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Original Research

Clinical Manifestation of Osteogenesis Imperfecta in Indonesian Patients: A Multi-Centre Study

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Abstract

Osteogenesis Imperfecta (OI) is a rare genetic disorder caused by mutations in genes that encode collagen, with varying clinical presentations. While some studies in Indonesia have reported OI's clinical features and treatments, there is a lack of comprehensive national data, with limited awareness and access to specialized care for affected individuals. This collaborative study, involving multiple centres across Indonesia, aims to address data fragmentation by analyzing patient characteristics, clinical manifestations, and radiographic features of OI. This multi-centre study included 85 patients diagnosed with OI by expert clinicians across eight centres in Indonesia. Patients with alternative possible diagnoses were excluded. Data were collected through interviews, clinical evaluations, and medical records, focusing on patient characteristics, clinical manifestations, and radiographic features. Of 85 patients (43 males, 42 females), the most common age group was 0-5 years. Low birth weight (<2500 g) was observed in 31.25%, preterm pregnancies in 23.75%, history of miscarriages in 15.6%, advanced maternal age in 12.5%, and family history of OI in 30.9%. Fractures were the most frequent clinical feature (88.75%), followed by blue sclera (84.7%) and dentinogenesis imperfecta (35.4%). Deformities in the lower limbs were most prevalent (83.1%). Radiographic analysis showed bowing of long bones (97%), fractures (93.5%), and osteopenia (82.1%) as the most common manifestations. The study provides an overview of clinical and radiographic characteristics of OI in Indonesia and supports improved awareness to optimize patient outcomes.

Keywords

Osteogenesis Imperfecta; collagen; genetic disorder; Indonesia

1. Introduction

Osteogenesis Imperfecta (OI) is a rare genetic disorder affecting connective tissue with a prevalence of 1 in 15,000 to 20,000 births [1]. Mutations in the *COL1A1* and *COL1A2* genes, which encode type I collagen, are the most common causes of OI, leading to reduced collagen quality or quantity and compromised bone strength [2]. In addition, other mutations, including autosomal recessive forms, contribute to the wide clinical variability observed in OI [3]. Factors such as mutation type, gene location, and altered amino acids further complicate OI's phenotypic presentation, making counselling and management challenging [4, 5].

While previous studies on OI in Indonesia have provided valuable insights into its clinical characteristics and treatment, most have been limited in scope. Several case reports described individual presentations [6-8] and treatments [9], while a study in Surakarta profiled 13 patients' age, symptoms, and treatments [10]. A larger study from Jakarta in 2019 analyzed 41 patients, focusing on clinical features and bisphosphonate treatment [11]. Despite these contributions, comprehensive national data on OI's incidence and demographic and clinical patterns remain unavailable [11]. The limited awareness of OI among healthcare professionals [11] and the general population [12], along with restricted access to diagnostic tools and specialized care [11], pose significant challenges for early diagnosis and effective management of OI in Indonesia. Notably,

despite the diagnostic limitations, two case reports by Setijowati et al. [13] and Cayami et al. [14] reported novel OI-causing mutations in Indonesian patients.

Given Indonesia's diverse population, with more than 250 ethnic groups, variability in OI manifestations may be expected [15]. However, the disease has not been well characterized at a national level. This study will be the first in Indonesia to include multi-center data collection and will represent the largest cohort of OI patients to date. By consolidating this data, we aim to provide a broader perspective on the demographic, clinical, and radiological characteristics of OI in Indonesia and, in turn, to support a more comprehensive understanding of OI in Indonesia and to improve awareness and management of this condition.

2. Materials and Methods

This cross-sectional study was conducted from October 2019 to October 2024 across multiple referral hospitals in Indonesia, including Palembang, Aceh, Riau, Semarang, Surakarta, Surabaya, Makassar, and Papua, to ensure a geographically diverse cohort. Participants were included if they had a clinical diagnosis of Osteogenesis Imperfecta established by experienced pediatric endocrinologists. The diagnosis was based on a combination of bone fragility and characteristic skeletal and extraskeletal features. A history of recurrent fractures with minimal or no trauma typically reflects bone fragility. Skeletal features included limb shortening, bone deformities, radiological findings such as osteopenia, cortical thinning, bone bowing, fractures, and Wormian bones. Extraskeletal features included blue sclerae, dentinogenesis imperfecta, hearing loss, joint hypermobility, and myopia. Given the retrospective nature of the study, imaging protocols were not standardized. To improve diagnostic specificity, alternative conditions that may mimic OI, such as abuse, rickets, and secondary osteoporosis, were excluded from the study.

They were then re-evaluated using questionnaires and medical record review for patient characteristics (age, gender, miscarriage history, full-term pregnancy history, advanced maternal age, birth weight, and family history of OI) and clinical manifestations (dentinogenesis imperfecta, myopia, scleral hue, and hearing loss, time and location of first fracture, deformity of vertebrae, chest, and extremities, and ambulation). Radiographic data (bowing, osteopenia, Wormian bones, fractures, cortical thinning) were obtained from electronic medical records.

The data collected were thoroughly reviewed for completeness before being organized and tabulated for analysis.

2.1 Ethics Statement

Ethical Clearance was obtained with the approval and consideration of Komisi Etik Penelitian Kesehatan (KEPK) of the Faculty of Medicine, Diponegoro University and RSUP. Dr. Kariadi Semarang (No.16188/EC/KEPK-RSDK/2024). All data obtained by researchers was kept confidential and used for research purposes. Research subjects who chose not to continue the study did not receive any consequences. All patients or parents signed the informed consent forms.

3. Results

3.1 Patient's Characteristics

A total of 85 patients (43 males, 42 females) with OI from eight different centres across Indonesia were investigated. There were 58 patients from the centre in Semarang, seven from Surabaya, seven from Makassar, five from Surakarta, four patients from Palembang, two from Aceh, one from Riau, and one from Papua. Table 1 presents data on patient's gender, age distribution and maternal pregnancy history (see Table 1). This study showed that the most prevalent age group was 0-5 years, followed by 6-10 years and 11-15 years. Low birth weight (<2500 g) was detected in 25 patients (31.25%). Family history is seen in 25 patients (30.9%). Of those, 5 patients (6.1%) were from consanguineous marriages. Among the maternal risk factors associated with OI, preterm pregnancies are associated with the highest prevalence, with an incidence rate of 19 (23.75%). This was followed by the history of miscarriages, which has an incidence rate of 13 (15.6%), and advanced maternal age (over 35 years), with an incidence rate of ten (12.5%).

Table 1 Patient's Characteristics.

Characteristic	Number of Patients	%	95% CI*
Gender (*n* = 85)			
Male	43	50.6	40.0-61.2%
Female	42	49.4	
Age at research (*n* = 85)			
0-5	54	63.5	
6-10	16	18.8	
11-15	11	12.9	
16-20	2	2.35	
21-25	0	0	
26-30	0	0	
31-35	1	1.2	
>35	1	1.2	
Low Birth Weight (*n* = 80)			
<2500	25	31.25	21.4-41.1%
≥2500	55	68.75	
Miscarriage History (*n* = 83)			
Yes	13	15.6	7.8-23.4%
No	70	84.4	
Not Full-term pregnancy history (*n* = 80)			
Yes	19	23.75	14.4-33.1%
No	61	76.25	
Maternal age (*n* = 80)			
<20 years old	6	7.5	
20-35 years old	64	80	
≥35 years old	10	12.5	5.3-19.7%
Family history (*n* = 81)			

Yes	25	30.9	20.8-40.9%
Yes + Consanguinity	5	6.1	0.9-11.3%
No	56	69.1	

* Confidence Interval.

3.2 Clinical Features

Among the various clinical manifestations of OI, the most frequently observed was fractures at various sites, affecting 88.75% of patients. Fracture timing was recorded for 80 participants. Most fractures occurred between the ages of 1 and 5 years (36.25%), followed by the first year of life (33.75%), in-utero (12.5%), and after age 5 (6.25%). Meanwhile, 11.25% reported never experiencing a fracture. The femur was the most common fracture site (33.3%), followed by the cruris (24.4%), humerus (17.9%), antebrachii (3.8%), and multiple locations (8.9%). Lower extremity deformities were the most prevalent (83.1%), followed by upper extremity deformities (53.0%), sternal deformities (23.8%), and vertebral deformities (20.2%). Ambulation status showed 27.7% of participants could walk normally, while others required ambulatory aids (21.7%), used a wheelchair (14.5%), were limited to sitting (22.9%), or were confined to lying (13.2%) (see Table 2).

Table 2 Clinical Features.

Characteristic	Number of Patients	%	95% CI*
Time of First Fracture (*n* = 80)			
In-utero	10	12.5	5.3-19.7%
0-1 year old	27	33.75	23.4-44.1%
1-5 years old	29	36.25	25.7-46.8%
>5 years old	5	6.25	0.9-11.6%
Never Experienced	9	11.25	4.3-18.2%
Location of First Fracture (*n* = 78)			
Femur	26	33.3	22.9-43.8%
Cruris	19	24.4	14.8-33.9%
Humerus	14	17.9	9.4-26.5%
Antebrachii	3	3.8	0.0-8.1%
Mixed (≥2 fractures)	7	8.9	2.6-15.3%
No fractures	9	11.5	4.4-18.6%
Deformity			
Vertebrae (*n* = 84)	17	20.2	11.6-28.8%
Sternum (*n* = 84)	20	23.8	14.7-32.9%
Upper Extremities (*n* = 83)	44	53.0	42.3-63.7%
Lower Extremities (*n* = 83)	69	83.1	75.1-91.2%
Ambulation (*n* = 83)			
Lying	11	13.2	6.0-20.5%
Sitting	19	22.9	13.9-31.9%
Wheelchair	12	14.5	6.9-22.0%
Ambulatory assisting device	18	21.7	12.8-30.6%
Normal	23	27.7	18.1-37.3%

Blue Sclerae (*n* = 85)			
Yes	72	84.7	77.1-92.4%
No	13	15.3	
Myopia (*n* = 78)			
Yes	3	3.8	0.0-8.1%
No	75	96.2	
Hearing Loss (*n* = 79)			
Yes	3	3.8	0.0-8.0%
No	76	96.2	
Dentinogenesis Imperfecta (*n* = 79)			
Yes	28	35.4	24.9-46.0%
No	51	64.6	

As for the extraskeletal clinical manifestations, blue sclera is seen in 84.7% of patients, followed by dentinogenesis imperfecta at 35.4%, myopia at 3.8%, and hearing loss at 3.8% (see Table 2).

3.3 Radiographic Features

From 85 patients, we were only able to obtain radiological data from 34 patients. However, based on available data, bowing of long bones was found in 97% of patients, followed by fractures in 93.5% of patients. Osteopenia was present in 82.1% of patients, wormian bones were observed in 45.8%, and cortical thinning was noted in 44.4% (see Table 3). Of the 27 patients (14 males and 13 females) who underwent evaluation for cortical thinning, 12 were found to have cortical thinning. Among these 12 patients, 58.3% were male and 41.6% were female.

Table 3 Radiographic Features.

Radiographic Features	Number of Patients	%	95% CI*
Bowing (*n* = 34)	33	97	91.5-100.0%
Osteopenia (*n* = 28)	23	82.1	67.9-96.3%
Wormian Bones (*n* = 24)	11	45.8	25.9-65.8%
Fracture (*n* = 31)	29	93.5	84.9-100.0%
Cortical Thinning (*n* = 27)	12	44.4	25.7-63.1%
Male	7	58.3	30.4-86.3%
Female	5	41.6	13.7-69.6%

4. Discussion

Osteogenesis Imperfecta remains underreported in Indonesia, with limited studies describing the clinical characteristics of affected individuals. Recent advances in the classification of genetic skeletal disorders have further underscored that OI is a highly heterogeneous condition, encompassing an expanding spectrum of genes beyond type I collagen, including those related to collagen processing, osteoblast differentiation, and bone mineralization. This molecular complexity may partly explain the variability in clinical manifestations observed across populations [16]. In this context, the present study provides valuable insights into OI in Indonesia by examining a cohort of

patients from 8 different provinces, highlighting clinical characteristics, including demographic distribution, skeletal manifestations, and extraskeletal features.

In this study, we observed that OI is distributed almost equally between males and females, consistent with most studies that reported OI affected both sexes equally [11, 17]. Given the autosomal inheritance pattern of most OI, a balanced sex distribution is expected.

The majority of patients in this cohort were children, consistent with other local studies from Surakarta [10], but notably higher than in the Italian cohort. This pattern may be attributed to the relatively low awareness of OI among medical professionals [11], as the condition has only recently been more recognized. Furthermore, since pediatric endocrinologists collected the data, the true prevalence in adults remains unknown and may be better captured in orthopaedic studies.

In our study, a positive family history was identified in approximately one-third of all patients. This proportion is comparable with findings from Jakarta [11], but somewhat lower than those reported from other countries (See Table 4). The relatively lower rate of inherited cases in our study may reflect the contribution of sporadic (de novo) and autosomal recessive OI, both of which present without a known family history.

Table 4 Characteristics comparison of OI in several countries.

Characteristics	Indonesia	Vietnam [18]	Taiwan [19]	China [20]	Ukraine [21]	Brazil [22]	Spain [23]	Italy [24]
Female-to-male ratio	1:1.02 (*n* = 85)	1:1.39 (*n* = 146)	2.2:1 (*n* = 48)	1:1.35 (*n* = 61)	1.17:1 (*n* = 143)	1.24:1 (*n* = 76)		1.15:1 (*n* = 568)
Children	95.2% (aged 0-15 years old)	70.55% (aged 0-15 years old)	56.25% (aged 0-15 years old)		54.23% (aged 0-17 years old)			50.4% (aged 0-17 years old)
Family History	30.9% (*n* = 81)		47.9% (*n* = 48)		38.71% (*n* = 93)	44.6% (*n* = 74)		35.9% (*n* = 568)
Blue Sclerae	84.7% (*n* = 85)	80.14% (*n* = 146)	75% (*n* = 48)	80.3% (*n* = 61)	87.32% (*n* = 139)	93.4% (*n* = 76)	87.5% (*n* = 40)	78.9% (*n* = 568)
Dentinogenesis Imperfecta	35.4% (*n* = 79)	60.96% (*n* = 146)	35.4% (*n* = 48)	32.8% (*n* = 61)	54.68% (*n* = 139)	27.6% (*n* = 76)	22.5% (*n* = 40)	15.7% (*n* = 568)
Hearing Loss	3.8% (*n* = 78)	17.81% (*n* = 146)	8.3% (*n* = 48)	1.6% (*n* = 61)	22.38% (*n* = 139)		17.5% (*n* = 40)	17.1% (*n* = 568)
Spine deformity	20.5% (*n* = 83)	62.3% (*n* = 146)	54.1% scoliosis (*n* = 48)		77.3% (*n* = 141)		42.5% (*n* = 40)	41% (*n* = 568)
Chest wall deformity	24.1% (*n* = 83)	50.68% (*n* = 146)			34.75% (*n* = 141)		10% (*n* = 40)	11.1% (*n* = 568)
Upper limb deformity	53.1% (*n* = 83)	54.8% (*n* = 146)			65.96% (*n* = 141)			5.8% (*n* = 568)
Lower limb deformity	83.2% (*n* = 83)	82.8% (*n* = 146)			81.56% (*n* = 141)			15.5% (*n* = 568)
Normal Ambulation	27.7%	39.73%	64.5%		74.29%			

Low birth weight (<2500 gr) appeared to be substantially more frequent in our cohort compared to reports from Vietnam with only 14.38% [18]. This difference may be attributed to the overall prevalence of low birth weight, which is higher in Indonesia (10%) compared to Vietnam (8.2%) [25]. Although the proportion of low birth weight in our study is still significantly higher than the overall low birth weight proportion in the general population (10%). In addition, higher proportion of preterm birth may partly contribute to the increased prevalence of low birth weight in our population, as premature infants have a shorter duration for intrauterine growth and skeletal development. Previous studies have identified potential associations between certain genetic variants, including *COL1A1*, and miscarriage [26]. However, as our study did not assess underlying genetic analysis, the significance of this finding remains unclear.

4.1 Clinical Features

Fractures in our cohort predominantly involved the femur and cruris, consistent with findings from other populations [18, 21]. This contrasts with fracture patterns commonly seen in healthy children from an epidemiological study in the UK, where the upper limbs are more commonly affected [27, 28]. This difference reflects the underlying collagen defect in OI, which leads to impaired bone strength and structural integrity, particularly affecting weight-bearing bones [3, 29]. Additionally, a study from Spain suggested that fracture patterns may vary according to the disease severity, with femoral fractures becoming more prominent in moderate to severe forms of OI [30].

The prevalence of spinal and chest wall deformities in our cohort was lower than that reported in other studies [18, 21, 24]. This may indicate younger patient population, as these deformities tend to progress over time [30, 31]. Upper and lower limb deformities were significantly less frequent in Italy than in our study. In addition, ambulation rates in our study were also lower compared to other populations. These findings suggest differences in disease severity and access to early intervention. Bisphosphonate therapy, which is widely used in children with OI, has been shown to improve bone mineral density and reduce fracture risk, potentially limiting the progression of skeletal deformities [32]. In our setting, bisphosphonate therapy is part of the standard management of OI and widely administered. However, its effect on long-term functional outcomes remains variable, likely because it primarily targets bone resorption and does not address the underlying defects in collagen synthesis and bone matrix integrity [33]. Furthermore, differences in timing of initiation may influence clinical outcomes. However, detailed data on treatment patterns were not systematically collected in this study, which limits further interpretation.

Blue sclera remained one of the most consistent clinical manifestations of OI across populations (see Table 4) with other local studies from Jakarta reporting similar trends [10, 11], supporting its role as a reliable phenotypic marker despite regional variation. In contrast, dentinogenesis imperfecta showed variable prevalence across populations (see Table 4) [10], suggesting possible differences in phenotypic expression. The low prevalence of hearing loss is likely because hearing loss typically manifests after the age of 30, whereas our cohort included participants mostly under the age of 15 [33].

4.2 Radiographic Features

Radiographic data were available for 34 out of 85 patients, as imaging was not consistently performed in all cases due to variations in accessibility and completeness of medical records in each

centers. Based on the available data from the medical database, the most prominent radiographic features observed were bone bowing and fractures, followed by osteopenia in our population. These findings align with the key characteristics of OI and are pathognomonic when seen in combination [34].

Wormian bones were observed in nearly half of our patients, consistent with a study in Montreal reporting 58% of their patients had Wormian bones. Notably, their study also indicated that the presence of Wormian bones is strongly associated with more severe phenotypes [35].

Cortical thinning was observed in a substantial proportion of patients, with higher prevalence in males. This contrasts with a previous study, which reported that male mice exhibit significantly greater cortical bone thickness than their female counterparts, attributed to differences in growth hormone levels and sex steroids. This discrepancy may be due to the fact that the patient sample in this study consists mainly of younger patients, where puberty tends to start earlier in girls, at around 8-13 years old, than in boys, at around 9-14 years old and at puberty, GH tends to increase [36, 37].

4.3 Limitation

A key limitation of this study is the potential for recall bias, as a large proportion of data were collected through questionnaire-based evaluation. Participants may have difficulty accurately recalling past medical events. Additionally, patients included in the study may have been selected from centres with the availability of pediatric endocrinologists, potentially excluding those with undiagnosed OI. Survival bias may have also influenced the findings as individuals with a more severe OI may not survive to be included in the study. Another challenge in this study is the difficulty in classifying OI accurately, as many patients did not attend regular clinical follow-ups. Given the genetic heterogeneity of OI, reliance on clinical and radiological manifestations alone may introduce diagnostic uncertainty. Incomplete radiographic data may introduce selection bias, as patients with available imaging may not be fully representative of the overall cohort. The relatively small sample size in comparison to the broader Indonesian population [8] presents another limitation, as it remains uncertain whether the findings are fully representative of the population at large. In addition, the descriptive design of this study limited the ability to perform comparative statistical analyses between subgroups, which may be explored in future studies with larger sample sizes. Despite these limitations, it is important to note that this is the largest study reporting OI conducted in the region, providing valuable insights to OI within the country.

5. Conclusions

This study presented the characteristics, clinical features and radiographic features of OI in Indonesia, addressing the gap in the current literature on the condition in the region. The implications of this study, such as its use as a foundation for genetic counselling and future genotype-phenotype studies, can also raise awareness among healthcare professionals and the general population, ultimately contributing to improved patient treatment and quality of life.

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Author Contributions

F.K.C. and A.U. conceptualized and designed the study. Data collection and processing were conducted by F.K.C., A.U., S.L., A.G.M., R.D.A., M.F., N.R., R.A., Y.H., and A. Data analysis and interpretation were performed by F.K.C., A.U., and S.L. The manuscript was drafted by S.L., with critical revisions and feedback provided by F.K.C. and A.U. All authors gave the final approval for the manuscript.

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Competing Interests

The authors have declared that no competing interests exist.

AI-Assisted Technologies Statement

Artificial intelligence (AI) tools were used solely for basic grammar correction and language refinement in the preparation of this manuscript. Specifically, Grammarly Proof was employed to improve the readability and linguistic clarity of the English text. All scientific content, data interpretation, and conclusions were developed independently by the author. The authors have thoroughly reviewed and edited the AI-assisted text to ensure its accuracy and accept full responsibility for the content of the manuscript.

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