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Research paper

In- and out-of-hospital mortality for myocardial infarction during the first wave of the COVID-19 pandemic in Emilia-Romagna, Italy: A population-based observational study

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ABSTRACT

Background: The COVID-19 pandemic has put several healthcare systems under severe pressure. The present analysis investigates how the first wave of the COVID-19 pandemic affected the myocardial infarction (MI) network of Emilia-Romagna (Italy).
Methods: Based on Emilia-Romagna mortality registry and administrative data from all the hospitals from January 2017 to June 2020, we analysed: i) temporal trend in MI hospital admissions; ii) characteristics, management, and 30-day mortality of MI patients; iii) out-of-hospital mortality for cardiac cause.
Findings: Admissions for MI declined on February 22, 2020 (IRR -19.5%, 95%CI from -8.4% to -29.3%, $p = 0.001$), and further on March 5, 2020 (IRR -21.6%, 95%CI from -9.0% to -32.5%, $p = 0.001$). The return to pre-COVID-19 MI-related admission levels was observed from May 13, 2020 (IRR 34.3%, 95%CI 20.0%-50.2%, $p<0.001$). As compared to those before the pandemic, MI patients admitted during and after the first wave were younger and with fewer risk factors. The 30-day mortality remained in line with that expected based on previous years (ratio observed/expected was 0.96, 95%CI 0.84−1.08). MI patients positive for SARS-CoV-2 were few (1.5%) but showed poor prognosis (around 5-fold increase in 30-day mortality). In 2020, the number of out-of-hospital cardiac deaths was significantly higher (ratio observed/expected 1.17, 95%CI 1.08−1.27). The peak was reached in April.
Interpretation: In Emilia-Romagna, MI hospitalizations significantly decreased during the first wave of the COVID-19 pandemic. Management and outcomes of hospitalized MI patients remained unchanged, except for those with SARS-CoV-2 infection. A concomitant increase in the out-of-hospital cardiac mortality was observed.
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RESEARCH IN CONTEXT

Evidence before this study

Since the COVID-19 pandemic started to spread globally, several studies have been carried out to understand it and investigate its effect on society. Some of the works focusing on myocardial infarction (MI) have reported a significant reduction in daily hospital admissions for MI. Others showed an increase in out-of-hospital cardiac arrests. Less information is available about the management and mortality of MI patients throughout COVID-19 pandemic, and it is still unclear if the reduction in daily admissions for MI is linked to the increased out-of-hospital cardiac deaths.

Added value of this study

The present analysis is based on the data of the Emilia-Romagna region, one of the most severely hit areas of Italy. Our team had access to all the citizens' clinical data and hospitals' database of the region, including in- and out-of-hospital mortality. The data showed a reduction in admissions for MI from February 22 to May 13, 2020. However, during that period, patients with MI who were admitted to hospital were treated with the same gold standards as before the pandemic, which meant no significant variation in the 30-day mortality rates. The number of MI patients positive for SARS-CoV-2 infection was not significantly high (1.5% of the cases), but their prognosis was worse, with 30-day mortality exceeding 30%. In 2020, the number of out-of-hospital cardiac deaths was significantly increased, peaking in March and April 2020.

Implications of the available evidence

Our research confirmed that a well-organized MI network can offer gold-standard treatments even during a devastating pandemic, resulting in a not significant variation in 30-day mortality. On a less positive note, we observed a substantial increase in out-of-hospital cardiac deaths, together with the reduction in hospital admissions for MI. These data should reinforce the need for social, media, and political campaigns to reassure the population regarding the safety and efficacy of well-organized emergency networks even during a pandemic.

1. Introduction

Emilia-Romagna is a North of Italy region with around 4.5 million inhabitants, more than 50 hospitals and a well-structured public emergency service [1-3]. The network for the myocardial infarction (MI), involving more than 50 emergency rooms, 17 spoke cardiology units and 10 hub centres with 24/7 cardiac catheterization services, is one of the flagships of the regional health service [1-4]. The COVID-19 pandemic has had a profound effect on the regional health system, inducing changes in organization and assistance to face more than 100,000 cases and 4400 deaths during the first wave. Worldwide, it has been reported that the COVID-19 outbreak has had an enormous impact on MI management [5-12]. Delayed hospital presentations have become common [5]. Some networks had to introduce unexpected changes in pathways and treatments (i.e., pharmacological instead of mechanical coronary reperfusion) [6,7]. In addition, several studies highlighted a significant decline in the number of hospital admissions for MI, and the national lockdowns imposed by authorities have been advocated as potential causes [8-12].

The current investigation has been carried out to describe the performance of the Emilia-Romagna MI network and the whole spectrum of the consequences on it due to COVID-19 pandemic. For this purpose, from January 2017 to June 2020, the trend and the changes in hospital admission for MI, the 30-day mortality of MI patients (with or without concomitant COVID-19), as well as the out-of-hospital mortality for cardiac cause, were analysed and compared.

2. Methods

2.1. Data collection

The AMI-Co (Acute Myocardial Infarction during Coronavirus disease 2019) is a population-based, observational study. The identification of patients admitted to hospital for MI is based on administrative data generated at hospital discharge from all hospitals of the Emilia-Romagna (Italy) (supplemental online). Since 1999, discharge hospital records were tracked in a single electronic database. The records contain detailed information concerning patient details, hospitalization, primary and secondary diagnoses, and diagnostic/therapeutic procedures performed. MI diagnosis, as well as the diagnostic and therapeutic procedures, were defined according to the International Classification of Diseases, 9th Revision (ICD-9). A detailed list of methods and ICD-9 codes is available in the supplemental appendix (Supplemental Table 1). The data extraction was in line with a validated protocol periodically applied for national (https://pne.agenas.it/), and regional (https://assr.regione.emilia-romagna.it) audits of the healthcare system. Mortality rates of patients admitted to hospital for MI were obtained by analysis of hospital discharge records and mortality registry (supplemental online). Similarly, mortality registry was used to identify subjects who died out-of-hospital for cardiac cause (supplemental online). The identification of all subjects positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was performed by the interrogation of the dedicated regional database. Access to this information has enabled us to cover the entire resident population of the region and ensures a complete follow-up and the identification of the cause of death (supplemental online). The review boards approved the protocol (Comitato Etico di Area Vasta Emilia Centro, approval id #381−2020). Since the study was based on data drawn from routine daily practice, no informed consent was required.

2.2. Procedures and definitions

In addition to standard baseline characteristics (age, sex, residence, etc.) and comorbidities (arterial hypertension, hyperlipidaemia, diabetes mellitus, chronic kidney disease, chronic obstructive pulmonary disease, prior cardiovascular events, etc.), the following variables were collected: date of admission, clinical presentation (ST-segment elevation MI or non-ST-segment elevation MI), use of primary percutaneous coronary intervention (PCI) in STEMI patients, first medical contact to balloon time, use of invasive strategy in NSTEMI patients, timing from admission to coronary angiography in NSTEMI patients, SARS-CoV-2 infection. SARS-CoV-2 infection was confirmed by CE-marked reverse-transcriptase-polymerase-chain-reaction assay from nasopharyngeal swab specimen. The analysis was performed in referral laboratories of the region.

The first objective of the present investigation was to describe the temporal trends in the number of hospital admissions for MI. Accordingly, all patients admitted for MI from January 2017 to June 2020 were identified. The second objective was to outline the characteristics, management, and 30-day mortality of MI patients admitted in the 2020 and compare this with the same information from previous years (pre-COVID-19 normality, from January 2017 to December 2019). MI patients admitted in the 2020 were divided in three subgroups (the selection is based on trend of the pandemic in

Emilia-Romagna and on our time series analysis): from January 1 to February 21 (before pandemic), from February 22 to May 13 (first wave of the pandemic), from May 14 to June 30 (after the first wave of the pandemic). The number, treatments, and outcomes of patients admitted to hospital primarily for acute MI but also diagnosed positive for SARS-CoV-2 infection were reported separately. Finally, the third objective was to describe variations in the occurrence of out-of-hospital mortality for cardiac cause from January 2017 to June 2020. The cause of death was retrieved from death certificates. Briefly, the cases were identified in presence of one of the ICD-10 codes of myocardial infarction. A detailed description of the methodology and codes allowing the identification of cardiac death is available in the supplemental online.

2.3. Statistical analysis

A detailed description of the statistical methods is available in the supplemental online. Briefly, continuous variables were reported as mean ± standard deviation (SD) and compared using Student's t-tests or Mann-Whitney tests. Categorical variables were expressed as number and percentage and compared using χ^2 tests. To describe the trend of daily hospital admissions for MI and the impact of COVID-19 pandemic, a population-based interrupted time series design and segmented regression analysis were carried out. After verifying the absence of overdispersion, checking residual deviances, Poisson models were applied to estimate time series trends (general population and subgroups). The models included time, weekly and annual seasonality of MI hospitalizations as covariates. The residual autocorrelation was checked through Ljung-Box test. Subsequently, an iterative procedure was carried out to detect any significant disruptions in the trend. The breakpoints identified were included as covariates in additional Poisson models, to assess the related incident rate ratio (IRR) between hospitalizations observed and expected. Further Poisson models were carried out to analyze, in different time range, the IRR between MI hospital admissions observed in 2020 and those expected, based on 2017−2019 data. To assess 30-day mortality, a multivariable logistic regression, including the variables listed in Table 1 as covariates, was performed. Data from the years 2017−2019 were entered in the multivariable logistic regression and the model estimated were later applied to 2020 data to evaluate the expected deaths, adding the probability estimated for each patient. The ratio of number of deaths observed - to those expected (SMR) was measured to estimate any excess mortality that occurred in the time intervals of interest. The SMR 95%CI was calculated as 1.96 x standard error of SMR and if the 95%CI did not cross the 1 value, the SMR was considered statistically significant. Finally, to analyze out-of-hospital cardiac deaths, age-sex-specific rates detected in the first six months, from 2017 to 2020, were considered. The rates of out-of-hospital cardiac death were calculated as the ratio between the number of deaths stratified by sex and age group of 5 years and the amount of the resident population at the beginning of each year of the same age group and sex. IRR between observed and expected rates, stratified for temporal windows, was estimated through Poisson regression model with count of deaths, stratified by 5-year age classes and sex, as dependent variable, log of the amount of resident population, stratified by 5-year ag classes and sex, as offset and year 2020, expressed as dichotomous variable, 5-years age classes, sex and age-sex interaction, as covariates. All analyses were performed using R version 3.6.3 (The R Foundation for Statistical Computing, Wien) and SAS version 9.3 (SAS Institute, Inc. Cary, NC, USA).

2.4. Role of the funding source

There was no funding source for this study. The Executive Committee of the AMI-Co study (supplemental online) had full access to all the data and had final responsibility for the decision to submit for publication.

3. Results

From January 2017 to June 2020, 31,381 hospital admissions for MI were calculated. Of note, 12,164 (38.7%) admissions were for STEMI, whereas 19,217 (61.3%) for NSTEMI. The daily average number declined from 2017 to 2019, with the typical seasonal variability (Fig. 1, supplemental Fig. 1). As compared to the expected trend, an abrupt reduction in daily MI admissions was observed on February 22, 2020 (IRR −19.5%, 95%CI from −8.4% to −29.3%, p = 0.001) (Fig. 1). A further significant reduction was observed on March 5, 2020 (IRR −21.6%, 95%CI from −9.0% to −32.5%, p = 0.001) (Fig. 1). A first inversion in the tendency is observed on April 17, 2020 (IRR 23.4%, 95%CI 9.2%−39.5%, p = 0.0008) (Fig. 1), with a further increase in admissions from May 13, 2020 (IRR 34.3%, 95%CI 20.0%−50.2%, $p<0.001$) (Fig. 1). Repeating the analyses on the national lockdown window (from March 9 to May 4) did not change the findings (IRR −31.9%, 95%CI from −36.5% to −27.0%, $p<0.001$).

In 2020, 3728 patients were admitted to hospital for MI. Of note, 3672 (98.5%) of them were negative for SARS-CoV-2 infection (Table 1), whereas 56 (1.5%) resulted positive for SARS-CoV-2 infection (Table 2). Looking at MI patients negative for SARS-CoV-2 infection, those hospitalized during and after the pandemic's first wave were younger and with fewer risk factors and prior cardiac events, as compared to those admitted before pandemic (Table 1). Similar findings were observed comparing the MI patients of the year 2020 with those of the years 2017−2019 (temporal window February 22 − May 12) (Supplemental Table 3). For what concerns the treatments, the timing for invasive strategy was shorter in NSTEMI patients admitted after the onset of the pandemic (Table 1). From 2017 to 2020, 30-day mortality of MI patients remained unchanged, ranging around 8.5% (Fig. 2). After correction for potential confounding factors (Supplemental Table 4), we did not find significant variations in the 30-day mortality of the MI patients hospitalized and treated in 2020 (Fig. 2). The number of observed deaths in 2020 was in line with that expected on data of years 2017−2019 (ratio observed/expected 0.96, 95%CI 0.86−1.11) (Fig. 2, Supplemental Table 5). The ratio observed/expected was constant before, during and after the first wave of the pandemic, as well as during the national lockdown (Fig. 2).

Looking at MI patients who were confirmed positive for SARS-Cov-2 infection (Table 2), we found that, as compared to others, they were older and with more history of heart failure (Table 2). In addition, they were under-treated and with a longer hospital stay (15.2 ± 14.3 vs. 7.2 ± 6.9, respectively) (Table 2). At follow-up, 18 (32%) of them died, being SARS-CoV-2 infection an independent predictor of 30-day mortality (OR 5.1, 95%CI 2.9−8.8, $p<0.001$) (Supplemental Table 6). Respiratory failure, cardiogenic shock and bleeding complications were the most common final events in these patients.

From January 2017 to June 2020, 4510 deaths for cardiac cause were counted out-of-hospital (Supplemental Table 7). The daily number of out-of-hospital cardiac death throughout the years is shown in Fig. 3. The mean age (80±12 years) and the percentage of male sex (55.7%) in the subjects who died did not vary throughout the years (Supplemental Fig. 2). The same pattern was observed for main cardiovascular risk factors (Supplemental Fig. 2). An abrupt increase in the number of out-of-hospital cardiac deaths was observed in 2020 (Fig. 3). After correction for age and sex and as compared to the expected number based on 2017−2019 data, we confirmed the increase in the number of out-of-hospital cardiac deaths in 2020 (ratio observed/expected 1.17, 95%CI 1.08−1.27) (Fig. 3, Supplemental Table 8). The excess of out-of-hospital cardiac deaths was concentrated from February to April 2020, with the peak in April 2020 (ratio observed/expected 1.62, 95%CI 1.32−1.98) (Fig. 3). Repeating the

Table 1
Patient characteristics of MI patients negative for SARS-CoV-2 infection admitted in 2020.

	Timing of hospitalization on 2020 though COVID-19 pandemic				
	Before (*n* = 1343)	First wave (*n* = 1301)	After (*n* = 1028)	p1	p2
Age, years	72.8 ± 13	71.5 ± 13	71.0 ± 13	0.013	0.003
< 65 years, no. (%)	342 (25.5)	377 (29)	341 (33.2)	0.027	<0.01
65–74 years, no. (%)	341 (25.4)	335 (25.7)	225 (21.9)		
75–84 years, no. (%)	394 (29.3)	384 (29.5)	290 (28.2)		
≥85 years, no. (%)	266 (19.8)	205 (15.8)	172 (16.7)		
Male sex, no. (%)	885 (65.9)	866 (66.6)	666 (64.8)	0.717	0.573
Comorbidities, no. (%)					
Diabetes	298 (22.2)	299 (23)	215 (20.9)	0.626	0.455
Hypertension	804 (59.9)	542 (41.7)	354 (34.4)	<0.001	<0.001
Hyperlipidaemia	839 (62.5)	604 (46.4)	409 (39.8)	<0.001	<0.001
Prior MI	235 (17.5)	185 (14.2)	147 (14.3)	0.021	0.036
History of HF	295 (22)	248 (19.1)	176 (17.1)	0.065	0.003
Peripheral artery disease	67 (5)	52 (4)	44 (4.3)	0.219	0.418
Cerebrovascular disease	87 (6.5)	98 (7.5)	80 (7.8)	0.288	0.219
COPD	62 (4.6)	45 (3.5)	51 (5)	0.131	0.696
Chronic kidney disease	155 (11.5)	119 (9.1)	103 (10)	0.043	0.238
History of cancer	8 (0.6)	11 (0.8)	8 (0.8)	0.447	0.591
Charlson Index >2	214 (15.9)	206 (15.8)	161 (15.7)	0.944	0.857
Hospitalization					
STEMI, no. (%)	529 (39.4)	521 (40.0)	395 (38.4)	0.73	0.633
Anterior location STEMI	259 (48.9)	266 (51.1)	197 (49.9)	0.478	0.762
Inferior location STEMI	230 (43.5)	217 (41.7)	170 (43.0)	0.549	0.894
Coronary angiography	496 (93.7)	490 (94.1)	372 (94.2)	0.762	0.651
Primary PCI	426 (80.5)	420 (80.7)	320 (81.0)	0.725	0.891
FMC-balloon time, minutes *	85±40	87±45	86±43	0.565	0.784
NSTEMI, no. (%)	814 (60.6)	780 (60.0)	633 (61.6)	0.736	0.633
Coronary angiography within 24 h	425 (52.2)	416 (53.3)	358 (56.5)	0.690	0.111
Coronary angiography 24–72 h	191 (23.4)	219 (28.1)	183 (28.9)	0.040	0.022
PCI	491 (60.3)	479 (61.4)	392 (62.0)	0.693	0.570
Admission to ICU	220 (16.4)	225 (17.3)	177 (17.2)	0.53	0.589
Admission to CCU	820 (61.1)	795 (61.1)	643 (62.5)	0.979	0.459
Intra Aortic Balloon Pump	31 (2.3)	35 (2.7)	17 (1.7)	0.529	0.262
Duration CCU stay, (days)	2.8 ± 3.7	2.8 ± 3.9	2.8 ± 3.5	0.742	0.923
Duration hospital stay, (days)	8 ± 8.2	7.5 ± 7.7	6.9 ± 6.2	0.092	<0.001

Before is defined as the temporal range from January 1 to February 21, 2020. The first wave was from February 22 to May 13, 2020. The time range after the first wave was from May 14 to June 30, 2020.
p1 is for the comparison between before and first wave subgroups. p2 is for the comparison between after and before subgroups.
* : data is available in 58% of the cases.
MI: myocardial infarction. HF: heart failure. COPD: chronic obstructive pulmonary disease. STEMI: ST-segment elevation MI. PCI: percutaneous coronary intervention. FMC: first medical contact. NSTEMI: non ST-segment elevation MI. ICU: intensive care unit. CCU: cardiac care unit.

analysis in the national lockdown window confirmed the results (Fig. 3).

4. Discussion

The key insights of our analysis are:

i. in Emilia-Romagna, one of the regions of the North Italy most severely hit by the COVID-19 pandemic, the diffusion of SARS-CoV-2 infection has been associated with a significant reduction in hospital admissions for MI,
ii. during the first wave of the pandemic, patients with MI admitted to hospital were younger and with less risk factors and comorbidities; they continued to receive gold-standard treatments and their 30-day mortality, after adjustment for potential confounding factors, was in line with historical values,
iii. the number of MI patients with concomitant SARS-CoV-2 infection was limited (1.5%, 95%CI 1.1%–1.9%), but they were undertreated, and their prognosis was poor,
iv. concurrently with the spreading of the SARS-CoV-2 infection and the reduction in hospital admission for MI, a significant increase in out-of-hospital cardiac deaths was observed.

From the beginning of the COVID-19 pandemic, hospitals observed an alarming reduction in admissions for time-dependent diseases, including MI [8-12]. Although reproducible across the countries, this observation left several unmet gaps in knowledge. First, data was mainly collected in high-volume hub centres, and less information was available from spoke hospitals or entire MI network. Second, the outcome of the patients admitted for MI during the outbreak was not systematically reported and their prognosis is still unclear. Third, no studies clarified the out-of-hospital consequences.

The current investigation aimed to fill these gaps, and its major strengths are: i) data were extracted from a homogenous hub and spoke MI network including more than 30 hospitals; ii) the analysis was not limited to pre-established arbitrary temporal windows, but the historical series starting from January 2017 was reported; iii) crucial information about management and outcome (30-day-mortality) of MI patients was available (considering both negative and positive for SARS-CoV-2 infection); iv) in-hospital data were enriched with out-of-hospital cardiac death to depict the whole spectrum of the consequences of the COVID-19 pandemic on the MI network.

We confirmed the significant reduction in hospital admissions for MI. The numbers started to decrease from February 22, 2020, the day when the first documented Italian case of SARS-CoV-2 infection was

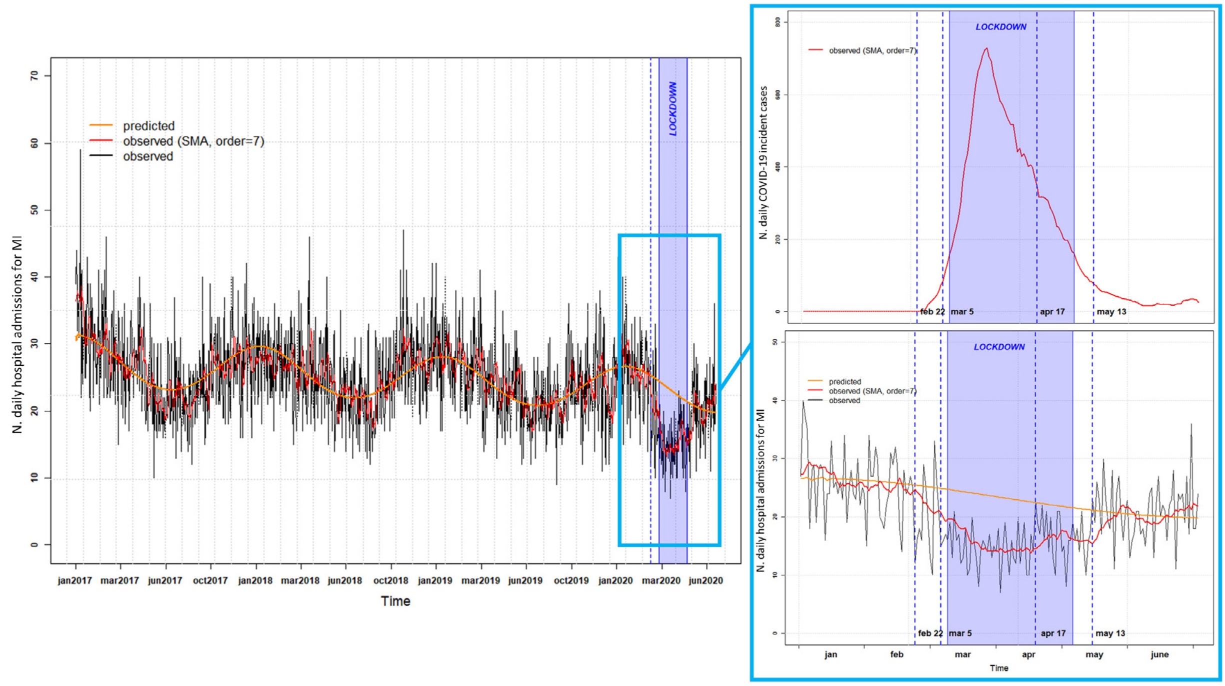

Fig. 1. Daily number of admissions for MI.
The graph on the left represents the number of daily hospital admissions for MI from January 2017 to June 2020. The orange line is the expected trend (based on seasonality), whereas the red line is the observed trend. The first six months of the year 2020 are highlighted in the light blue box. The upper portion of the light blue box shows the trend of cases who resulted positive for SARS-CoV-2 infection. The lower portion shows the trend of daily hospital admissions for MI in the first six months of the 2020. The violet range represents the national lockdown (from March 9 to May 3, 2020). The dotted black lines the dates associated with significant changes in the trend of daily admission for MI. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

reported. The fall in hospital admissions for MI can be explained by two main hypotheses. The first is that the lifestyle changes caused by pandemic and lock-down (staying home, less stress, less air pollution) triggered fewer coronary events. The opposite theory suggests that the fear of contagion and the misinterpretation of the “stay-at-home” government campaign might have hindered people’s decision to go to hospital in case of MI symptoms. Although not trying to draw final conclusions from a debate that has not ended, what evolves from our data (start of the reduction in hospital admission for MI before the national lockdown, lack of relationship with local number of COVID-19 cases and return to pre-pandemic statistics coinciding with the end of the pandemic’s first wave) is that the second hypothesis may be more plausible.

After looking at the previous studies about the outcome of MI patients admitted during the pandemic, the results seemed conflicting [9, 12-14]. A large retrospective registry focused on STEMI patients undergoing primary PCI across European centres suggested an increase in-hospital mortality [12]. In this registry, the characteristics of MI patients admitted during pandemic were similar to those of their control cohort [12]. Despite this, the in-hospital outcome was worse [12]. Similarly, a survey involving Italian cardiac care units found a higher fatality rate during the pandemic [9]. Our study did not confirm this finding for the Emilia-Romagna region. MI patients admitted during the pandemic were, on average, younger and with fewer cardiovascular risk factors. This finding could be interpreted as a result of the presence of more striking symptoms at presentation in younger people coupled with a greater fear of contagion in older and comorbid patients. After adjustments for potential confounding factors, we found that 30-day mortality of MI patients admitted during the pandemic was in line with that of the previous years. This finding is interesting and noteworthy in several ways. The Regional Authority for Health and Welfare re-organized the activities of the hospitals during the pandemic by significantly reducing elective procedures and surgery activities. However, the networks for the management of the time-dependent disease, including the MI network, have not been modified. Although longer follow-up is necessary to confirm our findings, it seems that a well-established and organized MI network is able to work efficiently also during a pandemic, without significant changes in mortality. Unfortunately, the same consideration cannot be applied to MI patients with confirmed SARS-CoV-2 infection. They were a limited number of cases (1.5% 95%CI 1.1%−1.9%) and tended to show a late presentation. Fewer invasive procedures were used (both primary PCI for STEMI patients and invasive strategy for NSTEMI patients). These features translate into a dramatically higher 30-day mortality (32% vs. 8% of MI patients negative for SARS-CoV-2 infection, $p<0.001$).

As mentioned before, previous studies had identified the trend of a lower number of admissions due to MI [8-12]. However, the question of its out-of-hospital consequences was left unsolved. Analyses focused on the number of out-of-hospital cardiac arrests highlighted a significant increase during the first wave of the pandemic [15,16]. Looking at MI hospitalization and out-of-hospital cardiac death at the same time, we found an opposite trend. While the first decreased with a nadir in March and April, the second increased with a peak in the same months. Although we may not demonstrate an indissoluble association between phenomena, we can suppose that a large part of these out-of-hospital cardiac death can be the missing MIs not admitted to hospital. We believe that this could be due to media campaigns around Italy to prevent the spread of the virus, targeting, and influencing, especially older patients with more risk factors and comorbidities. Hence, older people perceived that they had a higher risk of death in case of a SARS-CoV-2 contagion and were thus more reluctant to call emergency services in case of MI symptoms. This attitude led to a significant increase in out-of-hospital cardiac deaths.

We are aware that our research may have some limitations. First, the hospital admissions for MI were inferred from ICD-9 codes, which

Table 2
Patient characteristics of MI patients positive for SARS-CoV-2 infection.

	Positivefor SARS-CoV-2 (*n* = 56)	Negativefor SARS-CoV-2 (*n* = 2808)	p
Age, years	76.1 ± 13	71.5 ± 13	0.002
< 65 years, no. (%)	8 (14.3)	834 (29.7)	<0.001
65–74 years, no. (%)	14 (25)	683 (24.3)	
75–84 years, no. (%)	20 (35.7)	826 (29.4)	
≥85 years, no. (%)	14 (25)	465 (16.6)	
Male sex, no. (%)	36 (64.3)	1859 (66.2)	0.764
Comorbidities, no. (%)			
Diabetes	13 (23.2)	617 (22)	0.824
Hypertension	23 (41.1)	1187 (42.3)	0.857
Hyperlipidaemia	19 (33.9)	1304 (46.4)	0.063
Prior MI	9 (16.1)	432 (15.4)	0.888
History of HF	17 (30.4)	528 (18.8)	0.029
Peripheral artery disease	4 (7.1)	124 (4.4)	0.328
Cerebrovascular disease	5 (8.9)	204 (7.3)	0.636
COPD	3 (5.4)	114 (4.1)	0.627
Chronic kidney disease	6 (10.7)	274 (9.8)	0.811
History of cancer	0 (0)	20 (0.7)	0.526
Charlson Index >2	13 (23.2)	443 (15.8)	0.132
Hospitalization			
STEMI, no. (%)	26 (46.4)	1102 (39.2)	0.276
Anterior location STEMI	13 (50.0)	564 (51.2)	0.905
Inferior location STEMI	7 (26.9)	465 (42.2)	0.119
Coronary angiography	20 (76.9)	1035 (94.0)	0.003
Primary PCI	17 (65.3)	895 (81.2)	<0.001
FMC-balloon time, minutes *	95±55	87±45	0.373
NSTEMI, no. (%)	30 (53.6)	1706 (60.8)	0.276
Coronary angiography within 24 h	7 (23.3)	947 (55.5)	<0.001
Coronary angiography within 24–72 h	9 (30.0)	481 (28.2)	0.738
PCI	15 (50.0)	1054 (61.8)	0.260

The group of MI patients negative for SARS-CoV-2 infection were admitted from February 2020 to June 2020.
* : data is available in 61% of the cases.
MI: myocardial infarction. HF: heart failure. COPD: chronic obstructive pulmonary disease. STEMI: ST-segment elevation MI. PCI: percutaneous coronary intervention. FMC: first medical contact. NSTEMI: non ST-segment elevation MI.

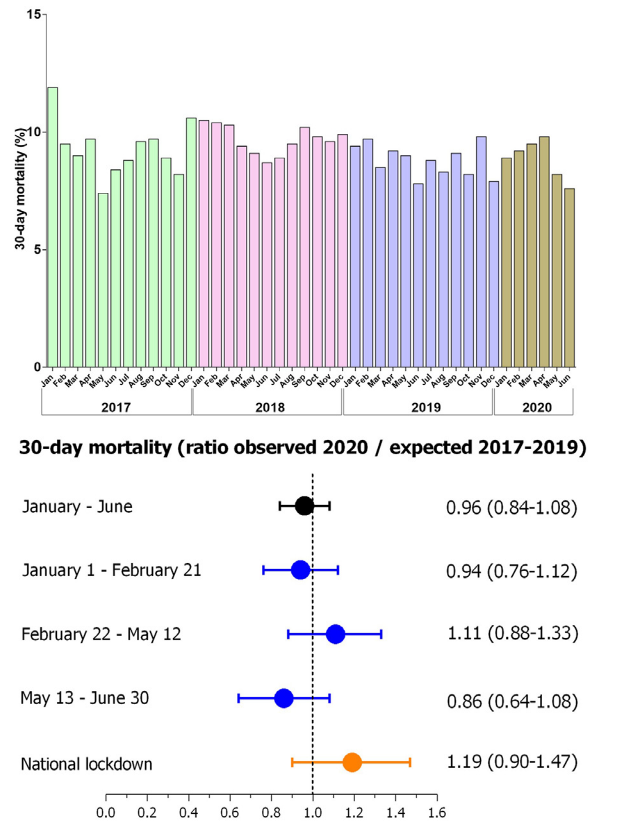

Fig. 2. Thirty-day mortality of patients hospitalized for MI.
The upper portion of the Figure shows the monthly 30-day mortality of patients admitted to hospital for MI from January 2017 to June 2020. The lower part of the Figure shows the ratios between observed and expected 30-day deaths of MI patients. The expected number was computed based on data from the years 2017–2019 and after adjustment for confounding factors.

could result in partial. However, our methodology has been applied in several previous analyses and periodic audits verified with source data the consistency of the information [1-4]. Second, some MI cases with concomitant SARS-CoV-2 infection could have gone undiagnosed, especially in the last week of February and in the first week of March. However, this number should be small because screening for SARS-CoV-2 was systematically applied in hospitalized subjects and the risk of bias on our findings should be considered limited. Third, the cause of out-of-hospital deaths was based on that reported in the death certificates. Although guidelines for the discrimination of the primary cause of death are well-established and applied in our region, we may not exclude some bias. This may have led us to overestimate cardiac causes of death or underestimate cases with asymptomatic concomitant SARS-CoV-2 infection. Nevertheless, the same methodology was applied over the years (from 2017 to 2020), therefore the risk of bias or misinterpretation should be minimal. Fourth, the trend of out-of-hospital cardiac arrest would have further enriched our findings and allowed a link between the reduction in MI admissions and the increase in out-of-hospital cardiac death. Unfortunately, this data is traced only in some areas of the region [17]. Of note, available evidence suggested a trend for the increase of the activations of the emergency service for out-of-hospital cardiac arrests [17]. Finally, it should be noted that the unequivocal proof that out-of-hospital death was cardiac (and not suspected cardiac) would require an autoptic evidence. Likewise, autoptic evidence and the demonstration that hospital admission of these subjects would have saved their life, would be necessary to prove that the increased out-of-hospital cardiac death was consequence of "missing MIs". Obviously, this is not feasible and goes beyond the scope of the present analysis.

In Emilia-Romagna, the first wave of the COVID-19 pandemic has been associated with a significant reduction in hospital admissions for MI. The patients admitted to hospitals continued to receive standard-of-care treatment without changes in 30-day mortality, except for those with concomitant SARS-CoV-2 infection who were undertreated and with a 5-time increased risk of death. Together with the reduction in MI hospital admissions, a significant increase in the out-of-hospital cardiac deaths was observed.

Author Contributions

Conceived and designed the research: Gianluca Campo, Giuseppe Di Pasquale, Gianni Casella, Rossana De Palma, Elena Berti, Daniela Fortuna.

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Performed statistical analysis: Daniela Fortuna, Federico Banchelli.

Handled funding and supervision: Giuseppe Di Pasquale, Gianni Casella, Rossana De Palma. Drafted the manuscript: Gianluca Campo, Gianni Casella, Massimo Piepoli.

Made critical revision of the manuscript for key intellectual content: Marcello Galvani, Alessandro Navazio, Giuseppe Boriani, Gabriele Guardigli.

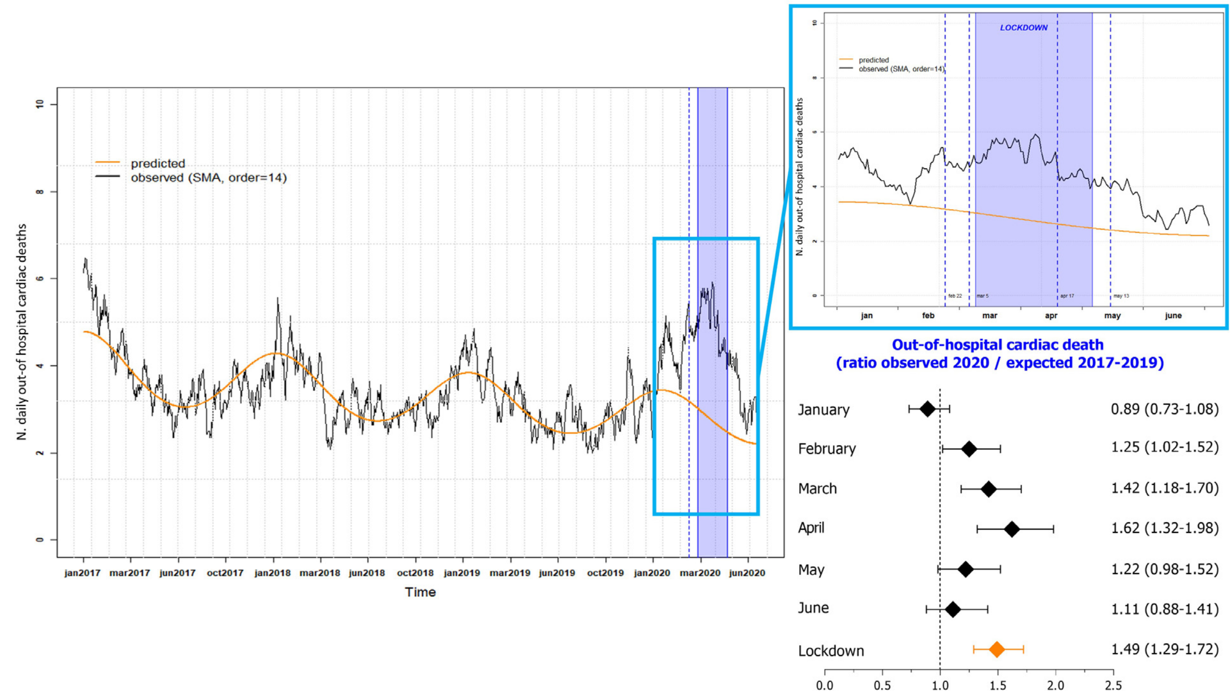

Fig. 3. Out-of-hospital cardiac death.

The graph on the left represents the number of out-of-hospital cardiac deaths from January 2017 to June 2020. The orange line is the expected trend based on seasonality. The black line is the observed trend. The first six months of the year 2020 are highlighted in the light blue box (upper right). The lower portion on the right shows the ratios between observed and expected out-of-hospital cardiac deaths. The expected numbers were computed based on data from the years 2017–2019 and after adjustment for age and sex. The national lockdown was from March 9 to May 3, 2020. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Data sharing statement

The data that support the findings of this study are available from the corresponding author (GC), upon reasonable request.

Declaration of Interests

The Authors have nothing to disclose.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.lanepe.2021.100055.

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