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Original Research Article

Risk of Benzodiazepine induced fractures in Elderly Using Cronbach's α-Coefficient

Praveen Khairkar[1], Andem Meghana Reddy[2], Edwin Luther[3], Vishwak Reddy[4], C Kamraj[5], Sumera Yasmeen[6], Pustakaala Dharneedhar[7], Ashwini Kamble[8*]

[1, 2, 4, 6, 7] Department of Psychiatry and Clinical Neurosciences,
[3]Department of Orthopedics, Kamineni Institute of Medical Sciences, Narketpally
[5]Department of Orthopedics, Kamineni Academy of Medical Sciences, Hyderabad, Telangana, INDIA
[8*]Department of Biochemistry, Kamineni Institute of Medical Sciences, Narketpally, Hyderabad, INDIA

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***Corresponding author: Dr Ashwini Kamble**
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Abstract

Objective: Our primary objective was for naturalistic evaluation of benzodiazepine use in elderly using Cronbach's alpha, odd's ratio and attributable risk of benzodiazepines for propensity of fractures. **Methods:** We used the naturalistic case-control qualitative as well as quantitative (mixed) study design and recruited 216 elderly patients above 60 years of either gender. We specifically included those who were prescribed with any benzodiazepines over last 6 months or more and we enquired if any of them had sustained a fracture of any nature or visited the emergency setting for any other medical purpose**. Results:** Out of 216 patients, only 31% patients had history of fractures who were using benzodiazepines. Fracture of femur neck (38%) was the most common site followed by tibia (17%), while the fracture of radius and humerus were least common 6% and 4% respectively. We observed the odd's ratio (1.117), Attributable risk (0.0239), Population Attributable risk (0.0206), Relative Risk (1.079), Cronbach's alpha (0.066) for propensity of risk of benzodiazepines induced fractures**. Conclusions:** We naturalistically evaluated the multiple risk ratios like odd's ratio to Cronbach's alpha and from sensitivity to specificity for association of benzodiazepines and bone fractures allowing the clinicians to have necessary vigilance.

Keywords: Attributable risk, Benzodiazepine, Fractures, Cronbach's alpha.

Introduction

People worldwide are now living longer than before as the relative percentage of elderlies to the demographic statistics is increasing each day. Fractures are common in elderly people, because of skeletal fragility resulting in significant morbidity and mortality[1]. Risk of falling increases with age and fall accounts for 90% of appendicular and hip fractures[2]. Around a third of people aged 65 or over probably fall at least once a year or so, but only 1% of falls in women result in hip fracture[3]. Many risk factors for hip fracture have been proposed or recognized apart from increasing age, factors like low body

weight, low intake of calcium and dairy products, age at menopause, osteoporosis, and a personal and family history of fractures, associated severe systemic complicated diseases, being handicap(s), and drugs like benzodiazepines or alcohol could also play a part[4].

In a recent analysis, 8.7% of US adults aged 65-80 years were prescribed benzodiazepines over the course of one year[5]. Benzodiazepines were prescribed to patients across diagnostic groups in elderly patients, with clonazepam being the most frequently prescribed followed by lorazepam[6]. A longitudinal observational trend of benzodiazepine uses in the UK showed that those aged between 60 and 70 years had 10%, 6%, and 7% rate of episodic, recurrent, and chronic use of benzodiazepines respectively[7]. Few studies[8] have documented the relationship of hip fracture with dosage of benzodiazepine rather than the half-life of the various formulations while others disputed the reliability or consistency in the contribution of benzodiazepines in causality of fractures in elderly. However, there is no meta-analysis conducted so far for pooled odd's ratio that benzodiazepines can contribute to fractures in elderly. Rather, the tangential meta-analyses by Max de Vries[9] and Seppala et al[10] who evaluated the association between risk of falling in elderly more than 60 years and their use of medications (cardiovascular medications and psychotropics). Using generic inverse variance method, pooling unadjusted and adjusted odd's ratios (OR), they qualitatively synthesized the data from 281 studies and their results showed (a pooled OR [95% confidence interval]): analgesics, 1.42 (0.91-2.23); nonsteroidal anti-inflammatory drugs (NSAIDs), 1.09 (0.96-1.23); opioids, 1.60 (1.35-1.91); anti-parkinson drugs, 1.54 (0.99-2.39); antiepileptics, 1.55 (1.25-1.92); and polypharmacy, 1.75 (1.27-2.41). The latter two classes probably embed benzodiazepine but without any certainties. Further another interesting meta-analysis[11] identified the rule of cognitive impairment in a risk of fall around older adults evaluating 27 studies over a period of 21 years (1988-2009). The authors identified the fixed effect using an inverse variance method and found that impairment on global measures of cognition was associated with any kind of fall but not necessarily restricted to hip fractures (summary estimates of OR [95% CI 1.56-2.90]). Pro-link between benzodiazepine uses and cognitive impairment in elderly is also well established by[12] in 5,423 participants with a mean follow up period of 4.78 years and they measured the cognitive decline using both Mini Mental Status Examination (MMSE) and Clinical Dementia Rating Sum of Boxes (CDR-SB) score and they further mentioned the poor cognitive performance in benzodiazepine users probably due to prodromal symptoms caused by pre-clinical dementia process. Thus, indirect association of benzodiazepine use in elderly, it's effect on their cognitive decline and likelihood of fracture without providing any reliable consistencies paves us the untouched opportunity to analyze in the present study for naturalistic evaluation of Cronbach's alpha, a most commonly used measure of internal consistency to determine if the reliability for association at acceptable level[13]. A coefficient alpha may be thought of as the mean of all possible split-half co-efficient corrected by the Spearman-Brown formula as follows.

The formula for coefficient alpha is

$$_{\alpha}= r_{\alpha}=\left(\frac{N}{N-1}\right)\left(1-\frac{\sum \sigma_i^2}{\sigma^2}\right)$$

Where r_{α} is coefficient alpha, N is the number of items, and σ^2 is the variants of the total test scores. As with all the reliability estimates, coefficient alpha can vary between 0 and 1.

In the present study our primary objective was for naturalistic evaluation of

benzodiazepine use in elderly using Cronbach's alpha, odd's ratio and attributable risk of benzodiazepines for propensity of fractures. Our secondary objective was to correlate the risk ratio of benzodiazepine fractures in elderly with clinical variables.

Methodology:

The sample Size Calculation

$$n = \frac{(1\text{-alpha}/2)^2\, p(1-p)}{d^2}$$

Wherein 1-alpha/2 = confidence interval
p = population proportion (12%)
d= margin of error (5%)

Thus, using above formula, the approximate minimal sample size was 168. The sensitivity, specificity, relative risk, positive predictive value, negative predictive value and Cronbach's α-coefficient were calculated.

We obtained the ethical institutional approval for this study in April 2019 (IEC/25/04/2019) and it was sent to ICMR research committee for their approval to further conduct the study. We used the naturalistic case-control qualitative as well as quantitative (mixed) study design and evaluated 216 elderly patients above 60 years of either gender from out-patient and in-patient settings of Department of Emergency Medicine, Orthopedics, Family Medicine and Geriatric Psychiatry from our institute for a period of 6 months. We specifically included those who were prescribed with any benzodiazepines over last 6 months or more and we enquired if any of them had sustained a fracture of any nature or visited the emergency setting for any other medical purpose. Patients were also asked for use and abuse of benzodiazepines and any temporal association of fractures with dose and timing of use of benzodiazepines. Further, we objectively screened for their past prescriptions after duly obtaining their consent. Clinical details about type and nature of fracture were noted from clinical records.

Statistical Analysis:

All the data were entered and evaluated in SPSS 23 version software. Descriptive statistics like chi-square test and frequency, percentage for the clinical variables were obtained. Specific categorical or continuous variables were evaluated using parametric or non-parametric tests. Cronbach's α-coefficient, Odds ratio and confidence interval for the risk of fractures secondary to use of benzodiazepines shall be obtained. A p value of significance shall be kept at 0.05 (2 tailed).

Results:

We screened a total of 216 elderly patients from department of Emergency Medicine and Orthopedics who fulfilled our inclusion and exclusion criteria. We noted that 40 among them were using benzodiazepines over the last 12 months but only 13 elderly patients sustained or had history of fractures while using them. We additionally screened 176 elderlies who were not using any sedatives/benzodiazepines just to identify if how many of them too have had bone fractures in last 12 months and to our observation, 53 of them sustained some or other fractures. Overall, most of our patients (53%) belonged to 60-65 years of age group, 21% patients were on benzodiazepine use and to our surprise, only 12% of patients were having greater than 75 years of age while 80% were not on benzodiazepine use. Details about their demographic and clinical parameters are illustrated in **Table 1.**

Overall, 19% patients had a history of benzodiazepine use while the remaining 81% patients had no history of benzodiazepine use. Most of our patients were on alprazolam (62%) followed by clonazepam (20%). Surprisingly, alprazolam is still prescribed at least 3 times more commonly than clonazepam and older chlordiazepoxide, a longer acting benzodiazepine is still being used at least

infrequently in elderly patients. Only 5% of patients were on high dose/dependence of benzodiazepines whereas 20% were on low dose, rests of them (70%) were on moderate/average dose while dose of drug used by 5% patients was unspecified. Interestingly, 10% of our patients were prescribed 2 or more benzodiazepines in past one week before fractures.

In our study, as further noted in Table 1, out of total 216 patients, only 31% patients had history of fractures whereas 69% patients had no history of fractures. Among those who had fractures, we observed that neck of femur (38%) was the most common site of fracture followed by fracture of tibia (17%), while the fracture of radius and humerus were least common (6% and 4% respectively). Among the type of fractures, the most common type was transverse fracture (21%) followed by non-displaced (17%) type. Spiral (1%) and Closed (4%) type of fractures was the least common. Most elderly people visited hospital for some, or the other surgical (37%) disorders followed up by orthopedic (22%) disorders and further followed by medical (15%) disorders. This reflects that orthopedic problem is the 2nd most common reason for their hospital visit. 60% are those patients who had no medical co-morbidities. However, 16% patients had two or more of the above co-morbidities and 12% patients had only Hypertension, 9% patients had only Diabetes mellitus.

Table 1: Socio-Demographic and Clinical Profile of Study Population

Variable	**Cases: With Benzodiazepine Use (n = 40)**		**Control: With Benzodiazepine Use (n = 176)**	
	Frequency	**Percentage**	**Frequency**	**Percentage**
Age				
60-65 yrs	24	60%	90	51%
66-70 yrs	7	18%	54	31%
71-15 yrs	4	10%	12	7%
>75 yrs	5	12%	20	11%
Gender				
Male	26	65%	114	65%
Female	14	35%	62	35%
Domicile				
Rural	27	68%	114	65%
Urban	13	32%	62	35%
Education				
Literate	14	35%	42	24%
Illiterate	26	65%	134	76%
Variable	**Patients with fractures (n = 66)**		**Patients without Fracture (n = 176)**	
	Frequency	Percentage	Frequency	Percentage
With Benzodiazepine Use				
	13	20%	27	18%
Without Benzodiazepine Use				
	53	80%	123	82%
Site	**Frequency**		**Percentage**	
Neck of Femur	25		38%	
Tibia	11		17%	
Shaft of Femur	4		6%	
Radius	4		6%	

Humerus	3	4%
Others	19	29%
Type of Fracture		
Transverse	14	21%
Non-displaced	11	17%
Comminuted	9	14%
Oblique	8	12%
Displaced	7	11%
Closed	3	4%
Spiral	1	1%
Others	13	19.70%

In our study, as further noted in Table 1, out of total 216 patients, only 31% patients had history of fractures whereas 69% patients had no history of fractures. Among those who had fractures, we observed that neck of femur (38%) was the most common site of fracture followed by fracture of tibia (17%), while the fracture of radius and humerus were least common (6% and 4% respectively). Among the type of fractures, the most common type was transverse fracture (21%) followed by non-displaced (17%) type. Spiral (1%) and Closed (4%) type of fractures was the least common. Most elderly people visited hospital for some, or the other surgical (37%) disorders followed up by orthopedic (22%) disorders and further followed by medical (15%) disorders. This reflects that orthopedic problem is the 2nd most common reason for their hospital visit. 60% are those patients who had no medical co-morbidities. However, 16% patients had two or more of the above co-morbidities and 12% patients had only Hypertension, 9% patients had only Diabetes mellitus.

Table 2: Table showing Odd's Ratio, Attributable Risk, Population Attributable Risk, Relative Risk, Sensitivity, Specificity, Cronbach's alpha of Benzodiazepine Use

Odd's Ratio	1.117
Attributable Risk	0.0239
Population Attributable Risk	0.0206
Relative Risk	1.079
Sensitivity	0.197
Specificity	0.82
Cronbach's alpha	0.066

In our sample, we found odd's ratio (1.117), Attributable risk (0.0239), Population Attributable risk (0.0206), Relative Risk (1.079), Cronbach's alpha (0.066) as illustrated in **Table 2 and Fig 1.** This signifies that benzodiazepine use results in a mild increase in risk of fracture in elderly. Use of benzodiazepines was found to be positively associated with both age of patient and site of fractures (Inter-Item Covariance Matrix) as illustrated in **Table 3.**

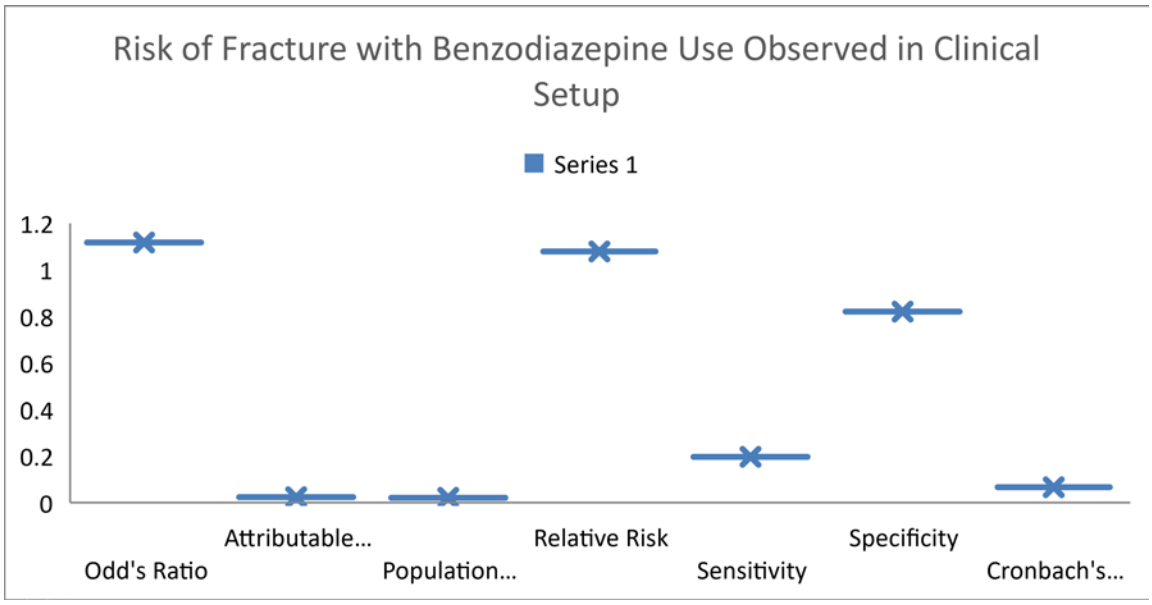

Fig 1: Graphical (Whisker plot) illustration of Odd's Ratio, Attributable Risk, Population Attributable Risk, Relative Risk, Sensitivity, Specificity, Cronbach's alpha of Benzodiazepine Use via Bar Chart.

Table 3: Inter-Item Covariance Matrix of Age of Patient, Site of Fracture and Benzodiazepine Drug Used by Patient

Inter-Item Covariance Matrix	Age of Patient	History of Benzodiazepine Use	History of Fracture
Age of Patient	1.02	0.005	-0.045
History of Benzodiazepine Use	0.005	0.152	0.004
History of Fracture	-0.045	0.004	0.213

Table 4: ANOVA with Friedman's Test

	Sum of Squares	df	Mean Square	Friedman's Chi-Square	Sig
Between People	94.068	215	0.438	3.455	0.178
Within People Between Items	1.642a	2	0.821		
Residual	203.691	430	0.474		
Total	205.333	432	0.475		
Total	299.401	647	0.463		

Grand Mean = 1.7623
Kendall's Coefficient of concordance W = 0.05
We further conducted ANOVA with Friedman's Chi Square test and found the association of Benzodiazepine with fracture with twice likelihood (Friedman's chi square 3.455). However, the significance of value remains questionable.

Table 5: Pearson's Correlation (r) of Fractures in Elderly with History of Benzodiazepine use

		History of Fracture	History of Benzodiazepine Use
History of Fracture	Pearson Correlation	1	0.02
	Sig. (2-tailed)		0.769
	N	216	216
History of Benzodiazepine Use	Pearson Correlation	0.02	1
	Sig. (2-tailed)	0.769	
	N	216	216

We further conducted ANOVA with Friedman's Chi Square test and found the association of Benzodiazepine with fracture with twice likelihood (Friedman's chi square 3.455) as seen in **Table 4**. However, the significance of value remains questionable. Since our sample has normal and parametric distribution, we evaluated correlation Pearson's moment coefficient (r) for identifying the strength of association as shown in **Table 5.** We found that a small degree of positive association (r=0.020, P=0.769) without clear significance as far as relationship with use of Benzodiazepines and fractures are concerned.

Table 6: Cohort Studies related to risk of fractures in elderly

Title of the Project	**Authors**	**Country**	**Year**	**Sample size**	**Findings**
1.Risk factors for hip fracture in white women [18]	Cummings SR, Nevitt MC, Browner WS, Stone K, Fox KM, Ensrud KE, et al.	Portland, Oregon; Minneapolis; Baltimore; and the Monongahela Valley, Pennsylvania,	1995 Mar	(n=9516) Hip fractures=192	Incidence of hip fracture ranged from 1.1 (95 percent confidence interval, 0.5 to 1.6) per 1,000 woman-years among women with no more than two risk factors and normal calcaneal bone density for their age to 27 (95 percent confidence interval, 20 to 34) per 1,000 woman-years among those with five or more risk factors and bone density in the lowest third for their age
2. Cognitive	Guo Z,	Sweden	1998	(n=1,608)	

impairment, drug use, and the risk of hip fracture in persons over 75 years old: a community-based prospective study [19]	Wills P, Viitanen M, Fastbom J, Winblad B		Nov	Hip fractures=134	
3. Central nervous system active medications and risk for fractures in older women [20]	Ensrud KE, Blackwell T, Mangione CM, Bowman PJ, Bauer DC, Schwartz A, et al	United States	2003 Apr	(n= 8127) Fracture=1256	No independent associations between benzodiazepine use or anticonvulsant use and risk for non-spine fracture -Narcotics (multivariate hazard ratio [HR], 1.40; 95% confidence interval [CI], 1.06-1.83) - Antidepressants (multivariate HR, 1.25; 95% CI, 0.99-1.58)
4.Benzodiazepine use and hip fractures in the elderly: who is at greatest risk? [21]	Wagner AK, Zhang F, Soumerai SB, Walker AM, Gurwitz JH, Glynn RJ, et al.	New Jersey	2004 July	(n=1,25,203) Eligible hip fractures=2312	-Incidence rate ratio [IRR]= 1.24; 95% confidence interval [CI], 1.06-1.44) -Short half-life, high-potency benzodiazepine (IRR, 1.27; 95% CI, 1.01-1.59) - during the first 2 weeks after starting a benzodiazepine (IRR, 2.05; 95% CI, 1.28-3.28 - during the second 2 weeks after starting a benzodiazepine (IRR, 1.88; 95%

					CI, 1.15-3.07) - for continued use (IRR, 1.18; 95% CI, 1.03-1.35)
5. Trends of benzodiazepine prescribing and the risk of hip fracture in elderly patients in Taiwan: A population-based study [22]	Chan ALF, Lin SJ	Taiwan	2010 Mar	N=62,023	Adjusted OR in the four years studied: 1.57, 1.38, 1.68, 1.45
6. Older adults' medication use 6 months before and after hip fracture: A population-based cohort study [23]	Kragh A, Elmståhl S, Atroshi I	Sweden	2011 May	n=2,043 (hip fractures) 1308=participant with drug exposure	Polypharmacy (≥5 drugs) increased 39.3%, excessive polypharmacy (≥10 drugs) increased 36.4%, and use of three or more psychotropic drugs increased 8.6%. After fracture, the use of all analyzed drugs including psychotropic, cardiovascular, opioid, and anticholinergic drugs increased significantly (P<.001)
7. Risk of fractures requiring hospitalization after an initial prescription for zolpidem, alprazolam, lorazepam, or diazepam in older adults [24]	Finkle WD, Der JS, Greenland S, Adams JL, Ridgeway G, Blaschke T, et al	United States	2011 Oct	Zolpidem (n = 43,343), Alprazolam (n = 103,790), Lorazepam (n = 150,858), Diazepam (n = 93,618).	(Rate ratios) (RRs) -Zolpidem= 2.55 (95% confidence interval (CI) = 1.78-3.65; P < .001) -Alprazolam= 1.14 (95% CI = 0.80-1.64; P = .42) -Lorazepam= 1.53 (95% CI = 1.23-1.91; P < .001) -Diazepam= 1.53 (95% CI = 1.23-1.91; P < .001)

					(Ratio of RRs) (RRR) - zolpidem relative to alprazolam= 2.23 (95% CI = 1.36-3.66; P = .006) -zolpidem relative to lorazepam= 1.68 (95% CI = 1.12-2.53; P = .02 -zolpidem relative to diazepam= 1.29 (95% CI = 0.72-2.30; P = .32)
8. Risk of hip fracture among older people using anxiolytic and hypnotic drugs: a nationwide prospective cohort study [25]	Bakken MS, Engeland A, Engesaeter LB, Ranhoff AH, Hunskaar S, Ruths S	Norway	2014 July	(n=906,422) Eligible hip fractures= 39,938	-Short-acting benzodiazepine anxiolytics (SIR 1.5, 95% CI 1.4-1.6) - Benzodiazepine-like hypnotics (z-hypnotics) @Night (SIR 1.3, 95% CI 1.2-1.4) @Day (SIR 1.1, 95% CI 1.1-1.2) - hypnotics (SIR 1.2, 95% CI 1.1-1.2) - anxiolytics (SIR 1.4, 95% CI 1.4-1.5)
9. Is use of fall risk- increasing drugs in an elderly population associated with an increased risk of hip fracture, after adjustment for multimorbidity level: a cohort study [26]	Thorell K, Ranstad K, Midlov P, Borgquist L, Halling A	Sweden	2014 Dec	(N = 38,407) had a hip fracture	-opioids (OR 1.56, 95% CI 1.34-1.82), -dopaminergic agents (OR 1.78, 95% CI 1.24-2.55), -anxiolytics (OR 1.31, 95% CI 1.11-1.54), -antidepressants (OR 1.66, 95% CI 1.42-1.95) - hypnotics/sedatives (OR 1.31, 95%

					CI 1.13-1.52)

Table 7: Case-Control studies related to risk of fractures in elderly

Title of the Project	Authors	Country	Year	Sample size	Findings
1. Benzodiazepines of long and short elimination half-life and the risk of hip fracture [27]	Ray WA, Griffin MR, Downey W	Canada	1989 Dec	Controls= 24,041 Cases=4501	Long half-life= RR=1.7(95% CI,1.5-2.0) Short half-life=RR=1.1(95%CI, 0.9-1.3)
2.Benzodiazepines and hip fractures in elderly people: case-control study [28]	Pierfitte C, Macouillard G, Thicoipe M, Chaslerie A, Pehourcq F, Aissou M, et al	Bordeaux, France	2001 Mar	Controls=817 Cases=245	OR=0.9, 95% CI 0.5-1.5 (Lorazepam) OR=1.8, 95% CI 1.1-3.1
3.Zolpidem use and hip fractures in older people [29]	Wang PS, Bohn RL, Glynn RJ, Mogun H, Avorn J	New Jersey	2001 Dec	Controls=4888 Cases=1222	Zolpidem (AOR=1.95; 95%CI 1.09-3.51) Benzodiazepines (AOR 1.46; 95% CI=1.21-1.76) Antipsychotic medications (AOR 1.61; 95% CI=1.29-2.01), Antidepressants (AOR 1.46; 95% CI=1.22-1.75)
4. Medication use and risk of falls [30]	Neutel CI, Perry S, Maxwell C	Canada	2002 Mar	N=227 (Case-crossover study)	OR=1.8 OR=11.4(new BZD)
5. Population-based study of the effectiveness of bone-specific drugs in reducing the risk of osteoporotic fracture [31]	Perreault S, Dragomir A, Blais L, Moride Y, Rossignol M, Ste-Marie LG, et al	Quebec, Canada	2008 Mar	Cases=3170 Controls=31700	Risk of fall or use of benzodiazepines, antidepressants, or narcotics increased the fracture risk by 23-77%
6.Benzodiazepine and risk of hip	Chang CM, Wu	Taiwan	2008	Controls= 1214 Cases=217	AOR = 1.7, 95% CI = 1.2-2.5.

fractures in older people: A nested case-control study in Taiwan [32]	ECH, Chang IS, Lin KM.		Aug		high during the first month (AOR = 5.6, 95% CI = 2.7-11.8) of exposure, doses higher than 3.0 mg/day in diazepam equivalents (AOR = 1.8, 95% CI = 1.1-3.1), and using short-acting benzodiazepines (AOR = 1.8, 95% CI = 1.3-2.7)
7. Risk factors for falls with severe fracture in elderly people living in a middle-income country: a case control study [33]	Coutinho ES, Fletcher A, Bloch KV, Rodrigues LC	Rio de Janerio, Brazil	2008 Aug	Control= 250 (44) Cases= 250 (19)	OR = 2.56, 95% CI=1.44-4.57; P value=<0.01
8.Fracture risk from psychotropic medications: a population-based analysis [34]	Bolton JM, Metge C, Lix L, Prior H, Sareen J, Leslie WD.	Canada	2008 Aug	Controls= 47,289 Cases=15,792	OR = 1.10; 95% CI, 1.04-1.16
9.Relationship between the Risk of Falling and Drugs in an Academic Hospital [35]	Tanaka M, Suemaru K, Ikegawa Y, Tabuchi N, Araki H	Japan	2008 Sep	N=4084 Falls=65	Hypnotics (OR 2.12; 95% CI, 1.25 to 3.52), Anxiolytic (OR 3.35; 95% CI, 1.83 to 5.82)
10. Risk for fractures with centrally acting muscle relaxants: an analysis of a national Medicare Advantage claims database [36]	Golden AG, Ma Q, Nair V, Florez HJ, Roos BA	United States	2010 Sep	Controls=8164 Cases=8164	Long-acting benzodiazepines= 1.9 (95% CI 1.49 to 2.43; $p < 0.001$), Short-acting benzodiazepines= 1.33 (95% CI 1.15 to 1.55; $p < 0.001$)
11. Impact of drug interactions, dosage, and duration of therapy on the	Zint K, Haefeli WE, Glynn RJ, Mogun H, Avorn	Pennsylvania	2010 Dec	Controls=85,990 Cases= 17,198	RR=1.2 (95%CI 1.1,1.2) Alprazolam=1.5 (1.3, 1.7), Lorazepam=1.9

risk of hip fracture associated with benzodiazepine use in older adults [37]	J, Stürmer T.				(1.7, 2.2) Zolpidem= 1.7 (1.4, 2.0) Interacting drugs were 2.1 (1.5, 2.8) Daily BDZ doses >1 [RR: 1.3 (1.2, 1.5)]
12. Zolpidem use and risk of fracture in elderly insomnia patients [38]	Kang DY, Park S, Rhee CW, Kim YJ, Choi NK, Lee J, et al	South Korea	2012 July	Cases=1508 (Case-crossover study)	(Zolpidem)adjusted odds ratio [aOR], 1.72; 95% CI, 1.37 to 2.16 (Benzodiazepine hypnotics) aOR, 1.00; 95% CI, 0.83 to 1.21
13.Potential Impact of Benzodiazepine Use on the Rate of Hip Fractures in Five Large European Countries and the United States [39]	Khong TP, de Vries F, Goldenberg J, Klungel O, Robinson N, Ibanez L, et al	Netherlands	2012		PAR=1.8 %, 95 % CI 1.1–2.6 (Germany); 2.0 %, 95 % CI 1.2–2.8 (United Kingdom); 5.2 %, 95 % CI 3.2–7.3 (Italy); 7.4 %, 95 % CI 4.5–10.0 (France); 8.0 %, 95 % CI 4.9–11.0 (United States); and 8.2 %, 95 % CI 5.1–12.0 (Spain).
14. Nonbenzodiazepine sleep medication use and hip fractures in nursing home residents [40]	Berry SD, Lee Y, Cai S, Dore DD	United States	2013 May	Cases=15,528 (Case-crossover study)	Non-benzodiazepine hypnotic drug (OR, 1.66; 95% CI, 1.45-1.90) - in new users (OR, 2.20; 95% CI, 1.76-2.74) - in residents with mild vs moderate to severe impairment in cognition (OR, 1.86 vs 1.43; P = .06) - with moderate vs total or severe functional impairment (OR,

					1.71 vs 1.16; P = .11) - with limited vs full assistance required with transfers (OR, 2.02 vs 1.43; P = .02) - in a facility with fewer Medicaid beds (OR, 1.90 vs 1.46; P = .05)
15. Association between use of benzodiazepines and risk of fractures: A meta-analysis [41]	Xing D, Ma XL, Ma JX, Wang J, Yang Y, Chen Y	China	2014	Meta-analysis (25 studies, including 19 case-control studies and 6 cohort studies)	RR = 1.25; 95% CI, 1.17-1.34; p < 0.001).
16. Benzodiazepines, Z-drugs and the risk of hip fracture: A systematic review and meta-analysis [42]	Donnelly K, Bracchi R, Hewitt J, Routledge PA, Carter B	United Kingdom	2017 Apr 27	Control=150 Cases=66	RR = 1.52, 95% CI 1.37-1.68; and RR = 1.90, 95% CI 1.68-2.13(BZD and Z-drugs resp.) (Short Term use)-RR = 2.40, 95% CI 1.88-3.05 and RR = 2.39, 95% CI 1.74-3.29(BZD and Z-drugs resp.)
17. Naturalistic Evaluation of Benzodiazepine Concurrent Use in Elderly for Cronbach's α-coefficient, Odd's Ratio and Attributable Risk of Fractures- A Pilot Study	Praveen Khairkar, Meghana Reddy A Edwin M Luther,	India	2019 Oct		OR=1.117, AR=0.0239, PAR=2.06% RR=1.079 Sensitivity=0.197 Specificity=0.82 Cronbach's alpha= 0.083

Discussion:

Unfortunately, poor quality of life in elderly population incurs huge burden on family and health care system and getting fractures serves a common reason for early mortality among them. Indeed, falls account for 87% of all fractures among people aged 65 years or older and it is accepted as a serious consequence and important public health issue[14]. The very first study linking the association of use of benzodiazepine with hip fractures was documented by Ray WA et al in 1989[15] by evaluating 4,501 cases and 24,041

controls. Their emphasis was more on comparison of short and long elimination half-lives of benzodiazepines and contrary to our understanding, RR with long half-life was observed to be 1.7 (95% CI, 1.5-2.0) whereas for short acting benzodiazepine, the RR was only 1.1 (95% CI, 0.9-1.3). From thereon, not many studies are conducted as noted by PubMed Advanced search (dated 28/01/2021), only 97 articles/abstracts related to term risk of fractures in elderly using benzodiazepine(s). Noteworthy among them was a study conducted by Khong TP et al in 2012[16] in 5 large European countries and United States who evaluated the potential impact of use of benzodiazepines on the rate of hip fractures and they observed the Population Attributable Risk (PAR) varying from as low as 1.8% in Germany to as high as 8.2% from Spain. Further Donnelly K et al[17] conducted a systemic review and meta-analysis in 2017 for comparative attribution of not only benzodiazepines but also Z-drugs commonly prescribed as safer alternatives to benzodiazepines and found that short term use of benzodiazepines has Relative Risk(RR) of 2.40 (95% CI 1.88-3.05) and Z-drugs has 2.39 (95% CI 1.74-3.29) reflecting that specific sub-group of benzodiazepines or even the safer heavens of non-benzodiazepines like Z-drugs are linked with at least twice the risk for occurrence of fractures and to our surprise, there is no such data published from India as yet. To our knowledge, the question of naturalistic evaluations and Sensitivity, Specificity and reliability of various Attributable or Relative Risk for the association of Benzodiazepines and fractures on clinical setting remained the gap which the present study intends to bridge. We in our naturalistic south Indian population found the following important statistical figures: Odd's Ratio (1.117), Attributable Risk (0.0239), Population Attributable Risk (0.0206), Relative Risk (1.079). We also identified Sensitivity and Specificity 0.197 and 0.82 respectively. None of the studies have tried to see correlation from Cronbach's alpha perspective using covariance matrix. We observed 0.083 value of Cronbach's alpha. Use of benzodiazepine is positively associated with site of fracture and not significantly associated with age in elderly fractures. (P-value=0.178). In evaluating this Cronbach's alpha, we would like to emphasize here that Cronbach's alpha is an index of the degree to which we estimate the reliability of a single factor. Therefore, Item sampling and other heterogenous tests serves as source of error variance and impacts invariably to value of Cronbach's coefficient of alpha by choosing to optimize the group of elderlies and the homogenous sample, our study has modest degree of internal consistency and this index of Cronbach's alpha distinctly help us to achieve the later. Comparative illustration of different studies is shown in table 6 and 7

Limitations:

In the present study, one should be cautious to interpret our population attributable risk and specifically the Cronbach's alpha because confounding factors like patient's BMI, bone density and the presence of additional drugs or dietary factors affecting the osteoporosis can also influence to the fractures risk in elderly. Secondly, being a cross-sectional study and that too being restricted to the hospital, we cannot actually reflect the true figures which we have seen using Covariance matrix and additional evaluation of large community samples and the prospective study design in future might take care of the responders' bias.

Conclusion:

There is substantial evidence within the literature showing that risk impact of benzodiazepine induced fracture is widespread within the orthopedic domain and therefore the relevance of addressing the clinical issue is incumbent upon all the orthopedic community who prescribe the

benzodiazepines. The present study has fair degree of accuracy in evaluating the multiple risk ratios arising from odd's ratio to Cronbach's alpha and from sensitivity and specificity for association of benzodiazepines and bone fractures allowing the clinicians in South Indian regions to have necessary vigilance. Finally, we conclude that this data would certainly add up for improving the validly used algorithms in health care systems and strengthening the later could help achieve predictable outcomes and to set the threshold for standard practice of restriction like the developed countries for benzodiazepines in elderly.

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Informed consent

Informed consent was obtained from all individual participants included in the study.

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