



Relationships Among 10-Year Fracture Risk Assessment, Comorbidity Burden, and Functional Status in Ischemic Stroke Survivors

İskemik İnmeden Sağ Kalanlar Arasında 10 Yıllık Kırık Riski Değerlendirmesi, Komorbidite Yükü ve Fonksiyonel Durum Arasındaki İlişkiler

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Abstract

Objective: Poststroke disabilities and comorbidities pose serious problems among the stroke survivors. We thought that the comorbidity burden and functional status may impact determining the fracture risk of patients with ischemic stroke. The aim of this study was to investigate the effect of comorbidity burden and functional status in determining the 10-year fracture risk of patients with ischemic strokes.

Materials and Methods: The cross-sectional study included 138 ischemic stroke survivors. Functional status [Functional Independence Measure (FIM)], comorbidity burden [Charlson Comorbidity index (CCI)] and fracture risk [The Fracture Risk Assessment Tool (FRAX)] were evaluated.

Results: The median age of the cases was 64 (49-83) years (53.6% male). As the CCI increased, motor (FIM-motor) and cognitive (FIM-cognitive) functions decreased. The decrease in FIM-motor and FIM-cognitive and the increase in the CCI increased statistically significantly the risk of major osteoporotic fracture (FRAX-MOFR) and hip fracture (FRAX-HFR) ($p<0.05$). The patients with a history of osteoporotic fractures were older, had lower FIM-motor and FIM-cognitive, and higher CCI ($p<0.05$). There was a significant relationship between FIM-motor, FIM-cognitive, and CCI, and FRAX-MOFR and FRAX-HFR. CCI was the independent variable.

Conclusion: In stroke survivors, levels of the motor and cognitive functions and comorbidity burden could predict the risk of hip and major osteoporotic fractures. Comorbidity burdens are independent variables.

Keywords: Comorbidity burden, functional status, fracture risk, FRAX, ischemic stroke

Öz

Amaç: İnme sonrası özürlülük ve komorbiditeler hayatta kalanlar arasında ciddi problemler oluşturmaktadır. İskemik inme hastalarında komorbidite yükü ve fonksiyonel durumun kırık riskini belirlemede etkili olabileceğini düşündük. Bu çalışmanın amacı iskemik inmeli hastalarda 10 yıllık kırık riskini belirlemede komorbidite yükü ve fonksiyonel durumun etkisini araştırmaktır.

Gereç ve Yöntem: Bu kesitsel çalışmaya 138 iskemik inmeli hasta dahil edildi. Fonksiyonel durum [Fonksiyonel Bağımsızlık Ölçütü (FIM)], komorbidite yükü [Charlson Komorbidite indeksi (CCI)] ve kırık riski [Kırılma Riski Değerlendirme skoru (FRAX)] değerlendirildi.

Bulgular: Olguların ortanca yaşı 64 (49-83) yıl (%53,6 erkek) idi. CCI arttıkça motor (FIM-motor) ve bilişsel (FIM-bilişsel) fonksiyonlar azaldı. FIM-motor ve FIM-bilişseldeki azalma ve CCI'daki artış, majör osteoporotik kırık (FRAX-MOFR) ve kalça kırığı (FRAX-HFR) riskini istatistiksel olarak anlamlı bir şekilde artırdı ($p<0,05$). Osteoporotik kırık öyküsü olan hastalar daha yaşlıydı, daha düşük FIM-motor ve FIM-bilişsel ve daha yüksek CCI'ya sahipti ($p<0,05$). FIM-motor, FIM-bilişsel ve CCI ile FRAX-MOFR ve FRAX-HFR arasında anlamlı bir ilişki vardı ve CCI bağımsız değişkendi.

Sonuç: İnmeden kurtulanlarda motor ve bilişsel işlev seviyeleri ve komorbidite yükü, majör osteoporotik kırık ve kalça kırığı riskini öngörebilir. Komorbidite yükü bağımsız değişkenlerdir.

Anahtar kelimeler: Komorbidite yükü, fonksiyonel durum, kırık riski, FRAX, iskemik inme

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Introduction

Stroke is one of the most important causes of morbidity and mortality worldwide. The most common type of stroke is an ischemic stroke, and its incidence increases with age (1,2). The overwhelming majority of stroke patients have at least one comorbidity. About 25% of them have five or more comorbidities. The most common stroke-related comorbidities are advanced age, hypertension, dyslipidemia, diabetes, obesity, atrial fibrillation, and smoking. Poststroke morbidity and comorbidities pose serious problems among survivors (2,3). Studies have reported a negative relationship between comorbidity burden and functional outcomes (4,5). It is essential to determine the comorbidity burden in predicting functional prognosis after acute diseases like stroke and hip fractures (5). It is not well understood how comorbidities affect stroke patients (3). Comorbidities such as heart diseases, chronic obstructive pulmonary disease, and dementia create the risk of falling and affect the incidence of fractures (6). Stroke is a significant risk factor for hip fracture, which increases the risk of hip fracture up to four times (7,8). Poststroke hip fracture has a negative effect on clinical outcomes. The rehabilitation program is delayed, recovery and hospital stay are prolonged, and the risk of morbidity and mortality increases (9). Studies have shown that stroke can increase the risk of falling, resulting in a hip fracture (8). The rate of stroke survivors experiencing a fracture in the first year after stroke is 3-6% (7). Moreover, the risk of hip fractures in stroke survivors is higher than that in healthy adults of the same age (10). It is estimated that 50% of stroke survivors fall within the first year after being discharged from the hospital, and as many as 40% fall repeatedly (11). High fracture rates among stroke survivors are not solely due to their high risk of falling. Additionally, stroke survivors have an increased risk of osteoporotic fractures due to sarcopenia and decreased bone mineral density (BMD), especially on the paretic side (8). However, the results of previously published studies are conflicting and the relationship between stroke and hip fracture risk is unclear (8,12). The Fracture Risk Assessment Tool (FRAX) approved by the World Health Organization (WHO) predicts the 10-year probability of hip and major osteoporotic fractures (13). One study linked severe disability after stroke and a higher FRAX risk score with an increased risk of hip fractures (7). The need to prevent post-stroke fractures, including the prevention of both falls and osteoporosis, and identify stroke patients at risk of fractures was emphasized (14). We thought that the burden of comorbidity and functional status in ischemic stroke patients might impact the prediction of their 10-year fracture risk. We could not find any research in this direction in the literature. This study aimed to investigate the effects of comorbidity burden and functional status in determining 10-year fracture risk in ischemic stroke survivors.

Materials and Methods

This cross-sectional study was performed at the Physiotherapy and Rehabilitation Clinic of a Training and Research Hospital (between 2019 and 2021). The study was planned in compliance with the principles of the Declaration of Helsinki and was approved by the Bursa Yüksek İhtisas Training and Research Hospital Ethics Committee (decision no: 2011-KAEK-25 2019/05-03, date: 22.05.2019). All Patients and/or their legal representatives were informed about the study, and they gave written and signed informed consent.

Male and female patients aged 40-85 years, with a stroke duration of six months or more, diagnosed with ischemic stroke, attending their rehabilitation programs in the physiotherapy and rehabilitation clinic, and not receiving osteoporosis treatment were included in the study. The exclusion criteria were determined as not having a significant cognitive function, being in a vegetative state, and having a stroke type other than ischemic stroke. Other exclusion criteria were refusal to participate in the study, being <40 years old, and being >85 years old.

The age, body mass index (BMI, kg/m²), and demographic data of each participant were recorded. The patient's comorbidities (such as diabetes, hypertension, dyslipidemia, chronic heart failure, myocardial infarction, cardiovascular disease, atrial fibrillation, cancer, chronic lung-liver-kidney diseases, peptic ulcer, and dementia) were learned from the patient or their companion. These data were verified using the necessary testing and imaging methods during clinical follow-ups, and these were obtained and recorded from the hospital records. The same investigator made the clinical observations and evaluations.

Data collection

Functional Independence Measure (FIM): It was used to assess functional status (15). FIM, which includes 13 motor and five cognitive elements, measures independence in daily life. The score for each item ranges from 1 (total dependency) to 7 (total independence). The maximum total motor score is 91, the maximum total cognitive score is 35, and the maximum total FIM score is 126. The Turkish version of FIM was found reliable and valid (16).

Charlson Comorbidity index (CCI): CCI contains 19 chronic diseases and has been used to predict mortality and functional outcomes in stroke cases (17). There is a weighted score between 1 and 6 determined for each disease. Additionally, 1 point is added for every ten years over the age of 40. The higher the overall score, the greater the burden of comorbidity. In this study, the patients were divided into four subgroups according to their CCI scores: group 1 (CCI score 2-3), group 2 (CCI score 4-5), group 3 (CCI score 6-7), and group 4 (CCI score ≥8) (18).

FRAX: Approved by the WHO, the FRAX tool predicts the 10-year probability of hip fractures (HFR) and major osteoporotic fracture (MOFR) (fracture of the hip, clinical spine, wrist, and humerus) (13). FRAX can be used in clinical practice in men or women aged 40 and above. Clinical risk factors for FRAX are as follows:

- Age,
- Sex,
- Weight (kg),
- Height (cm),
- Previous fragility fracture,
- Parent fractured hip,
- Glucocorticoid treatment,
- Current smoking,
- Alcohol consumption,
- Rheumatoid arthritis,
- Conditions causing secondary osteoporosis,
- Optional; BMD of the femoral neck.

Clinical risk factors are entered into the country-specific calculator, and the probability of fractures is calculated (<https://www.sheffield.ac.uk/FRAX>). The femoral neck BMD T-score was not included in the calculation in this study. The clinical risk factors were learned with the declaration of the patients and/or their companions. They were confirmed with the results of the necessary testing and imaging methods obtained from the hospital records. The patients were classified for MOFR according to FRAX: low- (<10%), moderate- (10-20%), and high-risk ($\geq 20\%$). Additionally, classification was made for HFR: high-risk $\geq 3\%$, and low-risk <3% (19). The patients were divided into those with and without a history of fractures. Intra-group

comparisons of the evaluation parameters were made.

Statistical Analysis

The IBM SPSS 23.0 statistical software was used in statistical analysis of data. Descriptive statistical methods such as frequency, percentage, mean, standard deviation, median, and min-max were used while analyzing the data. The data's compliance with normal distribution was evaluated using Shapiro-Wilk tests. Independent-samples t-test (t-test for independent groups) was used in the inter-group comparisons of the normally distributed variables. For the non-normally distributed variables, the Wilcoxon signed-rank test was used for the intra-group comparisons, and the Mann-Whitney U test was used for the inter-group comparisons. A comparison of different risk groups was made with the Kruskal-Wallis test. The relationships between the variables were analyzed using the Spearman correlation test. Multivariate regression analysis was used to analyze the independent predictors of HFR and MOFR. $p < 0.05$ was considered significant.

Results

This study included 138 patients who survived ischemic strokes (Figure 1). Of the 153 stroke survivors, seven were excluded

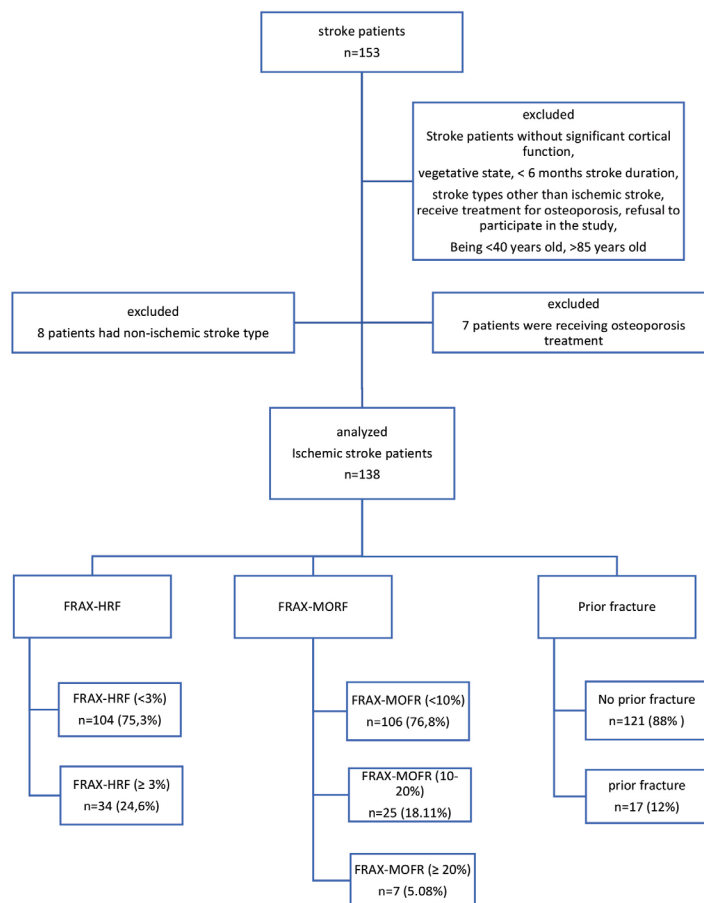


Figure 1. Flow chart

FRAX-HFR: Fracture Risk Assessment Tool-hip fracture, FRAX-MOFR: Fracture Risk Assessment Tool-major osteoporotic fracture

because they received treatment for osteoporosis, and eight were excluded because they had a non-ischemic stroke. The median age of the cases was 64 (49-83) years, 53.6% were male, and 46.4% were female. The median stroke duration was 14 (5-36) months, and the median length of stay in the intensive care unit was 2 (0-90) days. The demographic data, functional status, comorbidity burden, and FRAX scores of the cases are given in Table 1.

The functional statuses of the patients according to their CCI levels are shown in Figure 2: As CCI levels increase, a decrease is observed in motor and cognitive functions.

FRAX scores were obtained in 138 patients, and the patients were grouped according to their MOFR values (Table 2): 76.8%

of the patients had a low risk (<10%), 18% had a moderate risk (10-20%), and 5% had a high risk of MOFR. There was an increase in MOFR with increasing age. While 40.6% of the low-risk patients were women, 56% of the intermediate-risk patients and all high-risk patients were women ($p<0.05$). There was no significant difference between the groups regarding their BMI values ($p>0.05$). As MOFR increased, FIM motor, FIM cognitive, and FIM total scores decreased, while CCI total scores increased significantly ($p<0.05$) (Table 2).

According to the classification of the patients according to their HFR values, 75.36% had a low risk (<3%) and 24.63% had a high risk ($\geq 3\%$) (Table 3). There was no significant difference between the low- and high-risk groups in terms of their sex

Table 1. Demographic data, functional status, comorbidity burden and FRAX scores of patients with ischemic stroke

		n=138
Age		64 (49-83)
Gender n; %	Male n; %	74; 53.6%
	Female n; %	64; 46.4%
BMI (kg/m ²)		27.50 (19.80-41.39)
Smoker n; %	Current smoker n; %	30; 21.7%
	Ex-smoker n; %	40; 29%
	Non-smoker n; %	68; 49.3%
Income n; %	High n; %	33; 23.9%
	Moderate n; %	55; 39.9%
	Low n; %	50; 36.2%
Stroke side n; %	Right n; %	76; 55.1%
	Left n; %	62; 44.9%
Stroke duration (months)		14 (5-36)
Number of strokes		1 (1-4)
Intensive care period		2 (0-90)
Atrial fibrillation n; %		21; 15.2%
Hypertension n; %		117; 84.8%
Hyperlipidaemia n; %		50; 36.2%
FIM-motor		65.50 (13-91)
FIM-cognitive		31 (5-35)
FIM-total		97 (18-126)
CCI-total		4.5 (2-11)
CCI 2-3 n; %		42; 30%
CCI 4-5 n; %		52; 38%
CCI 6-7 n; %		11; 8%
CCI ≥ 8 n; %		33; 24%
FRAX-MOFR		6 (2.2-31)
FRAX-HFR		1.4 (0-16)
History of osteoporotic fracture n; %		17; 12.3%
Dominant hand	Right n; %	134; 97.1%
	Left n; %	4; 2.9%

Median (minimum-maximum); percentage: %, BMI: Body mass index, FIM: Functional Independence Measure, CCI: Charlson Comorbidity index, FRAX: Fracture Risk Assessment Tool, MOFR: Major osteoporotic fracture risk, HFR: Hip fracture risk

($p>0.05$). The high-risk group had significantly lower BMI values ($p<0.05$). As HFR increased, FIM motor, FIM cognitive, and FIM total scores decreased, while CCI total scores increased significantly ($p<0.001$) (Table 3).

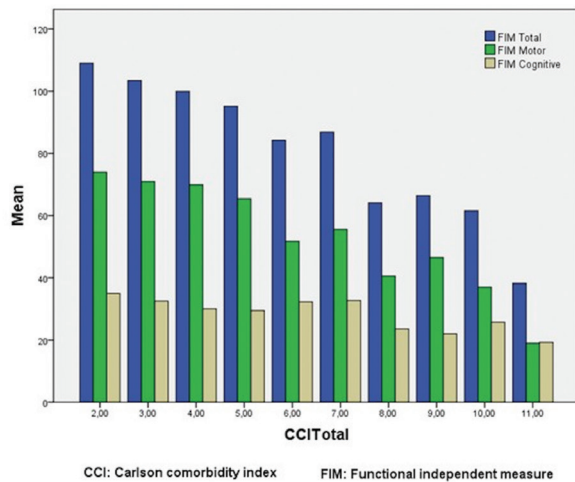


Figure 2. Functional status according to comorbidity rates
CCI: Charlson Comorbidity index, FIM: Functional independence measure

Cases with a history of osteoporotic fractures were significantly older. They had significantly lower FIM motor, FIM cognitive, and FIM total scores and significantly higher CCI total scores ($p<0.05$) (Table 4).

While MOFR showed a positive correlation with CCI total and age, it was negatively correlated with FIM motor, FIM cognitive, and FIM total scores. The multivariate regression analysis model was found to be significant for the CCI total scores of the patients. In the regression analysis, the following results were obtained: $p<0.001$, $R= 0.747$, regression model: $FRAX - MOFR = -1.834+0.846$ CCI total (Table 5).

While HFR showed a positive correlation with CCI total and age, it was negatively correlated with BMI, FIM motor, FIM cognitive, and FIM total scores. The multivariate regression analysis model was found to be significant for the CCI total scores of the patients. In the regression analysis, the following results were obtained: $p<0.001$, $R=0.735$, regression model: $FRAX - HFR = -1.057+0.514$ CCI total (Table 5).

Discussion

Our results showed that the functional status and comorbidity burden of stroke survivors could significantly predict their ten-

Table 2. Comparison of data according to major osteoporotic fracture risk levels

		FRAX-MOFR (<10%)	FRAX-MOFR (10-20%)	FRAX-MOFR ($\geq 20\%$)	p
n; %		106; 76.81%	25; 18.11%	7; 5.08%	
Gender	Male n; %	63; 59.4%	11; 44%	-	0.005*
	Female n; %	43; 40.6%	14; 56%	7; 100%	
Age		63 (49-82)	69 (57-83)	72 (65-83)	<0.001*
BMI (kg/m ²)		26.95 (19.80-41.30)	25.80 (20.80-36.70)	25.70 (23-33.30)	0.565
FIM-motor		68 (13-91)	40 (15-86)	32 (13-73)	<0.001*
FIM-cognitive		32.50 (5-35)	30 (5-35)	26 (5-35)	0.001*
FIM-total		98 (18-126)	68 (22-121)	52 (18-108)	<0.001*
CCI-total		4 (2-10)	8 (3-11)	10 (8-11)	<0.001*

Median (minimum-maximum), percentage: %; * $p<0.05$ significant, BMI: Body mass index, FIM: Functional Independence Measure, CCI: Charlson Comorbidity index, FRAX: Fracture Risk Assessment Tool, MOFR: Major osteoporotic fracture risk

Table 3. Comparison of data according to hip fracture risk levels

		FRAX-HFR ($\geq 3\%$)	FRAX-HFR (<3%)	p
n; %		34; 24.63%	104; 75.36%	
Gender	Male n; %	20; 58.8%	54; 51.9%	0.487
	Female n; %	14; 41.2%	50; 48.1%	
Age		73 (60-83)	62 (49-82)	<0.001*
BMI (kg/m ²)		25.75 (19.90-34)	27 (19.80-41.30)	0.028*
FIM-motor		37.50 (13-81)	69 (13-91)	<0.001*
FIM-cognitive		27 (5-35)	32.50 (5-35)	<0.001*
FIM-total		64 (18-101)	99 (18-126)	<0.001*
CCI-total		9 (6-11)	4 (2-9)	<0.001*

Median (minimum-maximum), percentage: %; * $p<0.05$ significant, BMI: Body mass index, FIM: Functional Independence Measure, CCI: Charlson Comorbidity index, FRAX: Fracture Risk Assessment Tool, HFR: Hip fracture risk

year fracture risk. Comorbidity burden was the independent variable in this study. The decreases in motor and cognitive functions and the increases in comorbidity burden increased the risk of hip and major osteoporotic fractures calculated by the FRAX tool. The patients with a history of osteoporotic fractures were older than those without a history of such fractures. Additionally, the patients with a history of osteoporotic fractures had lower cognitive and motor functions and higher comorbidity burdens than those without a history of such fractures.

An association has been established between stroke and an increased risk of low-trauma fractures (7,8,20). Post-stroke bone fractures are associated with higher morbidity and mortality (9). Although Lai et al. (12) found no relationship between stroke and hip fracture, the consensus is that stroke significantly and independently increases the risk of hip fractures (8). A population-based study demonstrating a significantly higher risk of hip fractures in all stroke types than controls, albeit at higher rates in hemorrhagic stroke, reported that stroke patients had a higher rate of comorbidity than controls. Additionally, a multivariate analysis was performed to adjust for age, sex,

geographic area, and comorbidities, and again, stroke patients were shown to have a significantly higher HFR than controls. Using the National Health Insurance Survey Database, the aforementioned retrospective study did not assess the functional status of patients or the degree of osteoporosis risk (2). Although one study of 186,171 men found that CCI \geq 3 was associated with increased HFR (21), another study in older people found no relationship between CCI and fracture risk (19). Additionally, the results of a meta-analysis showed a negative relationship between comorbidity burden and functional outcomes in stroke patients (5). Studies have reported that comorbidity burden and immobilization cause a significant increase in fracture risk (22,23). One study listed the independent predictors of poor rehabilitation outcomes after ischemic stroke as CCI>3, atrial fibrillation, and previous myocardial infarction (4). In this study, cognitive and motor functions were evaluated with FIM. Consistent with the literature, there was a negative correlation between comorbidity burden and functional outcomes. Furthermore, as the MOFR and HFR of the patients measured with the FRAX tool increased, it was observed that their comorbidity burden increased, and

Table 4. Comparison of data in patients with and without previous osteoporotic fractures

		No prior fracture n=121; 88%	Prior fracture n=17; 12%	p
Gender	Male n; %	65; 53.7%	9; 52.9%	0.952
	Female n; %	56; 46.3%	8; 47.1%	
BMI (kg/m ²)		26.70 (19.80-41.30)	27.70 (20.80-36.70)	0.460
Age		64 (49-83)	68 (60-83)	0.003*
Stroke duration (months)		14 (5-36)	15 (6-33)	0.963
Intensive care period		4 (0-5)	2 (0-4)	0.699
FIM-motor		67 (13-91)	42 (15-86)	0.001*
FIM-cognitive		32 (5-35))	30 (5-35)	0.262
FIM-total		97 (18-126)	75 (22-121)	0.003*
CCI-total		4 (2-11)	8 (4-11)	<0.001*

Mean \pm standard deviation, median (minimum-maximum), percentage: %, *p<0.05significant, BMI: Body mass index, FIM: Functional independence measure, CCI: Charlson Comorbidity index

Table 5. A- The relationships between FRAX-MOFR and data. B- The relationships between FRAX-HFR and data

	FRAX-MOFR				FRAX-HFR			
	Spearman correlation analysis		Multivariate regression analysis		Spearman correlation analysis		Multivariate regression analysis	
	r	p	β	p	r	p	β	p
Age	0.497	<0.001*	0.020	0.768	0.683	<0.001*	0.098	0.163
BMI (kg/m ²)	-0.131	0.126	0.052	0.360	-0.290	0.001*	-0.071	0.219
Stroke duration	0.025	0.773	-0.022	0.660	0.048	0.580	-0.019	0.705
FIM-motor	-0.388	0.000*	-0.615	0.139	-0.499	<0.001*	-0.506	0.234
FIM-cognitive	-0.349	0.000*	-0.197	0.226	-0.412	<0.001*	-0.177	0.288
FIM-total	-0.445	0.000*	0.725	0.159	-0.570	<0.001*	0.521	0.322
CCI-total	0.590	0.000*	0.393	<0.001*	0.768	<0.001*	0.504	<0.001*

Mean \pm standard deviation, median (minimum-maximum), percentage: %, *p<0.05 significant, BMI: Body mass index, FIM: Functional independence measure, CCI: Charlson Comorbidity index, FRAX: Fracture Risk Assessment Tool, MOFR: Major osteoporotic fracture risk, HFR: Hip fracture risk

their functional status decreased. Both HFR and MOFR increased in direct proportion to age. This result differed from studies reporting a higher incidence of hip fractures after stroke in those of a younger age (2). In the multivariate analysis including age, BMI, stroke duration, FIM, and CCI, the effect of CCI was significant for both MOFR and HFR.

A study performed on the elderly population reported that retardation in cognitive and physical functions was associated with higher FRAX scores (19). Additionally, studies have reported an inverse relationship between changes in BMD and the functional statuses of stroke survivors. As a person's functional status deteriorates, the degree of bone density loss increases (7,24). Previous studies with male and female participants have reported a relationship between overall fracture risk and severity of stroke, but no significant relationship has been found between hip fracture risk and stroke severity (20,25). In a cohort of postmenopausal women, worse functional outcome after stroke and a higher FRAX score were associated with an increased risk of subsequent hip fractures (7). Our results showed that those with a high risk of hip and major osteoporotic fractures had significantly lower motor and cognitive functionality levels. The population of our study consisted of men and women who survived strokes; however, the majority of those with high MOFR and HFR values were female. The mean age of the patients in our study was lower than that in the cohort study mentioned above.

Post-stroke fracture risk has been linked to decreased BMD and increased susceptibility to falls. The reduction in skeletal loading on the affected side causes an increase in osteoclastic activity. The decrease in postural stability and muscle strength due to immobility may indirectly lead to decreased skeletal mass and increased risk of falling. BMD may be lower in postmenopausal women (7,23). Studies have also shown that chronic diseases and related drugs can affect bone metabolism, predispose individuals to bone loss (osteoporosis), and thus, increase the risk of bone fractures (2). The incidence of any fracture was previously reported as 9%, while the incidence of hip fractures was 52% in a mean follow-up period of 2.54 years (maximum ten years) after stroke. In the same study, a >7-fold increased risk of fractures, including hip fractures, was found in the first year after hospitalization due to stroke. After this, the fracture risk decreased towards baseline risk levels except for people aged ≥ 80 years, but it still did not completely reach the baseline. The risk ratio for any fracture and hip fracture was reported to be the highest in younger age groups and women. In the study, X-ray or other independent assessments did not confirm fractures. All patients characterized by stroke were included, regardless of whether they were hemiplegic (23). In our study, the patient population consisted of hemiplegic stroke patients. Those with a history of osteoporotic fractures confirmed by imaging constituted 12% of the cases, they were older, and women had a higher proportion. Moreover, the mean stroke duration in this study was 17 months.

According to our knowledge, this is the first prospective study to assess 10-year fracture risk with the FRAX tool in ischemic stroke survivors and investigate the relationship of this variable with comorbidity burden and functional status levels. Previous studies have focused more on the risk of hip fractures in stroke survivors and followed a retrospective data collection path for this. This study also addressed the risk of major osteoporotic fractures. Although it is known that comorbidities such as atrial fibrillation and hypertension are common in stroke patients (26), the use of CCI did not allow us to consider these comorbidities. We thought that standardization might not be achieved in the measurement of femoral BMD, and confusion could occur since there is a difference between the hemiplegic side and hip fractures in those who had hip surgery. For this reason, femoral BMD was not included in the calculation in the FRAX tool. Future studies should target objective data, including BMD.

Conclusion

Currently, the evaluation and treatment of stroke survivors for fracture and/or osteoporosis is a neglected topic. Osteoporosis treatment is indicated if the FRAX index is $\geq 20\%$ for significant osteoporotic fracture risk and $\geq 3\%$ for hip fracture risk. Our results showed that motor and cognitive function and comorbidity burden could predict 10-year fracture risk (major osteoporotic fracture risk and hip fracture risk) measured by the FRAX index in stroke survivors. We think that assessing the functional status and comorbidities of stroke survivors may be as crucial as the FRAX index for predicting fracture risk. Future studies may focus on developing a new index, including functional status and comorbidity burden, on determining the risk of osteoporotic fractures and indications for treatment in stroke survivors.

Ethics

Ethics Committee Approval: The study was planned in compliance with the principles of the Declaration of Helsinki and was approved by the Bursa Yüksek İhtisas Training and Research Hospital Ethics Committee (decision no: 2011-KAEK-25 2019/05-03, date: 22.05.2019).

Informed Consent: All patients and/or their legal representatives were informed about the study, and they gave written and signed informed consent.

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Authorship Contributions

Surgical and Medical Practices: İ.A.K., M.K.A, Concept: İ.A.K., M.K.A, Design: İ.A.K., M.K.A, Data Collection or Processing: İ.A.K., M.K.A, Analysis or Interpretation: İ.A.K., M.K.A, Literature Search: İ.A.K., M.K.A, Writing: İ.A.K., M.K.A.

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References

- Orellana-Urzuá S, Rojas I, Líbano L, Rodrigo R. Pathophysiology of Ischemic Stroke: Role of Oxidative Stress. *Curr Pharm Des* 2020;26:4246-60.
- Zheng JQ, Lai HJ, Zheng CM, Yen YC, Lu KC, Hu CJ, et al. Association of stroke subtypes with risk of hip fracture: a population-based study in Taiwan. *Arch Osteoporos* 2017;12:104.
- Ofori-Asenso R, Zomer E, Chin KL, Si S, Markey P, Tacey M, et al. Effect of Comorbidity Assessed by the Charlson Comorbidity Index on the Length of Stay, Costs and Mortality among Older Adults Hospitalised for Acute Stroke. *Int J Environ Res Public Health* 2018;15:2532.
- Simić-Panić D, Bošković K, Milićević M, Rabi Žikić T, Cvjetković Bošnjak M, Tomašević-Todorović S, et al. The Impact of Comorbidity on Rehabilitation Outcome after Ischemic Stroke. *Acta Clin Croat* 2018;57:5-15.
- Kabboord AD, van Eijk M, Fiocco M, van Balen R, Achterberg WP. Assessment of Comorbidity Burden and its Association With Functional Rehabilitation Outcome After Stroke or Hip Fracture: A Systematic Review and Meta-Analysis. *J Am Med Dir Assoc* 2016;17:1066.e13-21.
- Duffield SJ, Ellis BM, Goodson N, Walker-Bone K, Conaghan PG, Margham T, et al. The contribution of musculoskeletal disorders in multimorbidity: Implications for practice and policy. *Best Pract Res Clin Rheumatol* 2017;31:129-44.
- Northuis CA, Crandall CJ, Margolis KL, Diem SJ, Ensrud KE, Lakshminarayan K. Association between post-stroke disability and 5-year hip-fracture risk: The Women's Health Initiative. *J Stroke Cerebrovasc Dis* 2020;29:104976.
- Luan L, Li R, Wang Z, Hou X, Gu W, Wang X, et al. Stroke increases the risk of hip fracture: a systematic review and meta-analysis. *Osteoporos Int* 2016;27:3149-54.
- Frost SA, Nguyen ND, Black DA, Eisman JA, Nguyen TV. Risk factors for in-hospital post-hip fracture mortality. *Bone* 2011;49:553-8.
- Ramnemark A, Nilsson M, Borssén B, Gustafson Y. Stroke, a major and increasing risk factor for femoral neck fracture. *Stroke* 2000;31:1572-7.
- Walsh ME, Sorensen J, Galvin R, Williams DJ, Harbison JA, Murphy S, et al. First year post-stroke healthcare costs and fall-status among those discharged to the community. *Eur Stroke J* 2018;3:254-62.
- Lai SW, Liao KF, Lai HC, Tsai PY, Lin CL, Chen PC, et al. Risk of major osteoporotic fracture after cardiovascular disease: a population-based cohort study in Taiwan. *J Epidemiol* 2013;23:109-14.
- Compston J. FRAX—Where are we now? *Maturitas* 2015;82:284-7.
- Ramnemark A, Nyberg L, Borssén B, Olsson T, Gustafson Y. Fractures after stroke. *Osteoporos Int* 1998;8:92-5.
- Hall KM, Hamilton BB, Gordon WA, Zasler ND. Characteristics and comparisons of functional assessment indices: disability rating scale, functional independence measure, and functional assessment measure. *The Journal of Head Trauma Rehabilitation* 1993;8:60-74.
- Küçükdeveci AA, Yavuzer G, Elhan AH, Sonel B, Tennant A. Adaptation of the Functional Independence Measure for use in Turkey. *Clin Rehabil* 2001;15:311-9.
- Jiménez Caballero PE, López Espuela F, Portilla Cuenca JC, Ramírez Moreno JM, Pedrera Zamorano JD, Casado Naranjo I. Charlson comorbidity index in ischemic stroke and intracerebral hemorrhage as predictor of mortality and functional outcome after 6 months. *J Stroke Cerebrovasc Dis* 2013;22:e214-8.
- Falsetti L, Viticchi G, Tarquinio N, Silvestrini M, Capeci W, Catozzo V, et al. Charlson comorbidity index as a predictor of in-hospital death in acute ischemic stroke among very old patients: a single-cohort perspective study. *Neurol Sci* 2016;37:1443-8.
- González Silva Y, Abad Manteca L, de la Red Gallego H, Álvarez Muñoz M, Rodríguez Carbajo M, Murcia Casado T, et al. Relationship between the FRAX index and physical and cognitive functioning in older people. *Ann Med* 2018;50:538-43.
- Kapral MK, Fang J, Alibhai SM, Cram P, Cheung AM, Casaubon LK, et al. Risk of fractures after stroke: Results from the Ontario Stroke Registry. *Neurology* 2017;88:57-64.
- Reyes C, Estrada P, Nogués X, Orozco P, Cooper C, Díez-Pérez A, et al. The impact of common co-morbidities (as measured using the Charlson index) on hip fracture risk in elderly men: a population-based cohort study. *Osteoporos Int* 2014;25:1751-8.
- Ensrud KE, Kats AM, Boyd CM, Diem SJ, Schousboe JT, Taylor BC, et al. Association of Disease Definition, Comorbidity Burden, and Prognosis With Hip Fracture Probability Among Late-Life Women. *JAMA Intern Med* 2019;179:1095-103.
- Kanis J, Oden A, Johnell O. Acute and long-term increase in fracture risk after hospitalization for stroke. *Stroke* 2001;32:702-6.
- Lazoura O, Groumas N, Antoniadou E, Papadaki PJ, Papadimitriou A, Thriskos P, et al. Bone mineral density alterations in upper and lower extremities 12 months after stroke measured by peripheral quantitative computed tomography and DXA. *J Clin Densitom* 2008;11:511-7.
- Lisabeth LD, Morgenstern LB, Wing JJ, Sanchez BN, Zahuranec DB, Skolarus LE, et al. Poststroke fractures in a bi-ethnic community. *J Stroke Cerebrovasc Dis* 2012;21:471-7.
- Pastuszak Ż, Koźniewska E, Stępień A, Piusińska-Macoch A, Czernicki Z, Koszewski W. Importance rating of risk factors of ischemic stroke in patients over 85 years old in the Polish population. *Neurol Neurochir Pol* 2018;52:88-93.