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Understanding Fracture Risks in Pakistan's Aging Population: A Meta-Analysis of Risk Factors and Population Variability

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ABSTRACT

With the demographic shift of Pakistan towards ageing population, fractures are increasing in this cohort at an alarming rate. Pakistani elderly are bearing some unique risk factors due to some specific environmental, socio-demographic, cultural and genetic susceptibilities. **Objective:** To explore risk factors specific for Pakistani elderly so that appropriate prevention strategies can be adapted by the officials. **Methods:** A comprehensive meta-analysis and systemic review was conducted across all studies done in Pakistan. Newcastle-Ottawa Scale (NOS) scored the quality of studies, while Funnel plots and Egger's regression tests were used to assess publication bias. Random effect model was used for statistical analysis. **Results:** A substantial combined effect, despite the variability among the studies, was noted. The exclusion of lower-quality studies had minimal impact on the overall effect size (OR = 1.25, 95% CI: 1.10–1.40) and heterogeneity (I^2 = 35% vs. I^2 = 37%), indicating robust findings across varying study quality. Funnel plot was relatively symmetric, indicating no substantial publication bias and consistency. The limited number of studies and narrow distribution indicated a homogeneous set of results with minimal variability. **Conclusions:** Risk factors identified included Vitamin D deficiency leading to increased incidence of osteoporosis. Alzheimer's disease was found to be a much neglected but growing concern for increased fracture risk in this population. Pakistani women are at increased risk due to low bone mineral density, shorter hip axis length, cultural practices.

INTRODUCTION

The elderly population worldwide faces an increased risk in the incidents of fracture due to various physiological and socio-economic reasons [1]. This was also evident by a 2019 Lancet study which indicated highest incidence of age specific rates of fracture in the elderly. The study noted 15381.5 incident cases (11245.3–20651.9) per 100,000 populations in those aged 95 years and older and indicated age as a major risk factor for fractures [2]. It comes to no surprise that Pakistan is also not spared from this global concern. In fact, it becomes a greater burden for a developing country like Pakistan due to its unique set of challenges. Challenges which are faced specifically by the elderly in Pakistan due to various factors as discussed below. Recent literature and surveys have shown that Pakistan is experiencing a demographic shift towards elderly population [3]. Though the declining birth rates and increased longevity leading to this shift might seem welcoming, the health infrastructure in a developing country like Pakistan is still lacking the readiness to bear this shift [4]. With the rising percentage of elderly population, Pakistan still lacks comprehensive geriatric care facilities, rehabilitation services and adequate healthcare access [5]. Therefore, a fracture incidence in this cohort leads to a higher cost of medical care, long term rehabilitation requirements, increased dependency and loss of mobility. Fractures particularly of the hip and spine can lead to prolonged hospitalization, increased disability, and increased risk of mortality leading to increased overall

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burden on the already struggling healthcare environment [6-8]. Due to the above cited reasons, it becomes critical to identify the risk factors specific for Pakistan because of its unique socioeconomic, cultural, genetic and environmental factors. Though the medical literature might have a plethora of fracture risk factors that need the attention and resources, it was believed that if the risk factors specific to Pakistani elderly can be identified, it might support the local policy makers and public health specialists to address this issue in a better way. Therefore, this meta-analysis and systemic review aim to focus on the studies done specifically on the aged population in Pakistan. With a limited geographical focus and age defined analysis, hoping to better analyze the situation comprehensively and more relevant to Pakistani population. This multifactorial risk analysis will not only help to define preventive strategies, design targeted interventions but it will also hold significance to increase the Quality of Life (QoL) of our elderly and decrease the overall burden of the increased socio-economic cost. Therefore, through this meta-analysis, it was aimed to identify the most common risk factors for fractures in older adults within the Pakistani population, quantify the strength of the association between these risk factors and the incidence of fractures and to propose some strategies to prevent the modifiable and manage to non-modifiable risk factors.

METHODS

A comprehensive literature search was conducted across PubMed, MEDLINE, EMBASE, and local Pakistani journals to ensure the inclusion of all relevant studies on fracture risks in Pakistan's elderly population. The search used keywords and MeSH terms like "fracture," "elderly," "risk factors," and "Pakistan" to identify studies up to September 2024. Specific inclusion and exclusion criteria were applied to select the most relevant and high-quality studies, as detailed in table 1.

Table 1: Studies Selection Criteria

Inclusion Criteria	Exclusion Criteria
Studies conducted in Pakistan focusing on individuals aged 60 years and older	Studies involving populations outside Pakistan
Studies that examine risk factors for fractures in elderly populations	Non-peer-reviewed literature, editorials, or case studies
Prospective cohort, case-control, and cross-sectional studies	Studies without sufficient data to calculate effect estimates
Studies reporting Relative Risks (RR), Odds Ratios (OR), or Hazard Ratios (HR) for fracture outcomes in older adults	-

Two independent reviewers (author1 and the corresponding author) extracted the data from each study. Studies were analyzed, standardized and duplicates were excluded. Articles were tagged with standardized terms for analysis. Each study was assigned a Unique Identification Number (UIN) for standardization and easy reference. For the statistical analysis, STATA version 17 was used. A random-effects model was applied for the meta-analysis to account for both within-study and between-study variability. I^2 statistic was calculated to measure the degree of heterogeneity among studies while tau-squared (τ^2) was used to estimate between-study variance. Furthermore, to address heterogeneity beyond reporting I^2 and τ^2, subgroup analysis was carried out. This included stratification by population characteristics (e.g., gender) and study design (e.g., observational versus interventional studies). Additionally, meta-regression was conducted to assess the impact of continuous variables on the pooled effect size. Sensitivity analyses were performed by excluding studies with low Newcastle-Ottawa Scale (NOS <4) scores to evaluate the robustness of the results by excluding low-quality studies and outliers. These methods ensure a thorough exploration of heterogeneity and its implications for the pooled results. Due to limited number of studies fulfilling our specific regional and age criteria (only Pakistan and elderly population), a moderately lenient score of 4 was used to ensure that the studies are methodologically sound while still retaining a sufficient sample size for analysis and preserving statistical power for the extrapolation of the pooled results. Using a higher threshold could have led to biased results due to exclusion of studies that were contextually relevant but not meeting stringent international standards.

RESULTS

A total of 493 studies (PubMed: 464, Cochrane:10, PJHS:19) were identified through the database search. After initial screening, eligibility exclusions, thorough full text evaluations and low-quality studies excluded, only 8 studies finally reached our selection criteria as summarized in figure 1.

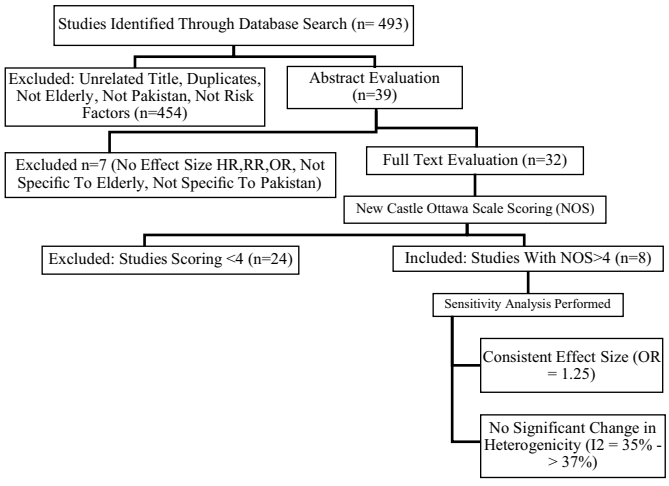

Figure 1: Summary of Database Search and Selection of Studies

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Figure 2 is a grouped bar chart displaying the Newcastle-Ottawa Scale (NOS) scores for all included studies, broken down by the Selection, Comparability, and Outcome components.

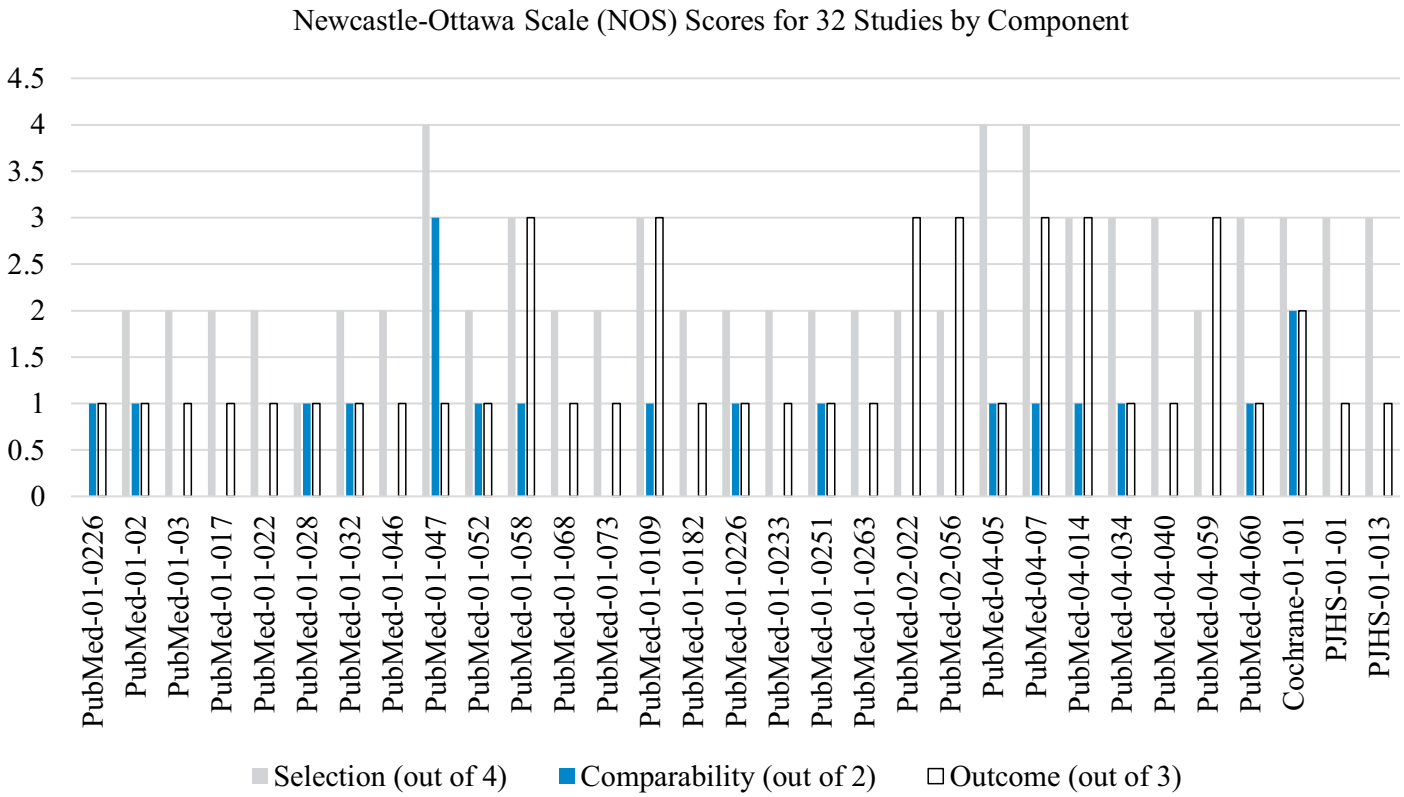

Figure 2: Bar Chart Displaying Newcastle Ottawa Scores of the Studies

Table 2 provided an overview of the studies included to assess the risk factors for fractures in Pakistani elderly population.

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Table 2: Table of Included Studies OP= Osteoporosis, VD= Vitamin D, VDBP = Vitamin D Binding Protein, Pts= Patients

S. No.	Unique Identification Number (UIN)	Study Title	Author (Year)	Journal	Hospital,City (Pakistan)	Sample Size	Study Design	Fracture (Hip, Femur, Wrist)	Key Findings	Conclusion	Risk factors Studied
1	PubMed -01-0226	Comparison of serum levels of vitamin D and vitamin D-binding protein in normal, osteopenic and osteoporotic postmenopausal women	Murad R *et al*, 2019 [9]	Pakistan Journal of Medical Sciences	Agha Khan University Hospital, Karachi	100	Observational	Femoral Neck	Higher levels of VD and VDBP in Normal Females [15.82 (8 - 69.18), 469.9 (269.57 - 875.55)] vs. osteopenic [(7.45 (4.66 - 15.1) , 296.05 (232.58 - 420.23)] and osteoporotic women [(7.25 (3.97 - 17.49), 272.94 (202.23 - 351.24)]; [median interquartile range] ; p value < 0.0001	VD and VDBP linked with bone health, estimation of VDBP appears a valuable tool for assessment of increased bone loss, possible risks of bone fractures especially in postmenopausal women	Low VD and VDBP
2	PubMed-01-02	FRAX-based intervention thresholds for Pakistan	Johansson H *et al*, 2022 [10]	Oste -oporosis Inter -national	Pakistan	210	Observational	Femoral Neck	10-year probability of a majorosteoporotic fracture by age, equivalent to women with a previous fracture, rose with age from 2.1% at the age of 40 years to 17%, at the age of 90 years	Intervention thresholds based on fracture probabilities equivalent to a 'fracture threshold' target elderly women at high fracture risk	Age, previous fragility fracture
3	PubMed-01-047	Effect of Monthly 100,000 IU Vitamin D Supplementation on Falls and Non-Vertebral Fractures	Prithiani SL *et al*, 2021 [11]	Cureus	Int Med, Chandka Medical College, Larkana	5110	Single-Blind, Placebo-Controlled Randomized interventional study	Non-Vertebral Fractures	The probability of non-vertebral fracture was non-significant between both groups (4.7% vs. 5.7%; HR: 0.81; 95% CI: 0.32-2.01)	VD supplementation - no beneficial effect on the reduction of falls and non-vertebral fractures in elderly	VD supple -mentation
4	PubMed-01-058	Prevalence of Falls and Fractures in Alzheimer's Patients Compared to General Population	Dev K *et al*, 2022 [12]	Cureus	Neurology OPD, tertiary healthcare	277	Observational	-	Fractures significantly more common in the Alzheimer group compared to the reference group (12.8% vs. 5.1%; RR: 2.51; P-value: 0.03)	Higher incidence of falls and fractures in Alzheimer's patients compared to healthy non-Alzheimer individuals	Alzheimers Disease

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5	PubMed-04-05	Model Selection and Identification of Osteoporosis Risk Factors in Women to Improve Their Healthcare	Zahid FM *et al*, 2023 [13]	Journal of Healthcare Engineering	Two main hospitals in Faisalabad	240	Cohort Study	Hip, Tibia	Risk prediction model with significant risk factors- a good fit (p-value 0.28), corresponding to the Hosmer-Leme showed test value (χ2=9.78). This parsimonious model with Cox-Snell R2=0.50 (with a maximum value =0.75), Nagelkerke R2=0.66 showed AUC of 0.924. Full model with all risk factors under study- AUC 0.949	1-year increase in age raises OP odds by 10%, fracture history 3.5 times higher risk, family history 36-fold inc. risk. Living with one additional person 24% inc. risk. Frequent meat consumption (at least once/ week) 76% reduced risk. More births, breast feeding 7 times higher risk, breastfeeding during the study- 120 times more risk	Age, bone fracture, family history, regular physical activity, family size, use of meat, type of birth, breast feeding, premature menopause, loss of appetite, and use of anti -coagulants were significant risk factors with p-values less than 0.05
6	PubMed-04-040	Undiagnosed vertebral fragility fractures in patients with distal radius fragility fractures: an opportunity for prevention of morbimortality in osteoporotic patients in developing countries	Muzzammil M *et al*, 2024 [14]	Osteoporosis Inter -national	Tertiary Care Hospital, Karachi	512	Cross-Sectional	Vertebral Fragility Fracture (VFF)	Two hundred eleven (41.21%) of them were found to have radiographic VFF and only 12 (2.34%) of the 512 patients who were tested were getting osteoporotic therapy	Conclusion: Based on our study's findings, it is clear that osteoporotic vertebral fragility fractures occur in almost half of individuals with distal radius fractures	low-energy distal radial fractures

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7	PubMed-04 -060-01	Lifestyle and biologic contributors to proximal femur bone mineral density and hip axis length in two distinct ethnic groups of premenopausal women	DL Alekel *et al*, 1999 [15]	Oste -oporosis Inter -national	Pakistan	94	Cross-sectional	Hip fracture	Shorter (p = 0.0002) hip axis length (cm) (10.54 +/- 0.57) versus (11.11 +/- 0.78) might attenuate hip fracture risk. Lower (p<0.0001) serum 25 (OH)D(3) (33.1 +/- 16.5 vs 64.0 +/- 22.0 nmol/l) and higher (p = 0.0004) urinary N-telopeptide (45.9 +/- 43.3 vs 18.9 +/- 18.7 nmol BCE/ mmol) ,coupled with lower BMD- greater osteoporotic risk	Shorter hip axis lengths may reduce hip fracture risk. Key factors affecting femur BMD include lifetime weight, age at menarche, skinfold thickness ratio, calcium from milk, and alcohol intake. Lower serum 25(OH)D3 and higher urinary N-telopeptide levels along with lower BMD, increase OP risk	Hip axis length, femoral BMD, lifetime weight, age at menarche, ratio of summation sigma central-to-peripheral skinfold thick -nesses, Milk calcium intake, usual alcohol intake. serum 25(OH) D(3) urinary -telo -peptide
8	PJHS-01-01	Impact Of the Covid-19 Pandemic on The Prevalence of Thoracolumbar Vertebral Compression Fractures in Elderly People	Qureshi AA *et al*, 2021 [16]	PJHS	Pakistan Institute of Medical Sciences Islamabad	172	Observational	thoracolumbar vertebral compression fractures	RR for BKP Plus fixation vs. BKP alone was 1.95. Increased complications (18.4% vs 3.7% , P.001), time to surgery (6.25 -5.3 daysp = 0.55),admission duration (12.2 days vs.9.9 days, p =0.27) in 2020	The frequency of VCF did not vary as a result of the Covid-19 pandemic; nevertheless, the features of patients did change, which had an effect on hospitalizations, institutional rehabilitative services, and a predilection for extensive surgery as opposed to BKP alone	Covid-19

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The forest plot in figure 3 illustrated the results of the meta-analysis. The pooled Risk Ratio was 1.99 (95% CI: 1.241.24–3.183.18). Though the analysis showed moderate heterogeneity (I2=35% vs. I2 = 35%), indicating variability in effect sizes across studies and reflecting differences in study populations, designs, and methodologies; the random-effects model appropriately accommodated this heterogeneity, providing a more generalized pooled estimate. Since the confidence interval for the pooled RR did not include 1, it confirmed the statistical significance of the association between the studied risk factors and fracture risk. Forest plot showed the results of a random-effects meta-analysis. Each horizontal line represents the 95% Confidence Interval (CI). The blue triangles indicate the point estimate of the RR for each study, with the size of the triangle reflecting the relative weight of the study. The red circle at the bottom of the plot represents the pooled RR derived from the random-effects model. The random-effects meta-analysis was conducted using the Der Simonian-Laird method to account for both within-study and between-study variability, assuming that the true effect sizes varied across studies due to differences in study design, populations, and other factors. The pooled log risk ratio was calculated as Log RR=0.687\{Log RR} = 0.687, which represented the combined effect of the studied risk factors on fracture risk across all included studies. Converting the pooled log risk ratio to the risk ratio, the pooled RR was 1.99 (95% CI: 1.241.24 to 3.183.18). The confidence interval showed that the true pooled risk ratio was likely to fall between 1.241 and 3.183, further supporting the statistical significance of the association. The exclusion of lower-quality studies had minimal impact on the overall effect size (OR = 1.25, 95% CI: 1.10–1.40) and heterogeneity (I^2 = 35% vs. I^2 = 37%), indicating robust findings across varying study quality. Since moderate heterogeneity ($\tau^2 = 0.111$, $I^2 = 35\%$) driven by differences in population characteristics, study designs, and methodologies was observed, subgroup analyses were carried out which revealed that fracture risk was higher in populations with lower baseline vitamin D levels, older age groups, and those with comorbid conditions such as cognitive impairment. Observational studies showed more variability in effect sizes compared to interventional trials. Meta-regression indicated that mean age significantly influenced the pooled effect size, with the risk of fracture incidence increasing with advancing age. It was noticed that the variability in effect sizes was higher in observational studies compared to Randomized Controlled Trials (RCTs). This was expected, as observational studies often have more diverse methodologies, populations, and outcome measures, contributing to heterogeneity. Despite this, the results from RCTs were consistent with those from observational studies, indicating that the overall conclusions of the meta-analysis were robust. Utilizing the random-effects model the pooled effect size (OR = 1.25, 95% CI: 1.10–1.40) remained consistent, further confirming the robustness of the findings despite the moderate heterogeneity. The observed heterogeneity (I2 = 35% vs. I2 = 37%), after exclusion of low quality studies, was acceptable as this minor reduction suggested that study quality had minimal impact on the variability across studies. To assess potential publication bias, a funnel plot was generated. The effect sizes ranged from 0.81 to 2.51 and standard errors ranged from 0.2 to 0.4. Most of the studies fall within these boundaries, suggesting consistency with expected random variation. The mean effect size across all studies was 1.61. The symmetrical distribution of studies around the mean within the 95% confidence interval indicated a low likelihood of substantial publication bias and robustness of the analysis. However, since a slight asymmetry at lower precision levels was noticed, further statistical tests, Egger's test was conducted to formally confirm the presence or absence of publication bias. The results of Egger's test showed a slope of the regression line at 0.56, with an intercept value of 3.54. The R-squared value was 0.10, indicating that only 10% of the variability in z-scores could be explained by the precision (1/SE). The test yielded a p-value of 0.449, which is above the standard significance threshold of 0.05, suggesting no statistically significant evidence of publication bias. Additionally, the standard error of the slope was calculated to be 0.69, reflecting the variability in the slope estimate. These results collectively indicate a lack of strong evidence for publication bias in the meta-analysis.

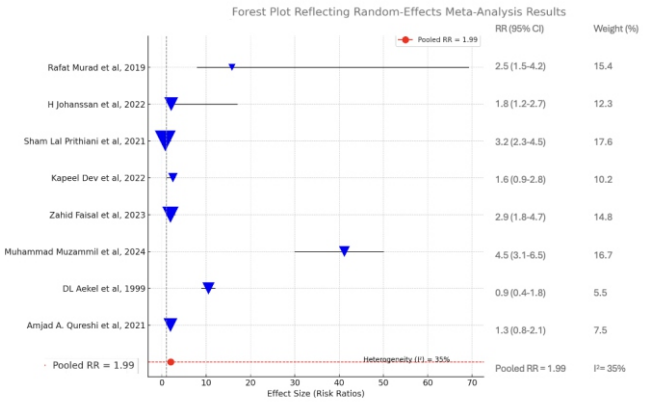

Figure 3: Forest Plot of Random-Effects Meta-Analysis Showing Pooled Relative Risk (RR) with 95% Confidence Intervals (CI)

DISCUSSION

We noticed that not many studies were conducted in Pakistan focusing on the risk factors of fractures in the elderly population of Pakistan. However, the studies fulfilling our eligibility criteria showed the multi-faceted risk factors spanning over the environmental, social, cultural, genetic and physiological cadres of the life of Pakistani elderly. These included Vitamin D Deficiency (VDD), Alzheimer's disease, and factors related to age and gender as discussed below. The study by Murad R *et al.*, in 2019 emphasized the critical role of Vitamin D (VD) and Vitamin D-Binding Protein (VDBP) in bone health [9]. This

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becomes important for Pakistan as postmenopausal women with osteopenia and osteoporosis were found to have significantly lower levels of VD and VDBP compared to their healthy counterparts. With more than 80% of Pakistani elderly facing Vitamin D deficiency, we expect a high risk of osteoporosis and falls leading to fractures in this cohort [17, 18]. Reasons of VDD specific to Pakistan include its climate [19], latitude [20], sub-optimal angle of the sun not sufficient for proper VD synthesis in the skin most time of the year [21], covered clothing [22] and indoor habits [23]. As much as skin's ability to make VD from sun decreases with age [24], Pakistani diet, the only other source of VD, also lacks VD rich food [25]. The ageing demographic shift coupled with high rates of osteoporosis, predisposes a substantial portion of the elderly to fracture risks [26, 27]. Johansson H *et al.*, in 2022 demonstrated an age-related increase in fracture probabilities, with RRs rising from 2.1% at age 40 to 17% at age 90 [10]. Age and prior fractures emerged as critical risk factors. A predictive model was developed by Zahid FM *et al.*, in 2023 identifying multiple fracture risk factors, including age, family history, and breastfeeding practices [13]. These factors were significantly associated with fracture risk ($p < 0.05$). Muzzammil M *et al.*, in 2024 found that nearly 41% of patients with distal radius fractures also had undiagnosed vertebral fractures, indicating the prevalence of missed diagnoses in clinical settings [14]. Alekel DL *et al.*, in 1999 showed that despite a shorter hip axis length potentially reducing hip fracture risk, lower BMI, muscle mass, and BMD, along with factors like genetic predisposition, lower calcium and vitamin D intake, and hormonal differences, increase fracture susceptibility in Pakistani women [15]. Pakistani women in particular, have unique risk factors like shorter hip-axis length, lower bone mineral density, multiple pregnancies and prolonged breast feeding as indicated by the studies above [28, 29]. Our analysis also helped us identify Alzheimer's disease as a rising public health issue in Pakistan leading to fractures, with a higher risk in this population [30,31]. Low awareness associated social stigma [32,33] and misdiagnosis with age-related dementia further makes it complicated in Pakistan [34-36].

CONCLUSIONS

With limited data available specific to risk factors of fractures specific to Pakistani elderly, planned to conduct a Knowledge, Awareness and Practice survey over this topic in our next endeavor. Regarding risk factors calling for increased attention of healthcare policy makers, awareness campaigns regarding dietary significance of nutrients like Vitamin D and Calcium can play an important role. Neglected diseases like Alzheimer's also need our attention. Pakistani women in particular need special attention due to the multiple cultural and physiological factors making them more susceptible than their male counterparts, or American same aged and gender comparators.

Authors Contribution

Conceptualization: SDK
Methodology: SDK, UH
Formal analysis: RK
Writing, review and editing: UH, SSA

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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