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ORIGINAL ARTICLE

Validation and Application of a Predictive Score of Acute Chest Syndrome

Christian Kassasseya, M.D.,[1,2] Sékou Kéné, M.D.,[2,3] Tatiana Besse-Hammer, M.D.,[4] Ruben Nzouakou, M.D.,[5] Hèzouwè Magnang, M.D.,[2,6,7] Paul Telfer, M.D.,[5] Jean-Benoit Arlet, Ph.D.,[2,8] Gonzalo de Luna, M.D.,[2,8] Louis Affo, M.D.,[2,9] Sandrine Dautheville, M.D.,[2,10] Stéphanie Ngo, M.D.,[2,11] Yanis Pelinski, Ph.D.,[2,12] Cindy Mescam,[2,12] Sabrina Djoumad, M.Sc.,[2,12] Anne-Laure Pham Hung d'Alexandry d'Orengiani, Ph.D.,[2,12] Armand Mekontso Dessap, Ph.D.,[2,13,14] Marc Michel, Ph.D.,[2,15] Frédéric Galactéros, Ph.D.,[2,12] Etienne Audureau, Ph.D.,[2,16,17] Aldiouma Guindo, Ph.D.,[2,3] Anoosha Habibi, M.D.,[2,12,18] Mehdi Khellaf, Ph.D.,[1,2] Dapa Diallo, Ph.D.,[2,3] and Pablo Bartolucci, Ph.D.[2,12,18]

Abstract

BACKGROUND Vaso-occlusive crisis (VOC) is the most common manifestation of sickle cell disease, and acute chest syndrome (ACS) is a frequent complication with a substantial risk of death. The aim of this study was to validate the previously developed PREdictive SEVerity (PRESEV) score for the occurrence of ACS in adult patients with sickle cell disease hospitalized for VOC and to assess the safety of outpatient management of patients with a low-risk score.

METHODS To validate the PRESEV score, a prospective observational study was conducted in 13 centers across 5 countries in Africa and Europe. The score ranges from 0 to 16, with values of 5 or less considered low risk. The safety of a low-risk score (≤5) for outpatient management was then assessed in 100 patients. The primary outcome was the occurrence of ACS.

RESULTS A total of 393 patients were included for the validation of the score: 206 (52.4%) from Europe and 187 (47.6%) from Africa. Of these, 76 patients (19.3%) developed ACS. Of the 50 patients (12.7%) with a low-risk score, 3 (6.0%) developed ACS (negative predictive value 94.0%). Of the 76 patients who developed ACS, 73 (96.1%) did not have a low-risk score (sensitivity 96.1%). A total of five deaths (1.3%) was recorded; no individuals who died had a low-risk score. Score performance was similar across both continents. When the score was used to guide outpatient management in 100 patients with VOC, one case of ACS (1.0%) was recorded.

CONCLUSIONS This international study validated the PRESEV predictive risk score to identify adult patients at low risk for ACS. (Funded by the Support for Actions against Red Blood Cell Diseases Association and others; trial registration number, IRB 00003835; ClinicalTrials.gov number, NCT03032055.)

Background

Vaso-occlusive crisis (VOC) is the main cause of hospitalization in patients with sickle cell disease (SCD),[1] and acute chest syndrome (ACS) is the major cause of death during hospitalization.[2-5] A previous multicenter study demonstrated that ACS develops after an average of 2.5 days of hospitalization.[6] However, there were no accurate and reliable predictors of risk for developing ACS during hospitalization.

The author affiliations are listed at the end of the article.

Pablo Bartolucci can be contacted at pablo.bartolucci@aphp.fr.

To address this unmet need, we previously conducted the PREdictive SEVerity (PRESEV I) prospective single-center study at Henri-Mondor Hospital (Créteil, France), involving adults with homozygous sickle hemoglobin (SS) or sickle beta-zero (S-β_0) thalassemia SCD who were admitted for VOC.[7] The objective was to determine whether or not ACS could be predicted using clinical and laboratory parameters assessed on arrival to the emergency department (ED). From 2006 to 2012, 247 patients with VOC requiring hospitalization were included. Of these, 19% developed ACS, on average, 2.8 days post admission (median [interquartile range]: 3 [2–3] days). A multivariable analysis identified four variables independently associated with the occurrence of ACS: reticulocyte count, hemoglobin level, white blood cell count, and a categorical pain score based on spine and pelvic pain (see the Supplementary Appendix, Methods and Fig. S1). These variables were used to develop a predictive score for ACS (PRESEV score), with an area under the curve of 0.805 (95% confidence interval, 0.734 to 0.877). The score ranges from 0 to 16, with values of 5 or below considered low risk, 6–10 considered intermediate risk, and 11 or more considered high risk (Table 1) (online calculator: https://presev2-app-btd2ymfhwsruhkb3ecmdca.streamlit.app). The PRESEV score demonstrated a negative predictive value of 98.9% in the low-risk group and a positive predictive value of 44.7% in the high-risk group. Hydroxyurea treatment did not have any impact on the score.

Table 1. PRESEV Score.*

Day-1 Variable	Points
Reticulocytes (10^9/l)	
≤216	0
>216	6
Spine and/or pelvis categorial pain scale†	
0 or 1	0
2	4
3	6
Leukocytes (10^9/l)	
≤11	0
>11	3
Hemoglobin (g/dl)	
>9	0
≤9	1
PRESEV score	
Risk	Predictive score
High	≥11
Intermediate	6–10
Low	≤5

* Acute chest syndrome predictive model derived from the PRESEV 1 study.
† 0 denotes no pain; 1, mild pain, no pain increases upon mobilization; 2, moderate pain, increased by mobilization; and 3, severe pain with disability.

In this study, our primary objective was to evaluate the accuracy of the PRESEV score at hospital admission across multiple centers and countries. Our secondary objective was to evaluate the safety of the PRESEV score in outpatient management with close monitoring for VOC in patients with a low-risk score (≤5). Ultimately, we speculate that this score could help avoid unnecessary hospitalizations, reduce length of stay, reduce the burden on hospital units, and reduce costs for patients and communities.[8]

Methods

DESIGN

The PRESEV 2 study was an international, multicenter prospective observational study, designed and conducted in accordance with the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines (ICH E6) for good clinical practice, the European directives on clinical trials (Directive 2001/20/EC), the Declaration of Helsinki, and applicable local regulatory requirements (IRB 00003835, NCT03032055). The database was declared to the Commission nationale de l'informatique et des libertés (CNIL n°7830264) and was approved by the ethics committee (protocol 2013/NICB).

PRESEV SCORE VALIDATION

Validation of the PRESEV score was conducted in 13 centers (Table S1) across two continents (Africa and Europe) and five countries (Mali, Togo, England, Belgium, and France) between January 2016 and February 2020.

Patients who consented to participate in the study were consecutively enrolled on the first day of hospital admission in the ED for a VOC. Although the study protocol allowed the inclusion of patients 2 years of age and above, the current analysis focuses exclusively on the adult subgroup (≥18 years). Additional inclusion criteria were genotype hemoglobin SS or S-β_0 thalassemia patients, with a severe VOC, defined as pain or tenderness affecting at least one part of the body (e.g., limbs, ribs, sternum, skull, spine, and/or pelvis), expected to require opioid analgesics and hospitalization for at least 24 hours, and not attributable

to other causes. Patients suffering from chronic comorbidities, including but not limited to pulmonary hypertension or other forms of end-organ disease, were eligible for inclusion. Eligible patients were required to provide written informed consent according to local regulations. Patients could only be included once.

The following patients were excluded from the study: patients with ACS on arrival at the ED, pregnant women, patients experiencing homelessness, patients deprived of their liberty by a court or administrative order, patients under guardianship, patients unable to understand the purpose and conditions of carrying out the study, patients unable to provide consent, and patients unable to participate in the entire study.

On arrival at the ED, the following data were collected: demographic information; medical history; vital signs; and the parameters of the PRESEV score, which comprised reticulocyte count, hemoglobin level, leukocyte count, and the categorical pain score. The categorical pain score was selected based on its prior validation and demonstrated practical relevance in the management of VOC.[7,9] Notably, in the PRESEV I study, the categorical pain score included seven body regions: the skull, the chest, the spine–pelvis region, and the four limbs. However, only spinal and pelvic pain were associated with the onset of ACS in the multivariate analysis.

VOC was treated according to each center's standard of care, without centralized recommendations regarding analgesia, oxygen therapy, or intravenous fluid management.

During hospital stay, pulmonary auscultation was performed at least once a day. An abnormality on auscultation was defined as crackles, bronchial breathing, and/or decreased breath sounds. Any new abnormality on auscultation had to be confirmed by a second physician. In cases of disagreement, a chest radiograph was performed.

At each daily clinical assessment during the patient's hospital stay, all data related to the progression of the disease were collected, including clinically relevant medical events and both pharmacological and nonpharmacological treatments. Dates of ACS diagnosis were documented, as well as the dates of transfusions. Adverse events that could compromise study continuation or influence study outcomes were systematically sought during follow-up visits through patient interviews and physical examination and were subsequently recorded.

If a patient was discharged before the fifth day of hospitalization, a phone call was made and/or a hospital visit was scheduled 3–7 days after discharge, to ensure complications did not develop after discharge. If no direct contact (phone call or hospital visit) could be established within 90 days of discharge, additional information was sought from medical records or, when available, from relatives. In accordance with a complete-case analysis approach, patients for whom no data could be obtained from any source were considered lost to follow-up and were secondarily excluded from the study.

Patients without the complete data that were required to calculate the PRESEV score were also secondarily excluded. Participants could additionally be withdrawn from the study for the following reasons: withdrawal of patient consent for any reason at any time, or occurrence of an adverse event that could interfere with the continuation of the study.

The primary outcome measure was the occurrence of an ACS, defined by the appearance of a clear positive auscultatory abnormality (new crackles or bronchial breathing), or the presence of new opacities on chest imaging (alveolar or interstitial) together with chest pain and/or decreased breath sounds, within the first 5 days following presentation to the ED. These criteria have been slightly adjusted from the previous study for several reasons: they have proven to be accurate, are easier to apply globally, and enable a reduction in x-radiation exposure.[10,11] To ensure accuracy in radiographic interpretation, investigators were instructed to differentiate new opacities suggestive of ACS from atelectasis. ACS, including assessment for potential pulmonary embolism, was managed according to each center's standard of care.

The physicians were blinded to the predictive score result. All charts were reviewed centrally and in a blinded fashion to ensure that patients were properly classified into ACS or no-ACS groups.

Secondary outcome measures were data at admission, including levels of hemoglobin, reticulocytes, leukocytes, platelets, C-reactive protein, urea, lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, and direct and total bilirubinemia, hospital length of stay, occurrence and timing of transfusion, hospitalization in intensive care unit, and death.

PRESEV SCORE SAFETY IN CLINICAL PRACTICE

The safety of the PRESEV score for outpatient management was evaluated across six French centers starting in February 2021 (Table S2). Home care was systematically

offered to patients with SCD presenting to the ED with a VOC, a low-risk PRESEV score (≤5), and a requirement for hospitalization for pain management, excluding those with a known opioid use disorder.

This study presents the data from the initial 100 patients enrolled in the home care protocol named DREPADOM that was recently implemented in France. The treatment plan encompassed oral opioid analgesia, oxygen therapy to maintain peripheral oxygen saturation of 98% or more, and intravenous hydration with a 5% glucose solution containing 4 g/l sodium chloride and 2 g/l potassium chloride (Bionolyte G5), 2 l/day. Monitoring was performed by community nurses, who conducted home visits two to three times daily, depending on the coordinating physician's evaluation. Vital signs monitored included blood pressure, heart rate, oxygen saturation by pulse oximetry, and respiratory rate. These were recorded on a secure online platform (Link4Life), with automatic alerts triggered for abnormal parameters. In addition, daily phone calls were made by the nurse coordinator to each of the patients. The entire service was supervised by an SCD expert, who checked the patient's parameters daily on the online platform and received immediate, automatic alerts in the event of an abnormal vital sign or a clinical concern observed by the nurse.

The SCD expert assessed the need to discontinue DREPADOM on a daily basis. In the event of a complication or abnormal vital sign, an immediate telephone consultation with the expert was arranged. If necessary, an ambulance was dispatched to the patient's home, and direct admission to a referral hospital was organized.

In the case of rehospitalization, the ACS diagnostic criteria were the same as those previously described for the validation of the score.

STATISTICAL ANALYSIS

The target sample size was determined to be 400 adults, evenly distributed: 200 participants from Europe and 200 from Africa. Based on a 20% incidence of ACS, as reported in the extant literature and observed in a previous study, it was estimated that this sample size would enable robust confirmation of the predictive value of the score with a 95% confidence interval for the area under the receiver operating characteristic curve of ±0.04.

The study population was described in terms of sociodemographic, clinical, and biochemical features. The ACS predictive score was calculated for each patient according to the formula defined in the pilot study.[7]

Results

INTERNATIONAL VALIDATION OF THE SCORE

A total of 419 patients with VOC requiring hospitalization fulfilled the inclusion criteria. Twenty-one patients (5.0%) were excluded due to missing data regarding the PRESEV score, all related to the reticulocyte count, four patients (1.0%) were excluded because they were discharged before day 5 without follow-up, and one patient was mistakenly included despite ACS criteria on arrival (crackles; Fig. 1).

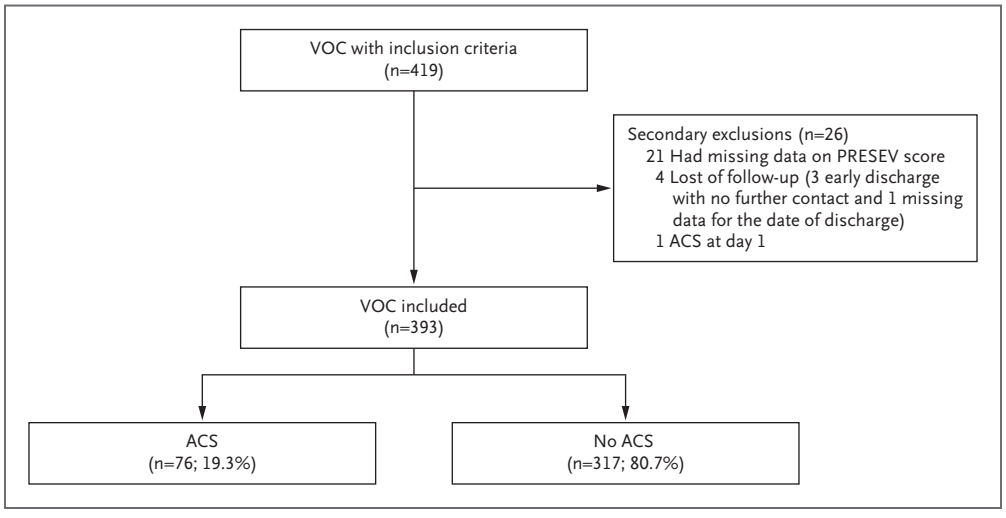

Figure 1. PRESEV Score Validation: Study Flowchart.

ACS denotes acute chest syndrome; and VOC, vaso-occlusive crisis.

Table 2. Characteristics of the 393 Patients Hospitalized with Vaso-Occlusive Crisis.*			
Characteristic	**Total**	**African Cohort**	**European Cohort**
	393 (100)	187 (47.6)	206 (52.4)
Age (years)	27 [23–33]	26 [22–31]	28 [24–35]
Male, n (%)	180 (45.8)	81 (43.3)	99 (48.1)
Genotype S-β_0 thalassemia†, n (%)	17 (4.3)	15 (8.0)	2 (1.0)
Hydroxyurea treatment‡, n (%)	150 (38.2)	7 (3.7)	143 (69.4)

* Results are expressed as n (%) or median [interquartile range]. S-β_0 denotes sickle beta zero.
† All other patients were genotype SS.
‡ Long-term therapy initiated prior to the current hospitalization.

The final study population therefore comprised 393 patients, 206 from Europe and 187 from Africa. The median age was 27 years of age (interquartile range, 23–33), with a slightly younger population in Africa (26 years [interquartile range, 22–31] vs. 28 years [interquartile range, 24–35]). The sex ratio (female-to-male) was 1.2:1 and was comparable on both continents. A total of 150 patients (38.2%) were treated with hydroxyurea, 143 of 206 (69.4%) in Europe and 7 of 187 (3.7%) in Africa (Table 2).

Of the 393 patients, 76 (19.3%) developed ACS (Fig. 1 and Table S3) with no apparent difference between African and European centers (Table S4). The median time to onset of ACS was 3 days (interquartile range, 2–4).

Patients' characteristics such as age, sex, and genotype were comparable between the ACS and no-ACS groups (Table 3; additional details are presented in Table S5). The number of patients receiving hydroxyurea treatment was also similar (39.5% in the ACS group vs. 37.9% in the no-ACS group; Table 3). The median (interquartile range) PRESEV score was 14 (10–16) in the ACS group compared with 10 (7–14) in the no-ACS group (Table 3).

PREDICTIVE SCORE

Among the 50 patients with a low-risk score, 3 (6.0%) developed ACS (negative predictive value, 94.0%; sensitivity, 96.1%). Among the 165 patients with a high-risk score (≥11), 46 (27.9%) developed an ACS (positive predictive value, 27.9%; specificity, 62.5%) (Table 4). The performance of the PRESEV score of 5 or less was comparable in identifying patients who went on to be free from ACS in patient cohorts from Africa and Europe (negative predictive value, 95.5% vs. 92.9%; sensitivity, 97.4% vs. 94.6%).

OUTCOMES

During their hospital stay, 56.6% of patients with ACS received a blood transfusion compared with 9.5% in the no-ACS group (Table S6). Of the 73 transfused patients, 3 (4.1%) were classified as low risk, representing 6% of the low-risk group (Table S7). Two of them were in Africa and one was in Europe. The indications for transfusion were as follows: two cases of VOC unresponsive to standard management and one case of VOC associated with severe anemia. None of these patients progressed to ACS or died during hospitalization. The percentage of patients who received at least one unit of red blood cells was 12.1% in Europe compared with 25.7% in Africa (Table S4).

Seven patients (9.2%) from the ACS group and one patient (0.3%) from the no-ACS group underwent intensive care unit admission, and none had a low-risk score (Tables S6 and S7). Two patients (0.6%) included in the no-ACS group with an intermediate PRESEV score were rehospitalized after discharge for an ACS. One patient (1.3%) died in the ACS group due to ACS, and four patients (1.3%) died in the no-ACS group: one from stroke; one from acute renal failure; and two from unknown cause, for which ACS could not be excluded. All the patients who died were in the African cohort, and none had a score lower than 8.

AMBULATORY MANAGEMENT OF VASO-OCCLUSIVE CRISES IN PATIENTS WITH A LOW-RISK SCORE

A total of 100 patients with severe VOC and a low-risk PRESEV score upon ED arrival were managed at home with DREPADOM between February 2021 and September 2024 (Fig. S2). The female-to-male ratio was 2:1, with a median age of 33 years (interquartile range, 27–40), and 72 patients (72%) received hydroxyurea treatment (Table 5). The median PRESEV score on ED arrival was 1 (interquartile range, 0–4). The median duration of home care was 2 days (interquartile range, 2–4). Eleven patients required readmission to the hospital, primarily for pain management, and one patient (1%) was diagnosed with ACS. There were no intensive care unit admissions or deaths.

Table 3. Demographic and Clinical Characteristics of the Patients at Baseline.*

Parameter	ACS Group	No-ACS Group	Missing Data
Number (%)	76 (19.3)	317 (80.7)	–
Characteristic			
Age (year)	27 [23–33]	27 [23–33]	0
Male, n (%)	42 (55.3)	138 (43.5)	0
African center, n (%)	39 (51.3)	148 (46.7)	0
Genotype S-β_0 thalassemia†, n (%)	5 (6.6)	12 (3.8)	0
Hydroxyurea treatment‡, n (%)	30 (39.5)	120 (37.9)	0
Clinical			
Temperature (°C)	37.0 [36.5–37.4]	36.9 [36.4–37.3]	16
Systolic blood pressure (mm Hg)	120 [110–130]	120 [110–130]	10
Transcutaneous O_2 saturation (%)	97 [95–98]	98 [95–99]	13
Breaths/minute	20 [18–22]	20 [18–20]	78
Arrival pain VAS (mm)	8 [7–9]	8 [7–9]	31
PRESEV score§	14 [10–16]	10 [7–14]	0
CPS spine — pelvis¶ (0–3)	3 [2–3]	2 [1–3]	0
Hemoglobin (g/dl)	8.4 [7.5–9.4]	8.7 [8.0–9.7]	0
Reticulocytes ($\times 10^9$/l)	270 [193–358]	241 [186–328]	0
White blood cells ($\times 10^9$/l)	15.3 [12.9–19.8]	13.0 [10.4–17.3]	0
Other parameters			
Platelet count ($\times 10^9$/l)	361 [278–446]	396 [295–516]	10
C-reactive protein (mg/l)	21 [8–56]	12 [6–28]	40
Lactate dehydrogenase (IU/l)	599 [428–824]	487 [370–695]	44
eGFR‖ (ml/minute/1.73 m^2)	118 [72–133]	125 [104–136]	14
Aspartate aminotransferase (IU/l)	46 [35–64]	41 [33–54]	25
Alanine aminotransferase (IU/l)	25 [19–35]	25 [18–35]	20
γ-Glutamyltransferase (IU/l)	29 [20–49]	30 [20–55]	26
Total bilirubin (mg/dl)	2.40 [1.40–3.39]	2.01 [1.40–3.01]	25
Direct bilirubin (mg/dl)	0.41 [0.2–0.65]	0.35 [0.22–0.53]	54

* Results are expressed as n (%) or median [interquartile range]. ACS denotes acute chest syndromes; CPS, categorial pain scale; eGFR, estimated glomerular filtration rate; IU, international unit; S-β_0, sickle beta zero; and VAS, visual analog scale.
† All other patients were genotype SS.
‡ Long-term therapy initiated prior to the current hospitalization.
§ The four PRESEV score parameters were selected through prior multivariable modeling in the original PRESEV study (see Supplementary Appendix, Methods).
¶ 0 denotes no pain; 1, mild pain, no pain increases upon mobilization; 2, moderate pain, increased by mobilization; and 3, severe pain with disability.
‖ Estimated glomerular filtration rate was calculated using the adjusted Chronic Kidney Disease Epidemiology equation. A selection of characteristics is presented here; the complete table is available in the Supplementary Appendix (Table S5).

Table 4. Predictive Model Performance on the Study Population.*

Predictive Score	ACS Group (n)	No-ACS Group (n)	Total (n)	
High risk, ≥11	46	119	165	PPV=27.9%‡
Intermediate risk, 6–10	27	151	178	
Low risk, ≤5	3	47	50	NPV=94.0%†
Total	76	317	393	
	Se=96.1%†	Sp=62.5%‡		

* ACS denotes acute chest syndrome; PPV, positive predictive value; NPV, negative predictive value; Se, sensitivity; and Sp, specificity.
† Low-risk score.
‡ High-risk score.

Table 5. Characteristics of the First 100 Patients Managed at Home with DREPADOM.*			
Characteristic	**Total**	**Rehospitalized**	**Not Rehospitalized**
	100 (100)	11 (11)	89 (89)
Age (years)	33 [27–40]	33 [26–33]	33 [27–40]
Male, n (%)	33 (33)	4 (36.4)	29 (32.6)
Hydroxyurea treatment†, n (%)	72 (72)	8 (72.7)	64 (71.9)
PRESEV score	1 [0–4]	2 [0–4]	1 [0–4]
Home care service			
Length (day)	2 [2–4]	2 [1–4]	3 [2–4]

* Results are expressed as n (%) or median [interquartile range]. No missing data. DREPADOM: home care protocol for vaso-occlusive crisis management.
† Long-term therapy initiated prior to the current hospitalization.

Discussion

In this multicenter study, with an overall ACS prevalence of 19.3%, the PRESEV score had a negative predictive value of 94% and a sensitivity of 96.1% to identify patients at low risk for developing ACS (PRESEV score ≤5). These values are slightly lower than those of the first study, which studied a homogeneous population from a single center.[7]

VOC is the leading cause of hospitalization for patients with SCD;[1] this crisis has as its most frequent severe complication ACS, which represents the main source of death in this population.[2-5] The majority of patients do not present with ACS on arrival to the ED, with ACS manifesting, on average, after 2.5 days of hospitalization.[6,7] Therapeutic trials that have aimed to shorten the duration of VOC have had no influence on the occurrence of ACS.[9,12] The tendency would, therefore, be to keep patients under hospital surveillance for at least 3 days.

Globally, EDs and hospitals are overcrowded.[13,14] This phenomenon has been observed for many years[15] and has already raised serious concerns in locations heavily affected by SCD, including Africa,[16] the United States,[17] Brazil,[18] France,[19] and India.[20,21] The coronavirus disease 2019 (Covid-19) pandemic accentuated the burden on health structures all over the world,[22] particularly in Africa.[23] During a pandemic, in overcrowded health care structures, quality of health care protocols deteriorates, leading to increased mortality[13] and a higher hospitalization rate, which further exacerbates hospital overcrowding, creating a vicious circle.[24]

The vast majority of ED visits for patients with SCD are related to pain associated with a VOC.[1] It, therefore, seems essential to address this issue by rapidly identifying those who do not require conventional hospitalization, without a substantial risk of complications. In this context, a predictive score for the occurrence of ACS that uses easily obtainable and widely available clinical information had previously been developed, and the primary aim of the present study was to validate this score in a multicenter cohort.

Although patients with recent or chronic transfusions were excluded from the PRESEV I study due to the potential impact of transfusions on hemoglobin and reticulocyte levels, we deliberately included them in this multicenter validation to assess the performance of the PRESEV score under real-life conditions. Moreover, any potential bias introduced by transfusion would likely lead to a reduced incidence of ACS, which could theoretically impact the negative predictive value of the score. Nevertheless, the score's performance remained consistent with that observed in our original study. Similarly, the presence of chronic kidney disease did not alter score performance; however, only 36 patients (9.4%) in our cohort had an estimated glomerular filtration rate under 60 ml/minute. Taken together, these findings support the robustness of the PRESEV score across a broad clinical spectrum.

This study was designed to validate the PRESEV score, which was originally developed in patients with SS or S-β_0 thalassemia genotypes. To ensure consistency with the initial cohort, patients with the SC genotype were excluded from this validation study. The SC genotype exhibits substantial differences in clinical presentation and in key biological parameters — such as hemoglobin, reticulocyte, and leukocyte counts — which is why we chose not to include patients with this genotype at this stage. A distinct predictive score will likely be required for this population.

The aim of this study was to validate the PRESEV score on an international scale, including in Africa, the region most affected by SCD worldwide.[21] To ensure the applicability and safety of the PRESEV score in resource-limited settings

such as sub-Saharan Africa, we adopted a pragmatic, clinically driven definition of ACS that does not systematically require chest imaging. Notably, our previous study demonstrated that auscultation alone — when crackles or bronchial breath sounds were present — achieved a sensitivity of 87.8% and a specificity of 99.5% for ACS diagnosis in a population where the overall prevalence of ACS was 16.8%, which provides additional data to support the use of the PRESEV score (Table S8).[10] This approach is also consistent with recent international guidelines that emphasize the importance of clinical assessment in diagnosing ACS.[11,25,26]

The ACS rate in our cohort (19.3%) was slightly higher than that observed in the original PRESEV study (16.8%), potentially suggesting that few, if any, cases of ACS were missed. A postdischarge follow-up protocol was also implemented to identify any late-onset ACS events. Only two patients (0.6%) from the no-ACS group were rehospitalized for ACS after discharge, further supporting the accuracy of our case identification. Among patients with a low-risk score, there were no intensive care admissions or deaths. All patients who died, regardless of the cause, had an intermediate- or high-risk score. In interpreting our data, it is important to note that, as the population prevalence of a disease increases, the negative predictive value tends to decrease. As such, the score may not function as well among populations with ACS prevalences greater than 20%.

This study has several limitations that should be acknowledged. First, we used a complete case analysis approach, excluding patients who were missing data required to calculate the PRESEV score (n=21) and those with incomplete follow-up (n=4). This method was chosen to preserve internal validity by ensuring that all analyses were based on complete and reliable data. However, it may have introduced selection bias if the excluded patients differed systematically from those included. The small number of excluded participants, representing less than 7% of the initial cohort, likely minimizes this risk. To further limit missing outcome data, all patients discharged before day 5 were re-evaluated in person or contacted by phone to confirm the absence of ACS. Based on previous studies[6,7] indicating that ACS occurs rarely after 5 days (median 3 [interquartile range, 2–3]), patients discharged without ACS after at least 5 days of hospitalization were not reassessed. Nonetheless, some residual uncertainty remains and should be considered when interpreting the results. While the absence of participating centers from Asia or the Americas may represent a limitation regarding geographic representativeness, the demographic and clinical characteristics of enrolled patients (sex, age, genotype) are consistent with those reported in large epidemiologic studies of SCD (Table S9), supporting the generalizability of our findings.

In conclusion, the PRESEV score, based on clinical and routine laboratory tests, was validated in an independent sample of patients from sites in Africa and Europe. These findings may be useful to physicians for identifying patients with a low risk of developing an ACS.

Disclosures

Author disclosures and other supplementary materials are available at evidence.nejm.org.

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Author Affiliations

[1] Emergency Department, Henri-Mondor University Hospital, Greater Paris University Hospitals, Créteil, France
[2] Erythrocyte Sickle Cell Disease Network, Créteil, France
[3] Sickle Cell Research and Control Centre, University of Bamako, Bamako, Mali
[4] Clinical Research Unit, Brugmann Hospital, Brussels, Belgium
[5] Department of Hematology, Royal London Hospital, Barts Health NHS Trust, London, UK
[6] National Center for Research and Care for Sickle Cell Patients, Lomé, Togo
[7] Faculty of Health Sciences, University of Lomé, Lomé, Togo
[8] Internal Medicine Department, French National Sickle Cell Disease Referral Center, European Hospital Georges Pompidou, Greater Paris University Hospitals, Paris Cité University, Paris, France
[9] Department of Internal Medicine, Louis-Mourier Hospital Colombes, Greater Paris University Hospitals, Paris Cité University, Paris, France
[10] Emergency Department, Hospital Tenon, Paris, France
[11] Internal Medicine Department, French National Sickle Cell Disease Competence Center, Delafontaine Hospital, Saint-Denis, France
[12] Sickle Cell Referral Center, Henri-Mondor University Hospital, Greater Paris University Hospitals, Paris-East Créteil University, Créteil, France
[13] Intensive Care Medicine and Resuscitation Unit, Greater Paris University Hospitals, Henri-Mondor University Hospitals, Créteil, France
[14] Cardiovascular and Respiratory Manifestations of Acute Lung Injury and Sepsis Research Group, Paris-East Créteil University, Créteil, France
[15] Internal Medicine Department, Henri-Mondor University Hospital, Greater Paris University Hospitals, Paris-East Créteil University, Créteil, France
[16] Department of Public Health, Henri-Mondor University Hospital, Greater Paris University Hospital, Créteil, France
[17] INSERM U955, Paris-East Créteil University, Créteil, France
[18] Laboratory of Excellence, Mondor Institute for Biomedical Research, Paris-East Créteil University, Créteil, France

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