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Letter to the Editor

Acute coronary syndromes during the first and the second wave of COVID-19☆

Dear editor,

The deleterious side effects of the coronavirus disease 2019 (COVID-19) pandemic on cardiovascular disease have been widely reported [1–3]. However, most data refer to March and April 2020. Particularly, patients with ST-elevation myocardial infarction (STEMI) and concomitant infection presented the worst outcome and a significant prolongation in time to seek medical attention [4,5].

In the Lombardy Region the situation during the first and the second wave of the COVID-19 pandemic was dramatic. In order to guarantee the treatment of time-dependent emergencies including acute coronary syndromes (ACS), the healthcare authorities of the Lombardy Region applied a model of centralization to some Macro-Hubs on March 8th, 2020. A detailed description of the modified network and of the results of its application during the first wave of COVID-19 have been previously published [6,7].

Since Lombardy was dramatically hit also during the second wave of the infection, the centralization model was further applied by health authorities on October 23th 2020.

In the present observational, retrospective multicenter study of prospectively collected data, we aimed to compare time to treatment and outcome of all consecutive patients with ACS, both STEMI and non (N)STEMI hospitalized at the same Macro-Hubs between the first (February 21th-May 7th 2020) and the second (November 2th-January 31th 2021) waves of COVID-19. The two study periods were based on the application of the decrees by the regional healthcare authorities.

Both periods of data collection started with a surge in cases of infection; the first was the same of the national lockdown when only essential activities were permitted, whereas, during the second period only non-pharmaceutical interventions to mitigate the spread of the infection have been applied.

The study complies with the Declaration of Helsinki and was approved by the Local Institutional Review Board of the participating center or patients gave their informed consent at admission for data collection and future publications in anonymous studies.

For patients with STEMI, we analyzed the time intervals "symptoms onset to first medical contact (FMC)" (intended as the diagnosis by 12-lead electrocardiogram) and "FMC to arrival at catheterization laboratory (cath-lab)".

Data were even compared between two pre-specified groups of patients based on testing or not positive for SARS-CoV-2.

The diagnosis of COVID-19 was based on positivity of nasopharyngeal swab, bronchoalveolar lavage, serological test or a pulmonary computer tomography diagnostic for interstitial pneumonia, as single test or in combination. Survival of patients was evaluated as in hospital all cause of death.

Categorical data are reported as absolute values and percentages, continuous variables are presented as median and interquartile range (IQR). Variables were compared by the chi-squared test or the Mann-Whitney test as appropriated; the cut-off adopted for statistical significance was $p < 0.05$.

Eight out of thirteen Macro-Hubs agreed to participate to both data collections, including a total of 664 and 861 patients during the first and the second wave respectively.

Table 1 reports the baseline characteristics of the populations. No difference was found in clinical presentation (53.5% STEMI), in most baseline characteristics, in rate of invasive strategy with coronary angiography (97%) and of percutaneous coronary intervention PCI (about 80%). In-hospital cardiogenic shock was higher during the first wave (8.1% vs 5.5%, p=0.04).

The proportion of patients with concomitant COVID-19 was not different (8.7% vs 6.6%, p=0.69). However, the rate of pneumonia (6.9% vs 3.5%, p=0.002), the need of non-invasive respiratory support strategies (5.7% vs 3.6%, p=0.05), and of invasive mechanical ventilation (4.8% vs 1.5%, p=0.002) were higher during first compared to the second wave.

For patients with STEMI, the median time "symptom onset to FMC" was not different between the two waves [95 (IQR 46-228) vs 80 (IQR 45-222) min, p=0.36], while median time "FMC to cath-lab" was significantly shorter during the second one [80 (IQR 48-128) vs 65 (IQR 35-109) min, p=0.01].

Overall, all cause of death was higher during the first compared to the second wave (8.4% vs 4.8%, p=0.004), but the difference was limited to patients presenting with STEMI (12.7% vs 6.1%, p=0.001); furthermore, mortality was higher both in patients with (32.8% vs 17.5%, p=0.06) and in those without COVID-19 (6.1% vs 3.9%, p=0.05).

The main finding of this analysis has been that during the second wave of COVID-19 in-hospital mortality of overall population was significantly reduced, the clinical manifestation of infection was less severe and the outcome of patients with concomitant COVID-19 improved; for patients with STEMI "time interval from diagnosis to cath-lab" was shorter.

A delay in STEMI treatment was the first observation reported as a consequence of the COVID-19 outbreak [8]; particularly, patients with STEMI and COVID-19 presented the longest time of assistance driven by a prolonged time from symptom onset to admission [5]. Our time to access was shorter compared to previous data; however, a comparison of different populations even outside the pandemic could be not appropriate and potentially misleading for differences in geographical

☆ The members of the COVID-19 Lombardy Macro-Hubs investigators are listed in the Appendix.

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Table 1
Baseline characteristics, time to catheterization laboratory, and in-hospital outcome of the two groups.

	First spread (Feb. 21th-May 7th 2020) N=664	Second spread (Nov 2th2020-Jan 31th 2021) N=861	*P value*
Median age (IQR)- years	69 (59-77)	67 (58-77)	0.08
Male sex, n (%)	508 (76.5)	641 (74)	0.26
Arterial Hypertension,, n (%)	465 (70)	561 (65.2)	0.04
Current smoking,, n (%)	261 (39.3)	220 (25.6)	<0.0001
Type 2 Diabetes,, n (%)	166 (25)	200 (23.2)	0.41
Dyslipidemia, n (%)	320 (48.2)	442 (51.3)	0.23
Prior MI, n (%)	152 (22.9)	171 (19.9)	0.15
Prior PCI, n (%)	162 (24.4)	189 (22)	0.27
Prior CABG, n (%)	33 (5)	52 (6)	0.39
STEMI at presentation, n (%)	346 (52)	474 (55)	0.24
NSTEMI at presentation, n (%)	318 (48)	387 (45)	0.25
LVEF %, median (IQR)	50 (41-55)	50 (40-55)	0.26
OHCA, n (%)	22 (3.3)	39 (4.5)	0.23
Cardiogenic SHOCK, n (%)	54 (8.1)	47 (5.5)	0.04
COVID-19, n (%)	58 (8.7)	57 (6.6)	0.69
Pneumonia, n (%)	46 (6.9)	30 (3.5)	0.002
No concomitant COVID-19, n (%)	10 (1.6)	7 (0.9)	0.23
Concomitant COVID-19, n (%)	36 (62)	23 (40.4)	0.02
NIRSS, n (%)	38 (5.7)	31 (3.6)	0.05
No concomitant COVID-19	16 (2.6)	19 (2.4)	0.81
Concomitant COVID-19, n (%)	22 (37.9)	12 (21.1)	0.049
IMV, n (%)	32 (4.8)	13 (1.5)	0.002
No concomitant COVID-19, n (%)	21 (3.4)	12 (1.5)	0.018
Concomitant COVID-19	11 (19)	1 (1.8)	0.0027
Coronary angiography, n (%)	645 (97)	834 (97)	0.99
Multivessel CAD, n (%)	342 (53)	425 (50.9)	0.42
Treatment with PCI, n (%)	532 (80)	686 (82.3)	0.25
Time to cath-lab for STEMI patients			
• *Median time interval "Symptoms to FMC" (IQR), min*	95 (46-228)	80 (45-222)	0.36
• *Median time interval "FMC to Cath-Lab" (IQR), min*	80 (48-128)	65 (35-109)	0.01
In Hospital death, n (%)	56 (8.4)	41 (4.8)	0.004
• *STEMI*	44 (12.7%)	29 (6.1%)	0.001
• *NSTEMI*	12 (3.8%)	12 (3.1%)	0.61
• *No concomitant COVID-19*	37 (6.1)	31 (3.9)	0.05
• *Concomitant COVID-19*	19 (32.8)	10 (17.5)	0.06

IQR = interquartile range; MI = myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery by-pass grafting; STEMI= ST-elevation MI; NSTEMI = non-persistent ST-elevation MI; LVEF = Left ventricle ejection fraction; OHCA = out of hospital cardiac arrest; NIRSS= non-invasive respiratory support strategies; IMV= invasive mechanical ventilation; CAD=coronary artery disease; FMC=first medical contact; Cath-Lab= catheterization laboratory

features and in network organization.

The improvement in time to treatment between the first to the second wave of COVID-19 is likely related to the application of standardized protocols for fast-track treatment of STEMI with separate pathways to avoid the spread of infection during hospitalization that have been reported in a position paper endorsed by scientific societies [9]. The implementation of the dedicated protocol allowed to obtain time of reperfusion, short-term clinical outcomes, and staff safety similar to the targets before the pandemic [10].

We have reported a striking difference in mortality between the two phases of the pandemic (8.4% vs 4.8%) driven by lower deaths among STEMI patients and among patients with COVID-19. An adverse impact of the pandemic more relevant on STEMI patients could be expected. In one of the earliest studies about the dramatic reduction in the number of hospitalizations for acute myocardial infarction across Italy during the first wave of the COVID-19 pandemic, total mortality was higher compared to the same week of the previous year in patients with STEMI, but not in those with NSTEMI [1]. Furthermore, it is well known that patients with STEMI and concomitant COVID-19 present a worse outcome: in the recent North American COVID-19 Myocardial Infarction Registry, in-hospital mortality of these patients was 33%, and they were more likely to present with cardiogenic shock but were less likely to receive invasive angiography compared to controls [4].

Beyond the higher rate of cardiogenic shock observed during the first wave, our data agree with the previous ones for the impressive high in-hospital mortality of patients with COVID-19 that nearly halved during the second wave. However, the improved outcome observed in COVID-19 patients is more likely due to specific improved therapeutics (e.g., steroids, improved ventilation strategies) rather than to any improvement in ACS pathways as can be observed from the significant reduction in the rates of pneumonia and in the need for non-invasive respiratory support strategies and invasive mechanical ventilation. Furthermore, we have previously reported that the presence of COVID-19 was independently associated with in-hospital mortality, age, STEMI presentation, an ejection fraction < 40%, out-of-hospital cardiac arrest and cardiogenic shock [7].

Small sample size, retrospective analysis and residual confounding bias can be considered as the main limitations of the present study. Furthermore, geographical differences do not allow to drawn any definitive conclusions and make our findings not necessarily representative of different areas in Italy or worldwide.

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Declaration of Competing Interest

All authors have nothing to disclose.

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