

Prevalence of Retinal Hemorrhages in Critically Ill Children



WHAT'S KNOWN ON THIS SUBJECT: The association of retinal hemorrhages (RHs) with abusive head trauma (AHT) is robust; 46% to 100% RHs are reported in AHT. There is potential selection bias with risk of circular reasoning because the majority of studies describing RH focus on AHT.



WHAT THIS STUDY ADDS: This is the first prospective observational study defining prevalence and distribution of RH in critically ill children excluding those with AHT. Severe multilayered RH were rare and observed in children with accidental fatal head injury, severe coagulopathy, severe sepsis, or a combination of these factors.

abstract

BACKGROUND: Retinal hemorrhages (RHs) with encephalopathy and subdural bleeding are considered suggestive of abusive head trauma (AHT). Existing studies describing RH focus on AHT and have potential selection bias. We undertook a prospective observational study to define the prevalence, distribution, and extent of RH in critically ill children.

METHODS: From February 2008 to December 2009, emergency intensive care admissions ≥ 6 weeks of age underwent dilated retinal examination by either a pediatric ophthalmologist or RetCam (retinal photograph) imaging after written informed consent. Patients with suspected or proven AHT, penetrating eye trauma, and elective admissions were excluded.

RESULTS: The prevalence of RH was 15.1% (24/159; 95% confidence interval [CI]: 9.5%–21%); 16/24 (66%) mild, and 2/24 (8%) moderate. Severe multilayered RH were seen in only 6 patients (3.7%), 3 with myeloid leukemia and sepsis, 2 with severe accidental head injury, and 1 with severe coagulopathy secondary to late onset hemorrhagic disease of newborn. There was no detectable impact of age, gender, seizures, coagulopathy or cardiopulmonary resuscitation on prevalence of severe multilayered RH; however, sepsis (odds ratio: 3.2; 95% CI: 1.3–8.0, $P = .018$) and coagulopathy (odds ratio: 2.8; 95% CI: 1.2–7.0, $P = .025$) were significantly associated with any RH. Only admission diagnosis was independently associated with severe multilayered RH on logistic regression.

CONCLUSIONS: RHs were seen in critically ill children with a prevalence of 15.1% (24/159); however, most were mild. Severe multilayered RH resembling those described in AHT were rare (6/24) and were only seen in patients with fatal accidental trauma, severe coagulopathy, sepsis with myeloid leukemia, or a combination of these factors. *Pediatrics* 2012;129:e1388–e1396

AUTHORS: Shruti Agrawal, MD, MRCPCH,^a Mark J. Peters, MBChB, PhD,^{a,b} Gillian G.W. Adams, FRCS (Ed), FRCOphthal,^{c,d} and Christine M. Pierce MRCP, FRCPC^a

^aPaediatric and Neonatal Intensive Care Units and ^cPaediatric Ophthalmology, Great Ormond Street Hospital for Children, London, United Kingdom; ^bCritical Care Group–Portex Unit, Institute of Child Health, University College London, London, United Kingdom; and ^dMoorfields Eye Hospital, London, United Kingdom

KEY WORDS

retinal hemorrhages, critical illness, trauma, coagulopathy, shaken baby syndrome, nonaccidental injury

ABBREVIATIONS

AHT—abusive head trauma
CI—confidence interval
CPR—cardiopulmonary resuscitation
OR—odds ratio
RH—retinal hemorrhage
SE—standard error

www.pediatrics.org/cgi/doi/10.1542/peds.2011-2772

doi:10.1542/peds.2011-2772

Accepted for publication Jan 24, 2012

Address correspondence to Shruti Agrawal, Paediatric Intensive Care Unit, Addenbrooke's Hospital, Hills Rd, Cambridge CB2 0QQ, United Kingdom. E-mail: shragrawal@gmail.com

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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FINANCIAL DISCLOSURE: Dr Peters has received fees from both prosecution and defense teams for providing expert opinion to Family and Criminal courts in cases of suspected nonaccidental head injury; Ms Adams has provided expert witness and court reports in cases of possible abusive head trauma in relation to the eye findings in these cases, has been paid a fee for these reports, and has instructed in civil and criminal cases; and Dr Agrawal and Dr Pierce have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: There was no funding required or used for this study. This work was undertaken at Great Ormond Street Hospital/University College London Institute of Child Health, which does receive a proportion of funding from the Department of Health's National Institute for Health Research Biomedical Research Centres funding scheme.

Nonaccidental injury causes significant morbidity and mortality in young children around the world; the exact prevalence of nonaccidental injury is difficult to ascertain; however, a recent review suggests that 4% to 16% of children are physically abused every year.¹ The estimated incidence of abusive head trauma (AHT) in children less than 2 years of age is 21 to 24 per 100 000 children, and AHT is the commonest cause of traumatic death in infancy.² A false-negative diagnosis of AHT may leave vulnerable children at risk; a false-positive diagnosis carries the risk of harm to the whole family, particularly the accused. The presence of retinal hemorrhages (RHs), subdural hemorrhages, and acute severe encephalopathy is considered highly suggestive but not pathognomonic of AHT.³

The association of RH with AHT is robust. In proven AHT, RHs have been recorded in 46% to 100% cases.⁴ A recent systematic review identified apnea and RH as the 2 features best able to discriminate accidental from abusive head injury.⁵ However, RHs have been postulated in a wide range of illnesses, and the list continues to expand as sicker infants are maintained on intensive care units and techniques for retinal examination improve.^{6–8} In the literature, RHs have been suggested to occur in association with cardiopulmonary resuscitation (CPR), intracranial hemorrhages, raised intracranial pressure, bleeding diathesis (congenital or acquired), and seizures,^{6,7} although the studies determining such an association have not revealed evidence to support all of these implicated etiologies with RH.^{9–18} Furthermore, RHs in abuse have been observed commonly to be flame-shaped, bilateral, and multilayered, unlike RH seen in other postulated etiologies.⁶

Because the majority of studies describing RH focus on patients with AHT, there is potential selection bias with

a risk of circular reasoning. We undertook a prospective study to define the prevalence, distribution, and extent of RH in critically ill children between 6 weeks and 16 years of age, excluding patients with AHT. We also report the impact of coagulopathy and admission diagnoses on this distribution as the secondary outcome measures.

METHODS

Study Design and Patients

All emergency admissions of infants and children >6 weeks of age (to exclude the possibility of any birth-related RHs) up to 16 years of age, to our tertiary 14-bedded PICU between February 2008 and December 2009 were considered for inclusion in this prospective observational cross-sectional study. Patients with any direct ocular trauma were excluded, as were the cases of suspected or proven AHT (any children younger than 2 years of age with head injury were actively investigated to rule out AHT as per the hospital protocol; a multiprofessional team then examined all the evidence and excluded AHT in all these patients before inclusion in the study). The study was approved by the local ethics committee (National Research Ethics Committee, UK, reference number 07/H0713/65), and written informed parental consent was obtained before recruitment.

Demographic data, admission diagnosis (1 of the 4 mutually exclusive diagnostic categories, namely, traumatic brain injury, sepsis, primary respiratory pathology and nontraumatic encephalopathy, based upon the primary illnesses leading to a PICU admission), hematologic investigations including coagulation profile (prothrombin time, activated partial thromboplastin time, and fibrinogen) and platelet count, signs of any external bleeding, use of blood products, cranial imaging findings, drugs administered while in the PICU, comorbidity,

CPR episodes before or after admission including duration of chest compressions, and occurrence of seizures before or after admission were noted for each patient. Coagulopathy was defined as prothrombin time more than 3 seconds above normal and/or twice normal partial thromboplastin time and/or platelet count <50 000/mm³.¹⁹

Procedures

The patients underwent dilated fundoscopic examination; either a wide-angle retinal photograph was taken by RetCam II (Clarity Medical Systems, Pleasanton, CA) or indirect fundoscopic examination was done by a pediatric ophthalmologist (either a consultant or fellow). Retinal photographs have been shown to have comparable specificity and sensitivity in identifying RH⁸ to standard clinical examination and photo documentation and are considered to be a major advance in the documentation of RHs in comparison with the traditional approach of hand drawings.²⁰ The retinal pictures were later reviewed by the consultant pediatric ophthalmologist (Ms Adams). RetCam was exclusively used by either trained PICU staff (Dr Agrawal, Dr Pierce, or Dr Peters) or a trained ophthalmologist; viscotears were used as an interface between the cornea and the camera, and 0.5% proxymetacaine drops were used if the patient was not fully sedated and paralyzed. Whenever possible, retinal photographs were taken. Indirect fundoscopy was reserved for the patients where there were practical difficulties in taking RetCam images (difficulty in opening eyes due to edema, very awake patients). The patients were recruited within first 48 hours of admission to our PICU unless the duty clinicians felt a transient loss of pupillary reactions after dilating drops might compromise neurologic monitoring. In these patients, eye examination was done as soon as was practically possible (usually within 72 hours).

Outcome Measures and Prespecified Subgroup Analysis

There is no universally accepted grading system for RH, and different studies have revealed different classifications.²¹ We classified the RH by using laterality (unilateral or bilateral), severity (<5 RH mild, 5–20 RH moderate, >20 RH severe), and as single or multilayered based on their location in the retina. The primary outcome measures were the prevalence and distribution of RH in critically ill children. Secondary analyses were carried out for the association of RH with admission diagnoses and coagulopathy. Comparisons were made in the 2 age groups (≤ 2 years, >2 years) and gender. We chose the age cutoff at 2 years because AHT most often involves children younger than 2 years.^{22–24}

Statistical Analysis

Analyses were performed with SPSS 19 for Mac (SPSS Inc, Chicago, IL). Prevalence is described with SEs of proportions and compared between potential risk groups with Fisher's exact test.²⁵ Multiple logistic regression analyses with RH ("any" or "severe") as the dependent variables were performed with the following covariates (implicated in the published literature when the frequency of event occurring was more than 10 in our study group): age, gender, diagnostic group, any CPR with chest compressions, and coagulopathy.

Role of Funding Sources

There was no funding for this study. This work was undertaken at Great Ormond Street Hospital/University College London Institute of Child Health, which does receive a proportion of funding from the Department of Health's National Institute for Health Research, Biomedical Research Centres funding scheme.

RESULTS

Of 356 families approached, a total of 161 consented to the study (Fig 1), final analyses were performed on 159 patients; 2 patients were excluded due to poor RetCam photographs in 1 patient and a scarred retina from treated retinopathy of prematurity in the second patient. Age, gender, and admission diagnoses did not differ significantly between recruited cases ($n = 161$) and those in whom consent was declined ($n = 195$). The median age of the study population was 18 months (range 1.5–190 months); and the boy to girl ratio was 1.2:1. RHs were seen in 24/159 cases (15.1%; 95% confidence interval [CI]: 9.5%–21%). The distribution of RH according to different age groups is given in Table 1.

Severity of RH

Mild RH

Mild RHs were seen in 16/159 (10%, 6.3%–16%) cases, of which 11 were unilateral and 5 bilateral; the majority

of these were single-layered (11/16; Table 2). Half of the mild RHs were seen in patients who were 24 months or less of age. Sepsis was the most frequent admission diagnosis in patients with mild RHs (7/39, 17.9%), followed by 3 patients each with accidental traumatic brain injury (3/29, 10.3%), respiratory illness (3/55, 5.4%), and non-traumatic encephalopathy (3/36, 8.3%; Table 2).

Moderate RH

There were 2 patients with moderate bilateral RH (2/159, 1.2%). One child had single-layered hemorrhages in the context of enteroviral sepsis-induced multiorgan dysfunction and acute respiratory distress syndrome. Another 3-year-old child had multilayered bilateral moderate RH after a witnessed accidental fall of a television onto his head (Table 2).

Severe RH

Six patients (6/159, 3.8%, 1.7%–8%) had severe RH; all the severe RHs were

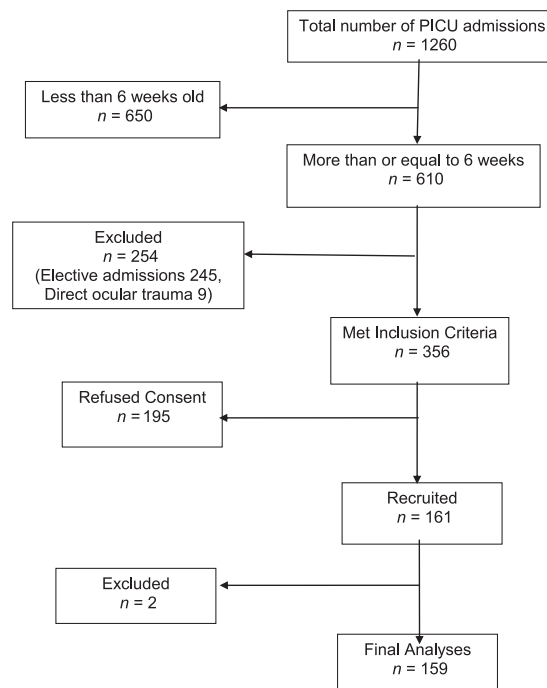


FIGURE 1

Flow chart showing study inclusion and exclusion criteria.

TABLE 1 Age Distribution and Presence of RH

Age, y	No. of Patients	Any RHs, <i>n</i> (%)	Severe RHs, <i>n</i> (%)	No RHs, <i>n</i> (%)
<1	51	8 (15.6)	2 (3.9)	41 (80.3)
1–2	32	4 (12.5)	2 (6.25)	26 (81.25)
2–3	12	2 (16.6)	0	10 (83.3)
3–5	16	2 (12.5)	0	14 (87.5)
5–10	21	4 (19)	2 (9.5)	15 (71.4)
>10	27	4 (14.8)	0	23 (85.1)

multilayered, and 5/6 were bilateral. The patient with severe unilateral multilayered RH had a severe coagulopathy due to late onset hemorrhagic disease of the newborn. This patient had an extensive, unilateral intracranial hemorrhage on the side of impact and ipsilateral RH after a low level witnessed fall from hammock (Table 2). Three patients with severe multilayered RH had leukemia (acute myeloid leukemia in 2 patients and juvenile myelomonocytic leukemia in 1 patient); all 3 patients were admitted to the PICU with severe sepsis, and 2 patients had associated severe coagulopathy; these patients also had leukemic retinal changes (exudates in all patients, pseudo-hypopyon in 1 patient). The other 2 patients with severe multilayered RH had fatal traumatic brain injury; 1 suffered 60 miles per hour pedestrian/car road traffic accident, and the second suffered witnessed complex fall down 10 steps with multiple impacts. This same child developed bowel perforation related to necrotizing enterocolitis. Four out of the 6 patients with bilateral severe multilayered RH were 2 years or less in age (Table 2); there was, however, no detectable impact of age or gender, admission diagnoses, or the presence of coagulopathy on the presence of severe multilayered RH (Tables 3 and 4).

Association of RHs With Coagulopathy and Diagnostic Groups

There was no detectable impact of age or gender on the prevalence of RH; however, sepsis as the admission diagnoses (odds ratio [OR]: 3.2; 95%

CI: 1.3–8.0, $P = .018$) and the presence of coagulopathy (OR: 2.8; 95% CI: 1.2–7.0; $P = .025$) were significantly associated with the occurrence of any RH (Tables 3 and 4). Respiratory failure as the admission diagnosis was associated with significantly fewer RH (OR: 0.23; 0.065–0.8, $P = .018$), whereas traumatic brain injury and nontraumatic encephalopathy had no detectable impact on the occurrence of RH (Table 4). On multivariate logistic regression analysis, diagnostic category was the only factor independently associated with occurrence of any RH ($P = .026$) and the presence of severe multilayered ($P = .017$) RH.

Coagulopathy was a common association with RH, being present in 11 out of 24 cases (Table 5). In the patients with coagulopathy, sepsis was the commonest admission diagnosis (27/42), and 7 of these patients had RH (5 mild, 2 severe; Table 5). There were 29 patients with traumatic brain injury, and 7 of these patients had RH (details in Table 3); among the 22 who did not have RH, 9 were involved in road traffic accidents, 10 had witnessed fall from a height, and 3 had miscellaneous reasons for traumatic brain injury (witnessed blunt trauma).

Among 17 patients who received CPR, 11 did so after in-hospital arrest and 6 out-of-hospital arrest. The mean CPR duration was 5.8 minutes (range, 2–25 minutes); the underlying etiology was respiratory disease in 8, sepsis in 4, nontraumatic encephalopathy in 3, and drowning and trauma in 1 patient each. No severe multilayered RHs were seen in any patients after CPR. Four patients had single-layered RH observed post

CPR; 3 of these (all unilateral) were in the context of severe coagulopathy, and 1 was after traumatic brain injury (bilateral mild RH; Table 2). No RHs were seen in patients post CPR without an associated coagulopathy or trauma.

We could not recruit patients with status epilepticus (either febrile or known epilepsy) due to their typically very short PICU stay. We, therefore, excluded seizures as an association from the final analysis because all the patients with seizures had multiple other risk factors for RH.

DISCUSSION

Studies in victims of child abuse demonstrate severe bilateral and multilayered RH in a high proportion (~85%) of AHT.^{5,20} RHs (together with a history of apnea) have been shown to discriminate accidental from abusive head injury more effectively than any other features.⁵ The majority of studies start from a suspicion of abuse and hence the incidence of RH in the population outside the neonatal age group is not known. There are few exceptions to this, such as the studies of Curcoy et al²⁶ who found no RH in 108 infants with apparent life-threatening events and in 2/182 (0.5%) infants admitted to hospital after convulsions.¹⁸

To our knowledge, ours is the first prospective study estimating the prevalence of RH in a population of critically ill children. Emergency admissions to a PICU are a highly relevant study population in that these cases are suffering from the pathologies considered as differential diagnoses for AHT. One of the key findings of our study is the level of complexity of the pathology present in cases in whom severe RHs are observed.

We report a 15.1% prevalence of the presence of any RH in critically ill children; however, severe bilateral multilayered RHs, similar to those reported as typical of abuse, are rare in this critically

TABLE 2 Details of Patients With RHs

	Age, mo	Gender	Admission Diagnosis	Coagulopathy	Seizures	QPR	Additional Details	Computed Tomography Head Scan	RHs	Papilledema
Mild RHs										
1	1.5	Girl	Respiratory failure	Yes	No	Yes	Pulmonary hypertension	None	Unilateral, single-layered	No
2	3	Boy	Sepsis	Yes	No	No	Severe combined immunodeficiency	Left subdural collection	Unilateral, single-layered	No
3	8	Girl	Respiratory failure	No	No	No	Bronchiolitis	None	Unilateral, single-layered	No
4	10	Girl	Respiratory failure	Yes	No	No	Pneumonia	None	Unilateral, single-layered	No
5	13	Boy	Sepsis	Yes	Yes	Yes	5 min in-hospital arrest, hemophagocytic lymphohistiocytosis, post bone marrow transplant	None	Unilateral, single-layered	No
6	55	Boy	Sepsis	Yes	No	Yes	4 min in-hospital arrest	Right cerebral infarction	Unilateral, single-layered	No
7	75	Girl	Nontraumatic encephalopathy	No	Yes	No	Cerebral aneurysm, intracranial hemorrhage, previous intraventricular hemorrhage	Subarachnoid hemorrhage	Unilateral, single-layered	No
8	125	Boy	Sepsis	Yes	No	No	None	None	Unilateral, single-layered	Left
9	36	Girl	Nontraumatic encephalopathy	No	No	No	None	Left transverse sinus thrombosis, bilateral temporoparietal hemorrhagic infarcts, left > right, midline shift	Unilateral, multilayered	No
10	141	Boy	Nontraumatic encephalopathy (picture 1)	No	Yes	No	Arterio-venous malformation	Extensive intraventricular and cerebellar bleed with acute hydrocephalus	Unilateral, multilayered	No
11	170	Girl	Traumatic brain injury (picture 2)	No	No	No	Hit by a car	Fracture basal skull and mastoid	Unilateral, multilayered	No
12	1.5	Girl	Sepsis	No	No	No	Severe combined immunodeficiency	None	Bilateral, single-layered	
13	3	Girl	Traumatic brain injury	Yes	No	No	Witnessed fall from steps from mom's arms	Right frontal, parietal fractures, subgaleal blood	Bilateral, single-layered	No
14	13	Girl	Traumatic brain injury	No	No	Yes	Hit by car—front seat passenger	Hypothalamic contusions, diffuse axonal injury, right frontal, temporal, zygoma, orbital fractures, subarachnoid blood	Bilateral, single-layered	No
15	54	Boy	Sepsis	Yes	No	No	Meningococcal disease	None	Bilateral, multilayered	No
16	100	Girl	Sepsis	No	No	No	Acute lymphoblastic leukemia, bone marrow transplant	None	Bilateral, multilayered	No
Moderate RHs										
17	36	Boy	Traumatic brain injury	No	No	No	Television fell on the head (child was shaking the television stand), witnessed	Left Subdural hemorrhage, Right occipital bleed, Fracture occipital bone	Bilateral, single-layered	No
18	161	Girl	Sepsis	No	No	No	Acute respiratory distress syndrome, multiorgan dysfunction syndrome	None	Bilateral, multilayered	Bilateral

TABLE 2 Continued

Age, mo	Gender	Admission Diagnosis	Coagulopathy	Seizures	CPR	Additional Details	Computed Tomography Head Scan	RHs	Papilledema
Severe RHs									
19	2	Girl	Traumatic brain injury	Yes	No	Witnessed fall from a low level hammock, late onset hemorrhagic disease of newborn	Right subdural hematoma	Unilateral, multilayered	No
20	6	Girl	Sepsis	Yes	No	Juvenile myelomonocytic leukemia	None	Bilateral, multilayered	No
21	14	Girl	Traumatic brain injury	No	Yes	Witnessed fall from stairs while being carried	Subarachnoid hemorrhage, small left subdural hemorrhage, edema, left uncal herniation, left posterior cerebral artery infarct, right middle cerebral artery infarcts	Bilateral, multilayered	No
22	24	Boy	Sepsis	Yes	No	Acute myeloid leukemia	None	Bilateral, multilayered	Bilateral retinal detachment
23	79	Boy	Sepsis	No	No	H1N1 infection, acute myeloid leukemia	None	Bilateral, multilayered	No
24	110	Boy	Traumatic brain injury (picture 3)	No	No	Pedestrian hit by car at 60 miles/h	Severe brain injury, mandibular and orbital fracture	Bilateral, multilayered	No

ill population (3.7%, 6/159). When severe multilayered RH did occur, it was exclusively in association with severe trauma, sepsis, coagulopathy, or any combination of these factors.

The authors of 2 recent reviews have described the association of severe bilateral extensive RH with AHT.^{4,5} There is a suggestion that the severity of RH is proportionate to the severity of the head injury^{4,27}; both children with traumatic brain injury in our study with severe multilayered RH died, possibly reflecting the severity of injury. The meta-analysis further quotes that the severity of RH is more important in predicting abuse than the mere presence of RH.⁴ It thus becomes important that all RH be fully described in the scientific literature with reporting of their extent and severity not just their presence.

Rigorous search for a coagulation abnormality is recommended to exclude coagulopathy as the cause of RH.¹⁵ Despite this, other than a handful of case reports and few small case series, there are no specific studies determining such an association.^{16,17,28–32} Leukemia is known to cause significant retinopathy in as many as two-thirds of the patients with myeloid leukemia³³; we saw severe RH in 3 patients with myeloid leukemia and severe sepsis. Other than the retinal lesions caused by leukemic infiltrates, the RHs in leukemia are thought to be associated with coagulation and platelet abnormalities.³⁴ Our study suggests an association between coagulopathy and the presence of RH; although the numbers involved in our study are small, it highlights the need for future studies looking closely at the association of coagulopathy and RH. We also found RH in 3 septic patients with a normal coagulation profile. It is difficult to comment whether this finding was related to a qualitative coagulation abnormality or an isolated effect of sepsis without a coagulation impact.

TABLE 3 Distribution of RHs by Putative Risk Factors

Risk Factor (<i>n</i>), Total, 159	Any RH (<i>n</i> = 24), <i>n</i> (%)	No RH (<i>n</i> = 135), <i>n</i> (%)	OR (95% CI) <i>P</i> (Fisher's Exact Test)	Severe RHs (<i>n</i> = 6), <i>n</i> (%)	No Severe RHs (<i>n</i> = 153), <i>n</i> (%)	OR (95% CI) <i>P</i> (Fisher's Exact Test)
Age, y						
≤2 (90)	12 (13.3)	78 (86.8)	0.73 (0.31–1.7)	4 (4.4)	86 (95.5)	1.6 (0.28–8.8)
>2 (69)	12 (17.4)	57 (82.6)	<i>P</i> = .51	2 (2.8)	67 (97.1)	<i>P</i> = .70
<1 (59)	11 (18.6)	48 (81.3)	1.5 (0.64–3.7)	2 (3.3)	57 (96.6)	0.75 (0.13–4.3)
>1 (100)	13 (13)	87 (87)	<i>P</i> = .34	4 (4)	96 (86)	<i>P</i> = .75
Gender						
Boy (87)	10 (11.4)	77 (88.5)	0.54 (0.22–1.3)	3 (3.4)	85 (97.7)	0.81 (0.16–4.1)
Girl (72)	14 (19.4)	58 (80.5)	<i>P</i> = .19	3 (4.1)	69 (95.8)	<i>P</i> = .8
CPR						
Performed (17)	4 (23.5)	13 (76.4)	1.9 (0.56–6.4)	0 (0)	17 (100)	0.60 (0.033–11.2)
Not performed (142)	20 (14)	122 (85.9)	<i>P</i> = .29	6 (4.2)	137 (96.4)	<i>P</i> = .74
Coagulopathy						
Present (42)	11 (26.2)	31 (73.8)	2.8 (1.2–7.0)	3 (7.1)	39 (92.8)	2.9 (0.57–15)
Absent (117)	13 (11.1)	104 (88.8)	<i>P</i> = .025	3 (2.5)	114 (97.4)	<i>P</i> = .34

ORs are presented for the presence of hemorrhages among those with the risk factor (<2 years, boy gender, CPR, and coagulopathy) to those without. In the face of the zero observations, ORs were estimated by adding 0.5 to each value. The percentages in parentheses have used the risk factors as the denominator.

TABLE 4 Distribution of RHs by Primary Reason for Admission

Risk Factor (<i>n</i>), Total, 159	Any RH (<i>n</i> = 24), <i>n</i> (%)	No RH (<i>n</i> = 135), <i>n</i> (%)	OR (95% CI) <i>P</i> (Fisher's Exact Test)	Severe RHs (<i>n</i> = 6), <i>n</i> (%)	No Severe RHs (<i>n</i> = 153), <i>n</i> (%)	OR (95% CI) <i>P</i> (Fisher's Exact Test)
Sepsis (39)	11 (28.2)	28 (71.7)	3.2 (1.3–8.0)	3 (7.6)	36 (92.3)	0.30 (0.059–1.59)
Other (120)	13 (10.8)	107 (89.1)	<i>P</i> = .018	3 (2.5)	117 (97.5)	<i>P</i> = .158
Respiratory failure (55)	3 (5.4)	52 (94.5)	0.23 (0.065–0.8)	0 (0)	55 (100)	0.14 (0–2.5)
Other (104)	21 (20.2)	83 (79.8)	<i>P</i> = .018	6 (5.7)	98 (94.2)	<i>P</i> = .09
Traumatic brain injury (29)	7 (24.1)	22 (75.8)	2.1 (0.78–5.7)	3 (10.3)	26 (89.6)	4.9 (0.93–26)
Other (130)	17 (13)	113 (86.9)	<i>P</i> = .15	3 (2.3)	127 (97.6)	<i>P</i> = .075
Nontraumatic encephalopathy						
Present (36)	3 (8.3)	33 (91.6)	0.44 (0.12–1.60)	0 (0)	36 (100)	0.25 (0.013–4.5)
Absent (123)	21 (17)	102 (82.9)	<i>P</i> = .29	6 (4.8)	117 (95.1)	<i>P</i> = .34

ORs are presented for the presence of hemorrhages among those with the risk factor (sepsis, etc) to those without. In the face of the zero observations, ORs were estimated by adding 0.5 to each value. The percentages in parentheses have used the risk factors as the denominator.

Lack of evidence of such an association calls for further studies looking at retinal changes in sepsis and extended coagulation profile tests within this setting.

Chest compressions are frequently discussed as a possible risk factor for RH.^{9–11} The reported incidence of RH in CPR varies from 2% (1/43) of in-hospital arrests to 41% (70/161) in a post-mortem study.^{9,10} In the first study, the only patient with RH post CPR had mild hemorrhages and associated coagulation abnormalities⁹; in the post-mortem study, all but 1 patient with RH post CPR had underlying diseases that could lead to RH.¹⁰ We observed no bilateral multilayered RH post CPR; indeed the only RH seen after CPR were in the context of trauma or coagulopathy.

Therefore, our study is consistent with the existing literature that CPR per se does not increase the prevalence of RH. Interestingly, we found a negative correlation of RH with respiratory failure due to primary respiratory system illnesses; suggesting that even severe respiratory illnesses requiring respiratory support does not result in RH. We could not find a similar population studied; however, this finding potentially reflects that primary respiratory illnesses in the absence of sepsis and coagulopathy do not cause RH. This compliments the available studies, which have not revealed any evidence to support respiratory illnesses as a cause for RH.^{7,35,36}

Our results substantiate the importance of defining the severity, distribution, and

extent of RH in any clinical setting. The overall prevalence of mild or moderate RH in critically ill children is 3 times that of the severe multilayered RH. The presence of severe multilayered RH in the absence of severe fatal trauma and/or severe coagulopathy warrants a thorough search for a cause including consideration of child abuse.

There are several limitations to our study. Ideally, we would present a control group of healthy children to provide a baseline incidence of RH. However, we suggest critically ill children are the appropriate study population because these are the cases in which serious inflicted head injury is a relevant differential diagnosis. We also could not recruit consecutive patients fulfilling the inclusion criteria due to consent

TABLE 5 Distribution of RHs by Diagnostic Category of Admission and Coagulopathy

Diagnostic Category	Median Age, mo	Coagulopathy (n = 42)			No Coagulopathy (n = 117)		
		No RH, n/N (%)	Any RH, n/N (%)	Severe RH, n/N (%)	No RH, n/N (%)	Any RH, n/N (%)	Severe RH, n/N (%)
Traumatic brain injury (n = 29)	36	0/2	2/2 (100)	1/2 (50)	22/27 (81.5)	5/27 (18.5)	2/27 (7.4)
95% CI of proportions	—	0–66	33–100	9–90	63–92	8–37	2–23
Sepsis (n = 39)	40.5	20/27 (74.7)	7/27 (25.9)	2/27 (7.4)	8/12 (66.6)	4/12 (33.3)	1/12 (8.3)
95% CI of proportions	—	55–87	13–45	2–23	39–86	14–61	15–35
Respiratory failure (n = 55)	11.5	6/8 (75)	2/8 (25)	0/8	46/47 (97.8)	1/47 (2.1)	0/47
95% CI of proportions	—	41–93	7–59	0–32	89–100	0–11	0–8
Nontraumatic encephalopathy (n = 36)	37.5	5/5 (100)	0/5	0/5	28/31 (90.3)	3/31 (9.7)	0/31
95% CI of proportions	—	57–100	0–43	0–43	5–97	3–25	3–25
CPR (n = 17)	13	5/8 (62.5)	3/8 (37.5)	0/8	8/9 (88.8)	1/9 (11.1)	0/9
95% CI of proportions	—	31–86	14–69	0–32	57–98	2–44	0–30

95% CIs for each proportion are given for each category.

refusal. The numbers involved in our study mean that we cannot preclude rare exceptions to the patterns we have observed; this has resulted in wide CIs when looking at the association of RH with individual risk factors and is a major limitation of our study. The fact that many of the patients involved had multiple coexisting risk factors makes it difficult to comment on the strength of association of individual risk factors with RH; however, this also is 1 of the strengths of our study highlighting the

pathologic complexity and presence of multiple risk factors required to cause RHs in a population of patients where AHT is a relevant differential diagnosis. This is an inherent shortcoming of studying rare events prospectively, involving consent in the complex environment of a PICU. Future studies with larger number of patients in individual diagnostic categories controlling as far as possible for relevant confounders are warranted to substantiate these results.

CONCLUSIONS

RHs in critically ill children have a prevalence of 15% (24/159); however, most are mild or moderate (18/24, 75%). Severe multilayered RHs are rare (6/24, 25%); their presence is associated with severe traumatic head injury, severe coagulopathy, severe sepsis, or a combination of these factors. Admission diagnosis is the only factor independently associated with presence of RH on multivariate analysis.

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