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 I² test, if no significant heterogeneity was observed (I² ≤ 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 | 172 (51.7) | Descriptive study | heart disease | 24 (7.2) |
| Cummings et al. (2020) | USA | 257 | 62 (51–72) | 171 (67%) | 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) |
| Study (2020) | Country | Sample Size | Age (Mean ± SD) | N (%) | Study Design | Disease | Cases (%) |
|-------------|---------|-------------|-----------------|-------|--------------|---------|-----------|
| 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 (53.7-75.8) | 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 et al. (2020) | Italy | 3988 | 63 (56-69) | 3188 (79.9) | Retrospective, observational cohort study | Heart disease | 533 (13.4) |
| Study                          | Country   | N   | Mean Age (SD) | N with Disease (%) | Study Type                        | Condition                          | N with Disease (%) |
|-------------------------------|-----------|-----|---------------|-------------------|-----------------------------------|-----------------------------------|-------------------|
| 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 (42.9)        | Single-institution retrospective study | Heart Disease                  | 39 (13.6)         |
| Pinto et al. (2020)           | Italy     | 1226| 71.7±14.5     | 733 (59.8)        | Observational cohort              | 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 (55.8)        | 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 t | Congestive Heart Failure          | 218 (14.7)        |
| Study                                      | Country  | Sample Size | Age Mean ± Standard Deviation | Number of Cases | Design               | Outcomes                                      | N (%)  |
|--------------------------------------------|----------|-------------|-------------------------------|-----------------|----------------------|-----------------------------------------------|--------|
| 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, prospective cohort study | Coronary heart disease                        | 12 (2.1)  |
| Parra-Bracamonte et al. (2020)             | Mexico   | 142,690     | 45 (34.0-57.0)                | 79,280 (56)     | NR                   | Cardiopathy                                   | 3,521 (2.0) |
| Pablos et al. (2020)                       | Spain    | 456         | 65±17.9                       | 182 (41)        | Retrospective         | 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         | 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      | 10,482      | 66                            | 6,239 (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         | CVD                                           | 85 (29.5)  |
| Gupta et al. (2020)                        | USA      | 2,626       | 63.99±16.49                   | 1,497 (57.00)   | Retrospective study  | CAD                                           | 5,16 (19.6) |
| Czernichow et al. (2020)                   | Europe   | 5,795       | 59.8±13.6                     | 3,791 (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  | 9,548       | 62.1                          | 4,182 (43.8)    | Ongoing statewide     | CVD                                           | 4,186 (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 (18.7) |
| 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) |
| Study                          | Country     | N     | Mean Age ± SD | Cases (%) | Study Design                                      | Disease(s)            | Incidence |
|-------------------------------|-------------|-------|---------------|-----------|--------------------------------------------------|-----------------------|-----------|
| 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)  |
| Study                          | Country   | Sample Size | Mean Age | Participants | Study Design          | Disease | Study Type | Study Type Details |
|-------------------------------|-----------|-------------|----------|--------------|------------------------|---------|------------|--------------------|
| Liu et al. (2020)             | China     | 77          | 63.6±3.6 | 48 (62)      | Retrospective study    | CVD     |            |                    |
| Al Kuwari et al. (2020)       | Qatar     | 5685        | 35.8±12.0| 5052 (88.9)  | Case series            | CVD     |            |                    |
| Balbi et al. (2020)           | Italy     | 340         | 68 (57–76)| 252 (74)     | Retrospective study    | CVD     |            |                    |
| Calmes et al. (2021)          | Belgium   | 493         | 58 ± 19  | 244 (49.49)  | NR                     | NR      |            |                    |
| Talavera et al. (2020)        | Spain     | 576         | 67.18±14.75| 325 (56.6)  | Retrospective cohort study | CVD     | Cardiological disorders | 154 (26.7) |
| Zinellu et al. (2020)         | Italy     | 105         | 72.0 (59.5-80.0)| 70 (66.67) | Retrospective study    | CVD     |            | 59 (56.19)        |
| Mallow et al. (2020)          | USA       | 21676       | 64.9±17.2| 11442 (52.8) | Retrospective cohort study | CVD     | 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)        |
| Study                                | Country | n   | Mean Age ± SD | n (%)  | Study Design                  | Condition                               | Cases  |
|--------------------------------------|---------|-----|---------------|--------|--------------------------------|------------------------------------------|--------|
| 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) |
| Study                        | Country | Sample Size | Age | Gender | Study Type                          | Disease                          | Cases |
|------------------------------|---------|-------------|-----|--------|-------------------------------------|----------------------------------|-------|
| Clift et al. (2020)          | UK      | 6083102     | 48.21±18.57 | 3035409 | 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) |
| Study (Year)                      | Country       | N  | Mean Age (Range)    | N (%) | Study Type                              | Condition                          | N (%) |
|----------------------------------|---------------|----|---------------------|-------|-----------------------------------------|------------------------------------|-------|
| 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) |
|Author et al. (Year) | Country | Sample Size | Mean ± Standard Deviation | Cases (Percentage) | Study Type | Disease |
|---------------------|---------|-------------|---------------------------|-------------------|------------|---------|
| An et al. (2020)    | Korea   | 228         | 44.97±19.79               | 107 (46.9)        | Cohort study | CVD     |
| Piazza et al. (2020)| USA     | 1114        | 50.6±18.3                 | 511 (45.9)        | Cohort study | CAD     |
| Rao et al. (2020)   | China   | 240         | 48 (23–87)                | 111 (46.250)      | Cohort study | CVD     |
| Tehrani et al. (2021)| Sweden. | 255         | 66±17                     | 150 (59)          | Retrospective analysis | Chronic heart failure |
| Hyman et al. (2020) | USA     | 755         | 63±13                     | 483 (64.0)        | Cohort study | Chronic heart failure or valve disorder |
| Hamilton et al. (2020)| UK     | 1032        | 71 (56–83)                | 569 (55.1)        | Retrospective review | Congestive Heart Failure |
| Liu et al. (2020)   | China   | 774         | 64 (54–73)                | 452 (58.4)        | Multicenter retrospective observational study | Chronic cardiac disease |
| Ganatra et al. (2020)| USA     | 2467        | 59 (18–101)               | 1032 (42)         | Retrospective study | CAD |
| Rubio-Rivas et al. (2020)| Spain | 12066       | 68 (56–79)                | 7052 (58.5)       | Cohort study | Chronic heart failure |
| Mendes et al. (2020)| Switzerland | 235    | 86.3±6.5                  | 102 (43.4)        | Retrospective monocentric cohort study | Heart failure |
| Nemer et al. (2020) | USA     | 350         | 64±16                     | 194 (55)          | Prospective | Congestive heart failure |
| Guo et al. (2020)   | China   | 350         | 43 (32–56)                | 173 (49.4)        | Retrospective, multicenter study | CVD |

*Note: CVD stands for Cardiovascular Disease.*
| Study                          | Country       | Sample Size | Mean Age (Range) | Mean Age (Range) | Study Design                  | Disease                     | Cases (Percentage) |
|-------------------------------|---------------|-------------|------------------|------------------|------------------------------|-----------------------------|--------------------|
| 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              | 240 (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)           |
| Study                      | Country          | Number | Age                  | Sex     | Study Type                        | Disease                | Outcome | Location                  |
|---------------------------|------------------|--------|----------------------|---------|-----------------------------------|------------------------|---------|---------------------------|
| Hippisley-Cox et al. (2020) | UK               | 8275949 | 48.47±18.41          | 4115973 | Prospective cohort study          | CVD                    | 433631 | (5.24)                    |
| Tomasoni et al. (2020)    | Italy            | 692    | 66.5±13.3            | 415     | Multicenter study                 | CAD                    | 148     | (21.4)                    |
| Elmunzer et al. (2020)    | North American   | 1846   | 59.9±16.4            | 1044    | Large-scale retrospective cohort study | Congestive Heart Failure | 284     | (15.4)                    |
| Polverino et al. (2020)   | Italy            | 3179   | 81.5±13.3            | 2171    | Nationwide observational study     | Coronary artery disease | 359     | (11.3)                    |
| Sharp et al. (2020)       | USA              | 21280  | 50 (34-66)           | 9053    | Retrospective cohort study        | Congestive Heart Failure | NA (NA) |                           |
| Stebbing et al. (2020)    | Italy&Spain      | 166    | 74.05±13.06          | 855     | Observational studies             | CVD                    | 48      | (28.9)                    |
| Fu et al. (2020)          | China            | 355    | 43.5*                | 193     | Hospital-Based Retrospective Cohort Study | Heart disease          | 20      | (6.2)                     |
| Sheshah et al. (2020)     | Saudi Arabia     | 300    | 49.7±13.2            | 259     | Single-center, retrospective study | Coronary Artery Disease | 10      | (3.3)                     |
| Bowe et al. (2020)        | USA              | 5216   | 70 (61–76)           | 4908    | Cohort study                      | CVD                    | 1588    | (30.0)                    |
| Study                        | Country          | Sample Size | Mean Age | SD/Range | Study Type                                                                 | Disease                                    | n   |
|------------------------------|------------------|-------------|----------|----------|-----------------------------------------------------------------------------|---------------------------------------------|------|
| 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) |
| Study                          | Country       | Sample Size | Mean Age | Median Age | Study Type                          | Disease            | CVD Incidence |
|-------------------------------|---------------|-------------|----------|------------|-------------------------------------|-------------------|---------------|
| 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\(\leq 59.1\) | 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 study | 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) |
| Study Authors and Year | Country | Sample Size | Mean Age or Range | Male (%) | Study Design | Disease | Cases (Prevalence) | Reference |
|------------------------|---------|-------------|-------------------|----------|--------------|---------|-------------------|-----------|
| 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) | |
| Abnach et al. (2021) | Morocco | 101 | 50 (32–63) | 75 (51.72) | Retrospective study | CVD | 16 (11.03) | |
| Eshrat et al. (2020) | Iran | 3188 | 55.05 ± 0.31 | 1925 (60.4) | Retrospective cohort study | CVD | 401 (12.6) | |
| Özyilmaz 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) | |
| Study                                    | Country      | n   | Mean Age ± Standard Deviation | Mean % (Min–Max) | Study Design                     | Disease                  | n (%)       |
|------------------------------------------|--------------|-----|-------------------------------|------------------|----------------------------------|--------------------------|-------------|
| 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) |
| Study                  | Country   | N     | Age (Mean ± SD) | CVD (95% CI) | Study Type                      | Diagnosis                  | Cases |
|-----------------------|-----------|-------|----------------|--------------|---------------------------------|----------------------------|-------|
| 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    |                   |

* denotes 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 kidney injury; CLD, chronic liver 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
Table 2: Subgroup analysis
| Variables | Effects | NO. Of studies | Subgroup analysis | Prediction interval |
|-----------|---------|----------------|-------------------|--------------------|
|           |         |                | Pooled ES (95% CI) | I², τ², P value    |
| Sample size |         |                |                   |                   |
| ≥1000     | HR      | 24             | 1.16 (1.03-1.32)  | I² = 88%, τ² = 0.0697 | P < 0.01 | 0.66-2.04 |
|           | OR      | 53             | 1.41 (1.32-1.51)  | I² = 84%, τ² = 0.0694 | P < 0.01 | 0.84-2.39 |
| <1000     | HR      | 41             | 1.63 (1.41-1.88)  | I² = 64%, τ² = 0.0957 | P < 0.01 | 0.86-3.10 |
|           | OR      | 83             | 1.57 (1.40-1.77)  | I² = 57%, τ² = 0.0967 | P < 0.01 | 0.84-2.95 |
| Age       |         |                |                   |                   |
| ≥60       | HR      | 41             | 1.42 (1.25-1.61)  | I² = 73%, τ² = 0.0914 | P < 0.01 | 0.76-2.65 |
|           | OR      | 78             | 1.49 (1.34-1.65)  | I² = 86%, τ² = 0.1144 | P < 0.01 | 0.75-2.95 |
| <60       | HR      | 23             | 1.18 (1.04-1.33)  | I² = 81%, τ² = 0.0181 | P < 0.01 | 0.77-1.80 |
|           | OR      | 58             | 1.30 (1.19-1.42)  | I² = 76%, τ² = 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)  | I² = 88%, τ² = 0.4301 | P < 0.01 | -       |
| Male (%)  |         |                |                   |                   |
| ≥50       | HR      | 44             | 1.41 (1.23-1.60)  | I² = 83%, τ² = 0.1123 | P < 0.01 | 0.71-2.80 |
|           | OR      | 94             | 1.33 (1.23-1.44)  | I² = 78%, τ² = 0.0558 | P < 0.01 | 0.83-2.14 |
| <50       | HR      | 21             | 1.25 (1.13-1.38)  | I² = 55%, τ² = 0.0179 | P < 0.01 | 0.92-1.69 |
|           | OR      | 36             | 1.42 (1.27-1.58)  | I² = 56%, τ² = 0.0431 | P < 0.01 | 0.92-2.20 |
| NA        | HR      | 0              | -                 | -                  | -       | -       |
|           | OR      | 8              | 2.25 (0.87-5.79)  | I² = 98%, τ² = 1.6735 | P < 0.01 | 0.08-65.97 |
| Study design |       |                |                   |                   |
| Retrospective/case series | HR | 38          | 1.50 (1.30-1.73)  | I² = 81%, τ² = 0.1067 | P < 0.01 | 0.76-2.96 |
|           | OR      | 88             | 1.37 (1.28-1.47)  | I² = 65%, τ² = 0.0269 | P < 0.01 | 0.83-2.14 |
| Prospective study | HR | 9           | 1.11 (0.74-1.67)  | I² = 88%, τ² = 0.2724 | P < 0.01 | 0.28-4.39 |
|           | OR      | 7              | 1.31 (0.84-2.06)  | I² = 77%, τ² = 0.2451 | P < 0.01 | 0.32-5.34 |
| Others | HR | 19          | 1.25 (1.12-1.39)  | I² = 63%, τ² = 0.0214 | P < 0.01 | 0.90-1.74 |
|           | OR      | 43             | 1.45 (1.24-1.70)  | I² = 93%, τ² = 0.1725 | P < 0.01 | 0.62-3.42 |
| Region |       |                |                   |                   |
| Europe | HR | 27          | 1.31 (1.17-1.47)  | I² = 83%, τ² = 0.0462 | P < 0.01 | 0.83-2.08 |
|           | OR      | 54             | 1.47 (1.33-1.64)  | I² = 75%, τ² = 0.0725 | P < 0.01 | 0.85-2.56 |
| North America | HR | 12          | 1.16 (1.02-1.33)  | I² = 52%, τ² = 0.0234 | P < 0.02 | 0.80-1.69 |
|           | OR      | 42             | 1.18 (1.08-1.29)  | I² = 77%, τ² = 0.0333 | P < 0.01 | 0.81-1.72 |
| Asia | HR | 24          | 1.64 (1.24-2.16)  | I² = 81%, τ² = 0.3015 | P < 0.001 | 0.51-5.30 |
|           | OR      | 37             | 1.55 (1.29-1.87)  | I² = 68%, τ² = 0.1272 | P < 0.01 | 0.73-3.29 |
| Others | HR | 2           | 2.12 (0.89-5.01)  | I² = 59%, τ² = 0.2289 | P = 0.12 | -       |
|           | OR      | 5              | 3.54 (0.86-14.60) | I² = 92%, τ² = 2.2244 | P < 0.01 | 0.02-691.66 |
| Disease |       |                |                   |                   |
| CVD     | HR      | 27             | 1.36 (1.15-1.61)  | I² = 79%, τ² = 0.1154 | P < 0.01 | 0.66-2.80 |
|           | OR      | 41             | 1.48 (1.24-1.76)  | I² = 91%, τ² = 0.1984 | P < 0.01 | 0.59-2.70 |
| Cardiac disease | HR | 25          | 1.40 (1.17-1.69)  | I² = 77%, τ² = 0.1141 | P < 0.01 | 0.68-2.90 |
|           | OR      | 38             | 1.43 (1.25-1.64)  | I² = 84%, τ² = 0.0762 | P < 0.01 | 0.80-2.55 |
| HF      | HR      | 4              | 1.23 (1.05-1.44)  | I² = 89%, τ² = 0.0173 | P < 0.01 | 0.63-2.39 |
|           | OR      | 31             | 1.46 (1.31-1.62)  | I² = 59%, τ² = 0.0290 | P < 0.01 | 1.01-2.10 |
| Outcomes     | Effect | HR    | 95% CI       | I²  | τ²    | P       | 95% CI       |
|--------------|--------|-------|--------------|-----|-------|---------|--------------|
| CAD          | HR     | 9     | 1.48 (1.14-1.93) | 70% | 0.0957| < 0.01  | 0.67-3.29    |
|              | OR     | 26    | 1.17 (1.02-1.35) | 52% | 0.0416| < 0.01  | 0.75-1.83    |
| Others       | HR     | -     | -             |     |       |         |              |
|              | OR     | 2     | 1.63 (1.05-2.53) | 33% | 0.0585| < 0.01  | -            |
| Mortality    | HR     | 55    | 1.39 (1.27-1.53) | 76% | 0.0597| < 0.01  | 0.85-2.30    |
|              | OR     | 98    | 1.44 (1.32-1.56) | 84% | 0.0840| < 0.01  | 0.80-2.57    |
| Severity     | HR     | 7     | 1.06 (0.70-1.60) | 88% | 0.2418| < 0.01  | 0.30-3.68    |
|              | OR     | 25    | 1.22 (1.03-1.43) | 66% | 0.0575| < 0.01  | 0.72-2.06    |
| Disease progression | HR | 3     | 1.65 (1.20-2.27) | 0%  | 0.000  | = 0.56  | 0.21-12.92   |
|              | OR     | 15    | 1.63 (1.31-2.04) | 68% | 0.0858| < 0.01  | 0.84-2.39    |

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

Meta-regression
| Variables          | HR Tau² | t-value | P-value | OR 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               | 0.7562  | 0.1143  | 0.1713  | 0.5027  |         |         |
| NR                | 0.0734  | 0.0351  | 0.7253  | 0.0997  | -0.1552 | 0.0449  |
| Male (%)          |         |         |         |         |         |         |
| >=50              | 0.1404  | 0.1206  | 0.1006  | 0.1674  |         |         |
| <50               | 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 |         |         |         |         |         |         |
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 3

Sensitivity analysis for pooled OR (A) and HR (B).
Figure 4

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

Supplementary Files

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