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Medicina Clínica xxx (xxxx) xxx–xxx

MEDICINA CLINICA

www.elsevier.es/medicinaclinica

Original article

Mortality risk factors in patients with SARS-CoV-2 infection and atrial fibrillation: Data from the SEMI-COVID-19 registry

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ARTICLE INFO

Article history:
Received 23 October 2021
Accepted 10 January 2022
Available online xxx

Keywords:
Atrial fibrillation
COVID-2019
Hospitalization
Risk factor
Mortality
Anticoagulation

ABSTRACT

Introduction: Atrial fibrillation and associated comorbidities pose a risk factor for mortality, morbidity and development of complications in patients admitted for COVID-19.
Objectives: To describe the clinical, epidemiological, radiological and analytical characteristics of patients with AF admitted for COVID-19 in Spain. Secondarily, we aim to identify those variables associated with mortality and poor prognosis of COVID-19 in patients with AF.
Methods: Retrospective, observational, multicenter, nationwide, retrospective study of patients hospitalized for COVID-19 from March 1 to October 1, 2020. Data were obtained from the SEMI-COVID-19 Registry of the Spanish Society of Internal Medicine (SEMI) in which 150 Spanish hospitals participate.
Results: Between March 1 and October 1, 2020, data from a total of 16,461 patients were entered into the SEMI-COVID-19 registry. 1,816 (11%) had a history of AF and the number of deaths among AF patients amounted to 738 (41%). Regarding clinical characteristics, deceased patients were admitted with a higher heart rate (88.38 vs 84.95; $p > 0.01$), with a higher percentage of respiratory failure (67.2% vs 20.1%; $p < 0.01$) and high tachypnea (58% vs 30%; $p < 0.01$). The comorbidities that presented statistically significant differences in the deceased group were: age, hypertension and diabetes with target organ involvement. There was also a higher prevalence of a history of cardiovascular disease in the deceased. On multivariate analysis, DOACs treatment had a protective role for mortality (OR:0,597) IC (0,402-0,888 ; $p = 0.011$).
Conclusions: Previous treatment with DOACs and DOACs treatment during admission seem to have a protective role in patients with AF, although this fact should be verified in prospective studies.

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2387-0206/

Factores de riesgo de mortalidad en pacientes con infección por SARS-CoV-2 y fibrilación auricular: datos del registro SEMI-COVID-19

Palabras clave:
Fibrilación auricular
COVID-2019
Hospitalización
Factor de riesgo
Mortalidad
Anticoagulación

R E S U M E N

Introducción: La fibrilación auricular y las comorbilidades asociadas a ella suponen un factor de riesgo de mortalidad, morbilidad y desarrollo de complicaciones en los pacientes ingresados por COVID-19.
Objetivos: Describir las características clínicas, epidemiológicas, radiológicas y analíticas de los pacientes con FA ingresados por COVID-19 en España. De forma secundaria, se pretende identificar aquellas variables que se asocian con mortalidad y mal pronóstico de la COVID-19 en pacientes que presentan FA.
Métodos: Estudio retrospectivo, observacional y multicéntrico de ámbito nacional de pacientes hospitalizados por COVID-19 desde el 1 de marzo al 1 de octubre de 2020. Los datos fueron obtenidos del Registro SEMI-COVID-19 de la Sociedad Española de Medicina Interna (SEMI) en el que participan 150 hospitales españoles.
Resultados: De un total de 16.461 pacientes en el registro SEMI-COVID-19, 1.816 (11%) tenían antecedente de FA y el número de fallecidos entre los pacientes con FA ascendió a 738 (41%). En cuanto a la clínica, los pacientes fallecidos ingresaron con una frecuencia cardíaca mayor (88,38 vs 84,95; p > 0,01), con mayor porcentaje de insuficiencia respiratoria (67,2% vs 20,1%; p < 0,01) y mayor taquipnea (58% vs 30%; p < 0,09). En el análisis multivariante, el tratamiento con ACOD tuvo un papel protector para la mortalidad por infección por COVID 19 (OR:0,597; IC (0,402-0,888; p = 0.011)
Conclusiones: El tratamiento previo con ACOD como el tratamiento con ACOD durante el ingreso parecen tener un papel protector en los pacientes con FA, aunque este hecho debería ser comprobado con estudios prospectivos.

Introduction

New coronavirus 2019 (COVID-19) disease, caused by SARS-CoV-2, has been and remains a challenge for health systems worldwide, given its high contagiousness and morbidity and mortality[1]. The pandemic caused by COVID-19 has affected more than 290 million people worldwide and has caused more than 5 million deaths as of January 2022[2]. Spain is one of the most affected countries in the world[3], with more than 7,164,906 million cases and more than 89,837 deaths since the start of the pandemic[2]. This has led the Spanish Society of Internal Medicine (SEMI) to create a registry with data on hospitalized patients throughout the country in which more than 150 hospitals have participated.

The magnitude of the pandemic has led to a truly scientific revolution, with studies to describe its clinical characteristics and risk factors, clinical trials to discover effective treatments and the development of vaccines in record time.

Among the risk factors described to date, cardiovascular disease has been associated with increased morbidity and mortality[4–7]. On the other hand, cardiovascular complications developed during admission in relation to COVID-19 are common and constitute a major cause of mortality[8–12].

However, the role of atrial fibrillation (AF) and its management in relation to COVID-19 remains to be determined and not many studies have been published to date.

AF is the most common sustained arrhythmia in the Spanish population, with an overall prevalence of around 4% and over 15% in patients over 80 years of age[13–15]. It is a risk factor for the development of heart failure, cardioembolic stroke and dementia[13,16], all of which have been independently associated with COVID-19 mortality. On the other hand, age, hypertension, diabetes mellitus, obesity and ischaemic heart disease are factors that increase the risk of developing AF and have all been described as poor prognostic factors in COVID-19. Bearing in mind all of the above, given the impact that both diseases independently have on global health and the evident relationship between them, this study aims to describe the clinical, epidemiological, radiological and laboratory characteristics of patients with AF admitted for COVID-19 in Spain.

A second aim is to identify those variables that are associated with mortality and poor prognosis of COVID-19 in patients with AF.

Material and methods

Study design

A nationwide retrospective, observational, multicenter study of patients hospitalized for COVID-19 was conducted from 1 March to 1 October 2020. The data were obtained from the SEMI-COVID-19 Registry, with the participation of 150 Spanish hospitals. The SEMI-COVID-19 registry has consecutively enrolled older patients with microbiologically confirmed COVID-19 disease using a reverse transcription polymerase chain reaction test obtained from a nasopharyngeal, sputum or bronchoalveolar lavage specimen.

For this study, we have selected patients with a history of AF during hospital admission for COVID-19.

Variables

Clinical, epidemiological, radiological, laboratory and therapeutic variables were analysed, as well as mortality during admission or early readmission, defined as a new episode of hospital admission within 30 days after discharge. Data were collected retrospectively using an online data capture system. The comorbidity burden of patients was established with the age-adjusted Charlson comorbidity index[17]. To establish functional status prior to hospital admission, the Barthel index was used[18] (independent or mild dependency: 100-91; moderate dependency: 90-61; severe dependency: ≤60). Patients were considered to have hypertension, diabetes mellitus or dyslipidaemia if they had a previous diagnosis in their medical history or were receiving medical treatment for them. Diabetes mellitus was classified into 2 subgroups: with target organ damage (brain, heart, kidney, or retina involvement) or without target organ damage. Chronic lung disease was defined as a previous diagnosis of chronic obstructive pulmonary disease or asthma. Atherosclerotic cardiovascular disease was defined by a previous history of ischemic heart disease (acute myocardial infarction, acute coronary syndrome, angina, or coronary revascularization). Neoplastic disease included all non-metastatic solid tumours (excluding non-melanoma skin tumours). Moderate-severe kidney disease was defined by a glomerular filtration rate below 45 ml/min/1.73 m^2 according to the CKD-EPI equation[10].

Table 1
Epidemiological, clinical, laboratory and radiological characteristics in patients with AF and COVID-19, classified into deceased and not deceased.

	Deceased N = 738	Not deceased N = 1,061	*p*
Comorbidities			
Age	83.30 ± 7.83	78.14 ± 10.63	<0.01
Male sex n (%)	465 (63.2)	600 (56.6)	<0.01
HBP n (%)	624 (84.7)	806 (76.1)	<0.01
Diabetes mellitus n (%)			
Without TO lesion	136 (18.5)	207 (19.1)	0.72
With TO lesion	113 (15.4)	99 (9.1)	<0.01
Dyslipidemia n (%)	419 (56.9)	565 (53.3)	0.131
BMI > 30n (%)	142 (22.0)	250 (25.6)	0.103
Charlson index	2.98 ± 2.37	2.08 ± 2.03	<0.01
Heart failure n (%)	277 (37.5)	291 (27.4)	<0.01
AMI n (%)	115 (15.6)	120 (11.3)	<0.01
Angina n (%)	74 (10.1)	59 (5.6)	<0.01
Stroke n (%)	100 (13.6)	105 (9.9)	0.017
PVD n (%)	97 (13.2)	77 (7.3)	<0.01
COPD n (%)	119 (16.2)	150 (14.2)	0.239
Dementia n (%)	200 (27.1)	165 (15.6)	<0.01
Clinical, laboratory and radiological characteristics			
HR bpm	88.38 ± 21.76	84.95 ± 18.93	<0.01
SBP mmHg	126.5 ± 25.09	130.73 ± 23.50	<0.01
SpO_2%	90.07 ± 7.51	93.43 ± 4.64	<0.01
RR>20 rpm n (%)	415 (58.0)	313 (30.0)	<0.01
Dyspnea n (%)	540 (73.6)	602 (56.8)	<0.01
Confusion n (%)	273 (37.1)	140 (13.3)	<0.01
Creatinine mg/dl	1.66 ± 1.23	1.25 ± 0.93	<0.01
Glucose (mg/dl)	150.01 ± 72.46	129.57 ± 61.91	<0.01
CRP (mg/L)	110.34 ± 97.45	76.17 ± 77.02	<0.01
Ferritin (ng/dl)	1.093.14 ± 1.386.62	691.01 ± 878.44	<0.01
INR	2.51 ± 2.53	2.41 ± 2.72	0.56
D-dimer (ng/dl)	2.556.6 ± 8.546.71	1.409 ± 5.064.883	<0.01
Bilateral pneumonia n (%)	385 (53.0)	488 (46.8)	<0.01
Pleural effusion n (%)	47 (6.5)	41 (3.9)	0.01
Usual treatment n (%)			
ACEI	219 (29.9)	221 (20.9)	<0.01
ARBs	189 (25.9)	309 (29.2)	0.129
ASA	97 (13.3)	116 (11.0)	0.135
Statins	324 (44.6)	490 (46.4)	0.456

ASA: acetylsalicylic acid; **ARBs:** angiotensin receptor blockers; **COPD:** chronic obstructive pulmonary disease; **CKD:** chronic kidney disease; **PVD:** peripheral vascular disease; **HR:** heart rate; **RR:** respiratory rate; **HBP:** high blood pressure; **AMI:** acute myocardial infarction; **HF:** heart failure; **ACEI:** angiotensin converting enzyme inhibitors; **BMI:** body mass index; **TO:** target organ; **CRP:** C-reactive protein; **SpO_2:** oxygen saturation; **SBP:** systolic blood pressure.

Moderate-severe liver disease was defined as grade B or C in the Child-Pugh classification. Obesity was defined by a body mass index $\geq 30\ kg/m^2$. Comorbidities were collected from the medical records of each hospital. Laboratory data (blood count, biochemistry, blood gases, coagulation) and imaging tests were collected on admission. Regarding anticoagulation, baseline anticoagulant treatment was classified into vitamin K antagonists (VKA) and direct oral anticoagulants (DOAC) since the frequency of low molecular weight heparin (LMWH) was negligible. However, 3 groups were differentiated in terms of anticoagulant treatment during admission: VKA, DOAC and LMWH. In-hospital complications included: admission to the intensive care unit, presence of acute respiratory distress syndrome, acute coronary syndrome, arrhythmia, *shock*, sepsis, acute renal failure, venous thromboembolism and acute arterial ischemia. Ventilatory support included invasive mechanical ventilation, non-invasive mechanical ventilation and high-flow oxygen.

Statistical analysis

Patients were divided according to the categorical variable of mortality into deceased or non-deceased. Categorical and continuous variables were expressed as absolute values and percentages and as medians (ranges), respectively. Differences between groups were analysed using the Student's t test or the Mann-Whitney U test for continuous variables or with Pearson's χ^2 for categorical variables. A value of $p < 0.05$ was considered statistically significant. The measure of association was presented as the *odds ratio* (OR) with a 95% confidence interval (95% CI). Subsequently, a multivariate analysis was performed expressed as adjusted OR, 95% CI. Logistic regression analysis was used to identify independent factors at admission for in-hospital mortality, including those variables with statistical significance in the bivariate analysis and with a percentage of missing values of less than 20%. The statistical analysis was done with the SPSS version 26.0 software (IBM SPSS Statistics ©).

Ethical aspects

All patients gave their informed consent. This study was conducted in accordance with the Helsinki Declaration and was approved by the Malaga Ethics Committee (Code: SEMI-COVID-19 03-27-20). The STROBE initiative for the publication of observational studies was followed (available at www.strobe-statement.org).

Results

A total of 16,461 patients were entered into the SEMI-COVID-19 registry between 1 March and 1 October 2020. Of these, 1816 (11%) had a history of AF. A total of 1,799 patients were finally analysed, as 17 were excluded due to lack of basic data for correct aetiology. The number of deaths among patients with AF was 738 (41%). The epidemiological, clinical, laboratory and radiological characteristics are shown in Table 1 Table 1. A specific table has been developed for anticoagulation treatment both before and during admission (Table 2 Table 2). Table 3 Table 3 shows the treatments

Table 2
Anticoagulant treatment at baseline and during admission for patients with AF and COVID-19. Classified as deceased and not deceased

	Deceased N = 738 (%)	Not deceased N = 1061 (%)	*p*
Baseline anticoagulant therapy			
No treatment	140 (19.1)	252 (23.8)	<0.01
VKA	360 (49.2)	384 (36.3)	<0.01
DOAC	212 (29.0)	405 (38.3)	<0.01
Anticoagulant treatment during admission			
LMWH	524 (72.1)	788 (74.6)	0.251
VKA	73 (10.1)	109 (10.4)	
DOAC	50 (6.9)	200 (19)	<0.01

DOAC: direct oral anticoagulants; VKA: vitamin K antagonists; LMWH: low molecular weight heparin.

Table 3
Treatments during admission and complications of patients with AF and COVID-19, classified as deceased and not deceased.

	Deceased N = 738 (%)	Not deceased N = 1061 (%)	*p*
Treatments during admission			
ACEI	82 (11.2)	124 (11.8)	0.724
ARBs	91 (12.6)	195 (18.6)	<0.01
ASA	75 (10.4)	96 (9.2)	0.396
Statins	109 (15.0)	240 (2.9)	<0.01
Ibuprofen	1 (0.1)	11 (1.0)	0.04
Other NSAIDs	20 (2.8)	37 (3.5)	0.03
Corticosteroids	320 (43.8)	387 (35.9)	<0.01
Lopinavir/ritonavir	302 (41.2)	481 (44.5)	0.17
Remdesivir	2 (0.3)	15 (1.4)	<0.01
Hydroxychloroquine	500 (68.4)	878 (81.1)	<0.01
Chloroquine	27 (3.7)	33 (3.1)	0.46
Colchicine	10 (1.4)	9 (0.8)	0.28
Tocilizumab	33 (4.5)	46 (4.3)	0.79
Complications			
Prone	93 (12.7)	58 (5.5)	<0.01
NIMV	58 (7.9)	35 (3.3)	<0.01
IMV	47 (6.4)	26 (2.5)	<0.01
HFO	85 (11.7)	48 (4.6)	<0.01
Bacterial pneum.	149 (20.2)	130 (12.3)	<0.01
ARDS	391 (53.4)	49 (4.6)	<0.01
HF	208 (28.2)	157 (14.8)	<0.01
AMI	23 (3.1)	6 (0.6)	<0.01
AKF	279 (37.9)	174 (16.4)	<0.01
PTE	4 (0.5)	8 (0.8)	0.578

ASA: acetylsalicylic acid; **NSAIDs:** nonsteroidal anti-inflammatory drugs; **ARBs:** angiotensin receptor blockers; **AMI:** acute myocardial infarction; **HF:** heart failure; **ACEI:** angiotensin converting enzyme inhibitors; **AKF:** acute kidney failure; **HFO:** high-flow oxygen therapy; **ARDS:** acute respiratory distress syndrome; **PTE:** pulmonary thromboembolism; **IMV:** invasive mechanical ventilation; **NIMV:** Non-invasive mechanical ventilation.

during admission and the complications. Table 4 Table 4 shows the logistic regression.

Numerous variables showed statistically significant differences in the deceased group. These were older and had a higher proportion of hypertensive and diabetic patients with target organ involvement. However, no statistically significant differences were found for dyslipidaemia and obesity, although there was a greater trend in the deceased group. A higher prevalence of cardiovascular history was also observed in the deceased: heart failure, acute myocardial infarction, angina pectoris, stroke, and peripheral vascular disease.

Clinically, deceased patients were admitted with a higher heart rate (88.38 vs. 84.95; $p < 0.01$), with higher percentage of respiratory failure (67.2 vs. 20.1%; $p < 0.01$), higher tachypnoea (58.0 vs. 30.0%; $p < 0.01$) and greater dyspnoea and confusion on admission (73.6 vs. 56.8%; $p < 0.01$ and 37.1 vs. 13.3%; $p < 0.01$, respectively). On the other hand, deceased patients had statistically significantly higher levels of creatinine, glucose, C-reactive protein (CRP), ferritin and D-dimer, as well as a higher percentage of bilateral pneumonia and pleural effusion. No differences were found in INR values (2.51 vs. 2.41; $p = 0.56$). Deceased patients showed higher rates of complications, except for pulmonary embolism (0.5 vs. 0.8; $p = 0.578$).

With regard to anticoagulant treatment, it is noteworthy that deceased patients had a lower frequency of treatment with DOACs, both at baseline (29 vs. 38.3%; $p < 0.01$) and during admission (6.9 vs. 19%; $p < 0.01$).

Table 4
Logistic regression analysis of factors associated with mortality in patients with AF admitted for COVID-19, including oral anticoagulation

	OR CI	*p*
Age	1.069 1.048–1.090	0.000
Sex (female)	0.726 0.518–1.018	0.63
Oxygen saturation>93%	0.956 0.929–0.985	0.003
Charlson index	1.112 1.035–1.194	0.004
D-dimer (ng/dl)	1.000 1.000–1.000	0.693
Serum creatine at admission (mg/dL)	1.354 1.157–1.584	0.001
C-reactive protein at admission (mg/L)	1.003 1.001–1.005	0.002
Direct oral anticoagulant	0.597 0.402–0.888	0.011

Finally, in the multivariate analysis, the following were independent factors for mortality: age, hypertension, Charlson index, and elevated heart rate, creatinine, CRP, ferritin and D-dimer values. Treatment with DOACs had a protective role for mortality (Appendix C Supplementary table of Annex B).

Discussion

The results of our research show that patients with COVID-19 infection with a history of AF may have a high mortality rate

during hospital admission. In our series, the mortality observed in this patient population exceeded 40% during the first waves of the COVID-19 pandemic. These findings have also been observed in other international multicenter registries such as HOPE, in which the researchers also observed a mortality rate of 43% for subjects with a history of AF[19].

AF associates a series of comorbidities that have been described as poor prognostic factors in COVID-19[19]. Our series showed a higher proportion of hypertensive, diabetic and patients with a history of cardiovascular disease (heart failure, acute myocardial infarction, angina, stroke and peripheral vascular disease) among the deceased. In terms of clinical characteristics at admission, the following were associated with worse prognosis: elevated heart rate, baseline oxygen saturation below 94%, tachypnoea and the presence of dyspnoea and confusion. These results are similar to those described in the literature in patients without AF[3]. Likewise, patients who had a significant inflammatory response on admission with increased lymphopenia and higher CRP, D-dimer, ferritin and creatinine levels had higher mortality[3,7].

Our research allows, at the time of admission, to identify a profile of patients with a history of AF and a high risk of mortality and complications. Given the high mortality rate in patients with AF, the mere fact of having AF poses a risk, which is increased in the case of advanced age, hypertension, previously established cardiovascular diseases, and a state of instability with respiratory failure and tachycardia with a high inflammatory response. The number of complications developed by AF patients was also quite high, all of them higher in the deceased group, as expected.

AF is the most common arrhythmia in patients with COVID-19 for two reasons: on the one hand, it is the most common arrhythmia in the general population and, on the other hand, COVID-19 favours its occurrence[8,10]. The mechanisms by which COVID-19 increases the frequency of AF are beginning to be understood, although they are not yet fully clear. Among the hypotheses proposed, the following have been postulated: reduced availability of ACE-II receptors, cytokine storm, endothelial damage, electrolyte disturbances, hypoxaemia and increased activity of the sympathetic nervous system as mechanisms favouring the onset of AF due to its effects on cardiac remodelling[11]. Recent studies show that patients with COVID-19 infection with a greater inflammatory reaction have a higher risk of developing AF, as occurs with influenza infection[20].

The role of anticoagulation in the treatment of COVID-19 is yet to be determined. Several studies have demonstrated the benefit of anticoagulation at prophylactic doses in relation to the prothrombotic state resulting from the massive inflammatory response occurring in COVID-19[11]. Recent published evidence in non-critically ill patients with COVID-19 shows that an initial strategy of therapeutic dose anticoagulation with heparin increased the likelihood of survival to hospital discharge compared to routine thromboprophylaxis[21].

One of the most relevant findings of our study is the observation of a higher proportion of patients treated with DOACs among the survivors, both at baseline and during admission. In fact, it behaves as a protective factor in the multivariate analysis. This finding is probably influenced by the fact that patients on baseline DOAC therapy are younger and in a better cardiorespiratory status, which allows them to tolerate the oral route well. However, maintaining the DOAC during admission was not associated with increased mortality. In this sense, some authors have also observed these findings of benefit from the use of DOACs in patients with COVID-19 infection who required hospital admission[22].

The indication to maintain DOAC therapy in patients with AF already taking it at baseline and DOAC therapy in the prevention of thromboembolic events in COVID-19 is an attractive option to consider in outpatient management or hospitalised COVID patients with good cardiopulmonary function. The main limitation would be its potential interaction with some of the treatments used at the beginning of the pandemic for COVID-19 such as lopinavir/ritonavir, although these treatments are currently out of use and no interactions have been described with corticosteroids, remdesivir or anti-inflammatory biologics (tocilizumab, baricitinib, etc.), which are the current reference treatments.

We believe that our study meets the objective of describing a clinical profile of patients with AF admitted for COVID-19 in Spain and identifying poor prognostic factors associated with morbidity and mortality: it is the first of its kind in Spain and one of the few worldwide. Despite this, it has several limitations. Firstly, this is a retrospective and observational study so, despite a multivariate analysis and a logistic regression, bias cannot be ruled out. On the other hand, the SEMI-COVID registry has involved a large number of investigators at different levels of care, which means heterogeneity in the inclusion of data, which, moreover, have been obtained from discharge reports and clinical records. Analysing only hospitalised patients gives a profile of greater severity and the data may not be fully translatable to the rest of AF patients. Despite these limitations, a large number of AF patients from all over the country have been analysed, as it is a multicentre registry, which has made it possible to draw up a risk profile in patients hospitalised for COVID-19. Future prospective studies are needed to confirm these initial data, given that only retrospective studies have been published to date.

Conclusions

AF and its associated comorbidities are a risk factor for mortality, morbidity, and the development of complications in patients hospitalized for COVID-19. Given the magnitude and importance of the pandemic, this has meant that COVID-19 has become the leading cause of death in patients with AF, replacing cardiovascular causes. On the other hand, the clinical, laboratory and radiological data associated with a worse outcome in AF patients are similar to those previously described in the overall population.

Both pre-treatment with DOACs and treatment with DOACs during admission seem to have a protective role in patients with AF, although this fact should be confirmed in prospective studies. In any case, with these findings, there is no indication to modify the treatment with DOACs for LMWH in hospitalized patients and the door is opened to carry out clinical trials with DOACs as prevention of thromboembolic events occurring in COVID-19.

Conflict of interests

The authors state that they have no conflict of interest in relation to this publication.

Acknowledgements

We thank all participants and investigators of the SEMI-COVID-19 Registry.

Annex A. List of investigators of the SEMI-COVID-19 Registry

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.medcli.2022.01.008.

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