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# **Association of Cardiovascular Disease With Coronavirus Disease 2019 (COVID-19) Severity: A Meta-Analysis**

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**Abstract:** Observational studies have reported an association between underlying cardiovascular diseases (CVD) and worse prognosis in COVID-19 patients, but this still remains unclear. We conducted a meta-analysis of recent studies that reported the association of CVD with worse prognosis and increased mortality in COVID-19 patients. Literature search through PubMed, the Cochrane Library, and Embase was completed by 2 reviewers from November 1, 2019 to April 20, 2020. Inclusion criteria were observational case-control or cohort studies on COVID-19 patients with a history of CVD included, which reported outcomes of COVID-19 infection severity, clearly outlined the definition of “severe disease” and with sample size >10. Data were abstracted independently by 2 authors. Studies were divided into 2 separate cohorts for analysis: severity (severe vs nonsevere) and mortality (non-survivors vs survivors). Data was pooled into a

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**meta-analysis to estimate pooled odds ratio (OR) with 95% confidence interval (95% CI) for each outcome. A total of 18 studies (n = 4858 patients) were included. Sixteen studies were from China, while 2 were from the United States. Pre-existing CVD was associated with a significantly increased risk of a severe form of COVID-19 (OR = 3.14; 95% CI 2.32-4.24;  $I^2 = 0\%$ ;  $Q = 8.68$ ,  $P = 0.73$ ) and overall risk of COVID-19 all-cause mortality (OR = 11.08; 95% CI: 2.59-47.32;  $I^2 = 55\%$ ;  $P = 0.11$ ). However, this study did not find a significant association between previous history of CVD and mortality in severe COVID-19 disease (OR = 1.72; 95% CI: 0.97-3.06,  $I^2 = 0\%$ ,  $P = 0.46$ ). Pre-existing CVD is associated with worse outcomes among patients with COVID-19. Clinicians and policymakers need to take account of these findings in implementing risk stratification models. (Curr Probl Cardiol 2020;45:100617.)**

## Introduction

**T**he ongoing pandemic of coronavirus disease 2019 (COVID-19) has been associated with high rates of morbidity and mortality. Clinical and biological predictors are needed for identifying the severity of COVID-19 infection and helping in judicious allocation of limited resources. Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in the United States, and has also been associated with worse outcomes in patients with influenza and bacterial pneumonias.<sup>1-3</sup> Emerging data have linked the presence of CVD with a worse prognosis in COVID-19 patients.<sup>4-6</sup> Likewise, COVID-19 is associated with a high inflammatory burden, the so called inflammatory or “cytokine storm,” inducing vascular inflammation, myocarditis, and cardiac arrhythmias,<sup>5</sup> which in turn can aggravate the damage to the heart.<sup>4</sup> However, a few and scattered studies, with widely varying results, have been published so far. The small sample size of patients with a previous CVD history in these studies further limits its applicability. Thus, we aimed to compile and analyze all results recently published on the influence of CVD in the severity of COVID-19 infection. To this end, we carried out a pooled analysis of current studies and evaluated the association between underlying or previous history of CVD conditions and outcomes of infection severity in COVID-19 patients.

## Methods

### *Study Protocol and Registration*

This systematic review and meta-analysis were conducted in strict conformity with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.<sup>7</sup> The protocol for this study has been reported in the International Prospective Register of Systematic Reviews (PROSPERO identifier: CRD42020180086).

### *Literature Search Strategy*

A comprehensive and systematic search of literature from November 1, 2019 to April 20, 2020 was conducted on the electronic databases Pubmed, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) to identify studies eligible for inclusion. The electronic search was carried out using the strategy as follows: (1) “COVID-19,” OR “SARS-CoV-2,” OR “coronavirus disease 2019”; (2) “cardiovascular disease,” OR “coronary artery disease,” OR “hypertension”; (3) 2 AND 3. No language restriction was made. When the articles were published by the same study group and there was an overlap of the search period, only the most recent article was included to avoid duplication of data. The PubMed function "related articles" was used to extend the search. Also, we searched major infectious disease, cardiovascular and general medicine journals reporting articles about COVID-19 infection to look for additional studies. We then performed hand-search of the bibliography of included studies, to detect other potentially eligible investigations.

### *Eligibility Criteria*

All studies were screened and assessed for eligibility by 4 independent reviewers (G.A., S.A., B.M.H, and I.C). Search results were screened by title and abstract, with those of potential relevance evaluated by full text. Studies were deemed eligible for inclusion if they fulfilled the following criteria: (1) observational case-control or cohort studies (2) COVID-19 patients with a history of CVD included; (3) outcomes of COVID-19 infection severity reported; (4) clearly outlined the definition of “severe disease” and (5) sample size > 10. Severe disease was defined in this analysis as a composite of: (1) Respiratory distress, respiratory rate  $\geq 30$  per minute; (2) Oxygen saturation on room air at rest  $\leq 93\%$ ; (3) Partial pressure of oxygen in arterial blood/fraction of inspired oxygen  $\leq 300$  mmHg; (4) Patients requiring mechanical ventilation/vital life support/intensive care unit admission; (5)

Death. Cardiovascular disease was defined as any cardiac pathology with the exception of hypertension. Reviews and studies with incomplete or irrelevant data were excluded. Any disagreements between reviewers arising during the eligibility assessment were settled through a consensus.

### *Data Extraction and Quality Assessment*

Data extraction was conducted by 4 independent reviewers (G.A., S. A., B.M.H, and I.C). For each study, the following information was extracted: the surname of the first author and the year of publication, the geographical region where the study was performed, the type of study (cohort or case-control), sample size, baseline demographic characteristics, proportion of patients with severe and nonsevere COVID-19, proportion of patients with underlying CVD, and mortality from COVID-19. Any variances were resolved by a consensus. Quality assessment and analysis of risk of bias of all selected full-text articles was performed using the Newcastle-Ottawa Scale for nonrandomized studies.

### *Outcomes of Interest*

The primary outcome of interest was the association between pre-existing CVD and COVID-19 severity. The secondary outcome was the association between underlying CVD and COVID-19 mortality. A tertiary outcome was the association between underlying CVD and mortality in patients with severe COVID-19 disease. Thus, a total of 3 separate meta-analyses were performed.

### *Statistical Analysis*

The statistical analysis was carried out using MetaXL (software Version 5.3, EpiGear International Pty Ltd., Sunrise Beach, Australia) and the Comprehensive Meta-analysis software (Version 3.3.070, Biostat, New Jersey). The strength of association between pre-existing CVD and COVID-19 severity and mortality was estimated using odds ratio (OR). A random-effects model (DerSimonian and Laird) was applied due to the heterogeneity in definition of CVD amongst the studies. The magnitude of heterogeneity among the included studies was assessed using the chi-squared test ( $\text{Chi}^2$ ) and I-squared statistic ( $I^2$ ). For the  $\text{Chi}^2$  test, a Cochrane's  $Q$   $P$  value of  $<0.10$  was considered significant. The values of the  $I^2$  statistic were interpreted as follows at a 95% confidence interval: 0%-40% might not be important, 30%-60% might indicate moderate heterogeneity, 50%-90% may represent substantial heterogeneity, and 75%-

100% may represent significant heterogeneity (37). Subgroups were used to compare cohort vs case-control studies. Publication bias was assessed by a funnel plot analysis. A random effects meta-regression using log OR was performed to evaluate the impact of baseline characteristics (age and sex) on association of CVD with disease severity in patients with COVID-19. Additionally, leave-one out sensitivity analysis was performed to assess the robustness of the results, and to further probe the sources of inter-study heterogeneity.

## Results

### *Study Identification*

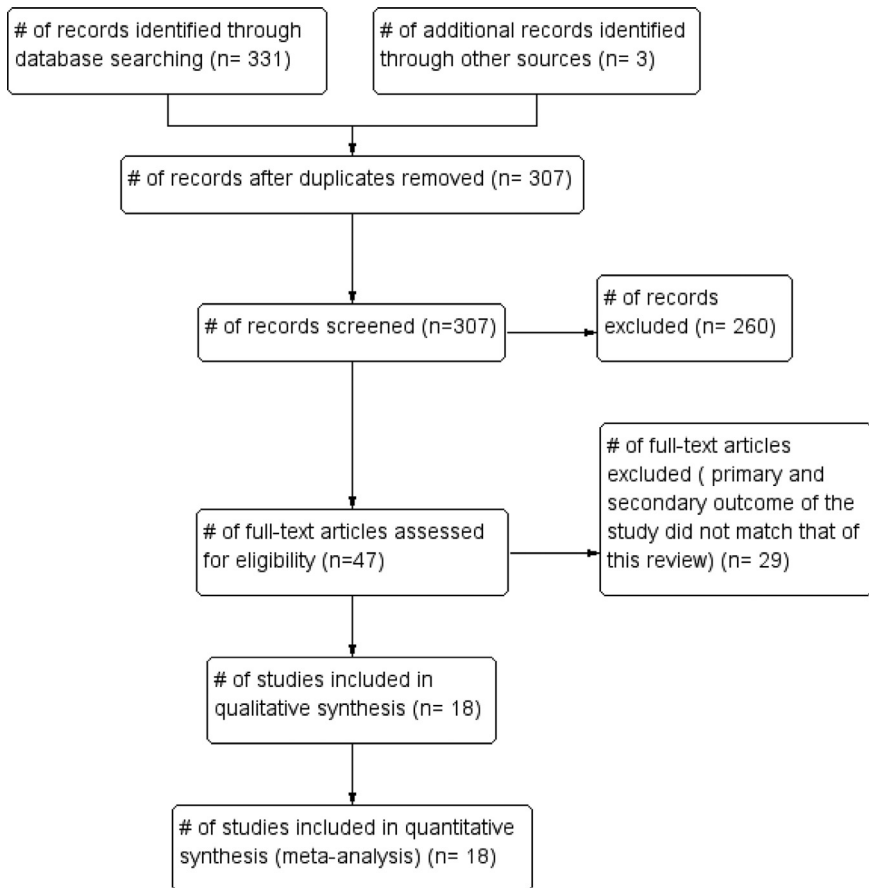
The initial search produced 331 potentially relevant articles. Following the removal of duplicates and primary screening, 47 articles were assessed by full text for eligibility in the meta-analysis. Of these, 29 were excluded because the primary and secondary outcome of the study did not match that of this review. Thus, a total of 18 articles were included in this systematic review and meta-analysis (Fig 1; Tables 1 and 2).

### *Characteristics of the Included Studies and Quality Assessment*

A total of 18 included studies (n = 4858 patients) were included. Sixteen studies were from China, while 2 were from the United States. Thirteen studies reported data on pre-existing cardiovascular diseases in patients with and without severe COVID-19,<sup>4,8-19</sup> 5 studies reported data on mortality in COVID-19 with and without pre-existing CVD,<sup>20-24</sup> while 1 study reported both.<sup>16</sup> Essential characteristics of the included studies are outlined in Tables 1 and 2. Summary of the Newcastle-Ottawa Scale for the included studies is provided in supplementary material.

### *Meta-Analysis of the Association Between CVD and COVID-19 Severity*

A total of 13 studies reported data on the association between pre-existing CVD and COVID-19 severity. In pooled analysis, CVD was found to be associated with a significantly increased risk of a severe form of COVID-19 in both case-control (OR = 3.33; 95% CI 2.11-5.27;  $I^2 = 0\%$ ;  $Q = 3.43$ ;  $P = 0.75$ ) and cohort studies (OR = 3.02; 95% CI 2.00-4.57;  $I^2 = 2\%$ ;  $Q = 5.12$ ;  $P = 0.40$ ), with the overall analysis revealing



**FIG 1.** Flow of studies through the systematic review.

very low evidence of inter-study heterogeneity (Cochran’s  $Q = 8.68$ ,  $P = 0.73$ ,  $I^2 = 0\%$ ). No significant change in the OR was seen in the leave-one-out sensitivity analysis (Fig 2; supplementary material).

### *Meta-Analysis of the Association Between CVD and Mortality in Severe COVID-19 Disease*

A total of three ( $n = 480$ ) studies reported data on mortality in patients with severe COVID-19 disease and pre-existing history of CVD. Pooled analysis of these studies did not find a significant association between previous history of CVD and mortality in severe COVID-19 disease (OR = 1.72; 95% CI: 0.97-3.06,  $I^2 = 0\%$ , Cochran’s  $Q = 1.56$ ,  $P = 0.46$ ). No heterogeneity was seen among the studies (Fig 4; supplementary material).

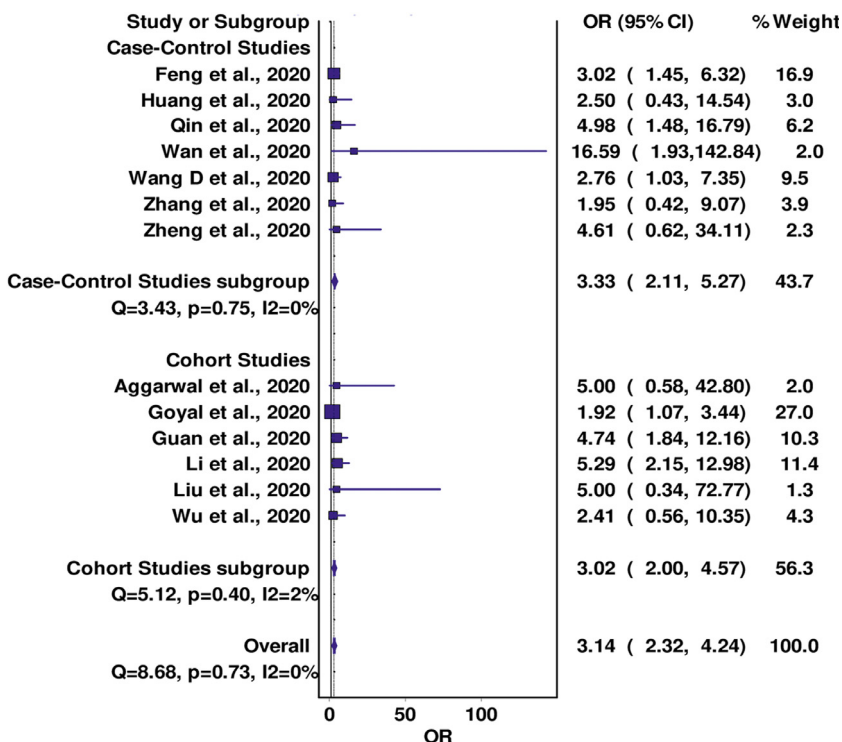
**TABLE 1.** Characteristics of patients included in the severity analysis cohort

Study	Country	Sample Size	Severe patients				Non-severe patients			
			n (%)	Age (yrs)*	Women (%)	CVD n (%)	n (%)	Age (yrs)*	Women (%)	CVD n (%)
Aggarwal et al. (2020)	Iowa, USA	16	8 (50%)	67 (38-70)	3 (38%)	5 (63%)	8 (50%)	68.5 (41-95)	1 (13%)	2 (26%)
Li et al. (2020)	Wuhan, China	548	269 (49.1%)	65	116 (43.1%)	28 (10.4%)	279 (50.9%)	56	153 (54.8%)	6 (2.2%)
Goyal et al. (2020)	New York, USA	393	130 (33.1%)	64.5	32 (28.2%)	25 (19.2%)	263 (66.9%)	61.5	117 (44.5%)	29 (11%)
Guan et al. (2020)	Outside Hubei, China	1099	173 (15.7%)	52 (40–65)	73 (42%)	10 (5.8%)	926 (84.3%)	45 (34-57)	386 (42%)	17 (1.8%)
Huang et al. (2020)	Wuhan, China	41	13 (31.7%)	49 (41-61)	2 (15%)	3 (23%)	28 (68.3%)	49 (41-57.5)	9 (32%)	3 (11%)
Liu et al. (2020)	Shenzen, China	12	6 (50%)	64	3 (50%)	3 (50%)	6 (50%)	43.3	1 (16%)	1 (16%)
Qin et al. (2020)	Wuhan, China	452	286 (63.3%)	61 (51-69)	131 (45.8%)	24 (8.4%)	166 (36.7%)	53 (41.25-62)	86 (51.8%)	3 (1.8%)
Wan et al. (2020)	Chongqing, China	135	40 (29.6%)	56 (52-73)	19 (47.5%)	6 (15%)	95 (70.4%)	44 (33-49)	43 (45.3%)	1 (1%)
Wang D et al. (2020)	Wuhan, China	138	36 (26.1%)	66 (57-78)	14 (39%)	9 (25%)	102 (73.9%)	51 (37-62)	49 (48%)	11 (10.8%)
Wu et al. (2020)	Wuhan, China	201	84 (41.7%)	58.5 (50-69)	24 (28.6%)	5 (6%)	117 (58.3%)	48 (40-54)	49 (41.9%)	3 (2.6%)
Zhang et al. (2020)	Wuhan, China	140	58 (41.4%)	64 (25-87)	25 (43%)	4 (6.9%)	82 (58.6%)	52 (26-78)	44 (54%)	3 (3.7%)
Feng et al. (2020)	Wuhan, China	476	124 (26.1%)	58 (48-67)	43 (34.7%)	17 (13.7%)	352 (73.9%)	51 (37-63)	162 (46%)	21 (6%)
Zheng et al. (2020)	Changsha, China	161	30 (18.6%)	57 (46.5-66)	16 (53.3%)	2 (6.7%)	131 (81.4%)	40 (31-51)	65 (49.6%)	2 (1.5%)



**TABLE 2.** Characteristics of patients included in the mortality analysis cohort

Study	Country	Outcome	Sample Size	Non-survivors				Survivors			
				n (%)	Age (yrs)*	Women (%)	CVD n (%)	n (%)	Age (yrs)*	Women (%)	CVD n (%)
Deng et al. (2020)	Wuhan, China	In-hospital mortality	225	109 (48.5%)	69 (62-74)	36 (33%)	13 (11.9%)	116 (51.5%)	40 (33-57)	65 (56%)	4 (3.4%)
Ruan et al. (2020)	Wuhan, China	In-hospital mortality	150	68 (45.3%)	67 (15-81)	19 (28%)	13 (19%)	82 (54.6%)	50 (44-81)	29 (35%)	0 (0%)
Wu et al. (2020)	Wuhan, China	In-hospital mortality	84	44 (52.3%)	68.5 (59.3-75)	15 (34.1%)	4 (9.1%)	40 (47.7%)	50 (40.3-56.8)	9 (22.5%)	4 (10%)
Yang et al. (2020)	Wuhan, China	28-day mortality after ICU admission	52	32 (61.5%)	64.6 (11.2)	11 (34%)	3 (9%)	20 (38.5%)	51.9 (12.9)	6 (30%)	2 (10%)
Zhou et al. (2020)	Wuhan, China	In-hospital mortality or discharge	191	54 (28.3%)	69 (63-76)	16 (30%)	13 (24%)	137 (71.7%)	52 (45-58)	56 (41%)	2 (1%)
Wang Y et al. (2020)	Shanghai, China	28-day mortality after ICU admission	334	211	69 (62-74)	36 (33%)	13 (11.9%)	133 (34.7%)	40 (33-57)	65 (56%)	4 (3.4%)



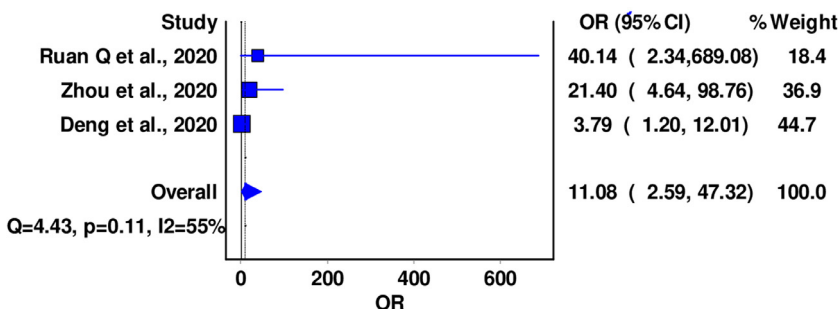
**FIG 2.** Forest plot for association between CVD and COVID-19 severity.

### *Meta-Analysis of the Association Between CVD and Overall COVID-19 Mortality*

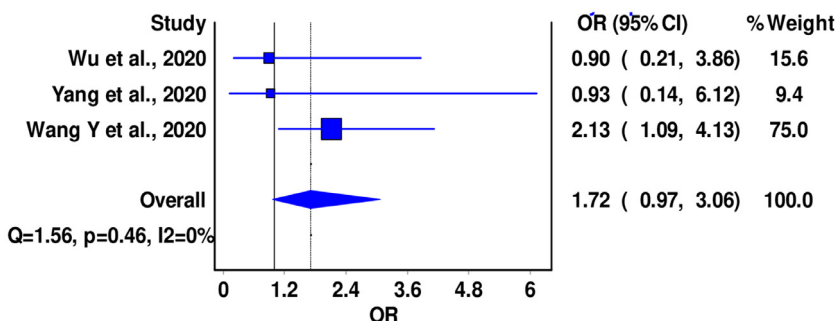
A total of 3 (n = 566) studies reported data on mortality in all hospitalized patients COVID-19 disease and pre-existing history of CVD. In the pooled analysis, previous history of CVD was associated with an ~11-fold increase in mortality (OR = 11.08; 95% CI: 2.59-47.32), with moderate level of inter-study heterogeneity ( $I^2 = 55%$ , Cochran's  $Q = 4.43$ ,  $P = 0.11$ ). No significant differences were noted in the leave-one-out sensitivity analysis (Fig 3; supplementary material).

### *Bias and Meta-Regression*

The potential for publication bias was evaluated in funnel plots (supplementary material). Only very mild asymmetry was noted in funnel plot for CVD and severity. The limited studies for both mortality analyses limited any determination of potential for publication bias in these



**FIG 3.** Forest plot for association between CVD and COVID-19 mortality.



**FIG 4.** Forest plot for association between CVD and COVID-19 mortality in patients with severe disease.

studies. Importantly, in meta-regression of odds of severe disease with underlying CVD, the age of patients in the severe group had no significant influence on calculated pooled odds ratio ( $P = 0.34$ ). However, interestingly, as the percentage of women in the severe group increased, so did the odds ratio of severe disease and CVD association ( $P = 0.02$ ).

## Discussion

Our results demonstrate that underlying or previous history of CVD is directly associated with both worse prognosis and severity outcomes in COVID-19 patients. CVD was found to be associated with around 3-fold increased odds of severe COVID-19 infection, and an 11-fold increase in all-cause mortality among COVID-19 patients.

There are several possible explanations for these findings. First, coexistence of COVID-19 may considerably enhance the severity of an underlying CVD, has already proven in some of the respiratory

infections.<sup>1-3</sup> Symptomatology of fever, cough, and imaging findings may divert clinicians' attention away from possible cardiovascular injury in patients with confirmed COVID-19. Several drugs being currently used to treat COVID-19 infection have been shown to have deleterious cardiovascular effects.<sup>25</sup> Chloroquine/hydroxychloroquine and azithromycin have been associated with prolonged QTc interval and risk of arrhythmias.<sup>26,27</sup> Conduction defects, ventricular arrhythmias, and heart failure have been reported with azithromycin and remdesivir therapy.<sup>28,29</sup> Lopinavir/ritonavir and interleukin therapies have been shown to be associated with ischemic heart disease and abnormalities in lipid profile.<sup>28,30</sup> Last but not the least, patients deemed to be either relatively stable or those with guarded prognosis may not be considered for invasive strategies to preserve healthcare resources and prevent spread of infection.

Our study has several limitations. First, since most studies were from Wuhan China, the potential of overlap, in which 1 patient could be included more than 1 study, is high. Further, we found limited number of studies with relatively small sample size during literature search. However, at this stage of ongoing pandemic, our findings may provide early insights into building models for risk stratification and help with judicious use of limited healthcare resources. Careful evaluation of the patients was performed in order to avoid an overlap between studies. We did not use any exclusion criteria due to the small number of studies. Sensitivity and publication bias analyses were performed to assess for heterogeneity. Since age and sex can be significant confounding variables, we performed a meta-regression to assess their impact on disease severity and mortality in COVID-19 patients.

The presence of CVD was found to be associated with COVID-19 severity and mortality. However, larger studies are needed to confirm these findings. Individuals with previous history of CVD, especially older individuals or those with other co-morbidities, should be aware that if they develop COVID-19 related symptoms, such as fever cough or dyspnea, or were previously exposed to persons with known or suspected COVID-19 infection, they should immediately refer to their healthcare service for receiving specific health and safety advices, or for being timely managed to prevent worsening of their clinical conditions. Finally, the general population should strongly avoid contact with people at higher risk for severe illness, such as those with underlying CVD.

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## Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:[10.1016/j.cpcardiol.2020.100617](https://doi.org/10.1016/j.cpcardiol.2020.100617).

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