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A Possible Case of β-Thalassemia From the Cemetery of Santa Maria Maggiore in Vercelli (Piedmont, Northern Italy,18th Century)

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ABSTRACT

In Italy's Piedmont region, the city of Vercelli has a history of malaria transmission due to favorable conditions for Anopheles mosquitoes, which may have influenced the genetic prevalence of thalassemia. This study investigates the skeletal remains of a nonadult individual from the Church of Santa Maria Maggiore in Vercelli, dating to the 18th century, and suggests possible pathological changes indicative of β-thalassemia. The skeletal analysis reveals extensive pitting, marrow hyperplasia, cortical thinning, scalloped epiphyses, and a distinctive "rib-within-a-rib" radiological appearance, which could be consistent with β-thalassemia major and intermedia. While thalassemia is currently prevalent in Piedmont, no prior paleopathological evidence of the condition has been reported. This study highlights the diagnostic challenges in identifying β-thalassemia in ancient populations due to similarities with other anemias and the absence of ancient DNA. The importance of combining skeletal analysis with historical and environmental contexts is emphasized to improve diagnostic accuracy. This research provides new insights into the historical presence of β-thalassemia in Vercelli and underscores the potential influence of environmental factors and genetic disorders.

1 | Introduction

Vercelli is an Italian city located in the eastern part of the Piedmont region. This area has been historically known for being conducive to developing Anopheles mosquitoes, which transmit protozoan parasites of the genus *Plasmodium* that cause malaria. The widespread prevalence of malaria in the Po Valley is closely linked to the expansion of agricultural land converted into rice paddies, whose waterlogged fields promote mosquito development. In modern times, activities related to rice cultivation, experimentation, and trade continue to form the foundation of the local economy, earning Vercelli the title of Italy's and Europe's rice capital.

With the advent of rice cultivation, public health and hygiene issues arose almost immediately. In Piedmont, particularly malaria-stricken Vercelli, a petition was submitted to Duke Carlo Emanuele I on August 8, 1583, to contest rice cultivation (Corbellini 2022).

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We certify that this manuscript consists of original, unpublished work which is not under consideration for publication elsewhere.

We confirm that the information regarding any prior publication or concurrent submission of any part of this work is accurate, and that no part of the manuscript is currently under consideration elsewhere.

This situation continued, with few changes, until the enactment of the 1934 Consolidated Health Laws in Vercelli. These laws included several articles specifically addressing rice cultivation, establishing minimum distances for rice paddies from populated areas, guidelines for water drainage, conditions for approving new installations, work rest periods related to cultivation, and standards for medical and pharmaceutical assistance, as well as the hygienic conditions of workers' housing and their health. Owners were mandated to provide free quinine to combat malaria among rice paddy workers, even in areas no longer affected by malaria (Mosca 2009).

In the 1700s, doctors wrote about the presumed immunity of specific individuals to malaria: "There are individuals who are immune due to intrinsic organic reasons. Despite being constantly bitten by mosquitoes, they never experience fevers, appear rosy, and have normal spleen and liver" (Celli 1909). At that time, Cooley's anemia had not yet been discovered, and the correlation between malaria and thalassemia was unknown.

Today, it is estimated that approximately 7000 people in Italy are affected by β-thalassemia, primarily residing in some areas of the South (Sicily, Sardinia, and Puglia) and the North (Lombardy, Piedmont, and Emilia-Romagna). Of these, 73% suffer from β-thalassemia major or transfusion-dependent thalassemia, making Italy one of the countries with the highest incidence of thalassemic patients worldwide (https://www.osservatoriomalattierare.it/malattie-rare/talassemia/19890-beta-talassemia-circa-settemila-le-persone-affette-dalla-patologia-in-italia).

This study aims to analyze a nonadult individual whose skeletal lesions suggest thalassemia, a group of hemoglobinopathies commonly found in malaria-endemic regions.

2 | Materials

The Church of Santa Maria Maggiore in Vercelli was built in the 18th century and continued to be used until the first half of the 19th century and features a unique burial space in its underground area (Figure 1A). The cemetery is structured on two levels: the first level includes individual tombs and family chapels designated for ecclesiastics and nobles, while the second level contains three communal ossuaries with hundreds of individuals. On the first level, there is a prominent local family that had a dedicated funerary space inside a chapel marked by its heraldic coat of arms (Fusco et al. 2023). According to historical sources, this important family settled in the area from the first half of the 17th century. Inside the chapel, built in 1777, the remains of two masonry tombs containing a total of eight adults and five nonadults (Funerary Unit 17 and Funerary Unit 18) were discovered. Funerary Unit 17 (FU17) contains two tiny, superimposed wooden coffins. The first coffin houses the remains of two adults and three infants, buried in a secondary deposition (Licata et al. 2024; Vanni et al. 2024). One of these infants, designated FU 17 C1#2 (hereafter referred to as #2), is the focus of this study due to pathological changes potentially related to its death. Not all skeletal elements of the infant are present, likely due to preservation issues associated with secondary depositions. Despite this, the skeletons show no fragmentation and exhibit excellent cortical preservation (Figure 1B).

3 | Methods

Age estimation for Infant #2 was conducted by evaluating the fusion of postcranial bones and measuring the diaphyseal length of the long bones (Cunningham et al. 2000; Young 1957). Due to the immaturity of the skeletal remains, sex determination was not performed.

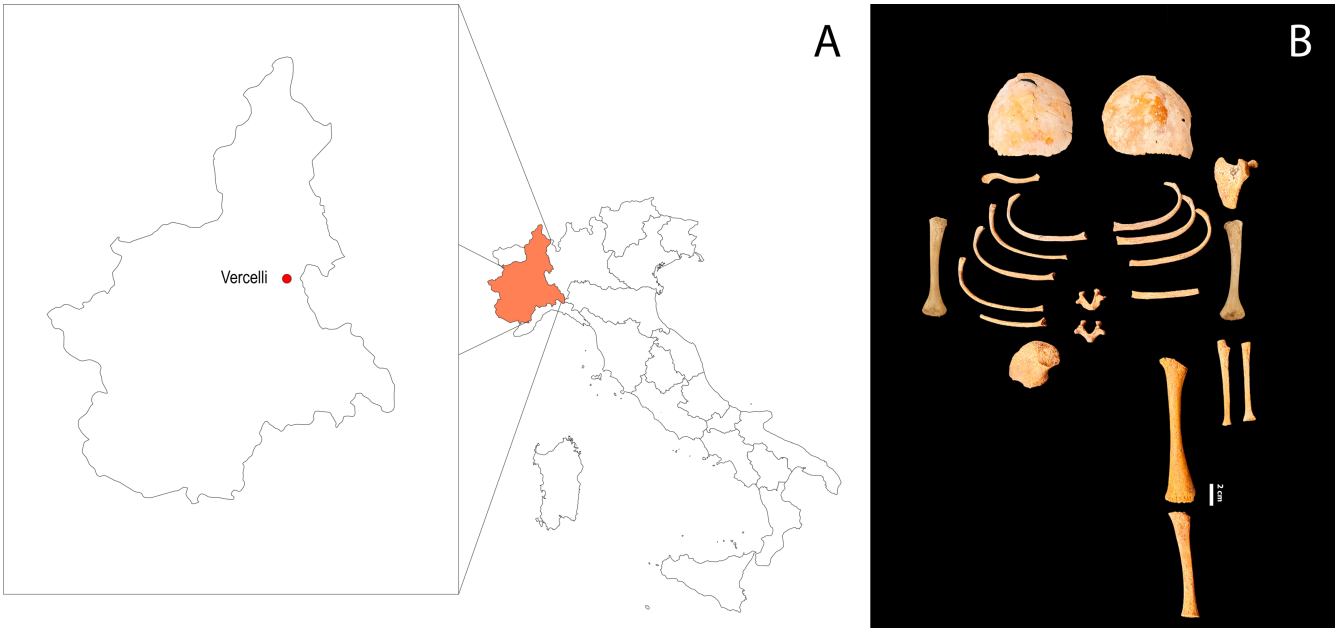

FIGURE 1 | (A) Geographical location of Vercelli in Italy. (B) Skeleton of non-adult individual #2. [Colour figure can be viewed at wileyonlinelibrary.com]

Pathological conditions were first macroscopically examined to identify any visible abnormalities. Radiographic analyses were carried out using a FMI TOP330HFAR radiographic machine. Differential diagnosis was then performed using the Appleby protocol to differentiate the observed pathological features from other conditions (Appleby et al. 2015).

4 | Results

Based on the diaphyseal length of the long bones, Infant #2 is estimated to be between 6 months and 1 year old.

The parietals were the only cranial bones that exhibited slight diffuse porosity. No other macroscopic or radiological alterations are observed in the skull. The long bones, including the humeri, left ulna, radius, tibia, and femur, exhibit extensive pitting in both the distal and proximal epiphyses. There is a marked widening of the medullary cavity with enlarged trabecular structure accompanied by thinning of the cortex, most pronounced in the radius, ulna, and humeri, wherein the proximal epiphyses, the cortex is almost completely destroyed. The cortex in the metaphyses appears reticulated. The distal femoral metaphyses are remodeled, resulting in a widened outline that lacks the usual concave flare. The epiphyseal margins of all long bones are scalloped and jagged (Figures 2A, 3A). Radiographically, osteopenia, thinning of the metaphyseal cortex, and trabecular thinning are observed (Figures 2B, 3B). Similar enlargement, alteration of the trabecular pattern, and smoothed margins are evident in flat bones such as the pelvis and scapulae. A fan-like organization of trabeculae is observable in the pelvis (Figure 3C).

The ribs are hypertrophic, with flared epiphyses. The thinning of the cortex is mostly in the posterior portions that show lace-like cortical rarefaction, with the underlying trabeculae exhibiting a diagonal arrangement. The most striking lesions observed are the hypertrophic and locally thickened ribs, showing an appearance like that of healing calluses (Figure 4A). These localized bone formations observed on radiographs do not reveal a distinct fracture line (Figure 4B). Instead, they resemble costal osteomas, with localized areas of cancellous new bone deposited on the top of the original cortex at the anterior midshaft. The radiographic aspect is that of "rib-within-a-rib" appearance, depicted by a band of radiopaque bone (Figure 4B).

5 | Discussion

Among the most notable manifestations in this individual are bone marrow hyperplasia, cortical thinning, osteopenia, and the radiological "rib-within-a-rib" appearance. These findings led us to consider several conditions in the differential diagnosis, including metabolic disorders such as vitamin D and C deficiencies, iron-deficiency anemia (IDA), hereditary spherocytosis (HS), congenital hemolytic anemias, such as sickle cell anemia (SCA), and different forms of thalassemia: major, intermedia, minor (β-TM, β-TI, β-Tm). Certain types of anemia that are commonly included in differential diagnoses have been deliberately excluded in this case. Forms of anemia resulting from toxicosis and congenital anomalies, such as Fanconi's anemia, Diamond–Blackfan anemia, and transient erythroblastopenia, are typically aplastic, as these conditions suppress erythropoietic activity and are unlikely to cause marrow expansion (Lewis 2018; Simonson and Kao 1991).

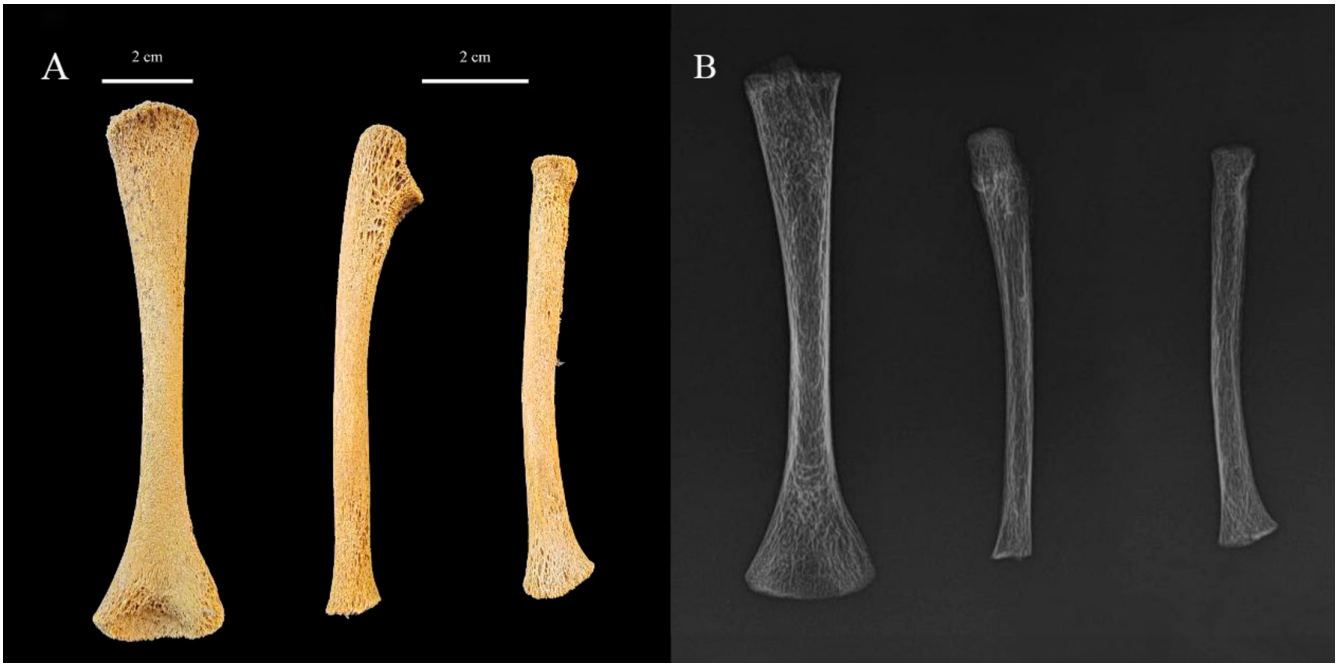

FIGURE 2 | (A) Humerus, ulna, and radius. Bones exhibit porosity and widespread pitting, particularly on the proximal end of the radius and ulna, indicating generalized osteopenia. The cortex is nearly absent in the proximal epiphyses, with smoothed margins. The cortex appears reticulated in the metaphysis. (B) Conventional radiograph showing osteopenia and thinning of the metaphyseal cortex. [Colour figure can be viewed at wileyonlinelibrary.com]

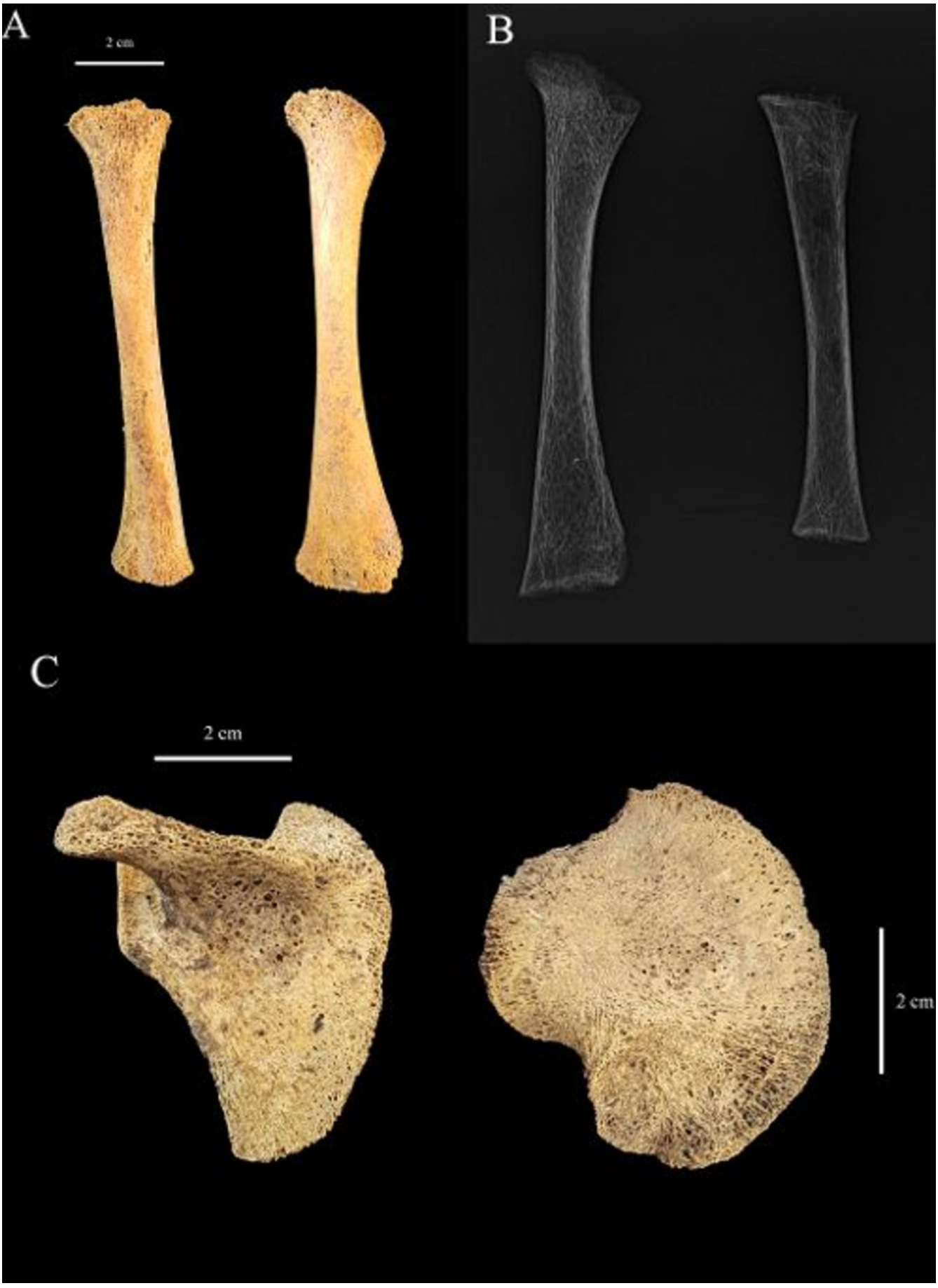

FIGURE 3 | Legend on next page.

FIGURE 3 | (A) The femur and tibia display porosity and cortical rarefaction. The epiphyseal margins are scalloped and jagged. The distal femoral metaphysis shows remodeling, resulting in a widened contour that lacks the usual concave flare. Thickened trabeculae are also visible. (B) A Radiograph highlights osteopenia and thinning of the metaphyseal cortex. The femur shows a widening of the epiphyseal and metaphyseal marrow spaces and alteration in the medullary cavity. (C) Left scapula and right ilium. Severe osteopenia is eviden,t with porosity and cortical thinning. The trabecular bone in the long bones and ilium is thickened and sparse. [Colour figure can be viewed at wileyonlinelibrary.com]

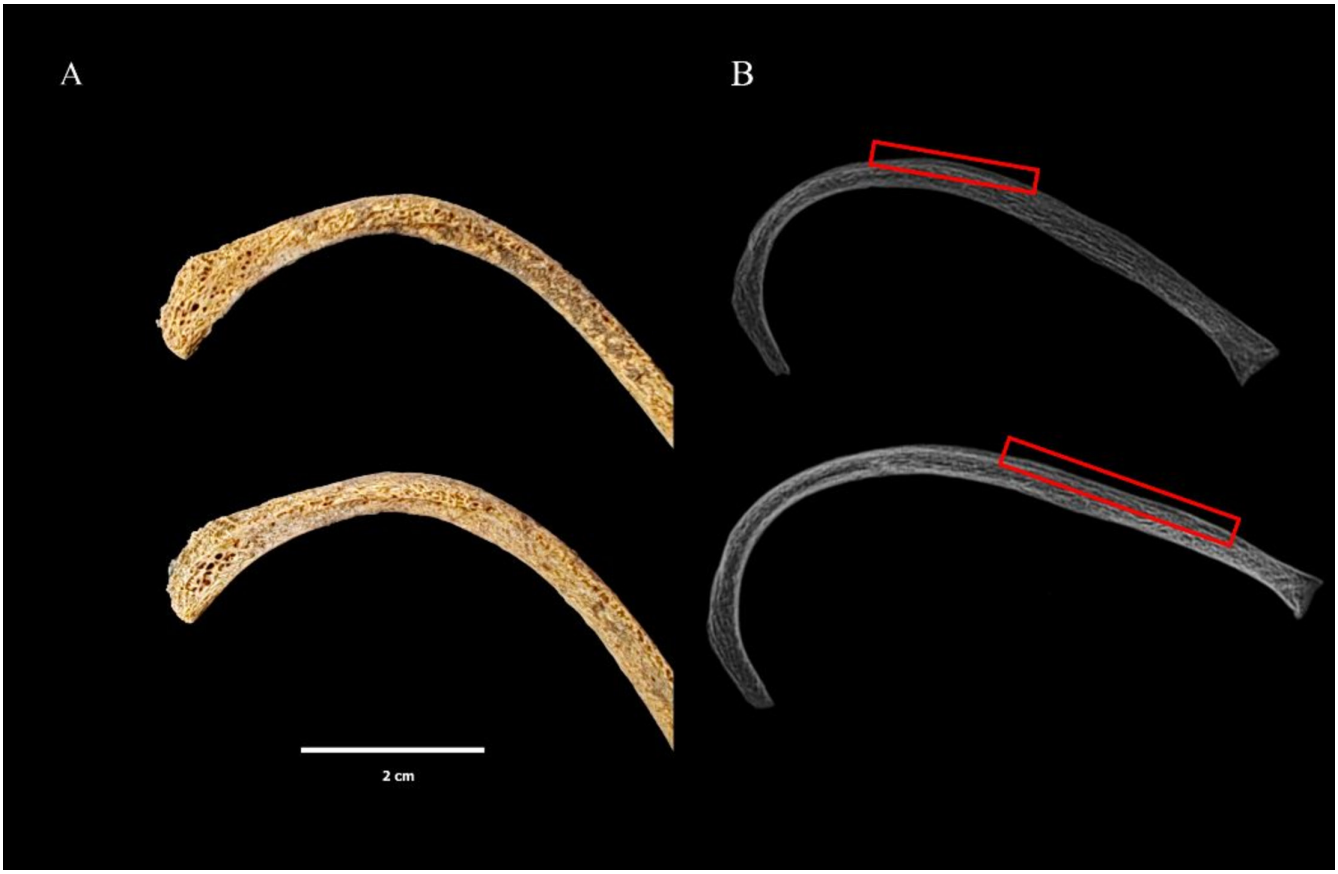

FIGURE 4 | (A) Ribs are thickened with accentuated pitting along the costal margin; the surface shows extreme lacelike cortical rarefaction. (C) X-ray image showing thick layers of subperiosteal new bone on the rib shafts, with ribs exhibiting a "rib-within-a-rib" appearance. [Colour figure can be viewed at wileyonlinelibrary.com]

Similarly, vitamin B12 deficiency anemia has been excluded from the differential diagnosis in Table 1, as infants typically have sufficient B12 stores for 2 to 3 years (Simpson 1991). Similarly, some rare conditions, such as polycythemia vera (PV) and cyanotic congenital heart disease (CCHD), have been excluded, as anemia in these cases typically represents the final stage of pathological alterations and hyperplasia primarily affects the diploe (Alonso-Gonzalez et al. 2023; Brickley and Ives 2008; Monge et al. 2024; Murray 1964; Walor et al. 2005).

Based on the evidence reported in Table 1, metabolic disorders such as vitamin D and C deficiencies have been ruled out, as well as IDA. Moreover, acquired anemias due to nutritional deficiencies are often associated with conditions such as scurvy and rickets (Lewis 2018). However, no manifestations of these diseases are present in the case under examination.

We have also excluded anemia due to malaria based on the available evidence. Although malaria does not cause direct skeletal lesions, it induces hemolytic anemia, which can contribute to the development of porous bone lesions (Schats 2023). Five types of porous skeletal lesions have been more frequently associated with malaria, primarily affecting the cranium, vertebral column, and the humeral and femoral necks (Smith-Guzmán 2015). In this child, many of the observed lesions on other bones do not align with those commonly linked to the disease. In malaria, porotic lesions are typically due to chronic or recurrent infections caused by *Plasmodium vivax* (Setzer 2014), since acute infections caused by *Plasmodium falciparum* leave minimal skeletal traces. There is limited clinical evidence for skeletal changes in chronic malaria cases, especially in very young individuals (Schats 2021). The authors are not aware of any cases of skeletal manifestations due to chronic malaria in children under 1 year of age, as in our case. It is highly unlikely that such a young child could have developed chronic malaria. We have also excluded hereditary spherocytosis (HS), as bone changes associated with HS are typically limited to the cranial diploë and rarely affect long bones (Perrotta et al. 2008).

TABLE 1 | Summary of the key features of each condition considered in differential diagnosis.

	Key features	Iron-deficiency anemia (IDA) [1, 2, 3, 4, 5,]	Hereditary spherocytosis (HS)[2, 6,7]	Sickle cell anemia (SCA)[8,9,2,3,7]	β-Thalassemia intermedia e major [10,11,2,7, 12,13]	Infectious disease (malaria) [14,15,16,17 18, 26, 27]	Vitamin D deficiency[1,2,7]	Vitamin C deficiency [1,2,7]	Vitamin B12 deficiency anemia [1,2,7]	Polycythemia vera (PV) [19, 20, 21, 23, 24]	Cyanotic congenital heart disease (CCHD) [19, 20, 7, 21, 25]	Fanconi's anemia (FA)[2, 22]	Diamond–Blackfan (DB) [22, 2]	Pathological changes in individual #2
Postcranium	Marrow hyperplasia	?	—	+	+	+	—	—	—	—	—	—	—	+
	Osteopenia	+	—	+	+	+	+	+	+	+	+	+	+	+
	Metaphyseal porosity	+	—	+	+	+	+	+	+	—	—	—	—	+
	Cortical thinning	+	—	+	+	+	+	+		+	+	—	—	+
	Metaphysis flask-shaped deformities	—	—	—	+	—	+	—	+	+	—	—	+	+
	Margins of long bones scalloped	—	—	—	+	—	+	+	—	—	—	—	—	+
	Periosteal new bone formation	+	—	+	—	+	+	+	—	—	+	—	—	—
	Necrosis	—	—	+	—	—	—	—	—	+	—	—	—	—
	Congenital malformations	—	—	—	—	—	—	—	+	—	+	+	+	
Pelvis	Fan-like trabeculae organization	—	—	—	+	—	—	—	—	—	—	—	—	+
Ribs	Trabeculae are arranged diagonally.	—	—	—	+	—	—	—	—	—	—	—	—	+
	Thickening and porosity	+	—	—	+	—	+	—	—	—	—	—	—	+
	Hypertrophic aspects, costal osteomas	—	—	—	+	—	—	—	—	—	—	—	—	+

(Continues)

TABLE 1 | (Continued)

	Key features	Iron-deficiency anemia (IDA) [1, 2, 3, 4, 5,]	Hereditary spherocytosis (HS)[2, 6,7]	Sickle cell anemia (SCA)[8,9,2,3,7]	β-Thalassemia intermedia e major [10,11,2,7, 12,13]	Infectious disease (malaria) [14,15,16,17 18, 26, 27]	Vitamin D deficiency[1,2,7]	Vitamin C deficiency [1,2,7]	Vitamin B12 deficiency anemia [1,2,7]	Polycythemia vera (PV) [19, 20, 21, 23, 24]	Cyanotic congenital heart disease (CCHD) [19, 20, 7, 21, 25]	Fanconi's anemia (FA)[2,22]	Diamond–Blackfan (DB) [22, 2]	Pathological changes in individual #2
Radiology	Opaque band within the affected rib longitudinal marrow expansion within the cortex	—	—	—	+	—	—	—	—	—	—	—	—	+
				While it typically affects the skull, vertebrae, tibia, and fibula, in this case, additional bones are involved.		Porous skeletal lesions primarily affecting the cranium, vertebra, the humeral and femoral necks, in this case, additional bones are involved.			Unlikely in #2, since the infant has sufficient capacity for 2–3 years.	Hyperplasia primarily affects the diploe	Hyperplasia primarily affects the diploe	Typically aplastic: suppress erythropoiesis; unlikely to cause marrow expansion	Typically aplastic: suppress erythropoiesis; unlikely to cause marrow expansion	

Note: Presence (+), absence (X), not definitive (?). 1. Brickley and Ives (2008), 2. Lewis (2018), 3. Steinbock (1976), 4. Arndt et al. (2005), 5. Walker et al. (2009), 6. Perrota et al., (2008), 7. Buikstra (2019), 8. Faerman et al. (2000), 9. Hershkovitz et al. (1997),10. Lagia et al. (2006), 11. Lawson et al. (1981), 12. Rohnbogner (2016), 13. Moseley (1974), 14. Schats (2023), 15. Schats (2021), 16. Smith-Guzmán (2015), 17. Gomes et al. (2022), 18. Coppola Bove et al. (2024) 19. (Simpson 1991). 20. Alonso-Gonzalez et al. (2023), 21. Monge et al. (2024) 22. Simonson and Kao (1991) 23. Oikonomidou et al. (2016), 24. Niscola et al. (2007), 25. Alonso-Gonzalez et al. (2023), 26. Smith-Guzmán (2015), 27. Schats (2023).

We also dismissed SCA based on the observed skeletal evidence. SCA typically affects the skull, vertebrae, tibia, and fibula (Buikstra 2019; Steinbock 1976), while in this case additional bones are involved. Moreover, SCA is characterized by new bone formation, osteomyelitis, and cortical thickening in the tibia and fibula, which can reduce the medullary cavity (Lewis 2018). In contrast, the individual under study exhibits cortical thinning with no signs of necrosis, further supporting the exclusion of SCA. Moreover, the most characteristic skeletal features of this pathology may not be evident before the age of 9 years (Ascenzi and Marinozzi 1958).

In thalassemia major and intermedia, one notable feature is the "hair-on-end" appearance, which indicates extensive bony proliferation of the outer table of the cranial vault and is particularly prominent in the most severe cases (Lagia et al. 2006). In our study, this manifestation is not observed in the parietal bones, the only skull bones present. However, this finding, although more commonly associated with thalassemia than other anemias, proves to be not as frequent, with a prevalence of only 0.08% in modern populations (Chaichun et al. 2021; Poyton and Davey 1968). This radiological appearance typically develops when clinical symptoms of hemoglobinopathies become evident after the sixteenth month of life, following the decline in fetal hemoglobin production (Jorge et al. 2016). Since #2 was between 6 months and 1 year of age, the absence of this radiological feature is consistent with the expected timing of its appearance.

Individuals with β-thalassemia major and intermedia could exhibit a range of postcranial lesions, including marrow hyperplasia and new bone formation that may cover the entire outer surface of the ribs, producing a "rib-within-a-rib" appearance. This phenomenon is described as costal osteomas caused by excessive marrow proliferation within a bony shell atop the original cortex, accompanied by localized erosions (Lawson et al. 1981). Erlenmeyer flask deformities, which notably affect the humerus and femurs, are also prevalent. These alterations are evident in #2, with the "rib-within-a-rib" appearance particularly indicative of β-thalassemia major and intermedia in patients without transfusions (Lagia et al. 2006; Pfeiffer et al. 1995). Consequently, the authors suggest that #2 may have been affected by β-thalassemia. The terms "major," "minor" and "intermedia" describe the severity of the condition and reflect its clinical phenotypes. Individuals with thalassemia minor usually experience mild anemia and are often unaware of their condition, as it generally does not cause significant health issues (Galanello and Cao 1998). The range of thalassemia intermedia includes conditions ranging from moderate microcytic hypochromic anemia with minimal splenomegaly and minimal facial bone alterations to severe anemia accompanied by hepatosplenomegaly and significant bone changes (Galanello and Origa 2010). Thalassemia major requires regular blood transfusions from infancy for survival and is associated with significant skeletal alterations, also observed in thalassemia intermedia. However, bone changes, such as rib alterations, are more common in untreated children with thalassemia intermedia (Pfeiffer et al. 1995).

Patients with thalassemia intermedia often survive into later life without blood transfusions, although this generally involves significant marrow proliferation and associated skeletal abnormalities (Sahni et al. 1991). This form of thalassemia is the most likely to be encountered in antiquity. Without treatment, children with β-thalassemia intermedia typically die before the age of 8 (Taher et al. 2006), while survival rates for β-thalassemia major are even lower (Weatherall and Clegg 2008). However, since #2 was younger than 1 year old, it is possible to suggest β-thalassemia major as a more likely diagnosis. This form is rarely found in archaeological records, even in regions where it is common today (Lagia et al. 2006).

Monge (Monge et al. 2024) identified only 18 possible cases of β-thalassemia in individuals under the age of 12 through a comprehensive literature review. Notably, most of these cases originate from Italy and the United Kingdom. In the Italian context, one of the earliest examples involves a 4–5-year-old child from Central Italy, dated to the 3rd century BCE (Facchini et al. 2004). Further cases include an 8-year-old child from the same region (Baggeri and Mallegni 2001), along with five additional individuals dated between the 1st and 3rd centuries CE (Yang 1997). According to Lewis, the presence of thalassemia in Roman Britain may be linked to migratory flows from the Mediterranean area (Lewis 2012).

Archaeological data on this pathology are limited, despite the WHO estimate of 270 million carriers of thalassemia syndromes, including 70 million with β-thalassemia (De Sanctis et al. 2017). This restricted sample is significant considering the hereditary nature of the disease and its earliest known occurrence dating back to the 4th to 3rd millennium BCE (Vlok et al. 2021).

β-Globin gene (HBB) mutations have been recognized as a positive selection for heterozygotes in malaria-endemic environments (Haldane 2006). In general, thalassemia follows the same geographical distribution as malaria, suggesting it evolved as a protection during childhood (Serjeant 2013).

Therefore, the presence of potentially β-thalassemic individuals in Vercelli is not surprising, given the historical spread of malaria in the marshlands and rice fields of the region.

Piedmont is one of the regions with the highest number of patients affected by thalassemia in Italy today (https://www.talassemicipiemonte.it/it/la-talassemia-o-morbo-di-cooley/).

However, no paleopathological evidence of β-thalassemia has been previously identified. A crucial role in identification arises from the difficulty in distinguishing between bone lesions caused by thalassaemic syndrome and those due to other acquired or genetic anemias (Ascenzi and Marinozzi 1958; Buikstra 2019; Murray 1964). Therefore, considering biological, historical, and environmental information is essential for differential diagnosis (Scianò et al. 2021).

6 | Limitations of the Study

The general skeletal response to various types of anemia, with similar skeletal manifestations, makes morphological diagnosis very challenging. Several scholars (Buikstra 2019; Galanello and Origa 2010) argue that the difficulty in diagnosing β-thalassemia, especially in ancient skeletons, is due to the extensive heterogeneity of β-thalassemias at the molecular level,

with more than 200 mutations reported to date, which can affect bones with significant variability (Lewis 2012).

Additionally, the skeletal remains analyzed in this study are incomplete, notably missing facial bones. Odontofacial manifestations are crucial for diagnosing thalassemia and differentiating it from other anemias (Lagia et al. 2006). In this case, only the parietal bones were available for examination, limiting our ability to fully assess these diagnostic characteristics.

Additionally, the absence of molecular or genetic testing restricts the possibility of definitively diagnosing the condition.

Furthermore, the historical context and environmental data provide valuable insights. However, they cannot account for individual variations in disease presentation or other interrelated factors that may have influenced the skeletal evidence.

7 | Conclusion

The analysis of the skeletal remains of infant #2 from Vercelli suggests the possible presence of β-thalassemia major, a hemoglobinopathy historically influenced by malaria endemic in the region.

The difficulty in diagnosing thalassemia in paleopathological contexts, given the similarity of bone lesions to other anemias, is further compounded when the cranium is absent, and no biomolecular confirmation is available. In such situations, osteological analysis remains a key tool and gains further value when integrated with historical and environmental information to support the differential diagnosis. Although the interpretation remains cautious, this case provides important insight into the potential presence of thalassemia in past populations, contributing new data from a region—Piedmont—where no previous osteoarchaeological evidence had been identified. It also underscores the importance of recognizing the noncranial skeletal manifestations of thalassemia in infants, which may easily be overlooked during analysis and recording.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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