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Covid-19 diagnosis and mortality in patients with non-ST-elevation myocardial infarction admitted in Italy during the national outbreak

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ABSTRACT

Introduction: We sought to assess the clinical impact of Covid-19 infection on mortality in patients with Non-ST elevation myocardial infarction (NSTEMI) admitted during the national outbreak in Italy.

Methods: We analysed a nationwide, comprehensive, and universal administrative database of consecutive NSTEMI patients admitted during lockdown for Covid-19 infection (March, 11th - May 3rd, 2020) and the equivalent periods of the previous 5 years in Italy. The observed rate of 30-day and 6-month all-cause mortality of NSTEMI patients with and without Covid-19 diagnosis during the lockdown was compared with the expected rate of death according to the trend of the previous 5 years.

Results: During the period of observation, 48,447 NSTEMI hospitalizations occurred in Italy. Among these, 4981 NSTEMI patients were admitted during the 2020 outbreak: 173 (3.5%) with and 4808 (96.5%) without a Covid-19 diagnosis. According to the 5-year trend, the 2020 expected rate of 30-day and 6-month all-cause mortality was 6.5% and 12.2%, while the observed incidence of death was 8.3% (p = 0.001) and 13.6% (p = 0.041), respectively. Excluding NSTEMI patients with a Covid-19 diagnosis, the 6-month mortality rate resulted in accordance with the prior 5-year trend. After multiple corrections, the presence of Covid-19 diagnosis resulted one of the independent predictors of all-cause mortality at 30 days [adjusted odds ratio (OR) 4.3; 95% confidence intervals (CI) 2.90–6.23; p < 0.0001] and 6 months (adjusted OR 3.5; 95% CI: 2.43–5.03; p < 0.0001).

Conclusions: During the 2020 national outbreak in Italy, a concomitant diagnosis of Covid-19 in NSTEMI was associated with a significantly higher rate of mortality.

1. Introduction

The coronavirus disease 2019 (Covid-19) infection has caused millions of deaths worldwide with a substantial impact on healthcare system and organization. Italy, that accounts about 59 million inhabitants, was the first European nation to be affected by Covid-19, with around 19 million confirmed total cases and >170,000 deaths to date [1,2]. The pandemic has mainly affected the North of Italy, where, especially in the first half of 2020, most confirmed cases of Covid-19 and related fatal events occurred [1,2].

Italy was the first western country to ratify a nationwide lockdown for Covid-19 [3], officially starting from March 11st and ending, after two addition decrees prolonging the national outbreak, on May 3rd 2020, restricting the movement of the population except for necessity, work, and health circumstances [4,5]. The national lockdown was the period with the widest spread of Covid-19 and the highest rate of mortality related to the infection, during which only health emergencies were admitted to hospitals in Italy [6].

Several studies have reported that hospitals admissions for acute myocardial infarction (MI), particularly for ST-elevation myocardial infarction, have been significantly reduced during the Covid-19 pandemic, with a concomitant increase in early mortality rate [7–10].

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without clear explanation of this phenomenon.

We aimed at analysing the clinical impact of Covid-19 infection on mortality in patients with Non-ST-elevation myocardial infarction (NSTEMI) admitted during the national outbreak and in the equivalent periods of the previous 5 years in Italy using a nationwide, comprehensive, and universal administrative database.

2. Methods

2.1. Study design

This was a retrospective cohort study that enrolled consecutive patients admitted to all public and private hospitals in Italy for a NSTEMI event during the national outbreak for Covid-19 (March, 11st - May 3rd, 2020) and the equivalent periods of the previous 5 years. We compared baseline characteristics, hospitalization rates and 30-day and 6-month all-cause mortality between NSTEMI patients admitted during the national outbreak for Covid-19 in 2020 and the prior 5-year equivalent periods. The Italian National Registry of Hospital Discharge Records (HDR), provided by the Italian Ministry of Health (MoH), and other administrative databases available through a collaboration with the Italian National Program for Outcome Evaluation (PNE-AGENAS) were used as sources of data.

2.2. Study population

All HDR of patients aged 18 to 100 years, resident in Italy, admitted during the study period and reporting diagnosis of NSTEMI were selected. For the purposes of this study NSTEMI patients were defined as patients reporting the ICD 9 CM codes 410.7 or 410.9 in primary diagnosis or the same codes in secondary diagnosis with any concomitant AMI complication within the primary diagnosis (ICD-9-CM codes 411, 413, 414, 426, 427, 428, 423.0, 429.5, 429.6, 429.71, 429.79, 429.81, 518.4, 518.81, 780.01, 780.2, 785.51, 799.1, 977.02 and 998.2) ('Outcomes evaluation National program [PNE] Ed. 2020; available at htt

Table 1

|                  | 2015 (N = 8660) | 2016 (N = 8822) | 2017 (N = 8796) | 2018 (N = 8536) | 2019 (N = 8652) | 2020 (N = 4981) | P     |
|------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-------|
| **Gender (%)**   |                 |                 |                 |                 |                 |                 |       |
| Male             | 534 (6.2)       | 570 (6.5)       | 512 (6.5)       | 543 (6.4)       | 525 (6.1)       | 281 (5.6)       | 0.345 |
| Female           | 966 (11.1)      | 939 (11.0)      | 908 (10.6)      | 844 (9.9)       | 801 (9.3)       | 394 (7.9)       | 0.609 |
| **Age (years)**  | 72.3 ± 13.1     | 72.2 ± 12.9     | 72.3 ± 12.7     | 72.1 ± 12.8     | 71.3 ± 12.7     | 66.3 ± 12.7     | 0.006 |
| **Hypertension (%)** | 3217 (37.1) | 3155 (35.8) | 3141 (35.8) | 3052 (35.8) | 3043 (35.2) | 1635 (32.8) | 0.046 |
| **Diabetes (%)** | 518 (6.4)       | 518 (6.4)       | 518 (6.4)       | 518 (6.4)       | 518 (6.4)       | 518 (6.4)       | 0.001 |
| **Heart failure (%)** | 1108 (12.8) | 1112 (12.6) | 1027 (12.6) | 986 (11.6) | 1015 (11.7) | 508 (10.2) | 0.137 |
| **Cerebrovascular disease (%)** | 959 (11.1) | 939 (10.6) | 908 (10.6) | 844 (9.9) | 801 (9.3) | 394 (7.9) | 0.069 |
| **Vascular disease (%)** | 624 (7.2) | 693 (7.9) | 651 (7.9) | 590 (6.9) | 599 (6.9) | 284 (5.7) | 0.023 |
| **Chronic coronary syndromes (%)** | 2055 (23.7) | 2056 (23.3) | 1970 (23.3) | 1855 (21.7) | 1901 (22.2) | 1059 (21.3) | 0.378 |
| **Arrhythmias (%)** | 1085 (12.5) | 1032 (11.7) | 1036 (11.7) | 962 (11.3) | 978 (11.3) | 562 (11.3) | 0.493 |
| **Anemia (%)**   | 534 (6.2)       | 570 (6.5)       | 512 (6.5)       | 543 (6.4)       | 525 (6.1)       | 281 (5.6)       | 0.345 |
| **Blood clotting defects (%)** | 16 (0.2) | 22 (0.2) | 23 (0.2) | 17 (0.2) | 15 (0.2) | 8 (0.2) | 0.792 |
| **Other hematological diseases (%)** | 50 (0.7) | 53 (0.6) | 59 (0.6) | 50 (0.6) | 59 (0.7) | 22 (0.4) | 0.180 |
| **Cardiomyopathy (%)** | 182 (2.1) | 196 (2.2) | 165 (2.2) | 163 (1.9) | 151 (1.7) | 93 (1.8) | 0.533 |
| **Rheumatic heart disease (%)** | 141 (1.6) | 140 (1.6) | 121 (1.6) | 121 (1.4) | 115 (1.4) | 67 (1.3) | 0.634 |
| **Endocarditis and acute myocarditis (%)** | 8 (0.1) | 12 (0.1) | 13 (0.1) | 11 (0.1) | 10 (0.1) | 9 (0.2) | 0.575 |
| **Other chronic heart conditions (%)** | 210 (2.4) | 256 (2.9) | 224 (2.9) | 228 (2.7) | 256 (3) | 125 (2.5) | 0.139 |
| **Chronic kidney disease (%)** | 822 (9.5) | 852 (9.7) | 826 (9.7) | 800 (9.4) | 786 (9.1) | 428 (8.6) | 0.402 |
| **Other chronic disease (liver, Pancreas, intestine) (%)** | 187 (2.2) | 182 (2.1) | 183 (2.1) | 152 (1.8) | 163 (1.9) | 78 (1.6) | 0.487 |

Abbreviations: CABG: coronary artery bypass grafting; MI: myocardial infarction; PCI: percutaneous coronary intervention.

* The p values refer to the comparison between the observed and expected rates of comorbidities in the 2020 study period.
The 30-day and 6-month all-cause mortality represented the main adverse outcomes.

2.3. Statistical analysis

Prevalence of risk factors and comorbidities were presented as counts and percentages; age was expressed as the mean ± standard deviation.

The number of expected NSTEMI events and the rates of the comorbidities and outcomes in 2020 national outbreak was estimated by a linear regression model using the number of NSTEMI events and the rates of the comorbidities and outcomes in the prior 5-year equivalent periods as predictors. The number of the actual and the expected events in the 2020 study period was compared by the Poisson test. The observed and expected rates of both comorbidities and outcomes were compared using the log-normal distribution property of the rate ratio (H0: observed rate / expected rate = 1).

The normal distribution of continuous parameters was tested with the Kolmogorov-Smirnov test. Variables with a skewed distribution were compared with the use of Wilcoxon rank sum tests. t-Test, Chi-square or Fisher exact tests were used to compare frequencies among Covid-19 and non-Covid-19 patients in the 2020 NSTEMI cohort, as appropriate.

To provide adjusted outcome data, age, gender, PCI performed ≤48 h from admission, and patients’ risk factors and comorbidities were included in the multivariate models as potential confounding factors; stepwise logistic procedures were used to identify independent associations with each of the considered outcomes. Since some chronic comorbidities recorded in the index hospitalization show a paradoxical protective effect [8], the same comorbidities recorded in the previous hospitalizations were also forced into the models.

All assumptions of statistical methods were explicitly checked. Statistical analyses were performed using SAS 9.4 (Cary, NC, USA).

3. Results

During the study period, 48,447 hospitalizations for NSTEMI occurred in Italy. In the almost 8 weeks of the 2020 national outbreak, 4981 NSTEMI patients were admitted at 365 centers in Italy: 173 (3.5%) with and 4808 (96.5%) without a Covid-19 diagnosis. Patients with a Covid-19 infection were older and more frequently had a history of rheumatic heart disease compared to NSTEMI patients without Covid-19 (Suppl. Fig. 1). In parallel, a significant decrease in the rate of CABG surgery than CABG (25.4% vs 46.3%; p < 0.0001) (Table 2).

After multiple corrections, the presence of Covid-19 diagnosis resulted one of the independent predictors of all-cause mortality at 30 days (adjusted odds ratio (OR) 4.3; 95% confidence intervals (CI) 2.90-6.23; p < 0.0001) (Suppl. Table 3) and 6 months (adjusted OR 3.5; 95% CI: 2.43-5.03; p < 0.0001) (Table 2).

### Table 2

| Logistic regression model for 6 months mortality. |
|--------------------------------------------------|
| Gender (F) | 1.6 | 0.9 | 0.856-0.967 | 0.002 |
| Age (years) | 1.1 | 1.1 | 1.074-1.081 | <0.0001 |
| COVID-19 | 3.4 | 3.5 | 2.434-5.026 | <0.0001 |
| Other hematological diseases, n (%) | 2.1 | 1.3 | 0.972-1.773 | 0.078 |
| Other previous cardiac surgery than CABG, n (%) | 1.6 | 1.3 | 1.094-1.552 | 0.003 |
| Previous vascular surgery | 2.1 | 1.3 | 1.153-1.448 | <0.0001 |
| Other chronic heart conditions | 2.2 | 1.2 | 1.041-1.431 | 0.014 |
| Anemia | 3.3 | 1.3 | 1.137-1.386 | <0.0001 |
| COPD | 2.5 | 1.2 | 1.081-1.303 | <0.0001 |
| Rheumatic heart disease, n (%) | 3.2 | 1.2 | 0.963-1.392 | 0.12 |
| Disorders of lipid metabolism | 1.0 | 0.8 | 0.712-0.889 | <0.0001 |
| Diabetes | 2.1 | 1.3 | 1.218-1.418 | <0.0001 |
| Heart failure | 3.5 | 1.6 | 1.442-1.692 | <0.0001 |
| Cerebrovascular disease | 2.4 | 1.4 | 1.258-1.492 | <0.0001 |
| Vascular disease, n (%) | 2.2 | 1.3 | 1.167-1.451 | <0.0001 |
| Other chronic disease (liver, Pancreas, intestine) | 1.7 | 1.1 | 0.889-1.292 | 0.469 |
| Chronic kidney disease | 3.3 | 1.4 | 1.268-1.524 | <0.0001 |
| Obesity | 1.2 | 1.1 | 0.874-1.278 | 0.567 |
| Previous PCI | 0.7 | 0.6 | 0.607-0.717 | <0.0001 |
| Previous cerebral revascularization, n (%) | 1.2 | 0.6 | 0.512-0.808 | <0.0001 |
| Malignant neoplasms | 2.3 | 1.7 | 1.562-1.843 | <0.0001 |
| Previous CABG | 0.8 | 0.7 | 0.643-0.813 | <0.0001 |
| PCI ≤48 h | 0.2 | 0.4 | 0.373-0.437 | <0.0001 |

Abbreviations: CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention.

According to the 5-year trend, the 2020 expected rate of 30-day all-cause mortality was 6.5%, while the observed incidence of death was 8.3% (p = 0.001). Excluding NSTEMI patients with a Covid-19 diagnosis, the observed incidence of 30-day mortality was 7.6% (p = 0.028 compared to the expected trend rate) (Fig. 2). Accordingly, the 2020 expected rate of 6-month all-cause mortality was 12.2%, while the observed incidence of death was 13.6% (p = 0.041); after excluding NSTEMI patients with Covid-19, the observed incidence of mortality at 6 months was 12.9% (p = 0.349 compared to the expected trend rate) (Fig. 3). The difference in the observed rates of 30-day and 6-month mortality among NSTEMI patients admitted during the 2020 lockdown with and without Covid-19 infection was particularly evident in the Northern Italy (Figs. 2 and 3).

After multiple corrections, the presence of Covid-19 diagnosis resulted one of the independent predictors of all-cause mortality at 30 days (adjusted odds ratio (OR) 4.3; 95% confidence intervals (CI) 2.90-6.23; p < 0.0001) (Suppl. Table 3) and 6 months (adjusted OR 3.5; 95% CI: 2.43-5.03; p < 0.0001) (Table 2).
4. Discussion

This retrospective analysis of nationwide administrative data documented a marked reduction of hospital admissions for NSTEMI during national outbreak for Covid-19 in Italy with a higher-than-expected all-cause death at both 1 and 6 months, compared with the mortality trend for NSTEMI of the same calendar period in the previous 5 years. Notably, when NSTEMI patients with a concomitant Covid-19 diagnosis were excluded from the analysis, the observed 6-month mortality rate resulted in accordance with the prior 5-year trend.

Several studies have already reported a significant decline of hospital admissions for acute MI during Covid-19 outbreak, with percentages ranging from 20 to 40% [7–10,14–20]. A recent study reported a reduction of MI admission of around 20% during the national lockdown in the 2 French provinces with a different medical campaign policy, with a faster normalization of MI incidence was observed in the province in which a large local media campaign was conducted [14]. In another study conducted in 22 centers in France, all located in major cities, a drop of MI as high as 30% was reported [15]. Notably, most studies conducted in Europe did not analyse a nationwide dataset but rather assessed the rate of admissions for MI in a sample of centers, mainly from large cities [7–10,16–20]. This aspect is crucial since in most countries, a migration of populations from the large cities to the countryside areas was observed during lockdown. Therefore, a large and universal assessment of MI cases, especially during lockdown, is essential to catch all variations in MI admissions and related fatal rates.

In our study, the first nationwide assessment of NSTEMI patients during Covid-19 pandemic, the reduction in admissions observed reached 40% as compared to the trends of the previous 5 years. This difference may be due to the greater social restrictions present in Italy at the time of the lockdown compared to other European countries. At the same time as the reduction in admissions for NSTEMI, there was a significant increase in in-hospital mortality. Multiple reasons have been hypotheses to explain this trend [7,8,21,22] such as reduction of air pollution and daily stressful lifestyle, or inefficiencies of the overloaded healthcare system. The main cause of the reduction in the number of hospitalizations for NSTEMI seems to be due to the patients’ fear of going to hospital for Covid-19 infection, especially in the lockdown period, where social containment was mandatory in conjunction with the progression of the pandemic and the highest rate of mortality due to Covid-19 infection. On the other hand, the higher rate of in-hospital mortality of acute MI patients admitted during national lockdown is an interesting observation never completely explained. As the proportion of NSTEMI patients referred to PCI was not decreased during that period, unlike the rate of CABG, it could reflect an overall higher proportion of patients being at “high risk” usually referred to surgery, a concomitant time delay in management leading to late reperfusion [18,21], an underuse of revascularization specifically in Covid-19 patients, as documented in our analysis, or a direct Covid-19-related impact on fatality. Our study is the first to suggest a direct correlation between the increased mortality observed in NSTEMI patients during lockdown and Covid-19 infection. In fact, when patients with concomitant Covid-19 infection were excluded from the series, the short- and medium-term fatality rate was in trend with the previous 5 years of observation.

4.1. Limitations

There are several limitations of using an administrative health claims
Fig. 2. Expected (exp.) and observed (obs.) mortality rate at 30 days (in the overall NSTEMI population and excluding those with Covid-19 infection) during the 2020 national outbreak and over the equivalent periods in the previous 5 years in Italy and by geographic regions.
Fig. 3. Expected (exp.) and observed (obs.) mortality rate at 6 months (in the overall NSTEMI population and excluding those with Covid-19 infection) during the 2020 national outbreak and over the equivalent periods in the previous 5 years in Italy and by geographic regions.
observed 6-month mortality was in trend with previous 5 years. Infection significantly increased the mortality rate; indeed, after with the 5-year expected trend. A concomitant diagnosis of Covid-19

5. Conclusions

During the 2020 national outbreak in Italy the rate of NSTEMI admissions was markedly reduced, while the number of PCI was consistent with the 5-year expected trend. A concomitant diagnosis of Covid-19 infection significantly increased the mortality rate; indeed, after excluding NSTEMI patients with a diagnosis of Covid-19 the rate of observed 6-month mortality was in trend with previous 5 years.

Further studies are warranted to understand the mechanisms underlying the association between Covid-19 and mortality in the NSTEMI context.

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Author contributions

Conceptualization: De Luca, Seccareccia, Baglio Data curation and Formal analysis: Rosato and D’Errigo Writing - original draft: De Luca Writing - review and editing: all authors.

Declaration of Competing Interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2022.11.008.

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