**RESEARCH ARTICLE**

# The effect of disability and gender mediated by depression on health-related quality of life of Greek stroke patients in the subacute rehabilitation phase: a prospective cohort study

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**Abstract**

**Background:** Stroke has been associated with compromised patient outcomes, such as a decreased quality of life. We aimed in the present study to evaluate the health-related quality of life (HRQoL) of hospitalized Greek stroke patients during the sub-acute rehabilitation period and assess the effect of demographic and clinical characteristics mediated by depressive symptom severity on HRQoL.

**Methods:** In a prospective study, a cohort of adult patients hospitalized in the sub-acute phase of their first stroke episode were assessed in the Rehabilitation Clinic of the University Hospital of Ioannina in Greece. Patients' functional status, depressive symptom severity, and HRQoL were evaluated twice, using the Patient Health Questionnaire 9 (PHQ-9), the Barthel Index (BI), and the World Health Organization Quality of Life Brief Version (WHOQOL-BREF), respectively. All patients received physical, occupational, and speech therapy during their rehabilitation.

**Results:** Fifty consecutive adult stroke patients were enrolled. We detected a statistically significant ($p < 0.001$) improvement in WHOQOL-BREF, especially in the "psychological health" and "environment" domains, BI, and PHQ-9 scores, between the initial and follow-up assessments. Mediation analysis revealed that baseline disability had both a significant direct (estimate =0.014, $p < 0.001$) and indirect (estimate =0.010, $p < 0.001$, PHQ-9 as mediator) effect on the total HRQoL score. Gender and stroke localization had significant direct effects on HRQoL total (estimate =-0.432, $p = 0.009$, and estimate =0.395, $p = 0.031$, respectively), while PHQ-9 mediation was insignificant. Antidepressant medications and stroke type did not play a substantial role in HRQoL.

**Conclusion:** By the end of the subacute rehabilitation phase, patients' HRQoL, functionality and depression severity improved. Additionally, baseline functionality, stroke localization, and gender directly or indirectly (mediated by initial depression severity) affected HRQoL, with male patients and patients with stroke non-involving the frontal lobe/basal ganglia showing a better HRQoL by the end of rehabilitation. HIPPOKRATIA 2023, 27 (1):12-17.

**Keywords**: quality of life, stroke, hospitalized patients, Barthel Index, Patient Health Questionnaire 9, WHOQOL-BREF, rehabilitation

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## Introduction

Cerebrovascular disorders are the third leading cause of mortality and the second leading cause of mortality and disability combined worldwide[1], which varies according to the degree of recovery, the location of the lesion, the patient's pre-morbid condition, and the level of support received[2]. Stroke can lead to various medical complications such as post-stroke depression (PSD)[3,4], which is the most common psychiatric disorder in stroke survivors[4]. PSD has been associated with severe consequences regarding patients' functionality, recovery, and quality of life[5] and has been linked to a variety of factors (e.g., stroke location)[4,6].

Health-related quality of life (HRQoL) is an index of well-being that includes various domains (e.g., physical, psychological, social, and environmental). It indicates patients' ability to fulfill their daily living satisfactorily[7]. The impact of stroke on people's lives is a challenge for the patients themselves (e.g., lower HRQoL), their families, and also for society, as it imposes a significant economic burden[2,8,9].

To our knowledge, there is no literature regarding the HRQoL of Greek stroke patients in the subacute (less than six months from stroke onset) rehabilitation phase or possible HRQoL predictors. Therefore, this study aimed to i) evaluate the HRQoL, functionality, and depression

of hospitalized Greek post-stroke patients during the subacute rehabilitation period, ii) explore any changes throughout time in these parameters, and iii) assess the direct and indirect (mediated by depression) effect of demographic and clinical characteristics on HRQoL.

## Materials and methods

*Study design, participants, and procedures*

We conducted a prospective cohort study between April 2015 and May 2018 and opted for a non-probability sampling technique, specifically purposive sampling. Sampling was carried out in the Rehabilitation Clinic of the University Hospital of Ioannina in Greece and specifically we enrolled patients who were hospitalized during the sub-acute stroke phase/stage (four to six weeks after initial admission to the Neurologic clinic of the hospital) and received intensive multi-disciplinary rehabilitation. During this three-year period, 219 patients attended the Rehabilitation Clinic in total, while the resulting sample consisted of 50 participants (28 male, 22 female) with a diagnosis of stroke who met the inclusion criteria and agreed to participate in this study. The study was approved by the hospital's Review Committee (Scientific Board of the University Hospital of Ioannina, decision No 18138, date 27/06/2013), and written informed consent was obtained from all participants before their enrolment in the study.

In order to determine participant eligibility, all 219 attending patients were clinically examined, and their medical histories were recorded. Patients were included in the study if they met the following criteria: patients i) aged between 18 and 70 years, ii) able to converse in Greek without previous mobility problems (including conditions such as respiratory and cardiac failure, myopathies, and other related pathologies capable of limiting patients' functionality at each level of mobility), who iii) suffered left-sided neurological deficits diagnosed following magnetic resonance imaging (MRI), computerized tomography (CT) scan, and bedside examination, iv) in the sub-acute phase of stroke, and iv) were hospitalized due to stroke. Children or subjects older than 70 years were excluded from the study, as well as those who i) had a history of previous stroke episode(s), ii) suffered a stroke involving the cerebral stem or the cerebellum, iii) were aphasic (without adequate language comprehension and speech production abilities) and would not be able to respond to the clinician's inquiries and understand the tests' items as well as patients with dementia [Mini-Mental State Examination (MMSE) score <24]. Also, we excluded patients with iv) a history of or ongoing/present psychoactive substance use/abuse or psychosis and v) an inability to cooperate and respond during the assessment.

Through the patient's medical history, we collected their demographic data (gender, age, marital status, and educational level), information regarding their stroke (type, location, and affected side), and other related medical information. The type of stroke was documented as either hemorrhagic or ischemic. The location of stroke was set either involving the frontal lobe/basal ganglia or not involving the frontal lobe/basal ganglia (based on CT or/and MRI findings) as patients with frontal lobe/basal ganglia stroke locations are reported in the literature to have a greater tendency for post-stroke depression[4,6].

Following intra- or inter-hospital transfer to the rehabilitation clinic, all patients were assessed twice, during their hospitalization. In particular, a baseline assessment was performed during the second week of attendance, and a follow-up assessment three months later. In addition, all patients underwent a psychiatric-psychological evaluation to assess the need for drug administration.

All patients received care from the clinic's interdisciplinary rehabilitation team. The program consisted of psychological and cognitive rehabilitation, physiotherapy, occupational therapy, speech and language therapy, and healthcare services provided by medical doctors (physiatrists, orthopedic doctors, and a psychiatrist), nursing staff, and other healthcare providers. The rehabilitation program consisted of four hours of therapy (occupational therapy, physiotherapy, speech therapy, and psychotherapy) daily for 12 weeks (since a statutory stay in a rehabilitation clinic is 8 to 12 weeks).

*Instruments*

The following instruments were administered:

1. The Greek version of the MMSE[10,11], a validated observer-rated measure of cognitive ability, was initially designed to screen older people for dementia[12]. The MMSE score ranges from 0 to 30, with a lower score indicating a more significant impairment in cognition (≥24, normal cognition)[12]. Upon admission to the rehabilitation clinic, all patients completed this tool. They were advised to answer without any external assistance.

2. The Greek version of the Patient Health Questionnaire-9 (PHQ-9), a multipurpose instrument for the evaluation of depression (screening, diagnosing, monitoring, and measuring severity), comprises nine items based directly on the nine diagnostic criteria for major depressive disorder in the Diagnostic and Statistical Manual (DSM)-IV. The PHQ-9 score ranges from 0 to 27 (0-3 for each item; 0: not at all, 1: several days, 2: more than half the days, 3: nearly every day), with higher scores indicating more severe symptoms [PHQ-9 classification groups according to total score 0-4: no depression, 5-9: mild, 10-14: moderate, 15-19: moderate-severe, and ≥ 20: severe (major) depression][13-15].

3. The Barthel Index (BI) assesses patients' functionality and rates their ability to engage in daily activities using ten variables describing daily living activities and mobility (e.g., feeding, bathing, and ascending/descending stairs). This index's score ranges from 0 to 100, with higher scores indicating greater independence. A score of 100 indicates no disability; generally, a score higher than 60 indicates the ability to live independently in the community[16,17].

4. The Greek version of the World Health Organization Quality of Life Brief Version (WHOQOL-BREF) is

utilized to assess patients' HRQoL. It comprises 26 items measuring four domains: physical health, psychological health, social relationships, and environment. Each item is rated on a 5-point Likert scale, and the instrument score ranges from 0 to 100, with higher scores indicating better HRQoL[18].

*Statistical Analysis*

Qualitative and demographic data are presented as absolute and relative frequencies (percentage), while quantitative variables are presented as means and standard deviation (SD). We used the Wilcoxon signed-rank test to compare the initial and reassessment scores between the PHQ-9 classification groups and the t-test to compare the BI, PHQ-9, and WHOQOL-BREF baseline and follow-up scores. Mediation analysis was performed to assess the mediating role of patients' initial PHQ-9 score between "BI score", "gender", "pharmacological treatment for depression", "stroke type", "stroke location", and "WHOQOL-BREF". More specifically, the four domains of WHOQOL-BREF, "WHOQOL-BREF total", and "WHOQOL-BREF change" (changes in total score). The statistical analysis was performed using the JASP (JASP Team, Amsterdam, The Netherlands) software, version 0.12.2. The statistical significance was set at a p-value of $<0.05$.

## Results

*Socio-demographic and clinical characteristics*

A total of 50 subjects with stroke who met the inclusion criteria were enrolled in this study. The sample's mean age was 56.76 ± 14.79 years, while 56 % of participants were male (n =28). Data regarding marital status, employment status, educational level, and clinical characteristics, e.g., type of stroke, are presented in Table 1.

*Barthel Index*

During the initial assessment, the patients' mean BI score was 47 ± 28.42. Upon completion of the rehabilitation program, the mean score was 65.8 ± 27.26. The difference between the two means was statistically significant ($p <0.001$; Table 2).

*Patient Health Questionnaire 9*

The initial PHQ-9 mean score was 9.74 ± 4.23; by the end of the rehabilitation program, the mean score was 5.04 ± 3.53. A statistically significant decrease was reported ($p <0.001$). Data regarding classification groups after the initial assessment and reassessment are presented in Table 2. We observed an improvement in the patient's depression severity between the initial and follow-up evaluation (Wilcoxon signed-rank test, z =-5.686, $p <0.001$, Table 2).

*WHOQOL-BREF Questionnaire*

Data regarding the patient's performance in the four domains (physical, mental, social relationships, environment) of the WHOQOL-BREF during the initial and follow-up assessment are presented in Table 2. Generally, a statistically significant ($p <0.001$) improvement in all four domains was observed during the reassessment. However, as shown in Table 2, the mean scores during both evaluations in all domains could be deemed average, with higher scores in the "psychological health" (1st assessment 51.66 ± 11.66, 2nd assessment 62.33 ± 11.29) and "environment" (1st assessment 57.75 ± 11.47, 2nd assessment 65.12 ± 10.64) HRQoL categories.

*Mediation analysis*

The initial BI score positively affects the total WHOQOL-BREF reassessment score (estimate =0.024, z

**Table 1:** Demographic data and clinical characteristics of the 50 consecutive adult patients hospitalized in the subacute phase of their first stroke episode were examined in the rehabilitation clinic and enrolled in the study.

| | |
|---|---|
| **Age** | 56.76 ± 14.79 |
| **Gender** | |
| Male | 28 (56) |
| Female | 22 (44) |
| **Marital status** | |
| Single | 12 (24) |
| Married | 31 (62) |
| Divorced | 3 (6) |
| Widowed | 4 (8) |
| **Education Status** | |
| Primary school | 21 (42) |
| High School | 25 (50) |
| University degree | 4 (8) |
| **Employment status** | |
| Retired before stroke | 17 (34) |
| Inactive because of stroke | 27 (54) |
| Part-time or voluntary work | 6 (12) |
| **Stroke type** | |
| Ischemic | 21 (42) |
| Hemorrhagic | 29 (58) |
| **Stroke localization** | |
| Involving frontal lobe/basal ganglia | 37 (74) |
| Non-involving frontal lobe/basal ganglia | 13 (26) |
| **Time post stroke (months)** | |
| 0-3 months post onset | 41 (82) |
| 3-6 months post onset | 9 (18) |
| 6+ months post onset | - |
| **History of depression** | 17 (34) |
| **Previous antidepressant medication** | 15 (30) |
| **Current antidepressant medication** | 34 (68) |
| **Time between evaluations (days)** (range) | 89.96 ± 5.54 (79-100) |

Values are presented as absolute frequency and percentage in brackets or means ± standard deviation and range where stated, SD: standard deviation.

**Table 2:** Comparisons of the mean scores on the Barthel Index, the Greek version of the Patient Health Questionnaire-9, and the Greek version of the World Health Organization Quality of Life Brief Version questionnaires before and after the rehabilitation program regarding the enrolled stroke patients hospitalized in the sub-acute phase in the rehabilitation clinic.

| | Initial Assessment | Follow-up | p value |
|---|---|---|---|
| **BARTHEL INDEX** | 47.00 ± 28.42 | 65.80 ± 27.26 | <0.001 |
| **PHQ-9** | 9.74 ± 4.23 | 5.04 ± 3.53 | <0.001 |
| Absence | 3 (6 %) | 24 (48%) | |
| Mild depression | 22 (44 %) | 4 (8%) | (Z =-5.686) |
| Moderate depression | 17 (34 %) | 22 (44%) | <0.001 |
| Moderately severe depression | 8 (16 %) | - | |
| **WHOQOL-BREF** | 4.88 ± 1.61 | 6.8 ± 1.61 | <0.001 |
| Physical Health | 45.50 ± 8.00 | 55.92 ± 10.03 | <0.001 |
| Psychological Health | 51.66 ± 11.66 | 62.33 ± 11.29 | <0.001 |
| Social Relationships | 50.50 ± 14.12 | 58.83 ± 13.19 | <0.001 |
| Environment | 57.75 ± 11.47 | 65.12 ± 10.64 | <0.001 |

Values are presented as absolute frequency and percentage in brackets or means ± standard deviation, PHQ-9: Patient Health Questionnaire 9, WHOQOL-BREF: World Health Organization Quality of Life Brief Version.

=7.048, p <0.001). More specifically, the initial PHQ-9 score significantly mediates this relationship (estimate =0.010, z =3.327, p <0.001), although BI still has a significant positive direct effect on the outcome variable (estimate =0.014, z =3.755, p <0.001). Gender seems to affect the total WHOQOL-BREF reassessment score significantly (estimate =-0.432, z =-2.615, p =0.009). This indicates that female patients are expected to have a lower total WHOQOL-BREF score, even after rehabilitation. With the inclusion of the mediator, the effect of gender on total WHOQOL-BREF was not significant (p =0.102). Moreover, a statistically significant direct effect was observed regarding location (estimate =0.395, z =2.159, p =0.031) with higher values for the total WHOQOL-BREF reassessment score in patients with stroke non-involving the frontal lobe/basal ganglia. The mediator $R^2$ is equal to 0.409, while the mediation model $R^2$ is equal to 0.666.

Furthermore, BI has a significant indirect effect (mediated by initial PHQ-9 score) on the "environment" and "social relationships" domains of the WHOQOL-BREF (estimate =0.009, z =2.634, p =0.008, and estimate =0.011, z =3.342, p <.0001, respectively). We found no significant direct effects. The model's $R^2$ is equal to 0.448 and 0.573, respectively. In addition, a statistically significant total effect was observed regarding stroke localization for the "environment" domain (estimate =0.570, z =2.205, p =0.027) as well as for the "social relationships" domain (estimate =0.591, z =2.435, p =0.015) with higher values for patients with stroke non-involving the frontal lobe or basal ganglia.

The initial PHQ-9 score significantly mediates the relationship between BI and the "psychological health" domain of the WHOQOL-BREF (estimate =0.010, z =3.204, p =0.001), even though the BI still has a significant direct effect on the outcome (estimate =0.010, z =2.345, p =0.019). In addition, gender seems to have a significant direct effect on "psychological health" (estimate =-0.504, z =-2.660, p =0.008). This indicates that female patients are expected to have lower scores in this domain, even after rehabilitation.

Both BI and gender have a significant direct effect on the "physical health" domain of the WHOQOL-BREF (estimate =0.020, z =4.590, p <0.001, and estimate =-0.795, z =-4.072, p <0.001, respectively). The model's $R^2$ equals 0.601 and 0.572 for "psychological health" and "physical health", respectively.

Finally, gender has a significant direct effect on the change observed in the total WHOQOL-BREF score (estimate =-0.728, z =-2.723, p =0.006). In contrast, BI has a significant indirect effect (mediated by initial PHQ-9 score) on this outcome (estimate =-0.009, z =-2.193, p =0.028). The model's $R^2$ is equal to 0.205.

## Discussion

We conducted a prospective study that enrolled 50 Greek hospitalized stroke patients who met the inclusion criteria during the subacute rehabilitation phase and found that patients' quality of life and functionality increased significantly while depression significantly decreased. Mediation analysis with functionality as the independent factor, quality of life as the outcome, and depression as the mediator showed that patients with initial (during admission) better functionality achieved a more acceptable HRQoL, both directly (in total WHOQOL-BREF score, and WHOQOL-BREF's "physical health" and "psychological health" domains, separately) and indirectly, when mediated by depression (in total WHOQOL-BREF score and WHOQOL-BREF's "environment", "social relationships", and "psychological health" domains separately). Furthermore, gender had a direct effect on HRQoL (WHOQOL-BREF total, "psychological health", "physical health", and WHOQOL-BREF change), indicating that male patients can achieve a more acceptable quality of life and show better improvement between initial assessment and reassessment, than female patients. In addition, stroke localization had a significant direct effect on HRQoL (in total WHOQOL-BREF score), indicating that patients with stroke not involving the frontal lobe/

basal ganglia may have a higher HRQoL than patients with stroke located in the frontal lobe or basal ganglia, by the end of rehabilitation. The relationship between antidepressant medication and stroke type with HRQoL was not significant.

Our study's results further extend previous findings. More specifically, in a prospective cohort study of patients in the first year after a stroke, higher HRQoL scores were independently associated with higher baseline HRQoL scores, lower disability, younger age, absence of depression history, and greater community participation[19]. In addition, Kapoor et al[20], in a telephone interview of stroke patients two to three years after their incident, concluded that functional impairment after a stroke is not the only parameter affecting their well-being. Factors such as cognitive impairment, social restrictions, and depression may all contribute to an unsatisfactory functional outcome and HRQoL for these patients.

Despite consistent positive evidence suggesting the use of antidepressant treatment in PSD[21,22], surprisingly, we found no indirect effect (mediated by depression) between functionality and HRQoL. It is possible that our patients would have benefited more from a combination of anti-PSD treatments since, according to Medeiros et al[23], the combination of pharmacological, psychosocial, and stroke-focused treatments obtains the best therapeutic results.

Regarding the importance of depression on the HRQoL of stroke patients, in a cross-sectional study, PSD was associated with significant post-stroke disability and poorer scores on all WHOQoL-BREF domains ($p < 0.05$)[24]. Similarly, Medeiros et al[23] concluded that PSD is associated with several adverse outcomes that decrease patients' quality of life. These results are also consistent with findings from other studies[25,26].

Kutlubaev and Hackett[27] highlighted that early recognition of depression in patients recovering from a stroke and the identification of those with a history of depression could effectively prevent increased disability after a stroke and facilitate stroke survivors' recovery. They also underlined the reciprocal relationship between functionality and depression. In our study, depression was seen in 60 % of the patients involved and decreased to 44 % at the end of the three-month follow-up period. An improvement in patients' functionality accompanied this improvement.

Available clinical data regarding the association between PSD and left frontal lobe and bilateral basal ganglia stroke lesion location have shown a strong correlation[4,6], while other published results have been contradictory. A recent systematic review highlighted the need for more longitudinal studies assessing stroke anatomical location and PSD rates to determine the exact connection[23]. In our study, the relationship between stroke localization and HRQoL was not significantly mediated by depression. Other factors, such as stroke severity and if the lesion is in the left or right hemisphere[4,23], may better mediate this relationship.

We only found two studies evaluating the relationship between infarct location and HRQoL. More specifically, De Haan et al[28] showed that patients with infratentorial strokes reported better overall functioning than patients with supratentorial strokes, while Lin et al[29] found that subcortical and brainstem infarct locations were associated with a lower HRQoL after a mild ischemic stroke. In our study, including only supratentorial right-sided stroke patients, patients with stroke not involving the frontal lobe/basal ganglia were also associated with a better overall HRQoL.

Although the current study has successfully demonstrated the mediating role of depression between functionality and HRQoL, the following three study limitations should be acknowledged: a) relatively small sample size, b) short follow-up period, and c) no control group. Thus, caution with the generalisability of the reported results is advised. We only included right-sided supratentorial stroke patients as we wanted to include a more homogenous group of patients and avoid left-sided lesions that might lead to aphasic signs and depressive symptomatology more frequently[30].

In order to avoid data heterogeneity, future randomized studies should take into consideration that patients' final (after rehabilitation) quality of life is often associated with the initial disability with the mediation of depression in stroke patients hospitalized in rehabilitation centers.

## Conclusions

In the last decade, there has been an increased clinical and research interest in stroke patients' HRQoL. In this study, we found that quality of life, disability, and depression improved significantly at the end of the subacute rehabilitation phase of Greek post-stroke patients. Mediation analysis revealed that depression is a vital mediation factor/mediator in the relationship between initial disability and patients' HRQoL after receiving three months of intensive rehabilitation therapy. In addition, female stroke survivors and involving the frontal lobe/basal ganglia should be under closer supervision during rehabilitation as their gender and the specific stroke location were associated with a lower HRQoL and less HRQoL improvement between initial assessment and reassessment. According to our findings, early psychological assessment and therapy are essential to improve these patients' functionality and quality of life.

## Conflict of interest

The authors have no conflict of interests to declare.

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