

International Prospective Registry of Acute Coronary Syndromes in Patients With COVID-19



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ABSTRACT

BACKGROUND Published data suggest worse outcomes in acute coronary syndrome (ACS) patients and concurrent coronavirus disease 2019 (COVID-19) infection. Mechanisms remain unclear.

OBJECTIVES The purpose of this study was to report the demographics, angiographic findings, and in-hospital outcomes of COVID-19 ACS patients and compare these with pre-COVID-19 cohorts.

METHODS From March 1, 2020 to July 31, 2020, data from 55 international centers were entered into a prospective, COVID-ACS Registry. Patients were COVID-19 positive (or had a high index of clinical suspicion) and underwent invasive coronary angiography for suspected ACS. Outcomes were in-hospital major cardiovascular events (all-cause mortality, re-myocardial infarction, heart failure, stroke, unplanned revascularization, or stent thrombosis). Results were compared with national pre-COVID-19 databases (MINAP [Myocardial Ischaemia National Audit Project] 2019 and BCIS [British Cardiovascular Intervention Society] 2018 to 2019).

RESULTS In 144 ST-segment elevation myocardial infarction (STEMI) and 121 non-ST-segment elevation acute coronary syndrome (NSTEMI-ACS) patients, symptom-to-admission times were significantly prolonged (COVID-STEMI vs. BCIS: median 339.0 min vs. 173.0 min; $p < 0.001$; COVID NSTEMI-ACS vs. MINAP: 417.0 min vs. 295.0 min; $p = 0.012$). Mortality in COVID-ACS patients was significantly higher than BCIS/MINAP control subjects in both subgroups (COVID-STEMI: 22.9% vs. 5.7%; $p < 0.001$; COVID NSTEMI-ACS: 6.6% vs. 1.2%; $p < 0.001$), which remained following multivariate propensity analysis adjusting for comorbidities (STEMI subgroup odds ratio: 3.33 [95% confidence interval: 2.04 to 5.42]). Cardiogenic shock occurred in 20.1% of COVID-STEMI patients versus 8.7% of BCIS patients ($p < 0.001$).

CONCLUSIONS In this multicenter international registry, COVID-19-positive ACS patients presented later and had increased in-hospital mortality compared with a pre-COVID-19 ACS population. Excessive rates of and mortality from cardiogenic shock were major contributors to the worse outcomes in COVID-19 positive STEMI patients.

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Since its outbreak in Hubei Province, China in December 2019, the novel severe acute respiratory syndrome coronavirus 2 has spread rapidly, resulting in a worldwide pandemic from this multisystem disease (1). The effect on ACS is 2-fold.

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First, viral infections such as influenza have been reported to exacerbate ACS (2). Multiple hypotheses for the higher incidence and greater adverse outcomes in ACS have been proposed, including arterial (macrovascular and microvascular) and venous thrombosis mediated by an endothelial inflammatory response, microvascular dysfunction, sepsis hypoxia, sympathetic nervous system overactivity, and cytokine and possible bradykinin release (3). Indeed, early reports suggest spontaneous thrombus development in the pulmonary and peripheral vasculature (4) and excess coronary thrombus formation may be causes for high mortality rates (5). However, nonobstructed epicardial coronary arteries with microthrombi or cellular inflammatory processes have also been observed (6), as have cases of myocarditis masquerading as ACS (7).

Second, early reports also demonstrated a marked decline in ACS admissions during the coronavirus disease 2019 (COVID-19) pandemic, together with a definite increase in mortality compared with non-COVID ACS patients (8-10). Although the proinflammatory nature of

COVID-19 and its subsequent complex interaction with the cardiovascular system make this an essential area of investigation, many of the clinical findings could be explained by patients' perception of potential harm in attending the hospital (COVID-19 fear). We proposed that the poorer outcomes in COVID-19-positive ACS patients were in part due to the logistical consequences of such understandable concerns.

We therefore established the International COVID-ACS Registry to document the demographic, procedural, and angiographic characteristics and in-hospital clinical outcomes of COVID-19-positive (or high index suspicion) patients admitted with ACS, paying particular attention to delays in standard management. We posited whether there was a link between previously published rates of increased mortality and factors, such as delayed presentation, that could affect adverse outcomes.

METHODS

STUDY DESIGN. The University Hospitals of Leicester (UHL) NHS Trust, in collaboration with the University of Glasgow Clinical Trials Unit, developed an online, web-hosted remote data entry system, allowing colleagues from international centers to prospectively enter anonymized data on patients who met the registry inclusion criteria. After seeking regulatory

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

COVID-19 = coronavirus disease 2019

MI = myocardial infarction

NSTE-ACS = non-ST-segment elevation acute coronary syndrome

N-STEMI = non-ST-segment elevation myocardial infarction

PCI = percutaneous coronary intervention

STEMI = ST-segment elevation myocardial infarction

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

advice from the UHL Clinical Audit Department, the study was registered as a health survey audit. No formal ethical approval was required. Each center entered its own data according to a site-specific user account with no patient identifiable data collected. Data transfer agreements were established between UHL, University of Glasgow, and sites as required. The inclusion criteria for the study were: 1) COVID-19 positive or a high index of clinical suspicion; and 2) invasive coronary angiography undertaken for suspected ACS. High-index clinical suspicion was defined as clinical status plus chest x-ray (CXR) or computed tomography (CT) findings suggestive of COVID-19 infection (11). The study comprised 55 centers located across 5 continents, with data collected from March 1, 2020, to July 31, 2020.

DATA COLLECTION. Patient demographics, including age, sex, and body mass index (BMI), were documented. Users recorded co-morbidities based on the International Classification of Diseases-10th Revision codes, including cardiovascular disease (hypertension, hyperlipidemia, diabetes mellitus, previous myocardial infarction [MI], previous percutaneous coronary intervention [PCI], and congestive cardiac failure), smoking status, and history of lung disease. Procedural and angiographic characteristics were noted, along with requirements for intensive care admission, inotropic/vasopressor support, invasive ventilation, and mechanical support. Timing data including symptom-to-admission, door-to-balloon, and door-to-angiography were also recorded. Symptom onset time was defined as the start of patient-reported cardiovascular symptoms (i.e., chest pain or dyspnea, but not cough or fever). Thrombotic occlusion at the time of angiography was graded using the TIMI (Thrombolysis In Myocardial Infarction) Thrombus Grade Score.

OUTCOMES. The primary endpoint was in-hospital all-cause mortality. Secondary endpoints included in-hospital repeat MI (Fourth Universal Definition of Myocardial Infarction) (12); heart failure, unplanned revascularization, and stroke (2017 Cardiovascular Endpoint Definitions for Clinical Trials Consensus Report) (13); cardiogenic shock (CGS) (systolic blood pressure <90 mm Hg for >30 min with signs of hypoperfusion, or need for inotropes); bleeding (Bleeding Academic Research Consortium criteria) (14); and stent thrombosis (Academic Research Consortium-2 Consensus Document) (15). We also reported total length of hospital stay.

COMPARATIVE GROUPS. COVID-ACS registry patients were subdivided into: 1) ST-segment elevation myocardial infarction (STEMI); and 2) non-ST-

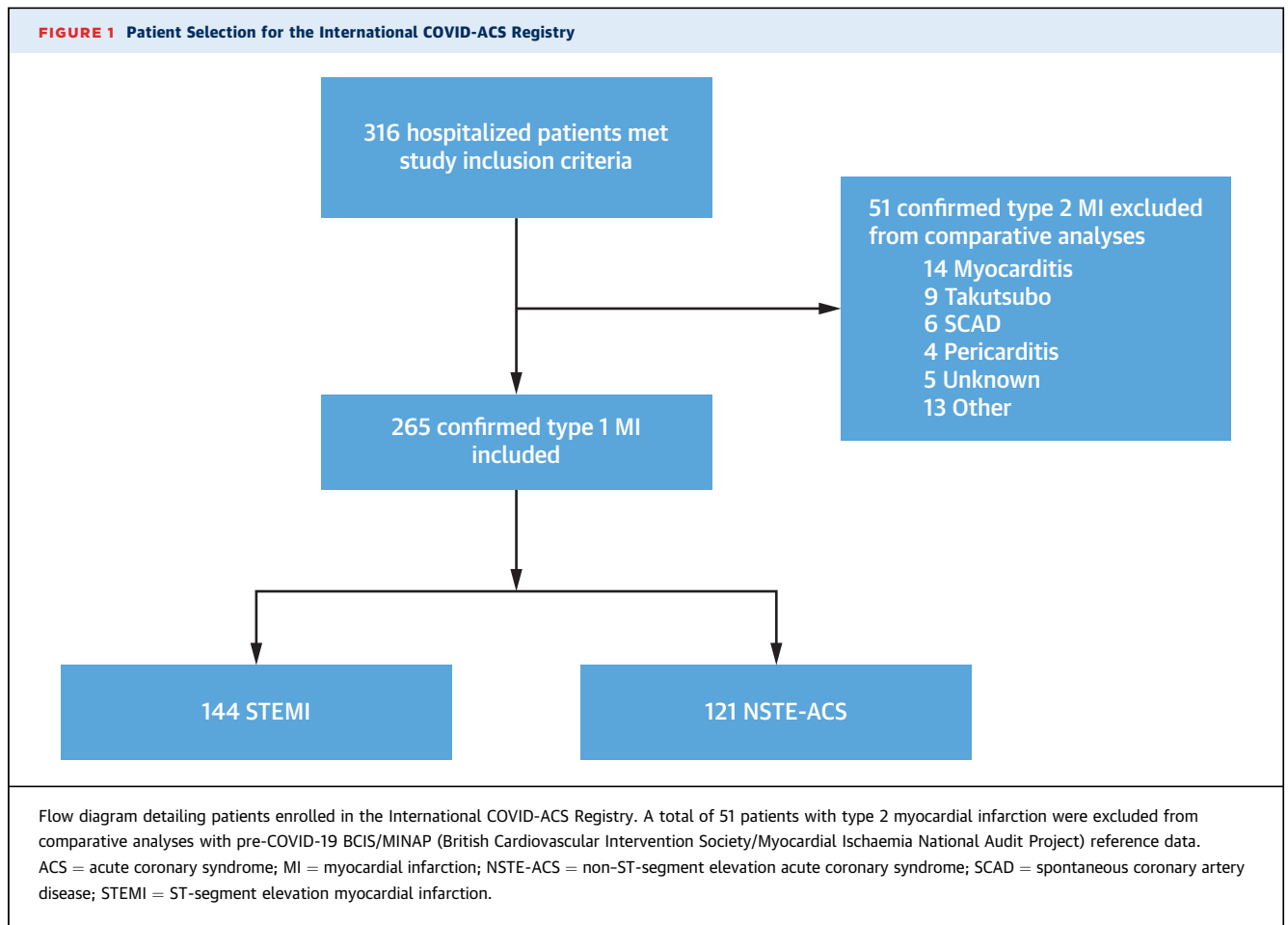
TABLE 1 Baseline Characteristics of Combined STEMI/NSTE-ACS COVID-ACS Registry Cohort (N = 265)*

Mean age, yrs	64.9 ± 12.9
Male	75.5 (200/265)
Hypertension	66.2 (174/263)
Hyperlipidemia	54.1 (131/242)
BMI, kg/m ²	27.5 ± 4.7
Diabetes	36.2 (92/265)
Smoking status	
Current smoker	27.1 (62/229)
Ex-smoker	27.1 (62/229)
Nonsmoker	45.8 (105/229)
Heart failure	19.3 (49/254)
Previous MI	20.2 (57/258)
Previous PCI	17.5 (46/263)
Chronic kidney disease (stages 3-5)	14.6 (38/260)
Lung disease	16.5 (42/254)
Previous stroke	7.2 (19/265)
COVID-19 positive	74.3 (197/265)
COVID-19 high index suspicion	25.7 (68/265)
Killip class III/IV on admission	17.4 (46/265)
Out-of-hospital cardiac arrest	5.3 (14/265)
Admission lactate, mmol/l	4.1 ± 7.3
Admission lactate >2.0 mmol/l	61.7 (58/94)
Presentation symptoms typical of ACS	81.4 (214/263)
Full PPE worn during procedure	90.9 (209/230)

Values are mean ± SD or % (n/N). Denominators not equal to n = 265 are due to incomplete data. *Excludes patients with type 2 myocardial infarction (see Figure 1).

ACS = acute coronary syndrome; BMI = body mass index; COVID-19 = coronavirus disease 2019; MI = myocardial infarction; NSTE-ACS = non-ST-segment elevation acute coronary syndrome; PCI = percutaneous coronary intervention; PPE = personal protective equipment; STEMI = ST-segment elevation myocardial infarction.

segment elevation acute coronary syndrome (NSTE-ACS) (including non-ST-segment elevation myocardial infarction [NSTEMI] and unstable angina). Because a key aim was to investigate possible delays in presentation to hospital and reperfusion therapy, we excluded type 2 MI COVID-ACS registry patients, as clinical outcomes in this group are not influenced by invasive coronary angiography and expeditious revascularization. Comparisons were thus performed between type 1 MI patients from our registry and pre-COVID STEMI and NSTE-ACS data from the U.K.-based British Cardiovascular Intervention Society (BCIS) National PCI Audit (April 1, 2018, to March 31, 2019), and English data from the Myocardial Ischaemia National Audit Project (MINAP) (2019) databases. All patients undergoing an invasive strategy for ACS in the United Kingdom are submitted to these robust and internationally acknowledged databases. The optimal comparative databases were BCIS for the STEMI population and MINAP for the NSTE-ACS population. We chose not to use concurrent COVID-19-negative ACS patients as control



subjects, because we recognized that systems of care were severely disrupted at this time and would not represent the pre-COVID standard. Furthermore, in-hospital events in BCIS and MINAP are similar to other internationally recognized national databases (16,17) and offer a reliable benchmark with which to compare outcomes in the COVID-ACS registry.

STATISTICAL ANALYSES. Descriptive statistics were presented for baseline demographics and characteristics. Frequency and percentage were reported for categorical variables, and mean \pm SD or median (interquartile range) were reported for continuous variables depending on their distributions. To compare the characteristics between the COVID-ACS and MINAP/BCIS datasets, Fisher exact test or chi-square tests were performed for categorical variables, and Student's *t*-test or Mann-Whitney *U* tests were used for continuous variables according to their distributions. To account for confounding factors and balance any differences in patient characteristics between the COVID-STEMI cohort and the BCIS STEMI database, a propensity score was derived using

logistic regression to predict whether patients were from COVID-ACS or BCIS, including age, sex, hypertension, hyperlipidemia, and diabetes. A propensity score-based inverse probability treatment weights method was then used to calculate the difference in mortality between patients recorded in the COVID-STEMI subgroup and BCIS STEMI databases, further adjusted for CGS status and ischemia time. A propensity score was not derived to compare NSTEMI-ACS cohorts due to the low number of clinical events observed in the registry subgroup.

RESULTS

In total, 316 hospitalized patients from 55 international centers across 5 continents were included: 238 (75.3%) from Europe, 35 (11.1%) from South America, 21 (6.6%) from Asia, 15 (4.7%) from Africa, and 7 (2.2%) from North America (Supplemental Table 1). Demographic variables and comorbidities for the combined STEMI/NSTEMI-ACS cohort are shown in Table 1.

TABLE 2 Baseline Demographics/Procedural Characteristics of COVID-STEMI and BCIS STEMI Subgroups

	COVID-STEMI Total (n = 144)	BCIS 2018-2019 (n = 24,961)	p Value
Mean age, yrs	63.1 ± 12.6	65.6 ± 13.4	0.018
Male	77.8 (112/144)	72.2 (17,972/24,961)	0.14
Hypertension	64.8 (92/142)	44.8 (9,456/24,961)	<0.001
Hyperlipidemia	46.0 (58/126)	28.9 (6,039/24,961)	<0.001
BMI, kg/m ²	27.3 ± 4.5	27.8 ± 5.5	0.18
Diabetes	34.0 (49/144)	20.9 (4,926/24,961)	<0.001
Current smoker	31.7 (39/123)	33.7 (7,645/24,961)	0.77
Heart failure	19.0 (27/142)	2.8 (569/24,961)	<0.001
Previous MI	16.4 (23/140)	13.0 (2747/24,961)	0.056
Previous PCI	13.9 (20/144)	10.2 (2,129/24,961)	0.034
Chronic kidney disease (stage 3-5)	9.9 (14/141)	3.6 (739/24,961)	<0.001
Lung disease	11.8 (16/135)	13.4 (2,763/24,961)	0.78
Stroke	7.6 (11/144)	5.7 (1,178/24,961)	0.11
COVID-19 positive	76.4 (110/144)	N/A	
COVID-19 suspected	23.6 (34/144)	N/A	
SBP at admission, mm Hg	119.5 ± 26.8	131.9 ± 27.5	<0.001
Heart rate at admission, beats/min	86.0 ± 22.0	78.5 ± 20.1	<0.001
Troponin T, ng/l	2224.0 (58.0-7,449.5)	899.0 (100.0-3,745.0)	0.15
Troponin I, ng/l	762.0 (50.0-23,037.0)	61.4 (14.6-1,118.4)	0.19
LVEF, %	39.7 ± 12.5	N/A	
Procedure			
Symptom onset to admission, min	339.0 (175.0-1,481.5)	173.0 (107.0-387.0)	<0.001
Door-to-balloon time, min	83.0 (37.0-336.0)	37.0 (31.0-109.0)	<0.001
Transradial access	74.3 (107/144)	87.4 (19,611/22,442)	<0.001
Nonobstructive CAD	2.8 (4/144)	N/A	
SYNTAX score	16.5 ± 9.1	N/A	
Thrombotic occlusion (TIMI grade 5)	37.5 (54/144)	N/A	
Use of aspiration thrombectomy	12.5 (18/144)	17.1 (3,754/21,915)	0.15
Complete revascularization	45.8 (66/144)	N/A	
Post-procedure			
ICU admission	45.8 (66/144)	N/A	
Ventilation	20.8 (30/144)	3.8 (863/22,442)	<0.001
Pressor support	27.1 (39/144)	4.6 (1,001/21,720)	<0.001
Mechanical support device, %	5.6 (8/144) (ECMO = 3, IABP = 5)	2.1 (459/21,720)	0.012

Values are mean ± SD, % (n/N), or median (interquartile range). Denominators not equal to n = 144 are due to incomplete data. Incomplete timing data was recorded in 9% (13 of 144) of COVID-STEMI patients. **Bold** p values indicate statistical significance.

CAD = coronary artery disease; ECMO = extracorporeal membrane oxygenation; IABP = intra-aortic balloon pump; ICU = intensive care unit; N/A = data unavailable; TIMI = Thrombolysis In Myocardial Infarction; other abbreviations as in [Table 1](#).

BASELINE CHARACTERISTICS. Of the 316 patients, 144 (54.3%) were diagnosed with STEMI and 121 (45.6%) with NSTEMI-ACS. These 2 groups formed the basis of the comparative analyses with MINAP/BCIS data. The study profile is outlined in [Figure 1](#).

The mean age of the STEMI/NSTEMI-ACS combined cohort was 64.9 ± 12.9 years; 75.5% were men; 66.2% had hypertension, 54.1% hyperlipidemia, 36.2% diabetes mellitus, 20.2% a previous MI, 19.3% prior history of heart failure, and 14.6% chronic kidney disease stage 3 to 5; and 27.1% were current smokers.

In total, 74.3% of patients tested positive for COVID-19 infection, with viral polymerase chain

reaction testing used in 98.9% of these cases. An additional 25.7% were defined as COVID-19 suspected (treated as positive despite a negative PCR test) due to a high index of clinical suspicion (clinical status plus CXR or CT findings compatible with COVID-19). On admission, 17.4% of patients were defined as Killip heart failure class III/IV, 61.7% had a serum lactate level >2.0 mmol/l, and 5.3% had experienced an out of hospital cardiac arrest.

Demographics, comorbidities, procedural characteristics, and post-procedural support requirements in the COVID-STEMI subgroup are shown in [Table 2](#). Compared with non-COVID STEMI patients (BCIS

TABLE 3 Baseline Demographics/Procedural Characteristics of COVID NSTEMI-ACS and MINAP NSTEMI-ACS Subgroups

	COVID NSTEMI-ACS Total (n = 121)	MINAP 2019 (n = 46,389)	p Value
Mean age, yrs	66.9 ± 12.9	70.2 ± 13.3	0.005
Male	79.3 (88/111)	65.5 (30,388/46,389)	0.002
Hypertension	68.3 (82/120)	57.8 (24,359/46,389)	<0.001
Hyperlipidemia	62.9 (73/116)	33.6 (13,895/46,389)	<0.001
BMI, kg/m ²	27.8 ± 4.9	28.2 ± 6.0	0.37
Diabetes	38.8 (47/121)	31.1 (14,101/46,389)	0.048
Current smoker	21.7 (23/106)	20.4 (8,834/46,389)	0.46
Heart failure	18.8 (22/117)	9.6 (3,968/46,389)	<0.001
Previous MI	24.6 (29/118)	29.1 (12,181/46,389)	0.75
Previous PCI	21.8 (26/119)	18.7 (7,684/46,389)	0.14
Chronic kidney disease (stage 3-5)	20.2 (24/119)	10.2 (4,214/46,389)	<0.001
Lung disease	21.8 (26/119)	19.2 (7,908/46,389)	0.18
Stroke	6.6 (8/121)	10.0 (4,121/46,389)	0.52
COVID-19 positive	71.9	N/A	
COVID-19 high index suspicion	28.1	N/A	
SBP at admission, mm Hg	122.0 ± 29.2	142.4 ± 27.3	<0.001
Heart rate at admission, beats/min	80.2 ± 18.7	79.6 ± 20.0	0.73
Troponin T, ng/l	60.0 (1.0-288.0)	144.0 (47.0-460.0)	0.37
Troponin I, ng/l	171.0 (39.75-1,279.0)	276.6 (47.1-1,371.4)	0.48
LVEF, %	48.6 ± 13.3	N/A	
Procedure			
Symptom onset to admission, min	417.0 (157.0-2,904.0)	295.0 (130.0-1,021.0)	0.012
Door-to-angiography time, h	48.5 (12.2-132.4)	57.7 (25.1-105.3)	0.49
Transradial access	77.7 (94/121)	88.0 (29,777/33,833)	0.002
Nonobstructive CAD	18.2 (22/121)	N/A	
SYNTAX score	19.3 ± 11.7	N/A	
Thrombotic occlusion (TIMI grade 5)	5.0 (6/121)	N/A	
Use of aspiration thrombectomy	0.0 (0/121)	2.41 (804/33,250)	0.12
Complete revascularization	42.7 (32/75)	N/A	
Post-procedure			
ICU admission	33.9 (41/121)	N/A	
Ventilation	11.6 (14/121)	0.4 (138/33,833)	<0.001
Pressor support	19.0 (23/121)	0.9 (306/32,666)	<0.001
Mechanical support device, %	0.8 (1/121) (IABP = 1)	0.6 (203/32,666)	0.52

Values are mean ± SD, % (n/N), %, or median (interquartile range). Denominators not equal to n = 121 are due to incomplete data. **Bold** p values indicate statistical significance. Abbreviations as in [Tables 1 and 2](#).

cohort), our COVID-STEMI subgroup was younger, with significantly more hypertension, hyperlipidemia, diabetes, heart failure, previous PCI, and renal dysfunction. Numerical but nonsignificant differences in cardiac troponin T and I were noted, although these analyses are limited by small numbers due to use of differing troponin assays at international centers (high-sensitivity vs. contemporary, troponin I vs. troponin T), whereas BCIS/MINAP collect only high-sensitivity troponin data.

Likewise, our COVID NSTEMI-ACS subgroup ([Table 3](#)) had a greater comorbidity burden with a significantly lower mean age than non-COVID NSTEMI-ACS patients from the MINAP cohort. Again, significantly higher incidences of hypertension, hyperlipidemia, diabetes, heart failure, and renal dysfunction were observed.

PROCEDURAL CHARACTERISTICS. Symptom onset to admission and door-to-balloon times were more than double in our COVID-STEMI subgroup compared with BCIS ([Table 3](#)). Incomplete timing data was recorded in 9% (13 of 144) of COVID-STEMI patients. Admission systolic blood pressure was significantly lower and admission heart rate was higher. Transradial access use was noted to be lower. Only 2.8% of this group was found to have nonobstructive coronary disease, with 37.5% reporting TIMI grade 5 intracoronary thrombus; 45.8% required intensive care admission and 20.8% mechanical ventilation—in some the indications were likely respiratory and not cardiac. The need for pressor support was 6-fold greater than in the pre-COVID national database, with twice as many requiring mechanical support devices.

TABLE 4 In-Hospital Outcomes of COVID-STEMI and BCIS STEMI Subgroups

	COVID-STEMI Total (n = 144)	BCIS 2018-2019	p Value
Death	22.9 (33/144)	5.7 (1,232/21,675)	<0.001
Myocardial infarction	5.6 (8/144)	N/A	
Heart failure	23.6 (34/144)	N/A	
Stent thrombosis	1.4 (2/144)	N/A	
Bleeding (Bleeding Academic Research Consortium 3-5)	2.8 (4/144)	0.26 (36/13,913)	<0.001
Stroke	2.1 (3/144)	0.14 (32/21,994)	0.002
Cardiogenic shock	20.1 (29/144)	8.7 (1,898/21,972)	<0.001
In-patient stay, days	6.4 (2.7-12.7)	3.0 (2.0-5.0)	<0.001

Values are % (n/N) or median (interquartile range). **Bold** p values indicate statistical significance. Abbreviations as in [Table 1](#).

Similarly, in the COVID NSTEMI-ACS subgroup, symptom onset to admission times were prolonged, and admission systolic blood pressure was lower. However, no significant delays in admission to angiography time were observed compared with the MINAP data, with a nonsignificant trend toward shorter in-hospital waits for the catheter laboratory noted (48.5 h vs. 57.7 h; $p = 0.49$). Post-procedural support requirement differences were also higher but were not required as frequently as with the COVID-STEMI subgroup.

IN-HOSPITAL OUTCOMES. Overall, in-hospital mortality in the study cohort was 15.5%. Among COVID-STEMI patients, the in-hospital mortality was 24.5% in those who were COVID-19 positive versus 18.2% in those with a high index of clinical suspicion ($p = 0.49$) ([Supplemental Table 2](#)). In-hospital mortality more than quadrupled in our COVID-STEMI subgroup (22.9% vs. 5.7%; $p < 0.001$) with higher rates of CGS (20.1% vs. 8.7%; $p < 0.001$) ([Table 4](#)). Rates of stroke (2.1% vs. 0.1%; $p = 0.002$) and bleeding (2.8% vs.

0.3%; $p < 0.001$) were also significantly elevated. Inpatient stay was twice as long in the COVID-STEMI patients (6.4 days vs. 3.0 days; $p < 0.001$) compared with BCIS.

For the COVID NSTEMI-ACS group, mortality was more than 4-fold greater compared with the pre-COVID MINAP NSTEMI-ACS cohort (6.6% vs. 1.2%; $p < 0.001$) ([Table 5](#)). For NSTEMI-ACS, in-hospital mortality was 5.7% in COVID-19-positive patients versus 8.8% in those with a high index of clinical suspicion ($p = 0.69$) ([Appendix 2](#)). Higher incidences of CGS (5.0% vs. 1.4%; $p = 0.007$) and bleeding (2.5% vs. 0.1%; $p = 0.006$) were also noted in the COVID NSTEMI-ACS group versus the MINAP NSTEMI-ACS reference cohort, as well as a significant prolongation in total hospital stay (6.9 days vs. 5.0 days; $p < 0.001$).

In terms of raw unadjusted data, for CGS patients, mortality was 58.6% in the combined COVID-ACS data and 32.8% in MINAP/BCIS, whereas for non-CGS patients, mortality was 13.9% in the combined COVID-ACS data and 3.0% in MINAP/BCIS. [Table 6](#) lists the reported cause of death, associated incidence of CGS, and related time delays.

MULTIVARIABLE PROPENSITY-BASED ANALYSES.

Adjustment using propensity score analyses for age, sex, hypertension, diabetes, and hyperlipidemia demonstrated that COVID-STEMI patients in our registry still had increased overall mortality compared with the reference patients (odds ratio [OR]: 3.33; 95% confidence interval [CI]: 2.04 to 5.42) ([Table 7](#)). Separate analyses stratified by CGS status show that, in patients with CGS, risk of mortality for COVID-ACS registry patients is greater compared with BCIS reference patients (OR: 1.83; 95% CI: 0.80 to 4.19), yet this is greatly increased in patients without CGS (OR: 4.16; 95% CI: 2.33 to 7.44).

Correcting for the potential confounders listed in the previous text, we also demonstrate that for every 10-min delay in total ischemia time (symptom-to-admission plus door-to-balloon), a 10% mortality risk increase is observed (OR: 1.10; 95% CI: 1.01 to 1.19). The confidence interval remained >1.0 for those with CGS (OR: 1.25; 95% CI: 1.09 to 1.45), whereas in those without CGS, this crosses the line of unity (OR: 1.04; 95% CI: 0.94 to 1.15). A further separate analysis showed a 48% increase in death in patients diagnosed with CGS (OR: 1.48; 95% CI: 1.27 to 1.72).

DISCUSSION

This international registry describes the demographics, procedural characteristics, and outcomes of COVID-19 ACS patients undergoing invasive coronary angiography and compares these to

TABLE 5 In-Hospital Outcomes of COVID NSTEMI-ACS and MINAP NSTEMI-ACS Subgroups

	COVID NSTEMI-ACS Total (n = 121)	MINAP 2019	p Value
Death	6.6 (8/121)	1.2 (378/32546)	<0.001
Myocardial infarction	4.1 (5/121)	N/A	
Heart failure	19.0 (23/121)	N/A	
Stent thrombosis	0.0 (0/121)	N/A	
Bleeding (Bleeding Academic Research Consortium 3-5)	2.5 (3/121)	0.12 (28/22,445)	0.006
Stroke	0.8 (1/121)	0.05 (18/33,352)	0.067
Cardiogenic shock	5.0 (6/121)	1.4 (461/33,342)	0.007
In-patient stay, days	6.9 (3.4-18.4)	5.0 (3.0-8.0)	<0.001

Values are % (n/N) or median (interquartile range). **Bold** p values indicate statistical significance. Abbreviations as in [Table 1](#).

historical cohorts. It provides mechanistic information on the excess mortality observed in COVID-19 ACS patients.

Compared with the pre-COVID era, we report: 1) significantly prolonged delays in patients seeking medical care, and longer door-to-balloon times in COVID-STEMI patients; 2) significantly higher rates of CGS, and requirement for intensive care unit admission and ventilatory and/or hemodynamic support; and 3) quadrupling of in-hospital mortality compared with our pre-COVID cohort databases. Moreover, both COVID-ACS subgroups were found to be younger and carried a greater burden of comorbidity.

To date, reports on concomitant COVID-19 infection in patients who present with ACS are limited to small observational studies of STEMI patients (6,18,19) (the largest included 78 patients), with a paucity of data in NSTEMI-ACS. In the most robust study, a single-center observation of 39 consecutive COVID-19-positive STEMI cases reported in-hospital mortality of 17.9% compared with 6.5% in COVID-19-negative control subjects. This was statistically nonsignificant, likely due to small numbers; however, higher thrombus burden was suggested for the increased mortality, which is notable as symptom-to-admission and door-to-balloon times did not differ (5).

Hence, contemporary data thus far have principally described the effects of the pandemic on COVID-19-negative ACS patients. The largest registry to date of 6,090 patients undergoing PCI (of whom 2,419 were in 2020) documented higher mortality (6.8% vs. 4.9%) and longer ischemia times in those treated during the COVID era (20). However, only 62 patients in this study were COVID-19 positive (in-hospital mortality 29.0%), with no further details provided. Our study focused on COVID-19-positive ACS cases, including time to treatment and potential mechanisms driving the elevated mortality rates in these patients.

Symptom-to-admission times and STEMI door-to-balloon times in our registry were significantly greater than the pre-COVID cohort and should be considered in the context of decreases in absolute hospitalizations for ACS during the COVID-19 pandemic (8,10,21)—most likely due to public fear of viral contagion (22). We assert that the delays seen in door-to-balloon time data may be due to restructured “COVID-19 pathways” and time spent donning appropriate PPE, which was utilized in more than 90% of cases from our registry. The nonsignificant trend to accelerated door-to-angiography times in our NSTEMI-ACS group is likely due to widespread

TABLE 6 Causes of Death Association With Cardiogenic Shock and Ischemia Times

Cause of Mortality (STEMI/NSTEMI-ACS)	Incidence of Cardiogenic Shock	Ischemia Time, min STEMI Only		
		CGS (n = 19*)	no CGS (n = 106*)	
Cardiovascular	58.5 (24/41)	75.0 (18/24)	1271.0 (355.0-2,760.0)	440.5 (208.0-1,701.0)
Respiratory	31.7 (13/41)	23.1 (3/13)		
Neurological	4.9 (2/41)	0.0 (0/2)		
Unknown	4.9 (2/41)	0.0 (0/2)		

Values are % (n/N) or median (interquartile range). *n = 19, n = 106 due to incomplete data. CGS = cardiogenic shock; IQR = interquartile range; other abbreviations as in Table 1.

suspension of elective catheter laboratory work (23), thus creating availability for acute cases.

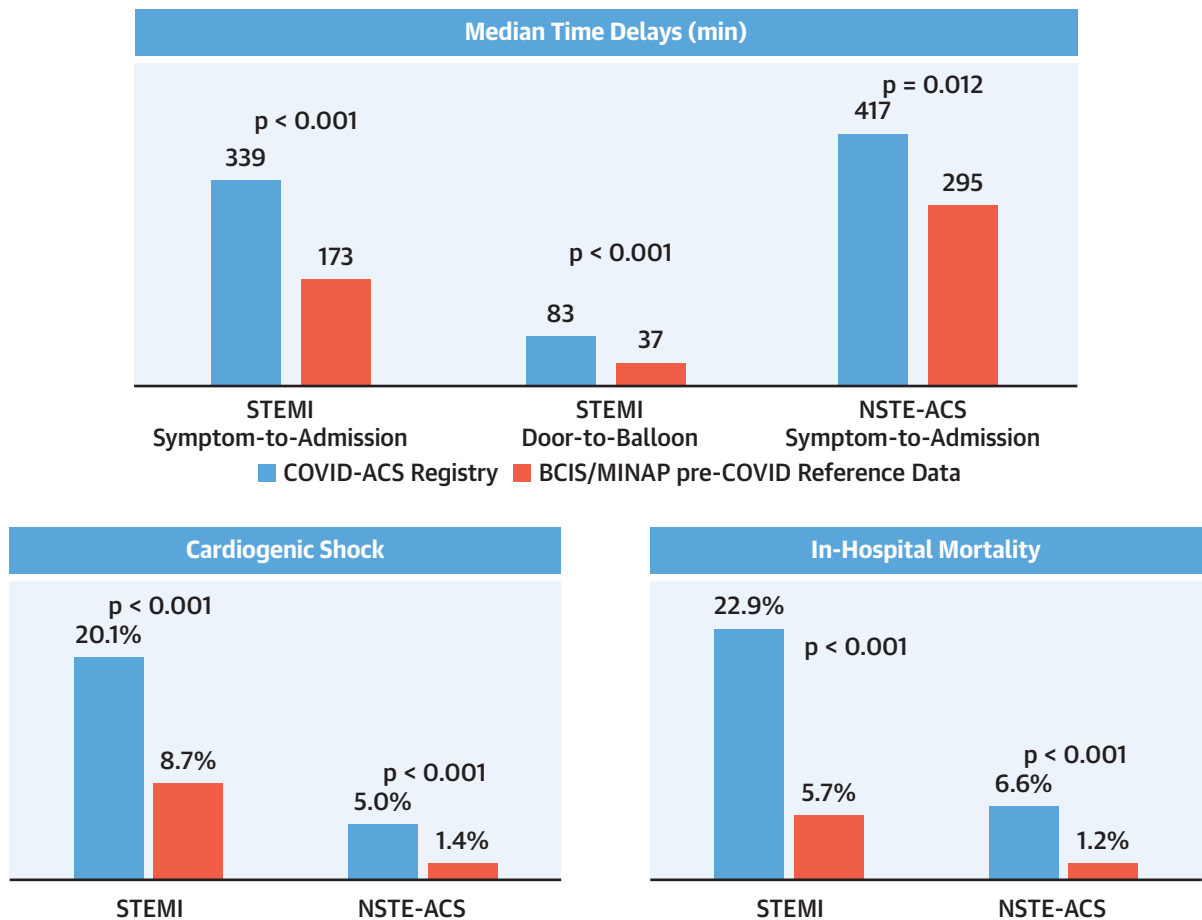
Our data support the notion that prolonged ischemia times were associated with poor outcomes, with a 10% increase in mortality for the COVID-ACS patients for every 10-min delay. This was exacerbated in those with CGS (25% increase/10 min), with the association still present in those without CGS (4%/10 min). For the STEMI cohort (ACS and reference database, COVID-19 positive and COVID-19 negative combined), experiencing CGS increased mortality by 48%.

Given the strong relationship between prolonged ischemia time and poorer outcomes in STEMI, the increased incidence of CGS is an important contributor to the higher rates of adverse outcomes and supports reported data of excess deaths due to CGS during the pandemic (22). Historical ACS longitudinal data describe the incidence of CGS as approximately 7% (24), one-half of the 13.2% in our study. The relationship of presentation times and onset of CGS is intuitive, but is not robustly reported. It is therefore reasonable to assert that prolonged ischemia times in our population were responsible for the high incidence of CGS, although consideration must be given to the hypothesis that higher CGS incidence could also be related to COVID-19 infection and potential pro-thrombotic mechanisms.

TABLE 7 Multivariate Propensity Analyses Comparing COVID-STEMI Patients With the BCIS Database

COVID-STEMI vs. BCIS	All Patients	CGS	Non-CGS
Overall mortality*	3.33 (2.04-5.42)	1.83 (0.80-4.19)	4.16 (2.33-7.44)
Total ischemia time (for every 10 min)†	1.10 (1.01-1.19)	1.25 (1.09-1.45)	1.04 (0.94-1.15)
CGS‡	1.48 (1.27-1.72)		

Values are odds ratio (95% confidence interval). COVID-STEMI and BCIS were matched for age, sex, hypertension, diabetes, and hyperlipidemia using a propensity score. Total ischemic time (symptom-to-admission plus admission-to-balloon) was right skewed, therefore a logarithm transformation with base 10 was performed. *Overall mortality: this adjusts for age, sex, hypertension, hyperlipidemia, diabetes, ischemia time, and CGS. †Mortality related to ischemia time. ‡Mortality related to presence of CGS. Abbreviations as in Tables 1 and 6.

CENTRAL ILLUSTRATION Time Delays and In-Hospital Outcomes in the International COVID-ACS Registry

Kite, T.A. *et al.* *J Am Coll Cardiol.* 2021;77(20):2466-76.

When compared with pre-coronavirus disease 2019 (COVID-19) reference data from the British Cardiovascular Intervention Society (BCIS) and Myocardial Ischaemia National Audit Project (MINAP) databases, patients enrolled in the International COVID-ACS registry were found to experience significant delays in presentation to hospital and time to reperfusion therapy, excess rates of cardiogenic shock, and greater in-hospital mortality. These novel data suggest 1 potential mechanism for the poorer outcomes observed in patients with acute coronary syndrome (ACS) and COVID-19, and yet again support the concept of "time is muscle" in myocardial infarction. Public health messaging during this and future pandemics should be clear—patients who experience cardiovascular symptoms should not delay in seeking medical attention. NSTEMI-ACS = non-ST-segment elevation acute coronary syndrome; STEMI = ST-segment elevation myocardial infarction.

Higher rates of hypertension, hyperlipidemia, diabetes mellitus, heart failure, and chronic kidney disease all may contribute to an elevated risk of major adverse cardiovascular events in COVID-19 ACS patients, consistent with other recent cohorts (25). However, our data suggest that these factors did not play a major role, because correcting for them still resulted in excess mortality. In a separate analysis stratified by CGS correcting for these confounders, the absolute differences in mortality between all STEMI patients who were either COVID-19 positive or negative with CGS was 25.8%, whereas it was only

10.9% in those without CGS. However, the relative risk of mortality with concomitant COVID-19 infection in patients without CGS was 4.16, but was 1.83 for those with CGS. Thus, COVID-19 significantly increases risk of death in patients without CGS, but in those who experience CGS, it is CGS that is the major determinant of mortality.

Thus, discriminating between the effects of acute MI and acute COVID-19 infection remains a significant challenge. However, the results from our International COVID-ACS Registry go further than previous studies and provide novel insights to support a hypothesis of

potential COVID-19 fear and a consequent reluctance to go to hospital, a reluctance that appears to have led to an increase in deaths from ischemic heart disease during the pandemic (26). This multicorbid population presented to hospitals significantly later and received less timely reperfusion therapy, thereby resulting in significantly higher rates of CGS and in-hospital mortality. This is supported by our data that suggest of those who died of cardiovascular causes, CGS was a key determinant, and CGS was associated with prolonged presentation times.

STUDY LIMITATIONS. Due to its observational design, we cannot exclude the presence of unknown confounding factors and selection bias for patients entered to the registry, given the ratio of number of patients enrolled to number of centers is relatively low. ACS patients who did not reach the catheter laboratory and those medically treated were not included. A total of 29.1% of patients enrolled tested negative for COVID-19 on viral RT-PCR testing, yet were treated as highly suspicious for COVID-19 due to CXR or CT findings supporting severe acute respiratory syndrome coronavirus 2 infection. Rates of false-negative COVID-19 RT-PCR results of up to 38% are well recognized (27); therefore, we considered it important that these patients were included in the study. Furthermore, there were no significant differences in mortality between these groups. We also acknowledge that COVID-19 can present heterogeneously. The results of propensity analysis confirm that delays in presenting to hospital and CGS were the main factors determining outcomes—however, other mechanisms such as impact of the COVID-19 virus itself on the cardiovascular system cannot be discounted. However, we did record overall mortality and perceived causes of death. Furthermore, we recognize that these are short-term data and that there is a lack of a concurrent COVID-19-negative control group—systems of care during the pandemic were disrupted at this time and would therefore not represent the pre-COVID standard. Moreover, our control group comprises only U.K. data and should not be considered truly reflective of practice at the international sites that participated in the study. However, over 75% of patients enrolled in the registry were from centers in Europe, and thus these data, which report similar in-hospital outcomes compared with other respected European databases (16,17), are likely to offer one of the best historical comparisons available.

CONCLUSIONS

This large multinational, observational study of COVID-19 ACS patients demonstrates novel mechanistic data indicating that these patients present later and have increased in-hospital mortality compared with a pre-COVID ACS population (**Central Illustration**). Importantly, COVID-19 ACS patients have excess rates of CGS, and adverse outcomes appear to be driven by delays in seeking medical care and timely reperfusion therapy, supporting yet again the concept of “time is muscle.” We should recognize that in patients with 2 diseases, differentiating one from the other may be difficult—thus, clear and simple public health messages for patients to present expeditiously to the hospital when they first experience symptoms of ACS are required during this and future pandemics.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND

PROCEDURAL SKILLS: ACS in patients with COVID-19 is associated with a poor prognosis, particularly when medical intervention is delayed.

TRANSLATIONAL OUTLOOK: More research is

needed to elucidate the mechanisms that trigger acute coronary syndromes in patients with COVID-19, their impact on the incidence and outcomes of cardiogenic shock, and implications for management.

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APPENDIX For supplemental tables, please see the online version for this paper.