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Characterizing low femoral neck BMD in Qatar Biobank participants using machine learning models

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Abstract

Background Identifying determinants of low bone mineral density (BMD) is crucial for understanding the underlying pathobiology and developing effective prevention and management strategies. Here we applied machine learning (ML) algorithms to predict low femoral neck BMD using standard demographic and laboratory parameters.

Methods Data from 4829 healthy individuals enrolled in the Qatar Biobank were studied. The cohort was split 60% and 40% for training and validation, respectively. Logistic regression algorithms were implemented to predict femoral neck BMD, and the area under the curve (AUC) was used to evaluate model performance. Features associated with low femoral neck BMD were subjected the statistical analysis to establish associated risk.

Results The final predictive model had an AUC of 86.4% (accuracy 79%, 95%CI: 77.98–80.65%) for the training set and 85.9% (accuracy 78%, 95% CI: 75.92–80.61%) for the validation set. Sex, body mass index, age, creatinine, alkaline phosphatase, total cholesterol, and magnesium were identified as informative features for predicting femoral neck BMD. Age (odds ratio (OR) 0.945, 95%CI: 0.945–0.963, $p < 0.001$), alkaline phosphatase (OR 0.990, 95%CI: 0.986–0.995, $p < 0.001$), total cholesterol (OR 0.845, 95%CI: 0.767–0.931, $p < 0.001$), and magnesium (OR 0.136, 95%CI: 0.034–0.571, $p < 0.001$) were inversely associated with BMD, while BMI and creatinine were positively associated with BMD (OR 1.116, 95%CI: 1.140–1.192, $p < 0.001$ and OR 1.031, 95%CI: 1.022–1.039, $p < 0.001$, respectively).

Conclusion Several biological determinants were found to have a significant global effect on BMD with a reasonable effect size. By combining standard demographic and laboratory variables, our model provides proof-of-concept for predicting low BMD. This approach suggests that, with further validation, an ML-driven model could complement or potentially reduce the need for imaging when assessing individuals at risk for low BMD, which is an important component of fracture risk prediction.

Clinical trial number Not applicable.

Keywords Bone mineral density, Femoral neck, Machine learning, Creatinine, Alkaline phosphatase, Qatar biobank

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Background

Low bone mineral density (BMD) is an extremely common pathology characterized by a deterioration in bone strength due to a loss of bone mass and damage to the bone tissue microarchitecture [1, 2]. Bone mass reaches a peak during adolescence, following which it is preserved until a phase of life when the equilibrium between osteoblasts (bone-forming cells) and osteoclasts (bone-resorbing cells) is altered. Normally, an equal amount of bone is lost and created, so any change to this balance - such as through high glucocorticoid levels, parathyroid hormone imbalance, or low calcium levels - can lead to a reduction in bone mass [1].

Bone density used to be measured using multiple methods such as heel, radius, and phalanges ultrasound, spine computerized tomography (CT), or radius and calcaneus densitometry, although dual-energy X-ray absorptiometry (DXA) is now the favored method. One crucial metric derived from DXA is the T-score, which compares an individual's BMD to that of a healthy young adult of the same sex. The World Health Organization (WHO) states that a T-score of -1 or above indicates normal bone density, while scores between – 1 and – 2.5 signify osteopenia (lower than normal bone density) and scores below – 2.5 indicate osteoporosis, a severe depletion of bone density that places individuals at a higher risk of fractures [3]. In our study, we use the term "low BMD" to describe individuals reaching an at-risk state for low BMD, defined as a T-score <-1 [4]. Typically, 30–40% of bone mass is lost by 70 years of age, i.e., bone density decreases with age, while bone quality indicates the propensity of the bone to fracture [2].

Low BMD is a significant public health problem due to associated morbidity and mortality, and the prevalence of osteoporosis is increasing in both males and females. In the USA, about 50% and 20% of White adult females and males aged over 50, respectively, are exposed to osteoporotic fractures in their lifetime. Moreover, over 10.2 million Americans are estimated to have osteoporosis and more than 43 million have a low BMD. The prevalence of fractures continues to increase as the population ages, and the number of new osteoporosis cases is expected to increase and exceed the number of new cases of breast cancer, prostate cancer, and myocardial infarction combined. By 2040, the incidence of yearly fractures is predicted to increase by 68% [5]. Osteoporosis prevalence has dramatically and disproportionately increased in men compared with women over the last few decades, increasing from 4 to 38% in males over 50 between the 1990s and mid-2000s [6]. The primary cause of morbidity is fragility fractures, and hip fractures of the femoral neck cause acute pain with loss of function that are often slow to recover and persistent.

Machine learning (ML) can simply be described as when a computer learns how to perform complicated jobs without being programmed. ML can identify patterns and data structures that humans cannot identify due to its capacity to process and interpret huge amounts of data. ML can learn in two main ways: predicting outcomes based on training data ("supervised" ML) and exploring outcome without training data ("unsupervised" ML). In the supervised approach, the algorithm learns from training data, labeled images, text, or alphanumerical data, consequently establishing prediction rules from these training data [7].

Recognizing individuals at high risk of low BMD is essential, because an early diagnosis provides access to clinical management and medications that can reduce the risk of subsequent fracture. Risk factors for fractures include a history of fractures, lower body weight, low serum vitamin D, and low BMD. Recognizing the importance of predicting fracture risk, the WHO fracture risk assessment tool (FRAX) was established to calculate the fracture risk according to a set of risk factors. The accuracies of this and other predictive tools are evaluated using the area under the receiver operating characteristic curve (AUC) metric, which reflects concordance between the predicted and actual fracture outcome [8].

Nevertheless, measuring BMD usually necessitates imaging, which is not only costly and time-consuming but also exposes patients to radiation. In this study, our objective was to develop an accurate screening tool for low BMD utilizing readily available clinical and/or laboratory data that could help with bone health management. Embedding such a tool into patient information systems would enable the identification of high-risk individuals, facilitating timely interventions and personalized management strategies. To achieve our objective, we applied ML to a dataset of 4829 healthy individuals with associated demographic and clinical laboratory data to predict low femoral neck BMD.

Methods

Ethical approval

Data were obtained from the Qatar Biobank (QBB). Ethical approval was granted by the QBB Ethics Committee under reference number [E-2021-QF-QBB-RES-ACC-00050-0172] and the Qatar University Institutional Review Board (QU-IRB) under reference number [1648-E/22]. Written informed consent was obtained from all participants by the QBB [9]. All procedures involving human participants were conducted in compliance with the ethical standards outlined in the 1964 Declaration of Helsinki and its subsequent amendments or comparable ethical guidelines.

Study participants

This was a cross-sectional observational study of 4829 healthy participants participating in the QBB. The QBB started recruiting in 2012 and recruited male and female Qatari nationals or long-term residents (living in Qatar for > 15 years) aged 18 and above, so all participants were 18 years or older. No exclusion criteria were applied. The data contained demographic variables, BMD values for multiple skeletal sites, using the GE Lunar Prodigy (GE Medical Systems, Madison, WI), and the results of 14 clinical tests. All laboratory tests were conducted at the QBB in accordance with international standard procedures.

The data were split into a model training dataset (2999 (60%) samples; 2572 normal and 427 low BMD) and a model validation dataset (1924 (40%) samples; 1639 normal and 285 low BMD). For the training dataset, the data were split into 10 equal folds for cross-validation (CV), where nine folds were used as a training dataset and the remaining fold was used as a test set to evaluate model performance. This step was repeated 10 times, and the performance parameters of all 10 rounds were averaged.

Table 1 Characteristics of the study population (4829 participants)

Parameter	Mean (SD)	Parameter	*N* (%)
Age (years)	34.2 (10.3)	Smoking status	
BMI (kg/m$^{2)}$	28.1 (5.9)	Smoker	970 (21.7)
Creatinine (µmol/L)	67.0 (14.4)	Non-smoker	2732 (61.2)
Alkaline phosphatase (U/L)	69.5 (19.0)	Past smoker	762 (17.1)
Total cholesterol (mmol/L)	4.82 (0.87)	Sex	
Calcium (mmol/L)	2.37 (0.09)	Male	2442 (50.6)
Phosphorus (mmol/L)	1.15 (0.16)	Female	2387 (49.4)
Uric acid (µmol/L)	294.6 (80.0)		
Creatine kinase (U/L)	104.9 (382.6)		
Magnesium (mmol/L)	0.83 (0.06)		
Fibrinogen (g/L)	3.2 (0.6)		
Dihydroxyvitamin D total (ng/ml)	16.5 (10.0)		
Free thyroxine (pmol/L)	13.7 (2.2)		
Thyroid stimulating hormone (mlU/L)	2.04 (3.09)		
Testosterone (nmol/L)	10.1 (10.4)		
Estradiol (pmol/L)	239.0 (286.7)		

Abbreviations: SD = standard deviation, N = frequency

T-score calculation

Femoral neck BMD T-scores were calculated after calculation of the mean and standard deviation (SD) of an ethnicity and sex-matched reference population aged between 25 and 35 with normal body mass index (BMI) of 18.5–24.9 using the following equation:

$$T-score=\frac{Individuals'\ BMD-\\ mean\ of\ reference\ population}{Standard\ devasion\ of\ reference\ population}$$

After calculating T-scores, a new feature "class" was added to classify each instance into normal BMD and low BMD based on T-scores, where "normal" was defined as a T-score ≥ -1 and "low" was defined as individuals at risk of low BMD (T-score < -1) [4]. This variable was our class of interest for model training, i.e., predicting normal or low BMD based on clinical and demographic predictors.

Features

We considered an extensive range of independent (or predictor) variables including demographic, anthropometric, lifestyle, and biochemical measures (see Table 1). Demographic data included sex (male, female) and nationality (Qatari and non-Qatari) as categorical variables. Age was considered as a continuous variable, denoted in years. Body mass index (BMI), a crucial metric of individual health, was considered a continuous variable measured in kg/m^2 and smoking was a categorical variable. An important anthropometric measure, hip-to-waist ratio, was considered as a continuous variable.

We also integrated a broad range of biochemical predictors, as shown in Table 1, which were treated as continuous variables.

Data management and cleaning

Data obtained from the QBB were preprocessed to ensure reliability and integrity for subsequent ML. First, data quality was assessed by identifying and addressing missing values that might contribute to incomplete and potentially biased models through imputation of missing data with the mean of the records. Inconsistent formatting, typographical errors, or non-numerical values or symbols were corrected by standardizing the format, removing symbols, and converting the text values to missing data.

Data were cleaned using Sublime Text (Sublime HQ Pty Ltd, Australia) before conversion to CSV and raffs format for subsequent analysis in WEKA (Waikato Environment for Knowledge Analysis, University of Waikato, New Zealand) software. Since the training data were unbalanced with a majority in the control group, we used the "DataBalancer" option in WEKA. This option applies several sampling techniques includes random under-sampling, random oversampling, and cluster-based sampling,

which adjust the distribution of instances across classes, helping to reduce model bias and improving the model's ability to generalize to both classes.

Performance measures

In this study, the dataset was partitioned into 60% for training and 40% for validation. The training set was used to train the model, while the validation set was used to evaluate the model's performance on unseen data. This partitioning ensured that the model could learn from the majority of the data while also being validated on a separate set to prevent overfitting.

Model performance was assessed using precision, recall, F-measure, and the area under the receiver operating characteristics (AUC-ROC) curve measures. The ROC curve measures the ability of a model to distinguish positive from negative instances, with the true positive rate (TPR) plotted against the false positive rate (FPR). An AUC closer to 1 indicates better model performance and classification accuracy.

Table 2 Features selected using the three different WEKA evaluators

CorrelationAttributeEval	InfoGainAttributeEval	GainRatioAttributeEval
Sex	Sex	Sex
Total testosterone	Total testosterone	Total testosterone
Creatinine	Estradiol	Estradiol
Estradiol	Creatinine	Creatinine
Uric acid	Uric acid	MQ_S1
MQ_S1	MQ_S1	Uric acid
BMI	BMI	Total cholesterol
Magnesium	Age	BMI
Age	Magnesium	Age
Fibrinogen	Fibrinogen	Calcium
Calcium	Alkaline phosphatase	Magnesium
Total cholesterol	Calcium	Fibrinogen
Alkaline phosphatase	Total cholesterol	Alkaline phosphatase
Phosphorus	Creatine kinase	Creatine kinase
Dihydroxyvitamin D	Phosphorus	Phosphorus
Free thyroxine	Dihydroxyvitamin D	Dihydroxyvitamin D
Thyroid stimulating hormone	Thyroid stimulating hormone	Thyroid stimulating hormone
Creatine kinase	Free thyroxine	Free thyroxine

Feature selection and model implementation

The filter method in WEKA was used for feature selection. Filter methods evaluate attributes independently based on statistical measures (chi-squared test, information gain, and variance threshold) of their association with the class of interest. Eighteen features were assessed using three different tests to select the most relevant features contributing to femoral neck BMD classification. After feature selection, the "Ranker" approach in WEKA was used to rank the selected features from those contributing most to BMD prediction to the least contributory.

Logistic regression was applied to classify individuals based on their BMD into two categories: normal and low BMD. Logistic regression was selected due to its robustness, simplicity, and ability to handle multiple predictors while providing an interpretable output. The model was trained using 60% of the data, and its performance was evaluated using the remaining 40% of the data as the validation set.

Finally, several experiments were performed to identify the lowest number of features providing good model accuracy with the highest F-measure and AUC-ROC value.

Statistical analysis

Logistic regression was performed in SPSS v.24 (IBM Statistics, Armonk, NY) to assess associations between each feature and BMD prediction at the femoral neck site. Model features were entered simultaneously to account for the effect of each feature in the presence of all other features. A p-value < 0.05 was considered significant. For models with a significant effect, the effect of each feature was also assessed at a p-value of < 0.05, and the odds ratio (OR) and confidence intervals (CI) as well as Wald χ^2 statistic were noted for each.

Results

Subject characteristics

The study enrolled 4829 healthy subjects from the QBB database, 2442 (50.6%) males and 2387 (49.4%) females. This distribution closely reflects the overall sex ratio in the Qatari population. Sex, a known predictor of BMD, was included as an important parameter in our model to account for its effect on bone health. Available data included multiple demographic parameters and clinical test results (Table 1).

Selecting features predictive of femoral neck BMD

Clinical features most associated with femoral neck BMD classification according to the three different WEKA attribute evaluators included demographic features (sex, age, BMI), testosterone, estradiol, creatinine, uric acid, magnesium, fibrinogen, and calcium (Table 2).

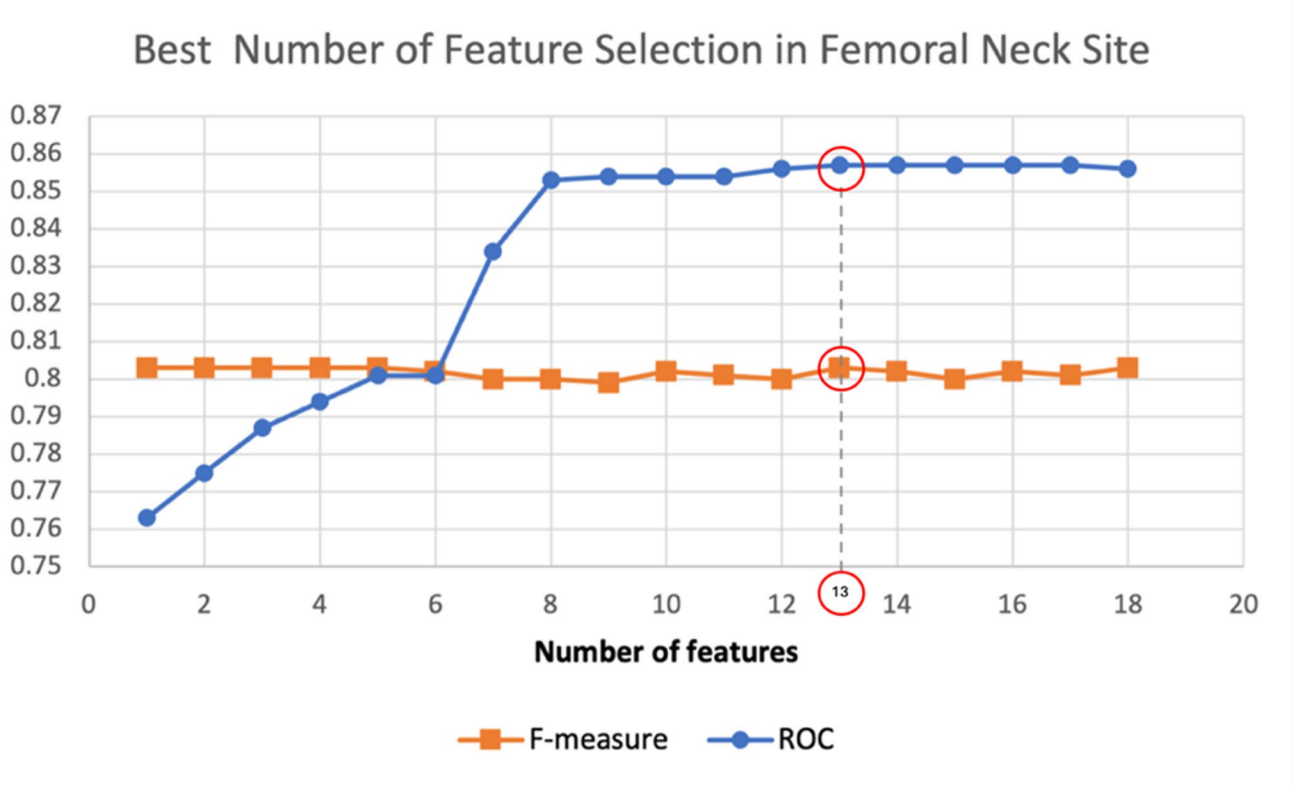

Fig. 1 The optimal number of features producing the highest F-measure and AUC-ROC

Table 3 Logistic regression accuracy metrics for associations with low femoral neck BMD for the training and validation models

Class	True positive rate	False positive rate	Precision	Recall	F-measure	ROC area
Training						
Normal	0.727	0.140	0.838	0.27	0.779	0.864
Low	0.860	0.273	0.759	0.860	0.806	0.864
Weighted Avg.	0.793	0.207	0.799	0.793	0.792	0.864
Validation						
Normal	0.842	0.341	0.841	0.842	0.841	0.859
Low	0.659	0.158	0.661	0.659	0.660	0.859
Weighted Avg.	0.783	0.283	0.783	0.783	0.783	0.859

Optimal feature number for model development

We next performed a series of experiments to determine the optimal number of features producing the highest F-measure for low BMI and the highest AUC-ROC value to reduce noise from features not strongly contributing to BMD prediction (Fig. 1). Thirteen features produced the best accuracy in classifying low femoral neck BMD from normal (F-measure = 0.803, AUC-ROC = 0.857): age, sex, BMI, smoking status, creatinine, alkaline phosphatase, total cholesterol, calcium, uric acid, magnesium, fibrinogen, testosterone, and estradiol.

Logistic regression as a classifier for femoral neck BMD

The final predictive model achieved an AUC of 86.4% on the training set and 85.9% on the validation set. The accuracy rates were 79% (95%CI: 77.98–80.65) for the training set and 78% (95% CI:75.92–80.61%) for the validation set. Additional performance metrics, including precision, recall, F-measure, and AUC (ROC curve), are provided in Table 3 for both datasets.

Identifying low-risk features

We next explored the bottom five attributes to ensure that they were not significantly contributing to model accuracy and therefore contributing noise (Table 4). These features degraded the prediction accuracy, producing an AUC of 0.528, so positively contributed to model accuracy.

Logistic regression

The model created using machine-identified features was significantly associated with femoral neck BMD (χ^2 [14,

Table 4 Logistic regression model performance using the bottom five attributes

Class	TP	FP	Precision	Recall	F-measure	ROC area
Normal	0.519	0.468	0.526	0.519	0.522	0.528
Low	0.532	0.481	0.525	0.532	0.529	0.528
Weighted Avg.	0.526	0.474	0.526	0.526	0.526	0.528

Table 5 The risk associated with ML-identified 13 predictors and femoral neck BMD

Predictor	Wald χ^2	df	*p*	Odds ratio	95% CI	
					Lower	Upper
Sex	235.663	1	**0.001**	0.023	0.014	0.037
Age	91.832	1	**0.001**	0.954	0.945	0.963
Smoking status	0.886	2	0.642			
Smoker	0.106	1	0.744	1.035	0.843	1.270
Past-smoker	0.877	1	0.349	1.113	0.890	1.391
BMI	179.493	1	**0.001**	1.166	1.140	1.192
Creatinine	49.270	1	**0.001**	1.031	1.022	1.039
Alkaline phosphatase	17.247	1	**0.001**	0.990	0.986	0.995
Total cholesterol	11.546	1	**0.001**	0.845	0.767	0.931
Calcium	0.215	1	0.643	0.803	0.316	2.035
Uric Acid	0.663	1	0.416	0.999	0.998	1.001
Magnesium	7.481	1	**0.006**	0.139	0.034	0.571
Fibrinogen	1.839		0.175	0.895	0.763	1.051
Total testosterone	1.203	1	0.273	1.007	0.994	1.020
Estradiol	1.273	1	0.259	1.000	1.000	1.001

Notes: Sex reference group = female. Smoking status reference group = non-smoker. $N = 4829$. p-values significant at an alpha level of less than 0.05 are in bold

n = N = 1333.622], $p < 0.001$). The model had a Nagelkerke R^2 of 0.397 and correctly classified 81.1% of cases. Males had a reduced likelihood of having a normal femoral neck BMD compared with females (OR 0.023); for every one-year increase in age, there was a decreased likelihood of having a normal femoral neck BMD (OR 0.954); and the likelihood of having a normal femoral neck BMD increased for every 1 unit increase in BMI (OR = 1.166). With respect to biochemical parameters, every unit increase in creatinine increased in the likelihood of having normal femoral neck BMD (OR = 1.031), while every unit increase in alkaline phosphatase (OR = 0.990), cholesterol (OR = 0.845), and magnesium (OR = 0.139) reduced the risk of normal femoral neck BMD (Table 5).

Sensitivity analysis

Given that accuracy increases were modest past the eighth feature and that the incremental accuracy added by the following 5 features was modest, we ran a sensitivity analysis with the eight features that provided the highest accuracy (Table S1). Sensitivity analysis revealed similar accuracy for case classification and Nagelkerke R-squared value. However, only four independent variables had significant effects out of the eight independent variables. The model containing the 13 features yielded seven independent variables with significant effects.

Discussion

Here, using demographic and laboratory attributes and machine learning, we established a predictive model for femoral neck BMD. In this first example of an ML-driven predictive model for low BMD, both demographic and laboratory variables were associated with BMD. This ML model identified a set of parameters that better estimated risk, potentially overcoming the need for traditional imaging. Furthermore, these markers were present in young individuals, paving the way for screening people early in life to prevent future harm. If implemented clinically, these parameters could form the basis of an easily implementable assessment of BMD based on routine measures that negate the need for DXA screening, thus reducing the time, costs, and radiation exposure associated with imaging. Sensitivity analysis with eight independent variables yielded similar accuracy as the thirteen-feature model, although the number of independent variables with significant effects was higher in the original model containing 13 features. Future research should examine the tradeoffs between accuracy and number of important independent variables related to femoral BMD.

The features identified by ML that were associated with femoral neck BMD had a significant global effect on the outcome with a reasonable effect size. Our finding that ML can be useful in the diagnosis of bone pathology is supported by several recent ML studies in the

osteoporosis field. For example [10], explored the predictive accuracy of several ML algorithms for fracture risk after percutaneous kyphoplasty, and found a good model with high accuracy. Another study used ML to predict osteoporosis risk in an Iranian population, again with good accuracy [11].

The early detection of bone health problems that might have long-term consequences requires accurate estimates of BMD in young people. Compared with traditional methods, ML models can analyze complex datasets and identify patterns that might be missed by conventional analyses. By identifying individuals at risk, bone health management could be tailored to the needs of young individuals. Our ML model showed that sex, age, smoking status, BMI, creatinine, alkaline phosphatase, testosterone, and estradiol contribute to femoral neck BMD. Our findings are consistent with Simpson et al. [12], who used a mechanobiological model to study the impact of age and sex on simulated 2D and 3D human femoral heads, finding that bone effects are mediated by local estrogen produced by chondrocytes and osteoblasts in men and postmenopausal women, rather than gonadal estrogen. For both sexes, bone density decreases with age as bone homeostasis starts to favor bone resorption. In men, bone mass peaks at about 20 years, followed by a gradual decrease of 0.5-1% per year, which, interestingly, coincides with the gradual decrease in testosterone seen with normal aging. A more significant drop in testosterone at around 50 years of age further accelerates bone loss in men [12–15]. For women, loss of bone mass starts a few years before menopause, mirroring the gradual decline in estrogen levels, which then accelerates to a 1–2% loss each year over 8–10 years as estrogen levels drop during menopause, before plateauing later [12].

We also detected a significant positive association between BMI and femoral neck BMD [16], consistent with a study from Hungary reporting a high prevalence of osteoporosis (21.6%) in females aged 50 and over in a population in which roughly two-thirds of people are overweight or obese. In that study, Vári et al. hypothesized that the positive correlation between BMI and BMD was due to mechanical loading [17]. Zhao et al. illustrated that, despite mechanical loading benefitting bone structure, an intriguing inverse relationship between fat mass and BMD persists in both Chinese and White populations even after adjusting for the mechanical loading effects of total body weight [18]. This intriguing finding, confirmed through further analyses within weight-stratified groups, suggests that factors beyond mechanical loading likely influence the observed interplay between bone and fat mass.

The observed association between smoking status and BMD, although not significant, highlights the crucial role played by smoking tobacco and bone health. Yuan et al. assessed the association between smoking and other habits and osteoporosis development using a Mendelian randomization approach, which revealed a significant positive association between smoking and fracture risk but not estimated BMD.

Several clinical laboratory features also contributed to classification of femoral neck BMD. As reported previously, testosterone and estradiol were both associated with BMD levels in the ML model but not statistical analysis. A recent study of a large number of adolescents aged 12–19 years investigated the relationship between sex hormones and BMD levels and detected a significant association between total BMD and testosterone in boys but not in girls. However, increased testosterone levels in girls were not only associated with infertility but also reduced BMD. Interestingly, estradiol was positively associated with BMD in both sexes [19], and Guisado-Cuadrado et al. found that the BMD levels were reduced in postmenopausal women compared to eumenorrheic women due to reduced sex hormone levels and consequent imbalanced bone formation and resorption. In addition, women using oral contraceptives for more than five years had lower BMDs, consistent with the effect of oral contraceptives in prolonged reduction of 17-β-estradiol levels [20].

Serum creatinine is often used as a biomarker of muscle mass since it is one of its breakdown derivatives [21, 22]. However, creatinine levels are also influenced by renal function and other factors. We detected a positive association between serum creatinine levels and femoral neck BMD, consistent with another study of healthy adults with normal renal function that reported significantly lower BMD in males and postmenopausal females with low serum creatinine, an effect that was even greater in males [23]. Another study confirmed these findings in individuals with normal kidney function, reporting that creatinine is an indicator of muscle health, with high muscle mass indicative of high creatinine, which plays a role in osteoporosis prevention [24].

Alkaline phosphatase, an enzyme that is primarily found in the liver, skeleton, and intestine [25, 26], was also associated with BMD in our ML model, with logistic regression analysis revealing a negative association between alkaline phosphatase and femoral neck BMD. This finding is consistent with another study examining associations between alkaline phosphatase and BMD levels in a population aged 20–59 years that detected a negative association between serum alkaline phosphatase and BMD [25] and an analysis of the NHANES dataset, albeit for lumber BMD [27]. Kang et al. examined the relationship between alkaline phosphatase levels and BMD in axial spondyloarthritis patients, finding that structural damage and low BMD were significantly associated with higher alkaline phosphatase levels, which enhanced

disease activity [26]. Quiescent osteoblasts are activated when BMD levels drop, resulting in the formation of unmineralized bone tissue and immature osteoblasts. The former then undergo self-reinforcing proliferation, consequently releasing high levels of bone-specific alkaline phosphatase and increasing serum alkaline phosphatase [25, 27].

Total cholesterol levels were also associated with BMD. The reasons for this are unclear. In postmenopausal females not taking hormonal therapy (but not premenopausal and postmenopausal women taking hormonal therapy), there is an inverse association between total cholesterol and total body BMD. This may be due to the relationship between estrogen levels and BMD [28]. Cholesterol is known to contribute to osteoblast and osteoclast homeostasis, with inhibition of cholesterol synthesis reducing expression of osteoblast precursor mRNA, consequently reducing osteogenic differentiation. Osteoblast differentiation is inhibited by free cholesterol through the inhibition of several bone matrix protein genes including *RUNX2*, *COL1A1*, and *A1P1* [29–31]. Further investigation of the mechanism underlying the association between total cholesterol and femoral neck BMD is required. Finally, magnesium levels were also associated with femoral neck BMD. Magnesium contributes to bone health and bone matrix maturation [32]. Although we found a negative association between magnesium and femoral neck BMD, several other studies have found the opposite [33–35] or no association [36, 37]. The exact impact of magnesium levels on femoral neck BMD remains uncertain, and further studies are needed to clarify the association.

Our study has some limitations. First, the cross-sectional design limited our ability to establish causal relationships between BMD and the identified variables. We split our data set to training and testing datasets, however, we did not have an independent test and validation datasets, so these findings should be regarded as preliminary and requiring further independent validation. Further longitudinal studies are necessary to elucidate the temporal dynamics and causal pathways underlying these factors and BMD. In addition, the validity of our findings relied on the accuracy and reliability of the dataset. Although extensive efforts were made to account for confounding variables, unmeasured factors such as dietary habits, physical activity levels, and medication use could potentially influence BMD and should be acknowledged as potential sources of bias. Finally, we developed models to predict BMD, but BMD has a complex relationship with the relevant clinical outcome of fracture risk. Future studies could develop the approach to develop a model that predicts fracture risk or examines the relationship between the parameters associated with BMD and fracture risk, for instance as measured using the FRAX tool.

Our analysis is strengthened by the large dataset, although we acknowledge volunteer bias as a "by design" limitation. However, there is no reason to suspect that volunteers who provide their data to the QBB have special characteristics that significantly differentiate them from the general population. Our study also includes a healthy cohort, which may impact the ML model, as far more subjects had normal BMD is than a low BMD, generating an imbalance in the data. Although we accounted for this in our analysis, over/under-sampling could still promote model overfitting. Future studies should try to use a more balanced population.

Conclusions.

Our study provides comprehensive insights into the demographic, clinical, and biochemical factors that influence BMD. These included sex, BMI, creatinine, alkaline phosphatase, total cholesterol, and magnesium. Although the number of features examined ($n = 13$) could also be analyzed using traditional statistical analyses, our study establishes the ML paradigm for future studies that include a much larger number of variables. Our findings consolidate existing knowledge and offer new perspectives that can help shape targeted strategies for preserving and enhancing bone health. Future research should validate these results in diverse populations and explore the application of these factors within predictive models to further enhance strategies for managing bone health.

Abbreviations

AUC-ROC	Area under the receiver operating characteristics
BMD	Bone mineral density
BMI	Body mass index
CI	Confidence interval
CT	Computerized tomography
DXA	Dual-energy X-ray absorptiometry
FPR	False positive rate
FRAX	Fracture risk assessment tool
ML	Machine learning
NHANES	National Health and Nutrition Examination Survey
OR	Odds ratio
QBB	Qatar Biobank
SD	Standard deviation
TPR	true positive rate
WHO	World Health Organization

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12891-025-08726-5.

Supplementary Material 1

Author contributions

Study conception and design: A.M.A. Data acquisition: A.M.A. Data analysis and interpretation: N.A.H., R.R., A.A.H. and M.A.H. First draft manuscript preparation: N.A.H. Editing of final draft: R.R., M.A.H., A.A.H. and A.M.A. All authors reviewed and approved the final version of the manuscript.

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Data availability
Data is not readily available as it the property of Qatar Biobank and share under clear agreement terms for the purposes of reporting data in grouped form for publication purposes. Therefore data is available from Qatar Biobank (https://www.qphi.org.qa/) upon request.

Declarations

Ethics approval and consent to participate
Data were obtained from QBB under reference number E-2021-QF-QBB-RES-ACC-00050-0172, and the study was conducted with the approval of QU-IRB under reference number 1648-E/22. Written informed consent was obtained from all participants by QBB.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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