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Original article

Long-term epidemiological insights into rickets: a nationwide population-based retrospective study

Chun-Hao Chu, MD[1,2,3], Ying-Chuan Chen, PhD[4], Pei-Yao Liu, PhD[4], Chun-Chieh Hu, MD[1], Yu-Lung Lin, PhD[5,6], Feng-Chih Kuo, MD, PhD[7], Chieh-Hua Lu, MD[7], Tzu-Ju Hsu, MS[8], Yu-Tung Hung, MS[8,9], Fuu-Jen Tsai, MD, PhD[10,11,12,13], Chien-Ming Lin, MD, PhD[1]

[1]Department of Pediatrics, Tri-Service General Hospital, National Defense Medical University, Taipei, Taiwan; [2]Department of Pediatrics, Zuoying Armed Forces General Hospital, Kaohsiung, Taiwan; [3]Master of Public Health Program, College of Public Health, National Taiwan University, Taipei, Taiwan; [4]Department of Physiology & Biophysics, National Defense Medical University, Taipei, Taiwan; [5]The Ph.D. Program for Translational Medicine, College for Medical Science and Technology, Taipei Medical University, Taipei, Taiwan; [6]International Ph.D. Program for Translational Science, College of Medical Science and Technology, Taipei Medical University, Taipei, Taiwan; [7]Division of Endocrinology and Metabolism, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical University, Taipei, Taiwan; [8]Management Office for Health Data, Clinical Trial Research Center, China Medical University Hospital, Taichung, Taiwan; [9]College of Medicine, China Medical University, Taichung, Taiwan; [10]School of Chinese Medicine, College of Chinese Medicine, China Medical University, Taichung, Taiwan; [11]Department of Medical Research, China Medical University Hospital, Taichung, Taiwan; [12]Division of Medical Genetics, China Medical University Children's Hospital, Taichung, Taiwan; [13]Department of Biotechnology and Bioinformatics, Asia University, Taichung, Taiwan

Background: Rickets is a growth disorder that imposes a global health burden and causes disability in affected children. However, issues related to the clinical epidemiology and mortality risk of nutritional versus hereditary rickets have not been fully investigated in large population studies, particularly in Asia.

Purpose: This study aimed to investigate the nationwide incidence, demographic characteristics, and mortality-related risk factors of pediatric rickets stratified by nutritional and hereditary subtypes.

Methods: This study utilized data of subjects aged 0–18 years taken from Taiwan's National Health Insurance Research Database. The database includes records of 31,488,321 individuals from January 1, 2008, to December 31, 2018. We analyzed all cases and conducted subgroup analyses of nutritional and hereditary rickets to examine how different etiologies affect the risk of mortality (ROM).

Results: Among the 1,551 patients with rickets, nutritional rickets accounted for twice as many cases as hereditary rickets. Nutritional rickets primarily affects preschoolers without sex-based differences, whereas hereditary rickets is often diagnosed later with a male predominance. ROM in rickets is associated with a low household income, anemia, chronic kidney disease (CKD), hyperparathyroidism secondary to renal tubulopathy, and a prolonged length of hospital stay (LOS). Between 2012 and 2018, the overall incidence of rickets increased and the mortality rates decreased.

Conclusion: Increasing incidence and decreasing mortality rates of rickets were noted, suggesting improvements in clinical awareness and disease management. influencing ROM, such as family income, anemia, CKD, hyperparathyroidism secondary to renal tubulopathy, and LOS are important considerations in the clinical care of rickets.

Key words: Nutritional rickets, Hereditary rickets, Incidence, Mortality rate

Key message

Question: What are the nationwide trends and mortality risk factors of nutritional versus hereditary rickets among children in Asia?

Finding: In 2012–2018, the incidence of rickets steadily increased, whereas mortality rates declined. Mortality is associated with a low household income, anemia, chronic kidney disease, secondary hyperparathyroidism, and a prolonged hospital stay.

Meaning: Early diagnosis and targeted interventions addressing social and medical vulnerabilities are critical to reducing ricket-related mortality.

Introduction

Rickets is a metabolic bone disease of the growing skeleton characterized by impaired apoptosis of hypertrophic chondrocytes and mineralization of the growth plate. Additionally, these impairments occur due to disruptions in the metabolism of key nutrients, including calcium, phosphorus, and/or vitamin D.[1)] Rickets can be classified

Corresponding author: Chien-Ming Lin, MD, PhD. Department of Pediatrics, Tri-Service General Hospital, National Defense Medical Center, No. 325, Cheng-Kung Road, Section 2, Neihu District, Taipei, 11490, Taiwan
✉ Email: ming.sandra@msa.hinet.net, https://orcid.org/0000-0001-7525-5743
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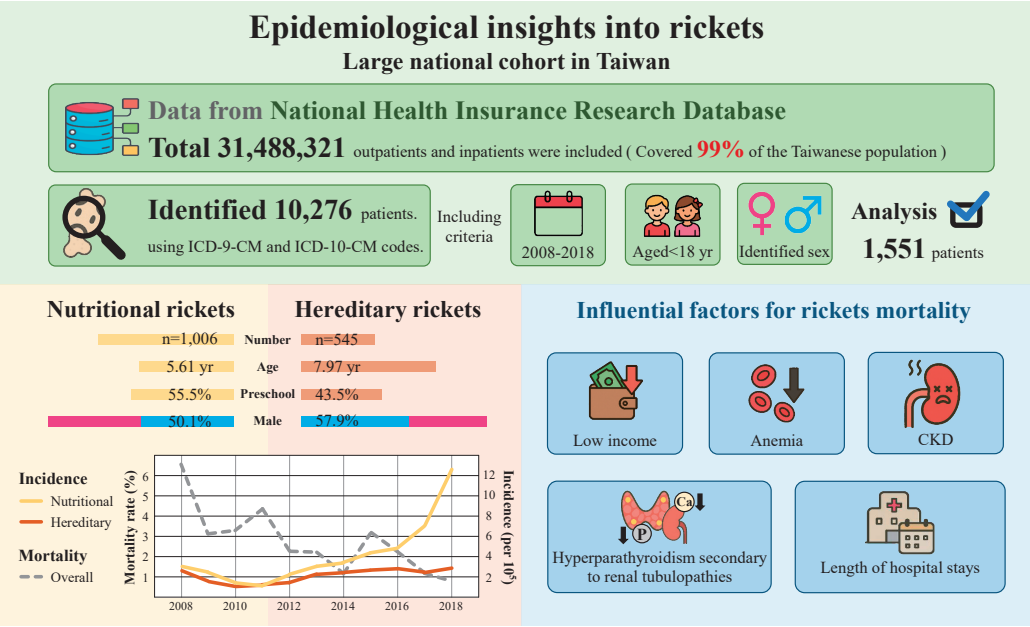

Graphical abstract

into 2 distinct categories: nutritional rickets and hereditary rickets.[2] Nutritional rickets typically results from deficiencies in vitamin D or calcium, while hereditary forms are associated with abnormalities of vitamin D metabolism.[3-5] Although nutritional rickets is more common than hereditary forms, the incidence and prevalence of rickets can vary across different study populations and time periods, also influenced by factors such as race, sunlight exposure, breastfeeding, socioeconomic factors, and geographical location.[6-8]

Despite increasing interest in the epidemiology of nutritional rickets in recent years, findings can be inconsistent due to differences in locations, cultures, or economic developments, with some cases not solely attributed to vitamin D deficiency.[9,10] Conversely, current studies focusing on the incidence and characteristics of hereditary rickets are limited. This study represents the first nationwide large-scale cohort investigation of rickets epidemiology in Taiwan, offering novel insights into the prevalence and characteristics of this condition. While the rarity and low incidence of hereditary rickets have limited its epidemiological research, our study concurrently examines the epidemiology of both nutritional and hereditary rickets to enhance our understanding of these distinct forms.

In this study, our objective was to comprehensively investigate the demographic characteristics, incidence, mortality rate, and potential factors associated with the ROM in the Chinese Han population affected by rickets. Furthermore, we aimed to enrich our understanding of rickets by comparing our findings with existing literature and data, thereby providing an up-to-date perspective on rickets epidemiology across diverse populations, regions, and cultures.[11] Understanding risk factors and gaining a thorough comprehension of rickets epidemiology are crucial for developing effective preventive strategies and targeted interventions to reduce the health burden of this disorder.

Methods

1. Source of data

Taiwan's National Health Insurance (NHI) is a nationwide medical financial support system commenced in 1995.[12] Over 99% of Taiwanese residents, approximately 23 million people, benefit from this system. The National Health Insurance Research Database (NHIRD) is derived from NHI and collects medical activities, including demographic data, disease diagnosis, prescriptions, surgeries, and expenses. This retrospective cohort study utilized outpatient and inpatient data obtained from the NHIRD. Participants were selected based on the codes from the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM).[13,14] The database review was conducted by the Management Office of Health Data at China Medical University Hospital's Clinical Trial Center. Rickets and associated variables were categorized based on clinical relevance and coded for statistical analysis using corresponding ICD codes. This classification was reviewed periodically by senior members of the research team for quality assurance.

2. Ethical considerations

The study was conducted anonymously to protect the privacy, rights, and interests of the participants. The NHIRD provided deidentified data, ensuring the concealment of identifiable personal information of the patients. As all identifying personal information was removed from the secondary files before analysis, patient consent was not required for accessing the NHIRD. However, some analyzed data were absent due to government regulations prohibiting transportation if the data variable unit is less than 3 units. This precaution aims to prevent the identification of extremely rare cases through alternative system analyses. All protocols were approved by the Institutional Review Board of the Research Ethics Committee of China Medical University Hospital (CMUH 110-REC3-133(CR-2)).

3. Study design and population

From January 1, 2008, to December 31, 2018, a total of 31,488,321 outpatients and inpatients were recorded in the NHIRD. Detailed information regarding the ICD-9-CM and ICD-10-CM codes used in the study is provided in Supplementary Table 1. Data from the "detailed documents of hospitalization medical expenses" and "registry for contracted medical facilities" were extracted from the NHIRD. The index date was defined as the date of the initial diagnosis of rickets for each patient. We identified a total of 10,276 patients with a diagnosis of nutritional rickets or hereditary rickets (nutritional rickets ICD-9: 268.0, 268.1, 268.9; ICD-10: E55.0, E55.9, E64.3; hereditary rickets ICD-9: 275.3; ICD-10: E83.30, E83.31, E83.32, E83.39). After excluding patients whose information was incompatible with rickets based on the timeframe before 2008 and after 2018 (n=1,795), those aged over 18 years (n=6,639), and those with unknown sex (n=291), we finally analyzed 1,551 participants with rickets (Supplementary Fig. 1). In the NHIRD, sex may be masked in specific cases (unknown sex) to comply with anonymization policies, particularly when subgroup sizes are small and pose potential re-identification risk.

4. Covariates

We examined the sociodemographic factors, including sex, age, monthly household income, season of disease onset, urbanization, and level of residence based on disease complexity. Patients were classified into subgroups according to these covariates: preschoolers (age 0–5), school-age children (age 6–10), and adolescents (age 11–18) by age; low income (New Taiwan dollar [NTD]<20,000), medium income (NTD 20,000–39,999), and high income (NTD≥40,000 by monthly household income; and urbanization levels ranging from 0 (low urbanization) to 3 (high urbanization).

5. Comorbidities

The baseline comorbidity history included prematurity, low birth weight, underweight, anemia, enthesopathy, osteoarthrosis, chronic kidney disease (CKD), hyperparathyroidism secondary to renal tubulopathies, and infectious lung diseases (Supplementary Table 1). These comorbidities were included as categorical variables in the models to investigate their impact on the mortality in patients with rickets.

6. Main outcome measures

We examined the overall incidence and mortality rate of rickets annually from 2008 to 2018. The distributions of sociodemographic factors, including age, season of disease diagnosis, and income levels, were analyzed. The annual incidence of rickets patients in the overall group and sex subgroups was investigated. Additionally, potential factors influencing the ROM were thoroughly evaluated among both survival and mortality groups. The length of hospital stay (LOS) among rickets patients was also examined to elucidate its correlation with the mortality rate.

7. Statistical analysis

For descriptive statistics, we used the chi-square test or Fisher exact test to analyze differences in categorical variables, and one-way analysis of variance for continuous variables. These tests were used to compare demographic characteristics and comorbidities between all participants and the mortality group, as shown in Table 1.

To identify independent factors associated with mortality, the Cox proportional hazards regression model was performed, incorporating relevant demographic and healthcare-related covariates described above (Table 2). Data are expressed as adjusted hazard ratios (HRs) with 95% confidence intervals (CI). All statistical analyses were performed using IBM SPSS Statistics ver. 22.0 (IBM Co., USA), with a 2-tailed P value<0.05 indicating statistical significance.

Results

1. Demographic characteristics and stratified analysis of rickets patients

Among the 1,551 index patients, male comprised 52.87% and females 47.13% (Table 1). The mean age was 6.44±6.09 years. Preschool-aged children represented the largest group (50.61%), followed by adolescents (34.04%) and school-aged children (15.34%). Most patients came from middle-income households (56.54%). While the occurrence of rickets did not vary significantly across seasons, and a high proportion of patients resided in areas characterized by higher levels of urbanization (level II: 32.17%,

Table 1. Demographic data and comorbidities of patients overall and by rickets group

Variable	Nutritional rickets		Hereditary rickets		Overall rickets	
	Value	*P* value	Value	*P* value	Value	*P* value
Demographic data (total population)						
Population/sex		0.67		0.96		0.49
Male	504 (50.10)		316 (57.98)		820 (52.87)	
Female	502 (49.90)		229 (42.02)		731 (47.13)	
Total	1006 (100)		545 (100)		1551 (100)	
Age (yr)	5.61±5.72	0.86	7.97±6.46	0.66	6.44±6.09	0.3
0–5	559 (55.57)		226 (41.47)		785 (50.61)	
6–10	156 (15.51)		82 (15.05)		238 (15.34)	
11–18	291 (28.93)		237 (43.49)		528 (34.04)	
Income level (USD)		**<0.001**		**<0.001**		**<0.001**
<20,000	138 (13.72)		109 (20.00)		247 (15.93)	
20,000–39,999	571 (56.76)		306 (56.15)		877 (56.54)	
≥40,000	297 (29.52)		130 (23.85)		427 (27.53)	
Season		0.4		0.27		0.16
Spring	233 (23.16)		123 (22.57)		356 (22.95)	
Summer	264 (26.24)		152 (27.89)		416 (26.82)	
Autumn	259 (25.75)		143 (26.24)		402 (25.92)	
Winter	250 (24.85)		127 (23.30)		377 (24.31)	
Urbanization level		0.93		0.77		0.7
0 (lowest)	137 (13.62)		44 (8.92)		185 (11.93)	
1	62 (6.16)		35 (7.10)		102 (6.58)	
2	303 (30.12)		180 (36.51)		499 (32.17)	
3	504 (50.10)		234 (47.46)		765 (49.32)	
Comorbidities (total population)						
Prematurity		0.64		0.37		0.61
No	831 (82.60)		500 (91.74)		1,331 (85.82)	
Yes	175 (17.40)		45 (8.26)		220 (14.18)	
Underweight		0.41		0.51		0.19
No	976 (97.02)		541 (99.27)		1,517 (97.81)	
Yes	30 (2.98)		4 (0.73)		34 (2.19)	
Anemia		**<0.001**		**<0.001**		**<0.001**
No	946 (94.04)		415 (84.18)		1,391 (89.68)	
Yes	60 (5.96)		78 (15.82)		160 (10.35)	
Enthesopathy		0.8		0.57		0.58
No	1003 (99.70)		542 (99.45)		1,545 (99.61)	
Yes	3 (0.3)		3 (0.55)		6 (0.39)	
Osteoarthrosis		0.65		0.3		0.33
No	997 (99.11)		535 (98.17)		1,532 (98.77)	
Yes	9 (0.89)		10 (1.83)		19 (1.23)	
Chronic kidney disease		0.74		0.17		**0.002**
No	1001 (99.50)		499 (91.56)		1,500 (96.77)	
Yes	5 (0.5)		46 (8.44)		51 (3.29)	
Hyperparathyroidism secondary to renal tubulopathies		0.09		**0.01**		**<0.001**
No	996 (99.01)		522 (95.78)		1,518 (97.87)	
Yes	10 (0.99)		23 (4.22)		33 (2.13)	
Infectious lung diseases		0.89		0.05		0.19
No	811 (80.62)		452 (82.94)		1,263 (81.43)	
Yes	195 (19.38)		93 (17.06)		288 (18.57)	
Length of days	3.51±15.89	**<0.001**	11.77±19.60	**<0.001**	6.41±17.72	**<0.001**
≤7	890 (88.47)		374 (68.62)		1,081 (69.7)	
>7	116 (11.53)		171 (31.38)		470 (30.3)	

(Contiuned)

Table 1. Demographic data and comorbidities of patients overall and by rickets group (continued)

Variable	Nutritional rickets		Hereditary rickets		Overall rickets	
	Value	*P* value	Value	*P* value	Value	*P* value
Demographic data (mortality)						
Population/sex		0.67		0.96		0.49
Male	12 (54.55)		30 (57.69)		42 (56.76)	
Female	10 (45.45)		22 (42.31)		32 (43.24)	
Total	22 (100)		52 (100)		74 (100)	
Age (yr)	6.68±6.81	0.86	8.35±6.28	0.66	7.85±6.44	0.3
0–5	11 (50.00)		20 (38.46)		31 (41.89)	
6–10	4 (18.18)		9 (17.31)		13 (17.57)	
11–18	7 (31.82)		23 (44.23)		30 (40.54)	
Income level (USD)		**<0.001**		**<0.001**		**<0.001**
<20,000	10 (45.45)		24 (46.15)		34 (45.95)	
20,000–39,999	9 (40.91)		16 (30.77)		25 (33.78)	
≥40,000	3 (13.64)		12 (23.08)		15 (20.27)	
Season		0.4		0.27		0.16
Spring	8 (36.36)		12 (23.08)		20 (27.03)	
Summer	6 (27.27)		15 (28.85)		21 (28.38)	
Autumn	5 (22.73)		18 (34.62)		23 (31.08)	
Winter	3 (13.64)		7 (13.46)		10 (13.51)	
Urbanization level		0.93		0.77		0.7
0 (lowest)	5 (22.73)		4 (7.69)			
1	5 (9.62)		7 (9.46)			
2	7 (31.82)		16 (30.77)		23 (31.08)	
3	10 (45.45)		27 (51.92)		37 (50)	
Comorbidities (mortality)						
Prematurity		0.64		0.37		0.61
No	19 (86.36)		46 (88.46)		65 (87.84)	
Yes	3 (13.64)		6 (11.54)		9 (12.16)	
Underweight		0.41		0.51		0.19
No	22 (100)		52 (100)		74 (100)	
Yes	0 (0)		0 (0)		0 (0)	
Anemia		**<0.001**		**<0.001**		**<0.001**
No	16 (72.73)		30 (57.69)		46 (62.16)	
Yes	6 (27.27)		22 (42.31)		28 (37.84)	
Enthesopathy		0.8		0.57		0.58
No	22 (100)		52 (100)		74 (100)	
Yes	0 (0)		0 (0)		0 (0)	
Osteoarthrosis		0.65		0.3		0.33
No	22 (100)		52 (100)		74 (100)	
Yes	0 (0)		0 (0)		0 (0)	
Chronic kidney disease		0.74		0.17		**0.002**
No	22 (100)		45 (86.54)		67 (90.54)	
Yes	0 (0)		7 (13.46)		7 (9.46)	
Hyperparathyroidism secondary to renal tubulopathies		0.09		**0.01**		**<0.001**
No	21 (95.45)		46 (88.46)		67 (90.54)	
Yes	1 (4.55)		6 (11.54)		7 (9.46)	
Infectious lung diseases		0.89		0.05		0.19
No	18 (81.82)		38 (73.08)		56 (75.68)	
Yes	4 (18.18)		14 (26.92)		18 (24.32)	
Length of days	32.32±79.90	**<0.001**	26.40±33.79	**<0.001**	28.16±51.40	**<0.001**
≤7	8 (36.36)		20 (38.46)		17 (22.97)	
>7	14 (63.64)		32 (61.54)		57 (77.03)	

Values are presented as number (%) or mean±standard deviation.
USD, United States dollars.
Boldface indicates a statistically significant difference with $P<0.05$.

Table 2. Hazard ratio of factors influencing mortality among index patients

Characteristic	Mortality			Adjusted HR[a)]	95% CI	*P* value
	No.	PY	MR (‰)			
Rickets						
Sex						
Female	32	3674.97	8.71	1.00	Reference	-
Male	42	4146.34	10.13	1.58	0.97–2.57	0.064
Age (yr)						
0–5	31	3921.98	7.90	1.00	Reference	-
6–10	13	1125.53	11.55	1.21	0.60–2.42	0.599
11–18	30	2773.80	10.82	0.67	0.37–1.20	0.178
Income level						
<20,000	37	1331.56	27.79	1.00	Reference	-
20,000–39,999	22	4429.27	4.97	0.13	0.07–0.24	**<0.001**
≥40,000	15	2060.48	7.28	0.27	0.15–0.51	**<0.001**
Season						
Spring	20	1867.64	10.71	1.00	Reference	-
Summer	21	2047.01	10.26	0.96	0.52–1.77	0.887
Autum	23	1704.25	13.50	1.07	0.58–2.00	0.822
Winter	10	2202.42	4.54	0.55	0.26–1.19	0.131
Urbanization level						
0 (lowest), 1	7	616.94	11.35	1.00	Reference	-
2	23	2687.99	8.56	1.16	0.49–2.76	0.739
3	44	4516.38	9.74	1.54	0.68–3.48	0.302
Length of days						
≤3	25	6181.45	4.04	1.00	Reference	-
>3	49	1639.86	29.88	4.82	2.90–8.02	**<0.001**
Nutritional rickets						
Sex						
Female	10	2266.63	4.41	1.00	Reference	-
Male	12	2253.02	5.33	1.02	0.38–2.75	0.976
Age (yr)						
0–5	11	2536.03	4.34	1.00	Reference	-
6–10	4	627.44	6.38	1.49	0.36–6.11	0.582
11–18	7	1356.18	5.16	0.83	0.25–2.68	0.749
Income level						
<20,000	11	744.23	14.78	1.00	Reference	-
20,000–39,999	7	2635.73	2.66	0.12	0.04–0.34	<0.001
≥40,000	4	1139.69	3.51	0.15	0.04–0.53	0.003
Season						
Spring	8	1146.59	6.98	1.00	Reference	-
Summer	6	1120.99	5.35	1.24	0.39–3.92	0.709
Autum	5	960.94	5.20	0.74	0.21–2.61	0.639
Winter	3	1291.13	2.32	0.47	0.12–1.89	0.286
Urbanization level						
0 (lowest), 1	2	360.62	5.55	1.00	Reference	-
2	8	1488.41	5.37	2.01	0.34–11.84	0.438
3	12	2670.63	4.49	2.97	0.48–18.48	0.244
Length of days						
≤3	9	4100.05	2.20	1.00	Reference	-
>3	13	419.61	30.98	13.50	4.95–37.05	<0.001
Heredity rickets						
Sex						
Female	21	1408.33	14.91	1	Reference	-
Male	31	1893.32	16.37	1.63	0.90–2.92	0.104
Age (yr)						
0–5	20	1385.95	14.43	1	Reference	-
6–10	10	498.09	20.08	1.16	0.51–2.64	0.729
11–18	22	1417.62	15.52	0.59	0.30–1.16	0.127
Income level						
<20,000	26	587.33	44.27	1	Reference	-
20,000–39,999	15	1793.54	8.36	0.14	0.07–0.29	**<0.001**
≥40,000	11	920.79	11.95	0.34	0.16–0.72	**0.005**
Season						
Spring	13	721.05	18.03	1	Reference	-
Summer	15	926.01	16.20	0.9	0.42–1.92	0.781
Autum	17	743.31	22.87	1.22	0.57–2.59	0.612
Winter	7	911.29	7.68	0.61	0.24–1.55	0.297
Urbanization level						
0 (lowest), 1	5	256.32	19.51	1	Reference	-
2	16	1199.59	13.34	1.07	0.38–3.03	0.896
3	31	1845.75	16.80	1.49	0.56–3.93	0.422
Length of days						
≤3	16	2081.40	7.69	1	Reference	-
>3	36	1220.25	29.50	3.03	1.65–5.54	**<0.001**

PY, person-years; MR, mortality rate; HR, hazard ratios; CI, confidence interval.
[a)]Adjusted HR estimated by the model including the variables of sex, age, income level, season, urbanization level, and hospital length of stay in days.
Boldface indicates a statistically significant difference with $P<0.05$.

level III: 49.32%).

A stratified analysis of all participants into nutritional rickets and hereditary rickets categories revealed twice as many cases in nutritional rickets compared to hereditary rickets (1,006 cases vs. 545 cases). Nutritional rickets showed an equal sex distribution, whereas hereditary rickets had a male-female ratio of 3:2. The mean age was younger in nutritional rickets (5.61±5.72 years vs. 7.97±6.46 years). Preschoolers predominated in nutritional rickets (55.57%), while adolescents were more prevalent in hereditary rickets (43.49%), suggesting a potential delay in diagnosing hereditary rickets. Family income, seasonal onset, and urbanization level were comparable across both categories.

2. Demographic characteristics and comorbidities among mortality group

We further analyzed the demographic characteristics and associated comorbidities among the mortality group. Male rickets patients (56.76%) and preschoolers (41.89%) exhibited a high tendency toward mortality (Table 1). A low family income level (<20,000 USD: 45.95%) was also noted among the mortalities. Additionally, the mortality

group had a higher proportion of patients with anemia (mortalities: 37.84% vs. total population: 10.35%), CKD (mortalities: 9.46% vs. total population: 3.29%), and hyperparathyroidism secondary to renal tubulopathies (mortalities: 9.46% vs. total population: 2.13%). Notably, the mortality group had a significantly longer LOS >7 days (77.03%, $P<0.001$), with a mean LOS of 28.16±51.4 days. Similar findings were observed when conducting a stratified analysis based on nutritional or hereditary rickets.

3. Risk of mortality in rickets patients stratified by covariates

The Cox proportional hazards regression model was employed to identify influential factors for rickets mortality (Table 2). After adjusting for variables, sex, age, season of diagnosis, and urbanization level did not significantly affect the ROM. However, patients with medium and high incomes had a significantly decreased ROM compared to those with low incomes (0.13-fold, $P<0.001$; 0.27-fold, $P<0.001$). Using the receiver operating characteristic (ROC) curve, we identified the optimal cutoff value of LOS for predicting mortality as 3 days for overall rickets (Supplementary Table 2). Furthermore, patients with a longer LOS (>3 days) had a 4.82-fold increased ROM compared to those without ($P<0.001$). Similar findings were observed in a stratified analysis of nutritional or hereditary rickets (Table 2).

4. Trend of the incidence rate in index patients

Supplementary Table 3 displays the trend of rickets occurrence among patients during the follow-up period. Overall, the incidence showed a mild decrease from 2008 (2.66 per 105 population) to 2011 (1.41 per 105 population), followed by an inflection point in 2012 (1.83 per 105 population), and an increasing trend thereafter (Fig. 1A). Additionally, the annual incidence in both sexes was similar to that of the overall population. The annual percentage change (APC) was significantly noted in total population (13.56, $P=0.002$) and both sexes (males=13.09, $P=0.004$; females=14.55, $P=0.002$). Regarding subgroups analysis, we found that the trend of the incidence rate in nutritional rickets (APC=17.9, $P=0.001$) aligned with that of overall rickets, while hereditary rickets exhibited a steady low incidence (APC=5.73, $P=0.028$) (Fig. 1B and C).

5. Trends of the mortality rate in index patients

The highest mortality rate among index patients occurred in 2008 (males, 17.65%; females, 8.11%) (Fig. 2A). Overall, there was a significant decreasing trend in mortality rates for rickets (-13.48, $P=0.002$), though there was a slight increase in males and a slight decrease in females (males=-3.50, $P=0.942$; females=-48.18, $P=0.353$) (Fig. 2A). A slight decrease in mortality rates was observed among the total population with nutritional rickets (APC=-46.20, $P=0.307$) (Fig. 2B). Similarly, there was also a slight decline among the total population with hereditary rickets (APC=-4.86, $P=0.293$), although its trend pattern appears to be influenced by the results for males (Fig. 2C). The detailed case numbers of annual mortality in index cases from 2008 to 2018 was shown in Supplementary Table 4.

6. LOS in rickets patients and determination of cutoff value

LOS was assessed to evaluate rickets severity and its correlation with mortality. Patients with hereditary rickets had significantly longer mean LOS compared to those with

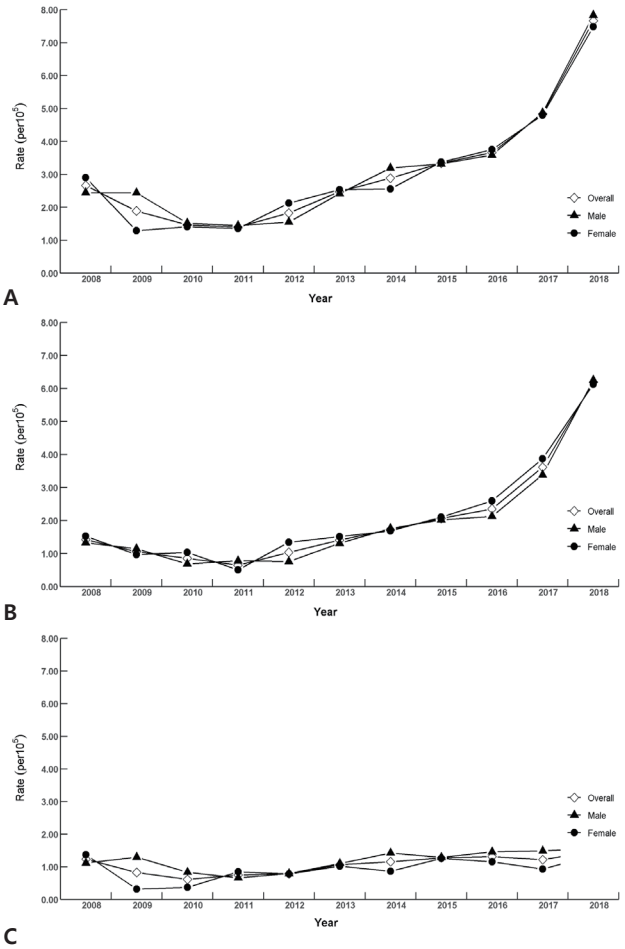

Fig. 1. Annual incidence rate among index patients. (A) Overall rickets. The total population increased significantly (annual percentage change [APC]=13.56; $P=0.002$). The male prevalence increased significantly (APC=13.09, $P=0.004$). The female prevalence increased significantly (APC=14.55, $P=0.002$). (B) Nutritional rickets. The total population increased significantly (APC=17.90, $P=0.001$). The male prevalence increased significantly (APC=18.01, $P=0.002$). The female prevalence increased significantly (APC=18.12, $P=0.002$). (C) Hereditary rickets. The total population increased significantly (APC=5.73, $P=0.028$). The male prevalence increased significantly (APC=5.48, $P=0.045$). The female prevalence increased slightly (APC=8.01, $P=0.097$).

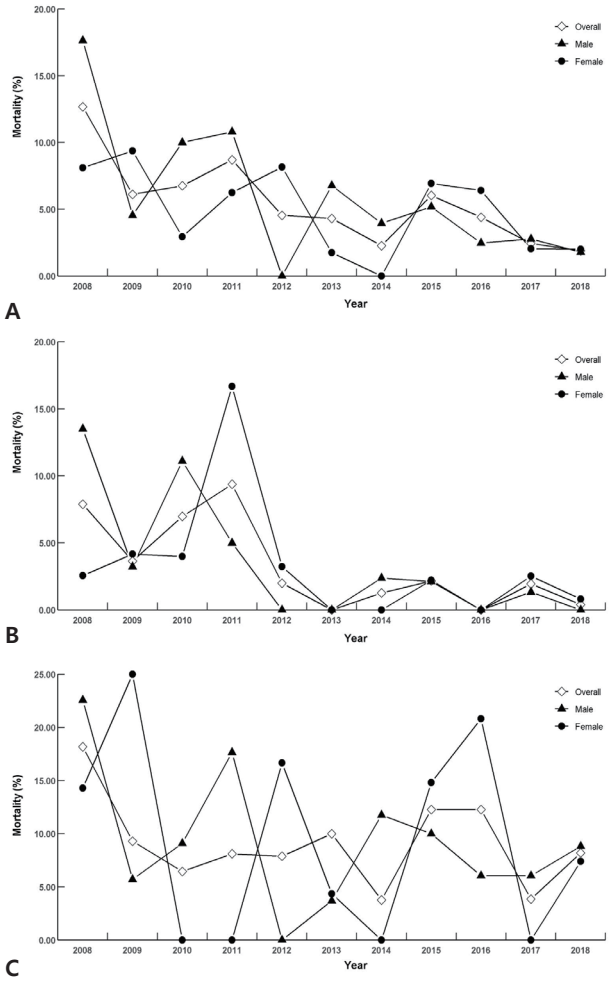

Fig. 2. Trend of proportional mortality among the index patients. (A) Overall rickets. The total population decreased significantly (annual percentage change [APC]=-13.48, *P*=0.002). The male prevalence increased slightly (APC=-3.50, *P*=0.942). The female prevalence decreased slightly (APC=-21.37, *P*=0.615). (B) Nutritional rickets. The total population decreased slightly (APC=-46.20, *P*=0.307). The male prevalence decreased slightly (APC=-66.82, *P*=0.140). The female prevalence decreased slightly (APC=-48.18, *P*=0.353). (C) Hereditary rickets. The total population decreased slightly (APC=-4.86, *P*=0.293). The male prevalence increased slightly (APC=8.99, *P*=0.864). The female prevalence decreased slightly (APC=-3.98, *P*=0.962).

nutritional rickets (11.77"±" 19.6 vs. 3.51"±" 15.89, *P*<0.001) (Table 1). The mortality group showed a higher mean LOS compared to the overall group (28.16±51.4 vs. 6.41±17.72, *P*<0.001). Notably, mortality cases in nutritional rickets had a significant longer mean LOS than those in hereditary rickets (32.32±79.9 vs. 26.4±33.79, *P*<0.001). The area under the ROC curves was 0.8085 for the overall group (95% CI, 0.760–0.857; *P*<0.001), 0.7414 for the nutritional groups (95% CI, 0.661–0.888; *P*<0.001), and 0.720 for the hereditary group (95% CI, 0.653–0.787; *P*<0.001) (Fig. 3).

Discussion

1. Summary of important results from the study

To our knowledge, there have been limited epidemiological studies on rickets, primarily focusing on the Caucasian population.[15,16] Our large-scale nationwide retrospective study aims to fill this gap by investigating the Asian population affected by nutritional or hereditary rickets and providing comprehensive epidemiological data, including factors influencing ROM and annual incidence.[6,8,9,17-21] In Taiwan, a developed country, the incidence of rickets increased from 2012 to 2018, potentially due to improved diagnostic capabilities rather than solely nutritional deficits. Overall, rickets slightly predominates in males and manifests during preschool or adolescence. ROM is linked to low income, anemia, CKD, hyperparathyroidism secondary to renal tubulopathies, and extended LOS. Early recognition and management of these factors are essential to avoid severe outcomes.

2. Comparison of studies on rickets epidemiology

The comparison of significant findings between the current study and previous studies is summarized in Table 3. Wheeler et al.[8] conducted a prospective cohort study to elucidate the temporal relationship between

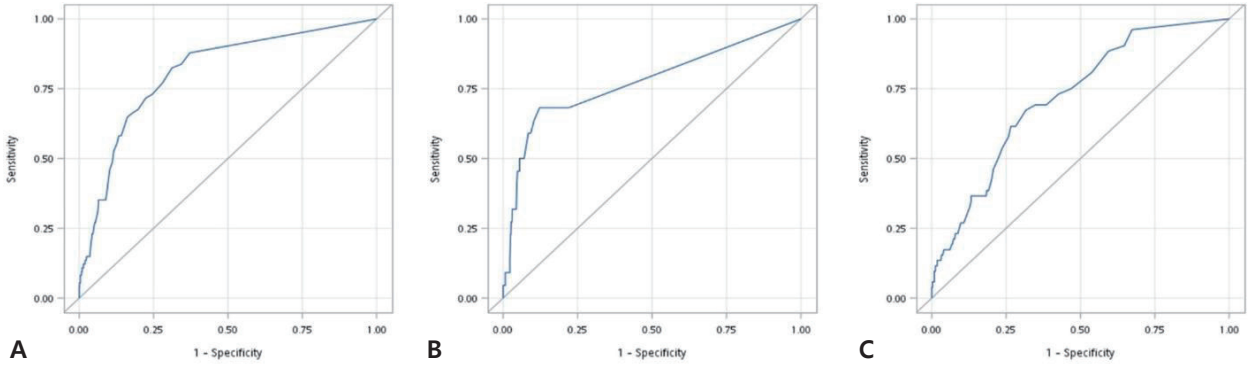

Fig. 3. Optimal cutoff value (CoV) of hospital length of stay (LOS) to predict mortality using receiver operating characteristic (ROC) curves. (A) Overall rickets. Area under the curve (AUC)=0.809, 95% confidence interval (CI)=0.760–0.857, *P*<0.001. Optimal CoV of LOS: 3 days. (B) Nutritional rickets. AUC=0.741; 95% CI, 0.661–0.888; *P*<0.001. Optimal CoV of LOS: 6 days. (C) Hereditary rickets. AUC=0.720, 95% CI, 0.653–0.787; *P*<0.001. Optimal CoV of LOS: 9 days.

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Table 3. Summary of studies of rickets epidemiology

Study	Design	Aim	Methods	Results	Strengths	Limitations
Current study	Nationwide retrospective cohort study	Epidemiological characteristics of nutritional and hereditary rickets. Also, analyze the ROM among rickets patients.	Statistical analysis based on the NHIRD in Taiwan from 2008 to 2018.	Late diagnosis and male predominance in hereditary rickets. ROM in rickets is associated with low socioeconomic status, anemia, CKD, hyperparathyroidism, and LOS. Increasing incidence and decreasing mortality rate during the study period.	Large pediatric subjects (n=1,551) enrolled from a nationwide database. Compare both nutritional and hereditary rickets in the same time. Focus on the Chinese Han population which was less be addressed.	Lacking of anthropometric data, biochemistry and endocrine parameters, and bone x-ray in the NHIRD.
Thacher et al.,[6] 2013	Retrospective cohort study (community-based population)	Temporal trends in incidence and risk factors of nutritional rickets	Research based on data from the Rochester Epidemiology Project cohort from 1970 to 2009.	Most of the cases aged <3 yr. Nutritional rickets is associated with black race, breast feeding, low birth weight, and stunted growth. The incidence has dramatically increased since 2000.	Long follow-up period of 40 yr. This study contains image evidence.	Exclusively focuses on nutritional rickets. A mixed-ethnicity study conducted in a well-developed county, which may lead to limited generalizability.
Wheeler et al.,[8] 2015	Prospective cohort study	Incidence and characteristics of vitamin D deficiency rickets	The New Zealand Pediatric Surveillance Unit conducted prospective surveillance among pediatricians for 36 months to monitor cases of vitamin D deficiency rickets.	Identified risk factors were darker skin pigmentation, Indian and African ethnicity, age <3 yr, exclusive breast feeding, and residing in southern latitudes. Incidence was higher in children <3 yr than those <15 yr.	A prospective study could decrease the information bias and recall bias.	Only focuses on nutritional rickets and small sample size (n=58).
Al-Atawi et al,[9] 2009	Retrospective cohort study (single medical center)	Clinical presentations and risk factors of nutritional rickets in Saudi infants.	Analyzing data of infants <14 mo who were diagnosed as nutritional rickets during a 10-yr period.	70% were exclusively breast-fed, and 23% were breast-fed until the age of 1 yr. The most frequent clinical presentation was hypocalcemic convulsions (34%) followed by chest infections (33%) and gastroenteritis (25%).	Included the biochemical analyses and image findings.	Only focuses on nutritional rickets and infants groups.
Hawley et al.,[17] 2020	Retrospective cohort study	Prevalence of XLH across the life course and overall survival among individuals with XLH.	A population-based cohort study using a large primary care database in UK from 1995 to 2016.	An increasing prevalence was noted during the study period.	Using a national database (represented 7% of the UK population). The first study focusing XLH prevalence and prognosis in adulthood.	Possible miscoding of the disease existed. Lack of genetic and image data. Only focuses on XLH.
Emma et al.,[18] 2019	Retrospective cohort study	An experts' opinion survey was conducted across Italian centers to gather data on XLH.	A questionnaire was developed to collect data from 10 centers on 175 patients diagnosed with XLH between 1998 and 2017.	The majority of patients were diagnosed between the ages of 1 and 5 years. Growth stunting, bone pain, dental abscesses, and dental malposition were common complications.	Multicenter research focused on XLH data, which was seldom addressed previously.	Lack of biochemistry, genetic or image data.
Mumtaz et al.,[19] 2022	Cross-sectional study	Risk factors of nutritional rickets in Pakistani children.	Making observation on 132 children with nutritional rickets, comparing their demographic data and socioeconomic status.	The majority of cases were aged from 1 to 3 years, male, lower socioeconomic status, lack of sun exposure, and poor nutritional conditions.	Enrich the epidemiological characteristics of rickets with the South Asia population.	Lack of control group. Small sample size.
Beck-Nielson et al.,[20] 2009	Retrospective cohort study	Incidence and prevalence of nutritional and hereditary rickets.	Patients aged 0–14.9 yr with a diagnosis of rickets in southern Denmark from 1985 to 2005 were identified and enrolled.	The incidence of nutritional rickets was found to be higher in the younger population, with a notable increase among immigrants.	A nationwide epidemiologic study	Only analyzed incidence of rickets without ROM investigation. Smaller sample size (n=112).
Meyer et al.,[21] 2017	Retrospective cohort study	To identify new cases of nutritional rickets in Norway	Use ICD-10 to clarify the newly diagnosed cases of nutritional rickets (<5 yr) during the period 2008–2012.	Total 42 patients were identified with a mean diagnostic age of 1.4 yr, and 93% had a nonwestern immigrant background.	A nationwide population-based study.	Only focuses on nutritional rickets and its incidence.

ROM, risk of mortality; NHIRD, National Health Insurance Research Database; CKD, chronic kidney disease; LOS, length of stay; XLH, X-linked hypophosphatemia; ICD-10, International Classification of Diseases, Tenth Revision.

nutritional rickets and risk factors such as darker skin pigmentation, Indian and African ethnicity, age under 3 years, and exclusive breastfeeding; however, the limited number of patients (n=58) from a specific region might restrict generalizability. Apart from 2 studies on X-linked hypophosphatemia,[17,18] most retrospective studies on nutritional rickets have identified factors such as black race, exclusive breastfeeding, low birth weight, males, lower socioeconomic status, lack of sun exposure, and poor nutritional condition as increasing the risks of rickets.[6,20,21] Notably, our study simultaneously investigated both hereditary and nutritional rickets, providing a broader perspective on the care of rickets. Unlike other studies with small sample sizes,[9,19] our nationwide retrospective study (1,551 cases) revealed a notable prevalence of rickets among pediatric patients, with a higher proportion diagnosed with nutritional compared to hereditary rickets. Our findings also suggest an increased overall incidence of rickets alongside declining mortality rates in recent years. However, these findings were limited by the lack of anthropometric data and detailed biochemical analysis. Future prospective research with larger sample sizes and comprehensive data is necessary to better understand the clinical characteristics and risk factors of rickets in diverse populations.

3. Male predominance and delayed diagnosis in hereditary rickets

Previous studies have reported a male predominance in rickets incidence[22,23]; however, our study offers a more nuanced perspective. While males outnumber females among rickets patients overall, subgroup analysis reveals that only hereditary rickets exhibit a male predominance, whereas nutritional rickets show a nearly equal sex distribution. Although the discrepancy between our findings and previous reports may be influenced by racial and genetic factors,[22,23] our results appear to better align with biological plausibility. Nutritional rickets primarily arises from individual nutritional status, indicating no inherent sex difference under similar environmental conditions.[24] Conversely, X-linked hypophosphatemia, a leading cause of hereditary rickets, may account for the higher likelihood of males being affected in this subgroup.[25]

Hereditary rickets is often diagnosed later, typically during adolescence. This delayed diagnosis reflected the real-world challenges in prompt diagnosis in Taiwan. Several factors may contribute to this delay: the clinical complexity and subclinical nature of rickets can lead to under-recognition or misdiagnosis until symptoms become more pronounced in later childhood or adolescence.[26] The limited use of genetic analysis in Taiwan might result in patients consulting multiple healthcare providers before receiving a confirmed diagnosis.[27] Additionally, restricted access to pediatric endocrinologists specializing in rickets contributed to diagnostic delays. Finally, familial variability in disease presentation[28] and a cultural reluctance among Taiwanese parents to seek medical care due to feelings of guilt or shyness may further delay diagnosis.

4. Poor socioeconomic status associated with mortality in rickets

In developing countries, the higher prevalence of rickets is often attributed to malnutrition stemming from poorer socioeconomic conditions.[29] However, our findings show that the most patients come from middle-income families with annual incomes exceeding 20,000 USD. This may be due to Taiwan's status as a developed country with relatively small income disparities.[30] Additionally, the majority of rickets-related deaths occurred in low-income families, aligning with previous studies that report increased rickets prevalence in developed countries, possibly linked to immigration or refugees issues that restrict access to nutritious food and healthcare resources. Consequently, higher incidences and increased severity of rickets cases ensue.[20,31]

5. Longer LOS, anemia, CKD, and secondary hyperparathyroidism increase mortality

Our study indicates that nutritional rickets generally presents with lower severity, evidenced by a shorter-than-expected average LOS compared to hereditary rickets. This suggests challenges in detecting and diagnosing hereditary rickets in Taiwan.[32] While nutritional rickets can often be resolved by improving nutritional status, hereditary rickets requires lifelong management due to genetic deficits.[5,33,34] Furthermore, our findings suggest that rickets patients with high disease severity face increased mortality risks, often associated with comorbidities such as anemia, CKD, and hyperparathyroidism secondary to renal tubulopathies. Possible explanations for these associations include the relationship between vitamin D deficiency and pulmonary infections like pneumonia, as well as the anemia's interference with treatment efficacy, leading to higher mortality rates among severely ill patients.[35] Additionally, complications related to CKD, such as bicarbonate wasting, alkaline urine, and renal tubular acidosis, can impede rickets treatment, potentially resulting in refractory cases.[36] Severe nutritional rickets may also contribute to secondary hyperparathyroidism,[37,38] increasing the risks of osteoporotic fractures and mortality due to disruptions in calcium and phosphorus metabolism.[39] Nonetheless, deaths in rickets are rarely a direct result of bone instability; they are usually caused by

associated comorbidities. To effectively reduce mortality, precise interventions should prioritize improving these main contributing comorbidities.

6. Incidence and mortality trends from a view of government policy and healthcare

From 2012 to 2018, the overall incidence of rickets in Taiwan showed a steady annual increase, largely driven by nutritional rickets rather than the stable occurrence of hereditary forms. Several factors may explain the rising incidence of nutritional rickets. The measurement of 25-hydroxyvitamin D levels has become more widespread in recent years.[40] In Taiwan, milk sold in containers is not fortified with vitamin D, and health supplements containing vitamin D are not commonly used by the general population. Given that over half of mothers and newborns were vitamin D deficient at birth,[41] another possible reason could be the increase in breastfeeding prevalence in Taiwan, which rose from 32.2% in 2008 to 49.9% in 2011 and continues to rise.[42] In 2012, the Taiwan government intensified efforts to promote breastfeeding through initiatives like advocating exclusive breastfeeding in maternity hospitals and establishing breastfeeding-friendly facilities in public areas. While exclusive breastfeeding offers significant benefits, it has also contributed to increased vitamin D deficiency prevalence.[43] Consequently, the Taiwanese government recently endorsed additional vitamin D supplementation, aligning with international recommendations.[44]

7. Hospital stay beyond 3 days as a clinical red flag

Beyond its statistical significance, prolonged hospitalization may also hold clinical implications as a red flag indicator for adverse outcomes. Our ROC analysis showed that a LOS >3 days was the optimal threshold for predicting mortality, with a sensitivity of 82.4% and specificity of 68.9% (Supplementary Table 2), and an AUC of 0.81 (Fig. 3). These findings are consistent with previous studies that demonstrated a positive association between extended LOS and mortality in pediatric patients.[45] In clinical settings, children with rickets who remain hospitalized beyond 3 days may warrant prompt multidisciplinary reassessment, including evaluation of comorbidities, nutritional status, or potential delays in treatment response. Nevertheless, LOS can be influenced by nonmedical factors such as discharge planning or resource availability, which may limit its specificity. Additionally, the possibility of reverse causality cannot be excluded—children with higher baseline severity or greater risk of death may have required prolonged hospitalization, rather than extended LOS being the cause of poor outcomes. Thus, further prospective research is still needed to validate its utility as a clinical indicator of elevated mortality risk in rickets.

8. Strengths and limitations

This study has several limitations. Firstly, the NHIRD did not provide comprehensive information such as body height, weight, body mass index, precise dosage of rickets medications, primary cause for admission, some socioeconomic details (e.g., educational level), and environmental factors (e.g., nutritional status). Secondly, biochemistry and endocrine parameters (e.g., serum electrolytes, parathyroid hormone, 25-hydroxyvitamin D, and 1,25-dihydroxyvitamin D) were unavailable in the NHIRD. Furthermore, given the absence of genetic testing data in the NHIRD, hereditary rickets was defined exclusively using ICD diagnostic codes for disorders of phosphate metabolism (ICD-9, 275.3; ICD-10, E83.30–E83.39). This methodology may result in misclassification bias, as genetic confirmation was not available for all patients and the diagnostic codes may have inadvertently included cases of secondary metabolic bone disorders, acquired malabsorption disease, nutritional deficiencies, and renal tubular disorders. Thirdly, imaging studies like bone surveys were not included, potentially affecting outcome analysis. Lastly, the outcomes of rickets treatment were not evaluated due to limitations in assessing intervention implications from NHIRD data. Despite these limitations, the NHIRD provides comprehensive population coverage, reducing the potential for recall and selection bias. However, further prospective studies with more detailed information are necessary to fully elucidate the impact of rickets and its treatments on normal growth and ROM.

In conclusion, our study highlights the demographic characteristics, ROM, and temporal trends in incidence and mortality among patients with rickets. We found that rickets primarily affects preschool-aged children. Hereditary rickets is less common than nutritional rickets and often diagnosed later, typically in adolescence. Significant mortality predictors include low family income and longer LOS. Despite rising incidence rates, mortality rates have decreased, underscoring the importance of targeted interventions and monitoring strategies to mitigate the burden of rickets and improve outcomes.

Footnotes

Supplementary materials: Supplementary Tables 1-4 and Supplementary Fig. 1 are available at https://doi.org/10.3345/cep.2025.00976.

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ORCID:
Chun-Hao Chu https://orcid.org/0000-0002-4079-3880
Ying-Chuan Chen https://orcid.org/0000-0001-8031-1893
Pei-Yao Liu https://orcid.org/0000-0002-6622-7844
Chun-Chieh Hu https://orcid.org/0000-0002-8814-6287
Yu-Lung Lin https://orcid.org/0009-0009-9245-8847
Feng-Chih Kuo https://orcid.org/0000-0003-3513-2487
Chieh-Hua Lu https://orcid.org/0000-0002-2179-9486
Tzu-Ju Hsu https://orcid.org/0000-0002-2949-6535
Yu-Tung Hung https://orcid.org/0000-0002-4255-6694
Fuu-Jen Tsai https://orcid.org/0000-0002-1373-245X
Chien-Ming Lin https://orcid.org/0000-0001-7525-5743

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