Early recognition of catastrophic antiphospholipid syndrome in patients with antiphospholipid syndrome based on a Chinese cohort study

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Abstract

Objective

Catastrophic antiphospholipid syndrome (CAPS) is a life-threatening form of antiphospholipid syndrome (APS) with high mortality. We try to develop a predictive model to achieve early recognition of CAPS.

Methods

Data of APS patients referred into Peking Union Medical College Hospital from May 2013 to October 2021 was collected. A binary logistic regression method was used to identify predictors of CAPS, coefficient B was assigned with score value in the development of prediction model, and risk-stratification was based on the calculated scores using the model.

Results

Twenty-seven CAPS (11.9%) occurred in 226 APS patients. CAPS was more likely to occur in male secondary APS patients with a history of hypertension, hyperlipidaemia, and arterial thrombosis, presented with haematological, nephrological and immunological abnormalities simultaneously. Hypertension history (OR 5.091, 95% CI 1.119–23.147), anaemia (OR 116.231, 95% CI 10.512–1285.142), elevated LDH (OR 59.743, 95% CI 7.439–479.815) and proteinuria (OR 11.265, 95% CI 2.118–59.930) were independent predictors for CAPS, and the scores were 1, 3, 3 and 2 points, respectively. The risk scores were divided into high-risk (6-9) and low risk (0-5), the risk for CAPS were 54.1% and 0.6%, with sensitivity of 0.963 and specificity of 0.886. The Nagelkerke's R^2 (0.739) and the Omnibus test (χ^2 =109.231, df=4, p=0.000) indicated the model has a good fit. The AUC of 0.971 indicated good discrimination. The calibration curve in internal validation showed good calibration of this predictive model.

Conclusion

A predictive model of CAPS was developed with hypertension, anaemia, elevated LDH and proteinuria. This model could help identify CAPS in high-risk patients, achieve early recognition and intervention to improve prognosis.

Key words

antiphospholipid syndrome, catastrophic antiphospholipid syndrome, diagnosis

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Introduction

Antiphospholipid syndrome (APS) is a clinical syndrome characterised with vascular thrombosis or/and pregnant morbidity in patients with persistent positive antiphospholipid antibodies (aPLs), which include lupus anticoagulant (LA), anti-cardiolipin antibody (aCL) and anti-β2 glycoprotein I (anti-β2GPI) (1). The clinical spectrum of APS includes thrombotic APS, obstetric APS, and a severe form called catastrophic APS (CAPS).

CAPS is a rare form of APS in less than 1% patients, characterised by microvascular thrombosis affecting multiple organs in a short period of time despite anticoagulant treatment. The "catastrophic" describes the life-threatening feature with high mortality. Though first-line treatment is combination therapy with glucocorticoid, heparin, and plasmapheresis or IVIG (2), the mortality rate is still as high as 37% in CAPS and even 48% in CAPS secondary to SLE (3). We have learned from CAPS Registry that majority of CAPS (53–65%) were triggered by a precipitating factor, including infection, surgery, malignancy, pregnancy related, lupus flare and so on (4). But there is barely any study investigating risk factors of CAPS in APS patients.

To improve the prognosis of CAPS, treatment might be started before CAPS diagnosis, since the current diagnosis of CAPS need at least 2 organs with signs of dysfunction. Thus, how to identify patients with high risk for CAPS would be important to achieve early recognition and initiate therapy. We conducted a study based on a single-centre 8-year APS cohort and hope to establish a predictive model for early recognition of CAPS.

Materials and methods

Study population

A single-centre study was conducted based on the APS cohort in Peking Union Medical College Hospital, Beijing, China. The PUMCH-APS cohort included APS patients referred into hospital from May 2013 to October 2021. The baseline was defined as the time of admission for APS or CAPS. Only the baseline admission was selected for each patient, and included just once in this study. The diagnosis of APS was established based on the 2006 revised Sydney classification criteria (5). CAPS was diagnosed according to the preliminary classification criteria published on 2003 (6). We included patients with both definite and probable CAPS. This study was approved by the Medical Ethics Committee of PUMCH.

Variables of interest

Demographic characteristics were collected from the medical history such as gender, age, height, weight, and body mass index (BMI). The cardiovascular risk factors included smoking, hypertension, diabetes, and hyperlipidaemia history, and was assessed following NICE guidelines as following: hypertension was defined as high blood pressure (>140/90 mmHg) on two occasions, diabetes was defined as high fast glucose level on two occasions, and hyperlipidaemia was defined as high cholesterol level.

Clinical indicators included disease duration, underlying diseases, and clinical manifestations of APS. Disease duration was defined as time from disease onset to baseline. APS patients with underlying diseases were defined as secondary APS, most common in systemic lupus erythematosus. The clinical manifestations contained in the classification criteria were collected. Venous thrombosis included deep vein thrombosis, pulmonary embolism, portal vein thrombosis, cerebral vein/sinus thrombosis and ophthalmic vein thrombosis. Arterial thrombosis was mostly stroke, myocardial infarction, visceral ischaemia, peripheral artery embolism, and retinal artery occlusion. They were diagnosed by imaging study or histopathology. Pregnancy morbidity was in accordance with APS classification criteria and included 3 types, unexplained fetal death at 10 weeks of gestation or later; premature birth prior to 34 weeks due to eclampsia, preeclampsia, or placental insufficiency; 3 consecutive unexplained spontaneous abortions prior to 10 weeks of gestation.

Detection of LA was concurrent with the recommended criteria from the International Society on Thrombosis and

Haemostasis (ISTH), using a three-step method and dilute Russell's viper venom time (dRVVT) based assay. The aCL and anti-β2GPI antibodies were detected by enzyme-linked immunosorbent assay (ELISA) using commercially available kits. Definition of a positive aCL or anti-β2GPI antibody was 40 or more GPL or MPL units, and tested on two or more occasions at least 12 weeks apart.

Other laboratory parameters at baseline included white blood cell count (WBC), haemoglobulin (HGB), platelet count (PLT), immunoglobulin (Ig), complement C3 and C4, creatine (Cr), lactate dehydrogenase (LDH), proteinuria and haematuria. In detail, anaemia was defined as HGB<120 g/L at admission, and obvious nutritional anaemia or bleeding were ruled out; thrombocytopenia was defined as PLT<100×10^9/L; hypocomplementaemia was considered if complement 3 below 0.730g/L or complement 4 below 0.100g/L. The cut-off creatine and LDH level were 90μmol/L and 250U/L respectively.

Statistical analysis

Continuous variables were shown as mean standard deviation (SD) and analysed using student's t test. Categorical variables were shown as frequency and analysed using χ^2 or Fisher's exact test. A binary logistic analysis was performed by selecting variables with $p<0.05$ in the univariate analysis. Continuous variables were changed into categorical variables for further analysis. Odds ratio (OR) and 95% confidence interval (CI) were used to describe the risk of CAPS for potential predictors.

A risk scoring system was established, the risk score was calculated using the regression coefficient B of each variable in the logistic regression model. A cumulative risk score was calculated for each patient. Receiver operating characteristic curve (ROC curve) was drawn, sensitivity and specificity were used to find the best cut-off of the scoring system. The performance of the model was assessed by Nagelkerke's R^2, Omnibus test, and area under the receiver operating characteristic curve (AUC). The internal validation was shown with calibration curve.

Table I. Demographic and clinical characteristics of APS patients in PUMCH-APS cohort.

	Total (n=226)	CAPS (n=27)	Non-CAPS (n=199)	*p*
Gender (M) (n/%)	78 (34.5)	14 (51.9)	64 (32.2)	**0.043**
Enrolment age (y)	36.2 ± 12.8	36.3 ± 15.2	36.2 ± 12.5	0.975
BMI (kg/m^2)	23.8 ± 4.2	22.8 ± 4.5	24.0 ± 3.8	0.133
Disease duration (m)	53.4 ± 72.8	49.7 ± 77.7	53.9 ± 72.3	0.777
Secondary APS (n/%)	66 (29.2)	14 (51.9)	52 (26.1)	**0.006**
Cardiovascular risk factors				
Smoking (n/%)	50 (22.1)	9 (33.3)	41 (20.6)	0.135
Hypertension (n/%)	52 (23.0)	16 (59.3)	36 (18.1)	**0.000**
Diabetes (n/%)	8 (3.5)	2 (7.4)	6 (3.0)	0.245*
Hyperlipidaemia (n/%)	21 (9.3)	6 (22.2)	15 (7.5)	**0.025***
APS diagnosis (n/%)				
Venous thrombosis	123 (54.4)	17 (63.0)	106 (53.3)	0.342
Arterial thrombosis	101 (44.7)	22 (81.5)	79 (39.7)	**0.000**
Pregnancy morbidity	73/148 (49.3)	5/13 (38.5)	68/135 (50.4)	0.412
LA	177 (78.3)	22 (81.5)	155 (77.9)	0.671
aCL-IgG/M	144 (63.7)	21 (77.8)	123 (61.8)	0.105
anti-β2GP1-IgG/M	178 (78.8)	23 (85.2)	155 (77.9)	0.384
Triple aPL positivity	113 (50.0)	17 (63.0)	96 (48.2)	0.218
WBC (×10^9/L)	7.0 ± 3.6	9.0 ± 6.3	6.6 ± 2.9	0.067
HGB (g/L)	124.5 ± 28.0	82.7 ± 20.4	130 ± 23.8	**0.000**
Anaemia(n/%)	79 (35.0)	26 (96.3)	53 (26.6)	**0.000**
PLT (×10^9/L)	123.9 ± 85.2	61.1 ± 67.1	132 ± 84.0	**0.000**
Thrombocytopenia (n/%)	104 (46.0)	24 (88.9)	80 (40.2)	**0.000**
IgG (g/L)	11.8 ± 3.9	12.4 ± 5.5	11.7 ± 3.6	0.539
C3(g/L)	0.94 ± 0.28	0.72 ± 0.32	0.96 ± 0.26	**0.000**
C4(g/L)	0.16 ± 0.08	0.13 ± 0.06	0.17 ± 0.08	**0.010**
Hypocomplementaemia (n/%)	60 (26.5)	16 (59.3)	44 (22.1)	**0.000**
Cr (μmol/L)	92.3 ± 94.8	224.5 ± 225.8	74.4 ± 28.4	**0.002**
Elevated Cr(n/%)	49 (21.7)	15 (55.6)	34 (17.1)	**0.000**
LDH (U/L)	256.7 ± 143.3	476.4 ± 227.0	226.9 ± 92.3	**0.000**
Elevated LDH(n/%)	79 (35.0)	25 (92.6)	54 (27.1)	**0.000**
Proteinuria (n/%)	46 (20.4)	18 (66.7)	28 (14.1)	**0.000**
Haematuria (n/%)	35 (15.5)	15 (55.6)	20 (10.1)	**0.000**
aGAPSS	9.98 ± 4.026	11.81 ± 3.253	9.73 ± 4.065	**0.002**
aGAPSS >10	123 (54.4)	21 (77.8)	102 (51.3)	**0.009**

*Fisher's test.

CAPS: catastrophic antiphospholipid syndrome; APS: antiphospholipid syndrome; BMI: Body Mass index; LA: lupus anticoagulation; aCL: anti-cardiolipin antibody; anti-β2GP1: anti-β2 glycoprotein 1; aPL: antiphospholipid antibody; WBC: white blood cell; HGB: haemoglobulin; PLT: platelet; IgG: immunoglobulin G; C3: complement 3; C4 complement 4; Cr: creatine; LDH: lactate dehydrogenase; aGAPSS: adjusted Global Anti-Phospholipid Syndrome Score.

All tests were two-tailed, and $p<0.05$ was considered statistically significant. All analyses were performed using SPSS v. 22.0 and R software (3.6.1).

Results

Baseline characteristics

A total of 226 APS patients were enrolled in this study, 11.9% (27 cases) were CAPS. Baseline characteristics were listed in Table I. CAPS group had more male patients than non-CAPS group (51.9% *vs*. 32.2%, $p=0.043$). Secondary APS was dominant in CAPS patients (51.9% *vs*. 26.1%, $p=0.006$). Hypertension (59.3% *vs*. 18.1%, $p=0.000$), hyperlipidaemia (22.2% *vs*. 7.5%, $p=0.025$) and arterial thrombosis (81.5% *vs*. 39.7%, $p=0.000$) were more common in CAPS patients. Most of the laboratory results were statistically significant between CAPS and non-CAPS patients. CAPS patients had lower HGB (82.7±20.4 *vs*. 130±23.8 g/L), lower platelet count (61.1±67.1 *vs*. 132±84.0 ×10^9/L), lower C3 (0.72±0.32 *vs*. 0.96±0.26 g/L), lower C4 (0.13±0.06 *vs*. 0.17±0.08 g/L), higher Cr (224.5±225.8 *vs*. 74.4±28.4 μmol/L), higher LDH (476.4±227.0 *vs*. 226.9±92.3 U/L) level, more proteinuria (66.7% *vs*. 14.1%) and more haematuria (55.6% *vs*. 10.1%) than non-CAPS patients. aGAPSS was higher in CAPS patients (11.81±3.253)

than non-CAPS patients (9.73±4.065). When converting continuous variables into categorical variables, anaemia (96.3% *vs*. 26.6%), thrombocytopenia (88.9% *vs*. 40.2%), hypocomplementemia (59.3% *vs*. 22.1%), elevated Cr (55.6% *vs*. 17.1%), elevated LDH (92.6% *vs*. 27.1%), and aGAPSS>10 (77.8% *vs*. 51.3%) were more prevalent in CAPS patients.

Predictors of CAPS in APS patients

A univariate binary logistic regression was performed. Gender, secondary APS, history of hypertension and hyperlipidaemia, arterial thrombosis, anaemia, thrombocytopenia, hypocomplementaemia, elevated creatine and LDH, proteinuria, haematuria, and aGAPSS were all significantly associated with CAPS in APS patients. The OR of each variable and *p*-value were shown in Table II. The variables in univariate logistic regression analyses were further performed with multivariate logistic regression analysis (forward LR stepwise method) to evaluate independent predictors for CAPS. History of hypertension (OR 5.091, 95% CI 1.119–23.147), anaemia (OR 116.231, 95% CI 10.512–1285.142), elevated LDH (OR 59.743, 95% CI 7.439–479.815) and proteinuria (OR 11.265, 95% CI 2.118–59.930) were independent predictors for CAPS and selected for the development of predictive model.

The prediction model of CAPS and internal validation

The OR and B regression coefficient in the multivariable analysis model was shown in Table III. The score of each variable was calculated as |B/Bmin|, thus the scores of hypertension, anaemia, elevated LDH and proteinuria were 1, 3, 3 and 2 points, respectively. The CAPS risk score was calculated for each APS patient, and the ROC curve of the predictive model was drawn (Fig. 1A). A score of 5 was the best cut-off point with the sensitivity of 0.963 and the specificity of 0.886. Figure 1B shows the cumulative risk score and the number of CAPS patients and non-CAPS patients, as shown in the figure, the CAPS rate generally increased when the risk score rose.

Table II. Predicting factors for CAPS in APS patients.

	Univariable analysis		Multivariable analysis	
	Odds ratio	*p*	Odds ratio	*p*
Gender (M)	2.272 (1.009-5.114)	0.047		
Secondary APS	3.044 (1.343-6.902)	0.008		
Hypertension	6.586 (2.820-15.382)	0.000	5.091 (1.119-23.147)	0.035
Hyperlipidaemia	3.505 (1.228-10.004)	0.019		
Arterial thrombosis	6.684 (2.430-18.382)	0.000		
Anaemia	71.623 (9.483-540.931)	0.000	116.231 (10.512-1285.142)	0.000
Thrombocytopenia	11.900 (3.467-40.844)	0.000		
Hypocomplementaemia	5.124 (2.218-11.839)	0.000		
Elevated creatine	6.066 (2.608-14.109)	0.000		
Elevated LDH	33.565 (7.688-146.534)	0.000	59.743 (7.439-479.815)	0.000
Proteinuria	12.214 (4.994-29.874)	0.000	11.265 (2.118-59.930)	0.005
Haematuria	11.187 (4.600-27.207)	0.000		
aGAPSS >10	3.328 (1.289-8.597)	0.013		

Table III. Odds ratio and B coefficient with multivariable logistic regression model and corresponding risk score.

Variables	Odds ratio	B coefficient	Score
Hypertension	5.091 (1.119-23.147)	1.627	1
Anaemia	116.231 (10.512-1285.142)	4.759	3
Elevated LDH	59.743 (7.439-479.815)	4.090	3
Proteinuria	11.265 (2.118-59.930)	2.422	2

Table IV. The risk stratification for CAPS according to the risk score system.

Risk stratification	Number of patients	CAPS (N)	CAPS (%)
High risk (6-9)	48	26	54.1
Low risk (0-5)	178	1	0.6
Total	226	27	11.9

The risk stratification for CAPS according to the risk score system was shown in Table IV. The risk score was divided into high-risk (6–9) and low risk (0–5), and the risk for CAPS were 54.1% and 0.6%. The Nagelkerke's R^2 (0.739) and the Omnibus test (χ^2 =109.231, df=4, p=0.000) indicated the logistic regression model had a good fit. The AUC was 0.971 (95% CI 0.942–0.999, SE=0.014, p=0.000) indicated the model had good discrimination.

The calibration curve in internal validation showed good calibration of this predictive model (Fig. 1C).

Discussion

CAPS is a life-threating form of APS, with multiple organ dysfunction in a short time. We conducted a cohort study to establish a predictive model for CAPS diagnosis, hope to achieve early diagnosis and start-up early intervention to improve final prognosis. In this study, we found CAPS patients were more likely to present in male secondary APS patients, with hypertension and hyperlipidaemia, with arterial thrombosis history, with haematological (anaemia, thrombocytopenia, elevated LDH), nephrological (proteinuria, haematuria, elevated Cr) and immunological (hypocomplementaemia) abnormalities simultaneously. The final predictive model consisted of hypertension (1 point), anaemia (3 points), elevated LDH (3 points) and proteinuria (2 points). The risk stratification was based on the risk scores, 0–5 were low risk (0.6%) and 6–9 were high risk (54.1%). The sensitivity and specificity of this predictive model were 0.963 and 0.886, and showed good discrimination and calibration.

The frequency of CAPS in APS is 1% in European cohort (7), and is 12% in PUMCH-APS cohort. Since PUMCH is a tertiary referral centre for APS, the occurrence of CAPS is higher. In PUMCH CAPS cohort, 51.9% were male patients, and 51.9% were secondary APS, nephrological abnormality

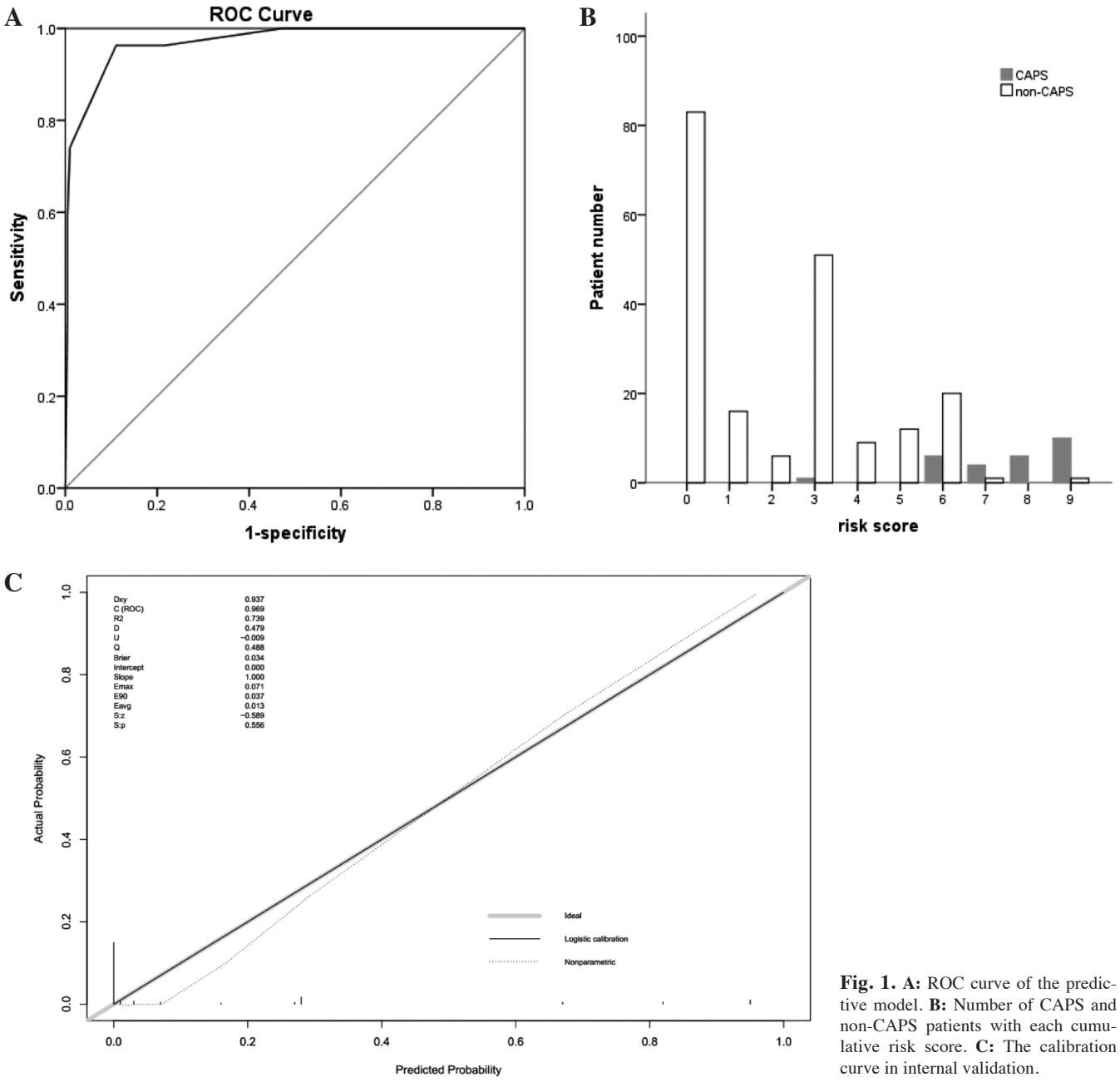

Fig. 1. A: ROC curve of the predictive model. **B:** Number of CAPS and non-CAPS patients with each cumulative risk score. **C:** The calibration curve in internal validation.

was in 66.7% patients, anaemia and thrombocytopenia occurred in almost 90% CAPS patients, indicating multiple organs involvement in CAPS patients and the severity of the disease.

APS secondary to SLE consisted 40% in CAPS Registry and 50% in PUMCH-CAPS cohort. Previous studies have shown that APS secondary to SLE were more likely to have poorer outcome (8), higher long-term damage (9) than PAPS patients. The comparison of secondary and primary APS in literature suggested arterial thrombosis had higher frequency in PAPS, while non-thrombotic manifestations including thrombocytopenia, haemolytic anaemia, livedo reticularis, valve heart disease were more prevalent in APS secondary to SLE (10, 11). Here we found secondary APS were more likely to have CAPS. Since CAPS associated with SLE were more likely to have severe cardiac and brain involvement leading to a higher mortality (48% *vs*. 33%) (3), we should be alert for CAPS in aPL positive lupus patients when there are multiple organs involvement, not just consider lupus flare.

Hypertension and hyperlipidaemia are traditional risk factors in cardiovascular disease. The pathogenesis of APS has a "second-hit" theory (12), the "first hit" injury induces endothelial dysfunction, the "second hit" potentiates thrombus formation (13). Infection (14) or surgery might be a "third hit" in the development of CAPS (15). Hypertension and hyperlipidaemia (16) could constitute a substantial first hit and activate the endothelium, allowing the promotion of thrombosis by aPLs. The important role of hypertension and hyperlipidaemia in pathogenesis of APS has been revealed by the aGAPSS (17) and validated in different

cohorts (18), hypertension was also included in our CAPS model (1 point). Hypertension was risk factor for arterial thrombosis in APS (19) but not for venous thrombosis (20), also explained the higher proportion of arterial thrombosis (81.5%) than venous thrombosis (63.0%) in our CAPS cohort.

CAPS is characterised with "thrombotic storm" and "cytokine storm", result a dramatic systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction (21). CAPS belongs to a spectrum of disorders called "thrombotic microangiopathy (TMA) syndrome", presented with thrombocytopenia, microangiopathic haemolytic anaemia (MAHA), and acute kidney injury (22). The diagnosis of CAPS should be considered in patients with MAHA plus acute multisystem involvement and double or triple aPLs at high titres (22), and the treatment should be more aggressive to reduce poor outcome. In our predictive model for CAPS, anaemia (3 points), elevated LDH (3 points) and proteinuria (1 point) was incorporated into the equation, indicating the sign of TMA should be valued as predictors for CAPS. To be noted, the laboratory results we collected were at baseline, which was the time of admission because of APS or CAPS. One reason was most patients were referred to our centre thus clinical data was thorough at admission. The other reason was that causes for anaemia in APS were various including haemolytic anaemia, lupus flare, chronic disease anaemia, or renal anaemia, mostly were not single factor. We believe the advantage of a predictive model is the integration of predictors, so the indicators at admission can reflect patients' disease risk status with the equation and given different weights for each predictor.

Hypocomplementaemia was more significant in CAPS patients, reflecting complement activation and consumption in CAPS. The activation of complement system plays a role in APS pathogenesis, and there is a crosstalk between complement and coagulation system (23), complement inhibition, for example eculizumab, is a promising treatment for APS and CAPS (24). Recent study has found CAPS patients have mutations in complement regulatory gene like atypic haemolytic uraemia syndrome (25), the triggers including infection pregnancy or surgery might lead to uncontrolled complement activation, and hypocomplementaemia might be an early sign for CAPS diagnosis.

Our study is noteworthy for several reasons. Firstly, the innovation of our study is worthy of attention. Risk stratification of APS patients will help physicians to identify CAPS in high-risk patients, recognise CAPS in an early stage and start intervention to improve prognosis. This is the first study focusing on predictors and risk stratification of CAPS in literature by far. The reason might be the rarity of this catastrophic disease, and the lack of a long-term follow-up APS cohort as control. Our CAPS study based on PUMCH-APS cohort, and the single-centre source ensured the intact medical records and the consistency of diagnosis. Additionally, the risk score stratification based on our predictive model is clinically practical, the model is simple, and the included variables are routinely collected, they will help rheumatologist recognise CAPS early. Finally, the predictive model has a good fit and discrimination.

Nevertheless, there are some limitations of our study. Firstly, the limited number of CAPS cases affect the stability of the model. Secondly, the single-centre study could not perform the external validation of this predictive model and we can only validate internally, dataset for external validation might be obtained in the future by conducting multicentre study.

In conclusion, a predictive model of CAPS was developed with history of hypertension, anaemia, elevated LDH and proteinuria. This predictive model showed good discrimination and calibration, could help early recognition of CAPS.

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