Central Nervous System Events in Children with Sickle Cell Disease Presenting Acutely with Headache

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Objective To determine the frequency of acute care visits and risk factors for central nervous system (CNS) events in children with homozygous sickle cell disease (SCD-SS) with an acute headache.

Study design This is a retrospective cohort study of acute care visits for headache in children with SCD-SS. The prevalence of headache visits, neuroimaging evaluation, and acute CNS events were calculated and clinical and laboratory variables assessed.

Results Headache was the chief complaint in 102 of 2685 acute care visits (3.8%) by children with SCD-SS. Acute CNS events were detected in 6.9% of these visits. Neuroimaging was performed in 42.2% of visits, and acute CNS events were identified in 16.3% of studies. Factors associated with acute CNS events included older age, history of stroke, transient ischemic attack, or seizure, neurologic symptoms, focal neurologic exam findings, and elevated platelets.

Conclusions Acute headache is common in pediatric SCD-SS and more frequently associated with acute CNS events than in the general pediatric population. A history of stroke, transient ischemic attack, seizures, neurologic symptoms, focal neurologic exam, or elevated platelet counts at presentation warrant confirmatory imaging studies. Whether a more limited workup is adequate for other children should be confirmed in a larger, prospective study. *(J Pediatr 2011;159:472-8)*.

Headache is a common complaint among children, especially those with sickle cell disease (SCD). A study by Niebanck et al[1] demonstrated an overall prevalence of frequent headache in children with SCD at a major US medical center of 32.4%, similar to that of all ethnically matched control subjects, but significantly higher in children younger than 13 years. A similar study demonstrated that 24.5% of Nigerian children and adolescents with SCD reported frequent headaches, significantly higher than healthy control subjects in that population.[2] Additionally, acute headache represents 0.5% to 1.2% of total Emergency Department (ED) visits in the general pediatric population.[3-5] Unlike the general pediatric population, children with SCD have a higher baseline risk of central nervous system (CNS) events, such as infarctive stroke, intracranial hemorrhage, or sinovenous thrombosis.[6-8] As a result, clinicians worry that an acute headache in a child with SCD presenting to the ED may foreshadow an acute CNS event. Head computerized tomography (CT) scans and/or a brain magnetic resonance imaging/angiography (MRI/A) are often undertaken to assess the etiology of the headache in this setting. These tests are time-consuming and expensive, and CT scans expose the patient to radiation that will contribute to the patient's cumulative lifetime exposure.[9,10] Outcomes data from headaches presenting to the acute care setting could help guide when a more extensive workup is warranted.

The objectives of this study were to determine the frequency of acute headache visits in children with homozygous sickle cell disease (SCD-SS) compared with previously reported data in the general pediatric population, to determine the rate of neuroimaging in the evaluation of acute headache in SCD-SS, and to determine the prevalence of acute CNS events among children with SCD-SS in an acute care setting with a chief complaint of headache. We also identified historical, clinical, and laboratory factors associated with acute CNS events in this context. We hypothesized that children with a history of stroke or high risk of stroke and those with neurologic symptoms or new neurologic exam finding at presentation would have a greater risk of an acute neurologic event. Clarifying which children with SCD-SS presenting with acute headache are at greatest risk for acute neurologic events could help practitioners utilize appropriate medical resources in the acute care setting more quickly and efficiently.

CNS	Central nervous system
CT	Computed tomography
ED	Emergency Department
HACU	Hematology Acute Care Unit
MRI/A	Magnetic resonance imaging/angiography
SCD	Sickle cell disease
SCD-SS	Homozygous sickle cell disease
TCD	Transcranial Doppler
TIA	Transient ischemic attack

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Methods

This study was approved by the Institutional Review Board at the Children's Hospital of Philadelphia. Requirement for informed consent was waived. Patients, 5 to 21 years of age, with SCD-SS who presented to the Children's Hospital of Philadelphia (460-bed teaching hospital) between June 1, 2001, and October 31, 2005, with a chief complaint of headache were included. These patients came through either the ED or to the Hematology Acute Care Unit (HACU), an inpatient service designed to facilitate efficient admission and discharge of hematology patients. Children younger than 5 years of age were excluded from this study because young children are less likely to report headache accurately.

The electronic medical record database was queried for visits of all patients with SCD-SS ages 5 to 21 years coming to the ED between June 1, 2001, and October 31, 2005 (1788 visits). The database was queried for "headache" or commonly used variations such as "HA" and "head pain" in the following search fields: "chief complaint," "current impression," from the nurse triage form, and the "discharge diagnosis" documented by the primary ED physician.

A total of 897 visits were also identified by searching the HACU database of SCD-SS patient admissions, ages 5 to 21 years, between June 1, 2001, and October 31, 2005. From this subset, all visits with headache listed in the chief complaint or final diagnosis were identified.

Data were obtained from the ED, HACU, hospital admission, and outpatient clinic charts. Clinical information regarding the acute headache presentation, including location, quality, intensity, and associated symptoms was collected.

The initial vital signs and neurologic exam findings for each visit were obtained from the physician ED note, admission history and physical exam, and the neurology consult note when present.

Information on the patient's history of headaches and family history of headache was obtained from both the outpatient clinic chart and from the acute visit record. All documented admissions from the previous 5 years for each patient were queried for history of headache.

Information on regular transfusion therapy, recent episodic transfusions, and hydroxyurea use as well as indications for these treatments was collected. Information was collected on other medications, particularly opiate and nonopiate pain medications and medications used to treat or prevent headaches.

Complete blood count and reticulocyte count were obtained from the initial laboratory studies for the acute visit. In addition, the complete blood count (and fetal hemoglobin level when available) was obtained from the most recent routine outpatient visit.

All official reports of brain MRI/A and CT scanning were reviewed from the current admission. CT scans obtained within 3 days after presentation and MRI scans obtained within 7 days after presentation were considered to be related to the acute headache event. Transcranial Doppler (TCD) results for both the most recent study and the highest historic time-averaged mean of the maximum velocity were obtained. Studies were analyzed using the highest time-averaged mean of the maximum velocity in the middle cerebral artery, distal internal carotid artery, and bifurcation, bilaterally, according to the Stroke Prevention trial in Sickle Cell Anemia (STOP) criteria.[11]

A history of overt stroke, silent stroke, transient ischemic attack (TIA), or seizures was obtained from the outpatient hematology chart. Prior head CT and MRI/A reports also were reviewed for evidence of past acute CNS events. Documentation of acute intracranial events, such as infarctive stroke, intracranial hemorrhage, or sinovenous thrombosis, for patients presenting with acute headache was obtained from the official interpretation of the CT or MRI/A scan by an attending neuroradiologist. Additionally, a database of all acute neurologic events/strokes in children with SCD was reviewed to ensure that all acute events presenting with headache were captured in our electronic medical record database query. No additional acute headache presentations were identified.

Data Analysis

Descriptive analyses including mean and standard deviation and proportions were used to describe patient characteristics. In exploratory analyses, continuous variables were compared between groups (CNS event and no CNS event) using *t* tests. The independence of categorical variables was assessed using Fisher exact tests. All statistical analyses were performed with Stata 9.0 software (StataCorp, College Station, Texas) and a P value of $< .05$ was considered statistically significant for all analyses.

Results

A total of 102 headache visits were identified in 73 patients with homozygous sickle cell (SCD-SS) disease (1 visit: 54 patients, 2 visits: 13 patients, 3 visits: 2 patients, 4 visits: 4 patients). Patient characteristics are shown in **Table I**. Of the total 102 acute headache visits, 85 acute headache presentations were evaluated initially in the ED, whereas 17 were evaluated initially in our HACU. The 85 ED visits for acute headache represented 4.8% of the total 1788 ED visits by children with SCD-SS during the study period, whereas the 102 total acute care visits represent 3.8% of the total 2685 acute SCD visits (includes ED and HACU visits). Of the 102 visits for acute headache, 60 (58.8%) were exclusively for headache, whereas 42 (41.2%) visits had an accompanying medical complaint of fever or vaso-occlusive pain episode.

Seven of the 102 (6.9%) headache visits were associated with acute intracranial pathology (**Table II**). One child (Patient 4) had two separate acute headache visits associated with CNS events. A brain CT and/or an MRI/A study were performed acutely in 42.2% of the 102 headache

Table I. Patient characteristics

Characteristic	All headache visits n = 102	No CNS events n = 95	Acute CNS events n = 7	*P* value
Demographic data				
Age at visit (years)	12.8 ± 4.2	12.5 ± 4.2	16.7 ± 2.9	.010
Sex (% female)	62 (60.8)	58 (61.1)	4 (57.1)	.838
Past headache/stroke history				
History of headaches	75 (76.5)	70 (76.9)	5 (71.4)	.665
On treatment for chronic headache	15 (17.7)	15 (19.0)	0 (0)	.240
Prior abnormal TCD	18 (20.2)[89]	18 (21.2)[85]	0 (0)[4]	.579
Bilateral max TCD velocity (cm/s)	163.6 ± 37.0[87]	163.6 ± 37.4[85]	163.3 ± 30.6[2]	.997
History of silent stroke	27 (31.4)[86]	26 (31.7)[82]	1 (25)[4]	1.0
History of overt stroke	12 (11.9)[101]	8 (8.51)[94]	4 (57.1)[7]	.003
History of TIA	10 (10.9)[92]	7 (8.1)[87]	3 (60.0)[5]	.008
History of seizure	6 (6.5)[93]	4 (4.6)[88]	2 (40.0)[5]	.032
Clinical presentation				
Nausea/vomiting	32 (34.0)[94]	29 (33.3)[87]	3 (42.9)	.686
Dizziness	18 (17.8)[101]	18 (19.0)[95]	0 (0)[6]	.588
Weakness-–generalized	11 (11.2)[98]	9 (9.9)[91]	2 (28.6)	.176
Photo/phonophobia	15 (16.7)[90]	14 (16.9)[83]	1 (14.3)	1.000
Vaso-occlusive pain	31 (30.4)	29 (30.5)	2 (28.6)	1.000
Fever	14 (13.7)	14 (14.7)	0 (0)	.589
Headache intensity scale (1-10)*	7.3 ± 2.2[52]	7.3 ± 2.2[47]	7.4 ± 3.2[5]	.924
Focal neurologic symptoms				
Ataxia	0 (0)[101]	0 (0)[95]	0 (0)[6]	
Vision change	10 (10.9)[92]	7 (8.2)[85]	3 (42.9)	.026
Weakness-–focal	5 (5.1)[98]	2 (2.2)[91]	3 (42.9)	.002
Numbness	3 (3.1)[96]	0 (0)[90]	3 (50.0)[6]	.001
Mental status change	2 (2.0)[98]	0 (0)[91]	2 (28.6)	.004
≥1 Focal neuro symptom	15 (14.7)	9 (9.5)	6 (85.7)	.001
Physical exam abnormality				
Mental status	2 (1.96)	0 (0)	2 (28.6)	.004
Cranial nerve	7 (6.9)	2 (2.1)	5 (71.4)	.001
Motor	4 (3.9)	2 (2.1)	2 (28.6)	.023
Reflexes	1 (1.0)	1 (1.1)	0 (0)	1.000
Coordination	3 (2.9)	2 (2.1)	1 (14.3)	.194
Sensory exam	6 (5.9)	1 (1.1)	5 (71.4)	.001
≥1 Neuro exam abnormality	10 (9.8)	5 (5.26)	6 (85.7)	.001
Hematologic data at presentation				
WBC ($\times 10^9$/L)	15.6 ± 7.0[99]	15.3 ± 6.3[92]	19.7 ± 13.0	.11
Hemoglobin ($\times 10^9$/L)	8.3 ± 1.5[99]	8.3 ± 1.5[92]	8.6 ± 1.6	.55
Platelets ($\times 10^9$/L)	433 ± 140[99]	421 ± 130[93]	619 ± 172[6]	.0006
Reticulocytes ($\times 10^9$/L)	9.1 ± 4.0[99]	9.1 ± 3.9[93]	8.4 ± 5.1[6]	.68

Data are presented as mean ± SD or n (%). If the number of patients analyzed for a respective characteristic differs from the value n represented in the column heading, a corresponding n value is represented in superscripted brackets.
≥1 focal neuro symptom represents all headache visits with at least one of the previously listed neurologic symptoms on presentation (ataxia, vision change, focal weakness, numbness, or mental status change); ≥1 neuro exam abnormality represents all headache visits with at least one of the previously listed abnormal neurologic exam findings (mental status, cranial nerve, motor, reflex, coordination, or sensory exam abnormality).
*Fifty patients had only qualitative descriptions of headache severity (eg, mild, moderate, severe, etc).

visits; the majority (81%) of those imaged underwent brain CT, but 19% had only brain MRI and 21% had both studies performed. The prevalence of acute CNS events among children who underwent neuroimaging studies was 16.3%.

A comparison of demographic, historic, and clinical features between children presenting with acute complaint of headache with and without acute CNS events is presented in Table I. Children with acute neurologic events were older and more likely to have a history of stroke, TIA, or seizure, at least one neurologic symptom at presentation, and new focal neurologic exam abnormalities at acute headache presentation. In addition, event platelet counts were higher in children with acute CNS events compared with those without CNS events. Although the change in all hematological measures from baseline did not reach statistical significance, the increase in white blood cell counts from baseline to the acute event tended to be higher in children with acute CNS events (11.4 to 19.7 $\times$ 10^9/L in children with CNS events compared with 11.9 to 15.3 $\times$ 10^9/L, P = .059). Neither hydroxyurea nor transfusion therapy had a statistically significant association with acute CNS events.

Discussion

Acute headache visits represent a larger proportion of acute care visits in children with SCD-SS compared with the general pediatric population by approximately 4-fold (Table III),[3-5] despite a similar reported prevalence of frequent, nonacute headache in children with SCD-SS compared with control subjects at the same institution (approximately 30%).[1]

Table II. Description of acute CNS events

Patient	Sex	Age	History of stroke /neurologic event	Headache presentation	Neurologic exam presentation	Highest TCD (cm/s)	Radiographic event
1	M	21	Overt stroke 11 years prior	Pain 9/10, left-sided, awakened from sleep, nausea, and emesis	Attention, concentration, and short-term memory deficits; became acutely somnolent	n/a	Sinovenous thrombosis with parenchymal hemorrhage
2	M	14	Prior TIA and seizure by report	Left occipital ×1 month, bilateral fronto-temporal ×2 weeks, emesis, dizziness, and blurred vision	Papilledema, bilateral cranial nerve VI palsy, decreased sensation to light touch on left occiput, left inner thigh, and buttock	131	Sinovenous thrombosis
3	F	19	Overt stroke 4 years prior	Acute onset frontal headache. Right hand and face numbness, and right hand weakness	Baseline right facial droop and ptosis, right upper extremity tingling and weakness, new 3+/5 right upper extremity strength	n/a	Acute anterior cerebral artery distribution infarctive stroke
4 Event No. 1	F	15	1st overt stroke 12 years prior, 2nd recurrence 3 years prior. Left middle cerebral artery distribution	Left frontal headache of 10/10 intensity ×1 hour, left-sided facial numbness, slurred speech, and drooling	Baseline right hemiparesis, left ptosis, and cranial nerve III palsy. New dysarthria, left facial weakness, and numbness, subsequent right facial weakness and numbness	183	New hemorrhage in left putamen and internal capsule, with surrounding edema. Progression of stenosis of left M1, left and right A1, moya-moya
4 Event No. 2	F	16	1st Overt stroke 13 years prior, 2nd recurrence 4 years prior, 3rd stroke 1 year prior	Severe frontal headache ×3 hours	Baseline left ptosis and cranial nerve III palsy, 4/5 right upper extremity weakness and hypertonia New vision loss in right eye, increased right-sided weakness, later obtunded	183	Massive intraventricular hemorrhage
5	F	14	Previous silent infarct noted on MRI 3 years prior	Bitemporal and right occipital 4/10 pain after acetaminophen administration. Premedication pain data unavailable. The patient did report this headache was inconsistent with typical SCD pain	No documented deficits	144	Focal pituitary hemorrhage without parenchymal infarct
6	M	14	Previous silent infarct noted on MRI 4.5 years prior	Frontal 5/10 headache ×1 day, nausea, generalized weakness, transient blurred vision	Partial left cranial nerve VI palsy, right pronator drift, and right-sided extinction to double simultaneous stimulation	195	Extensive left frontoparietal skull bone marrow edema and enhancement, underlying left-sided cortical vein thrombosis

Table III. Comparison of current study with other studies of headache presentation in the general pediatric population

		General pediatric population		
	Sickle cell Current study	Kan et al[3]	Burton et al[4]	Scagni et al[5]
Total headache visits	102	89 (130)†	269 (288)	550
% Headache visits of total acute care visits	3.8*	0.5 (0.7)	1.2 (1.3)	1.0
% Total headache visits imaged	42.2	0 (40.7)	0 (7.3)	8
% Abnormal imaging findings	16.3	0 (10)	0 (19)	25
% Total population with abnormal imaging findings	6.9	0 (3.8)	0 (1.4)	2, 0.5‡

Patients with traumatic headache or ventriculoperitoneal shunts were excluded to make the general populations more comparable to the current study population. Only abnormal findings detectable by head CT or MRI were considered.
*Includes visits directly to the ED and to the HACU, where the ED was bypassed (refer to Methods section).
†All values in parenthesis represent total study populations before adjusting for patients with traumatic headache or ventriculopeitoneal shunts.
‡Two percent represents the portion of the total population with abnormal imaging finding both related and unrelated to a cerebrovascular accident; 0.5% represents the portion of the total population specifically found to have cerebrovascular accident (one intracranial hemorrhage, one ischemic attack, and one venous sinus thrombosis).

Headaches severe or unusual enough to prompt acute care visits may simply be more common in this subpopulation of patients compared with the general pediatric population. Additionally, a hematologist often serves as the primary care provider for patients with SCD-SS. This could increase the rate of acute care evaluations because a hematologist may have a heightened concern for an acute neurologic event when a patient with SCD-SS develops an acute headache and may recommend urgent medical attention more frequently. Previous data also show that 74% of patients who utilize the ED frequently have a chronic illness[12]; thus, patients with SCD may seek acute care more frequently than the general pediatric population without a similar chronic illness.

Evidence of acute CNS pathology was detected in 6.9% of visits for acute headache in children with SCD, compared with 0.5% in the general pediatric population.[5] The spectrum of acute CNS pathology that has been reported in the general population (intracranial hemorrhage, ischemic stroke, and sinus venous thrombosis) was similar to that reported in the current study (Table III).[5] Thus, an increased rate of neuroimaging may be justifiable considering that acute CNS events were detected approximately 10 times more often in children with SCD-SS presenting with acute headache compared with the general pediatric population in the setting of a headache. Interestingly, venous thrombosis comprised 43% of the radiographically detected events in children with SCD-SS in our study. Because sinovenous thrombosis can be easily missed on brain CT in the absence of hemorrhage,[13] it is important to consider venous thrombosis in the symptomatic patient with SCD-SS and negative imaging studies.

In exploratory univariate analyses, we detected a number of factors associated with CNS events in the setting of an acute headache. Patients with acute CNS events were significantly older than those without events at acute headache presentation. One possible explanation is that the majority of events in our study were hemorrhagic rather than thrombotic, and hemorrhagic events are more common in young adults.[14] This is consistent with previous data that demonstrate headache is more predictive of a hemorrhagic stroke compared with thrombotic stroke.[15] A prior history of stroke, TIA, or seizures was significantly associated with an acute CNS event in children with sickle cell disease with acute headache. This finding was not surprising because it has been well described that patients with a history of overt stroke or TIA are at increased risk of neurologic events.[6,16,17] Based on this, we expected that children with abnormal TCD would be more likely to have acute CNS events. However, our data did not demonstrate this. This may reflect the relatively low specificity of abnormal TCD for stroke risk: Only about 40% of children with abnormal TCD will have a stroke in the absence of treatment.[18] Furthermore, children with abnormal TCD may not have as severe vasculopathy as those with a history of stroke, given that about 75% of children with abnormal TCD have normal magnetic resonance angiography studies.[19]

The strong association of focal neurologic symptoms and focal abnormalities on the physical exam further validates the importance of a thorough history and physical exam during the acute evaluation. However, the absence of focal signs and symptoms may not independently negate the need for further imaging, given that one of the seven children with an acute CNS event had no report of neurologic symptoms or focal findings on physical exam. This patient had a focal pituitary hemorrhage. Sudden headache is the most common presentation described in adults with pituitary hemorrhage, and although >60% of patients with pituitary hemorrhage also present with focal visual disturbances, a subset presents without focal neurologic symptoms.[20]

Platelet counts also were significantly higher during the acute headache presentation of SCD-SS patients with acute CNS events, and a trend toward significance was observed in white blood cell elevation from baseline in patients with acute CNS events. These data are consistent with the well-described proinflammatory and procoagulant environment observed in sickle cell disease.[21-24] Future prospective studies are warranted to determine the degree of activation of these platelets and to delineate if these platelets have a causal role in the acute CNS events or simply serve as a marker of an acute event.

There are several limitations to the interpretation and generalizability of the current study. As a retrospective analysis, the possibility of selection bias exists. Additionally, imaging studies were not performed on all patients. Thus, it is possible that more clinically subtle acute CNS events may have been missed; however, the majority of subjects had continued follow-up without further evidence of a neurologic event.

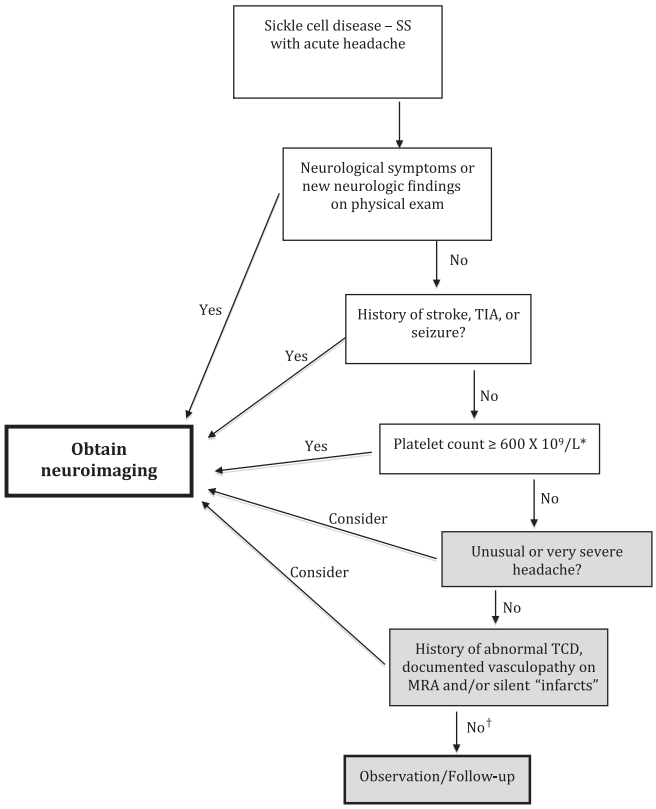

Figure. Algorithm for identifying children with homozygous sickle cell disease presenting with acute headache at increased risk of acute neurologic events. Statements contained within the *white boxes* are directly supported by this study; *gray boxes* are inferences that are not based directly on this study.*Approximates mean platelet count of patients having acute neurologic events. †Clinical judgment and other factors such as adequacy of patient follow-up should be considered in determining the need for neuroimaging.

Finally, the low number of events in this study precluded multivariate analysis. Nevertheless, our study highlights the relatively high rate of utilization of acute care services for headaches in the SCD population, the high rate of acute neurologic events in this setting, and the predictive value of historical data, hematologic data, and neurologic signs and symptoms.

Children with SCD-SS present to acute care settings with headache more frequently and undergo neuroimaging at a higher rate compared with the general pediatric population. Although the higher rate of acute CNS events may support increased imaging in this setting, a careful assessment of historic, hematologic, and clinical data may facilitate a more rational risk assessment and ultimately limit neuroimaging to patients at greater risk for acute CNS events. An approach for assessing the risk of acute CNS events in children with SCD-SS presenting with acute headache is summarized in the Figure. Children with SCD-SS presenting with acute headache who have associated neurologic symptoms, focal findings on physical exam and/or a history of stroke, TIA, or seizure should undergo neuroimaging. In the absence of this history and exam, patients with an elevated platelet count should also be considered for imaging. Although abnormal TCD and silent infarcts were not found to be associated with acute neurologic events in this study, a lower threshold for imaging patients with this history should be considered because these children have a higher baseline risk of stroke. Clinical judgment and other factors, such as atypical headache quality or severity, and assurance for follow-up should be weighed into the decision whether to image versus more conservative management in the absence of associated risk factors. The safety of a more limited workup in the absence of historic, hematologic, and clinical risk factors should be further explored in a larger prospective study. ■

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