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ORIGINAL RESEARCH

Serum LCAT as a Gender-Neutral Biomarker for Early Osteoporosis: A Multicenter Cohort Validation Study

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Purpose: This study aims to identify a novel biomarker for the early detection and prevention of osteoporosis.

Methods: A cross-sectional study (n=138, from 497 screened) was conducted at Nanjing Drum Tower Hospital (Sep 2023-Jun 2024). A second multicenter validation cohort (n=165) was collected (Jun 2024-Jan2025) from three hospitals, including 90 controls, 35 osteopenia, and 40 OP cases. Serum LCAT was measured via ELISA. Statistical analyses (*t*-tests, ANOVA, Mann–Whitney U) compared LCAT levels across bone health groups and genders. Correlations between LCAT and biochemical parameters were assessed, and ROC analysis evaluated diagnostic performance.

Results: Serum LCAT levels were significantly lower in both the osteopenia (n=32, p<0.01) and osteoporosis groups (n=50, p<0.001) compared with control group (n=56). The results from this second cohort support our previous cross-sectional findings, serum LCAT levels in controls (44.41 ± 14.16), osteopenia (32.15 ± 8.93) and osteoporosis (22.15 ± 7.07). In this multicenter study, serum LCAT levels were evaluated and found to be significantly decreased in the primary osteoporosis group compared to controls across all populations with notable differences by sex (males: U=207.5, p=0.0031; females: U=520.5, p=0.0001) and age (≤55 years: p=0.005; >55 years: p=0.0001). LCAT levels showed positive correlations with T/Z-scores, BMI, ALT, AST, LDL-C, and serum phosphorus, and negative correlations with age and serum creatinine. ROC analysis yielded an AUC of 0.822, with sensitivity and specificity of 75.9% and 78%, respectively. Moreover, serum LCAT levels exhibited significantly higher predictive value for osteoporosis than that of conventional serum 25-hydroxyvitamin D (25OHD) levels.

Conclusion: We demonstrate for the first time that reduced serum LCAT concentrations predict osteoporosis risk independently of confounding factors, qualifying it as a promising early-stage diagnostic biomarker. These findings establish LCAT as a demography-invariant diagnostic biomarker for early-stage osteoporosis, suggesting its potential utility in population-wide screening programs.

Keywords: osteoporosis, early detection, LCAT, hepatogenic factor, biomarker

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Introduction

OP is recognized as the most prevalent metabolic bone disorder in humans, distinguished by low bone mass and microstructural decline in bone tissue, as noted by the World Health Organization.[1] This condition can be categorized into two types: primary osteoporosis and secondary osteoporosis. Primary osteoporosis further divides into postmenopausal osteoporosis (PMOP), senile osteoporosis, and idiopathic osteoporosis. Secondary osteoporosis refers to that which occurs due to endocrine disorders, blood conditions, nutritional inadequacies, medications, or other diseases affecting individuals of various ages. Recent estimates suggest that over 18% of the global population suffers from osteoporosis.[2] In China, OP prevalence is approximately 23.57% among women and 12.22% among men.[3] Despite the availability of treatments aimed at diminishing morbidity and reducing diagnostic costs, there is a growing incidence of fractures and subsequent post-traumatic complications globally. Projections indicate that by 2050, the rate of hip fractures in men worldwide could surge by 310%, while for women, it may increase by 240%.[1] At present, the diagnosis of OP relies on bone mass evaluation via dual-energy X-ray absorptiometry (DEXA) and fracture risk assessment using online tools like FRAX.[4] Nonetheless, the accuracy of bone densitometry and risk calculations is inadequate for the early detection of the disease. Reports indicate that blood biomarkers may serve as a dependable method for the early diagnosis of osteoporosis. It has been reported that blood biomarkers can be used as a reliable means of early disease diagnosis. Most of the reliable blood biomarkers for OP such as type I collagen degradation products are not useful for early diagnosis of OP.[5] Serum osteocalcin, a bone-derived osteogenic factor, functions as a biomarker for osteoporosis by reflecting osteoblast activity. However, its diagnostic specificity and stability are significantly limited by diurnal fluctuations, renal function interference, and ectopic expression in non-osseous tissues.[6] Consequently, there is an immediate necessity to investigate early blood biomarkers for osteoporosis.

As the metabolic center of the human body, liver-centered organ crosstalk has received significant attention recently.[7] The liver can maintain the homeostatic balance of metabolism by secreting a large number of factors such as high-density lipoprotein (HDL), immunoglobulin A, bile acids, fibroblast growth factor 21 (FGF21), which distally regulate organs such as the intestine and brain. Once the above homeostatic imbalance is disrupted, metabolic diseases such as iron deficiency anemia, vitamin D deficiency, hypercholesterolemia, hepatic encephalopathy and so on will occur.[8] Currently, the inter-tissue metabolic regulation theories of liver-intestinal axis and liver-brain axis have been widely established internationally.[9–13] Our previous study clarified and deepened the regulatory mechanism of metabolic homeostasis of the liver-bone axis, and initially revealed how the liver-bone axis regulates metabolic homeostasis of the body under physiological and pathological conditions.[14] IIn our study, we found that chronic liver injury causes an imbalance in the metabolic homeostasis of the liver-bone axis by decreasing the secretion of the liver-derived factor LCAT, which triggers the loss of bone mass and ultimately leads to the development of osteoporosis. This suggests that LCAT can be used as a serum marker for osteoporosis, but whether it can be used for the early diagnosis of OP requires further study.

Considering these results, this research aimed to assess the initial circulating levels of LCAT in individuals diagnosed with primary osteoporosis, investigate its possible role as a biomarker for early detection and prevention of the condition, and examine its correlation with baseline data. Osteoporosis predominantly affects women, underdiagnosed men face significantly higher fracture-related mortality. Our study explores potential sex-based differences.

Materials and Methods

Study Design

Approval from the Research Ethics Review Committee of Nanjing Drum Tower Hospital, Nanjing Medical University First Affiliated Hospital, and its Affiliated Sir Run Run Hospital. Utilizing a cross-sectional design, serum samples and clinical information were gathered from patients diagnosed with bone loss and osteoporosis (n=82) who attended the Orthopedic Outpatient Department from September 2023 to June 2024. A comparison group (n=56) composed of individuals with normal bone mass was chosen from the Health Checkup Center. Finally, between June 2024 to January 2025, a second cohort was collected from Nanjing Drum Tower Hospital, Jiangsu Provincial Hospital, and Nanjing Medical University Affiliated Sir Run Run Hospital to further evaluate the potential of serum LCAT as a biomarker for the preliminary diagnosis of osteoporosis. A total of 165 samples were collected, including 90 cases

with normal bone volume and 40 diagnosed with osteoporosis. The classification of osteoporosis followed the diagnostic criteria established in 2022. Bone mineral density assessments were conducted using DEXA results focusing on the femur, hip joint, and LS (L1-L4). DEXA scans adhered to the ISCD (International Society for Clinical Densitometry) guidelines for calibration and operator training. All individuals provided written informed consent, and none were receiving any treatments that might affect bone density. The characteristics of the participants involved in the study are compiled in Tables 1 and 2.

Table 1 Baseline Characteristics of the Study Participants

Characteristics	NC (n=56)	OPE (n=82)	*P* value
Age (years)	55(35,62.5)	59(54.5,69)	0.534
Gender			0.502
Male	12(21.43%)	14(17.07%)	
Female	44(78.57%)	68(82.93%)	
BMI (kg/m^2)	24.31(22.36,29.88)	24.28(22.1,28.75)	0.766
FBG (mmol/L)	5.24±0.55	5.29±0.58	0.639
ALT (U/L)	18.85(15.55,24.62)	16.8(12.68,24.08)	0.24
AST (U/L)	24.04(20.47,29.2)	21.4(17.08,2615)	0.51
TC (mmol/L)	4.84±0.72	4.9±0.85	0.691
TG (mmol/L)	1.45±0.64	1.71±1.02	0.096
HDL-C (mmol/L)	1.41±0.4	1.36±0.38	0.461
LDL-C (mmol/L)	3.01±0.7	2.93±0.81	0.58
SCR (μmol/L)	56.57±9.28	57.96±11.36	0.442
P (mmol/L)	1.21±0.14	1.18±0.21	0.289
Ca (mmol/L)	2.33±0.11	2.34±0.12	0.935
LS-T	1.14±1.41	−2.31±0.85	**<0.001**
Serum LCAT (μg/mL)	30.10±9.87	17.49±5.71	**<0.001**
25 (OH) D(ng/mL)	28.05±9.93	19.72±8.13	**<0.001**

Notes: The data are expressed as mean ± standard deviation, median (quartile), or percentage. P values are determined by either the *t*-test or Chi-square test. Significant p values ($p < 0.05$) are highlighted in bold. The bold part is $P < 0.05$. NC for the bone mass healthy control group, OPE for osteopenia and OPO for osteoporosis.

Abbreviations: FBG, for fasting blood glucose; BMI, for body mass index; TC, for total cholesterol; TG, for triglycerides; ALT, for alanine aminotransferase; AST, for aspartate aminotransferase; HDL-C, for high-density lipoprotein cholesterol; LDL-C, for low-density lipoprotein cholesterol; SCR, for serum creatinine; LS, T-score for lumbar spine T-score; 25 (OH) D, for 25-Hydroxyvitamin D.

Table 2 Baseline Characteristics of the Second Cohort Participants

Characteristics	NC (n=90)	OPE (n=75)	*P* value
Age (years)	41.81±14.38	65.27±9.21	**<0.001**
Gender			0.32
Male	28(28.28%)	14(21.54%)	
Female	71(71.72%)	51(78.46%)	
BMI (kg/m^2)	22.28±2.22	22.87±2.60	0.12
ALT (U/L)	17.27±9.80	20.35±10.99	0.07
AST (U/L)	19.10±5.62	20.67±5.22	0.08
TC (mmol/L)	4.39±0.72	4.23±0.86	0.21
TG (mmol/L)	0.97±0.39	1.06±0.33	0.14
HDL-C (mmol/L)	1.460000±0.33	1.35±0.39	0.08

(*Continued*)

Table 2 (Continued).

Characteristics	NC (n=90)	OPE (n=75)	*P* value
LDL-C (mmol/L)	2.62±0.64	2.48±0.66	0.20
LS T-score	0.70±1.56	−2.21±1.0	**<0.001**
FN T-score	0.76±0.99	−1.63±0.83	**<0.001**
Hip T-score	0.93±0.83	−1.51±0.99	**<0.001**

Notes: The data are expressed as mean ± standard deviation, median (quartile), or percentage. P values are determined by either the *t*-test or Chi-square test. Significant p values ($p < 0.05$) are highlighted in bold. NC for the bone mass healthy control group, OPE for osteopenia and OPO for osteoporosis. The bold part is $P < 0.05$.

Abbreviations: BMI, for body mass index; TC, for total cholesterol; TG, for triglycerides; ALT, for alanine aminotransferase; AST, for aspartate aminotransferase; HDL-C, for high-density lipoprotein cholesterol; LDL-C, for low-density lipoprotein cholesterol; LS, T/Z-score for lumbar spine T/Z-score; FN, T/Z-score for Femoral Neck T/Z-Score.

Inclusion and Exclusion Criteria

The criteria for classifying osteoporosis adhered to the protocols specified in the Primary Osteoporosis Diagnosis and Treatment Guidelines (2022). To be eligible, all participants had to satisfy the following inclusion requirements: (1) Age of 18 years or older, (2) Availability of DEXA results, (3) Comprehensive clinical data. The exclusion criteria included: (1) A prior history of anti-osteoporotic treatment or any malignancy, (2) Significant skeletal deformities potentially interfering with the accuracy of DEXA measurements, (3) Recent use of drugs known to influence bone metabolism, (4) Other medical conditions that the researchers considered inappropriate for participation in this study.

Bone Density Measurement and Grouping Criteria

Bone mineral density assessments were conducted using DEXA results focusing on the femur, hip joint, and LS (L1-L4). Based on T- and Z-scores derived from the LS (L1-L4), participants were divided into three distinct categories: (1) Normal bone mass group: LS (L1-L4) T-score ≥ -1; (2) Osteopenia group: LS (L1-L4) $-2.5 <$ T-score < -1; (3) Osteoporosis group: LS T-score $-2.5 <$ T-score < -1, accompanied by fragility fractures in the proximal humerus, pelvis, or distal forearm, or a T-score ≤ -2.5. For women who have not yet reached menopause and men younger than 50, it is advisable to evaluate bone density levels utilizing Z-scores that correspond with the same ethnic background Furthermore, bone fractures that were linked to abnormal bone metabolism were also taken into account. All individuals provided written informed consent, and none were receiving any treatments that might affect bone density.

Determination of Serum LCAT Concentration and Lumbar Spine, Femoral Neck and Hip T/Z-Score

In this study, serum levels of LCAT were quantified using the Cloud-Clone Corp Assay Kit via enzyme-linked immunosorbent assay (ELISA). Lumbar spine (L1-L4) BMD was assessed with DEXA, concentrating on the specified area along the axial direction. The BMD values derived from DEXA were then transformed into T/Z-scores to assist in the diagnosis of osteoporosis. The Z-score is calculated as the difference between an individual's bone mineral density value and the average bone mineral density value of their peers, divided by the standard deviation of their peers' bone density values.

Clinical and Biochemical Assessments

An extensive clinical and biochemical assessment was performed, encompassing the measurement of various parameters by the Hospital's Department of Laboratory Medicine. These parameters included fasting blood glucose (FBG), body mass index (BMI), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total cholesterol (TC),

triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and serum levels of creatinine, phosphorus, and calcium.

Statistical Analysis

For this study, statistical evaluations were performed using IBM SPSS Statistics version 27.0, which was released by IBM in 2020 in Armonk, New York. Initially, Shapiro–Wilk Test assessment of data normality was carried out examination of normal distribution plots. Continuous variables conforming to a normal distribution were reported as mean ± standard deviation (SD), while those that did not follow a normal distribution were conveyed as median (quartile). Data were categorized according to T-scores, and appropriate statistical methods were applied. The independent sample *t*-test was used for comparisons between two groups with normally distributed data. One-way ANOVA was applied for comparisons of more than two groups. When data failed to satisfy the assumptions of normal distribution, non-parametric tests were instead employed.

To evaluate the correlation between LCAT levels and other clinical baseline variables, Pearson's correlation analysis was used for normally distributed data, whereas Spearman's rank correlation was implemented for non-normally distributed data. A p-value of less than 0.05 was considered statistically significant.

Results

Baseline Clinical Characteristics of All Participants

In this cross-sectional investigation, a total of 497 patients were screened, of which 359 were excluded, and 138 patients fulfilled the study eligibility criteria we enrolled a total of 56 participants with a normal bone density serving as controls, while 82 individuals demonstrating bone loss were categorized as the "osteopenia group" following established inclusion and exclusion guidelines (Figure 1). We assessed serum concentrations of the liver-derived protein LCAT, alongside

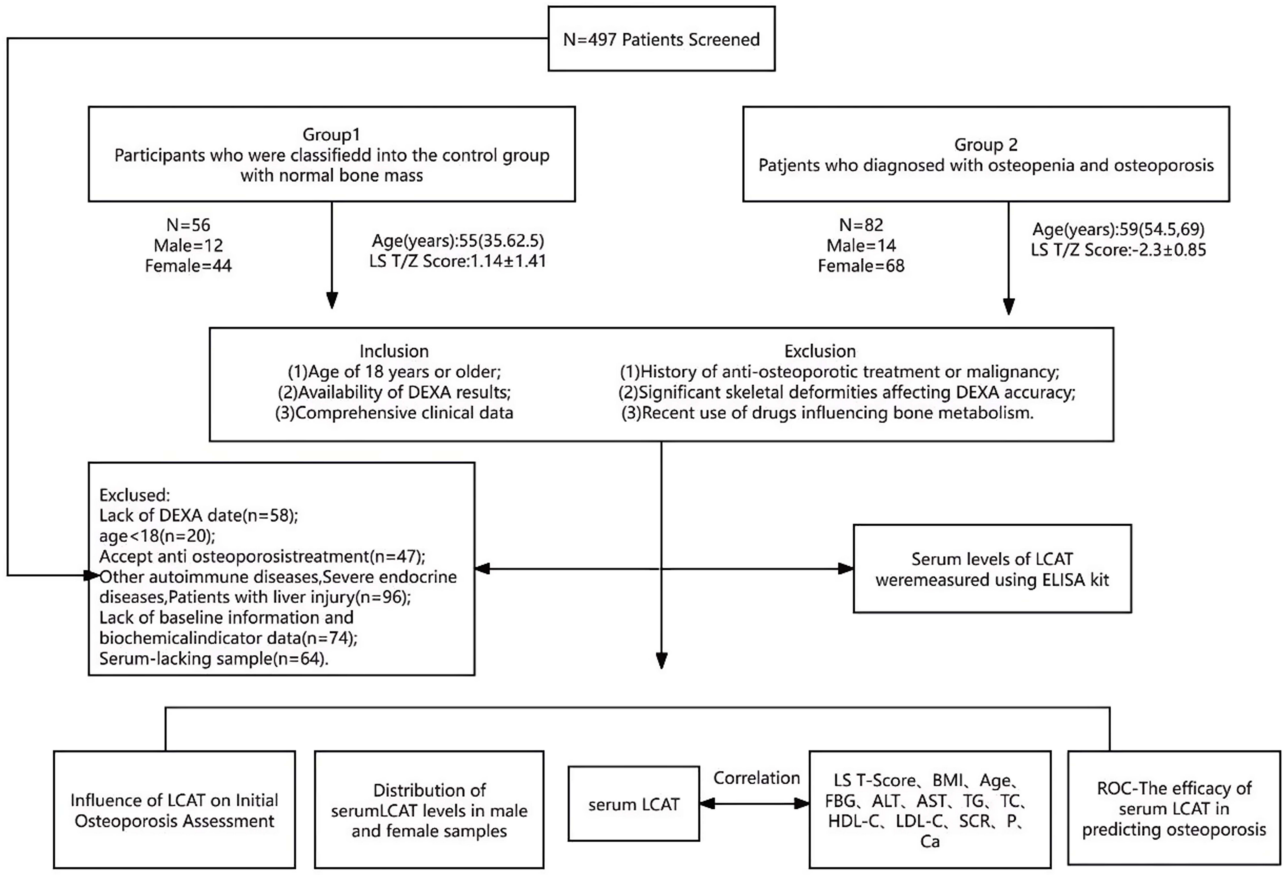

Figure 1 Flowchart of recruitment and follow-up.

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clinical parameters such as age, BMI, ALT, and AST within the two groups of patients. The analysis revealed that, with the exception of the LS, FN, Hip T/Z-score, serum LCAT and 25 (OH) D level, there were no statistically significant differences in other initial clinical traits. Importantly, both the lumbar spine T-score and serum LCAT levels in the bone loss group were markedly lower compared to those in the normal control group ($p < 0.001$, Table 1). The relevant clinical characteristics of the second cohort in Table 2.

Influence of Liver-Derived Factor LCAT on Initial Osteoporosis Assessment

In this research, we assessed the serum concentration of LCAT in samples collected from 32 individuals experiencing bone loss, 50 individuals diagnosed with osteoporosis, and 56 controls with normal bone density, utilizing an ELISA kit. When compared to the control group with normal bone density, LCAT serum levels showed a noteworthy decline in the osteopenia group (Figure 2), and were even lower in patients with osteoporosis. The LS T-score demonstrated a similar pattern, indicating significantly reduced values in the bone loss group relative to the normal group ($P < 0.0001$, Figure 2). As expected, a correlation between LCAT levels and the LS T/Z-score was observed ($P < 0.001$, $r = 0.6723$, Figure 2). The results from this second cohort support our previous cross-sectional findings, demonstrating that as bone loss progresses, serum LCAT levels significantly decrease in controls (44.41 ± 14.16), osteopenia (32.15 ± 8.93) and osteoporosis (22.15 ± 7.07). Furthermore, a significant positive correlation was observed between serum LCAT levels and T-scores for the Lumbar Spine ($R = 0.507$, $P < 0.001$), Femoral Neck ($R = 0.623$, $P < 0.001$), and Hip ($R = 0.601$, $P < 0.001$) (Figure 3).

Assess the Impact of Age and Sex Stratification on Liver-Derived LCAT's Predictive Value for Osteoporosis

Our study evaluated liver-derived LCAT as a potential diagnostic biomarker for osteoporosis, independent of age and sex. In two cohorts, serum LCAT levels were significantly lower in osteoporotic versus control groups after sex stratification (male: n=16, p=0.002; n=19,0.0026; female: n=68, p=0.0001; n=56, p=0.0002) and age stratification (age≤55 years: n=22, p=0.0001; U=169, p=0.0012; age>55 years: n=60, p=0.00013; U=125.1, p=0.001). Multivariate analysis demonstrated LCAT's persistent negative association with osteoporosis after adjusting for demographic confounders. These consistent results across populations support LCAT as a robust diagnostic marker unaffected by the traditional risk factors of advancing age and female sex. The findings suggest LCAT's potential clinical utility for osteoporosis screening (Figures 4 and 5).

The Correlation Between Serum LCAT Levels and Clinical Diagnostic Indicators

Serum LCAT concentrations were measured in two groups of individuals using an ELISA kit. The results indicated that patients who were undergoing bone loss had significantly lower serum LCAT levels when contrasted with the control group, with this disparity being statistically relevant. Across the entire sample population, serum LCAT levels demonstrated a positive relationship with T-score, BMI, ALT, AST, LDL-C, and blood phosphorus (Tables 3 and 4), while exhibiting a negative relationship with age and serum creatinine (SCR) (Tables 3 and 4).

The Efficacy of Serum LCAT in Predicting Osteoporosis

The role of serum LCAT in predicting osteoporosis is highlighted in (Figure 6), which presents the results of the ROC analysis. For serum LCAT levels, an area under the curve of 0.822 was observed regarding the prediction of osteoporosis-related bone loss and the area under the curve of serum 25 (OH) D was 0.74. The identified optimal cutoff point for serum LCAT concentration was 25.51, with a sensitivity of 75.9% and a specificity of 78% for the identification of bone loss linked to osteoporosis. This indicates that serum LCAT serves as a robust biomarker for detecting bone loss associated with osteoporosis.

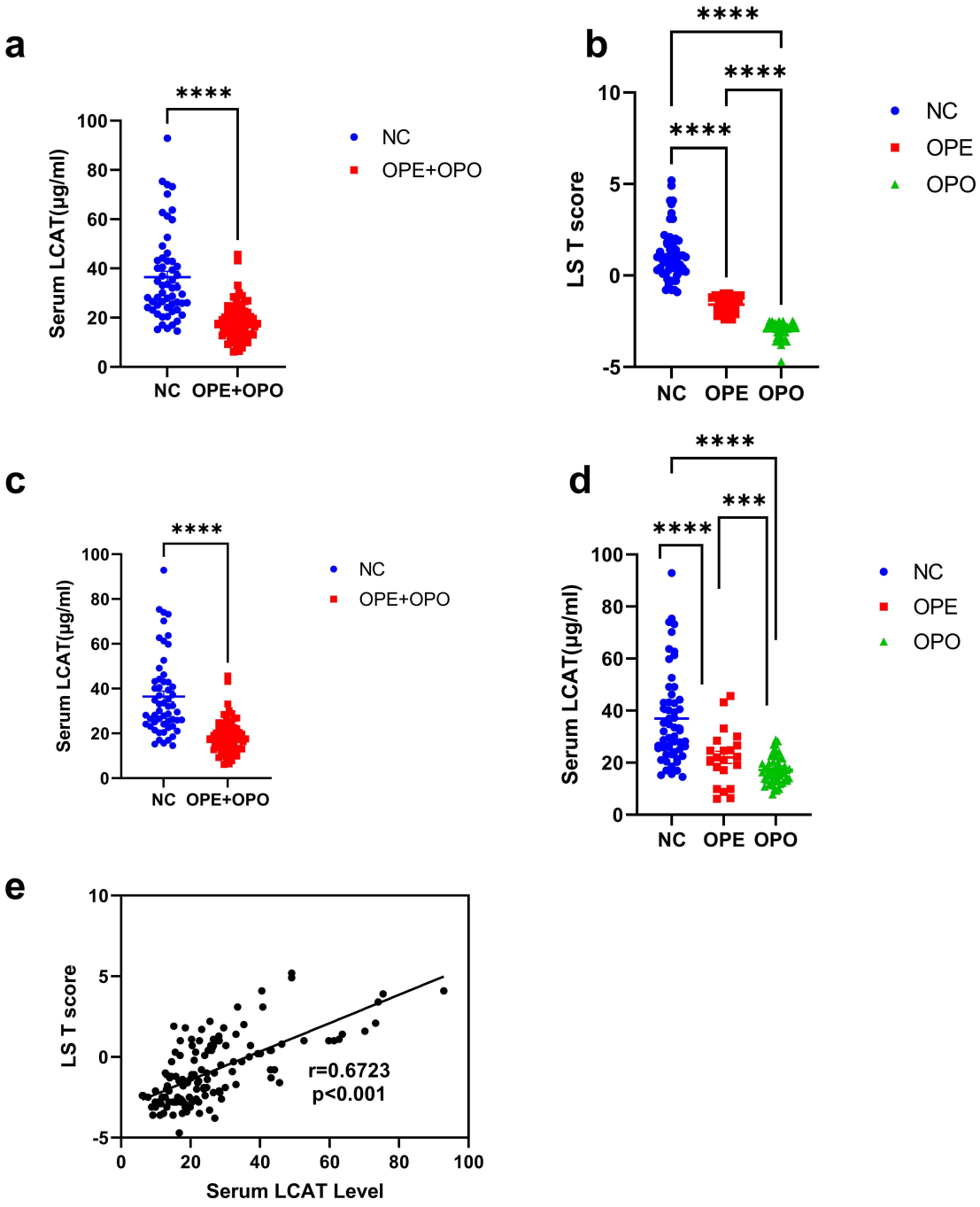

Figure 2 LCAT in serum is downregulated in OPE and OPO patients and the relationship between LCAT expression and LST-Score. (**a**) Statistical analysis of T-score of LS in population with normal and decreasing bone mass. (**b**) Lumbar spine T-score in patients with normal bone mass, decreased bone mass, and osteoporosis. (**c**) Expression of serum LCAT in patients with normal and decreased bone mass. (**d**) Detection of serum LCAT levels in patients with normal bone mass (n=56), osteopenia (n=32) and osteoporosis (n=50). (**e**) Correlation analysis of serum LCAT levels with lumbar spine T-scores. ***P < 0.001, ****P < 0.0001.
Abbreviations: NC, normal bone mass control; OPE, osteopenia; OPO, osteoporosis.

Discussions

Osteoporosis is a commonly encountered systemic metabolic bone disorder, often dubbed the "silent disease".[15] Diagnosis typically occurs only following the first fragility fracture, which presents considerable economic and social challenges. Recent research suggests that the global prevalence of osteoporosis stands at 18.3%,[16] with China reporting

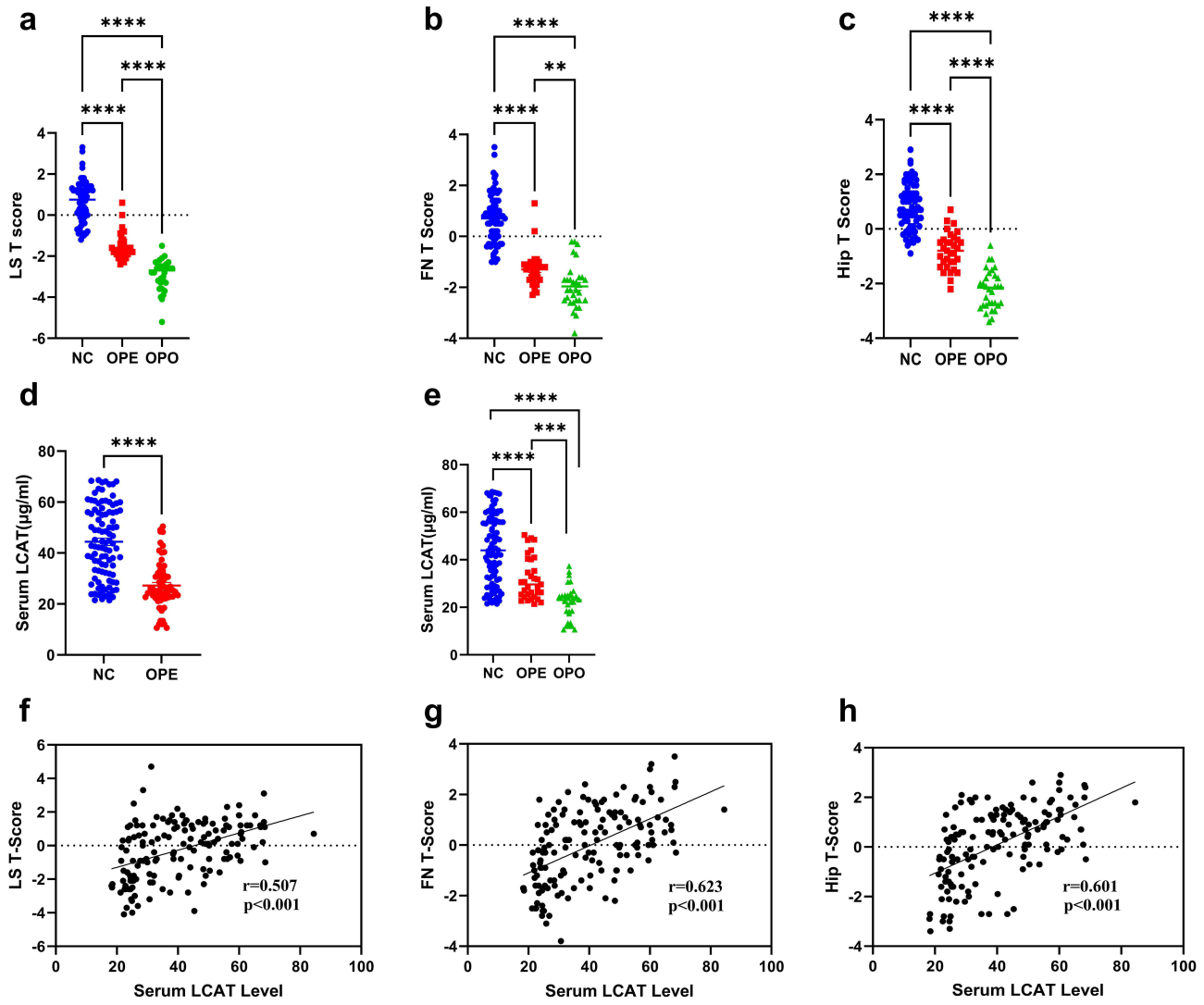

Figure 3 Multicenter Study Demonstrates Progressive Decline in Serum LCAT Levels with Accelerated Bone Loss and Reveals Significant Positive Correlations Between Hepatic-Derived LCAT and LS/Hip/FN T-Scores. (**a**) Statistical analysis of T-score of LS in population with normal bone mass, osteopenia, and osteoporosis. (**b**) Femoral Neck T-score in patients with normal bone mass, osteopenia, and osteoporosis. (**c**) Hip T/Z-score in patients with normal bone mass, osteopenia, and osteoporosis. (**d**) Expression of serum LCAT in patients with normal and decreased bone mass. (**e**) Detection of serum LCAT levels in patients with normal bone mass, osteopenia and osteoporosis. (**f**) Correlation analysis of serum LCAT levels with lumbar spine T-scores. (**g**) Correlation analysis of serum LCAT levels with Femoral Neck T-scores. (**h**) Correlation analysis of serum LCAT levels with Hip T-scores. NC for the bone mass healthy control group, OPE for osteopenia, OPO for osteoporosis. **P < 0.01, ***P < 0.001, ****P < 0.0001.

an overall prevalence of 20% as of 2015.[17] This underscores its importance as a significant public health issue globally. Being an age-associated metabolic condition, the incidence of osteoporosis is projected to rise significantly due to the aging global population, resulting in increased rates of morbidity, disability, and mortality.[18,19] Thus, early diagnosis and preventive strategies for osteoporosis are crucial.[20] Presently, the main technique for diagnosing osteoporosis relies on DEXA imaging to evaluate bone strength. Nevertheless, DEXA has notable limitations,[20–22] including high costs of equipment, exposure to radiation, restrictions in measuring bone density, and the risk of false-positive findings. Additionally, DEXA may not deliver a complete assessment of bone health status or the effectiveness of treatments across diverse populations. In recent years, the use of blood biomarkers has become more prominent in diagnosing and managing osteoporosis, as they can identify irregular bone metabolism at earlier stages, providing timely insights into disease status and information about bone density that DEXA may not reveal. New serum biomarkers have recently been launched in clinical diagnostics and research.[22–24] The fluctuations in serum biomarkers allow for real-time tracking of

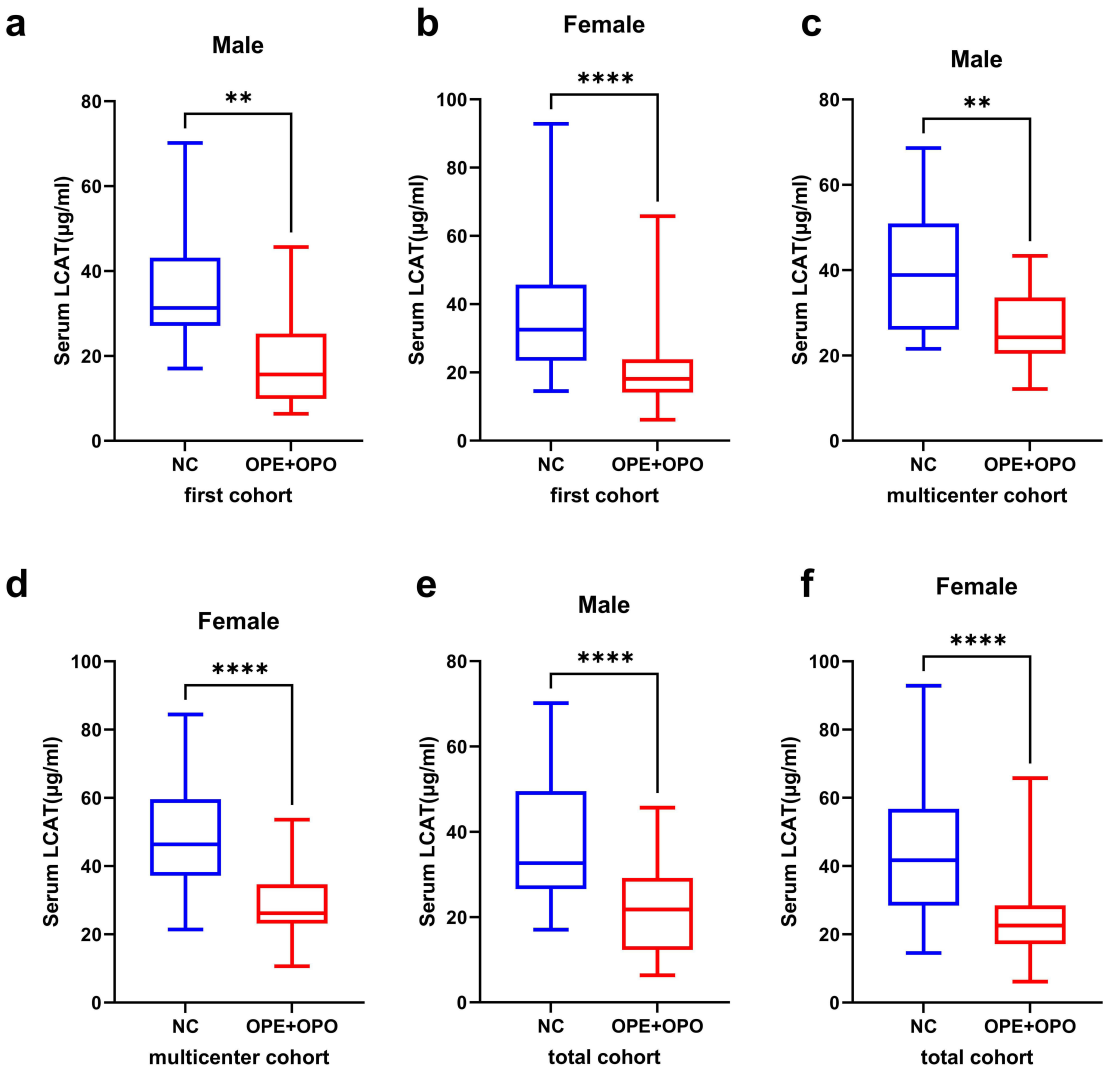

Figure 4 Serum LCAT Predicts Osteoporosis Risk Independent of Sex Stratification. (**a**) first cohort (Nanjing Drum Tower Hospital): Serum LCAT levels in male participants with normal bone mass (NC, n=12) compared to those with osteopenia (OPE) and osteoporosis (OPO) (n=14). (**b**) first cohort: Serum LCAT levels in female participants with normal bone mass (NC, n=44) versus those with OPE and OPO (n=68). (**c**) Multicenter cohort (Nanjing Drum Tower Hospital, Nanjing Medical University First Affiliated Hospital, and its Affiliated Sir Run Run Hospital): Serum LCAT concentrations in males with NC (n=29) with OPE and OPO (n=19). (**d**) Multicenter cohort: Serum LCAT concentrations in females with NC (n=61) with OPE and OPO (n=56). (**e**–**f**) total cohort analysis: Sex-stratified evaluation of serum LCAT's predictive capacity for osteoporosis, adjusted for age effects. Statistical significance. **P < 0.01, ****P < 0.0001.
Abbreviations: NC, normal bone mass control; OPE, osteopenia; OPO, osteoporosis.

treatment responses and disease advancement, facilitating the development of personalized treatment approaches. In contrast to invasive techniques such as tissue biopsies, assessments of blood biomarkers are generally less expensive, more accommodating for patients, and pose fewer risks. Despite significant progress in this area, there is still a pressing requirement to discover novel biomarkers that demonstrate high sensitivity and specificity for the early detection of conditions. This research indicates a pronounced decline in LCAT levels in osteoporosis patients as bone density diminishes. Importantly, serum LCAT levels show a substantial reduction during the initial phases of bone loss, suggesting a strong link between irregular serum levels of the liver-derived protein LCAT and the development and advancement of osteoporosis.

The liver is a key organ for metabolic processes within the human body, playing an essential part in maintaining homeostasis by interacting with various tissues and organs.[25,26] The liver is essential for the regulation of bone metabolism through the secretion of various proteins, cytokines, and enzymes, such as BMP9, IGF1, Hepcidin, and

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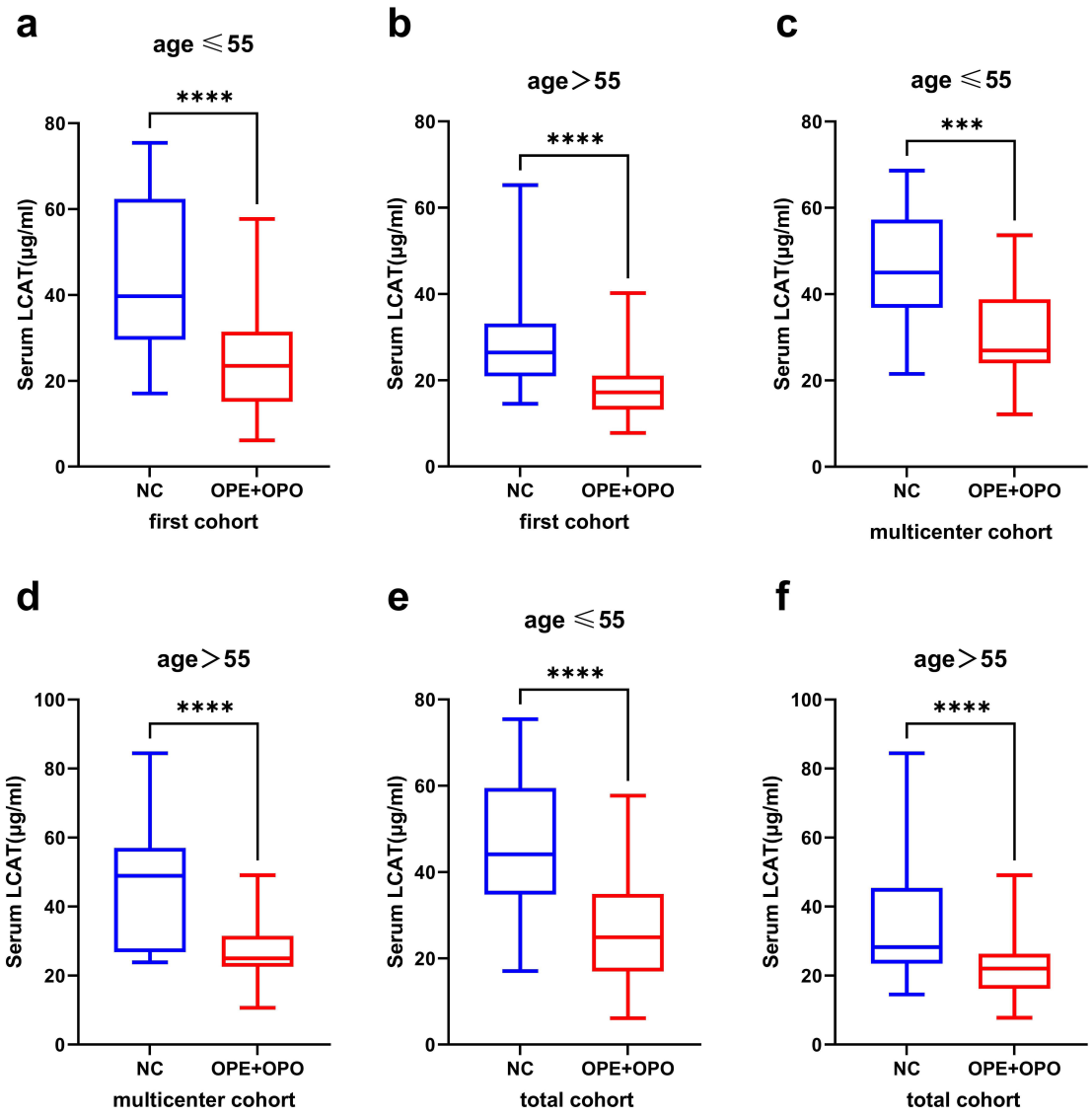

Figure 5 Serum LCAT distribution shows consistent discriminative capacity between controls and bone loss cohorts across all age strata. (**a**) First cohort (Nanjing Drum Tower Hospital): Comparison of serum LCAT levels between normal bone mass controls (n=28) and combined osteopenia and osteoporosis groups (n=24) in participants aged ≤55 years. (**b**) First cohort: Serum LCAT differences between NC (n=26) and combined OPE and OPO participants (n=60) aged >55 years. (**c**) Multicenter cohort (Nanjing Drum Tower Hospital, Nanjing Medical University First Affiliated Hospital, and its Affiliated Sir Run Run Hospital): LCAT concentration comparison between NC (n=70) and OPE and OPO (n=19) groups aged ≤55 years. (**d**) Multicenter cohort: LCAT levels in NC (n=20) versus OPE and OPO (n=56) participants aged >55 years. (**e–f**) Total cohort analysis: Age-adjusted, stratified evaluation of serum LCAT expression between bone-healthy and bone-loss groups across age strata. ***P < 0.001, ****P < 0.0001.
Abbreviations: NC, normal bone mass control; OPE, osteopenia; OPO, osteoporosis.

LCAT, which play a role in the recruitment and differentiation of osteoblasts and osteoclasts.[27–30]The skeleton acts as another important metabolic organ, influencing the activities of other organs through factors derived from bone.[31] In addition, factors that originate from bone, including Osteocalcin (OCN), Sclerostin, and Osteopontin (OPN), can affect liver metabolism via the endocrine system.[32–34]There exists a signaling pathway identified as the liver-skeleton signaling axis[8] where the liver and skeleton communicate through hormones, metabolic regulators, and signaling pathways to harmonize bone mineral metabolism and overall homeostasis. Research has shown that LCAT is a factor secreted by the liver that is intricately linked to cholesterol metabolism, serving a critical function in HDL metabolism and the process of cholesterol reverse transport.[35] The accumulation of cholesterol may result in dysfunctions of various organs and lead to diseases such as osteoporosis.[36] Moreover, prior studies from our team revealed that administering recombinant LCAT

Table 3 Pearson Correlation Analysis of LCAT with Respect to Indicators That Display a Normal Distribution Across the Entire Population

Variables	r	*P* value
Age (years)	−0.346	**<0.001**
Gender	0.018	0.833
FBG (mmol/L)	−0.071	0.411
TC (mmol/L)	0.017	0.846
HDL-C (mmol/L)	−0.15	0.079
LDL-C (mmol/L)	0.181	**0.033**
SCR (μmol/L)	−0.181	**0.033**
P (mmol/L)	0.253	**0.03**
Ca (mmol/L)	−0.031	0.721
LS-T/Z-score	0.608	**<0.001**

Note: The bold part is P < 0.05.
Abbreviations: FBG for fasting blood glucose; TC for total cholesterol; HDL-C for high-density lipoprotein cholesterol; LDL-C for low-density lipoprotein cholesterol; SCR for serum creatinine; LS T-score for lumbar spine T-score.

Table 4 Spearman Correlation Analysis of LCAT with Non-Normal Distribution Indicators in the Total Population

Variables	r	*P* value
BMI (kg/m2)	0.281	**<0.001**
ALT (U/L)	0.201	**0.018**
AST (U/L)	0.21	**0.014**
TG (mmol/L)	0.005	0.95

Notes: The bold part is P < 0.05.
Abbreviations: BMI, for body mass index; TG, for triglycerides; ALT, for alanine aminotransferase; AST, for aspartate aminotransferase.

protein through the tail vein facilitated enhanced cholesterol reverse transport[14] from the bone to the liver. Furthermore, LCAT significantly promotes the differentiation of osteoblasts while suppressing the maturation of osteoclasts, thus playing a key role in maintaining the balance of bone homeostasis. To explore the relationship between serum LCAT levels and osteoporosis, we assessed LCAT concentrations in the serum of osteoporosis patients and observed a notable decrease in LCAT levels when compared to individuals with normal bone density. Osteoporosis can occur at any age, but is most prevalent in postmenopausal women and elderly males. In this study, we included both type 1 (postmenopausal osteoporosis) and type 2 (senile osteoporosis) patients. Serum LCAT analysis revealed significantly decreased levels in both subtypes, suggesting that LCAT may serve as a potential diagnostic biomarker for osteoporosis across different subtypes. Additionally, LCAT levels were found to decline steadily alongside increased bone loss. Our examination further demonstrated a notable positive relationship between serum LCAT levels and LS T-scores. The prospective multicenter observational cohort study further validated the same trend. ROC analysis suggested that LCAT acts as

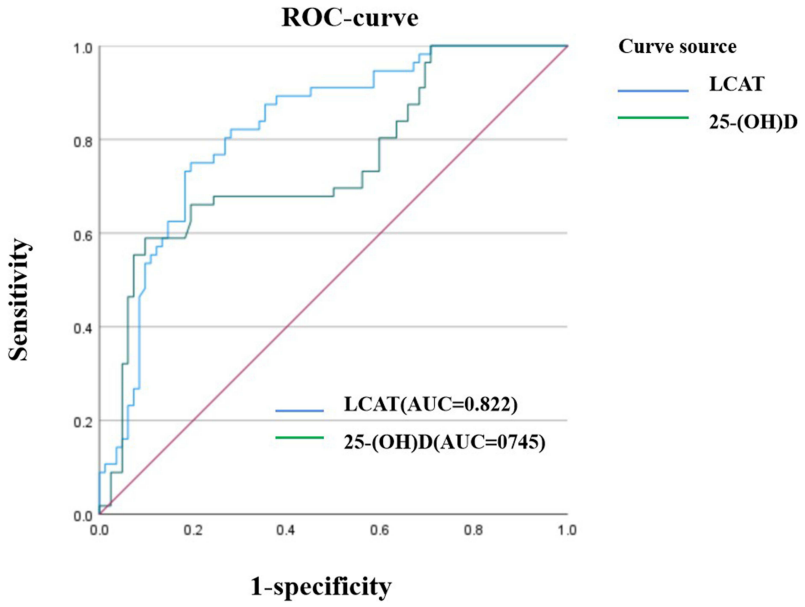

Figure 6 Subject area under the Operating Characteristic Curve (AUC) map of serum LCAT and 25 (OH) D level for the diagnosis of osteoporosis.

a trustworthy predictor of osteoporosis. Its predictive efficacy for osteoporosis exceeds that of serum 25(OH)D levels, establishing it as a novel serum marker for monitoring the progression of osteoporosis and facilitating early clinical diagnosis. After identifying the optimal cutoff value, LCAT exhibited high sensitivity and specificity for the diagnosis of osteoporosis. These results imply that serum LCAT could function as an innovative biomarker for diagnosing osteoporosis. Furthermore, this research contributes to our comprehension of the liver-bone axis, highlighting the significance of liver-derived components in forecasting metabolic bone disorders and offering new perspectives on the metabolic interactions between tissues, as well as the connections between the liver and bone.

Current studies primarily examine osteoporosis among women; nonetheless, there has been a considerable rise in the occurrence of osteoporosis in men along with related fragility fractures over recent decades.[37] Importantly, we have discovered that LCAT, a factor derived from the liver, acts as a biomarker independent of sex, effectively tracking disease progression in osteoporosis for both males and females. We further investigated the relationship between serum LCAT levels within the entire sample and different clinical baseline metrics. Our findings showed that serum LCAT levels positively correlated with T-scores, BMI, ALT, AST, LDL-C, and serum phosphorus, whereas they exhibited negative correlations with age and SCR. Research regarding the link between LCAT and clinical metrics is sparse. LCAT is essential in the metabolism of HDL-C, as individuals with higher HDL-C levels often display increased LCAT activity.[38] Notably, our research did not reveal a connection between LCAT and HDL-C, which could be linked to the prevalence of obesity in our sample. Patients who are obese may release elevated amounts of LCAT to balance the atypical cholesterol metabolism caused by lipid buildup; nonetheless, this adaptive response might not sufficiently raise HDL levels and might instead result in heightened LDL-C levels. Additionally, increased SCR levels observed in patients with chronic kidney disease are generally linked to reduced LCAT activity,[39] which is consistent with our findings. Additionally, earlier research has documented a marked decrease in LCAT activity among older individuals diagnosed with Alzheimer's disease and atherosclerosis,[40,41] implying a potential inverse relationship between LCAT activity and increasing age. Our initial findings revealed reduced serum LCAT concentrations in elderly patients suffering from osteoporosis; nonetheless, the small sample size and the influence of various confounding disease factors necessitate further verification of the relationship between LCAT levels and age. Importantly, our investigation also uncovered a positive association between serum LCAT levels and both ALT and AST. Ke Lu et al[14] observed that LCAT reduced liver damage and enhanced liver fibrosis in a HOD mouse model by facilitating reverse cholesterol transport from the bones to the liver. Following liver injury, levels of ALT and AST typically rise, serving as indicators of liver illness. We

hypothesize that during the early stages of liver damage, the liver compensates by producing a specific quantity of LCAT to alleviate the harm. Ultimately, our results established a positive association between lumbar T-scores and serum phosphorus levels, providing a foundation to propose LCAT as a promising diagnostic biomarker for osteoporosis.

The study has several limitations, primarily a smaller-than-ideal sample size. Research that incorporates a more extensive sample could help in establishing a standardized cutoff value for LCAT, which would lay a strong groundwork for its utilization as a clinical screening tool in diagnosing osteoporosis. Furthermore, the opportunity to monitor clinical serum LCAT levels during anti-osteoporosis therapies has yet to be explored. Further prospective trials with standardized interventions, confounder adjustment, and follow-up monitoring are needed. A significant strength of this investigation lies in its status as the first to assess and indicate that serum LCAT levels might act as an innovative biomarker for the early detection and prevention of osteoporosis.

Conclusion

In Conclusion, lower serum LCAT levels correlate with a heightened risk and rate of osteoporosis incidence. It shows considerable promise for the early prediction of osteoporosis, indicating its potential role as a novel auxiliary biomarker for early detection and prevention, regardless of gender differences. In subsequent studies, serum LCAT levels could be assessed to track the immediate effects of anti-osteoporosis interventions. Currently, the Hepatogenic factor LCAT exerts a dual regulatory function in bone metabolism: it facilitates osteoblast differentiation while simultaneously suppressing osteoclast maturation. Through its ability to modulate the equilibrium of bone remodeling processes, LCAT plays a crucial role in maintaining skeletal homeostasis, thereby acting as a protective factor against the development of osteoporosis. This emerging understanding highlights the potential therapeutic significance of LCAT in addressing bone-related disorders. Ultimately, it is essential to further explore whether LCAT could serve as a possible therapeutic target for osteoporosis management and to clarify the specific mechanisms by which it may enhance this condition.

Data Sharing Statement

The raw datasets generated during the current study are available from the **Yinhe Wang** upon reasonable request.

Ethics Statement

The study was conducted in accordance with the local legislation and institutional requirements. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committees and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study protocol was reviewed and approved by the Ethics Committees of: Nanjing Drum Tower Hospital (Approval No. 2024-772), Nanjing Medical University (Approval No. (2024) 637), The First Affiliated Hospital of Nanjing Medical University (Approval No. 2022-SR-171.A2).

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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