APPLICATION OF STRUCTURAL EQUATION MODELING TO DETERMINE FACTORS INFLUENCING COGNITIVE IMPAIRMENT, DEPRESSION, AND FATIGUE AMONG STROKE SURVIVORS

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This study explored the causal relationships between independent factors (individual factors, stroke characteristics) and post-stroke mental health issues through physiological and behavioral mediating factors. The study design is cross-sectional with a total of 162 stroke survivors treated at Vietnam's National Geriatric Hospital between June and December, 2021. We performed structural equation modeling analysis to calculate the standardization coefficient and correlation coefficient for our hypothesis. The structural model and standardized path coefficients had a goodness-of-fit indexes of Root-MeanSquare Error of Approximation (RMSEA) of 0.089, a comparative fit index (CFI) of 0.997, a Tucker-Lewis Index (TLI) of 0.954, and a standardized root mean-square residual (SRMR) of 0.019. Sleep disorder was positively associated with increasing post-stroke depression (Coef: 4.723; p<0.001) and fatigue status (Coef: 3.846; p<0.001). By contrast, alcohol use disorder was found as a factor that decreased fatigue status (Coef:-4.460; p = 0.005). Furthermore, post-stroke disability severity was significantly related to cognitive impairment (Coef: -3.229; p<0.001), depression (Coef: 1.559; p<0.001), and fatigue (Coef: 1.701; p = 0.002). The severity of post-stroke disability was associated with increasing cognition and mental health problems. Alcohol consumption and sleeplessness were found to be mediating effects between gender and age of stroke patients with changes in post-stroke depression and fatigue.

Keywords: Cognitive Impairment, Stress Disorder, Fatigue, Stroke, Structural Equation Modeling.

I. INTRODUCTION

Stroke is the leading cause of death and disability worldwide. It usually occurs suddenly when the blood supply to one or more brain regions is interrupted. During the first year, stroke survivors will experience abrupt and intense changes in physical and mental health. In most cases, these changes will have direct psychological, social, and economic impacts on patients and their families. Some negative changes in stroke patients' cognitive and mental health may influence their quality of life, raising the risks of stroke recurrence, suicidal ideation, or adverse effects on rehabilitation.[1]

Cognitive impairment, depression, and fatigue were found to be the most common symptoms among stroke survivors. According to a research carried out across 10 countries, stroke survivors who reported suffering cognitive impairment accounted for approximately

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30%.[2] Moreover, stroke characteristics of amounts and regions of the brain affected, and stroke mechanisms also found as the risks of cognitive impairment after stroke.[2] Additionally, fatigue and depressive symptoms are common and complicated sequelae after the stroke that share several risk factors, including functional limitations and sequela severity.[3,4] The aforementioned concerns may hinder stroke rehabilitation, exacerbate physical and psychological symptoms, and increase stroke recurrence and mortality. In recent years, many studies have found several factors that are significantly related to post-stroke depression such as medical history (i.e., predisposing illness and smoking), a history of mental disorders, and stroke characteristics.[3] Many other possible factors were also explored, including biological, psychological, social support, physical function, and cognition.[4] In summary, the risk factors for post-stroke mental health issues are complex and diverse. Moreover, post-stroke mental health issues can have adverse effects on cognitive function, functional recovery and survival. Therefore, it is important to study the risk factors for mental health after stroke.

Multivariate approaches have been used to identify the factors that influence the mental health status of stroke patients such as path models,[5] latent curve models,[6] and structural equation modeling (SEM).[7] However, the number of studies using the multivariate approach is limited and falls short of comprehensive exploration of related factors to cognitive impairment, depression, and fatigue after stroke. This study used SEM analysis to explore the causal relationships between independent factors (individual factors, stroke characteristics) and post-stroke mental health issues through mediator factors (physiology and behaviors) among Vietnamese stroke survivors. The hypothesis was that individual and stroke characteristics would be related to cognitive impairment, depression, and fatigue through the physiological and behavioral mediator variables.

II. METHODS

1. Research subjects/participamts

The inclusion criteria were:

1) diagnosed with cerebral stroke according to clinical criteria of the World Health Organization;

2) aged 45 years and over;

3) were treated and managed at the Central Geriatric Hospital in Vietnam;

4) suffered a stroke for one year since diagnosis; and

5) were independent in daily living activities before stroke.

The exclusion criteria were:

1) did not consent to participate in the study;

2) had disabilities from previous stroke events such as aphasia, pharyngeal paralysis, hemiplegia, etc.;

3) cases of consciousness disorders such as coma, poor cognition, or had Glasgow score ≤ 8, etc.;

4) had psychiatric disorders before stroke (depression, bipolar disorder, schizophrenia, substance addiction, etc).

2. Methods

Study setting, sample and sampling

This study used a cross-sectional design. From June to December 2021, a total of 162 stroke survivors at Vietnam's National Geriatric Hospital were recruited to participate in the study. A structured survey was used to directly interview stroke patients to ensure an objective assessment of their health status. Our survey was piloted among 10 stroke patients of different individual and stroke characteristics to test all

survey steps. Data collection commenced after the survey steps were thoroughly tested to assure the accuracy of the contents and patient assessment tools.

Measurement

The survey included the following main sections:

Outcome variables

- ***Cognitive impairment (Mini-Mental State Examination):*** cognitive impairment status was assessed using the Mini-Mental State Examination (MMSE) scale with 11 simple questions or tests that examine a variety of functions such as arithmetic, memory, and orientation. The number of correct items determines the score. The maximum score is 30 points. The generally accepted cut-off point for the presence of cognitive impairment is 24 or less.[8] Levels of cognitive impairment are classified as follows: normal cognition (≥ 24), mild cognitive impairment (20-23), moderate cognitive impairment (14-19), and severe cognitive impairment (0-13). The Cronbach's alpha for this scale was excellent at 0.90.

- ***Depression (Patient Health Questionnaire-9):*** The Patient Health Questionnaire-9 (PHQ-9) is a self-administered questionnaire that is part of the PRIME-MD diagnostic instrument for common mental disorders. Each item is scored on a scale from 0 to three, with "0" being "not at all" and "3" being "nearly every day". The total score ranged from 0 to 27. Classification of depression are as follows: none (0-4), mild (5-9), moderate (10-14), moderate-severe (15-19), and severe (20-27) [9]. The Cronbach's alpha was good at 0.87.

- ***Fatigue (Fatigue Severity Scale):*** The Fatigue Severity Scale (FSS) was designed as a common instrument for assessing the impact of fatigue. FSS is a short self-report questionnaire that contains nine statements about the severity of fatigue symptoms. Scoring is based on a 7-point Likert scale with '1' indicates 'strongly disagree' and '7' represents 'strongly agree.' In the overall score of 0-70, the levels of results are classified as follows: none-fatigue (1-3), moderate fatigue (3-5), severe fatigue (5-7) [10]. In our study, the Cronbach's alpha for items regarding answers was good at 0.89.

Independent Variables

- ***Demographic characteristics:*** Demographic data included age, gender, occupation, education, marital status.

- ***General health status:*** General health status of respondents included hospitalization, blood pressure at the time of survey, BMI, and Charlson Morbidity score.

- ***Stroke characteristics:*** Stroke characteristics included the number of strokes, paralysis severity at the time of survey, and stroke disability according to Modified Rankin Scale with 6 levels.

- ***Personal physiologic and behaviors:*** To evaluate the participant's physiological and behavioral health, we used the specialized scales for assessing the status of alcohol use, smoking, and sleep, as follows:

+ Alcohol use was assessed using the Alcohol Use Disorders Identification Test (AUDIT-C), a screening instrument for identifying those who are hazardous drinkers or have alcohol use disorders. The AUDIT-C has 3 questions. Each question is scored on a scale from 0 to 4, and the total score ranges from 0–12 points. It is considered positive in men for identifying hazardous drinking or having alcohol disorders. In women, the score of 3 or more is considered positive. In general, the higher score infers that a person's drinking may affect their health status.

+ Smoking status was assessed by the Fagerström Test for Nicotine Dependence. This instrument calculates the ordinary level of nicotine dependence concerning cigarette usage. In scoring, the “yes or no” items are scored as “1” or “0” and multiple-choice items are scored from 0 to 3. The total score ranges from 0 to 10. The classification of nicotine dependence is divided into three levels: none (0 points), very low and low (1-4 points), medium (5 points), high (6-7 points), and very high (8-10 points).

+ The Pittsburgh Sleep Quality Index was used to assess the sleep quality and disturbances over a 1-month time interval. This instrument consists of 7 components with 19 individual items. Each item is rated on a 0-3 scale, providing the total score in the range of 0 to 21 points. A lower score indicates a healthier sleep quality.

3. Data analysis

Data analysis was conducted using STATA version 16 (Stata Corp. LP, College Station, United States of America). Continuous variables were described using mean and standard deviation (SD), and categorical variables were represented by frequencies and percentages. To test the differences between the groups of participants, Whitney Wilcoxon test was used for continuous variables and $\chi 2$ test was used for categorical variables. Covariates for full models included demographics, general health status, stroke characteristics, and individual behaviors. Multivariate Tobit regression analysis was conducted to determine predictors associated with mental health issues in post-stroke patients. These regression models were then combined with stepwise forward methods to reduce the number of covariates using $p > 0.2$ as the threshold for excluding variables. A p-value <0.05 was considered statistically significant.

Structural equation modeling (SEM) was used to examine the association between demographic factors, stroke characteristics with cognitive impairment, depression, fatigue through mediation effects of physiology and personal behaviors. The roles of mental health issues were coded as continuous variables according to the total score of MMSE, PHQ-9, and FSS. Meanwhile, measurements of alcohol use and sleep disorder was treated as binary variables (no = 0, yes = 1). Multiple goodness-of-fit indices were used to assess the model including the absolute fit indices (Root-MeanSquare Error of Approximation (RMSEA), Standardized RootMean-Square Residual, (SRMR), Comparative Fit Index (CFI), and Tucker-Lewis Index (TLI)). CFI and TLI values >0.90 indicated acceptable model fit. Addionally, 90% confidence interval (CI) was included for RMSEA. The goodness of fit based on RMSEA and SRMR was classified into 3 levels with absolute values of 0.05, 0.06–0.08, and 0.08–1.0 reflecting good, satisfactory, and marginal fit.

4. Ethics approval

The study was approved by the Institutional Review Board for Ethics in Biomedical Research - Hanoi Medical University (Code: No 494/GCN-HDDDNCSYHN-DHYHN dated 12/05/2021). Before participating in this study, all participants or their relatives/guardians were requested to provide written informed consent following the Declaration of Helsinki.

III. RESULTS

Table 1. Demographic, Health status and Stroke characteristics of participants (n = 162)

Characteristics	Male		Female		Total		p-value
	n	%	n	%	n	%	
Total	85	52.5	77	47.5	162	100	
DEMOGRAPHIC CHARACTERISTICS							
Occupation							
Unemployment/retirement	62	72.9	47	61	109	67.3	0.107
Worker/farmer/officer	23	27.1	30	39	53	32.7	
Education							
Secondary school and lower	39	45.9	53	68.8	92	56.8	0.003
High school and upper	46	54.1	24	31.2	70	43.2	
Marital status							
Living with spouse	78	91.8	59	76.6	137	84.6	0.008
Single, widow/widower	7	8.2	18	23.4	25	15.4	
GENERAL HEALTH STATUS							
Hospitalization							
Inpatient	46	54.1	40	51.9	86	53.1	0.782
Outpatient	39	45.9	37	48.1	76	46.9	
Blood pressure at time of survey							
Normal blood pressure	55	64.7	52	67.5	107	66	0.704
High blood pressure	30	35.3	25	32.5	55	34	
BMI classifications							
Normal	47	55.3	36	46.8	83	51.2	0.159
Overweight/obese	31	36.5	27	35.1	58	35.8	
Underweight	7	8.2	14	18.2	21	13	
STROKE CHARACTERISTICS							
Number of strokes							
Once	49	57.6	57	74	106	65.4	0.029
Twice or more	36	42.4	20	26	56	34.6	
Stroke Classification							

Characteristics	Male		Female		Total		p-value
	n	%	n	%	n	%	
Cerebral infarction	55	64.7	49	63.6	104	64.2	0.887
Brain hemorrhage or unknown	30	35.3	28	36.4	58	35.8	
Paralysis severity at the time of survey							
None	20	23.5	15	19.5	35	21.6	0.743
Moderate	33	38.8	29	37.7	62	38.3	
Severe	32	37.6	33	42.9	65	40.1	
Stroke disability according to Modified Rankin Scale (Points)							
No symptoms (0)	7	8.2	8	10.4	15	9.3	0.760
No significant disbility (1)	26	30.6	18	23.4	44	27.2	
Slight disability (2)	18	21.2	13	16.9	31	19.1	
Moderate disability (3)	9	10.6	8	10.4	17	10.5	
Moderate severe disability (4)	18	21.2	23	29.9	41	25.3	
Severe disability (5)	7	8.2	7	9.1	14	8.6	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**p-value**
Age	72.6	9.7	74.2	9.5	73.3	9.6	0.003
Charlson morbidity score	2.7	1.2	0.9	2.7	2.7	1.0	0.452

Table 1 presents the demographic, general health status, and stroke characteristics of respondents. Amongst 162 stroke patients, the mean age was 73.3 (SD = 9.6) years, and 47.5% were female. A little more than half of the participants were inpatients (53.1%). About two-thirds of the participants suffered a first stroke (65.4%) and experienced one year or less since occurring stroke (62.3%). The rate of severe diability according to Modified Ranking Scale was 8.6%. The difference was statistically with $p<0.05$.

Table 2. Personal physiologic, Behaviors and Mental health issues including Cognitive impairment, Depression, and Fatigue among stroke survivors (n=162)

Characteristics	Male		Female		Total		p-value
	n	%	n	%	n	%	
PERSONAL PHYSIOLOGIC AND BEHAVIORS							
Smoking status and Nicotine dependence[1]							
Non-nicotine dependence	79	92.9	77	100	156	96.3	0.059

Characteristics	Male		Female		Total		p-value
	n	%	n	%	n	%	
Low & very low dependence	4	4.7	0	0	4	2.5	
High dependence	2	2.4	0	0	2	1.2	
Alcohol Use Disorders[2]							
Yes	25	29.4	1	1.3	26	16	<0.001
No	60	70.6	76	98.7	136	84	
Sleep Quality[3]							
Normal	30	35.3	16	20.8	46	28.4	0.041
Poor sleep	55	64.7	61	79.2	116	71.6	
MENTAL HEALTH ISSUES							
Cognitive Impairment[4] (point)							
Normal cognition (≥ 24)	27	31.8	17	22.1	44	27.2	0.434
Mild impairment (20-23)	16	18.8	19	24.7	35	21.6	
Moderate impairment (14-19)	18	21.2	21	27.3	39	24.1	
Severe impairment (0-13)	24	28.2	20	26	44	27.2	
Depression Severity[5]							
Non-depression	22	25.9	20	26	42	25.9	0.817
Mild depression	29	34.1	21	27.3	50	30.9	
Moderate depression	19	22.4	22	28.6	41	25.3	
Moderate-severe depression	8	9.4	6	7.8	14	8.6	
Severe depression	7	8.2	8	10.4	15	9.3	
Fatigue Severity[6]							
Non-fatigue	13	15.3	4	5.2	17	10.5	0.036
Moderate fatigue	72	84.7	73	94.8	145	89.5	

1. *Fagerström Test for Nicotine Dependence (FTND)*
2. *Alcohol Use Disorders Identification Test (AUDIT-C)*
3. *Pittsburgh Sleep Quality Index (PSQI)*
4. *Mini-Mental State Examination (MMSE)*
5. *Patient Health Questionnaire-9 (PHQ-9)*
6. *Fatigue Severity Scale (FSS)*

Table 2 shows the personal physiological, behavioral, and mental health problems of stroke survivors, including cognitive impairment, depression, and fatigue. A high proportion of participants (71.6%) reported having poor sleep quality, and 72.8% reported having cognitive impairment status ranging from mild to severe, with those who suffered severe impairment accounted for 27.2%. In terms of depression severity, 74.1% had depressive symptoms and 9.3% had severe depressed. The prevalence of fatigue was 82.1%. The differences were statistically significant with p<0.05.

The path coefficients and p-values of the structure equal model analysis were presented in **Figure 1.** Sleep disorders was positively associated with increasing the depression and fatigue status of stroke survivors. By contrast, alcohol use disorder was found as a factor that decreased the FSS score. Stroke disability was directly related to increasing the status of cognitive impairment, depression, and fatigue, but there was no relationship between paralysis severity and mental issues (MMSE, PHQ-9, and FSS).

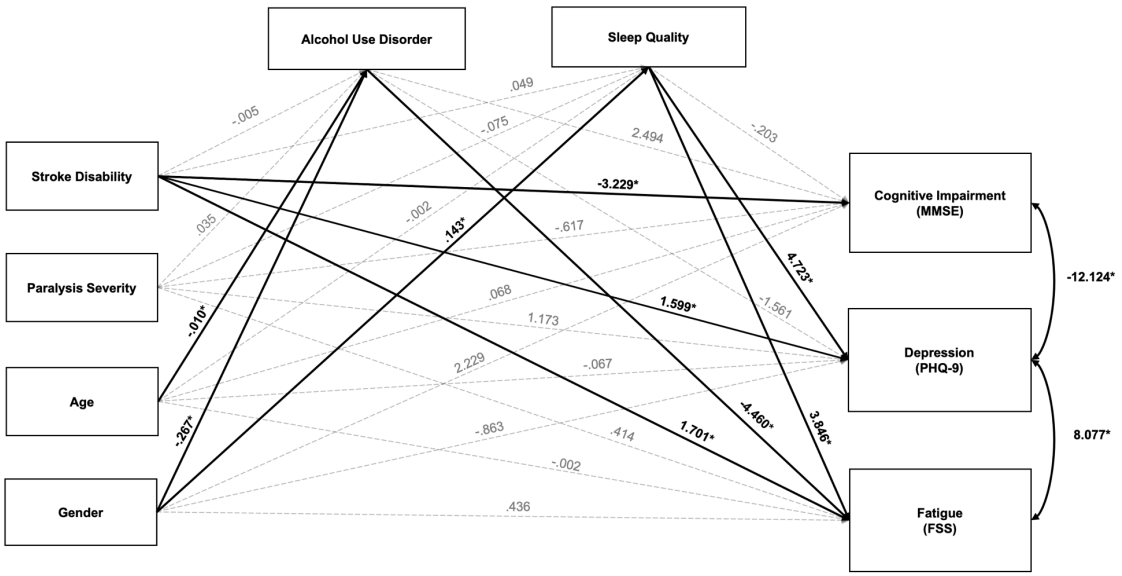

Figure 1. Structural model and standardized path coefficients (n=162, *: p<0.05)

The full model with structural and measurement components was presented in **Table 4**. For both PHQ9 and FSS scores, only sleep disorders were found to partially mediate associations between depression and fatigue status with gender among our participants. Meanwhile, alcohol use disorder had a mediating role between fatigue and gender and age. The index of goodness of fit of the model was RMSEA = 0.089, CFI = 0.997, TLI = 0.954, and SRMR = 0.019.

Table 4. Full models including the outcome and both tier-1 and tier-2 predictors

Structural component	Standardized path coefficient (p-value of unstandardized estimate)
Direct paths-tier 1 to the outcome	
Alcohol use disorder → Mini-Mental State Examination	2.494 (0.173)
Sleep disorder → Mini-Mental State Examination	-0.203 (0.881)
Alcohol use disorder → Patient Health Questionnaire-9	-1.561 (0.176)
Sleep disorder → Patient Health Questionnaire-9	4.723 (<0.001)
Alcohol use disorder → Fatigue Severity Scale	-4.460 (0.005)
Sleep disorder → Fatigue Severity Scale	3.846 (0.001)
Direct paths-tier 2 to tier 1	
Stroke disability → Alcohol use disorder	-0.005 (0.856)
Paralysis severity → Alcohol use disorder	0.035 (0.530)
Age → Alcohol use disorder	-0.010 (0.001)
Gender → Alcohol use disorder	-0.267 (<0.001)
Stroke disability → Sleep disorder	0.049 (0.187)
Paralysis severity → Sleep disorder	-0.075 (0.317)
Age → Sleep disorder	-0.002 (0.669)
Gender → Sleep disorder	0.143 (0.040)
Direct paths-tier 2 to the outcome	
Stroke disability → Mini-Mental State Examination	-3.229 (<0.001)
Paralysis severity → Mini-Mental State Examination	-0.617 (0.631)
Age → Mini-Mental State Examination	-0.068 (0.309)
Gender → Mini-Mental State Examination	2.229 (0.089)
Stroke disability → Patient Health Questionnaire-9	1.559 (<0.001)
Paralysis severity → Patient Health Questionnaire-9	1.173 (0.149)
Age → Patient Health Questionnaire-9	-0.067 (0.113)
Gender → Patient Health Questionnaire-9	-0.863 (0.298)
Stroke disability → Fatigue Severity Scale	1.701 (0.002)
Paralysis severity → Fatigue Severity Scale	0.414 (0.712)
Age → Fatigue Severity Scale	-0.002 (0.976)

Structural component	Standardized path coefficient (p-value of unstandardized estimate)
Gender → Fatigue Severity Scale	0.436 (0.702)
Measurement component	
Residual correlation	
Mini-Mental State Examination ↔ Patient Health Questionnaire-9	-12.124 (<0.001)
Mini-Mental State Examination ↔ Fatigue Severity Scale	8.077 (0.001)
Goodness of fit	
RMSEA (90% CI)	0.089 (0.000 - 0.200)
CFI	0.997
TLI	0.954
SRMR	0.019

CFI: comparative fit index; TLI: Tucker-Lewis Index; CI: confidence interval; RMSEA: root mean square error of approximation; SRMR: Standardized root mean squared residual

IV. DISCUSSION

This study analyzed the causal relationships between independent factors (individual factors, stroke characteristics) and post-stroke mental health issues through physiological and behavioral mediator factors among Vietnamese stroke survivors. The current findings are consistent with our initial hypothesis that stroke disability was significantly and positively correlated with mental health problems such as cognitive impairment, depression, and fatigue in stroke patients. In addition, physiological and behavioral factors fully mediated the relationship between demographic characteristics (age and gender) and the increase in all three mental health problems.

We found that stroke disability directly influenced the increase in cognitive impairment, depression, and fatigue after a stroke. Compared with the standardized path coefficients in the SEM model, the severity of disability had a greater impact on cognitive impairment than on depression and fatigue. This result was similar to prior studies showing that most of the worse functional disabilities on the modified Rankin scale were significantly associated with post-stroke cognitive impairment.[11] In China, a longitudinal survey among 185 stroke patients showed that disability severity of all patients (according to modified Rankin Scale scores 2-5) declined gradually over time, while those who suffered from cognitive impairment had an increased risk of disability severity.[12] Furthermore, our study also showed that there was a direct association between stroke disability and depression. However, the relationship between post-stroke depression and physical disability is likely complicated. According to Sharpe, severe disability after stroke can lead to depression, and early depression can predict later functional impairment.[13] We also found a

relationship between disability severity and post-stroke fatigue status.[14] Early post-stroke fatigue appears to be mostly determined by disability severity, while chronic fatigue is associated with complex medical comorbidities.[4] Hence, patients with post-stroke disabilities may suffer from chronic comorbid diseases, which not only cause negative emotions but also worsen rehabilitation.

The age and gender characteristics of stroke survivors influenced post-stroke fatigue through the mediating effects of alcohol use. Particularly, our results show that alcohol consumption among elderly stroke patients differs by gender. Previous studies reported that older females were more likely than older males to stop alcohol consumption after an adverse health event.[15] However, female participants who reported alcohol use disorder showed a positive relationship between alcohol use and reducing post-stroke fatigue status. This result appears to be in contrast to some previous evidence that indicates the level of alcohol consumption was not significantly associated with fatigue risk at any time point after stroke.[16] Although data on the beneficial effects of alcohol are currently lacking, it appears that psychosis in general and post-stroke fatigue, in particular, are also lowered by moderate alcohol consumption. Several constituents specific to alcoholic beverages, such as polyphenols, have been shown to protect against cerebrovascular disease. Additionally, the specific antioxidant properties of polyphenols could help prevent psychological disorders.[17]

The sleep quality of participants is a mediator between gender and mental health issues, including depression and fatigue. Our findings indicated that women were more likely to have poor sleep than men and also more likely to suffer from a higher risk of depression and fatigue. Depression and fatigue, which frequently develop in stroke patients, may also contribute to post-stroke sleep disturbance development. Furthermore, depression was associated with sleep quality at both acute and chronicpost-stroke stages, while fatigue appeared after the stroke event, usually related to functional impairment.[3,4] In addition, the effects of insomnia symptoms on depression and fatigue in women were higher than in men, which was supported by a 2014 study by Lee et al.[18] Notably, the bidirectional relationship between depression and fatigue and cognitive impairment was also observed in our study. Some previous investigators have shown that post-stroke fatigue is indirectly related to cognition impairment through depressive symptoms.[5]

Several implications can be drawn from the current study. First, disability severity significantly influenced mental health impairment. Hence, early rehabilitation for patients with severe post-stroke disability is crucial for improving their function and mental health during acute and chronic stroke. Second, physiological and behavioral factors were important mediators for changing mental health problems after stroke. Therefore, monitoring and adjusting these factors are necessary during the recovery process for stroke survivors to achieve the best physical and mental health. Finally, alcohol consumption was found as a beneficial factor that may decrease post-stroke fatigue status. However, studies on the beneficial effect of alcohol for stroke patients are currently lacking. Therefore, further investigation is needed to examine the effect of alcohol use in stroke patients.

When evaluating the findings of this study, some limitations should be considered. First, the cross-sectional design restricted our ability

to establish causal relationships. As a result, conclusions about the associations and effects in this study cannot be reached definitively. Longitudinal designs should be used in future studies to explore the impact of individual and stroke characteristics on cognitive impairment, depression, fatigue, and other mental health issues among survivors. Second, the majority of the participants were interviewed and evaluated in the hospital. Large-scale sampling is impossible due to the continuous effects of COVID-19 outbreaks, which might limit the generalizability of study findings. To extrapolate results for the larger population, further studies should be carried out with large sample sizes and representative samples. Last, the relationships between variables were scientifically described and defined through quantitative research methods. However, each stroke patient's information is a unique "life story". Therefore, a combination of quantitative and qualitative research can better provide a deeper understanding of post-stroke mental issues.

V. CONCLUSION

Our study found a high prevalence of stroke survivors who suffered from cognitive impairment, depression, and fatigue. Stroke disability was found to be directly associated with increasing cognitive impairment, depression, and fatigue after stroke. In addition, age and gender of stroke survivors impacted post-stroke fatigue through the mediating effects of alcohol use. The effect of insomnia symptoms on depression and fatigue was higher in women than in men, with alcohol use as a beneficial mediator.

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