

## Management of acute coronary syndromes during the COVID-19 outbreak in Lombardy: The “macro-hub” experience <sup>☆</sup>



Stefano Carugo <sup>a,\*</sup>, Marco Ferlini <sup>b</sup>, Diego Castini <sup>a</sup>, Aida Andreassi <sup>c</sup>, Giulio Guagliumi <sup>d</sup>, Marco Metra <sup>e</sup>, Carlo Lombardi <sup>e</sup>, Claudio Cuccia <sup>f</sup>, Stefano Savonitto <sup>g</sup>, Luigi Piatti <sup>g</sup>, Maurizio D’Urbano <sup>h</sup>, Corrado Lettieri <sup>i</sup>, Pietro Vandoni <sup>j</sup>, Maddalena Lettino <sup>j</sup>, Giancarlo Marenzi <sup>k</sup>, Matteo Montorfano <sup>l</sup>, Alberto Zangrillo <sup>m</sup>, Battistina Castiglioni <sup>n</sup>, Roberto De Ponti <sup>n</sup>, Luigi Oltrona Visconti <sup>b</sup>

<sup>a</sup> Cardiology Department, University of Milan, ASST Santi Paolo e Carlo, Milano, Italy

<sup>b</sup> Cardiology Department, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

<sup>c</sup> General Division Welfare, Lombardy Region, Italy

<sup>d</sup> Cardiovascular Department, ASST Papa Giovanni XXIII, Bergamo, Italy

<sup>e</sup> Cardiology Department, University of Brescia, ASST Spedali Civili, Brescia, Italy

<sup>f</sup> Cardiology Department, Poliambulanza Hospital, Brescia, Italy

<sup>g</sup> Cardiology Department, Manzoni Hospital, ASST Lecco, Italy

<sup>h</sup> Cardiology Department, Magenta Hospital, ASST Ovest Milanese, Italy

<sup>i</sup> Cardiology Department, Carlo Poma Hospital, ASST Mantova, Italy

<sup>j</sup> Cardiology Department, San Gerardo Hospital, ASST Monza, Italy

<sup>k</sup> IRCCS Centro Cardiologico Monzino, University of Milan, Milano, Italy

<sup>l</sup> Interventional Cardiology Unit, IRCCS San Raffaele, Milano, Italy

<sup>m</sup> Cardiac Surgery ICU, IRCCS San Raffaele, Milano, Italy

<sup>n</sup> Cardiology Department, Tradate Hospital, ASST Settelaghi Varese, Italy

### ARTICLE INFO

#### Article history:

Received 5 August 2020

Received in revised form 6 October 2020

Accepted 8 October 2020

Available online 3 November 2020

#### Keywords:

COVID-19

Sars-CoV2

Acute coronary syndromes

STEMI

NSTEMI

Macro-hubs

### ABSTRACT

**Background:** During the COVID-19 outbreak, healthcare Authorities of Lombardy modified the regional network concerning time-dependent emergencies. Specifically, 13 Macro-Hubs were identified to deliver timely optimal care to patients with acute coronary syndromes (ACS). Aim of this paper is to present the results of this experience.

**Methods and Results:** This is a multicenter, observational study. A total of 953 patients were included, presenting with STEMI in 57.7% of the cases. About 98% of patients received coronary angiography with a median since first medical contact to angiography of 79 (IQR 45–124) minutes for STEMI and 1262 (IQR 643–2481) minutes for NSTEMI.

A total of 107 patients (11.2%) had SARS-CoV2 infection, mostly with STEMI (74.8%). The time interval from first medical contact to cath-lab was significant shorter in patients with COVID-19, both in the overall population and in STEMI patients (87 (IQR 41–310) versus 160 (IQR 67–1220) minutes,  $P = 0.001$ , and 61 (IQR 23–98) versus 80 (IQR 47–126) minutes,  $P = 0.01$ , respectively). In-hospital mortality and cardiogenic shock rates were higher among patients with COVID-19 compared to patients without (32% vs 6%,  $P < 0.0001$ , and 16.8% vs 6.7%,  $P < 0.0003$ , respectively).

**Conclusions:** During the COVID-19 outbreak in Lombardy, the redefinition of ACS network according to enlarged Macro-Hubs allowed to continue with timely ACS management, while reserving a high number of intensive care beds for the pandemic. Patients with ACS and COVID-19 presented a worst outcome, particularly in case of STEMI.

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<sup>☆</sup> All authors take responsibility for all the aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

\* Corresponding author at: Cardiology Department, University of Milan, ASST Santi Paolo e Carlo, Milan, Italy.

E-mail address: [stefano.carugo@unimi.it](mailto:stefano.carugo@unimi.it) (S. Carugo).

### 1. Introduction

Lombardy is the most densely populated region in Italy, with approximately 10 million inhabitants. Since the first case of coronavirus disease 2019 (COVID-19) secondary to severe acute respira-

tory syndrome coronavirus 2 (SARS-CoV2) infection on February 21st 2020, an exponential spread of infections led four months later to more than 90 thousand cases diagnosed with the disease in Lombardy. The peak of infection was registered on March and April 2020, with a progressive but very slow decrease on May and June; unfortunately, more than 16,000 patients died [1].

Emergency situations, as the COVID-19 outbreak, may exert an adverse influence on the efficiency and effectiveness of time-dependent systems, with potential catastrophic consequences on clinical outcome: admissions for acute coronary syndromes (ACS) were significantly reduced during the COVID-19 pandemic across Italy, and appropriate time frames for primary percutaneous coronary intervention (PPCI) [2] for patients presenting with ST-elevation myocardial infarction (STEMI) might have been affected, with a potential increase in fatality and complication rates [3]. Recommendation on how to treat patients with ACS, affected or not by COVID-19 infection, have been issued in countries with a massive virus outbreak [4] and have been provided by national and international scientific societies [5].

On March 8th, the decree of the healthcare Authorities of Lombardy [6] urged a change in all of the regional networks for the treatment of time-dependent clinical and surgical emergencies (STEMI, stroke, major traumas, neurological, cardiac and vascular surgical emergencies) to concentrate urgent activities in few centers while expanding the numbers of intensive care beds dedicated for the COVID-19 patients, and avoid the default of other hospitals due to general overload. The standard STEMI network in Lombardy is divided in 8 areas, with an overall availability of 55 catheterization laboratories (cath-lab), most performing 24/7 PPCI. A detailed description of the modified network for STEMI during pandemic have been published previously [7]. In brief, a model of centralization to one or two "Macro-Hubs" in each area was applied according to the estimated patient transportation time, geographical features and capacity to admit all arriving patients. Further mandatory features were defined as follow: to perform PPCI to all incoming STEMI on a 24/7 basis; to guarantee a PPCI team (interventional cardiologists, nurses and related staff) available 24/7 in hospital (rather than on call); to provide separated pathways for STEMI patients with suspected/diagnosed COVID-19 from triage, through cath-lab to an isolated care unit. Thirteen "Macro-hubs" were therefore identified, with a variable number of spoke centers per Macro-Hub [7].

Aim of the present registry was to collect data about the management of patients with STEMI or non-STEMI (NSTEMI) hospitalized at the identified "Macro-Hubs" in Lombardy during the COVID-19 outbreak.

## 2. Methods

This study is a multicenter retrospective analysis of prospectively collected data. We included all consecutive patients with diagnosis of ACS hospitalized at each Macro-Hub from February 21st to May 7th 2020.

At each participating hospital, a principal investigator was responsible for data collection in a custom electronic database provided by the coordinating center (Division of Cardiology, University of Milan, ASST Santi Paolo e Carlo, Milan). At the end of the study the completed databases were submitted to the coordinating center to proceed with data analysis.

### 2.1. Study population

Eligible patients were identified for inclusion if they had received a diagnosis of ACS (either STEMI or NSTEMI). STEMI was defined as typical symptoms lasting for  $\geq 20$  min and persistent

ST-elevation of  $\geq 1$  mm (not known to be preexisting or resulting from a coexisting disorder) in greater than 2 contiguous leads and new or presumed-new left bundle-branch block. NSTEMI was defined as new ischemic symptoms and elevated cardiac biomarkers (high-sensitive I or T troponin above the upper limit of normal at each study site) with or without associated electrocardiographic changes (ST-depression, transient ST-elevation and T-wave inversion). The diagnosis of SARS-CoV2 infection was based on positivity of nasopharyngeal swab, bronchoalveolar lavage, serological test or a pulmonary TAC diagnostic for COVID-19 interstitial pneumonia, as single test or in combination.

Patients presenting with STEMI were directly admitted to the cath-lab to undergo primary PCI and they were all managed as potentially COVID-19 positive. After procedure, a swab test for SARS-CoV2 infection has been performed, and these patients were hospitalized in separated and dedicated rooms of the coronary care unit (CCU), until the result of the test was available. Healthcare professionals in this setting used appropriate personal protective equipment from admission in cath-lab to CCU.

Stable patients presenting with NSTEMI underwent a swab test for SARS-CoV2 infection at arrival in the Emergency Room and they had access to cardiology ward or CCU only after the result of the test was available, through a dedicated pathway if positive.

The study complies with the Declaration of Helsinki and was approved by the Local Institutional Review Board at each participating center.

### 2.2. Data collection

During the study the following data were collected: demographic characteristics; cardiovascular risk factors; previous cardiac events or procedures; site of STEMI (anterior versus others); values of hemoglobin and platelet count at admission; peak values of serum creatinine, lactate dehydrogenase and C reactive protein (CRP) during hospitalization; and, finally, echocardiographic left ventricular ejection fraction. The type of symptoms (chest pain versus dyspnea) and a clinical presentation with cardiogenic shock or cardiac arrest had to be reported.

Data about timing of symptoms onset, first medical contact (time of diagnosis by 12-lead electrocardiogram), hospitalization, access to cath-lab, details about type of revascularization (PCI or surgical) and extent of significant coronary artery disease at visual estimation had to be reported.

In hospital occurrence of death, recurrent myocardial infarction, stent thrombosis, heart failure and cardiogenic shock was further collected. Finally, data about pneumonia occurrence and the institution of non-invasive ventilation or endotracheal intubation with mechanical ventilation were collected.

### 2.3. Statistical analysis

Categorical data are reported as absolute values and percentages, continuous variables are presented as median and interquartiles range (IQR). Variables were compared by the chi-squared test or the Mann-Whitney test as appropriated.

The association between COVID-19 and mortality was investigated in a multivariate logistic regression analysis including presence of COVID-19 and the following covariates: age, sex, diabetes, arterial hypertension, previous myocardial infarction, STEMI as ACS of presentation, multivessel coronary artery disease, treatment with PCI at index event, left ventricular ejection fraction, occurrence of cardiac arrest, cardiogenic shock and pneumonia.

The softwares used for the analysis were SPSS 23 (SPSS Inc. Armonk, NY) and MedCalc Statistical Software version 16.2.0 (MedCalc Software bvba, Ostend, Belgium), the cut-off adopted for statistical significance was  $P < 0.05$ .

### 3. Results

Twelve out of thirteen Macro-Hubs agreed to participate and a total of 953 patients were included.

The baseline clinical characteristics of the population are summarized in Table 1. The median age was 69 (58–77) years (31.5% were  $\geq$  75 years old) and 23.4% were females.

STEMI was the clinical presentation in 57.7% of the cases, with anterior site in 52.2% of them. About 98% of patients received coronary angiography (98.7% of those with STEMI and 96.8% of those with NSTEMI), followed by myocardial revascularization with PCI in 84% of the cases (91.8% of those with STEMI and 68.2% of those with NSTEMI) and with coronary artery by-pass grafting in 3%.

About half of the patients (479, 50.3%) were transported to a Macro-Hub by the emergency medical service (EMS) whereas 169 self-presented at the emergency room of a Macro-Hub; 21 patients were already recovered at a Macro-Hub at the time of ACS; 268 were transferred by the spokes.

The median time from symptom onset to first medical contact (FMC) was 103.5 (IQR 56–240) minutes for STEMI and 164 (IQR 70–367) for NSTEMI; the time from FMC to hospital access was 65 (IQR 34–101) minutes for STEMI and 337 (IQR 127–553) for NSTEMI; the time from FMC to cath-lab was 79 (IQR 45–124) minutes for STEMI and 1262 (IQR 643–2481) minutes for NSTEMI; finally, the time from admission to cath-lab access was 12 (IQR 0–23) minutes for STEMI and 925 (IQR 182–2077) minutes for NSTEMI.

#### 3.1. Patients with COVID-19

A total of 107 patients (11.2%) presented a concomitant confirmed SARS-CoV2 infection with pneumonia in 60% of the cases. STEMI was the clinical presentation in most of these cases, a rate that was higher compared to COVID-19 negative patients (74.8%

**Table 1**  
Baseline characteristics of the overall population.

Variable	N = 953
Age, years (median IQR)	69 (58–77)
Age $\geq$ 75 years, n (%)	300 (31.5)
Females, n (%)	223 (23.4)
Arterial Hypertension, n (%)	641 (67.3)
Smoking, n (%)	367 (38.5)
Type 2 Diabetes, n (%)	230 (24.1)
Hyperlipidemia, n (%)	446 (46.8)
Previous MI, n (%)	207 (21.7)
Previous PCI, n (%)	218 (22.9)
Previous CABG, n (%)	50 (5.2)
LVEF, % (median IQR)	50 (40–55)
COVID-19 +, n (%)	107 (11.2)
<b>Clinical Presentation</b>	
STEMI, n (%)	550 (57.7)
NSTE-ACS, n (%)	403 (42.3)
<b>Blood samples</b>	
Hemoglobin at admission (gr/dl), (median IQR)	13.8 (12.4–15)
Platelets count at admission (n/mcl), (median IQR)	222 (184–272)
Serum creatinine max (mg/dl), (median IQR)	1.05 (0.86–1.36)
<b>Coronary Angiography and Revascularization</b>	
Coronary angiography, n(%)	933 (97.9)
STEMI, n (%)	543 (98.7)
NSTEMI, n (%)	390 (96.8)
PCI, n (%)	780 (83.6)
CABG, n (%)	31 (3.3)
Complete revascularization, n (%)	559 (59.9)

MI = myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery by-pass grafting; LVEF = Left ventricle ejection fraction; COVID-19 = coronavirus disease 2019; STEMI = ST-elevation myocardial infarction; NSTEMI = non-persistent ST-elevation myocardial infarction.

**Table 2**

Comparison between patients with acute coronary syndromes and concomitant or not coronavirus disease 2019 (COVID-19).

Variable	COVID-19 N = 107	No COVID-19 N = 846	P value
Age, (median IQR)	71 (61–77)	68 (58–77)	0.25
Female sex, (median IQR)	25 (23.4)	198 (23.4)	0.99
Arterial Hypertension, n (%)	79 (74)	562 (66.4)	0.12
Type 2 Diabetes, n (%)	32 (30)	198 (23.4)	0.13
Smoking, n (%)	17 (16)	350 (41.4)	<0.0001
LVEF, (median IQR)	45 (35–54)	50 (40–55)	<0.0001
Serum creatinine, mg/dl (median IQR)	1.15 (0.87–1.61)	1.03 (0.86–1.33)	0.02
Platelets, n/mcl (median IQR)	242 (187–296)	220 (184–269)	0.02
LDH, U/l, (median IQR)	478 (231–683)	291 (213–483)	0.001
<b>Clinical presentation</b>			
STEMI, n (%)	80 (74.8)	470 (55.6)	<0.001
NSTEMI, n (%)	27 (25.2)	376 (44.4)	<0.001
Chest pain n (%)	91 (85)	780 (92.2)	< 0.01
Dyspnea, n (%)	42 (40)	120 (14.2)	<0.0001
Shock, n (%)	2 (1.9)	8 (0.9)	0.37
Cardiac Arrest, n (%)	4 (3.8)	19 (2.2)	0.33
<b>Coronary Angiography and Revascularization</b>			
No significant CAD, n (%)	13 (12.5)	31 (6)	0.05
PCI, n (%)	84 (78.5)	696 (82.3)	0.34
CABG, n (%)	0 (0)	31 (3.7)	0.04
Complete revascularization, n (%)	54 (50.5)	505 (59.7)	0.06
<b>Clinical Outcome</b>			
Death, n (%)	34 (32)	49 (6)	<0.0001
MI, n (%)	0 (0)	6 (0.6)	0.42
Stent thrombosis, n (%)	0 (0)	5 (0.6)	0.42
Cardiogenic shock, n (%)	18 (16.8)	57 (6.7)	<0.001
Pneumonia, n (%)	64 (60)	25 (3)	<0.0001

LVEF = Left ventricle ejection fraction; SD = standard deviation; LDH = lactate dehydrogenase; STEMI = ST-elevation myocardial infarction; NSTEMI = non-persistent ST-elevation myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery by-pass grafting; MI = myocardial infarction.

vs 55.6%,  $P < 0.0002$ ). Table 2 reports the comparison between patients with and without COVID-19.

Although chest pain, with or without dyspnea, was the most common symptom at presentation in most cases, this symptom was significantly less common compared to patients without COVID-19 (85% vs 92%,  $P < 0.01$ ); on the contrary, the rate of dyspnea as prevailing symptom was higher in patients with infection (40% vs 14%,  $P < 0.0001$ ). Moreover, significantly more subjects with COVID-19 required endotracheal intubation (18% vs 4.3%,  $P < 0.0001$ ). Platelets count, creatinine and lactate dehydrogenase values were higher in patients with COVID-19.

Coronary angiography was performed in 97.2% of overall patients with COVID-19 and 80% underwent a PCI. The rate of patients without significant coronary stenosis was higher in patients with COVID-19 (12.5% vs 6%,  $P = 0.05$ ). No patients with STEMI was treated with fibrinolysis.

In hospital mortality was higher in patients with COVID-19 compared to patients without (32% vs 6%,  $P < 0.0001$ ), particularly in those with STEMI (38.7% vs 8.1%,  $P < 0.0001$ ). In-hospital occurrence of stent thrombosis and of recurrent MI was not different between the two groups; more patients with COVID-19 experienced cardiogenic shock during hospitalization (16.8% vs 6.7%,  $P < 0.0003$ ). At multivariate logistic regression analysis, the presence of COVID-19 resulted independently associated with in-hospital mortality likewise age, STEMI presentation, an ejection fraction  $< 40\%$ , the occurrence of cardiac arrest and shock, while treatment with PCI was associated with in-hospital survival (Table 3).

**Table 3**

Regression coefficients and odds ratios obtained by multivariate logistic regression model testing association between clinical variables and in-hospital mortality.

Variable	Regression coefficient (SE)	P value	Odds ratios (95% CI)
Age	0.054 (0.018)	0.002	1.05 (1.01–1.09)
Female sex	0.090 (0.437)	0.83	1.09 (0.46–2.58)
Diabetes	0.126 (0.412)	0.76	0.88 (0.39–1.98)
Arterial hypertension	0.270 (0.459)	0.55	1.31 (0.53–3.22)
Previous MI	0.621 (0.435)	0.15	1.86 (0.79–4.36)
STEMI	1.073 (0.518)	0.04	2.92 (1.06–8.07)
MVD	0.719 (0.403)	0.07	2.05 (0.93–4.52)
PCI at index event	−2.14 (0.501)	<0.0001	0.12 (0.04–0.31)
LVEF < 40%	1.64 (0.409)	0.0001	5.17 (2.31–11.5)
Cardiac arrest	2.25 (0.728)	0.002	9.54 (2.29–39.77)
Cardiogenic shock	2.94 (0.454)	<0.0001	19.10 (7.84–46.53)
Pneumonia	0.99 (0.553)	0.07	2.72 (0.91–8.04)
COVID-19	1.87 (0.576)	0.001	6.52 (2.10–20.18)

MVD = multivessel coronary disease; MI = myocardial infarction; PCI = percutaneous coronary intervention; LVEF = Left ventricle ejection fraction; COVID-19 = coronavirus disease 2019; STEMI = ST-elevation myocardial infarction.

Despite lack of statistical significance, time from symptoms onset to FMC was longer in patients with COVID-19, both in the overall population and in patients with STEMI: 150 (IQR 63–323) versus 120 (IQR 60–310) minutes ( $P = 0.63$ ) and 150 (IQR 46–297) versus 99 (IQR 57–236) minutes ( $P = 0.57$ ), respectively (Fig. 1). In the overall population, the time interval from FMC to cath-lab was significant shorter in patients with COVID-19 compared to patients without COVID-19 (87 (IQR 41–310) versus 160 (IQR 67–1220) minutes,  $P = 0.001$ ), due to a reduction in the time from FMC to hospital admission and from hospital admission to cath-lab (Fig. 1, panel A).

In patients with STEMI, the time interval from FMC to cath-lab was significantly lower in patients with COVID-19 compared to patients without COVID-19 (61 (IQR 23–98) versus 80 (IQR 47–126) minutes,  $P = 0.01$ ), due to a significant reduction of time from FMC to hospital admission (43 (IQR 13–84) versus 61 (IQR 31–100),  $P = 0.01$ ); time from hospital admission to cath-lab was short in both groups without a significant difference (10 (IQR 0–25) minutes vs 8.5 (IQR 0–23),  $P = 0.85$ ) (Fig. 1, panel B).

#### 4. Discussion

In the present registry, we report the experience of the Macro-Hubs that have been identified by the healthcare Authorities of Lombardy during the pandemic of COVID-19 to manage the time-dependent cardiac emergencies. We focused on ACS during two months with the highest daily increase of virus cases. The main findings of the data collection have been: more than half of treated patients presented with STEMI; nearly all patients received a timely coronary angiography; treatment times were in line with guidelines recommendations; patients with ACS and positive at SARS-CoV2 were mainly STEMI, and had significantly higher rates of cardiogenic shock and death compared to patients without infection.

The STEMI network of the Lombardy region has an overall availability of 55 cath-labs, most performing 24/7 PPCI, and a well distributed EMS for transportation of patients to PCI capable centers. The 13 Macro-Hubs identified at the beginning of the COVID-19 outbreak, perform 24/7 PPCI as hub even outside pandemic, though with a smaller area to serve and with a lesser number of spokes. Therefore, we think that it was not unexpected that numbers of STEMI were higher as compared to NSTEMI. In a recent multicentric, observational, nationwide survey carried out by the Italian Society of Cardiology, throughout a one-week period during the COVID-19 outbreak, the number of patients admitted to coronary care units with NSTEMI was lower than STEMI, mainly due to a

greater reduction of the NSTEMI numbers compared with the same week in 2019 [3].

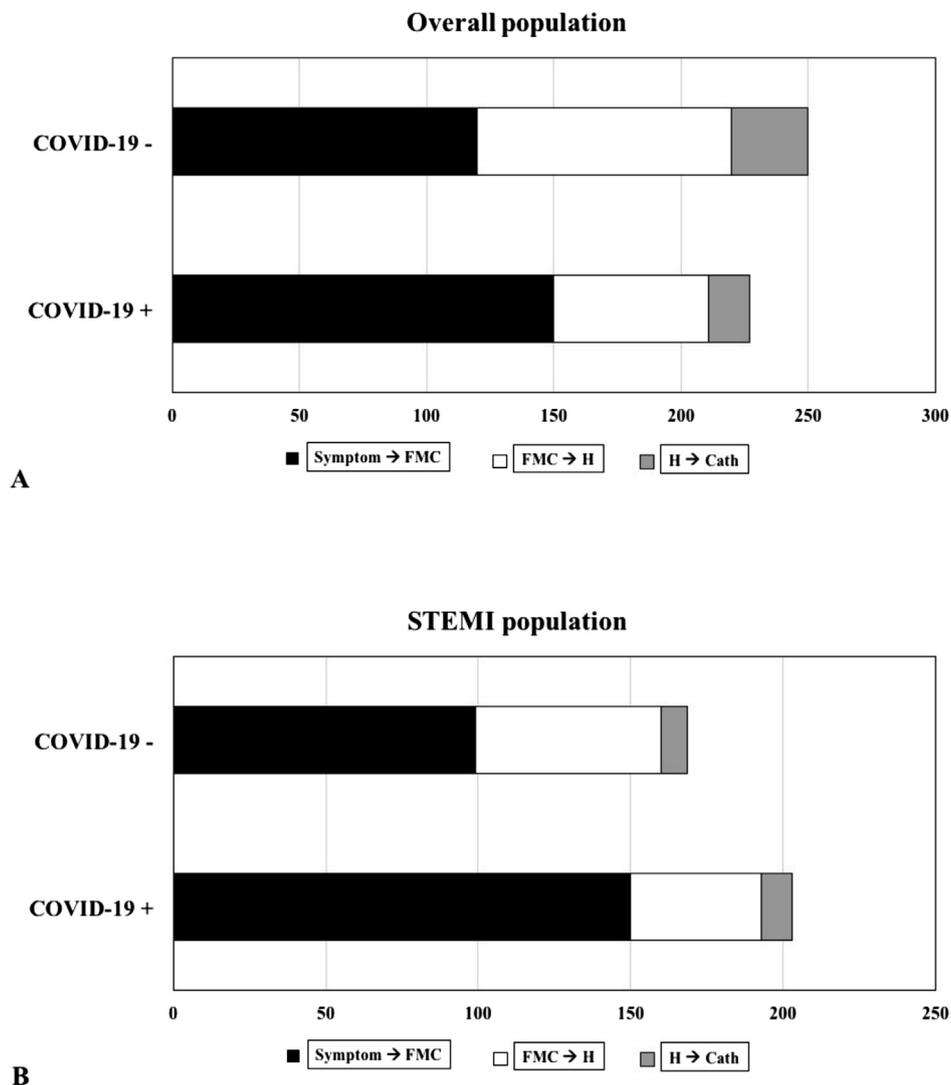
Furthermore, in the present registry, two-thirds of ACS accessed directly to a Macro-Hub, and most of them were transported by EMS: in case of STEMI, this likely allowed an acceptable time since FMC to cath-lab and to avoid fibrinolysis. Although a timing analysis for NSTEMI is more difficult for the heterogeneity of clinical presentation, time to invasive strategy was within 24 h, as recommended by guidelines in high risk patients. However, we cannot exclude that many patients with NSTEMI, not requiring urgent coronary angiography, were not referred by the spokes, resulting with a different time and type of treatment.

The overall rate of patients positive at SARS-CoV2 was comparable to the one reported in a previous Italian registry, but we found a lower rate of SARS-CoV2 positive subjects in NSTEMI population and a concomitant higher rate among STEMI [3].

Patients with COVID-19 had a higher mortality compared to those without COVID-19, particularly in case of STEMI. Beyond numerical or significant differences, confounding for imbalance in important baseline covariates must be considered in the interpretation of clinical outcomes. Patients with COVID-19 presented some features of higher risk related to the SARS-CoV2 infection, that was likely the cause of the worst outcome of this population: pneumonia was present in 60% of the cases, shock was 5 times greater and almost 20% of patients required an endotracheal intubation. Anyway, COVID-19 resulted to be independently associated with in-hospital mortality when evaluated in a multivariate logistic regression model together with age, STEMI presentation, cardiac arrest, shock and reduced left ventricular function.

About 12.5% of patients with COVID-19 had no significant coronary stenosis at angiogram; our finding is lower compared to the 39.3% initially reported by Stefanini et al. in 28 patients with confirmed COVID-19 who underwent an urgent coronary angiogram because of STEMI in Lombardy [8]. Although we cannot exclude that this difference could be a chance finding, patients with COVID-19 present evidence of myocardial injury, in some cases with abnormalities similar to myocarditis [9]. We agree with Italian colleagues that should be mandatory in such patients trying to differentiate between type 2 myocardial infarctions, myocarditis versus type 1 myocardial infarctions before coronary angiogram, to avoid inappropriate procedure and additional personnel exposure [8].

Our strategy of centralization had not a negative impact on time to treatment; in patients with COVID-19 we recorded a median time interval FMC to cath-lab even lower compared to patients without infection due to a reduction in time from FMC to hospital admission and from admission to cath-lab, perhaps due to the



**Fig. 1.** Time intervals (minutes) of care in patients with (+) and without (-) coronavirus disease 2019 (COVID-19) in the overall population (panel A) and in patients with ST-elevation myocardial infarction (panel B). STEMI = ST-elevation myocardial infarction; NSTEMI = non-persistent ST-elevation myocardial infarction; FMC = first medical contact; H = hospital access; Cath = access to catheterization laboratory.

worse clinical presentation of COVID positive patients. At the beginning of COVID-19 outbreak, a delay in treatment of patients presenting with STEMI was reported, mostly explained with lack of dedicated organization by the healthcare system or by the limited availability of EMS due to sick staff or systemic overload [10,11].

In our experience, beyond the already discussed modifications of the preexisting network, it is likely that an established and separated pathway for patients with suspected or diagnosed COVID-19, further reduced the time interval to treatment; however, we did not collect the previous information for each patient, making not feasible a separate analysis.

Time from symptoms onset to FMC was higher in patients with COVID-19, particularly for STEMI; although of non univocal interpretation, this finding might be related to the higher rate of dyspnea without chest pain as clinical presentation in these patients: an uncertainty in diagnosis of suffering heart attack may have caused a delay in seeking medical care.

The fear of infection, that has been supposed as the main cause of delay in STEMI presentation [10,12] may have played a more important role in patients without COVID-19.

However, different areas reported different results about time to treatment for STEMI during COVID-19 outbreak. In a national analysis carried out in Poland that investigated the impact of SARS-CoV2 pandemic on interventional cardiology procedures, a longer time delay has been observed in the STEMI cohort of COVID-19 patients for all the time intervals (pain to FMC and FMC to inflation or angiogram) [13]. In a single center experience from France, beyond a description of ACS admission during pandemic with a pattern of “U-shape” curve (initial dramatic decrease with return to normality 4 week after lockdown), it was found a significant increase in total ischemic time exclusively due to an increase in the symptom-onset to FMC time [14].

Finally, a reorganization of the network and an increase of fatigue by interventional cardiologists to guarantee a team available in hospital 24/7 was required to allow an acceptable treatment of ACS. Furthermore, although it was not investigated in the present study, it’s likely that local difficulties would be associated to the hospitalization of higher number of patients.

Therefore, at present, the model described should not be considered outside a situation of emergency as pandemic, and a new model of centralization could be redesigned.

#### 4.1. Study limitations

The relatively small sample size and the limitations inherent to the retrospective analysis of a clinical registry can be considered as the main limitations. We report only the management of ACS at 12 out of the 13 Macro-Hubs identified in Lombardy, so our finding may not be representative of different areas in Italy or worldwide [13,14]. Furthermore, no data are available about patients not transferred by the spoke centers, particularly with regard to NSTEMI.

We did not perform an analysis of troponin levels, as different hospitals used different biomarkers of myocardial injury (i.e. high-sensitivity, I or T-troponin) with upper limit of normal serum levels according to the local institutional laboratory: with these limitations we considered any analysis inconclusive and potentially misleading.

A separate analysis of timing to treatment in subgroup of patients with unknown/uncertain diagnosis of SARS-CoV2 infection was not carried out; however, we managed all STEMI patients in the acute phase as potentially positive and differences were unlikely.

We did not perform any comparison with data of the previous years to investigate the possible reduction in the number of ACS patients hospitalized during the pandemic; however, the present modified network, with a higher number of spokes, paradoxically increased the number of patients admitted to most of the Macro-hubs.

Finally, as previously mentioned, we did not perform any correction for covariates, and confounding bias on present results cannot be excluded.

#### 4.2. Conclusion

During the COVID-19 outbreak in Lombardy, the identification of some Macro-Hubs allowed to persist in the correct management of patients presenting with ACS.

Patients with ACS and positive at SARS-CoV2 had a much worst outcome, particularly in case of STEMI.

##### 4.2.1. Participating investigators

Marco Centola, Giulia Ferrante, Davide Marchetti (ASST Santi Paolo e Carlo, Milano), Claudio Montalto, Giuseppe Lanzillo (IRCCS Policlinico San Matteo, Pavia), Dario Pellegrini, Irene Pescetelli (ASST Papa Giovanni XXIII, Bergamo), Gloria Maccagni, Marianna Adamo (ASST Spedali Civili, Brescia), Sarah Cortinovi, Luisa Gentili (Poliambulanza, Brescia), Giuseppe Uccello (ASST Lecco), Claudio Vimercati, Silvia Affinito (ASST Ovest Milanese), Cristian Fava, Alfredo Fede (ASST Mantova), Stefano Rigetti, Ivan Calchera, Simone Tresoldi (ASST Monza), Nicola Cosentino, Gianpaolo D'Aleo (IRCCS Centro Cardiologico Monzino, Milano), Alberto Maria Cap-

pelletti (IRCCS San Raffaele), Roberta Giani, Claudio Licciardello, Federico Blasi (ASST Settelaghi Varese).

#### Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors

#### Declaration of Competing Interest

The authors declared that there is no conflict of interest.

#### References

- [1] <https://www.lombardianotizie.online/coronavirus-casi-lombardia/>.
- [2] K. Huber, B.J. Gersh, P. Goldstein, C.B. Granger, P.W. Armstrong, The organization, function, and outcomes of ST-elevation myocardial infarction networks worldwide: current state, unmet needs and future directions, *Eur. Heart J.* 35 (2014) 1526–1532.
- [3] S. De Rosa, C. Spaccarotella, C. Basso, et al., Reduction of hospitalizations for myocardial infarction in Italy in the COVID-19 era, *Eur. Heart J.* 41 (2020) 2083–2088.
- [4] J. Zeng, J. Huang, L. Pan, How to balance acute myocardial infarction and COVID-19: the protocols from Sichuan Provincial People's Hospital, *Intensive Care Med.* 46 (6) (2020) 1111–1113.
- [5] A. Chieffo, G.G. Stefanini, S. Price, et al., EAPCI Position Statement on Invasive Management of Acute Coronary Syndromes during the COVID-19 pandemic, *Eur. Heart J.* 41 (2020) 1839–1851.
- [6] <https://www.regione.lombardia.it/wps/wcm/connect/5e0deec4-caca-409c-825b-25f781d8756c/DGR+2906+8+marzo+2020.pdf?MOD=AJPERES&CACHEID=ROOTWORKSPACE-5e0deec4-caca-409c-825b-25f781d8756c-n2.vCsc>
- [7] M. Ferlini, A. Andreassi, S. Carugo, et al., Centralization of the ST elevation myocardial infarction care network in the Lombardy region during the COVID-19 outbreak, *Int. J. Cardiol.* 312 (2020) 24–26.
- [8] G.G. Stefanini, M. Montorfano, D. Trabattoni, et al., ST-Elevation Myocardial Infarction in Patients With COVID-19: Clinical and Angiographic Outcomes, *Circulation* 141 (2020) 2113–2116.
- [9] Q. Deng, B. Hu, Y. Zhang, et al., Suspected myocardial injury in patients with COVID-19: Evidence from front-line clinical observation in Wuhan, China, *Int J Cardiol* 311 (2020) 116–121.
- [10] C.-C. Tam, K.-S. Cheung, S. Lam, A. Wong, A. Yung, M. Sze, Y.-M. Lam, C. Chan, T.-C. Tsang, M. Tsui, H.-F. Tse, C.-W. Siu, Impact of Coronavirus Disease 2019 (COVID-19) Outbreak on ST-Segment-Elevation Myocardial Infarction Care in Hong Kong, China, *Circ: Cardiovascular Quality and Outcomes* 13 (4) (2020), <https://doi.org/10.1161/CIRCOUTCOMES.120.006631>.
- [11] A.K. Ardati, A.J. Mena Lora, Be Prepared, *Circ: Cardiovascular Quality and Outcomes* 13 (4) (2020), <https://doi.org/10.1161/CIRCOUTCOMES.120.006661>.
- [12] M. Roffi, G. Guagliumi, B. Ibanez, The Obstacle Course of Reperfusion for ST-Segment-Elevation Myocardial Infarction in the COVID-19 Pandemic, *Circulation* 141 (2020) 1951–1953.
- [13] Siudak Z, Grygier M, Wojakowski W, et al. Clinical and procedural characteristics of COVID-19 patients treated with percutaneous coronary interventions. *Catheter Cardiovasc Interv.* 2020;1–8. <https://doi.org/10.1002/ccd.29134>.
- [14] Marie Hauguel-Moreau M, Pilière R, Prati G et al. Impact of Coronavirus Disease 2019 outbreak on acute coronary syndrome admissions: four weeks to reverse the trend. *J Thromb Thrombolysis.* 2020 Jun 29 : 1–2. doi: 10.1007/s11239-020-02201-9 [Epub ahead of print].