# Association between serum albumin with geriatric nutritional risk index and osteopenia in Chinese elderly men: a nested case-control study

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**Running title:** Serum albumin with GNRIand osteopenia in men

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## ABSTRACT

**Background and Objectives:** Malnutrition is associated with a higher risk of osteoporosis. We aim to assess the relationship between serum albumin with geriatric nutritional risk index and osteopenia in Chinese elderly men. **Methods and Study Design:** This is a nested case-control study from a prospective cohort enrolled 1109 individuals who were followed for seven years. Demographic data, medical history, signs and symptoms, and laboratory parameters were collected and analysed. Nutritional status and Geriatric Nutritional Risk Index (GNRI) were assessed. The nutrition-related indexes predictive value for osteopenia development was analyzed through multivariate Cox regression analysis and by creating a receiver operating characteristic curve (ROC), calculating the area under the curve (AUC). Kaplan–Meier (K–M) method was further used to find the nutritional status level in the elderly men. **Results:** The ALB and GNRI correlated with the risk of osteopenia in Chinese elderly men. After adjusting for all covariates, people with higher ALB level (HR: 0.821; 95% CI: 0.790–0.852) and higher GNRI score (HR: 0.889; 95% CI: 0.869–0.908) had a smaller risk of osteopenia. ROC analysis showed that the AUC for ALB was 0.729 ($p<0.05$) and for the GNRI score was 0.731 ($p<0.05$). K-M curve indicated a significant difference in ALB level ($p<0.001$) and GNRI score ($p<0.001$) in the respective subgroups. **Conclusions:** This study found that lower ALB level and lower GNRI score are associated with a higher prevalence of osteopenia among elderly men in China.


**Key Words: osteoporosis, serum albumin, geriatric nutrition risk index, Chinese elderly men, nested case-control study**

## INTRODUCTION

With the rapid growth of aging population worldwide, osteoporosis (OP) has become a major public health problem which can cause bone fragility and an increased risk of fractures.[1] Osteopenia (low bone mass，LBM), as the early stage of OP, has also attracted more and more attention because of its large number of patients. The National Osteoporosis Foundation (NOF) estimates that 10.2 million Americans have OP and that an additional 43.4 million have LBM.[2] Meanwhile, in China, the overall prevalence rate of OP in people over 50 years old is 19.2%, and the prevalence rate in men is 6.0%; the overall prevalence rate in people with LBM who need prevention and treatment is 46.4%, and in men, it is as high as 46.9%.[3] Although the risk of fracture is greater among patients with OP than among those with LBM,

the much larger number of persons with LBM means that this group represents a substantial portion of the population at risk for fracture.[4] The consequences of fragility fracture may be more serious in men than in women. Studies have shown that the incidence and mortality of fragility fracture are higher in men (166.5‰ for men versus 77.3‰ for women).[5,6] Therefore, active prevention of LBM and OP can be beneficial to reduce osteoporotic fracture, prolong life expectancy and improve quality of life for the elderly.[7] Research on bone health in male remains to be improved. Traditionally, OP and LBM have been considered to be a female disease and have not received sufficient attention in men. Existing techniques for the diagnosis of OP and prediction models based on risk factors for predicting the risk of OP are mainly targeted at postmenopausal women.[8,9] In summary, we believe that it is more innovative and clinically meaningful to study the risk factor of LBM in middle-aged and elderly men.

As a multifactorial systemic disease, many other factors also contribute to LBM. Nutritional status have been associated with a reduction in bone mineral density (BMD).[10, 11] Considerable evidence has proven that malnutrition is an independent risk factor for elderly patients with OP; studies have reported that low body weight, hypoalbuminemia and low serum hemoglobin (Hb) levels can lead to an increased incidence of osteoporotic fractures.[12-14] Meanwhile, it has been reported that geriatric nutritional risk index (GNRI) was an independent risk factor for OP in the elderly and was negatively and non-linearly associated with the risk of OP in the elderly population.[15, 16] The GNRI is a clinical tool used to assess the risk of malnutrition and complications associated with nutritional status in older patients and is a crucial predictor of many diseases.[17] And the GNRI was calculated based on ideal body weight and serum albumin (ALB) levels.[17]

It is well known that elderly people are prone to malnutrition because of their specific metabolic characteristics and disease. However, to date, few studies have investigated the association between the nutritional status and LBM in elderly men. Moreover, no study has ever compared the predictive effect of different nutrition-related indexes on OP. Therefore, nutritional status should be taken into account in the management of elderly patients in order to reduce the incidence of OP and fragility fractures. The aim of our study was to investigate the relationship between ALB with GNRI and the risk of LBM in elderly non-malnutrition men.

## MATERIALS AND METHODS

### *Study participants*

Individuals of this cohort were enrolled during the period between March 2015 and September 2015, from the Second Medical Centre of Chinese PLA General Hospital. All enrolled individuals had comprehensive physical examination results and had a definite outcome of either LBM or not at recruitment. This study was approved by the Ethics Committee of Chinese PLA General Hospital (ID: S2021-094-01). The inclusion criteria were as follows: (i) individuals with normal BMD that were measured by dual-energy X-ray absorptiometry (DXA); (ii) age ≥ 45 years old; (iii)Chinese male individuals. Meanwhile, the exclusion criteria were as follows: (i)patients with history of LBM, OP, fragility fracture and anti-osteoporosis drugs use; (ii)patients combined with secondary OP. Finally, 1185 individuals without LBM or OP at the baseline were included for a 7-year non-interventional follow-up. For all participants, BMD is measured at annual follow-up visit by DXA at their routine physical examination. The follow-up period was from March 2015 to September 2022. Ultimately, 1109 individuals completed the second survey and were included in the study. The follow-up response rate was 93.6%, and the detailed research flow chart is shown in Figure 1.

### *Sample size calculation*

To compute the sample size for comparison of two proportions, the following formula was used:

$$n = \{[Z_{1-\alpha/2}\sqrt{[2\pi(1-\pi)]} + Z_{1-\beta}\sqrt{[\pi_1(1-\pi_1) + \pi_2(1-\pi_2)]}]\}^2 / (\pi_1 - \pi_2)^2$$

With power of 80%, confidence level of 95%, and proportion of occurrence of event in case of $\pi_1$ = 0.47 and in control under study of $\pi_2$= 0.2 (both provided based on previous study), and $\pi = (\pi_1 + \pi_2)/1 + k$, i.e., $\pi$=0.336 (for k = 4), the minimum sample size was found to be n = 218. Therefore, the sample size of our cohort is sufficient.

### *Clinical data*

The standardized self-administered questionnaires pertaining to personal history (histories of smoking, drinking, coffee, carbonated beverage and tea consumption), dietary habits (such as staple food, egg, red meat, white meat, dairy products, soy products) and exercise habits (exercise frequency, exercise duration, exercise intensity) were conducted by trained residents. We inquired about smoking, drinking, coffee, carbonated beverage and tea consumption as

'never' and 'past or current'. The height, weight, waist circumference (WC) and blood pressure (BP) were measured by uniformly trained investigators. The subjects wore thin shirts and stood upright on the bottom plate of a stadiometer to measure their height and weight. WC was measured at the thinnest part of the waist (the horizontal circumference of the waist through the umbilical point). Body mass index (BMI) was then calculated by weight (kg)/height ($m^2$). The BP was measured after the subjects rested for 10 min. An electronic sphygmomanometer (Omron) was used to measure BP three times, and the average value was taken as the data analysis. Blood samples with fasting for more than 8h were extracted to detect for blood routine (such as white blood cell count, red blood cell count, platelet count, Hb), electrolyte (such as serum calcium, serum phosphorus, serum magnesium), fasting blood glucose (FBG), hemoglobin A1c (HbA1c), liver function (ALB, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT), renal function (serum creatinine (Cr), blood urea nitrogen (BUN)), blood fat (triglyceride (TG), total cholesterol (TC), high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL)), coagulation function (such as prothrombin time (PT), activate part plasma prothrombin time (APTT), prothrombin time (TT), fibrinogen (FIB), thyroid function (thyroid stimulating hormone (TSH), total triiodothyronine (TT3), total thyroxine (TT4), free triiodothyronine (FT3), free thyroxine (FT4)), gonadal hormone (luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone (T), estradiol (E2), progesterone (P)) and bone turnover marker (osteocalcin (OST), type I procollagen amino-terminal peptide (P1NP), β isomer of C-terminal telopeptide of type I collagen (β-CTX), parathyroid hormone (PTH) and 25-hydroxy-vitamin D (25(OH)D), alkaline phosphatase (ALP)). The same day, blood samples with breakfast after 2h were extracted to detect for postprandial blood glucose (PBG). Any medical or fracture histories (such as hypertension, dyslipidemia, diabetes, coronary heart disease (CHD), cerebrovascular disease (CVD), chronic kidney disease (CKD), fatty liver disease (FLD)) and medication records (such as antihypertensive drugs, oral hypoglycemic drugs, insulin, statins, acid inhibitors, sleeping pills) were collected in detail from electronic medical records of these individuals. In order to minimize sampling bias, data were obtained by communicating effectively with medical workers and double checking with them.

***Assessment of nutritional status and LBM***

An individual's nutritional status is defined as "the condition of the body, resulting from the balance of intake, absorption, and utilization of nutrients and the influence of particular

physiological and pathological status".18, 19 Based on scientific understanding and previous clinical findings, the nutritional status include BMI, weight, lymphocyte (L), Hb, TP, ALB, TC, nutritional assessment tool such as the GNRI score, and so on.[17, 20, 21]

The GNRI is calculated using baseline body weight and ALB level as follows: 1.489 × ALB (g/L) + 41.7 × actual weight (kg)/ideal weight. Ideal weight was calculated using the Lorenz formula: height (cm) − 100 − ([height (cm) − 150]/4) for men. The actual weight/ideal weight ratio was regarded as 1, when the actual weight exceeded the ideal body weight. Individuals were classified into two nutrition risk groups based on the GNRI: no malnutrition (GNRI ≥ 100) and malnutrition (GNRI < 100).[17]

BMD scores were obtained from completed DXA scans to measure the left femoral neck by chart abstraction for each individual. At our hospital, we use a GE Lunar DXA. DXA can be used to assess BMD of the whole skeleton as well as specific sites. Areal BMD ($g/cm^2$) is measured since the scan is two dimensional. BMD is also described as a T-score which is unit of standard deviation (SD). The T-score describes the number of SDs by which the BMD in an individual differs from the mean value expected in young healthy individuals.[22] According to a working group of the World Health Organization (WHO), the definition of normal is T-score $\geq -1$, the definition of LBM is $-2.5 <$ T-score $< -1$, and the definition for OP is T-score $\leq -2.5$.[23]

***Statistical analysis***

Our statistical analyses were conducted with SPSS (version 26.0) and R (version 4.3.0) software. We apply multiple interpolation to deal with missing data. Continuous variables are described as mean ±SD or median (interquartile range (IQRs)). We used the Student's t-tests (normally distributed) or Mann Whitney test (non-normally distributed) for continuous variables between two groups. To explore the risk factors associate with LBM, univariable and multivariable Cox proportional hazards regression model was performed; and verify that all variables are consistent with the Proportional Hazards assumption. Model 1 was adjusted for no covariates. Model 2 was adjusted for age and BMI. Model 3 was adjusted for all the covariates. Moreover, we performed subgroup analyses using weighted stratified line regression models based on age and BMI. Receiver operating characteristic curves (ROC) were applied to assess the predictive properties of ALB or GNRI for LBM, to calculate the area under the receiver operating characteristic curve (AUC) and to calculate the optimal cut-off points of each variable. We divided the ALB or GNRI group into different subgroups

according to the optimal cut-off point. Kaplan–Meier (K–M) method was further used to find the nutritional status level in the elderly men. *p* values less than 0.05 were considered statistically significant in each statistical analysis.

## RESULTS

### *Baseline characteristics of participants*

First, 2,124 male participants were selected from the regular physical examinations in the Second Medical Centre of Chinese PLA General Hospital from March 2015 to September 2015. In our study, participants with history of LBM, OP, fragility fracture, anti-osteoporosis drugs use (n=822) and secondary OP (n=117) were excluded. Furthermore, after 7 years of follow-up, the loss rate of this cohort was 6.4% (n=76). A total of 1,109 participants were included in the final analysis (Figure 1).

The baseline characteristics of selected participants were compared between the LBM and non-LBM groups (Table 1). According to the diagnosis criteria for LBM, the incidence of LBM was 40.67% (451/1,109) and the incidence density of LBM was 79.0/1000 person-years in this study. Compared with patients with LBM, participants without LBM were more likely to have higher Hb level (152(144,159) vs. 148(141,155), $p<0.001$), higher ALB lever (46.2±2.5 vs. 45.2±2.4, $p<0.001$) and higher values of GNRI (112(109,115) vs. 109(106,111), $p<0.001$). And almost all individuals in our study had no significant anemia or hypoalbuminemia. Moreover, participants in the LBM group had lower BMI, lower PINP, lower BMD at left femoral neck (LNBMD), lower PROG, higher PBG and higher TT3 ($p < 0.05$, Table 1).

### *Associations of the nutritional status with LBM*

A multivariate Cox regression model was used to evaluate the relationship between the nutrition-related indexes and the 7-year LBM risk. The Hb level, ALB level and GNRI score showed a negative association with the risk of LBM in Model 1. After adjusting for confounding factors in Model 2 (age and BMI) and Model 3 (BMI, N, Cr, LDH, PBG, TT3, PINP, PROG, LNBMD, smoking, tea consumption, vitamin D supplement, exercise and FLD), the relationship between exposed variables and outcomes was still stable. When adjusting for all covariates, each unit of increased Hb level was associated with a decreased risk of LBM of 1.1%, each unit of increased ALB level was associated with a decreased risk of LBM of 17.9% and each unit of increased GNRI score was associated with a decreased risk of LBM of 11.1% (Table 2).

The association between Hb level, ALB level and GNRI score and risk of LBM is presented in Table 3. Higher Hb level was associated with a significantly lower risk of LBM when adjusting for age and BMI (HR: 0.446; 95% CI: 0.338-0.589; *p*-trend: ＜0.001) and after further adjustment for N, Cr, LDH, PBG, TT3, PINP, PROG, LNBMD, smoking, tea consumption, vitamin D supplement, exercise and FLD (HR: 0.503; 95% CI: 0.380-0.666; *p*-trend: ＜0.001) in the highest quartile of Hb level compared with the lowest. We observed a significant inverse association between ALB level, GNRI score and the risk of LBM. This association was significant in Model 1 and Model 2 (age and BMI), and after further adjustment for other factors, although the effect was slightly attenuated after further adjustment. The other factors–adjusted HRs of LBM for the highest quartile of level compared with the lowest were 0.212 (95% CI: 0.149-0.301; *p*-trend: ＜0.001) for ALB level and 0.229 (95% CI: 0.162-0.323; *p*-trend: ＜0.001) for GNRI score.

Furthermore, subgroup analysis by age or BMI, showed partial consistent results across categorized subgroups of the population, with low levels of ALB or GNRI consistently associated with an increased risk of LBM prevalence in the elderly men, all at $p < 0.05$. However, the Hb level didn't present a statistically significant negative association with the risk of LBM when the participants were older than 70 years (HR: 0.994; 95% CI: 0.981–1.007) or their BMI was less than 24 (HR: 0.999; 95% CI: 0.985–1.013) (Figure 3).

***Predictive properties of the nutritional status for LBM***

ROC curve analysis was performed with ALB or GNRI as the test variable and the presence of LBM as the status variable (Figure 4). The analysis yielded an AUC for ALB of 0.729, 95%CI of (0.699,0.758), with an optimal ALB threshold of 46.2 for predicting LBM, and a sensitivity of 66.5% and specificity of 67.3%; while an AUC for GNRI of 0.731, 95%CI of (0.701,0.760), with an optimal GNRI threshold of 110 for predicting LBM, and a sensitivity of 69.8% and specificity of 65.2%.

The comparisons of the cumulative probabilities of non-LBM for each group are shown in Figure 5. Follow-up data were obtained in all 1109 individuals. The mean follow-up time was 72 months with a follow-up time range of 7–87 months in our cohort. All individuals were non-LBM at follow-up. K–M curve indicated a significant difference in ALB level (Figure 4A, $p$＜0.001) and GNRI score (Figure 4B, $p$＜0.001) in the respective subgroups. The number of individuals are described in the risk table. An example prediction of LBM is as

follows: a male individual when ALB is higher than 46.2g/L or GNRI score is higher than 110, the risk of LBM is significantly reduced.

## DISCUSSION

Based on our prospective cohort, this study found that both ALB level and and the GNRI score were negatively correlated to the risk of LBM in this population. In addition, we demonstrated that the above associations were stable and not affected by age or BMI subgroups. To the best of our knowledge, this study is the first to explore the associations of the nutritional status, represented by ALB level and the GNRI score, with the risk of LBM in Chinese elderly men.

The relationship of BMD, fracture, and Hb levels is complex. Previously, several studies have concluded that Hb concentration is positively related with BMD.[24, 25] A possible mechanism underlying the link between Hb and OP may be hypoxemia, which has been reported to mediate the risk of OP.[26, 27] An experimental study showed that hypoxia resulted in a three-fold increase in osteoclast formation and a 10-fold stimulation of resorption pit formation.[28] Another possible explanation for the findings could be that erythropoietin (EPO) involves in the physiology of skeletal remodeling.[29] Conversely, a longitudinal study in older adults did not support the hypothesis that Hb levels are associated with BMD.[30] It is possible that age and ethnic differences in the study population, or the limited sample size, may have influenced the results. In this study, after adjusting the confounding factors, the relationship between the Hb level and LBM in male population presented a statistically significant negative association. However, the above association was not stable and affected by age and BMI subgroups. The possible reason is that our individuals were elderly men without anemia. It is well-know that low level of Hb is an important index of iron deficiency anemia when Hb was lower than 120g/L.[31] Anemia has been associated with low physical activity and disability,[32] as well as frailty,[33, 34] which could make it a marker of poor overall health. Therefore, most studies that found a positive association between Hb and BMD were analysed in anemic population. Our results suggest that Hb level cannot be used to predict LBM in individuals without anemia in clinical.

ALB is the most abundant plasmatic protein. It is only produced by the liver and the full extent of its metabolic functions is not known in detail. One of the main roles assigned to ALB is as an indicator of malnutrition.[35] As a reflection of nutritional status with regards to protein, ALB can be associated with BMD. Another important finding in the present study is that higher ALB protected our participants from the risk of LBM. In addition, we

demonstrated that the above associations were stable and not affected by age and BMI subgroups. In line with our findings, some studies revealed that the ALB concentrations were lower in the OP group than in the non-OP group.[20, 36] Likewise, hypoalbuminemia was associated with a higher risk of OP and future fractures.[37, 38] A possible explanation for this association is that low levels of ALB may directly activate osteoclasts and inhibit osteogenesis through its link with the nuclear factor-κB.[39] It has been indicated consistently in the literature that ALB is an important serum marker of malnutrition.[35] Meanwhile, hypoalbuminemia has a higher risk of OP in individuals with malnutrition. However, our study found that decreased ALB level also played a major role in LBM development for elderly men. Therefore, although individuals with malnutrition receive more attention in early OP detection, LBM in elderly men in good status of nutrition should also be taken into account. Our findings highlight the potential importance of ALB level in the LBM relationship in elderly non-malnutrition men, but more studies are necessary to further evaluate the nature of this association. In fact, the promotion of healthy habits, a balanced nutrient intake, and regular exercise is highly recommended in order to reduce the risk of OP.[40, 41] Thus, particular attention should be given to such interventions in order to improve elderly non-malnutrition men' health and healthy diet literacy.

The GNRI has been used as a significant tool to access the nutritional status of the elderly. Compared with the individual variables of ALB or BMI, the GNRI combines ALB with body weight and height, which can be more comprehensive and effective for evaluating systemic nutritional status. Remarkably, in this study, higher GNRI score was significantly associated with lower odds of LBM risk. This finding is congruent with a previous studies revealed that the GNRI value was positively correlated to the femur BMD and negatively correlated to the risk of OP. Besides, in a ROC analysis for predicting OP,[42] compared with ALB, BMI, and age, the GNRI had the largest area under the curve, indicating that the GNRI was a powerful indicator to improve the accuracy of diagnosis.43 There are several plausible mechanisms that might explain why the GNRI may be associated with BMD. First, several studies have shown that dietary protein supplements can increase insulin-like growth factor 1 (IGF-1) and decrease PTH and further reduce age-related BMD loss.[44, 45] Second, the intestinal absorption of calcium can be upregulated by the high intake of protein.[46] Third, optimal protein intake can help to resist loss of muscle and prevent sarcopenia in the elderly.[47, 48] Previous studies have demonstrated that, although many potential confounding factors were adjusted, the risk of BMD loss was still higher in the sarcopenic population.[49] As is known to all, muscles can influence bones through secreting bone factors and exerting physical forces.[50] Some

molecules secreted by skeletal muscle, such as IGF-1, interleukin-6, basic fibroblast growth factor, myostatin, and osteoglycin, have impacts on bone metabolism.[51] Physical forces are usually produced by gravity, locomotion, or external devices.[52] In short, the mechanism of the significant associations between GNRI and BMD and the risk of OP may be explained by an increase in IGF-1, a decrease in PTH, and resistance to muscle loss.

In ROC analysis for predicting LBM in middle-aged and elderly men, AUC values of ALB level and GNRI index were almost equal, and both could predict LBM in middle-aged and elderly men well. This indicates that ALB level is already an accurate indicator of diagnostic accuracy in the prediction of LBM. The GNRI index, adjusted for height and weight, did not show a greater predictive advantage on the basis of ALB levels.

Compared to ALB and GNRI, bone turnover markers (BTMs) provide a dynamic assessment of skeletal activity and are useful modalities for skeletal assessment. Because the bone metabolism of OP patients is in a high conversion state, all BMT are increasing.[2] Eastell et al. believed that PINP could not be used to determine the amount of bone loss and predict fractures in individuals.[53] However, PINP and β-CTX have an evident advantage when considering drug holidays for OP treatment.[54] Therefore, PINP and β-CTX currently lack specific clinical demonstrations to confirm their correlation with OP which requires further research and in-depth analysis. The value of using PINP to predict OP as not been confirmed. Some scholars believe that PINP and OP are not correlated,[55] while others believe that they are positively correlated.[56] The report indicated that PINP may be more effective than β-CTX for predicting LBM. Nguyen et al. reported that OP patients had higher levels of PINP and β-CTX, but only β-CTX was significantly correlated with BMD ($p < 0.01$).[57] Eastell et al. believed that PINP could not be used to determine the amount of bone loss and predict fractures in individuals.[53] However, PINP and β-CTX have an evident advantage when considering drug holidays for OP treatment.[38] Therefore, BTMs currently lack specific clinical demonstrations to confirm their correlation with OP which requires further research and in-depth analysis. To our knowledge, this is the first report on the association between baseline nutritional status and the risk of LBM in elderly men in good status of nutrition. This is also the first study to compare individuals with and without LBM using both ALB level and the GNRI score. Moreover, comprehensive information regarding potential covariates was collected at baseline. In addition, this study has some limitations. First, our study was an observational prospective nested case-control study; we controlled for numerous relevant confounders, but the possibility of residual confounding remains. Second, the serum data of the individuals was collected only once and not evaluates the progressive changes in serum

markers among individuals. Third, during follow-up, information about the dosage and duration of anti-osteoporosis drugs and other drugs that influence bone metabolism was not obtained, which might affect the evaluation of LBM risk. Follow-up large-scale studies are needed to confirm our results.

***Conclusion***

Our study found that lower nutritional status, represented by ALB level and the GNRI score, among elderly men in China is associated with a higher prevalence of LBM. The ALB level may be a good tool to identify Chinese elderly men who need further bone health nutritional support.

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**CONFLICT OF INTEREST AND FUNDING DISCLOSURE**

The authors declare that they have no conflict of interest.

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**Table 1.** Comparison of characteristic variables between LBM group and non-LBM group

| | Total (n=1109) | LBM (n=451) | non-LBM (n=658) | *p* value |
|---|---|---|---|---|
| Age (years) | 65 (59,75) | 66 (60,74) | 65 (59,75) | 0.291 |
| BMI (kg/m$^2$) | 25.0 (23.4,27.1) | 24.4 (22.9,26.1) | 25.2 (23.5,27.0) | < 0.001 |
| Waistline (cm) | 92.0 (87.8,98.0) | 92.0 (87.0,97.0) | 92.0 (88.0,98.0) | 0.283 |
| SBP (mmHg) | 125 (120,134) | 125 (120,134) | 126 (119,135) | 0.800 |
| DBP (mmHg) | 75 (70,80) | 75.00 (70,80) | 75 (70,80) | 0.410 |
| WBC (10e12/L) | 5.77 (4.82,6.68) | 5.77 (4.89,6.63) | 5.78 (4.81,6.72) | 0.954 |
| N (%) | 0.578±0.079 | 0.583±0.079 | 0.575±0.079 | 0.095 |
| L (%) | 0.322±0.076 | 0.318±0.076 | 0.325±0.075 | 0.569 |
| Hb (g/L) | 150 (143,157) | 148 (141,155) | 152 (144,159) | < 0.001 |
| TP (g/L) | 71.0 (69.0,74.0) | 71.0 (69.0,74.0) | 71.0 (69.0,74.0) | 0.196 |
| ALB (g/L) | 46.4±2.7 | 45.2±2.4 | 46.2±2.5 | 0.000 |
| GNRI | 110 (108,113) | 109 (106,111) | 112 (109,115) | < 0.001 |
| BUN (mmol/L) | 5.60 (4.80,6.60) | 5.50 (4.70,6.50) | 5.60 (4.80,6.70) | 0.210 |
| Cr (μmol/L) | 85.0 (77.0,94.0) | 84.0 (76.0,92.0) | 86.0 (78.0,95.0) | 0.004 |
| TC (mmol/L) | 4.26 (3.69,4.81) | 4.30 (3.70,4.87) | 4.22 (3.68,4.76) | 0.399 |
| TG (mmol/L) | 1.20 (0.93,1.69) | 1.20 (0.92,1.59) | 1.21 (0.93,1.72) | 0.404 |
| HDL (mmol/L) | 1.25 (1.07,1.46) | 1.27 (1.09,1.48) | 1.23 (1.06,1.45) | 0.064 |
| LDL (mmol/L) | 2.70 (2.17,3.26) | 2.73 (2.15,3.30) | 2.69 (2.19,3.21) | 0.702 |
| LDH (U/L) | 171 (154,189) | 169 (152,187) | 172 (156,191) | 0.042 |
| CK (U/L) | 109 (83,149) | 105 (81,145) | 110 (84,152) | 0.060 |
| CK_MB (U/L) | 12.3 (10.6,14.6) | 12.3 (10.4,14.5) | 12.3 (10.7,14.6) | 0.585 |
| GGT (U/L) | 22.0 (17.0,30.5) | 21.0 (16.0,30.0) | 23.0 (17.0,31.0) | 0.095 |
| ALP (U/L) | 60.0 (51.0,70.0) | 60.0 (51.0,70.0) | 60.0 (51.0,70.3) | 0.997 |
| AMY (U/L) | 67.0 (55.0,84.0) | 67.0 (55.0,85.0) | 67.0 (54.0,83.0) | 0.661 |
| HbA1c (%) | 5.70 (5.40,6.00) | 5.70 (5.50,6.10) | 5.70 (5.40,6.00) | 0.300 |
| FBG (mmol/L) | 5.56 (5.22,6.07) | 5.58 (5.21,6.11) | 5.55 (5.22,6.04) | 0.840 |
| PBG (mmol/L) | 8.25 (6.96,10.01) | 8.88 (7.61,10.95) | 7.77 (6.55,9.45) | 0.000 |
| TT4 (nmol/L) | 99.0±15.9 | 99.7±16.0 | 98.5±15.9 | 0.233 |
| TT3 (nmol/L) | 1.58 (1.43,1.74) | 1.60 (1.44,1.76) | 1.57 (1.42,1.72) | 0.033 |
| FT3 (pmol/L) | 4.71 (4.40,5.04) | 4.71 (4.41,5.05) | 4.73 (4.38,5.03) | 0.699 |
| FT4 (pmol/L) | 16.0 (14.7,17.4) | 15.9 (14.6,17.2) | 16.0 (14.7,17.4) | 0.302 |
| TSH (μIU/mL) | 2.06 (1.47,2.86) | 2.11 (1.50,2.81) | 2.04 (1.46,2.92) | 0.939 |
| OCN (ng/mL) | 15.0 (11.7,18.6) | 14.8 (11.4,18.6) | 15.3 (11.9,18.7) | 0.248 |
| PTH (pg/mL) | 37.9 (30.2,48.8) | 37.7 (29.6,49.2) | 38.2 (30.6,48.6) | 0.409 |
| PINP (ng/mL) | 32.87 (24.0,42.8) | 31.80 (23.5,41.3) | 33.61 (24.6,43.9) | 0.037 |
| β-CTX (ng/mL) | 0.28 (0.18,0.39) | 0.28 (0.18,0.38) | 0.29 (0.18,0.40) | 0.292 |
| 25(OH)D (ng/mL) | 21.6 (15.7,27.7) | 22.0 (16.6,27.4) | 21.4 (15.4,27.8) | 0.380 |
| TS (ng/mL) | 4.51 (3.40,5.78) | 4.55 (3.35,5.88) | 4.51 (3.42,5.71) | 0.836 |
| E2 (pmol/L) | 86.9 (60.3,114.7) | 85.3 (59.5,112.4) | 87.8 (60.8,116.7) | 0.369 |
| LH (mIU/ mL) | 7.1 (4.6,10.8) | 6.9 (4.4,10.2) | 7.3 (4.8,11.1) | 0.107 |
| FSH (mIU/ mL) | 11.7 (6.6,19.3) | 11.2 (6.6,18.3) | 12.0 (6.6,20.6) | 0.417 |
| PRL (μg/L) | 16.1 (9.3,23.0) | 15.2 (9.2,22.1) | 16.5 (9.5,24.1) | 0.220 |
| PROG (nmol/L) | 1.20 (0.64,1.92) | 1.12 (0.61,1.81) | 1.25 (0.65,1.98) | 0.039 |
| LNBMD (g/cm$^2$) | 0.97 (0.90,1.04) | 0.92 (0.87,1.00) | 1.00 (0.93,1.07) | 0.000 |
| Smoking | | | | |
| No | 627 (56.5%) | 186 (41.2%) | 441 (67.0%) | <0.00 |
| Yes | 482 (43.5%) | 265 (58.8%) | 217 (33.0%) | |
| Tea consumption | | | | |
| No | 350 (31.6%) | 84 (18.6%) | 266 (40.4%) | < 0.001 |
| Yes | 759 (68.4%) | 367 (81.4%) | 392 (59.6%) | |

25(OH)D, 25-hydroxy vitamin D; ALB, albumin; ALP, alkaline phosphatase; AMY, amylase; β-CTX, β isomer of C-terminal telopeptide of type I collagen; BMI, body mass index; BUN, blood urea nitrogen; CK, creatine kinase; CK_MB, creatine kinase isoenzyme MB; CKD, chronic kidney disease; Cr, serum creatinine; DBP, diastolic blood pressure; E2,estradiol; FPG, fasting plasma glucose; FLD, fatty liver disease; FSH, follicle-stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; GGT, gamma-glutamyl transpeptidase; GNRI, Geriatric Nutritional Risk Index; Hb, hemoglobin; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein cholesterol; L, lymphocyte; LBM, low bone mass; LDH, lactate dehydrogenase; LDL, low-density lipoprotein cholesterol; LH, luteinizing hormone; LHBMD, bone mineral density of left total hip; LNBMD, bone mineral density of left femoral neck; N, neutrophil; OCN, osteocalcin; PBG, postprandial blood glucose; PINP, serum carboxy-terminal propeptide of type I collagen; PRL, prolactin; PROG, progesterone; PTH, parathyroid hormone; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; TS, testosterone; TSH, thyroid stimulating hormone; TT3,total triiodothyronine; TT4,total thyroxine; WBC, white blood cells.

$p < 0.05$ (two-sided) was considered statistically significant.

**Table 1.** Comparison of characteristic variables between LBM group and non-LBM group (cont.)

| | Total (n=1109) | LBM (n=451) | non-LBM (n=658) | *p* value |
|---|---|---|---|---|
| Tea consumption | | | | |
| No | 350 (31.6%) | 84 (18.6%) | 266 (40.4%) | < 0.001 |
| Yes | 759 (68.4%) | 367 (81.4%) | 392 (59.6%) | |
| Milk | | | | |
| No | 362 (32.6%) | 136 (30.2%) | 226 (34.3%) | 0.144 |
| Yes | 747 (67.4%) | 315 (69.8%) | 432 (65.7%) | |
| Assisted walking | | | | |
| No | 1067 (96.2%) | 427 (94.7%) | 640 (97.3%) | 0.027 |
| Yes | 42 (3.8%) | 24 (5.3%) | 18 (2.7%) | |
| Calcium supplement | | | | |
| No | 712 (64.2%) | 294 (65.2%) | 418 (63.5%) | 0.570 |
| Yes | 397 (35.8%) | 157 (34.8%) | 240 (36.5%) | |
| Vitamin D supplement | | | | |
| No | 696 (62.8%) | 300 (66.5%) | 396 (60.2%) | 0.032 |
| Yes | 413 (37.2%) | 151 (33.5%) | 262 (39.8%) | |
| Exercise | | | | |
| No | 300 (27.1%) | 96 (21.3%) | 204 (31.0%) | 0.000 |
| Yes | 809 (72.9%) | 355 (78.7%) | 454 (69.0%) | |
| Diabetes | | | | |
| No | 786 (70.9%) | 316 (70.1%) | 470 (71.4%) | 0.624 |
| Yes | 323 (29.1%) | 135 (29.9%) | 188 (28.6%) | |
| Hypertension | | | | |
| No | 475 (42.8%) | 188 (41.7%) | 287 (43.6%) | 0.523 |
| Yes | 634 (57.2%) | 263 (58.3%) | 371 (56.4%) | |
| Dyslipidemia | | | | |
| No | 326 (29.4%) | 127 (28.2%) | 199 (30.2%) | 0.454 |
| Yes | 783 (70.6%) | 324 (71.8%) | 459 (69.8%) | |
| CKD | | | | |
| No | 1074 (96.8%) | 437 (96.9%) | 637 (96.8%) | 0.935 |
| Yes | 35 (3.2%) | 14 (3.1%) | 21 (3.2%) | |
| FLD | | | | |
| No | 799 (72.0%) | 288 (63.9%) | 511 (77.7%) | < 0.001 |
| Yes | 310 (28.0%) | 163 (36.1%) | 147 (22.3%) | |

25(OH)D, 25-hydroxy vitamin D; ALB, albumin; ALP, alkaline phosphatase; AMY, amylase; β-CTX, β isomer of C-terminal telopeptide of type I collagen; BMI, body mass index; BUN, blood urea nitrogen; CK, creatine kinase; CK_MB, creatine kinase isoenzyme MB; CKD, chronic kidney disease; Cr, serum creatinine; DBP, diastolic blood pressure; E2,estradiol; FPG, fasting plasma glucose; FLD, fatty liver disease; FSH, follicle-stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; GGT, gamma-glutamyl transpeptidase; GNRI, Geriatric Nutritional Risk Index; Hb, hemoglobin; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein cholesterol; L, lymphocyte; LBM, low bone mass; LDH, lactate dehydrogenase; LDL, low-density lipoprotein cholesterol; LH, luteinizing hormone; LHBMD, bone mineral density of left total hip; LNBMD, bone mineral density of left femoral neck; N, neutrophil; OCN, osteocalcin; PBG, postprandial blood glucose; PINP, serum carboxy-terminal propeptide of type I collagen; PRL, prolactin; PROG, progesterone; PTH, parathyroid hormone; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; TS, testosterone; TSH, thyroid stimulating hormone; TT3,total triiodothyronine; TT4,total thyroxine; WBC, white blood cells.
$p < 0.05$ (two-sided) was considered statistically significant.

**Table 2.** The characteristics of participants

| | Model 1[†] | | Model 2[‡] | | Model 3[§] | |
|---|---|---|---|---|---|---|
| | HR (95% CI) | *p*-value | HR (95% CI) | *p*-value | HR (95% CI) | *p*-value |
| Hb | 0.977 (0.971,0.983) | <0.001 | 0.979 (0.972,0.985) | <0.001 | 0.989 (0.980,0.998) | 0.012 |
| ALB | 0.787 (0.759,0.815) | <0.001 | 0.792 (0.764,0.822) | <0.001 | 0.821 (0.790,0.852) | <0.001 |
| GNRI | 0.867 (0.850,0.884) | <0.001 | 0.867 (0.850,0.884) | <0.001 | 0.889 (0.869,0.908) | <0.001 |

ALB, albumin; BMI, body mass index; CI, confidence interval; Cr, serum creatinine; FLD, fatty liver disease; GNRI, Geriatric Nutritional Risk Index; Hb, hemoglobin; HR, Hazard ratio; LDH, lactate dehydrogenase; LNBMD, bone mineral density of left femoral neck; PBG, postprandial blood glucose; PINP, serum carboxy-terminal propeptide of type I collagen; PROG, progesterone; TT3, total triiodothyronine.
[†]Model 1: no covariates were adjusted.
[‡]Model 2: age and BMI were adjusted.
[§]Model 3: age, BMI, N, Cr, LDH, PBG, TT3, PINP, PROG, LNBMD, smoking, tea consumption, vitamin D supplement, exercise and FLD were adjusted.

**Table 3.** HRs of LBM by quartiles of Hb, ALB and GNRI

| | Model 1[†] | | Model 2[‡] | | Model 3[§] | |
|---|---|---|---|---|---|---|
| | HR (95% CI) | *p*-value | HR (95% CI) | *p*-value | HR (95% CI) | *p*-value |
| Hb | | | | | | |
| Q1 (89-143) | | | | | | |
| Q2 (144-150) | 0.687 (0.540,0.874) | 0.002 | 0.704 (0.554,0.897) | 0.004 | 0.769 (0.603,0.979) | 0.033 |
| Q3 (151-157) | 0.588 (0.458,0.756) | 0.000 | 0.619 (0.481,0.796) | 0.000 | 0.762 (0.590,0.984) | 0.037 |
| Q4 (158-181) | 0.411 (0.312,0.542) | 0.000 | 0.446 (0.338,0.589) | 0.000 | 0.503 (0.380,0.666) | 0.000 |
| *p* for trend | <0.001 | | <0.001 | | <0.001 | |
| ALB | | | | | | |
| Q1 (37.1-44.7) | | | | | | |
| Q2 (44.8-46.4) | 0.602 (0.482,0.753) | 0.000 | 0.608 (0.487,0.761) | 0.000 | 0.738 (0.587,0.927) | 0.009 |
| Q3 (46.5-48.3) | 0.414 (0.322,0.533) | 0.000 | 0.434 (0.337,0.560) | 0.000 | 0.540 (0.415,0.704) | 0.000 |
| Q4 (48.4-53.9) | 0.166 (0.118,0.233) | 0.000 | 0.173 (0.123,0.243) | 0.000 | 0.212 (0.149,0.301) | 0.000 |
| *p* for trend | <0.001 | | <0.001 | | <0.001 | |
| GNRI | | | | | | |
| Q1 (87.74-107.67) | | | | | | |
| Q2 (107.68-110.48) | 0.650 (0.520,0.813) | 0.000 | 0.681 (0.543,0.854) | 0.000 | 0.779 (0.620,0.978) | 0.032 |
| Q3 (110.49-113.47) | 0.411 (0.319,0.528) | 0.000 | 0.457 (0.351,0.595) | 0.000 | 0.563 (0.432,0.735) | 0.000 |
| Q4 (113.48-121.96) | 0.177 (0.127,0.247) | 0.000 | 0.194 (0.138,0.273) | 0.000 | 0.229 (0.162,0.323) | 0.000 |
| *p* for trend | <0.001 | | <0.001 | | <0.001 | |

ALB, albumin; BMI, body mass index; CI, confidence interval; Cr, serum creatinine; FLD, fatty liver disease; GNRI, Geriatric Nutritional Risk Index; Hb, hemoglobin; HR, Hazard ratio; LDH, lactate dehydrogenase; LNBMD, bone mineral density of left femoral neck; PBG, postprandial blood glucose; PINP, serum carboxy-terminal propeptide of type I collagen; PROG, progesterone; TT3,total triiodothyronine.

[†]Model 1: no covariates were adjusted.

[‡]Model 2: age and BMI were adjusted.

[§]Model 3: age, BMI, N, Cr, LDH, PBG, TT3, PINP, PROG, LNBMD, smoking, tea consumption, vitamin D supplement, exercise and FLD were adjusted.

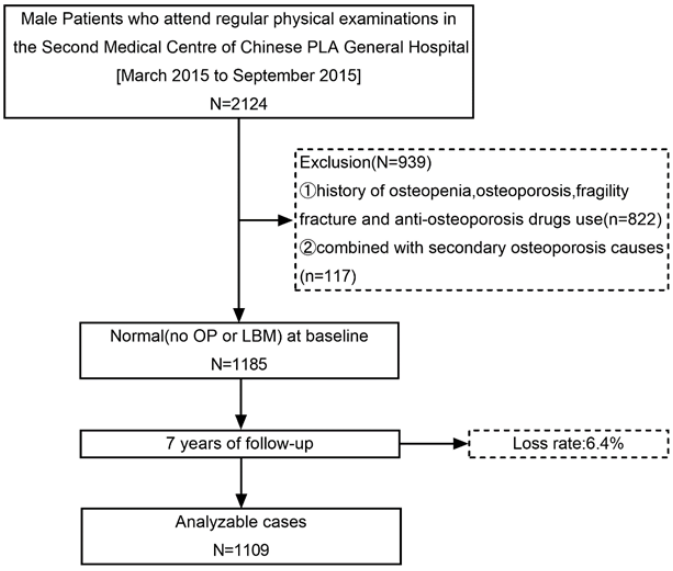



**Figure 1.** Flow diagram of study design. LBM, low bone mass; OP, osteoporosis.

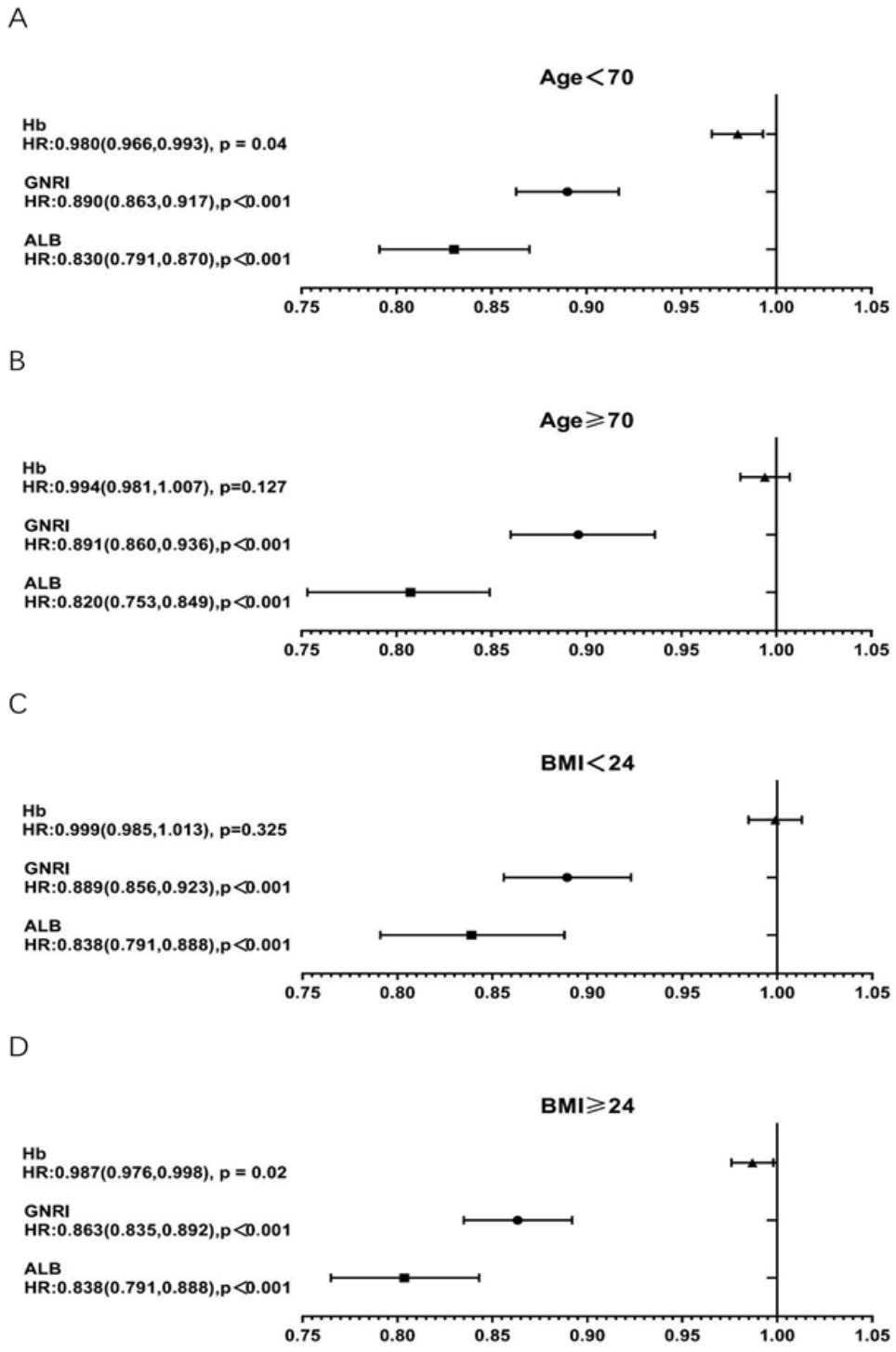



**Figure 2.** Associations of Hb, ALB and the GNRI with the risk of LBM stratified by age or BMI. (A)(B) subgroup analysis by age; (C)(D) subgroup analysis by BMI. ALB, albumin; GNRI, Geriatric Nutritional Risk Index; Hb, hemoglobin; LBM, low bone mass.

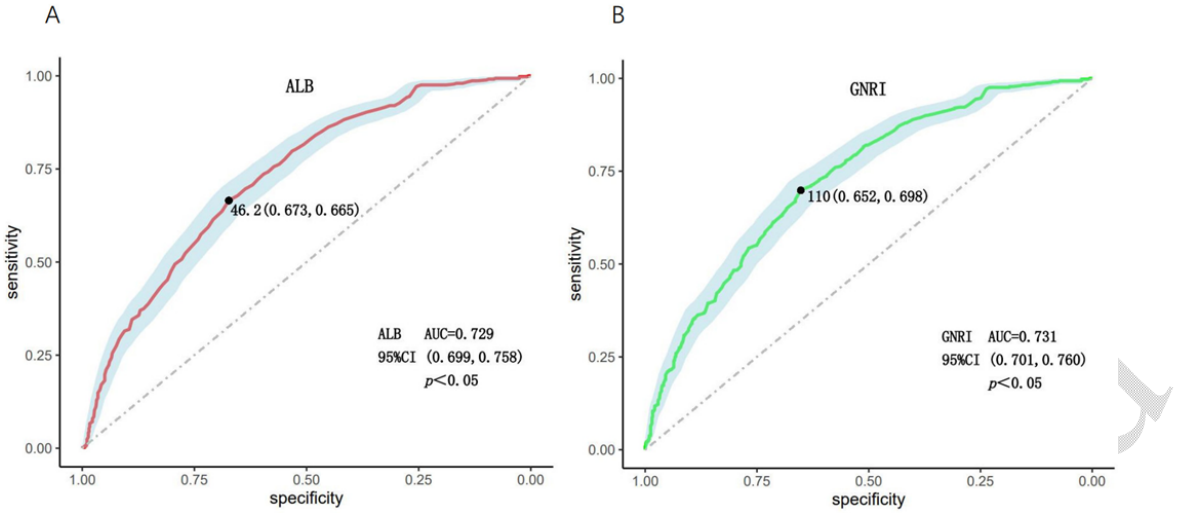
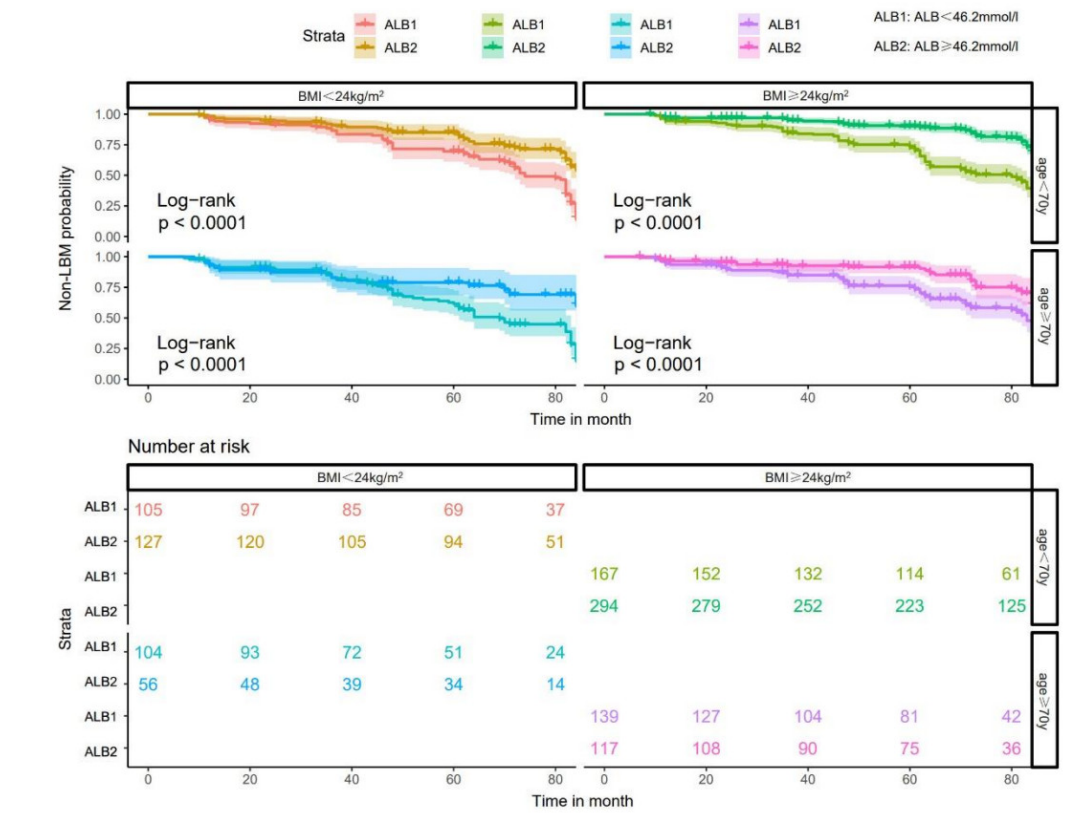



**Figure 3.** Receiver operating characteristic curve of LBM. The y-axis represents the sensitivity of the risk prediction, the x-axis represents the 1-specificity of the risk prediction. The 45° diagonal line serves as the reference line, since it is the ROC curve of random classification. Black dot indicates the best cut-off point. (A) ROC curves for the prediction for the risk of LBM using a serum ALB level; (B) ROC curves for the prediction for the risk of LBM using the GNRI score. ALB, albumin; AUC, area under the curve; CI, confidence interval; GNRI, Geriatric Nutritional Risk Index; ROC, receiver operating characteristic




B

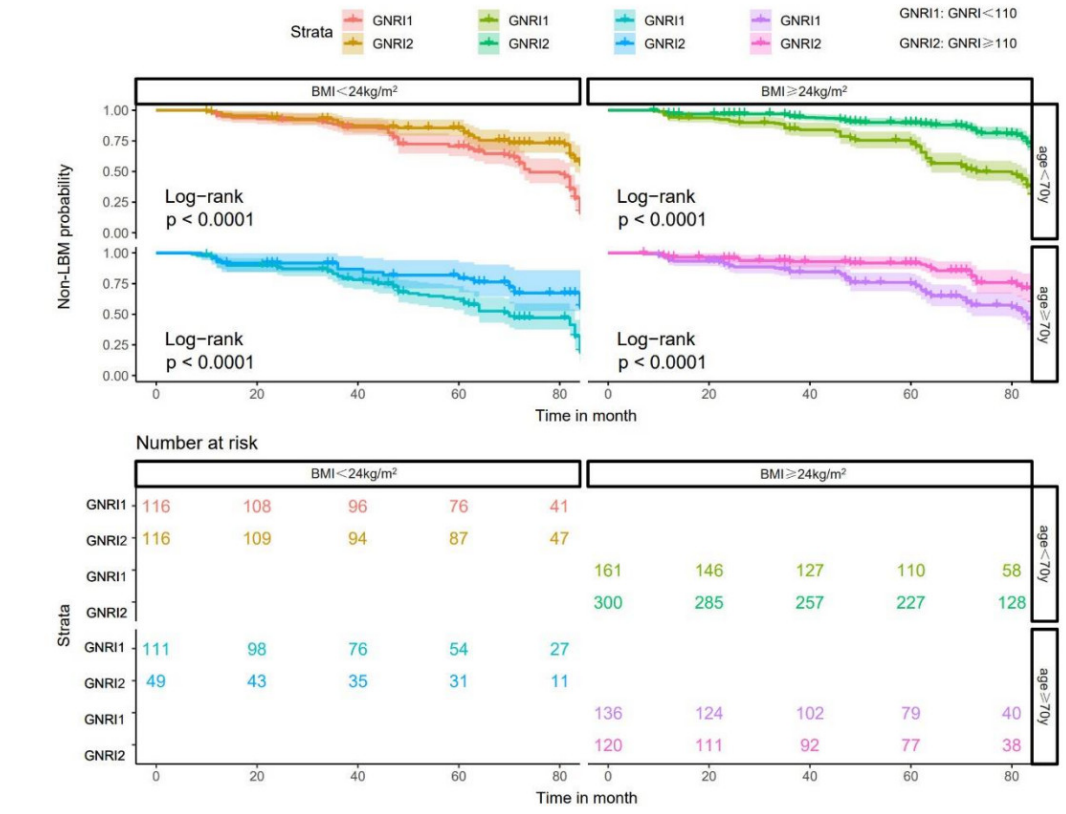



**Figure 4.** Kaplan–Meier curve analysis showing non-LBM probability. (A) The non-LBM probability for different serum ALB level in the subgroups; (B) The non-LBM probability for different GNRI score in the subgroups. ALB, albumin; BMI, body mass index; GNRI, Geriatric Nutritional Risk Index; LBM, low bone mass.