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Original Article

The safety of deferred coronary angiography in COVID-19 patients with acute coronary syndrome: the Barts COVID recovered pathway

Zhi Teoh[1*], Krishnaraj S Rathod[1,2*], Katrina Comer[1], Angelos Tyrlis[1], Fizzah A Choudry[1], Mick Ozkor[1], R Andrew Archbold[1], Oliver Guttmann[1], Andrew Wragg[1], Andreas Baumbach[1,2], Ajay K Jain[1], Anthony Mathur[1,2], Daniel A Jones[1,2]

[1]Barts Intervention Group, Interventional Cardiology, Barts Heart Centre, St. Bartholomew's Hospital, West Smithfield, London, EC1A 7BE, UK; [2]Centre for Cardiovascular Medicine and Devices, William Harvey Research Institute, Queen Mary University of London, London, UK. [*]Equal contributors.

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Abstract: Objective: To assess the safety and effectiveness of a novel pathway of deferrred invasive angiography in low-risk NSTEMI patients with concurrent COVID-19 infections; contrary to current UK guidelines recommending invasive coronary angiography in NSTEMI patients within 72 hours. Methods: This was a single-centre, observational study of all NSTEMI patients referred for inpatient coronary angiography at Barts Heart Centre, between March 2020 and June 2022. Demographic, procedural and outcome data were collected as part of a national cardiac audit. Results: 201 COVID positive NSTEMI patients were referred for angiography at Barts Heart Centre. 10 patients died from COVID related respiratory complications prior to angiography. Therefore, 191 patients underwent deferred angiography (median time 16 days from COVID diagnosis). The median GRACE score was 128 (IQR 86-153). Troponin levels were significantly elevated on initial COVID diagnosis compared to time of their procedure. 73% patients had a culprit lesion identified. 61.2% receiving PCI. Patients were followed-up for a median of 363 days (IQR 120-485 days) with MACE rates of 7.3%. This is comparable to the MACE event for NSTEMI patients (n=4529) without COVID at our institution treated during the same time-period (8.1%). Conclusion: This study demonstrates the safety and effectiveness of deferred coronary angiography on a COVID-Recovered pathway after a period of medical management for patients presenting with NSTEMI and concurrent COVID-19 infection. There was no adverse signal associated with the wait for angiography with similar MACE rates to the non-deferred NSTEMI cohort without COVID-19.

Keywords: Coronavirus-19, deferred angiography, non-ST elevation MI

Introduction

Indication for invasive coronary angiography in NSTEMI patients

All major clinical practice guidelines e.g. GIRFT, ESC, ACC/AHA [1-3] recommend early invasive coronary angiography for patients presenting with non-ST elevation myocardial infarction (NSTEMI). In acute coronary syndrome (ACS) patients, there is clear evidence of reduced rates of cardiac events from routine angiography-guided management compared with routine conservative or selective invasive management [4-6]. The optimal management strategy for patients with NSTEMI with concurrent coronavirus disease 2019 (COVID-19) infection, however, is not known.

COVID-19 infection and increased thrombogenicity

Infection with severe acute respiratory syndrome coronavirus-2 (SARS-COV-2), the causative virus for COVID-19, is associated with increased platelet aggregation and the release of inflammatory cytokines and pro-coagulant factors, resulting in a pro-thrombotic state. The incidence of thrombotic complications in patients with COVID-19 is up to 43% [7, 8].

COVID-19 and increased stent thrombosis

Importantly, percutaneous coronary intervention (PCI) in ACS (ST-Elevation myocardial infarction (STEMI) and NSTEMI) patients with COVID-19 is associated with worse outcomes than in

non-infected patients, with reported higher rates of in-hospital mortality [9, 10]. There are further reports of increased rates of stent thrombosis in COVID-19 patients undergoing primary PCI [11-14], with one large multi-centre cohort study, showing COVID-19 infection was independently associated with a five-fold increase in the rate of stent thrombosis [9].

Furthermore, infection prevention and control protocols in COVID-19 infected patients with NSTEMI delay invasive management beyond the recommended timeframe and are inefficient for the wider healthcare system.

The COVID recovered pathway

In response, we developed a regional clinical pathway for the delivery of deferred, early outpatient, coronary angiography in stabilised patients with NSTEMI who had concurrent COVID-19 infection "The COVID Recovered Pathway" with the aim of balancing these considerations in patient management.

Our aim was to assess the safety and effectiveness of patients put on this novel pathway. In this paper, we present the demographics, procedural information and outcomes for this novel pathway.

Methods

Inclusion criteria

We performed a single-centre observational cohort study of all NSTEMI patients referred for inpatient coronary angiography at Barts Heart Centre, a regional heart attack centre in London, between March 2020 and June 2022.

The diagnosis of NSTEMI was based on the universal definition of acute myocardial infarction and required symptoms and/or ECG changes without ST elevation coupled with elevation in plasma cardiac biomarker concentrations consistent with acute myocardial injury.

All patients were screened for SARS-CoV-2 on hospital admission by nasal/throat swab using real time-polymerase chain reaction and plasma antibody testing.

Patients with a diagnosis of NSTEMI who tested positive for COVID-19 were entered onto the COVID Recovered pathway.

Exclusion criteria

Patients presenting with ST-elevation myocardial infarction (STEMI), those who did not fulfil the universal definition for diagnosis of NSTEMI and those with chronic coronary syndrome (CCS) were excluded from the study. Also excluded were NSTEMI patients with very high risk features warranting immediate invasive angiography such as haemodynamic instability, cardiogenic shock, refractory chest pain despite maximal medical treatment, life-threatening arrhythmias, mechanical complications of myocardial infarction(MI), acute heart failure clearly related to their NSTEMI, ST-segment elevation in aVR with ST-depression >1 mm/6 leads.

Patients with contraindications to invasive coronary angiography i.e. active GI haemorrhage, pregnancy, acute stroke, hypertensive crisis, inability for patient cooperation and severe contrast allergy were also excluded from our study.

NSTEMI patients who were negative on COVID-19 screening were entered into a control cohort.

COVID-19 recovered pathway

This involved patients undergoing coronary angiography with follow-on PCI, if indicated, at least 10 days after the positive COVID-19 diagnosis. This time period was measured from the time-point of positive COVID-19 serology confirmation not symptoms. Patients were discharged for outpatient angiography unless there was evidence of further myocardial ischaemia during the index hospital admission. In the absence of contraindications, patients were treated with standard medical therapy which included aspirin, a P2Y12 inhibitor, high-intensity statin therapy, a beta-blocker, and an ACE-inhibitor. Patients were then followed up via outpatient pathways (30 day, 6 and 12 month review).

Ethics

The COVID Recovered Pathway was registered as a clinical audit with the Barts Quality and Safety Board. The study protocols were approved by the Barts Heart Centre Board and conformed to the ethical guidelines of the

1975 Declaration of Helsinki. All data was anonymized with removal of patient identifiers prior to analysis.

Data collection

Demographic and procedural data were collected prospectively as part of the National Cardiac Audit Programme. All patient-identifiable fields were removed. Formal ethical approval for this study was, therefore, not required. The national audit data fields include patient age, sex, ethnicity, height, weight, cardiovascular risk factors, time of symptom onset, and time of arrival at the invasive cardiac centre. Procedural data collected comprised number of diseased vessels, use of diagnostic devices such as intravascular ultrasound (IVUS), optical coherence tomography (OCT) or pressure wire and, where relevant, target vessel, use of aspiration thrombectomy, post-dilatation, and administration of a glycoprotein (GP) IIb/IIIa inhibitor.

Interventional procedures

For patients who underwent PCI, the interventional strategy was at the discretion of the operator, including the use of direct stenting, pre- and/or post-dilatation, and treatment of bystander, non-infarct related coronary artery stenoses. All patients undergoing PCI received a loading dose of aspirin 300 mg and either clopidogrel 600 mg or ticagrelor 180 mg prior to the procedure. All patients then received regular aspirin 75 mg per day and either clopidogrel 75 mg per day or ticagrelor 90 mg twice-daily or converted to Prasugrel 10 mg od (after reloading maintenance therapy). During PCI, unfractionated heparin was given at a loading dose of 70-100 U/kg with the ACT maintained >250 sec as per unit policy. ACTs were recorded at 10-15 minute intervals after the initial dose of heparin. GP IIb/IIIa inhibitors were used at the operator's discretion and according to local guidelines.

Study outcomes

The primary outcome was 12-month rate of major adverse cardiovascular events (MACE) consisting of a composite of all cause death, non-fatal stroke, non-fatal myocardial infarction or urgent myocardial revascularization. Follow-up began upon discharge after coronary angiography, however events following the index hospitalization for patients on the Recovered pathway were captured, documenting events which may have occurred prior to deferred coronary angiography. Clinical events during follow-up were assessed from electronic hospital and general practitioner records and from patients during structured virtual follow-up visits. Secondary outcomes included stent thrombosis, and the individual components of MACE, admission for decompensated heart failure, and any peri-procedural complication.

Statistical analysis

Comparisons were performed between the COVID-positive NSTEMI patients who underwent deferred coronary angiography on the COVID Recovered pathway and all other patients who underwent coronary angiography for NSTEMI over the same time-period (March 2020-June 2022). This control group consisted of 4,529 patients, all of whom were COVID-negative. Baseline clinical characteristics, angiographic findings, diagnosis, management, and 12-month MACE rates were compared between groups. Chi-squared analysis or Fisher's-exact test was used to compare categorical data between groups. The independent samples Student t-test or ANOVA test was used to compare normally distributed continuous data and the Mann-Whitney U test was used to compare skewed continuous data between groups. Kaplan-Meier curves were constructed for MACE during 12-month follow-up. Descriptive statistical analyses were performed using SPSS Statistics version 25.0 (IBM, New York). A 2-sided p-value <0.05 defined statistical significance. Variables are expressed as counts (percentages), mean ± standard deviation (SD), and median (lower quartile-upper quartile), as appropriate.

Results

During the study period, 4,730 patients with NSTEMI were referred for early invasive coronary angiography. Of these, 201 (4.2%) had concurrent COVID-19 infection at the point of referral and were treated on the COVID Recovered pathway. Ten patients died from COVID-19 related respiratory complications prior to discharge from their index hospitalisations. All these patients died from COVID-19 related respiratory complications.

Table 1. Baseline patient characteristics

	Recovered (n=191)	Control cohort- (n=4529)	*P* value
Baseline Characteristics			
Age (Mean ± SD)	63 yr ± 12.0	69.1 ± 11.5	0.0012
Male sex - no. (%)	74.9% (143/191)	67.1% (3039/4529)	<0.0001
Black, Asian, Minority Ethnic - no. (%)	52.9% (101/191)	35.6% (1612/4529)	<0.0001
Median BMI (IQR)	27.4 (24.7:31.1)	28.0 (26.1:29.9)	0.058
Past Medical History - no. (%)			
Hypertension	60.2% (115/191)	56.1% (2541/4529)	<0.0001
Hypercholesterolemia	64.9% (124/191)	40.7% (1843/4529)	<0.0001
Diabetes mellitus	40.8% (78/191)	36.4% (1649/4529)	0.0013
Smoking history	44.0% (84/191)	25.3% (1146/4529)	<0.0001
Previous MI	44.0% (84/191)	33.6% (1522/4529)	<0.0001
Previous PCI	37.2% (71/191)	27.4% (1241/4529)	<0.0001
Median GRACE score	128 (86:153)	135 (105:169)	0.106
Median laboratory values (IQR)- at time of procedure			
Troponin T - ng/L (initial COVID diagnosis/referral)	111.5 (54:455)	135 (64:745)	<0.0001
Troponin T - ng/L (at time of procedure)	27 (16:151)	NA	
White-cell count - 10^9/L	8.3 (6.9:10.2)	7.5 (5.8:9.2)	0.077
Lymphocyte count - 10^9/L	1.8 (1.4:2.3)	2.1 (1.7:2.6)	0.069
LDH - unit/L	229 (199:250)	145 (124:223)	0.053
D-Dimer - mg/L (0-0.5)	0.3 (0.3:0.7)	0.2 (0.1:0.4)	0.112
Fibrinogen - g/L	1.65 (0.55:5.04)	1.41 (1.02:2.69)	0.104
Ferritin - ug/L (30-400)	202 (84:263)	189 (131:287)	0.005
Creatinine - umol/L	81 (69:98)	77 (70:88)	0.230
Creatine kinase (CK) - u/L	85 (58:130)	81 (68:113)	0.398
C-reactive protein (CRP) - mg/L	4 (2:8)	3 (1:5)	0.276

Patient characteristics

The baseline clinical characteristics of the remaining 191 COVID-positive patients who entered the COVID recovered pathway are presented in **Table 1**. The mean age was 63 years, 143 (75%) were male and 90 (47%) were Caucasian. The median GRACE score was 128 (IQR 86-153). Compared to the COVID-negative NSTEMI control group, patients on the COVID Recovered pathway were less likely to be Caucasian (P<0.0001), were more often male (P<0.0001), and had more cardiovascular risk factors (P=0.0013). GRACE scores were similar in the two groups. The median peak plasma troponin concentration was significantly lower in patients on the Recovered pathway than in controls. At the time of coronary angiography, there were no significant differences between COVID-positive patients and controls in WCC, ferritin, or d-dimer concentrations.

Procedural characteristics

Patients on the Recovered pathway underwent coronary angiography a median of 16 (interquartile range 12-19) days after COVID-19 diagnosis. 10% remained as inpatients based on high-risk features with 90% being discharged prior to angiography. No patients suffered adverse events whilst waiting for angiography.

In one patient, arterial access could not be obtained so computed tomography coronary angiography was performed instead.

Final clinical diagnosis

Among the 191 patients in this group, 139 (73%) were confirmed to have acute coronary syndrome by invasive angiography with culprit coronary disease identified (**Table 2**). The remaining 52 (27%) patients were diagnosed with myocardial infarction with non-obstructive

Table 2. Outcomes

	Recovered (n-191)	Control Cohort (n=4529)	*P* value
Time for follow-up, median (IQR) - days	363 (120-485)	366 (131-463)	0.479
Median COVID-diagnosis to angiography (IQR) - days	16 (12:19)	NA	
Final Clinical Diagnosis - no. (%)			
Acute coronary syndrome	73.0% (139/191)	82.5% (3736/4529)	0.0065
MINOCA	27.0% (52/191)	13.1% (594/4529)	<0.0001
Myocarditis	11.5% (22/191)	4.9% (222/4529)	
Takotsubo	5.7% (11/191)	2.2% (100/4529)	
Unknown	9.9% (19/191)	6.0% (272/4529)	
Percutaneous coronary intervention - no. (%)	61.2% (117/191)	70.9% (3211/4529)	<0.0001
Coronary Artery Bypass Grafting - no. (%)	11.0% (21/191)	10.8% (489/4529)	0.103
Medical management - no. (%)	27.8% (54/191)	18.3% (829/4529)	<0.0001
IVUS Use	37.2% (71/191)	26.4% (1196/4529)	<0.0001
OCT Use	13.6% (26/191)	8.8% (399/4529)	<0.0001
Pressure Wire	3.1% (6/191)	5.6% (254/4529)	<0.0001
PCI vessel			<0.0001
LMS	1.6% (3/191)	1.0% (47/4529)	
LAD	27.7% (53/191)	26.6% (1205/4529)	
Cx	9.9% (19/191)	10.1% (457/4529)	
IM	1.0% (2/191)	2.9% (131/4529)	
RCA	9.9% (19/191)	12.3% (557/4529)	
Venous graft	3.1% (6/191)	2.9% (131/4529)	
Single anti-platelet	4.2% (8/191)	3.9% (177/4529)	0.003
NOAC only	5.2% (10/191)	3.6% (163/4529)	<0.0001
Warfarin only	1.0% (2/191)	1.0% (47/4529)	0.995
NOAC + single antiplatelet	2.1% (4/191)	1.1% (50/4529	0.698
DAPT	77.0% (147/191)	86.5% (3918/4529)	<0.0001
Triple therapy	7.9% (15/191)	4.8% (217/4529)	<0.0001
No anti-platelets/anti-coagulation	3.1% (6/191)	2.1% (95/4529)	0.466
Stent thrombosis (in PCI patients) - no. (%)	0.0%	0.11% (5/4529)	

coronary artery disease (MINOCA). Subsequent cardiac magnetic resonance imaging (MRI) suggested myocarditis in 22 (11.5%) of these patients and takotsubo cardiomyopathy in 11 patients (5.7%). Of those with confirmed NSTEMI, 117 (61.2%) underwent PCI, 21 (11%) underwent coronary artery bypass grafting (CABG), and 54 (28%) patients were managed medically. Most (77%) patients were discharged taking dual anti-platelet therapy (DAPT), 8% patients were treated with triple anti-thrombotic therapy (aspirin, clopidogrel and a novel oral anticoagulant) and in 3% of patients, all anti-thrombotic agents were stopped after coronary angiography. Patients on the COVID Recovered pathway were more likely to receive a final diagnosis of MINOCA compared to the NSTEMI control group. Consequently, they were less likely to undergo PCI and to receive DAPT.

Clinical outcomes

In-hospital outcomes: Among the patients who underwent deferred coronary angiography on the Recovered pathway, three (1.6%) patients developed MACE; one patient developed a cerebrovascular event after coronary angiography, one patient was referred for CABG but suffered a myocardial infarction (0.5% event rate) before surgery could be performed, and one patient died (0.5% event rate) from heart failure. In addition, one patient developed a retroperitoneal bleed after follow-on transfemoral PCI.

Table 3. 12-month clinical outcomes

	Recovered (n=191)	Control Cohort (n=4529)
Major adverse cardiovascular events	14 (7.3%)	367 (8.1%)
Cardiovascular death	2 (1.0%)	68 (1.5%)
Non-Cardiovascular Death	2 (1.0%)	70 (1.5%)
Unscheduled revascularisation	3 (1.6%)	115 (2.5%)
Cerebrovascular Accident (CVA)	2 (1.0%)	47 (1.0%)
Myocardial infarction	5 (2.6%)	114 (2.5%)
Stent thrombosis (in PCI patients)	0 (0.0%)	5 (0.16%)

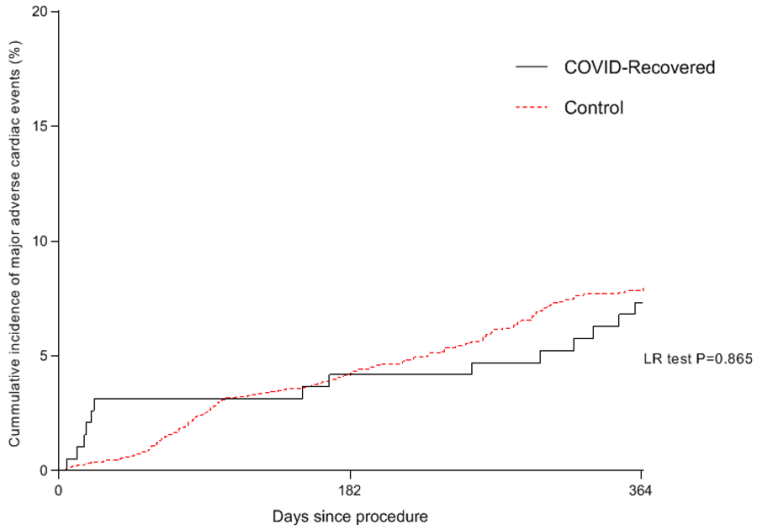

Figure 1. Kaplan-Meier curves of cumulative incidence of major adverse cardiovascular events over 1 year in COVID-recovered arm compared to control arm.

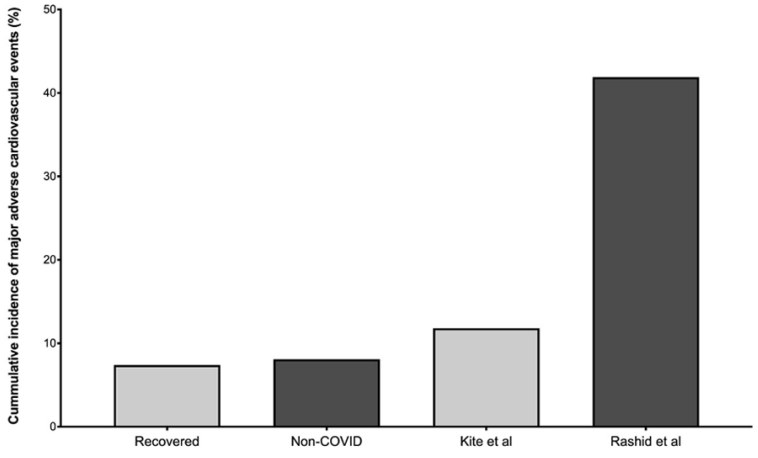

Figure 2. 12-month major adverse cardiovascular event rates in COVID-recovered versus non-COVID and compared to the current literature.

12-month outcomes: Patients were followed-up for a median of 363 (IQR 120-485) days. The combined primary outcome occurred in 14 patients in the COVID Recovered group, equating to a 12-month MACE rate of 7.3% (95% CI 2.8-10.2%) (**Table 3**). The individual components of MACE comprised 4 deaths (2 cardiovascular and 2 non-cardiovascular deaths), 5 NSTEMIs, 2 CVAs and 3 patients cases of urgent revascularisation for unstable angina. This is comparable to the MACE rate for the control NSTEMI patient population treated at our institution during the same time period (8.1% (95% CI 3-9.1%)) (**Figure 1**) and the literature [15, 16] (**Figure 2**). Secondary outcomes were made up of two non-cardiovascular deaths and two admissions for decompensated heart failure. There were no cases of stent thrombosis.

Discussion

This study is the first to assess the safety and effectiveness of a deferred coronary angiography pathway (COVID Recovered) in patients with NSTEMI and COVID-19 infection. Among 191 patients, deferred coronary angiography after a period of medical management was associated with equivalent 12-month clinical outcomes to patients without COVID-19 who underwent inpatient coronary angiography. The approach to patients with ACS and concurrent COVID-19 infection has varied from hospital to hospital throughout the world because of uncertainties regarding the benefits of early invasive management in patients with COVID-19, the risks of viral transmission to staff and other patients, the inefficiencies of individual patients waiting in hospital for procedures, and the knock-on effect of this on the scarce resource of bed availability during the pandem-

ic. The results of this study provide reassurance that initial medical stabilisation of patients with NSTEMI and COVID-19 infection with a view to outpatient coronary angiography 2-3 weeks later is a safe alternative to extended hospitalisation while infection prevention and control protocols are completed prior to invasive management.

The latest ESC guidelines recommend early invasive coronary angiography in patients with an established diagnosis of NSTEMI [1, 2]. However, in patients with concurrent COVID-19 infection that is associated with a pro-thrombotic state. Several studies reporting thrombotic complications in patients with severe COVID-19 found thrombotic rates ranging from 31% to 43% [7, 8]. Therefore, it is no surprise that invasive angioplasty is likely to carry significant more risks in patients with active COVID-19 patients. In patients with COVID-19 undergoing PCI for ST-elevation myocardial infarction (STEMI), stent thrombosis rates have been reported as high as 8.1% and in-hospital mortality up to 12.9% [9, 10]. One large, multi-centred retrospective cohort study, COVID-19 infection was independently associated with 5x increased risk of in-stent thrombosis [9].

Most previous studies of COVID-19 positive patients with ACS have focused on STEMI, with a relative lack of data concerning management of patients with NSTEMI. Data from two registries, however, both raise safety concerns regarding the early invasive management of patients with NSTEMI who have concurrent COVID-19 infection. In the International COVID-ACS Registry, in-hospital mortality rates were more than four-fold higher (6.6% vs. 1.2%; P<0.001) in 121 NSTEMI patients with COVID compared with a pre-pandemic NSTE-ACS cohort. In-hospital rates of MI and stroke of 4.1% and 0.8%, respectively, contributed to an in-hospital MACE rate of 11.5% in COVID-positive patients [15]. In the UK MINAP registry, 517 (4.0%) of 12,958 patients hospitalised with ACS were COVID-19-positive. These patients had considerably higher rates of in-hospital (24.2% vs. 5.1%) and 30-day mortality (41.9% vs. 7.2%) compared with non-COVID-19 ACS patients, with the highest rates seen at 30 days in the NSTEMI cohort (adjusted OR 8.45; 95% CI: 6.03-11.83) [16]. In our study, there were four deaths (two cardiovascular and two non-cardiovascular) among the 191 patients in the deferred coronary angiography group equivalent to a 2.1% 12-month mortality rate.

Although the benefit of immediate coronary angiography is established in patients presenting with STEMI, the timing and net benefit of immediate angiography is not so clear cut in patients with NSTEMI. Several large studies [17, 18] have failed to demonstrate a significant reduction in all-cause mortality or non-fatal MI for immediate (<24 hours) vs. deferred angiography (>36 hours) in the overall NSTEMI population. In the TIMACS trial, early invasive angiography have been shown to be beneficial in high-risk NSTEMI populations(defined by a GRACE score >140) as shown by the separation of the Kaplan-Meier curves for all-cause death, non-fatal MI or stroke, but not in the low-intermediate group [18]. Furthermore, the median time from randomization to angiography in the deferred angiography group was 50 hours. There have been no studies so far where NSTEMI patients had deferred angiography after at least 10 days (median 16 days).

The more recent VERDICT trial showed similar findings with a reduction in the primary composite outcome (comprising of all-cause death, non-fatal recurrent MI, hospital admission for refractory myocardial ischaemia or hospital admission for heart failure) for high risk NSTEMI (GRACE score >140) patients undergoing immediate angiography (within 12 hours of diagnosis) vs. delayed angiography (48-72 hours of diagnosis) [17].

Given the lack of proven benefit in immediate angiography for low-to-intermediate risk NSTEMI patients, combined with the increased thrombotic risk associated with COVID infection, we felt that it was reasonable to adopt a deferred angiography management strategy in these patients.

So far, there has been no other studies assessing the effect of deferring coronary angiography until recovery from COVID-19 in NSTEMI patients.

Our study has shown that this is safe and efficacious with only 14 (7.3%) out of 191 patients suffering a MACE. There were no deaths attributed to the wait for coronary angiography. There were no cases of stent thrombosis in the COVID-recovered group.

This study has several limitations. Firstly, this is an observational study with the inherent biases and confounders associated with this type of study. Secondly, severe COVID-19 infection may be associated with elevated plasma troponin concentrations due to myocardial injury which is not caused by an ACS, for example, due to myocarditis, sepsis, or pulmonary embolism [19]. Defining a cohort of "pure" NSTEMI is therefore potentially problematic in the context of concurrent COVID infection. Nevertheless, myocardial revascularisation rates were high in the study group and consistent with other NSTEMI cohorts, albeit slightly lower than among our control group. We believe that the diagnosis of NSTEMI was accurate in the majority of patients in our study group, but it is possible that the troponin elevations in a minority were due to causes other than myocardial infarction. This issue is not restricted to NSTEMI populations with concurrent COVID infection.

Conclusion

This study has demonstrated that deferring invasive coronary angiography for 2-3 weeks via a COVID 'Recovery pathway' is safe in stable NSTEMI patients who have concurrent COVID infection. These data have potential implications for the management of NSTEMI patients with COVID-19, providing an alternative to routine early invasive management with the potential to improve outcomes in this group of patients.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Daniel A Jones, Department of Cardiology, Barts Heart Centre, St. Bartholomew's Hospital, West Smithfield, London, EC1A 7BE, UK. E-mail: dan.jones8@nhs.net

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