



## Health Related Quality of Life and Dependency Among Stroke Survivors in a Tertiary Care Centre in Rajasthan

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### ABSTRACT

**Background:** Quality of life is an important health care issue in stroke survivors as disabilities associated with stroke causes permanent functional impairments leading to dependency in daily activities, issues with cognition and communication depressed mood, social isolation.

**Objectives:** To determine health related-quality of life and dependency among stroke survivors and its associated factors at a tertiary care hospital of Western Rajasthan.

**Methodology:** This cross-sectional, hospital-based study was conducted among 100 stroke survivors from May 2022 to December 2022. Patients aged more than 40 years, of either gender, with at least one year old history of stroke were included in the study. WHOQOL-BREF questionnaire and Barthel Index questionnaire were used to measure quality of life related to health and dependency of stroke survivors respectively.

**Results:** Domain scores was highest in environment (35.23±10.52) domains followed by physical health (30.67±9.79), social relationship (27.60±14.00) and psychological domain (22.77±10.08). Physical domain score was found to be less among female stroke patients (25.08±15.67) as compared to male stroke patients (31.51±8.40). Both physical (27.92±10.24) and psychological (20.75±9.63), quality of life was poor in upper lower SES patients. Psychological domain score was lowest among survivors with multiple comorbidities (22.14±9.58) as compared with survivors with single or no co-morbidity.

**Conclusion:** Factors like age, gender, socio-economic status, presence of multi-morbidities should be considered in framing health care set up and prioritization of rehabilitation in order to maximize recovery and improve health-related quality of life as well as reduce dependency.

**Keywords:** Health Related Quality of Life, WHO-BREF, dependency, stroke, survivors.

### INTRODUCTION

Stroke is a devastating event that affects every part of a person's life and results in significant loss of Disability Adjusted Life Years (DALYs), making it a significant cost burden on the healthcare system as well.<sup>1</sup> It is defined as "Rapidly developing clinical signs of a focal (or global) disturbance of cerebral function, with symptoms lasting 24 hrs or longer or leading to death, with no apparent cause other than of vascular origin" according to World Health Organisation (WHO).<sup>2</sup> Stroke burden rose from around 38 million Disability Adjusted Life Years (DALYs) globally in 1990 to 61 million in 2020. Between 1990 and 2019, there was a global rise of 70.0% (67.0–73.0) in the absolute number of incident strokes, 85.0% (83.0–88.0) in prevalent strokes, 43.0% (31.0–55.0) in stroke deaths, and 32.0% (22.0–42.0) in DALYs due to stroke.<sup>1</sup> Stroke is the fourth most common cause of death and the fifth most prevalent cause of disability in India, according to annual morbidity and mortality data. In rural areas, the estimated adjusted prevalence rate of stroke

ranges from 84 to 262/100,000, while in urban areas, it ranges from 334 to 424/100,000.<sup>3</sup>

Quality of life (QOL) is an important health care issue in stroke survivors as disabilities associated with stroke causes permanent functional impairments leading to dependency in daily activities, issues with cognition and communication, depressed mood, social isolation. Individuals with stroke-related disability, their families, and ultimately the economies of lower- and middle-income countries are all impacted.<sup>4,5</sup> The assessment of a patient's quality of life is frequently included in the overall assessment of the effects of a stroke, and this information can be used to identify the aspects of a patient's life that are most negatively impacted by the condition and to plan efficient therapeutic and rehabilitation interventions. To assess quality of life, a multifaceted approach is required. Physical, functional, psychological, and social health are at least four of the elements that go into assessing quality of life.<sup>6,7</sup> Traditional epidemiological studies focused on mortality and recurrence, but not on quality-of-life issues.



The focus of stroke management has shifted from "adding years to life" to "adding life to years" since more individuals are surviving stroke. It is also important to evaluate the relationship between health status, and other socio-demographic and clinical factors. There are limited number of studies that have investigated in this field on the stroke survivors in India. Therefore, this study was aimed to determine health related-quality of life and dependency among stroke survivors and its associated factors at a tertiary care hospital of Western Rajasthan.

## Materials and Methods

This hospital-based, cross-sectional study was conducted by the Department of Community Medicine working together with the Department of Neurology at MDM Hospital of Dr. S.N. Medical College, a tertiary care institute situated in Jodhpur city in Western part of Rajasthan from May 2022 to December 2022 after the approval from Institutional Ethics Committee (SNMC/IEC/2022/535).

Among the patients who visited the OPD of Neurology Department, those aged more than 40 years, of either gender, with at least one year old history of stroke (time since diagnosis and initiation of treatment) was included in the study. Those patients with aphasia, who were not able to respond to questions or communicate properly, patients with history of neurological disorder or psychiatric illness prior to stroke, stroke caused due to trauma and patients with CT findings of stroke mimics i.e. seizure, intracranial tumour, migraine, metabolic encephalopathy were excluded from the study.

Using the formula for sample size for estimate of a single sample proportion with absolute precision, the sample size was determined at 95% Confidence Interval and 10% absolute error.

$$N = \frac{(Z_{1-\alpha/2})^2 P(1-P)}{E^2}$$

Where,

$Z_{1-\alpha/2}$  = Standard normal deviate for 95% Confidence Interval (taken as 1.96)

P = Expected proportion of stroke patients with poor quality of life (taken as 60% as reported by Sahu RK et al. 2021<sup>8</sup>)

E = Absolute allowable error (taken as 10%)

On using the above formula, the sample size was calculated to be 92, which was rounded-off to 100 stroke patients.

Consecutive sampling was done till sample size was achieved.

A semi-structured proforma was used for data collection which consisted of four parts.

Part A: Socio-demographic characteristics that included age, gender, occupation, education, marital status, family type, socio-economic status etc.

Part B: Clinical and stroke related characteristics

Part C: WHOQOL-BREF questionnaire<sup>9</sup>

There are 26 questions in the WHOQOL-BREF questionnaire that measure quality of life connected to health. The psychological, social, environmental, and physical health domains are all included in this questionnaire. Two more items that assessed a person's general perception of their health and quality of life were included. The domain score is determined by taking the average scores of the items in each domain. In order to make domain scores similar with the values used in the WHOQOL-100, the mean score is then multiplied by 4. To determine what is regarded as the final score in that specific domain, the transformed score is applied to the raw scores obtained from the questionnaire. The WHOQOL-BREF Quality of Life measure has no cut-points, therefore the final score can be anywhere from 0 to 100, with higher scores denoting higher quality.

Part D: Barthel Index<sup>10</sup> questionnaire for assessing the dependency of stroke survivors.

The Barthel Index is a set of ten questions that evaluate several aspects of daily life and mobility, including clothing, walking, climbing stairs, eating, bathing, transferring from a wheelchair to a cot and back, and incontinence of the bladder and bowel. The patient's level of dependence on assistance is the basis for scoring; a score of 0–20 indicates "total" dependency, a score between 21 and 60 indicates severe dependence, a score between 61 and 90 indicates moderate dependence, a score between 91 and 99 indicates mild dependence, and a score of 100 indicates complete independence.

Socio-economic status was assessed using Modified Kuppuswamy's scale<sup>11</sup> for the year 2022.

## Data entry and Statistical Analysis

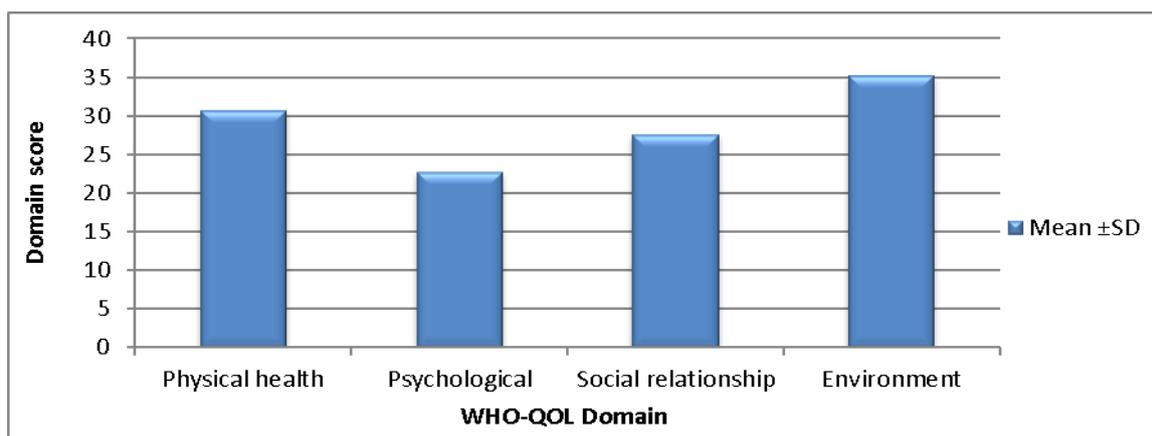
A master chart in MS Excel was created using the data gathered in the semi-structured proforma. The Chi square test was used to analyze the categorical variables, which were reported as frequency (n) and percentage (%). Continuous variables were compared between two groups using the Student's t-test and between more than two groups using an ANOVA. The continuous variables were represented as mean and standard deviation (Mean ± SD). Probability (p) value of <0.05 was considered statistically significant. IBM SPSS version 21 for Windows (IBM Inc. Armonk, New York, USA) statistics software was used for all statistical analysis.



**Table 1:** Distribution of study subjects according to socio-demographic and clinical characteristics (N=100)

Characteristics		Male (n=86)	Female (n=14)	Total n (%)
		n (%)	n (%)	
Age range (years)	40-49	11(12.8)	0(0.0)	11(11)
	50-59	26(30.2)	3(21.4)	29(29)
	60-69	30 (34.9)	6(42.9)	36(36)
	70-79	19(22.1)	5(35.7)	24(24)
Marital status	Married	80(93.0)	12(85.7)	92(92)
	Unmarried	3(3.5)	0(0.0)	3(3)
	Widow/widower	3(3.5)	2(14.3)	5(5)
Residence	Rural	12(14.0)	1(7.1)	13(13)
	Urban	74(86)	13(92.9)	87(87)
Educational status	Illiterate	3(3.5)	9(64.3)	12(12)
	Up to secondary	49(57.0)	5(35.7)	54(54)
	Senior secondary	10(11.6)	0(0.0)	10(10)
	Graduate and above	24(27.9)	0(0.0)	24(24)
Socio-economic status	Upper	0(0.0)	0(0.0)	0(0.0)
	Upper middle	23(26.7)	0(0.0)	23(23)
	Lower Middle	23(26.7)	3(21.4)	26(26)
	Upper Lower	40(46.5)	11(78.6)	51(51)
	Lower	0(0.0)	0(0.0)	0(0.0)
Family type	Nuclear family	31(36.0)	3(21.4)	34(34)
	Joint family	55(64.0)	11(78.6)	66(66)
Addiction	Smoking*	61(70.9)	0(0.0)	61(61)
	Alcohol#	32(37.2)	0(0.0)	32(32)
	Smokeless tobacco <sup>§</sup>	24(27.9)	5(35.7)	29(29)
Comorbidity	HTN	82(95.3)	11(78.6)	92(92)
	DM	61(70.9)	7(50)	68(68)
	CAD	35(40.7)	7(50)	42(42)
	CKD	10(11.6)	1(7.1)	11(11)
	COPD	35(40.7)	2(14.3)	37(37)
Type of Stroke	Infarct	81(94.2)	10(71.4)	91(91)
	Haemorrhage	5(5.8)	4(28.6)	9(9)
Duration since Stroke	<5years	69(80.2)	12(85.7)	81(81)
	≥5 years	17(19.8)	2(14.3)	19(19)

\*,#,§ self-reported



**Figure 1:** Mean WHO-QOL domain scores among all patients

**Table 2:** Distribution of WHO-QOL Domain scores among different socio-demographic and clinical characteristics

Characteristics		Physical Mean $\pm$ SD	Psychological Mean $\pm$ SD	Social Mean $\pm$ SD	Environment Mean $\pm$ SD
Age (years)	40-49 years	31.45 $\pm$ 11.50	24.55 $\pm$ 12.00	30.64 $\pm$ 16.69	37.91 $\pm$ 13.48
	50-59 years	33.34 $\pm$ 8.12	24.48 $\pm$ 10.07	29.69 $\pm$ 12.94	37.72 $\pm$ 8.54
	60-69 years	30.14 $\pm$ 11.11	23.47 $\pm$ 9.48	28.28 $\pm$ 15.25	34.81 $\pm$ 11.20
	70-79 years	27.88 $\pm$ 8.32	18.83 $\pm$ 9.62	22.67 $\pm$ 11.34	31.63 $\pm$ 9.61
p value		0.027 (S)	0.087	0.463	0.384
Residence	Rural	28.64 $\pm$ 6.42	22.43 $\pm$ 8.00	22.86 $\pm$ 10.51	31.29 $\pm$ 7.81
	Urban	31.00 $\pm$ 10.22	22.83 $\pm$ 10.42	28.37 $\pm$ 14.39	35.87 $\pm$ 10.79
p value		0.406	0.892	0.173	0.131
Gender	Female	25.08 $\pm$ 15.67	18.31 $\pm$ 13.14	24.92 $\pm$ 12.21	32.85 $\pm$ 8.98
	Male	31.51 $\pm$ 8.40	23.44 $\pm$ 9.46	28.00 $\pm$ 14.27	35.59 $\pm$ 10.73
p value		0.027 (S)	0.087	0.463	0.384
Socio-economic status	Upper middle	34.13 $\pm$ 9.43	22.48 $\pm$ 10.91	35.04 $\pm$ 15.47	40.13 $\pm$ 12.26
	Lower Middle	33.00 $\pm$ 7.72	27.00 $\pm$ 9.23	29.00 $\pm$ 10.10	37.19 $\pm$ 9.04
	Upper Lower	27.92 $\pm$ 10.24	20.75 $\pm$ 9.63	23.53 $\pm$ 13.72	32.02 $\pm$ 9.41
p value		0.014 (S)	0.034(S)	6.105	5.840
Education	Illiterate	27.67 $\pm$ 11.30	15.75 $\pm$ 6.90	22.92 $\pm$ 6.66	30.42 $\pm$ 8.86
	Up to secondary	30.09 $\pm$ 9.87	23.89 $\pm$ 10.58	25.89 $\pm$ 13.25	33.72 $\pm$ 9.76
	Senior secondary	32.60 $\pm$ 7.23	24.00 $\pm$ 8.74	32.50 $\pm$ 15.55	37.00 $\pm$ 7.61
	Graduate/ PG	32.67 $\pm$ 9.75	23.25 $\pm$ 9.88	31.75 $\pm$ 16.63	40.29 $\pm$ 12.28
p value		0.445	0.081	0.139	0.021 (S)
Marital status	Widow	31.40 $\pm$ 7.76	20.20 $\pm$ 6.57	35.00 $\pm$ 14.95	38.80 $\pm$ 10.23
	Married	39.67 $\pm$ 9.60	35.67 $\pm$ 14.43	35.33 $\pm$ 13.05	39.67 $\pm$ 20.42
	Unmarried	30.34 $\pm$ 9.84	22.49 $\pm$ 9.91	26.95 $\pm$ 13.94	34.89 $\pm$ 10.25
p value		0.226	0.069	0.287	0.552
Type of family	Joint	32.50 $\pm$ 8.69	23.26 $\pm$ 9.18	27.38 $\pm$ 12.98	36.88 $\pm$ 10.40
	Nuclear	29.58 $\pm$ 10.35	22.23 $\pm$ 10.38	27.70 $\pm$ 14.81	34.58 $\pm$ 10.65
p value		0.164	0.628	0.916	0.307
Duration since stroke	<5years	30.60 $\pm$ 10.11	22.31 $\pm$ 9.84	27.68 $\pm$ 14.29	35.53 $\pm$ 10.57
	$\geq$ 5 years	30.95 $\pm$ 8.50	24.74 $\pm$ 11.14	27.26 $\pm$ 13.02	33.95 $\pm$ 10.48
p value		0.892	0.348	0.908	0.558
Co-morbidity	No comorbidity	44.00 $\pm$ 8.48	40.50 $\pm$ 13.43	47.00 $\pm$ 4.24	53.00 $\pm$ 4.24
	Single comorbidity	31.71 $\pm$ 12.42	23.71 $\pm$ 10.82	25.62 $\pm$ 6.50	34.06 $\pm$ 8.42
	Multiple comorbidity	30.12 $\pm$ 9.05	22.14 $\pm$ 9.58	27.53 $\pm$ 14.95	35.04 $\pm$ 10.69
p value		0.125	0.034(S)	0.124	0.050(S)
Smoking Status*	Smoker	28.59 $\pm$ 11.60	22.62 $\pm$ 11.39	26.74 $\pm$ 11.43	34.21 $\pm$ 9.73
	Non-smoker	32.00 $\pm$ 8.27	22.87 $\pm$ 9.25	28.15 $\pm$ 15.49	35.89 $\pm$ 11.02
p value		0.089	0.903	0.627	0.439
Smokeless Tobacco <sup>#</sup>	Yes	30.37 $\pm$ 9.52	22.63 $\pm$ 9.94	27.18 $\pm$ 14.88	35.24 $\pm$ 10.19
	No	31.41 $\pm$ 10.54	23.10 $\pm$ 10.59	28.65 $\pm$ 11.74	35.21 $\pm$ 11.47
p value		0.630	0.830	0.644	0.989
Alcohol habit <sup>§</sup>	Alcoholic	30.46 $\pm$ 10.09	22.79 $\pm$ 10.25	25.99 $\pm$ 14.05	34.84 $\pm$ 9.93
	Non-alcoholic	31.94 $\pm$ 8.16	23.26 $\pm$ 9.56	31.23 $\pm$ 13.63	36.42 $\pm$ 11.81
p value		0.476	0.832	0.086	0.491

\*,#,§ self-reported



**Table 3:** Distribution of Barthel Index score among different socio-demographic and clinical characteristics

Socio-demographic and clinical characteristics		N	Barthel Index	p value
Age	40-49 years	11	53.18 ±23.05	0.185
	50-59 years	29	55.69±18.55	
	60-69 years	36	54.31 ±16.04	
	70-79 years	24	45.83±14.72	
Gender	Female	14	45.00±18.14	0.096
	Male	86	53.68 ±17.26	
Residence	Rural	13	49.64 ±19.06	0.506
	Urban	87	53.02 ±17.34	
Socio-economic status	Upper middle	23	60.00±15.10	0.003 (S)
	Lower Middle	26	56.52±17.92	
	Upper Lower	51	46.96±16.88	
Education	Illiterate	12	47.92±17.24	0.248
	Up to secondary	54	25.04±17.95	
	Senior secondary	10	62.50±11.36	
	Graduate/PG	24	51.88±18.22	
Marital status	Widow	5	49.00±12.94	0.049 (S)
	Unmarried	3	51.96±17.50	
	Married	92	76.67±2.88	
Type of family	Nuclear	34	53.82±15.81	0.461
	Joint	66	53.09±18.13	
Duration since stroke	<5years	81	52.65±17.37	0.903
	≥5 years	19	52.11±18.65	
Co-morbidity	No comorbidity	2	57.50±10.60	0.681
	Single comorbidity	17	53.09 ±17.11	
	Multiple comorbidity	81	49.41± 20.37	
Smoking status*	Non-smoker	39	54.43±16.90	0.182
	Smoker	61	49.32±18.29	
Smokeless tobacco consumption <sup>#</sup>	Yes	29	48.62±19.02	0.153
	No	71	54.15±19.03	
Alcohol habit <sup>§</sup>	Non-alcoholic	68	56.77± 15.08	0.118
	Alcoholic	32	50.81± 18.39	

\*,<sup>#</sup>,<sup>§</sup> self-reported

## RESULTS

Out of a total of 100 stroke survivors, most of them were males (86%), while 14% were females where majority of the male subjects were aged 60-69 years (34.9%) and 50-59 years (30.2%), followed by 40-49 years (12.8%) and >70 years (22.1%). Among females, majority were aged 60-69 years (42.9%), followed by 70-79 years (35.7%), while only 3 (21.4%) were aged 50-59 years. Majority of participants, both male (93%) and female (85.7%) were married currently; majority were from urban residence (87%); most females were illiterate (64.3%); more than half (66%) belonged to joint family; maximum of males were smokers (70.9%); none of the females were alcohol addicts and smokers. Common co-morbidities among males were Hypertension (95.3%), Diabetes mellitus (70.9%), CAD (40.7%), COPD (40.7%) and CKD (11.6%). Similarly common

co-morbidities among females were Hypertension (78.6%), Diabetes mellitus (50%), CAD (50%), COPD (14.3%), and CKD (7.1%). Duration since stroke among most of the survivors (81%) were of less than 5 years (Table 1).

Figure 2 indicates that among all patients, the WHOQOL Domain scores was highest in environment (35.23±10.52) domains followed by physical health (30.67±9.79), social relationship (27.60±14.00) and psychological domain (22.77±10.08).

Table 2 shows that the distribution of WHO-QOL domain scores among different socio-demographic and clinical characteristics. A significant difference (p=0.027) in physical domain score was seen among female stroke patients (25.08±15.67) as compared to male stroke patients (31.51±8.40), which indicates a poor quality of life in the physical health domain of female stroke survivors



compared to male survivors. Both physical (27.92±10.24) and psychological (20.75±9.63), quality of life was poor in upper lower SES patients as depicted by a significant difference among these two domains. Psychological domain score was lowest among survivors with multiple comorbidities (22.14±9.58) as compared with survivors with single or no co-morbidity and this finding was statistically significant.

The distribution of Barthel Index score among different socio-demographic and clinical characteristics was shown in Table 3. Dependency was significantly higher in upper lower class SES patients and widows as Barthel Index score was lowest in upper lower SES class (46.96±16.88) and in widows (49.0±12.94) respectively.

Moderate positive correlation was found between Barthel Index and WHO-QOL physical domain ( $r=0.343$ ), Psychological domain ( $r=0.386$ ) and environmental domain ( $r=0.363$ ), while weak correlation was seen with social domain ( $r=0.270$ ) as depicted in Figures 2, 3, 4 and 5.

## DISCUSSION

This study is among few researches which assessed the quality of life and dependency among stroke survivors in western part of India using WHOQOL-BREF questionnaire and Barthel Index.

Stroke is known to be a common occurrence in elderly and as reported by Rajan B et al<sup>12</sup> in their study, one-third of their participants belonged to age group of 65-74 years with mean age of 61.3 years which is almost similar to our finding where mean age was found to be 61.76±9.18 years, with majority of patients in the age group of 60-69 years. A male preponderance was seen among the stroke survivors by previous research conducted by Oni OD et al<sup>13</sup> which is also replicated by our study findings. This can be explained by the fact of gender bias prevalent in the society which makes preferences in seeking health care for males as compared to females. Majority of females were also seen to be illiterate as compared to the males in this study which was similar to findings of Mahesh PKB et al.<sup>14</sup> As education influences the socio-economic status, it was observed in the present study that majority of the patients (both males and females) were in the upper lower socio-economic status of which 46.5% of males belonged to Upper lower class and 78.6% of females were in upper lower class. In our study common comorbidities prevalent among both males and females were Hypertension (92%), Diabetes Mellitus (68%), CAD (42%), COPD (37%) and CKD (11%). Similar spectrum of co-morbidities was observed in study conducted by Froes KSO et al.<sup>15</sup>

In the present study lowest scores of WHOQOL-BREF among the participants was in psychological domain (22.77±10.08), followed by social relationship (27.60±14.00), Physical health (30.67±9.79) and environment (35.23±10.52) domains. The presence of low mean scores in the psychological and social domains matches with the finding of Butsing N et al<sup>4</sup> and Kwok T et al<sup>16</sup>. These findings indicate that the psychological and

social aspects of health-related quality of life suffer the most. Survivors of strokes report feeling constrained in their efforts to reorganize their lives, and a decline in social interaction is linked to a worsening of their interpersonal relationships with friends and family. This illustrates why it's important to comprehend the variables linked to stroke survivors' quality of life when creating a goal plan to enhance quality of life and lessen adverse effects.

Stroke survivors with poorer overall health-related quality of life scores were more likely to be females, in the present study. The finding that male stroke survivors had significantly better physical health than females is similar to a previous study done by Oni OD et al.<sup>13</sup> The data available about the implications of socio-economic factors on stroke in Indian context are meagre. In the present study, physical and psychological quality of life were lowest in stroke patients of upper lower SES class as compared to other classes. Low socioeconomic class puts people at risk for having worse health because they have less access to medical treatment, worse living conditions, more stress, and difficulty adhering to management standards. The study by Jeon NE et al<sup>17</sup> have also indicated that a poor socioeconomic status—including illiteracy and low income—is linked to a lower quality of life in terms of health. Because co-morbidities including hypertension, diabetes, coronary artery disease, etc. are becoming more common, the burden of stroke is projected to rise in emerging nations, which could have a negative impact on quality of life.<sup>18</sup> A high degree of functional impairment resulting from comorbid conditions along with post stroke complications leads to a poor quality of life which is reflected by our study findings is also justified by other researches.<sup>13</sup>

A statistically significant Barthel Index score was found in relation to socio-economic status, with the highest dependency found in the patients of upper lower class. The dependency level of patients with lower income status is high because the patients may be deprived of proper medical facilities. Marital status significantly affected dependency levels in our study. The dependency level was high in both widow and unmarried, which can be due to the lack of family care and support which is present in married individuals. In our study, it was found that the poor quality of life was associated with the increased dependency level in all the four domains. Similarly, Haghgoo HO et al<sup>19</sup> also reported that the activities of daily life were related with level of depression and quality of life in patients with stroke.

## Strengths and Limitations

One of the limitations of our study is that because it was conducted in a hospital, results may not be generalizable to the general population, and recall bias cannot be completely ruled out. However, the authors have made efforts to study one of the least explored topics, i.e., health related quality of life and dependency among stroke survivors in this part of the country.



## CONCLUSION

This study showed that factors like older age, female gender, lower socio-economic status, education level, presence of multi-morbidities worsened the quality of life and level of dependency among the survivors. So, these factors must be considered in framing health care set up and prioritization of rehabilitation in order to maximize recovery and improve health-related quality of life as well as reduce dependency. Future population-based epidemiological studies on stroke should be done to analyse the risk factors, improve preventive measures against stroke and undertake necessary measures to maximize recovery and improve health-related quality of life as well as reduce dependency.

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### Author's contribution:

VA: Designed and generated idea, data collection, data curation; MV: Data analysis; GD: Data collection; RM: Designing idea, editing manuscript; \*GD: manuscript preparation, data analysis; TK: editing manuscript.

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