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Pandemic-Associated Delays in Myocardial Infarction Presentation in Predominantly Rural Counties With Low COVID-19 Prevalence

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Fewer ST-elevation myocardial infarctions (STEMIs) presentations and increased delays in care occurred during the COVID-19 pandemic in urban areas. Whether these associations occurred in a more rural population has not been previously reported. Our objective was to evaluate the impact of COVID-19 on time-to-presentation for STEMI in rural locations. Patients presenting to a large STEMI network spanning 27 facilities and 13 predominantly rural counties between January 1, 2016 and April 30, 2020 were included. Presentation delays, defined as time from symptom onset to arrival at the first medical facility, classified as ≥12 and ≥24 hours from symptom onset were compared among patients in the pre−COVID-19 and the early COVID-19 eras. To account for patient-level differences, 2:1 propensity score matching was performed using binary logistic regression. Among 1,286 patients with STEMI, 1,245 patients presented in the pre−COVID-19 era and 41 presented during the early COVID-19 era. Presentation delays ≥12 hours (19.5% vs 4.0%) and ≥24 hours (14.6% and 0.2%) were more common in COVID-19 than pre−COVID-19 cohorts (p <0.001 for both), despite a low COVID-19 prevalence. Similar results were seen in propensity-matched comparisons (≥12 hours: 19.5% vs 2.4%, p = 0.002; ≥24 hours 14.6% vs 0.0%, p = 0.001). In a predominantly rural STEMI population, delays in seeking medical care after symptom onset were markedly more frequent during the COVID-19 era, despite low COVID-19 prevalence. Considering delays in reperfusion have multiple adverse downstream consequences, these findings may have important implications in rural communities during future pandemic resurgences.
 (Am J Cardiol 2022;169:18−23)

Dramatic reductions in emergency room and acute coronary syndrome presentations were reported at the onset of the COVID-19 pandemic,[1−4] including a 38% decrease in ST-elevation myocardial infarction (STEMI) activations at 9 high-volume, primarily metropolitan STEMI centers. Reports from international metropolitan areas, including Hong Kong[5] and London,[6] demonstrated delays in symptom onset to first medical care were also present. It has been postulated that the high infection rates in these urban communities may have prevented patients with STEMI from seeking medical attention because of concerns of contracting the virus in the hospital setting.[5,6] However, these previous reports were limited to large urban areas, with high COVID-19 positivity rates. Whether the pandemic onset was similarly associated with delays in seeking STEMI care in more rural locations have not been previously reported. If found, delays in rural STEMI reperfusion are strongly linked to an increased short-term risk of morbidity and mortality secondary to decreased myocardial salvage, larger infarct size, and mechanical complications[7−10] and long-term implications including an increased the risk heart failure and the potential for downstream hospitalizations for heart failure.[8,9] This study was conducted to investigate if delays in STEMI presentation were evident in a more rural region with low COVID-19 prevalence during the early phase of the pandemic.

Methods

This study evaluated patients presenting to a large integrated health system STEMI network spanning 27 facilities and 13 predominantly rural counties in Michigan. The network consists of a traditional hub-and-spoke model with the cardiac catheterization laboratory of a single quaternary referral center serving as the hub where >300 primary percutaneous coronary intervention procedures are traditionally performed annually. Multiple hospitals and urgent care centers in rural counties serve as the spoke sites within the network from which patients with STEMI are emergently transferred to the hub hospital. Counties were classified as rural or urban based on a condensed version of the 2013 National Center for Health Statistics Urban-Rural Classification Scheme incorporating 2010 US Census Bureau data and is utilized by the Centers for Disease Control. In this study, "urban" was defined as large central metropolitan

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See page 23 for disclosure information.

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0002-9149/
https://doi.org/10.1016/j.amjcard.2021.12.052

area and large fringe metropolitan areas with "rural" encompassing the remaining counties.[11]

A longitudinal database of patients presenting for STEMI has been collected as part of ongoing institutional quality improvement efforts. Patients with STEMI treated within the network between January 1, 2016 and April 30, 2020 were included in the analysis. Patients who were already in the hospital at the time of STEMI onset were excluded. Patients were also excluded if the time of symptom onset or the time of arrival at the first facility was not recorded. Subsequent visits for individual patients were excluded if they had more than 1 and the original was included in the analysis. A waiver of consent and approval for the study were obtained from the local institutional review board.

Consistent with previous methodology,[1] March 1, 2020 was considered the onset of the COVID-19 pandemic in the United States, as this was the date New York City, the epicenter of infections in the United States, reported its first COVID-19 case. Patients presenting with STEMI from March 1, 2020 to April 30, 2020 were considered to take place in the early COVID-19 time period. This early COVID-19 timeframe was selected to provide a period during which there was widespread public knowledge of the pandemic, but infection rates in the study area remained relatively low. Patients presenting with STEMI between January 1, 2016 and February 29, 2020 were considered as presenting in the pre−COVID-19 time period.

The primary outcome of interest was the time from patient-recorded symptom onset to arrival at a first medical facility. These values were abstracted by trained study coordinators using consistent methods throughout the duration of the study time. Data were recorded in a secure quality improvement database. A categoric definition of ≥12 hours from symptom onset to care at a first medical facility was selected as the primary unit of analysis, based on previous data suggesting patients presenting ≥12 hours after symptom onset derive reduced mortality benefit from thrombolytic therapy[10] and experience significantly less myocardial salvage after primary percutaneous coronary intervention.[7] Presentation delays ≥24 hours were also reported as a second primary outcome, as guidelines do not support performing routine revascularization of the culprit lesion ≥24 hours after symptom onset because of lack of benefit.[12] Secondary outcome measurements included revascularization strategy (thrombolytic therapy, primary percutaneous coronary intervention, coronary artery bypass grafting, or no revascularization), use of mechanical circulatory support device, and mortality before discharge.

Characteristics of patients with STEMI in the pre−COVID era were compared with those during the early COVID era. Baseline variables, outcome measurements, and the proportion of patients with presentation delays ≥12 and ≥24 hours were compared by time periods. To provide perspective on the number of COVID-19 infections in the geographic region of the STEMI network, total infections within the 13 counties served by the network were plotted along with total infections within the 3 counties included in Metro Detroit, a major metropolitan COVID-19 hot-zone located in the same state as the study institution. Infections in each of these geographic regions were also plotted after adjusting total infections by population size.

A propensity score matched analysis was performed to account for patient-level differences that might result in longer presentation delays. Binary logistic regression was performed to calculate the propensity score to complete a 2:1 propensity-match subset of the data. The variables age, diabetes, and previous coronary disease were included in the binary logistic regression model to calculate the propensity scores as they have been associated with adverse events in COVID-19, which may plausibly influence patient decisions about seeking hospital-based care.[13,14] In order to account for potential differences in presentation delays in urban versus more rural locations, presentation at a hub or spoke facility was also included in the model. Finally, smoking status was included in the model, as the univariate analysis of baseline characteristics revealed a significantly differences in this variable between patients in the pre−COVID-19 and COVID-19 time periods. Swarm plots were created to visually depict time to presentation with of 12- and 24-hour presentation delays.

All continuous data were explored using histograms graphically to determine conformance to a normal distribution. Normally distributed continuous variables are shown as mean ± SD and analyzed using 2 sample independent *t* test comparing pre−COVID-19 and COVID-19 time periods. Non-normally distributed continuous variables are shown as median (twenty-fifth percentile to seventy-fifth percentile) and analyzed using Wilcoxon Rank Sum comparing pre−COVID-19 and COVID-19 time periods. Categoric variables are shown as count (% frequency) and analyzed using either chi-square or Fisher's exact test comparing pre−COVID-19 and COVID-19 time periods. All statistical analyses were generated using SAS (SAS Enterprise Guide software, version 7.1, SAS Institute Inc., Cary, North Carolina).

Results

Between January 1, 2016 and April 30, 2020, a total of 1,494 patients presented with a STEMI to 1 of 27 facilities across 13 counties within the study institution's STEMI network. Of these, 70 patients were excluded because they were in the hospital at the time of STEMI onset. An additional 115 patients were excluded because either the time of symptom onset or the time of arrival at the first facility was not recorded and 23 STEMI presentations were excluded as the patients had already presented with a STEMI during the study timeframe (Figure 1). Of the 1,286 patients included in the analyses, 1,245 and 41 presented with STEMI in the pre−COVID-19 (96.8%) and early COVID-19 time periods (3.2%), respectively. Baseline characteristics of the study population are presented in Table 1. Patients were predominantly male, white, and had multiple established cardiovascular risk factors. The predominant mode of transportation to the hospital was by ambulance and most cases presented to the hub location. No significant differences in baseline characteristics were identified between groups with the exception that patients in the early COVID-19 time period were more likely to be current/former smokers (68.3% vs 48.3%, $p = 0.01$) and were more likely to be transported to the hospital by ambulance rather than by private transportation ($p = 0.04$; Table 1).

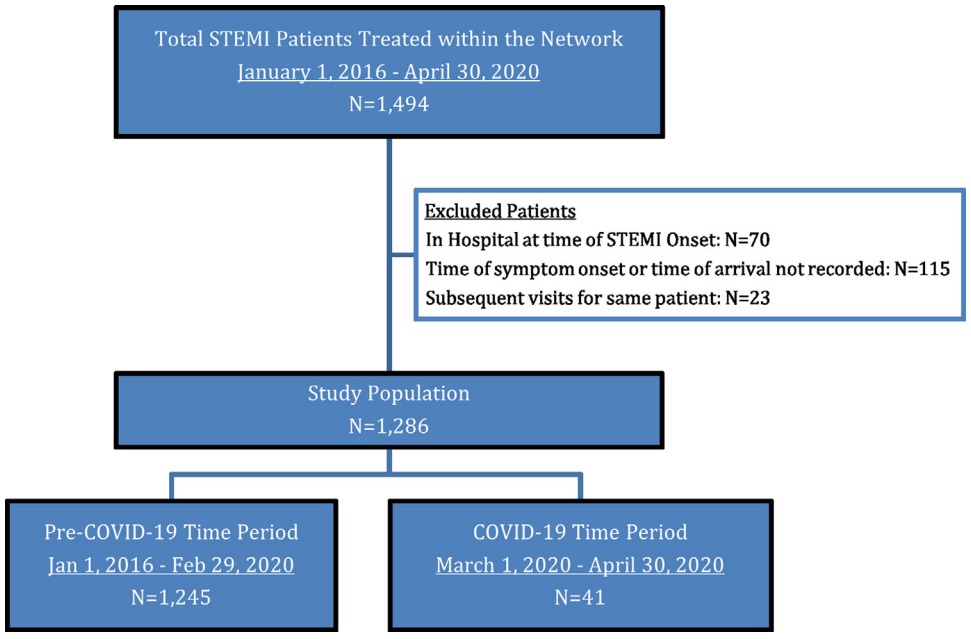

Figure 1. Flow chart of study population shown is the number of patients with STEMI treated with the STEMI network during the study period, patients excluded from the analysis, and the final study population according to those presenting with STEMI in the pre−COVID-19 and early COVID-19 time periods.

As of April 30, 2020, the median number of COVID-19 infections across the 13 counties in the STEMI network was 35 (interquartile range 11 to 98) per county and ranged from 2 infections in the least affected county to 1,479 infections in the most infected county. The total number of infections across all 13 counties was 2,306. In comparison, Metro Detroit reported 29,509 COVID-19 infections in the same time period; significant differences in COVID-19 infections normalized to population size were also evident (Figure 2). Over the course of the study period, various state-wide public health interventions were instituted, which are depicted in Figure 2.

Table 1
Baseline characteristics of the study population

Variable	Pre-COVID-19 Jan 2016 − Feb 2020 (N = 1,245)	Early COVID-19 Mar 2020 − Apr 2020 (N = 41)	p Value
Age (years)	63 ± 13	64 ± 12	0.45
Men	891 (71%)	30 (73%)	0.83
White	1,156 (93%)	38 (93%)	1.00
Height (cm)	173 ± 10	173 ± 10	0.99
Weight (kg)	90.5 ± 20.1	89.3 ± 18.9	0.71
Body mass index (kg/m^2)	30.3 ± 6.5	29.8 ± 5.4	0.63
Hypertension	822 (66%)	30 (73%)	0.34
Dyslipidemia	709 (57%)	22 (54%)	0.68
Diabetes mellitus	267 (21%)	11 (27%)	0.41
Current/former smoker	602 (48%)	28 (68%)	0.01
Currently on dialysis	11 (1%)	0 (0%)	1.00
Prior myocardial infarction	198 (16%)	8 (20%)	0.53
Prior PCI	249 (20%)	10 (24%)	0.49
Prior coronary artery bypass	70 (6%)	1 (2%)	0.72
Prior heart failure	38 (3%)	2 (5%)	0.37
Cerebrovascular disease	84 (7%)	4 (10%)	0.52
Peripheral arterial disease	75 (6%)	2 (5%)	1.00
Means of transport to presenting facility			
Self/family	594 (48%)	13 (32%)	0.04
EMS	650 (52%)	28 (68%)	
Presenting facility			
Hub hospital	807 (64.8)	30 (73.2)	0.27
Spoke Facility	438 (35.2)	11 (26.8)	

EMS = emergency medical services; PCI = percutaneous coronary intervention; STEMI = ST-elevation myocardial infarction.

Rates of presentation delays ≥12 and ≥24 hours after symptom onset in the early COVID-19 era and the pre−COVID-19 era are illustrated in Figure 3 among the 1,286 patients treated within the STEMI network during the study period. The odds of presentation delays ≥12 hours and delays ≥24 hours were 5.8 (95% confidence interval 2.5 to 13.2) and 106.5 (20.8 to 546.6) greater in the early COVID-19 era compared with the pre−COVID-19 era, respectively. The median (interquartile range) for the early COVID-19 era and pre−COVID-19 era were 1.9 (1.1 to 7.6) and 1.9 hours (1.1 to 3.9), respectively.

Subgroup analyses were conducted in the propensity-matched cohort to account for potential confounding variables. Comparison of baseline variables used for propensity score matching in the 2 groups are shown in Table 2, demonstrating appropriate matching of select variables. Swarm plots demonstrate time from symptom onset to emergency room presentation in graphical form (Figure 4). After propensity score matching, presentation delays ≥12 hours remained more common in the COVID-19 (19.5%) compared with the pre−COVID-19 time period (2.4%, p = 0.002). Presentation delays ≥24 hours were also more common in the COVID-19 time period (COVID-19 14.6% vs pre−COVID-19 0.0%, p = 0.001). Secondary outcome measurements were limited by low event rates in the propensity match analyses. No significant differences in cardiac arrest or revascularization strategy were observed, although this was likely due to low power. There was a small numeric

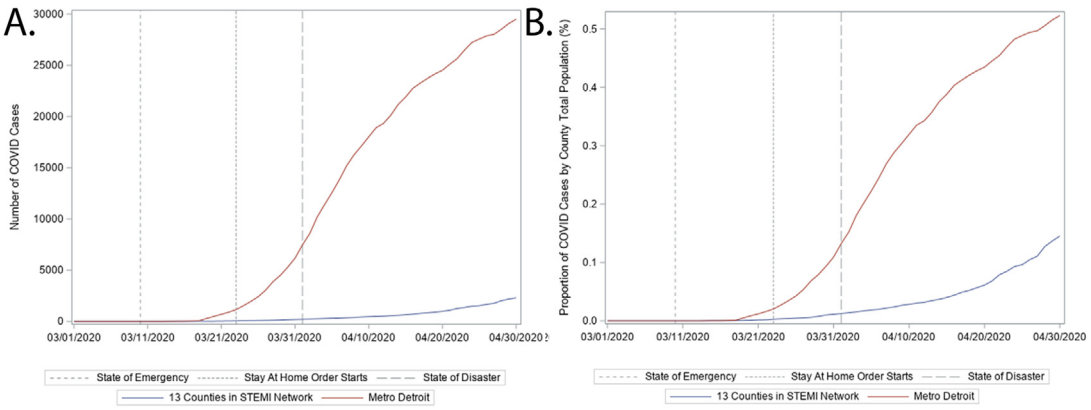

Figure 2. COVID-19 infections in counties of STEMI network and in Metro Detroit shown are the number of COVID-19 infections over time (*A*) and the number of infections normalized to total population size (*B*) in the 13 counties served by the STEMI network (*blue line*) and in Metro Detroit (*red line*). The dates that a state of emergency, stay at home order, and state of disaster were declared by the Governor of Michigan are noted by the vertical lines.

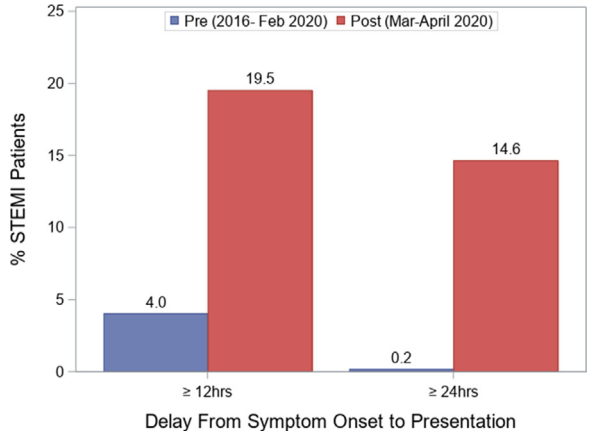

Figure 3. Percentage of patients with STEMI experiencing a presentation delay of ≥12 and ≥24 hrs from symptom onset in the pre−COVID and early COVID-19 eras. Shown is the percentage of patients having a delay of ≥12 and ≥24 hrs from symptom onset to presentation at a health care facility in patients presenting with an STEMI, stratified by the pre −COVID-19 and early COVID-19 eras. (p <0.001 for both). Feb = February; hrs = hours; Mar = March.

Table 2
Comparison of baseline variables used for propensity score matching in the pre-COVID-19 and early COVID-19 study groups

Variable	Pre-COVID-19 (N = 82)	Early COVID-19 (N = 41)	p Value
Age (years)	64 ± 11	64 ± 12	0.98
Men	55 (67%)	30 (73%)	0.49
Body mass index (kg/m^2)	30.1 ± 5.4	29.8 ± 5.4	0.72
Diabetes mellitus	31 (38%)	11 (27%)	0.23
Current or former smoker	54 (66%)	28 (68%)	0.79
Prior myocardial infarction	18 (22%)	8 (20%)	0.75
Prior PCI	22 (27%)	10 (24%)	0.77
Presentation			
Hub facility	58 (71%)	30 (73%)	0.78
Spoke facility	24 (29%)	11 (27%)	

PCI = percutaneous coronary intervention.

increase in the rates of mechanical circulatory support in the COVID-19 era, but the observed difference did not meet statistical significance. No in-hospital differences in mortality were observed between groups after matching (Table 3).

Discussion

This study builds on several previous findings demonstrating that the onset of the COVID-19 pandemic was associated with altered patterns of STEMI presentations. First, they suggest patients with STEMI in 13 predominantly rural counties presented late (≥12 hours) and very late (≥24 hours) after the onset of symptoms in the early months of the COVID-19 pandemic. Accordingly, in patients with STEMI, we observed a 5.8 times greater odds of presentation delays ≥12 hours and 106 times greater odds in those presenting ≥24 hours after symptom onset compared with historical controls. This observation remained largely unchanged after accounting for patient-level characteristics, suggesting the pandemic-associated STEMI delays previously demonstrated in densely populated urban centers extend to more rural locations. Second, we report that delayed STEMI presentations occurred in a geographic region with low COVID-19 prevalence yet during a time when knowledge of the pandemic was widespread. Despite the geographic area served by the STEMI network in this study having fewer than 1/10 the number of infections observed in Metro Detroit, significant delays in seeking medical care were nonetheless observed. This suggests much of the pandemic's effect on STEMI presentations may have been indirect in nature. One potential hypothesis for this finding is that the COVID-19 pandemic because of fears of contracting the virus in the medical setting; however, as this study did not survey patients with STEMI as to the underlying etiology of their delayed presentation, no definitive conclusion can be drawn as to the explanation. These delays, regardless of the cause, are of particular importance given the well-described associations between delayed coronary reperfusion therapy and worse clinical outcomes including elevated rates of heart failure.[8,9] Thus, physicians in areas with low COVID-19 rates should be vigilant for a possible influx of resultant ischemia-mediated heart failure in the months to years to come.

The observed increases in STEMI presentations ≥12 and ≥24 hours after symptom onset in the COVID-19 era in the present study are concerning, as presentation delays are well established to have numerous deleterious downstream consequences. Delays in revascularization of >12 hours are

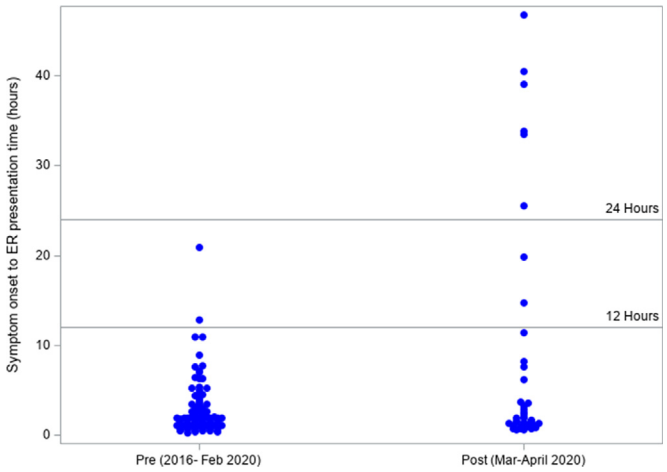

Figure 4. STEMI presentation delay in the pre−COVID-19 and early COVID-19 time periods. Shown are swarm plots of presentation delay in the propensity score matched cohorts in the pre−COVID-19 and early COVID-19 time periods. Presentation delays of 12 and 24 hours are marked as horizontal lines on the figure. ER = emergency room.

associated with larger infarct size, higher mortality rates, and in which reperfusion therapy results in substantially less myocardial salvage.[9,10] In patients with presentation delays ≥24 hours, routine administration of thrombolytics or percutaneous coronary intervention is not recommended because of limited benefit.[12] Larger transmural infarcts may also increase the risk of mechanical complications of myocardial infarction, including rupture of the ventricular septum, papillary muscle, or left ventricular free wall. These mechanical complications are associated with markedly elevated mortality rates and are rare in the reperfusion era.[15] A number of reports have anecdotally noted an increase in mechanical complications of STEMI during the COVID-19 pandemic,[16] and several reports have demonstrated increased risk of adverse cardiac events during the COVID-19 era[17] and in patients with COVID-19 infection,[18] possibly attributable to patients not seeking timely treatment for a myocardial infarction.

Outside of acute complications, presentation delays increase the risk of adverse downstream consequences in the long-term as well. Delays in reperfusion are a strong determinant of infarct size; with each 5% increase in myocardial infarct size, there is an associated 20% increase in subsequent hospitalizations for congestive heart failure.[9] Thus, there is a potential for increase in subsequent heart failure hospitalization resulting from the presentation delays observed in our study. Indeed, delays in reperfusion in STEMI exert a tremendous unfavorable effect on morbidity and mortality on patients and potential future economic impact on the health care system. Whether the delayed presentations among patients with STEMI in the COVID-19 pandemic will be followed by a deluge of heart failure hospitalizations in the future is not yet known, but newly established registries such as Get With the Guidelines may help to answer these important questions.[19] The ability of healthcare systems to weather the impact of an increase in heart failure patients within their communities may be disproportionate comparing large urban hospitals with those in more rural communities.

Table 3
Secondary outcomes of interest in propensity score matched groups

Variable	Pre-COVID-19 (N = 82)	Early COVID-19 (N = 41)	p Value
Cardiac arrest prior to cath lab	6 (7%)	4 (10%)	0.73
Revascularization strategy			
Thrombolytic	0 (0%)	0 (0.0)	NA
PCI	76 (93%)	36 (88%)	0.50
Coronary artery bypass	3 (4%)	3 (7%)	0.40
No revascularization	3 (4%)	2 (5%)	1.00
Mechanical circulatory support	10 (12%)	9 (22%)	0.16
Discharge status			
Alive	75 (92%)	40 (98%)	0.27
Deceased	7 (8%)	1 (2%)	

PCI = percutaneous coronary intervention.

The study is limited by inclusion of patients within a single STEMI network and geographic region, which spans 13 counties and received patients from 27 referring facilities during the study period. The inclusion of patients from a single STEMI network, with a homogenous ethnic makeup, has the potential to limit the generalizability of the study results. Although the retrospective observational study design is strengthened by use of propensity score matching, underlying unmeasured residual confounding cannot be excluded. Further studies are needed to determine whether the onset of the pandemic is associated with larger infarct sizes, which was not measured in our study and is outside the scope of this manuscript. Finally, this study is underpowered to detect clinically meaningful differences in short- and long-term adverse clinical consequences from delayed presentations. Therefore, the study focuses on quantifying presentation delays rather than adverse clinical outcomes between groups.

In summary, this study demonstrated 5-fold and 73-fold higher rates of presentation delay ≥12 hours and ≥24 after symptom onset in patients with STEMI in a rural population despite low COVID-19 prevalence. Considering delays in reperfusion are well established to have multiple adverse downstream clinical consequences, these findings may have important implications in rural communities.

Disclosures

The authors have no conflicts of interest to declare.

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