Outcomes of out-of-hospital cardiac arrest in patients with SARS-CoV-2 infection: a systematic review and meta-analysis

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Introduction   Out-of-hospital cardiac arrests increased during the COVID-19 pandemic and a direct mechanism of cardiac arrest in infected patients was hypothesized. Therefore, we conducted a systematic review and meta-analysis to assess outcomes of SARS-CoV-2 patients with out-of-hospital cardiac arrest.

Methods   PubMed and EMBASE were searched up to April 05, 2021. We included studies comparing out-of-hospital cardiac arrests patients with suspected or confirmed SARS-CoV-2 infection versus noninfected patients. The primary outcome was survival at hospital discharge or at 30 days. Secondary outcomes included return of spontaneous circulation, cardiac arrest witnessed and occurring at home, bystander-initiated cardiopulmonary resuscitation, proportion of nonshockable rhythm and resuscitation attempted, and ambulance arrival time.

Results   In the ten included studies, 18% (1341/7545) of out-of-hospital cardiac arrests occurred in patients with SARS-CoV-2 infection. Patients with out-of-hospital cardiac arrest and SARS-CoV-2 infection had reduced rates of survival (16/856 [1.9%] vs. 153/2344 [6.5%]; odds ratio (OR) = 0.33; 95% confidence interval (CI), 0.17–0.65; $P = 0.001$; $I^2 = 28\%$) and return of spontaneous circulation (188/861 [22%] vs. 640/2403 [27%]; OR = 0.75; 95% CI, 0.65–0.86; $P < 0.001$; $I^2 = 0\%$) when compared to noninfected patients. Ambulance arrived later (15 ± 10 vs. 13 ± 7.5 min; mean difference = 1.64; 95% CI, 0.41–2.88; $P = 0.009$; $I^2 = 61\%$) and nonshockable rhythms (744/803 [93%] vs. 1828/2217 [82%]; OR = 2.79; 95% CI, 2.08–3.73; $P < 0.001$; $I^2 = 0\%$) occurred more frequently.

SARS-CoV-2 positive patients suffered a cardiac arrest at home more frequently (1186/1263 [94%] vs. 3598/4055 [89%]; OR = 1.86; 95% CI, 1.45–2.40; $P<0.001$; $I^2 = 0\%$) but witnessed rate (486/890 [55%] vs. 1385/2475 [56%]; OR = 0.97; 95% CI, 0.82–1.14; $P = 0.63$; $I^2 = 0\%$) and bystander-initiated cardiopulmonary resuscitation rate (439/828 [53%] vs. 1164/2304 [51%]; OR = 0.95; 95% CI, 0.73–1.24; $P = 0.70$; $I^2 = 53\%$) were similar.

Conclusions   One-fifth of out-of-hospital cardiac arrest patients had SARS-CoV-2 infection. These patients had low rates of return of spontaneous circulation and survival and were characterized by higher nonshockable rhythms but similar bystander-initiated cardiopulmonary resuscitation rate.

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Introduction

Since December 2019, the world has been fighting a rapidly evolving outbreak of SARS-CoV-2, a novel coronavirus responsible for the coronavirus disease (COVID-19), started in the Chinese province of Hubei [1,2]. This outbreak was declared by the WHO a pandemic and caused unprecedented challenges for healthcare systems worldwide. In most cases, COVID-19 patients were characterized by mild respiratory symptoms, but the number of patients requiring hospital and intensive care unit (ICU) admission rapidly overwhelmed hospital capacity [3]. In addition to the enormous growth in COVID-19 cases, the incidence of out-of-hospital cardiac arrest (OHCA) increased in numerous countries [4–6]. Prehospital emergency medical services (EMS) struggled to adapt to preserve the time-sensitive nature of their service to care both for COVID-19 patients and other emergencies [7–9].

The COVID-19 pandemic affected the whole system-of-care of OHCA, compromising each link of the chain of survival [10] and worsening outcomes [5,10–13]. Hospitals'

reorganization and the effect of lockdown on psychological, physical, and social wellbeing likely altered access to healthcare services. Postponing outpatient visits or delaying access to the emergency department may have left undiagnosed potentially evolving conditions like myocardial infarction [14,15], contributing to increased mortality. Also, fear of infection may have reduced rates of bystander-initiated cardiopulmonary resuscitation (CPR) [16], and CPR guidelines were updated both for laypeople and healthcare providers [17–19].

SARS-CoV-2 infection can directly trigger a cardiac arrest due to multiple complex mechanisms. The most plausible trigger is the sudden deterioration of acute respiratory failure, but myocardial involvement, endothelial injury, thromboembolism and myocarditis are also possible [20]. While the impact of COVID-19 on the system-of-care of OHCA was previously and extensively described [18–20], characteristics and outcomes of patients with cardiac arrest and concomitant SARS-CoV-2 infection are still poorly investigated, in particular in the out-of-hospital setting. Early studies in COVID-19 patients with in-hospital cardiac arrest reported low survival rates ranging from 0% to 12% [21–23]. Such low survival rates raised concerns regarding starting resuscitation, considering the risk of exposing healthcare providers to the virus and the already overwhelmed ICUs. Therefore, we conducted a systematic review and meta-analysis to study the outcomes of patients with cardiac arrest occurring in the out-of-hospital setting and a suspected or confirmed infection with SARS-CoV-2.

Methods

This systematic review and meta-analysis were conducted in accordance with the preferred reporting items for systematic reviews and meta-analyses [24]. The protocol was submitted and registered in the prospective international register of systematic reviews (PROSPERO) with the registration number CRD42021243540.

To formulate the review question, the PICO (population, intervention or exposure, comparison, outcome) framework was used: Among adults with OHCA during the COVID-19 pandemic (P), does confirm or suspected SARS-CoV-2 infection (E), compared to noninfection (C), affect survival at hospital discharge or at 30 days (O)?

Search strategy

Two authors systematically and independently searched PubMed and EMBASE for the keywords 'out-of-hospital cardiac arrest', 'cardiac arrest', 'severe acute respiratory syndrome coronavirus 2', 'COVID-19' and 'SARS-CoV-2' up to 5 April 2021. The complete search strategy is available in the Supplement. To identify additional manuscripts, references of included studies and review articles were screened.

Study selection

We included studies comparing OHCA patients with confirmed or suspected SARS-CoV-2 infection to OHCA patients without confirmed or suspected SARS-CoV-2 infection in the same study period according to definitions used by study authors. Studies reporting only the number of OHCA patients with concomitant SARS-CoV-2 infection were also included. Considered the review question, the context of a global pandemic, and that most data are obtained from ongoing registries, we decided to include observational cohort studies with both a prospective and a retrospective design. Systematic reviews, literature reviews and editorials were excluded.

Articles were independently assessed for eligibility by two investigators at the title/abstract level. If they met inclusion criteria, full-text manuscripts were retrieved for definitive selection. Disagreements were resolved by agreement with the supervision of a third investigator.

Outcomes

The prespecified primary outcome was survival at hospital discharge or at 30 days. Secondary prespecified endpoints were bystander-CPR, use of an automated external defibrillator, proportion of shockable rhythm, time to EMS arrival, return of spontaneous circulation (ROSC), survival at hospital admission (sustained ROSC until arrival at the emergency department) and survival with favorable outcome defined as a cerebral performance category (CPC) or a score on the modified Rankin Scale less than two (Supplementary Table 3–4, Supplemental digital content 1, *http://links.lww.com/EJEM/A322*) [25,26].

Data extraction and risk of bias assessment

For each study, two investigators independently used a standardized form to extract first author, year of publication, period and country of the study, sample size, number of COVID-19 deaths, rates of bystander-CPR, ROSC, survival outcomes, baseline characteristics of patients, interventions performed in the prehospital setting and EMS arrival time. The cumulative incidence of COVID-19 deaths per one million population during the study period was calculated. Definition of SARS-CoV-2 infection and COVID-like symptoms used by each study author is reported in Table 1. Authors were contacted to obtain additional data.

We assessed the risk of bias of included studies using the tool Risk Of Bias In Nonrandomized Studies – of Interventions (ROBINS-I) [27]. The grades of recommendation, assessment, development and evaluation (GRADE) approach were used to assess the certainty of evidence [28].

Statistical analysis

We calculated pooled odds ratios (ORs) and 95% confidence intervals (CI) using the Mantel−Haenszel method

Table 1 Characteristics of studies included ordered by first author

Study	Journal	Country/region	Study period	Sample size	Definition of OHCA with COVID-19
Baert *et al.*, (2020) [30]	Scand J Trauma Resusc Emerg Med	France	1 March to 31 April 2020	1005	Laboratory confirmation or suggestive symptoms (fever with respiratory symptoms)
Baldi *et al.*, (2020) [13]	Eur Heart J	Lombardy, Italy	21 February to 20 April 2020	490	Laboratory confirmation (pre- or postmortem) or suggestive symptoms (fever ≥3 days with cough, dyspnoea, or both)
Ball *et al.*, (2020) [11]	Resuscitation	Victoria, Australia	16 March to 12 May 2020	380	Laboratory confirmation
Fothergill *et al.,* (2020) [31]	Resusc Plus	London, UK	1 March to 30, April 2020	3122	Laboratory confirmation or suggestive symptoms
Kim *et al.*, (2020) [32]	Infect Chemother.	Daegu, Korea	19 February to 31 March 2020	80	Laboratory confirmation (after CPR)
Marijon *et al.*, (2020) [5]	The Lancet	Paris, France	16 March to 26 April 2020	521	Laboratory confirmation or suggestive symptoms (fever lasting >48 h with cough, dyspnoea, or both)
Navalpotro-Pascual *et al.*, (2021) [33]	Emergencias	Madrid, Spain	1 March to 30 April 2020	313	Laboratory confirmation or suggestive symptoms
Sayre *et al.*, (2020) [34]	Circulation	King County, USA	26 February to 15 April 2020	537	Laboratory confirmation (pre- or postmortem) or suggestive symptoms (fever or respiratory illness or COVID-19 exposure)
Sultanian *et al.* (2020) [35]	Eur Heart J	Sweden	16 March to 20 July 2020	422	Laboratory confirmation, suspected infection, or recent infection (5% of cases)
Uy-Evanado *et al.* (2020) [36]	JACC: Clin Electro-physiol	Oregon and California, USA	1 March to 31 May 2020	278	Laboratory confirmation

for dichotomous outcomes. We estimated the mean difference (MD) and 95% CIs outcomes using the inverse variance (I-V) method for continuous outcomes. Statistical heterogeneity hypothesis was tested with Cochrane Q statistic and I^2 value. Independently from the amount of statistical heterogeneity, we decided to apply a random effect model. We recognized the impact of disparities between systems and of the pandemic itself on these systems. Statistical significance was set at the two-tailed level of 0.05 for hypothesis testing of effect and 0.10 for hypothesis testing of heterogeneity. When only a median and interquartile range (IQR) were available, we calculated mean and SD with the method described by Wan *et al.* [29]. Results of pooled analyses were presented with forest plots. Publication bias for the primary outcome was investigated by visual estimation of the funnel plot. All analyses were performed using RevMan version 5.3.

Results
Study characteristics
Our search strategy in electronic databases returned 239 records. After the removal of duplicates and nonpertinent records examined at the title and abstract level, we retrieved 37 full-text documents for detailed assessment. Ten studies were definitively included (Fig. 1) [5,11,13,30–36]. List and details of excluded studies are available in Supplementary Table 1, Supplemental digital content 1, *http://links.lww.com/EJEM/A322*. Among included studies, six compared characteristics and outcomes of patients with OHCA infected with SARS-CoV-2 with those not infected [13,30–33,35]. All included studies reported the prevalence of SARS-CoV-2 infection among patients with OHCA [5,11,13,30–36]. All studies were conducted between 19 February 2020 and 20 July 2020 and were observational cohort studies with a retrospective design or a retrospective analysis of registries data.

Six studies were conducted in Europe [5,13,30,31,33,35], two in North America [34,36], one in Australia [11] and another one in Asia [34]. Characteristics of studies included in this systematic review and meta-analysis are described in Table 1. A summary of main findings is reported in Table 2.

Association of SARS-CoV-2 infection with main outcomes
The primary outcome of survival at hospital discharge or at 30 days and ROSC were assessed in six studies for a total of 5432 patients [13,30–33,35]. Overall, patients with SARS-CoV-2 suffering an OHCA had reduced rates of survival at hospital discharge or at 30 days (primary outcome) when compared with patients not affected by SARS-CoV-2 (Fig. 2a; 16/856 [1.9%] vs. 153/2344 [6.5%]; OR = 0.33; 95% CI, 0.17–0.65; *P* = 0.001; I^2 = 28%). Visual inspection of funnel plot did not suggest the presence of publication bias (Supplementary Fig. 1, Supplemental digital content 1, *http://links.lww.com/EJEM/A322*). Only two studies reported the secondary outcome survival with favorable outcomes [33,35] and pooled analysis was not performed.

ROSC was less frequently achieved (Fig. 2b; 188/861 [22%] vs. 640/2403 [27%]; OR = 0.75; 95% CI, 0.65–0.86; *P* < 0.001; I^2 = 0%) in patients with OHCA and infection with SARS-CoV-2.

All the included studies were assessed as serious risk of bias according to ROBINS-I assessment. The most frequent source of bias was reporting unadjusted results for confounding factors and participant selection. Risk of bias assessment and GRADE table are included in the Supplementary Table 1, Supplemental digital content 1, *http://links.lww.com/EJEM/A322* and Supplementary Table 2, Supplemental digital content 1, *http://links.lww. com/EJEM/A322*, respectively.

Fig. 1
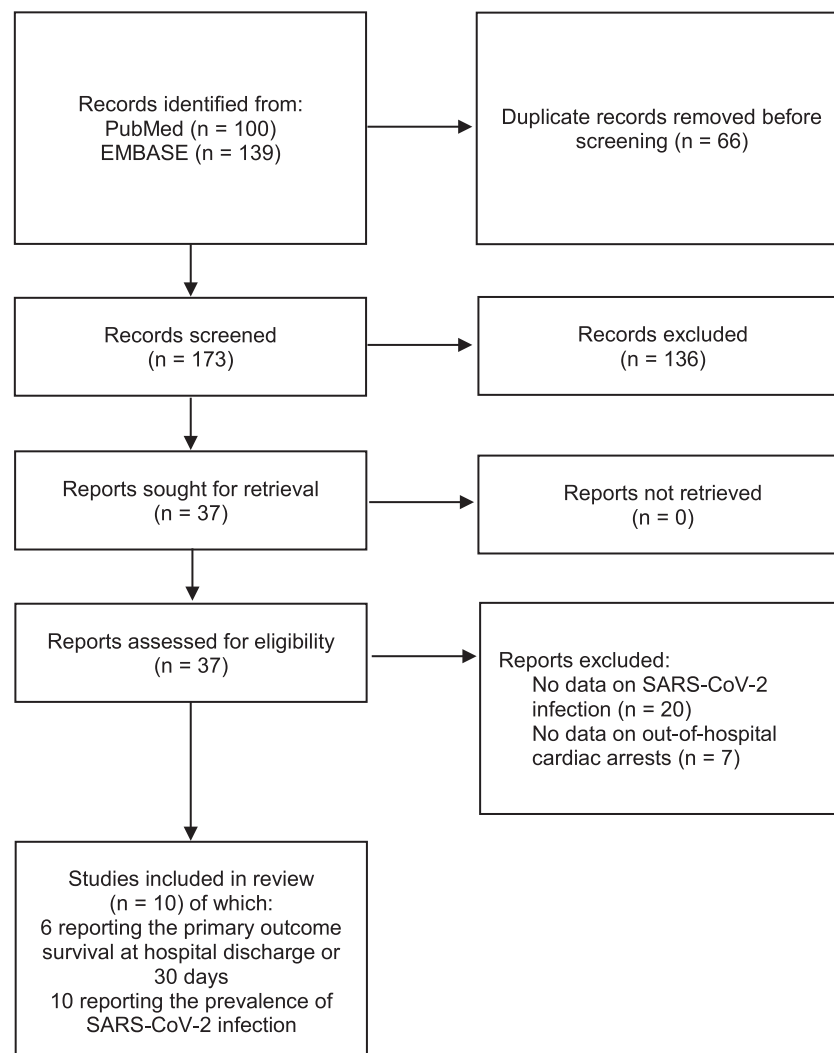
Flowchart of the literature search according to preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines.

Characteristics of out-of-hospital cardiac arrest patients

Baseline characteristics were reported in six studies for a total of 5432 patients [13,30–33,35]. Age (Supplementary Fig. 1A, Supplemental digital content 1, *http://links.lww.com/EJEM/A322*; 71 ± 16 vs. 72 ± 16; MD = −1.07; 95% CI, −2.15 to 0.02; $P = 0.053$; $I^2 = 6\%$) and proportion of males (Supplementary Fig. 1B, Supplemental digital content 1, *http://links.lww.com/EJEM/A322*; 784/1272 [62%] vs. 2587/4160 [62%]; OR = 0.90; 95% CI, 0.70–1.17; $P = 0.44$; $I^2 = 59\%$) of OHCA patients affected by SARS-CoV-2 were similar to those not infected with SARS-CoV-2.

Data for first monitored rhythm, bystander-CPR, bystander-witnessed, location of arrest, and time to EMS arrival were available in five studies (5352 patients) [13,30,31,33,35] while rates of EMS attempted resuscitation in four studies (4930 patients) [13,30,31,33].

The first monitored rhythm in OHCA patients with SARS-CoV-2 infection was more likely to be nonshockable (pulseless electrical activity or asystole) when compared with patients without SARS-CoV-2 infection (Fig. 3a; 744/803 [93%] vs. 1828/2217 [82%]; OR = 2.79; 95% CI, 2.08–3.73; $P < 0.001$; $I^2 = 0\%$).

Bystander-witnessed OHCAs were similar between patients with or without SARS-CoV-2 (Supplementary Fig. 1C, Supplemental digital content 1, *http://links.lww.com/EJEM/A322*; 486/890 [55%] vs. 1385/2475 [56%]; OR = 0.97; 95% CI, 0.82–1.14; $P = 0.63$; $I^2 = 0\%$). Likewise, rates of bystander-CPR were not different between OHCA patients with and without confirmed or suspected SARS-CoV-2 (Fig. 3b; 439/828 [53%] vs. 1164/2304 [51%]; OR = 0.95; 95% CI, 0.73–1.24; $P = 0.70$; $I^2 = 53\%$). Patients with SARS-CoV-2 infection were more likely to suffer OHCA at home (Supplementary

Table 2 Summary of main findings

Outcomes	No. of studies	SARS-CoV-2 infection	No infection	Effect size[a] (95% CI)	P value	I^2 (%)
Primary outcome						
Survival to hospital discharge or 30 days, n (%)	6	16/856 (1.9%)	153/2344 (6.5%)	0.33 (0.17–0.65)	0.001	28%
Secondary outcomes						
Return of spontaneous circulation, n (%)	6	188/861 (22%)	640/2403 (27%)	0.75 (0.65–0.86)	<0.001	0%
Age, years (SD)	6	71 (16)	72 (16)	−1.07 (−2.15 to 0.02)	0.053	6%
Male, n (%)	6	784/1272 (62%]	2587/4160 (62%)	0.90 (0.70–1.17)	0.44	59%
Home location, n (%)	5	1186/1263 (94%)	3598/4055 (89%)	1.86 (1.45–2.40)	<0.001	0%
Nonshockable rhythms, n (%)	5	744/803 (93%)	1828/2217 (82%)	2.79 (2.08–3.73)	<0.001	0%
Bystander-witnessed, n (%)	5	486/890 (55%)	1385/2475 (56%)	0.97 (0.82–1.14)	0.63	0%
Bystander-initiated CPR, n (%)	5	439/828 (53%)	1164/2304 (51%)	0.95 (0.73–1.24)	0.70	53%
EMS response times, minutes (SD)	5	15 (10)	13 (7.5)	1.64 (0.41–2.88)	0.009	61%
EMS attempted resuscitation, n (%)	4	680/1175 (58%)	1760/3753 (47%)	1.25 (0.69–2.25)	0.46	91%

CPR, cardiopulmonary resuscitation; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
[a]Odds ratio for dichotomous outcomes and mean difference for continuous outcomes.

Fig. 2

(a) Survival at hospital discharge or at 30 days
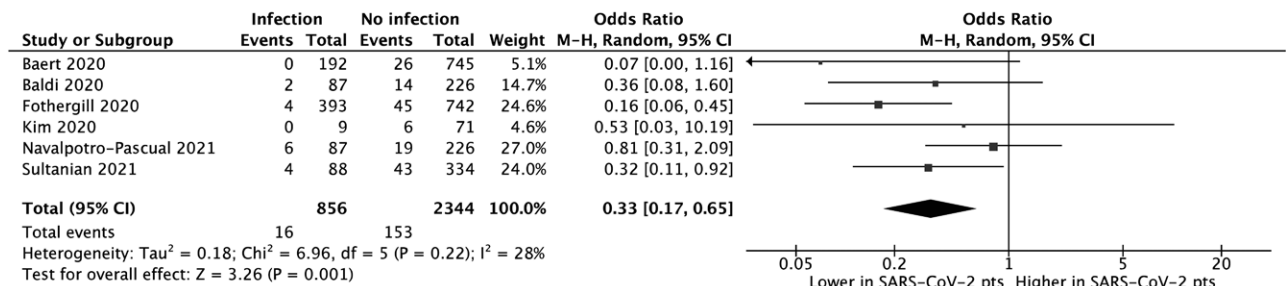
(b) Return of spontaneous circulation
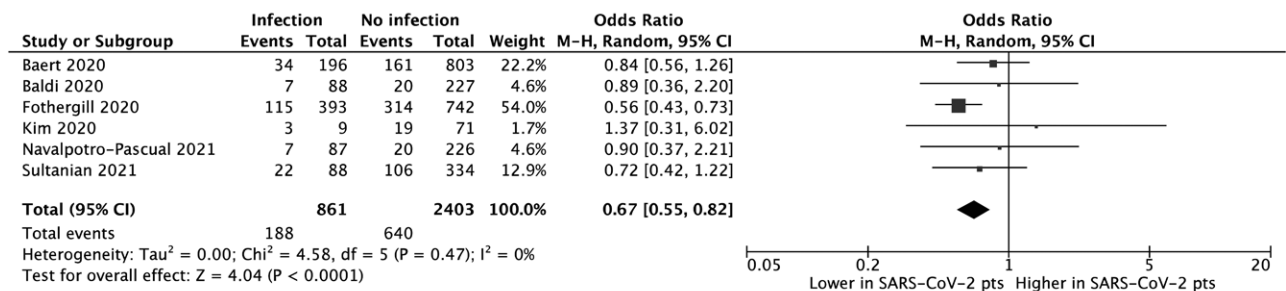
Forest plot for the primary outcome rate of survival at hospital discharge or at 30 days (a) and for return of spontaneous circulation (b). CI, confidence interval; df, degrees of freedom; M–H, Mantel–Haenszel.

Fig. 1D, Supplemental digital content 1, *http://links.lww. com/EJEM/A322*; 1186/1263 [94%] vs. 3598/4055 [89%]; OR = 1.86; 95% CI, 1.45–2.40; *P* < 0.001; I^2 = 0%).

EMS response times to OHCAs in patients with SARS-CoV-2 were longer (Fig. 3c; 15 ± 10 vs. 13 ± 7.5 min; MD = 1.64; 95% CI, 0.41–2.88; *P* = 0.009; I^2 = 61%) while the proportion of cases with resuscitation attempted by EMS was similar (Supplementary Fig. 2, Supplemental digital content 1, *http://links.lww.com/EJEM/A322*; 680/1175 [59%] vs. 1760/3753 [47%]; OR = 1.25; 95% CI, 0.69–2.25; *P* = 0.46; I^2 = 91%) when compared to patients without SARS-CoV-2.

Prevalence of SARS-CoV-2 among out-of-hospital cardiac arrest

All ten studies reported the prevalence of SARS-CoV-2 infection, among which nine a laboratory-confirmed SARS-CoV-2 test was available [5,11,13,30–34,36] (Table 3). Overall, during the COVID-19 pandemic, 18% (1341/7545) of OHCA involved patients with confirmed SARS-CoV-2 infection or COVID-like symptoms (e.g. fever associated with respiratory symptoms). OHCA patients with confirmed SARS-CoV-2 infection were 2.6% (171/6668; nine studies), while COVID-like symptoms were present in 17% (1082/6288, eight studies [5,13,30–34,36]) of OHCAs (Table 3).

Fig. 3

(a) Non-shockable rhythms

Study or Subgroup	Infection Events	Total	No infection Events	Total	Weight	Odds Ratio M–H, Random, 95% CI
Baert 2020	189	197	727	806	15.4%	2.57 [1.22, 5.41]
Baldi 2020	80	88	198	226	12.4%	1.41 [0.62, 3.24]
Fothergill 2020	366	393	596	742	45.9%	3.32 [2.16, 5.11]
Navalpotro–Pascual 2021	35	37	94	109	3.7%	2.79 [0.61, 12.84]
Sultanian 2021	74	88	213	334	22.6%	3.00 [1.63, 5.54]
Total (95% CI)		**803**		**2217**	**100.0%**	**2.79 [2.08, 3.73]**
Total events	744		1828			

Heterogeneity: Tau^2 = 0.00; Chi^2 = 3.32, df = 4 (P = 0.50); I^2 = 0%
Test for overall effect: Z = 6.89 (P < 0.00001)

Odds Ratio M–H, Random, 95% CI
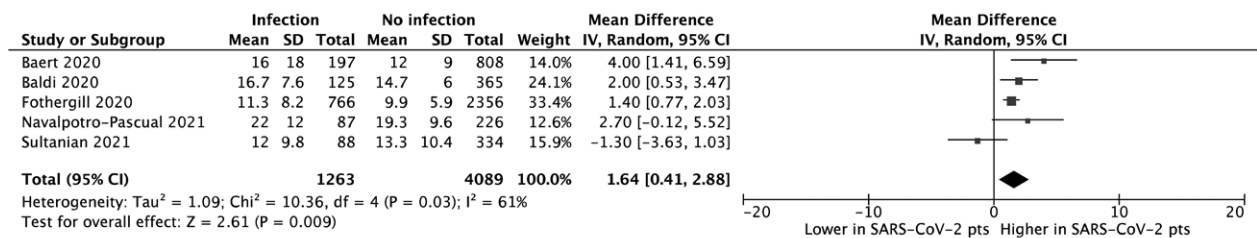0.05   0.2   1   5   20
Lower in SARS–CoV–2 pts   Higher in SARS–CoV–2 pts

(b) Bystander-initiated cardiopulmonary resuscitation

Study or Subgroup	Infection Events	Total	No infection Events	Total	Weight	Odds Ratio M–H, Random, 95% CI
Baert 2020	99	197	401	808	25.8%	1.03 [0.75, 1.40]
Baldi 2020	13	63	76	194	11.2%	0.40 [0.21, 0.79]
Fothergill 2020	257	393	461	742	29.2%	1.15 [0.89, 1.49]
Navalpotro–Pascual 2021	30	87	84	226	16.0%	0.89 [0.53, 1.49]
Sultanian 2021	40	88	142	334	17.7%	1.13 [0.70, 1.81]
Total (95% CI)		**828**		**2304**	**100.0%**	**0.95 [0.73, 1.24]**
Total events	439		1164			

Heterogeneity: Tau^2 = 0.05; Chi^2 = 8.56, df = 4 (P = 0.07); I^2 = 53%
Test for overall effect: Z = 0.38 (P = 0.70)

Odds Ratio M–H, Random, 95% CI
0.05   0.2   1   5   20
Lower in SARS–CoV–2 pts   Higher in SARS–CoV–2 pts

(c) Time to arrival (minutes) of emergency medical services

Study or Subgroup	Infection Mean	SD	Total	No infection Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Baert 2020	16	18	197	12	9	808	14.0%	4.00 [1.41, 6.59]
Baldi 2020	16.7	7.6	125	14.7	6	365	24.1%	2.00 [0.53, 3.47]
Fothergill 2020	11.3	8.2	766	9.9	5.9	2356	33.4%	1.40 [0.77, 2.03]
Navalpotro–Pascual 2021	22	12	87	19.3	9.6	226	12.6%	2.70 [−0.12, 5.52]
Sultanian 2021	12	9.8	88	13.3	10.4	334	15.9%	−1.30 [−3.63, 1.03]
Total (95% CI)			**1263**			**4089**	**100.0%**	**1.64 [0.41, 2.88]**

Heterogeneity: Tau^2 = 1.09; Chi^2 = 10.36, df = 4 (P = 0.03); I^2 = 61%
Test for overall effect: Z = 2.61 (P = 0.009)

Mean Difference IV, Random, 95% CI
−20   −10   0   10   20
Lower in SARS–CoV–2 pts   Higher in SARS–CoV–2 pts

Forest plot for the rate of (a) nonshockable rhythms, (b) bystander-initiated cardiopulmonary resuscitation and (c) time to arrival of emergency medical services. CI, confidence interval; df, degrees of freedom; M–H, Mantel–Haenszel.

Table 3   Prevalence of SARS-CoV-2 infection among out-of-hospital cardiac arrests

Study	Country/region	Incidence of COVID-19 deaths[a]	SARS-CoV-2 confirmed or suspected, n (%)[b]	SARS-CoV-2 confirmed, n (%)	SARS-CoV-2 suspected, n (%)
Baert et al., 2020 [30]	France	373	197/1005 (20%)	27/1005 (2.7%)[c]	170/1005 (17%)[c]
Baldi et al., 2020 [13]	Lombardy, Italy	1250	125/490 (26%)	19/490 (3.9%)	106/490 (22%)
Ball et al., 2020 [11]	Victoria, Australia	2.8	0/380 (0%)	0/380 (0.0%)	n/a
Fothergill et al., 2020 [31]	London, UK	607	766/3122 (25%)	66/3122 (2.1%)	700/3122 (22%)
Kim et al., 2020 [32]	Daegu, Korea	35	9/184 (4.9%)	9/184 (4.9%)	0/184 (0.0%)
Marijon et al., 2020 [5]	Paris, France	521	42/521 (8.1%)	17/521 (3.3%)	25/521 (4.8%)
Navalpotro-Pascual et al., 2021 [33]	Madrid, Spain	1279	87/313 (28%)	9/313 (2.9%)[c]	78/313 (25%)[c]
Sayre et al., 2020 [34]	King County, USA	139	26/527 (4.9%)	23/527 (4.4%)	3/527 (0.6%)
Sultanian et al., 2020 [35]	Sweden	556	88/877 (10%)	n/a	n/a
Uy-Evanado et al. 2020 [36]	Oregon and California, USA	107	1/126 (0.8%)	1/126 (0.8%)	0/126 (0.0%)
Total			1341/7545 (18%)	171/6668 (2.6%)	1082/6288 (17%)

COVID-19, coronavirus disease 19; OHCA, out-of-hospital cardiac arrest; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
aPer one million of population during the study period.
bSum of confirmed and suspected cases, mutually exclusive.
cAdditional data provided by study authors.

Discussion

This systematic review and meta-analysis of cohort studies found that ROSC and survival at hospital discharge or at 30 days were poor among OHCA with SARS-CoV-2 infection and lower than patients without infection. Patients with OHCA and concomitant SARS-CoV-2 infection were characterized by a higher rate of nonshockable rhythms and prolonged EMS arrival time. However, rate of CPR initiated by a bystander and resuscitation attempted by EMS were similar. Notably, about one out of five OHCAs involved a patient with SARS-CoV-2 infection.

The association between COVID-19 pandemic and the occurrence of cardiac arrest is still far from being understood, but several direct and indirect mechanisms were proposed. OHCA may increase if patients delay presentation to the emergency department or EMS activation due to COVID-19 fears for time-dependent conditions (e.g. acute coronary syndromes). Cancelation of elective hospital activity and overload of healthcare services may have left undiagnosed severe conditions that may have potentially contributed to increasing OHCA with worse outcomes. Another reason for an increase in OHCA incidence is the direct effect of SARS-CoV-2 infection. We found a substantial amount (18%) of patients suspected or confirmed to be infected with SARS-CoV-2. The prevalence ranged among studies from 0.0% in Australia [11] to 28% in Spain [33] and this probably reflects the different incidence of COVID-19 cases shown in Table 3. In Lombardy, Paris, and London, the percentage of excess OHCAs directly imputable to SARS-CoV-2 infection was respectively 74% [13], 33% [5] and 55% [31], suggesting a direct effect between the infection and the occurrence of cardiac arrest. When interpreting our findings, limited access to COVID-19 testing should be considered.

In patients infected with SARS-CoV-2, the disease can progress to respiratory failure and ultimately precipitate into cardiac arrest. A rapid deterioration in COVID-19 patients with apparently mild respiratory discomfort was described [37]. In the context of OHCA, hypoxemic respiratory failure likely occurred acutely in nonhospitalized patients. Hypoxia is considered one of the usual causes of cardiac arrest with nonshockable rhythms and it was the leading etiology of arrest among in-hospital cardiac arrests in COVID-19 patients [38]. This might explain the lower proportion of shockable rhythms we observed among patients with confirmed or suspected SARS-CoV-2. Moreover, we observed a delayed EMS arrival, probably due to wearing of personal protective equipment. The risk of contracting SARS-CoV-2 during resuscitation depends on the prevalence and the probability of transmission. Therefore, the correct use of full personal protective equipment is of paramount importance for EMS to safely perform resuscitation maneuvers

but may prolong response time and affect overall performance due to the time needed for dressing and fatigue. Another link between SARS-CoV-2 infection and cardiac arrest is the possible involvement of the heart and, more extensively, of the cardiovascular system. In a cohort of in-hospital cardiac arrests in COVID-19 patients, pulmonary embolism and cardiac arrhythmias accounted for over 20% of cases [38]. Likewise, there may be delayed sequelae of the infection that may increase the burden of cardiovascular disease among the population.

Critically ill patients admitted with COVID-19 pneumonia have poor survival rates [39,40]. Early studies showed even worse survival rates when an in-hospital cardiac arrest occurs in these patients. The first study from Wuhan reported a 30-day survival of 2.9% [21] while two single-center studies from the US showed 0% in-hospital survival [22,41]. A multicenter study across 86 US intensive care units showed 12% survival to hospital discharge [23]. Similarly, among OHCA, we found an overall survival to hospital discharge or 30 days of only 1.9%, and among studies, it ranged between 0.0% and 8.9%. These low survival rates among IHCAs raised concerns regarding starting resuscitation in those patients, also considering the risk of exposing healthcare providers to the virus and the already overwhelmed ICUs. Analogous low rates of survival among OHCAs observed in this meta-analysis could raise similar concerns regarding initiating resuscitation maneuvers in OHCA patients with concomitant SARS-CoV-2 infection. These results should not be generalized: healthcare providers should continue assessing each patient individually for their chances of survival and favorable outcome and, in the setting of a pandemic, consider the expected use of resources, if appropriate.

The possible hypoxic cause of cardiac arrest in SARS-CoV-2 patients questioned the efficacy of providing chest compression-only bystander-CPR. The updated guidelines during the COVID-19 outbreak recommend chest compression-only CPR for adults to reduce the viral transmission risk and standard CPR for children. Fear among laypeople of contracting an infectious disease while performing CPR is possible and may have increased in the COVID-19 pandemic [16]. Despite this and lower bystander-CPR rates reported in some European countries during 2020 [5,13,36,42], we found no differences in bystander-witnessed and bystander-CPR rates in patients with SARS-CoV-2 infection. However, we observed that SARS-CoV-2 positive patients were more likely to suffer a cardiac arrest at home. In such cases, instructing bystanders to start CPR immediately may be reasonable considering that likely they had already been exposed to COVID-19 or they were themselves infected. It is unknown if patients with SARS-CoV-2 infection received CPR by first responders alerted through mobile phone technology [43,44]. During the pandemic, most regions limited the dispatch of first responders [45,46]

but the impact of these changes on patients outcomes is yet to be investigated.

Limitations

This systematic review and meta-analysis provide relevant information for clinicians and researchers involved in cardiac arrest and could support the development of guidelines for CPR in the context of airborne disease transmission, but it has some limitations. The main limitation is the impossibility to discriminate different severity of SARS-CoV-2 infection among patients with OHCA. Also, we could not separate patients between confirmed and suspected infection, and therefore they were analyzed together. The second limitation is the absence of data from other countries, particularly from those with a different incidence of COVID-19. A third limitation is the lack of adjustment for confounders among included studies. Also, the design of studies could be problematic as they were all observational cohort studies with a retrospective design or a retrospective analysis of registries data. Moreover, they were not primarily designed to compare infected with noninfected patients and cardiac arrest registries were not ready to effectively capture COVID-19 status. Evidence certainty was categorized as low.

Future studies should be focused on investigating the causative factor of OHCA, including postmortem data, to appreciate more clearly the mechanisms and pathophysiology of OHCA in the context of SARS-CoV-2 infection. Also, new studies should be conducted on subsequent COVID-19 waves when access to COVID-19 tests were higher, and EMS and hospitals were more prepared. A more systematic and comprehensive laboratory testing for SARS-CoV-2 infection among OHCAs could provide a definitive estimation of SARS-CoV-2 actual prevalence. We understand how complex testing patients is in the setting of resuscitation, and we congratulate the authors who were able to provide these data during a pandemic.

Conclusion

Patients with OHCA and confirmed or suspected SARS-CoV-2 infection had lower rates of survival at hospital discharge or at 30 days and ROSC when compared with OHCAs without confirmed or suspected infection. These patients more frequently presented with non-shockable rhythms and received delayed treatments due to increased EMS arrival time, but CPR initiated by bystanders were not affected. One OHCA patient every five was suspected or confirmed to be infected with SARS-CoV-2.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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