

openheart Undiagnosed SARS-CoV-2 infection and outcome in patients with acute MI and no COVID-19 symptoms

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ABSTRACT

Objective We aimed to determine the prevalence and outcome of occult infection with SARS-CoV-2 and influenza in patients presenting with myocardial infarction (MI) without COVID-19 symptoms.

Methods We conducted an observational study from 28 June to 11 August 2020, enrolling patients admitted to the National Institute of Cardiovascular Disease Hospital, Dhaka, Bangladesh, with ST-segment elevation MI (STEMI) or non-ST-segment elevation MI who did not meet WHO criteria for suspected COVID-19. Samples were collected by nasopharyngeal swab to test for SARS-CoV-2 and influenza virus by real-time reverse transcriptase PCR. We followed up patients at 3 months (13 weeks) postadmission to record adverse cardiovascular outcomes: all-cause death, new MI, heart failure and new percutaneous coronary intervention or stent thrombosis. Survival analysis was performed using the Kaplan-Meier method.

Results We enrolled 280 patients with MI, 79% male, mean age 54.5±11.8 years, 140 of whom were diagnosed with STEMI. We found 36 (13%) to be infected with SARS-CoV-2 and 1 with influenza. There was no significant difference between mortality rate observed among SARS-CoV-2 infected patients compared with non-infected (5 (14%) vs 26 (11%); p=0.564). A numerically shorter median time to a recurrent cardiovascular event was recorded among SARS-CoV-2 infected compared with non-infected patients (21 days, IQR: 8–46 vs 27 days, IQR: 7–44; p=0.378).

Conclusion We found a substantial rate of occult SARS-CoV-2 infection in the studied cohort, suggesting SARS-CoV-2 may precipitate MI. Asymptomatic patients with COVID-19 admitted with MI may contribute to disease transmission and warrants widespread testing of hospital admissions.

INTRODUCTION

COVID-19, caused by SARS-CoV-2, is associated with symptoms such as fever, cough, shortness of breath and pneumonia and may lead to death.¹ The risk of complications increases with age and chronic comorbidities including obesity, diabetes

Key questions

What is already known about this subject?

► There is ample information by now about asymptomatic COVID-19 cases and also among SARS-CoV-2 infected patients with myocardial infarction. We also know that an individual is usually tested for SARS-Cov-2 infection on meeting WHO clinical criteria for suspected COVID-19.

What does this study add?

► The study adds baseline data about the prevalence of occult SARS-CoV-2 infection among asymptomatic MI cases. Also, it provides baseline data on clinical adverse cardiovascular endpoints: all-cause death, new MI, heart failure and new percutaneous coronary intervention or stent thrombosis after 3 months (13 weeks) of MI episode. The study also indicates futures research studies to determine clinical impact of SARS-CoV-2 infection on MI.

How might this impact on clinical practice?

► Our findings highlight the need for screening of all patients and adopting preventive measures for frontline healthcare workers, including cardiologists, to avoid transmission of SARS-CoV-2 in hospital environments.

mellitus, cardiovascular disease and chronic heart failure.^{1,2} SARS-CoV-2 causes cardiac and vascular pathology through the direct invasion of cardiomyocytes³ and has been related to coronary thrombosis and cardiac arrest.⁴ Observational studies show up to 20% of patients with SARS-CoV-2 infection suffer from impairment of myocardial and cardiac function.^{5–7} Influenza also carries an increased risk of cardiovascular events as confirmed by recent observational studies.⁸

Coinfection with SARS-CoV-2 and influenza virus leading to adverse cardiovascular events has been described,^{9,10} but we have not found reports of occult SARS-CoV-2 infection in patients with myocardial infarction (MI).

Undiagnosed influenza has been reported to occur in over 12% of patients presenting with MI.¹¹ The goal of this study was to determine the prevalence and 3-month (13 weeks) outcomes of SARS-CoV-2 infection in patients with acute MI not meeting the WHO clinical criteria for suspected COVID-19 of acute onset fever and cough or acute onset of any three or more of: fever, cough, general weakness/fatigue, headache, myalgia, sore throat, coryza, dyspnoea, anorexia/nausea/vomiting, diarrhoea and altered mental state.¹²

METHODS

During the first wave of the COVID-19 pandemic, we conducted a prospective longitudinal observational study at the National Institute of Cardiovascular Diseases (NICVD) Hospital, Dhaka, enrolling participants from 28 June to 11 August 2020. The NICVD is the largest public tertiary care cardiac hospital in Bangladesh, providing treatment for ST-segment elevation MI (STEMI) and non-ST segment elevation MI (NSTEMI) in patients throughout Bangladesh. Study activity was suspended from 29 July to 5 August during the Eid al-Adha holiday.

Physicians reviewed hospital admission records from emergency rooms and visited cardiology wards to identify study candidates hospitalised with STEMI/NSTEMI who did not show symptoms meeting the WHO clinical criteria for suspected COVID-19 and who had not been tested for COVID-19. Stable patients were screened for inclusion criteria: (1) admitted within the past 24 hours with diagnosis of STEMI or NSTEMI; (2) ≥ 18 years of age; (3) no suspected COVID-19 according to WHO criteria; and (4) willing and able to give informed consent for participation.

Sample size calculation

During the peak influenza season in July 2019, a hospital-based influenza surveillance system in Bangladesh indicated more than 20% occult influenza infections among patients with underlying cardiovascular disease.¹³ To estimate the frequency of laboratory-confirmed influenza virus and SARS-CoV-2, we assumed that the prevalence of either infection would be $\sim 20\%$. Accordingly, a sample size of 246 patients with 5% precision and a 95% CI was sufficient to determine the prevalence of occult influenza or SARS-CoV-2 infection among patients with MI. Assuming a dropout rate of up to 15% during follow-up, we enrolled 280 patients with MI to the study.

Data collection

After obtaining consent, study physicians used an electronic case report form to record baseline sociodemographic data; medical history including body mass index, smoking status, chronic conditions, type of MI, previous coronary revascularisation procedures and hospital admissions in the past 14 days; and clinical and laboratory-related information such as location of MI based on ECG/echocardiogram, cardiac troponin I (cTn-I) level at admission and real-time reverse transcriptase-PCR (rRT-PCR)

test results for influenza virus and SARS-CoV-2. For clinical variables, study physicians reviewed hospital medical records and verified information by clinical examination. Medical technologists collected nasopharyngeal (NP) swabs for influenza virus and SARS-CoV-2 testing within 24 hours postadmission.

Three months (13 weeks) after STEMI/NSTEMI admission, participants/family members were contacted by phone to record target clinical endpoints including: (1) death from any cause, (2) new MI, (3) heart failure or (4) new unplanned percutaneous coronary intervention and/or stent thrombosis. If more than one endpoint occurred during the follow-up period, we selected the first occurring event for the endpoint analysis. Reported endpoints were verified from hospital records.

Blood sampling, swab sampling and laboratory analysis

Three millilitres of venous blood drawn from the median cubital vein for measurement of cTn-I were transported in cool boxes within 6 hours of collection to icddr. NP swabs were collected, and influenza virus was identified by rRT-PCR and typed and subtyped using primers and probes supplied by the USA Centres for Diseases Control and Prevention. Presence of SARS-CoV-2 RNA was also identified in NP swabs by rRT-PCR targeting ORF1ab-specific and N-gene-specific primers and probes following the protocol of the Chinese Center for Disease Control and Prevention.¹⁴ Amplification was carried out using the iTaq universal probes one-step kit in a Bio-Rad CFX96TM Real-Time PCR detection system (Bio-Rad Laboratories, Inc, California, USA).

Data analysis

We stored electronic case report data on a local server and used Stata V.13 (StataCorp LP, College Station, Texas, USA) for analysis. We used descriptive statistics to document sociodemographic information, medical history, clinical data, symptoms and laboratory investigations. Categorical variables were summarised using frequency and percentage. For numerical variables with symmetrical distribution, we used mean and SD and for asymmetrical distribution, median and IQR. We analysed cardiovascular clinical endpoints at 3 months using descriptive statistics. Subjects were grouped according to the SARS-CoV-2 infection result (negative or positive). We analysed categorical variables using Pearson's χ^2 tests and the Mann-Whitney U test for continuous variables to determine the significance of any association with COVID-19 disease in a bivariate analysis.

Survival analysis was conducted using time to event data. We recorded the time from STEMI/NSTEMI admission to the first incidence of an adverse cardiovascular clinical endpoint during the follow-up period. We calculated survival estimates by the Kaplan-Meier method and applied the log-rank test to compare cases with adverse outcomes with respect to SARS-CoV-2 infection. We considered significance at $p \leq 0.05$.

Table 1 Sociodemographic and clinical characteristics of patients with MI on 28 June to 11 August 2020 at NICVD, Dhaka, Bangladesh

Characteristics	Patients with MI (n=280)	SARS-CoV-2 infected (n=36)	No infection n=244	P value
Age in years, mean (\pm SD)	54.5 (11.8)	54.5 (13.2)	54.5 (11.6)	0.954
<40	26 (9.3)	3 (8.3)	23 (9.4)	Ref.
40–64	193 (68.9)	24 (66.7)	169 (69.3)	0.899
\geq 65	61 (21.8)	9 (25.0)	52 (21.3)	0.683
Male, n (%)	220 (78.6)	30 (83.3)	190 (77.9)	0.456
Location of residence, n (%)				
Suburban	136 (48.6)	1 (2.8)	41 (16.8)	Ref.
Urban	102 (36.4)	13 (36.1)	89 (36.5)	0.091
Rural	42 (15.0)	22 (61.1)	114 (46.7)	0.020*
Education, years of school attendance, n (%)				
None	67 (23.9)	8 (22.2)	59 (24.2)	Ref.
1–5	132 (47.1)	16 (44.4)	116 (47.5)	0.971
6–10	29 (10.4)	2 (5.6)	27 (11.1)	0.500
11–12	27 (9.6)	6 (16.7)	21 (8.6)	0.180
\geq 13	25 (8.9)	21 (8.6)	21 (8.6)	0.606
Travel history to COVID-19 hotspot n (%)	49 (17.6)	3 (8.3)	46 (18.9)	0.119
Medical history				
Body mass index†, mean (\pm SD) ¹	23.4 (3.6)	23.9 (3.6)	23.3 (3.6)	0.389
Overweight (BMI† >25)	84 (30.0)	11 (30.6)	73 (29.9)	0.938
Diabetes mellitus, n (%)	107 (38.2)	9 (25.0)	98 (40.2)	0.099
Smoking status, n (%)				
Never smoked	112 (40.0)	17 (47.2)	95 (38.9)	Ref.
Former smoker	53 (18.9)	10 (27.8)	43 (17.6)	0.508
Current smoker	115 (41.1)	9 (25.0)	106 (43.4)	0.098
Hyperlipidaemia, n (%)	47 (16.8)	6 (16.7)	41 (16.8)	0.984
Hypertension, n (%)	136 (48.6)	19 (52.8)	117 (48.0)	0.589
Previous myocardial infarction, n (%)	35 (12.5)	4 (11.1)	31 (12.7)	0.787
Previous PCI, n (%)	13 (4.6)	1 (2.8)	12 (4.9)	0.569
Previous coronary artery bypass graft, n (%)	5 (1.8)	1 (2.8)	4 (1.6)	0.630
STEMI, n (%)	140 (50.0)	18 (50.0)	122 (50.0)	–
NSTEMI, n (%)	140 (50.0)	18 (50.0)	122 (50.0)	–
Hospital admission in the past 14 days, n (%)	15	3 (8.3)	12 (4.9)	0.396
Discharge medications, n (%)				
ASA	256 (97.0)	33 (94.3)	223 (97.4)	0.320
P2Y ₁₂ inhibitor	255 (96.2)	34 (97.1)	221 (96.1)	0.909
β -blocker	177 (66.8)	22 (62.9)	155 (67.4)	0.596
ACEI/ARB	176 (66.4)	24 (68.6)	152 (66.1)	0.772
Statin	262 (98.9)	34 (97.1)	228 (99.1)	0.300
Nitrate	207 (78.1)	29 (82.9)	178 (77.4)	0.466
Diuretic	60 (22.6)	8 (22.9)	52 (22.6)	0.974
Azithromycin	12 (4.5)	1 (2.9)	11 (4.8)	0.610

*Significant at $p \leq 0.05$.†Body mass index=kg/m².

ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers; ASA, acetylsalicylic acid; MI, myocardial infarction; NICVD, National Institute of Cardiovascular Diseases; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; SD, standard deviation; STEMI, ST-segment elevation myocardial infarction.

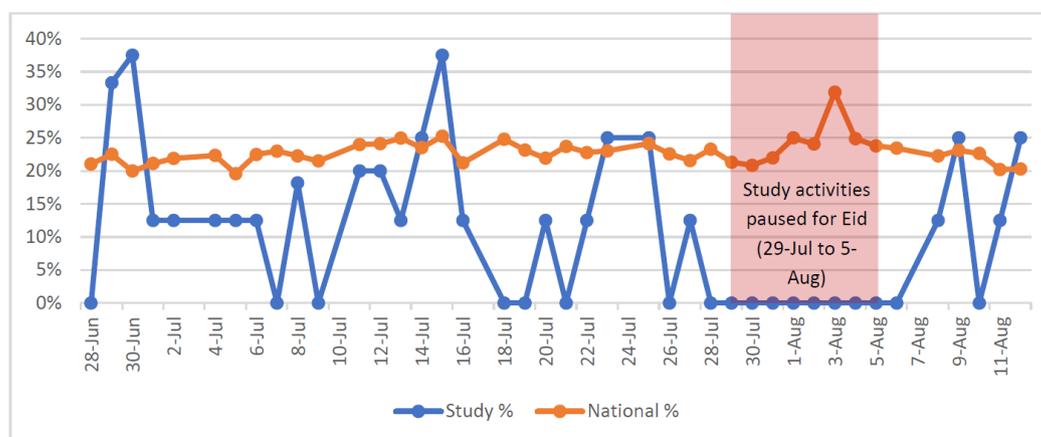


Figure 1 Daily test positivity rate for SARS-CoV-2 infection in Bangladesh and study hospital (National Institute of Cardiovascular Diseases) from 28 June to 11 August 2020.

Table 2 Clinical symptoms and laboratory parameters of patients with MI on 28 June–11 August 2020 at NICVD, Dhaka, Bangladesh

Characteristics	Total of patients with MI (n=280)	SARS-CoV-2 infected (n=36)	No infection (n=244)	P value
Symptoms, n (%)				
Retrosternal chest pain	166 (59.3)	22 (61.1)	144 (59.0)	0.811
Fever	5 (1.8)	1 (2.8)	4 (1.6)	0.630
Cough	31 (11.1)	5 (13.9)	26 (10.7)	0.564
Shortness of breath	38 (13.6)	5 (13.9)	33 (13.5)	0.952
Sore throat	9 (3.2)	3 (8.3)	6 (2.5)	0.062
Runny nose	2 (0.7)	–	2 (0.8)	0.586
Headache	12 (4.3)	1 (2.8)	11 (4.5)	0.632
Diarrhoea	6 (2.1)	–	6 (2.5)	0.342
Cardiac arrhythmia	6 (2.1)	1 (2.8)	5 (2.1)	0.778
Body ache	24 (8.6)	2 (5.6)	22 (9.0)	0.489
Weakness	131 (46.8)	23 (63.9)	108 (44.3)	0.028*
Influenza virus, n (%)				
Type and subtype	A/H3	–	A/H3	–
SARS-CoV-2, n (%)				
Cardiac troponin I, pg/mL, median (IQR)	14389 (2831–43241)	10087 (3548–41005)	14529 (2339–43533)	0.714
Subtype of MI, n (%)				
Anterior	38 (27.1)	5 (27.8)	33 (27.1)	Ref.
Anteroseptal	31 (22.1)	3 (16.8)	28 (23.0)	0.666
Inferior	50 (35.7)	6 (33.3)	44 (36.1)	0.872
Extensive anterior	18 (12.9)	3 (16.7)	15 (12.3)	0.713

*Significant at $p < 0.05$.

MI, myocardial infarction; NICVD, National Institute of Cardiovascular Diseases.

RESULTS

Sociodemographic and medical characteristics

We enrolled 280 patients 23–95 years of age (mean 54.5 (11.8)), in which 220 (79%) were male, 140 (50%) with STEMI and 140 with NSTEMI (table 1). The daily positivity rate was higher than the national average⁷ on 8 days of the 6-week study period (figure 1).

Symptoms and laboratory findings

Among the 280 participants, SARS-CoV-2 positivity in subjects with STEMI and NSTEMI was similar (18/140, 13%). We conducted this study during peak influenza season (May–September) in Bangladesh,¹⁵ but detected only a single influenza case on the 29th epidemiological

Table 3 Endpoints after 3 months post-MI by SARS-CoV-2 infection during COVID-19 pandemic (28 June–12 November 2020) in Bangladesh

Endpoints	Total of patients with MI (n=280)	SARS-CoV-2 infected (n=36)	Uninfected (n=244)	P value
All-cause death, n (%)	31 (11.1)	5 (13.9)	26 (10.7)	0.564
Recurrent MI, n (%)	12 (4.3)	1 (2.8)	11 (4.5)	0.632
Heart failure, n (%)	4 (1.3)	0	4 (1.6)	0.439
Revascularisation, n (%)	20 (7.1)	4 (11.1)	16 (6.6)	0.322
All endpoints, n (%)	67 (23.9)	10 (27.8)	57 (23.4)	0.990

MI, myocardial infarction.

week of 2020 (12 July 2020). Clinical symptoms and laboratory parameters on admission are shown in [table 2](#).

Cardiovascular endpoints at 3 months (13 weeks) follow-up

Overall, there were no significant differences in outcome between SARS-CoV-2 positive and SARS-CoV-2 negative patients. At 3 months (13 weeks), we observed numerically higher mortality among SARS-CoV-2 positive patients compared with SARS-CoV-2 negative patients (14% vs 11%, $p=0.564$) ([table 3](#)). We also recorded a numerically higher proportion of revascularisation procedures among SARS-CoV-2 positive than negative patients (4 (11%) vs 1 (7%), $p=0.437$). The proportion of recurrent MIs was numerically higher (11 (5%) vs 1 (3%), $p=0.632$) among SARS-CoV-2 negative participants, and no SARS-CoV-2 negative participant developed heart failure. In the survival analysis, we found a shorter median time to cardiovascular event among SARS-CoV-2 positive patients compared with SARS-CoV-2 negative patients (21 days, IQR: 8–46 vs 27 days, IQR: 7–44) ([figure 2](#)). There

was no difference in the composite endpoint at 3 months between patients with and without SARS-CoV-2 infection ($p=0.378$).

DISCUSSION

During the 6-week study period, we found a substantial rate of undiagnosed SARS-CoV-2 infection in patients with MI who would not have been routinely tested. We have not found previous reports of prevalence of SARS-CoV-2 infection among MI patients without symptoms consistent with WHO criteria for of SARS-CoV-2 infection. However, asymptomatic SARS-CoV-2 infections have been reported since early January and February 2020 in China and Germany,^{16 17} and a recent review confirmed that almost half of all SARS-CoV-2 infections are asymptomatic.¹⁸ Our study was conducted during the first wave of the COVID-19 pandemic when the Bangladesh testing positivity rate was at a peak of 20%.⁷ Our study findings suggest the possibility of occult SARS-CoV-2

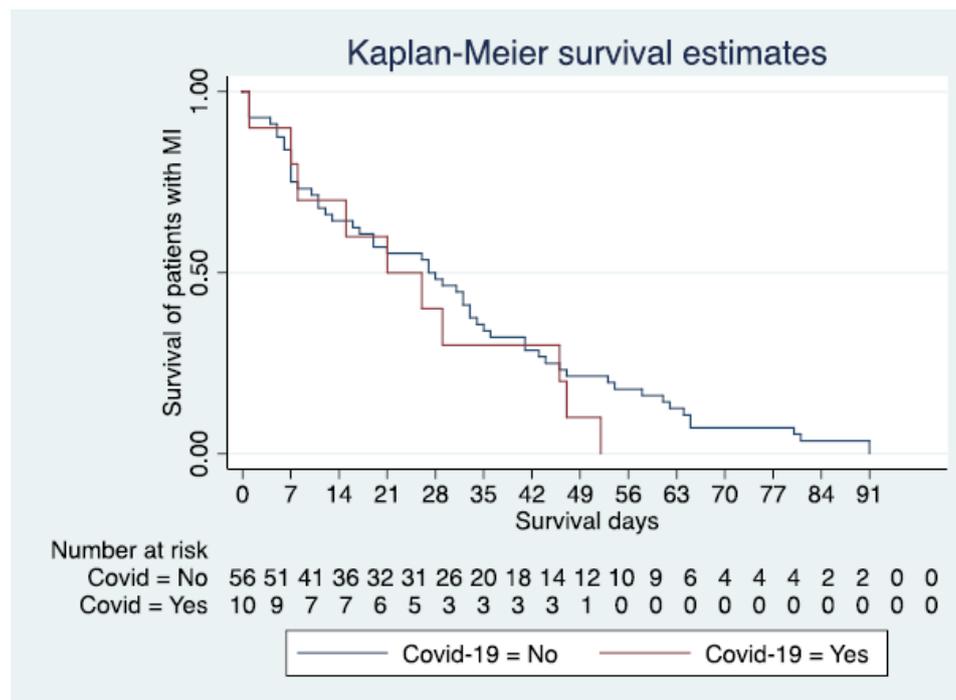


Figure 2 Three-month (13 weeks) survival rate of patients with MI in Bangladesh during COVID-19 pandemic (June–November 2020).

virus infection precipitating MI as illustrated by recent evidence^{19 20} and leading to poorer outcomes.^{21 22} Larger studies with control groups are needed to evaluate this.

A review of studies of asymptomatic cases of SARS-CoV-2 infection in populations from Iceland, Italy, Hong Kong, USA, Japan and Greece suggested that 40%–45% of those infected with SARS-CoV-2 may remain asymptomatic.¹⁸ Most of these studies imply an epidemiological link of close contact with confirmed COVID-19 cases. The majority of our study participants did not report travel history to an identified COVID-19 hotspot. Asymptomatic cases are a threat to public health, hindering control of the pandemic.^{18 23} Since we enrolled participants who did not meet clinical criteria for suspected COVID-19, it was anticipated that we would not find significant differences in presenting symptoms of participants testing positive and negative for SARS-CoV-2 infection. As reported in previous studies, some cases with detectable SARS-CoV-2 may show only cardiac manifestations, without the typical presentation of fever and cough.^{24 25} We found generalised weakness as the second most frequent symptom (47%) after chest pain (59%), and generalised weakness was reported significantly more often among SARS-CoV-2 infected participants. A comprehensive review of cardiovascular implications related to COVID-19 reported that, in mild SARS-CoV-2 cases, cough, runny nose and sneezing often appear with anosmia, ageusia and gastrointestinal symptoms.^{26–28} However, most of these non-specific symptoms were absent in our participants with STEMI/NSTEMI testing positive for SARS-CoV-2 and were numerically more prevalent in COVID-19 free patients.

Surprisingly, given the absence of routine influenza vaccination in Bangladesh,²⁹ we found only one influenza-positive participant during the normal peak influenza season. While studies in other parts of the world report influenza coinfection with SARS-CoV-2,^{10 30} we found no such cases among patients with MI. This absence of influenza during the peak season may be explained by social distancing measures together with shutdown of offices, businesses and educational institutes.

Our study provides important insight into the vital aspect of leaking cTn-I due to myocardial injury in association with SARS-CoV-2 infection. Studies published in March 2020 reported myocardial injury assessed by high cardiac troponin levels to be an independent risk factor for increased mortality in patients with MI testing positive for COVID-19.^{5–7} In our study, subjects without SARS-CoV-2 infection had a higher median level of cTn-I than subjects with SARS-CoV-2 infections. The findings may imply that SARS-CoV-2 infection-related leaking cTn-I in STEMI/NSTEMI has little effect on outcome.

Dual antiplatelet therapy (DAPT) with acetylsalicylic acid and P2Y₁₂ inhibitors was the predominant postdischarge therapy for our study participants. DAPT has proven to have markedly reduced fatal and non-fatal ischaemic events after percutaneous coronary interventions among patients with MI.³¹ However, in our study

participants, no primary percutaneous coronary intervention was performed as providing guideline-recommended treatment is not often possible for patients with MI in Bangladesh.³² Furthermore, a medical registry system was not available to document post-MI medication adherence by patients, and we reported findings after 3-month (13 weeks) follow-up. All these factors may have contributed to an increased frequency of adverse cardiovascular outcomes among our study participants.

At 3 months (13 weeks) post-STEMI/NSTEMI, we found numerically higher all-cause mortality and revascularisation rates and a shorter median time to an adverse cardiovascular event among laboratory-confirmed patients with COVID-19. During the COVID-19 pandemic, studies in China and Egypt have shown an increasing trend in mortality among patients with STEMI,^{27 33} and also reinfarction and need for revascularisation were significant outcomes.³³ Our study appears to be the first to report cardiovascular outcomes among SARS-CoV-2 infected patients at 3 months (13 weeks) post-MI. Nevertheless, future studies describing long-term prognosis among SARS-CoV-2 infected STEMI cases and NSTEMI cases are warranted.

Strengths of our study include that the outcomes registered were validated by reviewing treatment physician's prescription notes by the study physicians. Second, we excluded patients suspected of having SARS-CoV-2 infection based on WHO clinical criteria in order to identify cases that would not otherwise have been tested for SARS-CoV-2. Third, all rRT-PCR tests and cTn-I assays were performed in ISO 15189 and ISO 15190 accredited laboratories of the icddr,b.

Our study has several limitations. It was conducted in a single hospital in a resource-limited setting where guideline-recommended treatment for STEMI/NSTEMI is not routinely provided; hence, this may have profoundly influenced the outcomes registered. Also, the low number of SARS-CoV-2 positive patients reduced the potential to observe differences in outcomes among SARS-CoV-2 positive and negative patients. We also lacked a control group, such as patients admitted for other conditions for comparison of infection rates.

The substantial rate of occult SARS-CoV-2 infection among patients with MI suggests that SARS-CoV-2 may precipitate MI. Our findings highlight the need for screening of all patients and adopting preventive measures for frontline healthcare workers, including cardiologists, to avoid transmission of SARS-CoV-2 in hospital environments. Larger studies are needed to determine clinical impact of SARS-CoV-2 infection on MI.

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Contributors ZA wrote the paper and performed data analysis. OF, CRM and ZA conceived the study, and MJU and AKMMI were responsible for patient inclusion.

ZA, OF, FC, MAA, MaR and PKG developed study protocol. MuR, MEH and MKS performed laboratory analysis. PKG developed data visualisation and was responsible for statistical analyses. MaR, SC and CRM provided critical feedback. All authors have read and approved the final manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The study was approved by the icddr,b institutional review board prior to enrolling participants, and informed written consent to participate in the study was obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data generated during the study are subject to a data access policy of icddr,b and are available from icddr,b's research administration on reasonable request through the corresponding author.

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