Cardiac arrest and coronavirus disease 2019

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Purpose of review
The impact of the coronavirus disease 2019 (COVID-19) on the cardiovascular system has been highlighted since the very first weeks after the severe acute respiratory syndrome coronavirus 2 identification. We reviewed the influence of COVID-19 pandemic on cardiac arrest, both considering those occurred out of the hospital (OHCA) and in the hospital (IHCA).

Recent findings
An increase in OHCA incidence occurred in different countries, especially in those regions most burdened by the COVID-19, as this seems to be bounded to the pandemic trend. A change of OHCA patients' characteristics, with an increase of the OHCA occurred at home, a decrease in bystander cardiopulmonary resuscitation and automated external defibrillator use before Emergency Medical Service (EMS) arrival and an increase in non-shockable rhythms, have been highlighted. A dramatic drop in the OHCA patients' survival was pointed out in almost all the countries, regardless of the high or low-incidence of COVID-19 cases. Concerning IHCA, a reduction in survival was highlighted in patients with COVID-19 who sustained a cardiac arrest.

Summary
Cardiac arrest occurrence and survival were deeply affected by the pandemic. Informative campaigns to the population to call EMS in case of need and the re-allocation of the prehospital resources basing on the pandemic trend are needed to improve survival.

Keywords
automatic external defibrillator, cardiac arrest, cardiopulmonary resuscitation, coronavirus disease 2019, severe acute respiratory syndrome coronavirus 2

INTRODUCTION

The first cases of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus were firstly described in China in December 2019 [1]. The clinical syndrome caused by this virus, called 'coronavirus disease 2019' (COVID-19) [2], has a wide spectrum of severity, from asymptomatic patients to patients with severe pneumonia and acute respiratory distress syndrome (ARDS) requiring mechanical ventilation [3]. The COVID-19 impact on the cardiovascular system has been highlighted since the first weeks after its identification [4,5▪].

OUT-OF-HOSPITAL CARDIAC ARREST AND CORONAVIRUS DISEASE 2019

A dramatic surge in out-of-hospital cardiac arrest (OHCA) was highlighted, for the very first time, in Lombardy Region [6▪], Italy, one of the first regions, outside of China, deeply affected by COVID-19 pandemic. Using data from the Cardiac Arrest Registry of the Lombardia Region (Lombardia CARe), a 58% increase of OHCA incidence compared with the same period of the previous year was pointed out during the first 40 days after the first diagnosed case of COVID-19. The increase in OHCA was particularly evident in the provinces more affected by COVID-19, i.e. Lodi and Cremona provinces, which experienced an increase in OHCA of 187% and 143% respectively as compared to 2019. This result was then confirmed analyzing the first 2 months of pandemic in the same territory [7▪] as the difference in cases of OHCA between 2020 and 2019 per 100

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KEY POINTS

- An increase in out-of-hospital cardiac arrest (OHCA) was highlighted during the pandemic especially in regions with high-incidence of coronavirus disease 2019 (COVID-19).
- The OHCA increase seems to be correlated to the COVID-19 incidence in a given area and recognize both infection-related and pandemic-related possible causes.
- An increase in OHCA occurred at home, a decrease in bystander cardio-pulmonary resuscitation and automated external defibrillator use before Emergency Medical Service arrival and an increase in not-shockable rhythms were highlighted.
- A dramatic decrease in OHCA survival occurred both in regions with high- and low-incidence of COVID-19 cases.
- Patients with COVID-19 who sustained a cardiac arrest, both out-of-hospital and in-hospital, had a lower chance of survival than non-COVID-19 patients.

000 inhabitants and the trend of COVID-19 cumulative incidence per 100000 inhabitants were found to be strongly and statistically significantly correlated. The same evidence was also proved in different part of the world during the first pandemic wave. In Europe, data from Paris area [8▪] reported a 2-fold increase in OHCA incidence immediately before and during the weeks after Paris lockdown; similarly in England, both in London [9▪] and in North East England [10] where an increase in OHCA incidence strongly correlated with the daily number of COVID-19 cases was noticed in March–April 2020. Moving to America, an increase in OHCA during the first pandemic wave was pointed out not only in New York City, the most important USA outbreak of COVID-19 during the first wave, where a 3-fold increase in OHCA was highlighted [11▪,12], but in also in areas other than the United States of America [13–16,17▪▪], as in Canada [18] and in Brazil [19]. A slight increase was observed also in some areas in Asia, as in Singapore [20]. However, some other studies in Europe [21,22,23▪,24▪], USA [25,26▪,27,28], Asia [29,30] and Australia [31▪▪,32] reported a stable incidence of OHCA in the period from March to May 2020. These inhomogeneous results more than a seeming contradiction are owed to an important regional variation probably due to different COVID-19 incidence.

Concerning this aspect, the first evidence about the weight of COVID-19 in explaining this regional variation came from the USA, where the higher the county-level of COVID-19 mortality rate per million residents, a surrogate of COVID-19 incidence, the higher the OHCA incidence [17▪▪]. Similar results were reached in the Lombardy Region [33▪], where the correlation between OHCA and COVID-19 incidence was confirmed not only during the first, but also during the second pandemic wave, highlighting how this correlation was found to be statistically significant only in those provinces whose cumulative incidence of COVID-19 overcame those of the whole territory. This trend stressed the importance of the burden of COVID-19 cases in a given area on the occurrence of OHCAs. Other studies, from several cities in different continents, reinforced this concept showing a direct association between the local prevalence COVID-19 and the frequency of OHCA only in those cities with a high impact of the pandemic, whereas less impacted cities revealed an unchanged (or even diminished) OHCA incidence [34].

CHANGING IN OUT-OF-HOSPITAL CARDIAC ARREST PATIENTS' CHARACTERISTICS AND OUTCOME

Not only the incidence, but also the profile of OHCA patients, has been deeply affected by COVID-19 pandemic. Firstly, an increase of in-home OHCA was pointed out during the outbreak regardless of the degree of the increase of OHCA incidence [7▪–9▪,20] and it was perfectly consistent with the 'lock-down' and 'stay-at-home' order which was issued globally during the first pandemic wave [35]. Moreover, in many areas, an increase in unwitnessed OHCA was highlighted [7▪,8▪,20], probably due to the fact that many people spent the quarantine in different rooms or houses than their relatives. The spectrum of etiologies of OHCA has also been influenced by the pandemic, with an increase of medical etiology [7▪,9▪,36], especially in those regions who experienced an increase in OHCA. Similarly, in these areas, the rate of OHCA with a shockable presenting rhythm decreased in favor of not-shockable ones [7▪,8▪,11▪,13,36]. Both these changes may be explained considering that many of the exceeding OHCA in 2020 were due to COVID-19 [6▪]. Such a medical condition may lead to a respiratory failure and the resulting hypoxia is one of the most likely cause of cardiac arrest [37–39], especially in the most affected areas where many patients were treated at home, because of the overcrowding of health facilities, and so they may have suffered a rapid deterioration of the clinical situation till the cardiac arrest [40].

This hypothesis is supported by meta-analysis focused on COVID-19 patients suffering from OHCA, in whom the percentage of not-shockable

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rhythms is significantly higher than in non-COVID-19 OHCA patients [41,42▪▪]. In addition to the location and the cause of cardiac arrest, also bystanders' initiated actions and the Emergency Medical Service (EMS) response have been affected by the pandemic. A decrease in cardio-pulmonary resuscitation (CPR) initiated before EMS was observed worldwide [7▪–9▪,20,23▪,24▪,27,43], both in areas with high and low-incidence of COVID-19. This is probably due to both the decrease of OHCA occurred in public places, where bystanders are most likely to initiate CPR, and the fear in performing CPR [44,45]. Albeit this fear was already present before the pandemic [46], especially about the performing mouth-to-mouth ventilation [47], the peculiar transmission route of SARS-CoV-2 through droplets exacerbated it. It will probably be one of the most important negative legacies of the COVID-19 pandemic that we will have to fight in the near future [48]. Similarly, also a reduction in automated external defibrillator (AED) use before EMS arrival was highlighted in almost all the countries regardless of COVID-19 incidence [7▪,8▪,24▪,27,31▪▪]. The reasons for that are probably the same of the reduction of bystanders CPR. It should also be considered that during pandemic, especially during the first pandemic wave, many first responder (FR) systems were suspended or restricted to some FR categories [49▪,50▪], probably contributing to the decrease in CPR and AED use before EMS. Beyond the intervention by bystanders and first responders, also the EMS intervention was affected by the outbreak. An increase in EMS intervention time was observed both in countries with high- and low-incidence of cases [7▪,9▪,20,27,29,30,31▪▪] and probably was owed to both the overload of the EMS, especially in high incidence countries [51], and the need for wearing personal protective equipment (PPE) [52]. This delay, if on the one hand seems not to have affected the capability of the EMS to properly treat the patients [53], on the other has probably contributed to increase the rate of patients with a non-shockable rhythm [54].

One of the most alarming and terrible factors concerning this topic is the dramatic reduction in the outcome of OHCA during the pandemic [8▪,9▪,10,11▪,13,17▪▪,23▪,27,29,30,31▪▪,36,42▪▪,43,55,56,57▪▪,58]. This affected all the outcomes commonly used for OHCA following Utstein recommendations [59], as the return of spontaneous circulation (ROSC), the survival at hospital admission and the survival at hospital discharge or at 30days, with and without good neurological outcome. If such a reduction was quite expected in the most hit countries with a higher proportion of COVID-19 related cardiac arrests characterized by an awfully poor outcome [7▪,37,60], it is truly alarming that a worsening of patients' outcome was observed almost in all the countries at low-incidence of COVID-19, as for example in Victoria Region in Australia [31▪▪], where a 54% reduction in survival at hospital discharge was highlighted. The reasons are probably to be found in all the changes discussed above and their overcoming represents the most important challenge for resuscitation science in the coming years.

CAUSES OF THE INCREASE IN OUT-OF-HOSPITAL CARDIAC ARREST INCIDENCE DURING PANDEMIC

The respiratory failure due to SARS-CoV-2 infection, as shown before, may explain some of the OHCAs during the pandemic, but it was unable to explain the whole, dramatic, increase observed in the areas with high-incidence of COVID-19 cases. We believe that it is possible to define two main categories of causes at the basis of OHCAs increase during the pandemic: the infection-related and the pandemic-related causes. Among the first group, besides the pneumonia induced respiratory failure, also pulmonary embolism [61] may play a role. This occurrence was an under-known issue during the first months of the pandemic, but then it has been demonstrated to be a potential and possibly life-threatening complication of COVID-19. Moreover, the myocardial injury, diagnosed in a high proportion of patients hospitalized for COVID-19 [4,5▪,62], may have acted in the occurrence of cardiac arrest also among patients at home. The myocardial damage during SARS-CoV-2 infection can be either a primary cardiac damage, as in type 1 myocardial infarction promoted by viral infection [63,64▪] and in SARS-CoV-2 related myocarditis [65,66], or a secondary cardiac damage, like in type 2 myocardial infarction, favored by the inflammatory response and fever leading to an increase in the body's metabolic demands [67]. Furthermore, also the acute de-compensation of chronic heart failure (HF) and de-novo HF as a consequence of myocardial injury may have had a role in increasing OHCAs. The last mechanism of the infection-related causes may be the occurrence of primary ventricular arrhythmias in COVID-19 patients. These arrhythmias may be favored by the effect of hydroxychloroquine and azithromycin [68], which were proposed as a treatment for COVID-19 during the first pandemic wave [69] despite some effects on QT interval. This gains even more importance if you consider that QT interval was found to be longer than expected also in COVID-19 patients not receiving these drugs [70]. One of the possible explanations is that inflammatory cytokines activation during SARS-CoV-2 infection, particularly interleukin-6 (IL-6), can suppress IKr

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(rapid delayed rectifier channel) in heterologous cells and myocytes resulting in prolonged repolarization [71]. Whatever the mechanism, the prolongation of the QT interval can promote the development of malignant ventricular arrhythmias [72], which can lead to cardiac arrest.

Concerning the pandemic-related causes, the unprecedented reduction in outpatient visits experienced during the lockdown, especially in the first pandemic wave, had a detrimental effect on chronic patients [73,74]. However, undoubtedly, the major role was played by the fear of in-hospital infection [75], that lead many patients to delay the EMS call [76,77▪] or prevented them to call the EMS at all in case of time-dependent diseases (i.e. myocardial infarction, stroke, etc.) [78▪,79]. This was perfectly in line both with the reports concerning the reduced rate of hospital admissions for acute coronary syndrome (ACS) during the COVID-19 outbreak [80▪,81,82] and concerning the impressive reduction in emergency department (ED) patient attendance during lockdown period [83]. This fear of in-hospital infection is probably more evident in the areas with high-incidence of COVID-19 cases, as the population knew the load of people hospitalized for COVID-19 in the hospital of their area [33▪]. Such a behavior may have led to at-home deterioration of time-dependent diseases until the OHCA occurrence, stressing the importance of information campaigns focusing on the importance of early EMS activation in case of real need to prevent COVID-19 from being a disease that kills at home.

IN-HOSPITAL CARDIAC ARREST AND CORONAVIRUS DISEASE 2019

Hospitalized patients with COVID-19 may develop in-hospital cardiac arrest (IHCA) for several reasons.

Up to one-third may develop severe hypoxemia needing non-invasive respiratory support, invasive mechanical ventilation or extracorporeal membrane oxygenation [84,85]. Thus, refractory hypoxemia can be a leading cause of IHCA in this patients' population [86]. Potential consequences of mechanical ventilation, such as pneumothorax due to barotrauma, and the above mentioned pathophysiological COVID-19 related events (i.e. thromboembolism, myocarditis) also contribute as potentially reversible causes of IHCA. Moreover, cardio-respiratory comorbidities have been identified as risk factors for the most severe form of COVID-19 and death [87]. Pandemic peaks have led to un-precedent number of admission of patients with acute respiratory failure and critical care resources have been less than demands worldwide. This has contributed to suboptimal assistance to hospitalized COVID-19 patients, with increased risk of unrecognized deterioration and death [88].

A recent systematic review including 10 studies and 1179 patients with COVID-19 who developed IHCA and who received CPR attempts [89▪] estimated an overall rate of IHCA of 4.1%. It is important to note that all the included studies concerned the first wave of pandemic and that the IHCA incidence may have differed among pandemic timeframes in different geographic settings [86]. The non-shockable were the most common presenting rhythms (89%) and the overall rate of ROSC after CPR attempts was 32.9%. The overall mortality rate (in-hospital or at 30 days) was 89.9%, whereas the favorable neurological status [Cerebral Performance Category (CPC) score 1–2] at 30 days was very low (6.3%). The mortality rate was roughly similar between COVID-19 patients who developed IHCA in ICU vs. wards (86% vs. 95%). A subgroup analysis from three studies showed that patients with COVID-19 who developed IHCA have a significantly higher risk of death after CPR attempts than comparable non-COVID-19 ones (odds ratio [OR] 2.34).

IHCA in COVID-19 have other two peculiarities. The first is the risk of infection by healthcare providers who attempt CPR. Indeed, the World Health Organization lists CPR as an aerosol generating procedure [90] and specific algorithm by relevant societies have been released. Once started,the CPR performance can be suboptimal due to PPE and fatigue [91], leading to worse outcome in this patients' population [92,93].

The second is that prone position has been extensively used as respiratory support co-intervention in both awake and intubated patients [94]. This resulted into an un-precedent number of IHCA occurring in prone patients. The best strategy to attempt CPR in this situation is unclear (i.e. prone CPR vs. turning supine first), and this adds difficulties to a prompt response to IHCA [95▪]. Finally, although a universal do-not-resuscitate order for COVID-19 hospitalized patients cannot be justified by the data, it is pivotal to consider as early as possible the appropriateness of CPR attempt. Data from UK demonstrated that 44% of patients presenting to hospitals with COVID-19 have a do-not-resuscitate order established at the admission to the emergency department or throughout the hospital stay [96]. This underlines the need for an early comprehensive triage to reduce useless or unwanted CPR attempt in IHCA of patients with COVID-19 [97].

CONCLUSION

Cardiac arrest occurrence and survival were deeply affected by the pandemic. Public information

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campaigns to call EMS in case of need are required as well as sufficient prehospital resources to respond at times of peak demand.

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Conflicts of interest

There are no conflicts of interest.

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