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RESEARCH PAPER

Health-related quality of life in older patients surviving ICU treatment for COVID-19: results from an international observational study of patients older than 70 years

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Abstract

Background: health-related quality of life (HRQoL) is an important patient-centred outcome in patients surviving ICU admission for COVID-19. It is currently not clear which domains of the HRQoL are most affected.
Objective: to quantify HRQoL in order to identify areas of interventions.
Design: prospective observation study.
Setting: admissions to European ICUs between March 2020 and February 2021.
Subjects: patients aged 70 years or older admitted with COVID-19 disease.
Methods: collected determinants include SOFA-score, Clinical Frailty Scale (CFS), number and timing of ICU procedures and limitation of care, Katz Activities of Daily Living (ADL) dependence score. HRQoL was assessed at 3 months after ICU admission with the Euro-QoL-5D-5L questionnaire. An outcome of ≥4 on any of Euro-QoL-5D-5L domains was considered unfavourable.
Results: in total 3,140 patients from 14 European countries were included in this study. Three months after inclusion, 1,224 patients (39.0%) were alive and the EQ-5D-5L from was obtained. The CFS was associated with an increased odds ratio for an unfavourable HRQoL outcome after 3 months; OR 1.15 (95% confidence interval (CI): 0.71–1.87) for CFS 2 to OR 4.33 (95% CI: 1.57–11.9) for CFS ≧ 7. The Katz ADL was not statistically significantly associated with HRQoL after 3 months.

Conclusions: in critically ill old intensive care patients suffering from COVID-19, the CFS is associated with the subjectively perceived quality of life. The CFS on admission can be used to inform patients and relatives on the risk of an unfavourable qualitative outcome if such patients survive.

Keywords: Intensive Care Unit (ICU), frailty, Quality of Life, Survival, Older people, COVID-19

Key Points

- Three-month survival of patients ≥70 years admitted to the Intensive Care Unit for COVID-19 is limited (39%).
- Half of the surviving patients have severe to extreme problems on at least one of the Health-related quality of life (HRQoL) domains.
- Frailty is associated with severe to extreme problems on the HRQoL outcome.

Introduction

In 2019, the novel corona virus (SARS-CoV-2) caused a worldwide pandemic. Particularly older patients (>70 years) became severely ill and a disproportionate number needed admission to an intensive care unit (ICU) [1]. Despite improvements in treatments, a large proportion of these older patients still succumb to the disease and the 30-day survival is 59% [2].

Patients who survive the ICU admission often experience serious sequelae: post-traumatic stress disorder, anxiety, depression, muscle weakness, cognitive impairment and many others [3]. Additionally, a significant number of patients developed what is now named 'long-covid', which has a strong influence on the physical and mental aspects of life and well-being. Such unwanted side effects of ICU-treatment may profoundly impact the quality of life of surviving patients [3, 4]. However, which adverse outcomes have the largest impact on self-perceived, health-related quality of life is currently unclear. Without such information, we cannot properly intervene to prevent poor quality of life. Moreover, many older patients (and their relatives) prioritise a good quality of life over long-term survival [5]. Vice versa, there is a strong relationship between quality of life after ICU survival and the self-reported unacceptable outcome one year after intensive care treatment [6]. We might even consider intensive care treatment disproportionate if it only causes suffering and anguish while not reaching the personal goal of a good quality of life [7]. For all these reasons, an assessment of the patient's pre-ICU functional abilities at ICU admission and assessments for post-intensive care syndrome-related problems has been advocated [8].

This prospective multinational, observational study aims to report on outcomes of the various domains of the self-reported health-related quality of life assessment of former critically ill COVID-19 patients. A second aim is to study whether adverse outcomes are associated with frailty.

Methods

Design and settings

This multicentre, prospective study is part of the Very old Intensive care Patients (VIP) project (www.vipstudy.org) and was endorsed by the European Society of Intensive Care Medicine. In short, the 'COVID-19 in very old intensive care patients' (COVIP-study) was conceived in the first months of 2021 when the first wave hit Europe. Basically, it was an observational study looking at patients' demographics, treatment modalities while admitted to the ICU and outcomes of these patients up to 3 months after admission to the ICU [2]. Such research was already performed in a general but older ICU population (>80 years old) [2, 9, 10]. As a consequence, research protocols could swiftly be adapted to the COVID-19 population and ethical clearance was swift because it had already been evaluated, albeit in another domain of patients. The study was registered at ClinicalTrials.gov (ID: NCT04321265) and adhered to the European Union General Data Privacy Regulation (GDPR). This investigation aimed to understand which factors are associated with survival and quality of life in older COVID-19 patients (the so-called COVIP-study, COVID-19 in VIP) [2]. As in the previous VIP studies [2, 9, 10], national coordinators recruited the ICUs, coordinated national and local ethical permissions, and supervised patient recruitment at the national level. Ethical approval was mandatory for study participation and was obtained for each country separately. Usually, informed consent was mandatory for inclusion, but in some countries, this was not required with the reference to the critical condition and difficulties with patients consent.

Study population

The COVIP-study recruited consecutive patients with a positive COVID-19 test and aged 70 years or older who were admitted to an ICU. The dataset was extracted from the COVIP study database on 14th of May 2021 and contained patients from 19th March to 4th February 2021. Prospective data collection commenced at ICU admission. The admission day was defined as day 1, and all consecutive days were numbered sequentially from that date.

Data collection

The methods have been described in previous publications [2]. In short, all centres used a uniform online electronic case report form (eCRF). Of each patient, we recorded (i) information present on admission (i.e. gender, weight, length, days in hospital prior to ICU admission, days with symptoms

prior to hospital admission, comorbidities, medication use, habitat before admission, arterial blood gasses on admission, sequential organ failure assessment (SOFA), the clinical frailty scale (CFS) and the Katz activities of daily living), (ii) we collected data on treatments provided to (or withheld from) the patient while being admitted to ICU (i.e. mechanical ventilation, prone positioning, tracheostomy performed, vasoactive drugs used, use of renal replacement treatment used, use of non-invasive ventilation, use of extra-corporeal membrane oxygenation, use of antimicrobials, and life sustaining treatments withheld or withdrawn while being in the ICU) and (iii) outcomes of the patients (i.e. survival to ICU discharge, ICU length of stay, vital status at 30 days, vital status at 3 months and EuroQoL quality of life questionnaire at 3 months).

Records of patients for whom data were not complete were completed using multiple imputations (see Statistical section). For the SOFA score on admission, each element was entered and the eCRF calculated the total score. Furthermore, we assessed the need for non-invasive or invasive ventilation, prone positioning, tracheostomy, vasopressor use and renal replacement therapy. The CRF also documented any limitation of life-sustaining therapy during the ICU-stay.

Frailty and comorbidities

The frailty level prior to the acute illness and hospital admission was assessed using the CFS [2, 9, 10].

Data storage

The eCRF and database were hosted on a secure server in Aarhus University, Denmark.

Health-related quality of life

The quality of life was assessed by the EurQol-5D-5L questionnaire at 3 months post-discharge. This is a self-reported assessment of generic health that consists of five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), each with five levels of functioning (e.g. n 'no problems', 'slight problems', 'moderate problems', 'severe problems' and 'unable to'/'extreme problems' for all of these dimensions) (see Supplementary Table 1, Supplementary data are available in *Age and Ageing* online). This health state classifier can describe 3,125 unique health states that are often reported as vectors ranging from 11,111 (full health) to 55,555 (worst health). Numerous societal value sets have been derived from population-based valuation studies around the world that, when applied to the health state vector, resulting in a preference-based score that typically ranges from states worse than dead (<0) to 1 (full health), anchoring dead at 0. In addition, the measure includes a visual analogue scale where health is rated by the patient on a scale from 0 (worse imaginable health) to 100 (best imaginable health) [11].

On each of the 5 domains of the Euro-QoL-5D-5L patients can answer on 5 different levels (from level 1: no problem to level 5: extreme problems) (see Supplemental Table 1, Supplementary data are available in *Age and Ageing* online). The self-perceived quality of life is by definition subjective, and therefore, there is no normative value at which one can dichotomise quality of life into 'good' or 'poor' [12]. For study purpose, we defined a level 4 answer or worse ('I have severe/extreme problems') as an outcome considered 'unfavourable'.

Statistical analysis

Descriptive data were computed based on all case records, showing the amount of missing data per variable. Continuous data points were expressed as median ± interquartile range. Differences between independent groups were calculated using the Mann–Whitney U-test. Categorical data are expressed as numbers (percentage). The Chi-square test was applied to calculate differences between groups.

Multiple variables showed missing data. For the multivariable analysis of associating CFS to HRQoL (see below), the complete cases considering all required variables numbered 585 of the total 1,224 patients (47.8%). We used multiple imputation techniques to avoid the bias due to loss to follow-up when a complete case analysis would have been performed. A total of 100 imputed datasets were generated by multiple imputations through chained equations using the 'mice' package in R v4.1.0. All imputation models allowed for non-linear associations of any included continuous variables.

Univariate and multivariable logistic regression analyses were performed to assess associations with baseline variables and the studied HRQoL outcomes. We chose the covariables for the multivariable model (age, gender, Katz, SOFA score and CFS) based on clinical experience and previous literature [2, 9, 10]. In analyses where CFS was shown per level, CFS 7, 8 and 9 were combined because there were too few patients in CFS 8 and 9 to allow a proper analysis of these levels separately. Rubin's rules were used when pooling the results from the imputed datasets. All tests were two-sided, and a P-value of <0.05 was considered statistically significant. R version 4.1.0 was used for all statistical analyses.

Results

Study population

In total, 3,140 patients ≥70 years old were included in the COVIP-study. Ninety days after inclusion (ICU admission), 1,224 were still alive of which 707 (57.8% of the survivors) answered the quality of life questionnaire. Figure 1 depicts the flow of patients and Table 1 summarises the demographics of all the patients that were included in the study versus those who survived up to 3 months (but did not answer versus those who answered the questionnaire).

The patients who answered the questionnaire were statistically similar to those who did not answer this questionnaire except for age. Those who did not answer the questionnaire were younger (non-responders were 73 versus 74 years of the responders, $P = 0.003$). All other variables were equally distributed among responders and non-responders.

Table 1. Patient demographics

Patient characteristic	Total population	missing data from total population	Responders	Non-responders	*P* value for difference between responders and non-responders
N	1,224		707	517	
Age (years)	74 [72–77]	4	74 [72–77]	73 [71–77]	0.003
Sex (male)	856 (70%)	3	487 (69%)	369 (71%)	0.444
BMI	28 [25–31]	76	28 [25–31]	28 [25–31]	0.599
Proven COVID-19	1,198 (98%)	6	693 (98%)	505 (98%)	0.978
Hospital stay prior to ICU admission (days)	2 [1–5]	9	2 [1–5]	2 [1–5]	0.13
Duration of symptoms prior to hospital admission	7 [4–10]	97	7 [4–10]	7 [4–10]	0.5
Diabetes	360 (29%)	6	212 (30%)	148 (29%)	0.664
Heart failure	135 (11%)	11	87 (12%)	48 (9%)	0.122
Hypertension	802 (66%)	9	456 (64%)	346 (67%)	0.355
Ischemic heart disease	239 (20%)	14	137 (19%)	102 (20%)	1
Pulmonary failure	250 (20%)	5	156 (22%)	94 (18%)	0.11
Clinical Frailty Scale 1	119 (10%)	68	78 (11%)	41 (8%)	0.366
CFS 2	354 (29%)		222 (31%)	132 (26%)	
CFS 3	427 (35%)		239 (34%)	188 (36%)	
CFS 4	151 (12%)		93 (13%)	58 (11%)	
CFS 5	43 (4%)		27 (4%)	16 (3%)	
CFS 6	40 (3%)		27 (4%)	13 (3%)	
CFS 7	21 (2%)		14 (2%)	7 (1%)	
CFS 8	1 (0%)		1 (0%)	0 (0%)	
CFS 9	0 (0%)		0 (0%)	0 (0%)	
SOFA-score	4 [3–7]	20	4 [3–7]	4 [2–7]	0.129
Intubated	775 (63%)	5	448 (63%)	327 (63%)	0.947
Duration of invasive mechanical ventilation (days)	14 [8–27]	26	14 [7–26]	14 [8–27]	0.478
Prone positioning	394 (32%)	454	227 (32%)	167 (32%)	0.858
Initiation of prone positioning after admission to the ICU (days)	0 [0–0]	4	0 [0–0]	0 [0–0]	0.001
Vasoactive medication	735 (60%)	9	430 (61%)	305 (59%)	0.566
Duration of vasoactive medication (days)	4 [2–9]	39	5 [2–10]	4 [2–8]	0.015
RRT	109 (9%)	3	68 (10%)	41 (8%)	0.345
Duration of RRT (days)	6 [2–15]	6	11 [3–18]	4 [2–8]	0.006
Non-invasive ventilation	303 (25%)	7	192 (27%)	111 (21%)	0.025
Duration of non-invasive ventilation (days)	1 [1–3]	19	1 [1–3]	1 [1–3]	0.140
ECMO	2 (0%)	0	2 (0%)	0 (0%)	0.548
Length of stay on the ICU (days)	12 [6–27]	22	13 [6–27]	12 [6–27]	0.717

BMI means Body Mass Index, SOFA means Sequential Organ Failure Score, RRT means renal replacement therapy, ECMO means Extracorporeal Membrane Oxygenation. All continuous variables are represented as median with [interquartile range].

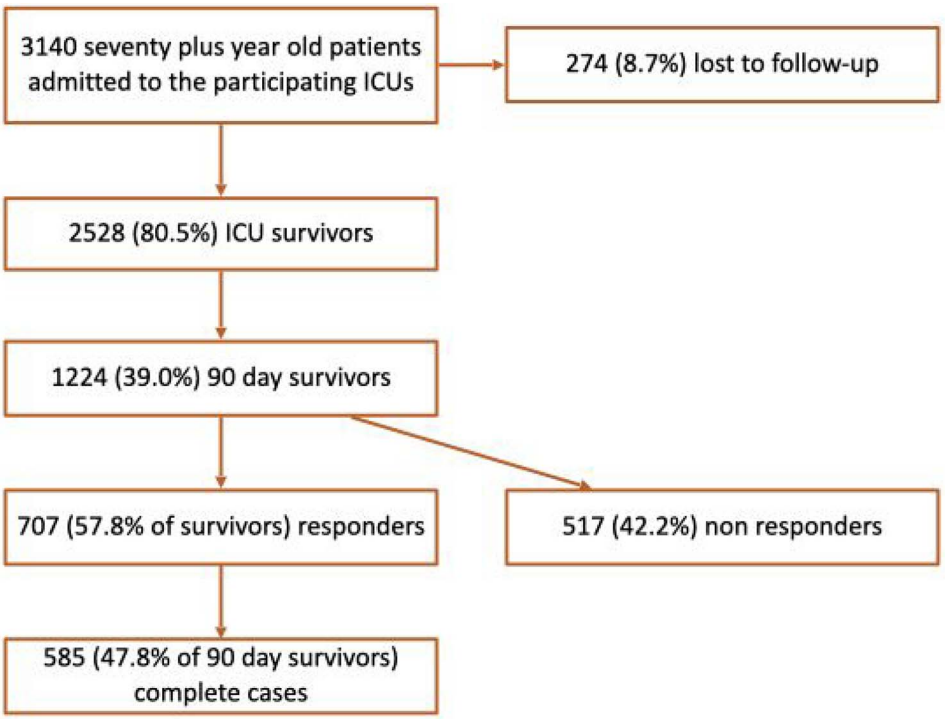

Figure 1. Flow of patients.

Health-related quality of life

The EQ-5D-5L questionnaire was completed by or completed for $n = 707$ patients. In $n = 441$ (62.4%), the questionnaire was completed by the patients, in $n = 146$ (20.7%) by family or care-givers, in $n = 114$ (16.1%) extracted from hospital records or by $n = 6$ (0.8%) through other means. The patients that did answer the questionnaire ($n = 707$) showed that $n = 182$ patients (25.7%) complained of having an impairment at a level 4 or 5 answer ('I have severe/extreme problems') in at least one of the five domains (see Figure 2). After correction for various variables in the multivariable analysis, the odds of having a complaint of level 4 or worse were correlated with increasing frailty scales: the odds for CFS 2 were 1.17 (95% confidence interval (CI): 0.72–1.91) and increased to an odds of 4.22 (95%CI: 1.06–16.8) for patients with CFS 7 and over (combined group) (see Table 2). If the patients with a CFS 1–3 are combined into the reference group ('non-frail') then patients with CFS 4–5 have an odds of 1.61 (95%CI: 1.13–2.3) and patients with a CFS $\geqq 7$ have an odds of 2.99 (95%CI: 1.43–6.25) of having a complaint of equal to or more than a level 4 in any of the domains. The differences between these groups are summarised in a spider graph depicting all 5 domains (see Figure 3).

Discussion

In this multicentre study in patients older than 70 years admitted to an ICU with COVID-19 found that only 39% of the patients survived up to 90-days. Even worse, within the group of surviving patients 48% ($n = 592$) experienced 'severe problems' or 'extreme problems' in at least one of the five domains of the EQ-5D-5L questionnaire. 'Severe problems' were mentioned by 41% ($n = 496$), and 'extreme problems' on one of the five domains in 30% ($n = 371$). There was a clear association between the level of frailty before hospitalisation and reporting severe problems in any one of the 5 domains of the health-related quality of life questionnaire. Particularly pre-frail and frail patients (defined as a CFS of 4 or above) showed an independent association with persisting problems after 90 days leading to a diminished quality of life.

The association between frailty before acute ICU admission and outcome at 90-days was as expected. Frailty is defined as 'a clinically recognisable state of increased vulnerability resulting from ageing-associated decline in reserve and function across multiple physiologic systems such that the ability to cope with acute stressors is comprised'. Being admitted with a severe disease such as COVID-19 definitely fulfils the criteria of an acute stressor. However, this research is one of the first to show which proportion of older patients with COVID-19 will have persisting problems and their severity. Previous research in a small cohort of a slightly younger ICU population (mean age 65 years) showed that 67% of the surviving patients had a decreased HRQoL and 62% had a decline in functional status [13]. These patients were asked to recall their quality of life prior to becoming ill and compare it to their current functioning and self-perceived quality of life. A small Italian observational

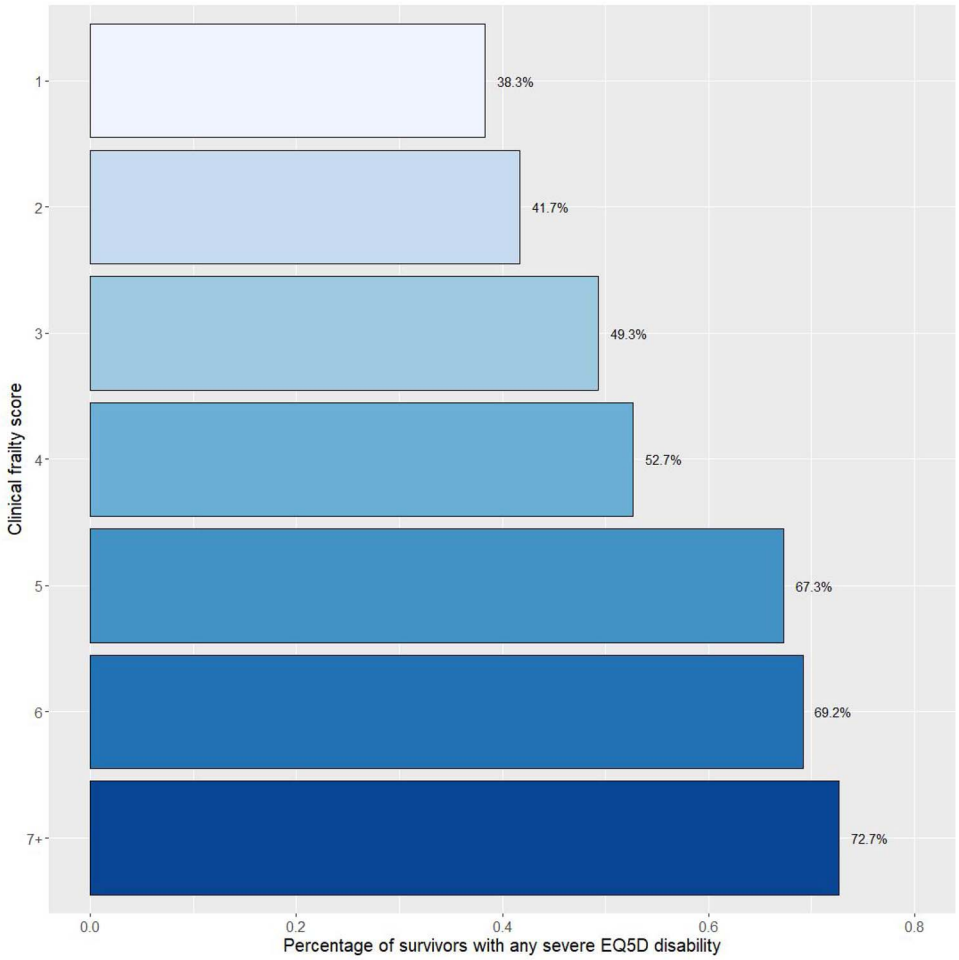

Figure 2. Association between CFS and severe or worse complaints on any of the 5 domains of the Quality of Life questionnaire. Percentage of patients complaining of any impairment more than or equal to level 4 answer ('I have severe complaints . . . ') on one of the 5 domains of the Health-Related Quality of Life questionnaire (EuroQoL-5D-5L). Based on data after multiple imputation.

Table 2. Odds of having at least one outcome in the quality of life domains of ≧level 4 (moderate to extreme complaints) corrected for Katz, age, gender and day 1 SOFA score

CFS score	OR	95%CI lower limit	95%CI upper limit	*P*-value
2	1.17	0.72	1.91	0.526
3	1.62	1.01	2.6	0.046
4	1.89	1.08	3.29	0.025
5	3.77	1.66	8.59	0.002
6	4.17	1.71	10.17	0.002
7+	4.22	1.06	16.78	0.041

study looked at the HRQoL of surviving adult patients and compared that to age- and gender-matched controls [3]. In that study, survival at 90-days was 58% and the response rate among survivors was impressive; 78% of the surviving patients answered their questionnaire. They showed that surviving COVID-19 patients had a HRQoL that was (statistically) worse than an age- and gender-matched control patients not affected by COVID-19. However, in another, younger age group (mean age 48 years), the HRQoL was reduced in one third of the patients, but the patients assessed their overall health-related quality of life as expressed by an visual analogue scale (the EQ-VAS) to be equivalent to normative values for the general adult Italian population [14]. The authors of that study realised that this rather young and

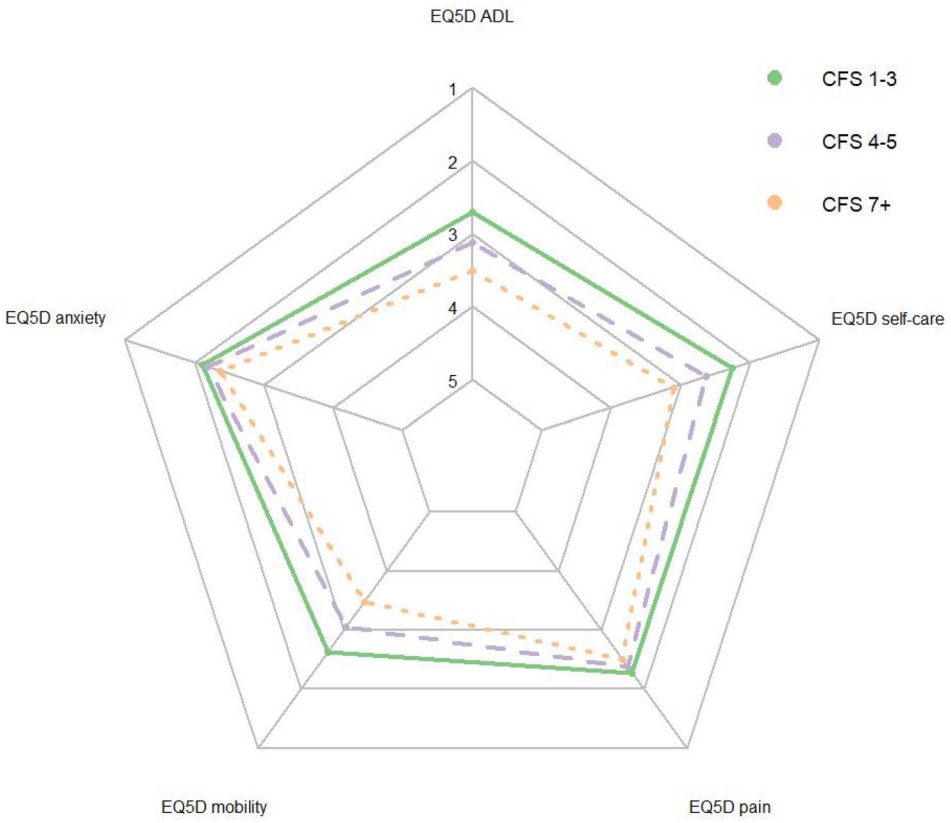

Figure 3. Spider graph depicting outcome of quality of life in non-frail, pre-frail and frail patients. Patients with a CFS 1-3 are considered 'non-frail' (green line). Patients with a CFS 4-5 are considered 'pre-frail' (purple line) and patients with CFS 7+ are considered 'frail' (orange line). On the QoL domains, 1 denotes 'no problems', 2 'slight problems', 3 'moderate problems', 4 'severe problems' and 5 'extreme problems'.

previously healthy population might not be representative for a frailer population.

However, this points towards one of the most important limitations of self-perceived and self-reported HRQoL: it is subjective, cultural and changes over time [12]. While the Euro-QoL questionnaire tries to objectify certain persisting complaints, the normative societal values for the HRQoL index are different for various countries. This implies that various countries, religions and/or cultures value outcomes differently. It, therefore, remains difficult to compare outcomes between individuals or between countries. This is illustrated by the fact that many European countries do not yet have a normative societal value sets to calculate an HRQoL index based on the EQ5D five-level variant, specially stratified by age. We have chosen to circumvent this limitation by assessing which proportion of patients will have severe problems in one of the five domains of the HRQoL. We find this to be clinically relevant regardless of country and might be used to counsel older patients or their relatives. Many critically ill patients and particularly their relatives want to know the chances of survival and their health-related quality of life if they survive COVID-19. Depending upon the level of frailty prior to admission, we can now inform which proportion of patients will have persisting problems (see Supplementary Table 2, Supplementary data are available in *Age and Ageing* online).

Limitations and strengths

One of the major limitations of this study is that it has been performed in a 'selected ICU population'. This means that the patients had been subject to triage decisions prior to ICU admission. Some patients have been considered to be 'too good' or 'too bad' for ICU admission and these patients were never part of the study population. This might result in a potentially biased study population, with a better outcome than the overall patient group of ≥70 years. This, however, is reality in every day ICU care and is true for every ICU study. Indeed, the starting point of our study was the older patient that had been admitted to the ICU.

The follow-up was limited to 3 months. Some disabilities require more time to improve and it is, therefore, conceivable that some of the patients will experience further improvements of their present health-related quality of life.

Another limitation is that in most countries, written informed consent was mandatory. We know, from previous research, that this results in a selected study population that is less ill than when written informed consent would not have been necessary (the real ICU population will be more severely ill) [15].

And finally, association should not be confused with causation. The fact that frail patients with end up with more severe problems in the health-related quality of life domains

does not mean that frailty is causing this or will always cause this.

However, the strong features of this observational cohort are that it is performed in many European countries, is quite large and represents a diverse mixture of cultures and religions. The results of this research can be translated into advice for older patients in whom are admitted to the ICU and want to discuss outcome trajectories. Again, particularly, older patients (and their relatives) prioritise a good quality of life over long-term survival [5]. Future research might focus on a certain quality of life that is unacceptable for individual patients and we need to establish predictors for such unwanted outcomes.

Conclusion

Half of the older critically ill old patients who have survived COVID-19 reported severe to extreme problem after 3 months, which was associated with the level of frailty: frail patients had a larger proportion of patients experiencing severe to extreme problems on any of the HRQoL domains. Such information is important to convey to older patients (or their relatives) when they need to be admitted to the ICU.

Supplementary Data: Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

Acknowledgements: Individual participant data that underlie the results reported in this article are available to investigators whose proposed use of the data has been approved by the COVIP steering committee. The anonymised data can be requested from the authors if required, provided that both parties will adhere to all the legal GDPR requirements.

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