



Brief Resolved Unexplained Events: Analysis of an Apparent Life Threatening Event Database

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ABSTRACT

OBJECTIVE: To identify the proportion of patients previously diagnosed with apparent life-threatening events (ALTE) who would meet criteria for brief resolved unexplained events (BRUE) and to identify rates of adverse outcomes in subgroups: ALTE not meeting criteria for BRUE, lower-risk BRUE, and higher-risk ALTE.

METHODS: We performed a secondary analysis of a single-center prospective registry of patients diagnosed with ALTE in a tertiary care emergency department from March 1, 1997 to October 31, 2007. We identified the proportion of patients meeting criteria for BRUE, and the proportion of patients with BRUE meeting lower-risk criteria. We assessed outcomes of patients in subgroups.

RESULTS: Seven hundred and sixty-two patients were included. Adverse outcomes included recurrent ALTE (n = 49), aspiration (n = 9), trauma (n = 8), and death (n = 4). Three hundred and twenty-six of 762 (42.8%) met criteria for BRUE. Seventy of 326 (21.5%) met criteria for lower-risk

BRUE. Adverse outcomes occurred in 40 of 436 (9.2%) with ALTE not meeting criteria for BRUE, 2 of 70 (2.9%) with lower-risk BRUE, and 23 of 256 (9.0%) with higher-risk BRUE. Of 4 patients who died, 1 had an ALTE not meeting criteria for BRUE and 3 had non-lower-risk BRUE. The BRUE risk criteria identified all BRUE patients that died or had substantial morbidity as higher-risk.

CONCLUSIONS: Less than half of patients with ALTE meet criteria for BRUE. Of those who do, one-fifth is lower-risk. In this series, the risk-stratification in the BRUE criteria identified those patients at highest risk of adverse outcomes. Further research is required to risk-stratify patients with BRUE.

KEYWORDS: abuse; ALTE; BRUE; cardiac arrhythmia; low-risk; seizures; significant outcomes; trauma

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WHAT'S NEW

In this evaluation of a prospective registry, a minority (40%) of patients with Apparent Life Threatening Events met criteria for Brief Resolved Unexplained Events (BRUE). Patients with lower-risk BRUE may have a lower rate for adverse outcomes.

IN 2016, THE American Academy of Pediatrics published a clinical practice guideline renaming Apparent Life-Threatening Events (ALTE) to Brief Resolved Unexplained Events (BRUE).¹ This guideline provided a new definition for BRUE along with management recommendations for lower-risk patients. ALTE was defined in 1986 as a frightening episode to the caregiver with apnea, choking, gagging, or changes in color, or muscle tone.² BRUE refers to a more specific diagnosis of exclusion in which a well-appearing infant less than 1 year has an event with cyanosis or pallor, changes in breathing, tone, or responsiveness.¹

The degree of overlap between these 2 conditions remains unestablished: nearly all cases of BRUE fit under

the previous rubric of ALTE, though the reverse is not always true. Two previous analyses investigating this question have been limited by their retrospective design and limited numbers.^{3,4} A more rigorous analysis of a cohort of patients with ALTE would allow better identification of health outcomes and provide evidence regarding the applicability of previous ALTE research to the current era.

In this study, we utilize data from a prospective registry of patients diagnosed with ALTE to identify the proportion of patients who meet BRUE criteria. In addition, we aim to report the rates of adverse outcomes of patients in 3 groups: ALTE not meeting criteria for BRUE, lower-risk BRUE, and higher-risk BRUE.

METHODS

DATA SOURCE

We performed a secondary analysis of a single-center prospective observational study performed in a tertiary-care pediatric institution between March 1, 1997 to

October 31, 2007. Published subsets of this cohort have reported rates of retinal hemorrhages,⁵ serious bacterial infections,⁶ and all-cause mortality⁷ in patients with ALTE. Prior to this analysis, approval was obtained from the University of Pittsburgh Institutional Review Board as an exempt study.

PATIENT INCLUSION AND EXCLUSION

For the parent study, patients diagnosed with ALTE by the treating emergency department (ED) physician were consented during the time of hospital encounter or soon after discharge by telephone. Patients were considered for inclusion if they were well-appearing during initial evaluation and if they met diagnostic criteria for ALTE: an event in a child <24 months who was well-appearing at the time of ED evaluation and who met diagnostic criteria for ALTE.² During the course of the study, informed consent was required for certain aspects of data collection (ie, dilated retinal examinations and testing for serious bacterial infections). However, even if these aspects were refused by caregivers, the requirement of consent was waived for medical record review and outcomes tracking.

DATA ABSTRACTION

Clinical, historical, diagnostic testing, and outcome data were collected. Clinical and historical data included age, sex, race/ethnicity, medical history, previous ALTE, the presence of apnea, duration of apnea, changes in mental status, color, or muscle tone, associated choking or gagging, number of events, provision of cardiopulmonary resuscitation, and the presence of a prodrome (ie, symptoms consistent with a viral infection, such as nasal congestion, cough, etc). Laboratory data included results of complete blood counts, venous blood gas testing, hepatic function testing, and toxicology testing. Radiologic data included the results of chest radiography, skeletal survey, brain computerized tomography, and upper gastrointestinal series. Clinical testing included the results of electrocardiograms, electroencephalography, and esophageal pH probe testing. The decision to obtain testing or admit was at the discretion of treating providers. Outcome data included diagnoses, revisits, and adverse outcomes both during the initial visit and follow-up medical record review (including ED and subspecialty visits, but not primary care physician visits) for 6 months after the initial event. Diagnoses included recurrent ALTE/apneic/cyanotic events, gastroesophageal reflux, bronchiolitis, upper respiratory tract infections, seizures, abuse, choking episode, infection/sepsis, swallowing disorder, breath-holding spell, metabolic disorder, and cardiac disease. No further patient contact occurred after obtaining consent. Data were collected in paper charts by study members and were entered into a database using SPSS Statistics (IBM Corporation, Armonk, NY).

OUTCOMES

Our primary outcome was the proportion of patients with ALTE who met criteria for BRUE.¹ Secondary

outcomes included the proportion of BRUEs meeting criteria for lower- and higher-risk events and adverse outcomes within 3 categories: patients with ALTE without meeting criteria for BRUE, patients with ALTE who met criteria for higher-risk BRUE, and patients with ALTE who met criteria for lower-risk BRUE.¹ We described rates of adverse outcomes in each group and calculated the relative risk with 95% confidence interval (CI) of adverse outcomes in patients with lower-risk and higher-risk BRUEs.

One important characteristic to differentiate patients with ALTE and BRUE is the presence or absence of a physical finding or historical characteristic suggestive of significant disease. To classify patients into ALTE or BRUE groups, patients with choking episodes and those with discharge diagnoses of gastroesophageal reflux, upper respiratory infection, and bronchiolitis were considered to be factors excluding patients from a diagnosis of BRUE.

ANALYSIS

We applied diagnostic criteria for BRUE to the study cohort to identify the proportion of patients who met BRUE criteria. For those with BRUE, we stratified patients into higher- and lower-risk groups. We reported adverse outcomes in groups: ALTE not meeting criteria for BRUE (ALTE only), lower-risk BRUE, and higher-risk BRUE by calculating relative risk. Analyses were conducted with R version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

PARENT STUDY INCLUSION

Seven hundred and sixty-two patients were included from the study cohort. Median age was 1.5 months (interquartile range, 0.8–3.0 months); 51.6% were girls (Table 1).

PATIENTS MEETING CRITERIA for BRUE and LOWER-RISK BRUE

Of 762 patients with ALTE, 436 patients with ALTE did not meet criteria for BRUE (57.2%), 70 met criteria for lower-risk BRUE (9.2%), and 256 met criteria for higher-risk BRUE (33.6%) (Figure, Table 2).

ADVERSE OUTCOMES

Forty of 436 (9.2%) of patients with ALTE only, 23 of 256 (9.0%) with higher-risk BRUE, and 2 of 70 (2.9%) with lower-risk BRUE had adverse outcomes. Among those with infectious disease and BRUE, one was diagnosed with pneumonia during admission on a repeat chest radiograph done several days after admission, another was diagnosed with pneumonia on chest radiograph at presentation, and a third had a lumbar puncture with pleocytosis thought to be due to aseptic meningitis. All were well appearing during initial evaluation. The relative risk of adverse outcomes in the

Table 1. Demographics of Population Overall and in Subgroups

	All Patients (n = 762)	ALTE, Not BRUE (n = 436)	Lower-Risk BRUE (n = 70)	Higher-Risk BRUE (n = 256)
<i>Historical/clinical characteristics and admissions, with number of records with data</i>				
Median age, months (IQR); n = 762 (100%)	1.5 (0.8–3)	1.25 (0.60–2.6)	3 (2.3–5.0)	1.3 (0.5–2.8)
Previous history of ALTE; n = 762 (100%)	38 (5.0)	23 (5.3)	0 (0.0)	15 (5.9)
Number of girls (%); n = 762 (100%)	393 (51.6)	224 (51.4)	35 (50.0)	134 (52.3)
Race (%); n = 762 (100%)				
Caucasian	535 (70.7)	314 (72.2)	49 (70.0)	172 (68.3)
African American	158 (20.9)	91 (20.9)	18 (25.7)	49 (19.4)
Asian	2 (0.3)	1 (0.2)	0 (0.0)	1 (0.4)
Other	24 (3.2)	13 (3.0)	0 (0.0)	11 (4.4)
Unknown	38 (5.0)	16 (3.7)	3 (4.2)	19 (7.5)
Prematurity (%); n = 762 (100%)				
≤36 weeks	177 (23.3)	88 (20.3)	9 (12.9)	80 (31.2)
<32 weeks	48 (6.3)	16 (3.7)	0 (0.0)	32 (12.5)
Associated choking (%); n = 718, (94.2%)	339 (47.2)	339 (78.8)	0 (0.0)	0 (0.0)
Presence of prodrome (%); n = 758, (99.4%)	179 (23.6)	97 (22.4)	20 (29.0)	62 (24.2)
Color change (%); n = 762 (100%)*	499 (65.5)	268 (61.5)	49 (70.0)	182 (71.1)
Irregular breathing (%); n = 762 (100.0%)	578 (76.4)	313 (71.8)	52 (74.3)	213 (83.2)
Change in tone (%); n = 726 (95.3%)	412 (56.7)	236 (56.5)	37 (56.9)	139 (57.2)
Altered responsiveness (%); n = 762 (100%)	306 (40.2)	174 (39.9)	36 (51.4)	96 (37.5)
CPR done (%); n = 733 (96.1%)	106 (14.5)	45 (10.7)	0 (0.0)	61 (24.4)
More than 1 event (%); n = 727 (95.4)	165 (22.7)	96 (22.9)	0 (0.0)	69 (28.4)
Admissions (%); n = 762; (100%)	700 (91.9)	387 (88.8)	66 (94.3)	247 (96.5)
<i>Clinical testing, n (%)[†]</i>				
Chest radiography; n = 624, (81.9%) [†]	531 (85.1)	282 (81.7)	55 (87.3)	194 (89.8)
CBC performed	637 (83.6)	335 (76.8)	63 (90.0)	239 (93.4)
Hepatic function panel	360 (47.2)	180 (41.3)	39 (55.7)	141 (55.1)
Venous blood gas	408 (53.5)	220 (50.5)	38 (54.3)	150 (58.6)
Urine toxicology screen	317 (41.6)	173 (39.7)	34 (48.6)	110 (43.0)
Skeletal survey; n = 757, (99.3%) [†]	32 (4.2)	9 (2.1)	3 (4.3)	20 (7.8)
Head computerized tomography; n = 758, (99.5%) [†]	152 (19.9)	63 (14.4)	23 (32.9)	66 (25.8)
Upper GI series; n = 597, (78.3%) [†]	92 (15.4)	60 (17.1)	6 (12.0)	26 (13.3)
pH probe testing; n = 596, (78.2%) [†]	21 (3.5)	10 (2.9)	0 (0.0)	11 (5.6)
EKG; n = 758, (99.5%) [†]	642 (84.7)	379 (87.7)	52 (74.3)	211 (82.4)
EEG; n = 720, (94.5%) [†]	248 (34.4)	111 (27.2)	30 (45.5)	107 (43.5)
<i>Results of laboratory testing</i>				
Hemoglobin (g/dL); median (IQR)	11.9 (10.8–14.1)	12.1 (11.0–14.4)	11.3 (10.5–12.4)	12.0 (10.5–14.8)
White blood cell count (cells x 10 ⁹ /L); median (IQR)	11.2 (9.0–13.9)	11.1 (9.1–13.7)	11.3 (8.4–14.2)	11.1 (9.1–13.9)
Abnormal chest radiography	–	Cardiomegaly (1), diaphragm eventration (1), hyperinflation (2), infiltrate/atelectasis (16), possible fractures (2) other (3)	Infiltrate/ atelectasis (1)	Cardiomegaly (1), diaphragm eventration (1), infiltrate/atelectasis (12), possible fractures (3)

ALTE indicates apparent life-threatening event; BRUE, brief resolved unexplained event; CPR, cardiopulmonary resuscitation.

*Color change for ALTE defined as any color change reported by parent, whereas color change for BRUE is defined as cyanosis or pallor only.

[†]Number in "All patients" column represents the total number for which performance of testing was documented.

lower-risk compared to the higher-risk BRUE group was 0.32 (95% CI, 0.08–1.32; $P = .11$). The relative risk of adverse outcomes in patients with lower-risk BRUE compared to patients with ALTE only was 0.33 (95% CI, 0.08–1.33; $P = .12$). While patients in the lower-risk BRUE group were not entirely free of adverse outcomes, the BRUE risk criteria identified all of the BRUE patients that died or had substantial morbidity (Table 2).

Of four patients who died, one was 2 months old who did not meet criteria for BRUE because of gastroesophageal reflux. This infant died of suspected sudden infant death. The second patient was 4 months old who met criteria for higher-risk BRUE because of having multiple events who had suspected sudden infant death. The third was a 2 weeks old who presented for an apneic episode and who met criteria for higher-risk BRUE on the basis of age and having had cardiopulmonary resuscitation. This

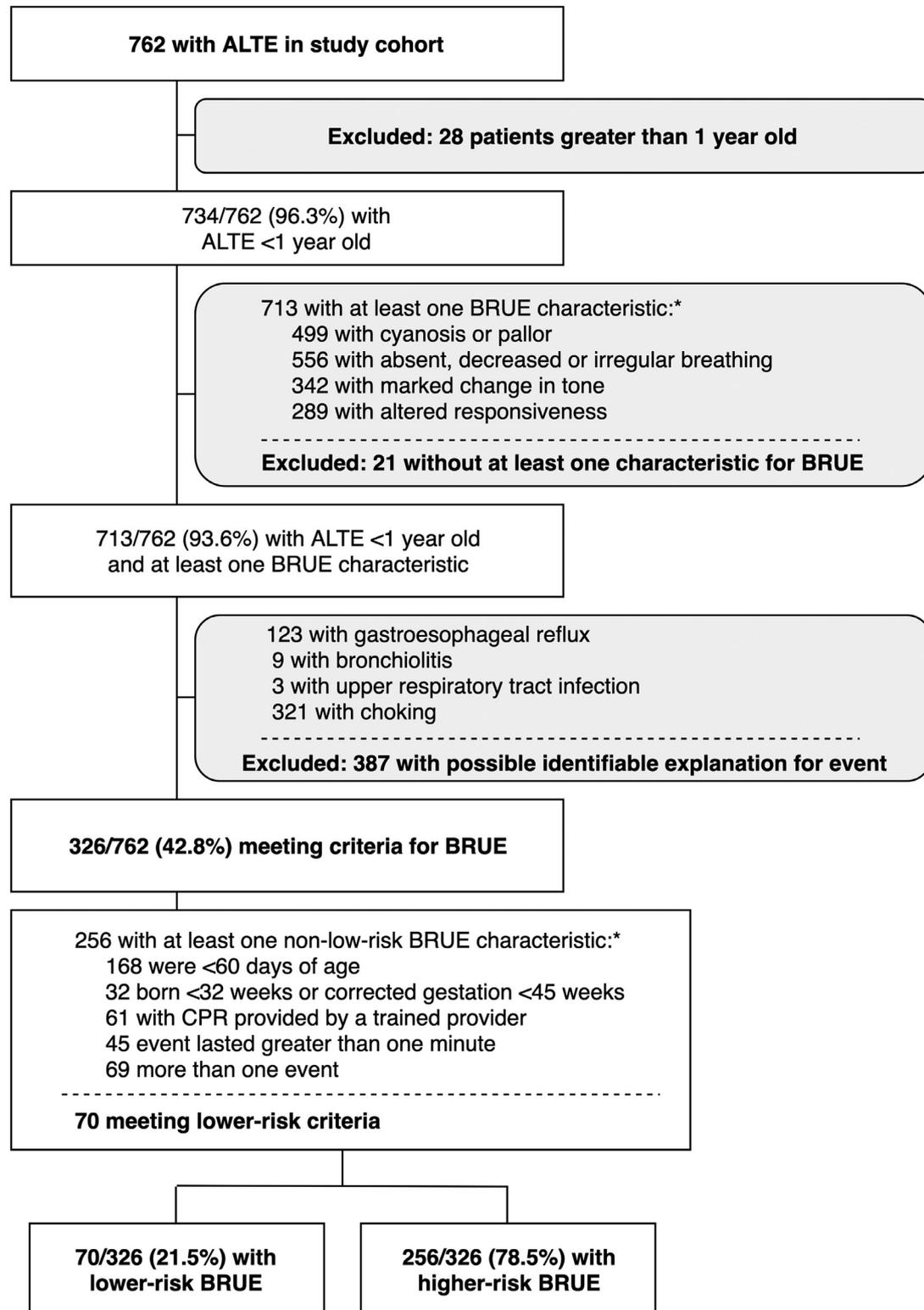


Figure. Identification of patients with BRUE among patients with ALTEs. ALTE indicates apparent life-threatening event; BRUE, brief resolved unexplained event; CPR, cardiopulmonary resuscitation. *Because patients had more than one characteristic meeting criteria, numbers do not sum to 100%.

infant was diagnosed with ketoglutaric aciduria and died of cardiac arrest 4 weeks later. The fourth was 2 months old who met criteria for higher-risk BRUE because of having multiple events. This child died after discharge due to suspected child abuse. All 4 infants underwent autopsy.

DISCUSSION

In this secondary analysis of a cohort of patients with ALTE, two-fifths of patients meeting diagnostic criteria for ALTE also met criteria for BRUE. Of those who met criteria for BRUE, one-fifth met criteria for lower-risk events. Rates of adverse outcomes in patients with ALTE only was

Table 2. Diagnoses in Patients With ALTE, Higher-Risk BRUE, and Lower-Risk BRUE

Event	Initial Encounter	Follow Up
ALTE without BRUE 40/436 (9.2)		
Recurrent ALTE	10	20
Aspiration events	8	1
Central sleep apnea	2	3
Trauma	2	1
Subglottic stenosis	1	1
Infection/sepsis	2	0
Seizure disorder	2	0
Positive urine toxicology testing	2	0
Pertussis	1	0
SIDS	0	1
Obstructive sleep apnea	0	1
Lower-risk BRUE: 2/70 (2.9%)		
Recurrent ALTE	0	2
Obstructive sleep apnea	0	1
Higher-risk BRUE: 23/256 (9.0)		
Recurrent ALTE	12	5
Trauma	4	1
Infection/sepsis	3	0
Hydrocephalus	0	1
Genetic/metabolic disorder	2	1
Seizure disorder	0	2
Subglottic stenosis	0	1
SIDS	0	1
Munchausen syndrome by proxy	0	1
Central sleep apnea	2	1

ALTE indicates apparent life-threatening event; BRUE, brief resolved unexplained event; SIDS, sudden infant death. Some patients had multiple adverse outcomes.

similar to the rate of events in patients with higher risk BRUE (9.2 versus 9.0%), and the rate of events in patients with lower-risk BRUE appeared to be lower.

Two-fifths of patients with ALTE met BRUE criteria. To date, previous studies that have attempted to identify patients with ALTE meeting clinical criteria for BRUE reported differing rates. Meyer et al reported that 20 of 91 (23.0%) of patients with ALTE met BRUE criteria.³ Colombo et al reported that 49 of 84 (58.3%) patients admitted to a single-center for ALTE met criteria for BRUE.⁴ Both of these studies were retrospective and utilized International Classification of Disease coding to identify cases, leading to potential selection bias. A third study, which prospectively enrolled 32 patients referred to an ambulatory sleep center following an ALTE episode, found that 26 (81.3%) met criteria for an ALTE.⁸ This higher figure may relate to the data source of this study coming from a sleep center rather than an ED, leading to selection of a different patient population.

We found that 21.5% of patients with BRUE met lower-risk criteria. This figure lies between that reported by Meyer et al (1 of 20, 5%) and Colombo et al (16 of 49, 32.7%).^{3,4} In the study by Colombo et al 12.1% with higher-risk BRUE (3 with seizures and 1 with prolonged QT syndrome) and 12.5% of patients with lower-risk BRUE (2 with seizures) had adverse outcomes comparable to those in our study.⁴ The higher rate of adverse outcomes in the lower-risk group by Colombo may be due to its inclusion of only those patients admitted to the hospital, who may have a higher rate of pathology.

Our findings carry multiple implications. As only a minority of ALTE meets criteria for BRUE, the ability to translate previous research to current day practice may be limited. Additionally, these results suggest that the rate of adverse outcomes in patients who may have been formerly diagnosed with ALTE is high: even though these patients may not be diagnosed with BRUE, a thorough evaluation is warranted to identify risk factors for deleterious outcomes in this population. Given this and the similarities between the ALTE and higher-risk BRUE groups, further investigation may be warranted in reviewing the characteristics composing the BRUE definition.

The findings from this study are subject to limitations. Though this was a secondary analysis of a prospective database, it retrospectively applies the BRUE criteria to patients with ALTE. Results may not be generalizable to other centers, particularly nonacademic sites. While data from this study are older, it uses a prospective registry and is better able to identify BRUE events compared to other studies. A prospective data study on patients with ALTE would be difficult to perform due to changes in nomenclature. Beyond the inclusion requirement that infants be well-appearing on initial evaluation, historical, and physical exam details were limited in the parent study. Some data were missed with respect to event characterization. There was a larger fraction of missing data with respect to diagnostic testing. However, to characterize an event as a BRUE does not require testing. Low-risk BRUE is not expected to have testing performed. Adverse outcomes data may have been missed because of various rates of testing, which were determined by clinical provider. As no further contact occurred with patients or families, it would not be known if they had adverse events that did not prompt a return to clinical care, or if patients were evaluated at different institutions. This is particularly challenging because of the rarity of adverse events in patients with ALTE and BRUE. It was not known if cardiopulmonary resuscitation was provided by a trained provider. When we repeated our analysis without this variable, overall results were similar (not shown). For patients with recurrent ALTE, we were unable to classify if those events would meet BRUE criteria. Despite these limitations, this study provides valuable data regarding the rates of adverse outcomes in this population.

CONCLUSIONS

Approximately two-fifths of patients formerly diagnosed as ALTE met criteria for BRUE. Of those with BRUE, one-fifth met criteria for lower-risk BRUE. The rate of adverse outcomes in patients with lower-risk BRUE appeared to be lower than in those with higher-risk BRUE. Furthermore, the BRUE criteria correctly identified those patients with outcomes having the highest morbidity and all cases with subsequent mortality. Further prospective research is needed to identify outcomes of patients with BRUE in order to more safely risk-stratify this population.

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Authorship statement: Dr Ramgopal designed the study, drafted the initial manuscript, collected data, carried out the analysis, and drafted the manuscript.

Dr Soung designed the study, collected data, and revised the manuscript for intellectually important content.

Dr Pitetti conceptualized the study and critically revised the manuscript for intellectually important content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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