COVID-19 Infection and Psychosocial Symptoms in First Year Post-Stroke Patients – a secondary analysis of the UPACT observational study

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Background: Annually 12.2 million adults worldwide suffer a stroke, this can result in physical and psychosocial issues like depression, anxiety, and fatigue. These symptoms are very similar to those in individuals from the general population during the COVID-19 pandemic. Psychosocial symptoms are known to have a negative impact on the recovery of stroke survivors. However, little is known about the impact of a COVID infection post-stroke on psychosocial outcomes.

Aim: This study aimed to investigate a relationship between COVID-19 infection and depression, anxiety, and fatigue symptoms in first year stroke survivors with and without a COVID-19 infection post-stroke.

Method: Retrospective study using cross-sectional data from the UPACT study. Patients with a stroke in the last year in one of five Dutch hospitals participated. The primary outcomes of the current study consisted of depression, anxiety, and fatigue. This information was analyzed for secondary analysis using Quantile regression for two study groups: the COVID group and non-COVID group.

Results: 572 stroke survivors were included, 126 experienced a COVID infection. There was significant influence of COVID infection on anxiety, not on depression or fatigue. Daily functioning capability and time since stroke were associated with improved psychosocial symptoms. Previous depression or anxiety, cerebral infarction, sex, or age were associated with an increase in (some of the) psychosocial symptoms.

Conclusion: COVID infection had a significant influence on anxiety. Influential factors on psychosocial scores varied greatly between study groups, leading to cautionary interpretation of the current findings. Further research is necessary to consider if tailored rehabilitation programs could benefit stroke survivors.

Practical implications: Even though the COVID pandemic is no longer present, post-stroke COVID-infections can still occur. If COVID infections rise or a pandemic occurs again in the future, stroke rehabilitation may need adjustment, particularly around anxiety.

Keywords: *stroke, COVID-19, depression, anxiety, fatigue, rehabilitation.*

INTRODUCTION

Every year, nearly 12.2 million new strokes occur worldwide[1]. One in every four adults over the age of 25 will suffer a stroke in their lifetime[1]. Stroke, meaning cerebral infarction or cerebral hemorrhage, is a major health event. A cerebral infarction occurs when part of the brain is cut off from blood supply, caused by small artery occlusions[2], while a cerebral hemorrhage occurs when there is a sudden bleed into the nervous tissue of the brain[3]. Both prevent nutrients and oxygen from reaching certain areas of the brain, potentially resulting in deterioration of brain cells, brain damage and other complications like long- and short-term physical or psychosocial residual symptoms[4].

Psychosocial symptoms can occur during hospitalization and months or years afterwards[5]. The occurrence of post-stroke depression varies, but current literature states 11 to 41% experience it up until two years post-stroke[6,7]. Anxiety prevalence ranges between 20% and 24% in the first-year post-stroke[8,9], and 25% to 82% of stroke survivors report post-stroke fatigue as a common symptom in the first two years[10]. The psychosocial symptoms that are seen following a stroke are very similar to psychosocial impairments in individuals from the general population during the COVID-19 pandemic, regardless of COVID infection. However, mental health symptoms like depression, anxiety and fatigue that develop during the first stages of COVID infection were reported across all healthy age groups and can persist even after the acute stage[11–15].

Depression, anxiety, and fatigue symptoms negatively impact health-related quality of life (HRQoL), and have been connected to frequent hospitalization, increased healthcare costs, higher mortality, and less rehabilitation compliance in stroke survivors[4,16]. While COVID infections are associated with a deterioration in pre-existing mental health outcomes[13], with 10% of symptoms post-COVID becoming chronic[14]. Presence of these symptoms could be an obstacle to the rehabilitation process of stroke survivors, potentially through non-compliance [16]. Rehabilitation is an integral part of the recovery process and of returning to society post-stroke[17]. The process of post-stroke rehabilitation focuses on improving overall functioning and achieving the highest levels of independence in all aspects of everyday life through an adjustable rehabilitation plan[17]. While there are rehabilitation methods for psychosocial symptoms post-stroke, there currently is no specific post-COVID treatment for psychosocial problems[17,18]

The combination of stroke and COVID-19 on the emergence of psychosocial symptoms has been scarcely researched. Current studies focusing on stroke, COVID-19 and psychosocial issues show a rise in post-stroke depression[11], anxiety[11,19,20], low HRQoL[21], increased fatigue[12,15] and higher levels of mental health symptoms[12,21]. These studies only focused on

the difference of psychosocial symptoms in stroke patients before and after the pandemic, they did not study any relation between COVID infection during or after stroke and the impact on psychosocial symptoms. Despite the similarity of psychosocial symptoms seen after stroke and COVID-19, no recent research was found examining whether individuals who solely experienced a stroke and individuals who experienced a COVID infection post-stroke differ in the development of psychosocial symptoms. By examining these issues, we can gain a better understanding of the psychosocial challenges that individuals face after a stroke. It is therefore necessary to investigate if a COVID infection post-stroke influences psychosocial symptoms in stroke survivors.

AIM

This study aimed to investigate a relationship between COVID-19 infection and depression, anxiety, and fatigue symptoms in first year stroke survivors with and without a COVID-19 infection post-stroke.

METHOD

Design

A retrospective study with secondary analysis was performed with cross-sectional data from the UPACT study. Data for the UPACT study were collected from June 2021 until April 2022. This research was conducted by the Department of Nursing Science at UMC Utrecht and the Proactive Care for Older People Living at Home Lectorate at the Hogeschool Utrecht. The study's purpose was to better understand the difficulties and concerns patients experience in the first-year post-stroke and whether individuals require therapy for these problems and concerns. We conducted a secondary analysis of UPACT study data regarding psychosocial outcomes to better understand the influence of a COVID infection. Data for this analysis was reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement[22]. This reporting method was developed to give a complete and accurate data report of an observational study[22].

Population and Domain

A convenience sample was used in the UPACT study. All stroke patients who were hospitalized in one of the five Dutch affiliated hospitals in the last year were asked to participate through their healthcare provider. This includes one academic hospital and four general hospitals. The population comprises all adult first-year stroke survivors, with a cerebral hemorrhage or cerebral infarction. Transient Ischemic Attack (TIA) patients were excluded due to a difference in symptom severity, treatment, and rehabilitation methods[23,24].

Procedures and Data collection

Study parameters related to various aspects of pre- and post-stroke life were merged into a questionnaire in the UPACT study. This thesis only used the participant characteristics, depression, anxiety, and fatigue parts of the UPACT questionnaire. Eligible participants received a patient information letter from their healthcare provider, an information letter from the researchers, an informed consent form and the questionnaire by mail. Responses were collected through mail or online. Participants were not involved in the data collection for this thesis, due to the use of UPACT study data. The Hospital Anxiety and Depression Score (HADS) and the Checklist Individual Strength (CIS) were used in the questionnaire to assess depression, anxiety, and fatigue symptoms post-stroke.

Study outcomes

To assess symptom severity of anxiety and depression the HADS was used, which is validated for the stroke population[25]. The HADS assesses core symptoms of anxiety and depression and is divided into two subscales, an anxiety scale (HADS-A) and depression scale (HADS-D). Each subscale addresses feelings in the previous four weeks and is made up of seven statements, each statement consists of a four-point scale from strongly agreeing to strongly disagreeing. The more symptoms one has, the higher the score. A score of 0 to 7 is defined as 'no depression or anxiety', 8 to 10 as a 'possible depression or anxiety', and 11 to 21 as 'presumable depression or anxiety'[25,26].

Fatigue was assessed with the CIS and is a valid and reliable scale to measure fatigue[27]. This questionnaire consists of twenty questions. Eight questions regard the subjective feeling of fatigue (CIS-f). These questions were used in data collection. Each of these items can be scored on a seven-point Likert scale with one end of the scale meaning: 'yes, that is true' and the other meaning: 'no, that is not true'. This gives a total score of 8 to 26 for 'normal fatigue', 27 to 34 for 'moderate fatigue', and 35 to 56 for 'severe fatigue'[27].

Study determinants

The participant characteristics consist of sex, age, marital status, educational level, type of stroke (cerebral hemorrhage or cerebral infarction), time since stroke (in months), previous episodes of depression and anxiety, and if the participant experienced a COVID infection post-stroke. *Daily functioning* before and after stroke was measured with the EuroQol 6D (EQ-6D), which has been validated for stroke patients[28]. Participants had to fill out the EQ-6D with their knowledge of their daily functioning before stroke and the current situation. The EQ-6D, also called the EQ-5D-5L+C[28] questionnaire, is used to score six dimensions of health: daily activities, pain or discomfort, mobility, selfcare, anxiety and/or depression and cognition. Each dimension has five levels: no problems, slight problems, moderate problems, severe problems,

and extreme problems. These dimension scores add up to a score between 0 and 24. The total amount of points is recalculated to a scale of 0-100 by multiplying with 4,16 (100/24). A score of 100 means the best health imaginable and a score of zero means the worst health imaginable. A difference between the before and after scores (EQ-6D_diff) was calculated to visualize the increase or decrease in daily functioning since stroke.

Data analysis

Statistical analysis was performed using IBM SPSS for Windows (V.28.0). No imputation was performed, because both the overall percentage of missing data and the maximum percentage of missing data in individual variables was less than 5%[29].

The UPACT study consisted of 580 participants, this sample size allowed regression analysis of all study variables by the '20:1 rule' where the ratio of the sample size to the number of variables in the model should be at least twenty to one[30]. Before statistical analysis the data was checked on various assumptions necessary to perform linear regression analysis. This includes checking for outliers, linearity, normality, homoscedasticity, and multicollinearity[31]. The outcome variables were not normally distributed, and thus, Quantile regression analysis was used to diminish biased results. In contrast to linear regression, which uses the least squares method to calculate the conditional mean, quantile regression estimates the conditional median of the target[32–34]. Two separate regression analyses were performed: one to assess the relationship between COVID infection and each outcome, and secondary analyses stratified by COVID infection. The final model was created by backward stepwise selection of significant predictors (*alpha* < 0.1).

The study groups are referred to as the *COVID group* and *non-COVID* group. The COVID group refers to the group of stroke survivors who also experienced a COVID-19 infection post-stroke, the non-COVID group solely experienced a stroke. Categorical variables were retained in case of ≥ 1 significant subgroup in the full model.

Ethical issues

The study was conducted according to the Code of Conduct for Medical Research (Gedragscode Gezondheidsonderzoek)[35], in accordance with the EU GDPR[36], Declaration of Helsinki[37], and the Wet Geneeskundige Behandelovereenkomst (WGBO)[38]. The medical ethics review committee confirmed the UPACT was a non-WMO study. Informed consent was provided by all participants, and therefore this secondary analysis required no METC approval as anonymous data from de UPACT study were used.

RESULTS

Description of the participants

The UPACT study had a response rate of 22.3% and the final sample size consisted of 580 stroke survivors. Eight participants were excluded for the current study because these participants did not answer the question regarding COVID infection and thus could not be included in either study group. This study included 572 stroke survivors of which 126 participants experienced a COVID infection. Table 1 shows the participant characteristics for the total sample, the non-COVID group (78%) and the COVID group (22%). Participants in the total sample had a mean age of 70 (SD ± 12) while the mean age in the COVID group was 67 (SD ± 13). Most of the participants in the total sample were male (55.9%) with a high educational level (32.9%). This differed slightly from the COVID group which had a higher percentage of males (61.9%). Most of the patients experienced a cerebral infarction (444, 77.6%) and a minority a hemorrhage (84, 14.6%). The percentage of patients with a cerebral hemorrhage was slightly higher (16.7%) in the COVID group. For all other characteristics the distribution of participants between study groups was approximately the same, except for some small differences in educational levels.

Questionnaire results

According to participant responses in the total sample most of the participants experienced no depression (72.0%), no anxiety (75.3%), and normal fatigue (40.0%) (Table 2). The COVID group had a higher percentage of patients with possible depression (13.8%), suspected depression (16.3%), possible anxiety (14.9%) and suspected anxiety (10.5%) compared to the non-COVID group. There was no notable difference in fatigue scores between study groups.

Table 1. Participant characteristics of the total sample, non-COVID group and COVID group

Participant characteristics	*Total sample* (n = 572)	*Non-COVID Group* (n = 446)	*COVID Group* (n = 126)
Sex, n (%)			
Female	249 (43.5)	201 (45.1)	48 (38.1)
Male	320 (55.9)	242 (54.3)	78 (61.9)
Age, mean ± SD	70 ± 12	71 ± 12	67 ± 13
Marital status, n (%)			
Single	80 (13.9)	64 (14.3)	16 (12.7)
Married/cohabiting	397 (69.4)	308 (69.1)	89 (70.6)
Divorced/widowed	90 (15.7)	70 (15.7)	20 (15.8)
Educational level, n (%)			
Lowest (primary education)	22 (3.8)	20 (4.5)	2 (1.6)
Low (primary vocational education)	113 (19.8)	91 (20.4)	22 (17.4)
Average (secondary vocational education)	144 (25.2)	113 (25.3)	31 (24.6)
High (higher professional education)	188 (32.9)	149 (33.4)	39 (30.9)
Other	16 (2.8)	14 (3.1)	2 (1.6)
Type of stroke, n (%)			
Cerebral hemorrhage	84 (14.6)	63 (14.1)	21 (16.7)
Cerebral infarction	444 (77.6)	346 (77.6)	98 (77.8)
Unknown	26 (4.5)	23 (5.2)	3 (2.4)
Months since stroke, mean ± SD	7.9 ± 3.2	7.8 ± 3.27	8 ± 2.9
Previous depression episodes, n (%)			
Yes	86 (15.0)	67 (15.0)	19 (15.1)
No	476 (83.2)	371 (83.2)	105 (83.3)
Previous anxiety episodes, n (%)			
Yes	51 (8.9)	40 (9.0)	11 (8.7)
No	511 (89.3)	398 (89.2)	113 (89.7)
EQ-6D before stroke, mean ± SD	91 ± 13.4	90.7 ± 13.6	92.4 ± 12.5
EQ-6D after stroke, mean ± SD	80.8 ± 18.8	81.4 ± 18.5	78.6 ± 19.6
EQ-6D difference, mean ± SD	-10.5 ± 17.9	-9,5 ± 17,6	-14,1 ± 19

Numbers that do not add up to the required group totals or percentages that do not add up to 100% are the consequence of missing data.

Table 2. Categorical results from the depression, anxiety, and fatigue questionnaires

Depression, anxiety, and fatigue	*Total sample* (n = 572)	*COVID Group* (n = 126)	*Non-COVID Group* (n = 446)
HADS-D, n (%)	n = 549 (95.9)	n = 123 (97.6)	n = 426 (95.5)
Total score, median	3	4	3
No depression, n (%)	412 (72.0)	86 (68.2)	326 (73.1)
Possible depression, n (%)	67 (11.7)	17 (13.5)	50 (11.2)
Suspected depression, n (%)	70 (12.2)	20 (15.9)	50 (11.2)
HADS-A, n (%)	n = 530 (92.7)	n = 114 (90.5)	n = 416 (93.3)
Total score, median	3	4	3
No anxiety, n (%)	431 (75.3)	85 (67.5)	346 (77.6)
Possible anxiety, n (%)	55 (9.6)	17 (13.5)	38 (8.5)
Suspected anxiety, n (%)	44 (7.7)	12 (9.5)	32 (7.2)
CIS-f, n (%)	n = 534 (93.3)	n = 114 (90.5)	n = 420 (94.2)
Total score, median	30	30	30
Normal fatigue, n (%)	229 (40.0)	48 (38.1)	181 (40.6)
Moderate fatigue, n (%)	90 (15.7)	19 (15.1)	71 (15.9)
Severe fatigue, n (%)	215 (37.6)	47 (37.3)	168 (37.7)

Numbers that do not add up to the required group totals or percentages that do not add up to 100% are the consequence of missing data.

Influence of COVID infection

COVID did not influence depression and fatigue, but there was a significant increase in HADS-A in stroke survivors with COVID (Table 3).

Table 3. Univariable regression of COVID influence on study outcomes

	β	Std. Error	95% CI	
HADS-D	.694	.213	-.191	1.580
HADS-A**	.836	.422	.007	1.666
CIS-f	1.059	1.510	-1.908	4.025

** Variable has a significance of $p < 0.05$

Comparison of psychosocial outcomes between the COVID group and non-COVID group

Depression (HADS-D)

In both study groups, daily functioning (EQ-6D) was significantly associated with HADS-D (Table 4). A low, average, and high educational level was associated with a lower HADS-D in

the non-COVID group. Conversely, in the COVID-group, only the lowest educational level had a minimally significant association with an increase in HADS-D. Furthermore, having a cerebral infarction significantly increased the HADS-D in the COVID group.

The models differed between groups; the low, average, and high educational levels, next to previous depression and anxiety were associated with the HADS-D in the non-COVID group, while in the COVID group the lowest educational level, time since stroke and cerebral infarction were associated with HADS-D.

Table 4. Quantile regression model of variables associated with HADS-D

Parameter	β	Std. Error	95% CI	
Non-COVID group				
(Intercept)**	4.571	1,2735	2.067	7.076
EQ-6D_diff**[a]	-.103	.0134	-.129	-.077
Educational level=Lowest[b]	-2.143	1.5868	-5.264	.978
Educational level=dLow**	-3.000	1.3297	-5.615	-.385
Educational level=Average*	-2.571	1.3172	-5.162	.019
Educational level=High**	-3.000	1.3082	-5.573	-.427
Previous depression**[b]	2.286	.7878	.736	3.835
Previous anxiety**[b]	2.571	1.0495	.507	4.635
COVID Group				
(Intercept)	3.846	3.4388	-3.006	10.698
EQ-6D_diff**[a]	-.137	.0274	-.192	-.083
Time since stroke**	-.522	.1760	-.873	-.171
Educational level=Lowest*[b]	8.329	4.4043	-.447	17.105
Educational level=Low	-.586	3.2888	-7.139	5.967
Educational level=Average	-1.003	3.2182	-7.416	5.409
Educational level=High	-.447	3.1982	-6.820	5.926
Cerebral infarction	3.192	.9925	1.215	5.170

Step one of the quantile regression model included the variables sex, age, marital status, educational level, type of stroke, time since stroke, previous episodes of depression, previous episodes of anxiety, and daily functioning.

* Variable has a significance of $p < 0.1$

** Variable has a significance of $p < 0.05$

[a] EQ6D_diff = the difference score between the EQ6D before stroke and post-stroke.

[b] Overall variable had one more category which was set to zero because it was the reference category.

Anxiety (HADS-A)

In both study groups daily functioning (EQ-6D) and previous depression were significantly associated with HADS-A (Table 5). Daily functioning was associated with a lower HADS-A, while previous depression was associated with a higher HADS-A. The non-COVID group differed from the COVID group with sex and previous anxiety being associated with a higher HADS-A, while all educational levels were independently associated with a lower HADS-A.

Table 5. Quantile regression model of variables associated with HADS-A

Parameter	β	Std. Error	95% CI	
Non-COVID group				
(Intercept)**	4.400	1.3072	1.829	6.971
EQ-6D_diff**[a]	-.048	.0126	-.073	-.023
Sex**[b]	1.000	.4445	.126	1.874
Educational level=Lowest**[b]	-4.600	1.4837	-7.518	-1.682
Educational level=Low**	-4.200	1.2463	-6.651	-1.749
Educational level=Average**	-3.800	1.2272	-6.214	-1.386
Educational level=High**	-4.000	1.2167	-6.393	-1.607
Previous depression**[b]	2.600	.7349	1.155	4.045
Previous anxiety**[b]	4.800	.9653	2.901	6.699
COVID Group				
(Intercept)**	2.000	0.5601	.890	3.110
EQ-6D_diff**[a]	-.120	.0229	-.165	-.075
Previous depression**[b]	4.500	1.1212	2.277	6.732

Step one of the quantile regression model included the variables sex, age, marital status, educational level, type of stroke, time since stroke, previous episodes of depression, previous episodes of anxiety, and daily functioning.

** Variable has a significance of $p < 0.05$

[a] EQ6D_diff = the difference score between the EQ6D before stroke and post-stroke.

[b] Overall variable had one more category which was set to zero because it was the reference category.

Fatigue (CIS-f)

In both study groups daily functioning (EQ-6D) was significantly associated with a lower CIS-f (Table 6). In the non-COVID group previous depression was significantly associated with an increased CIS-f, while in the COVID group higher age was associated with an increased CIS-f.

Table 6. Quantile regression model of variables associated with CIS-f

Parameter	β	Std. Error	95% CI	
Non-COVID group				
(Intercept)**	25.000	1.2001	22.641	27.359
EQ-6D_diff**[a]	-.360	.0566	-.471	-.249
Previous depression**[b]	12.500	2.6797	7.232	17.768
COVID Group				
(Intercept)	-2.571	10.5326	-23.456	18.313
EQ-6D_diff**[a]	-.363	.0987	-.559	-.167
Age**	.405	.1503	.107	.703

Step one of the quantile regression model included the variables sex, age, marital status, educational level, type of stroke, time since stroke, previous episodes of depression, previous episodes of anxiety, and daily functioning.

** Variable has a significance of $p < 0.05$

[a] EQ6D_diff = the difference score between the EQ6D before stroke and post-stroke.

[b] Overall variable had one more category which was set to zero because it was the reference category.

DISCUSSION

Our study was the first to report on the influence of COVID-infection in post-stroke patients on psychosocial symptoms. We found a significant association between COVID infection and anxiety, but not for depression or fatigue. Both study groups seemed to vary on factors that were associated with psychosocial outcomes. Overall, participants' psychosocial scores improved if they had a higher daily functioning capability (EQ-6D) and if some time had passed since the stroke. Additionally, we found positive associations between previous episodes of depression and all psychosocial scores in the non-COVID group. In this group sex and previous episodes of anxiety were positively associated with anxiety. Previous episodes of depression were positively associated with fatigue. Other positive associations were found in the COVID group, time since stroke and a cerebral infarction were associated with depression, previous episodes of depression with anxiety and higher age with fatigue.

Several studies considered the COVID-19 pandemic in stroke survivors and showed an impact on psychosocial outcomes[12,19–21,39,40]. It is therefore remarkable that solely anxiety was found to have been impacted by COVID infection in the current study, when previous research regarding psychosocial problems during the pandemic showed depression, anxiety and fatigue all being impacted[12]. A recent study also found that stroke survivors experienced anxiety during the COVID pandemic[19]. However, unlike the current study it did not consider COVID infection as a potential indicator for anxiety. The model we examined included COVID as a univariable predictor, which could imply that there are still potential confounders that have not been considered, making it difficult to adequately explain the current finding. However, the severity of the stroke may have had an impact on this finding; either the severity of the stroke in our sample size may have been lower than in prior studies one year after the stroke, or the stroke survivors who chose not to fill out the questionnaire were significantly more ill, omitting crucial information about a group that may have been more severely affected by a COVID infection.

A similarity between study groups was the consistent influence of daily functioning (EQ-6D) on the outcomes, a higher EQ-6D score, and thus better daily functioning was associated with a decrease in depression, anxiety, and fatigue scores. Most studies focus on the impact of the psychosocial problem as being impactful on daily functioning[41–43], but the results of this study suggest that better daily functioning capability could also lessen the development of psychosocial problems.

The notable differences between groups were primarily the opposite educational levels being significant for depression. The lowest educational level was significant in the COVID group while the low, average, and high educational levels were significant in the non-COVID group.

This difference is explainable by the fact that the lowest educational level category only consisted of two participants in the COVID group, making it easier to find a significant result in this category which could potentially have altered our outcome.

When we examined each study group separately, we saw that previous episodes of depression were consistently associated with an increase in psychosocial outcomes in the *non-COVID group*. Previous episodes of anxiety had the same effect on depression and anxiety scores. This is a known phenomenon in stroke survivors, where previous episodes of depression or anxiety can be an amplifying factor for re-development of depression or anxiety post-stroke[44,45]. Notably, sex seemed to be associated with an increase in anxiety. Anxiety manifests differently in men and women due to a difference in reproductive hormones and social expectations, sex can therefore be of influence on the severity of anxiety individuals experience[46,47]. Furthermore, educational levels from primary education up to higher education were associated with a decrease in depression scores, this decrease was also seen in anxiety scores, where all educational levels were significant. Education as an influential factor for depression is supported by research stating that individuals with an education, be it primary education or higher education are less likely to develop depression than individuals with no educational background, and more education hours and a higher socioeconomic status lessen depression development[48,49].

While examining the *COVID group* we first saw that the number of months post-stroke were associated with a decrease in depression scores. The probability of developing depression decreases the longer it has been after the stroke because, in most circumstances, more recovery has taken place[16]. Secondly, cerebral infarction was associated with an increase in depression scores. A recent study contradicts this finding, stating that the risk of depression development was over twofold higher in individuals with a cerebral hemorrhage compared to cerebral infarction[50]. The current finding however could mean that the combination of COVID infection after a cerebral infarction could be a possible amplifying factor for depression. This finding should however be interpreted with caution, as it has not been examined further. Furthermore, previous episodes of depression were associated with an increase in anxiety scores. This connection is supported by earlier evidence, stating that a previous depression could negatively impact re-development of anxiety and vice versa[44,51]. Lastly, fatigue was negatively influenced by a higher age, which could be explained by the increased COVID severity in elderly patients when compared to the younger population, which according to previous research increases fatigue[52].

A strength of this study is that it was the first to investigate a possible relationship between COVID infection and psychosocial issues in stroke survivors. While other studies focused

solely on the impact of the pandemic, this study explored the influence a COVID-infection on psychosocial issues. This study also used a large database of stroke survivors, making it possible to perform regression analysis, corrected for potential confounders. Furthermore, for statistical analysis the choice for Quantile regression was made because no linear regression analysis was possible due to skewed data. This method made it easier to analyze the skewed data and interpret the results, while maintaining valid results.

Nonetheless, there are several limitations to the present study. Quantile regression has not been integrated fully into SPSS, giving multiple analysis complications. Using the Akaike Information Criterion (AIC) to compare regression models, calculate correlation and impact of COVID infection per study group was not possible. There were also no possibilities to formally test any hypotheses and compare study groups on differences in study outcomes through model testing, which was preferable. However, the current models were correctly constructed by using a manual backward stepwise regression based on significance of potential confounders. As a result, statistical analysis became more exploratory, which could have slightly reduced the validity of study results. The cross-sectional research design could also have influenced our outcomes, this design does not give a hundred percent certainty if our predictors precede the outcomes and could also be correlated with them. Other potential limitations could be that the original database gave a better overview of participants, some variables not included in this research could have made each individual case clearer. For example, previously experienced strokes were not included in this research as the focus lay predominantly on the recent stroke, but this variable could have impacted psychosocial outcomes. Also, a definitive COVID infection status for the participants was difficult to establish because self-reported information about the infection could be inaccurate. What makes it difficult to discern if the outcomes are related to the COVID infection is the time period. The pandemic and its rules and quarantines, taking away COVID infection, could also have had an impact on the outcomes as was seen in earlier research[12,21,39]..

Future research regarding this topic should perform analyses on psychosocial symptoms in an accommodating analysis program that allows full model testing, where SPSS did not allow this for quantile regression, and should confirm infection status of participants. It could also be useful to perform a multivariable regression with COVID infection included as a variable, instead of making two study groups. This could increase the chance of finding the impact of the infection on psychosocial outcomes and could lead to a better picture about the severity of these symptoms. Furthermore, additional research should investigate the changes that perhaps have to be made to rehabilitation programs if COVID infection increases the chances of developing psychosocial problems post-stroke.

This study indicates that a post-stroke COVID infection can increase psychosocial symptoms. This finding could influence the rehabilitation of stroke survivors based on the explorative results. Especially anxiety was significantly influenced by COVID infection, this could endanger rehabilitation compliance[16]. Even though the COVID pandemic is no longer present, post-stroke COVID-infections can still occur. However, the amount of patients will not be sufficient to initiate tailored treatment programs for rehabilitations. If a pandemic occurs in the future, our study implies that stroke rehabilitation may need adjustment, specifically around anxiety. If COVID infections increase, further research should be performed around this topic and extra attention should be directed to stroke patients who experience a COVID infection post-stroke. The rehabilitation programs need to act preventative with the knowledge we have about increased possibility of developing psychosocial issues, instead of treating these issues after surfacing.

In conclusion, COVID infection had a significant influence on anxiety, but not on depression and fatigue, although there was a numerical increase in scores. Influential factors on psychosocial scores varied greatly between study groups, leading to cautionary interpretation of the current findings. Psychosocial scores improved with better daily functioning and if some time had passed since the stroke. Furthermore, age, sex, cerebral infarction and previous episodes of depression or anxiety were associated with (some of the) psychosocial outcomes. In case of a future pandemic or an increase in COVID infections, future research should target development of tailored rehabilitation programs for patients with post-stroke COVID.

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