Outcomes among patients admitted for non-ST segment myocardial infarction in the pre pandemic and pandemic COVID-19 era – Israel Nationwide study

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Abstract:

Background: Since the beginning of the COVID-19 pandemic in 2019, several countries have reported a substantial drop in the number of patients admitted with non-ST segment myocardial infarction (NSTEMI). We aimed to evaluate the changes in admissions, in-hospital management and outcomes of patients with NSTEMI in the COVID-19 era in a nationwide survey.

Methods: A prospective, multicenter, observational, nationwide study involving 13 medical centers across Israel aimed to evaluate consecutive patients with NSTEMI admitted to intensive cardiac care units (ICCs) over an 8-week period during the COVID-19 outbreak and to compare them with NSTEMI patients admitted at the same period 2 years earlier (control period).

Results: There were 624 (43%) NSTEMI patients, of them 349 (56%) hospitalized during the COVID-19 era and 275 (44%) during the control period. There were no significant differences in age, gender and other baseline characteristics between the two study periods.
During the COVID-19 era, more patients arrived at the hospital via an emergency medical system (EMS) compared with the control period (p = 0.05). Time from symptom onset to hospital admission was longer in the COVID-19 era as compared with the control period [11.5 hours (IQR2.5-46.7) vs. 2.9 hours (IQR 1.7-6.8), respectively, p-value <0.001]. Nevertheless, time from hospital admission to reperfusion was similar in both groups. Rate of coronary angiography was also similar in both groups. In-hospital mortality rate was similar in both the COVID-19 era and the control period groups (2.3% vs. 4.7%, respectively, p=0.149) as was the 30-day mortality rate (3.7% vs. 5.1%, respectively, p=0.238).

Conclusions: In contrast to previous reports, admission rates of NSTEMI were similar in this nationwide survey during the COVID-19 era. With longer time from symptoms to admission, but with the same time from hospital admission to reperfusion therapy and with similar in-hospital and 30-day mortality rates. Even in times of crisis, adherence of medical systems to clinical practice guidelines, ensures the preservation of good clinical outcomes.
Introduction:

The COVID-19 pandemic is an ongoing global pandemic of coronavirus disease 2019, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1). Since the beginning of the pandemic, several studies from all around the world have reported significant reductions in acute myocardial infarction (MI) hospitalizations and catheterization laboratory activation rates (2-6). The reduced number of admissions during this period was assumed to have resulted in increases in out-of-hospital deaths and long-term complications of MI and missed opportunities to offer secondary prevention treatment for patients with coronary heart disease (7-9). Others suggest that limited physical activity due to social restrictions and especially stressful situations may cause an increase in ACS admission rates (10-12). Whereas much of the data regarding COVID-19 and MI have focused on ST segment elevation MI (STEMI) (13), it is well known that the risk for severe illness with COVID-19 increases with age, with older adults at the highest risk (8). Therefore, a focus on non-ST segment elevation MI (NSTEMI) rather than STEMI is of great importance, especially in the elderly population, as it is more prevalent among them (14). Previous studies have shown almost without exception that during national and international crises related to military, economic or natural disasters, there is an increase in the number of cardiovascular events (10-12). In contrast, most of the studies during the COVID-19 pandemic found a decrease in the number of hospital admissions but on the other hand an increase in
cardiovascular mortality (6, 9). Therefore, the decrease in the number of cardiovascular events in hospitalized patients, may represent a decrease in arrival and admission to hospitals and not a true decrease in the cardiovascular event rate. Hence, the aim of the current study was to examine this theory in a relatively small country environment with robust public medical services by conducting a nationwide survey during the first COVID-19 pandemic surge and to compare this data to a data from a parallel period two years earlier.

**Methods:**

We conducted a prospective, multicenter, observational, nationwide study involving 13 medical centers across Israel aimed to compare NSTEMI patients admitted to intensive cardiac care units (ICCs) over an 8-week period during the COVID-19 outbreak starting from March 9, 2020, through April 30, 2020, with NSTEMI patients admitted at the parallel period of time 2 years earlier during the Acute Coronary Syndrome Israeli Survey (ACSIS) 2018.

All participating centers have percutaneous coronary intervention (PCI) facilities operating 24/7. Data were anonymously documented in each ICCU by a local coordinator and prospectively submitted into an electronic form. The institutional review board of each participating center (Shaare Zedek Medical Center, Sheba Medical Center, Soroka University Medical Center, Rabin Medical Center, Shamir Medical Center, Hillel Yaffe Medical Center, Galilee Medical Center, Wolfson Medical Center, Barzilai Medical Center, Rambam Medical Center, Ziv Medical Center, Sourasky Medical Center and Samson Assuta Ashdod University Hospital) approved the study and waived the need for individual informed consent based on strict safeguarding of participant anonymity by de-identifying patients during database entry. All experiments were performed in accordance with relevant guidelines and regulations.
Data collection

Patient data from the control period was obtained from the ACSIS 2018. In brief, ACSIS is a biannual survey which has been conducted in all ICCUs in Israel during March-April by the Israeli Working Group on Acute Cardiac Care of the Israel Heart Society since 2000 (15). During these two-monthly (March-April) periods, detailed data regarding all consecutive acute MI patients are prospectively collected from all ICCUs and cardiology wards in all public hospitals in Israel. For the current study, we used data from the corresponding period in 2018 (March 9 through April 30) from 13 medical centers that participated in the COVID-19 period survey. The incidence of newly confirmed coronavirus cases in Israel was based on the Ministry of Health records (13).

We recorded the number of patients admitted to each ICCU with STEMI and NSTEMI during the above-named period. The diagnosis of acute MI was defined as clinical symptoms compatible with myocardial ischemia and troponin elevation. STEMI was diagnosed based on the presence of persistent ST-segment elevation ≥ 1mm in at least two consecutive inferior or lateral leads, or 2 mm in at least two precordial leads on the admission electrocardiogram. Otherwise NSTEMI was diagnosed. For each patient admitted with acute MI, we collected demographic data, clinical characteristics, main angiographic, and echocardiographic parameters. Time from symptom onset to hospital admission and time from hospital admission to reperfusion (defined at the time of guidewire passage), were documented for each patient. Patients' clinical status on hospital admission was assessed by the Killip classification.

The following in-hospital complications were recorded: sustained ventricular arrhythmia, second degree or higher atrioventricular block, pulmonary congestion requiring administration of intravenous diuretics, mechanical ventilation, major bleeding, and in-
hospital mortality. The primary combined outcome of this study was a composite of sustained ventricular arrhythmia, pulmonary congestion, and/or in-hospital mortality.

The health care system in Israel

Healthcare in Israel is universal and participation in a medical insurance plan is compulsory. All Israeli residents are entitled to basic health care as a fundamental right. The Israeli healthcare system is based on the National Health Insurance Law (1995), which mandates all citizens resident in the country to join one of four official health insurance organizations, known as Kupat Holim (Health Maintenance Organization) which are run as not-for-profit organizations and are prohibited by law from denying any Israeli resident membership.

Changes in the NSTEMI treatment pathway related to the COVID-19 pandemics in Israel

As in other countries (16), at the beginning of the COVID-19 pandemic in Israel, a task force of the Israeli heart society was established in order to provide guidelines for medical stuff treating patients suffering from COVID-19 and STEMI or NSTEMI. In general, for COVID-19 patients having NSTEMI during their hospitalizations, the guidelines recommended coronary angiography only if the patients were very high-risk patients (i.e., hemodynamic instability, recurrent chest pain, malignant arrhythmia pulmonary congestion related to the MI and cardiogenic shock). Furthermore, elective cases were differed, and shift-based allocation of staff members and physicians to operate the catheterization laboratory were made. Door to balloon time and was not measured for COVID-19 patients suffering STEMI.

Statistical analysis

Categorical variables are compared by the chi-square test. The distribution pattern was tested with Shapiro-Wilk test. Normally distributed continuous variables are compared by the
Student’s t-test. Non-normally distributed variables are compared using the Mann-Whitney-Wilcoxon test. Mean admission rates for AMI-related hospitalizations were calculated by dividing the number of cumulative events by the number of days for each time period. Incidence rate ratios (IRR) comparing the COVID-19 period (2020) to the control period (2018) were calculated using unadjusted Poisson regression to model the number of acute MI-related hospitalizations per day in the entire cohort and in the NSTEMI sub-group. A two-sided p-value of <.05 was considered statistically significant. All analyses were performed with R software version 3.4.4 (R Foundation for Statistical Computing).

**Results:**

The study cohort comprised 1466 patients, of whom 774 (52.8%) were hospitalized during the COVID-19 era between March 9 and April 30, 2020, as compared with 692 (47.2%) who were admitted during the corresponding period in 2018. There were 624 NSTEMI patients (43%), including 349 (56%) hospitalized during the COVID-19 era and 275 (44%) in 2018, representing about 27% increase in NSTEMI admission rate during the COVID-19 era.

**Acute myocardial infarction hospitalization rates and COVID-19 incidence**

The mean overall weekly acute MI admission rate was 14.9 during the study period and 13.3 during the control period (IRR 1.1, 95% Confidence Interval [CI] 0.2-5.8, p-value = 0.91). Results remained similar when only NSTEMI admissions were analyzed: 6.71 during the study period and 5.29 during the control period (IRR 1.3, 95% Confidence Interval [CI] 0.3-5.6, p-value = 0.78). (Figure 1).

**Baseline characteristics**
Baseline characteristics of NSTEMI patients are presented in Table 1. Approximately 76% were male and the median age was 67 years (IQR 58-76). There were no significant differences in age, gender and other baseline characteristics between the two study periods.

**Clinical presentation**

During the COVID-19 era, more patients arrived at the hospital via an emergency medical system (EMS) compared with the control period (p = 0.005) (Figure 2). Time from symptom onset to hospital admission (patient-related delay) was substantially longer in the COVID-19 era as compared with the control period [11.5 hours (IQR 2.5-46.7) vs. 2.9 hours (IQR 1.7-6.8), respectively, p-value <0.001] (Table 2). Yet, time from hospital admission to reperfusion (system-related delay) was similar in both groups [21.9 hours (IQR 7.6-51.5) in the COVID-19 era vs. 18.9 hours (IQR 9-42) in the control period, p=0.34]. The differences in the ischemic time remained consistent when the cohort was divided according to the month of admission, gender and age.

Killip classification upon admission was similar in both the COVID-19 era and the control period groups (Killip I 79% vs. 84%; Killip II 11.5% vs. 8.8%; Killip III 6.9% vs. 4.8% and Killip IV 2.6% vs. 2.4%, respectively, p value =0.48) (Table 2).

**Angiographic Findings and Ejection fraction**

Overall, 560 (89.7%) patients admitted with NSTEMI underwent coronary angiography during hospitalization, 89.4% in the COVID-19 era vs. 90.2% in the control period group, p=0.85. Angiographic findings were slightly different between the COVID-19 era and the control period groups but did not reach statistically significance (no vessel disease 9% vs. 5.9%; 1 vessel disease 19.3% vs. 27.6%; 2 vessel disease 30.4% vs. 31%; 3 vessel disease 41.3% vs. 35.5%, respectively, p=0.09). Interestingly, PCI was performed in higher rates in
the COVID-19 era group (91.3% vs. 59.7%, respectively, p<0.001). Ejection fraction (EF) at admission was also similar between the COVID-19 era and the control period groups with roughly half of the patients with preserved (>=50%) EF (48.2% vs. 52%, respectively, p=0.3) (Table 2).

**In-hospital and 30-day outcomes**

In-hospital mortality rate was similar in both the COVID-19 era and the control period groups (2.3% vs. 4.7%, respectively, p=0.149) as was the 30-day mortality rate (3.7% vs. 5.1%, respectively, p=0.238). Interestingly, composite end point rate for ventricular arrhythmia, heart failure and in-hospital mortality, was higher in the control period group as compared with the COVID-19 era group (14.2% vs. 6.9%, respectively, p=0.004). We found no significant differences in the distribution of anti-thrombotic, lipid lowering and novel oral glucose lowering medications upon discharge from the index hospitalization. Lastly, length of hospitalization was higher in the COVID-19 era with a median of 4(2,5) days as compared with 3(2,4) days in the control group (p<0.001).

**Discussion:**

Statement of principal findings

In this prospective, multicenter, observational, nationwide study, we found 3 major findings regarding NSTEMI patients during the COVID-19 pandemic: 1) The weekly cumulative incidence of hospitalized NSTEMI cases before and during the COVID-19 pandemic was similar 2) despite longer time from symptoms onset to admission (patient delay), the number of patients who were treated with early invasive approach, the time to catheterization (system delay) and the percent of patients who underwent coronary intervention were not
compromised in the COVID period 3) NSTEMI patients sustained similar in-hospital and 30-day mortality rate during both the COVID and the control periods.

Interpretation within the context of the wider literature

In contrast to our findings, several studies have reported reduction in admission rate for ACS and decreased use of coronary procedures in various countries affected by the COVID-19 pandemic, with up to ~40% reduction in ACS admission rate (9, 17-23). This apparent discrepancy might be explained by the fact that Israel characterized by relatively high accessibility of medical services including high number of hospitals with PCI capabilities with homogeneous distribution along the country. In addition, Israel has a mandatory health care law and all citizens are required by law to be members of one of the health maintenance organization, which has greatly increased the availability of primary care medicine and subsequently the vaccinations. All of the above contributed to the availability and accessibility of the medical systems in Israel at a relatively early stage of the crisis. We believe that the reduction seen in other countries in admission rate for ACS was probably not genuine due to a decrease in incidence of ACS, but rather due to the number of patients seeking medical treatment and receiving proper treatment due to ACS. This might explain why in Israel there was no reduction in admission rate of NSTEMI patients. Hence, the small area with the high medical services accessibility, might encourage patients, even during times of global crisis, to reach medical assistance. Nevertheless, although admission rates were similar, there was a longer time from symptoms onset to admission, which is in line with other studies during the COVID-19 pandemic, probably demonstrating the impact of the pandemic on health seeking behavior due to fears of contracting COVID-19 and the ensuing impact of delayed medical intervention (24-25). Interestingly, there was no difference in 30-day mortality rate between NSTEMI patients during the pandemic as compared with
NSTEMI patients before the pandemic. Again, these findings are in contrast with other studies which suggested increased mortality rate and more complicated course of ACS patients during the first phase of the COVID-19 pandemic (26-27). Moreover, although those who presented to hospitals were younger, had less comorbidities, they, nevertheless, had higher 30-day mortality rate (28). Although NSTEMI patients in our study had a longer time from symptoms onset to admission and longer length of hospitalization, they had similar delay from hospital admission to reperfusion therapy and similar rate of reperfusion therapy according to contemporary guidelines. Hence, because those were NSTEMI patients (and not STEMI patients) and the difference was in hours (on average 8 hours) and not in days, it did not lead to worse outcomes and hence, similar 30-day mortality rate (although longer length of hospitalization) compared with the non-pandemic period.

Implications for policy, practice and research:
Lastly, there are large data suggesting a prognostic importance of complying with medical guidelines (29-31). Moreover, studies have shown that in NSTEMI patients, adherence to guidelines reduces mortality in the first three years after infarction (32). In countries who can adhere to guidelines even in times of crisis, such as in the COVID-19 pandemic, it seems that outcomes will be better as well.

Strengths and limitations
Our study has several limitations: First, this is an observational study reporting on associations, and thus no causation can be inferred. Second, our report reflects patients who arrived at the hospital alive, we did not focus on patients with out of hospital cardiac arrest (OHCA) and there were several studies who suggested an increase in cases of OHCA observed. Third, results of Covid-19 testing were available for only a quarter of our cohort,
and therefore we cannot exclude that underlying coronavirus infection contributed to the incidence of acute myocardial infarction in our study.

Conclusions:
The current study provides an in-depth prospective insight into the characteristics, management and clinical outcomes of consecutive patients presenting with NSTEMI during the Covid-19 pandemic. In contrast to other, larger countries, in Israel, admission rates of NSTEMI were not reduced during the COVID-19 pandemic, with longer time from symptoms to admission, but with the same time from hospital admission to reperfusion therapy and with similar in-hospital and 30-day mortality rates. Even in times of crisis, adherence of medical systems to clinical practice guidelines, as presented by the rate and time from hospital admission to reperfusion therapy, ensures the preservation of good clinical outcomes.
References:

1. Naming the coronavirus disease (COVID-19) and the virus that causes it”. World Health Organization (WHO).

2. De Rosa S, Spaccarotella C, Basso C, Calabrò MP, Curcio A, Filardi PP, Mancone M, Mercuro G, Muscoli S, Nodari S, Pedrinelli R, Sinagra G, Indolfi C. Reduction of hospitalizations for myocardial infarction in Italy in the COVID-19 era. Eur Heart J 2020 Jun 7;41(22):2083-2088.

3. Wilson SJ, Connolly MJ, Elghamry Z, Cosgrove C, Firoozi S, Lim P, Sharma R, Spratt JC. Effect of the COVID-19 pandemic on ST segment-elevation myocardial infarction presentations and in-hospital outcomes. Circ Cardiovasc Interv. 2020 Jul;13(7):e009438.

4. Bhatt AS, Moscone A, McElrath EE, Varshney AS, Claggett BL, Bhatt DL, Januzzi JL, Butler J, Adler DS, Solomon SD, Vaduganathan M. Declines in hospitalizations for acute cardiovascular conditions during the COVID-19 pandemic: A multicenter tertiary care experience. J Am Coll Cardiol 2020 Jul 21;76(3):280-288.

5. Tam CF, Cheung KS, Lam S, Wong A, Yung A, Sze M, Lam YM, Chan C, Tsang TC, Tsui M, Tse HF, Siu CW. Impact of Coronavirus disease 2019 (COVID-19) outbreak on ST-segment elevation myocardial infarction care in Hong Kong, China. Circ Cardiovasc Qual Outcomes. 2020 Apr;13(4):e006631.

6. Solomon MD, McNulty EJ, Rana JS, Leong TK, Lee C, Sung SH, Ambrosy AP, Sidney S, Go AS. The Covid-19 pandemic and the incidence of acute myocardial infarction. N Engl J Med. 2020 Aug 13;383(7):691-693.
7. Mafham MM, Spata E, Goldacre R, Gair D, Curnow P, Bray M, Hollings S, Roebuck C, Gale CP, Mamas MA, Deanfield JE, de Belder MA, Luescher TF, Denwood T, Landray MJ, Emberson JR, Collins R, Morris EJA, Casadei B, Baigent C. COVID-19 pandemic and admission rates for and management of acute coronary syndromes in England. Lancet. 2020 Aug 8;396(10248):381-389.

8. https://www.cdc.gov/aging/covid19-guidance.html.

9. Metzler B, Siostrzonek P, Binder RK, Bauer A, Reinstadler SJR. Decline of acute coronary syndrome admissions in Austria since the outbreak of COVID-19: the pandemic response causes cardiac collateral damage. Eur Heart J. 2020;41:1852-1853.

10. Leor J, Poole WK, Kloner RA. Sudden cardiac death triggered by an earthquake. N Engl J Med. 1996;334(7):413-9.

11. Meisel SR, Kutz I, Dayan KI, Pauzner H, Chetboun I, Arbel Y, David D. Effect of Iraqi missile war on incidence of acute myocardial infarction and sudden death in Israeli civilians. Lancet. 1991;338(8768):660-1.

12. Allegra JR, Mostashari F, Rothman J, Milano P, Cochrane DG. Cardiac events in New Jersey after the September 11, 2001, terrorist attack. J Urban Health. 2005;82(3):358-63. Epub 2005 Jul 6.

13. Fardman A, Zahger D, Orvin K, Oren D, Kofman N, Mohsen J, Tsafrir O, Asher E, Rubinshtein R, Jamal J, Efraim R, Halabi M, Shacham Y, Fortis LH, Cohen T, Klempfner R, Segev A, Beigel R, Matetzky S. Acute myocardial infarction in the Covid-19 era: Incidence, clinical characteristics and in-hospital outcomes-A multicenter registry. PLoS One. 2021 Jun 18;16(6):e0253524. doi: 10.1371/journal.pone.0253524. PMID: 34143840; PMCID: PMC8213163.

14. Montalescot G, Dallongeville J, Van Belle E, Rouanet S, Baulac C, Degrandsart A, Vicaut E; OPERA Investigators. STEMI and NSTEMI: are they so different? 1 year outcomes in acute myocardial infarction as defined by the ESC/ACC definition (the OPERA registry). Eur Heart J. 2007 Jun;28(12):1409-17. doi: 10.1093/eurheartj/ehm031. Epub 2007 Apr 5. PMID: 17412730.
15. Asher E, Abu-Much A, Goldenberg I, Segev A, Sabbag A, Mazin I, Shlezinger M, Atar S, Zahger D, Polak A, Beigel R, Matetzky S; Platelets and Thrombosis in Sheba-PLATIS Study Group. Incidence and Clinical Features of Early Stent Thrombosis in the Era of New P2y12 Inhibitors (PLATIS-2). PLoS One. 2016 Jun 16;11(6):e0157437. doi: 10.1371/journal.pone.0157437. PMID: 27310147; PMCID: PMC4911066.

16. Wojakowski W, Bartuś S, Grygier M. Challenging clinical and organizational scenarios in cardiovascular diseases during the SARS-CoV-2 pandemic in Poland. Can we do better? Postepy Kardiol Interwencyjnej. 2020 Jun;16(2):121-122.

17. De Filippo O, D’Ascenzo F, Angelini F, et al. Reduced rate of hospital admissions for ACS during Covid-19 outbreak in northern Italy. N Engl J Med 2020; 383: 88–89.

18. De Rosa S, Spaccarotella C, Basso C, et al. Reduction of hospitalizations for myocardial infarction in Italy in the COVID-19 era. Eur Heart J 2020; 41: 2083–88.

19. Rodríguez-Leor O, Cid-Álvarez B, Ojeda S, et al. Impacto de la pandemia de COVID-19 sobre la actividad asistencial en cardiología intervencionista en España. REC Interv Cardiol 2020; 2: 82–89.

20. Garcia S, Albaghdadi MS, Meraj PM, et al. Reduction in ST-segment elevation cardiac catheterization laboratory activations in the United States during COVID-19 pandemic. J Am Coll Cardiol 2020; 75: 2871–72.

21. Solomon MD, McNulty EJ, Rana JS, et al. The COVID-19 pandemic and the incidence of acute myocardial infarction. N Engl J Med 2020; published online May 19. https://doi.org/10.1056/NEJMc2015630.

22. Mafham MM, Spata E, Goldacre R, Gaird D, Curnow P, Bray M, Hollings S, Roebuck C, Gale CP, Mamas MA, Deanfield JE, de Belder MA, Luescher TF, Denwood T, Landray MJ, Emberson JR, Collins R, Morris EJA, Casadei B, Baigent C. COVID-19 pandemic and admission rates for and management of acute coronary syndromes in England. Lancet. 2020 Aug 8;396(10248):381-389.

23. Siudak Z, Dudek D, Grygier M, Araszkiewicz A, Dąbrowski M, Kusa J, Hawranek M, Huczek Z, Kralisz P, Roleder T, Wojakowski W, Parma R, Malinowski KP, Bartuś S.
Interventional cardiology in Poland in 2020 - impact of the COVID-19 pandemic. Annual summary report of the Association of Cardiovascular Interventions of the Polish Cardiac Society and Jagiellonian University Medical College. Postepy Kardiol Interwencyjnej. 2021 Jun;17(2):131-134.

24. Perrin N, Iglesias JF, Rey F, Benzakour L, Cimci M, Noble S, Degrauw S, Tessitore E, Mach F, Roffi M. Impact of the COVID-19 pandemic on acute coronary syndromes. Swiss Med Wkly. 2020 Dec 31;150:w20448. doi: 10.4414/smw.2020.20448. PMID: 33382905.

25. Joo Hor Tan, Jieli Tong, Hee Hwa Ho, Delayed presentation of acute coronary syndrome with mechanical complication during COVID-19 pandemic: a case report, European Heart Journal - Case Reports, Volume 5, Issue 2, February 2021, ytaa506, https://doi.org/10.1093/ehjcr/ytaa506.

26. Primessnig U, Pieske BM, Sherif M. Increased mortality and worse cardiac outcome of acute myocardial infarction during the early COVID-19 pandemic. ESC Heart Fail. 2021 Feb;8(1):333-343. doi: 10.1002/ehf2.13075. Epub 2020 Dec 6. PMID: 33283476; PMCID: PMC7835606.

27. Petrović M, Milovančev A, Kovačević M, Miljković T, Ilić A, Stojšić-Milosavljević A, Golubović M. Impact of COVID-19 outbreak on hospital admissions and outcome of acute coronary syndromes in a single high-volume centre in southeastern Europe. Neth Heart J. 2021 Apr;29(4):230-236. doi: 10.1007/s12471-021-01554-x. Epub 2021 Mar 11. PMID: 33704668; PMCID: PMC7950419.

28. Jianhua Wu, Mamas Mamas, Muhammad Rashid, Clive Weston, Julian Hains, Tom Luescher, Mark A de Belder, John E Deanfield, Chris P Gale, Patient response, treatments, and mortality for acute myocardial infarction during the COVID-19 pandemic, European Heart Journal - Quality of Care and Clinical Outcomes, Volume 7, Issue 3, July 2021, Pages 238–246, https://doi.org/10.1093/ehjqcco/qcaa062.

29. Farmakis, I. T.; Zafeiropoulos, S.; Pagiantza, A.; Boulmpou, A.; Arvanitaki, A.; Nevras, V.; Tampaki, A.; Markidis, E.; Papadimtriou, I.; Karvounis, H.; Giannakoulas, G. Guideline Adherence Is Associated with Long-Term All-Cause Mortality in Patients after an Acute
Coronary Syndrome. Eur. Heart J. 2020, 41 (Supplement_2).
https://doi.org/10.1093/ehjci/ehaa946.2972.

30. Ricci-Cabello, I.; Vásquez-Mejía, A.; Canelo-Aybar, C.; Niño de Guzman, E.; Pérez-Bracchiglione, J.; Rabassa, M.; Rigau, D.; Solà, I.; Song, Y.; Neamtiu, L.; Parmelli, E.; Saz-Parkinson, Z.; Alonso-Coello, P. Adherence to Breast Cancer Guidelines Is Associated with Better Survival Outcomes: A Systematic Review and Meta-Analysis of Observational Studies in EU Countries. BMC Health Serv. Res. 2020, 20 (1), 920. https://doi.org/10.1186/s12913-020-05753-x.

31. Voortman, T.; Kiefte-de Jong, J. C.; Ikram, M. A.; Stricker, B. H.; van Rooij, E. J. A.; Lahousse, L.; Tiemeier, H.; Brusselle, G. G.; Franco, O. H.; Schoufour, J. D. Adherence to the 2015 Dutch Dietary Guidelines and Risk of Non-Communicable Diseases and Mortality in the Rotterdam Study. Eur. J. Epidemiol. 2017, 32 (11), 993–1005. https://doi.org/10.1007/s10654-017-0295-2.

32. Shah, B. R.; O’Brien, E. C.; Roe, M. T.; Chen, A. Y.; Peterson, E. D. The Association of In-Hospital Guideline Adherence and Longitudinal Postdischarge Mortality in Older Patients with Non-ST-Segment Elevation Myocardial Infarction. Am. Heart J. 2015, 170 (2), 273-280.e1. https://doi.org/10.1016/j.ahj.2015.05.007.
### Table 1. Baseline characteristics of NSTEMI patients before and during COVID-19 pandemic

| Baseline characteristic | Total N=624 | COVID-19 era, N=349 | Control period, N=275 | P value |
|-------------------------|------------|---------------------|-----------------------|---------|
| Age, years median (IQR) | 62 (54,71) | 67 (60,76)          | 66 (56,76)            | 0.165   |
| Male (%)                | 477 (76)   | 271 (77)            | 206 (75)              | 0.48    |
| Diabetes Mellitus, N (%)| 287 (34)   | 176 (50)            | 127 (46)              | 0.352   |
| Hypertension, N (%)     | 460 (55)   | 197 (72)            | 253 (73)              | 0.883   |
| Dyslipidemia, N (%)     | 529 (63)   | 200 (73)            | 246 (71)              | 0.55    |
| Current smoker, N (%)   | 422 (50)   | 96 (35)             | 118 (34)              | 0.84    |
| Prior CKD, N (%)        | 60 (7.1)   | 49 (18)             | 63 (18)               | 1.0     |
| Prior MI, N (%)         | 188 (22)   | 116 (42)            | 122 (35)              | 0.078   |
| Prior CABG, N (%)       | 28 (3.3)   | 29 (11)             | 42 (12)               | 0.673   |
| Prior PAD, N (%)        | 36 (4.3)   | 25 (9.1)            | 26 (7.4)              | 0.55    |
| Prior CHF, N (%)        | 45 (5.4)   | 35 (12.7)           | 38 (11)               | 0.56    |
| Prior stroke/TIA, N (%) | 69 (8.2)   | 27 (9.9)            | 35 (10)               | 1.0     |

STEM=ST-segment elevation myocardial infarction; IQR=Interquartile range; CKD=Chronic kidney disease; MI=Myocardial infarction; CABG=Coronary artery bypass grafting; PAD=Peripheral artery disease; CHF=Congestive heart failure; TIA=Transient ischemic attack.
Table 2. Clinical presentation and angiographic findings in NSTEMI patients before and during the COVID-19 pandemic

| Characteristic                                      | Total  | COVID-19 era | Control period | P value |
|-----------------------------------------------------|--------|--------------|----------------|---------|
|                                                     | N=624  | N=349        | N=275          |         |
| Time from symptom onset to hospital admission (hours), median (IQR) | 6.7 (0.5, 26) | 11.5 (2.5,47) | 3 (1.7,6.8) | <0.001  |
| Mode of transportation:                             |        |              |                | 0.005   |
| Mobile ICCU, N (%)                                   | 225 (36.1) | 129 (37)    | 96 (34.9)      |         |
| Regular ambulance, N (%)                             | 109 (17.3) | 67 (19.2)   | 42 (15.3)      |         |
| Private car, N (%)                                   | 226 (36.2) | 108 (30.9)  | 118 (42.9)     |         |
| In-patient, N (%)                                    | 64 (10.3)  | 45 (12.9)   | 19 (6.9)       |         |
| Killip class at admission:                           |        |              |                | 0.482   |
| 1, N (%)                                            | 450 (81.2) | 240 (78.9)  | 210 (84)       |         |
| 2, N (%)                                            | 57 (10.3)  | 35 (11.5)   | 22 (8.8)       |         |
| 3, N (%)                                            | 33 (6.0)   | 21 (6.9)    | 12 (4.8)       |         |
| 4, N (%)                                            | 14 (2.5)   | 8 (2.6)     | 6 (2.4)        |         |
| Total angiography during hospitalization, N (%)      | 554 (89.7) | 304 (89)    | 250 (90.2)     | 0.851   |
| Number of diseased vessels:                          |        |              |                | 0.091   |
| 1, N (%)                                            | 118 (22.5) | 62 (19.3)   | 56 (27.6)      |         |
|                          | 1, N (%) | 2, N (%) | 3, N (%) | MINOCA, N (%) | PCI (% out of patients with ANGIO) | EF, median (IQR) | Length of hospitalization (days), median |
|--------------------------|----------|----------|----------|---------------|-----------------------------------|-----------------|------------------------------------------|
|                          | 161 (30.7) | 98 (30.4) | 63 (31)  | 41 (7.8)      | 433 (77.3)                        | 50 (40,57)      | 3 (2,5)                                  |
| PCI (% out of patients   |          |          |          |               | 285 (91.3)                        | 48 (40,55)      | 4 (2,5)                                  |
| with ANGIO)              | 148 (59.7) |          |          |               | <0.01                             | 50 (40,60)      | 3 (2,4)                                  |
| EF, median (IQR)         |          |          |          |               |                                   | 0.107           |                                          |
| Length of hospitalization|          |          |          |               |                                   | <0.001          |                                          |

ICCU=intensive cardiac care unit; MINOCA=myocardial infarction with non-obstructive coronary arteries; EF=ejection fraction;
Figure 1. Weekly cumulative incidence (%) of hospitalized NSTEMI cases before and during the COVID-19 pandemic.
Figure 2. Distribution of NSTEMI patients according to the mode of transportation before and during the COVID-19 pandemic

ICCU=Intensive cardiac care unit; NSTEMI=non ST-segment elevation myocardial infarction.

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- **Ethics and other permissions**
The institutional review board of each participating center (Shaare Zedek Medical Center, Sheba Medical Center, Soroka University Medical Center, Rabin Medical Center, Shamir Medical Center, Hillel Yaffe Medical Center, Galilee Medical Center, Wolfson Medical Center, Barzilai Medical Center, Rambam Medical Center, Ziv Medical Center, Sourasky Medical Center and Samson Assuta Ashdod University Hospital) approved the study and waived the need for individual informed consent based on strict safeguarding of participant anonymity by de-identifying patients during database entry. All experiments were performed in accordance with relevant guidelines and regulations.

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- **Data Availability Statement**

  The data that support the findings of this study are available from Sheba Medical Center, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Sheba Medical Center