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Prevalence, characteristics and outcome of cardiac manifestations in critically-ill antiphospholipid syndrome patients

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Heart
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MINOCA

Aims: Antiphospholipid syndrome (APS) is a rare autoimmune disease defined by thrombotic events occurring in patients with persistent antiphospholipid antibodies. Cardiac manifestations in critically-ill APS patients are poorly investigated. We conducted a study to assess the prevalence, the characteristics and the prognosis of cardiac manifestations in thrombotic APS patients admitted to intensive care unit (ICU).

Methods and results: A French, national, multicentre, retrospective study, conducted, from January 2000 to September 2018, including all APS patients admitted to 24 participating centres' ICUs with any new thrombotic (arterial, venous or microvascular) manifestation. Cardiac manifestations were defined as any new cardiac abnormalities relying on clinical examination, cardiac biomarkers, echocardiography, cardiac magnetic resonance (CMR) and coronarography. One hundred and thirty-six patients (female 72%) were included. Mean age at ICU admission was 46 ± 15 years. Cardiac manifestations were present in 71 patients (53%). In patients with cardiac involvement, median left ventricular ejection fraction (LVEF) was 40% [28–55], troponin was elevated in 93% patients, coronary angiogram ($n = 19$, 27%) disclosing a coronary obstruction in 21%. CMR ($n = 21$) was abnormal in all cases, with late gadolinium enhancement in 62% of cases. Cardiac manifestations were associated with a non-significant increase of mortality (32% vs. 19%, $p = 0.08$). After 1-year follow-up, median LVEF was 57% [44–60] in patients with cardiac involvement.

Conclusion: Cardiac involvement is frequent in critically-ill thrombotic APS patients and may be associated to more severe outcome. Increased awareness on this rare cause of myocardial infarction with or without obstructive coronary artery is urgently needed.

1. Introduction

Antiphospholipid syndrome (APS) is a systemic autoimmune disease defined by thrombotic and/or obstetrical events occurring in patients with persistent antiphospholipid antibodies (aPLAs) [1]. In rare cases APS patients require intensive care unit (ICU) admission because of organ dysfunctions caused by macrovascular and/or microvascular thromboses [2]. Catastrophic antiphospholipid syndrome (CAPS) is the most severe complication of APS with mortality rates ranging from 26 to 50% [3–6]. Classification criteria for CAPS have been established in the early 2000 [7] but lack sensitivity and fail to identify patients with poor outcome [2,8]. Early recognition of CAPS is crucial to improve patients' outcome with early and tailored therapeutic interventions. Severe thrombotic APS frequently affects kidney, heart and central nervous system [5]. The precise frequency, clinical picture and outcome of APS-related cardiac involvement is lacking, especially in patients requiring ICU admission.

We conducted this study to determine the prevalence, characteristics and outcome of cardiac manifestations in thrombotic critically-ill APS patients.

2. Methods

2.1. Patients

This French, national, multicentre, retrospective study, conducted from January 2000 to September 2018, included all APS patients admitted to 24 participating centres' ICUs with any new thrombotic (arterial, venous, or microvascular) manifestation. APS patients admitted to the ICU without any new thrombotic manifestation were not included. APS was defined using the APS international diagnosis criteria available at the time of each patient's ICU admission [9–11]. Patients with newly diagnosed APS who died in the ICU and had a unique aPLa determination (namely, without aPLa positivity confirmed after 6 or 12-week depending on APS criteria available at the time of their admission to ICU) could be included as described in CAPS criteria. Lupus anticoagulant (LA) detection was performed according international guidelines [12]. Most patients had LA positivity identified before heparin introduction or while being under treatment with vitamin K antagonists. LA positivity was interpreted with caution in patients concomitantly receiving anticoagulant (especially heparin) or having high laboratory markers of inflammation.

APS-related thromboses were diagnosed clinically, using conventional imaging (Doppler ultrasound, echocardiogram, computed-

tomography scan, arteriography and magnetic resonance imaging) or through the analysis of any histopathological sample, as previously reported [2,3]. Organ involvement was defined as any new thrombotic event involving an artery or vein and large or small vessels in the corresponding organ. Microvascular involvement when histopathological proof could not be obtained was diagnosed as follows: kidney (50% serum creatinine rise, severe systemic hypertension ($>180/100$ mm Hg) and/or proteinuria (>500 mg/24 h), after exclusion of differential diagnoses, especially lupus nephritis), lung (bronchoalveolar lavage or computed-tomography scan revealing intra-alveolar haemorrhages after exclusion of differential diagnoses, especially cardiogenic pulmonary oedema), and brain (delirium, coma, seizure or status epilepticus after exclusion of differential diagnoses).

Cardiac manifestations were defined as any new cardiac abnormalities relying on clinical examination (i.e. any new clinical signs of heart failure), cardiac biomarkers (i.e. elevated troponin and/or NT-pro-BNP), echocardiography (i.e. unpreviously known altered left ventricle ejection fraction (LVEF), valvulopathy, intracardiac thrombus ...), cardiac magnetic resonance (CMR) and coronarography (i.e. new coronary obstruction).

2.2. Data collection

Standardised forms were used to collect the following information: epidemiological parameters; APS clinical, biological and therapeutic history; clinical manifestations; laboratory findings; in-ICU treatments; complications; and outcomes. Patients were classified according to previously published CAPS criteria [7,8]. The Damage Index of APS (DIAPS) was calculated for every survivor 6 months post-ICU discharge with available follow-up, as previously reported, with every item weighted the same (1 point) [13]. Systemic lupus erythematosus was classified according to American College of Rheumatology criteria [14]. Acute myocardial infarction (MI) and myocardial infarction with no obstructive coronary arteries (MINOCA) were defined according to the fourth universal definition of MI and the European Society of Cardiology position paper [15,16].

2.3. Statistical analyses

Results for categorical variables, expressed as number (%), were compared with χ^2 tests; those for continuous variables, expressed as mean \pm standard deviation or median [interquartile range (IQR)25–75], were compared using Student's t-test or Wilcoxon's rank test. First, we conducted a descriptive analysis of the 136 patients' clinical

Table 1

In-ICU antiphospholipid syndrome-related cardiac manifestations.

Variables	n = 71
Clinical presentation	
Dyspnea	34 (49)
Pulmonary crackles	23 (33)
Chest pain	12 (17)
Lower limb oedema	7 (10)
Syncope	3 (4)
Murmur	12 (17)
Electrocardiogram	n = 54
Right bundle branch block	8 (11)
Left bundle branch block	4 (7)
Q waves	5 (9)
Repolarization abnormalities	21 (39)
ST-segment elevation	5 (9)
ST-segment depression	9 (17)
Negative T waves	10 (18)
Coronary territory	
Anterior	11 (46)
Inferior	2 (8)
Lateral	7 (29)
Diffuse	4 (17)
Atrial fibrillation	7 (13)
Ventricular Tachycardia or fibrillation	3 (5)
Low-degree atrio-ventricular block	1 (2)
Complete heart block	1 (2)
Echocardiography	n = 67
LVEF before admission, %	60 [60-60]
LVEF on ICU admission, %	40 [28-55]
Libman-Sacks endocarditis	8 (17)
Intra-cardiac thrombus	2 (3)
Wall-motion abnormality	15 (27)
Left ventricular dilatation	18 (33)
Right ventricle dysfunction	8 (19)
TAPSE, mm	19 [9-21]
Troponin	n = 67
Troponin > ULN	62 (93)
Troponin, fold over ULN	46 [5-199]
NT-pro-BNP	n = 27
NT-pro-BNP > ULN	27 (100)
NT-pro-BNP, fold over ULN	34 [10-110]
Coronary angiography	n = 19
Time from symptoms to angiography, days	3 [1-12]
Mo notroncular lesions	2 (12)
Bitroncular lesions	3 (18)
Tritroncular lesions	0 (0)
Recent occlusive thrombosis	4 (21)
CMR imaging	n = 21
Abnormal	21 (100)
Time from ICU admission to CMR, days	0 [-0.5-9.5]
LVEF, %	44 [40-58]
Wall motion abnormality	8 (38)
LVEDV, mm	55 [49-61]
Late gadolinium enhancement	13 (62)
Sub-endocardial	11 (85)
Sub-epicardial	0 (0)
Trans-mural	2 (15)
Myocardial oedema	5 (24)
Classification	
Type 1 myocardial infarction	4 (6)
MINOCA	15 (21)
Suspected MINOCA	20 (28)
Undetermined	32 (45)

Abbreviations: APS, antiphospholipid syndrome; BNP, brain natriuretic peptide; CMR, cardiac magnetic resonance; ICU, intensive care unit; LVEDV, left ventricular end diastolic volume; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MINOCA, myocardial infarction with non-obstructive coronary arteries; TAPSE, tricuspid annular plane systolic excursion; ULN, upper limit of normal. Continuous variables are expressed as mean \pm standard deviation or median [interquartile range (IQR)]; categorical variables are expressed as n (%).

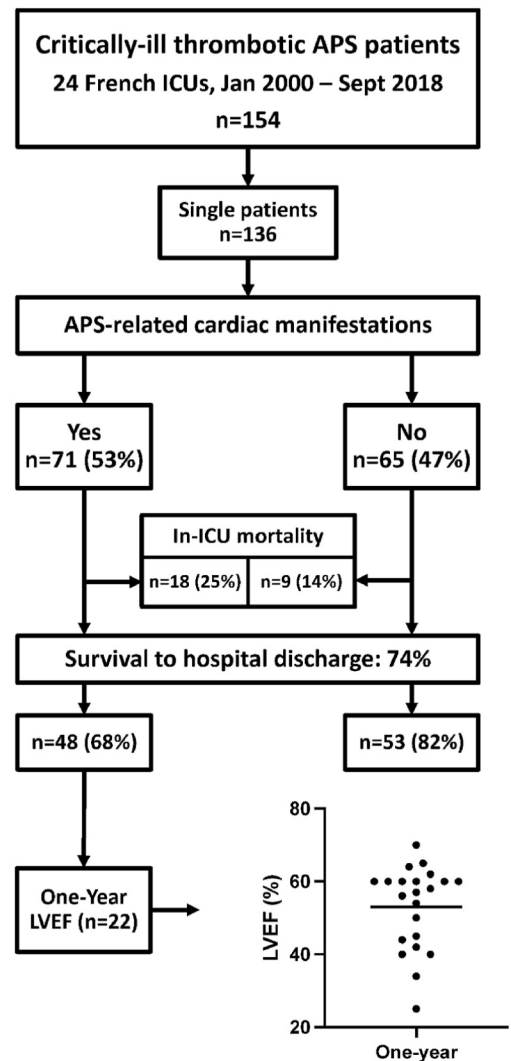


Fig. 1. TITLE: Study Flow-Chart. CAPTION: Abbreviations: APS: anti-phospholipid syndrome; ICU: intensive care unit; LVEF: left ventricular ejection fraction. The dot-plot shows the distribution of LVEF at one-year follow-up in 22 patients.

characteristics, laboratory findings, thrombotic manifestations, in-ICU organ-failure treatment(s), APS-specific treatment(s), complications and outcomes. In 71 episodes with cardiac manifestations, we conducted a descriptive analysis of clinical characteristics, biomarkers, electrocardiograms, echocardiography, cardiac magnetic resonance and coronary angiography findings. Then, we compared patients' data and outcomes according to cardiac manifestation (heart+ and heart-groups). For patients with multiple ICU admissions, only last episode was considered in statistical analyses. Statistical significance was defined as $p < 0.05$. Analyses were computed with R software 4.0.2 version (R project for Statistical Computing).

2.4. Ethical considerations

The database is registered at the "Commission Nationale de l'Informatique et des Libertés" (no. 918031, decision DR-2018-090) and was approved by the Ethics Committee of the French Intensive Care Society (reference CE SRLF17-30). The investigation conforms with the principles outlined in the Declaration of Helsinki. In accordance with the ethical standards of our hospital's institutional review board, the Committee for the Protection of Human Subjects, and French law, written informed consent was not needed for demographic, physiological and hospital-

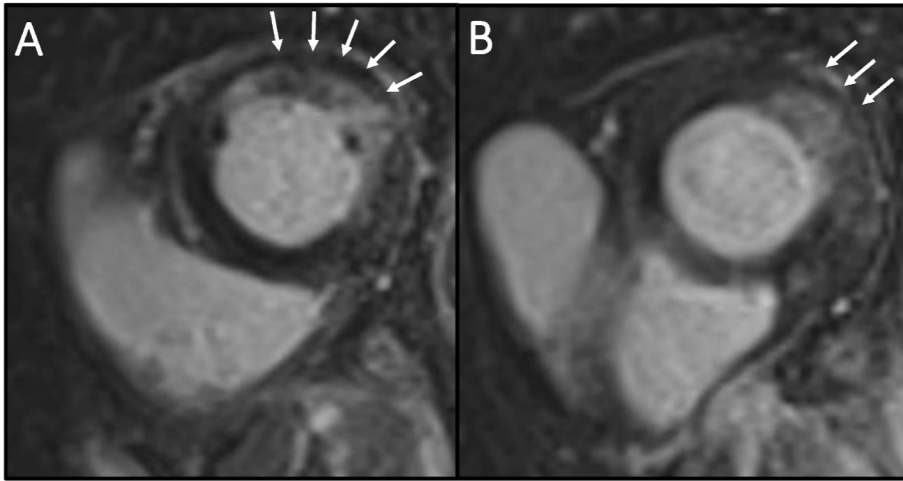


Fig. 2. TITLE: Cardiac Magnetic Resonance Imaging of a Critically-ill APS Patients with MINOCA. CAPTION: Mid short-axis magnetic resonance imaging sequences 15 min after gadolinium injection showing (A) subendocardial (ischemic-like pattern) late gadolinium enhancement of the anterior and antero-lateral walls (white arrows), and (B) subendocardial to transmural late gadolinium enhancement of the antero-lateral wall (white arrows). Abbreviations: MINOCA: myocardial infarction with non-obstructive coronary arteries.

outcome data analyses because this observational study did not modify existing diagnostic or therapeutic strategies; however, patients were informed of their inclusion in the study.

3. Results

3.1. Cardiac manifestations

One-hundred and thirty-six single patients with 154 episodes meeting the inclusion criteria, female-to-male sex ratio 2.8 and 46 ± 15 years old at admission, were included. APS-related cardiac manifestation was reported in 71 (53%) patients (Table 1). The flow-chart reporting the study population and main outcomes is reported in Fig. 1. Clinical findings included: dyspnea 49%, pulmonary crackles 33%, chest pain 17% and lower limb oedema 10%. Electrocardiogram revealed repolarization abnormalities in 39% patients. Repolarization abnormalities were mainly located in the anterior (46%) and lateral (29%) territories and were diffuse in 17% of patients. Troponin and NT-pro-BNP levels were elevated in respectively in 93% and 100% of patients with a median [IQR] levels: troponin 46 [5–199] and NT-pro-BNP 34 [10–110] fold upper normal limit. LVEF at admission $\leq 50\%$ was reported in 61% of these patients. Median [IQR] lowest in-ICU LVEF was 40% [28–55]. Libman-Sacks endocarditis was reported in 8 patients. Coronary angiography was performed in 19/71 episodes (27%), disclosing new coronary obstruction in 4/19 patients (21%) (Supplemental Table 1). CMR imaging was performed in 21/71 (30%) and was always pathologic, with late gadolinium enhancement in 62% cases, affecting sub-endocardial layers in 11/13 patients (85%) and being transmural in 2/13 (15%) (Fig. 2). Overall, cardiac manifestations could be classified as: type 1 myocardial infarction 6%, myocardial infarction with nonobstructive coronary arteries 21%, suspected myocardial infarction with nonobstructive coronary arteries 28% and undetermined 45%. Myocardial histology was available for three patients: autopsy $n = 1$, surgical biopsy during left ventricle device implantation $n = 1$, endomyocardial biopsy followed by the explanted heart $n = 1$. The autopsy and surgical biopsy revealed ischemic necrosis with capillary thromboses while the endomyocardial biopsy disclosed unspecific myocardial changes while the explanted heart revealed ischemic necrosis with normal coronary vessels. Among patients with cardiac involvement, in-ICU and in-hospital mortality rates were 25% and 32%. Cause of death were: multi-organ failure ($n = 7$, 30%), in-hospital cardiac arrest ($n = 5$, 22%), limitations of advance life support ($n = 5$, 22%), brain death ($n = 6$, 26%).

3.2. Comparison according to cardiac manifestations

Comparisons between heart+ and heart-groups are reported in Table 2 and Table 3. Demographic and APS characteristics were not statistically different between the two groups aside a higher frequency of LA in heart + group (97% vs. 86%, $p = 0.02$). The frequency of infection as a precipitating factor was not different between heart + and heart - group (27% vs. 31%, $p = 0.8$, respectively). Patients from heart + group trended to be sicker as suggested by higher day-0 Sequential Organ Failure Assessment (SOFA) score (7 vs. 6, $p = 0.08$), more frequent use of inotrope (25% vs. 2%, $p < 0.001$), vasopressors (56% vs. 31%, $p = 0.004$), mechanical ventilation (55% vs. 40%, $p = 0.09$), VA-ECMO (11% vs. 2%, $p = 0.03$) and higher in-hospital mortality (32% vs. 19%, $p = 0.08$). Survival analysis did not show significant different outcome between heart+ and heart-groups (Fig. 3). Specific APS treatments were given evenly to both groups. Eight patients had a refractory cardiogenic shock requiring VA-ECMO and half could be weaned with a bridge-to: recovery ($n = 1$), transplantation ($n = 1$) or left ventricle assist device ($n = 2$). Six-months DIAPS score was higher in patients with cardiac manifestations ($p < 0.001$).

3.3. Comparison according to vital status

Among patients with cardiac involvement, factors associated with poor outcome were classical in-ICU prognosis factors such as: old age, high day-0 SOFA and SAPS-II score, use of mechanical ventilation, extrarenal epuration, epinephrine and norepinephrine (Table 4). Cardiac-related specific features (troponin level, LVEF lowest value, dobutamine use) were not associated with the outcome, nor was the type of cardiac manifestation (MINOCA, MI, Libman-Sacks, undetermined). Notably, in this subgroup of patients with cardiac manifestations, all patients that survived received in-ICU anticoagulation treatment, which was the only in-ICU treatment significantly associated with an improved outcome (Table 4). The distribution of cardiac clinical, laboratory and morphologic involvements according vital status is reported in Fig. 4.

3.4. Left ventricular function after 1-year follow-up

LVEF dichotomous value (below or above 50%) was assessed after 1-year follow-up in 47 patients from the heart + group: 22/47 (47%) having a $LVEF \leq 50\%$. Among the 22 patients with quantitative value of LVEF available at one-year, LVEF was 57 [44–60] % and the median LVEF change compared to in-ICU value was 15% ($p < 0.001$, Fig. 5). The rate of recovery was low as only 6/27 (22%) patients with in-ICU $LVEF \leq 50\%$ had a $LVEF > 50\%$ after one-year follow-up. Factor associated with one-year $LVEF \leq 50\%$ were: low LVEF value before and in-ICU,

Table 2

In-ICU antiphospholipid syndrome characteristics and organ involvement with comparison according to cardiac manifestations.

Variable	All patients n = 136	Heart + n = 71	Heart-n = 65	p-value
Female	98 (72)	54 (76)	44 (68)	0.4
Age, years	46 ± 15	46 ± 14	46 ± 17	0.9
Body-mass index, kg/m ²	25.9 ± 5.7	25.4 ± 5.7	26.5 ± 5.5	0.3
APS characteristics				
APS known before ICU admission	107 (79)	57 (80)	50 (77)	0.8
APS follow-up duration, months	100 [29–217]	105 [26–218]	98 [51–205]	0.5
Venous APS	94 (70)	48 (69)	46 (71)	1
Arterial APS	59 (44)	33 (47)	26 (40)	0.5
Obstetrical APS	38 (28)	25 (35)	13 (20)	0.08
APS biological findings				
Lupus anticoagulant	124 (91)	69 (97)	55 (85)	0.02
Anti-cardiolipin IgG	100 (74)	55/69 (77)	45 (69)	0.4
Anti-cardiolipin IgM	28 (21)	9/69 (13)	19 (29)	0.04
Anti-β ₂ GPI IgG	81 (60)	47/69 (67)	34 (52)	0.1
Anti-β ₂ GPI IgM	18 (13)	7/69 (10)	11 (17)	0.4
Triple aPLA positivity	71 (52)	43 (60)	28 (43)	0.06
Definite APS	123 (92)	64/69 (93)	59 (91)	0.9
Previous APS treatment				
Any treatment	104 (77)	58 (82)	46 (71)	0.2
Antiplatelet therapy	43 (32)	26 (37)	17 (26)	0.2
Anticoagulant	96 (71)	51 (72)	45 (69)	0.9
Systemic lupus erythematosus	46 (34)	22 (31)	24 (37)	0.6
Precipitating event	101 (74)	56 (79)	45 (69)	0.2
In-ICU APS manifestations				
No CAPS	71 (53)	32 (45)	38 (59)	0.3
Probable CAPS	54 (40)	33 (47)	22 (34)	0.2
Definite CAPS	9 (7)	4 (6)	5 (8)	0.7
Number of extra-cardiac organs involved	2 [2,3]	2 [2,3]	2 [2,3]	0.8
Small vessel occlusion	30 (22)	13 (18)	17 (26)	0.3
Non-coronary macrovascular thrombosis	91 (67)	51 (72)	40 (62)	0.3
Arterial	54 (40)	32 (45)	22 (34)	0.2
Venous	64 (47)	34 (48)	30 (46)	0.9
Organ involved				
Kidney	79 (59)	44 (62)	37 (57)	0.6
Lung	43 (32)	22 (31)	21 (32)	1
Central nervous system	49 (37)	27 (38)	23 (35)	0.9
Skin	33 (24)	14 (20)	19 (29)	0.3
Peripheral vessel(s)	35 (26)	20 (28)	15 (23)	0.6
Liver	30 (22)	15 (21)	15 (23)	0.9
Adrenal gland	32 (24)	18 (25)	14 (22)	0.7
Spleen	18 (13)	13 (18)	5 (8)	0.08
Gastrointestinal tract	15 (11)	9 (13)	6 (9)	0.6
Eye	7 (5)	5 (7)	2 (3)	0.4
Pancreas	5 (4)	3 (4)	2 (3)	1
Fever	76 (57)	38/69 (55)	38 (59)	0.7
Haematological manifestation				
Anaemia	126 (94)	64/69 (93)	62 (95)	0.8
Thrombocytopenia	125 (92)	66/68 (97)	59/64 (92)	0.3
Lowest haemoglobin, g/dL	7.1 [6.4–8.7]	7 [6.3–8.2]	7.2 [6.5–8.9]	0.4
Lowest platelet count, G/L	38 [21–63]	38 [18–70]	36 [23–60]	1
Length of stay				
In-ICU stay, days	10 [5–21]	10 [5–25]	11 [5–21]	0.9
In-hospital stay, days	35 [21–59]	36 [21–64]	32 [21–56]	0.7

Abbreviations: APS, antiphospholipid syndrome; aPLA, antiphospholipid antibody; β₂GPI, β₂-glycoprotein-1; BNP, brain natriuretic peptide; CAPS, catastrophic APS; ICU, intensive care unit; IgG or IgM, immunoglobulin G or M. Continuous variables are expressed as mean ± standard deviation or median [interquartile range (IQR)] and compared with Student's t-test or Wilcoxon's rank test; categorical variables are expressed as n (%) and compared with χ² tests.

left ventricle dilation, right ventricular dysfunction but not in-ICU troponin highest value and parameters associated with patient's severity: high SOFA and SAPS-II scores, use of inotropes/vasopressor, mechanical ventilation and VA-ECMO (Table 5). Noteworthy, adrenal gland-related APS involvement was associated with favorable cardiac outcome.

4. Discussion

Antiphospholipid syndrome is a rare autoimmune disease affecting mainly young women and responsible for a large range of thrombotic and non-thrombotic manifestations. Given its rarity and the

pleomorphic nature of its cardiac manifestations (coronary thrombosis, MINOCAs, Libman-Sacks endocarditis ...), the diagnosis and management of APS remains a challenge. We present herein a real-life picture of APS-related cardiac involvement during acute thrombotic episodes.

Our series shares similarities but also differs from previous reports. Noteworthy, we included critically-ill thrombotic APS patients, some not meeting CAPS classification criteria while other series from literature only included definite/probable CAPS patients. The gender distribution, the frequency of systemic lupus erythematosus and lupus anticoagulation were comparable with previous reports [5]. The frequency of thrombocytopenia in our patients was higher (92% vs. 67%) than in the CAPS registry, probably reflecting a selection bias toward

Table 3
In-ICU scores, treatments and outcomes according to the presence of an APS-related cardiac manifestation.

Variable	All n = 136	Heart + n = 71	Heart-n = 65	p-value
ICU scores				
Day-0 SAPS II	32 [18–45]	36 [18–49]	31 [16–41]	0.2
Day-0 SOFA score	7 [4–9]	7 [4–9]	6 [3–9]	0.08
Charlson score	2 [1–4]	2 [1–4]	1 [1–3]	0.2
In-ICU organ failure treatments				
Vasopressors	60 (44)	40 (56)	20 (31)	0.004
Dobutamine	19 (14)	18 (25)	1 (2)	<0.001
Norepinephrine	44 (32)	26 (37)	18 (28)	0.3
Epinephrine	17 (12)	13 (18)	4 (6)	0.04
VA-ECMO	9 (7)	8 (11)	1 (2) ^a	0.03
Mechanical ventilation	65 (48)	39 (55)	26 (40)	0.09
Renal replacement therapy	54 (40)	31 (44)	23 (35)	0.4
APS specific treatments				
Anticoagulant	130 (96)	68 (96)	62 (95)	1
Antiplatelet therapy	41 (30)	26 (37)	17 (26)	0.2
Corticosteroids	110 (81)	62 (87)	48 (74)	0.05
Intravenous immunoglobulins	45 (33)	26 (37)	19 (29)	0.4
Plasmapheresis	55 (40)	34 (48)	21 (32)	0.08
Rituximab	17 (13)	12 (17)	5 (8)	0.1
Ecuzumab	6 (4)	5 (7)	1 (2)	0.2
Cyclophosphamide	10 (7)	3 (4)	7 (11)	0.2
Triple therapy ^b	78 (57)	45 (63)	33 (51)	0.2
Number of treatments	3 [2–4]	3 [2–4]	3 [2–4]	0.009
Outcomes				
In-ICU mortality	27 (20)	18 (25)	9 (14)	0.1
In-hospital mortality	35 (26)	23 (32)	12 (19)	0.08
Day-180 survival	80 (71)	42 (67)	38 (76)	0.3
DIAPS	2 [1–3]	3 [2–4]	1 [1–3]	<0.001
Day-365 survival	72 (67)	36 (61)	36 (75)	0.2

Abbreviations: DIAPS: antiphospholipid syndrome damage index; ICU: intensive care unit; SAPS II: simplified acute physiology score II; SOFA: sequential organ failure assessment; VA-ECMO: veno-arterial extra-corporeal membrane oxygenation. Continuous variables are expressed as mean \pm standard deviation or median [interquartile range (IQR)] and compared with Student's t-test or Wilcoxon's rank test; categorical variables are expressed as n (%) and compared with χ^2 tests.

^a Indication for VA-ECMO in the Heart - group: severe pulmonary embolism.

^b Defined as the association of anticoagulation, corticosteroids and whether IgiV or plasmapheresis.

sicker patients inclusion in our series. Mean age (46 vs. 38 years), the frequency of APS known at admission (80 vs. 50%) and survival (74 vs. 63%) were higher in our cohort [5]. Importantly, the frequency of cardiac involvement is similar in the CAPS registry and in our study, affecting half patients. However, given the absence of precise definition of cardiac involvement in the CAPS registry report, it is harsh to compare with our data the following reported frequency of heart failure (44%), myocardial infarction (30%) and valvulopathy (28%) [5].

Myocardial ischemia is the leading cause of cardiac manifestation in APS patients. Both macrovascular or microvascular coronary thromboses can occur as in any other organ during CAPS. While being infrequent, macrovascular coronary obstruction (21% of patients undergoing a coronary angiography and 6% of patients with cardiac manifestations) should not be overlooked owing the beneficial effect of coronary revascularization. Most APS patients with cardiac involvement had proven or suspected MINOCA. MINOCA refers to clinical signs and symptoms consistent with acute myocardial infarction and coronary arteries that angiographically normal or nearly normal [15,17,18].

There is an increasing awareness of a MINOCA in APS. In a recent study of 40 APS patients with acute myocardial infarction, 8 were MINOCAs [19] similar to our results. Sacre and colleagues reported a high prevalence (~30%) of ischemic-like LGE patterns in patients with APS [20]. The low frequency of coronary angiography performed in this series can be easily explained by the low probability of coronary obstruction in many patients (no chest pain, no ST segment elevation or depression) and the difficulties or risks associated with an unneeded coronary angiography (intra or interhospital transport in critically-ill patients, acute renal failure ...). Yet, the mechanism of cardiac manifestations remains unclear in a significant number of patients. The association between favorable cardiac outcome and adrenal involvement suggests that some cardiac manifestation could be related to acute adrenal crisis. Unraveling the pathophysiology of cardiac involvement in this setting is not straightforward since only a few patients could undergo both cardiac magnetic resonance and coronary angiogram. In this purpose, myocardial histology could theoretically be helpful. However, the diagnostic yield of endomyocardial biopsy for the identification of capillary thrombosis is unknown while the consequences of a hemorrhagic complication in CAPS can be dreadful.

The frequency of Libman-Sacks endocarditis seemed higher in patients from the CAPS registry (13% of all episodes) while we report only 8 patients (6% of all episodes) [5]. However, the frequency of APS-related valvular involvement strongly differs across studies owing to the absence of clear definition. Severe cases of Libman-Sacks endocarditis requiring surgery have been previously reported, although in our series most patients had mild valvular insufficiency not directly accountable for the clinical presentation [21–23].

In the CAPS registry, cardiac involvement was the second cause of death (20%) [5]. Similarly to our findings, they found only a nonsignificant trend toward increase mortality in patients with cardiac involvement [24]. In our series, 19/35 (54%) patients died from a multiple organ failure or a cardiac arrest, of whom 12/35 (34%) had a cardiac involvement. Determining the exact reason of death is always difficult facing CAPS patients with multiorgan involvement.

Loop-diuretics and inotropes/vasopressive drugs are the cornerstone symptomatic treatments of cardiogenic shock. Patients refractory to these interventions may need temporary circulatory support (TCS, mainly VA-ECMO) and ultimately a bridge-to-long term ventricular assist device or cardiac transplantation. Specific APS treatments include: high level of anticoagulation, antiplatelets therapy, plasma exchanges and a large range of drugs with immunosuppressive consequences (corticosteroids, rituximab, cyclophosphamide ...). Both the thrombotic manifestations of APS and these specific treatments significantly increase the complications (thrombotic, hemorrhagic and infectious) associated to TCS and its bridging strategies. The very possibility of TCS or transplantation is therefore frequently questioned in these patients. Our results suggest that these strategies are valid and can be offered in patients with APS thrombotic episodes-related refractory cardiogenic shock.

There are very few reports on long-term outcomes of critically-ill APS patients. After one-year of follow-up, more than half patients were alive. LVEF significantly increased in most patients and complete recovery of cardiac function (>50%). Yet, when restricting the analysis to the subgroup of patients with in-ICU altered LVEF, few had complete cardiac recovery. This finding, altogether with their increased DIAPS score, suggest that cardiac involvement during acute thrombotic APS episodes not only aggravates mortality but may also induces chronic cardiac morbidity highlighting the need for long term assessment and follow up.

Our study has limitations and strengths. First, it has a retrospective,

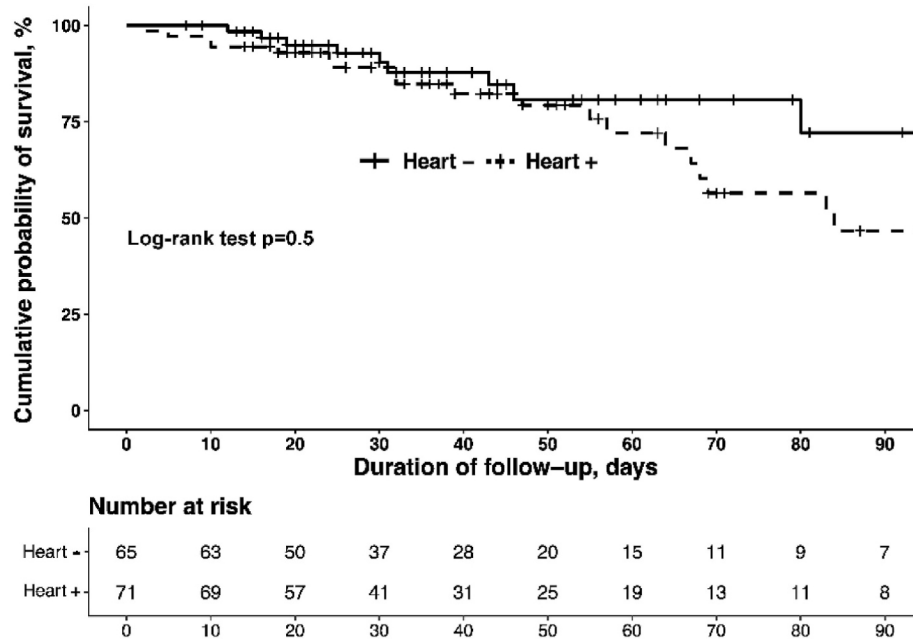


Fig. 3. TITLE: Kaplan-Meier Estimated Cumulative Probability of Survival Curves According to Cardiac Manifestations. **CAPTION:** Probabilities of survival were compared using the Log-rank test.

Table 4

Factors associated with vital status at hospital discharge in APS thrombotic patients with cardiac manifestations.

Variable	Survivors n = 48	Nonsurvivors n = 23	p-value
Female	38 (79)	16 (70)	0.6
Age, years	42 [32–50]	55 [45–64]	0.003
Day-0 SAPS II	26 [13–41]	45 [38–67]	<0.001
Day-0 SOFA score	5 [3–9]	11 [7–14]	0.001
Clinical findings	35 (73)	16 (70)	1
Electrocardiogram	18/35 (51)	14/19 (74)	0.1
Echocardiography	32/43 (74)	13/19 (68)	0.8
Troponin, fold over ULN	27 [3–150]	52 [8–150]	0.6
NT-pro-BNP, fold over ULN	17 [8–77]	117 [55–596]	0.04
Coronary occlusion	2/16 (12)	2/3 (67)	0.1
CAPS criterion			
No	21 (44)	14 (61)	0.3
Probable	25 (52)	7 (30)	0.1
Definite	2 (4)	2 (9)	0.6
Number of organs involved	2 [2,3]	3 [1–4]	0.4
In-ICU organ failure treatments			
Vasopressors	20 (42)	20 (87)	<0.001
Dobutamine	12 (25)	6 (26)	1
Norepinephrine	13 (27)	13 (56)	0.02
Epinephrine	5 (10)	8 (35)	0.02
VA-ECMO	4 (8)	4 (17)	0.4
Mechanical ventilation	19 (40)	20 (87)	<0.001
Renal replacement therapy	11 (23)	20 (87)	<0.001
APS specific treatments			
Anticoagulant	48 (100)	20 (87)	0.03
Antiplatelet therapy	21 (44)	9 (39)	0.8
Corticosteroids	42 (88)	20 (87)	1
Intravenous immunoglobulins	18 (38)	8 (35)	1
Plasmapheresis	21 (44)	13 (57)	0.4
Rituximab	3 (6)	1 (4)	0.6
Eculizumab	3 (6)	2 (9)	0.7
Cyclophosphamide	3 (6)	0	0.5
Triple therapy ^a	12 (25)	4 (17)	0.6
Classification			
Type 1 myocardial infarction	2/16 (12)	2/3 (67)	0.1
MINOCA	14 (29)	1 (4)	0.1
Suspected MINOCA	12 (25)	8 (35)	0.2

Abbreviations: APS, antiphospholipid syndrome; BNP, brain natriuretic peptide; CAPS, catastrophic APS; ICU, intensive care unit; LVEF, left ventricular ejection fraction; MINOCA, myocardial infarction with normal coronary arteries; SAPS, simplified assessment physiology score; SOFA, sequential organ failure assessment; ULN, upper-limit normal; VA-ECMO, veno-arterial extra-corporeal membrane oxygenation. Continuous variables are expressed as mean \pm standard deviation or median [interquartile range (IQR)] and compared with Student's t-test or Wilcoxon's rank test; categorical variables are expressed as n (%) and compared with χ^2 tests.

^a Defined as the association of anticoagulation, corticosteroids and whether IgIV or plasmapheresis.

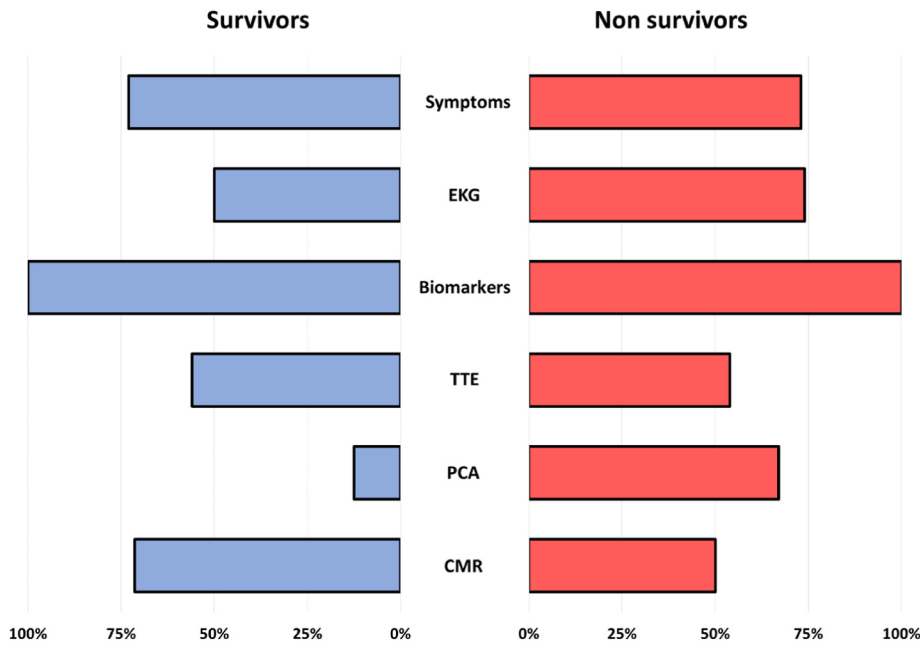


Fig. 4. TITLE: Rates of Abnormal Clinical, Biological and Morphological Features in Patients with Cardiac Manifestations According to their Vital Status. **CAPTION:** Among patients with cardiac involvement, cardiac manifestations were equally distributed across patients with favorable and poor outcome. Although non-significant, coronary occlusion was more frequent in patients that died (2 out of 3 coronary angiographies) than in patients that survived (2 out of 16 coronary angiographies) (OR = 11.2 95%CI [0.4-874], p = 0.1). TTE was considered abnormal in case of Libman-sacks endocarditis, wall motion abnormality, LVEF<50% or intra-cardiac thrombus. EKG was considered abnormal in case of right or left bundle branch block, any repolarization abnormality, high degree conduction disorder or ventricular arrhythmia. CMR was considered abnormal in case of late gadolinium enhancement. Biomarkers were considered abnormal in case of elevation of NT-proBNP and/or troponin. **ABBREVIATIONS:** CMR cardiac magnetic resonance; EKG, electrocardiogram; TTE *trans*-thoracic echocardiography; PCA, percutaneous coronary angioplasty.

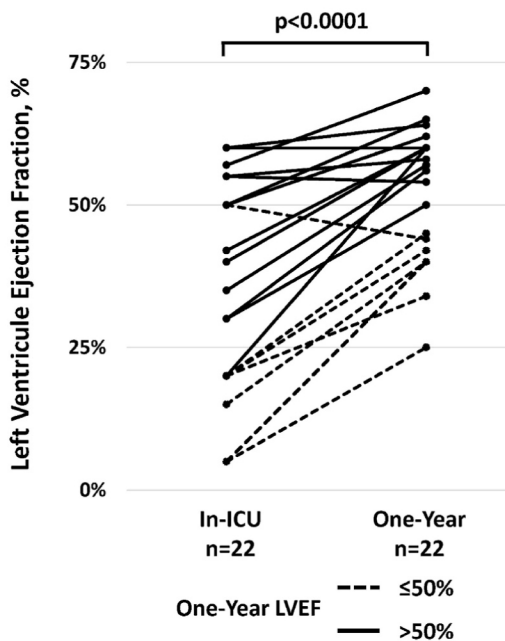


Fig. 5. TITLE: In-ICU and One-Year Follow-Up LVEF Assessment. **CAPTION:** In-ICU and follow-up LVEF values were available in 22 patients. Seven had an LVEF below 50% (dashed lines) and 15 above 50% (plain lines) at one-year follow-up. **ABBREVIATIONS:** APS: antiphospholipid syndrome; ICU: intensive care unit; LVEF: left ventricular ejection.

observational design but many patients with a very rare disease came from 24 ICUs in participating centres. Second, patient inclusion lasting >20 years means inevitable heterogeneity of diagnoses and management, especially given the advances in cardiac imaging, but most

patients (73%) were included during the last decade. Third, the significant number of missing cardiac investigation data (cardiac magnetic resonance, coronary angiograms, follow-up echocardiography) may under or overestimate the true frequency of APS-related cardiac involvement. Indeed, some troponin increase or electrocardiogram abnormalities could be related to APS-related extracardiac manifestations. Last, a lack of power may have prevented to show significant differences in terms of prognosis, however this is the largest series focusing on APS-related cardiac event reported to date.

In conclusion, cardiac involvement is frequent in critically-ill thrombotic APS patients, found in more severe APS patients and may be associated to more severe outcome. Increased awareness on this rare cause of myocardial infarction with or without obstructive coronary artery is now urgently needed.

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Authorship contributions

- LDA, MPdC and ZA contributed in study design, data collection, statistical analysis conduction and interpretation and manuscript writing.
- All others authors contributed in data collection.
- MPdC is the guarantor of this study.

Declaration of competing interest

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Table 5Factors associated with one-year left ventricle ejection fraction $\leq 50\%$.

Variable	One-Year LVEF>50% n = 25	One-Year LVEF $\leq 50\%$ n = 22	p-value
Female	22 (88)	16 (73)	0.3
Age, years	42 \pm 13	43 \pm 13	0.6
Day-0 SAPS II	10 [10–35]	34 [26–49]	<0.001
Day-0 SOFA score	4 [2–7]	7 [5–11]	<0.001
APS biological findings			
Lupus anticoagulant	25 (100)	21 (96)	0.5
Anti-cardiolipin IgG	17 (68)	20 (91)	0.08
Anti- β_2 GP1 IgG	19 (76)	15 (68)	0.7
Triple aPLA positivity	17 (68)	15 (68)	1
Systemic lupus erythematosus	10 (40)	5 (23)	0.2
LVEF before admission, %	60 \pm 0	49 \pm 16	0.04
In-ICU cardiac manifestations			
Lowest LVEF value, %	52 \pm 9	28 \pm 13	<0.001
LVEDV, mm	48 \pm 5	60 \pm 10	0.04
Right ventricle dysfunction	0/15 (0)	6/17 (35)	0.02
Troponin, ULN	116 \pm 180	81 \pm 87	0.9
CMR LGE	6/10 (60)	7/7 (100)	0.2
In-ICU APS manifestations			
CAPS criterion			
No	9 (36)	12 (54)	0.3
Probable	14 (56)	10 (46)	0.7
Definite	2 (8)	0 (0)	0.5
Number of organs involved	4 [3,4]	3 [2–4]	0.2
Organ involved			
Adrenal gland	10 (40)	2 (9)	0.02
Fever	9 (36)	17 (77)	<0.001
C-reactive protein, mg/L	111 [86–192]	184 [106–240]	0.8
Haematological manifestations			
Anaemia	21 (84)	22 (100)	0.1
Thrombocytopenia	21/22 (96)	21 (96)	1
Specific treatments			
Anticoagulant	18 (72)	15 (68)	1
Antiplatelet therapy	10 (40)	11 (50)	0.6
Corticosteroids	21 (84)	20 (91)	0.7
Triple therapy ^a	6 (24)	4 (18)	0.7
In-ICU treatments			
Vasopressors	5 (20)	16 (73)	<0.001
Dobutamine	2 (8)	10 (46)	<0.001
Norepinephrine	5 (20)	9 (41)	0.2
Epinephrine	0 (0)	5 (23)	0.02
VA-ECMO	0 (0)	4 (18)	0.04
Mechanical ventilation	6 (24)	13 (59)	0.02
Renal replacement therapy	4 (16)	7 (32)	0.3
Classification			
Type 1 myocardial infarction	0	2 (9)	1
MINOCA	4 (16)	10 (45)	1
Suspected MINOCA	6 (24)	6 (27)	0.7

Abbreviations: aPLA, anti-phospholipid antibody; APS, antiphospholipid syndrome; β_2 GP1, β_2 -glycoprotein-1; IgG or IgM, immunoglobulin G or M; CAPS, catastrophic APS; CMR, cardiac magnetic resonance; ICU, intensive care unit; LGE, late gadolinium enhancement; LVEDV, left ventricular end diastolic volume; LVEF, left ventricular ejection fraction; SAPS, simplified acute physiology score; SOFA, sequential organ failure assessment; VA-ECMO, veno-arterial extra-corporeal membrane oxygenation; ULN, upper limit of normal value. Continuous variables are expressed as mean \pm standard deviation or median [interquartile range (IQR)] and compared with Student's t-test or Wilcoxon's rank test; categorical variables are expressed as n (%) and compared with χ^2 tests.

^a Defined as the association of anticoagulation, corticosteroids and whether IgIV or plasmapheresis.

5. Acknowledgements

none.

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