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The Use Of Microrna Ratios To Predict Fractures In Older Women: The Opus Study

Introduction: Biomarkers may add to our ability to predict fracture risk in older women Circulating microRNAs (miRNAs) have emerged as promising minimally invasive biomarkers for bone fragility. This study assessed whether serum miRNA ratios can predict incident vertebral and nonvertebral fractures using a machine learning (ML)-based approach independent of established risk factors such as prior fracture and BMD. **Methods:** We analyzed 1,128 postmenopausal women aged 55 to 80 from the population-based OPUS Study with baseline serum profiled using the osteomiR® miRNA kit, which quantifies 19 miRNAs by RT-qPCR. All pairwise miRNA ratios were computed to evaluate predictive value for incident fractures. During 6-year follow-up, 126 women sustained nonvertebral and 43 vertebral fractures. Logistic regression models including clinical covariates were compared to models that added miRNA ratios to the baseline model —individually in logistic regression and as selected combinations in ML-based Elastic Net. The baseline model included age, BMI, total hip and lumbar spine BMD, prevalent fracture status, and spike-in control (UniSp4). Model performance was evaluated using AUC and Net Reclassification Improvement (NRI). **Results:** For nonvertebral fractures, individual miRNA ratios added to logistic regression improved AUC from 0.599 to 0.662 (ANOVA $p < 0.001$) and NRI = 0.081 for hsa-miR-17-5p/hsa-miR-29b-3p, which had an odds ratio (OR) of 1.478 ($p < 0.001$). The best ML model (AUC = 0.671, NRI = 0.114), using 20-fold cross-validation and Elastic Net alpha = 1 (indicating pure L1 lasso regularization), selected four miRNA ratios: hsa-miR-17-5p/hsa-miR-29b-3p, hsa-miR-143-3p/hsa-miR-29b-3p, hsa-miR-19b-3p/hsa-miR-29b-3p, and hsa-miR-188-5p/hsa-miR-550a-3p, with ORs ranging from 1.041 to 1.315. For vertebral fractures, the individual ratio hsa-miR-17-5p/hsa-miR-152-3p improved AUC from 0.608 to 0.635, with NRI = 0.128 and OR = 1.406 ($p < 0.001$). The best ML model (AUC = 0.639, NRI = 0.096), using

10-fold cross-validation and alpha = 1, selected four miRNA ratios: hsa-miR-144-5p/hsa-miR-152-3p, hsa-let-7b-5p/hsa-miR-451a, hsa-miR-133b/hsa-miR-152-3p, and hsa-miR-152-3p/hsa-miR-23a-3p, with ORs ranging from 0.608 to 1.459. Adding bone turnover markers (BTMs), alone or in combination with miRNA ratios, did not yield any improvement in model performance using the same methodology—whether added individually or as combinations selected via Elastic Net. **Discussion:** Circulating miRNA ratios derived from qPCR can enhance fracture risk prediction beyond clinical models. ML-based selection of informative ratios, followed by de novo logistic regression refitting with the baseline model, improved both discrimination and reclassification. These findings support integrating circulating miRNA biomarkers into clinical tools for assessing fracture risk in older women.

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