COVID-19 Related Cardiovascular Comorbidities and Complications in Critically Ill Patients: A Systematic Review and Meta-analysis

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ABSTRACT

OBJECTIVE: This systematic-review and meta-analysis aimed to assess the prevalence of cardiovascular comorbidities and complications in ICU-admitted coronavirus disease 2019 (COVID-19) patients.

DATA SOURCES: PubMed and Web of Science databases were referenced until November 25, 2020.

DATA EXTRACTION: We extracted retrospective and prospective observational studies on critically ill COVID-19 patients admitted to an intensive care unit. Only studies reporting on cardiovascular comorbidities and complications during ICU therapy were included.

DATA SYNTHESIS: We calculated the pooled prevalence by a random-effects model and determined heterogeneity by Higgins' I^2 test.

RESULTS: Of the 6346 studies retrieved, 29 were included in this review. The most common cardiovascular comorbidity was arterial hypertension (50%; 95% confidence interval [CI], 0.42-058; $I^2 = 94.8\%$, low quality of evidence). Among cardiovascular complications in the ICU, shock (of any course) was most common, being present in 39% of the patients (95% CI, 0.20-0.59; $I^2 = 95.6\%$; 6 studies). Seventy-four percent of patients in the ICU required vasopressors to maintain target blood pressure (95% CI, 0.58-0.88; $I^2 = 93.6\%$; 8 studies), and 30% of patients developed cardiac injury in the ICU (95% CI, 0.19-0.42; $I^2 = 91\%$; 14 studies). Severe heterogeneity existed among the studies.

CONCLUSIONS: Cardiovascular complications are common in patients admitted to the intensive care unit for COVID-19. However, the existing evidence is highly heterogeneous in terms of study design and outcome measurements. Thus, prospective, observational studies are needed to determine the impact of cardiovascular complications on patient outcome in critically ill COVID-19 patients.

KEYWORDS: COVID-19, critical care, cardiovascular system, hemodynamic, heart

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Introduction

The COVID-19 pandemic is ongoing, and increasing numbers of patients need ICU treatment for COVID-19. In the early phase, COVID-19 presents as a respiratory disease, but several lines of evidence suggest that COVID-19 is a systemic disease leading to deleterious outcomes, because it can induce multiorgan dysfunction and failure.[1] An interim guideline by the World Health Organization (WHO) [https://www.who.int/publications-detail/clinical-management-of-covid-19] grades COVID-19 by disease severity:

1. Mild disease
2. Moderate disease with pneumonia
3. Severe disease with severe pneumonia
4. Critical disease with acute respiratory distress syndrome (ARDS)
5. Critical disease with sepsis or septic shock

The overall case-fatality rate ranges from 1% to 4% in all patients,[2] and up to 20% of COVID-19 patients admitted to a hospital present with a critical disease[3] and require intensive care treatment. In this subset of patients, the ICU mortality of COVID-19 patients is up to 50%.[4] This substantial mortality is not explained by pulmonary symptoms alone, but may be caused by other organ involvement especially the kidneys and heart.[5] Early reports on COVID-19 have shown a high prevalence of chronic cardiovascular comorbidities and cardiovascular medication in patients with severe cases. There is ongoing research on whether these comorbidities lead to a higher susceptibility to suffer from a more severe form of COVID-19. Interestingly, cardiac enzyme levels are within the normal range early on in the course of disease, but the levels of troponin and other cardiac injury markers can increase at later stages.[6,7]

COVID-19 infection numbers follow an exponential increase. As a response to this global threat, substantial research efforts are aiming for a rapid knowledge gain regarding the pathophysiology and treatment of COVID-19. To obtain an overview of the number of COVID-19-related publications, we scanned PubMed for COVID-19-related publications

from January 17 to May 25, 2020. In this time period, 16,123 COVID-19 references were found in PubMed, which accounts for 63.7% of the publications indexed in this database during this time span (Supplemental Figure 1). Logarithmic data of published literature and reported COVID-19 cases are linearly correlated with each other ($r = 0.9939$; $P < .0001$). This highlights the need for a systemic assessment of available evidence.

Given that COVID-19 is associated with increased mortality in patients with pre-existing cardiovascular comorbidities, we analyzed the available evidence for COVID-19-related cardiovascular complications in critically ill adults.

Methods

Protocol and registration

This systematic review and meta-analysis was conducted according to the guidelines of the "Preferred Reporting Items for Systematic Reviews and Meta-Analysis" (PRISMA) statement.[8] The review protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD42020189270).

Eligibility criteria

Studies that met the following criteria were considered eligible for inclusion: (1) original articles, research letters and letters to the editor reporting on the prevalence of cardiovascular disease and complications; (2) studies of critically ill patients; (3) studies with adult patients (age ⩾18 years); (4) studies of patients admitted to intensive care units; and (5) written in English. Reviews, meta-analyses, case reports and duplicate publications were excluded. Published abstracts without retrievable full texts were excluded.

Information sources and search strategy

PubMed and Web of Science databases were searched for publications using the search terms "covid-19" or "SARS-CoV-2" and "characteristics", "critical" and "care" or "intensive" and "care" (search date May 25, 2020). Peer Review of Electronic Search Strategies checklist was used to design the search strategy.[9] We used Endnote X9 (Clarivate Analytics, Inc.) to manage the retrieved publications. Duplicate publications were identified by automatic search and manually confirmed.

Study selection

We selected pertinent studies according to the PRISMA flowchart. After the removal of duplicate studies, 2 authors (HM and MK) independently evaluated the titles and abstracts for relevant studies. The included studies were further evaluated by full-text review based on the eligibility criteria. Disagreements for study selection were solved by discussions and the consensus of 2 authors (HM and MK) and further discussions with the third author (PR).

Data extraction

All data were extracted by HM and verified by MK afterwards. The following data were extracted into a standardized table: author, digital object identifier (DOI), the country and location of data origin, study period, total reported ICU/critically ill patients, age distribution, deceased patients, Sequential Organ Failure Assessment (SOFA) score, total patients with comorbidities (hypertension, cardiovascular disease, coronary heart disease, arrhythmia, and congestive heart failure), and total patients with cardiovascular complications (shock, the use of vasopressors, arrhythmia, cardiomyopathy, acute cardiac injury diagnosed by biomarkers and cardiac arrest). All included studies were scored for their quality by the MetaXL Ver. 5.3 add-in for the Microsoft Excel quality indicators template as described.[10] This quality indicator assessment included the following topics: the degree of the definition of the target population, the diagnostic criteria, the methods of case ascertainment, the administration of measurement protocol, the catchment area and the prevalence measure used. The results of quality scoring are provided in Supplemental Data.

Analyses of prevalence

We used the MetaXL Ver 5.3 add-in for Microsoft Excel (EpiGear international, Australia) to perform all meta-analyses of prevalence.[11] To obtain as comprehensive of an overview as possible, studies with small case numbers were also left in the analyses. Therefore, high heterogeneity was assumed, and random-effects meta-analyses (after DerSimonian and Laird) and quality-effects meta-analyses (after Doi and Thalib) that included quality scoring were used.[10,12] Pooled prevalence is reported with the lower and upper 95% confidence intervals (CIs). Heterogeneity was assessed by calculating Cochran's Q and Higgins' I^2. We defined the grade of heterogeneity based on Higgins' I^2 calculation as follows: no heterogeneity ($I^2 = 0\%$), low heterogeneity ($I^2 = 25\%$-49%), moderate heterogeneity ($I^2 = 50\%$-74%) and severe heterogeneity ($I^2 > 75\%$).[13]

All presented pooled prevalence values were calculated based on the random-effects model. As a second line of evidence, we also calculated pooled prevalence values based on the quality-effects model; this did not result in significant differences. Pooled prevalence values based on the quality-effects model are reported in Supplemental Data.

Results

Study selection

We scanned PubMed and Web of Science to identify the relevant publications. Then, we selected studies based on the relevance in the title and abstracts according to the PRISMA flow chart (Figure 1). After the removal of publications not fulfilling the inclusion criteria, 29 studies published up to May 25, 2020 were left for final inclusion in the meta-analysis.[3,14-41]

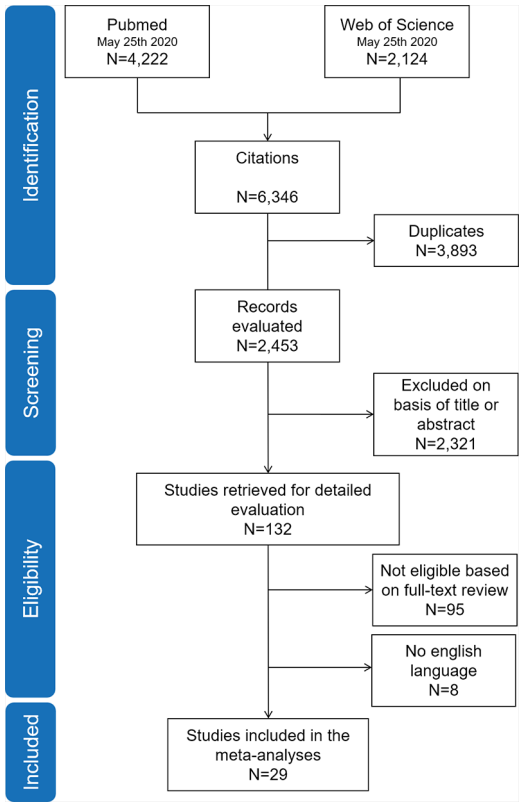


Figure 1. Flow-chart of study selection. Flow-chart in accordance with the guidelines of the "Preferred Reporting Items for Systematic Reviews and Meta-Analysis" (PRISMA) statement.

Study description

After selecting the relevant studies (Table 1), we screened the study protocol and study type. We found 5 prospective cohort studies, 1 prospective cross-sectional study and 20 retrospective cohort studies relevant for the analysis. In 2 reports the study design remained unclear by the analysis of the full texts.[30,31] Thus, a total of 4381 patients could be included in the meta-analysis. The number of patients in the individual studies varied between 8 and 1591.[24,27] One study did not specify patient disposition (regular floor or critical care unit) in the full text but reported on ventilated patients.[23] Direct communication with the first author of this report revealed that all ventilated patients were treated in an ICU. Thus, this report was included in the analyses. Three other studies did not explicitly report on "ICU patients" but on critically ill patients. We assumed that the treatment of critically ill patients took place in an intensive care setting; therefore, we included these studies in the analyses.[3,31,38]

To gauge socioeconomic differences among the studies, we analyzed the geographic regions of the included studies (Supplemental Figure 2): Fifteen reports published from mainland China (952 patients), 8 reports were from the United States of America (1675 patients), 4 reports were from Europe (Italy, Spain, and Denmark: 1728 patients) and 2 reports were from Asia outside of mainland China (Thailand and the Republic of South Korea: 26 patients).

Study quality and publication bias

Next, we scored each study based on 6 quality indicators. In 4 studies it was not possible to determine definitively how the diagnosis of COVID-19 was made.[18,29,30,37] Detailed results of the quality scoring are given in Supplemental Data. The corresponding funnel plots for cardiovascular comorbidities and complications revealed an asymmetric distribution of the studies. This suggests a publication bias of the included studies (Supplemental Data).

Baseline patient parameters

We analyzed the baseline parameters of the patients included in the different studies. The median age of the patients was between 49 (41-63) years and 73 (48-91) years.[26,37] The authors of 6 studies reported the SOFA score as a measurement of disease severity. The median SOFA score ranged from 3 (2-7 points) to 11 (8-13 points).[19,20] Twenty-one studies reported overall mortality, which ranged from 0% to 70.6% (20, 30, 40). The studies used different end-points for assessment, such as ICU mortality, in-hospital mortality, 15-day mortality, and 28-day mortality.[14-17,19-21,23-30,32,34-37,39]

Prevalence of cardiovascular comorbidities in critically ill patients

Several retrospective analyses reported that patients with severe COVID-19 have a pre-existing cardiovascular comorbidity. Thus, in the first analysis, we determined the prevalence of cardiovascular comorbidities in the ICU patient population (Figure 2). After screening the available information in the included studies, we focused on the following: arterial hypertension, cardiovascular diseases (not further specified), coronary artery disease, pre-existing arrhythmias (e.g., arterial fibrillation) and congestive heart failure.

Arterial hypertension was reported in 22 studies,[3,15,17-21,23-33,35,37,39,41] with a prevalence from 15% to 69%.[3,26] Using Higgins' I^2 test, we found severe heterogeneity among the studies (I^2 94.8%; $P < .005$). The random-effects meta-analysis resulted in a pooled prevalence of 50% (95% CI 41%-58%). Sixteen studies listed cardiovascular disease as a comorbidity without further specification of the different entities,[3,15,18-20,24-27,29,32-34,37-39] and the prevalence ranged from 0% to 77%.[3,25,27,38] Again, Higgins' I^2 test resulted in severe heterogeneity (I^2 98.9%; $P < .005$), with a pooled prevalence of 21% (95% CI 7%-38%) in the random-effects meta-analysis model. Similarly, coronary heart disease had a pooled prevalence of 19% (95% CI 11%-29%) in 5 studies,[3,21,23,35,41] ranging from 10% to 31%.[21,41] The I^2 test revealed severe heterogeneity among the different studies (I^2 87.9%; $P < .005$).

Congestive heart failure was present in a total of 429 patients[14,15,21,28,35] upon admittance to the ICU, which resulted in a pooled prevalence of 5% (95% CI 0%-15%) in the random-effects meta-analysis model.[14,15] However, as with all other

Table 1. Key characteristics of all included studies.

STUDY	STUDY DESIGN	COUNTRY	LOCATION	PERIOD OF TIME	TOTAL ICU PATIENTS	AGE	MORTALITY
Arentz et al. (2020),[14] JAMA	Prospective cohort	USA	Kirkland, Washington, Evergreen Hospital	2020-02-20 to 2020-03-05	21	70 (43-92)	52.4%
Barrasa et al. (2020),[15] Anaesth Crit Care Pain Med	Prospective cohort	Spain	Vitoria	2020-03-04- to 2020-03-31	48	63.2 ± 12	12.5% (at 28 days)
Bhatraju et al. (2020),[16] NEJM	Retrospective cohort	USA	Seattle region	2020-02-24 to 2020-03-09	24	64 ± 18	50% (in-hospital)
Cao et al. (2020),[17] Intensive Care Med	Retrospective cohort	China	Wuhan, Zhongnan Hospital	2020-01-03 to 2020-02-01	18	66 (54-76)	33.3%
Chu et al. (2020),[18] J Infect	Retrospective cohort	China	Hangzhou, First Affiliated Hospital	2020-01 to 2020-02-23	33	65.2 ± 16.6	nr
Cummings et al (2020),[19] Lancet	Prospective cohort	USA	New York, Presbyterian Hospitals	2020-03-02 to 2020-04-01	257	62 (51-72)	39.3% (in-hospital)
Du et al (2020)[20] Ann Am Thorac Suc	Retrospective cohort	China	Wuhan	2019-12-25 to 2020-02-15	51	68.4 ± 9.7	70.6% (15 days)
Ferguson et al. (2020)[21] Emerg Infect Dis	Retrospective cohort	USA	Northern California, San Francisco Bay Area	2020-03-13 to 2020-04-01	21	67.6 (42.2-70.1)	14.3% (in-hospital)
Gold et al (2020)[22], MMWR	Retrospective cohort	USA	Georgia	2020-03-01 to 2020-03-30	119	nr	nr
Goyal et al (2020),[23] NEJM, Pt. with invasive ventilation	Retrospective cohort	USA	New York City, Manhattan	2020-03-03 to 2020-03-27	130	nr	14.6%
Grasselli et al (2020),[24] JAMA	Retrospective cohort	Italy	Lombardy ICU network	2020-02-20 to 2020-03-18	1591	63 (56-70)	61.3% (405/661)
Hong et al. (2020),[25] YMI	Retrospective cohort	South Korea	Daegu, Yeungnam University Medical Center	up to 2020-03-29	13	63.2 ± 10.1	30.8%
Huang et al. (2020),[26] Lancet	Retrospective cohort	China	Wuhan, Jinyintan Hospital	2019-12-16 to 2020-01-02	13	49 (41-61)	38.5%
Ling et al., (2020),[27] Crit Care Resusc	Retrospective cohort	China	Hong Kong	2020-11-22 to 2020-02-11	8	64.5 (42-70)	12.5%
Myers et al. (2020),[28] JAMA	Retrospective cohort	USA	Kaiser Permanente Northern California	2020-03-01 to 2020-03-31	113	63 (53-73)	50%
Pedersen et al. (2020),[29] Dan Med J	Retrospective cohort	Denmark	Roskilde, Zealand University Hospital	2020-03-11 to 2020-04-01	16	69.5 (56-84)	60%

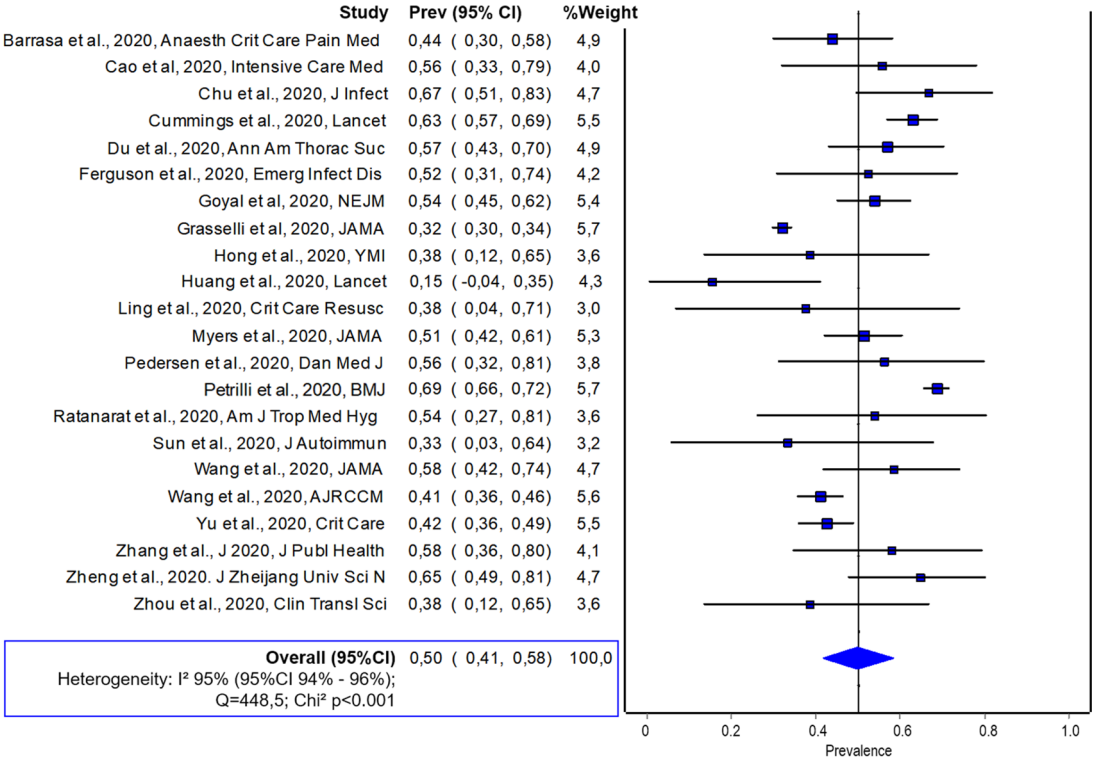
(Continued)

Table 1. (Continued)

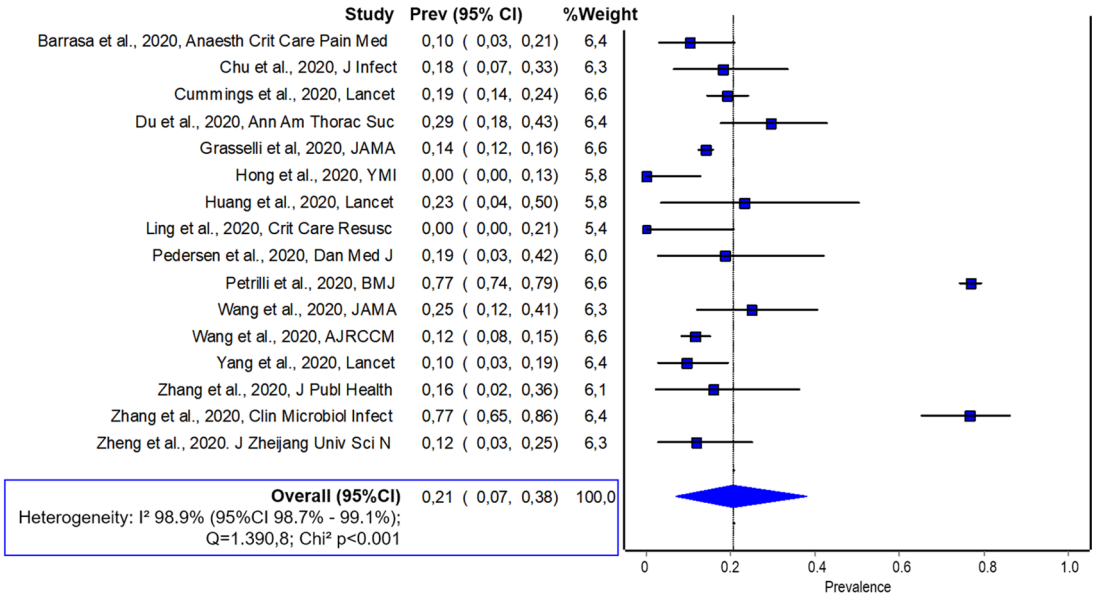
STUDY	STUDY DESIGN	COUNTRY	LOCATION	PERIOD OF TIME	TOTAL ICU PATIENTS	AGE	MORTALITY
Petrilli et al. (2020),[3] BMJ, Critical Illness	Prospective cohort	USA	New York City, NYU Langone Health	2020-03-01 to 2020-04-08	990	68 (58-78)	nr
Ratanarat et al. (2020),[30] Am J Trop Med Hyg	nr	Thailand	Bangkok, Siriraj Hospital	nr	13	58 ± 15	0%
Sun et al. (2020),[31] J Autoimmun, Crit Ill	nr	China	Beijing, Chinese PLA General Hospital	nr	9	63 (34-79)	nr
Wang et al. (2020),[32] JAMA	Retrospective cohort	China	Wuhan, Zhongnan Hospital	2020-01-01 to 2020-01-28	36	66 (57-78)	24%
Wang et al. (2020),[33] AJRCCM	Retrospective cohort	China	Wuhan, Tongji Hospital	2020-01-25 to 2020-02-25	344	64 (52-72)	nr
Yang et al. (2020),[34] Lancet	Retrospective cohort	China	Wuhan, Yin-tan Hospital	2019-12 to 2020-01-26	52	59.7 ± 13.3	61.5%
Yu et al. (2020),[35] Crit Care	Prospective cross-sectional	China	Wuhan, 16 hospitals	2020-02-26 to 2020-02-27 (cross-sectional)	226	64 (57-70)	40.9%
Zangrillo et al. (2020),[36] Crit Care Resusc	Prospective cohort	Italy	Milan, San Raffaele Scientific Institute	2020-02-20 to 2020-04-02	73	61 (54-69)	19.2%
Zhang et al. (2020),[37] J Publ Health	Retrospective cohort	China	Huazhong, Liyuan Hospital	2020-01-16 to 20-02-20	19	73 (48-91)	42.1%
Zhang et al. (2020),[38] Clin Microbiol Infect, Critical Patients	Retrospective cohort	China	Wuhan, Renmin Hospital	2020-01-11 to 2020-02-06	64	67.1 (58.3-76.8)	nr
Zheng et al. (2020),[39] J Zheijang Univ Sci N	Retrospective cohort	China	Hangzhou, First Affiliated Hospital	2020-01-22 to 2020-03-05	34	66 (58-76)	0%
Zheng et al. (2020),[40] J Clin Virol	Retrospective cohort	China	Chengdu, Public Health Clinical Medical Center	2020-01-16 to 2020-02-20	32	63.8 ± 16.5	nr
Zhou et al. (2020),[41] Clin Transl Sci	Retrospective cohort	China	Huangshi, Huangshi Central Hospital	2020-01-28 to 2020-03-02	13	67.4 ± 13.4	nr
					4,381		

"nr": not reported; Age is presented as either the mean ± the standard deviation or the median (interquartile range); mortality is given for ICU mortality if not noted separately.

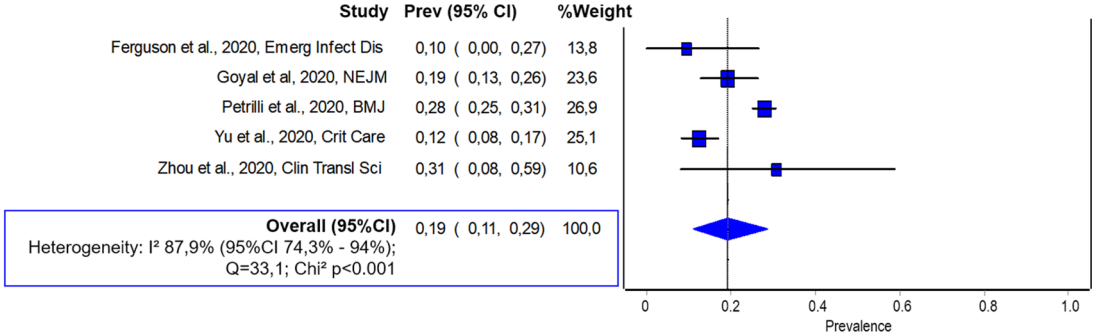
Arterial Hypertension



Cardiovascular diseases in general



Coronary heart disease



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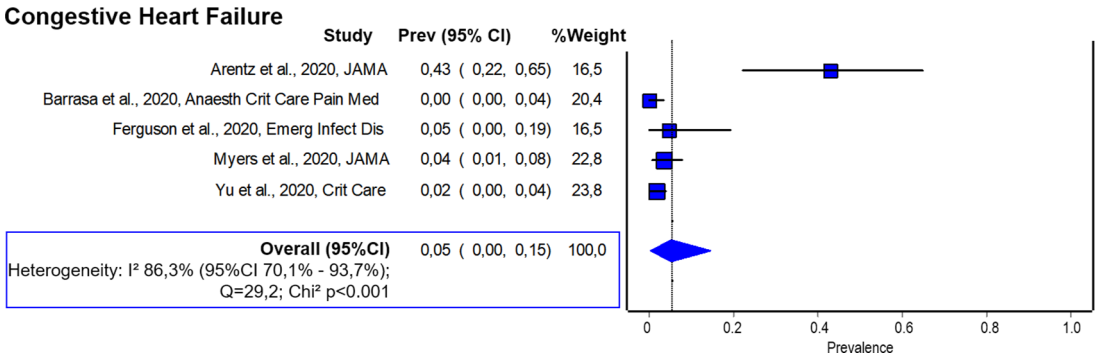

Figure 2. Forrest plots of pooled prevalence values for cardiovascular comorbidities in critically ill patients.

comorbidities, severe heterogeneity was found among the studies (I^2 86.9%; $P < .005$). In a total of 30 patients in 2 reports, chronic arrhythmia was present in the admitted patients with a prevalence of 11% and 14%, respectively,[21,31] but the number of patients was too small for a meta-analysis.

Prevalence of cardiovascular complications and therapy during ICU therapy

Several studies have indicated that COVID-19 might lead to an increase in cardiovascular complications. We analyzed the prevalence of shock, new-onset arrhythmia, cardiomyopathy, cardiac injury, or cardiac arrest in critically ill COVID-19 patients. Figure 3 presents the results of the meta-analysis.

Using the random-effects model, shock occurred in 39% (95% CI 20%-59%) of 751 analyzed patients in 6 publications.[22,25,26,32,33,35] The prevalence ranged from 16% to 71%.[22,35] Higgins' I^2 test resulted in severe heterogeneity (Figure 3). Vasopressors were required in 74% (95% CI 58%-88%) of 625 patients in 8 reports (ranging from 35% to 94%[15,34]) to maintain the mean arterial pressure target.[14-16,19,21,23,34,36] One study reported only a subset of patients (36). Again, there was severe heterogeneity among the studies.

New arrhythmias in the ICU occurred in 24% (95% CI 14%-36%) of 504 patients from 6 studies.[17,21,23,32,35,36] The reported prevalence ranged from 9% to 44%.[36] Higgins' I^2 test resulted in severe heterogeneity. We also screened for new-onset cardiomyopathy in the ICU. Three reports including 66 patients reported newly detected cardiomyopathies during ICU therapy.[14,16,21] One study reported on only a subset of 9 patients screened for cardiomyopathy.[16] The prevalence ranged from 0% to 3%.[14,16] Due to the small case numbers, a meta-analysis was not performed.

Acute cardiac injury developed in 30% (95% CI 19%-42%) of 927 patients in fourteen publications,[14-18,20,21,25,26,32,35,39] with 1 study reporting on only a subset of patients.[21] Higgins' I^2 test revealed severe heterogeneity among the studies. One study reported a prevalence of cardiac arrest of 8%.[36]

Subgroup analyses of cardiovascular injury by country

We performed an additional subgroup analysis for the prevalence of acute cardiac injury during ICU therapy in the data from mainland China or the USA and Western Europe (Figure 4). The pooled prevalence of acute cardiac injury in the random effects model was 6% (95% CI 0%-17%) in patients in the USA and Western Europe (4 studies, 107 patients) with a moderate heterogeneity.[14,16,21] In patients from mainland China, the pooled prevalence was 39% (95% CI 27%-50%) (9 studies, 807 patients) with severe heterogeneity.[17,18,20,26,32-35,39]

Discussion

Approximately 10% of COVID-19 patients require intensive care treatment and early on in this pandemic several studies reported that COVID-19 might lead to cardiovascular complications during ICU treatments.[42] However, the prevalence of cardiovascular complications remains unclear in critically ill patients. We performed a systematic-review and meta-analysis on the prevalence of cardiovascular comorbidities and complications in patients with critical COVID-19 treated in the ICU.

Our major findings were that half of ICU patients (50%) with COVID-19 had arterial hypertension as a pre-existing comorbidity; shock of any cause was the most common cardiovascular complication in the ICU (39%), and 74% of COVID-19 patients required vasopressors during the course of ICU stay. Despite exponential growth in the number of publications over the last few months, studies on the ICU population are very heterogeneous in design, patient population and outcome parameters.

Patients with COVID-19 present primarily with respiratory symptoms, such as dyspnea, cough and fever. Approximately 20% of COVID-19 patients develop severe disease,[6] some so severe that VV-ECMO is used as a rescue therapy.[43,44] We found that almost 40% of patients developed shock during their ICU stay. We found that the main cardiovascular complication in COVID-19 patients in the ICU was shock of any cause, corresponding to vasopressor use in 74% of the patients admitted to the ICU. Recent studies showed that COVID-19 leads to multiorgan failure,[45] including kidney failure, liver failure and encephalopathy[16,46] alongside a dysregulated immune response.[47-50] Thus, some authors classify COVID-19-induced shock as septic shock.[51,52]

In fact, COVID-19 leads to an increase in cytokines in the systemic circulation, sparking a dramatic response of the innate

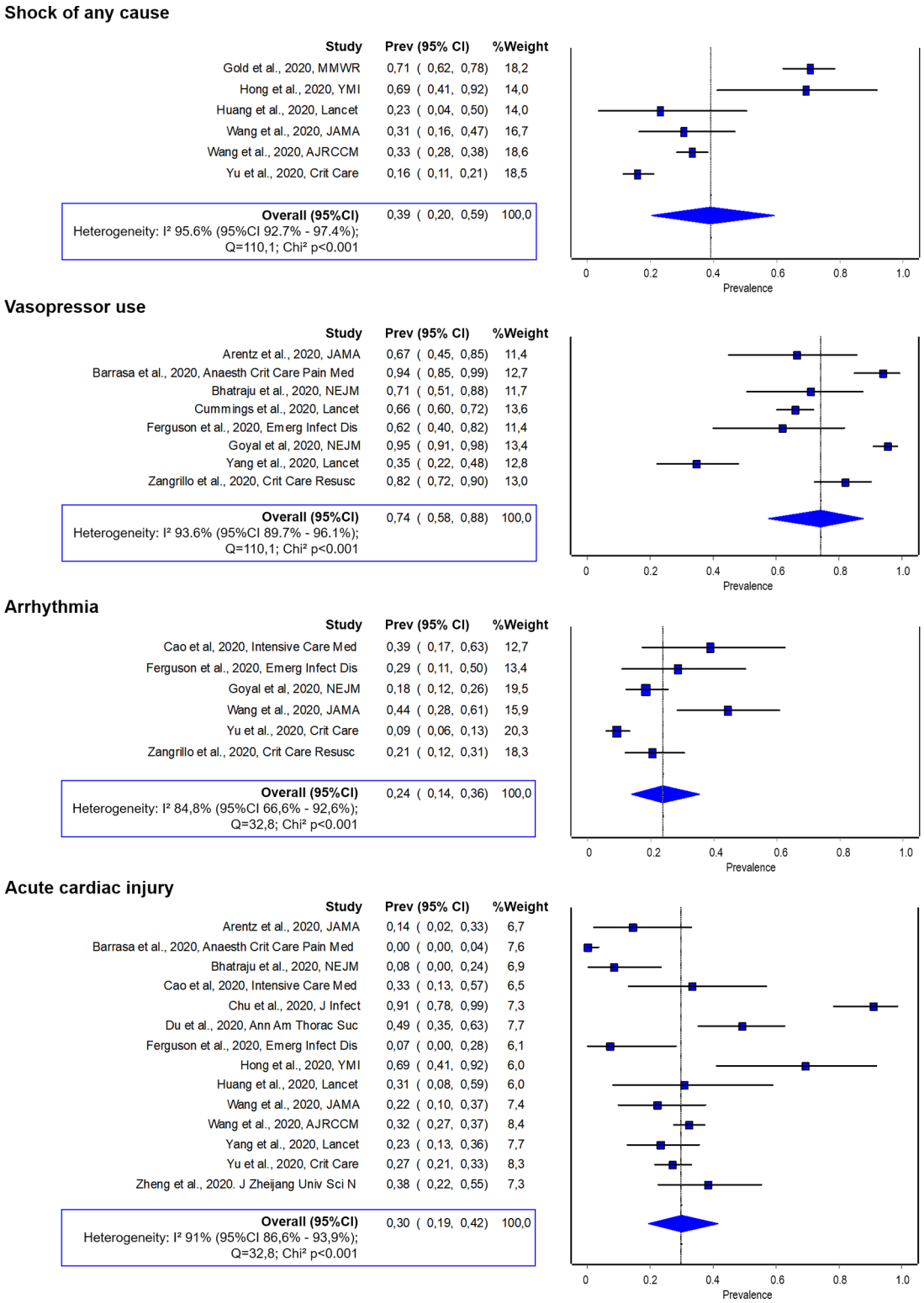

Figure 3. Forrest plots of pooled prevalence values for cardiovascular complications and therapy during ICU therapy.

and adaptive immune systems,[53] which in turn decreases vascular resistance, requiring vasopressors and leading to hemodynamic instability. However, we miss prospective studies using extended hemodynamic monitoring to proof that the loss of arterial vascular tone or other reasons lead to COVID-19-induced shock. Another explanation is that COVID-19 can be accompanied by bacterial superinfection with septic shock. However, no bacterial pathogen grew in blood cultures and sputum samples in a small observational study in critically ill individuals, which does not support septic shock as a cause.[16]

Cardiac injury was more prevalent in China than in the USA/Europe; the pooled prevalence of cardiac injury was

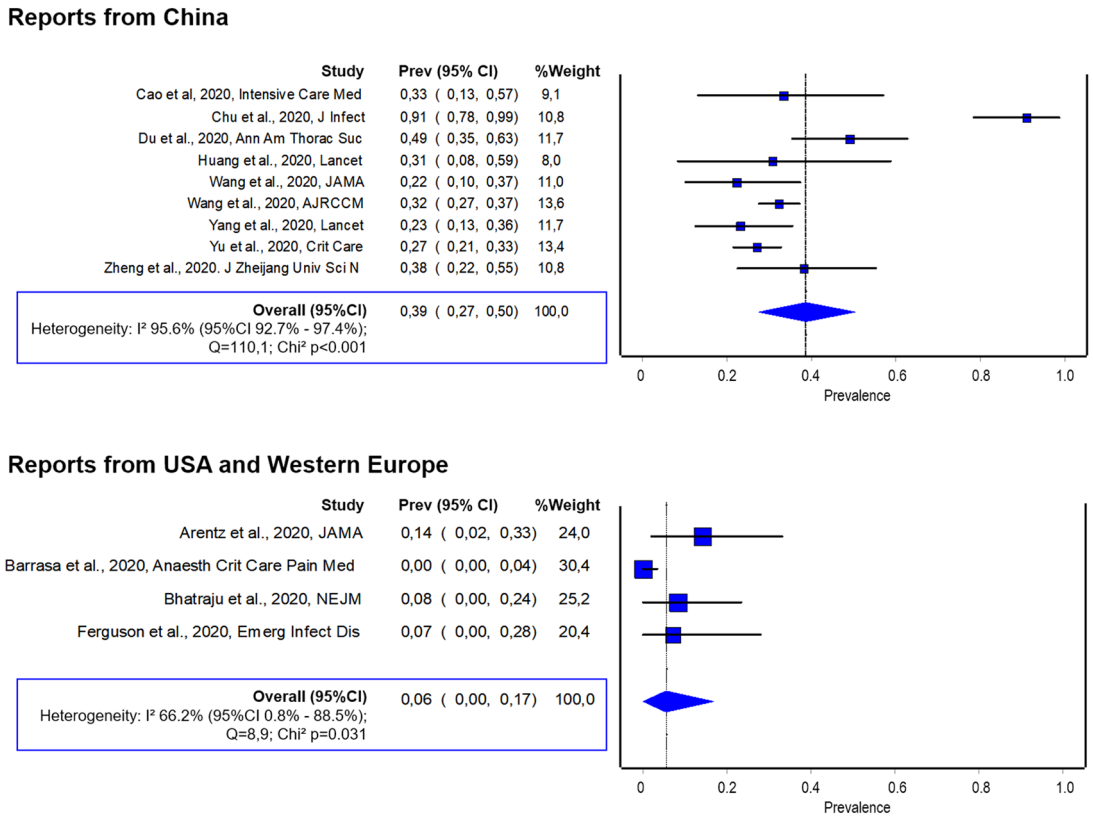

Figure 4. Forrest plots of pooled prevalence values for subgroup analyses of cardiovascular injury by country.

30%, most often determined by an increase in cardiac injury markers, such as an increase in troponin or creatine kinase.[54] Decreased cardiac function could also contribute to the development of vasopressor need and shock. However, a recent study on echocardiographic changes during COVID-19 found mainly changes in the RV systolic function with right ventricular dilatation.[55,56] Other reports found only a moderate increase in these markers.[57] Since the SARS-CoV-2 receptor ACE-2 is expressed in the heart, infection could lead to viral myocarditis, which could explain cardiac injury. However, in a case report using cardiac biopsies the authors found only low-grade myocardial inflammation and an absence of myocyte necrosis,[58] a phenomenon often present in severe systemic inflammation. Myocardial ischemia could also contribute to cardiac injury in these patients based on coronary artery disease (CAD). Nineteen percent of patients admitted to the ICU had pre-existing CAD, which, in part, explains the increase in cardiac injury, since the loss of peripheral vascular resistance during shock could lead to a supply-and-demand myocardial ischemia.

We found that the pooled prevalence of arrhythmias during ICU therapy was 24%, which is higher than that found in early, single-center reports on COVID-19. Here, the authors described arrhythmias in 16,7% of hospitalized patients.[32] In 1 report, the authors specified arrhythmias as "malignant" in 5.9% of patients.[7] Given the potential life-threatening nature of arrhythmias, this could contribute to ICU mortality when ICU staff are functioning in emergency mode during peak times of the epidemic because treatment might be delayed.

Fifty percent of patients admitted to the ICU suffered from arterial hypertension, whereas this value was only 15% for general hospitalized COVID-19 patients.[26] The reason why arterial hypertension increases the likelihood of detrimental outcomes in COVID-19 remains unclear. Thus, studies are required to determine whether arterial hypertension or the medication used for its treatment affects the clinical course of COVID-19.

Recent pathological investigations on the major pathophysiological changes induced by COVID-19 in adults found strong inflammation of the endothelium.[59] Clinically, this can lead to a Kawasaki-like disease, which is more pronounced in children with COVID-19.[60]

Our meta-analysis has several limitations. First, the results of the meta-analyses are limited by the quality of the included studies. Severe heterogeneity was present in all analyses, therefore, the results need to be compared and interpreted carefully. This also underlines the need for stringently designed studies. Currently, there is exponential growth in the number of publications on COVID-19 in the different databases (Supplemental Figure 1), yet the heterogenic nature of these studies limits the generalizability of the findings of the different reports. The search strings "covid-19" and "SARS-CoV-2" used in this meta-analysis might have missed very early studies on this disease that used namings like

"2019nCoV" or "novel corona." Another weak point in our analysis is that the included publications were not designed to study disease prevalence in different patient collectives. Data were extracted from the results of observational studies of patients admitted for COVID-19 treatment. Thus, a selection bias could be present, and the readers need to keep this in mind. Another factor is, that the different studies report results from all over the world. This inherently increases heterogeneity because there are differences in ICU infrastructure and staffing as well as differences in the reporting of the different comorbidities and complications. Furthermore, studies indicate that genetic factors might contribute to the severity of COVID-19.[61] In addition, most patient collectives were of retrospective nature. For this reason, we reported prevalence alone in this meta-analysis rather than investigating outcomes (such ICU mortality related to the different complications). All these limitations strongly underline that we need well-designed prospective observational trials to obtain a concise overview of cardiovascular comorbidities and complications in ICU patients to reduce the unacceptably high ICU mortality of COVID-19.

Despite these limitations, this systematic review and meta-analysis provides a comprehensive overview of cardiovascular diseases and complications in critically ill COVID-19 patients. These results help researchers and clinicians to better understand observations at the bedside and, at the same time, call for a careful comparison of different studies.

In conclusion, cardiovascular comorbidities and complications are common in critically ill COVID-19 patients. Thus, the ICU care team needs to prepare for hemodynamically unstable COVID-19 patients.

Take-Home Message

Fifty percent of ICU-treated COVID-19 patients have arterial hypertension as a pre-existing cardiovascular disease, and almost 40% of patients develop shock of different etiologies in response to COVID-19.

A 140-Character Tweet

COVID-19 leads to vasopressor demand in 74% and subsequent shock in almost 40% of patients in the ICU.

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Author Contributions

MK and HM developed the concept of the meta-analysis and performed the literature search, study screening, data extraction, data analysis, and data interpretation. MK and HM drafted the manuscript. PR performed data interpretation and critical revision of the manuscript. All authors approved the final manuscript.

Availability of Data and Material

All data can be shared by the authors upon a reasonable request.

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Supplemental Material

Supplemental material for this article is available online.

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