

SYSTEMATIC REVIEW AND META-ANALYSIS

# Prevalence of Cardiovascular Comorbidities in Coronavirus Disease 2019, Severe Acute Respiratory Syndrome, and Middle East Respiratory Syndrome: Pooled Analysis of Published Data

Yang Liu, MD\*<sup>1</sup>; Shaohui Wu, MD\*<sup>2</sup>; Mu Qin , MD<sup>3</sup>; Weifeng Jiang, MD<sup>4</sup>; Xu Liu, MD, PhD<sup>5</sup>

**BACKGROUND:** Coronavirus disease 2019 (COVID-19) is spreading widely around the world. We conducted this meta-analysis to explore the prevalence of cardiovascular comorbidities in COVID-19, severe acute respiratory syndrome (SARS), and Middle East respiratory syndrome (MERS) cases.

**METHODS AND RESULTS:** Relevant reports updated to April 17, 2020, were searched from PubMed, Embase, Web of Science, and the Cochrane Library with no restriction on language. A random-effects model was used in this meta-analysis to obtain pooled proportions of cardiovascular comorbidities in COVID-19, SARS, and MERS. A total of 22 studies (12 for COVID-19, 4 for SARS, and 6 for MERS) were included in this analysis, and the average age of patients with COVID-19, SARS, and MERS was 46.41±1.79, 39.16±2.25, and 52.51±4.64 years, respectively. Proportions of cardiovascular comorbidities in coronavirus diseases were as follows: COVID-19: proportion of hypertension was 17.1% (95% CI, 13.2%–20.9%), proportion of cardiac disease was 4.5% (95% CI, 3.6%–5.5%) and proportion of diabetes mellitus was 8.5% (95% CI, 5.5%–11.4%); SARS: proportion of hypertension was 4.5% (95% CI, 2.0%–7.0%), proportion of cardiac disease was 2.1% (95% CI, 0.6%–3.7%) and proportion of diabetes mellitus was 3.7% (95% CI, 1.0%–6.4%); MERS: proportion of hypertension was 30.3% (95% CI, 18.3%–42.2%), proportion of cardiac disease was 20.9% (95% CI, 10.7%–31.1%), and proportion of diabetes mellitus was 45.4% (95% CI, 27.3%–63.5%).

**CONCLUSIONS:** The prevalence of cardiovascular comorbidities varies among different coronavirus-associated diseases. With the development of time, proportions of cardiovascular comorbidities in COVID-19 need further attention.

**Key Words:** cardiovascular comorbidities ■ COVID-19 ■ Middle East respiratory syndrome ■ pooled analysis ■ prevalence ■ severe acute respiratory syndrome

The outbreak of novel coronavirus-infected pneumonia (coronavirus disease 2019 [COVID-19]) attributable to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has affected all 31 provinces in China and 43 countries and territories around the world.<sup>1–3</sup> The absolute number of new cases and severe cases have been increasing rapidly

daily because of enhanced transmissibility of the virus. The World Health Organization declared COVID-19 a public health emergency of international concern on February 1, 2020. The novel coronavirus 2019 (2019-nCoV) was isolated from biologic samples and identified as genus *Betacoronavirus*, placing it alongside other severe acute respiratory syndrome (SARS) and

Correspondence to: Mu Qin, MD, and Weifeng Jiang, MD, Department of Cardiology, Shanghai Chest Hospital, Shanghai Jiao Tong University, 241 Huaihai West Road, Shanghai, China. E-mail: qinmue@163.com, jiangweifeng83@sina.com

\*Dr Yang Liu and Dr Wu contributed equally to this work.

For Sources of Funding and Disclosures, see page 9.

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## CLINICAL PERSPECTIVE

### What Is New?

- The prevalence of cardiovascular comorbidities varies among different coronavirus-associated diseases.
- The proportions of hypertension, cardiac disease, and diabetes mellitus in Middle East respiratory syndrome were all higher than those in coronavirus disease 2019 and severe acute respiratory syndrome. Coronavirus disease 2019 had an apparently higher prevalence of hypertension than severe acute respiratory syndrome.

### What Are the Clinical Implications?

- Knowing the prevalence of cardiovascular comorbidities in coronavirus disease 2019, severe acute respiratory syndrome, and Middle East respiratory syndrome would be helpful in realizing not only the connection between cardiovascular comorbidities and coronavirus-associated diseases but also the discrepancies among different coronavirus-associated diseases.
- Conclusions about coronavirus disease 2019 could provide some assistance in fighting the epidemic.

## Nonstandard Abbreviations and Acronyms

<b>2019-nCoV</b>	novel coronavirus 2019
<b>ACE2</b>	angiotensin-converting enzyme 2
<b>COVID-19</b>	coronavirus disease 2019
<b>MERS</b>	Middle East respiratory syndrome
<b>SARS</b>	severe acute respiratory syndrome

Middle East respiratory syndrome (MERS).<sup>4</sup> 2019-nCoV is a new strain of coronavirus not previously identified in humans. Coronaviruses are zoonotic and are a large family of viruses that cause illness ranging from the common cold to more severe diseases, such as MERS and SARS.<sup>5</sup> In 2002, the SARS epidemic originated from an animal market in South China and then affected more than 8000 people, with 916 deaths in 29 countries,<sup>6</sup> and the mortality was nearly 11%. After the emergence of SARS, MERS was the second coronavirus resulting in a major global public health crisis. It first emerged in 2012 in Saudi Arabia when a 60-year-old man presented with severe pneumonia.<sup>7</sup> Since 2012, 2494 laboratory confirmed cases of MERS have been reported, and 858 associated deaths have occurred (34.4% case-fatality ratio).<sup>8</sup> COVID-19 appears to have greater infectivity and a lower case fatality rate when compared with SARS and MERS.<sup>9</sup> Between countries,

case fatality rates of COVID-19 vary significantly, but it could range from about 0.17% to 15.34%.<sup>10</sup>

The present study was undertaken to provide a systematic evaluation and detailed estimate of the prevalence of cardiovascular comorbidities (hypertension, cardiac disease, and diabetes mellitus) in SARS, MERS and COVID-19 cases. Lessons learned from the MERS and SARS outbreaks can provide valuable insight into how to handle the current epidemic. This assessment may aid the public health sector while formulating policies for surveillance, preparedness, and response to COVID-19.

## METHODS

The authors declare that all supporting data are available within the article.

### Search Strategy

We searched MEDLINE via PubMed, Embase, Web of Science, and the Cochrane Library, with no restriction on language for articles published until April 17, 2020. The keywords of the search included “COVID-19,” “2019 novel coronavirus,” “SARS,” and “MERS.”

### Selection of Articles

Articles were eligible for inclusion if they met the following criteria: (1) those that were clinical studies or consecutive cases about human; (2) required clinical data could be extracted from articles; and (3) at least 3 cases were reported in an article. Articles that met the following criteria were excluded: (1) reports published as review articles, letters, editorials, conference abstracts, vaccination trials, or family-based studies; (2) studies that did not contain data of specific comorbidities; and (3) articles containing data that were also included by other larger studies (eg, if data of article A were also included in article B, which contained more patients, article A would be excluded, while article B would be included).

### Data Extraction

Two researchers (Y.L., S.W.) extracted data independently for each identified article, and any disagreements were resolved by discussion. The following data were recorded: first author's name, year of publication; screening time; number, age, and sex of participants; and number of cardiovascular comorbidities, referring to hypertension, cardiac disease (mainly referred to coronary heart disease), and diabetes mellitus.

### Quality Assessment

We used the Newcastle-Ottawa Scale to assess the quality of included articles.<sup>11</sup> Assessment scores of 0

to 3, 4 to 6, and 7 to 9 indicated poor, fair, and good studies, respectively.

## Statistical Analysis

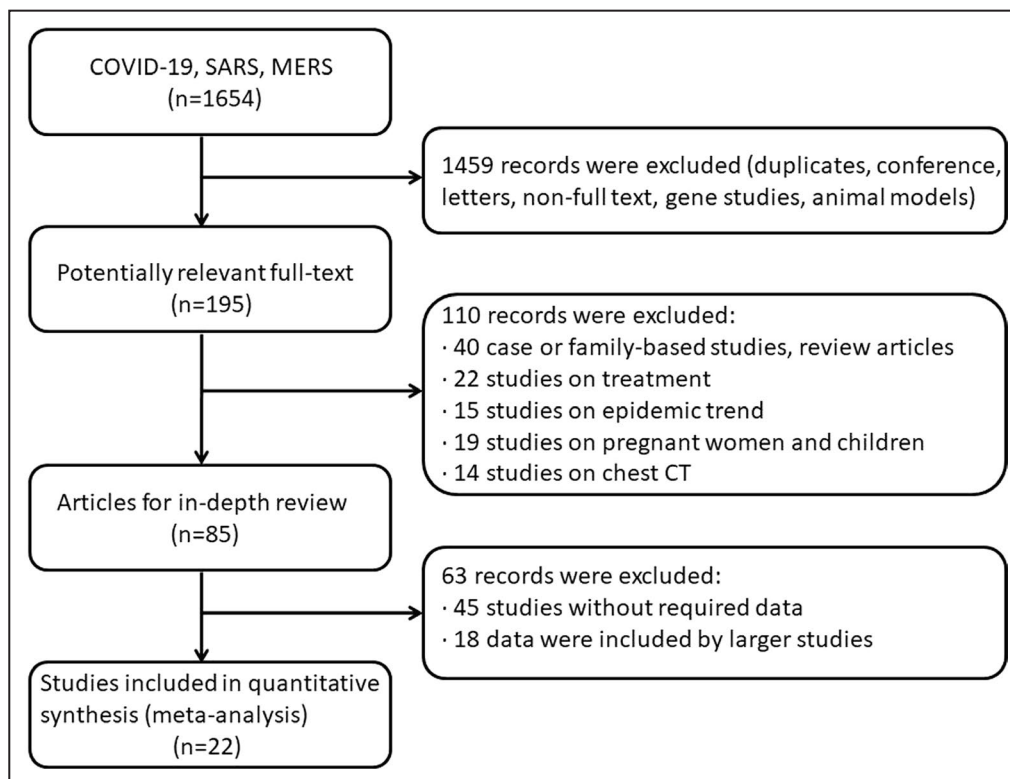
Weighted average was used to calculate the average age. Publication bias was assessed by Egger's test. The meta-analysis of proportions (and 95% CIs) of cardiovascular comorbidities was calculated for the identified studies. Meta-analysis was conducted by using the Stata version 15.0 (Stata Corporation, College Station, TX). Since it was assumed that the relationship between the comorbidities and coronavirus-associated disease varies across populations, a random-effects model (I-V heterogeneity) was used, unless there was no significant heterogeneity among studies. Heterogeneity of results across studies was assessed by a standard chi-square test with significance set at  $P < 0.10$  and an  $I^2$  statistic with significance set at  $I^2 > 50\%$ . ( $I^2$  statistic is heterogeneity's quantitative evaluation. It is calculated by the formula  $I^2 = [(Q - df) / Q] \times 100\%$ , where  $Q$  is the chi-square statistic and  $df$  is the degrees of freedom).

## RESULTS

We identified 1654 reports; 85 full-text articles were retrieved for in-depth review. A total of 22 studies that

reported the prevalence of cardiovascular comorbidities in COVID-19<sup>12–23</sup> ( $n = 51\,268$  cases from 12 studies) and SARS<sup>24–27</sup> ( $n = 1608$  cases from 4 studies) and MERS<sup>28–33</sup> ( $n = 597$  cases from 6 studies) were selected. All cases included in this meta-analysis were laboratory-confirmed cases. Figure 1 shows the selection of articles. All 22 articles were available as full reports (all in English). The assessment of the quality of reports is given in Table 1. Characteristics of included studies are given in Table 2. The average age of SARS cases ( $39.16 \pm 2.25$  years; range, 37.04–42.3 years) was significantly younger than COVID-19 cases ( $46.41 \pm 1.79$  years; range: 44.0–57.8 years;  $t$  test  $P < 0.0001$ ), and the average age of COVID-19 cases was significantly younger than MERS cases ( $52.51 \pm 4.64$  years; range, 35.92–64.5 years;  $t$  test  $P < 0.0001$ ). Certainly, the average age of SARS cases was significantly younger than MERS cases ( $t$  test  $P < 0.0001$ ).

Meta-analysis of the identified studies showed that the proportion of hypertension, cardiac disease, and diabetes mellitus in COVID-19 was 17.1% (95% CI, 13.2%–20.9%;  $I^2 = 96.3\%$ ; Egger's test  $P = 0.283$ ), 4.5% (95% CI, 3.6%–5.5%;  $I^2 = 77.4\%$ ; Egger's test  $P = 0.583$ ), and 8.5% (95% CI, 5.5%–11.4%;  $I^2 = 96.2\%$ ; Egger's test  $P = 0.177$ ) (Figure 2). For SARS, hypertension was present in 4.5% (95% CI, 2.0%–7.0%;  $I^2 = 78.7\%$ ; Egger's test  $P = 0.128$ ), cardiac disease in 2.1% (95%



**Figure 1.** Flowchart diagram of the systematic search and study selection strategy.

COVID-19, coronavirus disease 2019; CT, computed tomography; MERS, Middle East respiratory syndrome; and SARS, severe acute respiratory syndrome.

**Table 1. Characteristics and Quality Assessment of Included Studies**

Study	Year	Study Design	Selection	Comparability	Outcome	Quality Score (0–9)
COVID-19						
NCPERET et al <sup>12</sup>	2020	Retrospective	★★★	★	★★★★★	8
Di Qi et al <sup>13</sup>	2020	Retrospective	★★★	★	★★★	7
Guyi Wang et al <sup>14</sup>	2020	Retrospective	★★★	★	★★★★★	8
Min Cao et al <sup>15</sup>	2020	Retrospective	★★★	★	★★★★★	8
Songqiao Liu et al <sup>16</sup>	2020	Retrospective	★★★	★	★★★★★	8
Xu Chen et al <sup>17</sup>	2020	Retrospective	★★★	★	★★★★★	8
Zhibing Lu et al <sup>18</sup>	2020	Retrospective	★★★	★	★★★★★	8
Yucai Hong et al <sup>19</sup>	2020	Retrospective	★★★	★	★★★★★	8
Sijiao Wang et al <sup>20</sup>	2020	Retrospective	★★★	★	★★★★★	8
Yongtao Zheng et al <sup>21</sup>	2020	Retrospective	★★★	★	★★★★★	8
Bo Yuan et al <sup>22</sup>	2020	Retrospective	★★★	★	★★★★★	8
Christopher M. Petrilli et al <sup>23</sup>	2020	Retrospective	★★★	★	★★★★★	8
SARS						
Hsiao-Ling Chang et al <sup>25</sup>	2006	Retrospective	★★★	★	★★★★★	8
Hai-Ying Lu et al <sup>24</sup>	2005	Retrospective	★★★	★	★★★★★	8
Ping Tim Tsui et al <sup>27</sup>	2003	Retrospective	★★★	★	★★★★★	8
Nelson Lee et al <sup>26</sup>	2003	Retrospective	★★★	★	★★★	7
MERS						
Khalid A. Alburikan et al <sup>28</sup>	2020	Retrospective	★★★	★	★★★★★	8
Yaseen M. Arabi et al <sup>32</sup>	2014	Retrospective	★★★	★	★★★★★	8
Ziad A. Memish et al <sup>33</sup>	2014	Retrospective	★★★	★	★★★	7
Jaffar A. Al-Tawfiq et al <sup>30</sup>	2014	Retrospective	★★★	★	★★★	7
WHO <sup>31</sup>	2013	Retrospective	★★★	★	★★★	7
Abdullah Assiri et al <sup>29</sup>	2013	Retrospective	★★★	★	★★★★★	8

COVID-19 indicates coronavirus disease 2019; MERS, Middle East respiratory syndrome; NCPERET, Novel Coronavirus Pneumonia Emergency Response Epidemiology Team; SARS, severe acute respiratory syndrome; and WHO, World Health Organization.

CI, 0.6%–3.7%;  $I^2=78.8\%$ ; Egger's test  $P=0.165$ ), and diabetes mellitus in 3.7% (95% CI, 1.0%–6.4%;  $I^2=88.4\%$ ; Egger's test  $P=0.137$ ) (Figure 3). MERS exhibited different proportions as follows: hypertension in 30.3% (95% CI, 18.3%–42.2%;  $I^2=59.9\%$ ; Egger's test  $P=0.066$ ), cardiac disease in 20.9% (95% CI, 10.7%–31.1%;  $I^2=89.2\%$ ; Egger's test  $P=0.027$ ), and diabetes mellitus in 45.4% (95% CI, 27.3%–63.5%;  $I^2=95.4\%$ ; Egger's test  $P=0.062$ ) (Figure 4).

## DISCUSSION

Twenty-two studies were included in this meta-analysis, and we found out that the prevalence of cardiovascular comorbidities varies among different coronavirus-associated diseases. The proportions of hypertension, cardiac disease, and diabetes mellitus in MERS were all higher than those in COVID-19 and SARS. It could also be obtained from the meta-analysis that COVID-19 had an apparently higher prevalence of hypertension than SARS.

As MERS was prevalent mainly in the Middle East, the varying rates of cardiovascular comorbidities between MERS and COVID-19 and SARS cases may relate to their different patterns of regional spread. Another reason for this difference may relate to the highest average age of MERS cases given that older age is a known risk factor for hypertension, cardiac disease, and diabetes mellitus. Remarkably, a cardinal difference among SARS, MERS, and COVID-19 is the frequency of cardiovascular involvement. The viral illness could cause a general consequence of the imbalance between infection-induced increased metabolic demand and reduced cardiac reserve, along with superimposed pneumonia will directly and indirectly affect the cardiovascular system. The viral illness can also potentially destabilize coronary plaques and deteriorate the heart failure through several mechanisms including systemic inflammatory responses, which have been recently documented with COVID-19.<sup>34</sup> Both SARS and MERS have been linked to acute myocarditis, acute myocardial infarction, and rapid-onset heart failure. Reversible, subclinical diastolic left ventricular

**Table 2. Characteristics of Included Studies**

Study	Year	Patients (N)			Age (y)	Hypertension (N)	Cardiac Disease (N)	Diabetes Mellitus (N)
		All	Male	Female				
COVID-19								
NCPERET et al <sup>12*</sup>	2020	44 672	22 981	21 691	45.9	2683/20 812	873/20 812	1102/20 812
Di Qi et al <sup>13</sup>	2020	267	149	118	48.0	20	NA	26
Guyi Wang et al <sup>14</sup>	2020	242	119	123	45.0	36	9	15
Min Cao et al <sup>15</sup>	2020	198	101	97	50.1	42	12	15
Songqiao Liu et al <sup>16</sup>	2020	620	326	294	44.48	96	13	40
Xu Chen et al <sup>17</sup>	2020	291	145	146	46.0	39	12	22
Zhibing Lu et al <sup>18</sup>	2020	123	61	62	57.8	41	15	14
Yucai Hong et al <sup>19</sup>	2020	140	71	69	45.66	36	4	12
Sijiao Wang et al <sup>20</sup>	2020	165	92	73	44.0	24	8	12
Yongtao Zheng et al <sup>21</sup>	2020	30	13	17	44.5	3	1	3
Bo Yuan et al <sup>22</sup>	2020	417	198	219	45.4	63	28	32
Christopher M. Petrilli et al <sup>23</sup>	2020	4103	2072	2031	52.0	983	235	614
Total/weighted average (SD)		51 268	26 328	24 940	46.41 (1.79)			
SARS								
Hsiao-Ling Chang et al <sup>25</sup>	2006	346	128	218	42.3	23	19	30
Hai-Ying Lu et al <sup>24</sup>	2005	801	389	412	37.04	21	8	9
Ping Tim Tsui et al <sup>27</sup>	2003	323	127	196	41	16	3	8
Nelson Lee et al <sup>26</sup>	2003	138	66	72	39.3	NA	4	5
Total/weighted average (SD)		1608	710	898	39.16 (2.25)			
MERS								
Khalid A. Alburikan et al <sup>28</sup>	2020	348	216	132	52	73	24	76
Yaseen M. Arabi et al <sup>32</sup>	2014	12	8	4	59	6	4	8
Ziad A. Memish et al <sup>33</sup>	2014	12	6	6	35.92	4	NA	5
Jaffar A. Al-Tawfiq et al <sup>30</sup>	2014	17	11	6	60.7	NA	11	13
WHO <sup>31</sup>	2013	161	104	57	50.0	NA	12	16
Abdullah Assiri et al <sup>29</sup>	2013	47	36	11	64.5	16	13	32
Total/weighted average (SD)		597	381	216	52.51 (4.64)			

COVID-19 indicates coronavirus disease 2019; MERS, Middle East respiratory syndrome; NA, not available; NCPERET, Novel Coronavirus Pneumonia Emergency Response Epidemiology Team; SARS, severe acute respiratory syndrome; and WHO, World Health Organization.

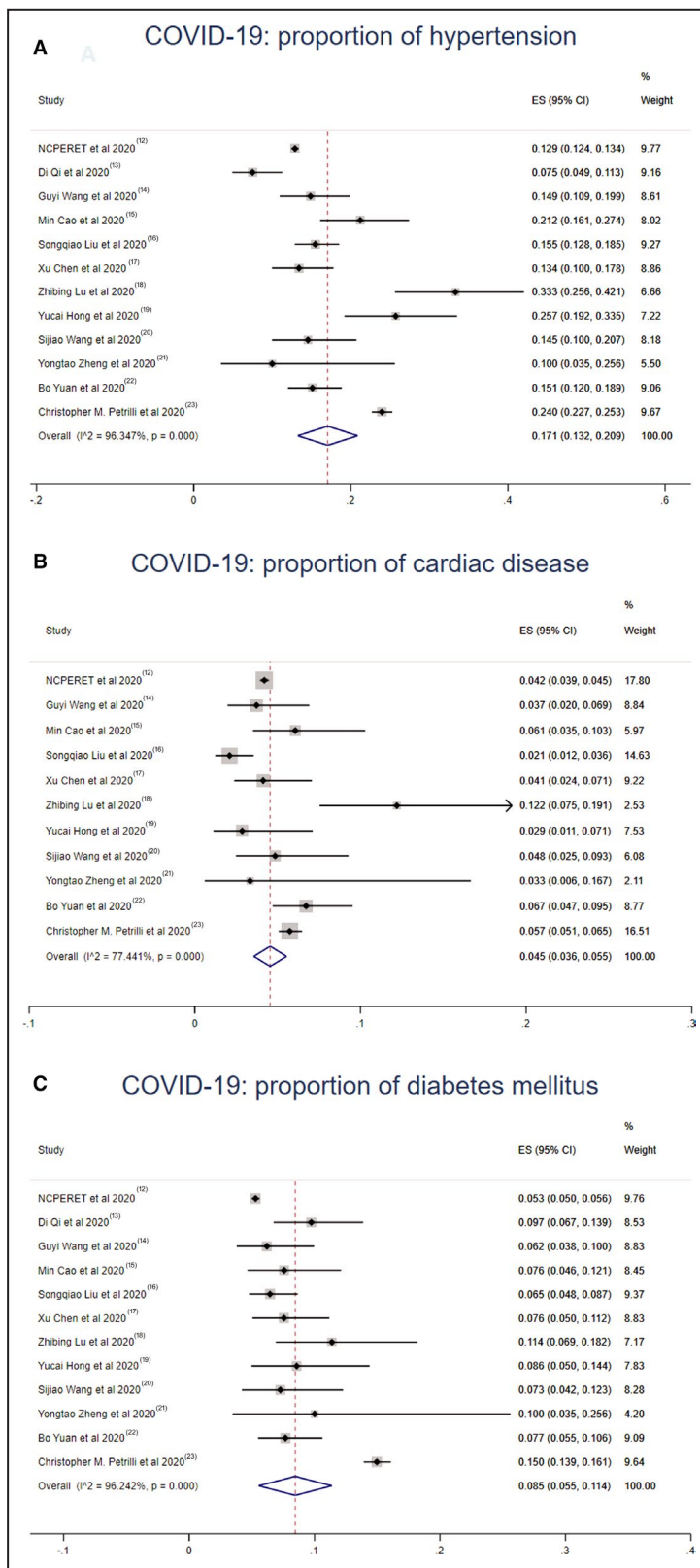
\*Only 20 812 patients were used to calculate percentages of hypertension, cardiac disease, and diabetes mellitus.

impairment in acute SARS even among those without underlying cardiac disease appears common, likely the result of systemic inflammatory immune response; however, lower ejection fraction upon admission was predictive of later mechanical ventilation.<sup>35</sup>

According to previous research on SARS-CoV, cardiac disease, and diabetes mellitus increased the risk of death by twice as much as other risk factors.<sup>36</sup> A large study from mainland China indicated that the overall case fatality rate of COVID-19 was 2.3%, but the mortality reached 10.5% in patients with underlying cardiovascular disease.<sup>37</sup> For patients with underlying cardiovascular disease, including hypertension, coronary heart disease, and cardiomyopathy, viral illness can damage myocardial cells through several mechanisms including direct damage by the virus, systemic inflammatory responses, destabilized coronary plaque, and aggravated hypoxia.<sup>38</sup> Patients with

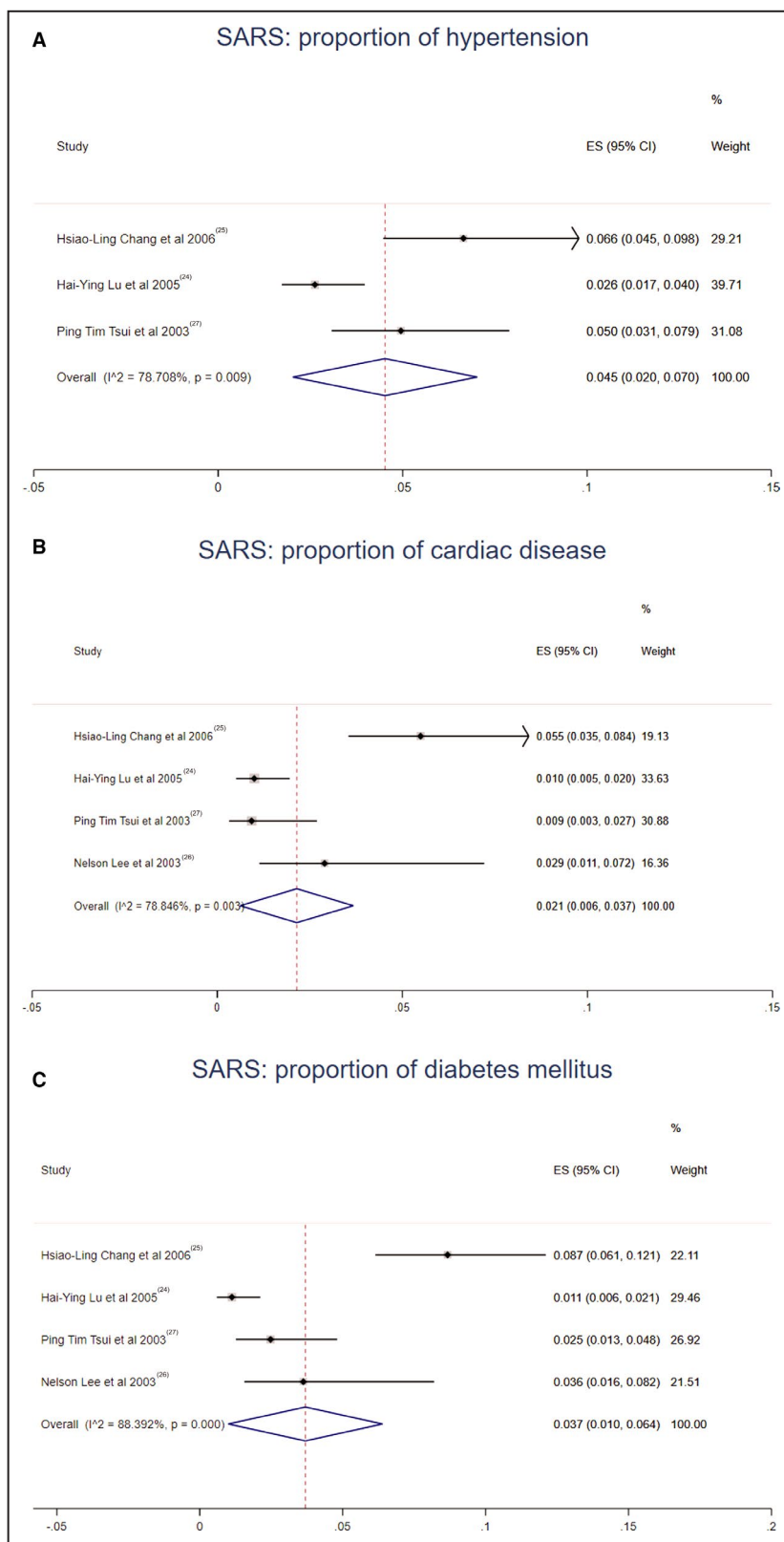
cardiovascular disease are more susceptible to cardiac injury after COVID-19 infection. Cardiac injury can in turn further aggravate the pneumonia and increase the severity of symptoms. Therefore, patients with cardiovascular disease account for a large proportion of deaths from COVID-19.<sup>39</sup>

Proportion of hypertension was very different between COVID-19 and SARS according to this analysis. Despite the evidence suggesting an influence of age on proportion of hypertension, the rate of hypertension in COVID-19 cases (average age 46.41±1.79 years) was still nearly 4-fold higher than that in the SARS cases (average age 39.16±2.25 years) (17.1% versus 4.5%). In accordance with a report,<sup>40</sup> the prevalence of hypertension at 40 to 49 years of age was 22.1% and that at 35 to 39 years of age was 12.6% in China. The ratio between them was 1.8, which was lower than the ratio of hypertension prevalence between COVID-19

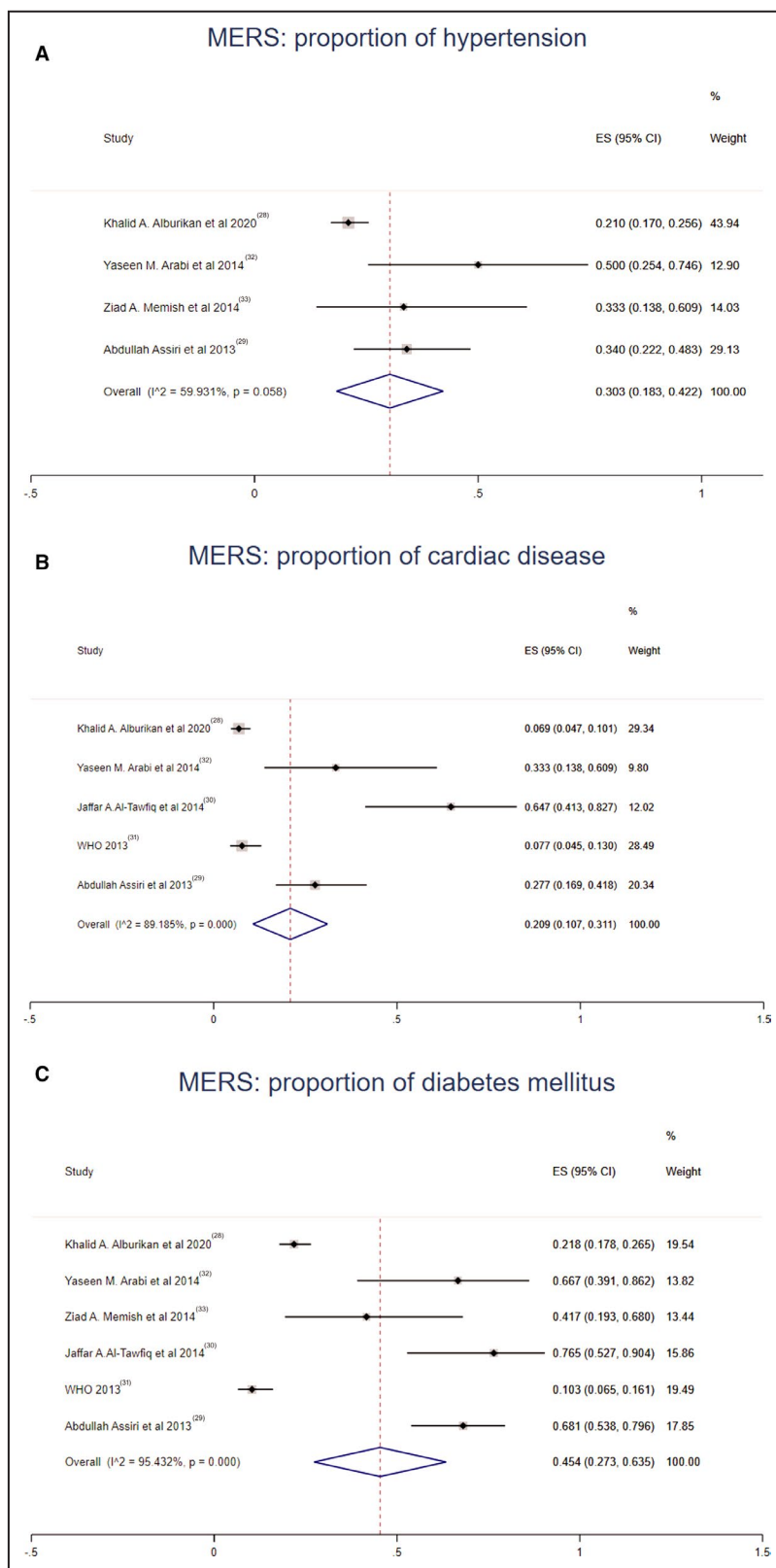


**Figure 2. Meta-analysis of the proportion of cardiovascular comorbidities in COVID-19 cases.**

Values represent proportions of hypertension (A), cardiac disease (B), and diabetes mellitus (C) in COVID-19 cases and the 95% CIs. COVID-19 indicates coronavirus disease 2019; NCPERET, Novel Coronavirus Pneumonia Emergency Response Epidemiology Team.



**Figure 3. Meta-analysis of the proportion of cardiovascular comorbidities in SARS cases.** Values represent proportions of hypertension (A), cardiac disease (B), and diabetes mellitus (C) in SARS cases and the 95% CIs. SARS indicates severe acute respiratory syndrome.



**Figure 4. Meta-analysis of the proportion of cardiovascular comorbidities in MERS cases.**

Values represent proportions of hypertension (A), cardiac disease (B), and diabetes mellitus (C) in MERS cases and the 95% CIs. MERS indicates Middle East respiratory syndrome; and WHO, World Health Organization.



and SARS (3.8). Therefore, there may be some other reasons contributing to the difference of hypertension prevalence between COVID-19 and SARS apart from age.

Scientists have confirmed that 2019-nCoV uses the same cell entry receptor, angiotensin-converting enzyme 2 (ACE2), as SARS coronavirus.<sup>41</sup> This finding has important implications for our understanding of 2019-nCoV transmissibility and pathogenesis. ACE2, the receptor for SARS-CoV-2 and SARS coronavirus, is a surface molecule localized on arterial and venous endothelial cells, arterial smooth muscle cells, and epithelia of the small intestine and the respiratory tract.<sup>42</sup> In the respiratory tract, ACE2 receptor is expressed on the epithelial cells of alveoli, trachea, and bronchi, bronchial serous glands, and alveolar monocytes and macrophages.<sup>43</sup> Downregulation of ACE2, as occurs during COVID-19 infection, is believed to contribute to pathological changes in the lung. Expression of the ACE2 receptor is also found in many extrapulmonary tissues including heart, kidney, endothelium, intestine, and liver. SARS-CoV-2 could invade cells of the above tissues and injure these organs.<sup>44,45</sup> Target cells of the MERS coronavirus infection in the lung include pneumocytes, multinucleated epithelial cells, and bronchial submucosal gland cells.<sup>46</sup> All of these cells express a multifunctional cell surface protein, called dipeptidyl peptidase 4 (also known as CD26), constituting the primary entry receptor of MERS coronavirus.<sup>47</sup> Dipeptidyl peptidase 4, the entry receptor of MERS coronavirus, is widely expressed on epithelial cells in the kidney, alveoli, small intestine, liver, and prostate, suggesting that the range of MERS coronavirus tissue tropism is broader than SARS coronavirus and 2019-nCoV.

There are several limitations in this meta-analysis. First, the studies included in this analysis indicated a wide among-studies variance in the prevalence of comorbidities, which may have facilitated the appearance of significant heterogeneity. Furthermore, the large variation among studies in the sample size (30–44 672 2019-nCoV cases, 138–801 SARS cases and 12–348 MERS cases) may be additional sources of heterogeneity. Third, different studies may define cardiac disease slightly differently, which may increase heterogeneity to some extent. For example, some studies referred only to coronary heart disease, while other studies included several cardiac diseases. Last but not least, further studies are needed to illustrate the discrepancy of the prevalence of comorbidities among different coronavirus diseases more accurately.

As COVID-19 is spreading in many regions of the world currently, it is reasonable to advise patients with comorbidities of the potential increased risk and to encourage additional, reasonable precautions in geographies with active COVID-19 transmission. It is important for patients with comorbidities to remain

current with vaccinations, including the pneumococcal vaccine given the increased risk of secondary bacterial infection; it would also be prudent to receive influenza vaccination to prevent another source of fever, which could be initially confused with coronavirus infection. Currently, no specific antiviral treatment is available for 2019-nCoV, and further research is imperative for identifying appropriate therapeutic targets.

## ARTICLE INFORMATION

Received March 29, 2020; accepted June 17, 2020.

### Affiliations

From the Department of Cardiology, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China.

### Sources of Funding

This research was supported by Grants from the Nature Science Foundation of China (No. 81770324).

### Disclosures

None.

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