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► **To cite this version:**

Marc Pineton de Chambrun, R. Larcher, Frédéric Pène, Laurent Argaud, Julien Mayaux, et al.. In-Hospital Mortality-Associated Factors of Thrombotic Antiphospholipid Syndrome Patients Requiring Intensive Care Unit Admission. *Chest*, 2019, 157 (5), pp.1158-1166. 10.1016/j.chest.2019.11.010 . hal-02387757

HAL Id: hal-02387757

<https://hal.science/hal-02387757>

Submitted on 18 Jun 2020

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In-Hospital Mortality-Associated Factors in Patients With Thrombotic Antiphospholipid Syndrome Requiring ICU Admission

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BACKGROUND: The antiphospholipid syndrome (APS) is a systemic autoimmune disease defined by thrombotic events that can require ICU admission because of organ dysfunction related to macrovascular and/or microvascular thrombosis. Critically ill patients with thrombosis and APS were studied to gain insight into their prognoses and in-hospital mortality-associated factors.

METHODS: This French national, multicenter, retrospective study included all patients with APS and any new thrombotic manifestations admitted to 24 ICUs (January 2000-September 2018).

RESULTS: During the study period, 134 patients (male/female ratio, 0.4) with 152 APS episodes were admitted to the ICU (mean age at admission, 46.0 ± 15.1 years). In-hospital mortality of their 134 last episodes was 35 of 134 (26.1%). The Cox multivariable model retained certain factors (hazard ratio [95% CI]: age ≥ 40 years, 11.4 [3.1-41.5], $P < .0001$; mechanical ventilation, 11.0 [3.3-37], $P < .0001$; renal replacement therapy, 2.9 [1.3-6.3], $P = .007$; and in-ICU anticoagulation, 0.1 [0.03-0.3], $P < .0001$) as independently associated with in-hospital mortality. For the subgroup of definite/probable catastrophic APS, the Cox bivariable model (including the Simplified Acute Physiology Score II score) retained double therapy (corticosteroids + anticoagulant, 0.2 [0.07-0.6]; $P = .005$) but not triple therapy (corticosteroids + anticoagulant + IV immunoglobulins or plasmapheresis: hazard ratio, 0.3 [0.1-1.1]; $P = .07$) as independently associated with in-hospital mortality.

CONCLUSIONS: In-ICU anticoagulation was the only APS-specific treatment independently associated with survival for all patients. Double therapy was independently associated with better survival of patients with definite/probable catastrophic APS. In these patients, further studies are needed to determine the role of triple therapy.

KEY WORDS: antiphospholipid syndrome; catastrophic antiphospholipid syndrome; ICU; systemic lupus erythematosus

ABBREVIATIONS: aPLA = antiphospholipid antibodies; APS = antiphospholipid syndrome; CAPS = catastrophic antiphospholipid syndrome; IVIg = IV immunoglobulins; SAPS = Simplified Acute Physiology Score; SLE = systemic lupus erythematosus; SOFA = Sequential Organ Failure Assessment

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The antiphospholipid syndrome (APS) is a systemic autoimmune disease defined by thrombotic and/or obstetrical events occurring in patients with persistent antiphospholipid antibodies (aPLA).¹ Rarely, patients with APS require ICU admission for organ failure attributable to macrovascular and/or microvascular

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FUNDING/SUPPORT: The authors have reported to *CHEST* that no funding was received for this study.

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main complications of APS. Criteria for the diagnosis of CAPS have been proposed.¹ Its prognosis is poor, with 37% to 50% mortality.^{1,2}

We recently reported that less than one-half of patients with APS and an in-ICU thrombotic event had “definite/probable CAPS” according to the international CAPS classification.³ In this study, “definite/probable CAPS” and “nonclassified as CAPS” groups had the same laboratory findings, received the same APS-specific treatments, and shared the same prognosis. Those results suggested that differentiating patients with thrombotic APS admitted to the ICU according to CAPS criteria may not be pertinent for in-ICU diagnosis and prognosis.

Knowledge about patients with severe thrombotic APS mainly relies on data obtained from the European CAPS Registry (henceforth referred to as the CAPS registry).² Although very useful, those data did not detail in-ICU parameters known to be associated with in-hospital mortality of critically ill patients (eg, severity scores, organ failures). The current study was conducted to identify the in-hospital mortality-associated factors of critically ill patients with thrombotic APS requiring ICU admission.

Patients and Methods

Patients

This national, multicenter, retrospective French study, conducted from January 2000 to September 2018, included all patients with APS admitted to the ICUs of the 24 participating centers with any new thrombotic (arterial, venous, or microvascular) manifestation; those without any new thrombotic manifestation were not included. APS was defined according to the 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 (or 6-week interval before 2006) were included. APS-related thromboses were diagnosed clinically, using conventional imaging (Doppler ultrasound, echocardiogram, CT scan, arteriography, and MRI) or histologic examination of any specimen, as previously reported.¹ 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 sample or, when histopathologic proof could not be obtained, was diagnosed after exclusion of differential diagnoses, as follows: kidney (50% serum creatinine rise), severe systemic hypertension (> 180/100 mm Hg) and/or proteinuria (> 500 mg/24 h), after excluding lupus nephritis in particular, lung (BAL or CT scan revealing intra-alveolar hemorrhages after eliminating cardiogenic pulmonary edema), heart (clinical, biologic, or radiologic evidence of myocardial infarction in the absence of explanatory coronary obstruction or thrombosis), and brain (delirium, coma, seizure, or status epilepticus).

Data Collection

The following information was collected on standardized forms: epidemiologic parameters; APS clinical, biologic, and therapeutic history; clinical manifestations; laboratory findings; in-ICU treatments; complications; and outcomes. Patients were classified according to previously published CAPS criteria.¹ The APS Damage Index was calculated for every survivor with available follow-up 6 months following ICU discharge, as previously reported⁷; every item was accorded 1 point. Systemic lupus erythematosus (SLE) was classified according to American College of Rheumatology criteria.⁸

Statistical Analyses

Results for categorical variables, expressed as number (%), were compared by using χ^2 tests; results for continuous variables, expressed as mean \pm SD or median [25th-75th percentile interquartile range (IQR)], were compared by using the Student *t* test or the Wilcoxon rank test. Normality of continuous variables was assessed with the Shapiro-Wilk test, and nonnormally distributed continuous variables were compared by using the Wilcoxon rank test.

The primary outcome was hospital mortality, defined as the occurrence of death during the hospital stay consecutive to the first ICU admission and prior to the discharge of the patient at home. First, patient characteristics were subjected to descriptive analysis (laboratory findings, thrombotic manifestations, in-ICU organ-failure treatments, APS-specific treatments, complications, and outcomes). We next

Results

The 152 Thrombotic APS Episodes

The 134 patients (male/female ratio, 0.4; mean age at admission, 46.0 \pm 15.1 years) had 152 episodes requiring ICU admission during the study period (e-Table 1). Prior to ICU admission, patients had venous (69.4%) or arterial (45.5%) APS, triple aPLA positivity (53%), took anticoagulants (70.9%), and/or underwent antiplatelet therapy (32.1%). One-third also had SLE. For 73.9%, a factor precipitating thrombosis could be identified prior to ICU admission, predominantly: anticoagulant withdrawal (47.5%), switch of vitamin K antagonist to heparin (34.3%), surgery (33.3%), infection (30.3%), hemorrhagic event (25.3%), pregnancy (19.2%), and invasive procedures (17.2%). Reasons for ICU admission are reported in e-Table 2. Sixty-one (45.5%) patients were classified as “definite/probable CAPS,” and 73 (54.5%) were classified as no CAPS. The all-episode in-hospital mortality was 35 of 152 (23%), and overall in-hospital mortality for the patients’ last episodes was 35 of 134 (26.1%).

In-Hospital Mortality-associated Factors

Last Episodes of the 134 Study Patients: Among the general characteristics, preadmission APS clinical manifestations, laboratory findings, treatments, and associated SLE frequencies (Table 1), the only factor that differed was that nonsurvivors were

compared differences in the mean/median values and frequencies of patient characteristics according to their vital status at hospital discharge. A Cox proportional hazards model, including the variables associated with in-hospital mortality (entry threshold, $P < .05$), was then run by using backward-stepwise variable elimination (exit threshold, $P > .10$). All potential explanatory variables included in the multivariable analyses were subjected to collinearity analysis with a correlation matrix. When collinearity was found (variance inflation factor > 5), only one of the two variables could be included in the model. Statistical significance was defined as $P < .05$. Analyses were computed by using IBM SPSS Statistics version 22.0 software (IBM SPSS Statistics, IBM Corporation).

Ethical Considerations

The database is registered with 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.

significantly older than survivors at admission. Nonsurvivors had significantly higher median Charlson Comorbidity Index scores, day 0 Simplified Acute Physiology Score (SAPS II), and day 0 Sequential Organ Failure Assessment (SOFA) score. The only day 0 SOFA scores ≥ 3 significantly associated with in-hospital mortality were renal and neurologic failures.

Pregnancy was a significantly more frequent precipitating factor for survivors, and hemorrhagic events were more common for nonsurvivors (Table 2). CAPS criteria were comparable for survivors and nonsurvivors. APS-attributable macrovascular or arterial macrovascular thromboses and heart, CNS, and GI tract involvements were significantly associated with mortality.

Anemia, thrombocytopenia, schizocytes, and low haptoglobin level frequencies did not differ between survivors and nonsurvivors (e-Table 3). Nonsurvivors’ median [25th-75th percentile interquartile range] hemoglobin nadir (6.7 [6.1-7.1] g/dL vs 7.5 [6.5-8.9] g/dL; $P = .004$) and platelet count (23 [11-64] G/L vs 47 [27-78] G/L; $P = .003$), compared with those of survivors, were significantly lower; their pH, fibrinogen concentrations, and prothrombin times were significantly lower; and their arterial lactate, troponin, serum creatinine, and procalcitonin and D-dimer levels were significantly higher.

TABLE 1] Comparisons of Characteristics of Patients With APS According to In-Hospital Mortality

Characteristic	Survivors (n = 99)	Nonsurvivors (n = 35)	P Value
Female sex	71 (71.7)	25 (71.4)	.9
Age, y	42.3 ± 14.4	56.4 ± 12.1	< .0001
BMI, kg/m ^{2a}	26.2 ± 5.4	24.1 ± 7.9	.1
APS			
Follow-up duration, mo	102.0 [37.0-217.0]	63.0 [1-175]	.06
Venous	70 (70.7)	23 (65.7)	.6
Arterial	43 (43.4)	18 (51.4)	.4
Obstetric	31/71 (43.7)	6/24 (24)	.1
Immunology findings			
Lupus anticoagulant	90 (90.9)	32 (91.4)	.9
Anti-cardiolipin IgG	75 (75.8)	23 (65.7)	.2
Anti-cardiolipin IgM	22 (22.2)	6 (17.1)	.5
Anti-β ₂ GP1 IgG	63 (63.6)	17 (48.6)	.1
Anti-β ₂ GP1 IgM	12 (12.1)	7 (20)	.3
Triple positivity	54 (54.5)	17 (48.6)	.5
Treatment prior to the episode			
Any	75 (75.8)	28 (80)	.6
Antiplatelet agent	30 (30.3)	13 (37.1)	.5
Anticoagulant	71 (71.7)	24 (68.6)	.7
Systemic lupus erythematosus	34 (34.3)	12 (34.3)	.9
APS diagnosed prior to ICU admission	79 (79.8)	26 (74.3)	.5
Charlson Comorbidity Index score	1.0 [1.0-3.0]	4.0 [1.0-6.0]	< .0001
In-ICU stay duration, d	9.0 [3.0-19.0]	16.0 [6.0-37.0]	.02
In-hospital stay duration, d	32.0 [20.0-53.0]	46.0 [19.0-83.0]	.1
Day 0 SAPS II	28.0 [13.0-39.0]	45.0 [37.0-59.0]	< .0001
Day 0 SOFA score ^b	5.0 [3.0-8.0]	9.0 [6.0-13.0]	< .0001
Renal failure	26/98 (26.5)	21/34 (61.8)	< .0001
Hematologic failure	21/98 (21.4)	13 (37.1)	.07
Cardiovascular failure	21/98 (21.4)	12 (34.3)	.1
Neurologic failure	13/98 (13.3)	12 (34.3)	.006
Respiratory failure	14/98 (14.3)	7 (20)	.4
Hepatic failure	2/98 (2.0)	0	.4

Continuous variables are expressed as mean ± SD or median [interquartile range] and compared by using the Student *t* test or the Wilcoxon rank test; categorical variables are expressed as No. (%) and compared by using χ^2 tests. APS = antiphospholipid syndrome; β_2 GP1 = anti- β_2 -glycoprotein-1 antibodies; SAPS = Simplified Acute Physiology Score; SOFA = Sequential Organ Failure Assessment.

^aA total of 92 survivors and 32 nonsurvivors.

^bFailure of each organ was defined as a SOFA score \geq 3.

Nonsurvivors, compared with survivors, received in-ICU vasopressive drugs, mechanical ventilation, renal replacement therapy, packed RBC, and platelet transfusions significantly more frequently (Table 3). In-ICU anticoagulant use was significantly more frequent for survivors, and rituximab infusions were significantly more frequent for nonsurvivors. Median numbers of APS-specific treatments were comparable between survivors and nonsurvivors. Survivors received

double therapy (corticosteroids + anticoagulant) significantly more often than nonsurvivors, who had higher, but nonsignificant, triple therapy (double therapy + IV immunoglobulins (IVIg)/ plasmapheresis) use.

According to the Cox proportional hazards model univariable and multivariable analyses of in-hospital mortality-associated factors (Table 4), age \geq 40 years,

TABLE 2] Comparisons of the Precipitating Events, APS Thrombotic Findings, and CAPS Criteria According to In-Hospital Mortality

Variable	Survivors (n = 99)	Nonsurvivors (n = 35)	P Value
Precipitating events	76 (76.8)	23 (65.7)	.2
Days from event to first symptoms	8.0 [2.0-7.0]	4.0 [0.0-10.0]	.05
Days from event to ICU admission	11.0 [5.0-22.0]	12.0 [5.0-22.0]	.8
Infection	21/76 (27.6)	9/23 (39.1)	.3
Treatment	4/76 (5.3)	0	.3
Surgery	25/76 (32.9)	8/23 (34.8)	.9
Invasive procedure	13/76 (17.1)	4/23 (17.4)	.9
Pregnancy	18 (23.7)	1 (4.3)	.04
Hemorrhagic accident	15/76 (19.7)	10/23 (43.5)	.02
Anticoagulant withdrawal	37/76 (48.7)	10/23 (43.5)	.7
VKA to heparin switch	27/76 (35.5)	7/23 (30.4)	.7
None observed	7/76 (9.2)	2/23 (8.7)	.9
CAPS criteria			
No CAPS	52 (52.5)	21 (60)	.4
Probable CAPS	42 (42.4)	11 (31.4)	.3
Definite CAPS	5 (5.1)	3 (8.6)	.4
Days between first and third organ involvements	5.0 [0.0-12.0]	6.0 [2.0-28.0]	.09
No. of involved organs	3 [2-4]	3 [2-4]	.07
Histologic proof	19 (19.2)	12 (34.3)	.07
Thrombotic manifestation			
Macrovascular thrombosis	60 (60.6)	29 (82.9)	.02
Arterial	33 (33.3)	24 (68.6)	< .0001
Venous	43 (43.4)	20 (57.1)	.2
Organ involved by thrombosis			
Kidney	54 (54.5)	23 (65.7)	.3
Heart	41 (41.4)	23 (65.7)	.01
CNS	31 (31.3)	18 (51.4)	.03
Skin	27 (27.3)	6 (17.1)	.2
Adrenal gland	25 (25.3)	5 (14.3)	.2
Lung	35 (35.4)	12 (34.3)	.9
Alveolar hemorrhage	22/31 (71)	5/7 (41.7)	.1
Peripheral vessel	19 (19.2)	15 (42.9)	.006
Liver	23 (23.2)	6 (17.1)	.4
Spleen	10 (10.1)	8 (22.9)	.06
GI tract	7 (7.1)	8 (22.9)	.01
Eye	7 (7.1)	0	.1
Pancreas	4 (4.0)	1 (2.9)	.8
Fever	55 (55.6)	23 (65.7)	.3

Continuous variables are expressed as mean \pm SD or median [interquartile range]; categorical variables are expressed as No. (%). CAPS = catastrophic antiphospholipid syndrome; VKA = vitamin K antagonist. See Table 1 legend for expansion of other abbreviation.

mechanical ventilation, renal replacement therapy, and in-ICU anticoagulation were retained as factors independently associated with in-hospital mortality. The

Kaplan-Meier estimated probabilities of survival did not differ regardless of whether patients were receiving triple therapy (Fig 1).

TABLE 3] Comparison of the In-ICU Organ Failures and APS-specific Treatments According to In-Hospital Mortality

Variable	Survivors (n = 99)	Nonsurvivors (n = 35)	P Value
In-ICU treatments			
Vasopressors	30 (30.3)	27 (77.1)	< .0001
Dobutamine	10 (10.1)	6 (17.1)	.3
Norepinephrine	23 (23.2)	20 (57.1)	< .0001
Epinephrine	6 (6.1)	9 (25.7)	.002
VA-ECMO	4 (4.0)	4 (11.4)	.1
Mechanical ventilation	34 (34.3)	31 (88.6)	< .0001
Duration, d	5 [3.5-10]	10.5 [2.7-29.2]	.2
Reason for mechanical ventilation			
Respiratory	13/29 (44.8)	8/29 (27.6)	
Neurologic	9/29 (31.0)	9/29 (31.0)	
Circulatory	7/29 (24.1)	12/29 (41.4)	
Renal replacement therapy	25 (25.3)	24 (68.6)	< .0001
Duration, d	11.0 [3.0-27.5]	18.0 [3.2-38.0]	.3
Blood transfusion	57 (57.6)	28/34 (82.4)	.009
Platelet transfusion	15 (15.2)	18/34 (52.9)	< .0001
APS-specific treatments			
No. of treatments	3 [2-4]	3 [2-4]	.7
None	1 (1.0)	1 (2.9)	.4
Anticoagulant	98 (99)	30 (85.7)	.001
Antiplatelet agent	28 (28.3)	8 (22.9)	.5
Corticosteroids	83 (83.8)	25 (71.4)	.1
Pulses	46/83 (55.8)	12/25 (48)	.5
IV immunoglobulins	35 (35.4)	11 (31.4)	.7
Plasmapheresis	34 (34.3)	16 (47.5)	.2
Rituximab	9 (9.1)	9 (25.7)	.01
Eculizumab	4 (4.0)	2 (5.7)	.7
Cyclophosphamide	9 (9.1)	1 (2.9)	.2
Triple therapy	59 (59.6)	16 (45.7)	.2
Double therapy	83 (83.8)	21 (60)	.004

Continuous variables are expressed as mean \pm SD or median [interquartile range]; categorical variables are expressed as No. (%).VA-ECMO = venoarterial extracorporeal membrane oxygenation. See Table 1 legend for expansion of other abbreviation.

Patients With Definite/Probable CAPS: According to univariable analysis of in-hospital mortality-associated factors (e-Table 4), the main significant factors (hazard ratio [95% CI]) identified were: day 0 SAPS II \geq 35 (10.4 [2.3-47.0]), macrovascular arterial thrombosis (3.3 [1.6-6.7]), GI involvement (3.7 [1.3-10.7]), vasopressive drugs (9.9 [2.2-44.6]), mechanical ventilation (84.1 [1.1-6510]), renal replacement therapy (5.7 [1.8-18.3]), in-ICU anticoagulation (0.1 [0.03-0.4]), corticosteroids (0.2 [0.06-0.5]), double therapy (0.1 [0.04-0.4]), triple therapy (0.2 [0.07-0.7]), platelet nadir < 20 G/L (1.7 [1.7-15.6]), and arterial lactate levels \geq 5 mmol/L (9.5 [3.0-29.8]).

Univariable and bivariable analyses of in-hospital mortality-associated factors for patients with definite/probable CAPS are presented in e-Table 5. Bivariable analyses (hazard ratio [95% CI]), including day 0 SAPS II \geq 35, retained the following factors as independently associated with in-hospital mortality: in-ICU anticoagulation (0.3 [0.07-0.9]), corticosteroids (0.3 [0.1-0.8]), and double therapy (0.2 [0.07-0.6]); triple therapy (0.3 [0.1-1.1]), IVIg (0.5 [0.1-7.8]), and plasmapheresis (0.8 [0.2-2.3]) were not retained as such. Moreover, in-ICU anticoagulation (0.1 [0.03-0.4]) and corticosteroids (0.02 [0.07-0.6]) were independently associated with in-hospital mortality. The Kaplan-Meier estimated

TABLE 4] Cox Proportional Hazards Model Univariable and Multivariable Analyses of In-Hospital Mortality-Associated Factors

Factor	Univariable Analysis			Multivariable Analysis		
	HR	95% CI	P Value	HR	95% CI	P Value
Age ≥ 40 y	7.7	2.3-25.1	.001	11.4	3.1-41.5	< .0001
Day 0 SAPS II ≥ 35	5.3	2.3-12.2	< .0001	0.6	0.2-1.9	.4
Day 0 SOFA score ≥ 5	4.0	1.5-10.2	.004
Charlson Comorbidity Index score ≥ 4	3.7	1.9-7.3	< .0001
APS involvement						
≥ 30 d between first and third organ involvements	2.4	1.1-5.4	.027
Histologic proof	1.9	0.9-3.8	.07
Macrovascular arterial	2.7	1.1-6.5	.03
Heart	2.2	1.1-4.4	.03
CNS	1.9	0.9-3.6	.07
GI	2.5	1.1-5.6	.02
Spleen	2.3	1.0-5.0	.05
In-ICU treatments						
Vasopressors	5.9	2.7-13.0	< .0001	1.1	0.3-3.4	.9
Mechanical ventilation	10.8	3.8-30.6	< .0001	11.0	3.3-37	< .0001
Renal replacement therapy	5.1	2.4-10.7	< .0001	2.9	1.3-6.3	.007
Corticosteroids	0.5	0.2-1.1	.094	0.6	0.3-1.2	.1
Anticoagulation	0.1	0.05-0.4	< .0001	0.1	0.03-0.3	< .0001
Double therapy	0.4	0.2-0.7	.003
Rituximab	2.2	1.0-4.7	.04
Platelet transfusion	3.7	1.9-7.2	< .0001
Packed RBC transfusion	2.8	1.2-6.8	.02
Laboratory findings						
Arterial lactate ≥ 5 mmol/L	5.5	2.7-11.2	< .0001
Platelets < 20 G/L	4.2	2.1-8.3	< .0001
Hemoglobin < 6.5 g/dL	2.4	1.1-4.8	.02
Infection	3.6	1.7-7.7	.001

The multiple Cox proportional hazards model included the involvement of three or more organs, evolution ≤ 1 week, histologic proof, and arterial and venous macrovascular thrombosis. It used backward-stepwise variable elimination (with the variable exit threshold set at $P > .10$). All potential explanatory variables included in the multivariable analyses were subjected to collinearity analysis with a correlation matrix. Variables associated with one another were not included in the model. Statistical significance was defined as $P < .05$. HR = hazard ratio. See Table 1 legend for expansion of other abbreviations.

probabilities of survival of patients with definite/probable CAPS (e-Fig 1) reported 82% day 90 in-hospital survival with double therapy vs 52% without it (log rank test, $P < .0001$).

Discussion

We recently reported that CAPS criteria do not adequately describe many patients with APS and a thrombotic event requiring ICU admission, who have “near-CAPS,” meaning they display microangiopathic process without being classified as definite/probable CAPS.³ Most of the information on patients with severe APS comes from the CAPS registry that included only

patients with definite/probable CAPS.^{2,9-14} Herein, we report the in-hospital mortality-associated factors of patients with APS and a thrombotic event requiring ICU admission, including the subset of those classified as CAPS.

Our analyses identified several new prognosis factors. First, Charlson Comorbidity Index score, day 0 ICU SAPS II, day 0 SOFA score, and renal and neurologic failures were strongly associated with in-hospital mortality, highlighting the importance of severity of APS organ involvement, an item not included in CAPS criteria. Second, APS macrovascular arterial thrombosis was strongly associated with patient prognoses,

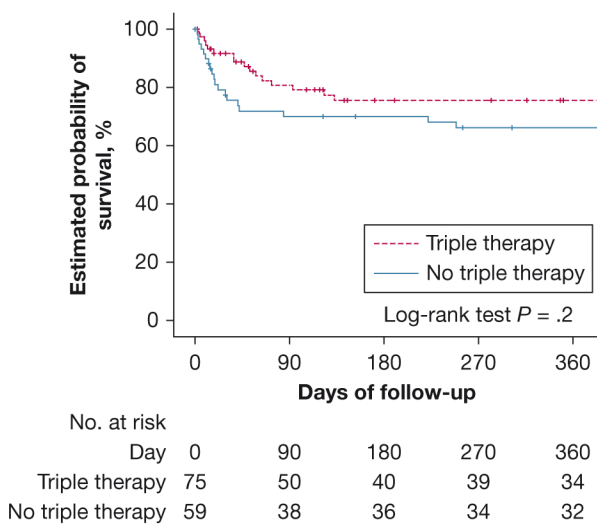


Figure 1 – Kaplan-Meier estimated probability of survival for the 134 patients with antiphospholipid syndrome whose last episodes required ICU admission. Comparison according to triple therapy use is shown.

suggesting that macrovascular thrombosis is a critical factor in patients with CAPS, although it was previously reported to be infrequent. Third, most patients had concomitant low hemoglobin and platelet counts, and persistent thrombocytopenia, regardless of threshold, during the first 28 in-ICU days was strongly associated with death. These findings suggest an APS-related diffuse, thrombotic, microangiopathic process in these critically ill patients.

Together with higher D-dimer levels in nonsurvivors, these results support the importance of thrombotic microangiopathy markers in outcomes of patients with thrombotic APS. We believe that thrombocytopenia and D-dimers could be useful monitoring markers for these patients with APS. Last, a hemorrhagic event as a precipitating factor, absence of in-ICU anticoagulation, and platelet or packed RBC transfusion were all associated with worse outcomes, suggesting that hemorrhagic complications seriously affect the prognosis. Maintaining full anticoagulation in patients with very low platelet counts can be difficult, especially when associated with hemorrhagic complications, but seems essential for survival.

Triple therapy is the recommended first-line treatment of CAPS.⁹ However, herein, it was not significantly associated with better survival in critically ill patients with thrombotic APS. For the subgroup of patients with definite/probable CAPS, double and triple regimens were associated with survival in the univariable analysis. However, the bivariable analyses (including the day

0 SAPS II) showed that survival was linked to in-ICU anticoagulation and corticosteroids, not to IVIg or plasmapheresis. Our findings indicate that corticosteroids should probably be added to in-ICU anticoagulation to treat patients with definite/probable CAPS. Frequent fever and elevated C-reactive protein levels in all patients with thrombotic APS suggest a marked inflammatory state that could explain corticosteroid efficacy. Neither plasmapheresis nor IVIg affected the prognosis of definite/probable CAPS; that finding could be explained by a lack of power compared with CAPS registry data, however. These data give support to using corticosteroids in addition to anticoagulation in patients with definite/probable CAPS; the role of triple therapy requires further evaluation.

Several other rescue therapies have been proposed to treat patients with refractory CAPS.¹⁰⁻¹³ Rituximab, administered to 18 of the 134 study patients, was significantly associated with mortality. This outcome probably reflects the intrinsic severity of the patients' disease rather than a deleterious rituximab effect. Antiplatelet therapy, used as an add-on treatment for one-third of the patients, was not associated with mortality. Last, too few patients received eculizumab or cyclophosphamide to make conclusions regarding their usefulness. Taken together, the data are insufficient to make conclusions regarding the role of such treatments in these patients.

In the data from the CAPS registry, CAPS mortality has fallen from 50% to 37% over the past two decades.^{2,14,15} Mortality of the definite/probable CAPS subgroup was lower than that previously reported, knowing that all the study patients required ICU admission, whereas that information is not available in the CAPS registry. Most of the study patients were admitted to the ICU after 2010, and therefore this lower in-ICU mortality rate may be derived from our better understanding of CAPS, generalization of triple therapy as a standard of care, and improved intensive care management; it may also reflect that most of these patients were managed in APS referral centers. As we previously reported,³ prognoses of CAPS and no-CAPS patients were similar, suggesting that CAPS criteria may not be a perfect fit for identifying the most severe critically ill thrombotic patients.

In addition to triple therapy, the CAPS registry found several mortality-associated factors: SLE,¹⁶ older age, renal involvement, and malignancies.¹⁷ We confirmed that age is an important prognosis determinant for patients critically ill with thrombotic APS but did not

find SLE to be associated with outcome; nevertheless, the percentages of patients with APS-SLE were similar in the CAPS registry and the current study.

Our study has limitations and strengths. First, it has a retrospective, observational design, but many patients with a very rare disease came from 24 ICUs in participating centers. Second, patient inclusion lasting > 20 years means inevitable heterogeneity of diagnoses and management, although most patients were included during the last decade. Third, CAPS and no-CAPS patients were included but that enabled description of

the real-world picture of patients with thrombotic APS requiring ICU admission and analysis of in-hospital mortality-associated factors.

Conclusions

According to our analyses, in-ICU anticoagulation was the only APS-specific treatment independently associated with survival. Double therapy was independently associated with better survival of critically ill patients with definite/probable CAPS. In these patients, further studies are needed to determine the role of triple therapy.

Acknowledgments

Author contributions: M. P. d. C. had full access to all the study data and takes responsibility for the integrity of the data and the accuracy of the data analysis, including and especially any adverse effects. M. P. d. C. and Z. A. contributed to study design, data collection, statistical analysis conduction and interpretation, and manuscript writing. C.-E. L. and A. C. contributed to study design, statistical analysis interpretation, and manuscript writing. All other authors substantially contributed to the acquisition of data and provided final approval of the manuscript.

Financial/nonfinancial disclosures: None declared.

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