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Prognostic performance of serum protein markers in assessing mortality risk for North African pediatric population hospitalized with complicated severe acute malnutrition

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ABSTRACT

Background: Complicated severe acute malnutrition (SAM) continues to kill numerous pediatric populations at the global level. Yet, significant progress has been achieved in the clinical management and treatment of this lethal condition in the pediatric population. **Aims:** To determine the prognostic performance of selected serum protein markers in predicting high-risk mortality in a pediatric population with complicated SAM. **Subjects and Methods:** This non-interventional cohort prognostic accuracy study included 59 pediatric patients (aged 6 – 60 months) with complicated SAM admitted to Moulay Ali Cherif Regional Hospital, Errachidia, Morocco, during the period from 01.02.2021 to 02.11.2022. Only the SAM pediatric population with medical complications were included in the study. SAM was defined as weight-for-height or weight-for-length z-score < -3 standard deviations, bilateral edema of nutritional origin, or mid-upper arm circumference < 11.5 cm. The enrolled pediatric population received standard inpatient care as per World Health Organization protocols for nutritional rehabilitation of SAM. The pediatric population was divided into two groups, deceased (n=10) and survivors (n=49), based on their outcomes during their hospital stay. Blood samples upon admission were obtained to assess levels of transthyretin, transferrin, albumin, retinol-binding protein, fibronectin, and C-reactive protein. Diagnostic accuracy was assessed using the area under the curve (AUC), the sensitivity, specificity, positive predictive value, and negative predictive value. **Results:** At a threshold of (≤ 0.13 g/L), transthyretin displayed the best performance of all nutritional markers, with an AUC of 0.71, good sensitivity (80.4%), and specificity (73%). While transferrin, albumin, retinol-binding protein, fibronectin, and C-reactive protein presented good to excellent sensitivity and negative predictive value, their performance was rated "fail" to "poor" (0.5 ≤ AUC < 0.7) with a "poor" positive predictive value. **Conclusion:** Low levels of transthyretin (≤ 0.13 g/L) demonstrated a prognostic advantage compared to other biomarkers such as transferrin, albumin, retinol-binding protein, fibronectin and C-reactive protein suggesting transthyretin's potential as a prognostic marker for predicting pediatric population with complicated SAM at high mortality risk.

Keywords: biochemical markers; death; predictive accuracy; undernutrition.

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1 Introduction

Severe acute malnutrition (SAM) refers to critical forms of pediatric malnutrition diagnosed using anthropometric criteria such as weight-for-height z-scores and mid-upper arm circumference (MUAC) [1]. SAM results from inadequate calorie, protein, vitamin, and mineral intake [2] and affects pediatric populations aged 6 – 60 months during the transition from breastfeeding to complementary foods [2, 3]. Suboptimal feeding and limited food access precipitate SAM [4-6], which affects 13.6 million pediatric populations globally [7]. Despite government initiatives, SAM remains highly prevalent, including Morocco, where it is common in pediatric hospitals [8-10]. As malnutrition compromises immunity, it accounts for 45 – 60% of the under 5 years of

pediatric population deaths in low- and middle-income countries [11-13].

Progress in the prevention and treatment of SAM has led to the development of enhanced management protocols. Guided by the World Health Organization (WHO), United Nations International Children's Emergency Fund, and collaborative partners, standardized guidelines now exist for the identification and care of SAM [1-14]. However, despite the presence of these standardized guidelines for the identification and management of SAM [1-14], mortality rates consistently reach high levels, particularly ranging from 25 – 30% in African nations [7-15]. Although guidelines show promise for improving outcomes, optimal implementation strategies remain unclear [1-16]. The risk of mortality in complicated, where SAM can exceed 50% in some regions [15]. The factors contributing to persistently high mortalities remain unclear, and guideline adherence alone may be insufficient [17,18]. Accurately determining high-risk patients requiring hospital treatment is critical to reduce mortality [1-19]. Numerous studies have evaluated prognostic markers of risk of death [20-26], but there is no consensus on definitive predictors.

In recent studies, the significance of prealbumin and various serum proteins as prognostic indicators for the identification of high-risk pediatric populations has garnered attention [27, 28]. Despite this recognition, few studies have examined biomarkers specifically within the context of SAM [21, 29-32]. The aim of our study was to comprehensively assess the prognostic efficacy of selected serum protein markers for predicting in-hospital mortality among pediatric populations admitted with complicated SAM.

2 Subjects and Methods

2.1 Study design

This was a non-interventional prognostic accuracy cohort study [33] that aimed to assess the performance of serum protein markers in predicting in-hospital mortality among the pediatric population with complicated SAM. The study was conducted at the pediatric intensive care unit of the Moulay Ali Cherif regional hospital, in the city of Errachidia, Morocco. The hospital's pediatric unit has 25 beds, accepting all inpatient referrals from the outpatient diagnostic center, transfers from other facilities, and emergency consultations. The pediatric population aged 6 to 60 months admitted to the pediatric department with complicated SAM were enrolled. SAM was defined as WFH (weight-for-height) z-score < -3 standard deviations (SD) or bilateral edema of nutritional origin or MUAC <11.5 cm [1]. Pediatric patients presented with medical complications, severe edema, poor appetite (failed appetite test), or one or more danger signs outlined in the Integrated Management of Childhood Illness guidelines, were diagnosed with complicated SAM [34]. These danger signs were classified into different categories: general danger signs (e.g.; inability to drink or breastfeed, vomiting, convulsions or fits), breathing problems (e.g.; rapid breathing, severe chest indrawing), circulation issues (e.g.; lethargy or unconsciousness, two or more signs of severe dehydration) and other signs (e.g.; high fever, hypothermia, jaundice in newborns, red or purplish skin or rashes with fever, blood in stool, blood in vomit, swelling or redness around the umbilicus, difficulty breastfeeding, or inability to feed) [34].

The enrolled pediatric population received standard inpatient care as per WHO protocols for nutritional rehabilitation of SAM [1-14]. Mothers were asked to stay with their children during medical and nutritional rehabilitation. The diagnosis and management of the malnourished pediatric population constitute a public health priority of the Ministry of Health and Social Protection (MHSP) of Morocco [35]. According to the National Nutrition Program of the MHSP [35], children under the age of five who attend a healthcare facility or hospital are subject to a complete nutritional assessment, and any child presenting with malnutrition is required to be admitted to the hospital for the management of his nutritional issue. The present study was non-interventional, meaning that no intervention was carried out by the researchers, and the recruited pediatric population was hospitalized for routine care to manage their nutritional disorders and health status as recommended by the MHSP [35]. On admission, each child underwent a structured history, physical examination including anthropometry (weight and height), and biological tests as per routine care.

2.2 Sample size justification

We investigated the prognostic performance of serum protein markers using the receiver operating characteristic (ROC) curve area under the curve (AUC). Considering significance level, test power, and null hypothesis value (No discriminatory performance), the significance level (type I error probability) was set to 0.05, test power (type II error probability) to 0.10, expected AUC to 0.74, and null hypothesis value to 0.5, implying no discriminatory power. The required significance level and test power sample size were determined by inputting these specified significance levels into MedCalc software version 9.3.0.0 [36]. The software provides an estimated sample size required to achieve the desired levels of significance and power. In this case, the calculated sample size was 59.

2.3 Inclusion and exclusion criteria

All hospitalized pediatric population aged (6 – 60 months) with complicated SAM were included in the study if their parents or caregivers provided written informed consent to

participate and were requested to stay during the treatment of their children until discharge from the hospital.

2.4 Medical assessment and anthropometric measurements

Comprehensive medical assessments were conducted during hospitalization, including evaluations for underlying diseases and abnormalities as an integral care package. Additionally, each child underwent a structured history, a complete physical examination, and sociodemographic and anthropometric measurements. Medical data including diseases diagnosed at admission and routine biological analysis were recorded from medical records. Anthropometric measurements of body weight, height, length, and MUAC were performed in duplicate within 24 hours of admission, using standard techniques, recording the mean value to minimize errors. A dietitian carried out all measurements precisely following standardized protocols, assisted by two nurses [37]. Body weight was measured without shoes and minimal clothing using a calibrated digital scale (KINLEE-20, accuracy 5 g) adjusted before each use. Infants/toddlers were weighed naked, without diapers, and length was measured using a professional infantometer (SECA model number 416, SECA, Germany) to the nearest millimeter. Standing height was measured with wall-mounted stadiometer for able-bodied pediatric population and recumbent length was used for others, both recorded to the nearest millimeter. MUAC was measured with a plastic tape to 0.1 cm, and head circumference with flexible tape to 0.1 cm. Age was obtained from interviews with mother and age/sex anthropometric measurements were converted to z-score indices (weight-for-age, height-for-age, weight-for-height) using of the WHO Anthro software (version 3.2.2) [38].

2.5 Blood sampling

After hospitalization, each child underwent a series of biological tests to monitor their health and nutritional status. Five milliliters of blood samples were collected via the radial artery and drawn within the first 24 hours for blood biochemistry analysis as part of standard routine testing. Blood was centrifuged at 1500 rpm for 15 minutes to separate serum. A 400-microliter aliquot of serum was transferred to a separate Eppendorf tube and immediately frozen at -20°C. Frozen serum samples were stored in this manner until batch analysis of the serum proteins could be performed. Serum levels of transthyretin, transferrin, albumin, retinol-binding protein (RBP), and fibronectin were measured using an immunonephelometric assay on a Dade Behring BN-100 automated analyzer (Germany). C-reactive protein (CRP) concentrations were determined by immunoturbidimetric assay using a Hitachi 911 analyzer, (Roche, France).

2.6 Main assessed outcomes

The primary outcome was in-hospital mortality. Explanatory variables were serum protein levels upon admission.

2.7 Statistical methods

Statistical analyses were performed using MedCalc software, version 9.3.0.0. A p-value <0.05 was considered statistically significant. Continuous data were presented as mean ± SD. The Kolmogorov-Smirnov test assessed the normality of continuous variables. Mean differences in parametric data were analyzed using Student's t-test. The Chi-Square test was used to analyze sex differences. To assess the effect size of the difference between the two groups, Cohen's d coefficient was used. Cohen's d was interpreted as follows: a small effect size was represented by d = 0.2, a moderate effect size by d = 0.5, and a large effect size by d = 0.8. ROC curves [39] determined optimal cutoff points for serum protein biomarkers to predict mortality. AUC was calculated by plotting test sensitivity (proportion of true positives among deceased patients) against 1-specificity at different cutoff concentrations. An AUC of 0.50 indicated predictive performance equal to chance. AUC values were interpreted as: 0.90 – 1.0 = excellent; 0.80 – 0.90 = good; 0.70 – 0.80 = fair; 0.60 – 0.70 = poor; 0.50 – 0.60 = fail [40]. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for each mortality risk threshold and classified as: "Poor" (50 – 60%); "Insufficient" (60 – 70%); "Fair" (70 – 80%); "Good" (80 – 90%); "Excellent" (90 – 100%) [41].

2.8 Ethical consideration

The study was approved by the ethics and research committee of the regional directorate (Number: S17-2021-1). In addition, the legal representative of the parents or guardians was totally informed of the purpose of this study and the importance of the research, under the supervision of qualified physicians. Confidentiality was also ensured in accordance with the guidelines of the Declaration of Helsinki [42]. Subsequently, written consent was obtained from parents or guardians for the participation of their pediatric population.

3 Results

As presented in Table 1, 59 pediatric individuals were enrolled for nutritional rehabilitation. They were divided into two groups based on clinical outcomes: Group 1 (n = 10) experienced in-hospital mortality at a mean age of 16.55 months. Group 2 participants (n=49) successfully recovered and were discharged in good clinical condition at a mean age of 20.12 months. Compared to the deceased group, the recovered group showed significantly greater height with a large effect size and a significantly higher percentage of boys.

Table 1. Comparison of baseline characteristics of the deceased and recovered groups on admission to the hospital

Physical and clinical characteristics	Recovered group (n=49)	Deceased group (n=10)	P	Value of Cohen's d
Age (month)	20.12 ± 8.02	16.55 ± 4.33	0.18	0.47
Weight (Kg)	7.89 ± 2.74	8.22 ± 2.45	0.72	–0.12
Height (cm)	79.35± 13.33	65.82 ±12.00	0.005	1.17
Head circumference (cm)	44.11 ± 2.37	41.34 ± 2.88	0.002	1.09
Mild-upper arm circumference (cm)	11.89 ± 1.26	10.89 ± 2.21	0.051	0.61
Z-score height-for-age	-2.89 ± 2.02	-2.41 ± 2.10	0.50	–0.24
Z-score weight-for-age	-2.92 ± 0.99	-3.35 ± 0.78	0.206	0.49
Z-score weight-for-height	-2.80 ± 1.89	-3.21 ± 1.23	0.514	0.26
Boy 35 (59.32%)	28(82.00)	7(20.00)	0.006	-
Girl 24 (40.67%)	21(87.50)	3(12.50)	0.028	-

The deceased group also displayed significantly lower head circumference measurements with a large effect size. However, we did not observe any significant differences in age, body weight, and nutritional status, as assessed by MUAC, Z-score height-for-age, Z-score weight-for-age, and Z-score weight-for- height, between the two groups.

All serum protein concentrations were below the reference range in both the deceased and recovered groups. Among all serum proteins studied, only transthyretin showed a

Table 2. Comparison of serum protein concentration between recovered and deceased pediatric population on hospital admission

Serum protein concentration (Normal range)	Recovered group (n=49) (mean± SD) C.V (%)	Deceased group (n=10) (mean± SD) C.V (%)	P
Transthyretin (0.15 – 0.30) g/L	(0.124 ± 0.023) 18.54	(0.101 ± 0.052) 51.48	0.036
Transferrin (2 - 4) g/L	(1.89 ± 0.830) 43.91	(1.37 ± 0.440) 32.11	0.062
Albumin (> 35) g/L	(27.00 ± 8.56) 31.7	(22.02 ± 3.21) 14.57	0.078
Retinol-Binding Protein (0.033-0.07) g/L	(0.024 ± 0.082) 341.66	(0.032 ± 0.01) 31.25	0.761
Fibronectin (0.030 - 0.195) g/L	(0.261± 0.132) 50.57	(0.199 ± 0.108) 54.27	0.174
C-reactive protein (<10) mg/L	(36.23 ± 20.51) 56.61	(45.23 ± 13.45) 29.73	0.194

C.V: coefficient of variance

Table 3. Prognosis values and performance of biochemical markers for predicting pediatric population at risk of death

Cutoff value	Sensitivity (95% C.I)	Specificity (95% C.I)	Positive Predictive Value (%)	Negative Predictive Value (%)	AUC
Transthyretin ≤ 0.13 g/L	80.4 (40.4-89.3)	73.0 (63.3-78.1)	39.50	82.90	0.71
Transferrin ≤ 1.36 g/L	83.4 (53.2-96.5)	44.0 (32.0-59.4)	30.10	90.50	0.68
Transferrin < 1.23 g/L	53.8 (25.2-80.7)	62.0 (47.2-75.3)	29.12	94.34	-
Albumin ≤ 35.23 g/L	100.0 (76.1-100.0)	27.6 (15.5-44.4)	27.10	100.0	0.67
Albumin < 24.00 g/L	45.4 (18.9-75.2)	64.5 (49.3-79.2)	27.20	81.30	-
Retinol-Binding Protein ≤ 0.031 g/L	100.0 (65.8-100.0)	18.1 (7.6-30.1)	30.60	100.0	0.56
Fibronectin ≤ 0.198 g/L	100.0 (69.7-100.0)	36.1 (20.2-53.7)	33.9	100.0	0.63
Fibronectin < 0.10 g/L	27.0 (6.9-55.6)	76.7 (53.3-89.2)	26.00	70.30	-
C-reactive protein > 46.34 mg/L	80.0 (36.0-92.5)	50.3 (39.0-59.0)	20.30	89.30	0.52

CI: confidence interval; AUC: Area under the curve

significantly lower concentration in the deceased group compared to the recovered group.

ROC curve analysis showed that a transthyretin threshold of ≤0.13 g/L provided the best diagnostic performance for distinguishing deceased patients from survivors, with a sensitivity of 80.4% and a specificity of 73.0%. Although transferrin, albumin, RBP, and fibronectin had good to excellent sensitivity, their AUC values between 0.5 and 0.7 indicated "fail" to "poor" performance diagnostic utility. The CRP level had a sensitivity of 80.0% in identifying deceased patients. However, with an AUC of 0.52, CRP exhibited "poor" overall performance in distinguishing deceased from surviving patients.

4 Discussion

In the present study, a transthyretin level ≤0.13 g/L was identified as the optimal threshold for predicting mortality risk, with an AUC of 0.71, a sensitivity of 80.4%, and a specificity of 73.0% as shown in Table 3. These findings are consistent with those of a previous studies showing that low transthyretin levels, particularly <0.11 g/L, were associated with increased mortality risk and length of hospital stay [27, 28]. Our results were also consistent with previous studies demonstrating the prognostic utility of transthyretin, particularly for survival, in conditions such as pediatric SAM, [21] dialysis, [43] cardiovascular disease, [44] cancer, [45, 46,] and critically ill patients [47]. Our research provides additional evidence to support the value of transthyretin as a prognostic biomarker for survival in complicated SAM.

Similar to transthyretin, transferrin possesses a short half-life and is considered a useful indicator for monitoring rapidly occurring changes in visceral protein levels and evaluating the effectiveness of nutritional therapy [30]. Previous studies identified serum total transferrin thresholds indicating increased death risk in the SAM pediatric population [29]. Achieving transferrin <1.7 g/L was associated with a significant increase in the relative risk of death of 2.5 among hospitalized patients [31]. In this study, a transferrin level ≤1.36 g/L demonstrated an interesting specificity of 83.4% for predicting mortality, with an excellent NPV of 90.5% (Table 3). However, transferrin showed "poor" overall performance in distinguishing deceased from surviving patients, with an AUC of 0.68. Additionally, another study found transferrin < 1.23 g/L clearly correlated with increased morbidity and mortality [48]. In the present study, a transferrin threshold < 1.23 g/L exhibited a sensitivity of 53.8% and a specificity of 62.0% for predicting mortality among the admitted pediatric population with complicated SAM. The "poor" predictive performance of transferrin may be attributed to decreased levels in inflammatory states along with a blunted synthesis response in relation to mortality [49], that reduces specificity. Additionally, it would be beneficial to conduct longitudinal studies to evaluate the impact of changes in transferrin levels over time on prognosis and survival outcomes in the SAM-affected and unaffected pediatric population.

Concentrations of circulating transport protein, traditionally albumin, have defined clinical protein deficiency [50]. This indicator of protein deficiency is also associated with a higher risk of death in hospital, and a decreased albumin concentration correlates with morbidity/mortality [51, 52]. In the present study, no significant difference was observed in serum albumin levels between deceased and cured SAM groups (Table 2), as reported elsewhere [53]. However, previous studies reported 30 – day mortality rates of 25% with serum albumin < 34 g/L, increasing to 62% mortality in cases of extreme hypoalbuminemia defined as ≤ 20 g/L [54]. In this study, an albumin threshold of ≤ 35.23 g/L demonstrated excellent sensitivity of 100% but "poor" overall predictive performance with an AUC of 0.68, comparable to transferrin. Lower albumin thresholds have been associated with increased mortality risk in prior studies [54, 55]. Specifically, albumin <24 g/L was associated with higher death risk [55]. Using this threshold, sensitivity declined to 45.4% though specificity increased to 65.3% in our sample (Table 3). This suggests serum albumin may not be an appropriate prognostic indicator in our population.

RBP constitutes a crucial visceral protein for evaluating nutritional status in SAM [56]. Additionally, RBP has been proposed as an indicator of protein repletion response in critically ill infants receiving parenteral nutrition [57]. In our investigation, there was no statistically significant difference in admission RBP levels between deceased and surviving SAM patients (Table 2), consistent with previous research results [29]. The current study demonstrates high sensitivity of 100.0% but low specificity of 18.1% for mortality prediction, which supports previous findings [21]. Although the NPV of RBP was excellent, the AUC (0.56) indicates a "fail" overall prognostic performance (Table 3). The potential role of RBP as a prognostic indicator has not been exhaustively explored or widely disseminated in the scientific literature potentially due to its characterization as a negative acute-phase protein (APP) [58]. RBP functions as an APP, and its levels experience a temporary decline during inflammation, indicating a reduction in RBP synthesis [58]. As evidenced by our observation of elevated CRP levels in the studied groups at admission (Table 2). Further investigations directly exploring the dynamics of RBP suppression across a spectrum of inflammatory states with varying severity could help substantiate the hypothesized association between inflammation and reduced RBP levels. Clarifying the nature of this relationship could facilitate the interpretation of RBP

levels in the context of inflammation and more precisely define the conditions under which RBP may be significantly affected and unreliable as a prognostic biomarker.

While fibronectin is not considered a primary marker of nutritional status, some data suggests that it may be useful in predicting preoperative risk. Kirby et al. [59] found elevated fibronectin in surgical patients experiencing postoperative morbidity and mortality. Additionally, Sandberg et al. [32] showed fibronectin levels below 0.10 g/L associated with high mortality risk. In our study, fibronectin levels at admission in the cured and deceased SAM groups were within normal limits and above the threshold of 0.10 g/L (Table 2). Using a cutoff of <0.10 g/L, we found fibronectin had "poor" prognostic performance (AUC=0.63) with a "poor" sensitivity of 27.0% compared to other markers (Table 3). This suggests limited utility for fibronectin as a predictor of risk of death in complicated SAM. Further research should carry on exploring the relationships between fibronectin, nutritional status, and clinical outcomes.

Numerous studies have demonstrated that elevated levels of various inflammatory biomarkers are associated with increased mortality risk across diverse clinical conditions [60, 61]. In the present study, we evaluated the prognostic performance of CRP to identify pediatric populations at high risk of death. Both surviving and deceased SAM pediatric populations exhibited elevated CRP levels at admission (Table 2). A CRP threshold of > 46.34 mg/L provided a good specificity of 80% for mortality risk. However, overall performance ability was "fail" (AUC=0.524), consistent with previous studies showing that CRP >10 mg/L did not predict inpatient mortality [62, 63]. This suggests CRP may have limited utility as an independent risk stratification marker in this population. One study in Uganda found higher CRP (>15 mg/L) associated with increased mortality risk, [60] indicating a potentially complex relationship between CRP and mortality in SAM that requires further elucidation. The short half-life of CRP and lack of response to feeding initiation may limit its prognostic efficacy. Further research should continue investigating the correlations between CRP, nutritional status, inflammation, and clinical outcomes in SAM to establish the role of CRP as a prognostic tool.

The main strengths of this study include the prospective prognostic design, which allowed the collection of predictor data at admission without knowledge of outcomes. This approach avoided potential biases associated with retrospective designs in which predictor data were collected after outcomes were well defined. To the bet of our knowledge, this is the first study evaluating the prognostic performance of serum protein markers (transferrin, albumin, fibronectin, transthyretin, RBP) for in-hospital mortality in a pediatric population with complicated SAM. However, the study provides crucial information on serum protein markers that are predictive of mortality and the potential for mortality reduction in pediatric populations with complicated SAM. Our reduced sample size, particularly in the deceased group, may limit generalizability. Multi-center studies in different complicated/uncomplicated SAM populations could help combat high SAM mortality rates. Moreover, given the multifaceted nature of complicated SAM, biomarkers of immune function, inflammation, and oxidative stress could provide further prognostic insight into mortality risk. In particular, the influence of inflammation on micronutrient biomarker levels represents a significant gap in current knowledge that warrants further investigation [64]. Since infection and inflammation are already present in several SAM cases, a better understanding of how inflammatory status impacts nutritional biomarkers could significantly improve the interpretation of these markers and prediction of mortality. Further research is critically required to clarify the relationship between inflammation, biomarker levels, and outcomes to improve prognostic capabilities and reduce preventable deaths from complicated SAM.

5 Conclusion

Among the serum protein markers evaluated, serum transthyretin ≤0.13 g/L exhibited the highest discriminative performance for mortality risk in the pediatric population admitted with complicated SAM, with an AUC of 0.71. Transthyretin also demonstrated an interesting sensitivity of 80.4% and specificity of 73% at this cutoff. Despite good to excellent sensitivity and NPV for transferrin, albumin, RBP, fibronectin, and CRP, their PPV were uniformly low. This suggests that these biomarkers may "fail" to detect several high-risk patients despite negative screening results. Early assessment of transthyretin level could enable risk stratification upon hospital admission and may help reduce inpatient mortality among pediatric patients with complicated SAM. Further research should explore additional biomarkers, incorporating markers of immune function, inflammation, and oxidative stress, as well as alternative clinical endpoints. This may provide more comprehensive prognostic information given the diverse pathologies associated with complicated SAM.

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H.B; conceived and designed the study, and undertook the literature research, performed the data analysis, carried out the statistical analysis, prepared, reviewed, and drafted the manuscript. The author approved the final version before submission. The author has read and agreed to the published version of the manuscript

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