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RESEARCH ARTICLE

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Frailty and health-related life quality in long-term follow up of intensive care patients above 65 years old: Protocol for a Norwegian prospective, observational multicenter study

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Abstract

Background: Frailty is strongly correlated with mortality in intensive care unit patients, yet routine screening among intensive care patients is rarely performed.

The aim of this study is to assess frailty and health-related quality of life (HRQoL) in patients before intensive care admission and to compare this with outcomes after 3 and 12-months. The Clinical Frailty Scale and EQ-5D-5L will be used to assess frailty and HRQoL, respectively.

Methods: This is an ongoing, prospective observational study including patients from five Norwegian ICU's. Inclusion criteria are patients aged ≥65 years requiring invasive mechanical ventilation for ≥24 h. The Clinical Frailty Scale and EQ-5D-5L are administered at baseline (before critical illness) and at 3- and 12-months post-inclusion. Additional data collected includes patient characteristics, ICU treatment details, illness severity and mortality. The EQ-5D-5L will be compared to Norwegian population norms and assessed for measurement properties.

Results: Inclusion started July 2022 and will be stopped at 350 patients. The study will be completed in 2025.

Conclusion: The study will assess the feasibility and measurement properties of the Clinical Frailty Scale and EQ-5D-5L in ICU survivors by telephone at long-term follow-up study and will give additional information on the frailty and HRQoL of intensive care survivors.

Clinical trial registration: The study is registered in ClinicalTrials.gov NCT06012942. Protocol version 2.7.1, 19.05.2023.

KEYWORDS
critical care, EQ-5D-5L, frailty, HRQoL, mortality, post-PICU syndrome

1 | INTRODUCTION

Intensive care treatment is resource demanding and further understanding of outcomes in survivors will inform economic evaluation including cost-effectiveness.[1] The overall intensive care unit (ICU) mortality rate is 16%.[2] Intensive care survivors can suffer from persistent physical, cognitive and mental problems termed post-intensive care syndrome (PICS). Complications that occur after ICU treatment include muscle wasting, polyneuropathy, post-traumatic stress syndrome and frailty.[3] Prognostic factors related to outcome could be related to frailty and HRQoL before critical illness.[3] Frailty is defined as a condition characterized by age-related loss of biological reserves, failure of homeostatic mechanisms and vulnerability to a range of adverse outcomes including falls, disability, hospitalization, cognitive decline, and dependency.[4] Frailty correlates strongly with mortality, yet routine screening in intensive care patients is rarely performed.[5]

The Clinical Frailty Scale (CFS) is a 9-point clinical assessment of frailty that has been linked to prolonged hospital stay, complications and short-term mortality among ICU patients.[6–8] However, the impact of CFS scores on long-term outcomes following ICU treatment remains largely unexplored.[9]

The Euroqol EQ-5D-5L, is a generic HRQoL measure recommended as a screening tool to identify long-term impairment after critical illness and PICS.[10,11] The EQ-5D-5L assesses health across five dimensions of mobility, self-care, usual activities, pain/discomfort, anxiety/depression, and general subjective health.[12,13]

Norwegian general population norms for EQ-5D-5L have been recently published and are used as reference data for score interpretation.[14]

For ICU survivors, the long-term benefit in terms of functional outcome and quality of life is uncertain and may be related to the degree of critical illness and extent of intensive care treatment.[15] The aim of this national multicenter observational study is to observe frailty in ICU survivors aged 65 years or older and to describe how frailty, EQ-5D-5L and other factors related to ICU treatment influences long-term outcomes.

2 | METHODS

2.1 | Study settings

The study is a prospective, observational multicenter clinical study in Norway coordinated from the University hospital of North Norway, Tromso. The study will enroll patients from ICUs at five hospitals across the four health regions: University hospital of North Norway, Akershus University hospital, Haukeland University hospital, St Olav University hospital, Nordland hospital. All hospitals are general ICUs with 5–10 beds.

Inclusion criteria

- All ICU patients ≥65 years old requiring invasive mechanical ventilation ≥24 h.

Exclusion criteria

- Patient or relatives not giving consent to participation in the study.
- Patient or relatives not able complete Norwegian language questionnaires.
- Patient not available for follow-up due to living abroad.

2.2 | Study variables

The timeline and list of variables for data collection are described in detail in Table 1.

At the point of enrolment (ICU admission), the eligibility of all patients is screened. Baseline variables such as demographics, cause for admission and comorbidity are recorded. Any decisions on treatment limitations are also noted. Baseline CFS and EQ-5D-5L are assessed.

During the ICU stay, the patient's diagnoses and sequential organ failure assessment (SOFA) are recorded. Type of ICU treatment is noted.

TABLE 1 Time schedule of assessments and list of variables.

Time point	Enrolment ICU admission	Study period ICU stay	ICU/hospital discharge	3-m follow up	12-m follow-up
Enrolment					
Eligibility screen	x				
Informed consent		x		x	x
Allocation		x			
Baseline variables					
Demographics		x		x	x
Cause for admission		x			
Comorbidity[a]		x		x	x
Decision on treatment limitation	x				
Hospital variables					
Diagnoses		x	x		
Severity score (SOFA)		x	x		
Time on ventilator			x		
ICU LOS			x		
Treatment intensity[b]			x		
Readmission ICU			x	x	x
Hospital LOS			x	x	x
Discharge destination			x	x	x
Outcome variables					
Mortality			x	x	x
Cause of death			x	x	x
CFS		x		x	x
EQ-5D-5L		x		x	x

Abbreviations: CFS, clinical frailty scale; EQ-5D-5L, Euroqol-5D-5L; ICU, intensive care unit; LOS, length of stay; SOFA, sequential organ failure assessment.

[a]Measured with comorbidity and polypharmacy score (CPS) which is a sum of known comorbidities and pre-admission medications.

[b]Treatment intensity defined as need for dialysis, tracheostomy, ecmo, vasopressor, ICP monitoring in addition to mechanical ventilation.

At ICU discharge, the number of days ventilator days, the length of stay and discharge destination are recorded. Outcome variables such as mortality are registered.

At the 3- and 12-month follow-ups, the patient's demographics and comorbidity are reassessed. The patient's readmissions to the ICU, hospital LOS, and discharge destination are again recorded. Outcome variables such as mortality, cause of death, CFS, and EQ-5D-5L are reassessed.

2.3 | Patient-reported outcome measures

2.3.1 | Primary outcomes

The CFS summarizes the overall level of fitness or frailty of an older adult following consultation with an experienced clinician.[6] The most recent and widely used version is a nine-point scale and includes both frailty and terminal illness.[16,17] The CFS is also available in self-completed and telephone interview versions.[18] Clinical judgment is used to determine the appropriate CFS level and scoring aids are available.[19] The CFS was found to be associated with mortality in old Norwegian ICU patients.[20]

The EQ-5D-5L is a widely used generic HRQoL instrument that assesses five dimensions of health that are of broad relevance: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has five levels of no problem, slight problems, moderate problems, severe problems, and extreme problems/unable to do. The five responses give a health state represented by five-digits (e.g., 12,231) starting with mobility. Health states are scored to give an index using a scoring algorithm from a value set derived from valuation tasks typically undertaken with general population samples.[3] National recommendations will be followed in scoring the index. Used alongside the EQ-5D, the EQ VAS is a 20 cm visual analog scale "assessing your own health today" with endpoints labeled "Best imaginable health state" (100) and "Worst imaginable health state" (0). EQ-5D-5L norm data is available for the Norwegian general population which aids the interpretation of EQ-5D-5L scores for health problems. The instrument has undergone testing for measurement properties in Norwegian patient populations.[14]

Changes in both the CFS and EQ-5D-5L scores will be assessed from prior to ICU treatment and at 3 and 12 months after ICU admission.

- Changes in Clinical frailty score from prior to ICU treatment and at 3 and 12 months after ICU admission.
- Changes in EQ-5D-5L prior to ICU treatment and at 3 and 12 months after ICU admission.

2.3.2 | Secondary outcomes

Association between pre-ICU CSF, age, ICU readmission, ICU LOS, intensive care treatment (ventilator time, dialysis, ICP measurement, prone position, extracorporeal membrane oxygenation), SOFA score, comorbidities and long-term (3 and 12 months) CFS, EQ-5D-5L and mortality.[14,21]

2.4 | Data collection and management

CFS and EQ-5D-5L data before current critical illness will be collected from the patient and/or relative during the ICU stay.

The following demographic and clinical data will be retrieved from the medical records: weight, height, smoking, cause for admission, comorbidity, decision on treatment limitation, severity score all days in the ICU, time on ventilator, length of stay, ICU treatment, ICD-10 intensive care diagnoses, number of readmissions to hospital and ICU, discharge destination, mortality, ICD-10 cause of death.

The patients will be followed up by telephone interview after hospital discharge for purposes of collecting CFS and EQ-5D-5L data at 3 and 12 months.

Consent forms will be stored locally at each site. Data for all sites are collected locally and managed using REDCap electronic data capture tools.[21] The research members of the central study site, Tromso, have access to data from all sites.

Three trained research nurses will collect follow-up data by telephone for all sites and input data in REDCap. About 2 weeks before the planned follow-up phone call, the research nurses will send the patient or the patient's relative that have consented to the study, a form containing EQ-5D-5L and CFS. Research nurses will have access to the CFS and EQ-5D-5L collected during the ICU stay.

2.5 | Statistical analysis

Continuous variables will be presented as mean and standard error (SE) or median and interquartile range (IQR), categorical variables as counts (%).

Patients not meeting inclusion criteria and loss to follow up will be recorded along with the reasons.

CFS and EQ-5D-5L reporting will follow published recommendations.[22,23] Prior to statistical analyses, CFS and EQ-5D-5L scores will be assessed for normality by examining histograms and bar plots; in addition, skewness parameters will be estimated to assess normality of the distribution. We will also check the data for outliers.

Based on the normality assumption and sample size (the number of patients that survived up to the time-point of follow-up) the comparison of the means between baseline and follow up will be performed by either a paired *t*-test or a nonparametric Wilcoxon signed-rank test depending on the distribution of data.

If we find a statistically significant difference between baseline CFS and CFS measured 12 months following ICU admission, we will also employ a logistic regression approach where baseline CFS will be a predictor, while binary mortality variables (1-died, 0-survived up to 12 months) will be a response.

In the other secondary analysis, we plan to test the secondary outcome variables by multiple linear/logistic regression with a change in EQ-5D-5L/mortality as a response variable and the other covariates: age, ICU readmission, ICU LOS, intensive care treatment (ventilator time, dialysis, intracranial pressure measurement, prone position, extracorporeal membrane oxygenation) as predictors.

Prior to the linear and logistic regression models, we will assess if sample size of patients surviving up to 12 months is sufficient to run models with all the desired covariates. In case of a small sample sizes, we would consider removing some of the covariates or reduce the number of categories for categorical covariates.

For the logistic and linear regressions, we will also consider including the random effect of data collection center (a hospital). The need for this random effect will be tested by a likelihood-ratio test.

Also, for the logistic and linear regression models (if performed), we will run a conventional model validation check, such as residual analyses and influence diagnostics.

Due to many statistical tests that we outlined for the study, we may need to adjust the statistical analysis for multiple testing bias. We will consider applying a *p*-value correction by Benjamini and Hochberg.[24]

The testing of measurement properties for the EQ-5D-5L will follow the COSMIN guideline including the use of a priori hypotheses in tests of construct validity.[23,25,26]

3 | ETHICS AND DISSEMINATION

The study was approved by the Norwegian Regional Committee for Medical and Health Research Ethics (REC), and informed consent is obtained from the next of kin and later by the patient whenever appropriate, according to local regulations (172,784/REK North). The study is registered in ClinicalTrials.gov; NCT06012942.

Written informed consent is given by patient or patients next of kin. Patient is included by deferred consent if the patient dies in the acute phase.

The results will be disseminated through peer-reviewed publications, social media, patient organizations and conferences.

4 | DISCUSSION

Despite the importance of frailty in ICU treatment prioritization and patient follow-up, detailed frailty mapping is not routinely performed. This project will provide insights into the relationship between ICU treatment and long-term functional impairment, contributing to personalized follow-up for post-critical illness in frail elderly patients. This could assist in patient selection for ICU treatment, avoiding age discrimination and customizing rehabilitation treatment. It could also contribute to frailty mapping and guideline preparation.

The study includes patients above 65 years old, a particularly vulnerable group, but this may limit generalizability. The CFS score has only been evaluated for patients above 65 years old. The CFS score, used for frailty assessment, is subject to interpretation and may vary between observers. To mitigate this, we have limited the number of observers and exclude distinctly uncertain cases. Follow-up information sometimes comes from relatives, sometimes from patients, which could affect reliability. We strive to obtain agreed information from both. Despite potential bias due to fewer data points at higher short-term mortality rates, follow-up at 3 and 12 months allows for studying outcomes over time.

5 | CONCLUSIONS

This research project will enhance understanding of frailty and HRQoL in ICU survivors, optimizing the treatment process following critical illness. Moreover, the data collected will inform the evidence base for the appropriateness of the CFS and EQ-5D-5L in this care setting. Given the increasing treatment of older ICU patients and the lack of ICU personnel, focusing on frailty in ICU survivors is timely. The results could have an important impact on patient care and ICU resource allocation.

AUTHOR CONTRIBUTIONS

SKF, BAK and HF conceived and designed the study protocol. SKF and BAK administered the study protocol. RK, PK, DB, OK Fossum contributed to the protocol. SKF, BAK, HF, BS, ME, AMG wrote ther data analysis plan. SKF wrote the first draft of the manuscript. All authors contributed to manuscript editing and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interests.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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