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Effect of SARS-CoV-2 infection on out-of-hospital cardiac arrest outcomes – systematic review and meta-analysis

Artur Krawczyk[1,A-F], **Lukasz Szarpak**[2,3,B-C,E-F], **Nicola Luigi Bragazzi**[4,C,E-F], **Basar Cander**[5,C,E-F], **Stepan Feduniw**[6,E-F], **Michal Pruc**[7,1,B,D,F], **Jarogniew Luszczki**[8,E-F], **Jaroslaw Chmielewski**[9,E-F], **Michal Kowalczyk**[10,E-F]

[1] *Polish Society of Disaster Medicine, Warsaw, Poland*
[2] *Baylor College of Medicine, Houston, United States*
[3] *Maria Sklodowska-Curie Medical Academy, Warsaw, Poland*
[4] *York University, Toronto, ON, Canada*
[5] *Bezmialem Vakif University, Fatih/Istanbul, Turkey*
[6] *University Zürich, Zürich, Switzerland*
[7] *International Academy of Ecology and Medicine, Kyiv, Ukraine*
[8] *Institute of Rural Health, Lublin, Poland*
[9] *Institute of Environmental Protection – National Research Institute, Warsaw, Poland*
[10] *Medical University, Lublin, Poland*
A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of the article

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Abstract
Introduction and Objective. The COVID-19 pandemic caused by the SARS-CoV-2 virus has recently presented the world with an unprecedented challenge. The purpose of this systematic review and meta-analysis is to investigate the relationship between SARS-CoV-2 infection and out-of-hospital cardiac arrest (OHCA) by comparing data from infected and non-infected individuals. The study adds to our understanding of the broader effects of the pandemic on public health and emergency care by examining the influence of COVID-19 on OHCA.
Materials and method. A comprehensive systematic literature search was performed using PubMed, EMBASE, Scopus, Web of Science, the Cochrane Library and Google Scholar from 1 January 2020 – 24 May 2023. Incidence rates and odds ratios (ORs) or mean differences (MDs) with 95% confidence intervals (CIs) for risk factors were recorded from individual studies, and random-effects inverse variance modelling used to generate pooled estimates.
Results. Six studies, involving 5,523 patients, met the criteria for inclusion in the meta-analysis. Survival to hospital admission, defined as admission to the emergency department with sustained return of spontaneous circulation (ROSC), among patients with and without on-going infection was 12.2% and 20.1%, respectively (p=0.09). Survival to hospital discharge/30-day survival rate was 0.8% vs. 6.2% (p<0.001). Two studies reported survival to hospital discharge in good neurological condition; however, the difference was not statistically significant (2.1% vs. 1.8%; p=0.37).
Conclusions. Compared to the non-infected patients, the ongoing SARS-CoV-2 infection was associated with worse OHCA outcomes.

Key words
out-of-hospital cardiac arrest, OHCA, COVID-19, SARS-CoV-2, infection, outcomes, survival rate

Abbreviations
ACLS: advanced cardiovascular life support; **ARDS:** acute respiratory distress syndrome; **CI:** confidence interval; **CPC:** Cerebral Performance Categories; **CPR:** cardiopulmonary resuscitation; **CVD:** cardiovascular disease; **EMS:** emergency medical service; **IHCA:** in-hospital cardiac arrest; **MD:** mean difference; **NOS:** Newcastle Ottawa Scale; **OHCA:** out-of-hospital cardiac arrest; **OR:** odds ratio; **ROSC:** return of spontaneous circulation; **PPE:** personal protective equipment; **PRISMA:** preferred reporting items for systematic reviews and meta-analysis; **SARS-CoV-2:** severe acute respiratory syndrome coronavirus 2; **SHA:** survival to hospital admission; **SHD:** survival to hospital discharge; **VTE:** venous thromboembolism

INTRODUCTION

In recent years, the world has faced the unprecedented challenge of the coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1, 2]. COVID-19 has emerged as a significant contributor to morbidity and death rates worldwide [3, 4]. At first, it was thought that COVID-19 was an acute respiratory distress syndrome (ARDS) [5]. However, it has now become apparent that COVID-19 is, in fact, a disease that affects a variety of organs. The illness is characterized by a cytokine storm which leads to endothelial

✉ Address for correspondence: Lukasz Szarpak, Baylor College of Medicine, Houston, TX, United States
E-mail: lukasz.szarpak@gmail.com

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inflammation and dysfunction [6–11]. It also leads to microvascular and macrovascular thrombosis, both of which have the potential to cause damage to organs other than the lung [12–15]. Even after making a full recovery from the acute illness, patients who had been exposed to COVID-19 had a greater chance of experiencing unfavourable cardiovascular outcomes, according to a number of studies [16–18]. The high COVID-19 exposure rate among the general population suggests that these studies may portend an important and urgent public health crisis.

One area of concern is the impact of the SARS-CoV-2 infection on its potential influence on out-of-hospital cardiac arrest (OHCA) outcomes [19]. OHCA refers to a sudden loss of circulation outside a medical facility and represents a significant cause of mortality, with an average incidence of 55 per 100,000 person-years among adults worldwide [20]. According to an analysis by the International Liaison Committee on Resuscitation, the number of OHCAs that were treated by emergency medical services (EMS) and bystander cardiopulmonary resuscitation (CPR) progressively increased [21, 22]. Prompt intervention in the form of and defibrillation is crucial for successful resuscitation. Rapid response times by emergency medical service personnel, coupled with the delivery of high-quality CPR, have been shown to enhance survival rates. Moreover, the presence of bystander CPR can effectively double the chances of survival from OHCA [23].

The COVID-19 pandemic has had a significant influence on the outcomes of OHCA [24–28]. The pandemic may indirectly impact OHCA by affecting the community's and EMS agencies' capacity to respond effectively to such emergencies [29]. Evidence suggests that individuals may be avoiding calling emergency services or seeking medical attention for symptoms such as chest discomfort or shortness of breath during this period [30, 31]. Fear of contagion and concerns about transmission may discourage bystander involvement in community responses to OHCA [32, 33]. Previous studies demonstrate lower rates of bystander cardiopulmonary resuscitation and public AED usage, which corresponds to lower rates of sustained return of spontaneous circulation (ROSC), lower survival to hospital discharge, and in general, a higher incidence of OHCA during the COVID-19 pandemic compared to prior years [32, 34]. Furthermore, EMS agencies have implemented rigorous screening protocols for potential COVID-19 symptoms or known infections in all EMS calls, and new processes have been introduced to ensure that first responders have access to appropriate personal protective equipment (PPE), thereby maximizing their safety during interventions [35, 36].

The purpose of this systematic review and meta-analysis was to investigate the correlation between SARS-CoV-2 infection and OHCA by comparing the OHCA data of patients who were infected with SARS-CoV-2 and non-infected patients.

MATERIALS AND METHOD

Study design and registration. The meta-analysis was performed in agreement with the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement, and is registered in the International Prospective Register of Systematic Reviews database (PROSPERO) (CRD42023428473). There were no amendments or protocol deviations.

Eligibility criteria. Studies reporting comparative OHCA data among SARS-CoV-2 infected and non-infected patients within the same location were included. Exclusions included (a) articles other than original research articles (i.e., review articles, letters, editorials, conference papers), (b) case reports, (c) non-English, non-Polish, or non-Spanish language articles, and (d) articles relating to paediatric populations (age of 17 years of age or younger).

Data sources and search strategy. Two authors (AK and MP) independently searched PubMed, EMBASE, Scopus, Web of Science, and the Cochrane Library of Systematic Reviews databases from 1 January 2020 – 24 May 2022. For this purpose, combinations were used of the key words: 'out-of-hospital cardiac arrest', 'OHCA', 'cardiac arrest', 'out of hospital cardiac arrest', 'heart arrest', 'cardiopulmonary arrest', 'sudden cardiac death' 'severe acute respiratory syndrome coronavirus 2', 'SARS-CoV-', 'COVID-19', 'nCOV', and 'novel coronavirus'. Further surveillance searches were conducted using the related articles feature, and an extensive search undertaken of the unpublished literature, including the reference lists of all included studies and existing traditional systematic reviews, as well as grey literature (Google Scholar) on the impact of SARS-CoV-2 infection on OHCA outcomes. Duplicate results were removed. The remaining articles were independently screened by two authors (AK and MP) for the relevance of their abstracts. The full text of the remaining articles was assessed by applying the inclusion and exclusion criteria.

Data extraction. Two of the authors (AK and MP) independently extracted data. Disagreements were resolved consensus achieved through discussion with all authors. Standardized extraction forms were used that included: study parameters (i.e., author, country of origin, year, study design, age, gender); resuscitation parameters (i.e., witnessed cardiac arrest, bystander witnessed, bystander cardiopulmonary resuscitation (CPR), emergency medical service (EMS) arrival time, bystander defibrillation, advanced cardiovascular life support (ACLS) initiation, adrenaline and amiodarone administration); outcomes (return of spontaneous circulation, survival to hospital admission, survival to hospital discharge (SHD), SHD with favourable neurological outcome, overall mortality). Where the data were incomplete, corresponding authors were contacted for additional information.

The primary endpoint of the study was survival to hospital discharge, or the 30-day survival rate. Secondary outcomes were: survival to hospital admission, defined as admission to the emergency department with sustained ROSC; and survival to hospital discharge with a good neurological outcome assessed as Cerebral Performance Categories (CPC) score 1 or 2.

Risk-of-bias assessment. The quality and risk of bias assessments of the included studies were performed using the Newcastle-Ottawa Scale (NOS). This scale is based on an eight-item score divided into three domains. These domains assess selection, comparability, and ascertainment of the outcome of interest. The quality assessment of articles ranges from low scores (0–4) to moderate scores (5–6) to high scores (7–9), representing three different levels of study quality. NOS was used by two authors (AK and NLB) to independently evaluate the quality of the included studies and assess the risk of bias. The same set of decision rules was used by each reviewer to score the studies. Any discrepancies from the NOS were reviewed and resolved by discussion between all authors.

Statistical analysis and data synthesis. Statistical analyses were performed using Review Manager 5.4 (Nordic Cochrane Centre, Cochrane Collaboration) and STATA 16.0 (StataCorp LLC, Texas, USA). The incidence of dichotomous data was calculated using the odds ratio (OR) with a 95% CI and analyzed using the Mantel-Haenszel technique. The mean difference (MD) with a 95% confidence interval (CI) was used to represent continuous outcomes. To enable an analysis of results between studies, median values were converted to means, derived using a Hozo formula. The heterogeneity in the included studies was assessed using Cochran's Q chi-square and I^2 statistical analyses. The Higgin's I^2-indices of 0–25, 26–75%, and 75–100% indicate low, moderate, and high heterogeneity levels between studies, respectively [37]. Random effect models were used regardless of heterogeneity. The p-values were two-tailed, and statistical significance was set at 0.05. To assess the small-study effect, a regression-based Egger's test was performed. Due to the small number of investigations (n = 10), a funnel plot was not performed. A sensitivity analysis using leave-one-out was performed to test the robustness of the findings.

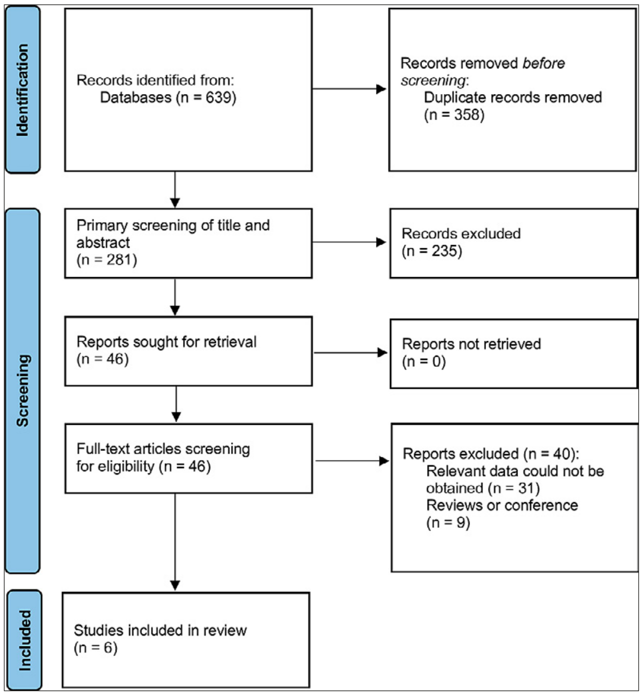

Figure 1. Flow diagram of search strategy and study selection

RESULTS

Study selection. A total of 639 studies were identified from the database search. Of these, 358 duplicate studies were removed; 235 studies were excluded after title and abstract screening, and 40 were excluded following full text screening based on the set inclusion criteria. Finally, six studies [38–43], involving 5,523 patients, met the criteria for inclusion in the meta-analysis. Figure 1 illustrates the study flow diagram. The studies were performed in France, Italy, Spain, Sweden, the United Kingdom, and the Republic of Korea, from 2020 – 2021. Their overall quality was excellent, with two studies scoring 9/9 on the NOS and the remaining four studies scoring 8/9 (**Tab. 1**).

Study characteristics. A total of 5,523 OHCA patients with comparative data segregating SARS-CoV-2 positive versus SARS-CoV-2 negative status were assessed in the six observational studies included in the meta-analysis (Tab. 1). Of those patients, 23.0% (1,273/5,523) occurred during the ongoing SARS-CoV-2 infection, and 77.0% (4,250/5,523) had negative tests for SARS-CoV-2. The mean age of patients with and without ongoing infection was 70.0±16.6 vs. 71.2±16.6 years (p=0.13). Cardiac arrest in patients with ongoing infection was more likely to occur at home than in patients without infection (94.8% vs. 89.1%, respectively (p<0.001). A detailed characterization of the etiology of cardiac arrest, the presence of witnesses and their undertaking of basic life-saving measures, as well as the specifics of the advanced resuscitation procedures performed by EMS, is presented in Table 2.

Outcomes. Survival to hospital admission, defined as admission to the emergency department with sustained ROSC, was reported in all studies. Pooled analysis of SHA among patients with and without ongoing infection was 12.2% and 20.1%, respectively (OR = 0.66; 95%CI: 0.40 to 1.07; p=0.09) (Fig. 2).

In contrast, the survival to hospital discharge/30-day survival rate was reported in five studies (0.8% vs. 6.2%) between patients with and without ongoing SARS-CoV-2

Table 1. Baseline characteristics of included trials

Study	Country	Study design	COVID-19 patients			Non-COVID-19 patients			NOS score
			No.	Age	Female gender	No.	Age	Female gender	
Baert et al., 2020	France	Multi-centre longitudinal prospective registry	197	67 ± 18	80 (40.6%)	808	69 ± 16	249 (30.8%)	9
Baldi et al., 2020	Italy	Multi-centre longitudinal prospective registry	125	76.98 ± 2.25	42 (33.6%)	365	76.75 ± 2.83	127 (34.8%)	9
Cho et al., 2020	Republic of Korea	retrospective observational study	10	73.3 ± 4.3	6 (60.0%)	161	72.3 ± 3.2	57 (35.4%)	8
Fothergill et al., 2021	UK	retrospective, observational study	766	70 ± 18	298 (38.9%)	2356	71 ± 19	985 (41.8%)	8
Navalpotro-Pascual et al., 2021	Spain	observational, prospective study	87	70 ± 2.7	33 (37.9%)	226	72.5 ± 3.3	91 (40.3%)	8
Sultanian et al., 2021	Sweden	observational registry-based study	88	66.5 ± 18.4	29 (32.9%)	334	70.6 ± 16.4	93 (27.8%)	8

Table 2. Pooled analysis of patients and resuscitation characteristics

Parameter	No. of studies	Event / Participants or Mean ± SD		Events		Heterogeneity between trials		p-Value for differences across groups
		Ongoing infection	No infection	OR or MD	95%CI	p-Value	I2 statistics	
Age	6	70.0 (16.6)	71.2 (16.6)	-1.18	-2.72 to 0.36	<0.001	88%	0.13
Female gender	6	488/1273 (38.4%)	1602/4250 (37.7%)	1.11	0.86 to 1.44	0.03	59%	0.42
Home location of CA	5	1020/1076 (94.8%)	3066/3442 (89.1%)	2.01	1.50 to 2.70	0.75	0%	<0.001
Time to EMS arrival	6	14.4 (10.4)	12.9 (9.1)	0.97	0.00 to 1.94	<0.001	96%	0.05
Medical aetiology of CA	5	799/840 (95.1%)	2195/2356 (93.1%)	2.77	0.41 to 18.61	<0.001	84%	0.29
Whitnessed arrest	5	459/703 (65.3%)	1181/1828 (64.6%)	1.00	0.83 to 1.21	0.43	0%	0.98
Bystander whitnessed	4	418/803 (52.1%)	1202/2249 (53.4%)	0.98	0.83 to 1.16	0.51	0%	0.80
Shockable rhythm	6	172/860 (20.0%)	526/2493 (21.1%)	0.75	0.45 to 1.24	0.01	66%	0.26
Bystander CPR	5	418/813 (51.4%)	1183/2410 (49.1%)	0.88	0.63 to 1.22	0.04	60%	0.43
Defibrillation during ALS	2	100/582 (17.2%)	390/1076 (36.2%)	0.37	0.25 to 0.56	0.18	45%	<0.001
Adrenaline given	3	465/569 (81.7%)	977/1302 (75.0%)	1.29	0.59 to 2.82	0.001	86%	0.52
Amiodarone given	2	6/176 (3.4%)	56/560 (10.0%)	0.35	0.15 to 0.85	0.38	0%	0.02
Mechanical chest compression	2	9/98 (9.2%)	134/387 (34.6%)	0.67	0.23 to 1.91	0.89	0%	0.45

CA - cardiac arrest; CI - confidence interval; CPR - cardiopulmonary resuscitation; MD - mean difference; OR odds ratio

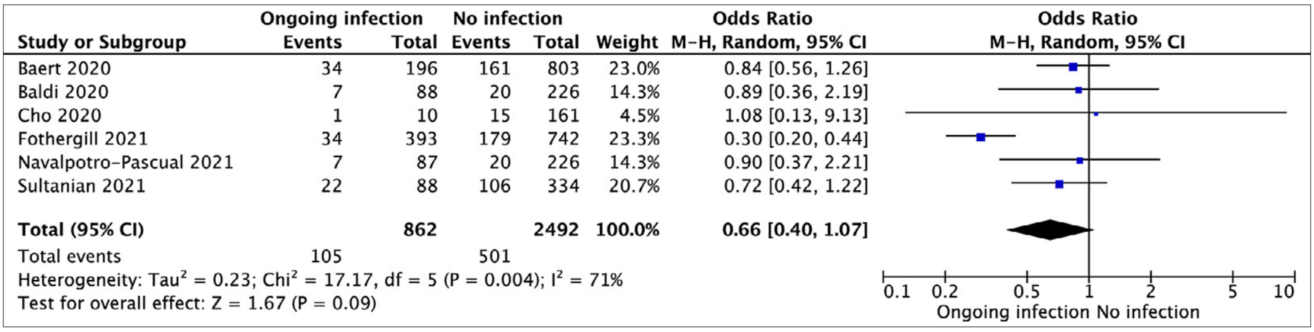

Figure 2. Forest plot of survival to hospital admission among patients with and without ongoing SARS-CoV-2 infection. The centre of each square represents the odds ratio for individual trials, and the corresponding horizontal line stands for a 95% confidence interval. The diamonds represent pooled results.
CI – confidence interval; OR – odds ratio

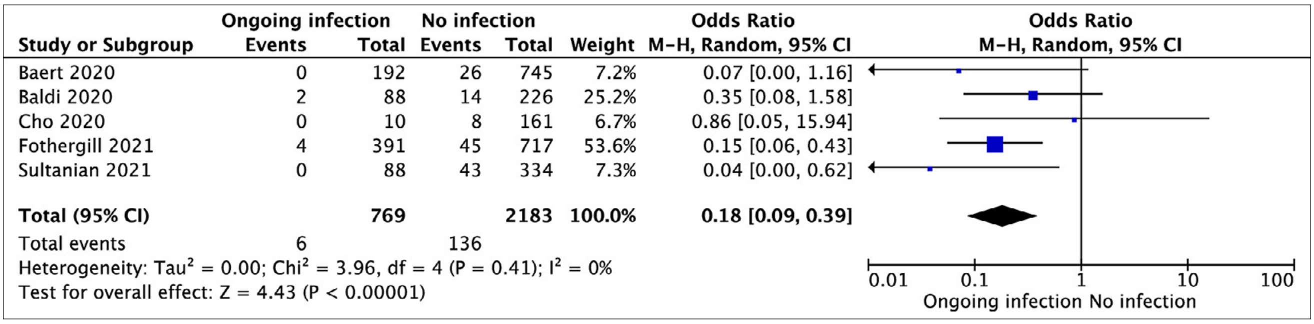

Figure 3. Forest plot of survival to hospital discharge or 30-day survival rate patients with and without ongoing SARS-CoV-2 infection. The center of each square represents the odds ratio for individual trials, and the corresponding horizontal line stands for a 95% confidence interval. The diamonds represent pooled results.
CI – confidence interval; OR – odds ratio

infection, respectively (OR = 0.18; 95%CI: 0.09 to 0.39; p<0.001) (Fig. 3).

Only two studies reported survival to hospital discharge in good neurological condition; however, the difference between patients with and without ongoing SARS-CoV-2 infection was not statistically significant (2.1% vs. 1.8%; OR = 2.12; 95%CI: 0.41 – 10.97; p=0.37).

DISCUSSION

The findings of the current study show that infection with COVID-19 had a detrimental influence on all the indicators examined, with the exception of surviving hospital discharge in a good neurological condition. Survival to hospital admission was 12.2% and 20.1%, respectively, for patients with and without persistent infection. Survival to hospital discharge or 30-day survival rates were 0.8% and 6.2%, respectively, while survival to hospital discharge in good neurological condition was not statistically significant.

There are many studies, including meta-analyses, that address the effect of the pandemic on out-of-hospital cardiac arrest, as well as in-hospital cardiac arrest, in both the adult and paediatric patient populations [24, 27, 44–47]. However, the presented meta-analysis demonstrated the influence of ongoing SARS-CoV-2 infection on out-of-hospital cardiac arrest outcomes.

From the beginning of the pandemic, the prevalence of OHCA increased grew in many parts of the world. Regarding differences in OHCA outcomes between the pandemic and pre-pandemic periods, Scquizzato et al. [44] in their meta-analysis indicate the COVID-19 pandemic affected the system of care for out-of-hospital cardiac arrest, and patients had worse short-term outcomes compared to the pre-pandemic period. Similar conclusions were reached by Teoh et al. [46] and Lim et al. [47], as well as other authors [19]. COVID-19 has had a significant and diverse impact on out-of-hospital cardiac arrest (OHCA). The COVID-19 pandemic has generated a unique set of issues for emergency medical services (EMS) and healthcare systems around the world, influencing the management, outcomes and overall care of OHCA patients [1, 48]. This can be rooted in many factors.

The potential for delayed recognition and response to cardiac arrest situations is one notable impact of COVID-19 on OHCA. The pandemic has intensified the strain on healthcare systems, with resources being diverted to COVID-19 management [1, 48]. The typical processes of EMS providers, emergency rooms, and hospitals have been significantly strained and disrupted [49–51]. This strain, combined with the constraints of PPE utilization and infection control measures, may result in delays in recognizing OHCA cases and commencing prompt resuscitation efforts [52].

A significant decline in bystander reaction rates and the beginning of cardiopulmonary resuscitation (CPR) for OHCA occurred during the pandemic [53]. Bystanders were hesitant to provide CPR due to fear of contracting COVID-19, ambiguity about virus transmission, and worries about performing mouth-to-mouth resuscitation [54, 55]. Furthermore, constraints on in-person CPR training courses and public health policies hampered the acquisition by general population of critical CPR skills and knowledge. These reasons have all contributed to a decline in bystander CPR rates, which could have had a substantial impact on OHCA survival results [56].

The COVID-19 pandemic placed a burden on EMS systems and hospital capacity, potentially disrupting the continuum of care for OHCA patients [57, 58]. EMS providers experienced difficulties maintaining response times, ensuring appropriate ambulance and personnel availability, and managing the increased demand for COVID-19-related crises. Hospital capacities were exceeded in many regions which caused delays in the transfer and admission of OHCA patients, as well as constraints in the availability of critical care services, such as intensive care unit (ICU) beds and specialized cardiac care [59, 60].

Even post-resuscitation care (PRC) is critical in determining the neurological outcomes and overall prognosis of OHCA patients [61, 62]. In contrast, the COVID-19 pandemic has added significant complexity and considerations to providing effective post-resuscitation care. Individuals who attain ROSC following OHCA may have a concurrent COVID-19 infection, necessitating specific infection control measures and treatment protocol adjustments in some cases [62]. To suggest appropriate therapy strategies, more study on the potential links between COVID-19 and post-cardiac arrest syndrome (PCAS), such as systemic inflammation, coagulopathy, and multi-organ failure, is required.

However, in the pandemic, changes were made to health care systems as well as to the delivery of CPR itself. Hence, in the opinion of the authors of the present review, it was important to compare OHCA patients with respect to a single period – that is, the COVID-19 pandemic period.

When assessing the impact of SARS-CoV-2 infection on OHCA survival, it is critical to remember the direct influence of the virus on the human body. Elevated cardiac biomarkers and imaging data indicate that SARS-CoV-2 infection causes myocardial injury [63, 64]. Direct viral invasion of cardiac cells, systemic inflammation, endothelial dysfunction, micro-vascular thrombosis, and immunological destruction are all possible mechanisms underlying myocardial injury. Myocardial injury may contribute to cardiac dysfunction, arrhythmias, and unfavourable cardiac events, thereby influencing the outcome of a cardiac arrest [65–69]. Furthermore, COVID-19 patients may have cardiac arrhythmias, such as atrial fibrillation, ventricular arrhythmias, and conduction abnormalities. These arrhythmias can increase the risk of cardiac arrest and lead to haemodynamic instability [70, 71]. Understanding the underlying mechanisms, risk factors, and suitable therapeutic techniques for arrhythmias in COVID-19 patients is critical for mitigating negative consequences.

Patients with COVID-19 are also at an elevated risk of venous thromboembolism (VTE) or microvascular thrombosis [72–74]. VTE, including deep vein thrombosis and pulmonary embolism, is more common in patients with COVID-19. This elevated risk is due to systemic inflammation, endothelial dysfunction, platelet activation, and hypercoagulability caused by the SARS-CoV-2 infection [15]. Prompt diagnosis, risk classification, and execution of effective thromboprophylaxis methods are critical for lowering CVD incidence and its impact on cardiac arrest outcomes. According to emerging research, SARS-CoV-2 infection can cause microvascular thrombosis, particularly in the pulmonary vasculature. Microvascular thrombus formation in the lungs may contribute to impeded gas exchange, aggravated hypoxaemia, and the development of ARDS, negatively impacting the prognosis of cardiac arrest patients [75, 76].

Given these effects of SARS-CoV-2 on the body, it is not surprising that the chances of sustained ROSC in OHCA patients are reduced, and thus also the chances of survival to hospital discharge.

Limitations. It is worth noting that the limited number of studies providing data on neurological outcomes in the context of ongoing infection indicates a need for further research in this area. Future investigations should aim to explore the impact of ongoing infection, including SARS-CoV-2 infection, on the neurological condition of patients after hospital discharge. This gap in our knowledge presents an opportunity for researchers and healthcare professionals to collaborate.

CONCLUSION

Compared to the non-infected patients, the SARS-CoV-2 infection was associated with worse OHCA outcomes.

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