ARTICLE

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Prevalence of osteoporosis among patients after stem cell transplantation: a systematic review and meta-analysis

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The prevalence of osteoporosis in post stem cell transplantation (SCT) is poorly defined. We performed a systematic review and meta-analysis to determine the prevalence of osteoporosis in patients with hematologic diseases who underwent SCT. PubMed, EMBASE, and Web of Science were searched (from inception to 30th April 2023) using Medical Subject Headlines to find studies that assessed the prevalence of osteoporosis among post SCT. Thirteen articles meeting the inclusion criteria were included in the analysis. The pooled prevalence rates of osteoporosis, osteopenia, and decreased bone mineral density (BMD) were determined to be 14.2% (95% CI 9.7–18.8), 36.0% (95% CI 23.8–48.2), and 47.8% (95% CI 36.6–58.9), respectively. Substantial heterogeneity was observed among the included studies (I^2 values ranged from 81% to 99%). Subgroup analyses revealed variations in prevalence based on gender, follow-up duration, age, region, sample size, and study quality. These findings suggest a high prevalence of osteoporosis in post-SCT patients. Given the negative impact of osteoporosis on prognosis and recipient survival, clinicians should prioritize preventive measures, early diagnosis, and effective treatments to minimize its impact.

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INTRODUCTION

Allogeneic or autologous stem cell transplantation (SCT) can cure a variety of malignant and nonmalignant hematologic diseases [1, 2]. With the advancements in treatment modalities and notable improvements in safety measures and supportive care, significant progress has been made in the field of transplantation over the past few decades, including an expansion of the age limit for transplantation, an increase in the availability of diverse donors, enhanced histocompatibility testing, safer conditioning regimens, more effective graft-versus-host disease (GVHD) prophylaxis, and improved management of opportunistic infections, all of which have led to a substantial increase in the number of transplant recipients and significantly extended the life expectancy of survivors [1]. The increasing patient population suffering from late effects of SCT, such as osteoporosis, a systemic condition characterized by impaired bone microarchitecture and reduced BMD resulting in bone fragility and increased fracture susceptibility [3, 4], where a 1 SD reduction in BMD approximately doubles the risk of fracture [3], often leads to functional decline, disability, chronic pain, significantly impacting patient's quality of life, functional independence, and increasing healthcare costs and mortality rates [5, 6].

Among patients undergoing transplantation, osteoporosis is a common disease that has been well-documented in solid organ recipients, especially renal [7], hepatic [8], lung [9, 10], and heart [11] transplant recipients, revealing its high prevalence and associated complications. However, its overall prevalence in post-SCT have not been well-described. Therefore, we decided to conduct a systematic review of existing studies in this field and perform a meta-analysis to investigate the global prevalence of osteoporosis in post-SCT, as this information is of significant importance for future service planning and resource allocation.

METHODS

Search strategy and selection criteria

We conducted this systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [12]. The study protocol was registered with the PROSPERO International Prospective Register of systematic reviews (CRD42023401230). We searched PubMed, EMBASE, and Web of Science for relevant observational studies on bone health in patients post-SCT, without language restrictions (Appendix 1), and ended on April 30, 2023. Additionally, we examined reference lists of previous reviews and key articles for additional studies.

Eligibility criteria and study selection

Two reviewers (Yumei Yang and Jinshu Guo) independently screened titles and abstracts for eligibility using EndNote (version X9.1) and subsequently conducted a full-text review.

Inclusion criteria were: (1) Randomized controlled trials (RCTs), cohort, or case-control studies; (2) Patients with hematologic diseases who underwent SCT as the study population; (3) Hematologic disease diagnosis based on International Classification of Diseases (ICD) criteria or medical professionals' assessment; (4) Outcome of interest being the prevalence of osteoporosis and/or osteopenia determined by dual-energy X-ray absorptiometry (DXA) or quantitative computed tomography (QCT); (5) Exposure variable including the reporting of BMD measured at specific

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sites (e.g., spine, hip) or total body. Alternatively, studies providing sufficient data to calculate the prevalence of osteoporosis and osteopenia were also considered. We excluded pediatric studies, non-English articles, case series, reviews, conference abstracts, guidelines, and studies with unclear or insufficient information. For studies published in multiple reports, we selected the one with the largest sample size and/or the longest follow-up times as appropriate.

Data extraction and quality assessment

We extracted the following data from each included study: first author, publication year, journal, country of recruitment, study design, duration of follow-up, mean or median age of transplantation, proportion of male participants, number of participants in the cohort and control groups, rates or numbers of osteoporosis and/or osteopenia cases, details of DXA/QCT assessments, evaluated sites, underlying hematologic disease, type of transplant, graft source, and criteria used to diagnose osteoporosis. In cases where data was missing, we contacted the corresponding authors for additional information. Two reviewers (Yumei Yang and Jinshu Guo) independently extracted the data from each study and resolved any discrepancies through discussion.

The methodological quality of the eligible studies was independently assessed by the two reviewers using the Newcastle-Ottawa Scale (NOS) tool [13]. We categorized studies with total scores of 0 to 3, 4 to 6, and 7 to 9 as low, moderate, and high quality, respectively [14].

Statistical analysis

The primary outcome of our meta-analysis was the prevalence of osteoporosis in post-SCT patients. The secondary outcomes included the prevalence of osteopenia and decreased BMD (osteoporosis and osteopenia). Each outcome, such as different follow-up durations or assessments at different sites, was considered as a separate study and included in the meta-analysis.

We calculated the prevalence and corresponding 95% confidence intervals (CIs) using percentages. To account for variations between studies, a random-effects model was utilized to compute a pooled estimation, which provided a more conservative estimate of the prevalence. Statistical heterogeneity between studies was evaluated using I^2, with values ranging from 0% to 100% [15]. Significant heterogeneity was defined as $I^2 \geq 50\%$ and $p < 0.05$ [16]. Subgroup analyses and meta-regression were conducted to explore potential sources of heterogeneity. Sensitivity analyses were performed by excluding individual studies to assess their impact on the overall results of the meta-analysis. Publication bias was assessed using funnel plots and, if applicable, Egger's test. A significance level of $p < 0.05$ was considered statistically significant. All statistical analyses were conducted using R software (version 4.1.2, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Identification of relevant studies

The search and selection process is shown in Fig. 1. We identified a total of 1423 articles from the 3 database searches. Of these, 97 full-text articles were retrieved for further screening and 84 articles were excluded, 13 articles were qualified for the final systematic review and meta-analysis [17–29].

Characteristics of included studies

Tables 1 and 2 provide a summary of the key characteristics of 13 articles related to osteoporosis in patients undergoing SCT [17–29]. These articles were conducted across multiple countries, with 3 articles from America [23, 25, 29], 3 from Canada [19, 21, 24], 2 from Germany [27, 28], and 5 from other countries including Spain [17], Switzerland [18], France [20], Sweden [22], and Italy [26]. Among the included studies, 10 were prospective cohort studies [17, 19, 20, 22, 23, 25–29], while 3 were retrospective cohort studies [18, 21, 24], with publication dates spanning from 1997 to 2022. The mean or median ages of the patients varied from 31.3 to 57 years [17–29], and the median follow-up duration after SCT varied from 4 months to 20 years [17–29]. The cohort sizes in the included articles ranged from 18 to 652 patients [17–29], with 12 articles reporting the proportion of males, which varied from 0% to 68% [17–20, 22–29].

The majority of patients included in the articles were diagnosed with hematologic diseases and underwent either allogeneic or autologous SCT using bone marrow or peripheral blood as graft sources, although cord blood was also occasionally utilized. Seven articles reported on the incidence or rate of graft-versus-host disease (GvHD) [17, 20, 22–25, 27], which ranged from 26% to 90%. The diagnostic criteria for osteoporosis, 12 articles followed the guidelines established by the World Health Organization (WHO) [17–20, 22–29], while 1 article did not specify the diagnostic criteria used [21]. When measuring BMD, 11 articles utilized DXA [17–20, 22–27, 29], while 1 article employed QCT [28], and 1 article did not mention the method used for BMD assessment [21].

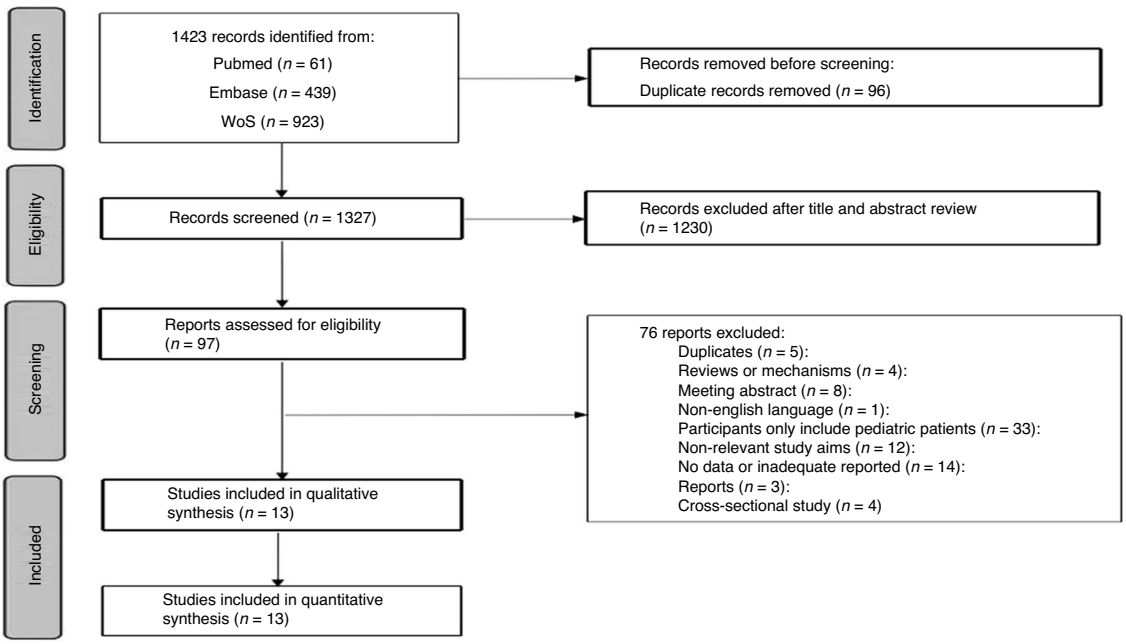

Fig. 1 PRISMA flow diagram.

Table 1. Characteristics of the included studies.

Study	Country	Study-type	From	TO	follow-up period	Males %	age(years)	Hematologic disease	Transplant type (%)	Graft source (%)	GVHD (%)	NOS
Leguy, 2022	France	PC	2005	2016	6 (6–7) m	55.8	47.8 ± 13.8	AML, ALL, CLL, NHL, HL, TL, MDS, MPD, CML	Allo-SCT (100)	BM (59.3), PB (37.6), Placenta (3.1)	GVHD = 65.1%	6
					38 (31–44) m							
Seneviratne, 2021	Canada	RC	1979	1998	20 y	NR	57 (37–77)	AML, ALL, CML, MDS, CLL, MM, NHL, AA	Allo-SCT (100)	BM (94), PB (6)	NR	6
Gubrianska, 2019	Sweden	PC	1994	2000	13.4 y (11–15) y	60	36.1 (22–58)	AML, CML	Allo-SCT (100)	BM (30), PB (70)	GVHD = 90%	6
Yao, 2010	America	PC	2006	2009	4 m	51	Auto-SCT: 57 (25–74), Allo-SCT: 45 (18–71)	AL, Lymphoma, Myeloma	Auto-SCT (52), Allo-SCT (48)	BM (13), PB (87)	aGVHD =85% (0–I = 28%, II-IV = 57%)	4
Abou-Mourad, 2010	Canada	RC	1981	2002	8.6 y (2.3–22.8) y	54.3	39 (14–57)	CML, AML, NHL, MDS, MM, ALL, AA, PNH, CLL, Myelofibrosis,	Allo-SCT (100)	BM (91.4), PB (7.7), BM + PB (0.9)	cGVHD = 53.1%	6
Yao, 2008	America	PC	2000	2005	4 m	59	41 (23–66)	AML, ALL, CML, MM, Lymphoma	Allo-SCT (100)	BM (24), PB (72), Cord blood (4)	aGVHD = 33% (<6 months), aGVHD = 42% (≥6 mouths)	4
Massenkeil, 2001	Germany	PC	1996	1999	6m	52	36 (17–56)	ALL, AML, MDS, CML	Allo-SCT (100)	BM (63), PB (37)	aGVHD = 56% (I–II 40%, III–IV 16%), cGVHD = 45%	4
					12 m							
Schulte, 2000	Germany	PC	1995	1997	12 m	59	37 ± 10 (18–58)	AML, ALL, CML, MDS, NHL	NR	BM (60), PB (40)	Not reported	6
					24 m							

Table 1. continued

Study	Country	Study-type	From	TO	follow-up period	Males %	age(years)	Hematologic disease	Transplant type (%)	Graft source (%)	GVHD (%)	NOS
Kashyap, 2000	America	PC	1995	1998	3–4 m	68	43 (31–54)	ALL, AML, CML, MDS, NHL, MPD, Myelofibrosis	Allo-SCT (100)	BM (100)	Not reported	5
					6–8 m							
					12–14 m							
Castañeda, 1997	Spain	PC	NR	NR	33.6 ± 34.5 m	0	31.3 ± 9.9	AML, CML, ALL,	Allo-SCT (52),	BM (100)	GVHD = 26%	6
					(7–158) m		(16–49)	NHL, HL, AA,	Auto-SCT (48)			
								RAEB				
Baumgartner, 2019	Switzerland	RC	2003	2014	55.2 m	60	49.7	ALL, AML, CLL,	Allo-SCT (100)	NR	NR	6
					(20.4–100.8) m		(39.1–58.8)	CML, MM, MPN,				
								MDS,				
								Lymphoma,				
								Secondary leukemia				
Schimmer, 2001	Canada	PC	1999	2000	4.2 y	55	49.6	NHL, HD, AML, MM	Auto-SCT (100)	BM or PB	NR	6
					(4.9m–11.4 y)		(23.5–68.2)					
Ria, 2007	Italy	PC	1999	2000	5.4 y	54	46 (25–68)	NHL, HL, MM, AL,	Auto-SCT (100)	NR	NR	9
					(4.3m–11y)			CLL,				
								WaldenstrÖm's macroglobulinemia				

PC prospectively cohort study, *RC* retrospectively cohort study, *CSC* cross-sectional studies, *NR* not reported,
AML acute myeloid leukemia, *ALL* acute lymphocytic leukemia, *AL* acute leukemia, *CML* chronic myeloid leukemia, *CLL* chronic lymphocytic leukemia, *NHL* non-Hodgkin lymphoma, *HL* Hodgkin lymphoma, *HD* Hodgkin's disease, *TL* T-Cell leukemia, *MDS* myelodysplastic syndrome, *MPD* myeloproliferative disorders, *AA* aplastic anemia, *PNH* paroxysmal nocturnal hemoglobinuria, *RAEB* refractary anemia with excess of blasts, *Allo-SCT* allogenic stem cell transplantation, *Auto-SCT* autologous stem cell transplantation, *BM* bone marrow, *PB* peripheral blood, *GvHD* graft-versus-host disease, *aGvHD* acute GvHD, *cGvHD* chronic GvHD.

Table 2. Prevalence of osteoporosis among SCT in 13 Articles.

Author	Year	Assessment time	Sites	DXA/ QCT	Criteria	Patients, *n*	OP, *n*	Osteopenia, *n*	Decreased BMD, *n*
Leguy et al.	2022	6 m	Total hip, Femoral neck, Lumbar spine	DXA	WHO	246	56	125	181
	2022	3 y	Total hip, Femoral neck, Lumbar spine	DXA	WHO	228	40	119	159
Seneviratne et al.	2021	20 y	NR	NR	NR	172	25	3	28
Gubrianska et al.	2019	10 y	Femoral neck, Total hip, Lumbar vertebrae (L1-L4), Total body	DXA	WHO	20	2	2	4
Yao et al.	2010	4 m	Lumbar spine (L2-L4)	DXA	WHO	197	9	51	60
	2010	4 m	Dual femur	DXA	WHO	197	12	55	67
Abou-Mourad et al.	2010	8.6 y	NR	NR	WHO	369	-	-	90
Yao et al.	2008	<6 m	Lumbar spine (L2-L4), Dual femur	DXA	WHO	27	-	-	13
	2008	≥6 m	Lumbar spine (L2-L4), Dual femur	DXA	WHO	19	-	-	9
	2008	6 m	Lumbar spine (L2-L4)	DXA	WHO	27	-	-	10
	2008	>6 m	Lumbar spine (L2-L4)	DXA	WHO	19	-	-	7
	2008	6 m	Dual femur	DXA	WHO	27	-	-	11
	2008	>6 m	Dual femur	DXA	WHO	19	-	-	9
Massenkeil et al.	2001	6 m	Lumbar spine(L1-3)	QCT	WHO	36	11	13	24
	2001	12 m	Lumbar spine(L1-3)	QCT	WHO	32	9	11	20
Schulte et al.	2000	1 y	Lumbar spine (L2-4), Proximal left femur (femoral neck, trochanter, Ward's triangle)	DXA	WHO	78	4	34	38
	2000	2 y	Lumbar spine (L2-4), Proximal left femur (femoral neck, trochanter, Ward's triangle)	DXA	WHO	35	3	13	16
Kashyap et al.	2000	3–4 m	Lumbar spine (L2-4)	DXA	WHO	21	-	4	4
	2000	6–8 m	Lumbar spine (L2-4)	DXA	WHO	18	-	7	7
	2000	12–14 m	Lumbar spine (L2-4)	DXA	WHO	21	-	8	8
	2000	3–4 m	Proximal left femur (femoral neck, trochanter, Ward's triangle)	DXA	WHO	21	-	3	3
	2000	6–8 m	Proximal left femur (femoral neck, trochanter, Ward's triangle)	DXA	WHO	18	-	6	6
	2000	12–14 m	Proximal left femur (femoral neck, trochanter, Ward's triangle)	DXA	WHO	21	-	10	10
Castañeda et al.	1997	33.6 m	Lumbar spine (L2-L4)	DXA	WHO	27	5	9	14
Baumgartner et al.	2019	55.2 m	NR	DXA	WHO	652	90	235	325
Schimmer et al.	2001	4.2 y	Lumbar spine(L1–L4), Femoral neck	DXA	WHO	64	5	34	39
	2001	4.2 y	Lumbar spine(L1–L4)	DXA	WHO	64	1	17	18
	2001	4.2 y	Femoral neck	DXA	WHO	64	5	30	35
Ria et al.	2007	5.4 y	Lumbar spine(L1–L4), Wrist	DXA	WHO	180	45	72	117
	2007	6 m	Lumbar spine(L1–L4)	DXA	WHO	180	58	74	132
	2007	24 m	Lumbar spine(L1–L4)	DXA	WHO	180	22	58	80
	2007	6 m	Wrist	DXA	WHO	180	38	67	105
	2007	24 m	Wrist	DXA	WHO	180	16	43	59

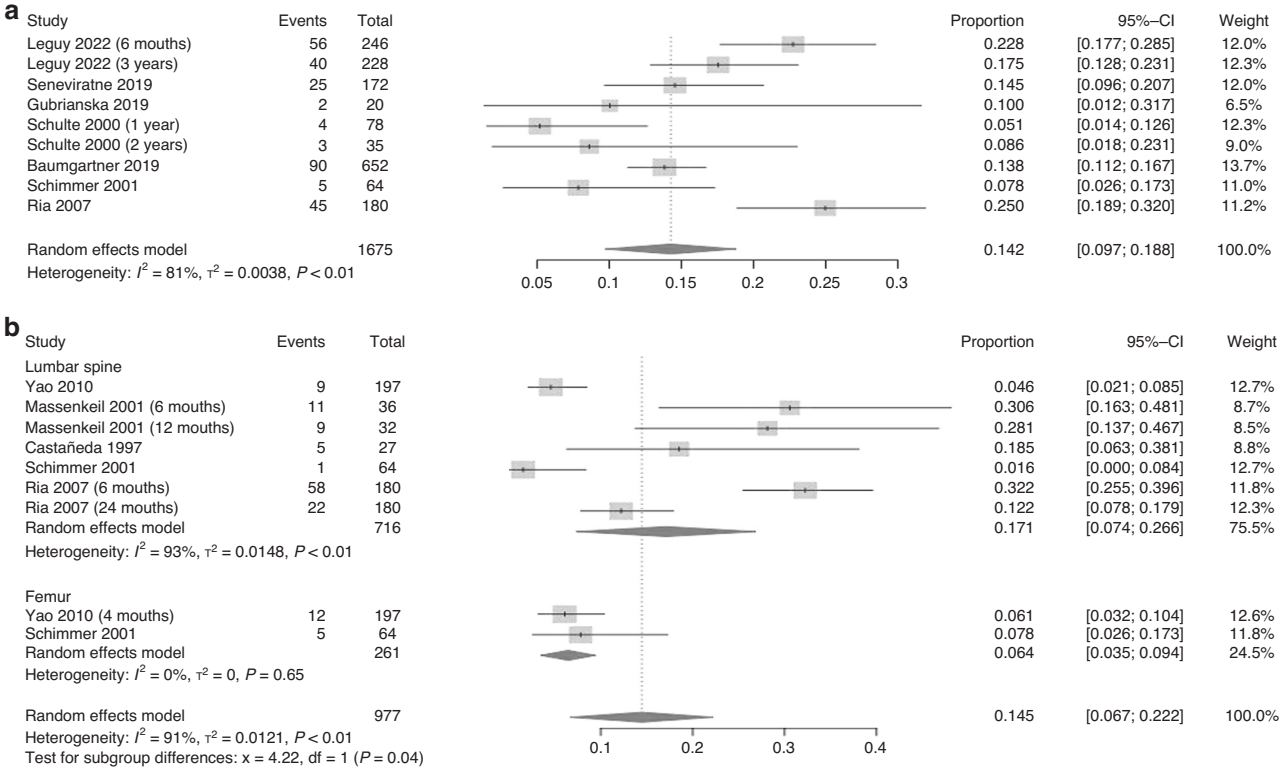

Fig. 2 Forest plot for the estimated osteoporosis prevalence in post-SCT. a The forest plot of overall osteoporosis prevalence in post-SCT. **b** The forest plot of osteoporosis prevalence in osteoporosis based on lumbar spine/femur. post-SCT post stem cell transplantation, CI confidence interval.

Risk of bias within studies

Details of the quality of the cohort studies as assessed by NOS are shown in Supplemental Table 1. Most studies included were ranked as moderate quality according to the NOS scale (4 to 6 stars out of 9).

Outcomes

Prevalence of Osteoporosis among post-SCT. The pooled prevalence estimate of osteoporosis from 9 studies (7 articles) [18–22, 26, 28] was14.2% (95% CI 9.7–18.8, $N = 1675$), with a significant evidence of between-study heterogeneity ($I^2 = 81\%$, $p < 0.01$) (Fig. 2a). Osteoporosis incidence rates in lumbar spine were reported in 7 studies (5 articles) [17, 19, 23, 26, 27], yielding a pooled prevalence rate of 17.1% (95% CI 7.4–26.8; $I^2 = 93\%$; $N = 716$). Only 2 studies (2 articles) reported osteoporosis incidence rates in femur [19, 23], resulting in a pooled prevalence rate of 6.4% (95% CI 3.5–9.4; $I^2 = 0\%$; $N = 261$) (Fig. 2b).

Sub-group analysis. The incidence of osteoporosis varied in SCT based on several factors within the subgroups analyzed (Table 3 and Figs. S1–9). In European studies [18, 20, 22, 26, 28], the incidence was 15.1% (95% CI 9.5–20.7) higher than the observed 11.5% (95% CI 4.9–18.0) incidence in America [19, 21] (Fig. S1). Incidence rates of osteoporosis were 13.1% (95% CI 8.5–17.6) for studies with a follow-up period of one year or longer [18, 19, 21, 22, 26, 28], and 22.8% (95% CI 17.7–28.5) for studies with a follow-up period of less than one year [20] (Fig. S2). Among SCT aged 45 years or older, the incidence was 16.9% (95% CI 12.1–21.6) [18–21, 26], while for those younger than 45 years, it was 6.3% (95% CI 2.2–10.4) [22, 28] (Fig. S3). Studies with a sample size exceeding 100 reported an incidence of 18.3 (95% CI 14.0–22.6) [18, 20, 21, 26], whereas studies with a sample size below 100 reported a lower incidence of 6.7% (95% CI 3.2–10.2) [19, 22, 28] (Fig. S4). A male proportion of less than 55% in the studies resulted in a higher incidence of osteoporosis among SCT (25.0%, 95% CI 18.9–32.0) [26], while a male proportion of 55% or greater had a lower incidence of 12.7% (95% CI 7.7–17.6) [18–20, 22, 28] (Fig. S5). High-quality studies indicated an incidence of osteoporosis of 25.0% (95% CI 18.9–32.0) among SCT [26], while moderate-quality studies reported a prevalence of 13.0% (95% CI 8.7–17.2) [18–22, 28] (Fig. S6). Subgroup analysis by publication year after 2010 reported a prevalence of 16.4% (95% CI 12.7–20.1), whereas studies with publication year before 2010 reported a lower incidence of 11.6% (95% CI 2.6–20.7) (Fig. S7). Study types and transplantation types showed similar prevalence to the overall prevalence (Figs. S8 and S9). However, despite these subgroup analyses, heterogeneity persisted within each subgroup.

Heterogeneity and meta-regression. To further explore the source of heterogeneity, a meta-regression method was employed. In the multivariate meta-regression analysis, variables including male proportion, age, and follow-up period were found to be statistically significant ($p < 0.0069$, $p = 0.0017$, $p = 0.0162$, respectively) (Table 4), collectively explaining 97.02% of the observed heterogeneity.

Sensitivity analysis. Sensitivity analyses were performed by excluding one study at a time to assess its impact on the pooled prevalence of osteoporosis in SCT. These analyses demonstrated that no individual study had a significant influence on the overall results (Fig. 3).

Publication bias. Funnel plots were visually examined to evaluate the presence of publication bias. The funnel plot observed in SCT demonstrated asymmetry, suggesting the potential presence of publication bias (Fig. 4).

Table 3. Subgroup analysis of the prevalence of osteoporosis in SCT.

Subgroups	Number of included studies	Osteoporosis			
		Prevalence	95%CI	I^2	*P* value
Regions					
Europe	7	15.10%	(0.09, 0.21)	84.10%	<0.01
North America	2	11.50%	(0.49, 0.18)	59%	0.12
Publication years					
<2010	4	11.70%	(0.03, 0.21)	62%	<0.01
≥2010	5	16.40%	(0.13, 0.20)	88%	0.03
Study type					
Prospective cohort study	7	14.20%	(0.08, 0.20)	85%	<0.01
Retrospectively cohort study	2	14.00%	(0.12, 0.16)	0%	0.81
Age					
<45 years	3	6.30%	(0.02, 0.10)	0%	0.69
≥45 years	6	16.90%	(0.12, 0.22)	79%	<0.01
Proportion of males					
<55%	1	25.00%	(0.19, 0.32)		
≥55%	7	12.70%	(0.08, 0.18)	80%	<0.01
Sample size					
<100	4	6.70%	(0.03, 0.10)	0%	0.82
≥100	5	18.30%	(0.14, 0.23)	77%	<0.01
Follow-up duration					
<1 year	1	22.80%	(0.18, 0.29)		
≥1 year	8	13.10%	(0.09, 0.18)	77%	<0.01
Study quality					
High	1	25.00%	(0.19, 0.32)		
Moderate	8	13.00%	(0.09, 0.17)	77%	<0.01
Transplant type					
Allo-SCT	5	16.40%	(0.13, 0.20)	62%	0.03
Auto-SCT	2	16.40%	(0.00, 0.33)	93%	<0.01

Table 4. Meta-regression analyses.

	No. of studies	Estimate	Standard error	*z* value	*P* value	95% CI
Intercept		0.4095	0.1224	3.3466	0.0008	(0.1697, 0.6494)
Regions	9	−0.0708	0.0385	−1.8391	0.0659	(−0.1463, 0.0047)
Follow-up period	9	−0.0787	0.0327	−2.4039	0.0162	(−0.1429, −0.0145)
Proportion of males	9	−0.1011	0.0374	−2.702	0.0069	(−0.1744, −0.0278)
Age	8	0.0849	0.0271	3.1316	0.0017	(0.0318, 0.1380)

Secondary outcomes. The meta-analysis included 9 studies (7 articles) with a total of 1675 patients to assess the prevalence of osteopenia post-SCT [18–22, 26, 28]. The reported prevalence of osteopenia was 36.0% (95% CI 23.8–48.2), with significant heterogeneity among studies ($I^2 = 99\%$, $p < 0.01$) (Fig. S10). Subgroup analysis for the lumbar spine (10 studies (6 articles)) yielded a pooled prevalence of 32.0% (95% CI 27.3–36.8, $N = 776$, $I^2 = 37\%$, $p = 0.11$) [17, 19, 23, 26, 27, 29], while femur analysis (5 studies (3 articles)) [19, 23, 29] resulted in a pooled prevalence of 33.3% (95% CI 21.0–45.5, $N = 321$, $I^2 = 73\%$, $p < 0.01$) (Fig. S11).

12 eligible studies (9 articles), involving 2090 patients, reported the prevalence of decreased BMD [18–22, 24–26, 28]. Using a random-effects model yielded a pooled decreased BMD prevalence of 47.8% (95% CI: 36.6–58.9, $I^2 = 97\%$, $p < 0.01$) (Fig. S12). Within the subset of 12 studies (7 articles) [17, 19, 23, 25–27, 29] comprising 822 patients, the pooled prevalence of decreased BMD in lumbar spine was 44.3% (95% CI 34.4–54.3, $I^2 = 91\%$, $p < 0.01$) (Fig. S13). Furthermore, analysis of 7 studies (4 articles) [19, 23, 25, 29] involving 367 patients provided data on the prevalence of decreased BMD in femur. The pooled prevalence for this subset was found to be 38.4% (95% CI 27.8–49.0, $I^2 = 70\%$, $p < 0.01$) (Fig. S13).

Results of the 'leave one-out' sensitivity analysis indicated that the no major differences in the magnitude of the summary results due to the influence of any single study were noted for the prevalence rates of total osteopenia (Fig. S14), and decreased BMD (Fig. S15).

The asymmetry funnel plot of osteopenia (Fig. S16) and decreased BMD (Fig. S17) in SCT indicated that the presence of potential publication bias. However, further assessment using Egger's test for decreased BMD did not reveal substantial asymmetry ($t = 0.28$, $P = 0.785$).

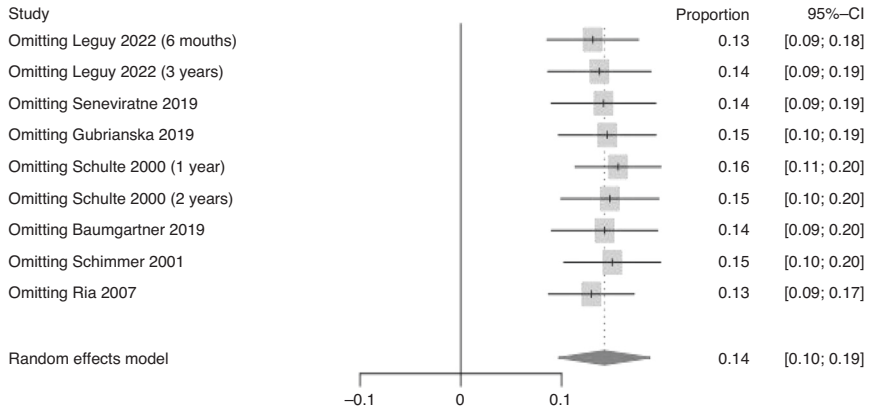

Fig. 3 Sensitivity analyses for osteoporosis by leave-one-out method.

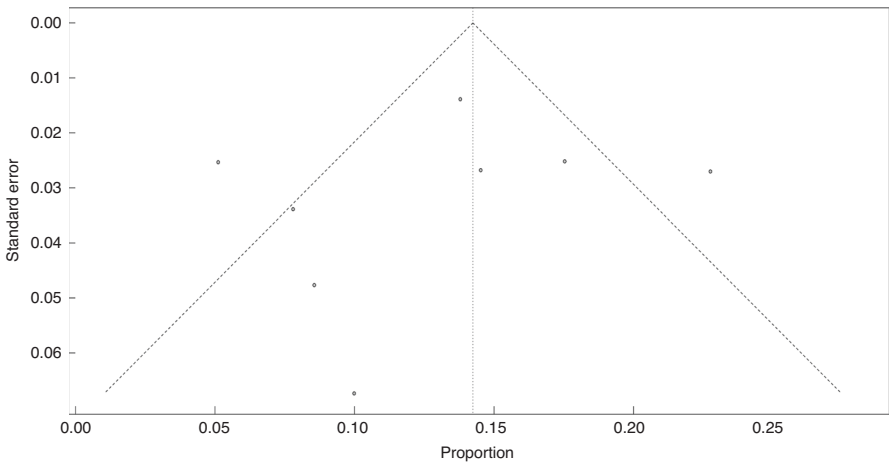

Fig. 4 Funnel plot analysis for assessing publication bias of osteoporosis in post-SCT studies.

DISCUSSION

Bone loss and subsequent osteoporosis is a global health crisis affecting approximately million population and is a common complication in post-SCT. Understanding the prevalence of osteoporosis and influencing factors in post-SCT is crucial for creating personalized interventions to improve outcomes. To best of our knowledge, this is the first meta-analysis provide an overview the prevalence of osteoporosis estimates among post-SCT, based on different countries, settings and populations to provide a comprehensive summary of the current research and addressing a critical gap in the current literature. Our results revealed a relatively high prevalence among post-SCT, with a total osteoporosis prevalence of up to 14.2% and a lumbar spine osteoporosis prevalence of up to 17.1%. Additionally, a significantly higher prevalence of osteopenia (36.0%), and decreased BMD (47.8%) were observed among post-SCT, with these findings also extending to the lumbar spine.

Osteoporosis is a common disease among patients undergoing transplantation as well as in post-SCT. Although only a limited number of studies published estimated the prevalence of OP in hematologic disease patients with SCT worldwide, some generalizations could be made.

Osteoporosis prevalence demonstrates gender disparities, with females exhibiting a higher susceptibility compared to males. A China study of adults aged 40 years or older reported a nearly fourfold in women (20.6%) compared to men (5.0%) [30], with this vulnerability escalating progressively with age [6]. Consistent with these findings, our SCT analysis confirmed higher osteoporosis prevalence when male ratio falls below 55% (25% vs. 13%). Gender disparity in osteoporosis persists across populations, emphasizing the need to consider gender-specific factors in prevention and management.

Age is a significant risk factor for decreased BMD [19, 26]. Ria et al. found a robust positive association between age and decreased BMD prevalence. In the 25–35-year age group, 35% had a T-score of -1 or below, indicating osteopenia or osteoporosis. This increased to 77% in individuals over 55 years [26]. Schimmer et al. reported that advanced age was the sole significant predictor of reduced bone density following autologous blood or marrow transplantation [19]. Our findings align: individuals aged 45+ in the SCT population had a higher osteoporosis incidence (16.9% vs. 6.3%) compared to those below 45 years old.

Osteoporosis incidence rates in SCT depend on follow-up duration, as it is influenced by the temporal sequence of transplant-related bone diseases [31]. Specifically, bone loss predominantly occurs within the initial 6–12 months, followed by gradual recovery [20, 26, 27]. Our sub-analysis revealed higher osteoporosis incidence within the first year post-SCT (22.8%), decreasing significantly thereafter (13.1%). A similar trend has been observed in patients undergoing solid organ transplant, where bone loss occurs within the initial months to one year, followed by gradual recovery [32].

Osteoporosis prevalence varies by region, with Europe (15.1%) higher than North America (11.5%). Factors contributing to this difference include sample sizes, genetics [3] and race [33],

population density, socioeconomic status [5], healthcare services [3], risk factor management, and preventive measures [4].

Bone loss correlates with glucocorticoid use duration and intensity [34]. While steroid exposure is uncommon after auto-SCT, it strongly correlates with BMD loss following allo-SCT, potentially increasing the susceptibility to osteoporosis in allo-SCT patients. However, studies show inconsistent findings regarding BMD changes in allo-SCT versus auto-SCT patients. Yao et al. observed similar BMD loss in both groups, despite steroid dosage being a notable risk factor for BMD changes following allo-SCT, explaining only a minor portion of the overall variation [23]. Similarly, our subgroup analysis, showed comparable osteoporosis prevalence (16.4%) in both allo-SCT and auto-SCT, highlighting the multifactorial nature of SCT-related osteoporosis risk.

In this meta-analysis, post-SCT osteoporosis incidence (14.2%) was comparatively lower than after solid organ transplantations (18–61%) [7, 8], likely underestimated due to various factors. Firstly, due to disease progression, relapse, GVHD, serious infection, and secondary cancer, among other factors, SCT experience a significantly higher excess mortality rate compared to the general population [24, 35]. As a result, the number and scale of research in this field are highly limited. Small sample sizes hinder statistical power, as evident in our sub-analysis showing lower osteoporosis prevalence in studies with <100 participants (6.7%) versus ≥100 (18.3%). Furthermore, majority of included studies focused on younger blood and marrow transplant survivors, but as the population of older long-term survivors grows, post-transplantation osteoporosis incidence is expected to rise. Moreover, worldwide variation is seen in osteoporosis prevalence, with higher burdens in Asia and Africa compared to Europe and North America [36]. Despite comprehensive database searches, studies were lacking in Asian and African countries. Immaturity of research may also contribute to underestimation.

Limitations and recommendations for future research

Some limitations should be considered to guide future research in this area. Firstly, given the different observed outcomes of osteoporosis in post-SCT, certain patients were repeatedly included in meta-analysis may introduce bias and compromise the accuracy of findings. Additionally, limited studies in certain subgroups may affect result reliability. Consequently, it is imperative to exercise cautious interpretation, and future investigations are essential to substantiate the observed effects. Secondly, the underling disease of the patients in the different studies are not uniform and the primary outcomes not consistent, that makes the overall heterogeneity across the eligible studies was high, and subgroup analyses did not identify significant variables affecting this heterogeneity, but further meta-regression showed that male proportion, age, and follow-up period were the main sources of heterogeneity, explaining 97.02% of it. Future studies should pay more attention to these potential factors to better understand their contributing to osteoporosis prevalence following SCT. Thirdly, in addition to the classical risk factors of osteoporosis (e.g., age, gender, …), various factors such as glucocorticoid therapy, immunosuppressive therapy, intensive chemotherapy, and radiotherapy have been found to contribute to the development of post-SCT osteoporosis [34, 37]. However, due to a lack of relevant studies and data, we did not extensively discuss these factors. More studies will be needed to elucidate in the future. Fourth, this study might be limited by language bias, as only articles published in English were included. Finally, also, like most other meta-analysis, the overall findings from the meta-analysis were limited by the quality of the primary studies, many including studies were unpaired cohort studies in different geographic regions which were the main lead to a moderate quality of studies, it is necessary for future investigators to consider these issues when designing, executing, and analyzing their study.

CONCLUSION

In conclusion, this systematic review and meta-analysis revealed that osteoporosis is a common comorbidity in SCT. It is essential for clinicians caring for regular monitoring of BMD status in this vulnerable group of patients as well as the necessity of preventive approaches, early diagnosis, and timely intervention to improve outcomes.

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AUTHOR CONTRIBUTIONS

YYM and PS conceived of the study concept and design. YYM and SJG performed the literature search, study selection and collected all data. YYM and PS contributed to the data analysis and interpretation of results. YYM drafted the manuscript, RX, XJY, and YPL revised the manuscript critically for important intellectual content. All authors reviewed the manuscript and approved the final submitted version.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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