Graduate thesis

NTNU
Norwegian University of Science and Technology
Faculty of Medicine and Health Sciences
Department of Neuromedicine and Movement Science

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Relationship between In-Hospital Frailty and Health-Related Quality of Life 3 and 18 months after Stroke: A prospective Cohort study

A part of the Norwegian COgnitive impairment After STroke (Nor-COAST) study

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ABSTRACT

BACKGROUND: With an ageing population and improvements in treatment more people will survive their stroke and it is crucial to focus on long-term outcome and quality of life among stroke survivors. Stroke survivors are known to have worse health-related quality of life (HRQoL) than the general population, but less is known about characteristics associated with decreased HRQoL by time following stroke. This study aim to examine how in-hospital frailty is related to HRQoL and change in HRQoL between three and 18 months post stroke.

METHOD: We studied acute stroke patients as a part of the Norwegian COgnitive impairment After STroke study (Nor-COAST), a multicentre prospective cohort. The participants were included at admission from May 2015 to March 2017, and followed up at three and 18 months post stroke. In-hospital frailty state was assessed using a modified version of the Fried phenotype model (0p = robust, 1-2p = pre-frail, 3-5p = frail). Clinical and demographic information were collected, including age, sex, stroke severity, and pre-stroke cognitive and physical state. HRQoL at three and 18 months follow-up was assessed using the five-level version of the EuroQol five-dimensional descriptive system (EQ-5D-5L) and the EuroQol visual analogue scale (EQ-5D VAS). We conducted linear mixed effect regression analyses unadjusted and adjusted for sex, age and stroke severity to investigate the association between in-hospital frailty and post-stroke health-related quality of life.

RESULTS: Of the 815 patients enrolled in the Nor-COAST study, 625 were included in our analyses. Mean age was 71.7 years (SD = 11.6; range = 33-96); 263 (42.1%) were female. Frailty prevalence was 10.4%, while 58.6% were prefrail. The robust group had significant higher measures in EQ-5D-5L index and EQ-5D VAS at three and 18 months ($p < 0.001$, all measures). The frail group had a significantly larger decrease in EQ-5D-5L index score compared to the robust group (-0.056; 95% CI -0.104 to -0.009; $p = 0.021$). There was no difference in change in EQ-5D VAS score between the groups.

CONCLUSION: This study suggests that stroke patients with in-hospital frailty suffer from worse post-stroke HRQoL, and they are also experiencing a larger decrease in their HRQoL compared to the robust patient.

TRIAL REGISTRATION: ClinicalTrials.gov (NCT02650531)

ABBREVIATIONS

ADL	- Activities of Daily Living
BMI	- Body Mass Index
CT	- Computer Tomography
EADL	- The Nottingham Extended Activities of Daily Living scale
EQ-5D-3L	- The three-level EuroQol five-dimension
EQ-5D-5L	- The five-level EuroQol five dimension
EQ-5D VAS	- The EuroQol five dimension Visual Analogue Scale
GDS	- The Global Deterioration Scale
HRQoL	- Health-Related Quality of Life
MCI	- Mild Cognitive Impairment
MMSE	- Mini-Mental State Examination
MoCA	- Montreal Cognitive Assessment
MRI	- Magnetic Resonance Imaging
mRS	- modified Rankin Scale
NIHSS	- National Institute of Health Stroke Scale
Nor-COAST	- Norwegian COgnitive impairment After STroke study
PROMs	- Patient Reported Outcome Measures
QoL	- Quality of Life
WHO	- World Health Organization

DECLERATIONS

Ethics approval and consent to participate

The Nor-COAST study is conducted according to the Declaration of Helsinki. Written informed consent was obtained from all participants prior to data collection. The study was approved by the Regional Committee for Medical and Health Research Ethics in North, REK Nord (REC number 2015/171).

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are not available since we do not have consent to share data according to Norwegian legal regulations for research.

Competing interests

The authors declare that they have no competing interests.

Funding

The Nor-COAST study is funded by the Norwegian Health Association. Additional funding was provided by the Department of Neuromedicine and Movement Science, Faculty of Medicine and Health Science, NTNU Norwegian Univeristy of Science and Technology.

Authors' contributions

ISW, IS, PT and MSE has been involved in the planning and design of this research, ISW as medical student and IS and PT as supervisors. SL has been involved in planning and writing of statistical analyses. MSE has been involved in writing of the discussion. ISW has analysed and interpreted the data. ISW, IS and PT have been the major contributors in writing the manuscript. All authors read and approved the final manuscript.

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1 INTRODUCTION

Stroke survivors are in several studies found to have worse health-related quality of life (HRQoL) than the general population[1-3]. In Norway, we have seen a decrease in stroke incidents the last years, but with an aging population, it is reason to believe that this trend will turn[4, 5]. As the health-care advances, more people are expected to survive their stroke and live with long-term sequela post-stroke[6]. This actualize the need for knowledge about factors that are related to HRQoL following stroke and how to help people live good lives in the longer term.

1.1 Health-related quality of life

Health-related quality of life (HRQoL) is the subjective quality of an individual's health status and daily life, in terms of their physical, mental and spiritual well-being[7]. It is a multi-dimensional concept expressing their satisfaction with their current functional level[8]. According to WHO, different factors such as an individual's cultural background, social relationships, level of independence and economic and environmental features, as well as their physical health and psychological state, can affect their HRQoL[9]. As HRQoL involves several subjective elements, there have been more focus the later decades on patient reported outcome measures (PROMs) to better capture HRQoL-information[10-13]. Notably, physician-reported measures have been shown to not accurately correlate with PROMs, which emphasizes the importance of collecting information about HRQoL directly from the patient[10, 14]. Further, the use of PROMs as a measurement for HRQoL in a stroke setting could provide us with better information regarding the individual factors responsible for a stroke survivor's degree of HRQoL, and therefore facilitate optimal care management and rehabilitation for each patient[12, 13, 15, 16].

Most of the studies examining the relationship between stroke and health-related quality of life have focused on the impact post-stroke factors have on the HRQoL-outcome, finding physical impairment, disability and dependence in ADL, post-stroke depression, cognitive impairment and age to be the independent factors most commonly influencing HRQoL[1, 2, 17-21]. There is a lack of knowledge regarding which patient groups at stroke-onset are in risk of experiencing a deterioration in HRQoL after their stroke. More awareness in this field could lead to better

rehabilitation programs post-stroke among exposed patient groups in order to prevent a deterioration in their HRQoL.

1.2 Frailty

Frailty is caused by a reduced reserve capacity in multiple physiological systems, as well as increased vulnerability to poor resolution of homeostasis after a stressor event, both endogenic and exogenic stress[22, 23]. Symptom are, among others, fatigue, decreased strength and endurance, and weight loss[24]. Frailty is associated with higher age, female sex, lower socioeconomic group, multimorbidity and cognitive and functional impairment[25-30]. Lately there has been an increased interest in reduced reserve capacity as a contributing factor for stroke aetiology and functional decline following stroke, but so far the body of knowledge concerning frailty and stroke is sparse[31].

As stroke is a big stressor event, it is reason to believe that frail persons suffering a stroke will experience a larger post-stroke deterioration compared to a non-frail person, both physical and cognitive. Taylor-Rowan *et. al* (2019) found pre-stroke frailty to be significantly associated with lower post-stroke cognition[32], and Landi *et. al* (2006) found frail stroke patients to present a lower function in activities of daily living (ADL) post stroke[33]. Moreover, persons with frailty are known to have larger degree of physical impairment and dependence in ADL and worse HRQoL than the general population [22, 24, 34-37]. Further, low physical functioning and frailty have been associated with low degree of subjective well-being[38, 39]. This provides reasons to believe that frail persons will show a lower HRQoL post-stroke than robust individuals.

It appears that only two other studies have investigated prevalence of frailty among acute stroke patients, finding a prevalence of 24.9%[40] and 28%[41] respectively. This current study is to our knowledge the first examining the relationship between in-hospital frailty at stroke onset with HRQoL after the stroke.

The overall aim of the present study is to investigate the prevalence of in-hospital frailty among stroke survivors and to which extent in-hospital frailty is associated with HRQoL at three and 18 months after suffering a stroke. Further we want to study how frailty is related to change in HRQoL from three to 18 months.

2 METHOD

2.1 Study design and Setting

This study is a substudy of the *Norwegian COgnitive impairment After STroke study* (Nor-COAST) study that is described in detail in a protocol paper [42].

The study is a multicentre, prospective cohort study recruiting patients hospitalized for acute stroke. The recruitment started 18.05.2015 and ended 31.03.2017. The participants were included from stroke units at five Norwegian hospitals: St. Olav University Hospital (Trondheim), Ålesund Hospital (Ålesund), Haukeland University Hospital (Bergen), Vestre Viken Hospital (Bærum) and Oslo University Hospital, Ullevål (Oslo).

2.2 Population

Eligibility criteria were: 1) Admittance to one of the five study centres within seven days after symptom debut. 2) Acute stroke diagnosed according to the World Health Organisation (WHO) criteria[43] or with findings of acute infarction or intra-cerebral haemorrhage on magnetic resonance imaging (MRI). Participants had to be 3) Scandinavian speaking, 4) over 18 years and 5) live in the catchment area of the recruiting hospitals. Exclusion criteria were expected survival less than three months.

All patients admitted to the participating stroke units were consecutively screened for eligibility and approached as soon as the stroke diagnosis was confirmed. Participants were assessed during hospital stay and followed up at three and 18 months after the stroke incident at the out-patient clinic or by telephone interview. Participants with measures on HRQoL at either three or 18 months were included in the analysis.

2.3 Measurements and outcomes

2.3.1 Demographics and clinical information

Demographic information was registered for each participant based on medical records and interviews with patients and/ or by proxy. Information about mortality was collected from the hospital electronic patient records, that are linked to the National Death registry.

Pre-stroke cognition and function was based on information from the patients' caregivers during the hospital stay. The Global Deterioration Scale (*GDS)* was used to assess pre-stroke cognition,

scoring the participant from 1 to 7 points; 1 point being no cognitive impairment, 3 points being mild cognitive impairment (MCI) and 4-7 points being mild to severe dementia[44]. In addition, they underwent assessments of their in-hospital cognitive function using the Montreal Cognitive Assessment (*MoCA*), scoring 0-30 points with a score of 26-30 points being normal[45]. Pre-stroke global function was assessed by using the modified Rankin Scale (*mRS*), scoring the participant 1-6 points; 1 point being no impairment, 5 points being extreme impairment and 6 points being dead.[46]. Pre-stroke function in instrumental activities of daily living (*i-ADL*) was assessed by the Nottingham extended ADL-scale (*EADL*)[47], scoring the patient 0-66 points; a high score suggesting better ability to undertake i-ADL[48].

2.3.2 Stroke characteristics

We classified the stroke as infarction or cerebral haemorrhage using CT and MRI scans. Stroke severity was assessed at day one post-stroke by the National Institutes for Health Stroke Scale (NIHSS), scoring 0-42 points with a high score indicating a severe stroke[49].

2.3.3 Frailty assessment

To measure frailty at baseline, we used a modified version of the five criteria specified in the Fried phenotype model[24] (Table 2), including the components exhaustion, unintentional weight loss, low energy expenditure, slow gait speed and weak grip strength. Information about exhaustion, weight loss and low physical activity was collected through retrospective self-report. Modified criteria were (1) unintended weight loss last six months, (2) a feeling of being constantly fatigued for more than one week pre-stroke, (3) engagement in physical activities less than once a week pre-stroke. Gait speed was assessed by measuring the participant's preferred gait speed based on the time used to walk 4 meters, with a duration of ≥ 6 seconds defining slow gait speed. Grip strength was evaluated using a Jamar handhold dynamometer. Each participant measured their grip strength in each hand three times, the highest value from the strongest hand was used. Low grip strength was defined using the value sets by Fried *et al*[24], stratified for sex and body mass index (BMI). In the case of missing data on a component, the participant was assigned 0 points (p) on that specific criteria. A frail state was defined as three or more criteria (3-5p), a pre-frail state was defined as one or two criteria (1-2p), while absence of criteria (0p) indicates a robust or non-frail state.

All frailty assessments at the index stay were performed at discharge or the seventh day for participants with longer hospital stays.

2.3.4 Quality of life Assessment

We used the five-level EuroQol five-dimentional descriptive system (EQ-5D-5L)[50] as measure of the participant's HRQoL at three and 18 months follow-up. The EQ-5D-5L consists of two parts: a 5-level descriptive health classifier questionnaire and a visual analogue scale (EQ-VAS).

The EQ-5D-5L questionnaire comprises the five dimensions ('5D') *Mobility, Self-Care, Usual Activities, Pain/Discomfort* and *Anxiety/Depression* of the participant's HRQoL, each with five levels of responses ('5L'); from 1p: "no problems" to 5p: "extreme problems". The participant is asked to indicate his/her health state that specific day, choosing the most appropriate statement in each dimension. In the 5L-questionnaire, the responses for the five dimensions can be combined in a 5-digit number describing the participant's health state, with '11111' meaning no problems in all dimensions to '55555' meaning extreme problems in all dimensions[51]. This health status can be converted into a single summary index. To find the participant's index score, we used the EQ-5D-5L Index Value Calculator Version 2.0, developed by the EuroQol Group, utilizing the value set from Denmark as there is no value set from Norway to this date. The crosswalk values in this calculator is based on the EQ-5D-3L index calculated by van Hout *et* al (2012)[52], with EQ-5D-5L index scores ranging from +1 to -0,624; 1 being the best health possible, 0 being dead and a score <0 representing a health condition worse than death.

The EQ-VAS provides information about the participants subjective health perception, scoring their health state that specific day on a visual scale from 0-100p; 0p being "the worst health you can imagine" and 100p being "the best health you can imagine".

Registration of EQ-5D-5L at three and 18 months post-stroke were performed at the outpatient clinic by self-report. Participants unable to attend the outpatient clinics were assessed through telephone interviews.

2.4 Analysis

We present descriptive statistics for the study population in terms of socio-demographic characteristics and pre-stroke clinical characteristics of physical and cognitive function, both in the total population and for the separate frailty groups. Categorical variables are presented as

frequencies and percentages, and continuous variables as mean and standard deviation (SD). Kruskal-Wallis test is used for continuous variables, and linear-by-linear association test is used for categorical variables.

We analysed differences in EQ-5D-5L index, EQ-5D VAS and EQ-5D-5L dimensions between frailty groups at three and 18 months respectively, as well as changes over time, using linear mixed effect regression. We used EQ-5D-5L index, EQ-5D-VAS and EQ-5D-5L dimensions respectively as dependent variable, frailty category and time between three and 18 months and their interaction as categorical covariates, and participant as random effect. We did this unadjusted, and adjusted for sex, age, and NIHSS-score. Normality of residuals was checked by visual inspection of QQ-plots. Statistical significance was defined as a p-value less than 0.05, and we report 95% confidence intervals (CI) where relevant. Analyses were conducted using SPSS 25.

3 RESULTS

As shown in Figure 1 a total of 815 patients were included in the Nor-COAST study, of whom a total of 625 (76.7%) had measures on EQ-5D-5L index at three and/or 18 months and were included in the analyses. Of these 578 (92.5%) had measures at three months and 493 (78.9%) had measures at 18 months. 446 (71.4%) had measures at both three and 18 months. 132 (21.2%) had measures only at three months and 47 (7.5%) had measures only at 18 months. Figure 1 presents a flow chart of the subjects analysed in this study.

Main reasons for drop-out were participants who were deceased, participants who refused further participation and participants with missing measures on EQ-5D-5L index. As shown in Figure 1 participants who were lost to follow-up at three and 18 months had higher prevalence of pre-frail and frail status as compared to those who remained in the study.

3.1 Patient characteristics

Mean age of included patients was 71.7 years (SD 11.6; range 33-96); 263 (42.1%) were female; mean NIHSS score was 2.8 (SD 4.1); mean pre-stroke mRS-score was 0.8 (SD 1.0); mean score on MoCA at day seven/discharge was 23.5 (SD 5.0).

The robust population was younger, comprised of less females, had better pre-stroke physical condition (mRS and EADL scores) and better pre-stroke cognition (GDS score), suffered from milder strokes and had better scores on MoCA-assessment compared to the pre-frail and frail population. They more seldom lived alone pre-stroke and had less home nursing. Table 1 presents demographic and clinical data for our study population.

The frailty distribution in our study population was 194 robust (31.0%), 366 pre-frail (58.6%) and 65 frail (10.4%) participants. Slow gait speed was the most common symptom with N = 217 (34.9%), while weight loss was the least common symptom with N = 67 (11.1%). Table 2 presents the distribution of the modified Fried-criteria in our study population.

3.2 Frailty and HRQoL

Results of the unadjusted and adjusted linear mixed regression analysis are presented in Tables 3 and 4 respectively.

3.2.1 Group differences in three and 18 months score

In both our unadjusted and adjusted model, we found between-group differences ($p < 0.001$) of EQ-5D-5L index score and EQ-5D VAS score at both three and 18 months with the robust group reporting better HRQoL.

3.2.2 Group differences in change in score

Figure 2 presents change in EQ-5D-5L index and EQ-5D VAS in each frailty group.

The robust group and the pre-frail group showed no change in EQ5D index between three and 18 months in the unadjusted model, but there was a decrease in the index score of the frail group (mean change -0.063, SE 0.022) (Table 3). After adjusting for covariates, the association between frailty and change in EQ-5D-5L index score remained significant with a mean change of -0.050 (SE 0.022) (Table 3). The frail group had a larger decrease in EQ-5D-5L index score compared to the robust group, with a between-group difference of -0.070 (95% CI -0.117 to -0.022, $p = 0.004$) and -0.056 (95% CI -0.104 to -0.009, $p = 0.021$) in the unadjusted and adjusted model respectively. We noted no significant difference in change in EQ-5D-5L index between the prefrail and the robust group. Furthermore, there were no between-group differences between the three frailty groups in change of EQ-5D VAS score in the unadjusted nor the adjusted model (Table 3).

3.2.3 Dimensions

We found between-group differences for all EQ-5D-5L dimensions at both three and 18 months except for Anxiety/Depression in the pre-frail group (Table 4). When considering within-group change, the robust group had no significant change in none of the dimensions. The pre-frail group had a significant worsening in Mobility and Self-Care (mean (SE): 0.12 (0.05); 0.07 (0.03) respectively). The frail group had a significant worsening in Mobility and Self-Care (mean (SE): 0.48 (0.12); 0.28 (0.09) respectively).

We also found the frail group to have a larger decrease in Mobility and Self-care compared to the robust group, with a between-group difference of 0.46 (95% CI 0.20 to 0.71, $p <0.001$) and 0.26 (95% CI 0.07 to 0.45, $p = 0.007$) respectively. We found no significant between-group differences between the pre-frail and the robust group in any of the dimensions.

3.3 Tables and figures

Figure 1 Trial profile.
Black frame represents the participants included. Red frame represents the analyses in the present study.

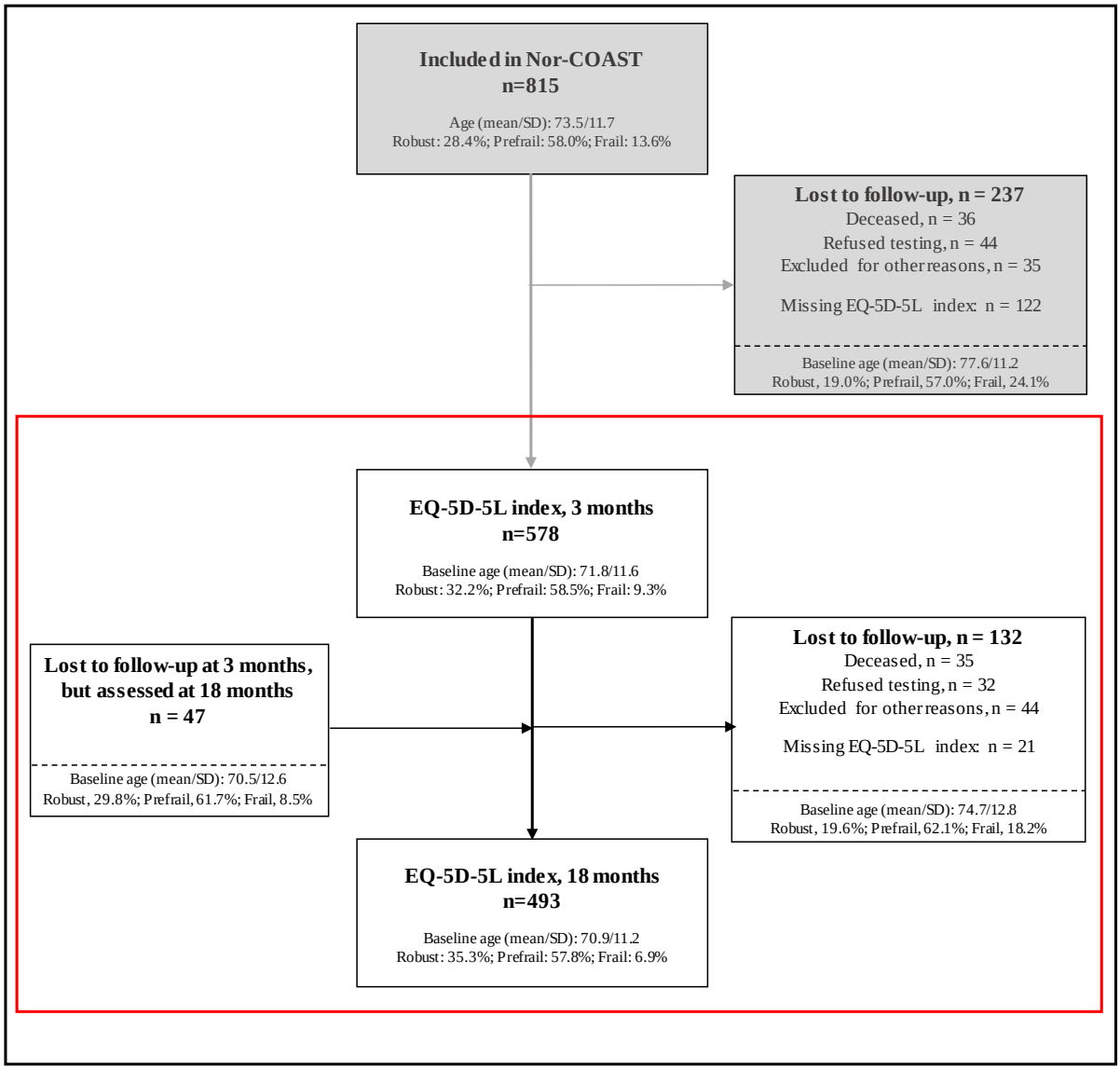


Table 1 Demographic baseline characteristics

	N	Total	Robust	Pre-frail	Frail	p-value[a]
Participants - n(%)	625	625 (100)	194 (31.0)	366 (58.6)	65 (10.4)	
Age						
Mean (SD)	625	71.7 (11.6)	65.6 (11.6)	73.3 (10.6)	81.1 (7.2)	<0.001
Range		33-96	34-92	33-96	58-95	
Sex	625					<0.001
Female		263 (42.1)	53 (27.3)	170 (46.4)	40 (61.5)	
Ethnicity	624					0.117
Caucasian		615 (98.6)	192 (99.5)	360 (98.4)	63 (96.9)	
Educational years	625					<0.001
Mean **(**SD)		12.4 (3.8)	13.7 (3.5)	12.1 (3.8)	10.2 (3.1)	
Home dwelling pre-stroke	625					<0.001
With home nursing		44 (7.0)	0 (0)	23 (6.3)	21 (32.3)	
Living situation	625					<0.001
Living alone		207 (32.5)	42 (21.6)	125 (34.2)	36 (55.4)	
mRS – *pre-stroke*	621					<0.001
Mean (SD)		0.8 (1.0)	0.4 (0.6)	0.8 (0.9)	1.8 (1.3)	
Nottingham EADL – *pre-stroke*	619					<0.001
Mean (SD)		57.6 (10.4)	62.0 (5.5)	57.1 (10.2)	46.9 (13.8)	
GDS - *pre-stroke*	619					<0.001
Mean (SD)		1.4 (0.8)	1.1 (0.4)	1.5 (0.8)	2.0 (1.2)	
Stroke classification						
Cerebral infarction	625	574 (91.8)	182 (93.8)	331 (90.4)	61 (93.8)	0.545
Cerebral haemorrhage		51 (8.2)	12 (6.2)	35 (9.6)	4 (6.2)	
NIHSS, day 1	617					<0.001
Mean (SD)		2.8 (4.0)	1.8 (3.9)	3.1 (4.0)	4.0 (3.9)	
MoCA – *in-hospital*	571					<0.001
Mean (SD)		23.5 (5.0)	25.4 (3.9)	23.2 (4.9)	19.4 (5.3)	

All measures are given as *n (%)* unless otherwise stated;

[a]Linear-by-linear associations for dichotomous output variables; Kruskal-Wallis test for continuous output variables;

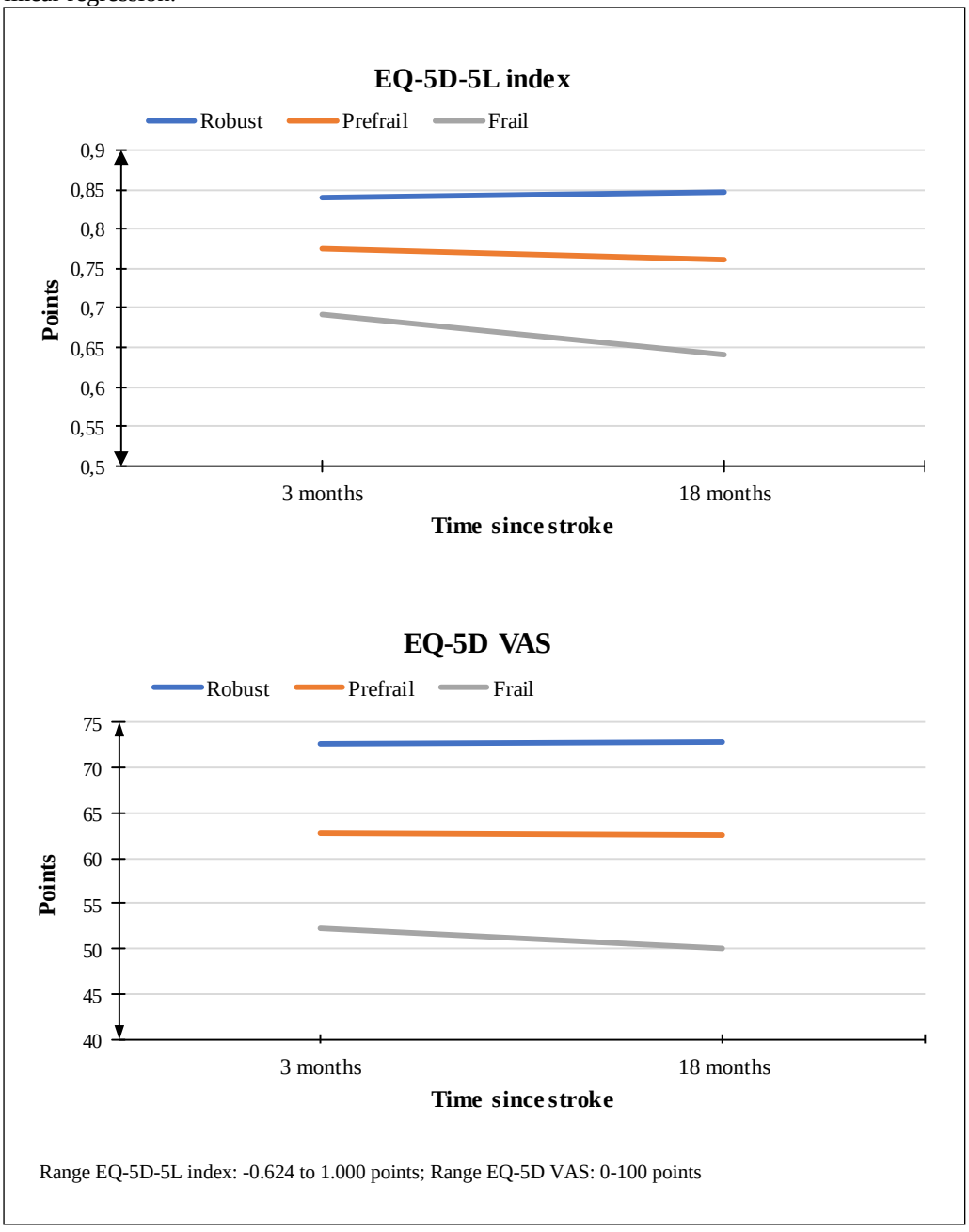
NIHSS National Institute of Health Stroke Scale, range 0-34p; *mRS* modified Rankin Scale, range 0-6p; *GDS* Global Deterioration Scale, range 0-7p; *MoCA* Montreal Cognitive Assessment, range 0-30p; *Nottingham EADL* Nottingham Extended Activities of Daily Living scale, range 0-66p

Table 2 Distribution of modified Fried criteria in the study population

Component	Operational definition	N	Total	Prefrail	Frail
Self-reported exhaustion	*Q1*: "Did you feel constantly fatigued for more than one week before the stroke?"	613	115 (18.7)	80 (22.2)	35 (54.7)
Low physical activity	*Q2:* "Did you engage in exercise/physical activities less than once a week before your stroke"	617	126 (20.4)	85 (23.4)	41 (63.1)
Weight loss	*Q3:* "Have you experienced unintentional weight loss the last 6 months"	606	67 (11.1)	46 (12.8)	21 (32.8)
Slow gait speed	Gait test 4 meters: ≥ 6 sec OR not able.	622	217 (34.9)	157 (42.9)	60 (90.9)
Weak grip strength	Grip strength limits defined by Fried[a] OR not able.	620	190 (30.6)	134 (37.2)	56 (84.8)

All measures are given as *n (%);*
BMI: Body mass index;
[a]Women: BMI ≤ 23.0 or missing, ≤ 17.0kg; BMI 23.1-26.0, ≤ 17.3kg; BMI 26.1-29.0, ≤ 18.0kg; BMI >29.0, ≤ 21.0kg; Men: BMI ≤ 24.0 or missing BMI, ≤ 29.0kg; BMI 24.1-28.0, ≤ 30.0kg; BMI >28, ≤ 32.0kg.

Figure 2 Development in EQ-5D-5L scores, for the three frailty groups. Based on mixed effect linear regression.



Range EQ-5D-5L index: -0.624 to 1.000 points; Range EQ-5D VAS: 0-100 points

Table 3: Relationship between frailty group and health-related quality of life score at 3 and 18 months respectively, and change in score between 3 and 18 months post-stroke. Linear mixed effect regression with EQ-5D score as dependent variable, and frailty category and time between 3 and 18 months and their interaction as categorical covariates, and patient as random effect.

	ROBUST		PRE-FRAIL				FRAIL			
					Difference from Robust				Difference from Robust	
Unadjusted	N	Mean (SE)	N	Mean (SE)	*Estimate (95% CI)*	*p value*	N	Mean (SE)	*Estimate (95% CI)*	*p value*
3 months										
EQ-5D-5L index	180	0.865 (0.012)	337	0.767 (0.009)	-0.098 (-0.128 to -0.069)	*<0.001*	61	0.659 (0.021)	-0.206 (-0.253 to -0.158)	*<0.001*
EQ-5D VAS	183	73.7 (1.3)	325	62.4 (1.0)	-11.3 (-14.5 to -8.0)	*<0.001*	60	50.8 (2.3)	-22.9 (-28.1 to -17.7)	*<0.001*
18 months										
EQ-5D-5L index	168	0.872 (0.013)	284	0.755 (0.009)	-0.117 (-0.147 to -0.086)	*<0.001*	41	0.596 (0.024)	-0.276 (-0.329 to -0.223)	*<0.001*
EQ-5D VAS	168	73.9 (1.4)	272	62.4 (1.1)	-11.5 (-14.9 to -8.1)	*<0.001*	38	48.5 (2.8)	-25.4 (-31.5 to -19.3)	*<0.001*
Change between 3 and 18 months										
EQ-5D-5L index	194	0.007 (0.011)	366	-0.012 (0.008)	-0.019 (-0.046 to 0.008)	*0.175*	65	-0.063 (0.022)	-0.070 (-0.117 to -0.022)	*0.004*
EQ-5D VAS	194	0.2 (1.3)	355	0 (1.1)	-0.3 (-3.6 to 3.9)	*0.880*	64	-2.3 (2.7)	-2.5 (-8.6 to 3.5)	*0.412*

Table 3 continues on next page

(Continued from previous page)

Adjusted for: age, gender, NIHSS-score

3 months										
EQ-5D-5L index	176	0.840 (0.12)	330	0.774 (0.009)	-0.067 (-0.097 to -0.037)	*<0.001*	60	0.691 (0.021)	-0.149 (-0.198 to -0.100)	*<0.001*
EQ-5D VAS	179	72.7 (1.4)	321	62.7 (1.0)	-9.8 (-13.3 to -6.3)	*<0.001*	59	52.3 (2.4)	-20.2 (-25.9 to -14.5)	*<0.001*
18 months										
EQ-5D-5L index	164	0.847 (0.012)	330	0.762 (0.009)	-0.084 (-0.115 to 0.054)	*<0.001*	40	0.641 (0.024)	-0.206 (-0.260 to 0.152)	*<0.001*
EQ-5D VAS	164	72.9 (1.5)	320	62.5 (1.1)	-10.3 (-13.9 to -6.7)	*<0.001*	37	49.9 (2.9)	-22.8 (-29.3 to -16.3)	*<0.001*
Change between 3 and 18 months										
EQ-5D-5L index	194	0.006 (0.011)	357	-0.011 (0.008)	-0.018 (-0.045 to 0.009)	*0.203*	64	-0.050 (0.022)	-0.056 (-0.104 to -0.009)	*0.021*
EQ-5D VAS	194	0.2 (1.4)	349	-0.2 (1.1)	-0.4 (-3.8 to 3.0)	*0.803*	63	-2.3 (2.8)	-2.5 (-8.7 to 3.6)	*0.416*

Dependent variable: EQ-5D-5L index and EQ-5D VAS respectively; Categorical covariate: frailty state; Random effect: patients;

Table 4 Adjusted linear mixed effect regression results for the relationship between in-hospital frailty and change in each EQ-5D-5L dimension 3 to 18 months post-stroke

	ROBUST		PREFRAIL				FRAIL			
					Difference from Robust				Difference from Robust	
	N	Mean (SE)	N	Mean (SE)	*Estimate (95% CI)*	*p value*	N	Mean (SE)	*Estimate (95% CI)*	*p value*
3 months										
Mobility	189	1.34 (0.06)	334	1.68 (0.05)	0.34 (0.19 to 0.50)	*<0.001*	62	2.33 (0.11)	0.99 (0.74 to 1.25)	*<0.001*
Self-care	189	1.11 (0.46)	333	1.25 (0.33)	0.14 (0.03 to 0.25)	*0.014*	62	1.67 (0.08)	0.55 (0.37 to 0.74)	*<0.001*
Usual Activities	189	1.45 (0.07)	334	1.80 (0.05)	0.36 (0.19 to 0.52)	*<0.001*	62	2.53 (0.11)	1.09 (0.82 to 1.35)	*<0.001*
Pain	187	1.62 (0.07	333	1.91 (0.05)	0.29 (0.12 to 0.46)	*0.001*	62	2.01 (0.12)	0.39 (0.11 to 0.68)	*0.007*
Anxiety	187	1.49 (0.06)	334	1.60 (0.04)	0.12 (-0.03 to 0.26)	*0.118*	61	1.72 (0.10)	0.25 (0.01 to 0.48)	*0.038*
18 months										
Mobility	175	1.36 (0.07)	282	1.79 (0.05)	0.43 (0.27 to 0.59)	*<0.001*	41	2.81 (0.13)	1.45 (1.17 to 1.73)	*<0.001*
Self-care	175	1.13 (0.05)	283	1.33 (0.04)	0.20 (0.08 to 0.31)	*0.001*	41	1.94 (0.09)	0.81 (0.60 to 1.02)	*<0.001*
Usual Activities	175	1.40 (0.07)	283	1.75 (0.05)	0.34 (0.17 to 0.51)	*<0.001*	41	2.64 (0.14)	1.24 (0.93 to 1.54)	*<0.001*
Pain	173	1.63 (0.07)	281	2.02 (0.05)	0.39 (0.21 to 0.57)	*<0.001*	41	2.26 (0.14)	0.63 (0.31 to 0.95)	*<0.001*
Anxiety	175	1.43 (0.06)	282	1.57 (0.04)	0.14 (-0.01 to 0.29)	*0.058*	41	1.73 (0.12)	0.31 (0.04 to 0.57)	*0.022*
Change										
Mobility	194	0.02 (0.06)	366	0.12 (0.05)	0.08 (-0.06 to 0.23)	*0.251*	65	0.48 (0.12)	0.46 (0.20 to 0.71)	*<0.001*
Self-care	194	0.02 (0.04)	366	0.07 (0.03)	0.05 (-0.05 to 0.16)	*0.351*	65	0.28 (0.09)	0.26 (0.07 to 0.45)	*0.007*
Usual Activities	194	-0.04 (0.07)	366	-0.06 (0.06)	-0.02 (-0.19 to 0.16)	*0.851*	65	0.11 (0.14)	0.15 (-0.16 to 0.46)	*0.335*
Pain	194	0.02 (0.07)	366	0.11 (0.06)	0.10 (-0.09 to 0.28)	*0.299*	65	0.26 (0.14)	0.24 (-0.08 to 0.56)	*0.142*
Anxiety	194	-0.06 (0.06)	366	-0.03 (0.05)	0.03 (-0.12 to 0.17)	*0.698*	65	0.00 (0.12)	0.06 (-0.19 to 0.31)	*0.642*

Dependent variable: Mobility, Self-care, Daily Activities, Pain and Anxiety respectively; Categorical covariate: frailty state; Random effect: patient;
Adjusted for: age, sex, NIHSS-score.
Range in each dimension: 1-5 points. Positive value in "change" represents a worsening

4 DISCUSSION

In this longitudinal descriptive cohort study on Norwegian stroke survivors, we found an in-hospital frailty prevalence of 10.4% and pre-frailty prevalence of 58.6%, using a modified version of the Fried phenotype model. Being frail or pre-frail was associated with lower HRQoL at three and 18 months.

HRQoL kept stable for the robust and pre-frail group, while the frail group reported reduced HRQoL, measured by EQ-5D-5L index, from three to 18 months post stroke. All groups kept stable in EQ-5D VAS score from three to 18 months. We found the dimensions Mobility and Self-Care, but not Usual Activities, Pain/Discomfort, or Anxiety/Depression, to be worsened from three to 18 months mainly among the frail, but also in the pre-frail participants. The robust group kept stable in all dimensions.

Historically there have been few studies investigating frailty in a stroke setting. A frailty prevalence of 10% is lower and a pre-frail prevalence of 60% is higher than what has been found in previous studies on acute stroke population [40, 41]. These studies used other frailty tools than the Fried criteria in their measures, which can explain these differences. The frailty prevalence among community dwelling elders has been shown to range from 4.0% to 59.1% depending on the population studied and the frailty measures used[53]. Compared to studies utilizing a version of the Fried criteria in high-income countries, frailty and pre-frailty prevalence in the present study is higher (10.4% vs 4.9-7.4%; 58.6% vs 40-49.7%) [54-58].

This is to the best of our knowledge the first study to investigate associations between in-hospital frailty and HRQoL after acute stroke. Our hypothesis that frail stroke survivors had lower HRQoL-scores compared to the robust group was confirmed. This is consistent with findings from non-stroke populations, suggesting a possible important clinical relationship between frailty and HRQoL[35, 37].

We also expected that frail participants would experience a larger decrease in HRQoL which was partly confirmed with a decrease in the EQ-5D-5L index, but no change in the EQ-5D VAS. There may be several explanations for this. First, the EQ-5D VAS rates the overall health status, including dimensions that are not part of the EQ-5D-5L questionnaire[59]. In addition, older

people are more likely to report a higher score in EQ-5D VAS[60] and the frail group had the highest mean age. Finally, frail people tend to better adapt to disability by means of the *response shift phenomena* [61, 62], meaning that while an increased disability will affect a frail person's EQ-5D-5L index negatively, it may not play any role in the subjective impression of their overall health.

An important note here is that we are lacking measures of EQ-5D-5L pre-stroke, which could lead to an underestimating of the true deterioration in HRQoL post-stroke. Despite adjusting for stroke severity in the analyses, we do not know to which degree the deterioration in HRQoL experienced by the frail participants is a direct consequence of the stroke incident, or whether it is a consequence of other mechanisms related to their frailty[63].

As shown in Figure 1, 23% of the participants in the Nor-COAST study, were lost to follow-up from baseline to three months, and 21% were lost to follow-up from three to 18 months. The participants excluded were older and had a higher prevalence of frailty and pre-frailty than the ones who remained in the study. The results in the present study therefore likely overestimate EQ-5L-5D scores and underestimate the decrease in HRQoL from three to 18 months.

The finding of deterioration in the Mobility and Self-Care dimensions among the pre-frail and frail population is supported by other non-stroke studies showing both groups to be at risk of experiencing worsening in physical function and ADL, notably a bigger risk among the frail[64, 65]. As the frail population is at risk of having a decline in ADL, it is somewhat surprising that they reported no significant change in the dimension of Usual Activities. However, as seen in Table 6, Usual Activities had the worst measure at three months, showing this dimension to also be associated with poor HRQoL among the frail. Thus, these three dimensions should be of importance in rehabilitation of frail stroke patients to ensure a better HRQoL.

The major strengths of our study are the large sample size, including more than 600 patients from five Norwegian stroke units representing different health regions in Norway, and a high percentage of the participants was assessed at the follow-ups with small amounts of missing data. However, the study population in the Nor-COAST study is slightly younger with smaller strokes and better pre-stroke mRS-score compared to the general Norwegian stroke population[5], presenting a possible selection bias where potential frail participants may not have been included due to worse health status.

One limitation may be that we used a modified version of the Fried criteria that has not been validated. However, both the differences in the group's baseline characteristics and clear findings regarding HRQoL are in line with previous research and indicate that our modified version has succeeded in classifying patients as robust, pre-frail or frail. Two of the Fried criteria – slow gait speed and low grip strength – had to be assessed post-stroke and may be influenced by the stroke incident[66, 67]. Considering stroke being an acute incident, only self-reported information about the premorbid state of a patient suffering stroke will be available for health professionals in a clinical setting, and assessments of the physical or cognitive state of the patient must be performed post stroke. At present there is little agreement on which methods that are the best for identifying persons with frailty, especially in an acute setting. Further discussion on how to combine both comprehensive assessments and simpler screening tools should be an important clinical issue.

We used the EQ-5D-5L to assess the participant's HRQoL at three and 18 months, which has shown valid among stroke patients[68]. An important limitation regarding the EQ-5D-5L index is that it has been derived from the index scores calculated for the 3-level version of the EQ-5D questionnaire (EQ-5D-3L), using a mapping function. Index scores based on mapping functions are less reliable than scores calculated directly from representative general population samples[52]. Another possible limitation is the use of value set from Denmark being the only Scandinavian country with a current value set. This may create a possible bias as we do not know to which degree a Norwegian value set will differ from the Danish set.

As this is, as far as we know, the first study to investigate in-hospital frailty and post-stroke HRQoL among acute stroke survivors, more studies should be performed in order to try to reproduce our findings. Further, intervention studies should be performed regarding rehabilitation and secondary prevention among the frail stroke population to ensure better quality of life over time post-stroke.

5 CONCLUSION

This study showed that more than half of stroke survivors are classified as frail or prefrail according to the Fried phenotype when assessed during the first week post stroke. We found participants with frailty and prefrailty to report lower levels of HRQoL at three and 18 months post-stroke compared to the robust participants, and while the robust participants reported stable HRQoL from three to 18 months, participants with frailty reported a decline in HRQoL related to reduced mobility and self-care. These results remained when adjusted for stroke severity, age and gender. These findings indicate that frailty should be addressed as an important factor in stroke rehabilitation and that further research is required to better target rehabilitation and secondary prevention towards the needs of stroke survivors with frailty and pre-frailty.

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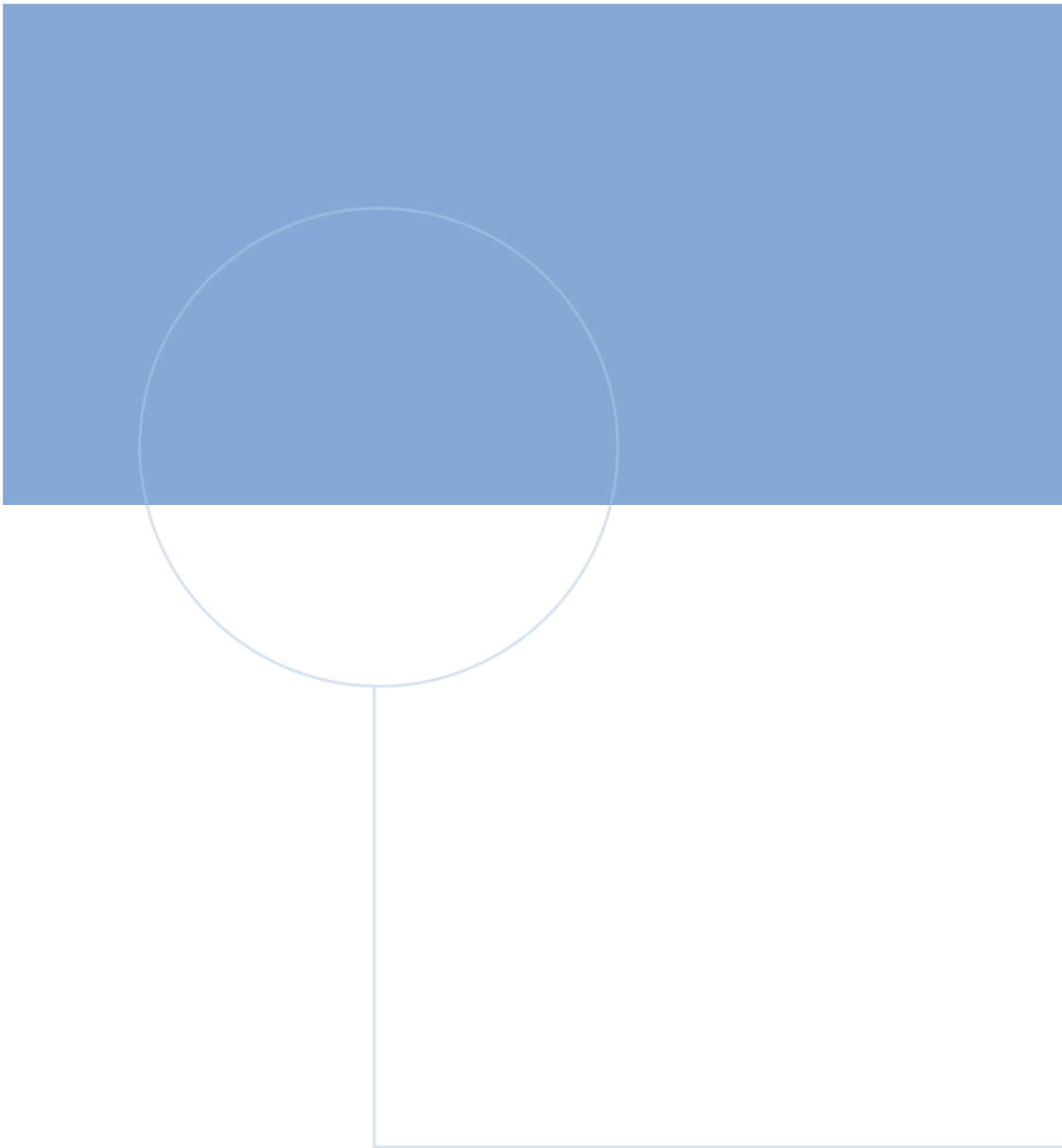

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