Post Stroke Fatigue; Frequency, Risk Factors, Radiological Topographic Localization and Impact on Quality of Life

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Abstract
Background: Stroke, a leading global cause of death, categorized as ischemic or hemorrhagic. Post-stroke fatigue (PSF) is common, impacting quality of life, rehabilitation, and survival, with hypertension and diabetes as contributing comorbidities. Identifying risk factors is complex due to the multifaceted nature of fatigue.
Objectives: Examine factors affecting PSF, disease frequency, and its impact on patient recovery and quality of life, focusing on Upper Egypt.
Patients and methods: Study involved stroke-fatigued 200 patients and 129 stroke patients without fatigue, at Qena University Hospital. Age ranged from 16 to 75, with a 3-month follow-up within a year after stroke onset. Assessments included demographics, risk factors, stroke severity (NIHSS), cognitive function (MoCA, Mini-Mental), insomnia symptoms (ATHENS), functional outcomes (Modified Rankin Scale, Barthel Index), depression and anxiety severity (Hamilton scales), fatigue (MFI), and overall quality of life (WHOQOL-BREF).
Results: Post-stroke fatigue linked to worse cognitive scores, severe stroke symptoms (higher NIHSS), more disability (Modified Rankin), higher fatigue (MFI), and slighter quality of life (WHQOOL). Depressive and anxiety scores were higher in fatigued patients (Hamilton). Male gender, education negatively correlated with fatigue ($P < 0.05$). No major correlations with age, rural areas, marital status, comorbidities.
Conclusion: Weariness is strongly linked to cognitive impairment in stroke patients. Higher NIHSS stroke severity is connected to fatigue, emphasizing stroke care. Fatigue impairs functional measures like the Modified Rankin Scale but not daily living (Barthel Index). Physical and environmental variables affect fatigue and quality of life. Post-stroke fatigue is caused by cognitive issues, stroke severity, and functional limitations.
Keywords: Stroke; Fatigue; Post-stroke Fatigue; Depression; Anxiety.

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Introduction

Stroke is classified into two main types: ischemic stroke and hemorrhagic stroke. It is a major cause of mortality worldwide, especially in low- and middle-income nations. In 2017, there were an estimated 11.9 million new cases of stroke. The prevalence of stroke was estimated to be 104.2 million, out of these cases, 6.2 million were fatal. Additionally, there were 132.1 million disability-adjusted life-years (DALYs) attributed to stroke **(Krishnamurthi et al., 2020).** In 2017, worldwide, IS accounted for 65% of all new cases of strokes, primary intracerebral hemorrhage (PICH) accounted for 26%, and subarachnoid hemorrhage (SAH) accounted for 9% **(Johnson et al., 2019; Zhan et al., 2023).**

Fatigue can be categorized as either objective or subjective. Objective fatigue refers to a noticeable and quantifiable decline in performance that occurs when a physical or mental task is repeated. On the other hand, subjective fatigue is characterized by a sense of early exhaustion, weariness, and reluctance to exert effort **(Staub & Bobousslavsky, 2001; Behrens et al., 2023).**

Post-stroke fatigue (PSF) is a troubling outcome of stroke, which can manifest as either a short-term or long-term condition **(Mutai et al., 2017; Kuppuswamy et al., 2023).** Survivors of stroke often experience concomitant medical illnesses, such as hypertension and diabetes mellitus, which can independently cause fatigue **(Mahon et al., 2018).** The lack of agreement on risk factors for post-stroke fatigue may be attributed to the complex and diverse nature of fatigue **(Parks et al., 2012; Jolly et al., 2023).**

Post-stroke fatigue (PSF) has a detrimental impact on the overall well-being, raises the risk of death, and hinders the process of stroke rehabilitation **(Wen et al., 2018)**. Considering the frequency of stroke and the widespread and harmful effects of PSF on quality of life, ability to live independently, and overall survival, it is crucial to prioritize effective management of PSF in stroke rehabilitation (**Shaik et al., 2024).** Furthermore, the level of weariness experienced by stroke survivors is affected by other symptoms associated with stroke, such as post-stroke depression (PSD) **(Byun et al., 2020).**

Post-stroke fatigue is commonly considered to be a primary kind of fatigue (**Larsson et al., 2023)**. However, we have suggested other contributing elements that are specific to post-stroke fatigue, including age, sex, residence, de-conditioning, physical handicap, disuse, sleep difficulties, adverse effects of medications, and depression (**Yadav & Joshi, 2022).**

In this research we will discuss relationship between considerable risk factors related to PSF, frequency of the disease and the impact of the disease on the quality of life and recovery of the patients in Upper Egypt.

Patients and methods

This was a prospective cohort study that was conducted on patients randomly seeking the medical care of the Neuropsychiatry Department of Qena University Hospital between July 2022 and April 2023. It received approval from the ethical committee under the number **SVU-MED-NAP020-1-22-1-306.**

Our inclusion criteria included patients with ischemic or hemorrhagic stroke, aged 16-75 years, of both genders. Exclusion criteria were patients with traumatic intracerebral hemorrhage, patients younger than 16 years of age or older than 70 years, patients with a history of anti-depressive drug intake before strokes and patients with recurrent strokes.

Stroke patients are those who experience a sudden onset of symptoms indicating a disruption in brain function, either in a specific area or throughout the entire brain. These symptoms persist for more than 24 hours or result in death and are not caused by any factors other than those related to blood vessel issues (**Aho et al., 1980**). Our study included 200 stroke cases complicated with fatigue and 129 cases with stroke not complicated with fatigue.

Patients were divided according to laterality of the affected site into right or left affect. Also, the patients were divided into supratentorial and Infratentorial groups. The 200 patients, ischemic and hemorrhagic stroke with fatigue together where the evaluation was done up to one year after stroke onset with follow up for 3 months.

The following demographic data were collected from all stroke patients: age, sex, residence, occupation and educational level as well as risk factor assessment including hypertension, diabetes, cardiac, smoking or illicit drugs. Laboratory investigation to rule out chronic diseases which may contribute to fatigue was done. Brain imaging by CT brain or MRI brain was done when indicated.

The stroke severity was measured by National Institutes of Health Stroke Scale (NIHSS) (**Brott et al., 1989**). Stroke outcome was evaluated by Modified Rankin scale and Barthel index (**Collin et al., 1988; Wilson et al., 2005**). Hamilton depression scale and Hamilton anxiety scale to assess the presence and severity of depression and anxiety, respectively, were also performed (**Hamilton, 1959; Hamilton, 196**). Cognitive function was assessed by Montreal cognitive assessment and mini mental state examination (**Folstein et al., 1975; Nasreddine et al., 2005**).

Athens' insomnia scale to assess the insomnia symptoms in patients with sleep disorders was carried out (**Soldatos et al., 2000**). Post stroke fatigue was evaluated by Multidimensional fatigue inventory scale (MFI) (**Smets et al., 1995**). The quality of life with post stroke fatigue was assessed by The World Health Organization Quality of Life (WHOQOL)-BREF (**The Whoqol Group, 1998**). Body mass index was calculated as a person's weight in kilograms divided by the square of height in meters (**Ramirez, 2005).**

MFI (**Smets et al., 1995**) and WHOQOL scale tests (**Sartorius, 1993)** were also used to assess patients.

In our study scales were utilized as following:

- **MoCA (Montreal Cognitive Assessment):** This scale was used to evaluate cognitive functioning and screen for mild cognitive impairment in stroke patients.
- **Mini-Mental:** Another cognitive assessment scale used in the study, the Mini-Mental scale, was employed to assess cognitive impairment and dementia in stroke patients.
- **NIHSS (National Institutes of Health Stroke Scale):** The NIHSS was used to evaluate the severity of a stroke and its impact on various neurological functions, aiding in the assessment of stroke-related impairments.
- **ATHENS (Assessment Tool for insomnia):** The questionnaire consists of eight items that assess many aspects of sleep, including the time it takes to

fall asleep, waking up during the night and early morning, total sleep time, the quality of sleep, the frequency and length of sleep-related complaints, the discomfort caused by insomnia, and how it affects daily functioning.

- **Modified Rankin Scale:** As a widely used scale, the Modified Rankin Scale helped assess functional outcomes and disability in stroke patients, providing valuable information on their level of independence.
- **Barthel Index:** The Barthel Index was employed to measure the level of independence in performing activities of daily living (ADL), offering insights into the functional abilities of stroke patients.
- **Hamilton Depression Scale:** This scale assisted in evaluating the severity of depression symptoms in stroke patients, shedding light on the emotional impact of stroke.
- **Hamilton Anxiety Scale:** The Hamilton Anxiety Scale was used to assess the severity of anxiety symptoms in stroke patients, providing information on their emotional well-being.
- **MFI (Multidimensional Fatigue Inventory):** With the MFI scale, we measured fatigue levels in stroke patients, enabling them to understand the impact of fatigue on the patients' quality of life.
- **WHOQOL-BREF (World Health Organization Quality of Life-BREF):** As a comprehensive tool, the WHOQOL-BREF assessed the overall quality of life in stroke patients, covering various domains such as physical health, psychological well-being, social relationships, and environmental factors.

Statistical analysis

The computer-generated data was analyzed using IBM SPSS version 22.0. Quantitative data was conveyed using percentages and numerical values. Prior to employing the median in nonparametric analysis or the interquartile range in parametric analysis, it was necessary to conduct Kolmogorov-Smirnov tests to verify the normality of the data. We employed a significance threshold of 0.05 to determine the statistical significance of the data. The Chi-Square test is employed to compare and analyze many groups. The Monte Carlo test can be employed to correct for any cells having a count below 5. The Fischer Chi-Square adjustment was utilized to analyze tables containing non-continuous data.

Results

Regarding comorbidities in the group with post stroke fatigue, 169 (85%) patients were hypertensive, 118 (59%) patients had diabetes, 85 (43%) patients had renal impairment, and 100 (50%) patients had cardiac impairment (**Fig.1**). The average BMI of our patients was 26.9 (SD = 2.1, Range = 21:38).

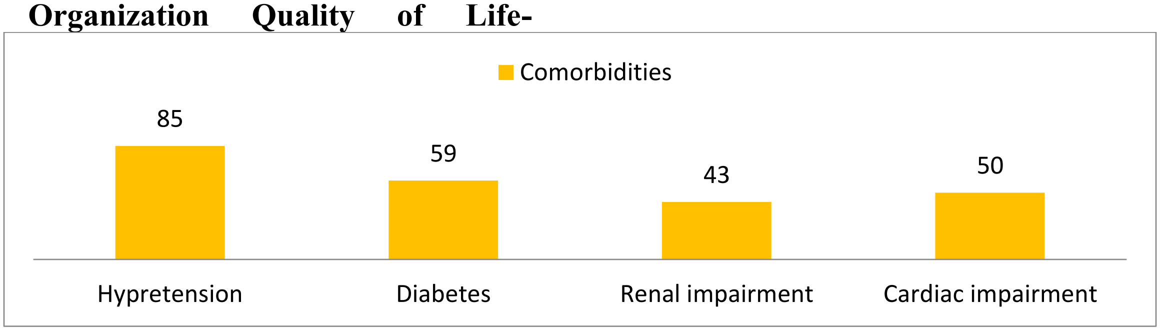

Fig.1. Comorbidities of patients.

The temporoparietal region was identified as the predominant site of stroke affection, accounting for 17% of the cases. The parietal region closely followed with a prevalence of 16.5%. Notably, brain stem involvement was observed in a 5.5% of cases. The frontal and thalamus regions also demonstrated a considerable frequency of stroke occurrence, comprising 3.5% and 6% of the cases, respectively. Fewer incidences of combined brain stem with cerebellum (0.5%) and parietothalamic (0.5%) regions **(Table.1; Fig.2).**

Table.1. Sites of stroke affection in patients.

Site	Number	Percentage
Basal ganglia	20	10%
Brain stem	11	5.5%
Brain stem & Cerebellum	1	0.5%
Cerebellum	5	2.5%
Frontal	7	3.5%
Frontoparietal	3	1.5%
Frontotemporoparietal	3	1.5%
Internal Capsule	10	5%
Occipital	9	4.5%
Parietal	33	16.5%
Parietothalamic	1	0.5%
Parietooccipital	4	2%
Temporal	6	3%
Temporoparietal	34	17%
Thalamus	12	6%

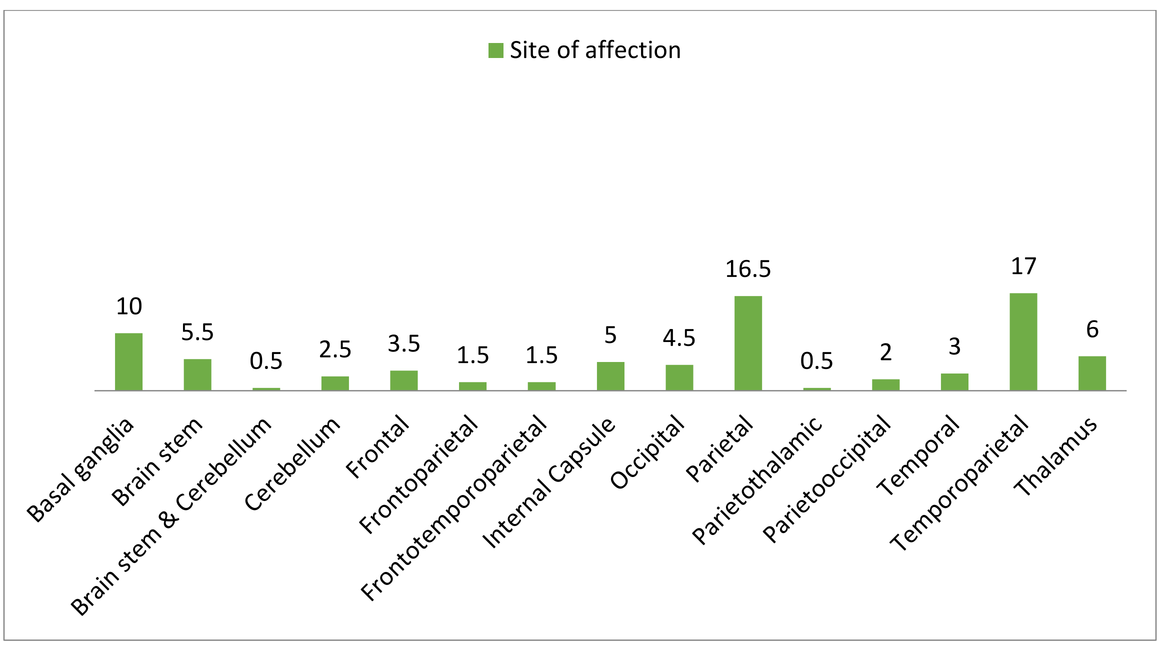

Fig. 2. Sites of stroke affection in patients.

The largest percentage of patients falls under Rankin Score 5, accounting for 28% of the cases, indicating a substantial level of disability among this subgroup. Additionally, significant portions of the population fall into the Rankin Score 3 and Rankin Score 4 categories, representing 26% and 24.5% of cases, respectively. On the other hand, a smaller percentage of patients achieved better functional outcomes, with Rankin Score 1 and Rankin Score 2 accounting for 5.5% and 16% of cases, respectively **(Table.2; Fig.3).**

Table 2. Modified Rankin Score.

Modified Rankin	Number	Percentage
1	11	5.5%
2	32	16%
3	52	26%
4	49	24.5%
5	56	28%

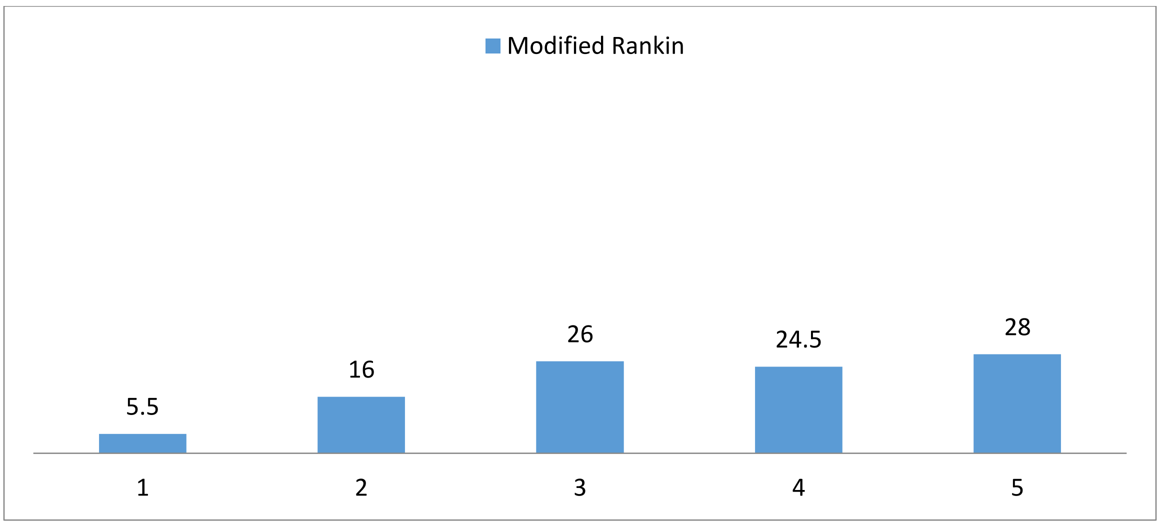

Fig.3. Modified Rankin Scale of Patients.

Regarding cognitive assessment, there were no significant differences between the two types of strokes in MoCA (Ischemic group: 17.3, Hemorrhagic group: 17.7, p = 0.66) and Mini-Mental scores (Ischemic group: 19, Hemorrhagic group: 19.5, p = 0.57). Similarly, stroke severity, as measured by NIHSS, showed no significant difference (Ischemic group: 7.2, Hemorrhagic group: 6.8, p = 0.37). However, in terms of sleep disorders, the ATHENS score was significantly better in the Hemorrhagic group (Ischemic group: 5.2, Hemorrhagic group: 4.1, p = 0.03), indicating superior performance. Regarding functional outcomes, the Modified Rankin Scale revealed a noteworthy finding, with the Hemorrhagic group exhibiting significantly better functional outcomes (Ischemic group: 3.7, Hemorrhagic group: 3.3, p = 0.02). On the other hand, there were no significant differences in activities of daily living, as measured by the Barthel Index (Ischemic group: 58.4, Hemorrhagic group: 61.3, p = 0.48). The study also investigated depression and anxiety, with the Hamilton Depression Scale and Hamilton Anxiety Scale showing no significant differences between the groups (Hamilton Depression Scale: Ischemic group: 9.7, Hemorrhagic group: 8.7, p = 0.14; Hamilton Anxiety Scale: Ischemic group: 7.7, Hemorrhagic group: 9.7, p = 0.74). Similarly, there were no significant differences in fatigue levels, as measured by MFI (Ischemic group: 47.5, Hemorrhagic group: 45.6, p = 0.38), and overall quality of life, as assessed by WHOQOL-BREF (Ischemic group: 67.8, Hemorrhagic group: 67.1, p = 0.8) **(Table.3; Fig.4).**

Table.3. Comparison between Ischemic & Hemorrhagic Groups Scales.

Variables	Ischemic group (SD)	Hemorrhagic group (SD)	p value
MoCA	17.3 (4.8)	17.7 (5.5)	.66
Mini-Mental	19 (6)	19.5 (6.6)	.57
NIHSS	7.2 (3.4)	6.8 (3.7)	.37
ATHENS	5.2 (3.4)	4.1 (3.7)	.03
Modified Rankin	3.7 (1.2)	3.3 (1.2)	.02
Barthel Index	58.4 (27.4)	61.3 (29.5)	.48
Hamilton Depression	9.7 (4.7)	8.7 (4.4)	.14
Hamilton Anxiety	7.7 (4.2)	9.7 (4.7)	.74
MFI	47.5 (15)	45.6 (16)	.38
WHOQOL-BREF	67.8 (17.7)	67.1 (18)	.8

SD: standard deviation

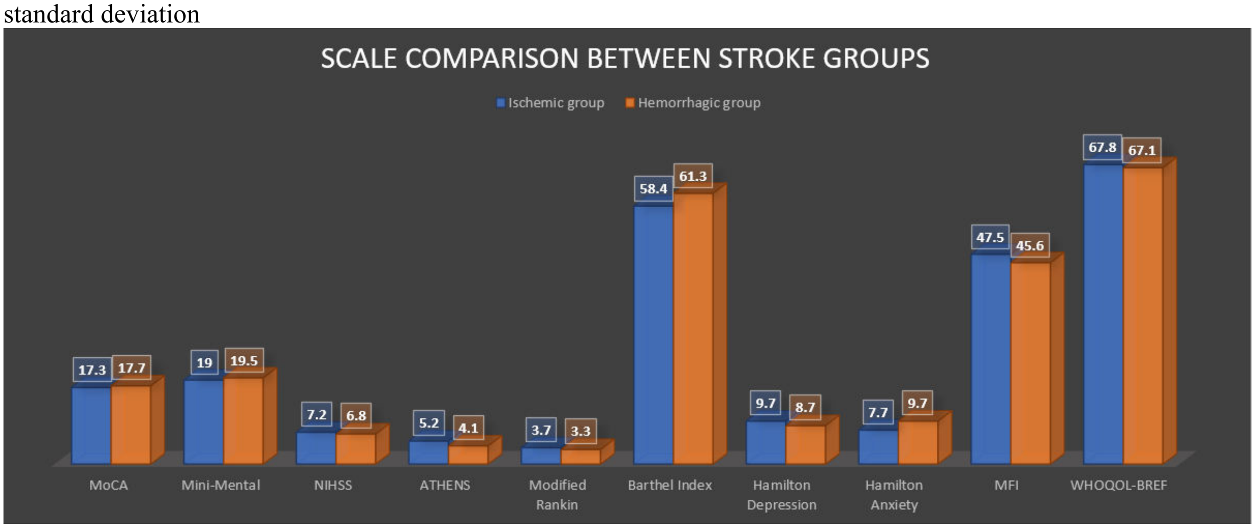

Fig.4. Comparison between Ischemic & Hemorrhagic Group Scales.

The findings revealed no significant differences between the post stroke fatigued patients and post stroke non fatigued patients in cognitive functioning, as measured by MoCA scores (Right group: 17.6, SD: 5; Left group: 17.5, SD: 5; p = .898) and Mini-Mental scores (Right group: 19.5, SD: 6; Left group: 18.9, SD: 6.3; p = .518). Additionally, stroke severity, assessed by NIHSS, showed no significant difference (Right group: 7.3, SD: 3.5; Left group: 6.7, SD: 3.5; p = .217). Furthermore, there were no significant differences in episodic memory (ATHENS) between the Right group (4.7, SD: 3.6) and the Left group (4.5, SD: 3.5; p = .792). Functional outcomes, measured by the Modified Rankin Scale, also exhibited no significant difference (Right group: 3.5, SD: 1.2; Left group: 3.5, SD: 1.2; p = .95). Activities of daily living, as assessed by the Barthel Index, showed similar levels of independence between the Right group (61.8, SD: 27.9) and the Left group (58.1, SD: 28.7; p = .375). Moreover, depression and anxiety levels, measured using the Hamilton Depression Scale and Hamilton Anxiety Scale, respectively, demonstrated no significant differences (Right group: 9.3, SD: 4.3; Left group: 9.1, SD: 4.8; p = .733 and Right group: 7.5, SD: 4; Left group: 7.6, SD: 4.8; p = .833). Additionally, there were no significant differences in fatigue levels, as measured by MFI (Right group: 46, SD: 14.1; Left group: 46.6, SD: 16.3; p = .811), and overall quality of life, assessed by WHOQOL-BREF (Right group: 68, SD: 17.9; Left group: 64.9, SD: 21.6; p = .752) between the Right and Left groups **(Table.4; Fig.5).**

Table 4. Comparison between the Right side affected & Left side affected Groups regarding Scales.

Variables	Right group (SD)	Left group (SD)	p value
MoCA	17.6 (5)	17.5 (5)	.898
Mini-Mental	19.5 (6)	18.9 (6.3)	.518
NIHSS	7.3 (3.5)	6.7 (3.5)	.217
ATHENS	4.7 (3.6)	4.5 (3.5)	.792
Modified Rankin	3.5 (1.2)	3.5 (1.2)	.95
Barthel Index	61.8 (27.9)	58.1 (28.7)	.375
Hamilton Depression	9.3 (4.3)	9.1 (4.8)	.733
Hamilton Anxiety	7.5 (4)	7.6 (4.8)	.833
MFI	46 (14.1)	46.6 (16.3)	.811
WHOQOL-BREF	68 (17.9)	64.9 (21.6)	.752

SD: standard deviation

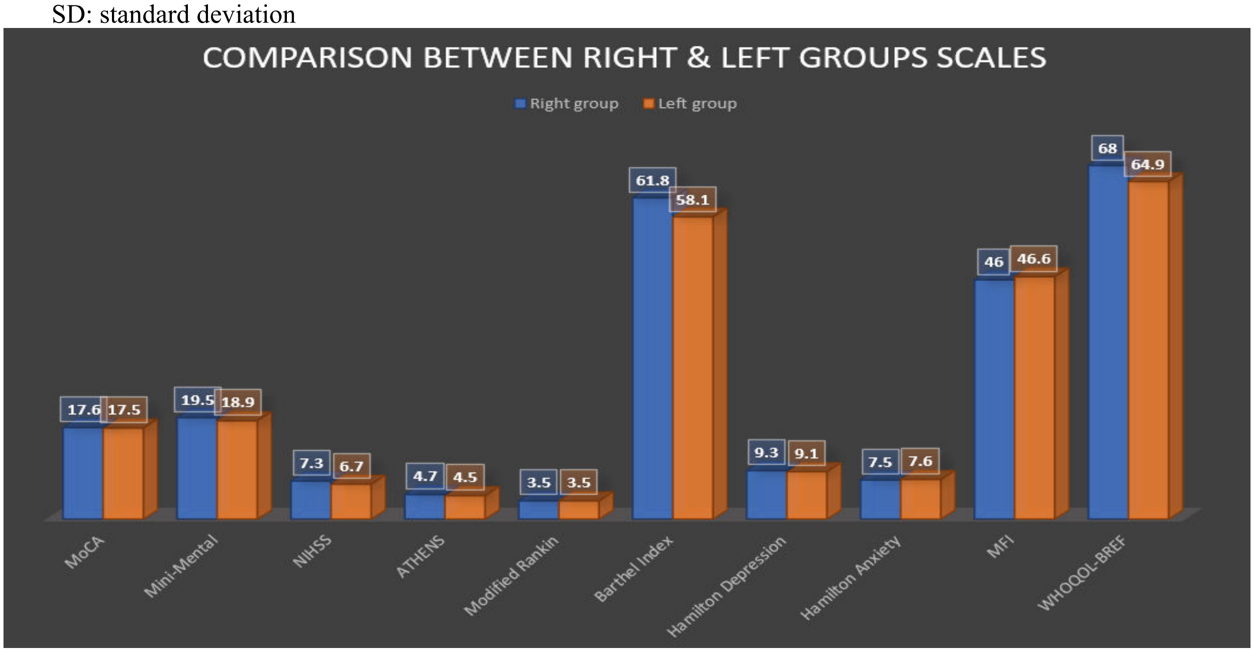

Fig.5. Comparison between Right & Left Group Scales.

The numerical data and significance revealed the following: The MoCA scores showed no significant difference between the Supratentorial group (17.3, SD: 5) and Infratentorial group (19.4, SD: 5.6; p = .096), indicating similar cognitive functioning. However, the Mini-Mental scores displayed a significant difference, with the Supratentorial group scoring lower (18.6, SD: 6) compared to the Infratentorial group (23.5, SD: 7; p = .002), suggesting better cognitive performance in the Infratentorial group. While the NIHSS scores showed no significant difference (Supratentorial group: 7.1, SD: 3.5; Infratentorial group: 5.5, SD: 1.7; p = .055), indicating comparable stroke severity, the Modified Rankin Scale scores revealed a significant difference (Supratentorial group: 3.6, SD: 1.2; Infratentorial group: 2.8, SD: 1; p = .006), indicating better functional outcomes in the Infratentorial group. Furthermore, the Barthel Index scores showed a significant difference (Supratentorial group: 59, SD: 27.7; Infratentorial group: 74.4, SD: 24.8; p = .025), indicating higher levels of independence in activities of daily living in the Infratentorial group. The Hamilton Depression Scale scores also displayed a significant difference (Supratentorial group: 9.4, SD: 4.5; Infratentorial group: 6.7, SD: 3.3; p = .012), suggesting higher levels of depression in the Supratentorial group. However, no significant differences were observed in episodic memory (ATHENS), anxiety levels (Hamilton Anxiety Scale), and fatigue (MFI) between the two groups. Interestingly, the WHOQOL-BREF scores showed a significant difference (Supratentorial group: 66.1, SD: 17.5; Infratentorial group: 74.8, SD: 15.7; p = .045), indicating better quality of life in the Infratentorial group **(Table 5; Fig. 6).**

Table 5. Comparison between Supratentorial & Infratentorial Groups Scales.

Variables	Supratentorial group (SD)	Infratentorial group (SD)	p value
MoCA	17.3 (5)	19.4 (5.6)	.096
Mini-Mental	18.6 (6)	23.5 (7)	.002
NIHSS	7.1 (3.5)	5.5 (1.7)	.055
ATHENS	4.8 (3.4)	5.4 (5.1)	.478
Modified Rankin	3.6 (1.2)	2.8 (1)	.006
Barthel Index	59 (27.7)	74.4 (24.8)	.025
Hamilton Depression	9.4 (4.5)	6.7 (3.3)	.012
Hamilton Anxiety	7.8 (4.3)	8.1 (5.4)	.75
MFI	47.3 (15.2)	40.1 (11.6)	.05
WHOQOL-BREF	66.1 (17.5)	74.8 (15.7)	.045

SD: standard deviation

We found a significant negative correlation between male gender and MFI (r= -0.21, P. Value= 0.003). Additionally, there was a significant negative correlation between education and MFI (r= -0.142, P. Value= 0.045). However, no significant correlations were found between MFI and age, rural areas, marital status, hypertension, diabetes, renal disease, or cardiac disease **(Table.6).**

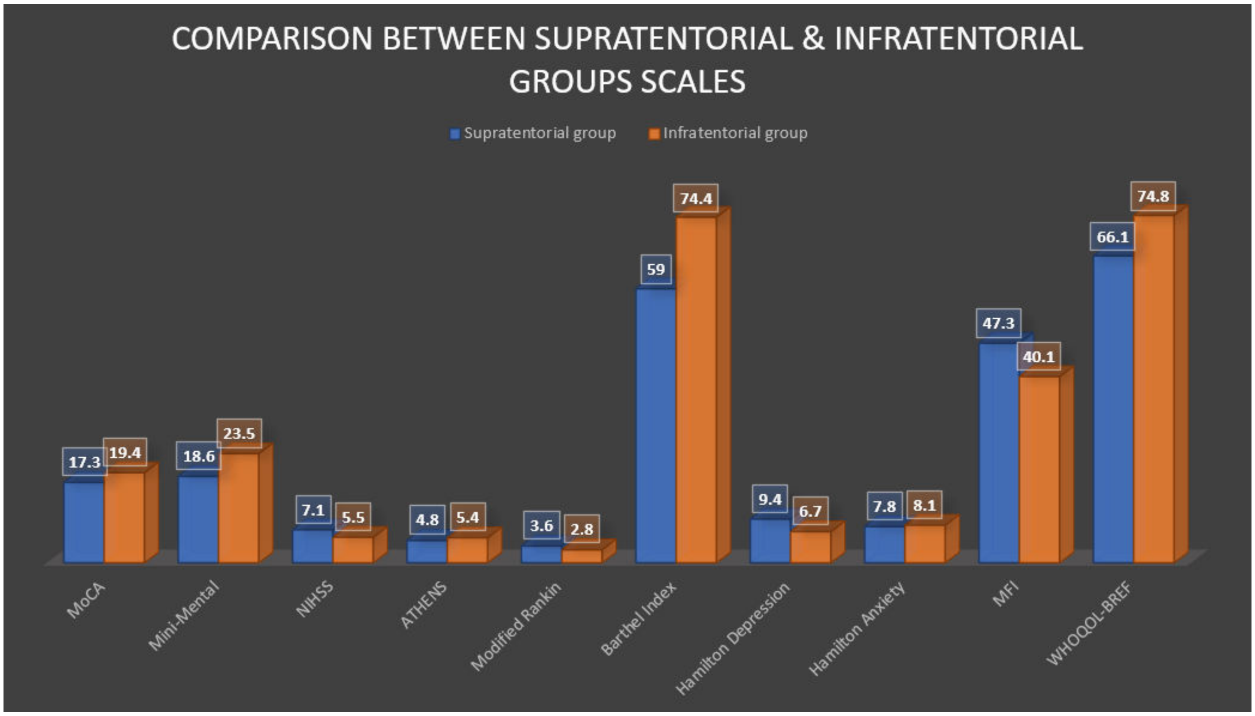

Fig.6. Comparison between Supratentorial & Infratentorial Groups Scales.

Table 6. Correlation between MFI and different stroke risk factors.

Variables		MFI
Male gender	r	-0.21
	p	0.003
Age	r	0.067
	p	0.349
Education	r	-0.142
	p	0.045
Rural areas	r	0.04
	p	0.56
Marital status	r	-0.1
	p	0.12
Hypertension	r	0.08
	p	0.29
Diabetes	r	0.002
	p	0.98
Renal disease	r	0.09
	p	0.22
Cardiac disease	r	0.03
	p	0.72

The Post stroke fatigued patients showed significantly lower scores in cognitive assessments (MOCA and Minimintal) compared to Post stroke non fatigued patients ($P < 0.001$*). Additionally, the Post stroke fatigued patients had higher scores on the NIHSS (National Institutes of Health Stroke Scale), indicating more severe stroke symptoms ($P < 0.001$*). Their BMI was also significantly higher than that of Post stroke non fatigued patients (P = 0.001*). Moreover, the Modified Rankin scores were notably higher in Post stroke fatigued patients, suggesting increased disability and dependence on others (P < 0.001*). The Post stroke fatigued patients reported higher levels of fatigue (MFI scores) (P = 0.006*) compared to controls. The WHQOOL (World Health Organization Quality of Life) assessment revealed that the cases had significantly lower scores in the Physical domain (P < 0.001*) and Environment domain (P = 0.011*), while the Total WHQOOL score was higher in controls (P < 0.001*). However, no statistically significant differences were found in the ATHENS score, as well as in the Psychological and Social domains of WHQOOL **(Table.7).**

Table 7. Comparison between post stroke fatigued patients and post stroke non fatigued patients regarding different assessment scales.

Variables	Fatigued patients (N = 200)	Non fatigued patients (N = 129)	P. Value
MOCA	18 (8-30)	22 (10-30)	MWU<0.00001 *
Minimintal	19 (8-30)	23 (10-30)	MWU<0.00001 *
NIHSS	7.09 ± 2.96	5.9 ± 2.74	t=0.00028*
ATHENS	5 (0-15)	4 (1-10)	MWU=0.13104
BMI	626 (18-38)	24 (20-32)	MWU=0.00138 *
Modified Rankin	3.71 ± 1.13	2.88 ± 1.08	t<0.00001*
Barthel index	60.83 ± 24.87	64.57 ± 25.38	t=0.18728
WHQOOL			
Physical	64.28 ± 16.7	74.4 ± 16.83	t<0.00001*
Psychological	88 (31-100)	88 (50-100)	MWU=0.06724
Social	87.79 ± 10.99	88.28 ± 8.95	t=0.67267
Environment	76.88 ± 17.42	81.88 ± 17.04	t=0.01088*
Total	81 (35-100)	88 (44-100)	MWU<0.00001 *

MWU: Mann-Whitney U, t: T. Test; *P<0.05 Statistically significant

For Hamilton depression, the median score for Post stroke fatigued patients is 7.5 (range: 2-19), higher than Post stroke non fatigued patients with a median of 7 (range: 2-15). The Mann-Whitney U test reveals a statistically significant difference (p=0.004) in overall depression levels between Post stroke fatigue and non-fatigued patients, indicating that cases tend to have slightly higher levels of depression. However, when examining the distribution of depression severity categories, the Chi-Square test shows no significant differences (p > 0.05) between the two groups regarding nil and mild categories. However, moderate depression was significantly prevalent among Post stroke fatigued patients. Regarding Hamilton anxiety, Post stroke fatigued patients have a median anxiety score of 5 (range: 2-19), slightly higher than Post stroke non fatigued patients with a median of 4 (range: 1-17). The Mann-Whitney U test indicates a statistically significant difference (p=0.003) in overall anxiety levels between Post stroke fatigued and non-fatigued patients, indicating that Post stroke fatigued patients tend to have slightly higher anxiety levels. However, similar to depression, the Chi-Square test shows no significant differences (p > 0.05) in the distribution of anxiety severity categories between Post stroke fatigued and non-fatigued patients **(Table.8).**

Table 8. Comparison between post stroke fatigued patients and post stroke non fatigued patients regarding Hamilton scales.

Variables	Fatigued patients (N = 200)	Non-fatigued patients(N = 129)	P. Value
Hamilton depression	7.5 (2-19)	7 (2-15)	MWU=0.00374*
Nil (0-7)	100 (50%)	74 (57.36%)	X^2=0.1914
Mild (8-16)	91 (45.5%)	55 (42.64%)	X^2=0.6097
Moderate (17-23)	9 (4.5%)	0 (0%)	f=0.0135
Hamilton anxiety	5 (2-19)	4 (1-17)	MWU=0.00278*
Nil (0-6)	124 (62%)	93 (72.09%)	X^2=0.0593
Mild (7-17)	74 (37%)	36 (27.91%)	X^2=0.0879
Moderate (18-23)	2 (1%)	0 (0%)	f=0.5218

MWU: Mann-Whitney U, $X^{2:}$ Chi Square test, f: Fisher Exact Test

Our study included 200 post stroke fatigued patients, the mean age of the patients was 62.4 years (SD = 10.9 years, Range of age = 16:75 years). 118 (59%) patients were males, and 82 (41%) patients were females. 108 (54%) patients were of urban areas and 92 (46%) patients were of rural areas. 162 (81%) patients were married, 37 (18.5%) were widows. 171 (86%) patients were non-educated, and 169 (84.5%) patients were unemployed. Our study included 100 (50%) patients with ischemic strokes and 100 (50%) patients with hemorrhagic strokes. The average age of the ischemic stroke group of patients is 63.4 years (SD = 9.7) and the average age of the hemorrhagic stroke group of patients is 61.3 (SD = 11.9).

Regarding the correlation analysis , a significant positive correlation between MFI & NIHSS (r = 0.75, p = .00), ATHENS (r = 0.5, p = .00), Modified Rankin (r = 0.68, p = .00), Hamilton Depression index (r = 0.75, p = .00), Hamilton Anxiety index (r = 0.55, p = .00). A significant negative correlation between MFI & MOCA (r = -0.44, p = .00), Mini-Mental (r = -0.64, p = .00), Barthel index (r = -0.55, p = .00), WHOQOL-BREF (r = -0.16, p = .02) (**Fig.7,** 8). A significant negative correlation between MFI and male gender (r = -0.21, p = 0.003) and between MFI and educational status (r = -0.142, p = 0.045). A non-significant correlation between MFI and age (r = 0.067, p = 0.349), rural areas (r = 0.04, p = 0.56), marital status (r = -0.1, p =

0.12), hypertension (r = 0.08, r = 0.29), diabetes (r = 0.002, p = 0.98), renal disease (r = 0.09, p = 0.22), and cardiac status (r = 0.03, p = 0.72).

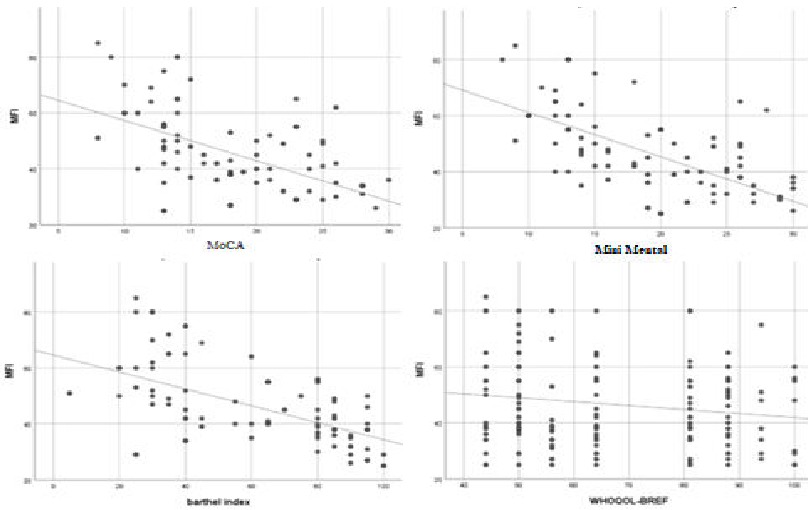

Fig.7. Negative Correlation between MFI and the other scales; MoCA, Mini-Mental, Barthel Index, & WHOQOL-BREF.

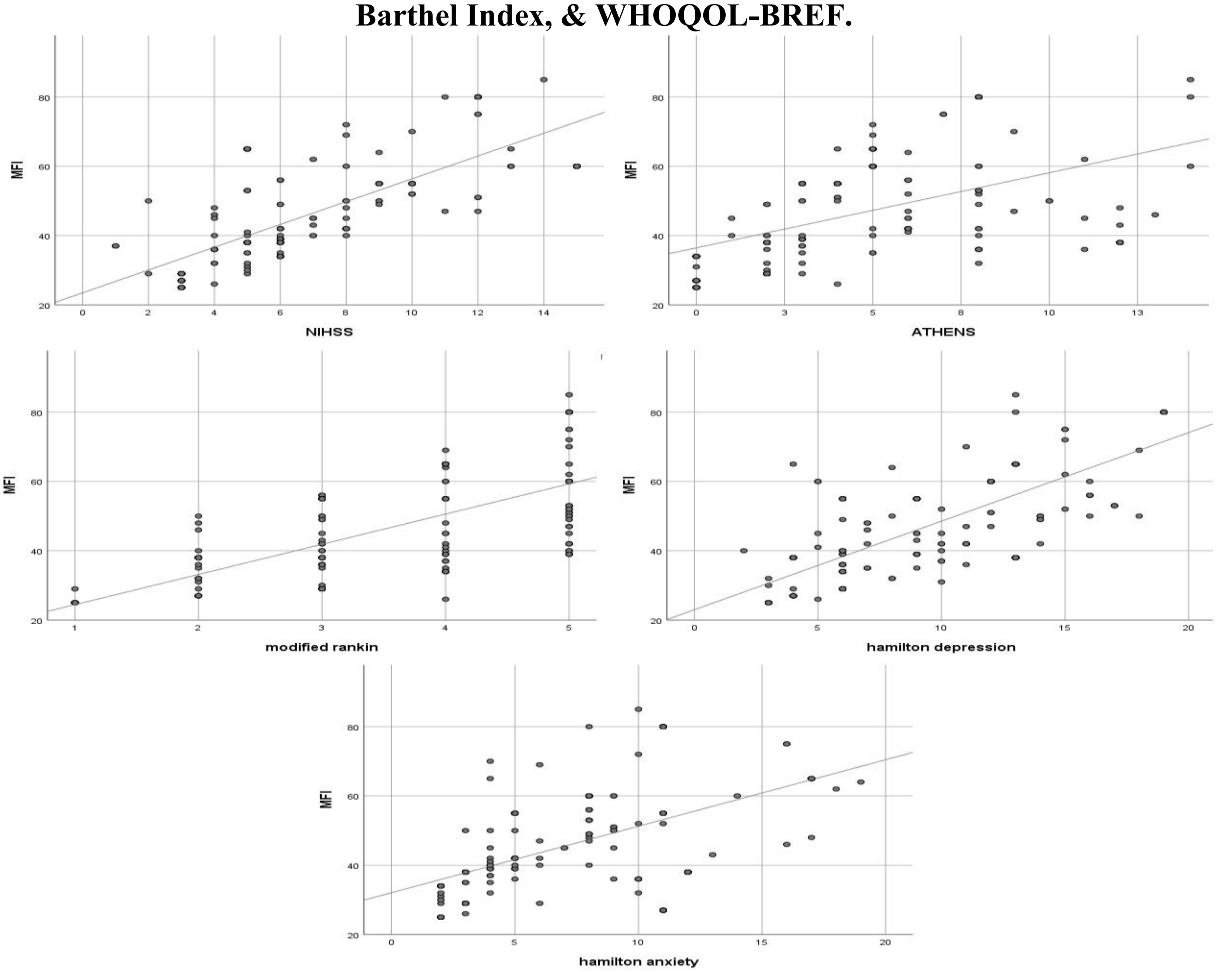

Fig.8. Positive Correlation between MFI and the other scales; NIHSS, ATHENS, Modified Rankin, Hamilton Depression, & Hamilton Anxiety.

Discussion

Medical professionals have long been aware that fatigue is a significant concern for a considerable number of stroke survivors under their supervision. The findings of this study indicate the risk factors for post-stroke fatigue and its impact on post-stroke quality of life. We identified more than 300 patients who satisfied our inclusion criteria and discovered that around two-thirds of the participants (200 patients). The included 200 patients, ischemic and hemorrhagic stroke had fatigue where the evaluation was done up to one year after stroke onset with follow up for 3 months. Nevertheless, as the current study mostly included patients with mild to moderate impairment, the prevalence of weariness among these patients appears very high, corroborating a review conducted by **Fred Stephen Sarfo et al. (2019).**

In our study we included 200 patients who had post stroke fatigue by MFI scale and never experienced fatigue before it and met our inclusion criteria. Our study included 100 (50%) patients with ischemic strokes and 100 (50%) patients with hemorrhagic strokes. The average age of the ischemic stroke group of patients is 63.4 years (SD = 9.7) and the average age of the hemorrhagic stroke group of patients is 61.3 (SD = 11.9). The higher age of the ischemic stroke patients is consistent with the literature as found in Salvadori et al., 2020 who reported the age of the ischemic stroke patients to be 75 years (SD= 12.5) and the hemorrhagic stroke patients to be 68.8 (SD = 15.4) **(Salvadori et al., 2020).**

In **Feigin et al., 2018**, most studied patients were males (118 patients, 59%) which is interesting given that there are regional variations in the sex distribution**,** but according to **Seshadri et al., 2006,** stroke was more common in females while men are more likely to develop coronary heart disease **(Leening et al., 2014).**

The majority of patients were urban (108 patients, 54%) further highlighting the urban-rural discrepancy in stroke incidence. It has been found that the mortality rate from stroke in rural areas is decreasing and increasing in urban areas, with the difference in magnitude being 15% in 1999 and increasing to 25% in 2010 **(Howard, 2013).**

The majority of our patients were married (162 patients, 81%). This is similar to the findings of Liu et al. who had a cohort of stroke patients whose 89.9% were married **(Liu et al., 2018).**

The majority of our patients were uneducated (171 patients, 86%). This is probably attributable to the community characteristics in which the study was conducted. However, this is alarming since previous literature found a discrepancy in the rate of all-cause mortality, specific stroke mortality, recurrent stroke, and cardiovascular events between illiterate and college-level-educated patients (16.7% vs 4.5%), (15.3% vs 3%), (8.9% vs 3.5%), and (10.9% vs 3.5%), respectively **(Che et al., 2020)**

Most of the patients (169 individuals, 85%) had hypertension. Hypertension is the primary risk factor for stroke. Researchers have discovered that for every 20 mm Hg increase in systolic blood pressure and 10 mm Hg increase in diastolic blood pressure, the mortality rates for stroke and ischemic disease double **(Lewington et al., 2002).** In addition, the United Kingdom transient ischemic attack (TIA) trial evaluated the blood pressure of patients who had been diagnosed with a stroke. A direct and reliable correlation between recurrent strokes and blood pressure was discovered. The data indicated that a reduction of five mmHg in diastolic blood pressure was associated with a decrease in stroke risk for approximately one-third of the population **(Rodgers et al., 1996; Sacco et al., 2006).**

According to our study, diabetes was the second most prevalent comorbidity, affecting 118 patients, which accounts for 59% of the total. Individuals with diabetes face a 1.5–3 times higher likelihood of experiencing strokes and have elevated mortality rates in comparison to the general population without diabetes. The primary cause of metabolic irregularities is attributed to proatherogenic risk factors, which include excessive fat accumulation in arteries, hypertension, and hyperglycemia (elevated blood glucose levels).

Additionally, those with hyperglycemia have a 1.5-fold higher chance of experiencing strokes. The development of atherosclerotic alterations in the blood arteries outside and inside the brain is mostly attributed to insulin resistance in cells and high levels of insulin in the blood, leading to the onset of diabetes. This process is not primarily influenced by elevated glucose levels or other risk factors **(Alloubani et al., 2018).**

Currently, there is limited research on the Sociodemographic Factors of post-stroke fatigue, and the results of the available studies are inconsistent. Several studies have found a link between post-stroke fatigue and pre-stroke depression, cognition, leukocytosis, myocardial infarction, diabetes, pain, and sleep disorders. However, other studies have not found a significant association between post-stroke fatigue and variables such as gender, marital status, education level, emotional state, excessive daytime sleepiness, waist circumference, hypertension, ischemic heart disease, atrial fibrillation, and diabetes **(Amélie Ponchel et al., 2015).**

Forty-six research examined the relationship between gender and PSF, with 33 of them reporting no statistically significant disparities between males and females. Twelve research indicated that there was a higher occurrence of PSF in females, while just one study showed that physical exhaustion was more prevalent in males. The analysis of 16 research found no significant correlation between educational degree and PSF **(Amélie Ponchel et al., 2015).**

In our study , female sex and education status were identified as risk factors of fatigue whereas age , marital status ,residence, special habits, employment and other medical comorbidities have not been identified as strong demographic risk factors of fatigue , which may be explained by the small sample size of this study.

We have studied the correlation between PSF and psychological factors as the great majority of studies found a correlation between PSF and poststroke depression, only few studies failed to observe this type of association **(Amélie Ponchel et al., 2015).** In this study we have found a significant positive correlation between MFI & depression; Hamilton Depression index ($r = 0.75$, $p = .001$).

Hamilton Depression was not significantly different between the group with stroke on the right side (Mean = 9.3, SD = 4.3) and the group that had stroke on the left side (Mean = 9.1, SD = 4.8) groups ($p = .733$), nor was it between supratentorial (Mean = 9.4, SD = 4.5) and infratentorial (Mean = 6.7, SD = 3.3) groups (p = .012), and it wasn't significantly different between different sites (p = .15). The Hamilton Depression index was found to be not significantly different between the ischemic and hemorrhagic group (9.7 vs 8.7, p = .14).

Depression and tiredness are distinct phenomena, and the exact connection between them is not well comprehended **(Duncan et al., 2012).** However, depression may contribute to the persistence of fatigue over a period of time **(Tang et al., 2014).** It is important to mention that these studies did not consistently account for a pre-existing history of depression prior to the occurrence of a stroke. While a study by **Naess et al. (2012)** suggested a potential association between prestroke depression and PSF, a separate study conducted by **Snaphaan et al. (2011)** did not find any such link.

Post-stroke, anxiety symptoms were prevalent. Our study utilized the Hamilton Anxiety Rating Scale (HARS) to evaluate anxiety symptoms. We established a cutoff of a mean HARS score of 14 or higher. Our findings revealed that approximately 30% of stroke survivors experienced post-stroke anxiety (PSA). This occurrence could be attributed to the fact that our sample consisted of stroke survivors with mild to moderate neurological impairments (median NIHSS score of 7). Additionally, individuals with severe neurological deficits or aphasia were excluded from our study. Patients who were not included in this study may have a higher likelihood of having PSA.

The Hamilton Anxiety index was found to be not significantly different between the ischemic and hemorrhagic group (7.7 vs 9.7, p = .74), which is consistent with the literature finding no difference between ischemic and hemorrhagic patients **(Alajbegovic et al., 2014).**

Hamilton Anxiety was not significantly different between the group with stroke on the right side (Mean = 7.5, SD = 4) and the group that had stroke on the left side (Mean = 7.6, SD = 4.8) groups (p = .833), nor was it between supratentorial (Mean = 7.8, SD = 4.3) and infratentorial (Mean = 8.1, SD = 5.4) groups (p = .75). However, there was significant correlation between mean Hamilton anxiety score and the affected part of the brain (p = .014). The mean Hamiton anxiety score was 8 in when stroke affected the basal ganglia, 8.6 when stroke affected the brain stem only, 11 when stroke affected both the brain stem & cerebellum, 7.2 when stroke affected the cerebellum only, 7 when stroke affected the cerebellum, 8 when stroke affected the frontal area, 11.3 when f stroke affected the frontoparietal area, 4.4 when stroke affected the fronto-temporo-parietal areas, 8 when stroke affected the internal capsule, 7 when stroke affected the occipital only, 17 when stroke affected the parietal only, 11 when stroke caused parietothalamic affection, 6.8 when stroke caused parietooccipital affection, 6.8 when stroke affected the temporal area, 8.9 when stroke caused temporooccipital affection and 9.6 when the stroke affected the thalamus.

Regarding the fatigue scale, MFI, it showed: a significant positive correlation between MFI & Hamilton Anxiety index (r = 0.55, p = .00).

Anxiety was associated with PSF in 13 studies but not in two other studies **(Amélie Ponchel et al. 2015).**

Regarding disability after stroke we found a significant positive correlation between MFI & Modified Rankin (r =

0.68, p = .001), which come in agree with another study **(Ying-Ye et al ., 2021)**

Modified Rankin score was found to be higher in the ischemic group than the hemorrhagic group (3.7 vs 3.3, p = .02) similar to the findings of Salvadori et al., 2020 (72% patients in the hemorrhagic stroke group having a score of 0 vs 67% of patients in the ischemic stroke group) but they also found no significant difference between the scores at admission vs at discharge for each group **(Salvadori et al., 2020).** Modified Rankin was not significantly different between the group with stroke on the right side (Mean = 3.5, SD = 1.2) and the group that had stroke on the left side (Mean = 3.5, SD = 1.2) groups (p = .95), nor was it between supratentorial (Mean = 3.6, SD = 1.2) and infratentorial (Mean = 2.8, SD = 1) groups (p = .006), and it wasn't significantly different between different sites (p = .247).

Prior study indicates a minimal correlation between the severity of a stroke and PSF, as reported by Sykepleien et al. in 2019. The results of our study indicated that the severity of stroke was a notable factor that heightened the incidence of post-stroke fatigue (PSF). The correlation coefficient (r) between NIHSS scores is 0.75, indicating a strong positive relationship. The p-value is 0.001, suggesting that this relationship is statistically significant.

A comprehensive literature analysis conducted in Norway indicated that there is either no link or a doubtful association between stroke severity and post-stroke fatigue (PSF). None of the research included in the review found any significant correlation between the severity of a stroke and PSF (Sykepleien et al., 2019). The inconsistent results could be attributed to variations in research methodology, the definition of exhaustion, or the size of the study population. Our study findings suggest that the greater severity of the stroke may have a substantial impact on PSF. We also found that NIHSS was not significantly different between the group with stroke on the right side (Mean = 7.3, SD = 3.5) and the group that had stroke on the left side (Mean = 6.7, SD = 3.5) groups (p = .217), nor was it between supratentorial (Mean = 7.1, SD =3.5) and infratentorial (Mean = 5.5, SD = 1.7) groups (p = .055), and it wasn't significantly different between different sites (p = .427). The NIHSS scores did not show a statistically significant difference between the ischemic and hemorrhagic groups (7.2 vs 6.8, p = .37). The NIHSS demonstrates moderate-to-high reliability when administered by both medical and non-medical personnel, and it is also useful in guiding therapy **(Wardlaw et al., 2003).** However, it has been observed that the average NIHSS score for individuals with good functional outcomes is significantly lower for posterior circulation strokes (mean baseline 7.3) compared to anterior circulation strokes (mean baseline 11.3). This finding emphasizes the importance of making acute stroke emergency management decisions based on a comprehensive neurological examination rather than relying solely on a single scale **(Kazi et al., 2021).**

Post-stroke and transient ischemic attack (TIA) sometimes result in the occurrence of sleep disturbances, which can potentially increase the risk of experiencing another stroke. Following a stroke, people report alterations in their sleep patterns. Approximately 30% of individuals experienced sleep difficulties within one year following a stroke, characterized by symptoms such as excessive daytime sleepiness, increased time taken to fall asleep, and a lack of feeling refreshed after sleep. Therefore, PSF was found to be correlated with sleep disturbances, as determined by questionnaires, in nine investigations, while three additional research did not find this association. Four research demonstrated a link between PSF and daytime sleepiness, but two other investigations did not discover this correlation **(Amélie et al,.2015).** In our study we found that ATHENS was not significantly different between the group with stroke on the right side (Mean = 4.7, SD = 3.6) and the group that had stroke on the left side (Mean = 4.5, SD = 3.5) groups (p = .792), nor was it between supratentorial (Mean = 4.8, SD = 3.4) and infratentorial (Mean = 5.4, SD = 5.1) groups (p = .478), and it wasn't significantly different between different sites (p = .419). ATHENS was found to be more in the ischemic group vs the hemorrhagic group (5.2 vs 4.1, p = .03). This is contrasted with the finding that the severity of insomnia is similar between both groups as can be found in the literature **(Okajima et al., 2020).**

A correlation between MFI & ATHENS (r = 0.5, p = .001),

Briefly; regarding the fatigue scale, MFI, it showed: a significant positive correlation between MFI & NIHSS (r = 0.75, p = .00), ATHENS (r = 0.5, p = .00), Modified Rankin (r = 0.68, p = .001), Hamilton Depression index (r = 0.75, p = .001), Hamilton Anxiety index (r = 0.55, p = .001) signifying that fatigue increases along with the increase of neurological deficit, insomnia, disability, depression, as well as anxiety, respectively.

Fatigue seems to be linked to the existence of cognitive impairment. Multiple studies have found no correlation between weariness and cognitive impairment **(Yang et al., 2015).** This can be attributed to the utilization of the Mini-Mental State Examination (MMSE) score in these studies, which has a lesser level of sensitivity compared to the Montreal Cognitive Assessment (MoCA) in evaluating cognitive impairment after a stroke **(Chestnut, 2010).**

Unlike the MMSE score, the MoCA scale enables the evaluation of executive and attentional processes, which are commonly impaired in vascular cognitive disorders.

In our study we have found a negative correlation between fatigue and MMSI and MoCA, we have to take into consideration depression may influence cognitive evaluations; which may affect our result. we have concluded that MoCA was similar between both ischemic and hemorrhagic groups (17.3 vs 17.7, p = .66). Used in the acute period, MoCA has a good predictive value for the development of poststroke cognitive impairment in the follow-up period **(Chiti & Pantoni, 2014).** MoCA was not significantly different between the group with stroke on the right side (Mean = 17.6, SD = 5) and the group that had stroke on the left side (Mean = 17.5, SD = 5) groups (p = .898), nor was it between supratentorial (Mean = 17.3, SD = 5) and infratentorial (Mean = 19.4, SD = 5.6) groups (p = .096).

Mini-Mental was not significantly different between the group with stroke on the right side (Mean = 19.5, SD = 6) and the group that had stroke on the left side (Mean = 18.9, SD = 6.3) groups (p = .518), but it was significantly different between supratentorial (Mean = 18.6, SD = 6) and infratentorial (Mean = 23.5, SD = 7) groups (p = .002), although it wasn't significantly different between different sites (p = .111). The MMSE was also found to be similar between both ischemic and hemorrhagic groups (19 vs 19.5, p = .57. MMSE deficits were more frequently observed in patients with left hemispheric lesions compared to those with right hemispheric lesions in the context of stroke (**Weaver et al., 2021).**

The results of the current study proved that there was a negative correlation between PSF and the functional recovery (Barthel Index) which come with an agreement to a review performed by Staub and Bogousslavsky. The study revealed that; Barthel Index was not significantly different between the group with stroke on the right side (Mean = 61.8, SD = 27.9) and the group that had stroke on the left side (Mean = 58.1, SD = 28.7) groups (p = .375), nor was it between supratentorial (Mean = 59, SD = 27.7) and infratentorial (Mean = 74.4, SD = 24.8) groups (p = .025), and it wasn't significantly different between different sites (p = .358). The Barthel Index did not show a statistically significant difference between the ischemic and hemorrhagic groups (58.4 vs 61.3, p = .48). **Hacke et al. (2005)** have found that a Barthel Index score of 75 or higher and a modified Rankin Score of 2 or below can be used to determine a positive outcome in patients with acute stroke. The sensitivity of this criteria is 75.0% and the specificity is 97.8%. **Uyttenboogaart et al. (2005)** proposed that a

Barthel Index of 90 and a modified Rankin Score of 2 or lower might be used to determine a positive outcome in patients with acute stroke. This criteria has a sensitivity of 90.7% and a specificity of 88.1%. A recent study conducted by **Zhou et al. (2021)** determined that the ideal cutoff scores for the Barthel Index were 100, with a sensitivity of 100% and a specificity of 95.3% for an adjusted modified Rankin Score of 1. Similarly, a cutoff score of 100 had a sensitivity of 98.1% and a specificity of 100% for an adjusted modified Rankin Score of 2,

The correlation between stroke type and PSF; including topographic radiology showed that MFI was not significantly different between the group with stroke on the right side (Mean = 46, SD = 14.1) and the group that had stroke on the left side (Mean = 46.6, SD = 16.3) groups (p = .811), nor was it between supratentorial (Mean = 47.3, SD = 15.2) and infratentorial (Mean = 40.1, SD = 11.6) groups (p = .05), and it wasn't significantly different between different sites (p = .231). The MFI was found to be not significantly different between the ischemic and hemorrhagic group (47.5 vs 45.6, p = .38). as they found no change in MFI between ischemic and hemorrhagic types of stroke (**Delva et al., 2017; Delva et al., 2018).**

Impact of post stroke fatigue on quality of life (measured by WHOQOL-BREF)in our study we found a negative correlation between PSF and WHOQOL-BREF, we also found that WHOQOL-BREF was not significantly different between the group with stroke on the right side (Mean = 68, SD = 17.9) and the group that had stroke on the left side (Mean = 64.9, SD = 21.6) groups (p = .752), nor was it between supratentorial (Mean = 66.1, SD = 17.5) and infratentorial (Mean = 74.8, SD = 15.7) groups (p = .045), and it wasn't significantly different between different sites (p = .102).

There was frequent insignificant differences between ischemic and hemorrhagic groups regarding scores of the used scales, however, a larger sample size of patients is recommended to further confirm that no difference between either groups truly exists. Furthermore, the Modified Rankin score is significantly higher in the ischemic group, which further supplements our recommendation of a larger sample size to detect any difference between both groups.

We also made a comparison of different scales between two groups post stroke fatigued patients and post stroke non fatigued patients to define if these risk factors are sensitive or specific for detection of post stroke fatigue we have found that The post stroke fatigued patients showed significantly lower scores in cognitive assessments (MoCA and Miniminta) compared to post stroke non-fatigued patients ($P < 0.00001$*). Additionally, the post stroke fatigued patients had higher scores on the NIHSS (National Institutes of Health Stroke Scale), indicating more severe stroke symptoms ($P = 0.00028$*). Their BMI was also significantly higher than that of non-fatigued patients ($P = 0.00138$*). Moreover, the

Modified Rankin scores were notably higher in post stroke fatigued patients, suggesting increased disability and dependence on others ($P < 0.00001$*). The WHQOOL (World Health Organization Quality of Life) assessment revealed that the fatigued patients had significantly lower scores in the Physical domain ($P < 0.00001$*) and Environment domain ($P = 0.01088$*), while the Total WHQOOL score was higher in non-fatigued patients ($P < 0.00001$*). However, no statistically significant differences were found in the ATHENS score, as well as in the Psychological and Social domains of WHQOOL.

For Hamilton depression, the median score for fatigued patients is 7.5 (range: 2-19), higher than non-fatigued patients with a median of 7 (range: 2-15). The Mann-Whitney U test reveals a statistically significant difference ($p=0.00374$) in overall depression levels between fatigued and non-fatigued patients, indicating that cases tend to have slightly higher levels of depression. However, when examining the distribution of depression severity categories, the Chi-Square test shows no significant differences ($p>0.05$) between the two groups regarding nil and mild categories. However, moderate depression was significantly prevalent among fatigued patients.

Regarding Hamilton anxiety, fatigued patients have a median anxiety score of 5 (range: 2-19), slightly higher than non-fatigued patients with a median of 4 (range: 1-17). The Mann-Whitney U test indicates a statistically significant difference ($p=0.00278$) in overall anxiety levels between fatigued and non-fatigued patients, indicating that fatigued patients tend to have slightly higher anxiety levels. However, similar to depression, the Chi-Square test shows no significant differences ($p>0.05$) in the distribution of anxiety severity categories between both patients.

Conclusion

The study highlights a significant link between fatigue and cognitive impairment in post-stroke patients. Higher stroke severity, as measured by NIHSS, is connected to increased fatigue, emphasizing the importance of effective stroke management. While fatigue correlates negatively with certain functional measures like the Modified Rankin Scale, it doesn't significantly impact overall daily living abilities (Barthel Index). Fatigue's association with quality of life domains, especially the Physical and Environment aspects, was noted. Post-stroke fatigue is related to cognitive issues, stroke severity, and functional constraints.

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