MEDICINA CLINICA

Brief report

SARS-CoV-2 infection: A predisposing factor for acute coronary syndrome[☆]

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ABSTRACT

Introduction: Several case series of ACS have been reported in COVID 19 patients. We aim to study its incidence, characteristics, and three-month prognosis. To put this incidence in perspective we compared it with the incidence of in-hospital ACS during the same period of 2019.
Methods: Observational multicenter cohort study of 3.108 COVID-19 patients admitted to two hospitals in Madrid between March 1st and May 15th, 2020. Ten patients suffered an ACS while being hospitalized for COVID 19 and were followed for three months. The ACS incidence in hospitalized patients during the same period of 2019 was also studied.
Results: The incidence of ACS in COVID-19 patients was 3.31‰, significantly higher than in the 2019 period, 1.01‰ ($p = 0.013$). COVID-19 patients that suffered and ACS frequently had a severe infection, presented with STEMI (80%), and had multivessel disease (67%). Mortality rate (30%) and hospital readmissions at three months (20%) were very high.
Conclusions: Severe COVID-19 patients develop ACS more frequently than expected. Although the overall incidence was low, it carried a poor immediate and three-month prognosis.

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Infección por SARS-CoV-2: un factor predisponente para síndrome coronario agudo

RESUMEN

Introducción: Se han reportado series de casos de SCA en pacientes COVID Nuestro objetivo fue describir su incidencia, características, y pronóstico a 3 meses. Para contextualizar esta incidencia se comparó con la incidencia de SCA intrahospitalarios durante el mismo periodo del 2019.
Métodos: Estudio observacional de cohortes multicéntrico, de 3.108 pacientes COVID-19 ingresados en dos hospitales madrileños, entre el 1 de marzo y 15 de mayo de 2020. Diez pacientes sufrieron un SCA durante la fase hospitalaria realizándose un seguimiento clínico de 3 meses. Se estudiaron asimismo los pacientes con SCA intrahospitalarios durante el mismo periodo del 2019.
Resultados: La incidencia de SCA en COVID-19 fue 3,31‰, significativamente superior a la del periodo 2019, de 1,01‰ ($p = 0,013$). Los pacientes COVID-19 con SCA, tenían una infección grave, mayoritariamente SCACEST (80%) y enfermedad multivaso (67%). La tasa de mortalidad (30%) y reingresos hospitalarios a 3 meses (20%) fueron muy elevadas.
Conclusiones: El SCA es una complicación más frecuente de lo habitual en COVID-19 grave pero poco común y con mal pronóstico inmediato y a 3 meses.

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C. de Cortina Camarero, E. Gómez Mariscal, V. Espejo Bares et al.

Medicina Clínica 157 (2021) 114–117

Introduction

The infection caused by the new severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) has caused a global pandemic that began in late 2019. The infection is usually mild or asymptomatic, but in the more severe spectrum, a respiratory condition occurs which may cause distress.[1] In this context, an exaggerated release of cytokines can be triggered, with a systemic hyperinflammatory response and multiple organ involvement.[2]

Cardiovascular system involvement is common, with different clinical manifestations such as ACS.[3] However, there is little information about the incidence of acute coronary syndrome (ACS) in patients with coronavirus disease 2019 (COVID-19), its treatment and prognosis, especially after initial hospitalisation.

Our main objective was to describe the incidence, characteristics, angiographic findings and immediate and 3-month prognosis of patients diagnosed with ACS in a large cohort of patients with COVID-19 admitted to 2 hospitals in the south of Madrid. Secondarily, it was compared with the incidence, characteristics, and therapeutic management of in-hospital ACS in the same time period of 2019 in a population of patients admitted to both hospitals for non-cardiological causes.

Methods

Between 1 March and 15 May 2020, 3108 patients with SARS-CoV-2 infection were admitted to the Hospital Universitario Fundación Alcorcón and the Hospital Universitario Infanta Leonor in Madrid with positive reverse transcriptase polymerase chain reaction ($_{rt}$PCR) for SARS-CoV-2 or highly suggestive clinical features with negative $_{rt}$PCR. No patient was excluded. All patients who suffered an ACS during the course of infection in the hospital admission period (ACS-COVID group) were registered in a specific database and assigned a numerical code. Their clinical data were obtained by reviewing electronic medical records. Severe or critical COVID-19 was defined according to previously published criteria.[4] Those patients with ACS and COVID-19 who were discharged were contacted by telephone or in person after three months of follow-up.

In-hospital ACS were reviewed over the same interval of 2019 (ACS-2019 group) in patients hospitalized for non-cardiological causes, and the incidence of ACS, baseline characteristics, management, and prognosis were compared between both populations.

Statistical analysis

Quantitative variables were expressed as mean and standard deviation or as median and interquartile range (IQR) and categorical variables as counts and frequency by percentage. The Student's t-test for independent variables was used for the comparison of means, the Mann–Whitney *U* test for the comparison of medians and Fisher's exact test for the comparison of categorical variables. Data were analysed with SPSS statistics (version 15.0, IBM, NY, USA).

The study was approved by the ethics committee of both institutions and a written informed consent was given to all patients.

Results

In the cohort of 3108 COVID-19 patients, during the study period, 10 patients were diagnosed with ACS during their hospital course, an incidence of 3.31‰. They were predominantly male, with a median age of 68 years (IQR 57–77) and mostly hypertensive (70%) (Table 1).

In the same period of 2019, 6952 patients were admitted to both centres, with 7 patients diagnosed with ACS during their admission, an incidence of 1.01‰. The difference in incidences between both populations was statistically significant ($p = 0.013$), highlighting a higher incidence of ACS among COVID-19 patients. The patients in the ACS 2019 group were older, with a more unfavourable cardiovascular risk profile and a history of coronary artery disease.

There was a higher proportion of NSTEACS in ACS-2019 patients, with similar rates of coronary angiography, but a lower percentage of multivessel disease (Fig. 1).

Laboratory markers of myocardial damage and inflammation were analysed with a tendency for higher elevation in ACS-COVID, especially D-dimer (3709, IQR 816–38,297 °C μg/l). At admission there were a greater number of complications and deaths in the ACS-COVID population, compared to ACS-2019 (Table 1).

In the ACS COVID group, there was a prevalence of respiratory symptoms, with pneumonia in almost all patients and criteria for severe or critical infection in 6 patients. The median time from

Table 1
Baseline and progression characteristics of the ACS COVID and ACS 2019 groups.

	ACS 2019 (n = 7)	ACS COVID (n = 10)	p
Sex-# (%)			0.593
Male	4 (57)	8 (80)	
Female	3 (43)	2 (20)	
Age (median, IQR)	74 (61–79)	68 (57–77)	0.31
Cardiovascular risk factors—# (%)			
HBP	6 (86)	7 (70)	0.603
DM2	2 (29)	1 (10)	0.537
DL	5 (71)	5 (50)	0.622
Smoking			0.741
Non smoker	1 (14)	3 (30)	
Active smoker	4 (57)	5 (50)	
Former smoker	2 (29)	2 (20)	
Obesity (BMI > 30 kg/m^2)-# (%)	3 (43)	2 (20)	0.608
Ischemic heart disease history-# (%)	4 (57)	1 (10)	0.101
Previous treatment-# (%)			
Antiplatelet agents	5 (71)	2 (20)	0.058
Anticoagulation	1 (14)	0	0.412
ACEI/ARBs	3 (43)	6 (60)	0.637
Statins	6 (86)	4 (40)	0.134
Mean time interval from symptom onset to ACS, days-(SD)	5.5 ± 6.3	9.7 ± 6.3	0.229
LVEF (%) – (mean, SD)	53 ± 8	51 ± 9	0.503
Segmental contraction abnormalities-# (%)	4 (57)	9 (90)	0.192
Laboratory parameters – (median, IQR)			

C. de Cortina Camarero, E. Gómez Mariscal, V. Espejo Bares et al.

Medicina Clínica 157 (2021) 114–117

Table 1 (*Continued*)

	ACS 2019 (n = 7)	ACS COVID (n = 10)	p
CPK (U/l)	328 (95−554)	404 (261−960)	0.562
TnI peak[a]			
Conventional TnI peak (ng/mL)	14 (3−38) (n = 6)	15 (11−31) (n = 6)	0.996
US TnI peak (ng/l)	NA	1204 (195−13496) (nº = 4)	
C-reactive protein (mg/l)	54 (15−81)	33 (12−127)	1
LDH (U/l)	375 (277−495)	436 (320−1852)	0.503
Ferritin (ng/mL)	192 (61−303)	769 (518−1892)	0.006
D-Dimer (µg/l)[b]	NA	3.709 (816−38.297)	
ACS type-# (%)			0.002
STEACS	0	8 (80)	
NSTEACS	7 (100)	2 (20)	
Coronary angiography-#/total population (%)	5 (71)	6 (60)	0.134
Findings in coronary angiography-#/total coronary angiography (%)			
Lesions > 70%	4 (80)	5 (83)	1
Multivessel disease	2 (40)	4 (67)	0.567
Revascularization-#/total population (%)	3 (43)	4 (40)	1
Severe complications-# (%)	0	2 (20) Acute pulmonary oedema Cardiogenic shock	0.228
Death during hospitalization-# (%)	0	2 (20) Cardiac rupture Respiratory failure	0.485
3-month follow-up-# (%)			
Death 3 months	0 (0)	3 (30)	0.228
Readmission 3 months	1 (14)	2 (20)	1

ARBs: angiotensin ıı receptor blockers, COVID-19: coronavirus disease 2019; CPK: creatine phosphokinase; SD: standard deviation; DL: dyslipidaemia; DM2: diabetes mellitus type 2; LVEF, left ventricular ejection fraction; Hb: haemoglobin; HBP: high blood pressure; ACEI: angiotensin converting enzyme inhibitors; BMI: body mass index; LDH: lactate dehydrogenase; NA: not available; IQR: interquartile range; ACS: acute coronary syndrome; STEACS: ST-elevation acute coronary syndrome; NSTEACS, non-ST elevation acute coronary syndrome; TnI: troponin ı, US: ultrasensitive.

[a] The cut-off point for conventional TnI was <0.07 ng/mL. The cut-off point for the US Tn was <57 ng/l for men and <37 ng/l for women.

[b] The D-dimer variable could not be compared between the ACS-COVID and ACS-2019 groups because it had too many missing values in the ACS-2019 group.
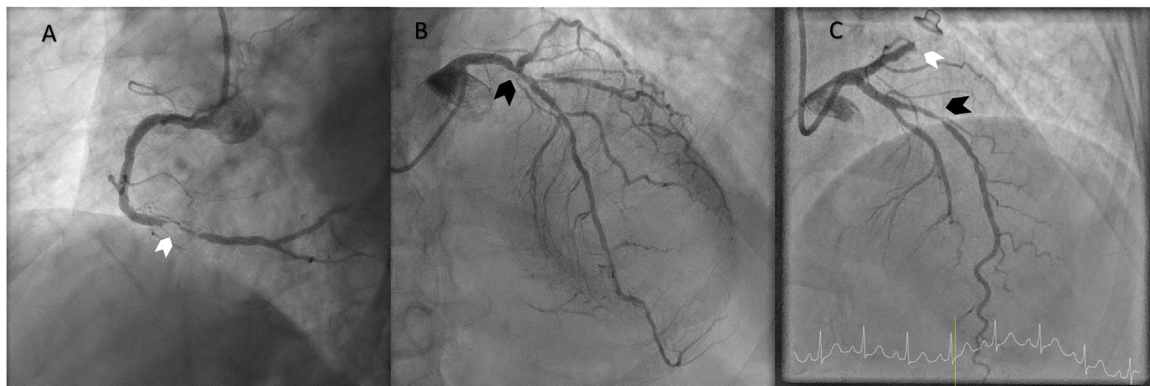

Fig. 1. Coronary angiograms of patients #5 and #8 in the ACS-COVID group, showing multivessel disease. A and B: Coronary angiography of patient #5, with inferior STEACS. Finding of a critical lesion in the distal right coronary artery (RCA) (A: white arrowhead) responsible for ST-elevation acute coronary syndrome (STEACS). In addition, there was diffuse disease in the left coronary artery, with a distal eccentric lesion in the left main coronary artery (LMCA) (black arrowhead) with moderate involvement of the proximal left anterior descending artery (LADA) and diffuse disease in the rest of the vessel, as well as significant disease in the first diagonal branch (B). C: Coronary angiography of patient #8, with inferolateral STEACS, with occlusion of the proximal circumflex artery (white arrowhead) and significant lesion in the middle LAD (black arrowhead).

COVID-19 onset to ACS was 9.7 days Most were treated with hydroxychloroquine and low molecular weight heparin (Table 2).

Progression during follow-up

The mean follow-up time in the ACS-COVID group was 113 °C ± 14 days, with 2 readmissions and 1 death from acute heart failure. Therefore, the 3-month mortality in the ACS-COVID group was 30%, with a readmission rate of 20% (Table 1).

Discussion

The findings of this study show that in a large population of 3108 patients with COVID-19, the incidence of ACS was 3.31‰, significantly higher than the incidence of in-hospital ACS in the same period of 2019, 1.01‰. ACS-COVID patients predominantly showed severe or critical COVID-19, with a high proportion of STEACS and elevated inflammatory parameters. A higher rate of conservative management stands out, with a common finding of multivessel coronary disease. At immediate and 3-month prognosis they are a very high-risk population, with a high mortality rate of 20% and 30% respectively, and a high readmission rate at 3 months (20%).

There is little information on the incidence, management, and prognosis of ACS in patients with COVID-19. The incidence of 3.31‰ in our study was higher than that reported in another Spanish series of 1.9‰,[5] but identical to that published in a Danish registry.[6]

The mean time interval between the onset of symptoms due to COVID-19 and ACS was approximately 10 days, underlining that this type of arterial thrombotic complications usually occurs in the late phase of the disease, with hyper-activation of inflammatory

C. de Cortina Camarero, E. Gómez Mariscal, V. Espejo Bares et al.

Medicina Clínica 157 (2021) 114–117

Table 2
Characteristics of COVID-19 in ACS-COVID patients.

	ACS-COVID (n = 10)
COVID-19 symptoms	
Respiratory	8
General	7
Gastrointestinal	4
Neurological	2
COVID-19 pneumonia	9
PCR confirmation	8
COVID-19 severity	
Mild	4
Severe	3
Critical	3
Treatment during admission	
Hydroxychloroquine	8
LMWH	8
Corticosteroids	5
Tocilizumab	2

COVID-19: coronavirus disease 2019; LMWH: low molecular weight heparin; PCR: polymerase chain reaction; ACS: acute coronary syndrome.

mechanisms.[7] In this sense, 60% of the patients in our series had a severe or critical COVID-19 infection. Laboratory tests showed that D-dimer levels were very high in association with a certain degree of coagulopathy, known as COVID-19-associated coagulopathy,[8] responsible for this type of arterial and/or venous thrombotic complications.

In terms of therapeutic management, the rate of coronary angiography was 60%, due to the severe condition of the patients, similar to other series, such as the Bangalore[9] series, of 50%.

Our follow-up mortality rate was 30% and readmission rate was 20%, implying that ACS in patients with COVID-19 is a marker of poor in-hospital and short-term prognosis. Should this be confirmed in further studies, this group of patients should be closely monitored after ACS.

To assess whether the incidence of ACS in the COVID-19 population was higher than other diseases that act as a *trigger* for a coronary event, a secondary objective was proposed so as to compare the incidence of ACS with that observed in the previous year period of 2019 in the total population of patients admitted for non-cardiological causes.[10] All patients admitted to both hospitals during the same time period were considered in order to avoid selection bias. The incidence of ACS was found to be higher in the ACS-COVID group, where there is a significant activation of inflammatory mechanisms, probably related to the aetiopathogenesis of coronary events.

Limitations

The number of ACSs is small, so the power to detect differences between the two populations is low. Some of the infarcts included

in the sample could be type 2, or even myocarditis, as not all cases had a coronary angiography. Finally, it is possible that the incidence of ACS was higher in relation to the diagnostic difficulty in this type of patient, with equivocal symptoms.

Conclusions

Patients with COVID-19 have a higher risk of ACS than patients hospitalised for other diseases. Although the incidence of ACS is low, this complication is associated with a poor immediate and 3-month prognosis.

Conflict of interests

The authors declare no conflict of interest.

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