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Cardiac arrhythmias in patients presenting with COVID-19, treated in Portuguese hospitals: A national registry from the Portuguese Association of Arrhythmology, Pacing and Electrophysiology.

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Arritmias Cardíacas em doentes com COVID-19, tratados em hospitais portugueses. Um registo nacional da APAPE

Resumo

Introdução e objetivos: Em dezembro de 2019, o SARS-CoV-2 foi descoberto como agente da doença COVID-19. As arritmias cardíacas são reportadas como frequentes, mas a sua incidência é desconhecida. O objetivo deste trabalho foi entender a incidência de arritmias em doentes COVID-19 tratados em hospitais portugueses e entender as suas implicações prognósticas.

Métodos: A Associação Portuguesa de Arritmologia, *Pacing* e Electrofisiologia (APAPE) conduziu um inquérito em hospitais portugueses, documentando a ocorrência de arritmias em doentes com COVID-19, as suas características clínicas, o uso de terapêutica experimental e o seu impacto no intervalo QT.

Resultados: Participaram vinte hospitais, reportando 692 doentes hospitalizados. Ocorreram episódios arrítmicos em 81 (11,7%), 64 (79%) com informação adicional. Documentaram-se arritmias de novo em 41 (64%) doentes, 45 (79%) do sexo masculino, idade mediana 73,5 (61-80,3) anos. Destes, 51 (79,7%) tinham comorbilidades associadas, maioritariamente hipertensão arterial (41, 64,1%). Dos 53 (82,3%) doentes sob terapêutica experimental, 7 (10,9%) tiveram aumento do intervalo QTc. Tiveram taquicardia ventricular 2 (3,1%) doentes, 5 (7,8%) bradicardia sinusal, 17 (26,6%) taquicardia paroxística supraventricular e 40 (7,8%) fibrilhação ou flutter auricular. Nenhum doente teve morte por causa arrítmica ou complicações associadas, à data do registo.

Conclusões: Numa população de doentes com COVID-19, a incidência de arritmias é elevada, mas não associada a aumento de mortalidade cardíaca, apesar da ocorrência mais frequente em doentes graves e com falência multiorgânica. Independentemente do uso de terapêuticas experimentais, a incidência de arritmias ventriculares é baixa e a fibrilhação auricular e outras arritmias supraventriculares são as arritmias mais prevalentes.

PALAVRAS-CHAVE

Arritmias; COVID-19; Portugueses; Terapêutica experimental; Prolongamento QT

Conflicts of interest: The authors have no conflicts of interest.

Funding: No funding was received for this study.

Abstract:

Introduction and objectives: In December 2019, SARS-CoV-2, was discovered as the agent of COVID-19 disease. Cardiac arrhythmias have been reported as frequent but their incidence is unknown. The aim of this research was to assess the real incidence of cardiac arrhythmias among COVID-19 patients admitted to Portuguese hospitals and to understand the underlying prognostic implications.

Methods: The Portuguese Association of Arrhythmology, Pacing and Electrophysiology (APAPE) conducted a survey in Portuguese hospitals to assess the occurrence of arrhythmias in COVID-19 patients, their clinical characteristics, the use of experimental therapies and its impact on QT interval.

Results: Twenty hospitals participated, reporting 692 hospitalized patients. An arrhythmic episode occurred in 81 (11.7%) and 64 (79%) had detailed information. New onset arrhythmias occurred in 41 (64%) patients, 45 (70.3%) male, median age 73.5 (61-80.3) years. There were 51 (79.7%) with associated comorbidities, mainly arterial hypertension (41, 64.1%). Of 53 patients (82.3%) under experimental therapy, 7 (10.9%) had an increased QTc interval. Regarding arrhythmias, two patients (3.1%) had ventricular tachycardia, 5 (7.8%) sinus bradycardia, 17 (26.6%) paroxysmal supraventricular tachycardia and 40 (62.5%) atrial fibrillation or flutter. Non-arrhythmic death syndrome nor related complications at the time of reporting.

Conclusions: In a population of COVID-19 patients, the incidence of cardiac arrhythmias is high but not associated with increased cardiac mortality, although it occurs frequently in extremely ill patients and with multiple organ failure. Regardless of the use of experimental drugs, the incidence of ventricular arrhythmias is low and atrial fibrillation and other supraventricular arrhythmias are the most prevalent arrhythmias.

Resumo:

Introdução e objetivos: Em dezembro de 2019, o SARS-CoV-2 foi descoberto como agente da doença COVID-19. As arritmias cardíacas são reportadas como frequentes, mas a sua incidência é desconhecida. O objetivo deste trabalho foi entender a incidência de arritmias em doentes COVID-19 tratados em hospitais portugueses e entender as suas implicações prognósticas.

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arritmias de novo em 41 (64%) doentes, 45 (79%) do sexo masculino, idade mediana 73.5 (61-80.3) anos. Destes, 51 (79.7%) tinham comorbilidades associadas, maioritariamente hipertensão arterial (41, 64.1%). Dos 53 (82.3%) doentes sob terapêutica experimental, 7 (10.9%) tiveram aumento do intervalo QTc. Tiveram taquicardia ventricular 2 (3.1%) doentes, 5 (7.8%) bradicardia sinusal, 17 (26.6%) taquicardia paroxística supraventricular e 40 (7.8%) fibrilhação ou flutter auricular. Nenhum doente teve morte por causa arritmica ou complicações associadas, à data do registo.

Conclusões: Numa população de doentes com COVID-19, a incidência de arritmias é elevada, mas não associada a aumento de mortalidade cardíaca, apesar da ocorrência mais frequente em doentes graves e com falência multiorgânica. Independentemente do uso de terapêuticas experimentais, a incidência de arritmias ventriculares é baixa e a fibrilhação auricular e outras arritmias supraventriculares são as arritmias mais prevalentes.

Keywords: Arrhythmias; ; ; , COVID-19, portuguese, experimental therapy, QT prolongation

Palavras-chave: Arritmias, COVID-19, portugueses, terapêutica experimental, prolongamento QT

Introduction:

In December 2019, an increasing number of cases of patients with pneumonia of unknown origin was detected in the Hubei province in China,^{1,2} and SARS-CoV-2, a novel coronavirus capable of human infection and transmission, was found to be responsible. The virus led to a pandemic, with more than 53.1 million reported infections and 1.3 million deaths³)to date. However, numbers may be in fact higher due to the virus being highly infectious and asymptomatic patients are capable of transmission.^{4- 6} COVID-19 disease presents with a wide range of symptoms but predominantly as an acute respiratory disease and fever.⁷ leading to hospitalization in about 10-15% of patients and critical intensive care (ICU) in 3-14.2% of

patients.⁷⁻¹¹ With growing knowledge about the disease, other clinical symptoms are constantly being reported. Respiratory failure, cytokine storm, thromboembolic phenomena and acute fulminant myocarditis are the predominant known causes of death¹²⁻¹⁴ with a 1.2-7.7% case-fatality rate worldwide to date. However, it may in fact be lower if the presumed asymptomatic undetected cases are accounted for, or higher, as in the elderly or in people with known associated diseases.^{3,7,10,15,16} In the latter group, cardiovascular comorbidities account for a higher mortality risk (10.5%)^{11,17,18}, as well as diabetes and chronic obstructive pulmonary disease. Cardiac arrhythmias have been reported as a frequent event in this population as the estimates account for 16.7% among hospitalized patients and 44% in ICU patients.^{19,20} In these patients, the effect of multiorgan damage and cardiac lesion on cardiac rhythm, as well as the effect of experimental therapies for treatment is yet unknown.

Objectives:

The aim of this research was to assess the real incidence of cardiac arrhythmias among COVID-19 patients admitted to Portuguese hospitals and to understand the underlying prognostic implications, in order to provide useful knowledge for the management of these patients.

Methods:

Study population

The Portuguese Association of Arrhythmology, Pacing and Electrophysiology (APAPE) conducted a survey between April 12 and May 10 of 2020 among affiliated Pacing and Electrophysiology laboratories in Portuguese hospitals to assess the occurrence of arrhythmias in patients infected with SARS-CoV-2 and their clinical characteristics. Confirmed COVID-19 patients, with at least one positive reverse transcriptase polymerase chain reaction test for SARS-CoV-2 and a milder clinical progression that resulted in hospital admission were included, irrespective of the predominant symptoms. In the subgroup of patients with continuous cardiac monitoring,

admitted to intensive or intermediate care units, the prevalence of arrhythmias, their type and outcome were assessed.

Patient evaluation and survey conducted

The reporting hospitals that agreed to participate were included in the study and were asked to report the number of patients admitted with COVID-19, the use of experimental therapies for the disease and the mode of QT interval monitoring, and the need for cardiologic evaluation (Figure 1). In the event arrhythmic episodes were detected, the investigators at each hospital were invited to report additional information, as detailed as possible (Figure 2). This included, comorbidities, clinical and laboratory evolution, arrhythmia type, new onset arrhythmia versus recurrent arrhythmia, therapy, any major adverse events during hospitalization, death, and its cause.

Statistical analysis

All analysis was performed using version 12 of STATA® (Statistics Data Analysis). Data are presented as median, lower and upper quartiles (Q1-Q3) for continuous variables and as absolute number and percentage for categorical variables.

Ethics disclosure

At each center, data were collected retrospectively using a standardized data collection form (Figures 1 and 2) sent to all the participating hospitals. Patient identification was registered in the participating centers but was not transferred to APAPE, so the compiled data remained anonymous.

This study complies within the Declaration of Helsinki rules.

Results:

Study population

Twenty hospital centers nationwide participated in the survey. During the study period, there were reports of 692 hospitalized patients with COVID-19. A subgroup of 393 (56.8%) patients were admitted to ICU or had continuous cardiac monitoring. In this subgroup of patients, 81 (20.6%) experienced an arrhythmic episode.

Experimental therapy

Among all hospitalized patients, 443 (64%) were under experimental therapy for COVID-19 (ritonavir/lopinavir, hydroxychloroquine or azithromycin). The QT assessment in these patients was performed daily in ICU or if the QT interval (QTc) were above 450ms and every other 48-72h in the remaining patients. Cardiologic assessment was needed in 65 (9.4%) patients (reasons for evaluation not detailed).

Patients with arrhythmias

In the subgroup of patients with arrhythmias, detailed additional information was available in 64 patients, of whom 45 (70.3%) were male, median age was 73.5 (61-80.3) years. There were 51 (79.7%) patients with associated comorbidities, median of 3 (1-4) (Table 1). Arterial hypertension was the most prevalent comorbidity, in 41 (64.1%) of patients, 23 (36%) patients had dyslipidemia, 22 (34.4%) patients were diabetic and 19 (29.7%) patients had previously diagnosed atrial fibrillation.

Among the monitored patients, 9 (14%) had left ventricular systolic dysfunction and one (1.6%) had right ventricular dysfunction. Acute cardiac injury occurred in 33 (51.6%) of the patients, non-ST elevation acute myocardial infarction in four (6.3%) and myocarditis in one (1.6%). Median peak value of cardiac Troponin I was 73.5 (28.9-278.3) pg/L. There were seven (10.9%) patients with significant electrolyte disorder at the time of arrhythmia onset.

There were 35 (54.7%) on mechanical invasive ventilation for respiratory failure and 33 (52%) had multiple organ failure. Only four (6.3%) patients developed cardiogenic shock, three in the

setting of acute cardiac injury of unknown cause with new onset left ventricle systolic dysfunction and one after non-ST elevation acute myocardial infarction. Myocardial biopsies and cardiac magnetic resonance were not performed.

In this arrhythmia subgroup, 53 patients (82.3%) were under experimental therapy for COVID-19, of whom 49 (76.6%) received hydroxychloroquine, 35 (54.7%) received azithromycin and 16 (25%) received lopinavir/ritonavir. Additionally, 49 patients (76.6%) were concomitantly taking other drugs that could prolong QT²¹ (median two, 1-3 drugs) of whom 19 (29.7%) were also on antiarrhythmic therapy with amiodarone. Only seven patients (10.9%) had an increased QTc interval, minimum 480ms and maximum 596ms.

An arrhythmic episode was a recurrence of a previously existing arrhythmia - atrial fibrillation (AF) - in 23 patients (35.9%) and new onset arrhythmia in 41 patients (64.1%). Regarding arrhythmic episodes, two patients (3.1%) had ventricular tachycardia, five (7.8%) patients sinus bradycardia, 17 (26.6%) paroxysmal supraventricular tachycardia and 40 (62.5%) AF or atrial flutter.

Patients with supraventricular arrhythmias, as opposed to those with the other types of arrhythmias, presented with more severe disease, being more frequently placed on mechanical ventilation (33, 57.9%), with hemodynamic instability (two, 3.5%) and cardiogenic shock (four, 7.0%) and with multiple organ failure 32 (56.1%) (Table 2), as reflected by higher absolute and relative frequencies. Both patients with ventricular tachycardia had QT prolongation but the clinical course was milder (Table 2).

Concerning outcomes, 20 (31.3%) patients died and the main identified cause was respiratory failure in 12 (60%) and refractory septic shock in four (20%), with only one patient (5%) dying of a direct cardiac cause (cardiogenic shock). None of the patients had arrhythmic dead syndrome nor was the arrhythmia episode found to contribute to their death.

Discussion

As SARS-CoV-2 is a newly detected coronavirus capable of infecting humans and causing COVID-19 disease, there is a lot of uncertainty regarding risk factors for disease outcome, as well as the best therapeutic strategies. Although acute pneumonia is the hallmark of the disease, there are several reports of additional direct organ damage from COVID-19, including acute heart failure and cardiac arrhythmias.^{13,14,22} Whether naturally resulting from the disease or from the treatment, its true incidence is still unknown. Currently, remdesivir and dexamethasone appear to be the most promising therapeutic drugs for treating COVID-19 patients, as they were demonstrated a reduction in disease duration and severity.²³⁻²⁷ At the time of data collection for this study, other experimental therapeutic targets for COVID-19 were in use and they have the additional potential to induce arrhythmias, as is the case of chloroquine/hydroxychloroquine.^{4,22}

In our registry, we aimed to assess the incidence of arrhythmic global events in COVID-19 patients as well as the potential harmful effects of experimental therapies on major cardiac adverse events.

These results show that in a population of patients hospitalized for COVID-19 in Portuguese hospitals, with cardiac continuous monitoring and admitted to intermediate or intensive care, there was a preponderance of male patients and a prevalence of older age groups. Likewise, patients with associated comorbidities,^{8,10,28-31} especially arterial hypertension, dyslipidemia, type 2 diabetes and atrial fibrillation are prone to severe disease.

The majority of patients were on experimental therapy for COVID-19, although not yet proven to be efficacious.^{22,32} This is particularly dangerous³³⁻³⁸ because a high percentage of these patients were also on other concomitant QT prolonging drugs. In our survey, more than 10% of patients displayed QT prolongation, although there was no evidence of polymorphic ventricular tachycardia, Torsade de Pointes or ventricular fibrillation. The incidence of prolonged QT was high,^{39,40} when compared with the 6% reported incidence in the normal population, but in line

with QT prolongation in populations with comorbidities such as diabetes, hypertension and ischemic cardiac disease, as is the case of our population.⁴¹ Additionally, this higher QT prolongation was probably due to the extremely high percentage of concomitant drugs (Table 1) and not related to electrolyte disturbances (which were low). This corroborates other studies that report the incidence of QT prolongation in patients taking these drugs.²¹ Since chloroquine/hydroxychloroquine are drugs that are still in use in COVID-19 studies, there is an increased need for a standardized QT interval monitoring protocol. Overall, the global incidence of arrhythmic events was high (11.7%), characterized mostly by new onset arrhythmias. Most patients with arrhythmias were critically ill patients with respiratory and multiple organ failure. These patients pose a greater challenge in management and had a bad outcome. The most frequent arrhythmic events were paroxysmal supraventricular tachycardia and AF, which can be associated with severe pulmonary disease and multiorgan failure per se, rather than cardiac lesion due to SARS2-CoV-2 and were not responsible for death events. Although patients with ventricular arrhythmias had an arrhythmic substrate (either a prolonged QT or severe left ventricle dysfunction) and the mortality rate was high, the cause of death was due to respiratory failure.

Regarding the impact of COVID-19 on other cardiovascular outcomes, in our study population, acute myocarditis had a low incidence, contrary to the previously reported information,^{8,13,42} as well as myocardial infarction. On the other hand, acute cardiac lesion occurred in more than half of the patients with severe disease with a non-despicable incidence (14.1% of patients) of left ventricle systolic dysfunction. Nevertheless, this did not lead to a significant impact on mortality since the leading cause of death was respiratory failure and septic shock. Direct cardiac causes of death in our population were low (cardiogenic shock or arrhythmias).

Limitations:

Our study has limitations. First, although most hospitals reported for the survey, we do not have full coverage across the country and there may be biases associated with differences between centers that report or do not report data to the survey. Second, as in all large-scale surveys, some data were missing and additionally, the complete information was not mandatory due to the high workload health care providers face due to the COVID-19 pandemic. Therefore, there was only information available on arrhythmias in the subgroup of monitored patients (56.8% of the population) and detailed information was limited to 79% of this subset.

Conclusions:

In a population of COVID-19 patients admitted to Portuguese hospitals, the incidence of cardiac arrhythmias is high and occurred mostly in extremely ill patients, who were either ventilated or had multiple organ failure, but was not associated with increased cardiac mortality. Regardless of the widespread use of experimental drugs to target SARS2-CoV-2 with the potential for QT prolongation, the incidence of ventricular arrhythmias is low and AF and other supraventricular arrhythmias were the most prevalent arrhythmias in COVID-19 patients.

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Registry collaborators

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Figures:



Avaliação da incidência e impacto de disritmias em doentes Covid-19

Este questionário, iniciativa da APAPE, destina-se à aferição da incidência dos vários tipos de disritmias em doentes com infeção por SARS-COV2 em território Português e do impacto das mesmas no seu *outcome* por forma a adequar eventuais revisões sobre a gestão destes doentes do ponto de vista arritmico.

O questionário abaixo, a preencher pelos laboratórios de *Pacing* e Electrofisiologia de Portugal Continental e Regiões Autónomas, idealmente completado com todos os dados, não é invalidado mesmo sem a possibilidade de preenchimento de todos campos. Desta forma, não deixe de enviar resposta tão completa quanto possível mas na impossibilidade de fornecer dados exatos, se possível estabeleça intervalos de dados.

Este registo será para publicação sob a forma de artigo científico. A APAPE agradece a sua importante contribuição e o nome do seu centro e investigador principal e responsável da unidade de cuidados serão referidos no mesmo.

- 1) Hospital: _____
- 2) Nome do investigador principal _____
- 3) Nome do responsável pelos doentes Covid-19 _____
- 4) Nome do médico responsável pela UCI _____
- 5) Número de doentes internados com COVID-19 _____

Se a resposta é 0, o seu inquérito está terminado

Se a resposta é diferente de 0 prossiga com questionário.

- 6) Número de doentes internados com COVID-19 com monitorização de ritmo (cuidados intensivos ou intermédios) _____
- 7) Número de doentes sob terapêutica experimental / *off label* com Cloroquina, hidroxicloroquina, Azitromicina e / ou ritonavir / lopinavir) _____
- 8) Número de doentes com disritmias documentadas: _____
- 9) Número de doentes com necessidade de *pacing* provisório _____
- 10) Periodicidade de monitorização QT em doentes sob terapêutica dirigida Covid-19 _____
- 11) Número de doentes com necessidade de avaliação por Cardiologia: _____



Figure 1: Electronic questionnaire regarding hospitalized patients used in the survey.



12) Perfil dos doentes com disritmias (preencher esta questão para cada um dos doentes)

- a. Idade _____ Género _____
- b. Comorbilidades *major* de risco (especificar) _____
- c. Disritmia
 - i. Taquicardia Ventricular monomófica _____
 - ii. Taquicardia Ventricular polimórfica / Torsade de Pointes _____
 - iii. Fibrilhação Ventricular _____
 - iv. Fibrilhação Auricular ou Flutter Auricular _____
 - v. Taquicardia Auricular ou TPSV _____
 - vi. Bradicardia Sinusal (≤ 40 bpm) _____
 - vii. Bloqueio aurículo ventricular ($\geq 2^\circ$ Grau Mobitz 2:1) _____
- d. Evento de disritmia *de novo* OU recidiva de disritmia de base? _____
- e. Ventilação mecânica invasiva? _____
- f. Falência multiorgânica (≥ 2 : respiratória, cardíaca, renal, neurológica, hemostase, hepática) _____
- g. Intervalo QTc admissão _____ / QTc máximo _____ / QTc evento _____
- h. Lesão Cardíaca Aguda? _____ Valor máximo Troponina _____
- i. Síndrome coronário agudo associado? _____ (STEMI / NonSTEMI)
- j. Miocardite aguda? _____
- k. Choque cardiogénico? _____
- l. Disfunção sistólica ventricular esquerda? (FEj _____% - se conhecida): _____
- m. Disfunção sistólica ventricular direita? _____
- n. Sob terapêutica com amiodarona? _____
- o. Alteração iónica grave? _____
- p. Sob terapêutica com cloroquina / hidroxicloroquina? _____
- q. Sob terapêutica com Azitromicina? _____
- r. Sob terapêutica com ritonavir / lopinavir? _____
- s. Sob terapêutica com outro fármaco prolongador do QT? _____
 - i. Quantos: _____
 - ii. Se relevante, especifique fármaco: _____
- t. Sob terapêutica com Dobutamina / Dopamina? _____
- u. Morte? _____
 - i. Causa Arritmica? _____
 - ii. Outra causa (se conhecida) _____



Figure 2: Electronic questionnaire for patients with arrhythmic episodes used in the survey.

Tables:

Table 1. Clinical and laboratory characteristics of patients with arrhythmias.

Clinical and Laboratory characteristics	n=64
Male gender	45 (70.3%)

Age	73.5 (61-80.25)
Previous arrhythmias	23 (35.9%)
Comorbidities	51 (79.7%)
Hypertension	41 (64.1%)
Diabetes	22 (34.4%)
Coronary artery disease	9 (14%)
Cerebrovascular disease	10 (16%)
Heart failure	7 (10.9%)
Dyslipidemia	23 (36%)
Chronic obstructive pulmonary disease	7 (10.9%)
Atrial fibrillation	19 (29.7%)
Chronic kidney disease	14 (21.9%)
Other comorbidities*	30 (46.9%)
Experimental therapy	53 (82.3%)
Lopinavir/ritonavir	16 (25%)
Hydroxychloroquine	49 (76.6%)
Azithromycin	35 (54.7%)
QT prolonging drugs	49 (76.6%)
Lopinavir /ritonavir	16 (25%)
Hydroxychloroquine	49 (76.6%)
Azithromycin	35 (54.7%)
Amiodarone	19 (29.7%)
Metoclopramide	8 (12.5%)
Quetiapine	12 (18.8%)
Olanzapine	3 (4.7%)
Haloperidol	6 (9.4%)
Other drugs	18 (28.1%)
QT prolongation	7 (10.9%)
Severe ionic disturbances	7 (10.9%)
Increased troponin I (pg/L)	48 (75%)
Left ventricle systolic dysfunction	9 (14.1%)
Right ventricle systolic dysfunction	1 (1.6%)
Acute cardiac lesion	33 (51.6%)
Acute coronary syndrome	4 (6.3%)
Acute myocarditis	1 (1.6%)
Hemodynamic instability	2 (3.1%)
Cardiogenic shock	4 (6.3%)
Mechanical ventilation	35 (54.7%)
Multiple organ failure	33 (52%)

*Neoplasm, Aortic Stenosis, Pulmonary embolism, Pulmonary hypertension, Obesity, Dementia, Hepatitis B, Peripheral artery disease

Table 2. Clinical and laboratory characteristics of patients, according to type of arrhythmias.

	SVT (n=57)	VT (n=2)	Sinus bradycardia (n=5)
Left ventricle systolic dysfunction	7 (12.3%)	1 (50%)	1 (20%)
Hemodynamic instability	2 (3.5%)	0	0
Acute cardiac lesion	30 (52.6%)	0	3 (60%)
ACS	4 (7.0%)	0	0

Myocarditis	0	0	0
Troponin I (pg/L)	75 (35.1-309.5)	10,1 (9-11.1)	114.9 (65.9 – 156.5)
Mechanical ventilation	33 (57.9%)	1 (50%)	1 (20%)
Cardiogenic shock	4 (7.0%)	0	0
Multiple organ failure	32 (56.1%)	0	0
Severe ionic disturbances	6 (10.5%)	0	1 (20%)
Prolonged QT interval	4 (7.0%)	2 (100%)	1 (20%)

Legend ACS: acute coronary syndrome; SVT: supraventricular tachycardia; VT: ventricular tachycardia.

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