Annals of Medicine

ISSN: 0785-3890 (Print) 1365-2060 (Online) Journal homepage: www.tandfonline.com/journals/iann20

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To cite this article: Lucia Merolle, Luca Ghirotto, Davide Schiroli, Giulietta Luul Balestra, Francesco Venturelli, Maria Chiara Bassi, Erminia Di Bartolomeo, Roberto Baricchi & Chiara Marraccini (2025) Risk of cancer in patients with thalassemia and sickle cell disease: a systematic review, Annals of Medicine, 57:1, 2522967, DOI: 10.1080/07853890.2025.2522967

To link to this article: https://doi.org/10.1080/07853890.2025.2522967

ANNALS OF MEDICINE
2025, VOL. 57, NO. 1, 2522967
https://doi.org/10.1080/07853890.2025.2522967

RESEARCH ARTICLE

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Risk of cancer in patients with thalassemia and sickle cell disease: a systematic review

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ABSTRACT

Background: Individuals with thalassemia or sickle cell disease (SCD) are at an elevated risk of developing cancer, yet the full extent of this risk remains inadequately characterised.

Methods: We conducted a systematic review using three databases (MEDLINE, EMBASE and Scopus) to compare the cancer risk in patients with thalassemia and SCD with that of the general population. Secondly, we assessed the impact of other putative risk factors in patients with thalassemia and SCD on cancer risk.

Results: Five studies from four countries were included, encompassing a total of 24,439 individuals overall. The risk estimates of developing cancer were highly variable, being affected by study design, population and comparators recruited, and type of cancer. The results showed an elevated cancer risk in SCD and thalassemia patient groups, with the highest incidence observed for hematologic malignancies (especially myeloid leukaemia in SCD patients). Patients with transfusion-dependent thalassemia had a significantly higher overall cancer risk, particularly hepatocellular carcinoma, compared to both non-transfusion-dependent patients and the general population. Other key factors seem to contribute to the increased cancer risk besides transfusion dependency, viral infections, and use of iron chelators. However, people with hemoglobinopathies appeared to be at lower risk of breast and prostate cancer compared to the general population.

Discussion: The findings are limited by variability among studies, including differences in control groups, inconsistent reporting of outcomes, and missing assessments of confounding factors. Therefore, future research with robust methods is essential to improve cancer surveillance and develop targeted prevention strategies for high-risk populations.

ARTICLE HISTORY
Received 13 January 2025
Revised 27 May 2025
Accepted 5 June 2025

KEYWORDS
Thalassemia; cancer incidence; sickle cell disease; systematic review

Introduction

Sickle cell disease (SCD) and thalassemia are inherited hemoglobin disorders that significantly impact life expectancy and quality of life. These diseases affect millions of people worldwide, particularly in the Mediterranean region, sub-Saharan Africa, India, and the Middle East [1–3].

Sickle haemoglobin is an abnormal haemoglobin caused by a point mutation in the beta (β) globin gene, which results in the substitution of a glutamic acid by a valine at position 6 of the β globin polypeptide chain [4]. SCD is the most common haemoglobinopathy occurring worldwide: it is a systemic disease that affects almost all the organs and leads to neurological, cardiac, pulmonary, hepatic, renal, ophthalmic, musculoskeletal and dermatological manifestations. Patients with homozygous sickle haemoglobin (SS) often present with severe symptoms, while those with a heterozygous mutant allele (SA) show minimal clinical symptoms. Mutations affecting genes in the α-globin or β-globin gene clusters, instead, affect haemoglobin synthesis and are responsible for thalassemia, which can be divided into three main clinical and haematological conditions of increasing severity (i.e. β-thalassemia carrier state, thalassemia intermedia, and thalassemia major) [5]. For patients with thalassemia major, blood transfusions serve as the primary treatment to relieve chronic anaemia resulting from ineffective erythropoiesis. In severe cases, patients undergo regular

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/07853890.2025.2522967.

blood transfusions along with continuous subcutaneous administration of iron-chelating agents to avert iron overload.

Advances in understanding the underlying mechanisms of these hemoglobinopathies and the use of more precise diagnostic tools, such as magnetic resonance imaging, have led to continuous improvements in therapeutic options, significantly increasing quality of life and life expectancy [6,7]. The increase in life expectancy in these patients may be accompanied by an increase in the prevalence of previously unrecognised age-related comorbidities [8].

Among these, the emergence of solid or hematological cancers is especially alarming: numerous case reports and original studies suggest a possible link between hemoglobinopathies and the development of solid and haematological malignancies [9–13]. Additionally, it is essential to explore whether these hemoglobinopathies and their clinical management increase the risk of cancer.

Besides the established cancer risk factors, patients with SCD or thalassemia may face additional risks that increase their likelihood of developing cancer. These risks include viral infections (for example, HIV or hepatitis C), oxidative damage caused by iron overload, and nonspecific immunomodulation resulting from frequent blood transfusions.

Iron can promote malignant transformation by inducing oxidative damage, leading to genotoxicity or immunological abnormalities, thus weakening cancer immune surveillance [14]. In patients with thalassemia major, in particular, inefficient erythropoiesis and frequent blood transfusions lead to a severe state of iron overload, potentially resulting in haemosiderin deposition in glomerular epithelial cells with an associated increased risk of renal cell carcinoma.

Iron overload is known to play a significant role in the pathophysiology of cancer through both direct and indirect mechanisms. Direct effects include DNA damage, where non-transferrin-bound iron generates reactive oxygen species (ROS), resulting in mutations in tumour suppressor genes, such as, and chromosomal strand breaks [15,16]. These alterations promote cellular proliferation and carcinogenesis, as evidenced by enhanced DNA synthesis and tumor growth in iron-enriched environments [16]. Indirectly, iron overload exacerbates oxidative stress, leading to lipid peroxidation that damages cell membranes and disrupts metabolic processes [17,18]. Additionally, iron-induced immunologic abnormalities, such as impaired lymphocyte proliferation and reduced macrophage tumoricidal activity, may diminish immune surveillance, further increasing cancer risk [19]. Collectively, these mechanisms highlight the dual role of iron in promoting cellular damage and creating a permissive environment for cancer development in patients with severe forms of thalassemia and SCD.

In addition to iron overload, chronic haemolysis and hemochromatosis have been proposed to increase the risk of developing clonal haematopoiesis, a premalignant condition that is, in turn, associated with myeloid cancers [20,21].

Similarly, chronic inflammation and oxidative stress, common features of both thalassemia and SCD [22–24], are key mechanisms involved in tumour initiation and progression [11]. Notably, the immune-anaemia axis has been proposed to correlate with cancer development [25,26]. Although still largely unexplored, this aspect may also be of primary importance for SCD and thalassemia patients.

Although some studies also suggested an association between the pharmacological treatments commonly used in hemoglobinopathies and an increased risk of cancer [27,28], evidence from long-term follow-up studies did not confirm this hypothesis [29]. Stem cell transplantation, which is potentially a curative approach, may also affect the risk of hematologic malignancies in SCD patients, particularly after graft rejection: it has been hypothesised that the shift from homeostatic to regenerative haematopoiesis in autologous cells exerts selective pressure, driving the clonal expansion and leukemogenic transformation of preexisting premalignant clones, ultimately leading to leukaemia [21]. Novel gene therapies and gene editing [21], which offer considerable hope for a more broadly applicable curative therapy for hemoglobinopathies, are currently under investigation. Genetic risk factors for myeloid malignancy development after curative therapy are presently being explored [30,31]. However, the limited number of patients treated to date, as well as the scarce data on long-term follow-up, prevent conclusions from being drawn concerning the cancer risk associated with this therapeutic approach.

Finally, disparities in the reporting of cancer incidences across the epidemiological studies available hinder a clear articulation of the current state of knowledge. This systematic review aims to synthesise the evidence on cancer risk in patients with SCD and thalassemia compared to the cancer risk in the general population. The secondary aim was to assess the impact of other putative risk factors, such as frequent blood transfusions or hematopoietic stem cell transplantation, on the risk of developing malignancies in people with SCD and thalassemia.

Materials and methods

Registration and review protocol

The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO 2024 CRD42024503935) and is publicly available at the following website link: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42024503935. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used to draft this review [32].

Information sources and search strategy

An experienced information specialist designed the search strategies for the MEDLINE, EMBASE, and Scopus databases based on a PECO-style approach. Only studies conducted on humans were searched, with no restriction on publication date. The search began on January 8, 2024, and the search strategies for each information source are reported in the Supplementary material – Search strategy.

Study selection process

The information specialist removed duplicates from the literature search results. Two independent researchers conducted an initial screening of titles and abstracts using Rayyan software [33]. References in literature reviews were also screened to identify other potentially relevant studies. Final eligibility was assessed through full-text evaluation based on the PECO framework's exclusion and inclusion criteria, summarised in Table 1. In particular, we labelled the main reason for exclusion according to the following criteria: 'foreign language' for studies not in English language; 'wrong population' for studies not involving human subjects or *in vitro* studies; 'wrong exposure' for studies not focus on individuals diagnosed with SCD or thalassemia; 'no comparator' for studies lacking of control group 'wrong comparator' for studies lacking a suitable control group; 'wrong outcome' for studies not assessing the incidence or prevalence of cancer in the included population; 'different study design' for studies that did not provide a proper comparison between exposed and unexposed population in terms of risk of cancer; 'wrong publication type' for studies that were not original research articles, such as editorials; 'reviews' for systematic, narrative and qualitative reviews. The results of the study selection process were documented based on the PRISMA flow chart [32].

Only studies published in English or Italian were included, without restriction on the publication period or geographic area.

Table 1. Inclusion and exclusion criteria.

PICOS strategy	Inclusion criteria	Exclusion criteria
P- Population	People of all sexes and ages. People from all geographical areas.	Studies not involving human participants.
E- Exposure	Thalassemia or sickle cell anemia (overall and by genotypes).	Studies on heterozygous patients (i.e. sickle cell trait or thalassemia trait).
C- Comparison	General population (Non-thalassemic or non-SCD- populations).	Studies with no control group reported.
O- Outcome	Primary outcome: incidence/prevalence of solid or hematological malignancies. Secondary outcome: overall survival of solid or hematological malignancies.	Studies that do not report data on the incidence or prevalence of hematological or solid malignancies.
S- Study design	Retrospective cohort studies, prospective cohort studies, cross-sectional studies, case-control studies, randomised controlled trials, and quasi-experimental studies.	Reviews, commentaries, editorials, conference proceedings, conference abstracts, and case reports.

Data extraction

Two reviewers independently conducted Data extraction using a standardised data extraction form created in Microsoft Office Excel. This form facilitated the systematic collection of relevant information and minimised the risk of data-collection bias. The extracted data included the following for each study: author, year of publication, country, study design, participant characteristics (number of exposed and unexposed participants, age, sex distribution, and nationality), information on exposure (i.e. condition), and control (i.e. healthy individuals, general population), primary outcomes (incidence or prevalence of malignancies), secondary outcomes (overall survival), length of follow-up, and relevant subgroup defining variables (i.e. Human immunodeficiency virus [HIV], Hepatitis C virus [HCV], Hepatitis B virus [HBV], blood transfusion dependency, drugs, iron chelating agents, iron overload markers, organ damage, stem cell transplant, cardiovascular comorbidities, and geographical macro-area). Authors of one of the SCD studies [34] were contacted through an academic social network to obtain missing data; however, no response was received.

The effect measures were those reported in the original studies for the incidence of malignancies. Effect measures were retained in the original metrics without conversion.

Risk of bias study

To critically evaluate the quality of the included studies, we used the Newcastle-Ottawa scale for Cohort

studies [35], which assigns a maximum score of nine points based on several aspects of the study design. Two independent authors (LM and CM) assessed the risk of bias. Disagreements were resolved through consultation with a third author (FV).

Synthesis methods

We summarized the characteristics of the included studies and presented the cancer incidence results in exposed and unexposed groups as reported in the original studies. Adjusted effect measures were reported when available rather than the crude measures. For studies not reporting incidence estimates but describing the number of observed events and the denominator in the exposed population (i.e. number of subjects or person-years), the crude incidence estimate was calculated. Because of the heterogeneity in the included populations, comparators, tumour site classifications, and the reported effect measures, no outcomes were deemed feasible for a meta-analysis. The results from the included studies were reported narratively and summarised in Table 2 to facilitate the critical appraisal of the available evidence, including subgroup considerations. No sensitivity analyses were conducted, and the certainty of the evidence was not assessed.

Results

Study selection

1,348 articles (drawn from EMBASE, Scopus, and MEDLINE) were identified using the search strategy described in the Materials and Methods section. After the preliminary screening and duplicate removal, 733 full-text articles were assessed for eligibility. Of these, 723 studies were excluded through abstract evaluation for not meeting the inclusion criteria, and five studies were excluded through full-text review, leaving five studies that met the eligibility criteria. The PRISMA flowchart in Figure 1 provides a detailed illustration of the selection process.

Characteristics of the included studies

Table 2 summarises the characteristics of the five included studies, all of which were cohort studies: two focusing on SCD patients [34,36], two focusing on thalassemia patients [37,38], and one focusing on patients with both conditions [39]. Of the studies on thalassemia patients, two focused on the differences between transfusion-dependent and non-transfusion-dependent disease [37,39]. In contrast, one focused on patients

Table 2. Main characteristics of the studies included in the systematic review.

Author year	Country	Study design	Type of exposure	Number of exposed, male (M), female (F)	Median age range (years)	Follow-up (years)	Unexposed subjects	Number of unexposed, male (M) female (F)	Median age range (years)	Viral infections (HBV/HCV)	Regular transfusion
Chung 2015 [32]	Taiwan	Longitudinal Nationwide Cohort Study	Thalassemia minor and major	2,655, 37.7% M 62.3% F	34.6	12	General Taiwanese population	10,620, 37.7% M 62.3% F	34.5	Control 215-120 Thalassemia	183 control 130
Santarone 2018 [33]	Italy	Monocentre retrospective cohort study	Transplanted thalassemia patients	122 61 M 61 F	10, (1-29)	30 y	Hematopoietic stem-cell donors for the transplant	122, 67 M 55 F	10 (1-48)	HSC donor 29 (24%) HBV 56 (46%) HCV Thalassemia patients: 33 (13%) HBV 139 (57%) HCV	YES
			Non-transplanted thalassemia patients	244 122 M 122 F	34, (24 – 39)						
Seminog 2016 [29]	England	Retrospective cohort study	SCD	7512, 54% M 46% F			Hospitalised people with minor medical and surgical conditions	118,821 M NA F NA	NA	NA	NA
Brunson 2017 [31]	USA	Retrospective cohort study	SCD	6,423	>30 years	22.2 person-year	General Californian population	NA	NA	NA	NA
Origa 2023 [35]	Italy	Multicentre retrospective cohort study	Thalassemia, SCD	4,631, 48% M 52% F	NA		General Italian population	NA	NA	YES (HCC patients only)	2579/3397 (transfused/total thalassemia patients)

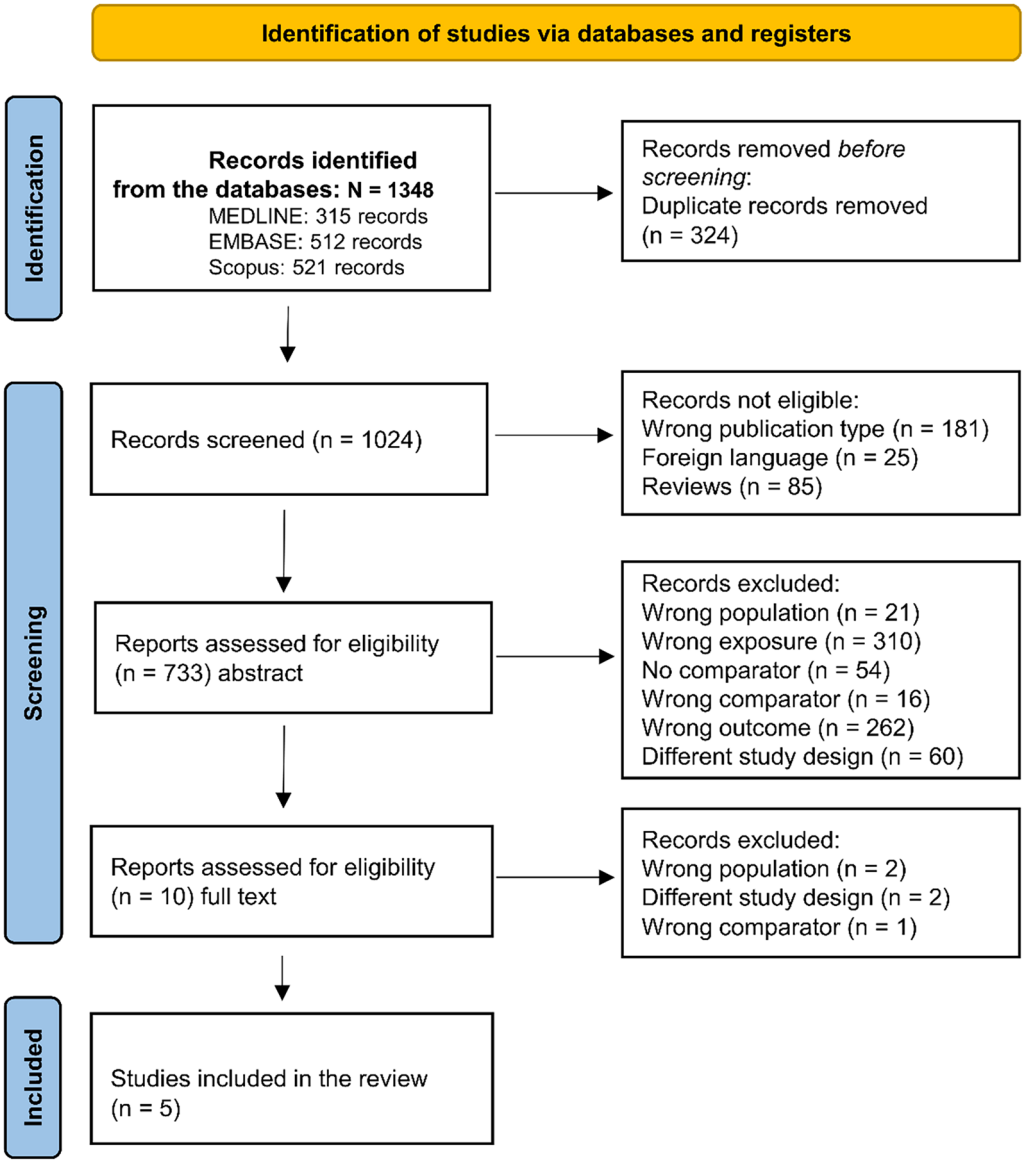

Figure 1. Flowchart illustrating the selection process for the five studies included in the review. The specific reason for exclusion has been defined according to the eligibility criteria described in Materials and methods.

who had undergone allogeneic hematopoietic cell transplantation (HCT) [38]. Two studies exclusively recruited patients with β-thalassemia [38,39], whereas Chung's analysis did not differentiate between thalassemia types [37]. Patients were identified through searches in local pathology registries [36], health insurance databases [37], hospital admission and discharge databases [34], internal registries of specialised centres [39], or registries of thalassemia patients who had undergone bone marrow transplantation [38].

The studies included in the review do not consistently report a precise diagnosis of hemoglobinopathy or explicitly state the severity of the condition. Two studies focusing on thalassemia patients [37,39] present the data categorising outcomes based on transfusion dependence, an indirect feature of β-thalassemia major. Finally, Santarone [38] divided the thalassemia patients into those who had undergone transplantation and those who had not.

Most of the studies were conducted in Europe, with one on the Black population in England [34], and two on Italian subjects [38,39]. One study was conducted in Taiwan [37], and the other in California (USA) [36].

Although all the included studies were cohort studies, they differed in their exposed population, comparators, and outcome assessments. The general population, deemed to be an unexposed group, was included in only two of the five studies [36,39]. The remaining three used hospitalised patients with minor medical or surgical conditions [34], stem cell donors [38], or the local, insured population without a diagnosis of thalassemia [37] as control cohorts.

While the registered protocol aimed initially to evaluate both the incidence and prevalence of cancer as primary outcomes, we could not assess prevalence since it was not reported in any of the eligible studies. Therefore, we were only able to synthetize data on cancer incidence. Incidence data were available in a limited number of studies. They were reported either as observed associations or, in three instances, as formal incidence estimates that utilized cumulative incidence or incidence rates. Furthermore, incidence was reported in a varied manner, either as a measure of the relationship between hazards (Hazard Ratio [HR], Relative Risk [RR]) [34,37] or as an incidence rate [36,38,39]. The secondary outcome, overall survival (OS), was reported in only one study [39]. Viral infections such as HBV and HCV, along with transfusion dependence, were reported in three of the five selected studies [37–39], and iron chelation therapy was assessed in two of the three studies on thalassemia patients [38,39].

Risk of bias study

The mean study quality score on the Newcastle-Ottawa Scale for assessing cohort studies was 6.8 out of 9 (SD = 1.5) [35]. Most studies did not adequately account for confounding factors: for instance, cirrhosis and viral infections, known risk factors for cancer development in the general population, were not adequately controlled in three of the five selected publications. Furthermore, additional therapies (i.e. transfusions or HCT) were not thoroughly investigated in the exposed cohort. On the contrary, since the mean age of thalassemia and SCD patients is usually lower than that of the general population, this factor has been appropriately considered by all the studies selected, which provided age-matched unexposed populations or age-adjusted results.

As previously discussed, all the studies reported the incidence of malignancies, whereas none documented prevalence, and only one reported OS. The median time to cancer diagnosis exceeded ten years. The duration of follow-up (at least 20 years, as reported by Santarone38] was considered sufficiently long in four studies. Table 3 provides detailed information on the quality assessment of the selected studies.

Results of individual studies

Table 4 summarizes the overall incidence of malignancies in patients with thalassemia and SCD.

This analysis yielded conflicting data for thalassemia patients. While Chung et al. [37] reported an increased risk of malignancy, the other two included studies reported a reduced risk of cancer compared to the control population (stem cell donors [38] or the general population [39], respectively). Chung et al. observed a 52% higher overall incidence of cancer in the Taiwanese thalassemia cohort of 2,655 patients (adjusted Hazard Ratio (aHR) = 1.54, 95% CI 1.15 to 2.07) [37], with 79 patients developing cancer during the follow-up period. Of these, 12 cases were haematological malignancies, indicating a 9-fold increased risk in this population (aHR = 5.32, 95% CI 2.18 to 13.0).

Santarone et al.recruited 488 patients in three subcohorts: 122 patients who had undergone transplantation, 244 non-transplanted patients, and 122 healthy Hematopoietic Stem Cell (HSC) donors. They observed a 30-year cumulative incidence of solid cancers amounting to 1.32% (95% CI 0.43–4.04, Table 4), corresponding to 3 out of 244 patients, compared to 1 out of 122 cases (3.23%, 95% CI 0.46–20.77, Table 4) in the control group of HSC donors. When considering the risk of developing cancer after HCT, they observed 8 out of 122 cases of cancer, corresponding to a significantly higher cumulative incidence of secondary solid cancers (13.24%, 95% CI 6.01–27.81) at 30 years post-transplant [38]. Unfortunately, the study did not report the incidence of solid cancers in the general population.

Table 3. Newcastle-Ottawa Assessment of the cohort studies considered in the systematic review.

	Study	Chung et al. 2015 [32]	Santarone et al. 2018 [33]	Seminog et al. 2016 [29]	Brunson et al. 2017 [31]	Origa et al. 2023 [35]
Selection	1. Representativeness of the exposed cohort	*			*	*
	2. Selection of the non-exposed cohort	*		*	*	*
	3. Ascertainment of exposure	*	*	*	*	*
	4. Demonstration that outcome of interest was not present at the start of the study	*	*	*	*	*
Comparability of the cohort based on the design and analysis	5a. Study controls for the main confounders (cirrhosis/liver damage, viral infections, HSC, transplantation.)		*			*
	5b. Study controls for any additional factor (transfusion, diabetes, drugs)					*
Outcome	6. Assessment of outcome	*	*	*	*	*
	7. Was follow-up long enough for outcomes to occur?	*	*		*	*
	8. Adequacy of follow-up of cohorts	*	*	*	*	*
	Total dcore	7	6	5	7	9

Table 4. Incidence of malignancies in patients with thalassemia and SCD (exposed) and related control groups (unexposed).

Author year	Population exposed	Exposed/total recruited	Groups of non-exposed	Groups of exposed	Incidence (cumulative, rates)	Observed association (aHR/ RR)	Observed malignancies in exposed (N)	Solid tumors	Hematologic tumors
Chung 2015 [32]	Thalassemia	2655/13275	Insured residents without a history of thalassemia	Patients diagnosed with thalassemia	Crude incidence rate 3.96 per 1000 person-years (79/19,960 p-ys) in exposed.	aHR = 1.54 (95% CI 1.15-2.07)	79	NA	N= 12 aHR 5.32 95% CI (2.18 to 13.0)
Santarone 2018 [33]	Thlassemia major (transplanted/non)	122	HSC donors (control group)	–	Cumulative incidence at 30 yrs. 3.23% (95% CI 0.46–20.77)	–	1	1	0
		122	–	Transplanted thalassemia patients	Cumulative incidence at 30 yrs. 13.24% (95% CI, 6.01–27.81)	–	8	8	0
		244	–	Non-transplanted thalassemia patients	Cumulative incidence at 30 yrs. 1.32% (95% CI 0.43–4.04)	–	3	3	0
Seminog 2016 [29]	Black people with SCD	7512/118821	Black English patients with minor medical or surgical conditions	Black people with SCD	Cumulative incidence 1,89%* (142/7512 exposed persons)	RR = 2.07 (95% CI 1.73-2.46)	142	NA	NA
Brunson 2017 [31]	SCD	6423	General population	Patients with SCD	Crude incidence rate 81.1 per 100,000* person-years (115/141,752 p-ys) in exposed.	Standardized incidence ratio 0.80 (95% CI 0.66-0.96)	115 SIR 0.80 (95% CI 0.66-0.96)	76 SIR 0.62 (95%CI 0.49-0.77)	31 SIR 1.72 (95%CI 1.17-2.44)
Origa 2022 [35]	Thalassemia, SCD	NA	Italian general population		Overall adjusted incidence rate 632 cases per 100,000 person-years	–	NA	NA	NA
		4631	–	Patients with Thalassemia and SCD	Overall adjusted incidence rate 442.1 (95% CI 339.7-700.5).	–	197	NA	21

*Proportions calculated by the review authors on data available from included studies.

Considering SCD patients [34,36], Seminog [34] reported a 2.07-fold increased risk of all cancers (RR = 2.07; 95% CI 1.76–2.46) in a cohort of 7,512 Black SCD patients in England, compared to 118,821 Black English patients with minor medical or surgical conditions (Table 4). Although the authors stated that they performed similar comparisons on SCD patients regardless of ethnicity, finding an RR of 1.4 (95% CI 1.2–1.6) compared to a broader control group, they did not provide detailed supporting data. In contrast, Brunson and colleagues [36] found that, among 6,423 Californian SCD patients, the overall standardised incidence ratio (SIR) of cancers was 0.80 (95% CI 0.66–0.96) compared to the general population. They observed a 38% reduced risk of solid tumours and a 72% increased risk of hematologic malignancies: among the 155 cancer cases observed, 76 were solid tumours (SIR = 0.62, 95% CI 0.49–0.77), and 31 were haematologic malignancies (SIR = 1.72, 95% CI 1.17–2.44) [36].

In an Italian cohort of 4,631 patients with hemoglobinopathies (3,397 with thalassemia, 815 with SCD, and 384 with other hemoglobin mutations) [39], Origa identified 197 cancers, of which 21 were hematological, with an incidence rate of 11.7 per 1,000. However, there was no statistically significant difference in the age-adjusted cancer incidence rate (442 cases per 100,000 person-years, 95% CI 339.7–700.5) compared to the general population (632 cases per 100,000 person-years, 95% CI), both when hemoglobinopathies were considered as a whole and after stratification by specific diseases. This study is also the only one among those selected reporting the secondary outcome, expressed as mortality rate by cancer, in hemoglobinopathies. In particular, the authors found that mortality from malignancy was similar to the general population, except for Hepatocellular Carcinoma (HCC), for which the Kaplan-Meier curve showed a particularly pronounced reduction in the probability of survival in transfusion-dependent thalassemia (TDT) patients [39].

Incidence stratified by type of cancer

Three of the five studies [34,36,37] were included to assess cancer risk stratified by type in individuals with thalassemia and SCD. Stratification by cancer type revealed further inconsistencies, driven by heterogeneity in tumour classification, the statistical methods applied, and population characteristics differing by ethnicity and specific diagnosis.

The stratified cancer risk for patients with thalassemia (Panel A) and SCD (Panel B) is summarised in Figure 2 and detailed in Table S1 of the supplementary

material. The study by Santarone et al. [38] was excluded from this subgroup analysis because it reported only cancers that developed after transplantation in thalassemia major patients. Similarly, the study by Origa et al. [39] was excluded because, although it reported adjusted incidence rates for various cancer subtypes, it did not stratify by specific haemoglobinopathy.

Only Chung et al. provided a detailed stratification of cancer incidence in thalassemia patients (Figure 2, Panel A), where they identified a significantly higher risk of developing both haematologic malignancies aHR = 5.32, 95% CI 2.18–13.0, as previously reported) and abdominal cancers, excluding the genitourinary system (aHR = 1.96, 95% CI 1.22–3.15), compared to a non-thalassemia population [37]. Regrettably, in addition to differentiating between transfused and non-transfused subjects, the authors evaluated thalassemia patients using a broad diagnostic category,

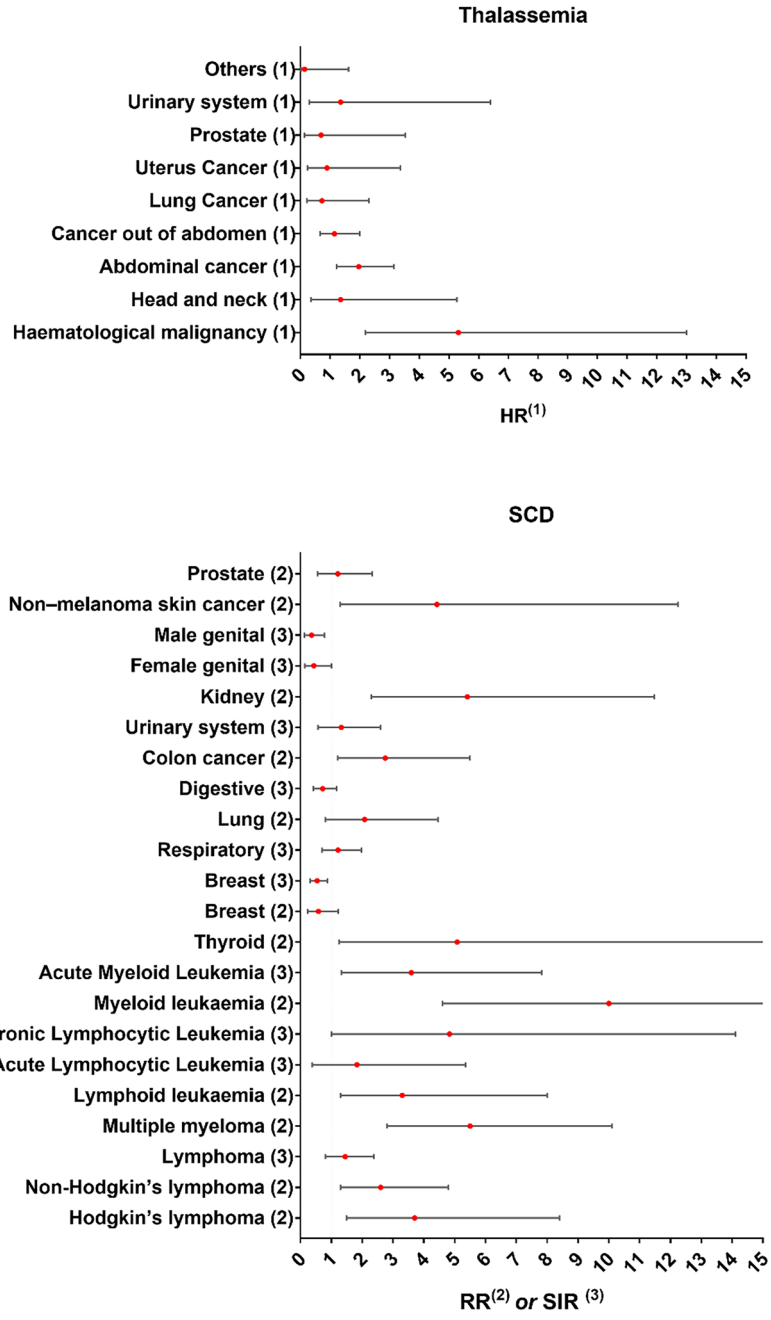

Figure 2. Risk of cancer in individuals with thalassemia (Panel A) or SCD (Panel B) compared to their respective general population/control groups, stratified by cancer type. The effect measures displayed in the Forest plots are reported as HR (1, chung 201532), SIR (3, brunson 201731) and RR (2, seminog 201629) with their corresponding 95% confidence intervals, according to the original study reports. Red dots indicate the point estimates, while horizontal bars extend from the lower to the upper limit of the 95% confidence interval for HR, RR, and SIR, respectively.

failing to distinguish among the various forms of the disease. This oversight is significant, as the different forms of thalassemia are associated with markedly diverse severity profiles and therapeutic requirements.

Both studies [34,36], focusing specifically on SCD patients, reported an increased risk of lung/respiratory and kidney/urinary system cancers. In contrast, the risk of breast cancer in females and prostate cancer in males was found to be lower than that of the control population (Figure 2, Panel B). Conversely, the findings for colon and digestive cancers showed an opposite trend. Notably, the Black English SCD population was found to have a higher risk of non-melanoma skin cancer (RR = 4.42, 95% CI 1.29–12.24) and thyroid cancer (RR = 5.08, 95% CI 1.25–15.41) (Figure 2, Panel B) [34]. Both studies [34,36] on SCD demonstrated that hematologic malignancies were more frequent in SCD patients. Seminog et al. [34] specifically reported significantly elevated RRs for Hodgkin's lymphoma (RR = 3.71, 95% CI 1.46–8.36), non-Hodgkin's lymphoma (RR = 2.63, 95% CI 1.34–4.76), multiple myeloma (RR = 5.46, 95% CI 2.78–10.05), lymphoid leukemia (RR = 3.33, 95% CI 1.26–7.97), myeloid leukemia (RR = 9.99, 95% CI 4.56–21.53), acute myeloid leukemia (RR = 11.05, 95% CI 3.86–30.17), and chronic myeloid leukaemia (RR = 11.35, 95% CI 2.25–52.74). However, these latter cancers were observed in a few patients and are not reported in Figure 2. Despite differences in the classification of haematologic diseases, Brunson et al. [36] also found an increased risk of these cancers in Californian SCD patients: leukaemia (SIR = 2.32, 95% CI 1.20–4.05), acute myeloid leukaemia (SIR = 3.59, 95% CI 1.32–7.82), chronic lymphocytic leukaemia (SIR = 4.83, 95% CI 1.00–14.11), acute lymphocytic leukaemia (SIR = 1.83, 95% CI 0.38–5.35), and lymphoma (SIR = 1.45, 95% CI 0.81–2.38).

Additional potential risk factors in patients with thalassemia and SCD

Transfusion dependence emerged as an additional risk factor for cancer in thalassemia patients. In the Taiwanese cohort, TDT patients had a higher risk of overall cancer (aHR = 6.70, 95% CI 3.29 to 13.6) compared to non-transfusion-dependent thalassemia (NTDT) patients. Further, the risk of developing haematological malignancies and abdominal cancer was found to be higher in the Taiwanese TDT patients, both when compared to NTDT (9.31 and 9.12, respectively) and to the control group (27.7-fold and 5.48-fold, respectively) [37].

In subjects with TDT, the likelihood of developing any type of neoplasm, including HCC, was significantly higher ($p < 0.001$), with an HCC incidence rate of 445 cases per 100,000 person-years, compared to 102 cases per 100,000 person-years in NTDT patients [39]. No significant difference was observed between the age-adjusted incidence rates of HCC in patients with SCD and the general population. In addition, male sex, anti-HCV antibody positivity, and HCV RNA detection emerged as significant risk factors for HCC in univariate analysis. All these factors, except anti-HCV positivity, were confirmed to be substantial in multivariate analysis [39]. Interestingly, no other tumours—whether solid or haematologic—were found to present a statistically higher risk in the Italian population of thalassemia and SCD patients [39].

Notably, HCT emerged as an additional risk factor (30-year cumulative incidence of 13.24%, as reported in Table 4). Eight transplanted patients were diagnosed with secondary solid cancer (SSC) at a median of 18 years after HCT and a median age of 33 years, with a median follow-up of 24 years [38]. The increased risk of secondary solid cancer was found to be four- to sixfold for patients treated with HCT compared with both hematopoietic cell donors and non-transplanted patients.

Although no additional potential risk factor was significantly associated with SCD patients, studies on SCD exhibit a critical source of bias related to how exposed and unexposed populations were selected, with registry size and data sources (for example, hospital records and specialised centres) contributing to discrepancies. Comparator populations rarely represented the general population, often including individuals with minor illnesses or pre-transplant donors, who may potentially distort results. Variability in the observation periods and evolving treatment protocols (for example, hydroxyurea and iron chelators) introduced further bias. Confounding factors were frequently underreported, complicating the interpretation of results, with only one study [19] acknowledging missing data in comparisons between Black and White SCD populations.

Discussion

This systematic review examined the existing literature on the risk of cancer in patients with thalassemia and SCD. Evidence from the included studies showed that patients with thalassemia and SCD have a different risk of developing cancer. However, inconsistencies in the results related to the reporting methods for the primary outcomes and the lack of appropriate adjustment for potential confounders hinder the accurate assessment of cancer risk in these patients compared to the risk in the general population.

Our systematic review revealed that patients with thalassemia (particularly those with TDT) are at higher risk of developing hematological malignancies and HCC, especially in the presence of hepatitis C virus (HCV) infection. Accordingly, NTDT patients, who experience less iron overload and fewer chronic liver infections, exhibit a lower cancer risk in general and HCC in particular compared to TDT patients [39]. Mortality from HCC was also found to be higher in thalassemia patients overall, and in TDT patients, in particular; however, OS from cancer, overall, was comparable to that of the general population [39].

Besides transfusion frequency, other significant risk factors for HCC identified include male sex, positivity to HCV RNA, and HCT. Regarding the increased risk of HCC in patients with thalassemia, a recent European study (not included in this systematic review due to the lack of an appropriate comparator) [40] confirmed the importance of iron overload and HCV infection in developing this disease. Iron overload, a common complication in thalassemia due to frequent blood transfusions and increased intestinal iron absorption, is known to promote oxidative stress, DNA damage, and fibrosis, creating a pro-carcinogenic environment in the liver. Chronic viral hepatitis accelerates liver fibrosis and cirrhosis, significantly increasing the risk of HCC. Thalassemia patients are particularly vulnerable to HCV due to historical exposure during blood transfusions before the implementation of rigorous screening protocols. Additional risk factors associated with lifestyle, such as smoking and alcohol consumption, further exacerbate liver damage by enhancing oxidative stress and inflammation, and their interplay with iron overload and viral infections may result in a synergistic effect for HCC development. It is worth noting, however, that positivity to HBV, obesity, alcohol abuse, and smoking were largely absent in the thalassemia patients cohort considered [40].

On the other hand, the incidence of thyroid cancer in thalassemia patients has yielded conflicting results. While Origa found no significant difference compared to the general Italian population [39], a previous study conducted in the same country (not included in this systematic review due to the absence of an appropriate comparator group) reported an increased risk of developing thyroid cancer in thalassemia patients [41].

Patients with SCD demonstrated a higher risk of hematological malignancies [34,36,39], a slightly reduced overall cancer risk, and a lower risk for certain solid tumours, such as breast cancer in females and prostate cancer in males [39]. In their study on a mixed population of patients with thalassemia and SCD, Origa reported only 11 cases of breast cancer compared with an expected 37, and just 1 case of prostate cancer compared with six expected cases. This suggests that breast cancer in women and prostate cancer in men are less common among individuals with hemoglobinopathies than in the general population. In this study, potential bias arising from the shorter average life expectancy of these patients, which limits their likelihood of reaching the advanced ages typically associated with solid tumour development, appears to have been mitigated with age adjustment in comparisons with the general population. Similar findings were observed in Seminog's research on Black English patients with SCD [34], indicating that the risk of breast and prostate cancer may be lower in these patients, potentially due to genetic or environmental factors associated with their conditions.

Besides the factors specifically related to the disease itself, it has been hypothesised that the genetic background and ethnicity of SCD patients, often of African descent, may also contribute to their susceptibility to certain types of cancer [34]. In these patients, high risks were reported for solid cancers of the stomach, colon, pancreas, prostate, and kidney. In contrast, risks were lower for non-melanoma skin cancer (RR = 0.6, 95% CI 0.3–1.0) and breast cancer in women (RR = 0.5, 95% CI 0.3–0.8), consistent with the lower risks observed in Black populations compared with White populations [34]. In particular, the lower incidence of skin cancers among individuals with SCD has been hypothesised to be associated with the protective effect of darker skin rather than the disease itself. On the other hand, the elevated risk of haematological malignancies, such as myeloid leukaemia and multiple myeloma, seems to be more strongly associated with SCD itself rather than ethnicity. For instance, the risk ratio for multiple myeloma calculated in the Black English population was almost half that of all English SCD patients, regardless of cultural background. While the same analysis, comprising all English SCD patients irrespective of ethnicity, had an RR of 8.9 [34]. SCD was also found to be strictly associated with renal medullary carcinoma [42], a rare tumour of the kidney first described in 1995 in a group of 34 patients, 33 of whom were young individuals with SCD [43].

Overall cancer mortality in patients with SCD had only been reported in Origa's study [39], and was found to be comparable to that of the general population, except for HCC. This finding appears to contrast with a previous study published by Brunson on a Californian cohort of SCD patients (not included in the final review) [44], where the authors observed a significantly worse OS compared with non-SCD cancer patients. Surprisingly, no differences were found when

stratifying by cancer type (hematological vs. solid tumours) in this study. The discrepancies between Origa's and Brunson's results may be partly due to differences in cancer classification:. For instance, Origa focused on tumour site-specific outcomes, whereas Brunson's analysis was limited to broader cancer categories (haematological vs. solid tumours). Moreover, geographic variations in HCC incidence may also play a role in the differences, as HCC is less common in North America than in Italy [40].

Both chronic inflammation and the use of hydroxyurea have been proposed as additional causative factors of the high incidence rate of haematological malignancies in patients with SCD. However, long-term follow-up studies have not yet confirmed this hypothesis [29,45,46]. Some authors attributed this increased risk to the high cellular turnover and chronic inflammation characteristic of SCD patients, which may result in a higher frequency of acute leukaemia and myelodysplasia mutations [47]. In fact, the chronic haemolysis and secondary haemochromatosis related to the pathophysiology of SCD lead to chronic inflammation and persistent bone marrow stress, predisposing patients with SCD to clonal haematopoiesis. This premalignant condition is significantly associated with an enhanced risk of developing myeloid cancers [20]. Clones generated by clonal haematopoiesis may be more resistant to radiation and/or chemotherapy, and as a result, they may preferentially expand after a failed transplant, leading to the myeloid malignancy detected following graft rejection [21]. Conversely, the reduced risk of solid tumours may be linked to the sickling of red blood cells, which could have antiangiogenic effects, limiting the growth of solid tumours [18].

Despite being potentially curative, HCT, gene therapy and gene editing have also been associated with a higher-than-expected incidence of myelodysplastic syndromes and acute myeloid leukaemia, particularly after graft rejection following non-myeloablative conditioning and myeloablative lentivirus-based gene therapy [48]. Genetic risk factors predisposing to myeloid malignancy are currently under investigation [30,31]. Unfortunately, we still have little data available, especially in the context of new gene therapies [49]. Few patients have been treated with these innovative therapies to date [50–54], or, the follow-up is not long enough yet to draw conclusions concerning the incidence of cancers, which, as we know, may occur several years after therapy.

Several essential considerations apply to the biases in the literature available on cancer risk in hemoglobinopathies, which may lead to confounding results. The classification of the exposed population poses a significant challenge in thalassemia studies, a disease where the type of mutation can result in profound differences in disease severity, complications, and the therapeutic approaches adopted. This bias does not apply to SCD studies, as all such patients are characterised by a homozygotic single-point mutation. Studies with large, robust samples [37] tend to provide more reliable results, while smaller studies recruiting fewer than 150 cases [38] lack statistical power and, therefore, reduce the generalisability of the findings. In many of the selected studies, the lack of a comparator truly representative of the general population contributed to different results in both thalassemia and SCD patients. Finally, the heterogeneity in the geographical distribution of the incidence of many cancers and the role of ethnicity in the likelihood of developing malignancies also affect the generalisability of the findings.

Limitations of this study

Despite the efforts to include studies in multiple languages, the focus on English-language publications may have introduced bias.

The heterogeneity of the research, characterised by substantial differences in study design, population characteristics, interventions, and outcomes, was a significant limitation, preventing direct comparisons and robust meta-analysis. The lack of studies from countries where SCD or thalassemia are most prevalent, such as Sub-Saharan Africa, parts of South Asia, and the Middle East, was another limitation in the systematic review. This geographic gap may be due to the limited research infrastructure, publication bias, or a lack of international visibility for studies conducted in these regions. The exclusion of these populations is significant since the genetic and environmental factors influencing the incidence and management of these conditions are highly variable across different settings. Including data from high-prevalence areas is crucial for developing a more comprehensive understanding of disease patterns and informing culturally appropriate healthcare interventions.

The inconsistent reporting of key secondary outcomes, such as overall survival, posed challenges, as many were either missing or inadequately detailed. Furthermore, the underreporting of therapeutic regimens and patient comorbidities limited the evaluation of treatment effects and the generalisability of findings.

Implication for research

With our systematic review, we highlighted that most of the literature on the risk of malignancies in hemoglobinopathies has significant limitations, including

inconsistent reporting of diagnosis and disease severity, and a lack of representative age-matched control groups.

Future research should first ensure standardised reporting of diagnosis, disease severity, and treatment protocols. To provide an accurate monitoring of cancer incidence, particularly for solid tumors, and assess overall survival, the studies should include large, diverse cohorts with long-term follow-up. Control groups must be representative of the general population, thereby avoiding biases that can arise from using selected populations. Age-matched and age-adjusted analyses are essential to account for the lower life expectancy of these patients. Confounding factors such as cirrhosis, viral infections, and additional therapies (e.g. transfusions, iron chelation, and iron overload) should be rigorously controlled. Data collection should be standardized across multiple geographic regions to account for ethnic and geographical heterogeneity in cancer incidence.

Additionally, studies should document cancer incidence by exposure, using transparent reporting methods and ideally population-based data. Collaboration with specialized centres and registries can enhance data quality, while ensuring robust statistical power requires sufficient sample sizes. This approach would improve the reliability and generalizability of findings, providing a clearer understanding of cancer risks in thalassemia and SCD populations.

Conclusions

The findings of this review have significant implications for managing and monitoring cancer in patients with SCD and thalassemia, particularly as concerns the influence of ethnicity, sex, age, region, and the timing of interventions such as transfusion regimens and iron-chelation therapy. The social context surrounding these patients increases their vulnerability and may contribute to a heightened risk of malignancies. Many individuals with these hemoglobinopathies often live in socially disadvantaged conditions, particularly in the Global South, while in Europe and the Americas, they predominantly affect ethnic minorities who face inequities in social determinants of health, including inadequate housing, precarious employment, limited educational opportunities, substandard care, and systemic discrimination [55–57].

Additionally, some secondary findings underscore the need to consider specific procedures for thalassaemia patients in future epidemiological studies on cancer incidence. Notably, transfusions and transplantation have been identified as potential risk factors, with transfusions demonstrating a clear association, while further investigation of transplantation is warranted.

Future research should focus on elucidating the mechanisms behind the elevated cancer risk in these populations using rigorous methodologies, incorporating general population controls, and accounting for critical confounding factors.

Acknowledgment

The authors would like to thank AVIS Comunale di Reggio Emilia for financially supporting this project with a generous contribution.

Ethical approval statement

No ethical approval was necessary for this systematic review since no primary data has been collected.

Author contributions

CRediT: **Lucia Merolle**: Conceptualization, Data curation, Methodology, Writing – original draft, Writing – review & editing; **Luca Ghirotto**: Conceptualization, Methodology, Writing – review & editing; **Davide Schiroli**: Data curation, Formal analysis; **Giulietta Luul Balestra**: Validation; **Francesco Venturelli**: Data curation, Formal analysis, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing; **Maria Chiara Bassi**: Data curation; **Di Bartolomeo Erminia**: Supervision; **Roberto Baricchi**: Supervision; **Chiara Marraccini**: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Protocol registration

The study is registered with the International Prospective Register of Systematic Reviews (PROSPERO 2024 CRD42024503935).

Funding

This study was partially supported by the Italian Ministry of Health – 'Ricerca Corrente Annual Program 2025' and by a liberal contribution of AVIS Comunale di Reggio Emilia.

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Data availability statement

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

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