CAPS criteria fail to identify most severely-ill thrombotic antiphospholipid syndrome patients requiring intensive care unit admission

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ABSTRACT

Purpose: Catastrophic antiphospholipid syndrome (CAPS), the most severe manifestation of antiphospholipid syndrome (APS), is characterised by simultaneous thromboses in multiple organs. Diagnosing CAPS can be challenging but its early recognition and management is crucial for a favourable outcome. This study was undertaken to evaluate the frequencies, distributions and ability to predict mortality of "definite/probable" or "no-

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CAPS" categories of thrombotic APS patients requiring admission to the intensive care unit (ICU).
Methods: This French national multicentre retrospective study, conducted from January 2000 to September 2018, included all APS patients with any new thrombotic manifestation(s) admitted to 24 ICUs.
Results: One hundred and thirty-four patients (male/female ratio: 0.4; mean age at admission: 45.4 ± 15.0 years), who experienced 152 CAPS episodes, required ICU admission. The numbers of definite, probable or no-CAPS episodes, respectively, were: 11 (7.2%), 60 (39.5%) and 81 (53.3%). No histopathological proof of microvascular thrombosis was the most frequent reason for not being classified as definite CAPS. Overall, 35/152 (23.0%) episodes were fatal, with comparable rates for definite/probable CAPS and no CAPS (23% vs. 28.8% respectively, $p = 0.4$). The Kaplan–Meier curve of estimated probability of survival showed no between-group survival difference (log-rank test $p = 0.5$). **Conclusions**: In this study**,** CAPS criteria were not associated with mortality of thrombotic APS patients requiring ICU admission. Further studies are need evaluate the adequacy of CAPS criteria for critically-ill APS patients.

1. Introduction

The antiphospholipid syndrome (APS) is a systemic autoimmune disease defined by thrombotic and/or obstetrical events that occur in patients with persistent antiphospholipid antibodies (aPLAs). [1]. In rare cases, APS patients are admitted to the intensive care unit (ICU) because of organ dysfunction caused by macrovascular and/or microvascular thromboses. Catastrophic APS (CAPS) is its most severe complication. Diagnostic criteria for CAPS have been proposed. [2]. CAPS is classified as definite in a patient with multiple (≥ 3) organ thromboses and microthrombotic involvement of at least one organ, developing within 7 days in a patient with persistently positive aPLAs. CAPS prognosis is severe with mortality ranging from 37% to 50%. [3].

In clinical in-ICU practice, although CAPS diagnosis can be challenging, its early recognition and management are crucial to improve outcome. Whether CAPS diagnosis covers all the thrombotic complications occurring in APS patients requiring ICU admission is unknown. Indeed, very few data are available on the distribution of CAPS criteria of APS patients admitted to the ICU and their associated mortality.

The objectives of this study were to evaluate the frequencies, distributions and prognoses of definite, probable or no-CAPS categories of thrombotic APS patients admitted to the ICU.

2. Methods

2.1. Patients

This French, national, multicentre, retrospective study, conducted, from January 2000 to September 2018, included all APS patients admitted to the 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. [4–6]. Patients with newly diagnosed APS who died in the ICU without aPLA positivity confirmed at a 12-week interval were included. Apart from these, all other patients had aPLA positivity persistence confirmed whether prior to ICU admission or during follow-up. Patients with evident competing thrombotic factors were not included in the study. 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]. 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 seen in any tissue biopsy or 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 intraalveolar haemorrhages after exclusion of differential diagnoses, especially cardiogenic pulmonary oedema), heart (clinical, biological or radiological evidence of myocardial infarction in the absence of explanatory coronary obstruction or thrombosis) and brain (delirium, coma, seizure or status epilepticus after exclusion of differential diagnoses).

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. [2]. The Damage Index of APS was calculated for every survivor 6 months post-ICU discharge with available follow-up, as previously reported [7], with every item weighted the same (1 point). Systemic lupus erythematosus was classified according to American College of Rheumatology criteria. [8].

2.3. Statistical analyses

Results for categorical variables, expressed as number (%), were compared with χ^2 tests; those for continuous variables, expressed as mean ± standard deviation or median [interquartile range (IQR)], were compared using Student's t-test or Wilcoxon's rank test. First, we conducted a descriptive analysis of the 134 patients' clinical characteristics during 152 episodes, laboratory findings, thrombotic manifestations, in-ICU organ-failure treatment(s), APS-specific treatment(s), complications and outcomes. Then, we compared the last episodes of each of the 134 patients according to their CAPS classification: "definite/probable CAPS" vs "no CAPS". Then, a Cox proportional hazards model, including the number of organs involved, the number of days to the first organ involvements, any histopathological proof and any new arterial or venous macrovascular involvement, was run using backward-stepwise variable elimination (variable exit threshold set at $p > 0.10$). All potential explanatory variables included in the multivariable analyses were subjected to collinearity analysis with a correlation matrix. When collinearity was found, only one of the two variables could be included the model. Statistical significance was defined as $p < 0.05$. Analyses were computed with IBM SPSS Statistics v22.0 software (IBM Corp, Armonk, NY, USA).

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). 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-

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. General characteristics of the 152 thrombotic APS episodes of 134 patients admitted to the ICU

The 134 APS patients' general characteristics during their 152 episodes are reported in Table 1. The male/female ratio was 0.4, with mean age at ICU admission (day 0) of 45.4 ± 15.0 years. One hundred and twenty-one (79.6%) episodes occurred in patients with definite APS known at ICU admission and median follow-up of 109 [32–222] months since diagnosis. Considering APS before admission, 107 (70.4%) were considered venous and 66 (43.4%) arterial APS phenotypes, 84 (55.3%) with triple aPLA positivity, 110 (72.4%) treated with anticoagulant and 50 (32.9%) antiplatelet therapy. In addition, 52 (34.2%) episodes occurred in a context of APS and systemic lupus erythematosus, with a precipitating event before ICU admission was identified for 114 (75%). A median [IQR] of 3 [2–4] organs were involved, proven microvascular thrombosis and macrovascular thrombosis were seen in 25% and 63.8% episodes. Episode-attributed in-ICU and in-hospital fatalities were 17.8% and 23%, respectively. Fifteen patients had more than on episode. The comparison between patients with a unique episode and patients with relapse is presented in Supplemental Table 1.

Table 1
General characteristics of the 134 APS patients' thrombotic and biological findings and outcomes of their 152 CAPS episodes.

Characteristic	Value
Demographic	
Women	96/134 (71.6)
Age, years	45.4 ± 15.0
Body mass index, kg/m^2	26 ± 6.5[a]
APS characteristics	
Months of follow-up	109 [32–222]
Venous APS	107 (70.4)
Arterial APS	66 (43.4)
Obstetrical APS	37/96 (38.5)
APS biological findings	
Lupus anticoagulant	138 (90.8)
Diluted Russell viper-venom time, fold over ULN, n = 79	1.7 [1.4–2.2]
Rosner index, fold over ULN, n = 66	2.0 [1.5–2.8]
Anti-cardiolipin IgG	115 (75.6)
Titer, fold over ULN, n = 101	6.9 [3.7–12.5]
Anti-cardiolipin IgM	30 (19.7)
Titer, fold over ULN, n = 27	3.3 [1.4–3.7]
Anti-β2GP1 IgG	95 (62.5)
Titer, fold over ULN, n = 87	5.1 [2.9–12.0]
Anti-β2GP1 IgM	20 (13.2)
Titer, fold over ULN, n = 18	3.2 [1.8–4.4]
Triple aPLA positivity	84 (55.3)
Definite APS	141 (92.8)
Treatment before episode	
Any treatment	119 (78.3)
Antiplatelet therapy	50 (32.9)
Anticoagulant	110 (72.4)
Systemic lupus erythematosus	52 (34.2)
APS known before ICU admission	121 (79.6)
Episode characteristics	
Precipitating events	114 (75.0)
Days to the first 3 organ involvements	5.0 [1.0–14.7]
Number of involved organs	3 [2–4]
Fever	91 (59.9)
Anemia	144 (94.7)
Thrombocytopaenia	134 (88.2)
Histological proof of microvascular thrombosis	38 (25.0)
Macrovascular thrombosis	97 (63.8)
Arterial	62 (40.8)
Venous	67 (44.1)
CAPS criterion	
No	81 (53.3)
Probable	60 (39.5)
Definite	11 (7.2)
Outcome	
In-ICU mortality	27 (17.8)
In-hospital mortality	35 (23.0)

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 χ^2 tests.
APS: antiphospholipid syndrome; β2GP1: β_2-glycoprotein-1; aPLA: antiphospholipid antibody; IgG or IgM: immunoglobulin G or M; ICU: intensive care unit; CAPS, catastrophic APS.
[a] Values available for 124 episodes at ICU admission.

3.2. Distributions of CAPS criteria and reasons for not being classified as definite CAPS

Distributions of episodes according to definite (7.2%), probable

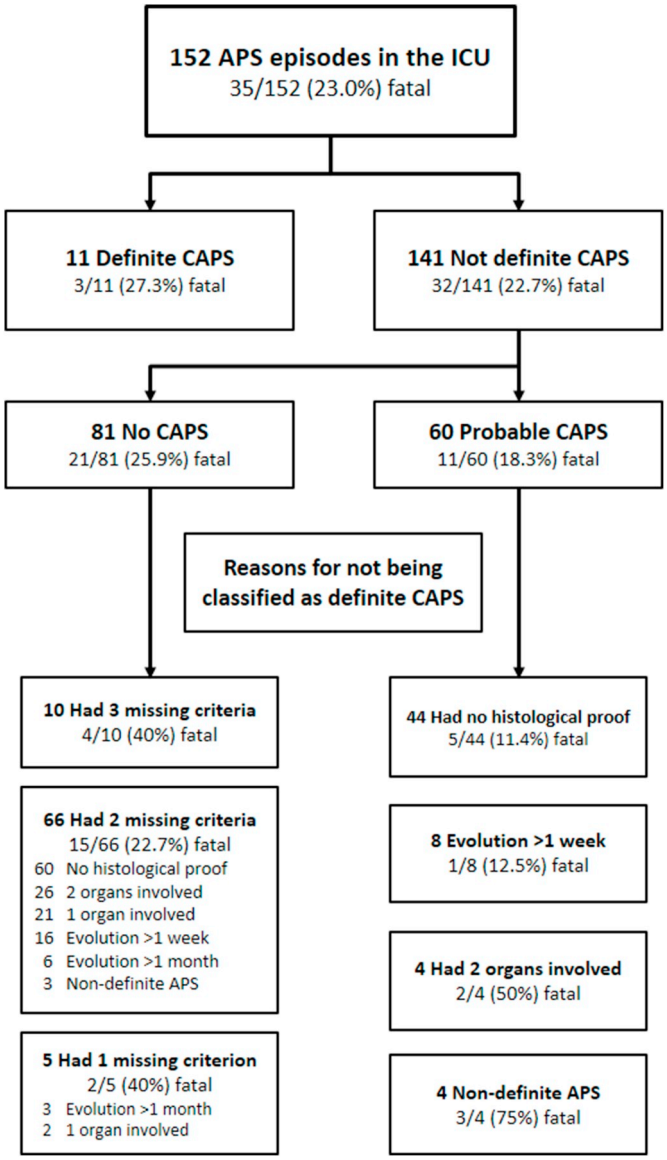

Fig. 1. Distributions of the 152 episodes of definite/probable and no catastrophic antiphospholipid syndrome (CAPS) requiring intensive care unit (ICU) admission, diagnosed in 134 antiphospholipid syndrome patients, and their attributed fatalities, with respective reasons for not being classified as definite CAPS.

Table 2
General characteristics of the 134 patients' last APS episode with comparison between definite/probable and no-CAPS patients.

Characteristic	All patients' last episode (n = 134)	Definite/probable CAPS (n = 61)	No CAPS (n = 73)	p value
Demographic				
Female	96/134 (71.6)	38 (62.3)	58 (79.5)	0.03
Age, years	46.0 ± 15.1	47.5 ± 13.9	44.7 ± 16.1	0.3
Body-mass index,[a] kg/m^2	25.6 ± 6.2	24.5 ± 4.6	26.6 ± 7.3	0.06
APS characteristics				
Months of APS follow-up	98 [28–214]	82 [16–210]	121 [41–215]	0.3
Venous APS	93 (69.4)	46 (75.4)	47 (64.4)	0.2
Arterial APS	61 (45.5)	28 (45.9)	33 (45.2)	0.9
Obstetrical APS	37/96 (38.5)	15/38 (39.5)	22/58 (37.9)	0.4
APS biological findings				
Lupus anticoagulant	122 (91.0)	56 (91.8)	66 (90.4)	0.8
Anti-cardiolipin IgG	98 (73.1)	42 (68.9)	56 (76.7)	0.3
Anti-cardiolipin IgM	28 (20.9)	15 (24.6)	13 (17.8)	0.3
Anti-β_2GP1 IgG	80 (59.7)	34 (55.7)	46 (63.0)	0.4
Anti-β_2GP1 IgM	19 (14.2)	12 (19.7)	7 (9.6)	0.1
Triple aPLA positivity	71 (53)	31 (50.8)	40 (54.8)	0.6
Definite APS	123 (91.8)	57 (93.4)	66 (90.4)	0.8
Treatment before CAPS episode				
Any treatment	103 (76.9)	46 (75.4)	57 (78.1)	0.7
Antiplatelet therapy	43 (32.1)	13 (21.3)	30 (41.1)	0.02
Anticoagulant	95 (70.9)	44 (72.1)	51 (69.9)	0.8
Systemic lupus erythematosus	46 (34.3)	17 (27.9)	29 (39.7)	0.1
APS diagnosed before ICU admission	105 (78.4)	46 (75.4)	59 (80.8)	0.4
In-ICU stay, days	10.0 [4.7–21.0]	10.0 [5.5–21.0]	10.0 [4.0–25.5]	0.7
In-hospital stay, days	34.0 [20.0–58.7]	36.0 [21.0–57.5]	32.0 [18.5–65.0]	0.7
Day-0 SAPS II	33 [17.5–45.2]	32.0 [18.0–45.5]	33.0 [16.0–47.5]	0.8
Day-0 SOFA score	6.5 [3.0–9.0]	7.0 [3.0–10.0]	6.0 [3.0–9.0]	0.7
Renal failure	48/133 (36.1)	23 (37.7)	25/72 (34.7)	0.7
Haematological failure	34/133 (25.6)	16 (26.2)	18/72 (24.2)	0.9
Cardiovascular failure	33/133 (24.8)	14 (23.0)	19/72 (26.4)	0.6
Neurological failure	25/133 (18.8)	10 (16.4)	15/72 (20.8)	0.5
Respiratory failure	21/133 (15.8)	8 (13.1)	13/72 (18.1)	0.4
Liver failure	2/133 (1.5)	0 (0.0)	2/72 (2.8)	0.2
Charlson score	2 [1–4]	2 [1–4]	2 [1–4]	0.5
Precipitating event	99 (73.9)	49 (80.3)	50 (68.5)	0.1

APS: antiphospholipid syndrome; CAPS: catastrophic APS; β2GP1: β_2-glycoprotein-1; aPLA: antiphospholipid antibody; IgG or IgM: immunoglobulin G or M; ICU, intensive care unit; day 0: day of ICU admission; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ-Failure Assessment.
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 χ^2 tests.
[a] Values available for 124 episodes at ICU admission.

(39.5%) or no-CAPS (53.3%) categories, and attributed fatalities are reported in Fig. 1. For probable CAPS episodes, the reasons for not being classified as definite CAPS were: no histopathological proof of microvascular thrombosis (73.3%), evolution > 1 week (13.3%), only two organs involved (6.7%) and non-definite APS (6.7%). Most of the no-CAPS episodes lacked 2 criteria for classifying them as definite CAPS (81.5%), with no histopathological proof (74.1%) and two (32.1%) or one (25.9%) APS-involved organs being the most frequent.

3.3. General characteristics

The general characteristics of the last APS episodes of definite/probable and no-CAPS patients are reported in Table 2. No-CAPS patients were significantly more likely to be women and tended to have higher body-mass indexes. Mean age at ICU admission, pre-admission last APS-episode characteristics and biological findings were comparable for the two groups. No-CAPS patients had significantly more frequently received antiplatelet therapy before admission. A non-significant trend towards more frequent association with systemic lupus erythematosus was found for no-CAPS patients. In-ICU and in-hospital lengths of stay, day-0 Simplified Acute Physiology Score II (SAPS II), Sequential Organ-Failure Assessment (SOFA) scores and Charlson comorbidity scores were comparable for the two groups.

3.4. APS thrombotic characteristics

APS thrombotic and biological findings of the last APS episodes of definite/probable and no-CAPS patients are reported in Table 3. Definite/probable-CAPS patients had a significantly higher median number of organs involved and frequencies of proven microvascular thrombosis renal, cerebral, cutaneous, adrenal gland and gastrointestinal involvement. Haematological manifestations were common, with anaemia (94.0%) and thrombocytopaenia (88.1%) being the most frequent, with no between-group differences.

3.5. Treatments and damage

Specific APS treatments and outcomes of the last APS episodes of definite/probable and no-CAPS patients are reported in Table 4. The overwhelming majorities of patients in both groups received anticoagulant and corticosteroids. Triple therapy, defined as the combination of anticoagulant, corticosteroids and plasmapheresis or intravenous immunoglobulins, was given to comparable percentages of definite/probable or no-CAPS patients. Definite/probable CAPS patients underwent plasmapheresis significantly more often than no-CAPS patients. Kidney failure (glomerular filtration rate < 60 mL/min) was the only statistically different damage between the two groups at hospital discharge, being more frequent in definite/probable CAPS patients, who also had a trend towards more frequent Budd–Chiari/portal or mesenteric vein thrombosis.

Table 3
Thrombotic and biological findings for the 134 patients' last APS episode with comparison between definite/probable and no-CAPS patients.

Variable	All patients' last episode (n = 134)	Definite/probable CAPS (n = 61)	No CAPS (n = 73)	p value
CAPS criterion				
No	73 (54.5)	0 (0.0)	73 (100.0)	NA
Probable	53 (39.6)	53 (86.9)	0 (0.0)	NA
Definite	8 (6.0)	8 (13.1)	0 (0.0)	NA
Days to first 3 organ involvements	5.0 [1.0–14.2]	5.0 [2.0–11.5]	5.0 [0.0–19.5]	0.7
Number of organs involved	3 [2–4]	4 [3,4]	2 [1–3]	< 0.0001
Histological proof of microvascular thrombosis	31 (23.1)	23 (37.7)	8 (11.0)	< 0.0001
Thrombotic manifestation				
Macrovascular thrombosis	89 (66.4)	48 (78.7)	41 (56.2)	0.006
Arterial	57 (42.5)	35/48 (72.9)	22/41 (53.7)	0.06
Venous	63 (47.0)	33/48 (68.8)	30/41 (73.2)	0.6
Organ involved				
Kidney	77 (57.5)	46 (75.4)	31 (42.5)	< 0.0001
Heart	64 (47.8)	33 (54.1)	31 (42.5)	0.2
Lung	47 (35.1)	22 (36.1)	25 (34.2)	0.8
Central nervous system	49 (36.6)	28 (45.9)	21 (28.8)	0.04
Skin	33 (24.6)	26 (42.6)	7 (9.6)	< 0.0001
Peripheral vessel(s)	34 (25.4)	17 (27.9)	17 (23.3)	0.5
Liver	29 (21.6)	14 (23.0)	15 (20.5)	0.7
Adrenal gland	30 (22.4)	22 (36.1)	8 (11.0)	0.001
Spleen	18 (13.4)	12 (19.7)	6 (8.2)	0.053
Gastrointestinal tract	15 (11.2)	11 (18.0)	4 (5.5)	0.02
Eye	7 (5.2)	5 (8.2)	2 (2.7)	0.1
Pancreas	5 (3.7)	4 (6.6)	1 (1.4)	0.1
Fever	78 (58.2)	35 (57.4)	43 (58.9)	0.8
Haematological manifestation	127 (94.8)	57 (93.4)	70 (95.9)	0.5
Anaemia	126 (94.0)	57 (93.4)	69 (94.5)	0.8
Thrombocytopaenia	118 (88.1)	56 (91.8)	62 (84.9)	0.2
Schizocytes	35/127 (27.6)	12/57 (21.1)	23/70 (32.9)	0.1
Haptoglobin < 0.1 g/L	26/98 (26.5)	13/46 (28.3)	13/52 (25)	0.7
Highest in-ICU LDH value, fold ULN (n = 111)	2.2 [1.7–3.6]	2.3 [1.7–3.8]	2.2 [1.7–3.5]	0.8
Lowest in-ICU value				
Haemoglobin, g/dL (n = 123)	7.1 [6.4–8.9]	7.1 [6.5–8.8]	7.0 [6.3–8.9]	0.9
Platelet count, G/L (n = 130)	44 [23–78]	44 [24–72]	44 [21–83]	0.9

APS: antiphospholipid syndrome; CAPS: catastrophic APS; ICU: intensive care unit; LDH: lactate dehydrogenase; ULN: upper limit of normal.
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 χ^2 tests.

3.6. In-hospital mortality

In-hospital mortality rates for definite/probable CPS vs no-CAPS were comparable. The Kaplan–Meier curves of their estimated probabilities of survival are shown in Fig. 2. The Cox proportional hazards model analysis of the association of APS characteristics and CAPS criteria with hospital mortality is reported in Table 5. According to univariable analyses: macrovascular thrombosis (hazards ratio (HR) 2.7 [95% confidence interval 1.1–6.5], p = 0.03), macrovascular arterial thrombosis (HR 3.3 [1.6–6.7], p = 0.001), and macrovascular arterial and venous thromboses (HR 2.6 [1.2–5.3], p = 0.01) were the only factors associated with in-hospital death. Multivariable analyses retained macrovascular arterial thrombosis (HR 3.6 [1.6–7.9], p = 0.001) and histological proof of microvascular thrombosis (HR 1.9 [1.0–4.1], p = 0.047) as being independently associated with hospital mortality. Noteworthy, triple aPLAs positivity was not associated with in-hospital mortality but patients with relapse were more likely to have triple aPLAs positivity.

4. Discussion

The clinical picture, management and prognosis of thrombotic APS patients requiring ICU admission had never been thoroughly examined previously. Herein, we described how these patients fit with the CAPS-definition criteria and how those criteria influenced their treatments and outcomes. CAPS criteria were devised to better recognise, understand and manage APS patients undergoing a dramatic "thrombotic storm". Moreover, they enabled our understanding of this condition to improve remarkably over the last two decades and, with "triple therapy" as the standard of care, CAPS mortality has fallen from 50% to 37%. [3,9,10].

According to the CAPS criteria, we could delineate two subgroups: definite/probable and no-CAPS patients. Comparison of the two subgroups showed that they were comparable except for parameters included in the CAPS-definition criteria: pre-ICU APS characteristics and treatments, and their initial severities and comorbidities, and haematological manifestations, including anaemia, thrombocytopaenia, lactate dehydrogenase levels, and low haptoglobin level or schizocyte frequencies. Other than plasmapheresis which was used more often for CAPS patients, patients in both groups received similar therapeutic regimens, suggesting that triple therapy has, indeed, been recognised as the standard of care for CAPS and is now given to ICU patients with "near-CAPS". That said, however, CAPS criteria might not suffice to decide therapeutic options for the physicians treating a thrombotic APS patient in the ICU. Pertinently, the low mortality that was similar for CAPS and no-CAPS patients supports using that pragmatic approach.

However, our findings raise the issue of the adequacy of CAPS criteria in clinical practice for identification and management of severely-ill thrombotic APS patients. Indeed, the similarity of the haematological patterns in both groups (very frequent anaemia and profound thrombocytopenia, highly evocative of APS microvascular involvement) suggests that many of our no-CAPS patients were probably near-CAPS patients. Near-CAPS and CAPS patients included herein shared the same prognosis, and, for such patients, fewer organs involved does not indicate less severe disease. Obviously, some of our no-CAPS patients were severely ill because of an isolated macrovascular thrombosis

Table 4
APS-specific treatments and outcomes of the 134 patients' last episodes with comparison between definite/probable and no-CAPS patients.

Variable	All patients' last episode (n = 134)	Definite/probable CAPS (n = 61)	No CAPS (n = 73)	p value
Specific treatments				
None	2 (1.5)	1 (1.6)	1 (1.4)	0.9
Anticoagulant	128 (95.5)	58 (95.1)	70 (95.9)	0.8
Antiplatelet therapy	36 (26.9)	18 (29.5)	18 (24.7)	0.5
Corticosteroids	108 (80.6)	51 (83.6)	57 (78.1)	0.4
Corticosteroid pulses	58/108 (53.7)	29 (47.5)	29/57 (50.9)	0.5
Intravenous immunoglobulins	46 (34.3)	19 (31.1)	27 (37.0)	0.5
Plasmapheresis	50 (37.3)	29 (47.5)	21 (28.8)	0.02
Rituximab	18 (13.4)	11 (18.0)	7 (9.6)	0.1
Eculizumab	6 (4.5)	4 (6.6)	2 (2.7)	0.3
Cyclophosphamide	10 (7.5)	3 (4.9)	7 (9.6)	0.3
Triple therapy[a]	75 (56)	38 (62.3)	37 (50.7)	0.2
Number of treatments	3 [2–4]	3 [2–4]	3 [2–4]	0.1
Outcomes				
Days of follow-up	375.0 [37.0–1144.7]	302.0 [33.5–1066.0]	458.0 [39.0–1152.0]	0.6
Damage				
GFR < 60 mL/min	36/99 (36.4)	23/47 (48.9)	13/52 (25.0)	0.01
End-stage renal disease	6/99 (6.1)	3/47 (6.4)	3/52 (5.8)	0.9
LVEF < 50%	23/99 (23.2)	10/47 (21.3)	13/52 (25.0)	0.7
Adrenal failure	12/99 (12.1)	7/47 (14.9)	5/52 (9.6)	0.4
Budd–Chiari/PVT/MVT	9/99 (9.1)	7/47 (14.9)	2/52 (3.8)	0.06
Neurological sequelae	14/99 (14.1)	7/47 (14.9)	7/52 (13.5)	0.8
Visual loss	8/99 (8.1)	6/47 (12.8)	2/52 (3.8)	0.1
DIAPS score after 6 months	2 [1–3.5]	3 [1–4]	2 [1–3]	0.2
Survival				
In-ICU mortality	27 (20.1)	12 (19.7)	15 (20.5)	0.9
In-hospital mortality	35 (26.1)	14 (23.0)	21 (28.8)	0.4
Day-28 survival	109/127 (85.8)	51/58 (87.9)	58/69 (84.1)	0.5
Day-90 survival	91/121 (75.2)	43/55 (78.5)	48/66 (72.7)	0.5
Day-180 survival	77/110 (70.0)	37/49 (75.5)	40/61 (65.6)	0.3
Day-365 survival	68/103 (66.0)	28/42 (66.7)	40/61 (65.6)	0.9

APS: antiphospholipid syndrome; CAPS: catastrophic APS; GFR, glomerular filtration rate; LVEF: left ventricular ejection fraction; PVT: portal vein thrombosis; MVT: mesenteric vein thrombosis; DIAPS: damage index APS.
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 χ^2 tests.
[a] Defined as the combination of anticoagulant, corticosteroids and plasmapheresis or intravenous immunoglobulins.

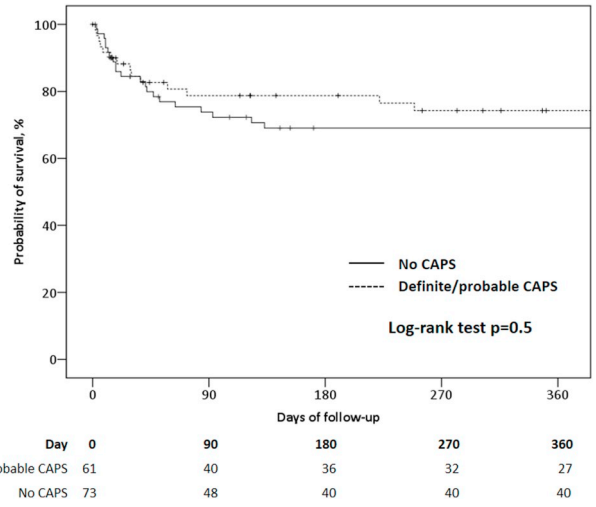

Fig. 2. Kaplan–Meier curve of the estimated probability of survival of the 134 patients with antiphospholipid syndrome admitted to the intensive care unit. CAPS: catastrophic antiphospholipid syndrome; day 0: day of intensive care unit admission.

(severe pulmonary embolism, cardiogenic shock related to coronary thrombosis…). Those patients could not—and should not—be considered CAPS patients, because the management required is not the same.

Most of the CAPS patients' data were derived from the European CAPS Registry that retrospectively included patients with definite or probable CAPS. [3,11–16]. Compared to CAPS Registry patients, our CAPS population was older (mean age 38 vs. 47.5 years) but had similar percentages of women (69% vs. 62.3%) and associated systemic lupus erythematosus (30% vs. 27.9%). APS was diagnosed during these ICU episodes for only 25% of our patients vs. 50% of the CAPS Registry. That finding probably reflects the particularities of the centres that participated in this study. The distributions and frequencies of involved organs in the CAPS Registry and our cohort, respectively, were quite similar: kidney (73% vs. 75.4%), heart (50% vs. 54.1%), central nervous system (56% vs. 45.9%) and skin (47% vs. 42.6%). The most notable differences between the CAPS registry and our CAPS patients, respectively, were: lung (60% vs. 36.1%) involvement which was defined differently for the two populations, adrenal gland involvement (10% vs. 36.1%), liver involvement (39% vs. 23%) and thrombocytopaenia (91.8% vs. 67%).

In the introduction of the international consensus statement on CAPS, it was stated that a minority of CAPS patients have macrovascular thrombosis. [2]. However, our findings revealed that macrovascular thrombosis was frequent in CAPS and seriously impacted patient's outcomes.

Mortality of our definite/probable CAPS patients was the lowest reported to date (19.7% vs. 37% for the CAPS Registry). Because our patients required ICU admission, it is difficult to appraise the extents of their CAPS severities vs those of CAPS Registry patients, for whom this information is not available. However, our lower frequencies of involvement of some organs (ie, lung or liver) could suggest less severe disease. On the other hand, ICU disease-severity scores that have been associated with ICU survival [17,18] are available for our patients but not CAPS Registry subjects. The CAPS-specific–treatment frequencies

Table 5
Univariable and multivariable (Cox proportional hazards model) analyses of the associations of the 134 APS patients' characteristics and CAPS criteria with in-hospital mortality.

	Univariable analysis			Multivariable analysis		
Variable	HR	95% CI	p value	HR	95% CI	p value
APS characteristics						
Known APS	0.7	0.3–1.5	0.4			
Venous APS	0.9	0.4–1.8	0.7			
Arterial APS	1.2	0.6–2.4	0.5			
Triple aPLA positivity	0.8	0.4–1.6	0.5			
Systemic lupus erythematosus	0.9	0.5–1.9	0.8			
CAPS criterion						
No	1.2	0.6–2.4	0.5			
Probable	0.7	0.3–1.4	0.3			
Definite	1.5	0.5–5.0	0.5			
≥3 organs involved	1.3	0.7–2.6	0.4	0.8	0.4–1.8	0.7
Evolution ≤1 week	0.9	0.5–1.7	0.7	1.3	0.6–2.7	0.4
Histological proof of microvascular thrombosis	1.9	0.9–3.8	0.07	1.9	1.0–4.1	0.047
Macrovascular thrombosis	2.7	1.1–6.5	0.03			
Arterial	3.3	1.6–6.7	0.001	3.4	1.7–6.9	0.001
Venous	1.6	0.8–3.2	0.2	1.6	0.8–3.2	0.2
Arterial and venous	2.6	1.2–5.3	0.01			
Episode characteristic						
Fever	1.5	0.8–3.1	0.2			
Anaemia	1.1	0.3–4.5	0.9			
Thrombocytopaenia	1.5	0.5–5.0	0.5			
Haptoglobin < 0.1 g/L	1.0	0.4–2.5	0.9			
Schizocytes	1.6	0.8–3.2	0.2			
Thrombotic microangiopathy[a]	1.1	0.5–2.4	0.7			

APS: antiphospholipid syndrome; CAPS: catastrophic APS; aPLA: antiphospholipid antibody; ICU, intensive care unit; CI, confidence interval; HR, hazards ratio.
The multiple Cox proportional hazard model, including ≥3 organs involved, evolution ≤1 week, histological proof, arterial and venous macrothromboses, using backward-stepwise variable elimination was run (with the variable exit threshold set at $p > 0.10$). All potential explanatory variables included in the multivariable analyses were subjected to collinearity analysis with a correlation matrix When collinearity was found, only one of the two variables could be included the model. Statistical significance was defined as $p < 0.05$.
[a] Defined as anaemia + thrombocytopaenia and haptoglobin < 0.1 g/L or schizocytes.

were similar herein and in the CAPS Registry, except for triple therapy, which was given more frequently to our patients (62.3% vs. 40.1%). The latter probably reflects the fact that most of our patients were admitted to the ICU after the CAPS Registry publication [12] supporting triple therapy use (72% admitted after 2010, data not shown).

Our study has both strengths and limitations. First, it is a retrospective, observational study but it included 24 ICUs in participating centres and many patients for a very rare condition. Second, the patient-inclusion period exceeded 20 years, with inevitable heterogeneity of diagnoses and management, but most of the patients were included during the last decade. Third, the study included CAPS and no-CAPS patients. However, it enabled us to describe the real-world picture of thrombotic APS patients requiring ICU admission and to examine the efficacy of the CAPS criteria.

Altogether, our results suggest that the CAPS criteria do not sufficiently encompass all the parameters responsible for thrombotic APS patients' disease severity in the ICU. The absence of items referring to organ dysfunction/failure in the CAPS criteria probably limited their ability to predict mortality. Albeit useful for the retrospective classification and comparison of patients, the CAPS criteria may be too stringent and not yet ready-to-use for the management of ICU patients. For physicians outside expert APS centres, the absence of CAPS criteria could be misleading and lead to rejection of the diagnosis for near-CAPS patients, thereby preventing them from receiving the appropriate aggressive treatment they indeed require. We think that, when confronted with a critically-ill thrombotic APS patient, CAPS criteria should be interpreted with caution and should not be the only elements taken into account to decide the intensity of the therapeutic management.

5. Conclusion

In this study, CAPS criteria were not associated with mortality of thrombotic APS patients requiring ICU admission. Further studies are needed evaluate the adequacy of CAPS criteria for critically-ill APS patients.

Authorship contributions

- MPdC and ZA contributed in study design, data collection, statistical analysis conduction and interpretation and manuscript writing.
- CEL and AC contributed in study design, statistical analysis interpretation and manuscript writing.
- All others authors contributed in data collection.

Disclosure of conflicts of interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://

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