



Uncovering the effects of COVID-19 on in-hospital cardiac arrest – a living systematic review and meta-analysis

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Abstract

Introduction and Objective. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused a global pandemic and had a negative impact on the entire health care system. To understand the effect of COVID-19 on outcomes of in-hospital cardiac arrest (IHCA), a systematic review and meta-analysis of studies was designed to compare the pre- and intra-pandemic periods of adult patients who suffered cardiac arrest, and additionally by performing a sub-analysis related to COVID-19 positive vs. negative patients in the same group of patients.

Materials and method. To evaluate the impact of COVID-19 on IHCA outcomes a systematic review and meta-analysis was performed. Pubmed (MEDLINE), Scopus, Embase, Web of Science, and Cochrane database were searched for articles published from 1 January 2020 – 8 April 2023.

Results. Return of spontaneous circulation events among IHCA patients in pre-COVID-19 and COVID-19 pandemic periods varied and amounted to 64.0% vs. 60.0%, respectively (OR=1.23; 95%CI: 1.19 to 1.26; p<0.001). Re-arrest occurrence was 4.5% vs. 4.9%, respectively (OR=1.24; 95%CI: 1.00 to 1.53; p=0.05). Survival to hospital discharge (SHD) was 25.1% compared to 20.9% for COVID-19 period (OR = 1.17; 95%CI: 0.96 to 1.41; p=0.12). During the COVID-19 period, SHD in COVID-19 positive patients was 14.0% compared to 25.9% for patients without COVID-19 (OR=0.72; 95%CI: 0.28 to 1.86; p=0.50). 30-day survival rate among COVID-19 positive vs. negative patients was 62.6% vs. 58.3%, respectively (OR = 0.99; 95%CI: 0.23 to 4.24; p=0.99).

Conclusions. Patients with SARS-CoV-2 infection had reduced rates of ROSC and SDH, as well as poorer neurologic outcomes and increased in hospital re-arrests during the COVID-19 period. However, the 30-day survival rate was similar in SARS-CoV-2 positive and negative patients.

Key words

outcome, survival rate, in-hospital cardiac arrest, COVID-19, SARS-CoV-2, IHCA

Abbreviations

CI – Confidence interval; IHCA – In-hospital cardiac arrest; MD – Mean difference; NOS – Newcastle Ottawa Scale; OR – Odds ratio; PEA – Pulseless electrical activity; PCR – polymerase chain reaction; ROSC – Return of spontaneous circulation; PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-analysis; SHD – Survival to hospital discharge

INTRODUCTION

The COVID-19 pandemic affected over 663 million patients worldwide and resulted in at least 6 million deaths. Accurately assessing the number of infected patients and pandemic-related deaths is challenging due to unreliable data during the initial stages of the pandemic when SARS-CoV-2 tests were not widely accessible [1–3]. Furthermore, in many countries,

COVID-19 has become a subject of significant political debate, leading to unreliable reporting of pandemic-related morbidity and mortality [4–6]. Nevertheless, an objective approach to reducing bias and estimating the actual number of pandemic-related deaths involves comparing mortality rates between the pre- and intra-pandemic periods [7, 8].

In-hospital cardiac arrest (IHCA) is associated with a high mortality rate and the risk of permanent damage to neurological function [3, 9], despite advances in training, technology, and guidelines. Sudden cardiac arrest is associated with serious disturbances in blood flow and metabolism, depending on its duration, causative causes, and

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comorbidities [10–15]. In recent decades, IHCA outcomes have steadily improved due to improvements in training, equipment availability, and the overall quality of medical care [16]. Of particular note is the creation of rapid response teams and the implementation of early warning systems which, in some managed care systems, have reduced the number of cases of sudden in-hospital cardiac arrest by half (cite).

In-hospital cardiac arrest (IHCA) accounts for most deaths while patients are hospitalized [17, 18]. Survival after an IHCA incident depends on several factors, including the quality and timing of the initiation of resuscitation efforts, comorbidities, the resuscitation setting (e.g., intensive care unit vs. general floor), and the initial cardiac rhythm. In both IHCA and out-of-hospital cardiac arrest, ventricular fibrillation treated with rapid defibrillation is associated with much higher patient survival than non-shockable rhythms.

COVID-19 has affected many of the factors that influence a positive resuscitation outcome: 1) the volume of patients strained the healthcare system, so that critically ill patients were placed in non-critical beds, which may have affected the initiation of resuscitation and available equipment, 2) the availability of protective equipment and the use of cumbersome equipment negatively impacted the quality of resuscitative efforts, 3) hypoxia caused pulseless electrical activity (PEA) [19–21].

To understand the effect of COVID-19 on outcomes of IHCA, a systematic review and meta-analysis of studies was designed to compare the pre- and intra-pandemic periods of adult patients who suffered cardiac arrest, and additionally to perform a sub-analysis related to COVID-19 positive vs. negative patients in the same group of patients.

MATERIALS AND METHOD

The article was written as a systematic review and meta-analysis, and was accordingly reported to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement [19]. The study protocol was defined *a priori* and registered in the PROSPERO register – International Prospective Register of Systematic Reviews under No. CRD42022382141.

Data sources and searches. A comprehensive literature search of Pubmed (MEDLINE), Scopus, Embase, Web of Science, and Cochrane electronic databases was conducted interperdently by two reviewers (KB and MP for the identification of relevant entries dated until 8 April 2023. Any disagreements between reviewers were resolved by discussion with a third reviewer (LS). The key word string ‘in-hospital cardiac arrest’ or ‘IHCA’ and ‘COVID-19’ or ‘SARS-CoV-2’ or ‘ncov’ or ‘novel coronavirus’ was used. Reference lists and citing articles from included studies were also screened. For reports by the same author, only the latest or the most intact were used to avoid overlapping queues. Where articles referred to the same group of patients, the article with the largest number of patients was used, while the remaining articles used outcomes not included in the main study. All references were managed and duplicates removed in EndNote (ver. X9, Clarivate Analytic).

Study selection. The search was limited to studies:

- 1) comparing cardiac arrest outcomes in the pre- and during COVID-19 periods or during COVID-19 periods among

patients stratified by COVID-19 status (i.e., either positive vs negative);

- 2) evaluating the clinical outcomes of cardiac arrest;
- 3) with accessible and essential data;
- 4) studies published in English.

Studies that did not meet the following criteria were excluded:

- 1) did not report any of the pre-specified outcomes;
- 2) did not present a comparative group;
- 3) not published in English;
- 4) reviews, conference abstracts, paediatric patients, animal experiments, case reports or case series, or comments.

Data extraction. Two reviewers (KB and MP) screened the published studies by extracting data from each manuscript using a predetermined standardized data form. A third reviewer (LS) reassessed the literature if the preliminary conclusions were uncertain. The information extracted from the studies included the following:

- 1) first author and publication date, country of origin, study design;
- 2) type of participant group;
- 3) case number; age, male gender;
- 4) IHCA outcomes.

Outcomes. The primary outcome was defined as the incidence of return of spontaneous circulation (ROSC). Secondary outcomes included: survival to hospital discharge (SHD), 30-day survival rate, SHD with a good neurological outcome, defined as 1–2 points on the Cerebral Performance Categories (CPC) Scale, as well as cardiac arrest recurrence.

Assessment of study quality. Two reviewers (KB and MP) independently assessed the quality of the included studies. If there were any differences between the reviewers, they were resolved by discussion with a third reviewer (ZR). The risk of bias within an individual cohort study was determined using the Newcastle Ottawa Scale (NOS) [23]. NOS measures the quality of a study based on three aspects: selection, comparability, and exposure. The maximum scores for these three aspects were 4, 2 and 3 stars, respectively. Studies with NOS scores ≥ 7 were considered to be high-quality studies.

Statistical analysis. All statistical analyses were performed using RevMan (ver. 5.4; Cochrane Collaboration, Oxford, UK). The pooled prevalence was estimated using the Mantel-Haenszel method. The results are presented as forest plots using odds ratios (ORs) with 95% confidence intervals (CIs). For dichotomous data and the mean difference (MD) for continuous data, with 95% CI. When data were reported as median with interquartile range, estimated means and standard deviations using the formula described by Hozo, were used [24]. Heterogeneity between studies was assessed by the I^2 test and assessed as low, moderate, or high, when I^2 was $<50\%$, $50\text{--}75\%$, or $\geq 76\%$, respectively [25]. The random-effects model was used for $I^2 > 50\%$; otherwise, the fixed effect model was employed. Egger’s test and funnel plots were used to assess potential bias and perform funnel plot tests for asymmetry to investigate potential publication bias if there were more than ten trials in a single meta-analysis. A 2-sided test was conducted to calculate all P values, and a P value was considered statistically significant when it was less than 0.05.

RESULTS

Study selection. The outline of the study selection process is depicted in a PRISMA diagram (Fig. 1). A total of 1,021 studies were identified from the primary literature retrieval. Among them, 374 studies were excluded because of duplication. After

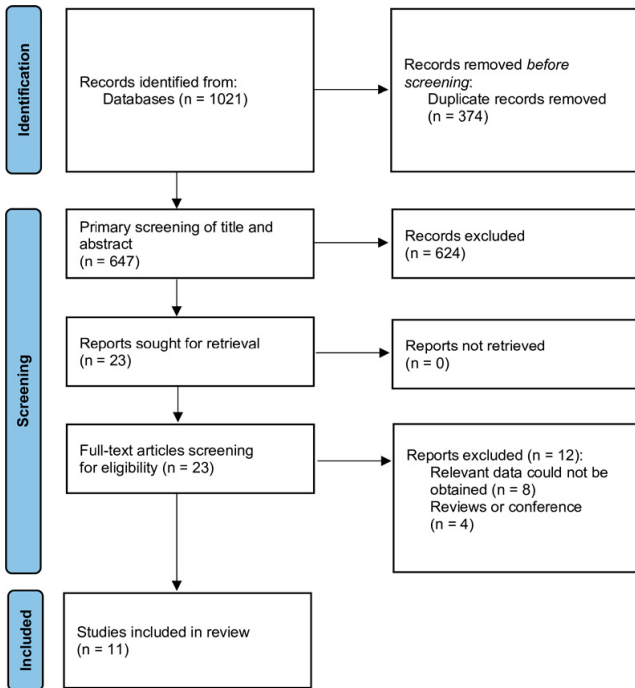


Figure 1. Flow diagram of the search strategy and study selection

reading the titles and abstracts, 624 irrelevant studies were also excluded. Of the remaining studies, another 23 were excluded because they were reviews, case reports, or not in English. Finally, the 11 included manuscripts [26–36] referring to 10 studies were included in the meta-analysis. Girotra et al. [28] and Gupta et al. [29] refer to the same population, however, Girotra et al. [28] analyze the IHCA for positive and negative COVID-19 pandemic patients, while Gupta et al. [29] compare the periods before and during the COVID-19 pandemic. Studies included in the meta-analysis were published between 2020 – 2022, and the countries included the USA, UK, Sweden, Singapore, Pakistan, Germany and China. Among those studies, eight reported IHCA outcomes between the pre-pandemic and COVID-19 pandemic periods (95,115 vs. 27,633 patients, respectively) [26, 27, 29, 32–35], and three studies during the COVID-19 period among SARS-CoV-2 positive vs. negative patients (6,225 vs. 20,401 patients, respectively) [28, 30, 34, 36]. The baseline characteristics are described in Table 1. The methodologic quality of the included trials was low, as summarized in Table 1.

Pre-COVID-19 vs. COVID-19 period meta-analysis. Seven studies reported ROSC among IHCA patients in pre-COVID-19 and COVID-19 pandemic periods. Pooled analysis showed that ROSC events among those periods varied and amounted to 64.0% vs. 60.0%, respectively (OR = 1.23; 95% CI: 1.19 to 1.26; $p < 0.001$) (Fig. 2).

In the pre-COVID-19 period, shockable rhythms occurred in 18.3% of cases during the first documented rhythm, compared to 16.1% during the COVID-19 pandemic period (OR = 1.30; 95% CI: 1.01 to 1.67; $p = 0.04$). Re-arrest occurrence was 4.5% vs. 4.9%, respectively (OR = 1.24; 95% CI: 1.00

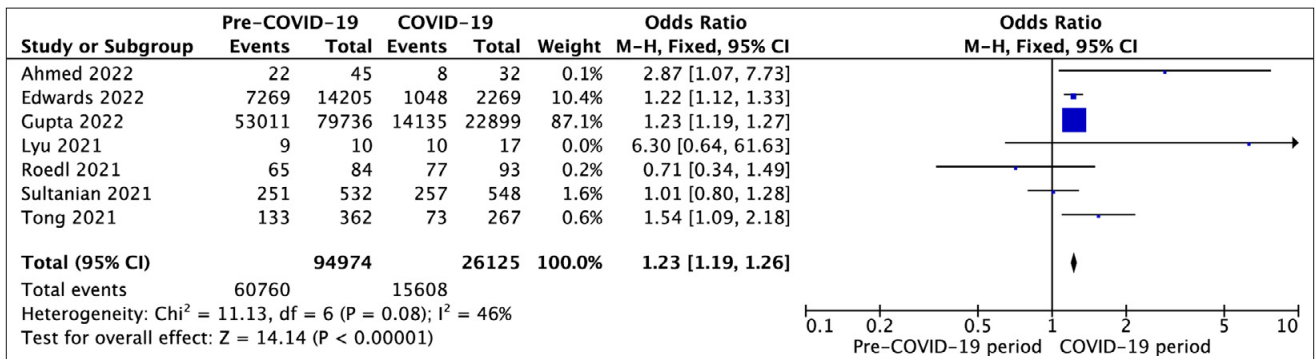


Figure 2. Forest plot of return of spontaneous circulation among patients with IHCA in pre-COVID-19 vs. COVID-19 periods. The center of each square represents the odds ratio for individual trials, and the corresponding horizontal line stands for a 95% confidence interval. The diamonds represent pooled results. CI – confidence interval; OR – odds ratio

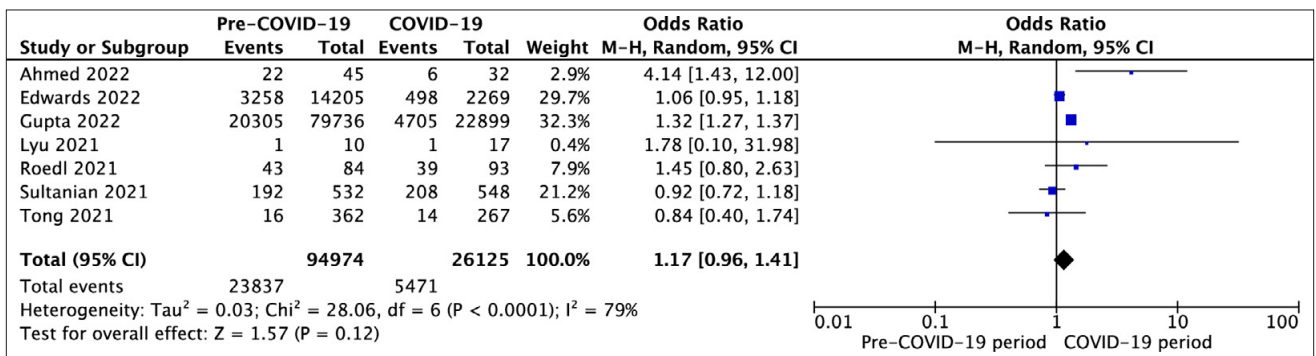


Figure 3. Forest plot of survival to hospital discharge among patients with IHCA in pre-COVID-19 vs. COVID-19 periods. The centre of each square represents the odds ratio for individual trials; the corresponding horizontal line stands for a 95% confidence interval. The diamonds represent pooled results. CI – confidence interval; OR – odds ratio

Table 1. Baseline characteristics of included trials

Study	Country	Study design	COVID-19 period										Score No.		
			Pre-COVID-19 period					COVID-19 period							
			No. of patients	Age	Gender, male	No. of patients	Age	Gender, male	No. of patients	Age	Gender, male	No. of patients			
Ahmed et al., 2022 [14]	Pakistan	Cross-sectional study	45	NS	24 (53.3%)	32	NS	20 (62.5%)	-	-	-	-	-	-	8
Edwards et al., 2022 [15]	UK	Retrospective, multicentre cohort study	14,205	71.4 ± 16.3	8536 (60.1%)	2,269	66.5 ± 17.0	1,449 (63.9%)	-	-	-	-	-	-	7
Girotra et al., 2022 [16]	USA	multicentre cohort study	-	-	-	24,915	NS	15,066 (60.5%)	5,916	NS	3,778 (63.9%)	18,999	NS	11,288 (59.4%)	8
Gupta et al., 2022 [17]	USA	multicentre cohort study	79,736	65.0 ± 15.5	46,920 (58.8%)	22,899	64.6 ± 15.3	13,731 (60.0%)	-	-	-	-	-	-	8
Holm et al., 2021 [18]	Sweden	Registry-based observational study	-	-	-	1,244	71.0 ± 13.2	788 (63.3%)	182	70.93 ± 12.43	114 (62.6%)	1,062	71.00 ± 13.32	674 (63.5%)	9
Lyu et al., 2021 [19]	Singapore	Retrospective study	34	70.8 ± 12.7	23 (64.8%)	46	65.0 ± 12.8	28 (66.4%)	-	-	-	-	-	-	8
Miles et al., 2020 [20]	USA	Cohort study	117	66.3 ± 3.5	67 (57.3%)	125	66.8 ± 3.2	82 (65.6%)	-	-	-	-	-	-	8
Roedl et al., 2021 [21]	Germany	Retrospective study	84	69.8 ± 3.5	60 (71.4%)	93	67.8 ± 3.5	60 (64.5%)	-	-	-	-	-	-	8
Sultatnian et al., 2021 [22]	Sweden	Registry-based observational study	532	70.1 ± 18.2%	327 (61.5%)	548	67.8 ± 18.9	351 (64.1%)	72	67.8 ± 13.0	49 (68.1%)	285	67.0 ± 20.8	192 (67.4%)	9
Tong et al., 2021 [23]	China	retrospective analysis of prospectively collected data	362	75.8 ± 3.2	240 (66.3%)	267	76.3 ± 3.2	154 (57.7%)	-	-	-	-	-	-	8
Yuriditsky et al., 2020 [24]	USA	retrospective observational study	-	-	-	110	-	81 (73.6%)	55	68.3 ± 1.8	48 (87.3%)	55	68.9 ± 5.1	33 (60.0%)	8

to 1.53; $p=0.05$). The pre-COVID-19 period had a hospital survival rate of 25.1% compared to 20.9% in the COVID-19 period (OR = 1.17; 95% CI: 0.96 to 1.41; $p = 0.12$) (Fig. 3).

COVID-19 positive vs. negative meta-analysis. ROSC among COVID-19 positive vs. negative patients was reported in three studies [28, 30, 34] in which they varied and amounted to 52.9% vs. 62.6%, respectively (OR = 0.59; 95% CI: 0.47 to 0.75; $p<0.001$).

SHD in COVID-19 positive patients was 14.0% compared to 25.9% for patients without COVID-19 (OR = 0.72; 95%CI: 0.28 to 1.86; $p=0.50$) [28,30,34]. Only one study [36] found that SHD with CPC 1–2 was 9.1% vs. 27.3% in COVID-19 positive vs. negative patients (OR = 0.27; 95% CI: 0.09 to 0.80; $p = 0.02$). 30-day survival rate was 62.6% vs. 58.3%, respectively (OR =0.99; 95%CI: 0.23 to 4.24; $p=0.99$) [30, 34].

DISCUSSION

To the best of the authors' knowledge, this is the largest and also the most up-to-date study to evaluate IHCA outcomes in pre-COVID-19 vs. COVID-19 periods, summarizing 11 studies and 122,748 patient outcomes. It was found that ROSC occurred less frequently, and fewer patients survived discharge from the hospital during the COVID-19 period. Moreover, recurrent cardiac arrests occurred more commonly during this period. During the COVID-19 period, ROSC occurred less frequently, and fewer patients survived until discharge when SARS-CoV-2 was positive, reinforcing the fact that the lower ROSC and SHD seen during the pandemic were due to the SARS-CoV-2 infection [37, 38]. However, the 30-day survival was similar between SARS-CoV-2 positive and negative patients.

Some reasons have been postulated for why COVID-19 increases the risk of sudden in-hospital cardiac arrest [39, 40], the primary among which is acute respiratory failure with rapid deterioration of the patient's condition, which in the absence of proper treatment, can quickly lead to IHCA.

To date, a limited number of papers have been identified analyzing the IHCA during the pandemic, including comparing the scope of measures taken, clinical characteristics of patients, survival rates, and parameters related to the measures taken and the quality of resuscitation to the period before the COVID-19 pandemic. The work on IHCA may help identify risk factors for IHCA in inpatients, provide data to facilitate proper patient qualification, change the management of patients' eligibility for resuscitation, and influence the course of resuscitation itself for IHCA.

Many authors have analyzed the causes of IHCA, the clinical characteristics of patients with COVID-19 in terms of their response to resuscitative measures, and the risk of its occurrence. In the initial period of the pandemic, how personnel responded, the necessity of donning and doffing personal protective clothing, which could affect the delay in the time of resuscitation efforts as well as the quality of resuscitation efforts themselves, were extremely important. Recommendations regarding video laryngoscopy and the use of mechanical chest compressions were also proposed [41, 42]. However, it is uncertain whether the use of these devices affects survival after in-hospital sudden cardiac arrest. Data are lacking on where the cardiac arrest occurred. It is essential to compare monitored and non-monitored wards [43]. The

extent of monitoring and the patient's condition during sudden in-hospital cardiac arrest can affect patient survival rates, including, in particular, surveillance of gas exchange.

The response of healthcare systems, including ambulatory care, emergency medical teams, capacity for hospitalizing patients, and the extent of inpatient care provided, depends mainly on the pandemic period and the number of critically ill patients, as does the capacity of the healthcare system as a whole to assist. In many hospitals, the capacity of emergency departments and intensive care units was completely exhausted, and critically ill patients were treated outside emergency departments or intensive care units, often by medical personnel who needed more optimal experience and clinical skills [27]. In many hospitals, operating theatres, post-anesthesia care units, internal medicine wards, and often every available room, including corridors adjacent to emergency departments and intensive care units, were adopted to treat patients with severe COVID-19, including severe respiratory failure requiring mechanical ventilation. The challenge for medical staff and those in charge of hospital operations was to ensure supplies, especially oxygen, the ability to monitor patients, and the need for certain drugs and invasive techniques [44].

Because there were insufficient ICU beds, doctors had to come up with guidelines for who could get treatment. Age and other health problems were two of the most important things that were looked at when deciding who could go to the ICU [44]. Several scientific societies have issued recommendations regarding patients' eligibility for ICU treatment in the case of the COVID-19 pandemic and limited space availability, as well as indications for undertaking resuscitation at both the pre-hospital and in-hospital stages [45–48].

The analyzed papers included various elements related to the characteristics of the patients, the method of confirming COVID-19 infection, the hospital ward where the cardiac arrest occurred, and the method of resuscitation. The method of confirming COVID-19 infection changed over time; in the early stages of the pandemic, only positive polymerase chain reaction (PCR) tests were considered reliable confirmation of infection; in later periods, rapid tests became available, which fundamentally changed the ability to confirm infection in a patient and determine whether a patient in whom resuscitation efforts were undertaken was actually infected with SARS-CoV-2, or merely clinically suspected [48].

Several studies assessed the impact of the need for medical personnel to use personal protective equipment on some basic elements associated with undertaking resuscitation activities, including the performance of medical procedures such as airway management, endotracheal intubation, the placement of intravenous access, and the quality of chest compressions. In several cases, it was shown that the use of PPE by medical personnel can worsen parameters related to the timing of individual procedures and the quality of the actions taken [49–53].

One of the primary factors associated with undertaking resuscitation and its effectiveness is the presence of potentially reversible causes, among them hypoxia [17, 54, 55]. In many patients with COVID-19, extreme hypoxia led to sudden cardiac arrest. In a situation where optimal therapy and circulation were maintained, it was not possible to ensure a sufficiently high arterial blood oxygen partial pressure with optimal mechanical ventilation. The effectiveness of resuscitation efforts was very limited.

A crucial element is an analysis of how resuscitation was undertaken, the indications for resuscitation, how it was carried out, the range of activities performed on individual patients and their duration, depending on the pandemic period. In the early days, many health systems implemented restrictions due to concerns about the safety of medical personnel. During this period, indications for initiating resuscitation efforts were limited, and recommendations for the use of personal protective equipment, the donning and rigorous use of which took time and may have been associated with delays in resuscitation efforts, were strictly adhered to. In subsequent stages, the availability of vaccination, changes in the characteristics of patients, the risk of death resulting from infection, and the availability of therapeutic methods may have affected the very qualification of patients and the manner and timing of resuscitation efforts in the hospital setting.

A factor that should also have been taken into account impeded the diagnosis and treatment of conditions, including delay in the diagnosis and treatment of potentially life-threatening conditions, including cancer, which resulted in an increase in mortality from selected conditions in some countries following a particular spike in COVID-19 cases, and limitations in the operation of out-patient and hospital care [56].

Limitations of the study. The main limitations of the meta-analysis performed include analyzing data from different centres with different patient characteristics and heterogeneous guidelines for undertaking and conducting resuscitation activities in the hospital setting during the COVID-19 pandemic. Of primary importance was that activities were undertaken in different hospital areas with different access to advanced resuscitation activities. The different ways of confirming the status of patients suspected of having COVID-19 infection were also limitations, as is the inability to confirm in many cases that COVID-19 led to sudden cardiac arrest and was the predominant cause. In most cases, autopsies were not performed for epidemiological reasons, making it impossible to analyze the causes of the onset of cardiac arrest. The papers analyzed often did not include patients who were not resuscitated, and lack data on cases in which resuscitation was not undertaken, including DNACPR recommendations. The data analyzed did not include parameters related to resuscitation quality, including chest compressions and the use of drugs. A limitation also relates to the nature of the data collected, including analyses of national registries and the resulting limitations and, moreover, often the location where the cardiac arrest occurred.

CONCLUSIONS

During the COVID-19 period, patients with SARS-CoV-2 infection had lower rates of ROSC and SDH, as well as poorer neurologic outcomes and an increase in hospital re-arrests. However, the 30-day survival rate was similar in both SARS-CoV-2 positive and negative patients.

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