COVID-19 kills at home: the close relationship between the epidemic and the increase of out-of-hospital cardiac arrests

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Aims	An increase in out-of-hospital cardiac arrest (OHCA) incidence has been reported in the very early phase of the COVID-19 epidemic, but a clear demonstration of a correlation between the increased incidence of OHCA and COVID-19 is missing so far. We aimed to verify whether there is an association between the OHCA difference compared with 2019 and the COVID-19 epidemic curve.
Methods and results	We included all the consecutive OHCAs which occurred in the Provinces of Lodi, Cremona, Pavia, and Mantova in the 2 months following the first documented case of COVID-19 in the Lombardia Region and compared them with those which occurred in the same time frame in 2019. The cumulative incidence of COVID-19 from 21 February to 20 April 2020 in the study territory was 956 COVID-19/100 000 inhabitants and the cumulative incidence of OHCA was 21 cases/100 000 inhabitants, with a 52% increase as compared with 2019 (490 OHCAs in 2020 vs. 321 in 2019). A strong and statistically significant correlation was found between the difference in cumulative incidence of OHCA between 2020 and 2019 per 100 000 inhabitants and the COVID-19 cumulative incidence per 100 000 inhabitants both for the overall territory (ρ 0.87, $P < 0.001$) and for each province separately (Lodi: ρ 0.98, $P < 0.001$; Cremona: ρ 0.98, $P < 0.001$; Pavia: ρ 0.87, $P < 0.001$; Mantova: ρ 0.81, $P < 0.001$).
Conclusion	The increase in OHCAs in 2020 is significantly correlated to the COVID-19 pandemic and is coupled with a reduction in short-term outcome. Government and local health authorities should seriously consider our results when planning healthcare strategies to face the epidemic, especially considering the expected recurrent outbreaks.

Graphical Abstract
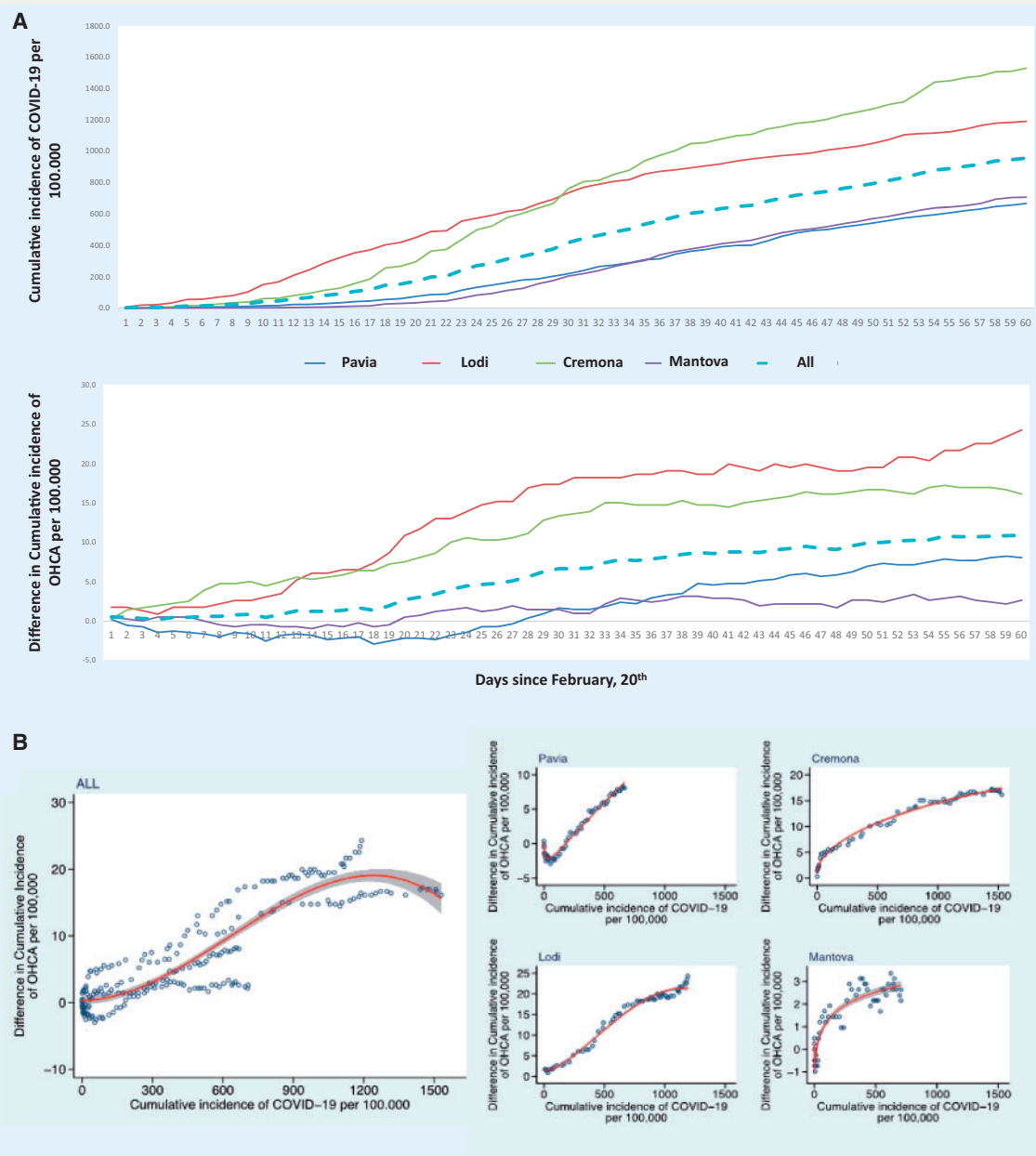
Introduction

A novel coronavirus, capable of human to-human transmission, emerged in China at the end of 2019[1] and was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[2] The resulting infection, called 'Coronavirus disease 2019' (COVID-19), has a wide spectrum of severity, from asymptomatic or pauci-symptomatic patients to patients with severe pneumonia and acute respiratory distress syndrome (ARDS) requiring mechanical ventilation.[3] Northern Italy was one of the first regions outside China to be significantly affected by COVID-19.[4] The first case of severe pneumonia due to SARS-CoV-2 without history of possible exposure abroad was

diagnosed in Codogno, Province of Lodi, Lombardy Region on 20 February 2020. Since then, the number of infections has been rapidly increasing, with a mortality rate higher than that of China,[5] and an increase in incidence of out-of-hospital cardiac arrest (OHCA) in the very early phase of the epidemic also being reported.[6] However, the correlation between the increase in OHCAs observed in 2020 and the COVID-19 epidemic curve still remain unproved. Our aim was to assess whether the difference in the number of OHCAs between 2020 and 2019 was statistically correlated with the COVID-19 epidemic trend and to look for clinical pre-hospital elements supporting this evidence.

Methods

Study population

The Lombardia Cardiac Arrest Registry (Lombardia CARe: NCT03197142) is a multicentre longitudinal prospective registry that has been registering all the OHCAs from the Province of Pavia since January 2015 and additionally from the Provinces of Lodi, Cremona, and Mantua Pavia since January 2019. All the data are collected following Utstein 2014 recommendations.[7] It was approved by the Ethical Committee of the Fondazione IRCSS Policlinico San Matteo (proc. 20140028219) and by all the others involved in the territory.

We considered all the OHCAs that occurred in these four provinces in the southern part of the Lombardy Region, in northern Italy, in the 2 months following the first documented case in the Lombardy Region (21 February 2020 to 20 April 2020) and those of the same time frame in 2019 (21 February 2019 to 21 April 2019, to account for the leap year). For the Province of Pavia, the mean value of OHCAs that occurred in the same time frame from 2015 to 2019 was also provided as historical reference. The daily new cases and the cumulative incidence of COVID-19, based on the confirmed cases announced by the National Department of Civil Defence/Protezione Civile Nazionale,[8] were also computed.

All the Emergency Medical System (EMS) electronic records have been reanalysed and the number of patients with suspected COVID-19 (fever for at least 3 days before OHCA associated with cough and/or dyspnoea) or with a diagnostic pharyngeal swab (performed before OHCA or after death) have been computed. Moreover, among the patients with suspected or diagnosed COVID-19, eventual gastrointestinal symptoms (vomiting or diarrhoea for at least 3 days) were assessed.

All the ECGs acquired in the field after the return of spontaneous circulation (ROSC) were evaluated for OHCA patients in 2020, and the QTc value was calculated with Bazett's formula. QTc was defined as prolonged if longer than 440 ms in males and 460 ms in females.[9]

We also counted the number of emergency calls received by the EMS dispatch centre and the resulting number of callouts for any pathology for both the 2020 and 2019 study periods. Among those, we counted, and compared with the previous year, those leading to a pre-hospital diagnosis of ST-segment elevation myocardial infarction (STEMI) according to the criteria recommended by the 2017 guidelines of the European Society of Cardiology.[10]

Data management

The data of the study are collected and managed using REDCap electronic data capture tools hosted at Fondazione IRCCS Policlinico San Matteo.[11,12] REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies, providing (i) an intuitive interface for validated data capture; (ii) audit trails for tracking data manipulation and export

procedures; (iii) automated export procedures for seamless data downloads to common statistical packages; and (iv) procedures for data integration and interoperability with external sources.

Statistical analysis

We present categorical variables as counts and percentage; we computed the difference in percentage between 2020 and 2019 together with its 95% confidence interval (CI) using a binomial regression model with identity link. We present continuous variables using the median and 25th–75th percentiles; we computed the difference in medians and 95% CI using quantile regression. We computed the Spearman R and its 95% CI to measure the strength of the correlation of difference in cumulative incidence in OHCAs between 2020 and 2019 per 100 000 inhabitants and COVID-19 cumulative incidence per 100 000 inhabitants for the entire series and for each province. To assess whether the 2020–2019 difference in incidence over time of OHCA paralleled that of COVID-19 in 2020, we used fractional polynomials within a generalized regression linear model to model the relationship of these two variables, and plotted the fitted and observed values. We assessed the interaction of the cumulative incidence of COVID-19 and OHCA difference and fitted the same models separately for each province. Given the risk of overfitting, these models are to be considered exploratory. Statistical analyses were performed with the MedCalc version 19.2 (MedCalc Software Ltd) and the Stata software (version 16, StataCorp, College Station, TX, USA). All tests were two-sided, and a P-value <0.05 was considered statistically significant.

EMS adaptation to the COVID-19 outbreak

During the COVID-19 outbreak, the number of BLS-D- and ALS-trained staffed vehicles increased by 40% (from 45 to 63) and by 29% (from 21 to 27), respectively. The EMS dispatchers and personnel were instructed to investigate for any possible symptoms related to COVID-19, both during the emergency call and at the patient's side from the caller, the relatives, and the eventual bystanders. Moreover, EMS personnel had been instructed to wear personal protective equipment (PPE; face shield, N95 face mask, and isolation gown) before starting resuscitation in case of doubt or if diagnosed for COVID-19. No specific changes in BLS or ALS protocols were adopted during the COVID-19 epidemic. See the Supplementary material online for details of the EMS description.

Results

The cumulative incidence of COVID-19 from 21 February to 20 April 2020 in the territory of the study was 956 COVID-19/100 000 inhabitants (Lodi 1190; Cremona 1529; Pavia 667; Mantua 706) and the cumulative incidence of OHCA was 31.7 cases/100 000 inhabitants, with a 52% increase compared with 2019 (490 OHCA in 2020 vs. 321 in 2019).

The increase in OHCA cases per 100 000 inhabitants was confirmed in each province, even if with different magnitude, according to the start of the epidemic (Lodi: +169%; Cremona: +106%; Pavia: +31%; Mantua: +12%) (Table 1). Notably, when considering the Province of Pavia as the historical reference, the mean incidence of OHCAs per 100 000 in the study period from 2015 to 2019 was 21.5 cases (95% CI 18.2–24.7).

Table 1 Relationship of COVID-19 per 100 000 inhabitants and OHCA difference between 2020 and 2019 cumulative incidences per 100 000 from days 1 to 60

Description					Model with fractional polynomials		
Province	Cumulative incidence per 100 000		% increase	Cumulative incidence per 100 000 COVID-19	Spearman's ρ	95% CI	P-value
	2020 OHCA	**2019 OHCA**					
All*	31.7	20.8	+52%	956	0.87	0.84–0.9	<0.001
Lodi	38.7	14.4	+169%	1,190	0.98	0.97–0.99	<0.001
Cremona	31.5	15.3	+106%	1,529	0.98	0.97–0.99	<0.001
Pavia	34.1	26	+31%	667	0.88	0.8–0.92	<0.001
Mantova	24.7	22.1	+12%	706	0.81	0.7–0.88	<0.001

*P for interaction with province <0.001.

Correlation between OHCA excess in 2020 and COVID-19

Statistical correlation

A strong and statistically significant correlation was found between the difference in cases of OHCA between 2020 and 2019 per 100 000 inhabitants and the trend of COVID-19 cumulative incidence per 100 000 inhabitants, both for the overall territory. In all cases, the association was strong, with a Spearman ρ >0.80 both for the entire case series and for each province (*Table 1*). Graphically, the overall association was best described by a polynomial including a square root followed by cubic transformation of the original variable. As a strong modifying effect by province of the relationship of the OHCA difference and COVID-19 cumulative incidence was present (*P* for interaction <0.001), we described each province separately; each had a different shape and slope of the corresponding curve (*Figure 1*).

Clinical findings

The comparison of the patient and OHCA characteristics between the two years is presented in *Table 2*. Of note, medical aetiology (94.9% vs. 89.4%; *P* = 0.006), home location (90.2% vs. 83.2%; *P* = 0.005), and unwitnessed OHCAs (53.5% vs. 45.8%; *P* = 0.037) were more frequent in 2020 compared with 2019; EMS arrival time was longer (15 min vs. 12 min; *P* < 0.001) and the outcome of patients with resuscitation attempted by EMS was worse in 2020 (pre-hospital ROSC 8.6% vs. 19.8%; *P* < 0.001 and survival at hospital discharge 5.1% vs. 9.5%; *P* = 0.06).

Among the 490 OHCA patients in 2020, 19 had a defined diagnosis of COVID-19 and 106 presented only suspected COVID-19 symptoms (fever for at least 3 days before OHCA associated with cough and/or dyspnoea). These 125 patients (25.5% of all OHCAs in 2020) represent 74% of the increase in OHCA in 2020, equally distributed in the four provinces (30 in Lodi, 32 in Cremona, 42 in Pavia, and 21 in Mantua). Moreover, among these 125 patients, gastrointestinal symptoms (vomiting or diarrhoea for at least 3 days) were also present in 9 (7.2%). The characteristics of these patients, as well as their comparison with unsuspected/undiagnosed patients, are presented in *Table 3*.

Out of the 27 patients transported with ROSC in 2020, a post-ROSC ECG was available and could be evaluated in 18 (67%), 6 of them with suspected or diagnosed COVID-19, with a median QTc value of 464 ms [interquartile range (IQR) 420–486]. Notably the QTc values was prolonged in 12 patients (4 of them with suspected or diagnosed COVID-19).

Finally, the number of emergency calls to the EMS dispatch centre and the resulting callouts increased by 94.1% (55 903 in 2020 and 28 794 in 2019) and by 20.3% (26 729 in 2020 and 22 212 in 2019) in 2020 compared with the same period in 2019. Among the overall emergency calls, those with a resulting diagnosis of STEMI were 43 in 2020 and 72 in 2019, with a reduction of 40.2%.

Discussion

Our study provides important insights into the impact of COVID-19 on OHCAs during the first 2 months of the epidemic from one of the first and most burdened areas worldwide. The main finding of our study is the strong and statistically significant correlation of the difference between the 2020 and 2019 OHCAs and the COVID-19 epidemic. Of note, the correlation was maintained even in the presence of a different phase of the epidemic, characterized by a more rapid rise at the beginning, towards a plateau in the latter part.

This aspect becomes even more evident when considering the different provinces separately, where specific shapes of the relationship were also shown when modelling using fractional polynomials. Interestingly, despite different shapes of the epidemic curve, the excess of OHCAs strictly followed the COVID-19 epidemic in all the phases of the epidemic in each province.

From our perspective, this latter finding, together with the high percentage of OHCA patients with suspected or diagnosed COVID-19, strongly supports the presence of a link between the infection and such a dramatic condition as that of cardiac arrest. Furthermore, considering only the Province of Pavia, from where we have collected OHCA data since January 2015, the number of OHCAs was quite stable in the same 2-month period from 2015 to 2019, so an impressive increase in OHCA as documented in 2020 would be unexplained except for the COVID pandemic with which it was in a strong statistical relationship. Different pathophysiological reasons may support this relationship, attributable both to infection- and pandemic-related issues.

Concerning infection-related issues, the first and more predictable reason is the occurrence of cardiac arrest due to respiratory failure
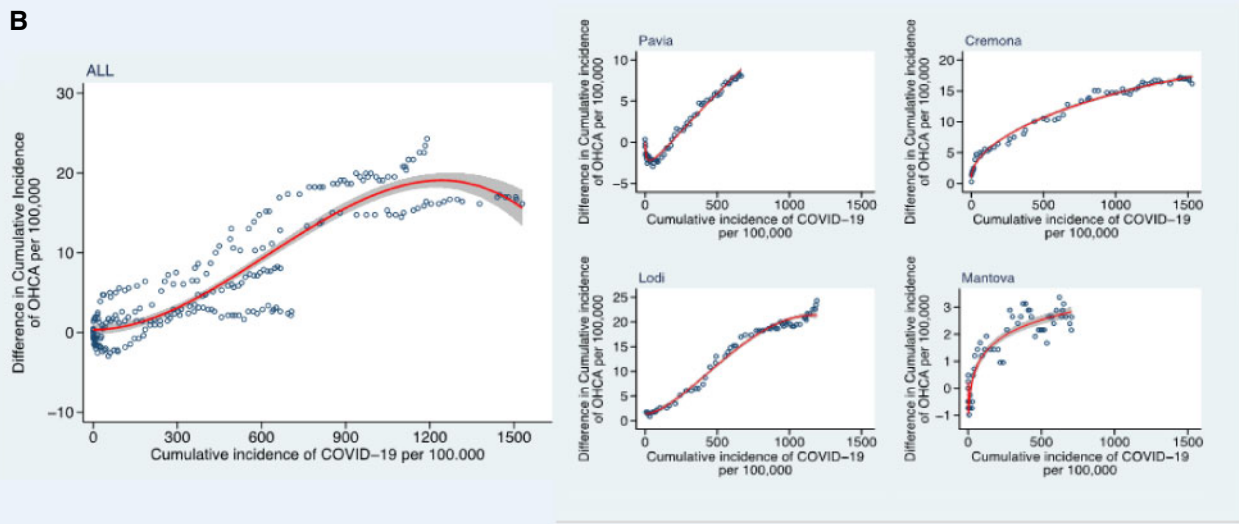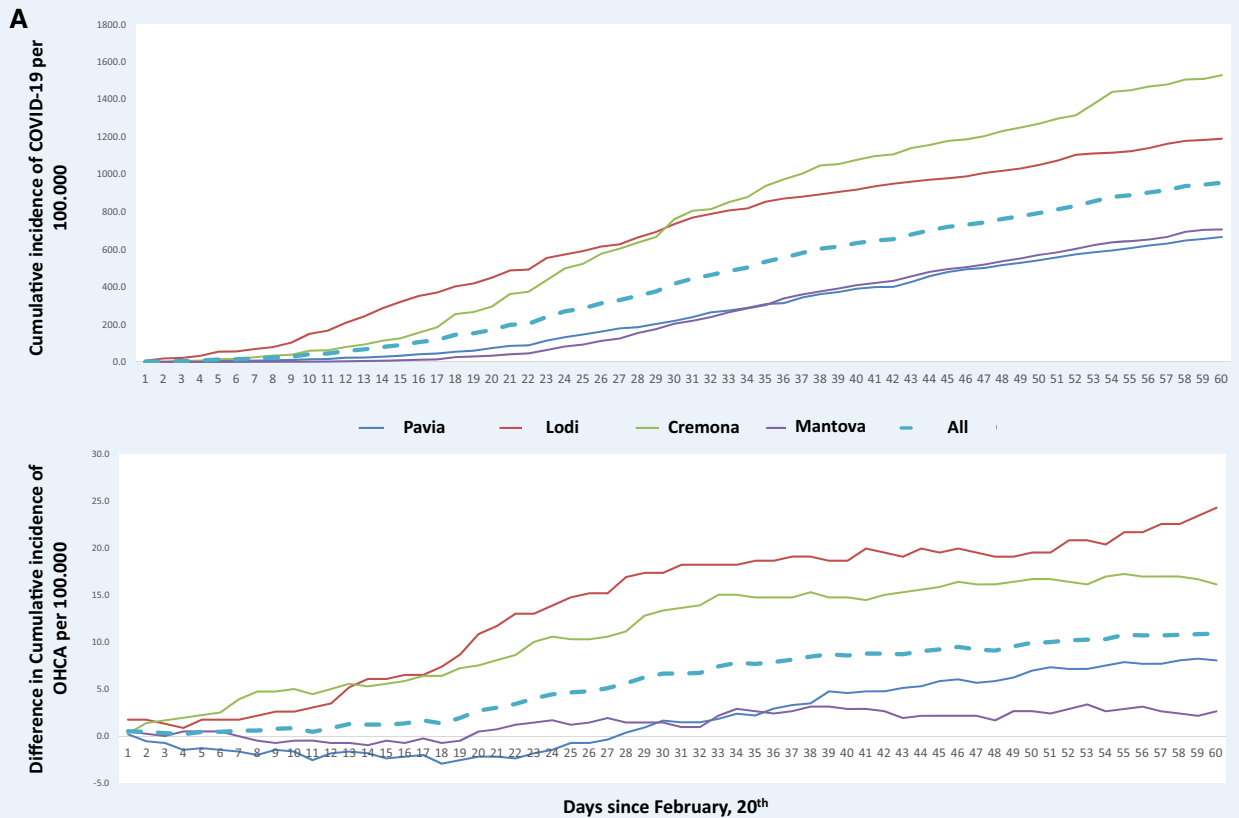
Take home figure *(A)* Over a period of 60 days from 20 February, the cumulative incidence of COVID-19 per 100 000 inhabitants in the four provinces and in the overall territory (dotted line) (upper part), and the trend of the difference of OHCA between 2020 and 2019 per 100 000 inhabitants in the four provinces and in the overall territory (dotted line) (bottom part). *(B)* The cumulative incidence of the difference in OHCA between 2020 and 2019 per 100 000 inhabitants as a function of the cumulative incidence of COVID-19 per 100 000 inhabitants, since 20 February 2020. Dots are the observed values. The red line is the function fitted using fractional polynomials. The shaded area is the 95% CI for the estimates.

caused by SARS-CoV-2, as it is the most feared life-threatening complication.[13,14] There are at least two elements supporting this theory. The former is the presence of suspected symptoms or of a defined diagnosis of COVID-19 before the event in 125 patients, representing

74% of the increase in OHCAs in 2020. The latter is that hypoxia is one of the causes known to be associated to non-shockable presenting rhythm,[15] being one of the 'five Hs and Ts'. This, along with the 3-min increase in EMS arrival time,[16] could explain the increase in

Table 2 Comparison between patients' and OHCAs' characteristics in 2020 and 2019 period

Variable	2020 (n = 490)	2019 (n = 321)	Difference (95% CI)*	P-value
Males, (%)	321 (65.5)	188 (58.6)	6.9 (0.1–13.8)	0.047
Age, years (IQR)	78 (67–84)	79 (67–86)	−1 (−3.2 to 1.2)	0.366
EMS arrival time, min (IQR)	15 (11–20)	12 (9–15)	3 (1.9–4.1)	<0.001
Aetiology of arrest, n (%)				
Medical	465 (94.9)	287 (89.4)	5.5 (95%CI, 1.6 to 9.4)	0.006
Trauma	13 (2.6)	28 (8.7)	−6.1 (−9.5 to −2.7)	<0.001
Drowning	0 (0)	0 (0)	−	
Overdose	1 (0.2)	1 (0.3)	−0.1 (−0.8 to 0.6)	0.77
Electrocution	0 (0)	0 (0)	−	
Asphyxia (external causes)	11 (2.3)	5 (1.6)	0.7 (−1.2 to 2.6)	0.47
OHCA location, n (%)				
Home	442 (90.2)	267 (83.2)	7 (2.2–11.9)	0.005
Nursing residence	21 (4.3)	23 (7.2)	−2.9 (−6.2 to 0.5)	0.09
Workplace	2 (0.4)	0 (0)	−0.4 (−1 to 0.2)	0.16
Street	17 (3.5)	23 (7.2)	−3.7 (−6.9 to −0.4)	0.026
Public building	3 (0.6)	5 (1.5)	−0.9 (−2.5 to 0.6)	0.22
Sport	0 (0)	1 (0.3)	−	
Other	5 (1)	2 (0.6)	0.4 (−0.8 to 1.6)	0.5
Witnessed status, n (%)				
Unwitnessed	261 (53.3)	147 (45.8)	7.5 (0.5–14.5)	0.037
Bystander witnessed	171 (34.9)	143 (44.5)	−9.6 (−16.5 to −2.8)	0.006
Witnessed by EMS	58 (11.8)	31 (9.7)	2.1 (−2.1 to 6.5)	0.32
Resuscitation attempted by EMS, n (%)				
Yes	314 (64.1)	222 (69.2)	−5.1 (−11.7 to 1.5)	0.13
No, dead on arrival	148 (30.2)	73 (22.7)	7.5 (1.3–13.6)	0.017
No, considered futile	28 (5.7)	26 (8.1)	−2.4 (−6 to 1.2)	0.2
Bystander CPR, n (%)[†]	89 (34.6)	87 (45.3)	−10.7 (−19.8 to −1.5)	0.02
Presenting rhythm, n (%)[‡]				
Shockable	36 (11.5)	37 (16.7)	−5.2 (−11.2 to 0.8)	0.09
Not shockable	278 (88.5)	185 (83.3)	5.2 (−0.8 to 11.2)	0.09
ACLS initiated, n (%)[‡]	138 (43.9)	138 (62.2)	−18.3 (−26.6 to −9.8)	<0.001
Amiodarone administered, n (%)[§]	17 (12.3)	16 (11.6)	0.7 (−6.9 to 8.4)	0.85
Adrenaline administered, n (%)[§]	120 (89.5)	119 (86.9)	2.6 (−0.5 to 10.4)	0.49
Mechanical CPR, n (%)[§]	9 (6.5)	23 (16.7)	−10.2 (−17.6 to −2.7)	0.008
Outcome, n (%)[‡]				
Death in the field	253 (80.6)	156 (70.3)	10.3 (2.9–17.7)	0.007
Transported with ongoing CPR	34 (10.8)	22 (9.9)	0.9 (−4.3 to 6.1)	0.73
Transported with ROSC	27 (8.6)	44 (19.8)	−11.2 (−17.3 to −5.1)	<0.001
Survived at hospital discharge, n (%)[‡]	16 (5.1)	21 (9.5)	−4.4 (−8.9 to 0.2)	0.06

EMS, emergency medical service; OHCA, out-of-hospital cardiac arrest; CPR, cardio-pulmonary resuscitation; ACLS, advanced cardiac life support (i.e. endotracheal intubation, administration of drugs, mechanical CPR); ROSC, return of spontaneous circulation.
*Differences are expressed as rate difference or mean difference and 95% confidence intervals.
[†]Among those in whom resuscitation was attempted by the EMS and excluding those witnessed by the EMS.
[‡]Among those in whom resuscitation was attempted by the EMS.
[§]Among those in whom ACLS was initiated.

non-shockable rhythm. However, questions arise as to why these patients developed respiratory failure at home. The rapid progression toward ARDS has been reported in single case reports describing a rapid worsening to respiratory failure, even in patients who were apparently stable a few hours earlier.[17,18] This could have been fatal to some patients, not leaving them sufficient time to activate the

emergency system. This phenomenon is truly alarming, especially considering that the age of the patients who suffered an OHCA during the epidemic is not particularly high and is similar to that in 2019. Moreover, in some cases, the severity of the clinical situation and the risk of its rapid progression could have been undervalued, with resulting at-home care attempts favoured by the impossibility of mass

Table 3 Characteristics of patients with OHCA suspected or diagnosed for COVID-19

Variable	COVID-19 suspected or diagnosed (n = 125)	COVID-19 not suspected or diagnosed (n = 365)	Difference (95% CI)*	P-value
Symptoms suspected (fever associated with cough and/or dyspnoea)	125 (100)			
Defined diagnosis of COVID-19	19 (15.2)			
Gastrointestinal symptoms	9 (7.2)			
Males, n (%)	83 (66.4)	238 (65.2)	1.2 (−8.4 to 10.8)	0.81
Age, years (IQR)	77 (70.2–83.7)	78 (67–84)	−1 (−4 to 2)	0.52
EMS arrival time, min (IQR)	16 (12–22.2)	14 (11–19)	2 (0.5–3.4)	0.007
Aetiology of arrest, n (%)				
Medical	125 (100)	340 (93.1)	–	
Trauma	0 (0)	13 (3.6)	–	
Drowning	0 (0)	0 (0)	–	
Overdose	0 (0)	1 (0.3)	–	
Electrocution	0 (0)	0 (0)	–	
Asphyxia (external causes)	0 (0)	11 (3)	–	
OHCA location, n (%)				
Home	119 (95.2)	323 (88.5)	6.7 (1.7–11.7)	0.008
Nursing residence	5 (4)	16 (4.4)	−0.4 (−4.4 to 3.6)	0.85
Workplace	0 (0)	2 (0.5)	–	
Street	1 (0.8)	16 (4.4)	−3.6 (−6.2 to −1)	0.007
Public building	0 (0)	3 (0.8)	–	
Sport	0 (0)	0 (0)	–	
Other	0 (0)	5 (1.4)	–	
Witnessed status, n (%)				
Unwitnessed	61 (48.8)	200 (54.8)	−6 (−16.1 to 4.1)	0.25
Bystander witnessed	39 (31.2)	132 (36.2)	−5 (−14.5 to 4.5)	0.31
Witnessed by EMS	25 (20)	33 (9)	11 (3.4–18.6)	0.005
Resuscitation attempted by EMS, n (%)				
Yes	88 (70.4)	226 (61.9)	8.5 (−1 to 17.9)	0.078
No, dead on arrival	27 (21.6)	121 (33.1)	−11.5 (−20.2 to −2.9)	0.009
No, considered futile	10 (8)	18 (4.9)	3.1 (−2.2 to 8.3)	0.25
Bystander CPR, n (%)[†]	13 (20.6)	76 (39.2)	−18.6 (−30.7 to −6.4)	0.003
Presenting rhythm, n (%)[†]				
Shockable	8 (9.1)	28 (12.4)	−3.3 (−10.7 to 4.1)	0.38
Not shockable	80 (90.9)	198 (87.6)	3.3 (−4.1 to 10.7)	0.38
ACLS initiated, n (%)[‡]	32 (36.4)	106 (46.9)	−10.5 (−22.5 to 1.4)	0.08
Amiodarone administered, n (%)[§]	3 (9.4)	14 (13.2)	−3.8 (−15.8 to 8.1)	0.53
Adrenaline administered, n (%)[§]	28 (87.5)	92 (90.2)	−2.7 (−15.5 to 10.1)	0.68
Mechanical CPR, n (%)[§]	2 (6.2)	7 (6.6)	−0.4 (−10 to 9.3)	0.94
Outcome, n (%)[‡]				
Death in the field	70 (79.5)	183 (81)	−1.5 (−11.3 to 8.4)	0.77
Transported with ongoing CPR	11 (12.5)	23 (10.2)	2.3 (−5.6 to 10.3)	0.57
Transported with ROSC	7 (8)	20 (8.8)	−0.8 (−7.7 to 5.9)	0.79
Survived at hospital discharge, n (%)[§]	2 (2.3)	14 (6.2)	−3.9 (−8.3 to 0.5)	0.08

EMS, emergency medical service; OHCA, out-of-hospital cardiac arrest; CPR, cardio-pulmonary resuscitation; ACLS, advanced cardiac life support (i.e. endotracheal intubation, administration of drugs, mechanical CPR); ROSC, return of spontaneous circulation.
*Differences are expressed as rate difference or mean difference and 95% confidence intervals.
[†]Among those in whom resuscitation was attempted by the EMS and excluding those witnessed by the EMS.
[‡]Among those in whom resuscitation was attempted by the EMS.
[§]Among those in whom ACLS was initiated.

hospitalization, despite extraordinary efforts of the local and national government to immediately increase ICU beds and the capacity of general wards.[19] Risk factors associated with the progression to ARDS have been identified in some populations,[18,20] but they were retrieved from critically ill patients with already confirmed COVID-19 pneumonia and they may not be appropriate for discriminating patients at risk among those treated at home. However, respiratory failure cannot be the only explanation for the increase in OHCAs. It cannot be excluded that some patients experienced arrhythmic sudden cardiac death (SCD) related to this infection. A non-negligible percentage of patients affected by COVID-19 in fact experienced myocardial injury,[21–23] and a series of mechanisms possibly leading to SCD have been proposed,[24] including the effect of hydroxychloroquine and azithromycin, which were proposed as a treatment for COVID-19,[25] on QT interval prolongation,[26] with the consequent risk of ventricular arrhythmias. Additionally, the infection itself could have played a role in prolonging the QTc values, as the elevated level of some cytokines, particularly interleukin-6 (IL-6), can suppress IKr in heterologous cells and myocytes, resulting in prolonged repolarization, and IL-6 also markedly blunted the hERG/IKr channel mRNA and protein expression.[27] Recent evidence highlighting that the QTc values might be at the upper limits or even prolonged in many patients with COVID-19, even before starting drugs potentially causing QTc prolongation, also seems to confirm this mechanism.[28] Notably, in four out of six patients of our population with suspected or diagnosed COVID-19 and a post-ROSC ECG available, a prolonged QTc was found. However, we found that also in non-suspected or diagnosed COVID-19 patients, the percentage of those with a prolonged QTc was similar, possibly caused by myocardial ischaemia. Indeed, it has been known for >40 years that a prolongation of the QT interval is associated with a major increase in the risk for ventricular arrhythmias and SCD either after a myocardial infarction[29] or in the general population.[30,31]

In addition, digestive symptoms (i.e. diarrhoea and vomiting) are present in a fair number of COVID-19 patients, especially in those with mild disease severity, with a delayed diagnosis and treated at home,[32] and they were also experienced by 7% of the suspected or diagnosed COVID-19 patients in our cohort. All these conditions may favour hypokalaemia, which can drive powerful electrophysiological effects on the myocardial cells, promoting life-threatening ventricular arrhythmias.[33] Moreover, recent data suggest that pulmonary embolism (PE) could be a complication in COVID-19 patients,[34] and this could have been another cause of OHCA in our population, consistent with a non-shockable presenting rhythm.

Last, but not least, considering the pandemic-related issues, another possible reason for the increase of OHCAs could reside in the increased deterioration at home, with electrical or mechanical complications of time-dependent cardiovascular disease that normally would have been treated earlier. This hypothesis is fully supported by our evidence of a 40.2% reduction in 2020 of the number of patients transported for STEMI, despite an increase in the number of all emergency calls managed by the EMS dispatch centre, which is absolutely in line with other experiences from northern Italy, Spain, and the USA,[35–37] and it leads to the conclusion that a considerable number of patients experienced a myocardial infarction at home, exposing themselves to an increased risk of SCD.[38] The two possible explanations for this issue could be the fear of being infected in the hospital or the desire to not further burden the health system, both resulting in non-activation of the emergency system. This brings about the need for specific information campaigns addressed at the population explaining the importance both of the quarantine and of early activation of the EMS in the case of effective need.

We also observed that the characteristics of OHCAs during the outbreak are different compared with those of a normal period. We highlighted an increase in medical aetiology over other types of aetiologies, and this further reinforces the hypothesis that the increase in the incidence of OHCAs is probably related to the direct (i.e. respiratory failure at home, SCD due to SARS-CoV-2 myocardial involvement or treatment) or indirect (i.e. lack of EMS activation in the case of time-dependent pathologies) effect of the COVID-19 epidemic. Moreover, consistently with the lockdown that was adopted in Italy,[39] there was an increase in the OHCAs that occurred at home coupled, however, with a decrease in bystander-witnessed OHCAs. This is probably the result of social distancing and, in some cases, of quarantine isolation, enforcing living in different rooms or in a different house from the rest of the family. A decrease of the bystander CPR rate was also observed, and it is probably due to the issue of the fear of infection. Furthermore, a 3-min median increase in EMS arrival time was observed, reasonably affecting the percentage of non-shockable presenting rhythm.[16] This delay was probably due both to the very high volume of rescues managed by EMS and to the time needed to put on PPE by EMS personnel. As a matter of fact, the EMS arrival time was longer for suspected/diagnosed COVID-19 patients than for the others. All the above aspects have led to a dramatic increase of OHCAs and, regretably, of people both dead on arrival, without any attempt of resuscitation by EMS, and dead in the field after a resuscitation attempt, highlighting COVID-19 as a disease that kills at home. This may also favour an underestimation of COVID-19 lethality, since the official statistics refer only to hospitalized patients,[40] excluding those who died at home.

We believe that our evidence could be very useful to other countries, in order to optimize the treatment of COVID-19 patients and organize the emergency medical response, especially considering that SARS-CoV-2 will definitely not be defeated in a few months and recurrent outbreaks are expected already in the coming months.[41]

Our study has some limitations. The first consists of the relatively short period of time analysed. However, although we have analysed only the first 60 days since the start of the epidemic, our results are already impressive and highlight the close relationship between the increase in OHCAs in 2020 and the COVID-19 epidemic. Moreover, in these 60 days, the epidemic curve has reached a plateau and, nevertheless, the relationship was maintained. The second relies on the impossibility of having the certainty of the causative diagnosis of cardiac arrest for each patient, as is typical for OHCA registries. However, we believe that the statistically strong correlation, supported by clinical elements such as the evidence that more than three-quarters of the 'extra' patients were highly suspected of or diagnosed with COVID-19, the reduction of 40.2% of the patients with a pre-hospital diagnosis of STEMI, and the changes in the characteristics of OHCAs, can be reasonably sufficient for confirming the direct or indirect role of COVID-19 in the observed increase in the incidence of OHCA. The third limitation could be the lack of information either about home therapy at the moment of OHCA or about the previous medical history or comorbidities of the patients.

Lastly, post-ROSC ECG was available only in 18 out 27 patients who achieved ROSC. This is because either the ECG was not performed by the EMS personnel or it was recorded but not transmitted to the dispatch centre or, even if transmitted, the file was unavailable due to technical issue.

Summarizing, the COVID-19 epidemic trend is associated with the difference between 2020 and 2019 OHCAs and is coupled with a reduction in the short-term outcome. Government and local health authorities should seriously consider our results when planning healthcare strategies to deal with the epidemic, not neglecting the pre-hospital issue of the emergency, especially considering the expected recurrent outbreaks.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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