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Weihe, Sarah; Mortensen, Camilla B.; Haase, Nicolai; Andersen, Lars P. K.; Mohr, Thomas; Siegel, Hanna; Ibsen, Michael; Jørgensen, Vibeke R. L.; Buck, David L.; Pedersen, Helle B. S.; Pedersen, Henrik P.; Iversen, Susanne; Ribergaard, Niels; Rasmussen, Bodil S.; Winding, Robert; Espelund, Ulrick S.; Bundgaard, Helle; Sølling, Christoffer G.; Christensen, Steffen; Garcia, Ricardo S.; Brøchner, Anne C.; Michelsen, Jens; Michagin, George; Kirkegaard, Lynge; Perner, Anders; Mathiesen, Ole; Poulsen, Lone M.

Published in:

Acta Anaesthesiologica Scandinavica

DOI (link to publication from Publisher):

[10.1111/aas.14108](https://doi.org/10.1111/aas.14108)

Publication date:

2022

Document Version

Accepted author manuscript, peer reviewed version

[Link to publication from Aalborg University](#)

Citation for published version (APA):

Weihe, S., Mortensen, C. B., Haase, N., Andersen, L. P. K., Mohr, T., Siegel, H., Ibsen, M., Jørgensen, V. R. L., Buck, D. L., Pedersen, H. B. S., Pedersen, H. P., Iversen, S., Ribergaard, N., Rasmussen, B. S., Winding, R., Espelund, U. S., Bundgaard, H., Sølling, C. G., Christensen, S., ... Poulsen, L. M. (2022). Long term cognitive and functional status in Danish ICU patients with COVID-19. *Acta Anaesthesiologica Scandinavica*, 66(8), 978-986. Advance online publication. <https://doi.org/10.1111/aas.14108>

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1.06.2022

1.11.1

Long term cognitive and functional status in Danish ICU patients with COVID-19

A nationwide, population-based, prospective cohort study

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the [Version of Record](#). Please cite this article as doi: [10.1111/aas.14108](https://doi.org/10.1111/aas.14108)

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Word count: 3000 (excl. abstract, tables, figures, and references)

Keywords: covid-19 , follow-up , cognitive , functional , frailty , fatigue , intensive care

Abstract

Background:

ICU admission due to COVID-19 may result in cognitive and physical impairment. We investigated the long-term cognitive and physical status of Danish ICU patients with COVID-19.

Methods:

We included all patients with COVID-19 admitted to Danish ICUs between March 10th and May 19th, 2020. Patients were contacted prospectively at 6 and 12 months for follow up. Our primary outcomes were cognitive function and frailty at 6 and 12 months after ICU admission, estimated by the Mini Montreal Cognitive Assessment, and the Clinical Frailty Scale. Secondary outcomes were 6- and 12-month mortality, health-related quality of life (HRQoL) assessed by EQ-5D-5L, functional status (Barthel Activities of Daily Living and Lawton-Brody Instrumental Activities of Daily Living), and fatigue (Fatigue Assessment Scale). The study had no information on pre-ICU admission status for the participants.

Results:

A total of 326 patients were included. The 6- and 12-month mortality was 37% and 38%, respectively. Among the 204 6-month survivors, 105 (51%) participated in the 6-month follow-up; among the 202 12-month survivors, 95 (47%) participated in the 12-month follow-up. At 6 months, cognitive scores indicated impairment for 26% (95% CI, 11.4 – 12.4) and at 12 months for 17% (95% CI, 12.0 – 12.8) of participants. Frailty was indicated in 20% (95% CI, 3.4 – 3.9) at 6 months, and for 18% (95% CI, 3.3 – 3.8) at 12 months. Fatigue was reported by 52% at 6 months, and by 47% at 12 months. For HRQoL, moderate, severe, or extreme health problems were reported by 28% at 6 months, and by 25% at 12 months.

Conclusion:

Long term cognitive, functional impairment was found in up to one-in-four of patients surviving intensive care for COVID-19. Fatigue was present in nearly half the survivors at both 6- and 12 months. However, pre-ICU admission status of the patients was unknown.

Editorial Comment:

In this prospective study of 326 individuals admitted to the ICU with COVID-19 in Denmark, 20-25% of individuals screened positive for cognitive impairment and frailty at 6 and 12 months.

Fatigue was common and health-related quality of life was reduced amongst responders. It should be noticed that a baseline status was not available prior to ICU admission and participation amongst survivors was roughly 50%. The results suggest that there is a high degree of reduced functional status and quality of life following ICU admission for COVID-19.

Word count: 298

Introduction

In December 2019, a new type of coronavirus, the Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) emerged in Wuhan, China, and started a pandemic.¹ The clinical manifestations of the human virus infection was called Corona Virus Disease-19 (COVID-19) and symptoms range from asymptomatic or mild symptoms to Acute Respiratory Distress Syndrome (ARDS) and multi-organ failure.²

The first patients with severe COVID-19 were admitted to intensive care units (ICU) in Denmark in March 2020.³ During this initial stage of the COVID-19 pandemic, in spring 2020, the Danish ICU COVID-19 Database was established to monitor critically ill patients suffering from COVID-19.⁴

Previous studies have shown that survivors of critical illness treated in the ICU may experience a decline in cognitive and functional status, which can last for a long time after discharge.⁵⁻⁷ This often includes an experience of fatigue and loss of health-related quality of life (HRQoL).⁸

We, therefore, anticipated that ICU patients with COVID-19 would experience similar cognitive and functional impairments after discharge.^{2,6} Consequently, the aim of the present study was to investigate cognitive and functional impairments, fatigue, and HRQoL in Danish ICU survivors of COVID-19 at 6 and 12 months after ICU admission.

Methods

Study design

This was a nationwide, population-based, prospective cohort study investigating the 6- and 12-month long-term outcomes of all patients admitted to a Danish ICU between March 10th to May 19th 2020 and retrospectively registered in the Danish ICU COVID-19 Database.⁴ The reporting of the study follows the STROBE guideline for reporting observational studies.

Ethics

The Danish Patient Safety Authority approved the establishment of the Danish COVID-19 ICU database and waived consent from the individual patients due to the retrospective nature of the database (ref. no. 31-1521-293).⁴

The Danish Data Protection Agency approved this study (REG-135-2020). National Ethics Committee waived consent (J.nr. 20-000013), because no ethical approval for this type of study is warranted in Denmark. The responsible investigator of the database granted permission to use the information from the database in this study. Furthermore, the Heads of each ICU with surviving patients at 6 months were contacted to gain acceptance to contact their individual patients.

The Danish ICU COVID-19 database

All patients with a positive polymerase chain reaction (PCR) test for SARS-CoV-2 either prior to or during ICU admission were registered in the Danish COVID-19 ICU database. Data registered included baseline characteristics, comorbidities, time on ventilator, vasopressor used, renal replacement therapy (CRRT), length of ICU and hospital stay, and mortality. (Appendix 1)

Patients and enrolment in the follow-up study

After acceptance from the participating ICUs, all their surviving patients were contacted by a secure online digital mailbox, e-Boks, providing information about their registration in the nationwide database during their admission to the ICU with COVID-19, and an invitation to participate in the follow-up study. If the patients had no access to e-Boks, contact was attempted by telephone. To optimize the opportunity to participate in the study, patients who did not reply within two weeks after the invitation by e-Boks were given a final attempt by telephone. All participants provided oral and written informed consent to the follow-up study upon first telephone contact.

Outcomes

The primary outcomes were cognitive function and frailty status at 6 and 12 months after ICU admission estimated by the Mini Montreal Cognitive Assessment (Mini-MoCA) and Clinical Frailty Scale (CFS). Secondary outcomes were 6- and 12-month mortality, self-rated HRQoL estimated by EuroQol (EQ)-5D-5L, functional status by Barthel Activities of Daily Living (ADL) score, and the Lawton-Brody Instrumental Activities of Daily Living (IADL) score, and fatigue by Fatigue Assessment Scale (FAS). Furthermore, the association between ventilator days and CFS, and MiniMoCA respectively were explored.^{9,10}

Data collection

Participants were interviewed by telephone at 6 and 12 (+/- 2) months after admission to the ICU. The interviews lasted approximately 20 minutes and were performed by the same interviewer (SW). The order of the questionnaires was: MiniMoCA, EQ-5D-5L, ADL, IADL, FAS, and CFS. All instruments were validated to be used in telephone interviews.

MiniMoCA version 2.1 is a validated questionnaire for assessing cognitive function. It consists of five cognitive domains; attention, verbal learning and memory, executive function/language, and orientation, covered by four subtests. The total score range from 0-15, and scores of 11 or above are considered normal.¹¹ A modified non-validated Danish translation has recently been made available and was used in this study.^{11,12}

EQ-5D-5L is a validated self-reporting HRQoL questionnaire exploring five domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The participants are asked to rate each domain into five levels, ranging from 1 indicating no problems to 5 indicating extreme problems. Furthermore, on the EQ-VAS, the participants mark their current overall health status on that particular day on a visual analog scale (VAS) between best and worst imaginable health (0-100).¹³ We used the Danish validated version for the study.

Barthel ADL describes the participants' function within ten items of ADL. The total score ranges from 0-20, a high score indicates high level of independence.¹⁴ A validated Danish translation was used in the study.¹⁵

Lawton-Brody IADL measures more complex activities necessary for living an independent life in one's own housing and consists of eight domains for women and five domains for men. Scores range from 0-8 for women and 0-5 for men; the higher scores the better function.¹⁶ A Danish version was used.¹⁷

The FAS describes the participant's level of fatigue by ten statements reflecting physical and mental fatigue.¹⁸ Each question is answered with scores 1-5 indicating how often the statement occurs. Total score ranges from 10-50, scores of 22 or higher indicate fatigue, and scores above 34 indicate extreme fatigue.¹⁹ A Danish validated version was used in this study.

CFS is a nine-level scale indicating the level of frailty. Based on the overall functional status and the medical history of the patient, the interviewer places the participant in one of nine categories: very fit, well, managing well, vulnerable, mildly frail, moderately frail, severely frail, very severely frail and terminally ill (scores 1-9).²⁰ Scores of 5 and above indicates frailty.²¹⁻²³ A case-based validated Danish translation of version 1.2 was used.²⁴

Furthermore, baseline characteristics, days on ventilator, use of vasopressors and renal replacement therapy, ICU and hospital Length of Stay were obtained from the Danish ICU COVID-19 database.

Statistics

No sample size calculation was performed because of the descriptive and hypothesis-generating nature of the study. Data was described with mean and standard deviation (SD) for normally distributed data and median and interquartile range (IQR) for nonparametric data, or proportions if relevant. A p-value less than 0.05 was considered statistically significant. Confidence intervals of the proportion were calculated using the binomial proportion. For correlation analysis, we used

the Pearson correlation analyses for normally distributed data measured on continuous scales. The Spearman rank order correlation was applied for ordinal data and nonparametric distributed data. The association between outcomes and predictive variables was performed by linear regression. Statistical analyses were made in R, version 3.6.3., *Vienna, Austria*.

Results

Twenty-nine Danish ICUs registered data on 326 patients in the Danish ICU COVID-19 database ⁴.

Two-hundred-four patients were alive 6 months after ICU admission, corresponding to a mortality of 37%. At 12 months follow-up the mortality rate was 38%.

Twenty-three ICUs had surviving patients at 6-month follow-up. Twenty-one ICUs granted permission to contact patients regarding the follow-up. One-hundred-eighty-nine patients received an invitation at 6 months, of whom 105 participated in the 6-month follow-up interview, and 95 participated in the 12-month follow-up interview. In total, 110 patients participated in one of the two follow-up interviews, among whom 90 participated in both (Figure 1). Patients from all five Danish regions participated (Table 1).

Baseline characteristics for the interviewed vs. non-interviewed participants were generally similar, except for the median age being higher for the interviewed participants (67 vs. 62 years). The proportion of participants needing mechanical ventilation was similar in the two populations (80% vs. 77%). However, the non-interviewed participants had a longer time on the ventilator (11.5 vs. 9.5 days) and they tended to have a higher use of dialysis treatment (18% vs. 14%). (Table 1)

The cognitive function measured by MiniMoCA had a median score of 13 (IQR 10-14) at 6 months and 13 (IQR 11-14) at 12 months. (Table 2) Twenty-six percent (n=27) had cognitive scores indicating impaired cognitive function (MiniMoCA <11) at 6 months, and 17% (n=16) at 12 months. (Appendix 2) Two participants could not cooperate to the investigation at the 6- and 12-months interviews due to impaired hearing.

Pearson correlation analysis showed a low correlation between cognitive function and time on ventilator at 6 and 12 months ($p = -0.03$ and -0.06 , respectively). In multiple linear regression analysis, we found no association between cognitive function and time on ventilator. (Appendix 5)

The participants presented a clinical frailty median score of 3 (IQR 3-4) at both 6- and 12-months interviews. (Table 2) Twenty percent (n=21) were scored as frail (>4) at 6 months, and 18% (n=17) at 12 months. (Appendix 3) The Pearson correlation analysis showed a low correlation between

CFS and time on ventilator at both 6 and 12 months ($p=0.28$ and 0.17 , respectively). We found a significant association between CFS and ventilator time in the multiple linear regression analysis at 6 months. (Figure 2) However, this association was not found at 12-months follow-up. (Appendix 5)

According to the EQ-5D-5L, the participants generally presented a high HRQoL in all five domains. (Appendix 4) The median for self-reported EQ-VAS was 70 (IQR 50-80) at 6 months, and 70 (IQR 51-80) at 12 months. (Table 2) EQ-VAS was reported below 50 by 28% ($n=29$) at 6 months and by 25% ($n=24$) at 12 months.

Generally, the participants had high scores in Barthel ADL and in Lawton-Brody IADL questionnaires, indicating the highest level of independence at both 6 and 12 months. Median score for Barthel ADL was 20 (IQR 20-20) at 6 and 12 months. (Table 2) Lawton-Brody IADL scores were reported gender specific, and with median 8 (IQR 7-8) and 5 (IQR 4-5) for females and males, respectively, at both 6 and 12 months. (Table 2)

At 6 months, 52% ($n=47$) of the participants had FAS scores indicating fatigue. Median score was 24 (IQR 14-37). At 12 months 47% ($n=45$) scored as fatigue, and median score was 23 (IQR 15-33). (Table 2) Younger participants reported fatigue more frequently. (Figure 3) Spearman correlation analysis showed a moderate correlation between age and FAS at 6 months ($p = -0.32$) and at 12 months ($p = -0.23$). We found no significant difference between gender. (Appendix 6)

Discussion

We present the results of a nationwide, population-based follow-up study of Danish ICU patients with COVID-19. At 6 and 12 months after ICU admission, the survivors showed cognitive impairments at both follow-up time points, frailty in about one-fifth of participants at both time-points. Participants presented a high level of independence and HRQoL at both time points. Nearly half the participants reported fatigue at both 6 and 12 months after their illness.

More than one in three of Danish COVID-19 patients admitted to ICU treatment had died within one year. Similar mortality has been reported in other and larger COVID-19 ICU populations.^{25,26} Furthermore, the mortality for unselected ICU populations,²⁷ and particularly for mechanically ventilated patients with ARDS, is within the same range.²⁸

One in four of the participants had cognitive impairments 6 months after ICU admission, and one in six at 12-month follow-up. Similar studies using MiniMoCA have found a higher prevalence of cognitive impairments. A Belgian follow-up study, found that 47% of COVID-19 ICU survivors had cognitive impairments, this was however estimated at 3 months.²⁹

Karnatovskaia et al found an association between time on ventilator and cognitive impairment,¹⁰ which we could not confirm. Generally, a challenge of ICU follow-up studies is that the pre-admission cognitive and functional status is rarely known. Consequently, we do not know if the presented impairments are related to the COVID-19 critical illness or not.

Twenty percent of the participants were scored frail at 6 months, and 18% at 12 months. Previous studies have reported a high association between frailty and 30-day mortality.^{22,27} Since we do not have pre-admission frailty status, there is a risk of the frailest patients dying within the first 6 months after ICU admission. Thus, our data might be biased showing less frailty than could be the case at an earlier time point. At 6 months we found that the longer time on the ventilator was associated with increased frailty. We could not retrieve these findings significant at 12 months. As we have relatively few patients in our study, these findings should be interpreted with caution. Additionally, causality is challenged because we do not have the pre-admission frailty status of the patients.

The participants reported high scores for ADL and IADL indicating the highest level of independency. This is dissimilar to other studies that have found a decline in ADL and IADL post-ICU, both short- and long-term.^{30,31} It is interesting that the physical functional status was overall good, especially when we consider that 26% have cognitive impairments and 20% are frail at 6 months. This might suggest that MiniMoCA and CFS are more sensitive tools in the follow-up context. The questions in ADL and IADL questionnaires are subjective, whereas the MiniMoCA is a more objective measure, and the CFS is an investigator-operated scale, synthesizing the information gathered during the interview. Another aspect is that 70% of our population is male, and as the Lawton-Brody IADL discriminates between genders and does not score the male's performance in the domains: laundry, food preparation, and housekeeping, some information regarding advanced skills is lost.

A major reported consequence after COVID-19 is short and long-term fatigue.³² We found that approximately 50% of the participants reported fatigue at 6- and 12-months follow-up. Our findings are in accordance with other COVID-19 follow-up studies investigating ICU and ward patients^{33–36}, which suggests that COVID-19 is associated with excessive fatigue. Unlike our study, a previous study found more females reporting fatigue than males.³⁷ We found a higher proportion of fatigue among the younger patients, and these findings are in accordance with a previous study of a mixed, non-COVID ICU population.³⁷ One explanation for this could be the different pre-admission status for participants of different ages. The older patient might have a lower pre-admission functional status than the younger patient and might even have experienced some degrees of fatigue prior to the critical illness. The younger participants may also still have an energy-consuming job, and the expectations of normal living might be higher than for the retired participants. A Dutch study investigated the ability to return to work after ICU treatment of COVID-19 and found 58% reported problems 1 year after.³⁶ Unfortunately, we do not have data on the resumption of work.

Overall, we found no major improvements in the functional status of the participants between 6- and 12- month follow-up. One explanation could be the participant's ICU length of stay. Studies

have shown that critical illness, ICU treatment, and long hospital stays leave the patients in a frailer state³⁸, which might impact the recovery time. As COVID-19 survivors have a very long ICU length of stay,^{3,4} it could be expected that their recovery in cognitive and functional domains will be a long process.

Follow-up studies rarely include all participants, and a concern in general is that non-responders could be either more or less impaired than the responders. Despite our efforts, 66 patients never responded to the invitation to join the follow-up study, and we do not know why. A Danish study exploring the characteristics of non-responders in a follow-up program after intensive care found the non-responders to have a higher age, a longer length of ICU stay, and more likely to be living alone.³⁹ Except for differences in time in ventilator and renal replacement treatment, general baseline characteristics in our study were similar between the interviewed vs. not interviewed participants. We did not find a relevant difference in age nor length of ICU stay between interviewed and non-interviewed. Unfortunately, we do not know the civil status of the participants and cannot explore this issue further.

This study represents the long-term impairments after COVID-19 during the first wave. Since therapeutic strategies have changed during the different waves of the pandemic, further studies are needed to investigate and compare the long-term impairments in COVID-19 patients from other waves, to reveal the long-term effects of the different treatments.

The strengths of our study are the broad representation of participants from all five Danish regions. Also, the baseline characteristics of the interviewed vs. non-interviewed are similar. Both indicate that this study might be representative of the total Danish COVID-ICU population. Furthermore, we have data from two time points making it possible to explore the dynamics in status over time. Another strength is that the same interviewer (SW) carried out all the interviews, which minimizes the interrater variability of the data.

This study has several limitations. Firstly, we have a relatively small sample size, which weakens our results. However, we invited the majority of patients who were still alive from the database.

Secondly, the proportion of lost-to-follow-up is relatively large for this study and it increases the risk of attrition bias. Finally, the lack of information on pre-admission cognitive and functional status for the participants is a limitation.

Conclusions

In this follow-up study of all Danish ICU patients with COVID 19 in the initial phase of the pandemic, we found cognitive impairments in 26% and 17%, at 6- and 12- months respectively. We found frailty in 20% and 18% of the participants, at 6- and 12- months, respectively. There was an association between time on ventilator and frailty at the 6-month follow-up. Furthermore, fatigue was a challenge for approximately 50% the survivors at both time points, especially in the younger participants. Based on retrospectively registered data in the Danish ICU COVID-19 database, no information on pre-admission cognitive and functional status on patients is available. In accordance with our data, there seem to be no changes in the impairments between 6- and 12-months follow-up.

1.06.2022

1.11.1

Funding

None

Conflict of interest

None of the authors declared any conflicts of interest.

Accepted Article

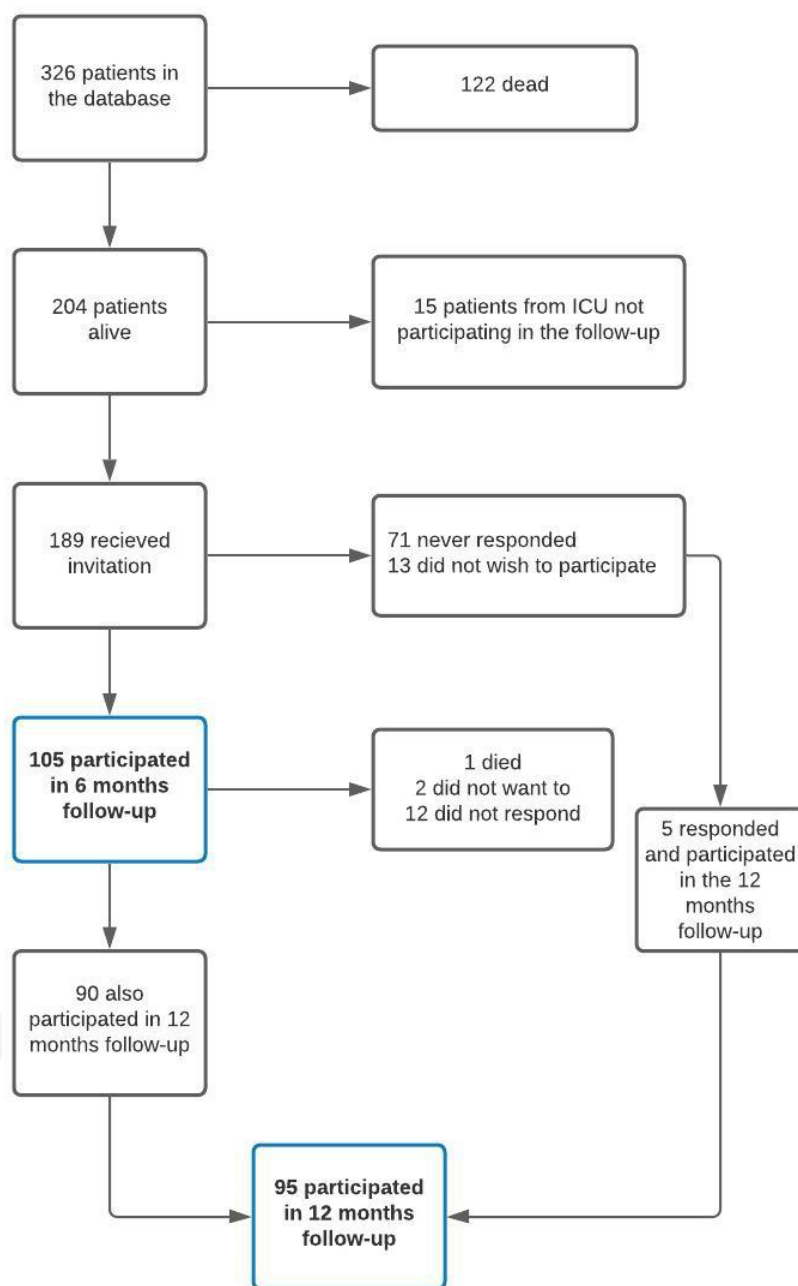
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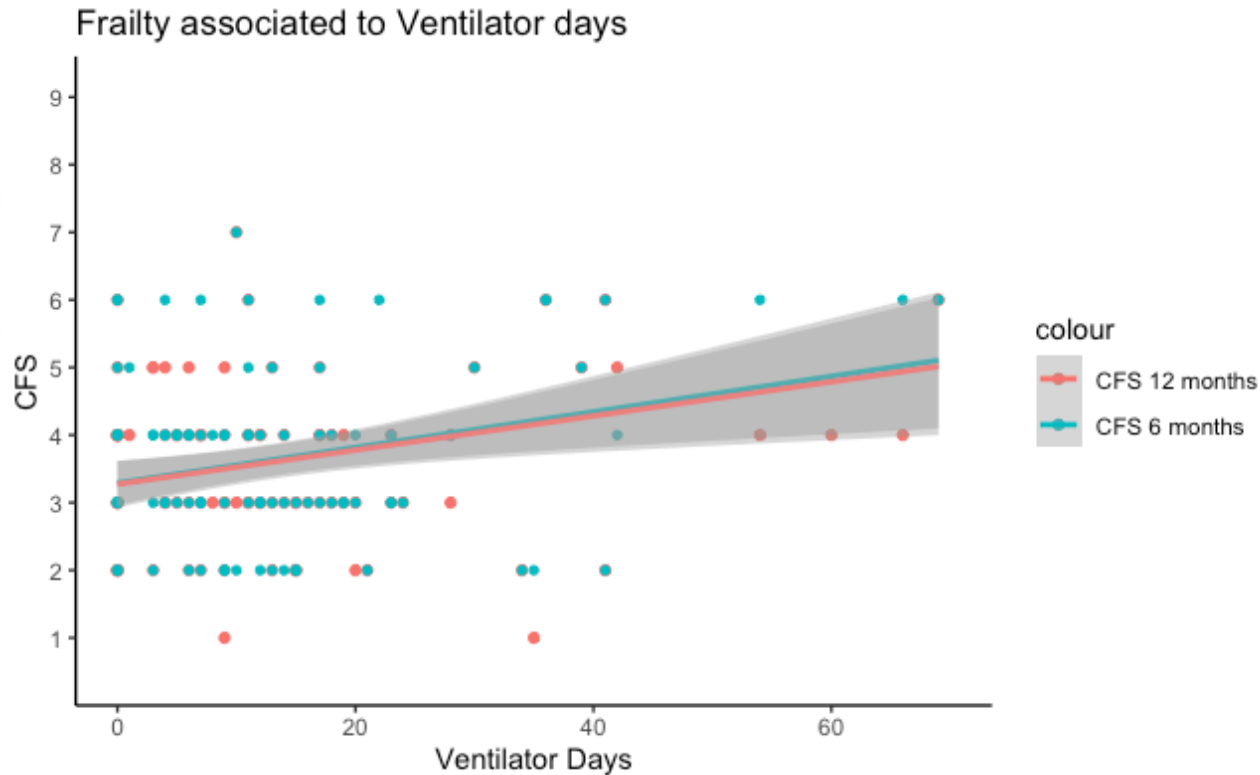
Figure 1



Legend

Participant flow diagram

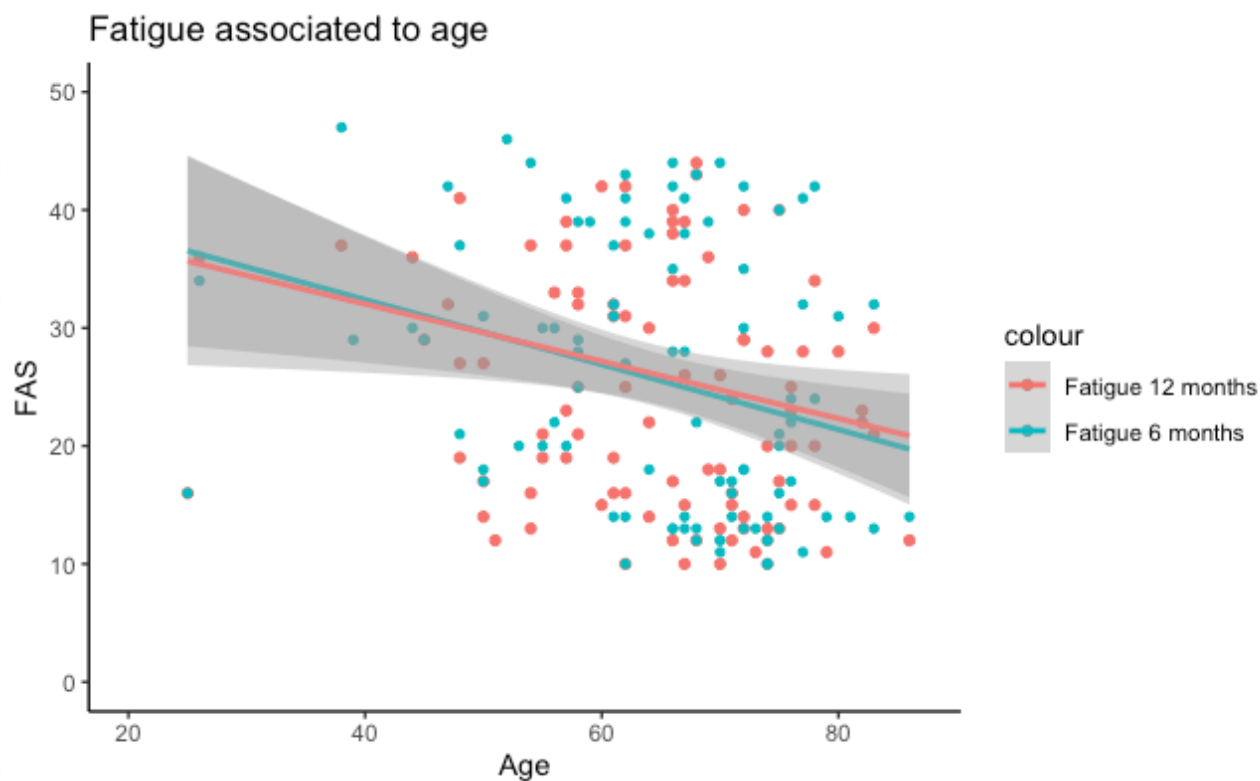
Figure 2



Legend

Ventilator days and Clinical Frailty Score (CFS) analysed in a linear regression model with 95% confidence intervals. Multiple linear regression analysis showed a significant association between frailty and ventilator days ($P=0.02$) at 6 months, but not at 12 months ($P=0.12$).

Figure 3



Legend

Age and Fatigue Assessment Scale analysed in a linear regression model with 95% confidence intervals. Multiple regression analysis showed that fatigue was negatively associated with age ($P=0.006$) at 6 months and at 12 months ($P=0.05$).

Table 1. Characteristics

	Interviewed n = 110	Not interviewed n = 94
Age, median (range)	67 (25 – 86)	62 (23 – 90)
Male, n (%)	77 (70%)	64 (68%)
Invasive mechanical ventilation, n (%)	88 (80%)	72 (77%)
Ventilator days median (IQR)	9.5 (4 – 17)	11.5 (3.3 – 18)
Renal replacement therapy, n (%)	15 (14%)	17 (18%)
ICU length of stay – days, median (IQR)	13.5 (8 – 21)	14 (7.3 – 23)
Comorbidity (any), n (%)	73 (66%)	59 (63%)
Hypertension	54 (49%)	41 (44%)
Ischaemic heart disease	13 (12%)	11 (12%)
Heart failure	3 (3%)	4 (4%)
Chronic pulmonary disease	16 (15%)	14 (15%)
Chronic kidney disease	13 (12%)	5 (5%)
Liver cirrhosis	0	0
Diabetes	22 (20%)	17 (18%)
Active cancer	2 (2%)	3 (3%)
Haematological malignancy	4 (4%)	2 (2%)
Immunosuppressed	8 (7%)	8 (9%)
Region, n		
Capital region	39	41
Zealand region	21	4
Northern region	10	10
Central region	25	17
Southern region	15	22

Table 2. Outcomes

	6 months (Median (IQR)) 105 participants	12 months (Median (IQR)) 95 participants
MiniMoCA	13 (10 – 14)	13 (11 – 14)
Clinical Frailty Score	3 (3 – 4)	3 (3 – 4)
EQ-5D-5L		
Q1 (Mobility)	1 (1-2)	1 (1 – 2)
Q2 (Self-care)	1 (1-1)	1 (1 – 1)
Q3 (Usual activities)	1 (1-2)	1 (1 – 2)
Q4 (Pain/Discomfort)	2 (1-3)	1 (1 – 2)
Q5 (Anxiety/Depression)	1 (1-2)	1 (1 – 1)
EQ-VAS	70 (50-80)	70 (51 – 80)
Barthel ADL	20 (20-20)	20 (20 – 20)
Lawton-Brody IADL		
Female	8 (7-8)	8 (7 – 8)
Male	5 (4-5)	5 (4 – 5)
Fatigue Assessment Scale	24 (14-37)	23 (15 – 33)

Legend

Abbreviations: The Mini Montreal Cognitive Assessment (MiniMoCA), Clinical Frailty Score (CFS), the Barthel Activities of Daily Living (Barthel ADL), the Lawton-Brody Instrumental Activities of Daily Living (IADL), the Fatigue Assessment Scale (FAS).