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## Influence of Different COVID-19 Pandemic Phases on STEMI: Experience From an Italian Hub Centre☆

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### ABSTRACT

**Introduction:** During Coronavirus disease 2019 (COVID-19) pandemic a reduction in ST-elevation acute myocardial infarction with an increase in in-hospital mortality has been observed. In our region the pandemic temporal trend was sinusoidal with peaks and valleys. A first outbreak was in March 2020, a reduction in May 2020 and a second outbreak in November 2020.

**Materials & methods:** Our hospital was reorganized as one of the 13 Macro-Hubs identified in Lombardy and we retrospectively analysed consecutive STEMI patients hospitalized in the three different phases of COVID-19 pandemic.

**Results:** We did not register any difference in the number of STEMI hospitalized in the three phases. At multivariate analysis for the entire population COVID-19 infection was the strongest independent predictor of in-hospital mortality. Focusing on COVID-19 patients they experienced a 5-time increased incidence of in-hospital mortality (COVID-19<sup>pos</sup> vs COVID-19<sup>neg</sup>, 47.1% vs 8.6%;  $p < 0.0001$ ) mainly driven by a higher incidence of respiratory complications (COVID-19<sup>pos</sup> vs COVID-19<sup>neg</sup>, 41.2% vs 6.2%;  $p < 0.0001$ ) with a similar incidence of cardiac death.

**Discussion:** Among STEMI admitted during different phases of pandemic, this study found an increased mortality in patients affected by COVID-19; the co-presence of COVID-19 infection leads to an increase of mortality mostly related to respiratory complications. Interestingly the different incidence in the general population of COVID-19 did not influence the incidence of STEMI.

**Conclusion:** In conclusion our data suggest the crucial need for an early and precise diagnosis of COVID-19 infection in STEMI to establish a correct management of these very high-risk patients.

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## 1. Introduction

Coronavirus disease 2019 (COVID-19) is a global pandemic affecting more than 181.176.715 patients worldwide (WHO data Report June 29th2021) and northern Italian regions were particularly affected. COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with a characteristic pulmonary involvement. This viral infection may have several manifestations including cardiovascular involvement. A recent study shows that 12% of patients hospitalized for COVID-19 have a direct myocardial injury [1]. During COVID-19 pandemic a reduction in ST-segment elevation myocardial infarction (STEMI) with an increase in in-hospital mortality has been observed,

explained mostly by a social and public fear relative to the risk of COVID-19 [2,3]. In our region the pandemic temporal trend was sinusoidal with peaks and valleys. A first outbreak was in March 2020 (248.12 cases for 100,000 inhabitants), a reduction in May 2020 (16.68 cases for 100,000 inhabitants) and a second outbreak in November 2020 (540.17 cases for 100,000 inhabitants; data from Italian Health Ministry). Our hospital was reorganized as one of the 13 Macro-Hubs for STEMI treatment identified in Lombardy [4]. Here we describe our experience in the three different phases of COVID-19 pandemic.

## 2. Methods

We retrospectively analysed consecutive STEMI patients hospitalized from March 15th, to April 15th 2020 (Pandemic-Peak 1; P–P1), from May 15th, to June 15th 2020 (Pandemic-Valley 1; P–V1) and from November 1st, to November 30th 2020 (Pandemic-Peak 2;

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P—P2). The study was performed in accordance with the Declaration of Helsinki and all patients signed a disclosure for the use of personal data collected anonymously. The diagnosis of SARS-COV-2 was performed by nasopharyngeal swab test. In-hospital all-cause mortality was the primary outcome. Cardiac death was defined in case of fatal arrhythmias, cardiogenic shock or mechanical complication. Respiratory pattern was registered at admission and monitored during the recovery. Respiratory complication was defined as respiratory impairment with need for an increase of ventilatory support with respect to the admission. This was defined as the need to up-grade the ventilatory support divided into four classes (no ventilatory support; increased oxygen intake; mechanical non-invasive ventilation; mechanical invasive ventilation). Respiratory complications, ischemic stroke, non-fatal MI, major bleeding, defined from type 3 to 5 according to Bleeding Academic Research Consortium (BARC) criteria and urgent unplanned revascularization were identified as in hospital adverse events [5]. Statistical analysis was performed with the SPSS 23 statistical package. Univariate and

multivariate analyses was performed by logistic regressions. A *p*-value <0.05 was considered statistically significant.

### 3. Results

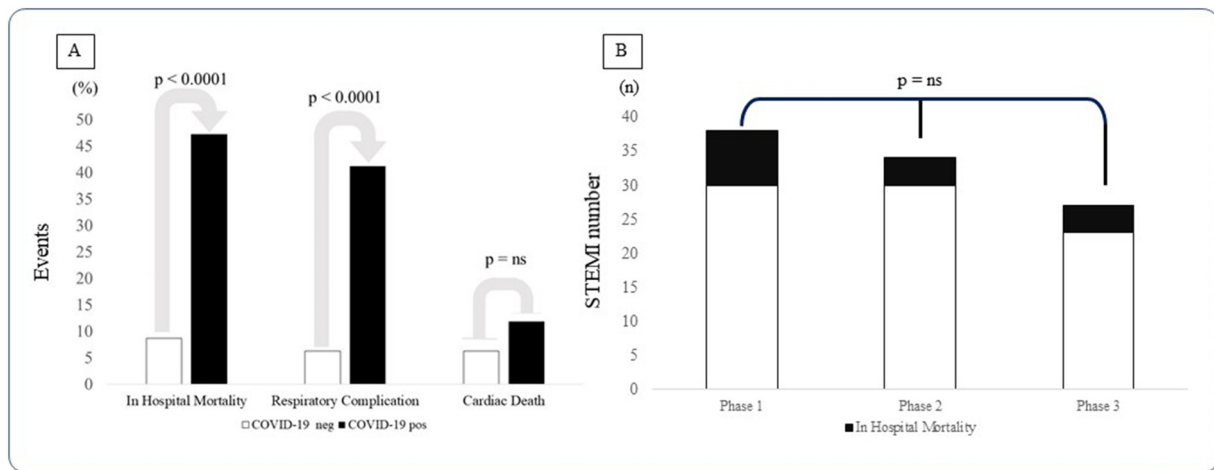
From a total of 99 STEMI patients, we divided our population in three groups according to the hospitalization period (*n* = 38 in P—P1, *n* = 34 in P—V1 and *n* = 27 in P—P2). The Table 1 displays a detailed overview of baseline clinical and demographical characteristics. The groups are superimposable with no differences regarding main cardiovascular risk factors, excluding a higher incidence of hypercholesterolemia and a minor, but significant, higher ejection fraction in the third group ( $48.7 \pm 9.0\%$  vs  $43.5 \pm 13.3$  vs  $50.3 \pm 9.4$ ; *p* = 0.04). The three groups differ for COVID-19 infection characterization. COVID-19 acute infection was detected only in P—P1 and P—P2 vs P—V1 patients (21.1% and 33.3% vs 0%; *p* < 0.002). During P—P1 patients received at most one test, during P—V1 all patients received one nasal swab test, conversely

**Table 1**

Shows baseline clinical, demographical and procedural characteristics of the population divided into the three phases; in-hospital outcome and multivariate analysis are reported at the bottom of the table.

Clinical characteristics	P-P1 (n = 38)	P-V1 (n = 34)	P-P2 (n = 27)	p-Value
Age (M-SD)	65 ± 11.2	68.3 ± 13.1	67.1 ± 13.6	ns
Male sex (%)	76.3	73.5	70.4	ns
BMI (kg/m <sup>2</sup> ) (M-SD)	26.6 ± 4.5	25.4 ± 3.1	27.3 ± 4.4	ns
Hypertension (%)	57.9	58.8	66.7	ns
Active smokers (%)	28.9	29.4	33.3	ns
Hypercholesterolemia (%)	21.1	20.6	48.1	0.03
Diabetes (%)	26.3	8.8	14.8	ns
Family history of CAD (%)	15.8	17.6	14.8	ns
Previous AMI (%)	13.2	5.9	18.5	ns
COPD (%)	7.9	11.8	3.7	ns
Ejection fraction (M-SD)	48.7 ± 9.0	43.5 ± 13.3	50.3 ± 9.4	0.04
Haemoglobin (g/dL) (M-SD)	13.4 ± 2.2	13.0 ± 1.7	13.9 ± 1.6	ns
Creatinine (mg/dL) (M-SD)	0.97 ± 0.27	0.93 ± 0.26	1.05 ± 0.41	ns
White Blood cells (10 <sup>3</sup> /uL) (M-SD)	11.7 ± 5.0	11.6 ± 6.8	10.2 ± 2.3	ns
Lymphocytes (10 <sup>3</sup> /uL) (M-SD)	1.8 ± 1.0	1.5 ± 0.6	2.0 ± 0.6	ns
HscTn-T (ng/L) (M-SD)	2558 ± 2000	3034 ± 2667	2218 ± 2360	ns
CK-MB (UI) (M-SD)	176 ± 114	230 ± 186	201 ± 167	ns
COVID 19 characterization				
COVID 19 positive (%)	21.1	0	33.3	0.002
not tested (%)	15.7	2.9	0	<0.001
Event characteristics				
Anterior MI (%)	37.8	50.0	44.4	ns
Hb O <sup>2</sup> saturation (%) (M-SD)	95.7 ± 8.0	97.7 ± 2.2	97.4 ± 1.6	ns
Killip class ≥3 (%)	10.5	14.7	3.7	ns
Out of hospital CA (%)	18.4	11.8	0	ns
Cardiogenic shock (%)	5.5	8.8	0	ns
Total ischemic time (min) (M-SD)	273 ± 340	222 ± 242	248 ± 211	ns
Door to balloon (min) (M-SD)	42.23 ± 16.28	38.16 ± 19.63	40.73 ± 18.15	ns
Procedural characteristics				
Radial access (%)	67.6	73.5	74.1	ns
Multivessel disease (%)	48.6	61.8	63.0	ns
IABP (%)	5.5	5.9	0	ns
Complete rev. during pPCI (%)	11.1	9.5	11.8	ns
In-hospital outcome				
Days of hospitalization	10.1 ± 5.1	11.6 ± 10.4	6.4 ± 2.5	0.03
Respiratory complications (%)	15.8	11.8	7.4	ns
In hospital MACE (%)	15.8	8.8	7.4	ns
In hospital cardiovascular death (%)	7.9	8.8	7.4	ns
In-hospital all cause death (%)	21.1	11.8	14.8	ns
Multivariate analysis in-hospital all cause death				
Variable	OR	CI	p	
Killip class >2	0.58	0.03–9.79	0.71	
Ejection fraction	0.88	0.81–0.96	0.008	
COVID 19 positive	12.61	2.18–72.77	0.005	

Abbreviations: BMI, body mass index; CAD, coronary artery disease; AMI, acute myocardial infarction; COPD, chronic obstructive lung disease; HscTn-T, high sensitivity cardiac troponine – T; CK-MB, creatin kinase-MB; Hb, haemoglobin; CA, cardiac arrest; IABP, intra aortic balloon pump; pPCI, primary percutaneous coronary intervention; CABG, coronary artery by-pass; ns, not significant.



**Fig. 1.** A: in-hospital mortality, respiratory complications and cardiac death in STEMI patients not affected (COVID-19 neg) vs affected (COVID-19 pos) by COVID-19 infection; B: total STEMI number and in-hospital mortality during the three pandemic phases.

during P—P2 all patients were tested repeatedly (number of swab nasal test/patient ratio  $0.95 \pm 0.57$  vs  $1.0 \pm 0.3$  vs  $1.9 \pm 0.93$  respectively,  $p < 0.0001$ ) and 15% of patients tested positive the third time. The three groups resulted superimposable also for procedural and event characteristics in particular no differences were present in the total ischemic time or door to balloon as expected by our previous experience where we evidenced that a well reorganized emergency system with dedicated pathways for COVID-19 positive or negative patients does not influence the reperfusion times even during pandemic [6]. In the majority of cases STEMI was anterior (37.8%, 50.0% and 44.4%). Out of hospital cardiac arrest, cardiogenic shock at admission and total ischemic time did not differed significantly among the three groups. Mean hospitalization duration was significantly reduced in the third phase, explained by a better organization of the entire health care system. P—P1 patients experienced a doubled in-hospital mortality respect to P—V1 patients (21.1% vs 11.8%). At multivariate analysis for the entire population COVID-19 infection was the strongest independent predictor of in-hospital mortality (OR 12.6 [95% CI] 2.18–72.77;  $p = 0.005$ ; Table 1). COVID-19 patients experienced a 5-time increased incidence of in-hospital mortality (COVID-19<sup>pos</sup> vs COVID-19<sup>neg</sup>, 47.1% vs 8.6%;  $p < 0.0001$ ) mainly driven by a higher incidence of respiratory complications (COVID-19<sup>pos</sup> vs COVID-19<sup>neg</sup>, 41.2% vs 6.2%;  $p < 0.0001$ ) with a similar incidence of cardiac death (COVID-19<sup>pos</sup> vs COVID-19<sup>neg</sup>, 11.8% vs 6.2%;  $p = ns$ ) (Fig. 1). As expected at univariate analysis there was a significant correlation between a higher grade of ventilatory support and in-hospital mortality (OR 2.138 [95% CI] 1.52–2.99;  $p = 0.001$ ). COVID-19 patients were like negative ones in terms of main risk factors (COVID-19<sup>pos</sup> vs COVID-19<sup>neg</sup>, age:  $65.6 \pm 14.5$  vs  $66.9 \pm 12$  y.o.; BMI:  $26.8 \pm 4.0$  vs  $26.3 \pm 4.1$  kg/m<sup>2</sup>; hypertension: 70.6 vs 58.0%; diabetes 11.8 vs 18.5; EF:  $44.3 \pm 12.0$  vs  $48.1 \pm 10.5$ ;  $p = ns$ ). Moreover, we registered a higher significant presence of COVID patients in the 2nd peak phases and the absence of COVID patients during the valley phase, with a similar number of STEMI registered (38 vs 34 vs 27; incidence STEMI/die: 1.19 vs 1.06 vs 0.90;  $p = ns$ ). (See Table 1.)

#### 4. Discussion

Among STEMI admitted during different phases of pandemic, this study found an increased mortality in patients affected by COVID-19. After the beginning of the pandemic, it has been clear that COVID-19 infection was not only a pulmonary infection, but it involves many different organs and systems [7]. Over the direct infection of lungs, COVID-19 determines an imbalance in the coagulative chain and immunologic system driving to a thrombophilic and auto-immune disorder. Several different manifestations of the infection derive from this substrate:

pulmonary embolism, diffuse endothelial dysfunction, myocardial and cerebral manifestations [8–10]. Regarding patients affected by acute coronary syndrome a recent study evidenced an increased mortality rate due to more severe complications during COVID-19 pandemic [11], but the author did not mention any differences between patients affected or not by COVID-19. Our data show that among STEMI patients the co-presence of COVID-19 infection leads to an increase of mortality. Interestingly the different incidence in the general population of COVID-19 did not influence the incidence of STEMI and this opens to a fascinating but speculative hypothesis: COVID-19 infection may be a comorbidity more than a consequence of STEMI. Nevertheless, an increased incidence of COVID-19 infection in the general population leads to a more frequent co-presence of the two pathologies with a dramatic effect on mortality rate. The increased risk of death seems to be related to extra-cardiac involvement of COVID-19 infection driven by a higher incidence of respiratory complications with a similar rate of cardiac death in COVID-19 patients compared to negative ones (Fig. 1). Nevertheless, the cardiac cause of in-hospital mortality for COVID-19 patient it is not “a priori” excluded in fact, even if we did not reach the significance due to the small sample size, there was clear trend of higher cardiovascular mortality in the COVID-19 patients. Even in the presence of an increased mortality trend during the pandemic peaks, the mortality rate in the different pandemic phases did not reach the statistical significance. This may be explained by the reduced numbers of cases for each period.

#### 5. Conclusion

The co-presence of STEMI and COVID-19, more than additive, seems to have an amplifying synergic effect on mortality. Our data suggest the crucial need for an early and precise diagnosis of COVID-19 infection in STEMI patients in order to establish a strict control and the best management of this high-risk sub population.

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