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Review Article

Primary Biliary Cholangitis–associated Osteoporosis: Contemporary Review of Pathogenesis and Management

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Abstract

Primary biliary cholangitis (PBC) is a chronic cholestatic disorder in which symptoms exert a direct influence on patients' quality of life. Beyond pruritus and fatigue, patients with PBC are also prone to developing osteoporosis (OP). This skeletal condition not only heightens the likelihood of fractures but is also associated with elevated mortality. With the overall prevalence of PBC rising, a parallel increase in OP incidence among these patients can be anticipated. Early recognition, preventive strategies, and appropriate therapeutic approaches are essential for preserving patients' quality of life. Nevertheless, current data on the management of OP in PBC remain limited. Most existing recommendations are extrapolated from studies on postmenopausal OP. However, these findings have not been effectively adapted into practical management protocols for PBC-related OP, largely due to distinct pathophysiological mechanisms between the two conditions. The absence of well-established preventive and therapeutic measures continues to represent a major obstacle in addressing OP among patients with PBC. This review offers a detailed synthesis of the epidemiology, underlying mechanisms, and therapeutic considerations of OP linked to PBC.

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Introduction

Primary biliary cholangitis (PBC) is an autoimmune-mediated, chronic intrahepatic cholestatic disorder defined by non-suppurative inflammation affecting the small intrahepatic bile ducts. The serological features of PBC patients include positive anti-mitochondrial antibodies and elevated cholestatic markers such as ALP and GGT, and the disease histopathologically manifests as non-suppurative inflammation of small bile ducts.[1,2] The etiology and pathogenic mechanisms of this disorder have not yet been completely clarified. In recent years, evidence has indicated that both the cytotoxic activity of $CD8^+$ T cells toward the bile ducts and immune regulation exerted by microbial metabolites contribute substantially to the progression of PBC.[3–7] Recent studies have also demonstrated the significant role of bile acid metabolism disorders in the pathogenesis of PBC.[8,9]

Osteoporosis (OP) represents a prevalent complication observed among patients with PBC.[10] This skeletal disorder is distinguished by diminished bone mass and deterioration of bone microarchitecture, potentially resulting in elevated fracture susceptibility.[11] Fragility fractures constitute the most substantial and severe consequence of OP, imposing considerable economic and psychological burdens upon families and society.[12,13] Although OP is common among patients with chronic liver disease, patients with PBC have the highest incidence rate of OP, followed by those with alcoholic liver disease, chronic hepatitis B, and metabolic liver disease.[14] Due to the fact that PBC patients often have symptoms of weakness and sarcopenia,[15] which increase the risk of falls, the risk of fractures is significantly elevated. Therefore, it is very important to timely summarize the literature related to PBC-associated OP and improve understanding of this disease.

The pathogenic mechanisms underlying PBC-associated OP demonstrate considerable complexity and multifactorial origins. Various contributing elements have been documented, encompassing heightened concentrations of inflammatory cytokines; insufficiencies in vitamin D (VD) and vitamin K (VK); and abnormally increased concentrations of bilirubin and bile acids.[16,17] However, concurrent OP among patients with PBC remains inadequately investigated. Consequently, relevant investigations concerning OP prevalence in PBC were synthesized, risk factors correlated with OP were identified, potential mechanisms governing OP development in PBC were systematically examined, and recent therapeutic advances in OP management were emphasized.

Prevalence and risk factors of OP in patients with PBC

Prevalence of OP in patients with PBC

The prevalence of OP in patients with PBC ranges from 20–50% (Table 1), with variations attributed to age, female proportion, and hepatic fibrosis severity within the studied populations. A meta-analysis demonstrated that OP was identified

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Table 1. Prevalence of osteoporosis in patients with PBC

Author	Year	States	PBC (n)	Media age	Female %	Cirrhosis %	Osteoporosis %
Keith. *et al*[18]	2001	USA	176	53	83.5%	59%	20%
Newton. *et al*[19]	2001	UK	272	62	94%	54%	31%
Juan Rodés. *et al*[20]	2005	Spain	142	54.3	100%	-	32.4%
GUAÑABENS. *et al*[75]	2010	Spain	185	55.7	100%	23%	37%
Hiroyuki. *et al*[22]	2017	Japan	128	61	100%	0	26%
Cançado. *et al*[25]	2021	Brazil	464	56	95.4%	32.7%	25.9%
Akihito. *et al*[23]	2021	Japan	117	68	82.1%	9.4%	28.2%
Wang. *et al*[21]	2023	China	268	56.7	88.1%	60.1%	45.5%

PBC, primary biliary cholangitis.

in 38% of 360 patients with PBC, while osteopenia was observed in 39%, and normal bone mass was documented in merely 23%.[10]

In the United States, OP was documented in 20% of 176 patients with PBC.[18] European population studies revealed OP prevalence rates of 31%[19] and 32.4%[20] in the United Kingdom and Spain, respectively. Regarding Asian populations, the overall OP prevalence in patients with PBC was reported as 45.5%[21] in China. Japanese studies indicated OP prevalence ranging from 20–30%.[22,23]

It was once speculated that the high incidence of OP in patients with PBC was due to the fact that most patients with PBC are postmenopausal women. However, one study[22] demonstrated that OP prevalence was substantially elevated in postmenopausal patients with PBC compared with matched postmenopausal controls. This finding emphasized the distinctive contribution of PBC to OP development.

Retrospective analysis revealed that OP prevalence in patients with PBC alone was comparable to that observed in patients with PBC–autoimmune hepatitis (AIH) overlap but substantially higher than that documented in patients with AIH.[24] In 2021, investigators determined that OP prevalence in the anti-mitochondrial antibody-positive group was similar to that in the anti-mitochondrial antibody-negative group.[25]

Patients with PBC not only exhibit elevated OP prevalence but also demonstrate increased fracture risk and substantially higher post-fracture mortality rates. One study documented[26] that patients with PBC experienced a 1.63-fold increased fracture risk. Additionally, mortality rates at 30 days and 1 year following fracture were markedly elevated in patients with PBC compared with controls who also sustained fractures.[27]

Risk factors for OP in patients with PBC

Risk factors for OP in patients with PBC include age and duration of disease, low body mass index, disorders of lipid metabolism, high bilirubin and bile acid levels, and severe liver fibrosis. Figure 1 shows the risk factors for OP in patients with PBC.

Advanced age represents a significant risk factor for OP development in patients with PBC. With advancing age, organ functionality deteriorates, and persistent inflammation induces hemodynamic alterations alongside renin–angiotensin–aldosterone system modifications, thereby disrupting bone remodeling processes. Recent research has reported that components of the RAAS are expressed in bone tissue, activating local RAAS reactions and leading to increased bone turnover and decreased bone density.[28] Furthermore, increased age correlates with elevated OP prevalence rates among patients with PBC.[21,22]

Additionally, disease duration constitutes another critical determinant in OP occurrence among patients with PBC. Researchers employing multivariate regression analyses have identified disease duration as an independent risk factor for OP development in patients with PBC.[29]

Reduced body mass index has been extensively documented as a risk factor for OP development in patients with PBC.[21] Malnutrition combined with diminished physical activity may decrease stress stimulation applied to bones, whereas mechanical stimulation and weight-bearing exercises are beneficial for maintaining bone structural integrity. Recent investigations have revealed that sarcopenia demonstrates strong associations with OP development.[30] One study documented that skeletal muscle index exhibited significant positive correlations with bone mineral density (BMD).[31,32]

Elevated lipid concentrations represent common abnormalities observed in patients with PBC.[32] Recent research has documented that serum triglyceride and cholesterol levels demonstrate negative correlations with BMD levels in elderly populations.[33] Whether abnormal lipid metabolism increases OP incidence in patients with PBC requires further investigation.

Abnormal bilirubin and bile acid concentrations are similarly associated with OP risk in patients with PBC[34] and primary sclerosing cholangitis. In a cohort comprising 238 patients with PBC, bile acid concentrations were markedly elevated in the osteoporotic group relative to non-osteoporotic patients.[35]

Hepatic fibrosis severity demonstrated significant associations with OP development in patients with PBC. Studies in MASLD have documented that advanced hepatic fibrosis exhibits negative associations with BMD[36] and that FIB-4 scores were markedly associated with elevated OP risk.[37] In a retrospective study involving 446 participants, multifactorial analysis revealed that FibroScan-detected liver stiffness constituted an independent risk factor for OP development in patients with PBC.[38] The more severe the liver fibrosis, the more severe the liver cell damage, which can lead to a decrease in insulin-like growth factor-1 (IGF-1), activation of inflammation, and acceleration of bone loss.

Mendelian randomization represents a recently developed bioinformatics analytical methodology that employs genetic variation as instrumental variables to examine causal relationships between exposures and outcomes. Two recent Mendelian randomization studies investigating PBC and OP have documented that PBC can result in increased OP risk.[39,40]

Pathogenesis of OP in patients with PBC

Bone homeostasis relies upon a dynamic equilibrium between osteoblast-mediated bone formation and osteoclast-induced

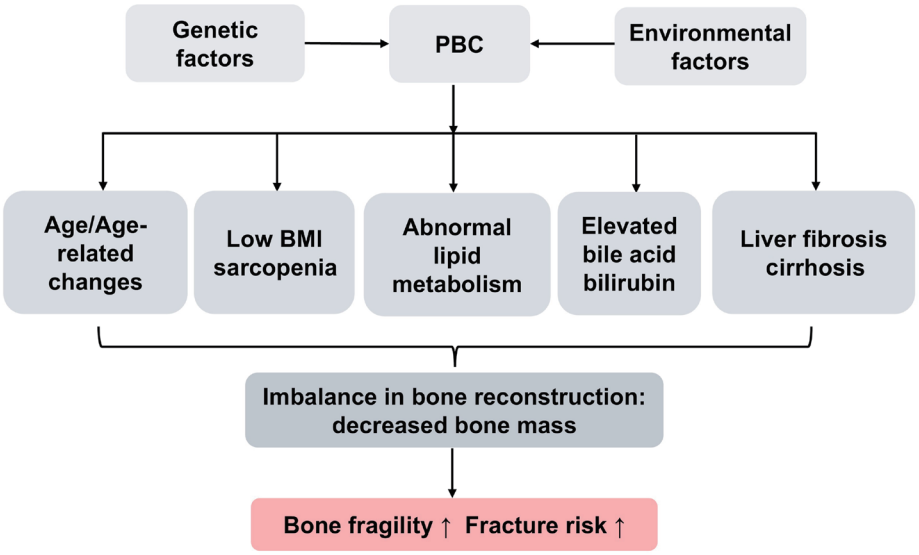

Fig. 1. Risk factors for osteoporosis in PBC patients. PBC, primary biliary cholangitis; BMI, body mass index; ↑, increase.

bone resorption. Several investigations have documented elevated bone resorption in patients with PBC. However, the preponderance of contemporary evidence indicates that osteoblast dysfunction and inadequate bone formation constitute the primary mechanisms underlying the pathogenesis of OP in PBC. Figure 2 synthesizes the principal factors contributing to the pathogenesis of OP in PBC.

Immune disorder

Osteoprotegerin (OPG) represents a pivotal signaling molecule within the receptor activator of nuclear factor-κB ligand (RANKL) pathway. Upon RANKL binding to receptor activator of nuclear factor-κB, essential transcription factors such as NFATc1 become activated, thereby governing osteoclast activation and differentiation processes.[41] OPG demonstrates the capacity to suppress bone resorption through its binding to RANKL, consequently preventing RANKL-mediated binding and inhibiting bone resorption mechanisms. Research has demonstrated that OPG concentrations were markedly elevated in the PBC cohort compared with control subjects, with further elevation observed in patients presenting with elevated bilirubin levels and high Mayo scores.[42] In 2016,

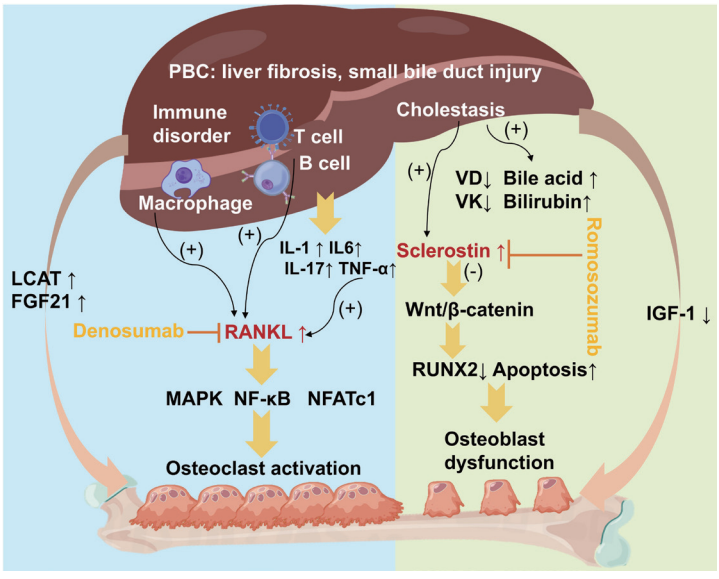

Fig. 2. Major factors in the pathogenesis of osteoporosis in PBC. In patients with PBC, activated macrophages, T cells, and B cells secrete elevated levels of IL-1, IL-6, and IL-17. This increases serum RANKL levels and enhances its binding to RANK. The RANKL–RANK complex subsequently activates osteoclast differentiation through the MAPK and NF-κB–NFATc1 signaling pathways. Denosumab can block the binding of RANKL to RANK, thereby inhibiting bone loss. On the other hand, cholestasis in PBC patients leads to increased secretion of osteonectin. Osteonectin inhibits osteoblast function via the Wnt/β-catenin pathway, resulting in impaired osteoblast activity. Romosozumab can suppress this process, thereby promoting osteogenesis. PBC, primary biliary cholangitis; LCAT, lecithin-cholesterolacyltransferase; FGF21, Fibroblast Growth Factor 21; RANKL, Receptor Activator for Nuclear Factor-κ B Ligand; IGF1, Insulin-like growth factor 1; RUNX2, Runt-related transcription factor-2; MAPK, mitogen-activated protein kinase; NFκB, nuclear factor kappa-B; NFATc1, nuclear factor of activated T cells 1. ↑, elevated levels; ↓, decreased levels.

investigators revealed that patients with PBC exhibited markedly increased hepatic RANKL expression levels relative to healthy controls.[43] These findings indicate that dysregulated expression of OPG/RANKL pathway–associated molecules within hepatic tissues of patients with PBC may constitute a critical factor contributing to OP development.

Research has established that patients with PBC demonstrate substantially increased Th17 cell populations,[44] with activated Th17 cells secreting considerable quantities of the cytokine IL-17, which possesses notable pro-inflammatory properties.[45] IL-17 has been shown to upregulate RANKL expression while simultaneously downregulating OPG expression, thus facilitating osteoclast differentiation and maturation processes and accelerating bone destruction mechanisms.[46] Furthermore, IL-17 stimulates macrophage production of various inflammatory mediators (e.g., TNF-α, IL-1, and IL-6), which indirectly enhance RANKL expression and promote bone destruction processes.[47]

Cholestasis

Compromised hepatic and intestinal recycling of bile acids, alongside bile acid metabolism disturbances in patients with PBC, generates a disruption in bile acid homeostasis, subsequently impairing lipid metabolism and compromising the absorption of fat-soluble vitamins, thereby resulting in VD and VK deficiencies among patients with PBC.[48] Diminished VD levels in patients with PBC contribute to calcium and phosphorus insufficiencies and inadequate osteogenic substrates, accompanied by secondary hyperparathyroidism induced through feedback mechanisms along the calcium–VD_3–PTH axis, which facilitates bone destruction. VK participates in osteocalcin activation through its role as a γ-carboxylase cofactor[49] and enhances bone formation. VK deficiency in patients with PBC contributes to bone microarchitecture deterioration and reduced bone density, whereas prolonged VK treatment partially ameliorates bone loss.[50]

Cholestatic retention compounds, including bile acids and bilirubin, may contribute to diminished bone formation through interference with osteoblast proliferation, differentiation, and mineralization processes. The introduction of elevated bile acid concentrations to osteoblast culture systems reduces the differentiation capacity of osteoblasts[34] and suppresses the expression of *RUNX2*, a gene promoting osteoblast differentiation. Elevated bilirubin concentrations similarly compromised the viability of cultured primary human osteoblasts.[51,52] Notably, ursodeoxycholic acid counterbalances the detrimental effects of these compounds on osteoblast viability, proliferation, mineralization, and apoptosis.[53,54] Nevertheless, clinical studies demonstrating ursodeoxycholic acid's effectiveness in preventing bone loss or reducing OP incidence remain absent.

Liver damage

IGF-1 synthesis is predominantly generated by hepatic tissue,[55] and compromised hepatic function observed in patients with PBC results in reduced IGF-1 concentrations,[56] thereby attenuating its capacity to enhance alkaline phosphatase activity and stimulate type I collagen synthesis within osteoblasts, as well as promote osteoblastic differentiation.[57] Experimental evidence has demonstrated that low-dose IGF-1 administration can augment bone mass and bone density in cirrhotic rat models.[58]

Sclerostin functions as a pivotal inhibitor of the Wnt/β-catenin signaling cascade, being predominantly synthesized by osteoblastic cells and potentially inhibiting bone formation processes.[59] Additionally, sclerostin expression has been identified within biliary ductal structures, particularly under cholangitic conditions. Research investigations have documented elevated serum sclerostin concentrations in patients with PBC compared with control subjects, with serum sclerostin demonstrating inverse correlations with bone formation biomarkers.[60] These findings potentially substantiate a contributory role for sclerostin in mediating the reduced bone formation associated with PBC.

Table 2. Diagnostic criteria for bone density measurement based on DXA

Diagnosis	T-value
Normal	T-value ≥ −1.0
Osteopenia	−2.5 < T-value < −1.0
Osteoporosis	T-value ≤ −2.5
Severe osteoporosis	T-value ≤ −2.5+ fragility fractures

DXA, dual-energy X-ray Absorptiometry.

Diagnosis of OP in patients with PBC

The internationally acknowledged diagnostic criterion for OP involves the assessment of BMD through dual-energy X-ray absorptiometry methodology.[61] OP is established when a T-score of ≤ −2.5 is obtained (Table 2).

Beyond BMD evaluation, various scoring instruments are available for rapid outpatient screening of osteoporotic risk, encompassing the International Osteoporosis Foundation Osteoporosis Risk One Minute Test, Fracture Risk Assessment, and the OSTA Index.

The IOF Osteoporosis Risk One Minute Test can be used to quickly screen high-risk patients for possible comorbidities of OP.[62] The main issues include age, whether the patient is underweight, whether there is a history of fractures, whether there is a sudden decrease in height, whether the parents have hip fractures, and whether there are other risk factors that may cause bone loss. If one answer is yes, the patient is considered at high risk of OP and needs to undergo bone density testing.

Fracture risk assessment[63] takes into account parameters such as bone density, age, height, weight, and OP risk factors. If the predicted incidence of hip fractures is ≥3% or the incidence of any major osteoporotic fracture is ≥20%, high-risk patients for osteoporotic fractures can be diagnosed, and drug treatment is recommended.

The OSTA risk index is a tool used to assess the risk of OP,[64] which is particularly suitable for Asians, especially postmenopausal women. The calculation formula for this index is: weight (kg) − age × 0.2. According to the value of the OSTA index, the risk of OP can be determined. OSTA > −1 indicates low risk, OSTA between −1 and −4 indicates moderate risk, and OSTA < −4 indicates high risk.

Management of OP in patients with PBC

At present, the management of OP in patients with PBC mainly refers to treatment methods for postmenopausal OP, and there is still a lack of high-quality clinical research on the treatment of OP in patients with PBC. The main treatment methods include basic calcium supplementation and VD therapy, commonly used bisphosphonates, estrogen replacement therapy, as well as emerging biologics and monoclonal antibodies.

VD and calcium

Calcium and VD administration is recommended to be main-

tained throughout the entire duration of OP management.[61] Nevertheless, limited clinical investigations have been performed, and definitive evidence confirming the effectiveness of calcium and VD supplementation in preventing bone deterioration among patients with PBC remains absent.

In 2006, research findings indicated that calcium and VD supplementation could substantially decelerate the progression of bone deterioration in patients with PBC and exert beneficial effects on bone mass preservation. A four-year prospective cohort investigation[65] similarly documented that calcium and VD_3 supplementation therapy failed to demonstrate significant OP improvement in female patients with PBC, yet successfully prevented and decelerated natural bone deterioration in these patients. However, VD needs to be converted into 1,25-dihydroxyvitamin D in the body to exert physiological effects, so directly supplementing with calcitriol can quickly increase VD levels in the body,[66] but the treatment effect for OP remains unclear.

Bisphosphonates and estrogen replacement therapy

Bisphosphonates are acknowledged as the primary therapeutic intervention for postmenopausal OP and function as anti-resorptive agents targeting bone metabolism. Nevertheless, the therapeutic effectiveness of bisphosphonates in ameliorating osteoporotic conditions among patients with PBC remains ambiguous.

A meta-analysis conducted by the Cochrane Library in 2011[67] encompassed six randomized trials incorporating 200 participants. The authors failed to identify any bisphosphonate demonstrating significant enhancement in fracture risk reduction or BMD improvement among patients with PBC. Other studies have demonstrated that bisphosphonates can effectively ameliorate osteoporotic conditions in postmenopausal patients with PBC.[68,69] The reasons for the inconsistent results may be the small sample size included in the meta-analysis and the fact that these patients with PBC had more severe disease, with most being cirrhotic. Treatment of PBC itself may improve the effectiveness of bisphosphonates in OP management.

Due to the association between bisphosphonates and esophagitis risk, clinical guidelines recommend cautious utilization in patients presenting with cirrhotic esophagogastric fundal varices. A 2022 investigation[70] evaluated the risk of variceal hemorrhage in cirrhotic patients with esophageal varices. The findings indicated that oral risedronate administration was efficacious in enhancing BMD among cirrhotic patients with esophagogastric varices without precipitating gastrointestinal bleeding complications.

Hormone replacement therapy represents a conventional therapeutic approach for OP management in postmenopausal women. However, hormone replacement therapy is associated with elevated risks of various adverse events. A meta-analysis[71] incorporating two clinical trials with 49 participants did not endorse estrogen replacement therapy for osteoporotic patients with PBC. One adverse reaction of estrogen replacement therapy is bile stasis, which exacerbates the condition of PBC patients. Therefore, estrogen replacement therapy is not recommended.

Denosumab

Denosumab has been sanctioned for managing postmenopausal OP characterized by elevated fracture susceptibility through its capacity to suppress osteoclast activation while diminishing bone resorption, thereby enhancing bone mass and mitigating vertebral and hip fracture risks.

In 2020, research documented[72] that ten osteoporotic patients with autoimmune liver disease (encompassing six PBC cases and four AIH cases) were administered subcutaneous denosumab at 60 mg biannually. After 36 months of treatment, progressive and substantial BMD enhancement was observed. Furthermore, denosumab has demonstrated favorable efficacy and safety profiles in patients with chronic liver disease, comparable to its performance in primary OP management.[68]

In a recent RCT study in Japan,[73] 41 patients with PBC were included: 21 patients were randomly assigned to receive denosumab monotherapy, and 20 patients received treatment with zoledronic acid. One year later, improvements in bone density showed that denosumab was not inferior to zoledronic acid in terms of efficacy and had fewer adverse reactions. Therefore, in clinical practice, patients with severe OP can be treated with denosumab.

Romosozumab

Romosozumab, a monoclonal antibody targeting sclerostin, has been approved for administration in patients at elevated fracture risk experiencing postmenopausal OP. Recent research documented[74] that underweight patients with PBC presenting with severe OP who were administered a reduced dose of romosozumab (3 mg/kg) exhibited substantial enhancement in lumbar spine bone density.

Conclusions

OP represents a prevalent complication among patients with PBC. The underlying pathogenesis is predominantly characterized by diminished bone formation, while certain investigations have additionally demonstrated enhanced bone resorption. The development of OP has been associated with the extent of hepatic fibrosis, advancing age, and the duration of cholestatic conditions. Dual-energy X-ray absorptiometry remains a widely utilized diagnostic modality for OP detection and should be implemented across all patients with PBC. Regarding therapeutic management, VD and calcium supplementation constitute the fundamental approach for OP prevention. Bisphosphonates may demonstrate efficacy in enhancing patients' BMD and mitigating fracture risk; however, robust evidence-based medical data remain necessary for confirmation. The therapeutic effectiveness of novel agents such as denosumab and romosozumab in managing OP among PBC populations requires additional comprehensive evaluation.

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Conflict of interest

YH has been an Editorial Board Member of *Journal of Clinical and Translational Hepatology* since 2013. The other authors have no conflict of interests related to this publication.

Author contributions

Study concept and design (YH, CG), acquisition of data (JL, CY, XL), drafting of the manuscript (JY, SS, TY), critical revision of the manuscript for important intellectual content (GG, CG), administrative, technical, or material support (YH), and

study supervision (YH). All authors have made significant contributions to this study and have approved the final manuscript.

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