



The Rate of Successful Cardiopulmonary Resuscitation in COVID-19 Patients: A Retrospective Cohort Study

Behrooz Banivaheb¹, Parmida Shahbazi¹, Nima Hemmati¹, Ashkan Yahyavi², Pegah Derakhshan¹, Seyed Mohammad Tabatabaei Jabali³, Ali Kabir^{1*}

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Abstract

Background: This study aims to provide information on the success rate of CPR in COVID-19 patients and some probable risk factors of mortality in these cases.

Methods: In this historical cohort design, the CPR success rate probable risk factors of 737 critically ill patients during the COVID-19 pandemic in 17 hospitals in the catchment area of Iran University of Medical Sciences, Tehran, Iran, was evaluated between Feb and Apr 2020. Data were extracted from a database that is a part of a national integrated care electronic health record system and analyzed with logistic and Cox regression models.

Results: COVID-19 cases were 341 (46.3%). The mean age in COVID-19 cases and non-COVID-19 patients were 70.0±14.6 and 63.0±19.3 years, respectively (P<0.001). The mortality was significantly higher in COVID-19 patients (99.1% vs. 74%, OR: 39.6, 95%CI: 12.4, 126.2). Cardiovascular diseases were the most frequent underlying disease (46.3% of COVID-19 cases and 35.1% of non-COVID-19 patients). Being a COVID-19 case (OR: 29.0, 95%CI: 8.9, 93.2), Intensive care unit admission (OR: 2.6, 95%CI: 1.5, 4.6) and age for each ten-year increase (OR: 1.2, 95%CI: 1.1, 1.4) were observed to be independent risk factors of mortality following CPR. The hazard ratio of being a COVID-19 patient was HR= 1.8 (95%CI: 1.5, 2.1).

Conclusion: Critically ill COVID-19 patients who undergo CPR have a decreased chance of survival in comparison to non-COVID-19 patients.

Keywords: Severe Acute Respiratory Syndrome Coronavirus 2, COVID-19, Cardiopulmonary Resuscitation, Mortality, Risk Factors

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Introduction

Coronavirus disease 2019 (COVID-19), a type of pneumonia induced by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first detected in Wuhan, China in December 2019. As of October 16th, 2020, the numbers of confirmed and deceased cases in the world

are 39,596,858 and 1,107,347, respectively (1). COVID-19 is an extremely communicable disease, where every case is responsible for infecting more than two other cases (2, 3).

Clinical course, risk factors of mortality, and outcomes

Corresponding author: Dr Ali Kabir, kabir.a@iumc.ac.ir

¹ Minimally Invasive Surgery Research Centre, Iran University of Medical Sciences, Tehran, Iran

² Research Center for Prevention of Cardiovascular Disease, Iran University of Medical Sciences, Tehran, Iran,

³ Department of Nutrition, School of Public Health, Iran University of Medical Sciences, Tehran, Iran

↑What is “already known” in this topic:

Successful cardiopulmonary resuscitation (CPR) in critically ill COVID-19 patients is thought to be very unlikely in a few recent studies. Furthermore, some risk factors have been reported to have a negative impact on the outcome of these patients.

→What this article adds:

This study provides a detailed comparison between COVID-19 and non-COVID-19 patients who underwent CPR in regards to their adjusted mortality risk and the risk factors contributing to mortality as the CPR outcome in these cases.

of patients with COVID-19 have been previously assessed in several studies. In a recent study, critically ill COVID-19 patients have been found to have poor clinical outcomes following cardiopulmonary resuscitation (CPR) (4) where, in a recent study, in 18 out of 136 patients (13.2%) return of spontaneous circulation occurred of whom, only four patients survived, and only one patient had a favorable neurological outcome in a 30-day follow-up (5). These studies show that approximately 40 to 50 percent of hospitalized patients with COVID-19 had at least one chronic comorbidity (6). Hypertension, diabetes and coronary heart disease were the most common ones. These studies also found older age to be a significant risk factor of mortality and an increased risk of developing ARDS and requiring mechanical ventilation in older patients (7).

The contradiction of guidelines and suggestions issued by different medical authorities on CPR in COVID-19 cases (8-10) and whether they list CPR as an aerosol-generating procedure or not, medical staff is worried about the safety of themselves and their associates and shortage of personal protective equipment are the most important issues brought up by several recent studies (11), which could impact the CPR success rate.

In a recently published editorial, authors stated that due to the imbalance of risk and benefit between patients and healthcare workers regarding CPR in COVID-19, some ethical challenges had risen. Doctors decide to perform CPR even if there is a very low possibility of survival because they prefer to do "everything possible" in order to be in less moral discomfort in their next clinical tasks, but some issues have been challenging this decision-making process since the COVID-19 outbreak has emerged. All these add to the debate of "there is no harm in trying" versus "there is little benefit for the patients and great risk for the staff" (12).

Ethical issues, guidelines for CPR in COVID-19 patients, and whether CPR is an aerosol-generating procedure have been discussed excessively in the literature. However, there is still a lack of ample evidence on the role of COVID-19 infection in CPR success rate; this study aims to investigate this issue in the patients who were hospitalized during the COVID-19 epidemic in Iran and compare the mortality in COVID-19 patients with other hospitalized cases in the same setting. As a secondary goal, some possible predictors of mortality such as the underlying conditions and the length of hospital stay (LOS) will be reported.

Methods

In this historical cohort study, 737 patients who underwent CPR in 17 hospitals in the catchment area of Iran University of Medical Sciences (IUMS) during the COVID-19 epidemic between February 20th and April 20th, 2020, were enrolled. These hospitals provide medical services for approximately 5 million people in the province of Tehran. The data was collected from the SEPAS system (an acronym for national electronic health records for every citizen) (13). In the SEPAS system, each individual must have three international classifications of disease (ICD) version 10 codes before discharge or death

namely initial impression, intermediate diagnosis and the final diagnosis. Eligibility criteria in this study were: undergoing CPR due to in-hospital cardiopulmonary arrest without an ICD 10 code for cardiopulmonary arrest (I46.9) as the initial impression during the COVID-19 epidemic and age over 18 years; the patients who underwent CPR before reaching the hospital and the patients who remained hospitalized at the end of the follow-up period were excluded. The sampling method was census. Participants were split into two groups, patients who had a probable or lab-confirmed diagnosis of COVID-19 plus clinical signs and symptoms requiring admission (cases), and patients who were admitted with other diagnoses (controls). Exposure was considered getting infected with SARS-CoV-2 based on WHO interim guideline for diagnosis and treatment of COVID-19 (14) which states that a confirmed case is "a person with laboratory confirmation of COVID-19 infection, irrespective of clinical signs and symptoms" and a probable cause is a patient who meets clinical criteria consisting of either the acute onset of fever and cough; or acute onset of at least three of the following signs or symptoms: fever, cough, general weakness or fatigue, headache, myalgia, sore throat, coryza, dyspnea, anorexia/nausea/vomiting, diarrhea, altered mental status; and is a contact of a probable or confirmed case. No specific matching was performed. The ICD 10 codes for COVID-19 (U07.1 and U07.2) were used to retrieve the data of cases. Considering that the database provides the possibility of recording more than one diagnosis for every patient, the absence of these codes in queries of non-COVID-19 patients meant that there was neither a clinical suspicion nor a positive PCR test for COVID-19 in the course of hospitalization, and patients were followed from admission up to a minimum of 120 days after discharge. Death was defined as the cessation of spontaneous blood circulation and breathing after at least 45 minutes of CPR. There were two dedicated code teams, one in the emergency unit and the other for the rest of the hospital wards. These teams consist of at least 5 members, a resident anesthesiologist or emergency medicine resident doctor, an intern, a first-year resident doctor, the chief resident doctor, a supervising nurse and another nurse in every hospital. The supervising nurse acts as the recorder of the events during the CPR process and the chief resident doctor is the leader of the team. In the emergency ward and in intensive care units (ICU), an attending doctor acts as the leader of the team. Upon the announcement of a crash code, the ward personnel immediately start the CPR process and notify the code team and CPR is assigned to the code team as soon as they arrive. Since wearing full PPE is mandatory for all the personnel working in COVID-19 wards based on the Iranian heart association guideline for CPR (15), there was no delay in the initiation of CPR due to the need for dressing in PPE. The main outcome measure was defined as recovery after CPR which was described by the spontaneous return of circulation without any serious neurological sequel at the point of discharge. The American Heart Association guideline (16) was used for performing CPR in all the hospitals.

All data consisting of age, gender, LOS, ICU admission,

chronic history of underlying conditions including cardiovascular diseases (CVD), chronic kidney diseases (CKD), chronic pulmonary diseases (CPD), diabetes mellitus (DM), and chronic use of immunosuppressant medications, and clinical outcome (death/recovery) were gathered from the database. All underlying diseases were assessed by the chronic use of medications related to each condition plus chronic history of receiving any form of dialysis in case of CKD. In the case of immunosuppressants, all cases who had a history of receiving any of the following classes were included: steroids, anti-proliferative agents, mammalian target of rapamycin inhibitors, and calcineurin inhibitors. SEPAS database receives information from IUMS hospitals, and the data gathering is an automatic process. An automatically generated code is allocated to each patient based on the ultimate condition of the patient (17). During the hospitalization of a patient, the data consisting of personal information, diagnosis, discharge information, all services, and administered medications, are entered in the hospital information system (HIS) by the physicians and nurses as a ward routine and then are instantaneously captured in real-time. Since the least amount of human involvement is present in the data entry process, and a machine captures the data, it is reliable and consistent. The database is maintained by the information technology department of IUMS. We gathered data from all eligible cases who were admitted to the hospitals and the system does not allow missing values for any of the included variables. There were no specific code statuses such as do not resuscitate or do not intubate and all the patients who require CPR underwent the process without any further considerations.

Statistical analysis

Categorical variables were described as frequencies, and continuous variables were described using mean and standard deviation (SD) or median and Interquartile range (IQR) values when applicable. Means for continuous variables were compared using independent samples t-test when the data were normally distributed with equal variances in subgroups; otherwise, the Mann-Whitney U test was implemented. Proportions for categorical variables were compared using the chi-square test. A logistic regression model was designed to adjust the variables. The dependent variable was considered mortality, and each variable with a P less than 0.2 was entered in the model by using the log-rank test to evaluate the univariate analysis

of significant or important variables in survival analysis before designing the Cox regression model. Hazard ratios (HR) were calculated, and the Kaplan-Meier curve was also used to show the survival of all patients who underwent CPR. SPSS version 16 was used (SPSS Inc., Chicago, Illinois) for analyzing the data. A P-value of less than 0.05 was considered statistically significant.

Ethical considerations

All patients were identified by a random computer-generated unique code, and no personal data was revealed to any party during the process of data extraction or analysis. This study was approved by the medical ethics committee of IUMS under the code: IR.IUMS.REC.1399.200.

Results

Among 737 participants, 445 (60.4%) were male. The patients' mean age was 66.2 ± 17.6 years. A history of an underlying condition was present in 416 (56.4%) patients. CVD was the most frequent underlying disease with a frequency of 40.3%, followed by CPD, DM, CKD, malignancy, the chronic use of immunosuppressants with 25.5%, 14.7%, 9.5%, 3.9%, and 0.7%, respectively. LOS had a median of 4 days, with an IQR of 6. The number of patients who were admitted to ICU was 412 (55.9%). The overall mortality percentage was 85.6%. The median follow-up duration was ten days (Range: 1-170, IQR=9).

Out of 737 patients, 341 (46.3%) were COVID-19 cases and 396 (53.7%) were non-COVID-19 patients. Mean age in case and control groups were 70.0 ± 14.6 and 63.0 ± 19.3 , respectively ($P < 0.001$), and 445 (60.4%) of patients were male with no significant gender difference between the two groups ($P = 0.987$). Median LOS was higher in COVID-19 than non-COVID-19 patients (median=5, IQR=6 vs median=2, IQR=5 days, $P < 0.001$). The frequency of mortality was significantly higher in COVID-19 patients (99.1% vs. 74%, OR: 39.60, 95%CI: 12.43, 126.16). CVD was the most frequent underlying condition, with 46.3% of cases and 35.1% of controls ($P = 0.002$), followed by CPD and DM (Table 1). The rate of ICU admission was also significantly higher in COVID-19 patients (61% vs. 51.5%, OR: 1.47, 95%CI: 1.09, 1.97) (Table 1).

No significant difference between the mortality of male and female patients was found ($P = 0.086$), but the deceased patients' mean age was significantly higher (68.1 ± 16.8 vs. 55.2 ± 18.7 , $P < 0.001$). The length of hospi-

Table 1. Baseline Characteristics in Patients with and without COVID-19 Diagnosis

Variable	COVID-19 case		P-value	Odds ratio (95% CI)
	Yes (n=341)	No (n=396)		
Male sex	60.4%	60.4%	0.987	1.00 (0.74, 1.34)
CVD [‡]	46.3%	35.1%	0.002	1.59 (1.18, 2.14)
CKD ^Ω	7.9%	10.9%	0.175	0.70 (0.42, 1.16)
CPD ^α	35.2%	17.2%	<0.001	2.61 (1.85, 3.69)
DM ^β	19.1%	10.9%	0.002	1.93 (1.27, 2.93)
Chronic use of immunosuppressants	1.1%	0.2%	0.167	4.68 (0.52, 42.15)
Malignancy	2.0%	5.5%	0.019	0.36 (0.15, 0.84)
ICU Admission ^μ	61.0%	51.5%	0.010	1.47 (1.09, 1.97)

[‡] Cardiovascular diseases, ^Ω Chronic kidney disease, ^α Chronic pulmonary disease, [‡] Confidence interval, ^β Diabetes mellitus, ^μ Intensive care unit

Table 2. Gender, Comorbidities, and Intensive Care Unit Admission in Deceased and Survived patients

Variable	Mortality		P-value	Odds ratio (95% CI)
	Yes (n=631)	No (n=106)		
Male sex	59.1%	67.9%	0.086	0.68 (0.44, 1.10)
CVD [‡]	44.0%	17.0%	<0.001	3.60 (2.14, 6.06)
CKD ^Ω	10.6%	2.8%	0.011	4.07 (1.25, 13.21)
CPD ^α	28.6%	6.6%	<0.001	5.68 (2.59, 12.48)
DM ^β	16.4%	3.7%	0.001	5.03 (1.81, 13.96)
Chronic use of immunosuppressants	0.6%	0.9%	0.541	0.67 (0.07, 6.05)
malignancy	4.4%	0.9%	0.105	4.87 (0.65, 36.22)
ICU Admission [‡]	60.6%	27.3%	<0.001	4.10 (2.59, 6.46)

[‡] Cardiovascular diseases, ^Ω Chronic kidney disease, ^α Chronic pulmonary disease, [‡] Confidence interval, ^β Diabetes mellitus, [‡] Intensive care unit

tal stay was also longer in deceased patients (median=4, IQR=7 vs. median=2, IQR=1, P<0.001). The frequency of mortality was significantly higher in patients with a history of underlying conditions except for the chronic use of immunosuppressants and malignancy (Table 2).

Multivariable analysis

To adjust variables, a logistic regression model was designed with mortality as the dependent variable and age, gender, being a COVID-19 case, LOS, CVD, CKD, CPD, DM, and malignancy as independent variables. LOS, CVD, CPD, DM, CKD and malignancy were not statistically significant in the model (P>0.05) although they were significant in univariate analysis (except for malignancy). Finally, being a COVID-19 case, ICU admission and age were independent risk factors of mortality in cases who underwent CPR, by ORs equal to 28.75, 2.49, and 1.27, respectively (Table 3).

Kaplan-Meier and Cox regression survival analyses were executed. The event was considered as death following CPR and time as the follow-up duration. The variables which having a P-value of less than 0.2 in univariate analysis and a P-value of less than 0.05 in the log-rank test were entered into the model using a "backward conditional method". These variables included being a COVID-19 case, CVD, CPD, gender, ICU admission, and age. Gender, CPD, and ICU admission were omitted from the

model in 4 consecutive steps. Being a COVID-19 case had the highest HR (HR= 1.72, 95%CI: 1.46, 2.011, P<0.001) followed by CVD (HR=1.69, 95%CI: 1.44, 1.99, P<0.001). In addition to being a COVID-19 case and having a history of CVD, age was statistically significant in the Cox regression model (HR= 1.08, 95%CI: 1.04, 1.13, P=0.001, for every 10-year increase). The Kaplan-Meier curve showed a survival rate of 14.4%, 0.9%, and 26.0% in all patients, cases and controls recorded at the end of the study, respectively (Table 4). The survival curve of COVID-19 patients and non-COVID-19 patients is demonstrated in Figure 1.

Discussion

In the setting of this study, more than 40% of CPR procedures were performed on SARS-CoV-2 infected patients. The odds of mortality following CPR was found to be significantly higher in COVID-19 patients both before and after adjustment. The results of this study yield that there is less chance of survival in COVID-19 cases, who become critically ill during the course of their disease and experience cardiac arrest requiring CPR, in comparison to other patients. This finding might be due to the higher frequency of underlying conditions among COVID-19 patients as well as the higher age average in this group. It is already established that having a higher age increases the risk of mortality in COVID-19 (18) as seen in this

Table 3. Logistic Regression Model For Prediction of Mortality in Cases under Cardiopulmonary Resuscitation

Variable	Adjusted Odds ratio (95% CI) [‡]	P
COVID-19 positive	28.75 (8.87, 93.21)	<0.001
CVD [‡]	1.34 (0.67, 2.65)	0.397
CKD ^Ω	2.79 (0.75, 10.40)	0.124
CPD ^α	1.69 (0.67, 4.25)	0.260
DM ^α	1.25 (0.38, 4.08)	0.704
malignancy	2.61 (0.26, 25.66)	0.409
ICU admission [‡]	2.49 (1.39, 4.45)	0.002
Age ^Ω	1.27 (1.14, 1.41)	<0.001
Gender	0.86 (0.52, 1.44)	0.588
LOS [‡]	1.00 (0.97, 1.04)	0.628

^Ω For every ten years [‡]cardiovascular diseases, ^Ωchronic kidney disease, ^αchronic pulmonary disease, [‡]confidence interval, ^αdiabetes mellitus, [‡]intensive care unit, [‡]length of hospital stay
Model was adjusted for cardiovascular diseases, chronic kidney disease, chronic pulmonary disease, diabetes mellitus, intensive care unit admission, age for each ten years of increase, gender and length of hospital stay

Table 4. The Survival Rate of all Patients, COVID-19^α Cases and Non-COVID-19 Cases Following CPR

Survival rate	2 nd day	6 th day	15 th day	The end of the study
overall	98.9%	86.2%	30.1%	14.4%
COVID-19 case	98.8%	82.7%	20.2%	0.9%
Non-COVID-19	99.0%	89.1%	38.6%	26.0%

^α Coronavirus disease 2019

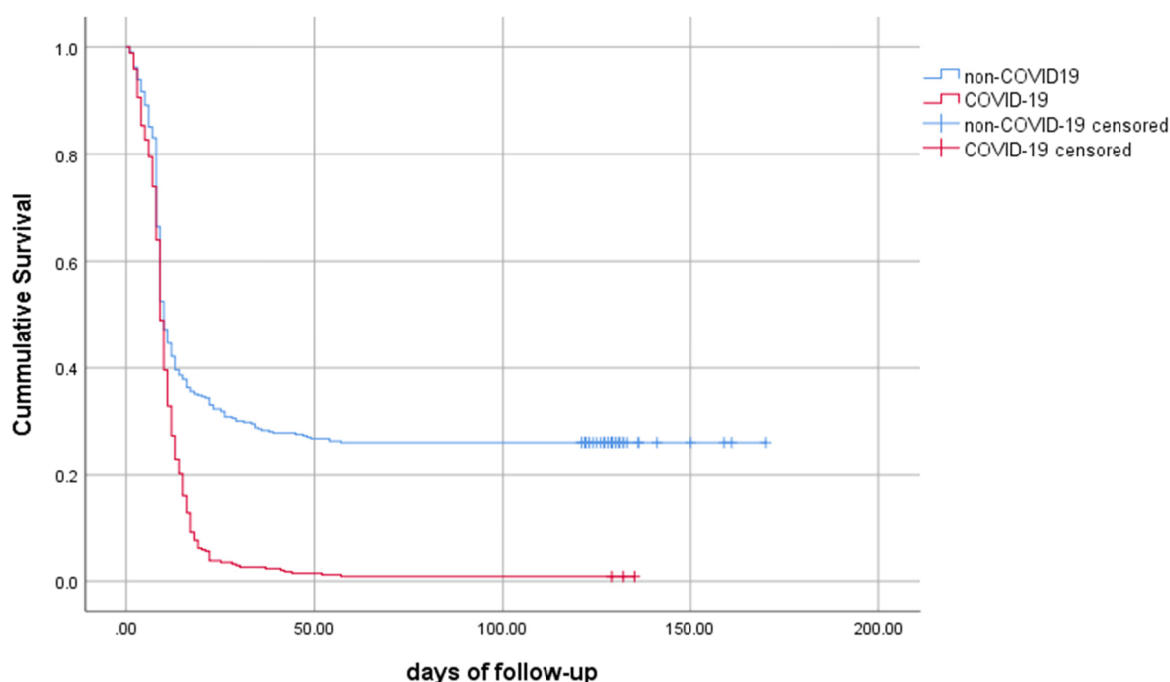


Fig. 1. The survival curve of non-COVID-19 and COVID-19 patients following cardiopulmonary resuscitation

study too. Besides, having a higher age leads to higher mortality following CPR (19). In this study, in the regression model, being a COVID-19 case had an OR of 35.0 (95%CI: 11.0, 112.3) when not adjusted for age, while the OR reduces to 29.0 after the adjustment for age is performed. A recent study with a smaller sample size also demonstrated the same significant risk of mortality following CPR in COVID-19 patients (5). After adjustment of variables in the regression model for successful CPR, age, ICU admission, and being a COVID-19 case remained probable risk factors of mortality. The high OR of being a COVID-19 case is probably the result of a small number of cases whose CPR was successful.

Older age and underlying conditions were demonstrated to be significant risk factors of mortality in COVID-19 patients in several recent studies (6, 7, 20). Results of this study also showed that these factors could lead to a higher risk of mortality in COVID-19 cases. One should take notice that this study only consisted of patients who underwent CPR, and they were typically expected to have higher frequencies of comorbid conditions and higher age average in comparison to other groups of patients according to previous investigations (21). The fact that the underlying conditions lost their significance in the logistic regression model might be due to the difference of general risk factors of mortality in COVID-19 patients compared to the risk factors which are related to CPR.

COVID-19 patients who underwent CPR were also more frequently admitted to ICU before undergoing CPR. This might be due to the fact that respiratory failure is the most common manifestation in COVID-19 patients who become critically ill, and respiratory support equipment is more efficiently available in ICU settings. The median of

LOS in COVID-19 patients who underwent CPR is five days which is close to what other studies have found (5) and longer in comparison to 2 days in controls. The reason could be because the studied hospitals also admit other patients with critical conditions in emergency wards resulting in a shorter LOS. In the logistic regression model, after the adjustment, LOS was not a statistically significant variable. This means that the LOS itself is possibly not a predictor of mortality in patients who underwent CPR.

It is worth mentioning that the success rate of CPR in patients with diagnoses other than COVID-19 was found to be 26%, which is higher than the average rate found by previous studies (21). This might be the consequence of data collection from tertiary and teaching hospitals with well-trained staff in this study. Although merely reporting the CPR success rate in COVID-19 patients is valuable, in order to provide a clearer comparison, a feasible option was to compare this rate with a relatively similar group of patients who underwent CPR in the same setting. We acknowledge that this control group was not the perfect one and this control group acts solely as a reference for comparison. Therefore, the interpretation of the results of the current study must be performed with caution. To the best of our knowledge, no other study has reported OR for mortality following CPR in COVID-19 patients, and there is still a shortage of evidence about this issue. We suggest later studies consider a larger sample size of COVID-19 cases with successful CPR to provide more information regarding this issue.

Performing CPR was found to be a challenge in COVID-19 patients in the literature. It is claimed that healthcare providers are concerned about performing CPR

on COVID-19 patients mainly because of a shortage of personal protection equipment and a lack of ample evidence on treatment and prophylaxis of possible infection. Due to the low success rate of CPR in poor prognosis patients, some authors are challenging the idea of whether to perform CPR on COVID-19 patients and suggested that new ethical codes should be established (11, 22). It should be taken into account that in our study, three COVID-19 patients survived after CPR and were discharged. Although the rate of successful CPR is low, it is evident that some patients survive after the procedure and it remains for the experts on the field to discuss the emerging ethical issues.

As far as we are aware, this is the first study to report the result of survival analysis on COVID-19 patients following CPR. The survival curve experiences a dramatic fall about the 10th to 15th day and reaches a plateau at about the 50th day. In non-COVID-19 patients, the same pattern can be observed but with a more dramatic fall in COVID-19 cases. The overall survival rate in previous studies was just above zero, which is in accordance with the results of our study (4, 5). The lack of control groups and small sample sizes were the most important limitations of these studies, which were addressed in the current study leading to relatively more accurate results.

We suggest further studies with case-control design to be performed in the future with COVID-19 patients who survived following CPR as cases and COVID-19 patients who did not survive as controls.

We had some limitations in our study, mainly due to the fact that the studies which use registries for data collection provide no control over the recording of the data as compared to non-registry studies. Firstly, the method of assessment of underlying conditions was the chronic use of medications related to each condition which can result in a slight underestimation of the number of cases. Some data in the resuscitation process were not recorded into the database, such as duration of resuscitation efforts, time to the first defibrillation, and time to the first injection of epinephrine and other medications. We do not know the precise interventions that patients had prior to cardiac arrest. Moreover, a PCR test was either not performed or came negative for non-COVID-19 patients therefore we suggest selecting non-COVID-19 patients more accurately by performing a PCR test for all the participants. The initial cardiac rhythm was not recorded into the database which is another limitation of this study. Furthermore, we suggest later studies choose their control group with regard to more prognostic and treatment factors. The strength of this study was its large sample size as well as being multicentric.

Conclusion

There may be very little chance of survival for critically ill COVID-19 patients who undergo CPR. Furthermore, older age and the severity of the disease were found to be risk factors of mortality in these patients.

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Conflict of Interests

The authors declare that they have no competing interests.

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