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ORIGINAL RESEARCH

Higher Rates of Thrombolysis Failure and Stent Thrombosis during the COVID-19 Upsurges. What Should We Learn at Recurrent Waves?

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ABSTRACT

Background: On-site thrombolysis as an alternative to transfer for primary PCI (pPCI) was utilized during COVID-19 first peak in many localities enforced by the overwhelming burden on the unprepared health systems. However, higher rates of thrombolysis failure and excess of STEMIs secondary to stent thrombosis were frequently reported during COVID-19's first peak, questioning a potential linkage to SARS-CoV-2-related prothrombotic status. The recent alarming spread of the new emerging SARS-CoV-2 variants in many regions threatens low- and middle-income countries with overwhelming crises similar to the commencement of the pandemic. In this retrospective analysis, we contrasted the clinical profiles, revascularization strategies, and outcomes of STEMI patients presenting to our system during the first COVID-19 surge (n=37), to STEMI presentations in the same interval of the previous year (n=77), to inspect the impact of COVID-19 on STEMI presentations and outcomes. **Results:** Patients' profiles were mostly comparable between the COVID-19-era- and the control- groups. Compared to the controls, STEMI patients during the COVID-19 had significantly higher rates of thrombolysis failure (5 (63%) vs. 3 (21%), p = 0.05) and of STEMIs due to stent thrombosis (5 (16%) vs. 2 (3%), p = 0.01). **Conclusions:** A prevalent prothrombotic milieu parallels SARS-CoV-2 upsurges, disproportionately exceeding numbers of confirmed SARS-CoV-2 infections. This prothrombotic status probably enhanced stent thrombosis and reduced the success of thrombolysis in STEMI cohorts. It is prudent to consider these observations in the unlucky event we faced recurrent upsurges dominated by the emerging SARS-CoV-2 variants.

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KEYWORDS COVID-19, STEMI, thrombolysis

Background

Since the World Health Organization (WHO) declared the coronavirus 2019 disease (COVID-19) as a pandemic in March 2020,[1] there has been an astonishing impact on ST-segment elevation myocardial infarction (STEMI) presentations and outcomes.[2–6]

Despite the reduced numbers of presentations observed at the beginning of the pandemic, STEMIs during the COVID-19 first peak were characterized by substantially worse prognosis and higher in-hospital mortality than usual.[2,7,8] Such observation was initially attributed to the common fears of contracting SARS-CoV-2 infections at healthcare facilities, suggesting that only sicker STEMI patients selectively presented (and very late) to medical services.[9] Nevertheless, alarming signals for increased thrombogenicity accompanying the COVID-19 syndrome started to be a big concern, with a possible worsening impact on STEMI presentations and prognosis.[10]

On the other hand, many health systems, particularly in low- and middle-income countries, were unprepared for the overwhelming burdens of such a crisis and were forced to implement resilient plans with many unstudied compromises. Prominent among these was appraising thrombolysis as an alternative reperfusion strategy for STEMIs, aiming to minimize patient transfer between facilities and reduce exhaustion of medical resources.

The emergence of the new and highly infective SARS-CoV-2 variants resulted in devastating spreads, that surpassed all preparations in many countries and resulted in recurrent crises, similar to what was met at the beginning of the COVID-19 pandemic, or even worse.[11]

Thereby, we opted to explore the influence of COVID-19 upsurges, and the presumably associated prothrombotic milieu on STEMI presentations and outcomes in the literature as well as in our single-center experience, aiming to appreciate what would guide future practices.

Methods

This is a retrospective observational analysis performed in Aswan Heart Center (AHC), Aswan, Egypt. AHC is the only 24/7 primary PCI (pPCI) center in a rural area, serving a population of 1.5 million inhabitants in South Egypt. AHC receives STEMI calls for pPCI, pharmaco-invasive, and rescue PCI from a network of 7 pPCI-non-capable

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facilities within a 130 km radius, with an average of 480 annual STEMI referrals.

In this single-center study, we evaluated the STEMI presentations through the period between May 1st to June 30th, 2020 [during the first COVID-19 surge in Egypt]. To contrast them with "non-COVID-surge" controls, we inspected STEMI presentations during the same interval (May 1st to June 30th) in 2019, to offset any seasonal or climatic confounders in our specific locality.

After attaining AHC institutional ethical committee approval (A--358-2020, acquired in 12/1/2021), patients' clinical data including age, gender, conventional risk factors for Coronary Artery Disease (CAD), data at presentation including initial assessment, baseline laboratory workup, procedural data, and outcomes, as well as post-discharge data [30-day clinical outcomes] were reviewed from medical files, tabulated and categorized by date of admission into the control group (May 1st to June 30th, 2019) and the COVID-19-surge group (May 1st-to-June 30th,2020). Any unclear or missing information were completed by contacting the corresponding patient by phone. Data were tabulated anonymously skipping personal identifiers, to waive the need for patients' consent.

Patients' presentation

Classically in the pre-COVID era, when a patient presents to any of our network centers with an established STEMI diagnosis[12], our center is notified by the patient data (personal data, time of pain onset to diagnosis, clinical profile, and risk factors, Killip class, echocardiographic data) with sharing of the ECG over smartphones. According to the clinical status and expected time to transfer, a decision is made for immediate transfer to our center for pPCI, or (if transfer time is >120 minutes and there are no contraindications to thrombolytics) to administer thrombolysis with either elective transfer for pharmaco-invasive strategy within 24 hours in cases of successful lysis or immediate transfer in cases of failed thrombolytic reperfusion.

During the COVID first peak and enforced by the shortage of personal protective equipment (PPE), our "hub and spoke" system adopted a conservative/modified protocol implying more utilization of pharmacological thrombolysis to minimize patient transfer and preserve PPE. In brief (but more details are in the discussion), onsite thrombolysis was administered for *uncomplicated non-anterior STEMIs* presenting to any pPCI-non-capable center in our network, with selective subsequent transfer to our center in cases of failed lysis (<50% resolution of ST and/or persistent chest pain) or post-MI complications (post MI heart failure or post-MI angina). All anterior STEMIs were routinely transferred (either immediately for pPCI or after lysis if the expected transfer time was >120 min). All STEMI patients with hemodynamic instability or thrombolysis contraindications were directly transferred for pPCI.

SARS-CoV-2 testing

By the beginning of the COVID-19 pandemic when thresholds for suspicion were still high, our center did not employ routine polymerase chain reaction (PCR) testing for all STEMI referrals, where testing was selectively ordered based on clinical suspicion.

With subsequent publications about confirmed PCR-positive cases who are asymptomatic (or minimally symptomatic),[13] it is very possible that some undiagnosed SARS-CoV-2 infections existed among our 2020 STEMI cohort. Additionally, there is growing evidence that patients who recovered from COVID-19 (and thus become PCR-negative) might have SARS-CoV-2-related late sequelae.[14,15] Hereby, we labeled the May-to-June 2020 STEMIs as the "COVID-era group", presuming that asymptomatic infections and post-recovery late sequelae were responsible for many of the observed differences during the COVID-19 upsurge compared with the controls in the pre-COVID-era, despite the low rate of PCR confirmed infections in our cohort.

Statistical analysis

Statistical package for social science (SPSS) software, version 22 for Microsoft Windows (SPSS Inc., Chicago, IL, USA) was used for data analysis. Categorical data were presented as frequency and percentages (n (%) and correlations among them were analyzed by Chi-square test. Continuous data were subjected to normality testing using the Shapiro-Wilk test and (if needed) visual assessment of histogram plots; and were presented as mean ± (standard deviation) or median [interquartile range], then were compared using independent samples t-test or Mann-Whitney test as appropriate. A probability p-value ≤ 0.05 was considered statistically significant.

Results

In the interval between May 1st, 2020 -to- June 30, 2020, our Center was consulted for 37 STEMI patients from our network Centers. Six patients (16%) underwent successful on-site thrombolysis for isolated lateral or inferior uncomplicated STEMI. According to the institutional protocol adopted during the crisis (represented in Figure 1 and detailed in the discussion), these 6 patients were managed medically in their centers, and because they led a complication-free hospitalization (no post-MI angina or heart failure), they were discharged from the admitting facility after a median of 3 days without transfer to our center. The remaining 31 STEMI patients met at least one of the predefined criteria for transfer. Figure 2 shows a flow chart of STEMI calls and transfers during the first COVID-19 peak.

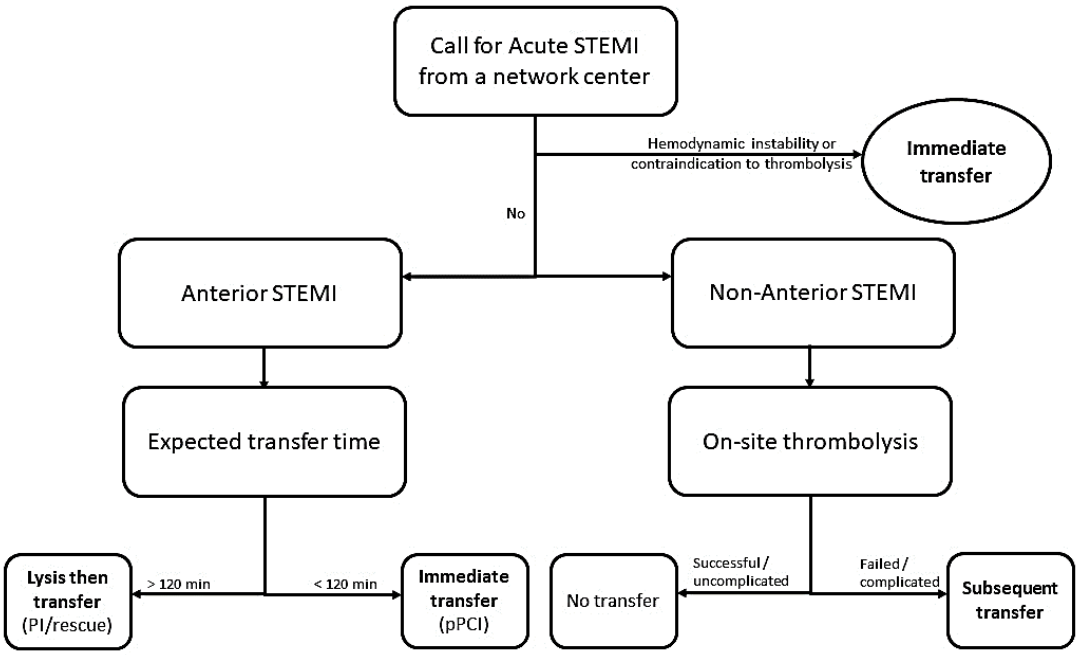

Figure 1 Local institutional policy adopted during the COVID-19 crisis.
PI, pharmaco-invasive strategy; pPCI, primary percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

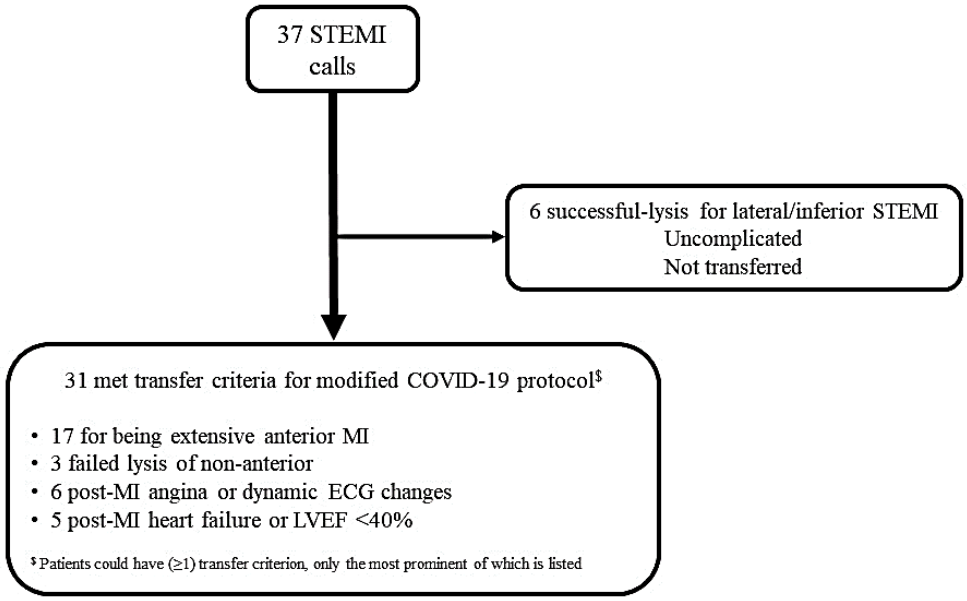

Figure 2 Flow chart for management and transfer during COVID-19 era.
STEMI, ST-segment elevation myocardial infarction.

In contrast to 37 STEMI calls during the COVID-19 surge (COVID-era group), there were 77 STEMI calls and referrals in the corresponding period in 2019, representing the reference workload (Control group). This represents a 52% reduction in STEMI calls to our center during the COVID-19 first peak in Egypt.

Clinical and demographic data of STEMI patients during the COVID era were comparable to the control group (represented in Table 1). The time delay from the first medical contact (FMC) to reaching the pPCI center and total ischemic time was significantly longer in the COVID- compared to the control group, (median [IQR]: 150 [90-360] vs 60 [50-150] minutes; p = 0.001, and 585 [345-1210] vs 412 [270-515] minutes; p = 0.01, respectively). There was no significant difference in patient-related time delays (pain onset-to-FMC).

Rates of attempting thrombolysis were comparable in the COVID- and the control-eras (8/37 [22%] vs 14/77 [18%] respectively, p = 0.6).

Table 1 Demographic and clinical features of the COVID-19-era and the control group

	COVID-19 era group N= 31	Control-group N= 77	*p* value
Age (years)	56 [49-65]	59 [50-69]	0.28
Male gender	25 (81%)	63 (82%)	0.54
Diabetes mellitus	14 (45%)	33 (43%)	0.83
Systemic hypertension	11 (36%)	37 (48%)	0.28
Smoker	20 (65%)	54 (70%)	0.65
Dyslipidemia*	10 (32%)	21 (27%)	0.17
Cumulative RF burden[$]	3 [2-4]	3 [3-4]	0.36

Data expressed as median [inter-quartile range] or frequency (percentage) as appropriate.
* Dyslipidemia = considered if total cholesterol, LDL-C, TG were ≥240, 125, 200 mg/dl respectively, or if diagnosis of dyslipidemia was previously documented.
[$] Cumulative RF burden = total number of risk factors per individual of the 6 conventional CAD RF (advanced age [>55 for males or >65 for females], male gender, diabetes, hypertension, smoking and dyslipidemia)

However, failure of thrombolysis was significantly more in the COVID-era (5/8 [63%] vs 3/14 [21%], p = 0.05). STEMI to be secondary to stent thrombosis (confirmed by angiography) was significantly more prevalent in the COVID-era (5 (16%) vs 2 (3%), p = 0.01). Noteworthy that among the 5 cases of definite stent thrombosis (ST) in the COVID group, 3 had very late (> 1 year) and 2 had late ST (both were >6 months from index PCI). Other data outlining patients' presentation, angiographic features, and outcomes are summarized in Table 2.

There were 5 (16%) SARS-CoV-2 infections confirmed by PCR testing during the COVID-19 era. There were no significant differences between the SARS-CoV-2 positive cases and other patients regarding risk factors, presentation, or outcomes, yet admitting the lack of precision in identifying COVID-19 asymptomatic or recovered cases in our COVID-era group.

Discussion

In the present study, we document the complex influence of the COVID-19 upsurge on STEMI referrals in a pPCI referral center in Egypt. Compared to the controls in the same period of the previous year, STEMI referrals during the COVID-19 first peak showed a significantly higher rate of thrombolysis failure and of STEMIs secondary to stent thrombosis (ST), which might point to a hypercoagulable status related to the COVID-19 era. Witnessing recurrent and more aggressive SARS-CoV-2 peaking waves dominated by the emerging new variants, we opted to further analyze these observations to guide practice in the face of recurrent crises.

New SARS-CoV-2 variants that are more serious, more infective, and potentially less responsive to contemporary vaccines,[16–18] have dominated many regions in the world causing overwhelming subsequent waves of SARS-CoV-2 infections exceeding what was seen during the first wave.[19,20] These upsurges in the rates of spread consumed all the reserves for many health systems and represented a national crisis, similar -or even worse than- what was met during the commencement of the pandemic. For the fears that such a devastating burden may enforce compromises and/or declines in essential medical services like primary PCI similar to the beginning of the pandemic, we liked to demonstrate the observations we had in our center during the first peak.

When COVID-19 started to peak in Egypt, our hub-and-spoke system developed a "modified STEMI reperfusion protocol" adaptive to the challenging situation, as many other national and international centers.[21–23] This adaptive protocol (Figure 1), employed onsite thrombolysis for uncomplicated non-anterior STEMIs presenting to any pPCI-non-capable Center in our network. Selective subsequent transfer for pPCI to our center took place in cases of failed lysis or post-MI complications. However, anterior STEMIs were routinely transferred (either immediately for pPCI or after lysis if the expected transfer time was >120 min). All STEMI patients with hemodynamic instability or lysis contraindication were directly transferred for pPCI.

Despite the temporal variation for COVID-19's first surge in different regions across the globe (that was in January-February 2020 in China, March-April 2020 in Europe and the USA, while May-June 2020 in Egypt), re-emergence of thrombolysis as an alternative reperfusion option was deemed necessary in many parts of the World.[3,6,22,24] Onsite thrombolysis for STEMIs presenting to pPCI-non-capable centers (as an alternative to immediate transfer), arguably had the advantage of minimizing patient transfer between hospitals, reducing consumption of PPE, reducing exhaustion of medical resources, and limiting exposure of healthcare personnel.

Table 2 Clinical data at presentation and angiographic data of the COVID-19-era and the control group

	COVID-19 era group	Control-group	*p* value
Pain to FMC (min)	240 [120-600]	240 [120-360]	0.71
FMC-to-pPCI center (min)	150 [90-360]	60 [50-150]	0.001
Total ischemic time (min)	585 [345-1210]	412 [270-515]	0.01
Peak-Troponin (ng/ml)	4.1 [2.0-8.8]	4.7 [2.2-9.2]	0.74
Peak-CKMB (u/L)	153 [87-323]	211 [102-373]	0.39
Pre-PCI LVEF (%)	40 [35-50]	45 [35-50]	0.43
Anterior MI	21 (68%)	42 (55%)	0.21
Inferior MI	9 (29%)	32 (42%)	0.22
Lateral MI	4 (13%)	4 (5%)	0.16
Isolated posterior MI	2 (7%)	4 (5%)	0.79
Initial thrombolysis strategy	8 (22%)	14 (18%)	0.6
Failed thrombolysis	5 (63%)	3 (21%)	0.05
Large thrombus burden	16 (52%)	29 (38%)	0.19
Culprit = ST	5 (16%)	2 (3%)	0.01
COVID-19 positive	5 (16%)	0	

Data expressed as median [inter-quartile range] or frequency (percentage) as appropriate.
CKMB: Creatinine-Kinase myocardial band; FMC: First medical contact; LVEF: Left ventricular ejection fraction; MI, Myocardial infarction; pPCI: primary percutaneous coronary intervention; ST: Stent thrombosis.

Nevertheless, in our practice, rates of failure of thrombolysis during the first COVID-19 peak were 3 folds as in the corresponding control group despite the comparable clinical profiles and patient-related delays (63% vs. 21%, p = 0.05).

This goes in line with the numerical higher rate of encountering large thrombus burden (according to TIMI classification[25]) in the COVID- compared to the control group. Similar data of thrombolysis failure, paralleled with longer hospital stays, increased patients' morbidity, and total mortality were reported from real practice and predictive models published amid the COVID-19 crisis.[26,27] These impactful findings raised a lot of concerns against expanding the utilization of thrombolysis as an alternative to pPCI.[24,28]

Additionally, there are many occasions during COVID-19 surges where thrombolysis would cause more harm than benefit. STEMI-mimicking diagnoses were increasingly reported in the COVID-19 experiences.[29,30] The rate of STEMI diagnoses found to have non-obstructive coronary arteries in subsequent angiograms (thus excluding type 1 MI) reached 39.3% in a case series published from Northern Italy during the first COVID-19 peak.[7] In addition, presentations of type 2 MI, which is possibly precipitated by hypoxemia, fever, intense systemic inflammation and tachycardia were frequently encountered among COVID-19 critically ill patients.[4,29] In such cases, thrombolysis would lead to pure harm devoid of any potential benefits, compared to the standard angiography-guided management.

Moreover, considering the high rate of thrombolysis failure mandating subsequent transfer for rescue PCI, thrombolysis-based strategies compared to the default immediate transfer for pPCI, lead to prolonged ischemic time, worsening patients' outcomes, increasing patients' morbidity and mortality and hospital stays and costs, while failing the expectations to preserve PPE and minimize medical team exposure. Accordingly, consensus statements released by the Society for Cardiovascular Angiography and Interventions (SCAI) and the American College of Cardiology (ACC) ensured that the priority of pPCI over thrombolysis should not be interchanged during the COVID-19 pandemic.[30,31]

Higher rates of stent thrombosis

In our COVID-era STEMI group, we encountered a higher-than-usual rate of type 4b MI, (proved by angiography to be due to stent thrombosis (ST)) compared to their corresponding control (16% vs. 3%, p = 0.001). All our five ST cases were >6 months post-PCI (3 had very late ST, and 2 had late ST), and none of them prematurely discontinued the P_2Y_{12} inhibitor therapy. Higher rates of ST were increasingly reported during the COVID-19 waves, despite not all of these cases having confirmed SARS-CoV-2 infections.[10,32] A report published amid the COVID-19 crisis stated that rates of ST reached up to 13% of the PCI workload, compared to a traditional annual rate of late and very late ST ranging between 0.2-to-2%.[10]

SARS-CoV-2-related thrombogenicity

Higher rates of thrombolysis failure, stent thrombosis, and large thrombus burden were repeatedly reported during COVID-19 surges and significantly exceeded the numbers of SARS-CoV-2 positive cases in the corresponding cohorts.[6,10,26,27] It should be suspected that such a consistent increase compared to conventional rates, is correlated to a hypercoagulable status common with -and perhaps persisting for some time after- SARS-CoV-2 infections. The high rate of asymptomatic SARS-CoV-2 infections and the growing evidence of late sequelae in recovered cases (i.e. after becoming PCR negative), can explain the discrepancy between the prevalent hypercoagulable manifestations "presumably related to COVID-19", as opposed to the fewer numbers of PCR-confirmed SARS-CoV-2 infections.[13,33]

SARS-CoV-2 infection has been affirmed as a systemic condition involving multiple organs rather than a simple respiratory viral illness.[34–36] Enhanced thrombogenicity is believed to play an important role in the pathogenesis of COVID-19 systemic inflammation and complications. Frequently, microthrombi were found disseminated in multiple organs (including the heart, liver, kidney besides lungs) in autopsies of COVID-19 mortalities suggesting a mechanistic role in disease fatality.[37,38]

The full pathogenesis of COVID-19-related enhanced thrombogenicity is not very clear, yet there are plenty of potentially involved pathways that are supported by clinical and/or lab findings. Direct viral invasion of the endothelial cells through the angiotensin-converting enzyme (ACE) receptors resulted in profound endothelial dysfunction and promoted cell damage, inflammation, and thrombosis.[39,40] In another report, SARS-CoV-2 RNA was detected in platelets of advanced COVID-19 cases, with proven hyperactive aggregation and adhesion functions of the infected platelets.[41] Additionally, the manifest systemic inflammation seen in COVID-19 cases, with a perceived procoagulant role of the cytokine storm has overwhelming evidence to support it. .[42–44] The SARS-CoV-2-associated overstimulation of Interleukin-6, other inflammatory mediators, and cytokines, was proportionally correlated to higher levels of fibrinogen in critically ill COVID-19 cases.[42] Moreover, these patients were consistently found to have abnormally high levels of other procoagulant factors (D-Dimer and factor VIII), paralleled with downregulation of natural anti-coagulants (including protein C, protein S, and antithrombin).[42–44] Lastly, the direct effect of inflammatory cytokines on atherosclerotic plaques can mediate local plaque destabilization and rupture with subsequent acute thrombotic occlusion. This theory is highly incriminated in SARS-CoV-2 linkage to promoting acute peripheral arterial ischemia, cerebrovascular accidents, and myocardial infarctions.[40,45] Thus, SARS-CoV-2-related procoagulant influence is ascertained, and it can explain the enhanced thrombogenicity, and subsequently, the reduced likelihood of successful lysis seen during COVID-19 surges.

Implications of the Contemporary Challenges

Admitting the contemporary threats of new or recurring crises by the emerging new variants, it might be wise for cardiologists to exert every effort to keep pPCI the default reperfusion strategy for STEMI (if it can be offered in a timely fashion), as the expected benefits from prioritizing "on-site thrombolysis" are plagued by high failure rate coupled with a non-justifiable excess bleeding risk for the

patients. Further studies are needed to evaluate if it might be wise to be more in favor of prolonging dual antiplatelet therapy in patients with previous PCI and high ischemic risk amid COVID-19 surges.

Limitations

This is a single-center study with a relatively small number of patients which represents one of the limitations in our study. The retrospective nature of the analysis represents another limitation. We admit the imprecise identification of the number of PCR-confirmed SARS-CoV-2 infections, due to the unemployment of routine PCR testing for all STEMI patients in our center by the earlier times of the pandemic. However, the common hypercoagulable manifestations during SARS-CoV-2 surges were consistently more prevalent than the number of confirmed cases, possibly explained by undiagnosed asymptomatic cases and/or because of late sequelae in recovered cases. Comparing rates of angiography-confirmed stent thrombosis involving all the STEMI patients during the pre-COVID era versus only the referred STEMI cases during the COVID-era (excluding the 6 medically managed cases) is another limitation in our study; however, we assume it would not defy the derived conclusion.

Conclusions

COVID-19 infections have been tied to systemic inflammation with a secondary prothrombotic status. During COVID-19 surges, prothrombotic manifestations are disproportionately more prevalent than the numbers of confirmed infections, possibly because of the high rates of undiagnosed asymptomatic cases or as late sequelae in recovered cases. The enhanced thrombogenicity witnessed amid COVID-19 surges perhaps promotes late and very late stent thrombosis and reduced success of thrombolytic reperfusion. Anticipating recurrent overwhelming waves with the emergence of SARS-CoV-2 new variants, it is very prudent to explore learning points from prior COVID-19 experiences to improve our management strategies.

Declarations

Ethics approval and consent to participate: Aswan Heart Center local institutional ethical committee approved this work.
Reference: Executive manager of Aswan Heart Center, Magdy Yacoub Foundation.
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Patients' consenting to participation: Weaved by virtue of the retrospective nature and full anonymization of personal information.
Consent for publication: Waived considering observational and retrospective nature.
Availability of data and material: Data can be provided (anonymized) upon need.
Competing interests: N/A.
Conflict of interest statement:
The authors declare no conflicts of interest.

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