Comorbidity Burden and Hip/Lumbar Bone Mineral Density

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ABSTRACT

Objective: To determine the association of the tested patients' comorbidities burden on the femoral hip and lumbar bone mineral densities and consequently on their osteoporotic fracture probabilities.

Methods: Firstly, we conducted the ROC and the sensitivity analysis to primary explore the optimal cut-off point of tested patients' bone densities. Secondly, each of the Binary Logistic Regression, ROC, and sensitivity analysis were sequentially and individually conducted for the tested patients' co-morbidities burden, as signified by Age-adjusted Charlson Co-Morbidity Index (AACCI), against the fH_BMD [<0.755 g/cm2 (0, negative state) and ≥0.755 g/cm2 (1, positive state)] and against the LBMD [<0.835 g/cm2 (0, negative state) and ≥0.835 g/cm2 (1, positive state)]. The studied patients were dichotomously categorized into 2 comparative cohorts; the cohort whose AACCI was <4 [Cohort I] versus the cohort whose AACCI was ≥ 4 [Cohort II]. The comparative investigating variables between the 2 tested cohorts were statistically analyzed by the Chi-Square Test (at p-value< 0.05).

Results: The optimal operating point of AACCI in this study were identified at 3.5 with youden's index and sensitivity of 85.16%, 85.2%. Of importance, the AUROC±SEM was significantly higher for the tested dependent variables of lumbar bone mineral density [0.958±0.012 (95% CI; 0.934-0.982)] than femoral hip bone mineral density [0.745±0.035 (95% CI; 0.676-0.814)].

Conclusion: We revealed that the tested participants whose AACCI exceeded 4 had significantly lower femoral and lumbar bone densities and higher risk for 10-year hip and major osteoporotic fractures comparing to the tested cohort who had a lower co-morbidity burden.

Keywords: Comorbidity burden; Osteoporosis; Dual-energy X-ray absorptiometry; Multiple logistic regression modeling; Rheumatological diseases; Bone mineral density.

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INTRODUCTION

Osteoporosis is a rheumatologically condition that is linked to a significant health issue, a severe decline in quality of life, and, consequently, a substantial financial burden. The most immediate consequence of osteoporosis is the occurrence of bone fractures. It is important to mention that the World Health Organization (WHO) estimates that the chances of experiencing at least one osteoporotic fracture, such as in the hip or vertebrae, in a developed country are approximately 30–40% over a person's lifetime. [1-3]

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Typically, femoral hip and vertebral bone mineral densities (fH_BMD and LBMD, respectively), along with their T and Z score derivatives, are predominantly used for diagnosing osteopenia and osteoporosis. Various diverse and valid assessment tools based on bone mineral density (BMD) are commonly employed to accurately estimate the risk of osteoporotic fractures, either in a specific or general manner. Specifically, the Fracture Risk Assessment Tool (FRAX) is widely used both nationally and internationally to address these concerns. When the risk of fractures in the femoral hip due to osteoporosis exceeds 3% or the risk of overall major osteoporotic fractures exceeds 20%, it is often considered a strong indication of a higher risk of fractures, even if the measured bone mineral densities (BMDs) are within the lower limits. [4-7]

In addition to BMDs and FRAX scores, there are other independent variables that can have a negative impact on bone quality and increase the likelihood of osteoporotic fractures. Non-modifiable risk factors include ageing, female gender, white ethnicity, and positive family history. Preventable or partially preventable factors such as a sedentary lifestyle, a diet low in protein density, insufficient intake of bone nutrients, inadequate consumption of vegetables and fruits, untreated chronic conditions, and the use of osteoblast inhibitors can have significant negative effects on osteoporosis and the risk of fractures. [8-13]

Comorbidities refer to the presence of additional medical conditions that coexist alongside a specific disease. Presently, there are multiple comorbidity indices with varying objectives. Various approaches can manage co-morbidities. An uncomplicated method involves tallying the patient's co-morbidities and calculating their total sum. We can use the counted co-morbidity tools as a discrete numerical value or as distinct categorical groups. A more intricate approach to evaluating co-morbidities involves assigning a weight to each comorbidity in order to quantify the overall burden of co-morbidities on the associated diseases based on hazard ratios. Assessing comorbidity burden is crucial in determining the prognosis of osteoporosis-related disabilities and costs, thus highlighting the significance of considering it in routine osteoporosis assessments. In addition, the patient's existing medical conditions may increase the likelihood of developing additional illnesses and worsen the patient's ability to function. There is limited understanding of the role of comorbidity burden estimation in functional prognosis, and the institution's electronic recording systems (ERSs) do not widely integrate these assessment tools. Depending on the objectives of the study and the specific outcomes of interest, these assessment tools for co-morbidities may yield varying responses. Nevertheless, it is crucial to systematically measure and assess the burden of comorbidity in order to effectively manage the primary diseases. [14-19]

Initially developed to predict patient mortality, the Charlson Co-Morbidity Index (CCI) and its modified version, the age-adjusted CCI (AACCI), have also undergone validation against patients' admission days and functionality. AACCI is currently one of the most commonly used weighted comorbidity assessment indexes. The AACCI encompasses 19 medical conditions, each assigned varying levels of importance, in addition to age. The clinical assessments and evaluations heavily rely on the overall weighted score. Unlike the AACCI, the Elixhauser Comorbidity Index (ECI) has undergone comparative validation against a range of patient outcomes. [20-23]

As the global population continues to age, the proportion of individuals with osteoporosis is expected to steadily increase, our main objective in this study was to thoroughly examine the Jordanian patients who visited the rehabilitation and rheumatology clinic to investigate the extent of correlations and the range of total variations in the patients' fH_BMD and LBMD, attributed to their comorbidity burdens.

METHODS:

This retrospective, non-interventional study included all individuals suspected of having osteoporosis who visited our rehabilitation clinic at Prince Rashid bin Al-Hasan Military Hospital, Royal Medical Services, Irbid, Jordan, between January 2023 and October 2023. Due to the retrospective nature of our research, the requirement for a signed consent form was waived. The Institutional Review Board (IRB) committee granted approval for this study on 12/12/2023, with the registration number 24_11/2023.

We performed a multiple logistic regression analysis using all potentially relevant factors, such as age, smoking status, gender, the Charlson Comorbidity Index (CCI), medical history, nutritional history, vitamin D level, and dual-energy X-ray absorptiometry (DEXA). Initially, we conducted separate univariate regression analyses to identify the significant variables. These significant variables were then included in our final logistic regression model.

Initially, we performed ROC and sensitivity analyses to primarily investigate the best threshold values for fH_BMD and LBMD in our tested patients. These thresholds were compared to the corresponding FRAX-based 10-year probabilities of hip and major osteoporotic fractures, which were set at 3% and 20%, respectively. Additional sensitivity indices, such as sensitivities, specificities, positive and negative predictive values, likelihood ratios, the Youden index, and the accuracy index, were also investigated alongside the optimal operating points. In our study, we utilised two specific thresholds, referred to as cutoffs, to divide the patients' fH_BMD values into two distinct groups: one group with fH_BMD values less than 0.755 g/cm2, and another group with fH_BMD values greater than or equal to 0.755 g/cm2. Similarly, we divided the LBMD values into two cohorts: one with LBMD values less than 0.835 g/cm2, and another with LBMD values greater than or equal to 0.835 g/cm2. Furthermore, the binary logistic regression, ROC, and sensitivity analysis were performed in a step-by-step manner for each patient's co-morbidity burden, as indicated by the age-adjusted Charlson Co-Morbidity Index (AACCI), in relation to the fH_BMD [<0.755 g/cm2 (0, negative state) and ≥0.755 g/cm2 (1, positive state)] and the LBMD [<0.835 g/cm2 (0, negative state) and ≥0.835 g/cm2 (1, positive state)]. The binary logistic regression analyses were performed to investigate the extent of correlations, the range of total variations in the dependent variable (VR), the percentage of cases that can be accounted for by the independent variables, and the predictive accuracy of the dependent variable. Additionally, this test was conducted to derive the essential coefficients for presenting the investigated binary logistic regression models. The ROC analyses were performed simultaneously to examine the area under the ROC curves (AUROCs) of the patients' AACCI in relation to the two dichotomized BMD outcomes of interest (fH_BMD and LBMD). The results of the ROC analyses were reported as AUROC±SEM. The optimal functional thresholds for the patients' AACCI were determined by identifying the highest differences in ∑Sensitivity+Specificty after subtracting from 1 unit, also known as Youden's index. The sensitivity indices for all accompanying factors were assessed simultaneously using the explored cutoffs. The probabilities of the patients' fH_BMD and LBMD being greater than or equal to 0.755 g/cm2 and 0.835 g/cm2, respectively, at the explored AACCI were determined either from the constructed binary logistic regression models or directly from the binary logistic regression illustrations. In this study, we divided the patients into two groups based on their level of co-morbidity: a group with a lower co-morbidity burden (Cohort I) and a group with a higher co-morbidity burden (Cohort II). We then compared the different variables of the patients between Cohort I and Cohort II. The first group, referred to as Cohort I, consisted of patients with an AACCI value less than 4. The optimal cutoff point for this group was determined to be 4. The second group, referred to as Cohort II, consisted of patients with an AACCI value greater than or equal to 4. The variables of interest in the two cohorts were compared using the Chi-Square Test, with a significance level of $p<0.05$. The results were expressed as numbers (percentages). The Chi-Square statistic (χ 2) was used to measure the difference between the observed and expected frequencies. Additionally, the goodness of fit (G-test of independence) was employed to assess how well the observed frequencies matched the expected frequencies, using the log of the likelihood ratio. Furthermore, the measure of the strength of associations was denoted as odds ratios (OR). The correlations, both interval by interval (Pearson, r) and ordinal by ordinal (Spearman, ρ), were represented as value± standard error of value

RESULT

There were a total of 206 cases that were processed. Out of these, 103 cases were classified as having a positive actual state (fH_BMD ≥0.755 g/cm2), 103 cases were classified as having a negative actual state (fH_BMD<0.755 g/cm2), and 3 cases were considered as missing data. A higher value of the AACCI signifies more compelling evidence of a negative actual state. The researchers examined the AUROC±SEM, which was found to be 0.745±0.035 (95% CI; 0.676-0.814). The study determined that the optimal performance of AACCI was achieved at a threshold value of 3.5, as indicated by Youden's index, sensitivity, and false positive rates of 50.49%, 89.3%, and 38.8%, respectively. In the case of the investigated AACCI versus LBMD, 155 cases were classified as having a positive actual status [LBMD≥0.835 g/cm2], 51 cases were classified as having a negative actual state [LBMD<0.835 g/cm2], and 3 cases were classified as missing data. A higher AACCI value indicates more compelling evidence for a negative current condition. The researchers examined the AUROC±SEM, which was found to be 0.958±0.012 (95% CI: 0.934-0.982). In this study, the optimal operating point of AACCI was determined to be 3.5 using Youden's index. The corresponding values for sensitivity and false positive rate were found to be 85.16% and 0.00%, respectively. The AUROC±SEM for the tested dependent variables of LBMD is [0.958±0.012 (95% CI: 0.934-0.982)]. was significantly higher than that of fH_BMD [0.745±0.035 (95% CI; 0.676-0.814)].

A binary logistic regression model was created to examine the relationship between the patients' AACCI and their fH_BMD ≥0.755 g/cm2. The model was constructed as [e (1.579-0.411×AACCI) /1+ e (1.579-0.411×AACCI)]. At an AACCI value of 3.5, the probability of a patient having fH_BMD ≥0.755 g/cm2 was determined to be 53.51%. The logistic-based model demonstrated statistical significance, with a chi-square value of 12.026 and a p-value of less than 0.0005. The variance accounted for in the dependent variable by our model ranges from 23.4% to 31.2%, depending on whether you use the Cox & Snell R2 or Nagelkerke R2 methods, respectively. Additionally, our model accurately classified 75.2% of the cases. The simulated association between the patients' AACCI and their LBMD ≥0.835 g/cm2 was analysed using binary logistic regression. The constructed formula for this association is [e (4.171-0.604×AACCI) /1+ e (4.171-0.604×AACCI)]. At the optimal AACCI value of 3.5, the probability of a patient having LBMD ≥0.835 g/cm2 was found to be 88.67%. The binary logistic regression model exhibited statistical significance, with a chi-square value of 36.47 and a p-value less than 0.0005. The proportion of the dependent variable that can be accounted for by our model varies from 42% to 62.3%, depending on whether we use the Cox & Snell R2 or Nagelkerke R2 methods, respectively. Additionally, our model accurately classified 85.9% of the cases.

The study found that the optimal cut-off points for fH_BMD and LBMD in predicting the risk of hip and major osteoporotic fractures were 0.755 g/cm2 and 0.835 g/cm2, respectively. The sensitivities and specificities of both measures were 100%, indicating their accuracy in identifying patients at risk. The positive and negative predictive values were 93.64% and 98.73% for fH_BMD, and 93.20% and 96.08% for LBMD, respectively. The likelihood ratios were 1571.43% for fH_BMD and 7850.00% for LBMD, indicating their strong association with fracture risk. The Youden and accuracy indices were 0.00% and 0.00% for both measures, respectively. Overall, the results demonstrate the effectiveness of fH_BMD and LBMD in predicting fracture risk based on the FRAX-based 10-year probability. The sensitivity indices for the patients' co-morbidity burden against fH_BMD≥0.755 g/cm2 and LBMD≥0.835 g/cm2 were as follows: 3.50 vs 3.50, 89.3% vs 85.2%, 61.17% vs 100.00%, 69.70% vs 100.00%, 85.14% vs 68.92%, 17.46% vs 14.84%, 230.00% vs NA, 50.49% vs 85.16%, and 75.24% vs 88.83%, respectively. The gender ratio tested in this study was determined to be 5.87 females for every male, with no significant variations observed between Cohort I and Cohort II [6.33 females to 1 male and 5.17 females to 1 male, respectively, (95% CI; 0.555-2.71), 0.035±0.071, χ 2=0.254, p-value=0.615]. Regarding the categorization of patients' ages, there was a higher proportion of patients in the age range of 50–59 years compared to the age range of 60–69 years. Specifically, 110 patients (53.4%) were in the 50-59 age range, while 96 patients (46.6%) were in the 60-69 age range. These differences were statistically significant when comparing Cohort I and Cohort II. In Cohort I, 99 patients (75.0%) were in the 50–59 age range, while 33 patients (25.0%) were in the 60–69 age range. In Cohort II, 11 patients (14.9%) were in the 50–59 age range, while 63 patients (85.1%) were in the 60–69 age range. The statistical analysis showed a significant difference between the two cohorts, with a value of 17.182 (95% CI; 8.10–36.444), a mean of 0.578±0.055, and a chi-square value of 68.907, with a p-value of 0.000. The patients' fH_BMD and LBMD, measured in grammes per square centimetre, were significantly distributed between the two tested cohorts. The distribution was as follows: 40 patients (30.3%) and 92 patients (69.7%) in one cohort, and 63 patients (85.1%) and 11 patients (14.9%) in the other cohort. The statistical analysis yielded a value of 0.076 (95% confidence interval: 0.036-0.159), with a standard deviation of -0.526±0.056, a chi-square value of 57.025, and a p-value of 0.000. Similarly, in terms of another parameter, the distribution was 0 patients (0.0%) in one cohort and 132 patients (100.0%) in the other cohort, and 51 patients (68.9%) and 23 patients (31.1%) in the respective cohorts. The statistical analysis yielded a value of 6.739 (95% confidence interval: 4.622-9.826), with a standard deviation of -0.766±0.041, a chi-square value of 120.906, and a p-value of 0.000.

In the studied patients, those with higher functionality status had a higher proportion compared to those with lower functionality status (115 patients, or 55.8%, vs. 91 patients, or 44.2%). Among the cohort with lower co-morbidity burden (Cohort I), there was a slightly higher proportion of patients with higher functionality status compared to those with lower functionality status (80 patients, or 60.6%, vs. 52 patients, or 39.4%), although this difference was not statistically significant. In contrast, the cohort with higher co-morbidity burden (Cohort II) had a slightly higher proportion of patients with lower functionality status compared to those with higher functionality status (39 patients, or 52.7%, vs. 35 patients, or 47.3%), although this difference was also not statistically significant. The odds ratio for this comparison was 0.583 (95% CI: 0.328–1.036), and the Pearson correlation (r) was -0.129±0.070, with a chi-square value of 3.406 and a p-value of 0.065. All the tested patients' analysis results and illustrations were clearly and fully presented in Tables 1-6 and Figures 1–5. The current study demonstrated that patients between the ages of 60 and 69 had a higher burden of co-morbidity compared to a cohort of the same gender and age, but with a lower co-morbidity burden [63 (85.1%) vs. 33 (25.0%), 17.182 (95% CI: 8.10-36.444), 0.578±0.055, $\chi 2$ = 68.907, p-value = 0.000].

DISCUSSION

In this study, the patients who had a higher co-morbidity burden were found to have significantly higher probabilities of experiencing 10-year femoral hip and other major osteoporotic fractures (FRAX≥3% or FRAX≥20%, respectively). Additionally, these patients were found to have a lower probability of femoral hip and lumbar bone densities compared to patients with a lower co-morbidity burden. The statistical analysis showed a strong association between higher co-morbidity burdens and these outcomes, with a p-value of 0.000. The results showed a significant difference between the two groups, with 49 participants (66.2%) in one group and 0 participants (0.0%) in the other group. The statistical analysis yielded a p-value of 0.000, indicating a highly significant result. The odds ratio was 0.159 (95% confidence interval: 0.111–0.228), and the chi-square value was 114.685 with a standard deviation of 0.042. The study found that there was a significant difference in the prevalence of osteoporotic fractures between two groups: 11 (14.9%) vs. 92 (69.7%) with a p-value of 0.076 (95% CI: 0.036-0.159), and 23 (31.1%) vs. 132 (100.0%) with a p-value of 6.739 (95% CI: 4.622-9.826). These findings were consistent with another study that highlighted the impact of co-morbidity burden on the risk of osteoporotic fractures in both non-elderly and elderly patients. [24-28] This study revealed that patients with a higher co-morbidity burden (Cohort II or those with an AACCI score ≥4) exhibited a higher prevalence of smoking, as well as a greater likelihood of receiving corticosteroidal administrations and having a family history of osteoporotic fractures, compared to patients with a lower co-morbidity burden (Cohort I or those with an AACCI score <4). The first comparison showed a significant difference between the two groups, with 38 (51.4%) in one group and 6 (4.5%) in the other. The calculated 95% confidence interval was 22.167 (8.682–56.593), and the mean difference was 0.548±0.058. The chi-square test resulted in a value of 61.845, with a p-value of 0.000. In the second comparison, there was also a significant difference between the groups, also a significant difference between the groups, with 24 (32.4%) in one group and 6 (4.5%) in the other. The calculated 95% confidence interval was 10.080 (3.888–26.134), and the mean difference was 0.379±0.065. The chi-square test resulted in a value of 29.634, with a p-value of 0.000. Lastly, the third comparison showed a significant difference between the groups, with 22 (29.7%) in one group and 3 (2.3%) in the other. The calculated 95% confidence interval was 18.192 (5.22–63.402), and the mean difference was 0.403±0.060. The chi-square test resulted in a value of 33.524, with a p-value of 0.000. A meta-analysis has confirmed that smoking is a risk factor for fractures, including hip fractures, and negatively affects bone architecture qualities. [29-31]

In this study, we examined the relationship between lower co-morbidity burdens and specific dietary factors, including a high protein density diet (≥2.5 g/100 Cal), regular consumption of fruits and vegetables, higher levels of vitamin D (≥30 ng/ml), and the absence of hyperthyroidism. The results of the statistical analysis are as follows: In the first comparison, there were 97 cases (73.5%) in one group and 32 cases (43.2%) in the other group, with a statistical measure of 0.275 (95% confidence interval; 0.151-0.501), a standard deviation of -0.300±0.068, a chi-square value of 18.527, and a p-value of 0.000. In the second comparison, there were 132 cases (100.0%) in one group and 53 cases (71.6%) in the other group, with a statistical measure of 3.491 (95% confidence interval; 2.781–4.382), a standard deviation of -0.450±0.047, a chi-square value of 41.712, and a p-value of 0.000. In the third comparison, there were 51 cases (38.6%) in one group and 12 cases (16.2%) in the other group, with a statistical measure of 0.307 (95% confidence interval: 0.151–0.626), a standard deviation of -0.233±0.062, a chi-square value of 11.227, and a p-value of 0.001. In the fourth comparison, there were 126 cases (95.5%) in one group and 32 cases (43.2%) in the other group, with a statistical measure of 27.563 (95% confidence interval; 10.774–70.508), a standard deviation of 0.593±0.056, a chi-square value of 72.328, and a p-value of 0.000. Previous studies have examined the impact of consuming fruits and green vegetables (FVC) on increasing alkalinity relative to acidity due to the presence of potassium salts from weak organic acids. An optimal ratio of potassium (PRO: K) in protein is linked to a reduced risk of renal acidosis and an increased likelihood of systemic calcium loading. [32-35]

Nevertheless, this study is subject to limitations due to its nature as an observational retrospective study, making it susceptible to recall and selection bias. The study was conducted at a single site and had a relatively small sample size. In this study, we did not collect data on other potential risk factors for gastrointestinal and hormonal-related negative confounders, as well as non-corticosteroidal drugs that are known to have detrimental effects on bone quantity and quality. Nevertheless, our study can provide additional support to other multi-site prospective studies that aim to investigate the relationship between the burden of co-morbidity and osteoporotic fractures, particularly in cohorts from Jordan or the Mediterranean region.

CONCLUSION

Overall, our study focused on a group of individuals from a small community who received rehabilitation treatment at Prince Rashid bin Al-Hasan Military Hospital, Royal Medical Services, Irbid, Jordan, from January 2023 to October 2023. We found that participants with an AACCI score higher than 4 had noticeably lower bone densities in the femur and lumbar region, as well as a higher risk of experiencing hip and major osteoporotic fractures within the next 10 years, compared to those with a lower burden of co-morbidities. Rheumatologists should priorities and implement the screening and management of comorbidity burdens in their patients. This can be achieved by developing effective strategies and addressing risk factors that can potentially be reversed.

Table 1. The sensitivity test's results for patients' femoral hip and lumbar bone mineral densities.

Prognostic Indicator	Cutoff	TPR	FPR	YI	TNR	PPV	NPV	NLR	PLR	AI
fH_BMD (g/cm^2)	0.755	100%	6.4%	93.64%	93.64%	93.20%	100.00%	0.00%	1571.43%	96.60%
LBMD (g/cm^2)	0.835	100%	1.3%	98.73%	98.73%	96.08%	100.00%	0.00%	7850.00%	99.03%

fH_BMD: Femoral hip bone mineral density, **LBMD**: Lumbar bone mineral density, **FRAX**: Fracture assessment tool, **TPR**: True positive rate (sensitivity), **FPR**: False positive rate, **YI**: Youden index, **TNR**: True negative ratio (specificity), **PPV**: Positive predictive value, **NPV**: Negative predictive value, **AI**: Accuracy index, **PLR**: Positive likelihood ratio, **NLR**: Negative likelihood ratio.

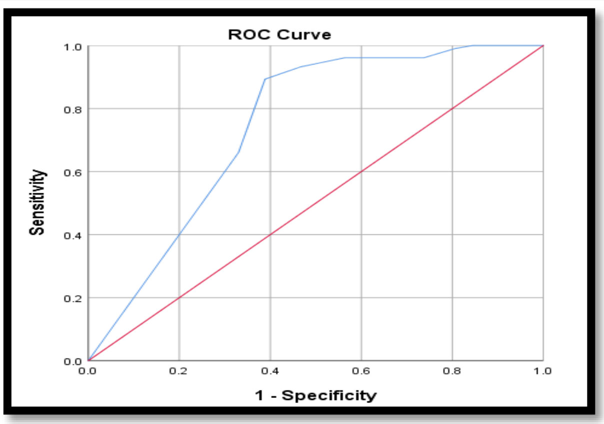
Table 2. The Binary Logistic Regression results for the patients' co-morbidities burden against patients' femoral hip and lumbar bone mineral densities.

Tested variables	B±SEM	Wald	Sig.	Exp(B)	95% C.I.for EXP(B) Lower	95% C.I.for EXP(B) Upper	χ2(df)	VR	%Cases
fH_BMD≥0.755 g/cm²									
Constant	1.579±0.298	28.092	0.000	4.851			(4) 12.026	23.4%-31.2%	75.2%
AACCI	-0.411±0.079	27.153	0.000	0.663	0.568	0.774			
LBMD≥0.835 g/cm²									
Constant	4.171±0.482	74.779	0.000	64.792			(4) 36.47	42%-62.3%	85.9%
AACCI	-0.604±0.085	50.318	0.000	0.546	0.462	0.646			

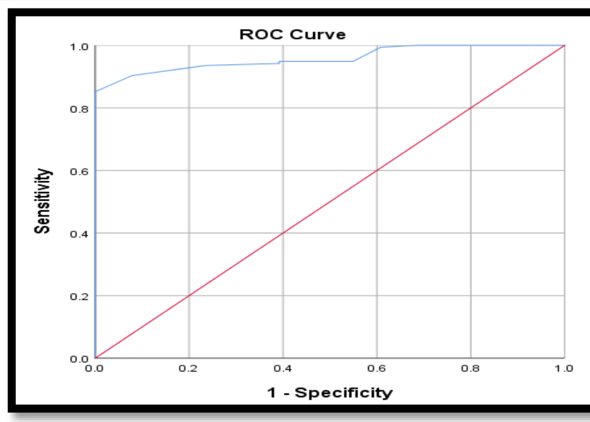
fH_BMD: Femoral hip bone mineral density, **LBMD**: Lumbar bone mineral density, **AACCI**; Age adjusted charlson comorbidity index**.**

Figure 1. The Receiver Operating Characteristic analysis for the patients' co-morbidities burden against patients' femoral hip and lumbar bone mineral densities

AACCI vs fH_BMD≥0.755 g/cm²



AACCI vs LBMD≥0.835 g/cm²



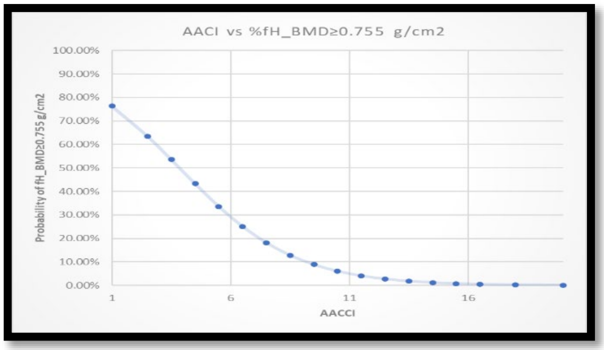
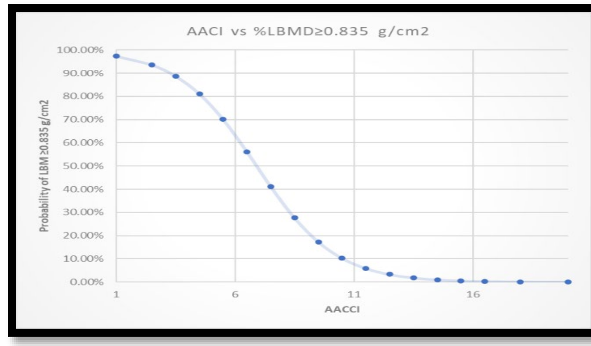
fH_BMD: Femoral hip bone mineral density, **LBMD**: Lumbar bone mineral density, **AACCI;** Age adjusted charlson comorbidity index.

Table 3. The sensitivity test's results for patients' femoral hip and lumbar bone mineral densities against probabilities of osteoporotic fracture.

OI	Cutoff	TPR	FPR	YI	TNR	PPV	NPV	NLR	PLR	AI
fH_BMD≥0.755 g/cm²	3.50	89.3%	38.8%	50.49%	61.17%	69.70%	85.14%	17.46%	230.00%	75.24%
LBMD≥0.835 g/cm²	3.50	85.2%	0.00%	85.16%	100.00%	100.00%	68.92%	14.84%	NA	88.83%

OI: Outcomes of interest**, TPR:** True positive rate (sensitivity). **FPR:** False positive rate. **YI:** Youden index **TNR:** True negative ratio (specificity). **PPV:** Positive predictive value. **NPV**: Negative predictive value**. AI:** Accuracy index. **PLR:** Positive likelihood ratio. **NLR**: Negative likelihood ratio**.**

Figure 2. The Binary Logistic Regression model's illustrations for the patients' co-morbidities burden against fH_BMD≥0.755 g/cm^2 and LBMD≥0.835 g/cm^2

AACCI vs fH_BMD≥0.755 g/cm^2	AACCI vs LBMD≥0.835 g/cm^2
	

fH_BMD: Femoral hip bone mineral density**, LBMD:** Lumbar bone mineral density, **AACCI;** Age adjusted charlson comorbidity index.

Table 4. Comparatively studied variables across Cohort I-II; Lower co-morbidity burden cohort (Cohort I) versus Higher co-morbidity burden cohort (Cohort II), in the studied patients.

	Cohort I AACCI<4 (132, 64.08%)	Cohort II AACCI≥4 (74, 35.92%)	Total (206, 100%)	OR	R ρ	χ^2 G-Test	p-Value
Gender							
Female	114 (86.4%)	62 (83.8%)	176 (85.4%)	1.226 (95% CI; 0.555-2.71)	0.035±0.071 0.035±0.071	0.254 0.250	0.615
Male	18 (13.6%)	12 (16.2%)	30 (14.6%)				
Female: Male	6.33: 1	5.17: 1	5.87: 1				
Age (Yrs.)							
50-59	99 (75.0%)	11 (14.9%)	110 (53.4%)	17.182 (95% CI; 8.10-36.444)	0.578±0.055* 0.578±0.055*	68.907 73.955	0.000
60-69	33 (25.0%)	63 (85.1%)	96 (46.6%)				
fH_BMD (g/cm^2)							
<0.755	40 (30.3%)	63 (85.1%)	103 (50.0%)	0.076 (95% CI; 0.036-0.159)	-0.526±0.056* -0.526±0.056*	57.025 61.423	0.000
≥0.755	92 (69.7%)	11 (14.9%)	103 (50.0%)				
FRAX							
<3%	99 (75.0%)	11 (14.9%)	110 (53.4%)	17.182 (95% CI; 8.10-36.444)	0.578±0.055* 0.578±0.055*	68.907 73.955	0.000
≥3%	33 (25.0%)	63 (85.1%)	96 (46.6%)				
FRAX							
<20%	132 (100.0%)	25 (33.8%)	157 (76.2%)	0.159 (955 CI; 0.111-0.228)	0.746±0.042* 0.746±0.042*	114.685 131.366	0.000
≥20%	0 (0.0%)	49 (66.2%)	49 (23.8%)				
LBMD (g/cm^2)							
<0.835	0 (0.0%)	51 (68.9%)	51 (24.8%)	6.739 (95% CI; 4.622-9.826)	-0.766±0.041* -0.766±0.041*	120.906 138.854	0.000
≥0.835	132 (100.0%)	23 (31.1%)	155 (75.2%)				
PD (g/100 Cal)							
Lower<2.5	35 (26.5%)	42 (56.8%)	77 (37.4%)	0.275 (95% CI; 0.151-0.501)	-0.300±0.068* -0.300±0.068*	18.527 18.386	0.000
Higher≥2.5	97 (73.5%)	32 (43.2%)	129 (62.6%)				
FVC							
Intermittent	0 (0.0%)	21 (28.4%)	21 (10.2%)	3.491 (95% CI; 2.781-4.382)	-0.450±0.047* -0.450±0.047*	41.712 47.403	0.000
Regular	132 (100.0%)	53 (71.6%)	185 (89.8%)				

.**CCI**: Age-adjusted Charlson Comorbidity Index., **PD**: Protein density, **FVC**: Fruit and vegetable content. **BMD**: Bone mineral density in g perm2, **FRAX**: Fracture risk assessment tool, **LBMD**: Lumbar bone mineral density.

Table 5 (Continued). Comparatively studied variables across Cohort I-II; Lower co-morbidity burden cohort (Cohort I) versus Higher co-morbidity burden cohort (Cohort II), in the studied patients.

	Cohort I AACCI<4 (132, 64.08%)	Cohort II AACCI≥4 (74, 35.92%)	Total (206, 100%)	OR	R ρ	χ^2 G-Test	p-Value
Functionality							
Relatively Functional	34 (25.8%)	16 (21.6%)	50 (24.3%)	NA	-0.036±0.063 -0.007±0.068	44.814 54.425	0.000
Partially Functional	46 (34.8%)	19 (25.7%)	65 (31.6%)				
Partially Non-Functional	19 (14.4%)	39 (52.7%)	58 (28.2%)				
Relatively Non-Functional	33 (25.0%)	0 (0.0%)	33 (16.0%)				
Functionality							
Lower	52 (39.4%)	39 (52.7%)	91 (44.2%)	0.583	-0.129±0.070	3.406	0.065
Higher	80 (60.6%)	35 (47.3%)	115 (55.8%)	(95% CI; 0.328-1.036)	-0.129±0.070	3.399	
Vit D level (ng/ml)							
10-19.9	33 (25.0%)	33 (44.6%)	66 (32.0%)	NA	-0.222±0.066* -0.240±0.067*	20.288 22.261	0.001
20.29.9	48 (36.4%)	29 (39.2%)	77 (37.4%)				
30-39.9	47 (35.6%)	8 (10.8%)	55 (26.7%)				
40-49.9	2 (1.5%)	4 (5.4%)	6 (2.9%)				
50-59.9	1 (0.8%)	0 (0.0%)	1 (0.5%)				
≥60	1 (0.8%)	0 (0.0%)	1 (0.5%)				
Vit D level (ng/ml)							
<30	81 (61.4%)	62 (83.8%)	143 (69.4%)	0.307	-0.233±0.062*	11.227	0.001
≥30	51 (38.6%)	12 (16.2%)	63 (30.6%)	(95% CI; 0.151-0.626)	-0.233±0.062*	11.965	
Alendronate							
No	99 (75.0%)	11 (14.9%)	110 (53.4%)	17.182	0.578±0.055*	68.907	0.000
Yes	33 (25.0%)	63 (85.1%)	96 (46.6%)	(95% CI; 8.10-36.444)	0.578±0.055*	73.955	
Menopausal age (Yrs)							
40-44.9	8 (7.3%)	7 (11.3%)	15 (8.7%)	NA	-0.029±0.075 -0.006±0.076	4.534 4.607	0.209
45-49.9	53 (48.2%)	24 (38.7%)	77 (44.8%)				
50-54.9	35 (31.8%)	27 (43.5%)	62 (36.0%)				
≥55	14 (12.7%)	4 (6.5%)	18 (10.5%)				
Smoking							
No	126 (95.5%)	36 (48.6%)	162 (78.6%)	22.167	0.548±0.058*	61.845	0.000
Yes	6 (4.5%)	38 (51.4%)	44 (21.4%)	(95% CI; 8.682-56.593)	0.548±0.058*	62.348	
Cs							
No	126 (95.5%)	50 (67.6%)	176 (85.4%)	10.080	0.379±0.065*	29.638	0.000
Yes	6 (4.5%)	24 (32.4%)	30 (14.6%)	(95% CI; 3.888-26.134)	0.379±0.065*	28.934	
fHx of fracture							
No	129 (97.7%)	52 (70.3%)	181 (87.9%)	18.192	0.403±0.060*	33.524	0.000
Yes	3 (2.3%)	22 (29.7%)	25 (12.1%)	(95% CI; 5.22-63.402)	0.403±0.060*	33.582	

CCBs: Calcium channel blockers, **BBs:** Beta-blockers**, ACEIs:** Angiotensin-converting enzyme inhibitors, **ARBs:** Angiotensin receptor blockers, **Cs:** Corticosteroids, **HTN:** Hypertension, **Anti-HTN:** anti-hypertension, **fHx:** Family history

Table 6 (Continued). Comparatively studied variables across Cohort I-II; Lower co-morbidity burden cohort (Cohort I) versus Higher co-morbidity burden cohort (Cohort II), in the studied patients.

	Cohort I AACCI<4 (132, 64.08%)	Cohort II AACCI≥4 (74, 35.92%)	Total (206, 100%)	OR	R ρ	χ^2 G-Test	p-Value
AACCI							
2	102 (77.3%)	0 (0.0%)	102 (49.5%)	NA	0.786±0.022* 0.888±0.012*	206.000 269.024	0.000
3	30 (22.7%)	0 (0.0%)	30 (14.6%)				
4	0 (0.0%)	12 (16.2%)	12 (5.8%)				
5	0 (0.0%)	13 (17.6%)	13 (6.3%)				
6	0 (0.0%)	9 (12.2%)	9 (4.4%)				
7	0 (0.0%)	1 (1.4%)	1 (0.5%)				
8	0 (0.0%)	4 (5.4%)	4 (1.9%)				
9	0 (0.0%)	4 (5.4%)	4 (1.9%)				
10	0 (0.0%)	10 (13.5%)	10 (4.9%)				
11	0 (0.0%)	5 (6.8%)	5 (2.4%)				
12	0 (0.0%)	7 (9.5%)	7 (3.4%)				
13	0 (0.0%)	1 (1.4%)	1 (0.5%)				
14	0 (0.0%)	1 (1.4%)	1 (0.5%)				
15	0 (0.0%)	2 (2.7%)	2 (1.0%)				
16	0 (0.0%)	2 (2.7%)	2 (1.0%)				
17	0 (0.0%)	2 (2.7%)	2 (1.0%)				
19	0 (0.0%)	1 (1.4%)	1 (0.5%)				
HTN							
No	91 (68.9%)	10 (13.5%)	101 (49.0%)	14.205	0.532±0.055*	58.289	0.000
Yes	41 (31.1%)	64 (86.5%)	105 (51.0%)	(95% CI; 6.632-30.423)	0.532±0.055*	63.316	
Anti-HTN							
CCBs	33 (80.5%)	0 (0.0%)	33 (31.4%)	NA	0.509±0.088* 0.611±0.089*	78.447 99.783	0.000
CCBs+BBs	0 (0.0%)	27 (42.2%)	27 (25.7%)				
CCBs+ACEIs or ARBs	2 (4.9%)	12 (18.8%)	14 (13.3%)				
CCBs+Thiazide	3 (7.3%)	17 (26.6%)	20 (19.0%)				
BBs+ACEIs or ARBs	2 (4.9%)	7 (10.9%)	9 (8.6%)				
ACEIs or ARBs+Thiazide	1 (2.4%)	1 (1.6%)	2 (1.9%)				
HT							
No	126 (95.5%)	32 (43.2%)	158 (76.7%)	27.563	0.593±0.056*	72.328	0.000
Yes	6 (4.5%)	42 (56.8%)	48 (23.3%)	(95% CI; 10.774-70.508)	0.593±0.056*	73.624	

AACCI: Age-adjusted Charlson Co-Morbidity index, **HTN:** Hypertension, **Anti-HTN:** anti-hypertension, **fHx:** Family history, **HT:** Hypothyroidism, **CCBs:** Calcium channel blockers, **BBs:** Beta-blockers **ACEIs:** Angiotensin-converting enzyme inhibitors **ARBs:** Angiotensin receptor blockers.

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