study	Heart disease	533 (13.4)

Deng et al. (2020)	China	264	64.5 (53.3-74.0)	130 (49.2)	Retrospective study	Coronary heart disease	32 (12.1)
Al-Salameh et al. (2020)	France	433	72±14.3	226 (52.1)	Observational cohort	CVD	99 (31.2)
Atkins et al. (2020)	UK	507	74.3±4.5	311 [61.3%]	NR	CHD	108 (21.5)
Yao et al. (2020)	USA	242	66.1±18.3	104 (42.98%)	Single-institution retrospective study	Heart Disease	39 (13.6)
Pinto et al. (2020)	Italy	1226	71.7±14.5	733 (59.8)	Observational cohort Study	CVD	NR (NR)
Chilimuri et al. (2020)	USA	375	63.0 (52.0-72.0)	236 (63)	Retrospective cohort study	CVD	62 (17)
Lian et al. (2020)	China	232	NR	108 (46.5)	Retrospective study	Heart disease	31 (13.36)
Zhao et al. (2020)	USA	641	58.9±17.5	358 (55.85)	Retrospective study	Heart failure	20 (3.12)
Wang et al. (2020)	USA	1827	52.7±21.1	500 (32.6)	NR	CVD	589 (32.2)
Garcia-Azoin et al. (2020)	Spain	576	67.18±14.75	326 (56.6)	Retrospective cohort study	Cardiac disease	154 (26.7)
Alkhatib et al. (2020)	USA	158	57±15.1	61 (38.6)	Retrospective cross-sectional analysis	Heart Failure	21 (13.3)
Hernández-Galdamez et al. (2020)	Mexico	211003	45.7±16.3	115442 (54.71)	Cross-sectional study	CVD	4949 (2.35)
Bellmann-Weiler et al. (2020)	Australia	259	66.8±14.3	157 (60.62)	Retrospective	CVD	152 (58.62)
Berenguer et al. (2020)	Spain	4035	70 (56 – 80)	2433 (61)	Retrospective nationwide cohort study	Chronic heart disease	932 (23.3)
Gottlieb et al. (2020)	USA	8673	41 (29 – 54)	4045 (46.6)	Retrospective case-control study	Congestive Heart Failure	218 (14.7)

Agarwal et al. (2020)	USA	1126	67.9±13.7	630 (49.3)	Retrospective	CVD	754 (59)
Shang et al. (2020)	China	2529	66	73 (64.6)	Retrospective	CHD	28 (24.8)
Shi et al. (2020)	Iran	386	59.46±15.82	236 (61.1)	Prospective, single-center study	CVD	97(25.1)
Posso et al. (2020)	Spain	834	60	400 (46.5)	Retrospective	Heart Failure	37 (37.4)
Shu et al. (2020)	China	571	50.0 (38.0- 59.0)	278 (48.7)	Single-center, retrospective cohort study	Coronary heart disease	12 (2.1)
Parra-Bracamonte et al. (2020)	Mexico	142690	45 (34.0-57.0)	79280 (56)	NR	Cardiopathy	3521 (2.0)
Pablos et al. (2020)	Spain	456	65±17.9	182 (41)	Retrospective observational matched cohort study	Heart failure	106 (23.2)
Zhang et al. (2020)	China	461	51 (38-64)	264 (57.3)	Multicenter study	Coronary heart disease	25 (5.4)
Fox et al. (2020)	USA	389	66.2±14.2	208 (46.5)	Single-center retrospective analysis	CAD	77 (19.79)
Vena et al. (2020)	Italy	317	71 (60-82)	213 (67.2)	Retrospective study	CVD	63 (19.9)
Ng et al. (2020)	USA	10482	66	6239 (59.5)	Retrospective study	Heart Failure	920 (8.78)
He et al. (2020)	China	288	48.5 (34.3-62)	131(45.5)	Single-center, retrospective cohort study	CVD	85 (29.5)
Gupta et al. (2020)	USA	2626	63.99±16.49	1497(57.00)	Retrospective study	CAD	516 (19.6)
Czernichow et al. (2020)	Europe	5795	59.8±13.6	3791 (65.4)	Prospective cohort study	HF	264 (4.55)
Sisó-Almirall et al. (2020)	Spain	322	56.7±17.8	161 (50.0)	Multicenter, observational descriptive study	HF	25(7.8)
Brenner et al*. (2020)	Germany	9548	62.1	4182 (43.8)	Ongoing statewide cohort study	CVD	4186 (43.8)
De Rossi et al.	Italy	158	66.38±13.44	113 (71.52)	Retrospective	Heart disease	33

(2020)					cohort study		(20.89)
Nimkar et al. (2020)	USA	327	71 (59–82)	182 (55.7)	Retrospective case series	Cardiac Disease	98 (29.9)
Klang et al. (2020)	USA	1320	74.48±12.88	772 (58.48)	Multicenter observational retrospective study	CHD	258 (19.55)
Emami et al. (2021)	Iran	1239	51.48±19.54	692 (55.9)	NR	CVD	132 (10.7)
Liu et al. (2020)	China	2044	62.0 (51.0–70.0)	1000 (48.92)	Mini-national multicenter, retrospective, cohort study	CHD	199 (9.76)
Giorgi et al. (2020)	Italy	2653	63.2	1328 (50.1)	Population-based prospective cohort	CHD	168 (7.1)
Feng et al. (2020)	China	114	63.96±13.41	71 (62.3)	Single-center, prospective study	CVD	31 (27.2)
Li et al. (2020)	China	199	67 (61-78)	89 (44.7)	Retrospective study	CVD	NR (NR)
Seiglie et al. (2020)	USA	450	63.32±17.13	259 (57.5)	Observational study	CHF	52 (11.56)
Tural Onur et al. (2020)	Turkey	301	57±18	206 (68.4)	Retrospectively	CVD	19 (6.3)
Anzola et al. (2020)	Italy	431	65±16	263 (61)	Prospective study	CVD	77 (18)
Ioannou et al. (2020)	USA	10131	61.6±15.9	9221 (91.0)	Longitudinal cohort study	CAD	2203 (21.7)
Bahl et al. (2020)	USA	1461	62.0 (50.0–74.0)	770 (52.7)	Multicentered cohort study	CVD	163 (11.2)
Kabarriti et al. (2020)	USA	5902	58 (44-71)	2768 (46.9)	Cohort study	CVD	1306 (22.1)
Jackson et al. (2020)	USA	51	60 (45–69)	29 (56.9)	Retrospective observational cohort	CAD	10 (19.6)
Desai et al. (2020)	Italy	575	64.8 (27-93)	380 (66.09)	Single-center, retrospective, observational study	CVD	155 (27.1)

Wang et al. (2021)	China	663	58 (44-69)	321 (48.4)	Retrospective	CVD	164 (24.7)
Solerte et al. (2020)	Italy	169	69±1.0	115 (68)	Multicenter, case-control, retrospective, observational study	CVD	53 (38)
Hayek et al. (2020)	USA	5019	60.42±14.86	3165 (63.06)	Multicenter cohort study	CAD	676 (13.47)
Chen et al. (2020)	China	2828	60.0 (50.0- 68.0)	1442 (51.0)	single-center Retrospective cohort study	CHD	181 (6.4)
Lee et al. (2020)	South Korea	5061	45.44±17.92	2,229 (44%)	Retrospective cohort study	CVD	49 (0.97)
Nachega et al. (2020)	South Africa	766	46 (34–58)	500 (65.6)	Retrospective cohort study	Heart disease	30 (3.9)
Rozaliyani et al. (2020)	India	4052	45.8±16.3	2169 (53.5)	Retrospective cohort study	Heart disease	148 (6.9)
Wang et al. (2020)	China	293	59.2 (42.8- 73.1)	138 (47.1)	Retrospective study	Coronary heart disease	21 (7.2)

Liu et al. (2020)	China	77	63.6±3.6	48 (62)	Retrospective study	CVD	15 (20)
Al Kuwari et al. (2020)	Qatar	5685	35.8±12.0	5052 (88.9)	Case series	CVD	250 (4.4)
Balbi et al. (2020)	Italy	340	68 (57–76)	252 (74)	Retrospective observational study	CVD	86 (25)
Calmes et al. (2021)	Belgium	493	58 ± 19	244 (49.49%)	NR	Cardiopathy	88 (18)
Talavera et al. (2020)	Spain	576	67.18±14.75	325 (56.6)	Retrospective cohort study	Cardiological disorders	154 (26.7)
Zinellu et al. (2020)	Italy	105	72.0 (59.5–80.0)	70 (66.67%)	Retrospective	CVD	59 (56.19)
Mallow et al. (2020)	USA	21676	64.9±17.2	11442 (52.8)	Retrospective cohort study	Severe heart disease	12000 (55.4)
Abbasi et al. (2020)	Iran	262	58 (43–67)	172 (65.6)	Retrospective cohort study	CAD	78 (29.8)
Craig-Schapiro et al. (2021)	USA	136	56.24±35.04	93 (68.38)	NR	CVD	52 (38.23)
Ryan et al. (2020)	USA	556	57±17	296 (53)	Retrospective case-control study	CVD	71 (13)
Serin et al. (2020)	Turkey	2217	47.66±17.23	1175 (53)	NR	CAD	165 (7.4)
Cao et al. (2020)	China	101	56.6±15.1	67 (66.3)	Retrospective, two-center study	CVD	21 (20.8)
Gupta et al. (2020)	USA	3099	62 (51–71)	2003 (64.6)	Multicenter cohort study	CAD	390 (12.6)

Raparelli et al. (2021)	Italy	3517	77.64±11.51	2346 (66.7)	Retrospective analysis	Congestive Heart Failure	539 (15.7)
Chinnadurai et al. (2020)	UK	215	74 (60–82)	133 (61.9)	Single-center observational study	CVD	93 (43.3)
Rajter et al. (2020)	USA	280	59.6±15.9	153 (64.6)	NR	cardiac Disease	43 (15.4)
Naaraayan ey al. (2020)	USA	362	71 (59–82)	200 (55.3)	Retrospective case series	Cardiac diseases	119 (32.9)
Cherri et al. (2020)	Italy	53	75 (68–83)	32 (60.4)	Retrospective study	Cardiopathy	20 (37.7)
Rodríguez-Molinero et al. (2020)	Spain	418	65.4±16.6	238 (56.9)	Observational cohort study	Heart failure	26 (6.22)
Clift et al. (2020)	UK	8256158	44.33±27.42	4111197 (49.8)	Cohort study	Heart failure	96225 (1.17)

Clift et al. (2020)	UK	6083102	48.21±18.57	3035409 (49.90)	Population based cohort study	Coronary heart disease	215069 (3.54)
Gamberini et al. (2020)	Italy	2540	66 (59–72)	300 (76.7)	Multicenter prospective observational study	Chronic ischemic heart disease	35 (9)
Omrani et al. (2020)	Qatar	1409	39.82±14.2	1167 (82.8)	Retrospective cohort study	Coronary artery disease	31 (2.4)
Yahyavi et al. (2020)	Iran	2553	58.1±17.9	1498 (58.7)	Retrospective cohort study	CVD	942 (36.9)
Guisado-Vasco et al. (2020)	Spain	607	69±22.0	394 (65.02)	Retrospective, observational, longitudinal study	chronic cardiac disease	133 (22.62)
Izzy et al.* (2020)	USA	5190	52 (36–66)	2378 (46)	NR	Coronary artery disease	257 (5)

Chow et al. (2020)	USA	412	55 (41-66)	244(52.9)	Retrospective, observational cohort study	CAD	52 (12.62)
Raines et al. (2020)	USA	440	60.8±14.07	393 (89.32)	Retrospective	CVD	364 (82.73)
Ramos-Rincon et al. (2020)	Spain	2772	86.3 (83.2- 89.6)	1367 (49.4)	Nationwide, multicenter, retrospective, observational study	CVD	855 (30.8)
Zhang et al. (2021)	China	222	51.5 (34.0- 65.3)	90(40.54)	NR	Chronic cardiovascular disease	44 (19.82)
de Souza et al. (2020)	Brazil	9807	70.21±8.37	4662 (47.5)	Retrospective population- based study	CVD	1192 (12.2)
Kolhe et al. (2020)	UK	1161	72.1±16.0	657 (56.59)	Retrospective cohort study	Congestive cardiac failure	207 (17.83)
Kim et al. (2021)	USA	10861	65 (54-77)	6468(59.6)	NR	CAD	1447 (13.3)
Giustino et al. (2020)	New York City & Milan	305	63 (53–73)	205 (67.2)	International, multicenter cohort study	Heart failure	24 (7.9)

An et al. (2020)	Korea	228	44.97±19.79	107 (46.9)	Cohort study	CVD	70 (30.7)
Piazza et al. (2020)	USA	1114	50.6±18.3	511 (45.9)	Retrospective observational cohort analysis	CAD	90 (8.1)
Rao et al. (2020)	China	240	48 (23–87)	111 (46.250)	Retrospective cohort study	CVD	43 (17.9)
Tehrani et al. (2021)	Sweden.	255	66±17	150 (59)	Retrospective analysis	Chronic heart failure	34 (13)
Hyman et al. (2020)	USA	755	63±13	483 (64.0)	Retrospective cohort study	Congestive heart failure or valve disorder	30 (4.3)
Hamilton et al. (2020)	UK	1032	71 (56–83)	569 (55.1)	Retrospective review	Congestive Heart Failure	129 (12.5)
Liu et al. (2020)	China	774	64 (54–73)	452 (58.4)	Multicenter retrospective observational study	Chronic cardiac disease	91 (11.8)
Ganatra et al. (2020)	USA	2467	59 (18–101)	1032 (42)	Retrospective study	CAD	184 (7.0)
Rubio-Rivas et al. (2020)	Spain	12066	68 (56–79)	7052 (58.5)	Cohort study	Chronic heart failure	809 (6.7)
Mendes et al. (2020)	Switzerland	235	86.3±6.5	102 (43.4)	Retrospective monocentric cohort study	Heart failure	66 (28.1)
Nemer et al. (2020)	USA	350	64±16	194 (55)	Prospective	Congestive heart failure	42 (12)
Guo et al. (2020)	China	350	43(32–56)	173(49.4)	Retrospective, multicenter study	CVD	15 (4.3)

Hilbrands et al. (2020)	Netherlands	305	60±13	189(62)	Observational study	Heart failure	64 (21)
Wang et al. (2020)	China	7283	64 (53–71)	3732 (51.2)	Retrospective observational study	CVD	161 (2.2)
Tang et al. (2020)	USA	752	73.9 (21.9–105.4)	323 (43)	Cohort study	Coronary heart disease	240 (31.91)
Annweiler et al. (2020)	France	77	88 (85–92)	39 (50.6)	Retrospective quasi-experimental study	Cardiomyopathy	42 (54.5)
Huang et al. (2020)	China	676	56.0 (39.0–68.0)	314 (46.4)	Retrospective study	Heart Disease	71 (10.5)
Poterucha et al. (2021)	USA	887	64.1	513 (58)	Retrospective study	CAD	104 (12.0)
Li et al. (2020)	China	100	62.0 (51.0–70.8)	56 (56.0)	NR	CVD	15 (15.0)
Prado-Galbarro et al. (2020)	Mexico	9487	31.37 (41.13–51.18)	5050 (53.2)	Observational study	CVD	171(1.8)
Shah et al. (2020)	USA	487	68.53±16.66	273 (56.06)	Retrospective review	Cardiomyopathy	16 (3.28)
Botta et al. (2021)	Netherlands	553	67.0 (59.0–73.0)	417 (75)	National, multicenter, observational cohort study	Heart failure	25 (5.0)
Di Domenico et al. (2020)	France	310	64 (52–76)	200 (64.5)	Single-center retrospective study	Heart disease	50 (16.2)
Ayaz et al. (2020)	Pakistan	66	50.6±19.1	40 (61)	Retrospective cohort study	Ischemic heart disease	10 (15)

Hippisley-Cox et al. (2020)	UK	8275949	48.47±18.41	4115973 (49.73)	Prospective cohort study	CVD	433631 (5.24)
Tomasoni et al. (2020)	Italy	692	66.5±13.3	415 (68.9)	Multicenter study	CAD	148 (21.4)
Elmunzer et al. (2020)	North American	1846	59.9±16.4	1044 (56.6)	Large-scale retrospective cohort study	Congestive Heart Failure	284 (15.4)
Polverino et al. (2020)	Italy	3179		2171 (68.3)	Nationwide observational study	Coronary artery disease	359 (11.3)
Sharp et al. (2020)	USA	21280	50 (34-66)	9053 (42.5)	Retrospective cohort study	Congestive Heart Failure	NA (NA)
Stebbing et al. (2020)	Italy&Spain	166	74.05±13.06	85 (51.2)	Observational studies	CVD	48 (28.9)
Fu et al. (2020)	China	355	43.5*	193 (54.37)	Hospital-Based Retrospective Cohort Study	Heart disease	20 (6.2)
Sheshah et al. (2020)	Saudi Arabia	300	49.7±13.2	259 (86.3)	Single-center, retrospective study	Coronary Artery Disease	10 (3.3)
Bowe et al. (2020)	USA	5216	70 (61–76)	4908 (94)	Cohort study	CVD	1588 (30.0)

Cheng et al. (2020)	China	220	59.5 (48.3-70.0)	106 (48.2)	Retrospective, observational study	CAD	22 (10.0)
Neumann-Podczaska et al. (2020)	Poland	50	74.8±9.4	35 (70.0)	Retrospective	Heart disease	26 (52.0)
Ken-Dror et al. (2020)	UK	429	70±18	242 (56.4%)	Prospective cohort study	chronic cardiac disease/congenital heart disease	103 (31.3)
Iannelli et al. (2020)	France	8286	59.1±12.6	4296 (51.8)	Retrospective	Cardiac failure	569 (6.9)
Sharifpour et al. (2020)	USA	268	63±15	149 (55.6)	Cohort analysis	CAD	36 (13.4)
Martins-Filho et al. (2020)	Northeast Brazil	1207	60 (46–73)	724 (60)	Retrospective cohort study	Heart failure	102 (8.45)
Lee et al. (2020)	Korea	7339	47.1±19.0	2970 (40.1)	Nationwide Population-Based Retrospective Study	CVD	455 (6.1)
Loffi et al. (2020)	Italy	1252	64.7±15.5	798 (63.74)	Retrospective, observational, single-center study	CAD	124 (9.9)
Grodecki et al. (2021)	USA	109	63.74±15.11	68 (62.39)	Prospective	Heart failure	16 (14.68)
Rossi et al. (2020)	Italy	590	76.2 (68.2–82.6)	399 (67.6)	Retrospective observational study	CVD	95 (16.1)
Khan et al. (2020)	Saudi Arabia	648	34±19	342 (52.8)	Retrospective cohort study	Cardiac diseases	23 (3.5)

Rutten et al. (2020)	Netherlands	1538	84±8.7	554 (36.02)	Prospective cohort study	CVD	53 (3.47)
Schuelter-Trevisol et al. (2020)	Brazil	211	51.2*	113 (53.6)	Cohort study	Chronic heart disease	27 (12.9)
FAI2R /SFR/SNFMI/SOFREMIP/CRI/IMIDIATE (2020)	France	694	56.1±16.4	232 (33.4)	Observational, multicenter, French national cohort study	Coronary heart diseases	68 (9.8)
Nyabera et al. (2020)	USA	290	77.6±8.3	150 (51.7)	Single-center retrospective cohort study	CAD	80 (27.6)
Ozturk et al. (2021)	Turkey	1160	60.5 (47–71)	627 (54.1)	Multicenter, retrospective, observational study	CVD	NR (NR)
Druyan et al. (2021)	Israel	181	62.71*	107 [59.1]	Single center study	Heart failure	10 (5.52)
Alguwaihes et al. (2020)	Saudi Arabia	439	55 (19–101)	300 (68.3)	Single-center retrospective study	CVD	44 (10.0)
Özdemir et al. (2021)	Turkey	101	49.60±18	55 (54.4)	Retrospective study	Chronic heart failure	10 (9.9)
Gue et al. (2020)	UK	316	73.42±15.97	192 (61.1)	Single-center retrospective cohort	CAD	48 (15.19)
Galiero et al. (2020)	Italy	618	65±15.2	379 (61.3)	Multicenter retrospective observational cohort study	Chronic Cardiac Disease	166 (26.9)
Rosenthal et al. (2020)	USA	64781	56.1±19.9	31968 (49.3)	Retrospective cohort study	Myocardial infarction	3717 (5.7)
Rethemiotaki et al. (2020)	the World Health Organization	44672	71*	22981 [51.44]	NR	CVD	92 (15.9)

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Pantea Stoian et al. (2020)	China	432	NR	NR	Multiple-case, multiple-center	Heart failure	30 (6.94)	
Zhou et al. (2020)	China	134	62.08±14.38*	85 (63.4)	Retrospective	Coronary heart disease	16 (11.94)	
Stefan et al. (2021)	Romania	37	64 (55–71)	19 (51)	Retrospective, observational, single-center study	Coronary heart disease	19 (51.0)	
Ahnach et al. (2021)	Morocco	101	50 (32–63)	75 (51.72)	Retrospective study	CVD	16 (11.03)	
Eshrati et al. (2020)	Iran	3188	55.05 ± 0.31	1925 (60.4)	Retrospective cohort study	CVD	401 (12.6)	
Özyılmaz et al. (2020)	Turkey	105	45 (20–87)	76 (72.3)	Single-center, retrospective, observational study	CAD	14 (13.3)	
Tan et al. (2020)	China	163	69.0 (62.0- 78.0)	109 (66.9)	Retrospective study	Chronic cardiac injury	25 (15.3)	
Ling et al. (2020)	UK	444	74 (63-83)	245 (55.2)	Cross- Sectional Multi-Centre Observational Study	Heart failure	54 (12.2)	
Zhong et al. (2020)	China	126	66.3±10.6	56 (44.4)	Retrospective observational study	CVA	21 (16.7)	
Izurieta et al. (2020)	USA	12613	80.5*	6496 (51.5%)	Retrospective cohort study	Congestive Heart Failure	3557 (28.2)	

Burrell et al. (2021)	Australia	304	63.5 (53–72)	140 (69%)	Prospective, observational cohort study	Chronic cardiac disease	40 (20)	
Li et al. (2020)	China	123	64.43±14.02	62 (50.41)	Retrospective study	CVD	26 (21.14)	
Caliskan et al. (2020)	Turkey	56	48±19.664	NR	Retrospective observational study	CAD	42 (7.4)	
Vafadar et al. (2021)	Iran	219	57.8±16.5	137 (62.6)	Retrospective cohort	Ischemic heart disease	46 (22.37)	
Working group for the surveillance and control of COVID-19 in Spain et al. (2020)	Spain	2612	83 (75–89)	14680 (56.2)	NR	CVD	11444 (59.9)	
Rashidi et al. (2021)	Iran, Germany, USA	1529	56 (32–80)	832 (54.4)	Multi-center prospective study	Cardiac disease	149 (9.7)	
Chaudhri et al. (2020)	USA	317	59.16±17.5	166 (52.37)	Single-center cohort study	Coronary artery disease	27 (12)	
Huh et al. (2021)	South Korea	219961	49.4 (18– 116)	104331 (47.4)	Retrospective case-control study	Chronic heart disease	32457 (14.76)	
Orioli et al. (2021)	Belgium	73	69±14	48 (66.67)	Retrospective study	CVD	32 (43.8)	
Gude-Sampedro et al. (2021)	Spain	10454	58.0±20.0	4172 (39.9)	Retrospective cohort study	Ischemic heart disease		
Monteiro et al. (2020)	USA	112	61 (45–74)	74 (66)	Retrospective, observational cohort study	CAD	17 (15)	
Lano et al. (2020)	France	122	73.5 (64.2– 81.2)	79 (65)	Observational cohort multicenter study	Congestive heart failure	13 (11)	
Lanini et al. (2020)	Italy	379	61.67±15.60	273 (72.03)	Longitudinal cohort study	CVD	19 (5.01)	
Schwartz et al. (2020)	Canada	56606	31*	29205 (51.59)	Cross- sectional study	CVD	4465 (7.89)	

Sun et al. (2021)	China	3400	61 (50-68)	1649 (48.5)	Retrospective cohort study	CVD	343 (10.1)
McGurnaghan et al. (2021)	Scotland	319349	79.9 (71.4–85.7)	180486 (56.5)	Cohort study	Any heart disease	696 (64.3)
Cetinkal et al. (2020)	Turkey	349	68.3±13.3	176 (50.43)	Retrospective single-center study	Heart failure	38 (10.89)
Xu et al. (2020)	China	61	63.62±10.78	33 (54.1)	Retrospective	Heart diseases	7 (11.5)
Lv et al. (2021)	China	409	50.47±12.43	188 (46)	Retrospective cohort Study	Heart disease	51 (12.5)
Guerra et al. (2021)	Spain	447	55.0±22.5	190 (46.4)	Retrospective single center study	Coronary artery disease	

*, 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: Subgroup analysis

Variables	Effects	NO. Of studies	Subgroup analysis		Prediction interval
			Pooled ES (95% CI)	I^2 / τ^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
	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.

Meta-regression

Variables	HR			OR		
	Tau²	t-value	P-value	Tau²	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						

Figures

Figure 1

Flow diagram of selection process.

Figure 2

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

Figure 4

Publication bias for pooled OR (A and B) and HR (C and D)

Supplementary Files

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