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ISSN: 2455-5479 DOI: https://dx.doi.org/10.17352/acmph

Research Article

Clinical features and outcomes of epidermolysis bullosa in thai children: A 20-Year review from a Tertiary Care Center

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Received: 04 October, 2022
Accepted: 04 November, 2022
Published: 05 November, 2022

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Keywords: Epidermolysis bullosa; Clinical features; Outcomes; Thai children

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Abstract

Background: Epidermolysis Bullosa (EB) is a heterogeneous genetic disorder with skin fragility. Only a few cases have been reported in Thailand. This study aims to determine the clinical characteristics, complications, and outcomes of EB stratified by subtype.

Methods: A retrospective single-center study of EB patients at the Dermatology Unit, Queen Sirikit National Institute of Child Health, was reviewed from January 1, 2002, to December 31, 2021. Diagnosis is based on clinical manifestations and some skin biopsies.

Results: There were 38 enrolled patients, age range from 0 to 25 years with a male-to-female ratio of 1.1:1. Family history of EB and consanguineous marriage were found in 6 cases and 2 cases, respectively. The most common type of EB was dystrophic EB (DEB) (26 cases) (68.4%), including recessive DEB in 15 cases (39.5%) and dominant DEB in 11 cases (28.9%). Other types were EB simplex in 10 cases (26.3%) and junctional EB in 2 cases (5.3%). Common complications were cutaneous bacterial infection (39.5%), anemia (31.6%), failure to thrive (18.4%), and protein energy malnutrition (15.8%). Musculoskeletal (21.1%), gastrointestinal (13.2%), and eye complications (7.9%) were exclusively found in DEB. Nineteen patients (50%) received regular follow-ups with a median duration of 9 months (range = 0.5 to 248 months). The mortality rate was 31.6% (6/19). Five cases died from bacterial sepsis, while one case died from metastatic squamous cell carcinoma.

Conclusion: DEB is the most common type of EB in Thai children, and bacterial sepsis is the predominant cause of death. Further multicenter and molecular genetic studies are recommended for a definite diagnosis.

Abbreviations

EB: Epidermolysis Bullosa; DEB: Dystrophic Epidermolysis Bullosa; EBS: Epidermolysis Bullosa Simplex; JEB: Junctional Epidermolysis Bullosa); KEB: Kindler Epidermolysis Bullosa; FTT: Failure to Thrive; SCC: Squamous Cell Carcinoma; DDEB: Dominant Dystrophic Epidermolysis Bullosa; RDEB: Recessive Dystrophic Epidermolysis Bullosa; AGA: Appropriate for Gestational Age; SGA: Small for Gestational Age; ASD: Atrial Septal Defect; VSD: Ventricular Septal Defect; GI: Gastrointestinal; NEBR: National Epidermolysis Bullosa Registry

Introduction

Epidermolysis bullosa (EB) is a prototype of genetic disorders with skin fragility [1-3] defined by skin blistering due to minimal mechanical trauma with disruption at the dermo-epidermal junctions, some of which are associated with significant morbidity and mortality. This disease occurs worldwide. It is estimated that the incidence varies in different countries between 1.4 – 41.3 per million live births [4-8]. According to the newest classification by consensus expert review in April 2019 [2], the four major classical EB types are EB simplex (EBS), skin cleavage within a basal layer of

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keratinocytes, junctional EB (JEB), skin cleavage through the lamina Lucida of the cutaneous basement membrane zone, dystrophic EB (DEB), skin cleavage at the sub-lamina data plane corresponding with the level of the anchoring fibrils and Kindler EB (KEB). EB is clinically and genetically heterogeneous, including a broad spectrum of severity with diversified subtypes. In severe cases, bullae and erosions can occur on any mucosal membrane and even be accompanied by extracutaneous involvement [1,2,9-12]. Complications and causes of death from EB, such as sepsis, pneumonia, respiratory failure, cardiomyopathy, undernutrition, failure to thrive (FTT), anemia, and squamous cell carcinoma (SCC) [1,9,13-19], have been elucidated extensively in the literature. Regardless, there are few case reports regarding the clinical features and outcomes of EB in Thailand [20-22].

The objectives of this study were to determine the clinical characteristics, complications, sequelae, and outcomes of EB patients in our hospital stratified by subtype.

Materials and methods

This retrospective study was conducted at the Dermatology Unit, Queen Sirikit National Institute of Child Health, the only Thai government hospital for children, in Bangkok, Thailand, over a 20-year period from January 1, 2002, to December 31, 2021. Eligibility for the inclusion of patients was based on the clinical features of blistering, peeling, erosions, or ulcerations from minimal mechanical trauma. All participants were systematically evaluated, diagnosed and, whenever possible, received skin biopsies to support the diagnosis and exclusion of another disease by the pediatric dermatologists at the institute. Classification of each type was primarily based on clinical signs and inheritance patterns, as described in Table 1.

Comprehensive data collection was identified from dermatology consultation notes, and inpatient and outpatient medical records. The demographic data, clinical features, extracutaneous manifestations, complications, sequelae, duration of follow-up, and outcomes were analyzed according

Table 1: Diagnostic criteria for classification of patients to each major type based on clinical signs [1,2,9].

Major type	Common subtype	Clinical signs					
		Onset	Blistering characteristics	Mucosa	Other cutaneous sign	Nail and hair	Complication and sequelae
EBS	Localized	Infancy to childhood or adolescence	Mainly confined to hands and feet (palms and soles), heal without scarring	Rare	Focal PPK (milder)	None	Improves with advancing age
	Intermediate	At birth to early infancy	Generalized	Mild	Focal PPK (mild to moderate)	Nail involvement (rare), hair is not affected	May be life-threatening in the neonatal period, but improved with advancing age
	Severe	At birth	Generalized and large blisters (newborn), and small, clustered, herpetiform blisters in later (infancy and childhood)	Oral, esophageal	Confluent PPK	Nail thickening and shedding (common), hair is not affected	
JEB	Severe	At birth (almost always)	Generalized blisters and large erosions	Oral, ocular, esophageal, GU, laryngeal and airway obstruction	Extensive perioral granulation tissue, atrophic scarring but no milia	Periungual erythema and granulation tissue, sloughing of the nails, anonychia Alopecia	Early death by 1-2 year of age FTT, anemia
	Intermediate	Similar to severe JEB, but less severe					
DEB	DDEB	At birth to early childhood	Limited blistering predominates on dorsum of hands, elbows, knees, and lower legs	Mild (20%)	Milia with scarring	Progressive nail thickening, dystrophy, or complete nail destruction (80%) Hair is not affected	Generally healthy FTT, PEM, anemia (less than RDEB)
	RDEB	At birth	Generalized, widespread	Mild to severe	Milia with scarring	Severe nails thickening, dystrophy, or destruction Alopecia	FTT, PEM, anemia, osteoporosis, pseudo-syndactyly, joint contracture, mitten deformity, cardiomyopathy, nephropathy, SCC
KEB		Neonate	Congenital acral blistering	Oral	Photosensitivity, generalized progressive poikiloderma, Scleroderma-like, webbing of the fingers and toes with digital tapering, PPK	Nail dystrophy	SCC, GI-GU problems; constipation; colitis; stenosis

EBS: Epidermolysis Bullosa Simplex; JEB: Junctional Epidermolysis Bullosa; DEB: Dystrophic Epidermolysis Bullosa; KEB; Kindler Epidermolysis Bullosa; DDEB: Dominant Dystrophic Epidermolysis Bullosa; RDEB: Recessive Dystrophic Epidermolysis Bullosa; PPK: Palmoplantar Keratoderma; FTT: Failure to Thrive; PEM: Protein-Energy Malnutrition; SCC: Squamous Cell Carcinoma; GI; Gastrointestinal; GU: Genitourinary

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to each subtype using the descriptive method with STATA statistical software (Version 14.0). This study was approved by the Research Ethic Review Committee of Queen Sirikit National Institute of Child Health (REC.058/2564).

Results

A total of 38 EB patients were enrolled, with an age range from 0 to 25 years. Skin biopsies were obtained from 14 patients (36.8%) to support the diagnosis of EB and rule out another vesiculobullous disease. The distribution of types of EB is summarized in Table 2. Based on typical clinical features, the most common type was DEB in 26 cases (68.4%) comprising dominant DEB (DDEB) (11/38, 28.9%) (Figure 1) and recessive DEB (RDEB) (15/38, 39.5%). Other major types were EBS in 10 cases (26.3%), localized EBS in 7 cases (7/38, 18.4%), intermediate EBS in 2 cases (2/38, 5.3%), and severe EBS (previously known as Dowling-Meara EBS) in 1 case (1/38, 2.6%). There were 2 cases of JEB (5.3%), 1 case of severe JEB (previously known as Herlitz JEB) (Figure 2), and 1 case of JEB with pyloric atresia. There was no Kindler EB. We also discovered EB with congenital absence of skin (Bart Syndrome) in 3 patients (Figure 3). All the Bart syndrome patients had typical cutaneous signs compatible with DEB. Table 3 shows the demographic data of all major EB categories. Twenty patients (52.6%) were male and 18 patients (47.4%) were female. The male-to-female ratio was 1.1:1. Family history of EB and consanguineous marriage were found in 6 cases (6/33, 18.2%) and 2 cases (2/32, 6.3%), respectively. Most of the patients had been born with no complications during labor. The deliveries were full-term (29/31, 93.5%) and appropriate for gestational age (AGA) (26/30, 86.7%). The geographical clustering of EB was crowded in Thailand's central (26/38, 68.4%) and northeastern regions (8/38, 21.1%).

Table 2: Types of epidermolysis bullosa.

Types of epidermolysis bullosa	Number (%) (*N* = 38)
Dystrophic epidermolysis bullosa (DEB)	26 (68.4)
Recessive DEB (RDEB)	15 (39.5)
Dominant DEB (DDEB)	11 (28.9)
Epidermolysis bullosa simplex (EBS)	10 (26.3)
EBS, localized	7 (18.4)
EBS, intermediate	2 (5.3)
EBS, severe	1 (2.6)
Junctional epidermolysis bullosa (JEB)	2 (5.3)
JEB, severe	1 (2.6)
Other JEB subtype: JEB with pyloric atresia	1 (2.6)

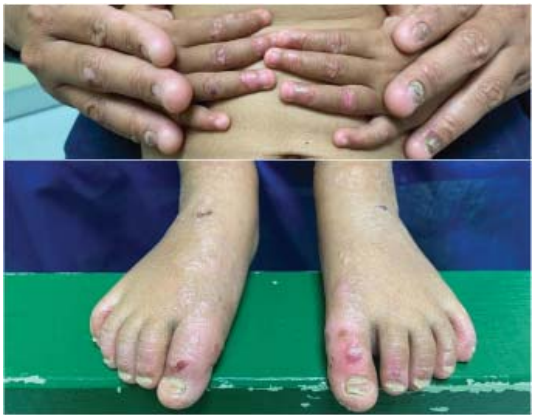

Figure 1: Dominant dystrophic epidermolysis bullosa. Blistering and scarring predominate on dorsum of hands, feet, and lower legs. Note the onychodystrophy on toenails as well as her mother's fingernails.

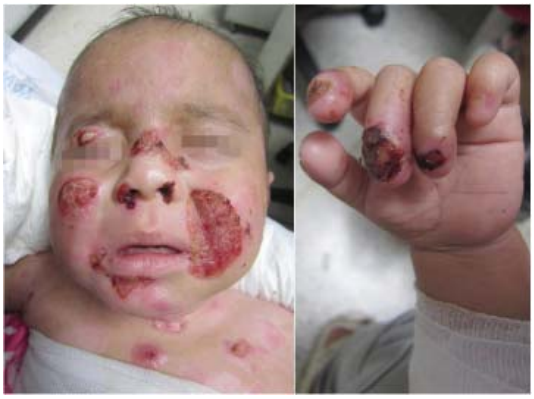

Figure 2: Junctional epidermolysis bullosa, severe (formerly Herlitz). Facial, perioral, perinasal blistering with formation of extensive granulation tissue is characteristic. Note that granulation tissue of his nailbeds and anonychia.

Figure 3: Epidermolysis bullosa with congenital absence of skin.

Table 3: Patient demographic data.

Demographic data	Type of Epidermolysis Bullosa, Number			
	Total	EBS	JEB	DEB
Sex				
Male	20	6	1	13
Female	18	4	1	13
Maturity				
Term	29	8	1	20
Preterm	2	0	1	1
Proportion				
AGA	26	7	2	17
SGA	4	1	0	3
Family history of EB	6	1	0	5
Consanguineous marriage	2	0	0	2

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Clinical manifestations of EB (Table 4)

Cutaneous signs were present at birth in about half of the patients (20/38, 52.6%), meanwhile, the onset of clinical signs appeared in neonates (34.2%), infants (10.5%), and children (2.6%). As recorded when the diagnosis of EB was established, the frequency of predominant cutaneous lesions over various body parts was found in the extremities (20/38, 52.6%); head and neck (5/38, 13.2%); trunk and buttocks (2/38, 5.3%); and general areas (11/38, 28.9%). Extensive granulation tissue was demonstrated in one JEB patient, while milia were found in 12 patients (12/38, 31.6%), all of whom were classified as DEB (12/26, 46.2%). Oral mucosal involvement was found in 12 cases (31.6%). In addition, laryngeal mucosal involvement causing upper airway obstructive symptoms were found in 2 cases with severe EBS and severe JEB. Enamel hypoplasia was found in 2 cases (5.3%). Nail changes were detected in half of the patients (19/38, 50%), predominantly in DEB (16/26, 61.5%), JEB (1/2, 50%), and EBS (2/10, 20%), respectively. Anonychia was the most common nail sign (23.7%), followed by onychodystrophy (18.4%), and hyperkeratotic nails (7.9%). Alopecia was absent in all patients. Four patients (1 JEB patient and 3 DEB patients) had congenital anomalies; pyloric atresia; pannus formation of both eyes; ASD, VSD; and unilateral renal agenesis.

Sequelae and complications of EB (Table 5)

According to the types of EB, punctum stricture, xerophthalmia, and limbal stem cell defects, ocular complications were reported in 3 DEB patients (3/26, 11.5%). A variety of gastrointestinal (GI) involvements such as stenosis, stricture, constipation, and dysphagia were notable in 5 cases of DEB (19.2%). Cardiomyopathy and chronic renal failure were found in 2 cases of RDEB. All musculoskeletal deformities such as pseudo-syndactyly, scarring contracture, and mitten deformity were found in DEB (19.2%, 7.7%, and 3.9%, respectively). All neurodevelopmental abnormalities such as delayed milestones and intellectual disability occurred in 3 DEB patients (2/26, 7.7%, and 1/26, 3.9%). Not uncommonly, cutaneous bacterial infection was a complication in all types of EB (40% in EBS, 50% in JEB, and 34.6% in DEB). Pneumonia occurred in 4 cases (10.5%), mainly in the DEB type. Nutritional complications revealed iron deficiency anemia in 12 cases (31.6%), FTT in 7 cases (18.4%), and protein energy malnutrition (PEM) in 6 cases (15.8%). A majority of malnutrition was categorized in DEB. Unfortunately, 1 RDEB patient developed biopsy-proven well-differentiated cutaneous SCC over a chronic unhealing wound on his left ankle when he was 18 years old (Figure 4). He underwent below-knee amputation and chemotherapy.

Table 4: Clinical manifestations of epidermolysis bullosa.

Clinical manifestations	Type of Epidermolysis Bullosa, Number (%)			
	Total (*N* = 38)	EBS (*N* = 10)	JEB (*N* = 2)	DEB (*N* = 26)
Age at onset of first clinical sign				
At birth	20 (52.6)	4 (40)	1 (50)	15 (57.7)
Neonate (< 1 month)	13 (34.2)	5 (50)	0	8 (30.8)
Infancy (1 - 12 month)	4 (10.5)	0	1 (50)	3 (11.5)
Childhood (> 12 month)	1 (2.6)	1 (10)	0	0
Predominant site of lesions				
Extremities	20 (52.6)	6 (60)	0	14 (53.8)
Generalized	11 (28.9)	1 (10)	1 (50)	10 (38.5)
Head and neck	5 (13.2)	2 (20)	1 (50)	1 (3.8)
Trunk and buttock	2 (5.3)	1 (10)	0	1 (3.8)
Granulation tissue	1 (2.6)	0	1 (50)	0
Milia	12 (31.6)	0	0	12 (46.2)
Congenital absence of skin	3 (7.9)	0	0	3 (11.5)
Oral cavity	14 (36.8)	2 (20)	2 (100)	10 (38.5)
Ulcer/erosion of oral mucosa	12 (31.6)	2 (20)	1 (50)	9 (34.6)
Enamel hypoplasia	2 (5.3)	0	1 (50)	1 (3.9)
Laryngeal mucosal involvement	2 (5.3)	1 (10)	1 (50)	0
Nail involvement	19 (50)	2 (20)	1 (50)	16 (61.5)
Hyperkeratosis	3 (7.9)	0	0	3 (11.5)
Onychodystrophy	7 (18.4)	1 (10)	0	5 (19.2)
Nail loss	9 (23.7)	1 (10)	1 (50)	8 (30.8)
Extracutaneous manifestation	4 (10.5)	0	1 (50)	3 (11.5)
Pyloric atresia	1 (2.6)	0	1 (50)	0
Pannus formation both eyes	1 (2.6)	0	0	1 (3.9)
ASD, VSD	1 (2.6)	0	0	1 (3.9)
Renal agenesis, unilateral	1 (2.6)	0	0	1 (3.9)

Table 5: Sequelae and complications of epidermolysis bullosa.

Sequelae and complications	Type of Epidermolysis Bullosa, Number (%)			
	Total (*N* = 38)	EBS (*N* = 10)	JEB (*N* = 2)	DEB (*N* = 26)
Eyes	3 (7.9)	0	0	3 (11.5)
Punctum stricture	1 (2.6)	0	0	1 (3.9)
Xerophthalmia	1 (2.6)	0	0	1 (3.9)
Limbal stem cell defect	1 (2.6)	0	0	1 (3.9)
Gastrointestinal tract	5 (13.2)	0	0	5 (19.2)
Stenosis	1 (2.6)	0	0	1 (3.9)
Stricture	1 (2.6)	0	0	1 (3.9)
Constipation	1 (2.6)	0	0	1 (3.9)
Dysphagia	2 (5.3)	0	0	2 (7.7)
Cardiomyopathy	1 (2.6)	0	0	1 (3.9)
Chronic renal failure	1 (2.6)	0	0	1 (3.9)
Musculoskeletal deformity	8 (21.1)	0	0	8 (30.8)
Pseudo-syndactyly	5 (13.2)	0	0	5 (19.2)
Scarring contracture	2 (5.3)	0	0	2 (7.7)
Mitten deformity	1 (2.6)	0	0	1 (3.9)
Neurodevelopment	3 (7.9)	0	0	3 (11.5)
Delayed milestones	2 (5.3)	0	0	2 (7.7)
Intellectual disability	1 (2.6)	0	0	1 (3.9)
Cutaneous bacterial infection	15 (39.5)	4 (40)	1 (50)	9 (34.6)
Pneumonia	4 (10.5)	0	1 (50)	3 (11.5)
Iron deficiency anemia	12 (31.6)	2 (20)	2 (100)	8 (30.8)
Nutrition	13 (34.2)	1 (10)	1 (50)	11 (42.3)
PEM	6 (15.8)	1 (10)	1 (50)	4 (15.4)
Failure to thrive	7 (18.4)	0	0	7 (26.9)
Squamous cell carcinoma	1 (2.6)	0	0	1 (3.9)

Outcome of EB

The median duration of follow-up was 9 months (ranging from 0.5 to 248 months). Nineteen patients (50%) received regular follow-ups at our institute. The mortality rate was 31.6%, as 6 of the 19 cases proved fatal during the investigation period. The fatality rate was highest in JEB (2/2, 100%), compared to RDEB (3/9, 33.3%), and EBS (1/4, 25%). Five cases (83.3%) comprising a single case of intermediate EBS, 2 JEB- and 2 of RDEB-patients died from uncontrolled blood culture-proven bacterial sepsis with disseminated intravascular coagulation, while one case (16.7%) diagnosed with RDEB

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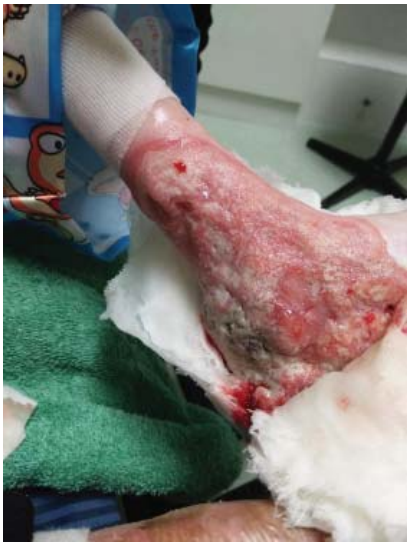

Figure 4: Biopsy-proven well-differentiated squamous cell carcinoma on left ankle in recessive dystrophic epidermolysis bullosa-patient.

was fatal due to metastatic SCC in the inguinal lymph nodes when he was 20 years old. Amongst the fatalities, the median life span was 6 months (ranging from 2 to 245 months). There were at least 13 survivors, which revealed good clinical recovery (61.5%; 8/13), stable clinical courses (30.8%; 4/13), and progressively deteriorated outcomes (7.7%; 1/13), who was diagnosed with RDEB and developed dilated cardiomyopathy.

Discussion

This first retrospective study of EB in Thailand over a 20-year period was designed to determine the epidemiology, clinical characteristics, spectrum of extracutaneous features, diversity of complications, and outcomes of this condition stratified by specific type. Based on our institute data, the most frequently diagnosed type was DEB (68.4%), which is consistent with most studies from tertiary care centers [14,17,23-25], where DEB was identified as the most frequently discovered type (59.8-77.2%). Notably, the proportion of EBS patients in this study (26.3%) was relatively lower, whereas the DEB percentage was relatively higher than the reports of the National Epidermolysis Bullosa Registry (NEBR) on information from the Netherlands, United States, Australia, New Zealand, England, and Wales [4,6-8]. According to research from the NEBR database [4,6-8], the outstanding type was EBS, which accounted for 45.7-53.7%. This was followed by DEB (34.7-35.2%). A comparison of the distribution of EB types in this work with previous studies conducted in other regions of the world during the last decade is summarized in Table 6; the chart also emphasizes differences in study periods, database sources, patient numbers, and additional diagnostic methods apart from clinical assessment. Several reasons could be explanations for these findings.

First, localized EBS is the most common clinical variant among EBS main subtypes. Although skin blistering develops in early infancy, it may not appear until early adulthood and is usually confined to the hands and feet. Lesions often heal without scarring and no obvious extracutaneous involvement [1,2], which might be misdiagnosed by a primary physician or pediatrician. Furthermore, the natural history of mild symptoms and tendency to blister gradually disappear in adolescence [1], which might be underestimated or neglectable in referring to tertiary care centers. Conversely, more DEB patients tend to be referred to tertiary hospitals than localized EBS patients due to greater severity with functional incapacity from extensive scarring [13,14,24]. We believe that the calculated EBS percentage will increase when the NEBR is fully set up in Thailand and truly reflects the nationwide statistics. Second, the diagnostic gaps of different EB types in low-outsource countries are problematic, which may affect the reliability of diagnosis. In the past, genetic testing or even immunofluorescence mapping was not feasible in all institutes. Nonetheless, modern methods for genetic testing in EB include next-generation sequencing and whole-exome sequencing, both of which are increasingly used in Thailand. Finally, global variations in populations, ethnicity, and inbreeding culture in some regions may affect the distribution of EB subtypes [26,27].

EB is also associated with many distinctive extracutaneous manifestations as well as various sequelae contributing to the disease burden. We found that clinical pictures such as external eyes (punctum stricture, limbal stem cell defect, xerophthalmia), dilated cardiomyopathy, gastrointestinal complications (dysphagia, constipation, structuring), chronic kidney disease, musculoskeletal deformities, iron deficiency anemia and failure to thrive appear in DEB, and RDEB specifically, more than other subtypes, which is consistent with a number of previous studies [2,9-14].

The fatality rate of EB from our institute was 31.6% and the highest in JEB (100%), comparable with a previous 11-year retrospective study from two centers in South Korea where Kim, et al. reported that five mortalities were caused by sepsis, failure to thrive, and severe metabolic acidosis with dehydration from a total of 30 patients; the highest mortality rate was noted in patients with JEB (up to 75%) [17]. As a matter of fact, bacterial sepsis is the most common cause of death during infancy in all subtypes of EB. Similarly, several studies supported sepsis as a major cause of early death in this work [11,15-17]. In addition, malabsorption with secondary failure to thrive, severe metabolic acidosis, tracheolaryngeal complications, or respiratory failure were other prominent causes of death [15-17].

Despite aggressive surgical resection in metastatic SCC, cardiomyopathy and chronic renal failure are the main causes of death in patients with RDEB who survive beyond childhood. The cumulative risks of SCC by age 20 start at 7.5%, then dramatically increase to 90.1% by age 55 with the median survival from the first diagnosis at only 2.4 years [18,19]. Our RDEB patient who developed metastatic SCC also had severe iron deficiency anemia, despite regular red-cell transfusions due to chronic blood loss from his wounds. Furthermore, he suffered from dysphagia because esophageal stricture led to insufficient intake of protein, energy, and nutrients. We highlight that comprehensive multidisciplinary care, despite no

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Table 6: Review of distribution of epidermolysis bullosa subtypes in selected studies during the last decade compared with present study.

Author and study period	This study 2003-2022	Kim [17] 2001-2011	Yu [23] 2021	Farokhforghani [24] 2017	Nanda [25] 2000-2017	Baardman [4] 1988-2018	Petrof [7] 2021	Fine [6] 1986-2002	Feinstein [14] 2011-2017	Kho [8] 2006-2008
Continent	Asia					Europe		North America		Australia
Country	Thailand	Korea	China (Chinese Han)	Iran	Kuwait	Netherlands	England & Wales	USA	USA & Canada	Australia & New Zealand
Database	Single center	Two centers	Single center	Burn research center	Single center	NEBR	NEBR	NEBR	EBCCOD from 17 EB centers	NEBR
Patient, N.	38	30	57	103	41	464	2,594	3,271	647	259
Distribution of EB type	1. DEB (68.4%) 2. EBS (26.3%) 3. JEB (5.3%)	1. DEB (70%) 2. EBS (17%) 3. JEB (13%)	1. DEB (77.2%) 2. EBS (21.1%) 3. JEB (1.8%)	1. DEB (75.7%) 2. JEB (12.6%) 3. EBS (8.7%) 4. KEB (2.9%)	1. EBS (46.3%) 2. DEB (41.5%) 3. JEB (12.2%)	1. EBS (45.7%) 2. DEB (34.7%) 3. JEB (18.8%) 4. KEB (0.9%)	1. EBS 17* 2. DEB 10.7* 3. JEB 1* 4. EB-NOS 0.6* 5. KEB 0.3*	1. EBS 1,711† 2. DEB 931† 3. EB-NOS 376† 4. JEB 139†	1. DEB (59.8%) 2. EBS (30%) 3. JEB (9.7%) 4. KEB (0.5%)	1. EBS (53.7%) 2. DEB (35.2%) 3. JEB (10.8%) 4. KEB (0.4%)
Additional diagnostic method apart from clinical assessment	Biopsy	IFM, TEM	Biopsy, Mutation analysis (WES, SS)	-	Biopsy, IFM, TEM, Mutation analysis (WES, SS)	IFM, TEM, Mutation analysis	IFM, Mutation analysis	IFM, EB-specific monoclonal antibody studies, TEM	IFM, TEM, Mutation analysis	IFM, TEM

NEBR: National Epidermolysis Bullosa Registry; EBCCOD: Epidermolysis Bullosa Clinical Characterization and Outcome Database; EBS: Epidermolysis Bullosa Simplex; JEB: Junctional Epidermolysis Bullosa; DEB: Dystrophic Epidermolysis Bullosa; KEB: Kindler Epidermolysis Bullosa; EB-NOS: Epidermolysis Bullosa-Not Otherwise Specified; IFM: Immunofluorescence Mapping; TEM: Transmission Electron Microscopy; WES: Whole Exome Sequencing; SS: Sanger Sequencing

* Point-prevalence per 1 million of the population in April 2021

† Prevalence from NEBR in January 2002

currently approved curative therapies, comprising protection from friction, avoidance of abrasion, control of secondary infection, pain and itch relief, nutritional supplementation, awareness of growth failure, long-term surveillance for SCC (starting in later adolescence), and psychosocial palliative will provide better outcomes for affected individuals and families, particularly in life-long, distressing RDEB.

This study had some limitations, including its single-center retrospective design. In Thailand, an official nationwide registry of EB has not yet been established. Consequently, we do not have data on all the known cases of EB in Thailand, and the findings may not reflect the overall data or be generalized to other healthcare settings. However, most EB in pediatric patients is diagnosed and treated at our center. It is important to note that nearly all patients were diagnosed and categorized by expert pediatric dermatologists into various types or subtypes of EB on the basis of clinical information, inheritance patterns, histopathology, and/or transmission electron microscopic study (in only one case), even though clinical identification of the major types of EB is unreliable exclusively in neonates [2,3]. Consequently, molecular genetic diagnosis should be encouraged to determine accurate subtypes, enable prompt genetic counseling, and improve prognostication [2,28].

Conclusion

DEB is the most common classical type of EB in Thai children. A wide range of extracutaneous manifestations and complications were seen in each subtype. Not uncommonly, bacterial sepsis was the predominant cause of death. Our report on this study of EB provides fundamental information that will contribute to use as a reference for clinical courses and prognosis in Thai patients with the eventual development of plans for future comprehensive management to improve quality of life and refine outcomes for patients with EB. Further multicenter and molecular genetic studies are recommended to confirm the findings of this study.

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Citation: Niltem E, Rujimethapass N, Sukhneewat C, Limpongsanurak W, Singalavanija S (2022) Clinical features and outcomes of epidermolysis bullosa in thai children: A 20-Year review from a Tertiary Care Center. Arch Community Med Public Health 8(4): 140-146. DOI: https://dx.doi.org/10.17352/2455-5479.000190

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Citation: Niltem E, Rujimethapass N, Sukhneewat C, Limpongsanurak W, Singalavanija S (2022) Clinical features and outcomes of epidermolysis bullosa in thai children: A 20-Year review from a Tertiary Care Center. Arch Community Med Public Health 8(4): 140-146. DOI: https://dx.doi.org/10.17352/2455-5479.000190