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Femoral hip osteoporotic fracture risk in Jordanian cohort and their relationships with hypertension and antihypertensive drugs

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Abstract

Background: Osteoporosis and hypertension (HTN) are frequent and often coexisting diseases among the elderly. Recent studies suggested that both diseases may share the same etiopathology. Moreover, the treatment of hypertension can either positively or negatively affect the bone mineral density (BMD) and consequently, either improving or worsening the patients' osteoporosis statuses, respectively.

Aim: The primary aim of this study is to determine the odd ratios, pearson and spearman correlations, and the distribution rates of the HTN statuses and their corresponding anti-HTN medications, in addition to other investigated comparative variables, across two categorized cohorts; the lower risk of femoral hip osteoporotic fracture (fHOPF) cohort [Cohort I] versus the higher fHOPF cohort [Cohort II], in Jordanian cohort.

Methods: The investigated studied participants were either allocated to non-HTN versus HTN cohorts (Cohort I vs Cohort II, respectively). Also, the anti-HTN medications were categorized into 6 major medication's group; Group I-VI. Both aforementioned categorized 2 patients' cohorts and 6 medications' groups were analyzed via chi square test to express the comparison results as distribution rates strength of associations (odd ratios), Pearson chi-square statistic (χ 2), Goodness of Fit (G-Test of independence), and Pearson (r) and Spearman (ρ) correlations. Patients who were on thiazide or thiazide like diuretics with ACEIs or ARBs had the lowest incidence rate of higher risk of fHOPF (50%), followed by patients who were on BBs with thiazide or thiazide like diuretics (66.7%), CCBs with thiazide or thiazide like diuretics (85%), CCBs with ACEIs or ARBs (85.7%), and lastly for patients who took CCBs with or without BBS (100%) [R & ρ [-0.390±0.081 &-0.362±0.068], χ 2 & G-Test [18.685 & 18.805], p-Value [0.002 &0.002]].

Results: Overall, 206 participants who were clinically diagnosed for osteoporotic fracture risk at our rehabilitation and rheumatology clinic between Sep 2021 and Nov 2021, were studied to investigate the differences of the various investigated independent variables across the 2 dichotomized HTN related cohorts; Cohort I-II. In this study, 49.03% (101 of the eligible patients) were allocated to the non-HTN affected cohort (Cohort I) and 50.97% (101 of the overall participants) were comparatively allocated to the HTN affected cohort (Cohort II).

Conclusion: The thiazide or thiazide like diuretics and ACEIs or ARBs, alone or in combination, may positively improve the femoral hip bone mineral densities and consequently mitigate the risk of osteoporotic fractures.

Keywords: Osteoporotic fracture; Hypertension; Antihypertensive drugs; Jordanian cohort

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1. Introduction

Hypertension affected patients, especially when accompanied with chronic kidney diseases, (CKD) are often have a higher probability of bone architectural distortion and consequently a higher likely of osteoporotic fracture. Indeed, the exaggerated rate of ageing related dual hypertension and osteoporosis cases are substantially elevated year by year in our society [1-3] .

Differently to CKD associated secondary hyperparathyroidism which is related to the excess phosphorus retention, hypertension associated secondary hyperthyroidism is primarily related to urinary calcium hypersecretion status. In both aforementioned mechanistic scenarios, a substantially quantity of calcium is released from bone, which may lower bone mineral density and subsequently the osteoporotic fracture risks. However, excess phosphate retention with/without excess calcium excretion, can increase FGF23 expression and consequently lower 1-α-hydroxylation of the endogenously circulated cholecalciferol or 25-OH-cholecalciferol. Both hypertension and chronic kidney diseases are known independent risk factors for osteoporosis complications [4-8].

Physiologically, bone resorption and deposition dynamic remodeling processes are closely regulated by various cytokines and hormones secretions which are demonstrated to be indirectly involved in the osteoporosis pathophysiology. For example, The Angiotensin II (AT II) in the renin-angiotensin system (RAS), is significantly induced the expression of RANKL (receptor activator of NF-κB ligand) in osteoblasts cells which accordingly leading to the activation of osteoclasts. It is known that the AT II receptors are substantially expressed in both osteoclast and osteoblast cultures, and AT II ultimately activates osteoclast cells which are the primary responsible for bone resorption. [9-12]

Recent clinical studies suggest that several antihypertensive drugs, particularly the angiotensin-converting enzyme inhibitors (ACEIs), AT II receptor blockers (ARBs), and the thiazide diuretics, are positively correlated with the BMDs. Blockage AT II at AT II receptors via either ACEIs or ARBs may mitigate the bone resorption rate at osteoclast culture level. Additionally, the researchers also propose that thiazide and thiazide like diuretics, such as hydrochlorothiazide and chlorthalidone, respectively, may shift the calcium balance into the positive direction, owing to its significant calcium reabsorption tendency, which may indirectly lower the osteoclasts related calcium resorption rate. The use of the aforementioned anti-HTN medications, either individually or in combination with each other, could have promising results in mitigation the ageing associated dual HTN and osteoporosis statuses. [13-17]

In this study, we primarily aimed to investigate the major differences across the 2 comparative tested cohorts; non-HTN affected cohort (Cohort I) and HTN affected cohort (Cohort II) regarding various multi-dimensional issues. Also, we aimed in this study to explore the differences of distributional rates of both the femoral hip bone mineral density (fH_BMD) and the femoral hip osteoporotic fracture (fHOPF) risk across the 6 selected anti-HTN medications' groups; calcium channel blockers (CCBs) [Group I], CCBs with beta-blockers (BBs) [Group II], CCBs with ACEIs or ARBs [Group III], CCBs with thiazide or thiazide like diuretics [Group IV], BBs with ACEIs or ARBs [Group V], and ACEIs or ARBs with thiazide or thiazide like diuretics. [Group VI].

2. Material and methods

This observational retrospective study was conducted for 206 participants who were clinically diagnosed for osteoporotic fracture risk at our rehabilitation and rheumatology clinic between Sep 2021 and Nov 2021 at Prince Rashid bin Al-Hasan Military Hospital, Royal Medical Services, Irbid, Jordan. Subjects who were previously diagnosed with chronic kidney disease [calculated glomerular filtration rate (GFR) <30 mL/ min/1.73m2), based on cockcroft equation], chronic liver disease [child-pugh score is B or C grade], inherited/metabolic bone disease [e.g., hyperparathyroidism/hypoparathyroidism, osteomalacia, pagets disease, osteogenesis imperfecta], or took anti-resorptive therapy [e.g., bisphosphonate, calcitonin, strontium ranelate, and teriparatide] were excluded from this study.

Hypertension (HTN) affected participant was defined for whose blood pressure ≥130/85mmHg or the participant is actively on anti-hypertensive medication. Information that was collected at the attended clinic, by a questionnaire, included age, actual body weight (ABW), height (Ht), HTN status or anti-HTN medication(s), menopausal age, functionality status, co-morbidity burden, smoking status, diet life-style, and history of family fracture. Co-morbidity burden was assessed via Age-adjusted Charlson Comorbidity Index (ACCI). Protein density (PD) [< or ≥ 2.5 g/100 Cal] and the fruit/vegetable consumption (FVC) pattern [intermittent versus regular] were approximated from the participants' diet life-style information.

Bone mineral density was measured using a dual-energy X-ray absorptiometry (DEXA) at the total lumbar spine (L1-L4) and left hip. DEXA scans of the anteroposterior spine and the proximal femoral hip participant's data were abstracted from the DEXA recorded database. These DEXA related database included primarily femoral hip T and Z-Scores, femoral hip BMD in g per cm2 (fH_BMD), Lumbar T and Z-Scores, Lumbar BMD (LBMD), 10-year risk of femoral osteoporotic fracture related FRAX score (<3% or ≥3%), and 10-year risk of major overall osteoporotic fracture related FRAX score (< or ≥20%). T-score values were used to determine the diagnosis of osteoporosis. A T-score within 1 SD (+1 or -1) of the young adult mean indicates normal bone density. A T-score of 1 to 2.5 SD below the young adult mean (-1 to -2.5 SD) indicates low bone mass. A T-score of 2.5 SD or more below the young adult mean (more than -2.5 SD) indicates the presence of osteoporosis. In this study, the higher probability of fHOPF was determined as either T-Score is <-2.5 (regardless of FRAX is < or ≥ 3%) or T-Score is between -1 and -2.5 but the FRAX is ≥3%. In contrast, the lower probability of fHOPF was determined as T-Score is between -1 and -2.5, and the FRAX is <3% or the T-Score is >-1 (regardless of FRAX is ≥ or <3%).

The investigated studied participants were either allocated to non-HTN versus HTN cohorts (Cohort I vs Cohort II, respectively). Also, the anti-HTN medications were categorized into 6 major medication's group; Group I-VI. Both aforementioned categorized 2 patients' cohorts and 6 medications' groups were analyzed via chi square test to express the comparison results as distribution rates strength of associations (odd ratios), Pearson chi-square statistic (χ 2), Goodness of Fit (G-Test of independence), and Pearson (r) and Spearman (ρ) correlations. The comparative investigated independent variables that were tested across the 2 patients' cohorts, including of particular both gender distribution rates and ratios, age ranges, vit D levels, nutritional indexes' statuses (PD and FVC patterns), smoking and corticosteroidal (Cs) statuses, anthropometrical variable of body mass index (BMI), and both the osteoporosis risk assessment instrument and tool (ORAI and OST, respectively). Statistical analysis was performed using Statistical Package for Social Science (SPSS) software version 23.0. Statistical significance was set at 5%.

3. Results

Overall, 206 participants who were clinically diagnosed for osteoporotic fracture risk at our rehabilitation and rheumatology clinic between Sep 2021 and Nov 2021, were studied to investigate the differences of the various investigated independent variables across the 2 dichotomized HTN related cohorts; Cohort I-II. In this study, 49.03% (101 of the eligible patients) were allocated to the non-HTN affected cohort (Cohort I) and 50.97% (101 of the overall participants) were comparatively allocated to the HTN affected cohort (Cohort II). Approximately, 33 (31.4%) of the HTN affected patients were on only CCBs (Group I) while approximately 27 (25.7%), 14 (13.3%), 20 (19.0%), 9 (8.6%), and 2 (1.9%) of the HTN affected participants were on CCBs+BBs (Group II), CCBs+ACEIs or ARBs (Group III), CCBs+Thiazide (Group IV), BBs+ACEIs or ARBs (Group V), and ACEIs or ARBs+Thiazide (Group VI), respectively.

The overall tested gender ratio (female to male ratio) in this study was assigned to 5.87: 1 with insignificant distributions across the non-HTN cohort (Cohort I) and the HTN cohort (Cohort II) [5.733: 1 and 6: 1, respectively, 0.956 (95% CI; 0.441-2.073), -0.008±0.070, χ^2=0.013, p-value=0.908]. Regarding the tested patients' age categorization, the age range (50-59) years had a lower proportional rate compared to the age range (60-69) years [23 (22.8%) and 38 (37.6%) vs 67 (32.5%), respectively] with significant distributions over Cohort I-II [42 (40.0%) and 72 (79.1%) vs 42 (40.0%) and 29 (27.6%), respectively, -0.372±0.060, χ^2= 30.760, p-value=0.000].

The higher risk grade of osteoporosis fracture (-20≤OST<-4) and also the moderate risk grade (-4≤OST<-1) had significantly higher proportional rates in Cohort II compared to Cohort I [10 (9.5%) and 41 (39.0%) vs 4 (4.0%) and 23 (22.8%), respectively, 0.221±0.066, χ 2= 10.685, p-value=0.005]. comparatively to the OST, the ORAI analysis also revealed that the high-risk grade (16≤ORAI≤25) and the moderate risk grade (9≤ORAI≤15) of osteoporosis were significantly higher distributed into the Cohort II compared the Cohort I [30 (33.0%) and 55 (60.4%) vs 18 (18.9%) and 40 (42.1%), respectively, 0.332±0.065, χ 2= 27.644, p-value=0.000]

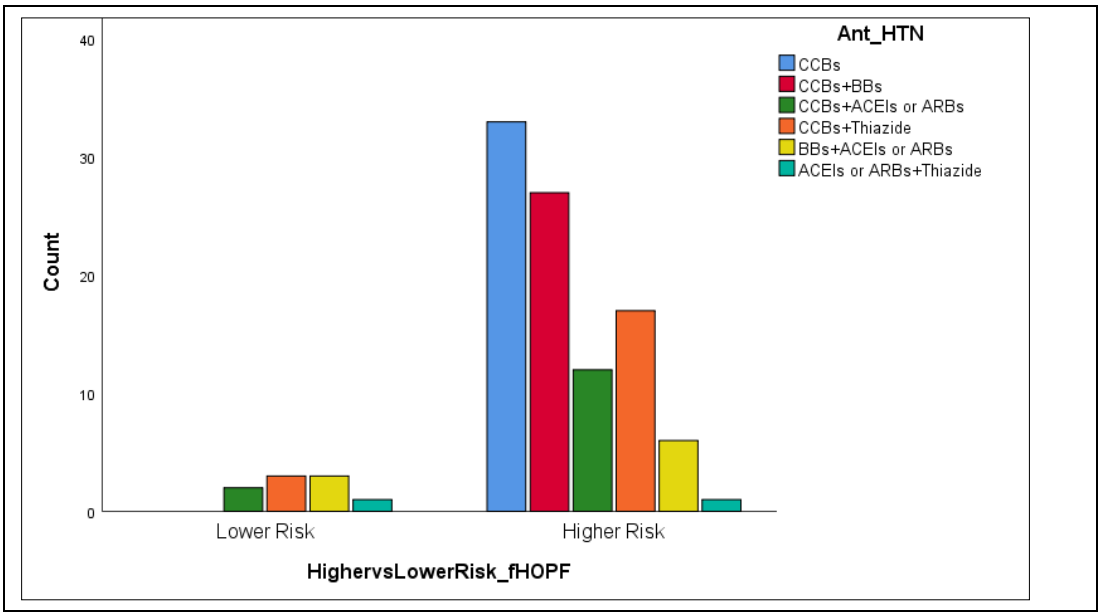
The low fHBMD (<0.755 g/cm^2) was significantly higher in the Cohort II than in the Cohort I [97 (92.4%) vs 6 (5.9%), respectively, 0.005 (95% CI; 0.002-0.016), -0.864±0.035, χ 2= 153.864, p-value=0.000]. Similarly, the higher risk of fHOPF was significantly higher in Cohort II compared to Cohort I [96 (91.4%) vs 0 (0.0%), respectively, 0.082 (95% CI; 0.044-0.153, 0.916±0.026, χ 2= 172.933, p-value=0.000]. investigated populations who were belonged to Cohort II had significantly lower distribution rates of higher functionality statues compared to populations who were belonged to Cohort I [31 (29.5%) vs 84 (83.2%), respectively, 0.085 (95% CI; 0.043-0.166), -0.540±0.058, χ 2= 60.074, p-value=0.000]. All the tested patients' analysis results and illustrations were clearly and fully presented in Table 1-4 and Figure 1-4.

Table 1 The comparatively studied variables of both femoral hip osteoporotic fracture (fHOPF) risk and femoral hip bone mineral density (fHBMD) across the 6 anti-hypertensive medications' groups (Group I-VI) for the Jordanian investigated patients, who attended to the rehabilitation clinic between Sep 2021 and Nov 2021 at the Prince Rashid bin Al-Hasan Military Hospital, Royal Medical Services, Irbid/Jordan

	CCBs	**CCBs + BBs**	**CCBs + ACEIs or ARBs**	**CCBs + Thiazide**	**BBs + ACEIs/ARBs**	**ACEIs/ARBs + Thiazide**	**Total**
	Group I	**Group II**	**Group III**	**Group IV**	**Group V**	**Group VI**	
	33 (31.43%)	**27 (25.71%)**	**14 (13.33%)**	**20 (19.05%)**	**9 (8.57%)**	**2 (1.9%)**	**105**
fHOPF	R & ρ [-0.390±0.081 &-0.362±0.068], χ 2 & G-Test [18.685 & 18.805], p-Value [0.002 &0.002]						
Lower Risk	0 (0.0%)	0 (0.0%)	2 (14.3%)	3 (15.0%)	3 (33.3%)	1 (50.0%)	9 (8.6%)
Higher Risk	33 (100.0%)	27 (100.0%)	12 (85.7%)	17 (85.0%)	6 (66.7%	1 (50.0%)	96 (91.4%)
FH_BMD (g/cm2)	R & ρ [0.399±0.081& 0.364±0.068], χ 2 & G-Test [20.060 & 18.224], p-Value [0.001 & 0.003]						
<0.755	33 (100.0%)	27 (100.0%)	13 (92.9%)	17 (85.0%)	6 (66.7%)	1 (50.0%)	97 (92.4%)
≥0.755	0 (0.0%)	0 (0.0%)	1 (7.1%)	3 (15.0%)	3 (33.3%)	1 (50.0%)	8 (7.6%)

Data results of the comparative variables between the 2 tested cohorts were statistically analyzed by Chi-Square Test (at p-value< 0.05) and expressed as Numbers (Percentage). The strength of associations was also described as odd ratios (OR). The Pearson chi-square statistic (χ 2) involves the squared difference between the observed and the expected frequencies. The Goodness of Fit (G-Test of independence) uses the log of the ratio of two likelihoods and tests the goodness of fit of observed frequencies to their expected. Both the interval by interval (Pearson, r) and the ordinal by ordinal (Spearman, ρ) correlations were expressed as value± standard error of value.

The studied patients were categorized into 6 comparative anti-HTN medications' groups; calcium channel blockers (CCBs) [Group I], CCBs with beta-blockers (BBs) [Group II], CCBs with ACEIs or ARBs [Group III], CCBs with thiazide or thiazide like diuretics [Group IV], BBs with ACEIs or ARBs [Group V], and ACEIs or ARBs with thiazide or thiazide like diuretics. [Group VI].



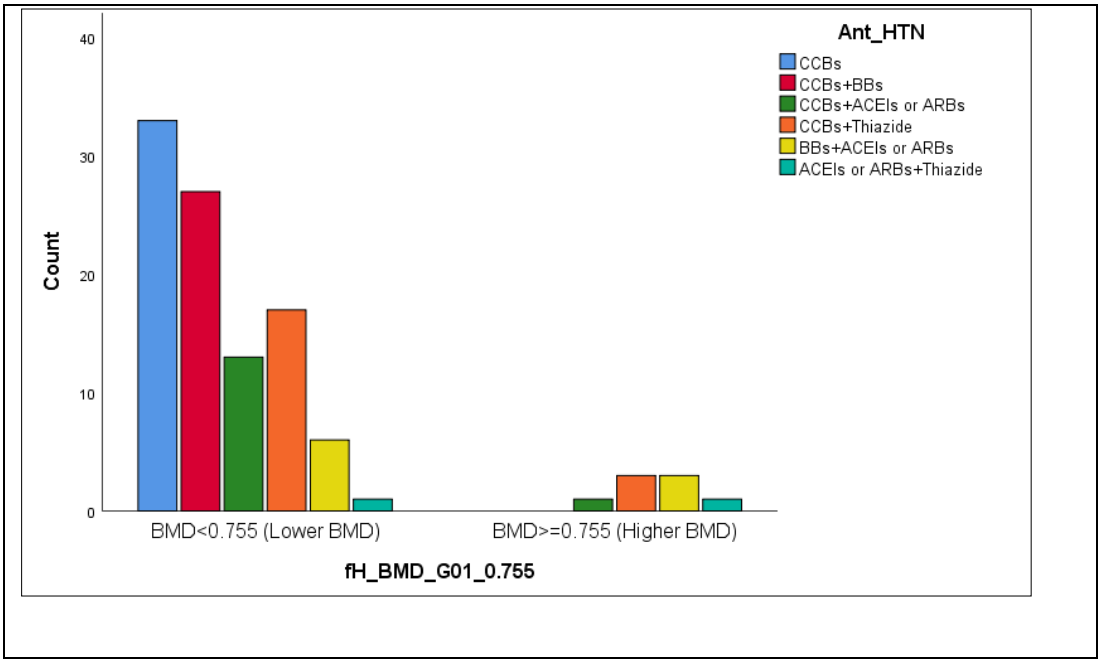
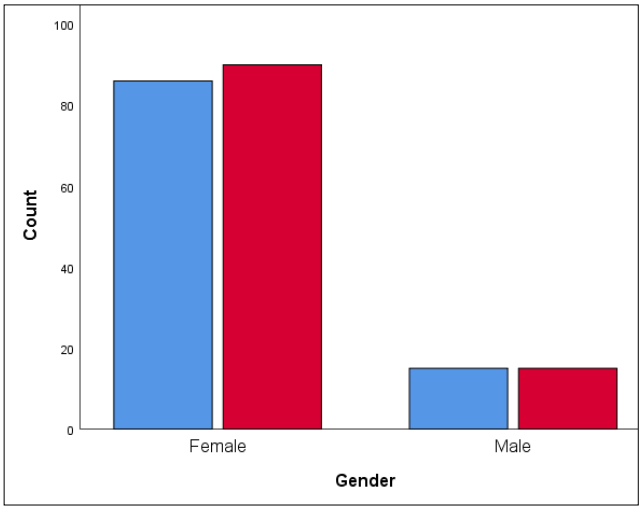


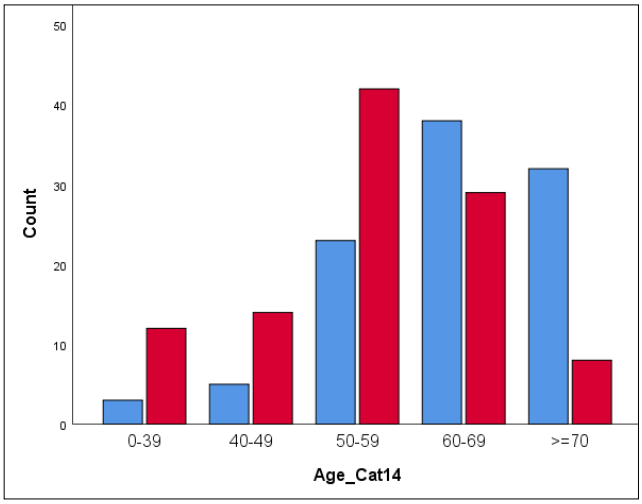
Figure 1 The bar charts' visualizations for the studied variables of both femoral hip osteoporotic fracture (fHOPF) risk and femoral hip bone mineral density (fHBMD) across the 6 anti-hypertensive medications' groups (Group I-VI) for the Jordanian investigated patients, who attended to the rehabilitation clinic between Sep 2021 and Nov 2021 at the Prince Rashid bin Al-Hasan Military Hospital, Royal Medical Services, Irbid/Jordan

Table 2 The comparatively studied variables across the Cohort I-II; Non-HTN affected cohort (Cohort I) versus HTN affected cohort (Cohort II), for the Jordanian investigated patients, who attended to the rehabilitation clinic between Sep 2021 and Nov 2021 at the Prince Rashid bin Al-Hasan Military Hospital, Royal Medical Services, Irbid/Jordan

	Non-HTN Cohort [Cohort I] (101, 49.03%)	**HTN Cohort [Cohort II] (105, 50.97%)**	**Total (206, 100%)**	**OR**	**R ρ**	**χ 2 G-Test**	**p-Value**
Gender							
Female	86 (85.1%)	90 (85.7%)	176 (85.4%)	0.956 (95% CI; 0.441-2.073)	-0.008±0.070 -0.008±0.070	0.013 0.013	0.908 0.908
Male	15 (14.9%)	15 (14.3%)	30 (14.6%)				
Female: Male	5.733: 1	6: 1	5.87: 1				
Age (Yrs)							
0-39	3 (3.0%)	12 (11.4%)	15 (7.3%)	NA	-0.372±0.060* -0.383±0.061*	30.760 32.412	0.000 0.000
40-49	5 (5.0%)	14 (13.3%)	19 (9.2%)				
50-59	23 (22.8%)	42 (40.0%)	65 (31.6%)				
60-69	38 (37.6%)	29 (27.6%)	67 (32.5%)				
>=70	32 (31.7%)	8 (7.6%)	40 (19.4%)				
Post-Menopausal age							
40-44.9	3 (3.6%)	12 (13.5%)	15 (8.7%)	NA	-0.028±0.076 -0.014±0.076	6.731 7.108	0.081 0.069
45-49.9	43 (51.8%)	34 (38.2%)	77 (44.8%)				

50-54.9	29 (34.9%)	33 (37.1%)	62 (36.0%)				
>=55	8 (9.6%)	10 (11.2%)	18 (10.5%)				
OST (-20-20)							
Low risk (-1-20)	74 (73.3%)	54 (51.4%)	128 (62.1%)	NA	0.221±0.066* 0.228±0.067*	10.685 10.848	0.005 0.004
Moderate risk (-4- -1)	23 (22.8%)	41 (39.0%)	64 (31.1%)				
High risk (-20--4)	4 (4.0%)	10 (9.5%)	14 (6.8%)				
LBMD (g/cm2)							
<0.835	0 (0.0%)	51 (48.6%)	51 (24.76%)	2.87 (95% CI; 2.314-3.56)	-0.563±0.040* -0.563±0.040*	65.199 85.102	0.000 0.000
≥0.835	101 (100.0%)	54 (51.4%)	155 (75.2%)				
Data results of the comparative variables between the 2 tested cohorts were statistically analyzed by Chi-Square Test (at p-value< 0.05) and expressed as Numbers (Percentage). The strength of associations was also described as odd ratios (OR). The Pearson chi-square statistic (χ 2) involves the squared difference between the observed and the expected frequencies. The Goodness of Fit (G-Test of independence) uses the log of the ratio of two likelihoods and tests the goodness of fit of observed frequencies to their expected. Both the interval by interval (Pearson, r) and the ordinal by ordinal (Spearman, ρ) correlations were expressed as value± standard error of value. The studied patients were dichotomously categorized into 2 comparative cohorts; Non-HTN affected cohort (Cohort I) versus HTN affected cohort (Cohort II).							
OST: The Osteoporosis self-Assessment Tool.			LBMD: Lumbar bone mineral density.				





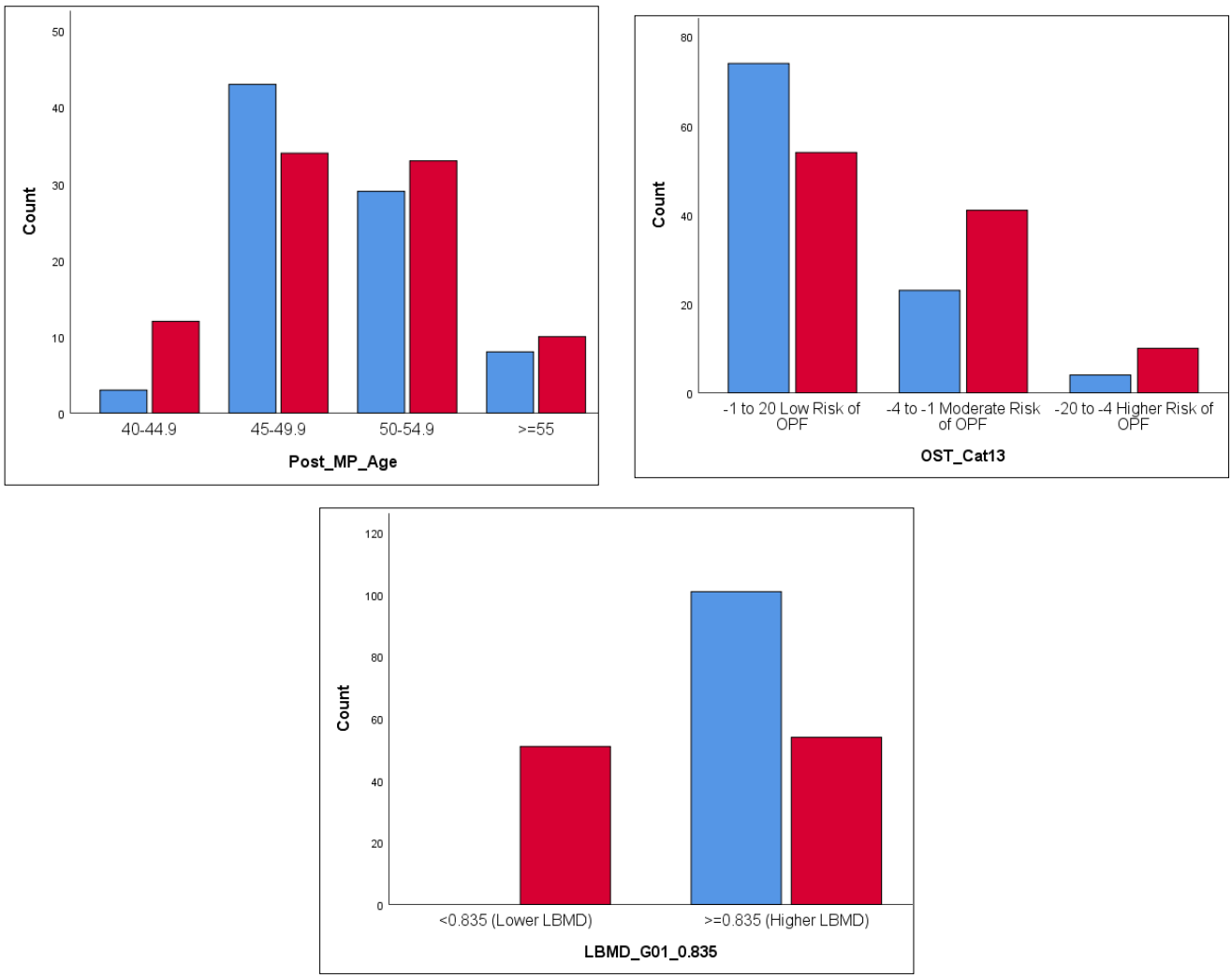


Figure 2 The bar charts' visualizations for the studied patients across the Cohort I-II; Non-HTN affected cohort (Cohort I) versus HTN affected cohort (Cohort II), for the Jordanian investigated patients, who attended to the rehabilitation clinic between Sep 2021 and Nov 2021 at the Prince Rashid bin Al-Hasan Military Hospital, Royal Medical Services, Irbid/Jordan

Table 3 The comparatively studied variables across the Cohort I-II; Non-HTN affected cohort (Cohort I) versus HTN affected cohort (Cohort II), for the Jordanian investigated patients, who attended to the rehabilitation clinic between Sep 2021 and Nov 2021 at the Prince Rashid bin Al-Hasan Military Hospital, Royal Medical Services, Irbid/Jordan

	Non-HTN Cohort [Cohort I] (101, 49.03%)	**HTN Cohort [Cohort II] (105, 50.97%)**	**Total (206, 100%)**	**OR**	**R ρ**	**χ 2 G-Test**	**p-Value**
ORAI (0-26)							
Low risk (0-8)	37 (38.9%)	6 (6.6%)	43 (23.1%)	NA	0.332±0.065* 0.329±0.067*	27.644 30.181	0.000 0.000
Moderate risk (9-15)	40 (42.1%)	55 (60.4%)	95 (51.1%)				

High risk (16-25)	18 (18.9%)	30 (33.0%)	48 (25.8%)				
fH_BMD (g/cm2)							
<0.755	6 (5.9%)	97 (92.4%)	103 (50.0%)	0.005 (95% CI; 0.002-0.016)	-0.864±0.035*	153.864	0.000
≥0.755	95 (94.1%)	8 (7.6%)	103 (50.0%)		-0.864±0.035*	183.493	0.000
ACCI							
<4	91 (90.1%)	41 (39.0%)	132 (64.1%)	14.205 (95% CI; 6.632-30.42)	0.532±0.055*	58.289	0.000
≥4	10 (9.9%)	64 (61.0%)	74 (35.9%)		0.532±0.055*	63.316	0.000
fHOPF risk							
Lower	101 (100.0%)	9 (8.6%)	110 (53.4%)	0.082 (95% CI; 0.044-0.153)	0.916±0.026*	172.933	0.000
Higher	0 (0.0%)	96 (91.4%)	96 (46.6%)		0.916±0.026*	223.198	0.000
Functionality							
Lower	17 (16.8%)	74 (70.5%)	91 (44.2%)	0.085 (95% CI; 0.043-0.166)	-0.540±0.058*	60.074	0.000
Higher	84 (83.2%)	31 (29.5%)	115 (55.8%)		-0.540±0.058*	63.803	0.000
Vit D (ng/ml)							
<30	45 (44.6%)	98 (93.3%)	143 (69.4%)	0.057 (95% CI; 0.024-0.136)	-0.529±0.054*	57.699	0.000
≥30	56 (55.4%)	7 (6.7%)	63 (30.6%)		-0.529±0.054*	63.426	0.000

Data results of the comparative variables between the 2 tested cohorts were statistically analyzed by Chi-Square Test (at p-value< 0.05) and expressed as Numbers (Percentage). The strength of associations was also described as odd ratios (OR). The Pearson chi-square statistic (χ 2) involves the squared difference between the observed and the expected frequencies. The Goodness of Fit (G-Test of independence) uses the log of the ratio of two likelihoods and tests the goodness of fit of observed frequencies to their expected. Both the interval by interval (Pearson, r) and the ordinal by ordinal (Spearman, ρ) correlations were expressed as value± standard error of value. The studied patients were dichotomously categorized into 2 comparative cohorts Non-HTN affected cohort (Cohort I) versus HTN affected cohort (Cohort II).

In this study, the higher probability of fHOPF was determined as either T-Score is <-2.5 (regardless of FRAX is < or ≥ 3%) or T-Score is between -1 and -2.5 but the FRAX is ≥3%. In contrast, the lower probability of fHOPF was determined as T-Score is between -1 and -2.5, and the FRAX is <3% or the T-Score is >-1 (regardless of FRAX is ≥ or <3%). The higher probability of fHOPF is considered as a Positive state and the lower probability of fHOPF is considered as a Negative State. For the tested categorical Tx related independent variable, 0 was assigned for the Cohort I and was considered the reference. While 1 was assigned for the Cohort II.

ACCI: Age-adjusted Charlson Comorbidity Index. ORAI: The Osteoporosis Risk Assessment Instrument.	fHOPF: Femoral hip osteoporotic fracture.

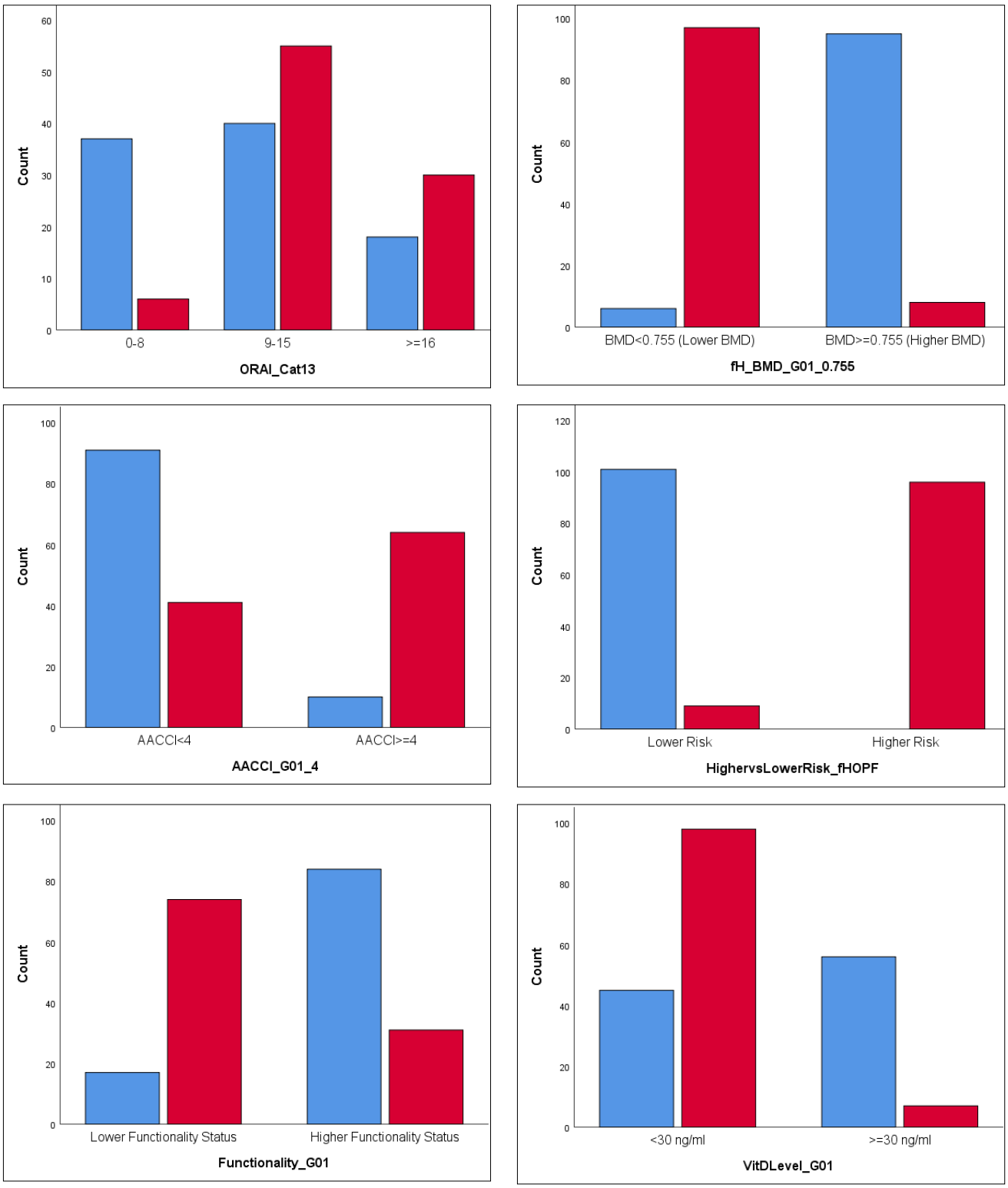
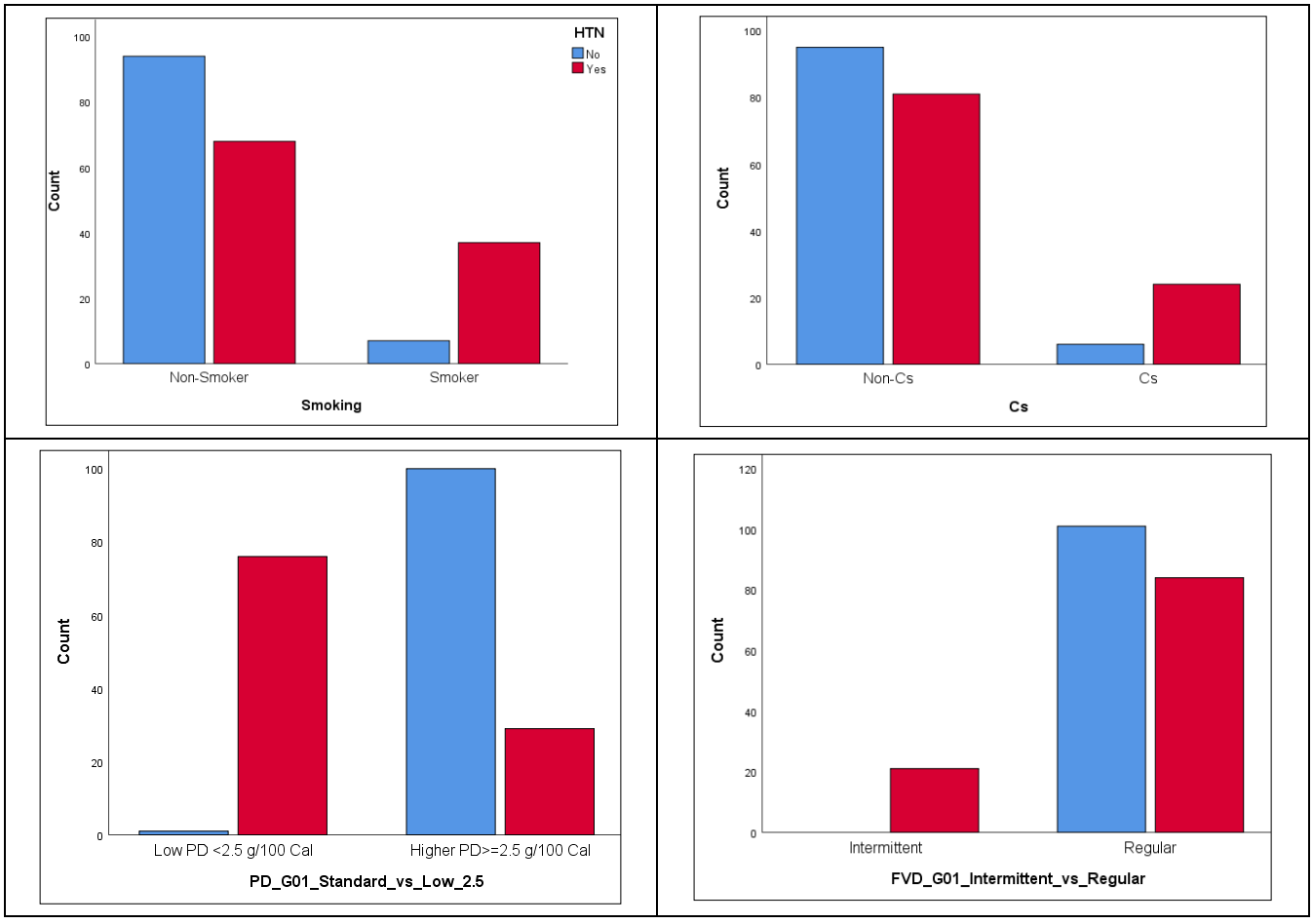


Figure 3 The bar charts' visualizations for the studied patients across the Cohort I-II; Non-HTN affected cohort (Cohort I) versus HTN affected cohort (Cohort II), for the Jordanian investigated patients, who attended to the rehabilitation clinic between Sep 2021 and Nov 2021 at Prince Rashid bin Al-Hasan Military Hospital, Royal Medical Services, Irbid/Jordan

Table 4 Comparatively studied variables across Cohort I-II; Non-HTN affected cohort (Cohort I) versus HTN affected cohort (Cohort II), for the Jordanian investigated patients, who attended to the rehabilitation clinic between Sep 2021 and Nov 2021 at Prince Rashid bin Al-Hasan Military Hospital, Royal Medical Services, Irbid/Jordan

	Non-HTN Cohort [Cohort I] (101, 49.03%)	**HTN Cohort [Cohort II] (105, 50.97%)**	**Total (206, 100%)**	**OR**	**R ρ**	**χ 2 G-Test**	**p-Value**
Smoking							
No	94 (93.1%)	68 (64.8%)	162 (78.6%)	7.307 (95% CI; 3.073-17.371)	0.345±0.058* 0.345±0.058*	24.559 26.552	0.000 0.000
Yes	7 (6.9%)	37 (35.2%)	44 (21.4%)				
Cs							
No	95 (94.1%)	81 (77.1%)	176 (85.4%)	4.691 (95% CI; 1.828-12.039)	0.240±0.060* 0.240±0.060*	11.840 12.602	0.001 0.000
Yes	6 (5.9%)	24 (22.9%)	30 (14.6%)				
PD (g/100 Cal)							
<2.5	1 (1.0%)	76 (72.4%)	77 (37.4%)	0.004 (95% CI; 0.001-0.029)	-0.738±0.040* -0.738±0.040*	112.09 137.33	0.000 0.000
≥2.5	100 (99.0%)	29 (27.6%)	129 (62.6%)				
FVC							
Intermittent	0 (0.0%)	21 (20.0%)	21 (10.2%)	2.202 (95% CI; 1.880-2.579)	-0.330±0.037* -0.330±0.037*	22.493 30.599	0.000 0.000
Regular	101 (100.0%)	84 (80.0%)	185 (89.8%)				
BMI (Kg/m2)							
<18.5	0 (0.0%)	44 (41.9%)	44 (21.4%)	NA	-0.670±0.049* -0.719±0.039*	114.919 142.943	0.000 0.000
18.5-24.9	23 (22.8%)	53 (50.5%)	76 (36.9%)				
25-29.9	75 (74.3%)	6 (5.7%)	81 (39.3%)				
30-34.9	1 (1.0%)	1 (1.0%)	2 (1.0%)				
≥35	2 (2.0%)	1 (1.0%)	3 (1.5%)				
Anti-HTN							
CCBs	0 (0.0%)	33 (31.4%)	33 (31.4%)	NA	NA	NA	NA
CCBs+BBs	0 (0.0%)	27 (25.7%)	27 (25.7%)				
CCBs+ACEIs or ARBs	0 (0.0%)	14 (13.3%)	14 (13.3%)				

CCBs+Thiazide	0 (0.0%)	20 (19.0%)	20 (19.0%)				
BBs+ACEIs or ARBs	0 (0.0%)	9 (8.6%)	9 (8.6%)				
ACEIs or ARBs+Thiazide	0 (0.0%)	2 (1.9%)	2 (1.9%)				
Data results of the comparative variables between the 2 tested cohorts were statistically analyzed by Chi-Square Test (at p-value< 0.05) and expressed as Numbers (Percentage). The strength of associations was also described as odd ratios (OR). The Pearson chi-square statistic (χ 2) involves the squared difference between the observed and the expected frequencies. The Goodness of Fit (G-Test of independence) uses the log of the ratio of two likelihoods and tests the goodness of fit of observed frequencies to their expected. Both the interval by interval (Pearson, r) and the ordinal by ordinal (Spearman, ρ) correlations were expressed as value± standard error of value. The studied patients were dichotomously categorized into 2 comparative cohorts; Lower risk fHOPF cohort (Cohort I) versus Higher risk of fHOPF cohort (Cohort II),							



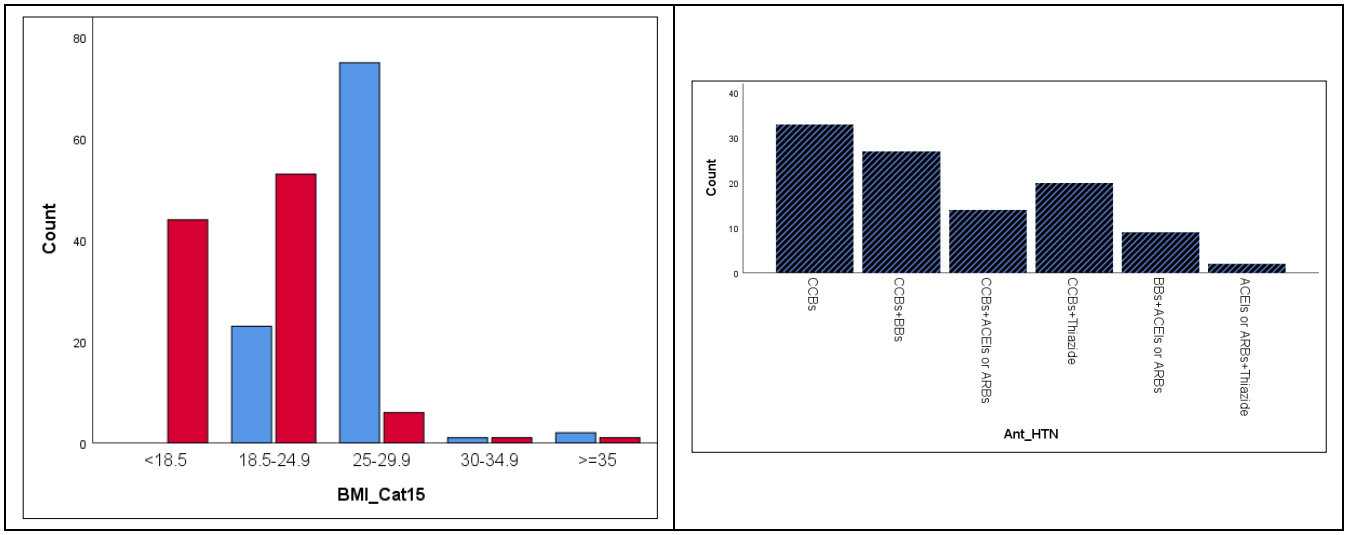


Figure 4 The bar charts' visualizations for the studied patients across the Cohort I-II; Non-HTN affected cohort (Cohort I) versus HTN affected cohort (Cohort II), for the Jordanian investigated patients, who attended to the rehabilitation clinic between Sep 2021 and Nov 2021 at Prince Rashid bin Al-Hasan Military Hospital, Royal Medical Services, Irbid/Jordan

4. Discussion

There are several main findings of our study, with important implications. Firstly, our study showing that the overall incidence of higher femoral osteoporotic fracture risk in HTN patients who were on at least one anti-HTN medication was 91.4%. Patients who were on thiazide or thiazide like diuretics with ACEIs or ARBs had the lowest incidence rate of higher risk of fHOPF (50%), followed by patients who were on BBs with thiazide or thiazide like diuretics (66.7%), CCBs with thiazide or thiazide like diuretics (85%), CCBs with ACEIs or ARBs (85.7%), and lastly for patients who took CCBs with or without BBS (100%) [R & ρ [-0.390±0.081 &-0.362±0.068], χ 2 & G-Test [18.685 & 18.805], p-Value [0.002 &0.002]]. Comparatively to the incidence rate of the higher risk of fHOPF, the incidence rate of fH_BMD ≥0.775 g/cm2 was highest for HTN affected patients who were belonged to Group VI, followed by Group V, Group IV, Group III, and lastly Group I-II [R & ρ [0.399±0.081& 0.364±0.068], χ 2 & G-Test [20.060 & 18.224], p-Value [0.001 & 0.003]].

Secondly, we showed in this study that there were significant correlations for the patients' co-morbidity burden, as assessed by ACCI, smoking, and corticosteroidal agents and the HTN status in these investigated participants who were at risk of osteoporotic fracture [(14.205 (95% CI; 6.632-30.42, 0.532±0.055, χ^2= 58.289, p-value=0.000), 7.307 (95% CI; 3.073-17.371), 0.345±0.058, χ2= 58.289, p-value=0.000), and (4.691 (95% CI; 1.828-12.039), 0.240±0.060, χ2= 11.840, p-value=0.000), respectively]. In contrast, we revealed in this study significant negative correlations of vit D levels and PD and FVC patterns regarding the HTN status [(0.057 (95% CI; 0.024-0.136), -0.529±0.054, χ2= 57.699, p-value=0.000), (0.004 (95% CI; 0.001-0.029), -0.738±0.040, χ2= 112.09, p-value=0.000), and (2.202 (95% CI; 1.880-2.579), -0.330±0.037, χ2= 22.493, p-value=0.000), respectively]

Generally, HTN affected patients often have higher osteoporotic fractures' risk than those without. A recent study by a team found that chlorthalidone may improve bone strength and reduce the risk of osteoporotic fractures. Previous studies had suggested that both ACEIs or ARBs and thiazide-type diuretics improve vertebral and non-vertebral bone mineral densities, little studies had compared various anti-HTN medications with each other, especially in the Mediterranean population, and this gave our study its uniqueness.

5. Conclusion

This single-center small non-sponsored and non-funded retrospective study which primarily aimed to explore the differences of distributional rates of both the femoral hip bone mineral density (fH_BMD) and the femoral hip osteoporotic fracture (fHOPF) risk across the 6 selected anti-HTN medications' groups revealed that the thiazide or thiazide like diuretics and ACEIs or ARBs, alone or in combination, may positively improve the femoral hip bone mineral densities and consequently mitigate the risk of osteoporotic fractures. However, this study was prone to recall and selection bias but it may adjunctively assist other multi-site prospective studies, especially in Jordanian or Mediterranean cohorts,

Compliance with ethical standards

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Disclosure of conflict of interest

There is no conflict of interest in this manuscript

Statement of ethical approval

There is no animal/human subject involvement in this manuscript

Statement of informed consent

Owing to the retrospective design of this study, the informed consent form was waived.

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