Transplant International

META-ANALYSIS

A systematic review and meta-analysis on the incidence of osteoporosis and fractures after liver transplant

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SUMMARY

Following liver transplant (LT), osteoporosis is a severe complication that causes morbidity. However, the incidence and risk factors of osteoporosis and fractures have not been well described. Single-arm meta-analysis of studies reporting osteopenia, osteoporosis, and fractures post-LT was performed with meta-regression for study period. Dichotomous variables, continuous variables and time-to-event variables were pooled in odds ratio, weighted mean difference and hazard ratio, respectively. For risk factors with limited data, a systematic review of literature was conducted. There was a significant increase in both osteoporosis and fractures compared to non-LT patients. Osteopenia, osteoporosis and incident fractures were newly diagnosed in 34.53% (CI: 0.17–0.56, $n = 301$), 11.68% (CI: 0.05–0.24, $n = 1251$) and 20.40% (CI: 0.13–0.30, $n = 4322$) of LT patients, respectively. Female gender ($P = 0.017$) increased risks of osteoporosis but not older age and BMI. Older age, lower pre-LT bone mineral density (BMD), presence of bone disease pre-LT were significant risk factors for fractures but not female gender, post-menopausal state, BMI, smoking and alcohol. There is a high incidence of skeletal complications post-LT. Older age, lower pre-LT BMD and presence of bone disease pre-LT are significant risk factors that are associated with incident fractures physicians should be cognisant of in liver transplant recipients.

Transplant International 2021; 34: 1032–1043

Key words
bone density, bone diseases, metabolic, postoperative complications, risk factors

Received: 23 January 2021; Revision requested: 11 March 2021; Accepted: 12 March 2021;
Published online: 19 May 2021

doi:10.1111/tri.13863

Introduction

Since the advent of liver transplant (LT) more than two decades ago, considerable progress in orthotopic liver transplantation has resulted in improved outcomes in long-term survival. However, the incidence of osteoporosis and fractures has been under described. Osteoporosis is a severe complication after liver transplantation. The majority of LT patients show accelerated loss of bone mass within the first six months after surgery, with an estimated decrease in median hip bone mineral density (BMD) of 7% [1–4] and increased risks of fractures [5–8]. Pain and immobility from these skeletal complications cause morbidity which can impact the quality of life for graft recipients [9–11].

Symptomatic osteoporosis with bone fractures post-LT is multifactorial, associated with pre- and post-LT factors. Previous reviews have shown that chronic liver diseases such as primary biliary cholangitis (PBC) and alcoholic cirrhosis contribute to hypogonadism, vitamin D deficiency, malabsorption, and low body weight which are risk factors for osteoporosis [12–14]. In addition, pre-existing bone disease has been suggested to be a determinant of bone status following transplantation. However, the pathogenesis of bone loss post-LT remains poorly understood with no correlation seen with liver function, indices of calcium and vitamin D metabolism or osteocalcin levels [12]. While immunosuppressive medications including glucocorticoid therapy may contribute to post-LT bone loss [12–14], more recent studies have failed to find a significant association between these factors and increased risks for skeletal complications [6,15,16]. At present, there is little agreement in the literature with regard to predictors of fracture in liver transplant recipients. Therefore, we aimed to perform a systematic review and meta-analysis to assess the incidence and risk factors for osteopenia, osteoporosis, and fractures in liver transplant patients.

Methods

Search strategy

A systematic search was conducted on Medline and Embase electronic databases on 7 December 2020 with reference to PRISMA guidelines [17]. The search terms included osteoporosis, osteopenia, fractures and liver transplant, and the full search used was *(exp osteoporosis/or (osteoporo* or osteopeni*).tw. or bone demineralization/or (bone* adj fragil*).tw. or fracture*.tw. AND (exp Liver Transplantation/or ((liver* OR hepat*) adj3 (transplan* OR graft*)).tw.)*. In addition, a sieve was conducted on the references of included articles. The title abstract sieving was done by three authors (WHL, CHN, ZGWO) after duplicates were removed with Endnote X9. A medical librarian was involved in the refinement of search strategy and retrieval of articles and the detailed search strategy can be found in Appendix S1 and File S1.

Study selection and extraction

Studies describing the incidence of osteopenia, osteoporosis, and fractures in patients after liver transplant were included in this review. Risk factors including age, body mass index (BMI), pre-LT bone mineral density (BMD) in lumbar spine (LS), and femoral neck (FN) as measured by dual-energy X-ray absorptiometry, gender, menopause state, smoking, etiology of liver disease (such as PBC and alcohol), and post-LT immunosuppressive regimens. No restrictions on population age and ethnicity were applied. Only original articles were included, and editorials, commentaries and reviews were excluded from the study. Studies reporting prevalence of osteoporosis and fractures after liver transplant without accounting for pre-transplant rates were excluded. Interventional studies on therapeutic regimes for post-LT bone health were also excluded.

The World Health Organization (WHO) criteria was used to define osteoporosis (T-score of 2.5 SD or less) and osteopenia (T-score between 1 SD and 2.5 SD) [18,19]. Fractures were defined by the individual studies as the obtaining of pairwise independent observer agreement on the semiquantitative evaluation of plain radiographs of patients. A structured proforma was used in the extraction of data and was conducted by two authors in a blinded pair (WHL, CHN). Data extraction was performed to extract study characteristics (study location, year, country, sample size), baseline characteristics (age, gender, body mass index, liver disease etiology, alcohol use, smoking), and post-LT outcomes (osteopenia, osteoporosis, total fractures, hip fractures, and vertebrae fractures). For continuous variables, unreported mean and standard deviations were converted using the pre-existing formula by Hozo *et al.* [20].

Statistical analysis and quality assessment

The analysis was conducted in STATA (Statacorp 16.1) and R (RstudioVer: 3.6.1). For the analysis of single arm binary variables, the generalized linear mix model was used to stabilize the variance and account for zero

events before the results were pooled in random effects [21]. Simulation studies have found the generalized linear mix model to be the most robust method of pooling single arm studies [21]. Thereafter, a meta-regression with logit expression to adjust for variables in the single arm meta-analysis was conducted and the coefficients were exponentiated to obtain the odds ratio (OR). In the analysis of dichotomous variables and time to event variables, a random effects model by Dersimonian and Laird was used to pool the results in OR [22]. Continuous variables were analyzed in weighted mean difference (WMD) [23]. Time to event data were analyzed using pooled hazard ratio (HR) to compare the development of osteoporosis and fractures between LT and non-LT patients.

Regardless of heterogenicity measures quantified in I^2 and Cochran Q test, all analysis were conducted in random effects with a P value of <0.05 denoting significance [24,25]. I^2 values of 0–40% were suggestive of insignificant degrees of heterogeneity, while values of 30–60%, 50–90%, and 75–100% were classified as moderate, substantial, and considerable heterogeneity, respectively [26]. Meta-regression was used to access the impact of study period on incidence of disease using the restricted maximum likelihood model [27]. When insufficient data were present for a meta-analysis, a systematic synthesis of literature was the preferred method to summarize the evidence. A visual representation of results was used to summarize the evidence with significance considered based on the individual articles' assessment method. Publication bias was assessed with visual inspection of the asymmetry of the funnel plot [28]. Quality assessment of included articles was done with the Joanna Briggs Institute (JBI) quality assessment scale which assesses the cohort selection, outcomes and follow-up validity to determine the extent to which a study has addressed the possibility of bias in its design, conduct, and analysis [29]. These can be found in Fig. S1 and Table S1, respectively.

Results

Summary of included articles

There were a total of 370 articles from the initial search strategy, with 288 remaining after removal of duplicates. A total of 178 were excluded based on the study title and abstract, and 110 full texts articles underwent full text review, of which 30 articles were subsequently included in the meta-analysis (Fig. 1). In summary, seven studies were conducted in the USA [30–36], four in Netherlands [1,37–39], three each in the United Kingdom [7,40,41], and Australia [42–44], two each in France [45,46], Taiwan [47,48], Spain [6,16], and Sweden [49,50], and one in Poland [13], Israel [3], China [51], Germany [15], and Norway [52], respectively. Twenty-nine articles were retrospective cohort studies, with the exception of one cross sectional study design. A total of 5071 patients underwent liver transplant, of whom 91 developed osteopenia, 127 developed osteoporosis, and 490 suffered fractures post-transplant. Based on the JBI quality assessment scale [29], 24 of the 30 included studies were of good quality, while six studies were of moderate quality (Table S1). A summary of the included studies can be found in Table S2. The summary of the results can be found in Table 1.

Development of bone disease

Longitudinal analysis

Studies were conducted longitudinally to observe the development of both osteoporosis and fractures after LT compared to sex- and age-matched non-LT patients. In one and two studies, respectively, there was a significant increase in both osteoporosis and fractures (HR: 5.58, CI: 1.54–20.19, $P = 0.009$ and HR: 4.74, CI: 2.21–10.18, $P < 0.0001$) compared to non-LT patients.

Incidence of bone disease after liver transplant

The main outcomes of the meta-analysis were the incidence of de novo osteopenia, osteoporosis and fractures. A total 34.53% (CI: 0.17–0.56) in 301 LT patients had a new diagnosis of osteopenia. Osteoporosis was newly diagnosed in 11.68% (CI: 0.05–0.24) among 1251 LT patients and a total of 20.40% (CI: 0.13–0.30) experienced an incident fracture among 4322 LT patients (Figs 2 and 3). Publication bias assessed by funnel plot was not asymmetrical (Fig. S1). A sensitivity analysis was done to analyze the incidence of hip and vertebral fracture separately. In total, hip and vertebrae fractures were present in 0.86% (CI: 0.00–0.02) in 3850 LT patients, and 10.92% (CI: 0.06–0.20) in 4065 LT patients, respectively (Fig. 4). Meta-regression was done to compare the rates of osteoporosis and fracture diagnosis with time. Study period was not significant for both osteoporosis and fractures ($\beta = -0.0081$, CI: -0.019 to 0.002, $P = 0.12$ and $\beta = -0.0071$, CI: -0.018 to 0.003, $P = 0.17$), respectively.

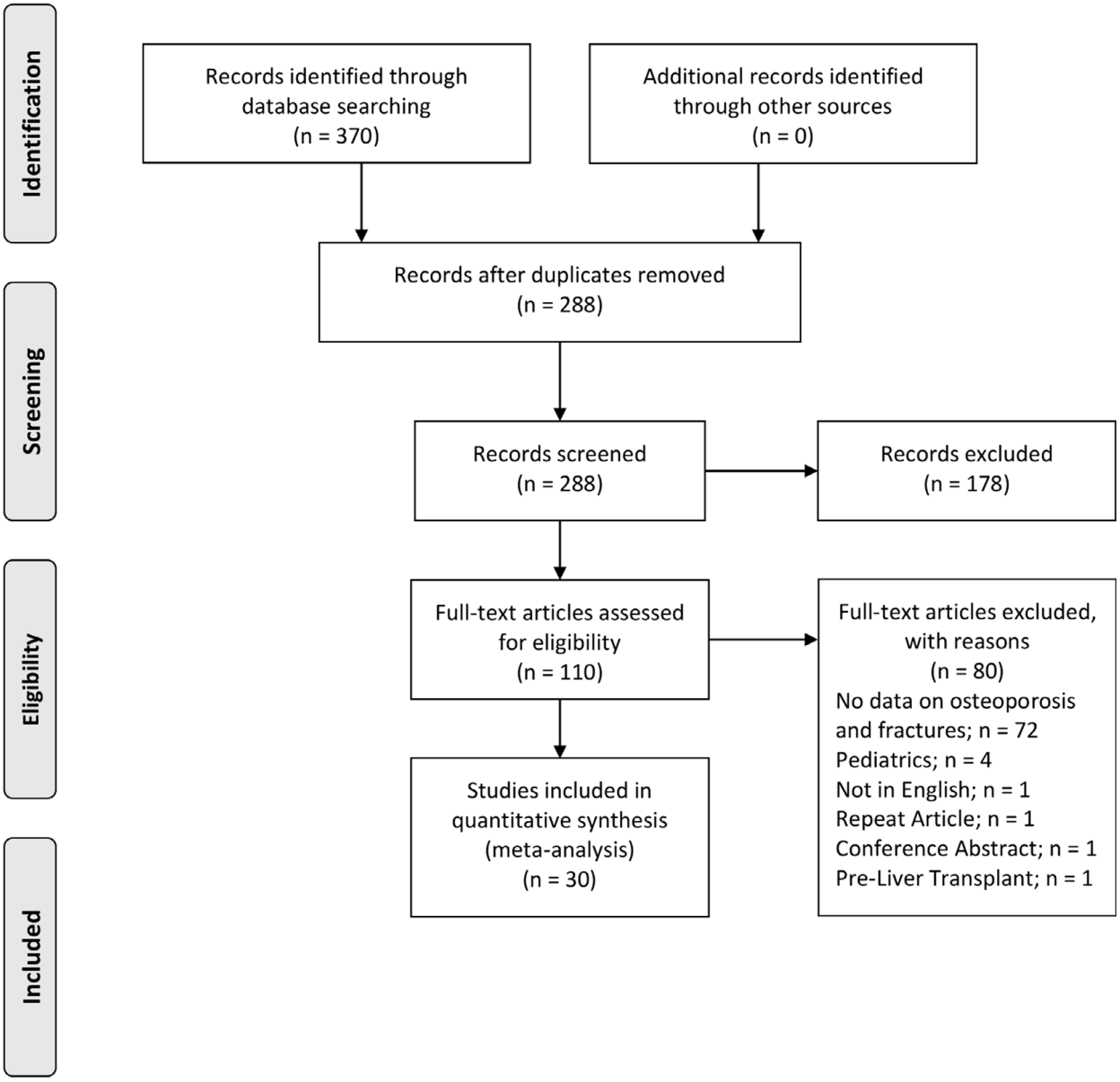

Figure 1 PRISMA flow diagram of included articles.

Risk factors for bone disease in LT patients

Osteoporosis

Non-modifiable: Older age was not significant for the development of osteoporosis among post-LT patients (WMD: 0.99, CI: 0.97–1.01, $P = 0.16$). The mean age compared ranged from 38.3 to 53.3 years old. However, female gender increased the odds of osteoporosis (OR: 1.41, CI: 1.09–1.83, $P = 0.017$). While PBC led to a twofold incidence in osteoporosis, the results were not significant (OR: 2.12, CI: 0.001–3716.50, $P = 0.42$). *Modifiable:* BMI was not a significant factor in the development of osteoporosis (OR: 1.11, CI: 0.12–10.11, $P = 0.65$).

Fractures

Non-modifiable: Age was a significant non-modifiable risk factor of fractures (WMD: 5.62, CI: 3.37–7.88, $P < 0.0001$). PBC as an underlying etiology appeared to influence the rate of fractures with four times increase odds of fractures (OR: 4.28, CI: 0.80–22.93, $P = 0.09$). Female gender and post-menopausal state did not influence the rate of fractures (OR: 1.27, CI: 0.75–2.16, $P = 0.37$ and OR: 7.36, CI: 0.78–69.58, $P = 0.08$).

Table 1. Summary of pooled analysis.

	No. of papers	Total sample size	Effect size	*P* value
Development after LT				
Osteoporosis	1	25	HR: 4.74 (CI: 2.21–10.18)	<0.0001*
Fracture	2	2226	HR: 5.58 (CI: 1.54–20.19)	0.009*
Incidence				
Osteopenia	3	301	34.53% (CI: 0.17–0.56)	–
Osteoporosis	11	1251	11.68% (CI: 0.05–0.24)	–
Fractures	24	4322	20.40% (CI: 0.13–0.30)	–
Vertebral fracture only	21	4065	10.92% (CI: 0.06–0.20)	–
Hip fracture only	14	3850	0.86% (CI: 0.00–0.02)	–
Regression with study period				
Osteoporosis	11	1172	−0.0081 (CI: −0.019 to 0.002)	0.12
Fractures	20	2047	−0.0071 (CI: −0.018 to 0.003)	0.17
Risk factors of osteoporosis in LT patients				
Age	8	1159	0.99 (CI: 0.97–1.01)	0.16
Female	8	1159	1.41 (CI: 1.09–1.83)	0.017*
BMI	3	755	1.11 (CI: 0.12–10.11)	0.65
PBC	3	594	2.12 (CI: 0.001–3716.50)	0.42
Risk factors of fractures in LT patients				
Age	6	782	5.62 (CI: 3.37 – 7.88)	<0.0001*
BMI	3	615	−0.049 (CI: −1.51 to 1.41)	0.95
BMD lumbar spine	4	218	−0.092 (CI: −0.16 to −0.026)	0.006*
BMD femoral neck	3	187	−0.11 (CI: −0.17 to −0.043)	0.001*
Gender	5	751	1.27 (CI: 0.75–2.16)	0.37
Menopausal	2	136	7.36 (CI: 0.78–69.58)	0.08
Smoking	1	518	1.88 (CI: 0.64–5.57)	0.25
Alcohol	2	609	0.59 (CI: 0.24–1.43)	0.24
PBC	1	27	4.28 (CI: 0.80–22.93)	0.09

BMI, body mass index; DM, diabetes mellitus; PBC, primary biliary cirrhosis.

Continuous data were calculated in weighted mean difference (WMD) while binary data were calculated using odds ratio (OR).

*$P < 0.05$ is statistically significant.

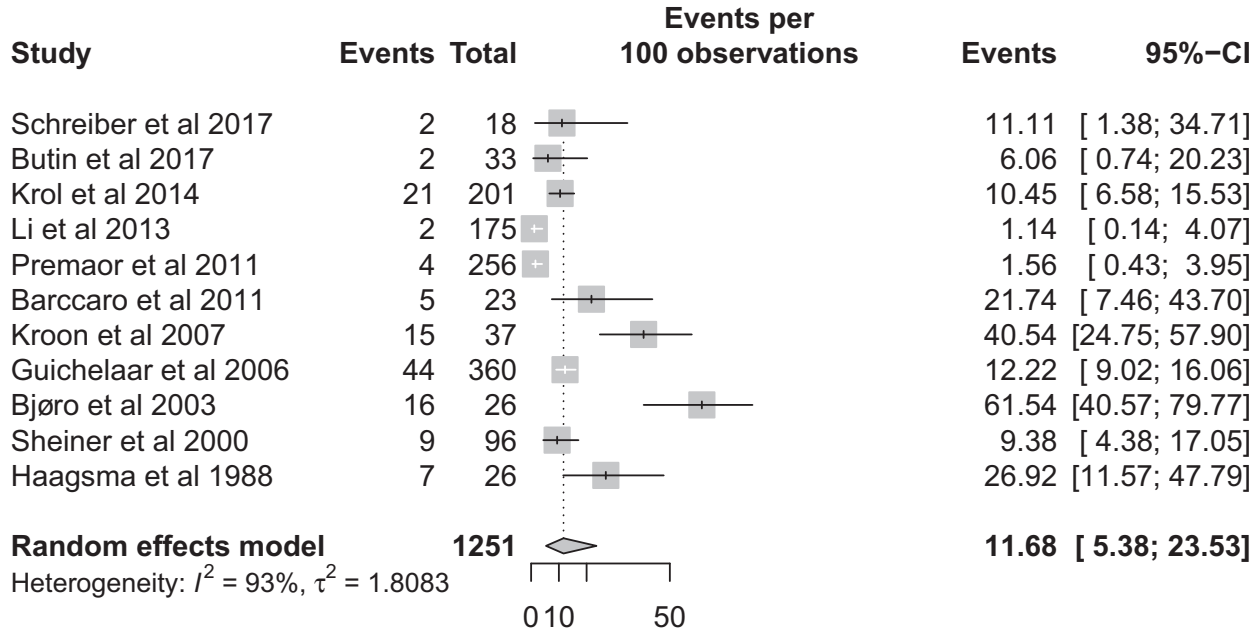

Figure 2 Forest plot of osteoporosis incidence.

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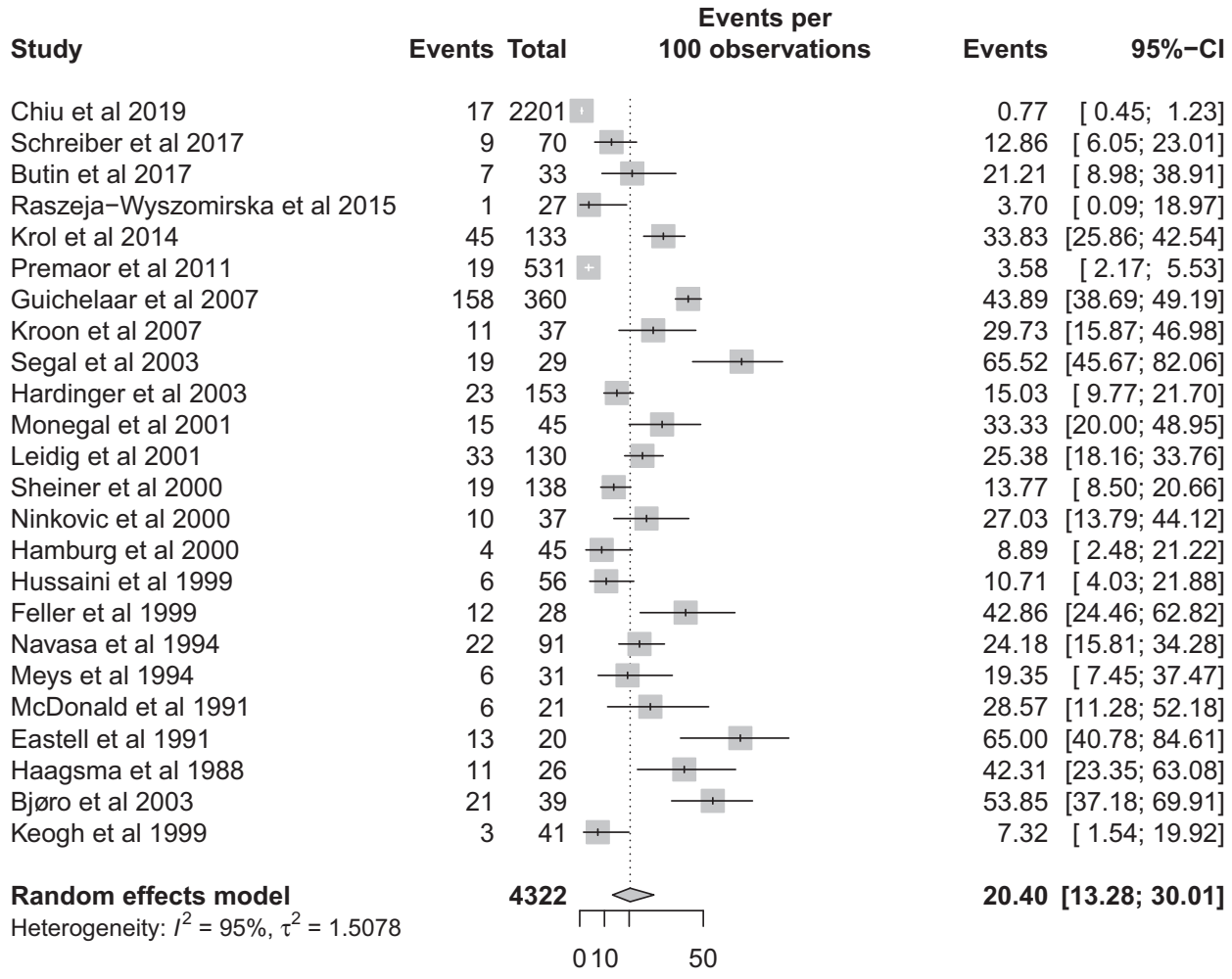

Figure 3 Forest plot of total incident fractures.

Modifiable: Lower pre-LT BMD from LS and FN significantly increased risk of incident fractures. (WMD: −0.092, CI: −0.16 to −0.026, $P = 0.006$ and WMD: −0.11, CI: −0.17 to −0.043, $P = 0.001$) The diagnosis of osteopenia and osteoporosis pre-transplant were also significant risk factors of incident fractures. However, BMI, smoking, and alcohol did not influence fracture rates.

Background immunosuppression

Nine studies reported effects of immunosuppression regime on fracture incidence in LT recipients [3,6,7,15,16,31,37,47,50]. For steroids, six studies reported non-significant effects [6,7,15,16,37,50], while two studies reported a significant increase in fracture rates [7,31]. Three studies which used cyclosporine reported non-significant increase in fracture rates [6,7,47], while one study reported significant effects [3]. For tacrolimus, two studies reported non-significant effects [7,47], while two studies reported significant increase in fracture rates [3,37] With mycophenolate mofetil and everolimus, two studies reported non-significant effects on fracture incidence for each medication, respectively [7,47]. For sirolimus and azathioprine, one study reported non-significant effects for each medication, respectively [7] (Fig. 5).

Bone modifying medications

Two studies reported effects of therapeutic bone medications on fracture incidence in LT recipients [7,15] with varying results. With vitamin D and calcium, Leidig *et al.* found a non-significant effect on fractures while Premaor *et al.* found a significant reduction with combined calcium and vitamin D supplements. For antiresorptive therapy, one study reported a significant decrease in fractures among patients given bisphosphonates [7].

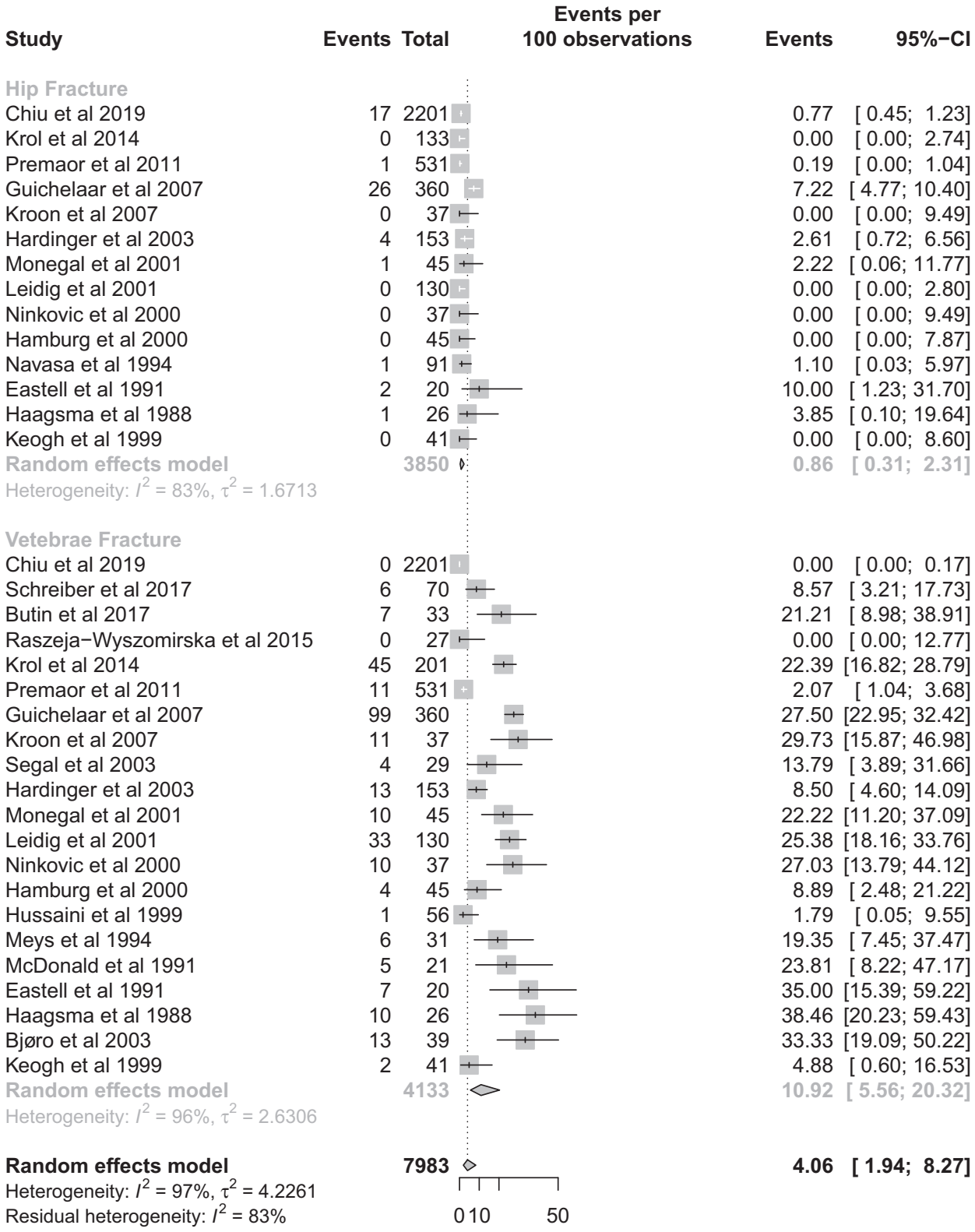

Figure 4 Forest plot of hip and vertebrae fractures.

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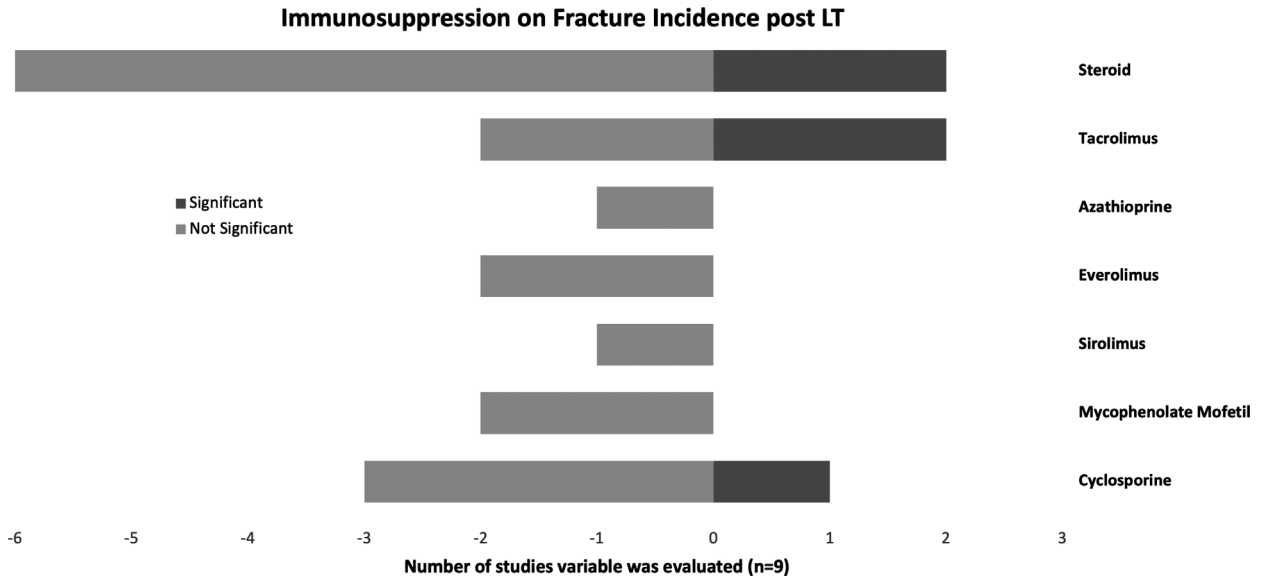

Figure 5 Summary of immunosuppression on fracture incidence post-LT.

Discussion

Our systematic review and meta-analysis studying osteopenia, osteoporosis and fracture risk in post-LT patients summarizes the published literature and highlights the current gaps in knowledge. Many transplant recipients who are on immunosuppressive therapy and have underlying bone disease have higher risks of skeletal complications [15,48]. In our meta-analysis, there was a five times increased risk of both osteoporosis and fractures in LT recipients compared to non-LT recipients. Among post-LT patients, the incidence of osteopenia, osteoporosis, and fractures was 34.53% (CI: 0.17–0.56), 11.68% (CI: 0.05–0.24), and 20.40% (CI: 0.13–0.30), respectively. While 11% of these patients had vertebral fractures, less than 1% of these patients had hip fractures. Studies assessing quality of life in LT patients found that those with osteoporosis or fractures faced more physical difficulties with work and daily activities [13,38]. Additionally, Kroon *et al.* [38] found that osteoporosis in LT patients tended to be associated with increased immobility. Considering the significant implications of bone health on post transplantation care, it is important to assess and target modifiable risk factors for osteoporosis and fractures during pre-transplant workup.

Female LT patients were found to have an increased risk of osteoporosis. Interestingly, age and BMI were not found to increase risk of osteoporosis in these patients. While older age was not significant for osteoporosis, it was a significant risk factor for incident fractures. The narrow mean age (range: 38.3–53.3 years old) and limited studies could have affected the significance. Previous epidemiologic studies have shown that advancing age leads to increase in fracture risk due to skeletal fragility [53]. Additionally, lower pre-transplant BMD and presence of osteopenia or osteoporosis pre-transplant were associated with an increased risk of post-LT fractures. Bone histology studies have demonstrated bone loss from hepatic osteodystrophy halting within 6 months of LT before subsequent progressive recovery of bone mass [16]. The prolonged recovery of BMD could be due to the increased severity of hepatic osteodystrophy pre-transplant leading to a higher rate of fractures in these patients. Several studies have also found positive correlations between BMD and physical activity in LT patients [13,43]. Lean tissue, composed predominantly of muscle, stimulates the skeleton by providing mechanical stress. Muscle mass is maintained by sex hormones and physical activity, both of which are frequently decreased pre-LT. In addition, sarcopenia is a frequent feature of LT patients [54,55], and muscle wasting is likely exacerbated by post-surgery immobility and deconditioning [56]. This suggests that prehabilitation for LT patients is important to maintain pre-LT BMD so as to lower risks of incident fractures. While not significant due to limited studies, graft recipients with PBC as an underlying etiology for LT had a two-times and four-times increase in odds for osteoporosis and fractures, respectively. PBC is a cholestatic disease where malabsorption of calcium and vitamin D, in addition to the interference of bilirubin levels in osteoblast function, may result in more severe pre-transplant osteoporosis

[57,58]. There was also a higher incidence of vertebrae fractures than hip fractures as glucocorticoid use likely affects trabecular bone present in vertebrae more than cortical bone which is present in the hip [59].

Our systematic review focusing on the effects of individual immunosuppressants was conflicting. Most studies demonstrated no significant association between immunosuppressants and post-LT fractures. Only two studies demonstrated a significant increase in fractures in post-LT patients on calcineurin inhibitors [3,37]. Surprisingly, only two studies demonstrated that steroids were associated with incident fractures [7,31]. These findings are similar to a systematic review of fracture risk in kidney transplant recipients by Naylor *et al.* [60] where the impact of steroid-sparing regimens on fracture rates was reported to be controversial. We postulate that this may be due to the heterogeneity of pre-transplant BMD, as well as evolving strategies for post-transplant immunosuppression over time [61]. Additionally, the relatively low dosage of steroids in LT patients could have reduced the contributory risk from steroids [62–64]. In addition, one of the studies that demonstrated a significant association of steroids with incident fractures was conducted over a long study period spanning 16 years from 1985 and included multiple immunosuppressant regimes [31]. Ideally, patient level data on steroidal dose would be used as the independent variable but was unavailable in the included articles for meta-regression to be conducted. The effect of immunosuppression remains unclear, and more studies are required to delineate the optimal regimens for patients at high risk of osteoporosis or fractures.

Medications affecting bone health such as calcium, Vitamin D, and antiresorptive therapy are important considerations in fracture incidence post-LT. While our systematic review demonstrated conflicting results, there appeared to be a reduction in incident fractures with the use of Calcium or Vitamin D, as well as bisphosphonates. Antiresorptive therapies such as bisphosphonates have been shown to be efficacious in reducing bone loss post-LT [65]. However, as the optimal bisphosphonate therapy has yet to be defined [66], these therapeutic modalities should be further assayed in adequately powered prospective controlled trials and evaluated in their efficacy in reducing osteoporosis and fracture incidence.

Clinical implications

Successful management of post-LT bone disease involves both optimization of bone health prior to transplant and prophylaxis against bone loss following transplantation. As older age, lower pre-transplant BMD and presence of osteopenia or osteoporosis pre-transplant are significant risk factors, bone densitometry should be conducted for all patients during the pre-LT workup [67]. This is in line with the Clinical Practice Guidelines by the European Association for the Study of the Liver (EASL). In addition, spinal radiographs for evidence of vertebral deformity or fracture risk calculators (FRAX or the Garvan Institute fracture risk tool) may also be utilized in elderly patients [68,69]. Further supportive measures including correcting vitamin D and calcium deficiency, good nutrition, increase in physical exercise and weight-bearing activities to optimize bone mass in osteoporotic patients can potentially help [66,70].

Strengths and limitations

To our knowledge, this is the first study to consolidate the risk factors and incidence of osteopenia, osteoporosis and fractures in post-LT patients as reported in 30 original studies. The review also provides direction for future studies on bone health in post-LT patients. However, in the analysis of incidence, we were limited in the interpretation by heterogeneity with a large I^2 value (>90%) [71,72]. Simulation studies have found that large sample sizes result in increased I^2 and can be an inaccurate measure of heterogeneity [73,74]. Longitudinal development of bone disease in LT patients compared to non-LT population should be taken with caution due to the limited studies. Insufficient data for osteopenia, comedications, risk factors such as immobilization, diabetes, cirrhosis related morbidity (hypogonadism, low IGF-1 levels, malnutrition, and sarcopenia), and other liver disease etiology prevented further analysis. Nevertheless, the findings highlight the need to address common risk factors to reduce the high incidence of post-LT bone disease. Finally, some studies may have underestimated fracture incidence as conventional spine radiographs without evaluation by semiquantitative methods tend to underreport mild grade fractures.

Conclusion

There is a high incidence of osteoporosis and fractures post-LT. This study provides evidence that older age, lower pre-transplant BMD and presence of osteopenia or osteoporosis pre-transplant are significant risk factors for incident fractures. As data on immunosuppression regimes remains conflicting, future studies should

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investigate the impact of individual immunosuppressive treatment on bone health in transplant recipients.

Funding

The authors have declared no funding.

Conflict of interest

The authors have declared no conflicts of interest.

Acknowledgements

We thank Ms Annelissa Mien Chew Chin, medical librarian of NUS Yong Loo Lin School of Medicine, for her aid in the refinement of our search strategy and the selection of articles. The manuscript, including related data, figures, and tables, has not been previously published and that the manuscript is not under consideration elsewhere.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. Detailed search strategy.

Figure S1. (a) Funnel plot for fractures. (b) Funnel plot for osteoporosis.

Table S1. JBI checklist for cohort studies.

Table S2. Summary of included studies.

File S1. PRISMA checklist.

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