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Kite, TA, Ludman, PF, Gale, CP orcid.org/0000-0003-4732-382X et al. (16 more authors) (2021) International Prospective Registry of Acute Coronary Syndromes in Patients With COVID-19. Journal of the American College of Cardiology, 77 (20). pp. 2466-2476. ISSN 0735-1097

https://doi.org/10.1016/j.jacc.2021.03.309

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

Thomas A. Kite[1], Peter Ludman[2], Chris P. Gale[3], Jianhua Wu[3], Adriano Caixeta[4], Jacques Mansourati[5], Manel Sabate[6], Pilar Jimenez-Quevedo[7], Luciano Candilio[8], Parham Sadeghipour[9], Angel Angel M. Iniesta [10], Stephen Hoole[11], Nick Palmer[12], Albert Ariza-Sole,[13] Alim Namitokov[14], Hector Escutia-Cuevas[15], Flavien Vincent[16], Otilia Tica[17], Mzee Ngunga[18], Imad Meray[19], Andrew Morrow[20], Md Minhaj Arefin[21], Steven Lindsay[22], Ghada Kazamel[23], Vinoda Sharma[24], Aly Saad[25], Gianfranco Sinagra[26], Annika Eriksson[27], Federico Ariel Sanchez[28], Marek Roik[29], Stefano Savonitto[30], Marija Vavlukis[31], Sivasankar Sangaraju[32], Richard Jabbour[33], Sharon Kean[34], Nick Curzen[35], Colin Berry[20,36], Gregg W. Stone[37], Bernard J. Gersh[38], Anthony H. Gershlick[1]

On behalf of the COVID-ACS Global Registry Investigators

Author affiliations

1. Department of Cardiovascular Sciences and the NIHR Leicester Biomedical Research Centre, Glenfield Hospital, University of Leicester, Leicester, UK
2. Institute of Cardiovascular Sciences, University of Birmingham, UK
3. Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds, Leeds, UK; Leeds Institute for Data Analytics, University of Leeds, Leeds, UK; Department of Cardiology, Leeds Teaching Hospitals NHS Trust, Leeds, UK
4. Division of Cardiology, Escola Paulista de Medicina, Universidade Federal de São Paulo; Hospital Israelita Albert Einstein, São Paulo, Brazil.
5. Department of Cardiology, University Hospital of Brest and University of Western Brittany, EA 4324 ORPHY, France
6. Cardiovascular Institute, Interventional Cardiology Department, Hospital Clinic, IDIBAPS, Barcelona, Spain
7. Interventional Cardiology Department, Hospital Clinico San Carlos, IdISSC, Madrid, Spain
8. Royal Free London NHS Foundation Trust, London, UK
9. Cardiovascular Intervention Research Center, Rajaie Cardiovascular Medical and Research Center, Iran University of Medical Sciences, Tehran, Iran
10. Department of Cardiology, Hospital Universitario La Paz, Madrid, Spain
11. Royal Papworth Hospital NHS Foundation Trust, Cambridge, UK
12. The Liverpool Heart and Chest Hospital, Liverpool, UK
13. Intensive Cardiac Care Unit, Bellvitge Univesity Hospital, L'Hospitalet de Llobregat, Barcelona, Spain
14. Scientific Research Institute – Regional Clinical Hospital #1 NA Prof. S.V. Ochapovsky, Krasnodar, Russia
15. Department of Cardiology, Regional Hospital ISSSTE Puebla, Puebla, Mexico
16. CHU Lille, Institut Cœur Poumon, Cardiology, Department of Interventional Cardiology for Coronary, Valves and Structural Heart Diseases, Inserm U1011, Institut Pasteur de Lille, EGID, Université de Lille, Lille, France
17. University of Oradea, Faculty of Medicine and Pharmacy, Department of Medical disciplines, 1 December Square, 410073, Oradea, Romania
18. Department of Medicine, Aga Khan University Hospital, Nairobi, Kenya
19. Peoples Friendship University of Russia, Hospital n\a V.V.Vinogradov, Moscow, RF
20. Department of Cardiology, Golden Jubilee National Hospital, Clydebank, UK
21. Department of Cardiology, National Institute of Cardiovascular Diseases & Hospital (NICVD), Dhaka, Bangladesh
22. Bradford Teaching Hospitals NHS Foundation Trust, Bradford, UK
23. Ghada A. Kazamel MD, PhD, cardiology department national heart institute. Egyp
24. Birmingham City Hospital, SWBH NHS Trust, Birmingham,UK
25. Zagazig University, Egypt. Department of Cardiovascular Medicine
26. Cardiovascular Department, University of Trieste, Trieste, Italy
27. (Annika)
28. (Federico)
29. Department of Internal Medicine and Cardiology, Medical University of Warsaw, Warsaw, Poland
30. Cardiovascular Department, Manzoni Hospital, Lecco, Italy

31. University Clinic for Cardiology, Medical Faculty, Ss' Cyrial and Methodius University, Skopje, Macedonia
32. University Hospitals Plymouth NHS Trust, Plymouth, UK
33. Cardiology Department, Imperial College Healthcare Trust, London, UK
34. Robertson Centre for Biostatistics, Institute of Health and Wellbeing, University of Glasgow, Glasgow, UK
35. Faculty of Medicine, University of Southampton, UK
36. British Heart Foundation Glasgow Cardiovascular Research Centre, University of Glasgow, UK
37. The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, NY
38. Dept of Cardiovascular medicine, Mayo Clinic College of Medicine

Corresponding author
Professor Anthony H. Gershlick
University of Leicester, University Hospitals of Leicester, NIHR Leicester Biomedical Research Centre, Glenfield Hospital, Groby Road, Leicester, LE3 9QP, United Kingdom
agershlick@aol.com
(+44) 0116 250 2677

Declarations of interest

Co-authors please list any here

Abstract

Background: Published data suggest worse outcomes in acute coronary syndrome (ACS) patients and concurrent COVID-19 infection. Mechanisms remain unclear. We report the demographics, angiographic findings, and in-hospital outcomes of COVID-19 ACS patients.

Methods: From 1st March-31st July 2020, anonymised data from 55 international centres were enrolled in a prospective, observational COVID-ACS Registry. Patients were COVID-19 positive (or high index clinical suspicion) undergoing invasive coronary angiography for suspected ACS. Outcomes were in-hospital major cardiovascular events (all-cause mortality, re-myocardial infarction, heart failure, stroke, unplanned revascularisation, or stent thrombosis). Results were compared to national pre-COVID-19 databases (Myocardial Ischaemia National Audit Project and British Cardiovascular Intervention Society 2018-2019).

Findings: In 141 STEMI and 121 NSTE-ACS patients, symptom-to-admission times were significantly prolonged (COVID-STEMI vs. MINAP/BCIS: median 339·0 vs. 173·0 minutes, p<0·001; COVID NSTE-ACS vs. MINAP/BCIS: 417·0 vs. 295·0 minutes, p=0·012). Mortality was significantly higher in both subgroups (COVID-STEMI: 22·9% vs. 5·7%, p<0·001; COVID NSTE-ACS: 6·6% vs 1·2%, p<0·001), which remained following multi-variate propensity analysis adjusting for co-morbidities (STEMI sub-group OR 3·33 (95% CI 2·04-5·42)). Cardiogenic shock (CGS) occurred in 20·1% vs. 8·7%, (COVID-STEMI vs. MINAP/BCIS, p<0·001) with a mortality of 58·6% (COVID-STEMI) vs. 32·8% respectively. After adjustment, CGS increased mortality by 48% (OR1.48 (1.27-1.72)).

Interpretation: These novel mechanistic data indicate COVID-19 positive ACS patients present later and have increased in-hospital mortality compared with a pre-COVID-19 ACS population. Excessive rates of CGS due to time delays may be mechanistically important.

Funding: The study was supported within Departments of Audit and the Clinical Trials Unit at The University of Glasgow.

INTRODUCTION

Since its outbreak in Hubei Province, China in December 2019, the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread rapidly, resulting in a worldwide pandemic from this multi-system illness[1]. The impact on acute coronary syndromes (ACS) is two-fold. Firstly, 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 vascular coagulopathy, with intra-coronary micro-thrombi, or a specific endothelial inflammatory reaction to the virus[3]. Indeed, early reports suggest excessive spontaneous thrombus formation in the coronary, pulmonary and peripheral vasculature due possibly to widespread endothelial inflammatory process[4]. Excess coronary thrombus formation has been suggested as a cause for higher mortality[5]. However non-obstructed epicardial coronary arteries with micro-thrombi or a cellular inflammatory process has also been observed[6], as has as a high incidence of myocarditis masquerading as ACS[7].

Early reports also demonstrated a marked decline in ACS admissions during the COVID pandemic, together with a definite increase in mortality compared to non-COVID ACS patients[8-10]. While the pro-inflammatory nature of COVID-19 and its subsequent complex interaction with the cardiovascular system, as described above, make this an essential area of investigation, many of the clinical findings could be explained by patients' perception of potential harm in attending hospital (COVID-19 fear). We proposed that the poorer outcomes in COVID-19 positive ACS patients were mostly due to such patient concerns.

The Global COVID-ACS Registry was established to document the demographic, procedural, angiographic characteristics, and in-hospital clinical outcomes in COVID-19 positive (or high index suspicion) patients admitted with ACS, paying particular attention to delays in standard management. We asked whether there was a link between previously published rates of fewer ACS presentation and factors likely to impact on adverse outcomes.

METHODS

Study design

The University Hospitals of Leicester 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 centres to prospectively enter anonymised data on patients that met the registry inclusion criteria. The study was considered a health survey as each centre entered their own data according to a site-specific user account with no patient identifiable data collected. After taking appropriate national regulatory advice, no ethical approval was sought. The inclusion criteria for the study were: 1) COVID-19 positive or a high index 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 centres located across 5 continents with collected data from 1st March 2020-31st July 2020.

Data collection

Patient demographics including age, sex, and body mass index (BMI) were recorded. Users recorded co-morbidities based on the International Classification of Diseases 10th revision (ICD-10) codes, including cardiovascular disease (hypertension, hyperlipidaemia, diabetes mellitus, previous MI, previous PCI, and congestive cardiac failure), smoking status, and history of lung disease. Procedural and angiographic characteristics were recorded. Requirements for intensive care admission, inotropic/vasopressor support, invasive ventilation, and mechanical support were also documented. We also asked whether full personal protective equipment was used. Data transfer agreements were established between the University of Leicester, University of Glasgow, and sites as required.

Outcomes

The primary endpoint was in-hospital all-cause mortality. Secondary endpoints included in-hospital repeat myocardial infarction (Fourth Universal Definition of Myocardial Infarction[12]), heart failure, unplanned revascularisation and stroke (2017 Cardiovascular Endpoint Definitions for Clinical Trials Consensus Report[13]), cardiogenic shock (CGS) (systolic blood pressure <90mmHg for >30 minutes 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 report total length of hospital stay.

Comparative groups

COVID-ACS patients were sub-divided into: 1) ST-elevation myocardial infarction (STEMI) and 2) NSTE-ACS (N-STEMI and unstable angina). Where available and appropriate, comparisons were made with pre-COVID STEMI and NSTE-ACS data from the UK-based British Interventional Cardiovascular Society (BCIS) (1st April 2018–31st March 2019), and English data Myocardial Ischaemia National Audit Project (MINAP) (2019) databases. All patients undergoing an invasive strategy for ACS in England are submitted to these robust and internationally acknowledged databases. The comparative databases were BCIS for the STEMI population and MINAP for the NSTE-ACS population, as each provided best comparators for those cohorts. We chose not to use a concurrent cohort of COVID negative ACS patients as controls, since we recognised that systems of care were disrupted at this time and would not represent the pre-COVID standard.

Statistical analyses

Descriptive statistics were presented for baseline demographics and characteristics. Frequency and percentage were reported for categorical variables, mean (standard deviation) or median (interquartile range) were reported for continuous variables depending on their distributions. To compare the characteristics between COVID-ACS and MINAP/BCIS datasets, Fisher exact test or Chi-squared tests were performed for categorical variables, and t-test or Mann-Whitney U tests were used for continuous variables according to their distributions. To account for confounding factors and to 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 ACS or BCIS including age, sex, hypertension, hyperlipidaemia, 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 cardiogenic shock (CGS) status and ischaemic time. A propensity score was not derived to compare NSTE-ACS subgroups as low rates of mortality and CGS were observed.

Role of the funding source

The Registry was set up from funding within the Universities of Leicester and Glasgow. There was no external funder.

RESULTS

In total, 316 hospitalised patients from 55 international centres 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 (participating centres **Appendix 1**). Demographic variables and comorbidities for the STEMI/NSTE-ACS cohort are shown in **Table 1**.

Baseline characteristics

Of the 316 patients, 144 (54.3%) were diagnosed with STEMI and 121 (45.6%) with NSTE-ACS. These two 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/NSTE-ACS combined cohort was 64·9 years (SD 12·9), 75·5% were male. 66·2% had hypertension, 54·1% hyperlipidaemia, 36·2% diabetes mellitus, 20·2% had a previous MI, 19·3% heart failure, and 14·6% chronic kidney disease stage 3-5. 27·1% were current smokers.

74·3% of patients tested positive for COVID-19 infection, with viral polymerase chain reaction testing used in 98·9% of these cases. 25·7% were defined as COVID-19 suspected (treated as positive despite a negative PCR test) due to high index of clinical suspicion (clinical status plus chest x-ray or computed tomography 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 suffered an out of hospital cardiac arrest (OHCA).

Demographics, co-morbidities, procedural characteristics and post-procedural support requirements in the COVID-STEMI subgroup are shown in **Table 2**. Compared to non-COVID STEMI patients (MINAP/BCIS cohorts), our COVID-STEMI subgroup were younger, with significantly more hypertension, hyperlipidaemia, diabetes, heart failure, previous PCI and renal dysfunction. Numerical but non-significant differences in cardiac Troponin T and I were noted, although these analyses are limited by small numbers and incomplete data.

Likewise, our COVID NSTE-ACS subgroup (**Table 3**) had a greater comorbidity burden with a significantly lower mean age than non-COVID NSTE-ACS patients from MINAP/BCIS cohorts. Again, significantly higher incidences of hypertension, hyperlipidaemia, diabetes, heart failure, and renal dysfunction were observed.

Procedural characteristics

Symptom onset to admission time and door-to-balloon time were more than double in our COVID-STEMI subgroup compared with the historical controls (Table 3), with admission systolic blood pressure significantly lower and admission heart rate significantly higher. Trans-radial access use was noted to be lower, perhaps reflecting a sicker patient cohort or that this is not the default access route in some countries. Only 2·8% of this group were found to have non-obstructive coronary disease, with 37·5% reporting the presence of intra-coronary thrombus. Nearly 50% required ICU admission and 20% mechanical ventilation (some would be due to the COVID-19 infection itself), and the need for pressor support was six times that of those in the pre-COVID National database, and twice as many requiring mechanical support devices.

Similarly, in the COVID NSTE-ACS subgroup, symptom onset to admission time was prolonged, and admission systolic blood pressure lower. However, no significant delays in admission to angiography time were observed compared with the MINAP/BCIS data, with a non-significant trend towards shorter in-hospital waits for the catheter laboratory noted (48·5hrs vs 57·7hrs, p=0·491). Post procedural support requirement differences were also higher but not required as frequently as with the COVID-STEMI sub-group.

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 vs. 18·2% in those with a high index of clinical suspicion (p=0.489). In-hospital mortality more than quadrupled in our COVID-STEMI study cohort (22·9% vs. 5·7% reference population, p<0·001) and with higher rates of CGS (20·1% vs. 8·7%, p<0·001). Rates of stroke (2·1% vs 0·1%, p=0·002) and bleeding (2·8% vs 0·3%, p=0·01) were also significantly higher (Table 4). In-patient stay was twice as long in the COVID-STEMI patients (6·4 days vs. 3·0 days; p<0·001) compared to reference group.

For the entire COVID NSTE-ACS group, mortality was more than four-fold greater compared with the pre-COVID MINAP/BCIS NSTE-ACS cohorts (6·6% vs. 1·2%, p<0·001) (Table 5). For NSTE-ACS, the in-hospital mortality was 5·7% in COVID-19 positive vs. 8·8% in those with a high index clinical suspicion (p=0·685). Higher incidences of cardiogenic shock (5·0% vs. 1·4%, p=0·007) and bleeding (2·5% vs. 0·1%, p=0·001) were also noted, as well as a statistically 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 COVID-ACS registry and 32.8% in MINAP/BCIS. For non-CGS patients, mortality was 13·9% in ACS registry 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 hyperlipidaemia, showed patients in our COVID-ACS registry still had increased overall mortality compared to the reference patients (OR 3·33 (2·04-5·42) (Table 7). Separate analyses stratified by CGS status show that in COVID positive/negative without CGS the OR is 4·16 (2·33-7·44) for overall mortality for the Registry compared to reference (BCIS/MINAP) patients. In COVID positive/negative in those patients with CGS the OR is 1·83 (0·80-4·19).

Correcting for the potential confounders listed above, we also show that for every 10 minutes delay in total ischaemia time (symptom-admission plus door-to-balloon) the OR was 1.10 (1.01-1.19), and for CGS the OR was 1.48 (1.27-1.72). The CI remained >1.0 for those with CGS (OR 1·25 (1·09-1·45)) whereas those without CGS the OR crossed the line of unity (1·04 (0·94-1·15)).

Discussion

This Global COVID-ACS registry constitutes the largest international analysis to date of COVID-19 ACS patients undergoing invasive coronary angiography. 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, ventilatory and/or haemodynamic support; and 3) quadrupling of in-hospital mortality compared to our pre-COVID cohort database.

Moreover, both COVID-ACS subgroups were found to be younger and carried a larger burden of comorbidity as compared with the ACS patients from the pre-COVID MINAP/BCIS national database.

Reports on concomitant COVID-19 infection in patients who present with ACS to date are limited to small observational studies of STEMI patients[6,16,17], with a paucity of data in NSTE-ACS. In a single centre study of 39 consecutive COVID-19 positive STEMI cases, Choudry et al reported in-hospital mortality of 17·9% compared to 6·5% in COVID-19 negative controls (statistically non-significant likely due to small numbers). Higher thrombus burden in patients with concurrent COVID-19 infection has been suggested, notable as symptom-admission and door-to-balloon times did not differ significantly in these analyses[5]. Furthermore, in a recent study of 517 COVID-19 positive ACS patients from the MINAP database, in-hospital mortality (adjusted OR 3·27, 95%CI 2·41-4·42) were confirmed, but again the reason(s) for increased mortality remained unclear[18].

Discriminating between the effect of acute myocardial infarction and acute COVID-19 infection remains a significant challenge. However, the results from our Global COVID-ACS registry go further than previous studies in providing novel insights to support a hypothesis of potential COVID fear and a consequent reluctance to attend hospital to explain the at least in part excess mortality rates demonstrated in our and other data. Our multi-variate propensity analyses (adjusting for potential confounders) suggest the chances of dying was 333% higher with than without COVID-19.

Our supposition is based firstly on demonstrating significant delays in patients attending hospitals, which has been previously reported in small single centre studies, with 3-4 times greater delays in symptom-first medical contact shown[19,20]. Our study confirms these findings in a larger data set, with the most notable time delays in our COVID-STEMI group. These observations can be considered in the context of reported significant decreases in absolute hospitalisations for ACS during the COVID-19 pandemic[8,10,21], most likely due to public fear of viral contagion[22]. Interestingly, door-to-balloon times in our COVID STEMI-ACS group were greater than two-fold longer than our pre-COVID cohort. This observation is supported by a Chinese study that reported an approximate 20-minute average delay in this metric[23]. Similarly, the ISACS-STEMI Registry (in press JACC) demonstrated increased ischaemia time and in-hospital mortality in STEMI patients during the COVID era. However, no mechanism was proposed.

We speculate that the delays seen with our data may be due to restructured "COVID-19 pathways" in healthcare systems and time spent donning appropriate PPE, which of interest was utilised in more than 90% of cases from our registry. Given the strong relationship between prolonged ischaemia time and poorer outcomes in STEMI, this in itself may be the mechanism driving higher incidence of adverse outcomes documented in our COVID-19 cohort, although other mechanistic cellular causes cannot be excluded.

Our data support the notion that prolonged ischaemia times were associated with poor outcomes, with a 10% increase in mortality for the COVID-ACS patients for every 10-minute delay and exacerbated in those with CGS (25% increase/10 minutes), with the association still present in those without CGS (4%/10 minutes). For the STEMI cohort, (ACS and reference databases, COVID positive or COVID negative) suffering CGS increased mortality by 48%.

In the separate analysis stratified by CGS, the absolute differences in mortality between those patients who were COVID-19 positive/negative with CGS was 25.8%, whereas this was only 10.9% in those without CGS. However, the relative risk mortality of COVID-19 infection on patients without CGS was 4.6 but for those with CGS this was 1.8. Thus, COVID-19 has a significant effect on mortality in patients without CGS but in those who suffer CGS, it is the CGS that influences their mortality.

The high incidence of CGS and its impact in our study is striking, and fits with the other reported data[22]. Non-COVID-ACS longitudinal data describe the incidence of CGS as approximately 7% [24], i.e. half the 13·2% in our study. Breaking these data down into NSTE-ACS and STEMI provides focus. CGS is reported to occur in 2·5% of NSTE-ACS,[25] half the finding in our study. In our non-COVID STEMI reference cohort CGS was seen in 8·7%, which is in keeping with the published data of less than 10%[26]. However, in our COVID-STEMI population this reached 20·1%. CGS is recognised as having a mortality of approximately 50%[27]. While the reference group incidence was lower than this at 32%, this was in-patient data and attrition to the approximate 50% will have occurred post discharge to 30 days. In our COVID-ACS group we propose that excess deaths were due to delayed presentation leading to worse myocardial injury and excess CGS.

The fact our study shows greater requirement for intensive care unit admission, ventilatory, and/or haemodynamic intervention supports these findings. Reports describing the incidence of CGS per se in COVID-19 infection are few and surrogates (heart failure) limited to case series or small retrospective studies. In a study of confirmed COVID-19, 23% had a clinical diagnosis of heart failure. Of half the patients who died, 52% (n=28) had developed heart failure versus 12% (n=16) in those who survived (p<0·001)[28]. Of 7 COVID-19 positive suspected STEMI patients, 4 developed CGS immediately after arrival at the hospital, with 3 eventually dying in-hospital[29].

The relationship of presentation times and onset of CGS is intuitive but not robustly reported. It is predicated on the severity of myocardial ischemia impairing ventricular function, leading to a spiral of reduced cardiac output, low blood pressure, further coronary ischaemia, contractility impairment and multi-organ failure. Duration of ischaemia is an important cause of irreversible myonecrosis[30] and associated with greater microvascular obstruction[31]. It is therefore not unreasonable to speculate that prolonged ischaemia times in our population were responsible for the high incidence of CGS, with its known high mortality.

Clearly, the interplay of ischaemic injury and concomitant COVID-19 infection in this group of patients remains difficult to define. Studies suggest that direct COVID-19 infiltration to myocardial cells, systemic inflammatory cytokine storm with pro-thrombotic milieu, and hypoxia-induced excessive intra-cellular calcium causing cardiac myocyte death may all play a role and precipitate a fulminant myocarditis and critical illness[32]. However, in the absence of robust pathological evidence to confirm these assertions, the prolonged ischaemia time and delay in appropriate and timely reperfusion may account for most of the excessive mortality in ACS due to the greater incidence of CGS. It is however impossible to exclude the possibility that the incidence and severity of CGS is higher because of excess thrombotic/cellular injury.

Higher rates of hypertension, hyperlipidaemia, diabetes mellitus, heart failure and chronic kidney all disease all may contribute to an elevated risk of MACE in COVID-19 patients, consistent with other recent ACS cohorts[18]. However, our data suggest that these factors were not playing a major part since correcting for them still resulted in excess mortality. Mortality rates were no different as to whether patients were COVID-19 proven or COVID-19 suspected.

Our data also differ in several key other elements as compared to previous studies. Non-obstructive coronary disease in COVID-STEMI populations have been reported in small cohorts to be 39% (n=11)[6] and 33% (n=3)[16] but we saw this in only 2.8% of our COVID STEMI-ACS group.

The role of a pro-thrombotic state requires consideration. Choudry et al reported 75% (n=21) of COVID-19 positive STEMI patients had significant thrombotic occlusion at angiography[5]. However, most STEMI patients present with thrombus as the final consequence of plaque rupture or erosion, so these data do not imply mechanisms. The rate of visible thrombus in our cohort was half their documented 37·5%. The difference may be due to the quantification used. Their report includes modified thrombus grade (MTG) (after first device) of 4 and 5, where 5=total occlusion. The 28·6% with MTG=5 only was similar to our 37·5%, and furthermore their use of aspiration thrombectomy of 17·9% (n=7) was broadly similar to the 12·5% (n=18) observed in our study. Difficulty in determining underlying plaque in the presence of a thrombotic occlusion is recognised. The presence of thrombus alone as a major mechanism causing the presentation event is therefore not supported by any data as yet published. Autopsy reports where it has seen prominently may reflect selection bias. Further mechanistic studies are required to define the precise role of COVID-19 infection in ACS.

As the largest study to date of COVID-19 ACS patients undergoing an invasive coronary strategy, our data suggest this multi-comorbid population of ACS patients presented to hospitals significantly later, received less timely reperfusion therapy, thereby resulting in significantly higher rates of CGS and in-hospital mortality. This is supported by our data, which suggest that of those who died with cardiovascular causes, CGS was a significant cause and those with CGS had longer presentation times. Our data support yet again the concept of “time is muscle” in ACS patients. We should recognise that in patients with two severe illnesses differentiating one from the other n=may be difficult for patients- thus the messages need to be clear and simple.

The messages for the future are that pro-active, very early public engagement are critical, and should include infection safety information and the need for patients to present expeditiously to hospital when they first

experience symptoms of ACS. Furthermore, hospital strategies have to be put into place to minimise treatment times in patients presenting with ongoing cardiac symptoms.

Limitations

This study has some limitations. Due to its observational design, we cannot exclude the presence of unknown confounding factors and selection bias for patients entered to the registry. 29·1% of patients 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 SARS CoV-2 infection. Rates of false negative COVID-19 RT-PCR results of up to 38% on the day of symptom onset are well recognised[33], therefore we considered it important that these patients were included in the study. Furthermore, there was no significant difference in mortality between these groups. We acknowledge that COVID-19 can present heterogeneously. However, we do record overall mortality and perceived causes of death.

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. We recognise that these are short term data and that there is a lack of a concurrent control group, however systems of care during the pandemic were disrupted at this time and therefore would not represent the pre-COVID standard.

Conclusions

This large multinational, observational, real-world study of COVID-19 patients hospitalised for suspected ACS who underwent coronary angiography demonstrated novel mechanistic data indicating COVID-19 positive ACS patients present later, and have increased in-hospital mortality compared with pre-COVID ACS population Importantly, COVID-19 patients have excess rates of CGS which may be mechanistically important. Adverse outcomes appear to be driven by delays in patients seeking medical care and timely reperfusion therapy,

Further efforts, including increasing public awareness campaigns to seek medical attention if cardiovascular symptoms develop and minimizing delays to treatment after hospital arrival, especially for those with STEMI are critical to attenuate time delays and improve outcomes following ACS during the present and future pandemics.

Research in Context

1. Evidence before this study

Separate small studies and case reports and with lack of reference pre-COVID comparative cohorts, indicated patients with COVID-19 and acute coronary syndrome present later and have higher mortality. Mechanistic understanding of the higher mortality was incomplete and focused on viral, myocardial or pro-thrombotic causes.

2. Added value of this study

These data show that patients really do present late as compared to a pre-COVID population and have a high incidence of myocardial injury with a significantly higher incidence of cardiogenic shock and higher mortality. The data suggest that the late presentation may at least play an important part in the natural history of COVID-ACS patients.

3. Implications of all the available evidence

These data have important implications for public health measures during such pandemics in the context of understandable public fear of COVID infection: these need to be simple, reassuring and repeated. “If you have chest pain, attend hospital where there are separate pathways to those used for COVID patients”.

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Table 1: Baseline characteristics of combined STEMI/NSTE-ACS COVID-ACS registry cohort*

Baseline Characteristic	COVID-ACS Total (n=265)
Age – mean (SD) (years)	64·9 (12·9)
Male sex – % (n)	75·5 (200/265)
Hypertension – % (n)	66·2 (174/263)
Hyperlipidaemia – % (n)	54·1 (131/242)
BMI – mean (SD) (kg/m^2)	27·5 (4·7)
Diabetes – % (n)	36·2 (92/265)
Smoking status	
· Current smoker – % (n)	27·1 (62/229)
· Ex-smoker – % (n)	27·1 (62/229)
· Non-smoker – % (n)	45·8 (105/229)
Heart failure – % (n)	19·3 (49/254)
Previous MI – % (n)	20·2 (57/258)
Previous PCI – % (n)	17·5 (46/263)
Chronic kidney disease (stages 3-5) – % (n)	14·6 (38/260)
Lung disease – % (n)	16·5 (42/254)
Previous stroke - % (n)	7·2 (19/265)
COVID-19 positive – % (n)	74·3 (197/265)
COVID-19 high index suspicion – % (n)	25·7 (68/265)
Killip Class III/IV on admission - % (n)	17·4 (46/265)
Out of hospital cardiac arrest - % (n)	5.3 (14/265)
Admission lactate - mean (SD) (mmol/L)	4·1 (7.3)
Admission lactate >2.0mmol/l - % (n)	61·7 (58/94)
Presentation symptoms typical of ACS - % (n)	81·4 (214/263)
Full PPE worn during procedure - % (n)	90·9 (209/230)

*Excludes patients with non-atheromatous ACS (see Figure 1). N/A = data unavailable.
Denominators not equal to n=265 are due to incomplete data.

Table 2: Baseline demographics/procedural characteristics of COVID-ACS and BCIS STEMI subgroups

	COVID-ACS Total (n=144)	BCIS 2018-2019 (n=24961)	P value
Age – mean (SD) (years)	63·1 (12·6)	65·6 (13·4)	**0·018**
Male sex – % (n)	77·8 (112/144)	72·2 (17972/24961)	0·136
Hypertension – % (n)	64·8 (92/142)	44·8 (9456/24961)	**<0·001**
Hyperlipidaemia – % (n)	46·0 (56/126)	28·9 (6039/24961)	**<0.001**
BMI, mean (SD) (kg/m^2)	27·3 (4.5)	27·8 (5.5)	0·184
Diabetes – % (n)	34·0 (49/144)	20·9 (4926/24961)	**<0·001**
Current smoker – % (n)	31·7 (39/123)	33·7 (7645/24961)	0·769
Heart failure – % (n)	19·0 (27/142)	2·8 (569/24961)	**<0·001**
Previous MI – % (n)	16·4 (23/140)	13·0 (2747/24961)	0·056
Previous PCI – % (n)	13·9 (20/144)	10·2 (2129/24961)	**0.034**
Chronic kidney disease (stage 3-5) – % (n)	9·9 (14/141)	3·6 (739/24961)	**<0·001**
Lung disease – % (n)	11·8 (16/135)	13·4 (2763/24961)	0·783
Stroke - % (n)	7·6 (11/144)	5·7 (1178/24961)	0·111
COVID-19 positive – %	76·4 (110/144)	N/A	
COVID-19 suspected – %	23·6 (24/144)	N/A	
Troponin T - median (IQR) (ng/L)	2224·0 (7391·5)	899·0 (3645·0)	0.148
Troponin I - median (IQR) (ng/L)	762·0 (22987·0)	61·4 (1103·8)	0.192
LVEF - mean (SD) (%)	39·7 (12·5)	N/A	
PROCEDURE			
Cardiac symptom onset to admission – median (IQR) (minutes)	338·0 (1306·5)	173·0 (280·0)	**<0·001**
Door to balloon time – median (IQR) (minutes)	83·0 (299·0)	37·0 (78·0)	**<0·001**
SBP at admission - mean (SD) (mmHg)	119·5 (26·8)	131·9 (27·5)	**<0·001**
HR at admission - mean (SD) (bpm)	86·0 (22·0)	78·5 (20·1)	**<0·001**
Trans-radial access - % (n)	74·3 (107/144)	87·4 (19611/22442)	**<0·001**
Non-obstructive CAD – % (n)	2·8 (4/144)	N/A	
Syntax Score - mean (SD)	16·5 (9·1)	N/A	
Thrombotic occlusion – % (n)	37·5 (54/144)	N/A	
Use of aspiration thrombectomy – % (n)	12·5 (18/144)	17·1 (3754/21915)	0·151
Complete revascularisation – % (n)	45·8 (66/144)	N/A	
POST-PROCEDURE			
ICU admission - % (n)	45·8 (66/144)	N/A	
Ventilation - % (n)	20·8 (30/144)	3·8 (863/22442)	**<0·001**
Pressor support - % (n)	27·1 (39/144)	4·6 (1001/21720)	**<0·001**
Mechanical support device - % (n)	5·6 (8/144) ECMO - 3, IABP - 5	2·1 (459/21720)	**0·012**

N/A = data unavailable. Denominators not equal to n=144 are due to incomplete data.

Table 3: Baseline demographics/procedural characteristics of COVID-ACS and MINAP NSTE-ACS subgroups

FINAL DIAGNOSIS: NSTE-ACS	COVID-ACS Total (n=121)	MINAP 2019 (n=46389)	P value
Age – mean (SD) (years)	66·9 (12·9)	70·2 (13·3)	**0·005**
Male sex – % (n)	79·3 (88/111)	65·5 (30388/46389)	**0·002**
Hypertension – % (n)	68·3 (82/120)	57·8 (24359/46389)	**<0·001**
Hyperlipidaemia –% (n)	62.9 (73/116)	33·6 (13895/46389)	**<0·001**
BMI, mean (SD) (kg/m^2)	27·8 (4·9)	28·2 (6.0)	0·371
Diabetes – % (n)	38·8 (47/121)	31·1 (14101/46389)	**0·048**
Current smoker – % (n)	21·7 (23/106)	20·4 (8834/46389)	0·459
Heart failure – % (n)	18·8 (22/117)	9·6 (3968/46389)	**<0·001**
Previous MI – % (n)	24·6 (29/118)	29·1 (12181/46389)	0·754
Previous PCI – % (n)	21·8 (26/119)	18·7 (7684/46389)	0·137
Chronic kidney disease (stage 3-5) – % (n)	20·2 (24/119)	10·2 (4214/46389)	**<0·001**
Lung disease – % (n)	21·8 (26/119)	19·2 (7908/46389)	0·179
Stroke - % (n)	6·6 (8/121)	10·0 (4121/46389)	0·519
COVID-19 positive – %	71·9 (87/121)	N/A	
COVID-19 high index suspicion – %	28·1 (34/121)	N/A	
Troponin T, median (IQR) (ng/L)	60·0 (287·0)	144·0 (413·0)	0.365
Troponin I, median (IQR) (ng/L)	171·0 (1239·3)	276·6 (1324·3)	0.481
LVEF - mean (SD) (%)	48·6 (13.3)	N/A	
PROCEDURE			
Cardiac symptom onset to admission – median (IQR) (minutes)	417·0 (2904·0)	295·0 (891·0)	**0·012**
Door to angio time – median (IQR) (hours)	48·5 (120·2)	57·7 (80·3)	0·491
SBP at admission, mean (SD) (mmHg)	122·0 (29·2)	142·4 (27·3)	**<0·001**
HR at admission, mean (SD) (bpm)	80·2 (18·7)	79·6 (20·0)	0·725
Transradial access - % (n)	77·7 (94/121)	88·0 (29777/33833)	**0·002**
Non-obstructive CAD – % (n)	18·2 (22/121)	N/A	
Syntax Score - mean (SD)	19·3 (11.7)	N/A	
Thrombotic occlusion – % (n)	5·0 (6/121)	N/A	
Use of aspiration thrombectomy – % (n)	0·0 (0/121)	2·41 (804/33250)	0·124
Complete revascularisation – % (n)	42·7 (32/75)	N/A	
POST-PROCEDURE			
ICU admission - % (n)	33·9 (41/121)	N/A	
Ventilation - % (n)	11·6 (14/121)	0·4 (138/33833)	**<0·001**
Pressor support - % (n)	19·0 (23/121)	0·9 (306/32666)	**<0·001**
Mechanical support device - % (n)	0·8 (1/121) IABP - 1	0·6 (203/32666)	0·518

N/A = data unavailable. Denominators not equal to n=121 are due to incomplete data.

Table 4: In-hospital outcomes of COVID-STEMI and MINAP/BCIS STEMI subgroups

OUTCOMES	COVID-STEMI Total (n=144)	MINAP 2019/BCIS 2018-2019	P value
Death – % (n)	22·9 (33/144)	5·7 (1232/21675)	<0·001
Myocardial infarction – % (n)	5·6 (8/144)	N/A	
Heart failure – % (n)	23·6 (34/144)	N/A	
Stent thrombosis – % (n)	1·4 (2/144)	N/A	
Bleeding (BARC 3-5) – % (n)	2·8 (4/144)	0·3 (36/13913)	0·001
Stroke - % (n)	2·1 (3/144)	0·1 (32/21994)	0·002
Cardiogenic shock – % (n)	20·1 (29/144)	8·7 (1898/21972)	<0·001
In-patient stay – median (IQR) (days)	6·4 (2·7-12·7)	3·0 (2·0-5·0)	<0·001

N/A = data unavailable

Table 5: In-hospital outcomes of COVID NSTE-ACS and MINAP/BCIS STEMI subgroups

OUTCOMES	COVID NSTE-ACS Total (n=121)	MINAP 2019/BCIS 2018-2019	P value
Death – % (n)	6·6 (8/121)	1·2 (378/32546)	<0·001
Myocardial infarction – % (n)	4·1 (5/121)	N/A	
Heart failure – % (n)	19·0 (23/121)	N/A	
Stent thrombosis – % (n)	0·0 (0/121)	N/A	
Bleeding (BARC 3-5) – % (n)	2·5 (3/121)	0·1 (28/22445)	0·001
Stroke - % (n)	0·8 (1/121)	0·1 (18/33352)	0·067
Cardiogenic shock – % (n)	5·0 (6/121)	1·4 (461/33342)	0·007
In-patient stay – median (IQR) (days)	6·9 (3·4-18·4)	5·0 (3·0-8·0)	<0·001

N/A = data unavailable

Table 6: Causes of death and associated conditions

STEMI/NSTE-ACS Mortality Cause	COMBINED % (n)	COMBINED Cardiogenic shock - % (n)	Ischaemia time – median (IQR), minutes STEMI ONLY	Ischaemia time (non-CGS) – median (IQR), minutes STEMI ONLY
Cardiovascular	58.5 (24/41)	75.0 (18/24)	STEMI + CV death + CGS 1271.0 (355.0-2760.0) (n=19*)	STEMI, no CGS 440.5 (208.0-1701.0) (n=106*)
Respiratory	31.7 (13/41)	23.1 (3/13)	STEMI + Resp death, no CGS 333.0 (222.0-2652.0) (n=8*)	-
Neurological	4.9 (2/41)	0.0 (0/2)	-	-
Unknown	4.9 (2/41)	0.0 (0/2)	-	-

*n=19, n=106, n=8 due to incomplete data

Table 7: Multivariate propensity analyses comparing the COVID-ACS Registry with the BCIS/MINAP database for

(a) overall mortality : this adjusts for age, sex, hypertension, hyperlipidaemia, diabetes, ischaemic time, CGS

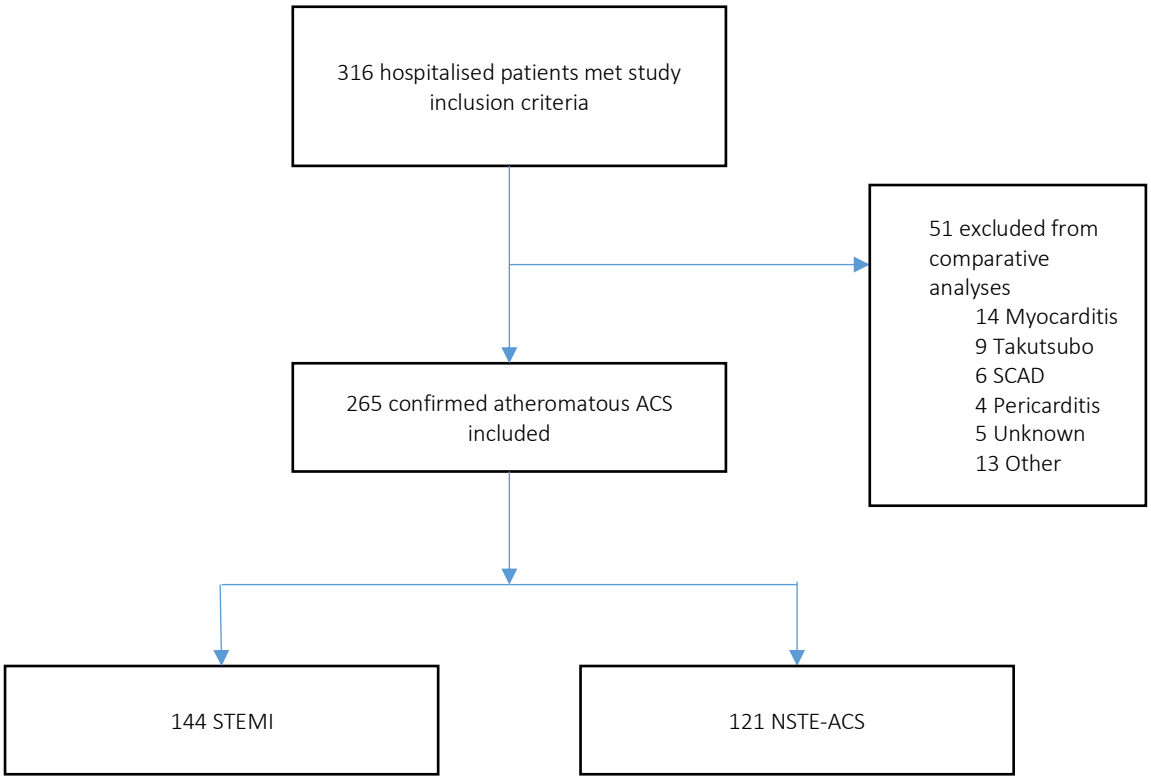
(b) mortality related to ischaemia time :

(c) mortality related to presence of presence of CGS (Odds ratio (95% CI))

	All patients	CGS	Non-CGS
COVID-ACS Registry versus reference population OVERALL Mortality	3.33 (2.04-5.42)	1.83 (0.80-4.19)	4.16 (2.33-7.44)
(b) Total Ischaemic time (for every 10 minutes)	1.10 (1.01-1.19)	1.25 (1.09-1.45)	1.04 (0.94-1.15)
(c) CGS	1.48 (1.27-1.72)		

COVID-ACS and BCIS/MINAP were matched for age, sex HTN, diabetes lipids using propensity score. Total ischaemic time (symptom-to-admission plus admission-to-balloon) was right skewed, therefore a logarithm transformation with base 10 was performed.

Figure 1: Patient selection



Appendix 1: Participating centres

We will complete this