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Efficacy of treatments tested in COVID-19 patients with cardiovascular disease. A meta-analysis

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Abstract

Background: The COVID-19 pandemic has spread globally infecting and killing millions. Those with cardiovascular disease (CVD) are at higher risk of increased disease severity and mortality. We performed a systematic review and meta-analysis to estimate the rate of in-hospital mortality following different treatments on COVID-19 in patients with CVD.

Methods: Pertinent articles were identified from the PubMed, Google Scholar, Ovid MEDLINE, and Ovid EMBASE databases. This study protocol was registered under PROSPERO with the identifier CRD42020183057.

Results: Of the 1673 papers scrutinized, 46 were included in the review. Of the 2553 patients (mean age 63.9 ± 2.7 years/o; 57.2% male), the most frequent CVDs were coronary artery disease (9.09%) and peripheral arterial disease (5.4%) and the most frequent cardiovascular risk factors were hypertension (86.7%) and diabetes (23.7%). Most patients were on multiple treatments. 14 COVID-19 treatments were compared with controls. The pooled event rate for in-hospital mortality was 20% (95% confidence interval (CI): 11–33%); certain heterogeneity was observed across studies.

Conclusions: COVID-19 is associated with a high in-hospital mortality rate in patients with CVD. This study shows that previous CVD determines mortality, regardless of the type of COVID-19 administered therapy. Treatments for at-risk patients should be administered carefully and monitored closely until further data are available.

Keywords

COVID-19, cardiovascular disease, therapy, comorbidity

Introduction

Coronavirus disease 2019 (COVID-19) is a pandemic that has recently hit the world, infecting millions and wreaking havoc on healthcare systems and economies. The World Health Organization (WHO) has described the virus causing COVID-19 as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

As of the 9 August 2021, the WHO had reported 202,296,216 confirmed cases of the COVID-19 resulting in 4,288,134 deaths.[1] At this time, the COVID-19 case to mortality rate has been found to vary significantly between countries due to population demographics, extent of testing, preparedness, and standard of care; however, the range is likely between 0.4 and 3.6%.[2]

Notwithstanding, there is a shared acceptance that disease severity and mortality rates increase with advanced age and with the presence of comorbidities. Specifically, it has been reported that patients suffering from cardiovascular diseases (CVD) and/or cardiovascular risk factors (CVRF) are more susceptible to developing severe COVID-19 infections, resulting in higher rates of intensive care unit (ICU) admission.[3,4]

Mechanistic information is lacking, but preliminary studies show that although SARS-CoV-2 is primarily a respiratory disease, the high presence of the viral entry receptor (human angiotensin-converting enzyme 2

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(ACE2) receptor) in heart tissue could explain the cardiotoxic manifestations of COVID-19.[5]

Although there is not currently a consensus on effective treatments against COVID-19, many drugs are being hastily trialed in hospitals internationally, based on in vitro or very small observational studies. Some of the current treatments being investigated that may have cardiotoxic effects include hydroxychloroquine (HCQ), azithromycin (AZ), remdesivir, and lopinavir/ritonavir.[5] Treatments currently being considered to lower the risk include convalescent plasma therapy as well as cell therapies using mesenchymal stem cells and allogenic cardiosphere–derived cells (CAP-1002).[6–8] The efficacy and safety of these drugs on COVID-19 patients with pre-existing CVD/CVRF has yet to be explored.

Despite ongoing efforts to find a safe and effective vaccine, COVID-19 cases continue to rise and information about COVID-19 treatments for more accurate decisions in clinical practice remains urgent and necessary. This systematic review and meta-analysis will provide a wide picture of evidence on the effectiveness and descriptive data of the side effects of COVID-19 treatments on patients with CVD.

Material and methods

Search strategy

This studies' protocol was registered under PROSPERO with the identifier CRD42020183057 and was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[9] and the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines.[10] Articles were identified from the PubMed, Google Scholar, Ovid MEDLINE, and Ovid EMBASE databases. Specific search terms were established, and the final search was completed in November 2020.

Study selection and inclusion criteria

Eligible articles that reported mortality rate in COVID-19 patients with CVD after testing specific reported treatment were included.

Studies were excluded if they met any of the following criteria: (1) inconsistency of data did not allow valid extraction; (2) data were duplicated; or (3) the trial/study was performed in a laboratory model. Two assessors (JB and SB-A) independently screened titles and abstracts to select studies for further examination. Any disagreement was resolved by discussion with a third author (CE). Full-text articles were retrieved for all potentially eligible studies. Statistical concordance testing was performed using Cohen's kappa coefficient to measure inter-rater agreement. Additionally, only studies from high impact journals were considered (impact factor ≥3.5) to reduce the number of uncontrolled case reports.

Outcomes

The primary outcome was in-hospital mortality rate. Secondary outcomes were the length of hospital stay as well as additional data on adverse reactions including electrophysiological alterations, sepsis, acute respiratory distress syndrome, and thromboembolisms.

Definitions of CVD/CVRF

The target population was those with a positive test for SARS-CoV-2 using a real-time reverse transcription polymerase chain reaction (RT-PCR) assay and those who had pre-existing CVD. Types of CVD include myocardial injury due to myocardial ischemia or non-ischemic processes, such as coronary artery diseases, atherosclerosis, myocarditis, cardiomyopathy, heart failure, and peripheral artery diseases. Types of CVRF included systemic hypertension, dyslipidemia, type I and II diabetes, obesity (defined as BMI > 30), and smoking habit (current or previous).

Adverse effects

A minority of the 39 articles reported adverse effects of treatments in detail. Among these, nine studies reported cardiovascular events such as QTc or thromboembolisms,[11–19] three studies reported gastrointestinal adverse effects,[20–22] five studies reported acute respiratory distress syndrome (ARDS),[11,20,22–24] nine studies reported a single adverse event,[14–16,23,25–28] eight specified two or three adverse events,[13,18–22,24,29] and four reported four or more specific adverse effects.[11,12,17,20]

Data extraction

The following variables were extracted from the included studies: study name, publication year, period of recruitment, study design, number of patients, age, proportion of male patients, hypertension, dyslipidemia, diabetes, obesity and smoking habit, in-hospital mortality, type of treatments, adverse outcomes, and hospital stay duration (length of hospital stay, LOS).

Statistical analysis

The analysis utilized a random effects model (inverse variance method). DerSimonian-Laird estimators were used to calculate between-study variance. Categorical variables were expressed as risk ratio (RR) with 95% confidence intervals (CIs.) I^2 and chi-square tests were used to assess studies' heterogeneity. When $I^2 > 50\%$ and $p \leq 0.05$, heterogeneity was considered to be significant. The publication bias was visualized by L'Abbé' plot and symmetry of funnel plot and was evaluated by Egger's test.

Subgroup analysis (pooling analysis) was also performed to compare mortality differences among the three groups: "CVD treated" versus "CVD un-treated" versus "no-CVD (treated and un-treated)." For the pooling analysis, the effect estimates were calculated as logit transformations ("plogit") with 95% CI.

Sensitivity analysis was also carried out to assess the robustness of the results with the trim-and-fill method.

Meta-regression was performed to assess the effects of covariates on the primary outcome of interest. Covariates included (a) sex, (b) age, (c) obesity, (d) diabetes, and (e) specific treatments.

Hypothesis testing for equivalence was set at a two-tailed level of 0.05. Analyses and data modeling were performed with R project (version 3.3.3. R project for Statistical Computing) and R studio (www.rstudio.com) using the *stat*, *metafor*, *meta*, and *lme4* packages.

Results

Of 1673 articles retrieved, 46 met the inclusion criteria (Figure 1: PRISMA flowchart), with 31[11–41] including patients with CVD from which 11 included a control group[11,25,26,29,31,32,34,36,37,40,41] and five were comparative studies, which all were included in the quantitative analysis.[11,25,31,36,37] The overall sample size was 2553 patients (pooled mean age 63.9 years; 42.8% female). We only the included studies with CVD patients; the sample size was 130 (mean age 63.9 ± 2.7 years; 55.3% male). There was 100% concordance between reviewers equating to a Cohen's kappa coefficient of $\kappa = 1$.

Patients' baseline characteristics are summarized in Table 1. The most frequent CVRF was hypertension (86.7%) followed by diabetes (23.7%). Dyslipidemia was reported in 1.37% of patients, obesity was reported with a frequency of 2.23%, and smoking habits were reported with a frequency of 2.98%. The most frequent CVD seen in patients was coronary artery disease at 9.09% and then peripheral arterial disease at 5.40%. History of heart failure was reported in 1.63% and undisclosed CVD was present in 1.17% of the patients.

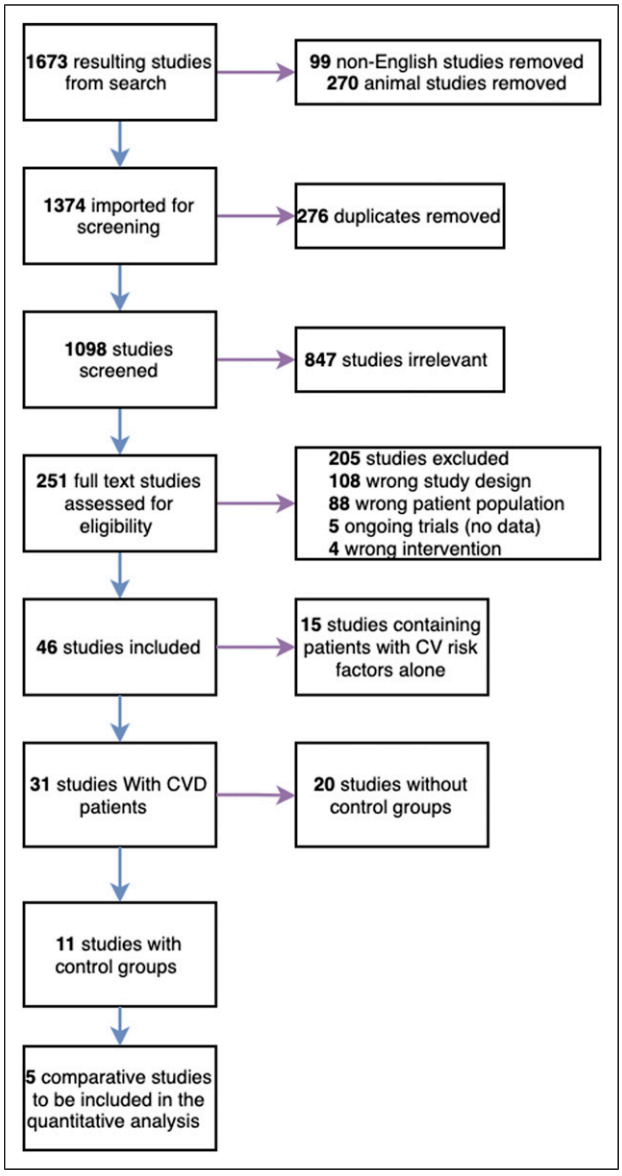

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart. CV: cardiovascular.

Primary outcome

In five of the 31 included studies,[11,25,31,36,37] the treatments involved corticosteroids, convalescent plasma, tocilizumab, oseltamivir, ribavirin, antibiotics, lopivanir/ritonavir, darunavir/ritonavir, HCQ, and CAP-1002 and RAAS inhibitors.

Mortality rate was significantly higher in the CVD treated group (RR: 1.52; 95% CI (1.05, 2.21), CVD treated vs overall population $p = 0.03$, $I^2 = 50\%$, $Chi^2 = 25.74$; p-value 0.02) (Figure 2).

Further statistical techniques were used to address this heterogeneity for our primary outcome. The

Table 1. Descriptive data.

Year of study	Country	First author	Study type	*N* (treated CVD)	*N* (control)	Male *N* (%)	Age, mean (SD)	Treatments	Hypertension, *N*	Diabetes, *N*	Dyslipidemia, *N*	Obesity, *N*	Smoking habit, *N*
2020	Italy	Inciardi, R. M.	Comparative study	53	46	45 (84.9)	68 (12)	Lopinavir/ritonavir, hydroxycholoroquine, darunavir/ritonavir, corticosteroid, tocilizumab, and antibiotics	40	16	23	13	11
2020	Italy	Sala, S	Case report	1	NA	0	43	Lopinavir/ritonavir and hydroxycholoroquine	0	0	0	0	0
2020	China	Guo, T.	Comparative study	66	121	32 (48.5)	58.5 (14.7)	Oseltamivir, ribavirin, broad-spectrum antivirals, antibiotics, and corticosteroids	33	17	0	0	7
2020	USA	Chorin, E.	Observational Study	251	NA	188 (74.9)	64 (13)	Hydroxychloroquine and azithromycin	54	27	0	0	0
2020	Brazil	Borba, M. G. S.	Observational Study	5	NA	3 (60)	51.1 (13.9)	Chloroquine diphosphate	3	2	0	1	0
2020	USA	Purohit, R.	Case report	1	NA	0	82	Antiaggregants and anticoagulants	1	0	1	0	0
2020	China	Duan et al.	Comparative study	10	10	6 (60)	53.4 (11.8)	Convelescent plasma transfusion, antivirals, antibiotics, and corticosteroids	3	0	0	0	0
2020	USA	Fried, J. A.	Case series	4	NA	2 (50)	49.3 (15)	Hydroxychloroquine, azithromycin, antibiotics, and antiaggregants and anticoagulants	2	2	1	0	0
2020	Italy	Gnecchi, M.	Case report	1	NA	1 (100)	16	Hydroxychloroquine, ibuprofen, and antivirals	0	0	0	0	0
2020	China	Zhang, P.	Comparative study	1128	522	603 (53.5)	64 (55–68)	ACE inhibitors, antivirals, antibiotics, corticosteroids, immunoglobuli, and traditional Chinese medicine	1128	240	0	0	0
2020	Spain	Pericas, J. M.	Case report	1	NA	1 (100)	43	Corticosteroids, tacrolimus, lopinavir/ritonavir, hydroxychloroquine, and azithromycin	0	0	0	0	0
2020	China	Dong, N.	Case series	4	NA	4 (100)	54.3 (12.1)	Antibiotics, interferon alpha, immunoglobin, ribavirin, and arbidol	1	2	0	0	0
2020	USA	Radbel, J.	Comparative report	1	1	0	69	Tocilizumab, hydroxychloroquine, azithromycin, and norepinephrine,	0	1	0	0	0
2020	USA	Singh, R.	Case report	1	NA	1 (100)	62	Hydroxychloroquine, ribavirin, lopinavir/ritonavir, tocilizumab, anakinra, and steroids	1	1	1	1	0
2020	USA	Singh, S.	Comparative study	6	34	5 (83.3)	56.3 (18.1)	Allogeneic cardiosphere–derived cell therapy, tocilizumab, lopinavir/ritonavir, and hydroxychloroquine	3	3	3	3	0

(continued)

Table 1. (continued)

Year of study	Country	First author	Study type	*N* (treated CVD)	*N* (control)	Male *N* (%)	Age, mean (SD)	Treatments	Hypertension, *N*	Diabetes, *N*	Dyslipidemia, *N*	Obesity, *N*	Smoking habit, *N*
2020	Italy	Toniati, P.	Case series	100	NA	70 (70.0)	62 (57–71)	Tocilizumab, lopinavir/ritonavir, remdesivir, hydroxychloroquine, azithromycin, and antibiotics (ceftriaxone or piperacillin/tazobactam)	46	17	0	31	0
2020	France	Woehl, B.	Comparative report	4	1	4 (100)	70.5 (5.2)	Anticoagulation treatment	3	1	2	2	1
2020	Spain	Amat-Santos, I. J.	Comparative study	4	6	2 (60)	82.3 (6.1)	Ramipril, antibiotics (azithromycin), corticoids, hydroxychloroquine, lopinavir/ritonavir, and tocilizumab	2	0	2	2	0
2020	The Netherlands	Bruggemann, R.	Case report	1	NA	1 (100)	57	Chloroquine diphosphate, nadroparin (LMWH), and antibiotics (amoxicillin)	1	0	0	0	0
2020	USA	Ferrey, A. J.	Case report	1	NA	1 (100)	56	Antimicrobial therapy, azithromycin, antibiotics (ceftriaxone), hydroxychloroquine, and tocilizumab	1	0	0	0	0
2020	China	Huang, L.	Case report	1	NA	1 (100)	79	Antibiotics, ganciclovir, human interferon α2b, methylprednisolone, and prednisone	1	0	0	0	0
2020	Austria	Lax, S. F.	Case series	9	NA	6 (66.7)	80.5 (75–91)	Anticoagulants, antiplatelets, antipyretics, antibiotics, antivirals, ACE inhibitors, enoxaparin (LMWH), and hydroxychloroquine	9	5	0	2	0
2020	Germany	Mathies, D.	Case report	1	NA	1 (100)	77	Hydroxychloroquine, antivirals, and antibiotics	1	1	0	0	0
2020	USA	O'Brein, C.	Case report	1	NA	0	82	Remdesivir, propofol, hydromorphone, norepinephrine, amiodarone, vancomycin, and antibiotics	1	0	0	1	0
2020	Norway	Overstad, S.	Case series	4	NA	4 (100)	51.8 (7.4)	Apixaban and antiaggregant and anticoagualnts	2	0	0	1	0
2020	USA	Asif, T	Case report	1	NA	0	70	Colchicine and norepinephrine	1	1	1	0	0
2020	USA	Singh, R.	Case report	1	NA	1 (100)	66	Hydroxychloroquine, oseltamivir, and lopinavir/ritonavir	1	0	0	0	0
2020	China	Gao, C.	Comparative study	850	140	443 (52.1)	64.2 (11.2)	RAAS inhibitors and non-RAAS inhibitors	850	228	0	0	57
2020	USA	Vilaro, J.	Case report	1	NA	1 (100)	50	Hydroxychloroquine, tocilizumab, and azithromycin	0	1	0	0	0
2020	USA	Wang, J.	Comparative report	2	1	1 (50)	67 (8)	Hydroxychloroquine, azithromycin, antiaggregant and anticoagualnts, and tissue plasminogen activator (tPA) treatment	2	1	1	0	0
2020	China	Yan, Y.	Comparative study	39	97	33 (84.6)	70 (62–77)	Corticosteroids	24	39	0	0	0
			Total:	2553		1460 (57.19)	63.96 ± 2.78		2214	605	35	57	76

USA: United States of America; RAAS: renin–angiotensin–aldosterone system.
Patients' descriptive data for each study.

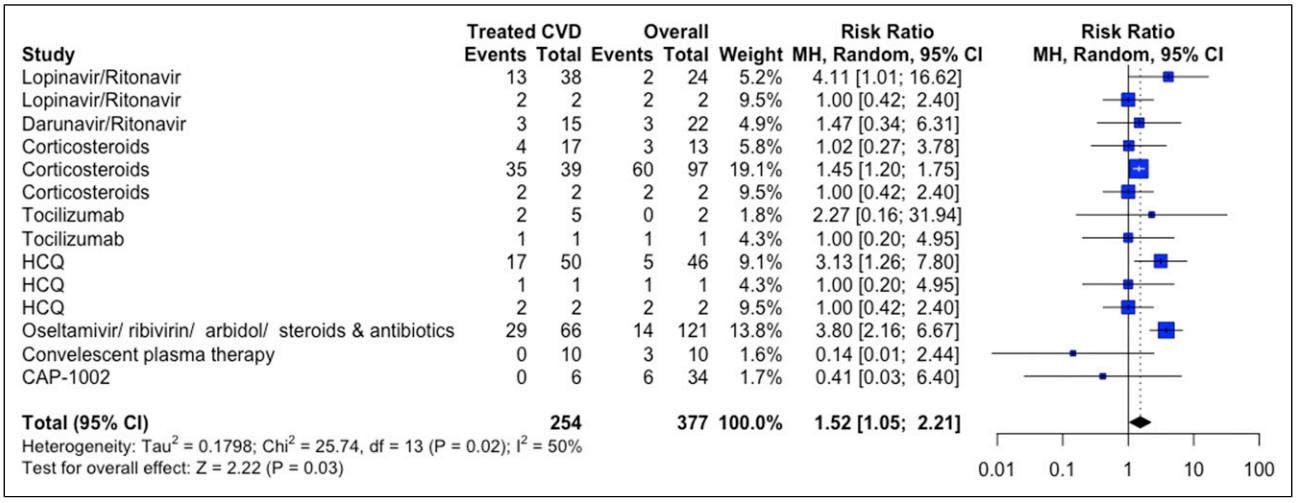

Figure 2. Forest plot of the mortality rate on CVD patients versus overall population. CVD: cardiovascular disease.

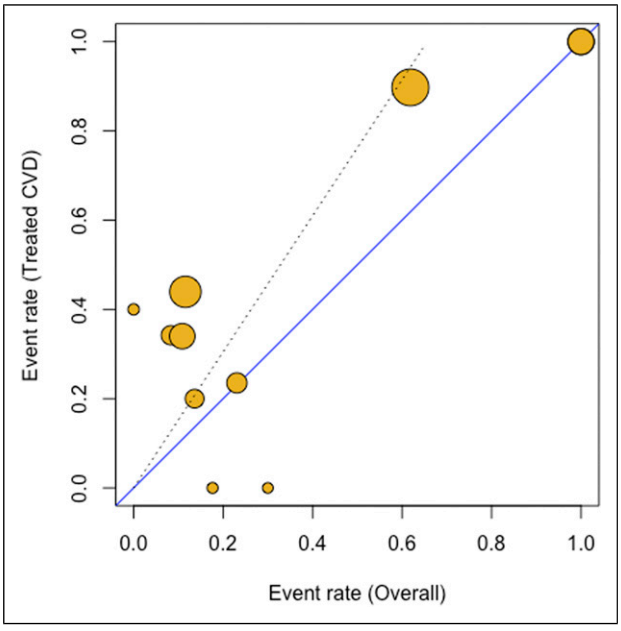

Figure 3. New L'Abbé plot. CVD: cardiovascular disease.

L'Abbé' plot showed a certain degree of heterogeneity in respect to the equality line (Figure 3). To further investigate the heterogeneity, linear regression test of funnel plot asymmetry with Egger test was performed that confirmed non-statistical significance (p-value = 0.71; Figure 4).

Subgroup analysis

Three of the 31 included studies treated CVD versus non-treated CVD patients.[30,34,35] Another four of the 46 included studies investigated treatments on CVD patients versus non-CVD patients,[11,25,31,41] which also provided insight. The treatments covered by these studies were convalescent plasma, corticosteroids, tocilizumab, antibiotics (including azithromycin) lopivanir/ritonavir, darunavir/ritonavir, oseltamivir, ribavirin, HCQ, and anticoagulant/antiplatelets.

Non-comparative pooled analysis of both treated CVD versus non-CVD patients (3.32, 95% CI 2.02, 4.93) and treated CVD versus non-treated CVD (8.53, 95% CI 0.79, 9.97) reported and strengthened the previous results. Regardless of the treatment, no mortality difference is reported in patients with previous CVD (p-value: 0.26; Figure 5; Tables 2; and 3)

Secondary outcome

Hospitality length, as a secondary outcome of the present study, was obtained and analyzed as an indirect outcome of disease severity. Six studies reported the outcome in this analysis.[11,25,31,36,37,41]

Comparative analysis of the length of hospitality showed, in line with our previous data, that there was no difference in terms of LOS comparing the treated CVD patients versus the overall patients in each study (0.79, 95% CI (−0.48, 2.05); p-value = 0.22) (Figure 6). This indicates that no treatment was capable of decreasing the hospitality length and indirectly the severity of the infection alone.

Additional data

Adverse effects, as additional data of the present study, were not classified by any standardized grade in any of the articles. Following the reported cases from the

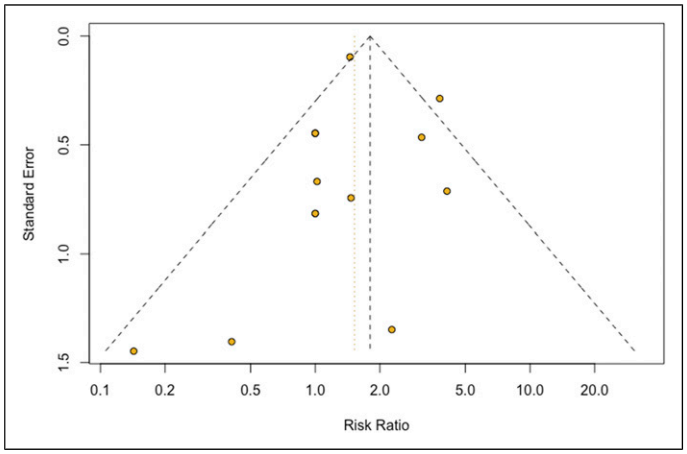

Figure 4. New funnel plot.

manuscripts, it can be concluded that, as shown in Table 1, patients with previous CVD showed higher adverse effects when treated with cardiosphere-derived cells CAP-1002 (100%) and antiplatelet/anticoagulants (61.9%). On the contrary, the treatments that revealed lower percentage of adverse effects on CVD patients were darunavir/ritonavir, oseltamivir, ribavirin, arbidol, steroids and antibiotics, convalescent plasma therapy, and other antihypertensive therapeutics (0%).

Discussion

In COVID-19 cases, it is important to recognize the clinical characteristics of patients in order to aid in early and rapid detection of infected persons, as well as to reduce patient mortality. Many antiviral drugs can cause cardiac insufficiency, arrhythmia, or other CV disorders during treatment of the disease, especially with antiviral therapy; therefore, the risk of cardiac toxicity needs be closely monitored.[42]

The main finding of this quantitative analysis is that CVD patients, despite specific treatments, were exposed to a significant higher mortality when compared to the overall population. These results remark the clinical relevance to reduce CVRF and ameliorate specific COVID-19 treatments to lower the risk of mortality in this group. Of note, data were collected from the first wave of COVID-19, meaning that there was no population vaccinated nor any modified SARS-CoV-2 strain infection that could blurry the results.

In line with our data, recent studies have demonstrated that patients suffering from CVD and its CVRF are more susceptible of being infected by SARS-CoV-2 and therefore are being admitted to ICU services. However, treatment management is still under study. In fact, diabetic patients treated with ACE inhibitors and angiotensin two receptor blockers, SGLT2 inhibitors, GLP-1 receptor agonists, pioglitazone, and insulin seem to increase the number of ACE2 receptors on the cells utilized by SARS-CoV-2 for penetration, but no evidence on worse prognosis has been shown.[43]

Although most of incorporated studies are single center, which may show admission bias as well as selection bias, in addition, all of the incorporated studies were retrospective analytical studies. We could not rule out the power of other confounding agents. Due to inadequate medical resources, only patients with relatively severe COVID-19 infection were admitted to hospital. Importantly, there may possibly be a selection bias when categorizing factors impacting the clinical consequences and mortality.

This is of interest in the clinical setting specially to remark the importance of the CVD treatment continuation as well as to find better and improved treatments in this population. Consequently, large population-based cohort study of patients with COVID-19 from different countries will be beneficial to recognize the clinical features and risk factors of the disease.

Limitations

This systematic review has a few limitations. When comparing the pooled results from different study designs it is important to consider any confounding factors that may account for any differences identified. For instance, if one set of studies was carried out on a younger cohort of patients, with a lower drug dosage, or with shorter duration of use, or relied on passive ascertainment

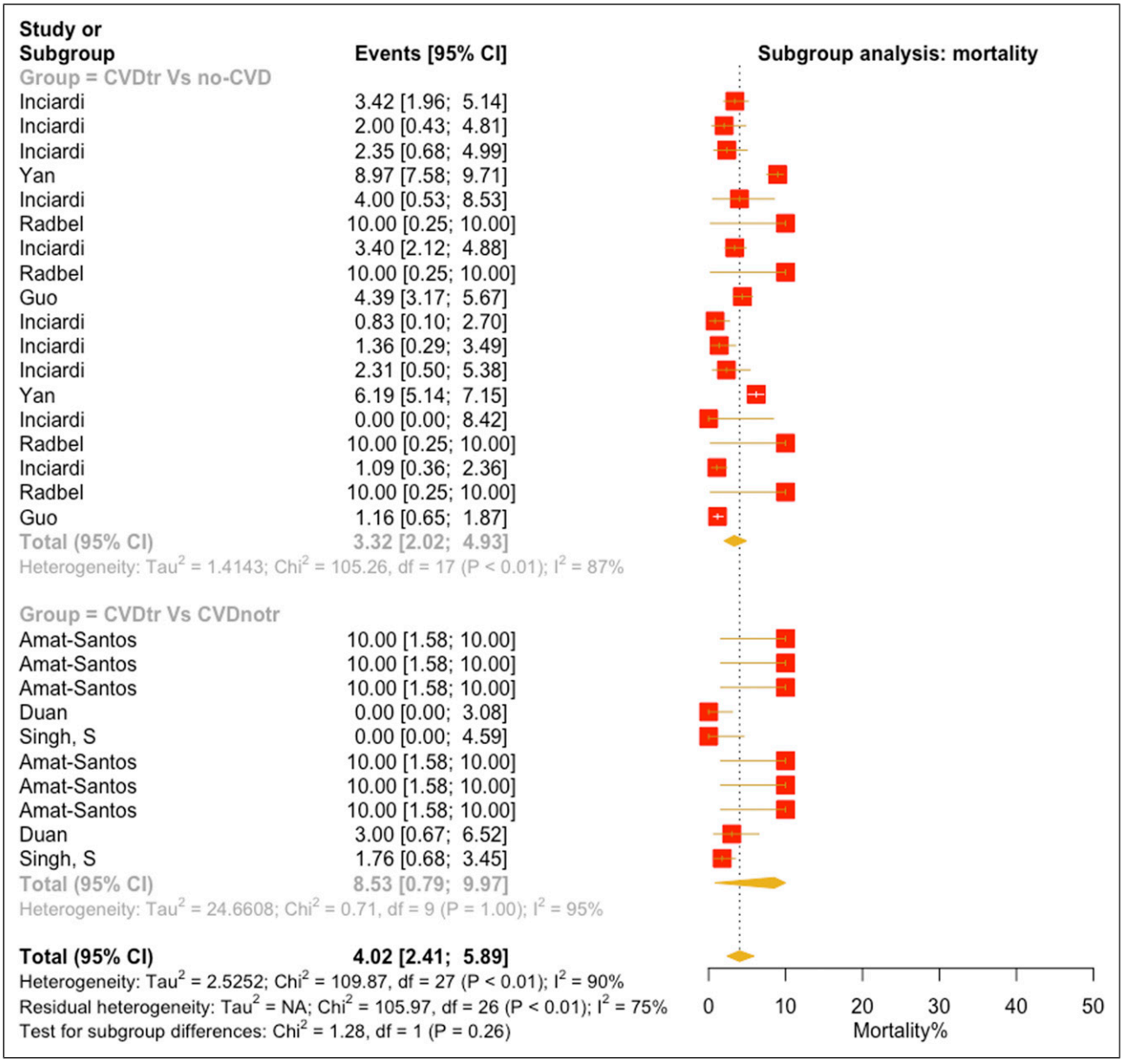

Figure 5. Forest plot of non-comparative pooled analysis of both treated CVD versus non-CVD patients and treated CVD versus non-treated CVD. CVD: cardiovascular disease; CVDtr: cardiovascular disease treated; CVDnotr: cardiovascular disease not treated; CI: confidence interval.

of adverse effects data, it might be expected that the magnitude of any outcome recorded would be lower.

Another constraint of our study is that we accepted information and data as reported by the authors. We did not attempt to source the primary studies, as this would have required extracting data from many papers and its consequential ethics approval. For instance, we relied on the authors' criteria of study design and data obtention, but are aware that authors may not all have used the same definitions. This is a particular problem with observational studies, where it is often difficult to determine the methodology used in the primary study and categorize it appropriately. In order to overcome this limitation, we chose to base our analysis on mortality as a patient countable number and we avoided manuscripts reporting number of patients in all groups, similarly with the second outcome.

Another important limitation to this review is the potentially unrepresentative sample used. Studies with limited number of patients as well as case-control studies comparing different treatments might have sampling bias. To overcome this issue, sensitivity analysis was

Table 2. Meta-regression model regarding treatments.

	Estimate	SE	*p*-value
Convalescent plasma	−1.0501	2.0471	0.608
Corticosteroids	1.1611	1.4435	0.4212
Darunavir/ritonavir	1.2788	1.6279	0.4321
HCQ	1.3616	1.4654	0.3528
Lopinavir/ritonavir	1.3401	1.4876	0.3677
Oseltamivir/ribavirin/arbidol/steroids and antibiotics	2.2302	1.4758	0.1307
Tocilizumab	1.1251	1.5995	0.4818

HCQ: hydroxychloroquine.
Meta-regression model regarding treatments. Estimates, standard error, and *p*-value are included.

Table 3. Meta-regression model regarding patient characteristics.

	Estimate	SE	*p*-value
Male	−0.0284	0.0291	0.3285
Hypertension	0.0938	0.0462	0.0424*
Diabetes	0.0011	0.0229	0.9599
Obesity	1.2866	2.0161	0.5234
Dyslipidemia	0.7488	1.1337	0.5089
Age	0.0334	0.0425	0.4326

Meta-regression model regarding patient characteristics. Estimates, standard error, and *p*-value are included *$p < .05$.

between the comparisons of different studies. This could be explained mainly due to the inclusion of case report studies which imply a small sample size. Moreover, it may be that particular types of outcomes can be identified more easily via particular types of study designs.

Future research

Where no randomized data exist, observational studies may be the only recourse. However, the potential value of observational data needs to be further

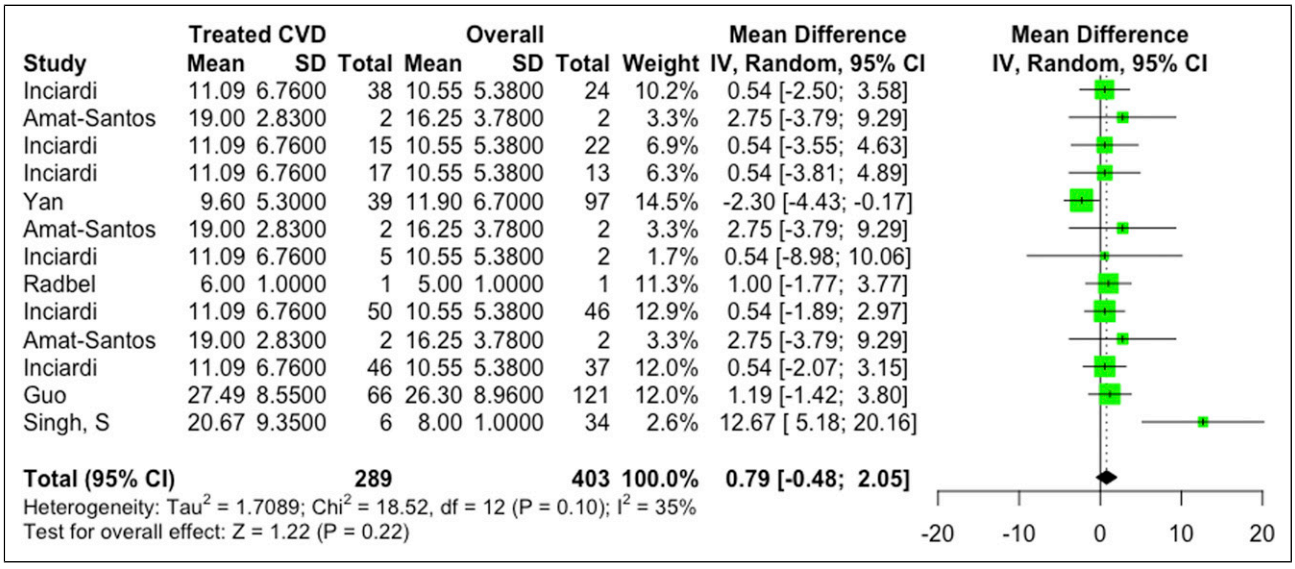

Figure 6. Forest plot of the comparative analysis of the length of hospitality. SD: standard deviation; CI: confidence interval.

performed. It should be noted that search was based on mortality, in which hospitality length and adverse effects are included as a secondary aim and are unlikely to present further analysis on this data.

In line with the previous limitations, and as showed in the Results section, there was considerable heterogeneity demonstrated, particularly in specific situations where existing treatments and their outcomes are short term or based on highly selected populations. Comparisons of risk estimates from different types of observational studies (e.g., case-control as opposed to cohort) merit further assessment.

Conclusions

Our findings have important implications for the present outstanding health situation to better understand the special needs of the CVD patients. Although there are strengths and weaknesses in every study, it can be said that CVD patients have a higher risk toward worse prognosis and no efficient treatment has been developed for those patients.

Declaration of Conflicting Interests

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Supplementary Comment

Searches were performed during October of 2020 using the following search terms: ((2019-ncov) OR (sars-cov-2) OR (sars-cov2) OR (COVID-19) OR (novel coronavirus)) AND ((cardiac) OR (cardiovascular disease*) OR (cardiovascular) OR (heart failure) OR (atherosclerosis) OR (arrhythmia*) OR (cardiomyopathy) OR (coronary artery disease*) OR (myocardial injury) OR (myocarditis) OR (venous thromboembolism)) AND (drug*) OR (therapy) OR (treatment*) OR (pharmaceutical preparations).

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Abbreviations

ACE2	Angiotensin-converting enzyme 2
AZ	Azithromycin
CAP-1002	Allogenic cardiosphere–derived cell therapy
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CVD	Cardiovascular disease
CVRF	Cardiovascular risk factors
HCQ	Hydroxychloroquine
ICU	Intensive care unit
LOS	Length of hospital stay
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RAAS	Renin–angiotensin–aldosterone system
RR	Risk ratio
RT-PCR	Real-time reverse transcription polymerase chain reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
tPA	Tissue plasminogen activator
USA	United States of America
WHO	World Health Organization