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The Silent Threats of Aging: Fear of Fragile Bones, Stiff Arteries, or Time's Inevitable Betrayal? An Age-Matched Study

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Abstract

Introduction: This study assessed the predictive power of femoral neck (FN) bone mineral density (BMD) and pulse wave velocity (PWV) for fracture and cardiovascular-related mortality over a three-year follow-up in a representative cohort.

Methods: A total of 142 participants (54 males, 38%), aged 56 ± 7.2 years, were enrolled in this prospective observational study. FN BMD was measured using dual-energy X-ray absorptiometry (DXA), and carotid-to-femoral PWV was determined via Doppler ultrasound.

Results: Mean PWV was significantly higher in non-survivors compared to survivors (10.9 ± 3.2 m/s vs. 8.6 ± 2.1 m/s, p = 0.0041). FN BMD was lower in non-survivors (0.658 ± 0.131 g/cm^2) than in survivors (0.852 ± 0.150 g/cm^2, p = 0.002). Logistic regression identified PWV as a strong determinant of mortality [coefficient: 0.1593; odds ratio (OR): 1.17; 95% confidence interval (CI): 1.04–1.32; p = 0.01], while FN BMD also showed significance (coefficient: –6.6336; OR: 0.0013; 95% CI: 0.000–0.156; p = 0.0064). However, in age-matched analysis, only PWV remained significant (OR: 2.77; 95% CI: 1.70–4.51; p < 0.0001]. Receiver operating characteristic (ROC) analysis demonstrated superior predictive accuracy for PWV [area under the curve (AUC): 0.958; cutoff: 11.3 m/s; sensitivity: 94.6%; specificity: 88.1%] compared with FN BMD (AUC: 0.560).

Conclusion: PWV showed outstanding accuracy for predicting all-cause mortality, outperforming FN BMD and remaining independent of age. These findings establish PWV as a robust prognostic marker for mortality risk, highlighting its potential role in improving clinical risk stratification for vascular aging and cardiovascular outcomes.

Keywords: Femoral Neck; Pulse Wave Velocity; Osteoporosis; Bone health; Arterial Stiffness.

Introduction

Aging is a complex and inevitable process that brings about various physiological changes, many of which occur silently, posing significant risks to health and quality of life [1]. Among these silent threats, two stand out for their profound impact: osteoporosis, characterized by gradual bone deterioration and a heightened risk of fractures, and arterial stiffness, a key factor in cardiovascular complications and increased mortality [2]. Both conditions are prevalent in aging populations and share common risk factors, including chronic inflammation, hormonal changes, renal function, nutritional deficiencies, genetic predispositions, and physical activity levels, and

diabetes [3]. Despite their different manifestations, osteoporosis and arterial stiffness may act independently or synergistically, increasing the likelihood of adverse outcomes such as fractures and cardiovascular death [2, 4]. Calcium mobilization from weakened bones to stiffer arteries highlights the interplay between osteoporosis and arterial stiffness in aging [5]. This process, involving calcium transfer to arterial walls, exacerbates bone fragility and promotes vascular calcification, linking these conditions through shared pathophysiological pathways [5, 6].

Or should we be more concerned about rigid and stiffer arteries, which silently escalate the risk of cardiovascular events and sudden death [6]? Alternatively, is it the natural aging process itself—the inevitable decline that encompasses both skeletal and vascular health—that poses the greatest threat? Each of these factors contributes to a broader picture of vulnerability, but understanding their individual and combined effects is essential for developing targeted strategies for risk reduction and treatment. The ramification of progressive arterial stiffening on cardiovascular outcomes is comprehensively established, but its influence on other health aspects in older adults, including bone and muscle conditions, remains less explored [6]. While arterial stiffening, bone mass decline, and muscle wasting are all age-associated changes influenced by overlapping risk factors, it remains uncertain whether they occur as independent parallel processes or stem from shared underlying mechanisms [6, 7]. Osteoporosis, often called the "silent disease," advances quietly without noticeable symptoms until a fracture occurs, resulting in significant health complications and a marked decline in quality of life [8].

Likewise, arterial stiffness, commonly assessed through pulse wave velocity (PWV), serves as a pivotal determinant of cardiovascular hazard and survival likelihood, frequently advancing silently until severe complications develop [9]. Early identification and management of these risks can greatly enhance health outcomes and lessen the impact of aging-related conditions. Bone mineral density (BMD) gradually decreases with age, mainly due to an imbalance in bone turnover.

In postmenopausal women, this decline speeds up as a result of lower estrogen levels, heightening the likelihood of developing osteopenia and osteoporosis [10]. In aging individuals, reduced BMD compromises bone integrity, increasing fracture susceptibility, particularly in the vertebrae, femur, and wrist [10, 11]. In the general population, arterial stiffening occurs gradually with age, driven by factors such as declining vascular elasticity and cumulative exposure to cardiovascular risk factors [12].

This manuscript aims to present findings from a three-year follow-up study conducted in a general population cohort, focusing on the long-term outcomes associated with osteoporosis and arterial stiffness. Specifically, the study examines the incidence of fractures and cardiovascular death, evaluating the predictive power of BMD and PWV. By analyzing these data, this research seeks to provide valuable insights into the interplay between skeletal and vascular health, emphasizing the importance of early detection and intervention in mitigating the risks associated with aging. In this study, a particular focus will be placed on distinguishing age as an inevitable process from the quality of bone and vascular health in relation to lethal outcomes during a three-year observational period, with the cohort being age-matched. This study highlights the need for a comprehensive approach to managing age-related conditions, addressing both bone and cardiovascular health to improve patient outcomes.

Methods

This prospective observational study, carried out at the Regional Hospital in Bitola, aimed to investigate the relationship between bone health and vascular rigidity in a general population. A total of 142 participants, comprising 54 males (38%), underwent assessments of bone mineral density using dual-energy X-ray absorptiometry (DXA) and arterial stiffness using carotid-to-femoral pulse wave velocity (PWV). The median age and body mass index (BMI) in the studied cohort were 56 years and 27.34 kg/m², in that order. Common comorbidities included hypertension (27.46%), smoking (38.73%), and diabetes (17.6%). The study monitored clinical outcomes over a three-year observation period, spanning from February 2, 2021, to March 15, 2024.

Table 1 Demographic Characteristics, Clinical Biomarkers, and Outcomes Comparison in Cardiovascular Death and Femoral Neck Fracture Fatal Outcomes Based on bone mineral density (BMD and pulse wave velocity (PWV) Values

Variables	All	CARDIOVASCULAR (PWV)		P	F_NECK fatal outcome (BMD)		P
	N = 142	Survived	Non-survived		Survived	Non - survived	
		N = 134	N = 8		N = 136	N = 6	
Age, years	56 (49 - 68)	57.47 ± 11.35	69.5 ± 6.43	0.0036	57.15 ± 11.26	72.67 ± 3.44	0.001
BMI, kg/m2	27.34 (24.15 to 31.18)	27.79 ± 4.32	27.32 ± 3.95	0.764	27.87 ± 4.39	25.29 ± 2.41	0.156
Hypertension, N (%)	39 (27.46%)	36 (26.47)	3 (37.5)	0.462	37 (27.21)	2 (33.330	0.744
Smoking, N (%)	55 (38.73)	52 (38.8)	3 (37.5)	0.005	53 (38.9)	2 (33.33)	0.075
Diabetes, N (%)	25 (17.6)	21 (15.7)	4 (50)	0.0137	26 (19.11)	3 (50)	0.0672
Fneck fracture (fatal outcome), N (%)	6 (4.22)	/		136	6	0.584	
Cardiovascular death endpoint, N (%)	8 (5.63)	134	8		/		
Fneck survival, months	35.12 ± 4.51	/	0.0035	36	32.3 ± 8.98	0.0013	
Cardiovascular survival, months	34.84 ± 5.42	36	34.94 ± 5.22		/		
BMD Fneck, g/cm2	0.837 (0.733 to 0.927)	0.846 ± 0.157	0.803 ± 0.082	0.803	0.852 ± 0.150	0.658 ± 0.131	0.002
PWV, m/s	9.4 (8.4 to 10.8)	8.6 ± 2.1	10.9 ± 3.2	0.0041	10.49 ± 2.7	11.1 ± 2.7	0.589

The results are presented as: mean and ± standard deviation (SD), median and 25th to 75th percentiles, number (N) and percent (%). BMI, body mass index; Fneck, femoral neck; BMD, bone mineral density and PWV, pulse wave velocity.

Notably, six fatal FN fractures (4.22%) and eight fatal cardiovascular events (5.63%) were documented, including three cases of acute myocardial infarction, two of ischemic stroke, two of sudden cardiac death, and one of decompensated heart failure. Fatal cardiovascular events were defined as deaths directly attributable to cardiovascular causes, confirmed by hospital records, death certificates, or autopsy reports where available. The six fatal FN fracture cases were due to non-cardiovascular complications: one patient died from bronchopneumonia due to prolonged immobilization, two patients succumbed to septicemia resulting from postoperative wound infections, one patient experienced acute respiratory failure, one developed sepsis following a urinary tract infection, and one suffered acute kidney injury with multi-organ failure.

The mean survival period for FN fracture endpoints was 35.12 months, while it was 34.84 months for cardiovascular-related events. The remaining patient characteristics and medical parameters are presented in Table 1, along with their comparison between survived and non-survived patients in both groups (with cardiovascular death and FN fracture death).

Bone mineral density of the FN (FN BMD) was measured using DXA, while carotid-to-femoral PWV propagation was evaluated using Doppler techniques. Carotid-to-femoral PWV was measured using color Doppler ultrasound with electrocardiogram (ECG) synchronization in a quiet, temperature-controlled room after a 10-minute resting period, with participants in the supine position and in a fasting state. The pulse transit time was determined as the time delay between the foot of the Doppler waveform at the carotid and femoral arteries, referenced to the R-wave of the ECG. The distance was measured as the direct surface distance between the carotid and femoral recording sites. Two consecutive measurements were obtained, and the mean value was used for analysis. The methods of DXA and carotid-to-femoral PWV measurement, as described in previous studies [2, 10–15], include determining arterial stiffness by evaluating the duration needed for the arterial pulse signal to travel across the carotid and femoral arteries (cfPWV), dividing the pulse transit time by the known distance between these two points. Patients with chronic unregulated diabetes on insulin therapy, rheumatoid arthritis, pulmonary disorders, malignancies, liver disease, or other persistent diseases affecting bone or heart health—such as recent and past cardiovascular events, heart attacks, or peripheral artery disease—were excluded from the study.

Statistical analysis

The dataset was processed using MedCalc® Statistical Software version 22.002 (MedCalc Software Ltd, Ostend, Belgium, https://www.medcalc.org; 2023). To compare continuous variables, an independent t-test was used for normally distributed data, whereas a non-parametric Mann–Whitney U test was applied for skewed distributions. We used age-matched residual-based matching to estimate the risk for cardiovascular fatal outcomes and FN fracture fatal outcomes. Age adjustment was performed using a residual-based matching approach, where the residuals from a linear regression model of each variable on age were computed and used in subsequent analyses, effectively removing the linear effect of age. Survival probabilities and the number at risk for cardiovascular fatal outcomes and FN fracture fatal outcomes were estimated across censored event-time analysis using the Kaplan-Meier method. To assess the model's capacity to differentiate surviving and non-surviving individuals, diagnostic performance was assessed using ROC (receiver operating characteristic) curves, identifying sensitivity, specificity, and optimal cutoff values. A logistic regression analysis was undertaken to determinate the predictive significance of PWV, FN BMD, and age concerning all-cause mortality.

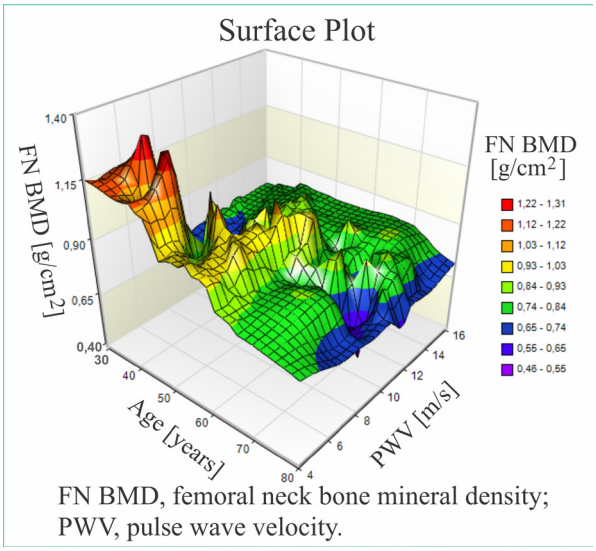
Results

The study evaluated 142 general population participants, examining relationships between femoral neck bone mineral density (FN BMD), pulse wave velocity (PWV), and clinical outcomes over a 36-month follow-up. Demographic, clinical, and procedural parameters, alongside survival outcomes, are summarized in Table 1, comparing survivors and non-survivors for both cardiovascular and FN fracture outcomes.

Patients who died from cardiovascular events were significantly older (69.5 ± 6.43 years, P = 0.0036), and those with fatal FN fractures were also older (72.67 ± 3.44 years, P = 0.001). BMI did not differ significantly for cardiovascular (P = 0.764) or FN fracture outcomes (P = 0.156). Hypertension prevalence was 27.46%, without significant group differences (P = 0.462 for cardiovascular, P = 0.744 for FN fractures). Smoking (38.73%) was significantly associated with cardiovascular mortality (P = 0.005) but not FN fractures (P = 0.075). Diabetes (17.6%) correlated with cardiovascular deaths (P = 0.0137) but not FN fracture mortality.

During follow-up, eight patients (5.63%) died from cardiovascular causes and six (4.22%) from FN fractures. Mean survival was 34.94 ± 5.22 months for cardiovascular deaths and 32.3 ± 8.98 months for FN fracture deaths (P = 0.0027). FN fracture patients had lower FN BMD (0.658 ± 0.131 g/cm² vs. 0.852 ± 0.150 g/cm², P = 0.002). Cardiovascular deaths had higher PWV (10.9 ± 3.2 m/s vs. 8.6 ± 2.1), and FN fracture patients also showed elevated PWV (11.1 ± 2.7 vs. 10.49 ± 2.7). These results indicate strong associations of age, arterial stiffness, and bone health with cardiovascular and FN fracture risk.

Figure 1 shows a 3D surface plot of FN BMD, PWV, and age, illustrating BMD decline with age and higher PWV, emphasizing interactions among vascular rigidity, aging, and bone health. Pearson correlations revealed a strong positive relationship between PWV and age (r = 0.765, p < 0.0001) and moderate negative correlations between PWV and FN BMD



FN BMD, femoral neck bone mineral density; PWV, pulse wave velocity.

Figure 1 – 3D Surface plot depicting the relationship between bone mineral density of the Femoral Neck, pulse wave velocity, and age in the study population

(r = −0.414, p < 0.0001) and age and FN BMD (r = −0.414, p < 0.0001).

Table 2 presents logistic regression results for all-cause mortality. Age was significant [P = 0.008, odds ratio (OR) = 1.071] but partially confounded by PWV due to multicollinearity (variance inflation factor, VIF = 5.732). Lower FN BMD was associated with higher mortality risk (P = 0.0064, OR = 0.0013, b = -6.6336), with a wide confidence interval (0.0000–0.1555).

Table 2 Predictive Value of Pulse Wave Velocity, Femoral Neck Bone Mineral Density and age for All-Cause Mortality

Backward Logistic Regression						
Number of events	14	9.86%	8 (cardiovascular events) + 6 (Femur neck fatal outcome)			
Number censored	128	90.14%				
Total number of cases	142	100.00%				
Null model -2 Log Likelihood	137.858					
Full model -2 Log Likelihood	128.839					
Chi-squared	9.02					
DF	1					
Significance level	P = 0.0027					
Covariate	Coefficient	SE	Wald	P	OR	95% CI of OR
PWV (m/s)	0.1593	0.06183	6.6356	0.01	1.1727	1.0388 to 1.3237
BMD Femur Neck (g/cm^2)	-6.6336	2.4351	7.421	0.0064	0.0013	0.0000 to 0.1555
Age (years)	0.06863	0.02589	7.027	0.008	1.071	1,0180 to 1,1268

PWV, pulse wave velocity; BMD, bone mineral density; DF, degree of freedom; SE, standard error; OR, odds ratio and CI, confidence interval.

Table 3 Age-Matched Predictive Value of Pulse Wave Velocity for All-Cause Mortality Using Residual-Based Matching

Backward Logistic Regression (PWV, age matched)						
Number of events	14	9,86%	8 (cardiovascular events) + 6 (Femur neck fatal outcome)			
Number censored	128	90,14%				
Total number of cases	142	100,00%				
Null model -2 Log Likelihood	91.42					
Full model -2 Log Likelihood	66.864					
Chi-squared	24.578					
DF	1					
Significance level	P < 0.0001					
Variable	Coefficient	SE	Wald	P	OR	95% CI of OR
Regresion_residual (PWV)	1.01872	0.24836	16.8254	< 0.0001	2.7697	1.7022 to 4.5064
Variable	b	SE	Wald	P		
Constant	-3.08051	0.48629	40.1292	< 0.0001		

PWV, pulse wave velocity; DF, degree of freedom; SE, standard error; OR, odds ratio; CI, confidence interval.

Table 4 Age-Matched Predictive Value of Femoral Neck Bone Mineral Density for All-Cause Mortality Using Residual-Based Matching

Backward Logistic Regression (PWV, age matched)						
Number of events	14	9,86%	8 (cardiovascular events) + 6 (Femur neck fatal outcome)			
Number censored	128	90,14%				
Total number of cases	142	100,00%				
Null model -2 Log Likelihood	91.42					
Full model -2 Log Likelihood	90.389					
Chi-squared	1.052					
DF	1					
Significance level	P = 0.3050					
Variable	Coefficient	SE	Wald	P	OR	95% CI of OR
Regresion_residual (BMD)	-2.09225	2.06044	1.0311	0.3099	0.1234	0.0022 to 7.0022
Variable	b	SE	Wald	P		
Constant	-2.24695	0.29022	59.9427	< 0.0001		

BMD, bone mineral density; DF, degree of freedom; SE, standard error; OR, odds ratio; CI, confidence interval.

PWV was a significant predictor (P = 0.01, OR = 1.1727, 95% CI 1.0388–1.3237).

Residual-based matching adjusted for age confirmed PWV as a strong predictor of adverse outcomes (OR = 2.7679, 95% CI 1.7022–4.5064), while FN BMD was not significant after age adjustment (OR = 0.1234, 95% CI 0.0022–7.0022) (Tables 3 and 4).

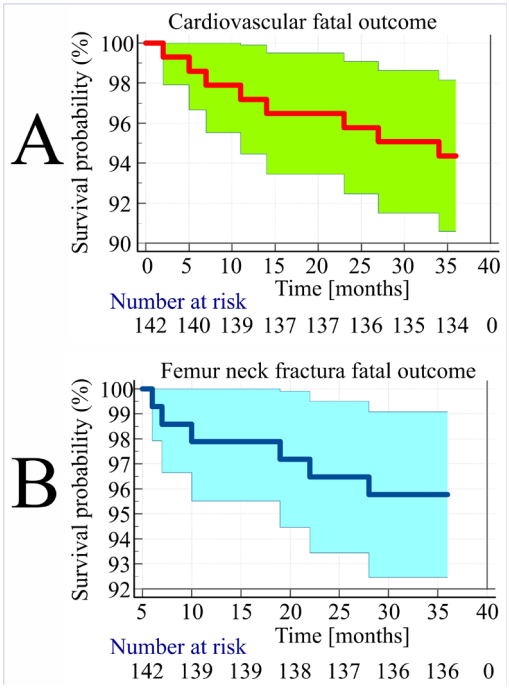


Figure 2 – Kaplan-Meier Survival Probability Curves for Fatal Outcomes Following Cardiovascular Events and Femoral Neck Fractures

Note: Each vertical decline represents a fatal event—8 in cardiovascular events and 6 in femoral neck fractures.

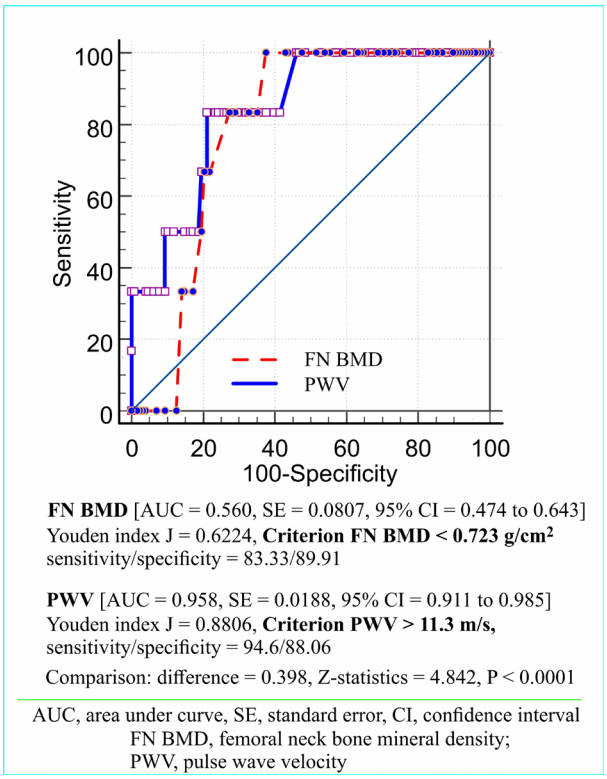


Figure 3 – Pairwise Comparison of Receiver Operating Characteristic Curves for Cardiovascular Death Predicted by Elevated Pulse Wave Velocity and Fatal Femoral Neck Fracture Predicted by Low Bone Mineral Density, Highlighting Significant Statistical Difference

Kaplan-Meier curves (Figure 2A, 2B) showed survival probabilities for cardiovascular and FN fracture deaths over 36 months. ROC analysis (Figure 3) demonstrated PWV had excellent discriminatory power for all-cause mortality [AUC = 0.985, J (Youden) index = 0.8806, cutoff 11.3 m/s, sensitivity 94.6%, specificity 88.06%], while FN BMD showed modest predictive ability (AUC = 0.560, J index = 0.6224, cutoff 0.723 g/cm², sensitivity 83.33%, specificity 89.91%). The optimal cutoff value was determined using the J (Youden) index, a summary measure of diagnostic performance calculated as sensitivity plus specificity minus one, which identifies the point maximizing the test's overall accuracy. The difference in predictive capability was significant (Z = 4.842, P < 0.0001), highlighting PWV as a superior prognostic marker compared to FN BMD.

Discussion

This study, which examined 142 patients, highlights the intricate interplay between skeletal and vascular health in predicting long-term outcomes, including fractures and mortality due to cardiovascular causes during a three-year observation period. Deceased individual in both the cardiovascular death group and FN fatal outcome group displayed a substantially higher age than survivors (p= 0.0036 and p =0.001, respectively). This indicates that advancing age correlates with an increased likelihood of mortality in both conditions. Advanced age plays a crucial role in cardiovascular-related death, partly due to the long-term influence of conventional predisposing elements. Studies confirm that while age's influence on risk decreases at very advanced ages, it remains a crucial factor in both short- and long-term mortality [16].

No meaningful difference was observed in BMI between survivors and non-survivors in either the cardiovascular or FN outcome groups (p =0.764 and p = 0.156, correspondingly), indicating that BMI may not be a predictor of mortality in these contexts. A notable difference was observed in smoking status between individuals who survived and those who did not in the cardiovascular group (p = 0.005), implying a conceivable nexus between tobacco consumption and lethal cardiovascular outcomes. Smoking significantly amplifies the likelihood of cardiovascular death, with a risk of coronary artery dysfunction that is two to four times higher and an excess mortality rate exceeding 70%, compounded by synergistic effects with traditional risk factors like hypertension, hypercholesterolemia, and diabetes. Nicotine and carbon monoxide exacerbate cardiovascular damage by impairing the myocardial oxygen supply/demand ratio, causing endothelial injury, and promoting atherosclerotic plaque development [17]. However, no substantial variation was identified in the FN group (p = 0.075).

Hypertension status alone may not distinguish survival outcomes in both groups. Non-survivors in both groups had lower BMD values compared to survivors, with a notable difference in the FN group (p = 0.0013). This suggests that lower BMD may be linked to poorer outcomes, particularly in FN fractures. PWV was markedly elevated in non-survivors compared to survivors only in cardiovascular estimated group (P = 0.0041), indicating that greater arterial stiffness correlates with an elevated risk of mortality [2, 11, 18].

In summary, age, smoking status, and clinical biomarkers (BMD and PWV) emerge as important factors associated with mortality in both cardiovascular and FN fracture outcomes.

The findings of this research underscore the critical role of vascular rigidity, quantified through PWV, in predicting overall mortality, surpassing the predictive value of bone strength as measured by BMD at the FN. PWV emerged as a robust predictor, with each 1 m/s increase linked to 17.27% higher likelihood of mortality. This finding aligns with previous evidence linking increased arterial stiffness to cardiovascular events, systemic inflammation, and mortality [19]. In contrast, while BMD demonstrated a protective effect—each 1 g/cm² increase reduced the odds of mortality by 99.87%—its predictive capacity appears secondary to that of arterial stiffness. This means that low, osteopenic, or osteoporotic bone, with each 1 g/cm² decrease in BMD, demonstrated a higher risk of mortality, highlighting the significant impact of bone density on health outcomes.

The observed interplay between arterial stiffness and bone strength may be mechanistically linked through calcium and phosphate metabolism [20]. Heightened oxidative imbalance plays a pivotal role in arterial mineral deposition, facilitating bone-like transformation and hardening of vascular cells in conditions like diabetes, atherosclerosis, and chronic kidney disease [21]. Additionally, oxidative stress-driven molecular cascades within vascular smooth muscle cells exacerbate arterial rigidity and disease progression [22]. Together with dysregulated bone remodeling and increased circulating calcium, oxidative stress contributes to the deposition of hydroxyapatite crystals in arterial walls, linking vascular calcification to both arterial stiffness and bone strength [20, 21, 22]. Bone remodeling, a natural process involving the resorption of aged bone and the deposition of newly synthesized bone matrix, becomes disrupted with aging and chronic diseases. Increased bone resorption can lead to a shift of calcium from bone into the bloodstream. Elevated circulating calcium levels contribute to vascular calcification, a hallmark of arterial stiffness [23]. This pathological process involves the deposition of hydroxyapatite crystals, typically found in bone, into the arterial walls, leading to loss of elasticity and increased vascular rigidity, heightened arterial stiffness, and a rise in PWV [24]. Advancing age leads to arterial stiffness, intimal thickening, and calcification, increasing cardiovascular risk. In postmenopausal women, declining estrogen exacerbates these changes by reducing its protective effects on endothelial function and inflammation. This accelerates vascular aging, promoting plaque development and calcification, highlighting the need for targeted strategies in this population [24].

Concurrently, bone weakening occurs due to reduced bone mineralization and structural deterioration. Factors such as declining estrogen levels in postmenopausal women, chronic inflammation, and oxidative stress exacerbate bone loss, further amplifying the mineral imbalance [23, 25]. The findings underscore that while both BMD and PWV are significant predictors, PWV emerges as a stronger and more independent marker of all-cause and cardiovascular mortality. Age reflects cumulative biological changes and exposure to risk factors, with a consistent, moderate effect on mortality risk. Its OR of 1.071 and narrower confidence interval, compared to BMD, suggests stability in its association with mortality. BMD has a stronger association, as indicated by the extreme OR, but its wider confidence interval makes its predictive value less precise, possibly due to sample size or measurement variability. PWV, a robust indicator of arterial stiffness and cardiovascular risk, shows a slightly stronger effect on mortality than age, but its overall predictiveness is less stable due to a higher P-value and wider CI. The results reveal that lower FN BMD is closely linked to a higher likelihood of fractures and mortality, reflecting the profound impact of skeletal fragility on patient outcomes [2, 26]. However, the predictive power of BMD, though statistically significant, is less precise, likely due to broader confidence intervals and a potential overlap with other variables, such as age [27].

After adjusting for age using residual-based matching, our findings indicate that loss of arterial elasticity, as measured by PWV, plays a more prominent role in predicting fatal events compared to bone health. The strong association between increased PWV and higher event risk emphasizes the importance of arterial stiffness in cardiovascular mortality. In contrast, BMD did not demonstrate a significant influence on the likelihood of fatal events, indicating that factors other than bone density might have a greater impact on mortality outcomes in this population. These results highlight the need to focus on arterial health, particularly in aging individuals, while considering that bone health may not be as critical a factor in fatal events when age is controlled.

In contrast, PWV, a direct indicator of vascular stiffness, demonstrates robust predictive power for both cardiovascular death and all-cause mortality [2, 27]. The results of Vlachopoulos et al. (2010) align with our findings [27]. They reported an increased risk for total cardiovascular events (RR: 2.26), CV mortality [relative risk (RR): 2.02], and all-cause mortality (RR: 1.90) in individuals with high PWV, with a 14-15% rise in the likelihood of adverse outcomes for every 1 m/s elevation in PWV. An RR > 1 indicates an increased risk of the outcome in the exposed group compared to the reference group. Similarly, our study found that each unit increase in regression residual of PWV was correlated with significantly higher odds of CV events (OR: 2.77, $p < 0.0001$). The OR of 2.77 (95% CI 1.70–4.51) indicates that higher PWV is significantly associated with increased odds of the outcome, with a 95% probability that the true effect lies within this range. Both studies confirm that elevated PWV is a significant determinant of cardiovascular outcomes, emphasizing its prognostic value [27].

Our findings closely align with Khoshdel et al. (2007), who reported that a one-level increment in arterial PWV correlated with a mortality RR of 2.41 with 95% CI ranging from 1.81 to 3.20 and a cardiovascular event RR of 1.69 (95% CI: 1.35–2.11). They also observed significant differences in PWV between survivors and non-survivors across populations with both low and high risk highlighting its utility in cardiovascular risk stratification [28]. The consistency between our results and those of Khoshdel et al. underscores the potential of PWV as a valuable tool for assessing systemic vascular health and guiding patient management.

The association remains consistent, with PWV showing an incremental risk increase per unit rise, independent of age and other confounders. Given the strong correlation between age and arterial stiffness, the higher reliability and specificity of PWV suggest that it captures the critical vascular contributions to aging-related mortality better than age alone [29].

Similar to the findings of Meaume et al. (2001), which identified aortic PWV as a robust and independent indicator of cardiovascular mortality in individuals aged over 70 years, our study highlights that PWV, with its higher reliability and specificity, better captures the critical vascular contributions to aging-related mortality than age alone [29].

This suggests that PWV provides a more precise measure of the vascular aging process, offering superior predictive value for cardiovascular outcomes. While bone fragility elevates the

likelihood of fractures and death, increased arterial stiffness, measured by PWV, silently reflects the long-term impact of vascular aging on cardiovascular health [2, 30, 31].

Our findings indicate that, while bone loss and cardiovascular conditions often coexist in the aging population [30], the precise cause-and-effect connection between vascular abnormalities and skeletal health remains uncertain. One possible explanation is that increased mobilization of calcium from bones undergoing osteoporotic changes leads to enhanced transfer and deposition onto vascular walls, creating calcifications in large blood vessels (e.g., the aorta) and thereby increasing their stiffness. Additionally, the dysregulation of bone remodeling during osteoporosis, defined by a disruption in the balance between bone resorption and formation, may contribute to altered calcium metabolism and vascular calcification. Further research is needed to elucidate these complex interactions and their clinical implications. Although associations between increased PWV and lower BMD were observed, these relationships appeared to diminish after accounting for confounding factors.

The interplay between vascular and bone health may be partly explained by shared processes such as bone turnover and vascular calcification, which together form a key pathway linking reduced BMD with increased arterial stiffness. During accelerated bone resorption, calcium and phosphate are released into the circulation, promoting deposition of calcium in the vascular wall and contributing to medial arterial calcification. This process reduces arterial elasticity and elevates PWV, reflecting a shared pathophysiological pathway between skeletal demineralization and vascular aging. Moreover, osteoporosis-related bone loss enhances circulating calcium-phosphate product levels, further accelerating vascular calcification and stiffening [10, 12]. Increased oxidative stress, disrupted calcium and phosphate homeostasis, and hyperglycemia can contribute to vascular calcification while impairing bone mineralization [32]. Additionally, inflammatory signaling molecules including interleukin-1β cytokine and necrosis-inducing factor increase the expression of a crucial osteoclast-activating ligand, contributing to bone loss and vascular calcification [33]. Furthermore, decreased estrogen levels, particularly in postmenopausal women, may contribute to both osteoporosis and arterial stiffness [34]. These shared pathways underscore the complex bidirectional relationship between vascular and bone health. This suggests that impaired vascular function might not be the main pathway connecting osteoporosis and cardiovascular disease. However, akin to the research conducted by Ruicong et al. (2024), which examined the intricate relationship linking vascular stiffness and bone health, aging is not merely a passage of time but a process marked by the interconnected decline of both bone and vascular systems, requiring further research to clarify these complex interactions [30].

Both stiff arteries and weak bones pose significant risks as we age, but their impact varies. Stiff arteries can lead to life-threatening cardiovascular events like heart attacks and strokes, while weak bones increase the risk of fractures, leading to disability and loss of independence. While both are silent threats, the immediate danger of arterial stiffness often outweighs the long-term complications of bone fragility, making cardiovascular health a critical focus in aging. This study highlights a significant inverse relationship between PWV and BMD, suggesting that greater arterial stiffness, reflected by higher PWV, is associated with lower BMD, thereby linking vascular aging with skeletal fragility. The inverse relationship observed between PWV and BMD further reflects this bidirectional interaction, where increasing arterial stiffness parallels declining bone density, underscoring a shared pathophysiological pathway between vascular and skeletal deterioration.

Conclusions

PWV reflects the cumulative effect of vascular aging, providing actionable insights for risk stratification and management of age-related conditions. Elevated PWV is a powerful indicator of cardiovascular risk, with each unit increase in its regression residual linked to a 2.77-fold higher likelihood of such events, underscoring its prognostic value. While BMD retains importance in predicting fracture outcomes, its predictive value is secondary to PWV, which offers a more direct marker for mortality risk. PWV demonstrates high sensitivity and good specificity in predicting all-cause mortality, outperforming FN BMD as a prognostic marker for mortality risk in this population.

The inverse relationship between PWV and BMD suggests shared pathophysiological pathways, underscoring the interconnected nature of vascular and skeletal health. These findings advocate for the integration of PWV measurement in clinical practice to complement osteoporosis management strategies, forming a holistic approach to mitigating risks associated with aging. Future research into the molecular mechanisms linking vascular calcification and bone resorption could further enhance our understanding and enable targeted therapeutic interventions.

Limitations of the study

One major limitation of this research is the limited cohort of 142 participants also the short follow-up duration of 36 months, during which only 8 fatal cardiovascular events and 6 FN fracture-related deaths were observed. These constraints may limit the generalizability and statistical power of the findings. Future research should include larger cohorts with follow-up periods exceeding five years to capture a higher number of fatal events, both cardiovascular and fracture-related, for more robust and comprehensive conclusions.

Author Contributions: *M. A.,* the lead physician, oversaw participant selection, study implementation, and medical history analysis. She identified pathophysiological links between bone health and arterial stiffness, supported findings with references, ensured data analysis aligned with results, and critically reviewed the manuscript for scientific rigor. She also conducted a comprehensive literature review and played a key role in the study's conception, data analysis, and discussion. *P. A.* contributed to data organization, statistical validation, and ensuring methodological accuracy. He assisted in refining the discussion by integrating relevant findings and enhancing the manuscript's clarity and coherence. *L. T.,* contributed by analyzing diagnostic imaging, interpreting data, and ensuring accurate result interpretation. She also managed data organization in Excel, enhancing the clarity and reliability of the findings. *B. T.* contributed by sourcing relevant literature, refining the discussion, enhancing tables, and improving language, spelling, and grammar. *K. S.* applied statistical methods, interpreted results, and provided key insights, ensuring a strong data-driven foundation for the study. *D. Z.,* an informatics and cloud expert, managed data collection, storage, and processing. He supervised statistical methods and contributed to result interpretation in the

discussion. All authors collaborated in writing, reviewing, and reaching a unanimous consensus on the final manuscript.

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Patient Informed Consent Statement: Written informed consent was obtained from all participants involved in the study, ensuring they understood the study's purpose, procedures, and their right to confidentiality.

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