− Main Text −

Background

Headlines about COVID-19 are dominated by risk of death, restrictions from new variants, novel therapeutics, and associated politics. However, less publicised are the long-term effects of COVID-19 for people up to two years from the start of Wave 1. Long-COVID is becoming better defined with national guidance based on limited evidence indicating a myriad of symptoms including physical and psychological sequalae (1). Although the physical health outcomes after COVID-19 have been explored, mental health outcomes have received less attention (2).

Risk factors for poor physical health outcomes include older age, multimorbidity, and living with frailty (3). It is unclear if the same risk factors may contribute to poor mental health outcomes. A recent systematic review published in the Journal of Affective Disorders by our group identified only weak evidence that COVID-19 survivors were at increased risk of psychiatric morbidity including anxiety, depression and post-traumatic stress disorder (4). However, the included studies rarely examined risk factors for poor outcome, and no studies investigated the effect of living with frailty. Frailty is a state of progressive physical and cognitive vulnerability where people are more likely to experience worse outcomes from an inflammatory insult such as illness or injury. Living with frailty increased the risk of death from the COVID-19 and was determined to be as important as age in the survival in from the first wave (3). Frailty also can predispose individuals to specific hospital presentations such as delirium (5). Effects may be direct (e.g., from the virus) and indirect (e.g. lockdowns, isolation, or unemployment). For those living with frailty, additional indirect effects may include deconditioning through home-based restriction orders, loneliness having been cut-off from community and family, and worse access to health services. Identifying the effect of the virus on mental health for those living with frailty can assist with developing clinical, social and economic responses. We aimed to explore the effect of frailty on mental health outcomes for survivors of COVID-19.

Methods

Study design

We undertook an observational cross-sectional study of patients admitted to hospital with COVID-19 in Wave 1 of the pandemic. Patients were contacted around one year after their hospital admission. We examined the effect of frailty on a spectrum of common mental health symptoms, specifically those of generalised anxiety, depression and trauma, as well as quality of life.

Setting

Patients were recruited from eight centres - seven were in the United Kingdom (Aberdeen Royal Infirmary, University Hospital of Wales in Cardiff, Ysbyty Ystrad Fawr in Caerphilly, Royal Gwent Hospital in Newport, Nevill Hall Hospital in Abergavenny, Southmead Hospital in Bristol, and Salford Royal Infirmary), and one in Italy (University Hospital of Modena Policlinico). The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human subjects/patients were approved in the United Kingdom by the Health Research Authority (20/LO/1236), and in Italy by the Ethics Committee of Policlinico Hospital Modena (Reference 369/2020/OSS/AOUMO). This manuscript follows the STROBE statement for reporting of cohort studies(17).

Participants

Eligible patients were identified from data held at each host site. Eligible participants were 18 years old or over and had been admitted to hospital as an emergency with a diagnosis of COVID-19 between 27th February 2020 and 6th June 2020. Patients were excluded if they had died during their hospital admission or after discharge.

Eligible patients were invited to participate in this study by postal letter. One week after letters were sent, participants were contacted by telephone to confirm receipt of the letter and enquire about their willingness to participate. If the letter had not yet been read, a further phone call was arranged. A data collection telephone call was arranged if the person agreed to participate. Verbal consent was taken over the phone at the start of the data collection phone call. A consultee was sought to provide assent for participants who lacked capacity to consent to participate. A friend, relative or carer was asked to assist with completion of the assessment scores for those who were unable to provide self-assessment scores.

Primary and Secondary Outcomes

The primary outcome the effect of frailty on participant-rated anxiety symptoms. Secondary outcomes included participant-rated: i) depressive symptoms; ii) trauma symptoms i.e., stress responses related to a traumatic event; iii) quality of life.

Variables

The primary outcome was participant-rated moderate/severe anxiety symptoms using the Generalised Anxiety Disorder-7 (GAD-7) with a cut-off score of ≥10 (Spitzer RL, et al; 2006). Secondary outcomes included: i) moderate/severe depressive symptoms measured by

participant-rated Patient Health Questionnaire-9 (PHQ-9) with a cut-off score of ≥10 (Kroenke K, et al 2001); ii) clinically significant trauma symptoms measured by a Trauma Screening Questionnaire (TSQ) with a cut-off score ≥6; iii) quality of life measured by ICEpop CAPability measure for Older people (ICECAP-O) score and the MRC Quality of Life.

Additional variables collected included demographics (age, sex) and physical comorbidities. Frailty was measured using the Clinical Frailty Scale (CFS) which is a judgment-based frailty tool assessed by a trained clinician based on participant's function two weeks prior to clinical presentation. It has been widely used throughout the pandemic and in other non-COVID settings. The CFS is scored using an ordinal hierarchical scale that numerically ranks frailty from 1 to 9. Version 2.0 of the CFS, updated in 2020, was used in this study with a score of 1 being very fit, 2 fit, 3 managing well, 4 living with very mild frailty, 5 living with mildly frailty, 6 living with moderate frailty, 7 living with severe frailty, 8 living with very severe frailty, and 9 terminally ill but not otherwise severely frail (6). CFS was categorized as: living without frailty (CFS 1-3), mild frailty (CFS 4-5), moderate to severe frailty (CFS 6-8). CFS 9 was not included given the definition of terminally ill may have other implications for mental health outcomes (Supplementary Table 1) (6).

Sample size justification

For the primary outcome of anxiety symptoms, we anticipated double the number of cases of moderate anxiety symptoms in those who were living with frailty (30%), compared to those without frailty (15%) (7)(8). We calculated a requirement of 242 patients to be followed up to detect this difference, with 80% power, and with a 5% significance level.

Data Sources

Data were collected from the index hospital admission using a combination of electronic and paper health records entered onto a standardised case reporting form. Follow-up data from nine months post admission were collected from the participants and entered directly into a case reporting form. All study personnel completed specific data collection training. Frailty scoring was standardised by mandatory completion of an open-access online training resource (18). The assessment of frailty was undertaken using question prompts available on a frailty app – the Acute Frailty Network Clinical Frailty Scale App (9). Each site uploaded data onto an infermed MACRO database housed within King's College London. The follow-up data were additionally uploaded by each site under the direction of the local site lead. User access control was maintained by King's Clinical Trials Unit (KCTU).

Data Analysis

Descriptive data for patients with no, mild, and moderate/severe anxiety were presented against the demographic and clinical characteristics during hospitalisation.

The primary outcome was moderate/severe anxiety at one year after admission. Patients were coded as none/mild anxiety (GAD-7 <10) versus moderately/severe anxiety (GAD-7 ≥10). Moderate/severe anxiety was analysed using a multilevel mixed-effects logistic regression, fitting a random effect to account for heterogeneity across hospital sites. Fixed effects were included to adjust for age group (<65, 65-79, ≥80 years old), sex (male, female), smoking status (never, ex-smoker, current smoker), diabetes (yes, no), coronary artery disease (yes, no), renal failure (eGFR ≥60, eGFR ≤60 ml/min/1.73m^2), disease severity using CRP (≥40 mg/L) (10), and frailty (CFS 1-3, 4-5, 6-8).

The secondary outcome of depression (PHQ-9) was analysed in a similar way to the primary outcome using a mixed-effects logistic regression. The secondary outcomes of trauma (TSQ), and quality of life (ICECAP-O, MRC QoL) were analysed using a mixed-effects linear regression adjusted for the same fixed effects as shown within the primary outcome analysis.

All analyses were converted to standardised effect sizes with 95%CI to compare the clinical importance of the findings. Analyses was carried out using Stata version 16.

Results

Participants

Of the 244 patients contacted, we consented 224 participants into the study. The median age was 65 years old (IQR 55-74, range 32-91). Two thirds (n=146, 65%) were male and a third female (n=78, 35%) (Table 1). The sample was predominately white (91.1%). The majority had never smoked (56.3%) or were ex-smokers (39.3%). The most common comorbidities were hypertension (46.4%), diabetes (22.3%), chronic kidney disease (19.6%), coronary artery disease (16.1%), and congestive cardiac failure (3.1%). Almost half (43.8%) of participants were classified as living with frailty (CFS 4-8). No patients were reported with CFS=9.

There were 25 participants (16.6%) with moderate/severe anxiety. Of those without frailty 9.9% experienced this, compared to 14.3% of those living with severe frailty (Table 1). One fifth (n=43, 19.2%) exhibited moderate/severe depressive symptoms (Supplementary Table 1). Of the 151 participants without frailty 13.2% (n=20) had moderate/severe depression compared to 21.4% (n=21/98) of those living with frailty. The mean ICE-CAP O (quality of life) score was for those without frailty 17.02 (SD 3.03), living with mild frailty 14.41 (SD

3.41), and for severe frailty 13.62 (SD 4.01). A similar pattern was seen in the MRC Quality of Life measure and Trauma Screening Questionnaire.

Primary Outcome Generalised Anxiety (GAD-7)

There was an association between frailty and anxiety for participants living with mild frailty (aOR=5.72, 95%CI 1.71-19.13, p=0.005) and severe frailty (aOR=6.73, 95%CI 1.64-27.7, p=0.008) compared to no frailty (Table 2). The effect of living with frailty is consistent with a small standardised effect size (SES) for CFS 4-5 and 6-8 on GAD-7 (SES=0.19 and SES=0.18, Figure 1). Similar findings were found in the unadjusted analysis between frailty and anxiety.

Secondary Outcomes

There was an association between frailty and depression for those living with mild frailty (aOR=4.87, 95%CI 1.59-14.91, p=0.006, SES=0.19), and severe frailty (aOR=5.20, 95%CI 1.32-20.48, p=0.02, SES=0.16) compared to no frailty. There was also an association between frailty and both measures of quality of life. For the MRC Quality of Life measure, the adjusted Mean Difference (aMD) between those without frailty and with mild frailty was 1.06 (95%CI 0.76 to 1.36, p<0.0001, SES=0.46, Table 4) and for those living with severe frailty (compared to not living with frailty) was 1.35 (95%CI 0.90 to 1.80, SES=0.40, p<0.0001). For the ICE-CAP O there was a reduction in quality of life for those living with mild frailty (aMD=2.04, 95%CI 1.09 to 2.98, SES=0.28, p<0.0001, Table 5), and severe frailty (aMD=4.61, 95%CI 3.27 to 5.94, SES=0.45, p<0.0001) compared to not living with frailty. There was also an association between trauma and frailty, for those living with mild frailty (aMD=1.16, 95%CI 0.47 to 1.85, SES=0.22, p=0.001) and severe frailty (aMD=2.13, 95%CI 0.53 to 2.50, SES=0.20, p=0.003).

Discussion

This is the first study to explore the effect of frailty on mental health outcomes after surviving COVID-19. The results indicate that frailty is associated with a significant level of mental health illness including moderate anxiety, moderate depression, post-traumatic stress, and a reduction in quality of life.

This study's findings of the effect of frailty on mental health outcomes are contrary to a recently published systematic review by our group, and published in the Journal of Affective Disorders examining COVID-19 survivors and the direct effect of the virus on common psychiatric symptoms (4). This showed a minimal to mild effect of COVID-19 infection on anxiety, depression, post-traumatic stress, and poor sleep. However importantly, frailty was

not examined in the review's included studies to be able to draw any conclusions. Future research into the long-term effects of COVID-19 should include psychiatric assessments, and consider frailty as a significant risk factor for poor outcomes. Interventional studies should ensure that people living with frailty are recruited as they may represent both the at-risk group and have the most to gain from treatment.

Psychological frailty is defined as experiencing mood disorders and emotional loneliness. The concept of frailty as a psychological condition is not well researched; mostly the focus is on physical frailty. Psychological frailty may result in decreased cognitive or mood resilience in the presence of life stressors which could lead to negative health outcomes in a similar fashion to the impact of illness on the trajectory of physical frailty. Frailty and loneliness are linked, with each state likely worsening the other (11,12). With worse mental health post COVID-19 infection we could anticipate a spiral of deteriorating physical and psychological health may occur. Future studies should look at the long-term trajectory and interaction of frailty, mental health outcomes, and mortality.

This study is unable to explain the causation of worse mental health and frailty. Studies examining non-COVID-19 populations have established a link between the two, and have acknowledged the possible bi-directional effect (13). This has been further recognised by the Royal College of Psychiatrist's report on frailty and outcomes for older people (14). The RCP also highlighted that current approaches in assessing frailty, through comprehensive geriatric assessment, often do not focus on mental health aspects. Our study provides useful evidence to ensure approaches to assess frailty should include mental health.

Interventions to reverse the effect in either direction are not yet clear. The best evidence for frailty modification in the community is through exercise and protein supplementation (15). These same treatments may also improve mental wellbeing. However, multicomponent interventions rather than single treatments are most likely to be beneficial given often multiple homeostatic systems involved and affected by frailty (16).

From a national perspective the WHO Mental Health Gap Action Programme has already identified that improvements in mental health services should be a joint responsibility between governments, health professionals, civil society, communities, and families (17). This firmly places the emphasis on whole-system approaches to enhancing mental health, with frailty also benefit from this encompassing approach. To action this systematic identification frailty tools should be embedded into routine clinical assessment as well as case finding through automatically generated electronic frailty scores.

Our results have implications for clinical practice. We suggest that people living with frailty after surviving COVID-19 should receive a mental health assessment and tailored support. The tools used within this study are well validated and are accessible and already widely used in routine clinical practice. Patients and carers should be made aware of this association of frailty and the risk of poor mental health to proactively access services if health deteriorates. The population within this study were all hospitalised, which may provide opportunity both for information provision on discharge from hospital, as well as provide an easily identifiable group for follow-up services.

Strengths and Limitations

A major limitation of our study is that mental health status was not measured at the index hospitalisation due to COVID-19, or a lack of a non-COVID comparator group to demonstrate if the mental health deterioration is due to the direct effect or the indirect effects of the virus. Indirect effects, such as social isolation through lockdowns, worse access to health services, or financial insecurity, may be more prominent in those living with frailty.

The tools we used in the study assessed for patient-rated symptoms rather than formal mental health diagnoses limiting the definitive prevalence of these issues. In addition we used a frailty tool that has not been extensively validated in the under-65 year old population (18). However, this study adds to the literature indicating that a consistent effect of frailty exists in younger people as well as older people. Strengths of the study are the range of common mental health diagnoses examined using well established community-based tools. This allows the results of the study to be directly applied to established frailty, mental health, and community-based services.

Summary

This study has demonstrated that living with frailty is associated with both psychiatric illness and a significant reduction in well-being one year after hospital admission due to COVID-19. These data provide opportunity for patients, families, carers, and health services to proactively identify deteriorating mental health in the year after hospital discharge from COVID-19.

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Declarations

Declarations of Interest

No authors have any declarations of interest

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Author Contributions

JH and BC conceived the study. BC and RS completed the analysis. All the authors were involved in the design of the study, interpretation of the data, drafting and reviewing the final manuscript.

Data Availability

The data is available on receipt of a statistical analysis plan that is approved by the study management group which is addressing a scientific and new research question.

Table 1 Population Characteristics

	Generalized Anxiety symptoms (GAD-7)			
	None (n=148)	**Mild (n=51)**	**Moderate or severe (n=25)**	**Total (n=224)**
Age				
<65	71 (65.1)	25 (22.9)	13 (11.9)	109 (48.7)
65-79	58 (67.4)	19 (22.1)	9 (10.5)	86 (38.4)
≥80	19 (65.5)	7 (24.1)	3 (10.3)	29 (12.9)
Sex				
Female	40 (51.3)	22 (28.2)	16 (20.5)	78 (34.8)
Male	108 (74.0)	29 (19.9)	9 (6.2)	146 (65.2)
Ethnicity				
White	140 (68.6)	44 (21.6)	20 (9.8)	204 (91.1)
Asian/Black	4 (66.7)	1 (16.7)	1 (16.7)	6 (2.7)
Missing	4	6	4	14 (6.3)
Smoking Status				
Never smokers	91 (71.1)	23 (19.0)	12 (9.9)	126 (54.0)
Ex-smokers	54 (61.4)	24 (27.3)	10 (11.4)	88 (39.3)
Current smokers	3 (30.0)	4 (40.0)	3 (30.0)	10 (4.5)
Missing	5	0	0	5 (2.2)
Diabetes				
No	122 (70.1)	34 (19.5)	18 (10.3)	174 (77.7)
Yes	26 (52.0)	17 (34.0)	7 (14.0)	50 (22.3)
Coronary artery disease (CAD)				
No	122 (64.9)	45 (23.9)	21 (11.2)	188 (83.9)
Yes	26 (72.2)	6 (16.7)	4 (11.1)	36 (16.1)
Hypertension				
No	67 (67.7)	21 (21.2)	11 (11.1)	99 (44.2)
Yes	14 (66.7)	3 (14.3)	4 (19.0)	21 (9.4)
Yes on treatment	67 (64.4)	27 (26.0)	10 (9.6)	104 (46.4)
Chronic Heart Failure (CHF)				
No	134 (66.0)	47 (23.2)	203 (10.8)	203 (90.6)
Yes	5 (71.4)	2 (28.6)		7 (3.1)
Missing	9	2	3	14 (6.3)
Reduced renal function (eGFR)				
≥60	115 (68.0)	40 (23.7)	14 (8.3)	169 (75.4)
<60	26 (59.1)	10 (22.7)	8 (18.2)	44 (19.6)
missing	7	1	3	11 (4.9)
Creative Reactive Protein (CRP)				
<40	49 (69.0)	16 (22.5)	6 (8.5)	71 (31.7)
≥40	99 (64.7)	35 (22.9)	19 (12.4)	153 (68.3)
Clinical Frailty Scale (CFS)				
CFS 1-3	97 (77.0)	23 (18.3)	6 (4.8)	126 (56.3)
CFS 4-5	41 (59.4)	16 (23.2)	12 (17.4)	69 (30.8)
CFS 6-8	10 (34.5)	12 (41.4)	7 (24.1)	29 (12.9)

Table 2: The association between clinical characteristics at hospital admission and one year moderate/severe anxiety, crude odds ratio (OR) and adjusted ORs (aOR) are presented with associated p-values

	Crude Odds Ratio (OR)		Adjusted OR (aOR)	
	OR (95%CI)	**p-value**	**aOR (95%CI)**	**p-value**
Age				
<65	Reference		Reference	
65-79	0.73 (0.28-1.90)	0.52	0.39 (0.12-1.29)	0.12
≥80	0.56 (0.13-2.45)	0.44	0.21 (0.04-1.10)	0.06
Sex				
Female	Reference		Reference	
Male	0.26 (0.11-0.64)	0.003	0.29 (0.11-0.76)	0.01
Smoking				
Never smokers	Reference		Reference	
Ex-smokers	1.10 (0.44-2.76)	0.83	0.95 (0.33-2.74)	0.93
Current smokers	3.94 (0.87-17.94)	0.08	1.58 (0.27-9.27)	0.62
Diabetes				
No	Reference		Reference	
Yes	1.20 (0.44-3.26)	0.72	0.70 (0.22-2.16)	0.53
CAD				
No	Reference		Reference	
Yes	0.84 (0.26-2.72)	0.77	0.94 (0.24-3.66)	0.93
eGFR				
≥60	Reference		Reference	
<60	1.89 (0.71-5.01)	0.20	2.11 (0.64-6.95)	0.22
CRP				
<40	Reference		Reference	
≥40	1.72 (0.63-4.69)	0.29	1.68 (0.59-4.84)	0.33
CFS				
CFS 1 - 3	Reference		Reference	
CFS 4 - 5	4.21 (1.50-11.79)	0.006	5.72 (1.71-19.13)	0.005
CFS 6 - 8	6.36 (1.95-20.74)	0.002	6.73 (1.64-27.71)	0.008

Table 3: The association between clinical characteristics and one year moderate depression, crude odds ratio (OR) and adjusted ORs (aOR) are presented with associated p-values

	Crude Odds Ratio (OR)		Adjusted OR (aOR)	
	OR (95%CI)	**p-value**	**aOR (95%CI)**	**p-value**
Age				
<65	Reference		Reference	
65-79	0.44 (0.18-1.07)	0.07	0.17 (0.05-0.57)	0.004
≥80	0.41 (0.12-1.33)	0.14	0.15 (0.03-0.66)	0.01
Sex				
Female	Reference		Reference	
Male	0.43 (0.20-0.92)	0.03	0.51 (0.22-1.19)	0.12
Smoking				
Never smokers	Reference		Reference	
Ex smokers	1.02 (0.46-2.25)	0.96	1.20 (0.48-2.99)	0.70
Current smokers	2.69 (0.58-12.59)	0.21	1.22 (0.20-7.34)	0.83
Diabetes				
No	Reference		Reference	
Yes	1.37 (0.60-3.14)	0.46	1.29 (0.48-3.43)	0.62
CAD				
No	Reference		Reference	
Yes	0.74 (0.28-1.90)	0.53	0.95 (0.30-3.00)	0.93
eGFR				
≥60	Reference		Reference	
<60	1.41 (0.61-3.30)	0.42	1.69 (0.60-4.76)	0.32
CRP				
<40	Reference		Reference	
≥40	1.78 (0.76-4.17)	0.19	1.41 (0.57-3.48)	0.45
CFS				
CFS 1 - 3	Reference		Reference	
CFS 4 - 5	2.52 (1.03-6.14)	0.04	4.87 (1.59-14.91)	0.006
CFS 6 - 8	3.81 (1.25-11.57)	0.02	5.20 (1.32-20.48)	0.02

Table 4: The association between clinical characteristics and one year trauma screening, crude mean difference (MD) and adjusted MD (aMD) are presented with associated p-values

	Crude Mean Difference (MD)		Adjusted MD (aMD)	
	MD (95%CI)	**p-value**	**aMD (95%CI)**	**p-value**
Age				
<65	Reference		Reference	
65-79	-0.84 (-1.46, -0.22)	0.008	-1.17 (-1.81, -0.53)	<0.001
≥80	-1.72 (-2.65, -0.78)	<0.001	-2.21 (-3.16, -1.25)	<0.001
Sex				
Female	Reference		Reference	
Male	-0.81 (-1.41, -0.21)	0.009	-0.61 (-1.89, -0.04)	0.04
Smoking				
Never smokers	Reference		Reference	
Ex smokers	0.08 (-0.53, 0.68)	0.81	0.12 (-0.46, 0.70)	0.69
Current smokers	1.36 (-0.06, 2.77)	0.06	0.41 (-0.91, 1.74)	0.54
Diabetes				
No	Reference		Reference	
Yes	-0.01 (-0.73, 0.71)	0.97	-0.13 (-0.81, 0.55)	0.70
CAD				
No	Reference		Reference	
Yes	-1.15 (-1.95, -0.36)	0.004	-1.10 (-1.90, -0.30)	0.007
eGFR				
≥60	Reference		Reference	
<60	0.24 (-0.53, 1.00)	0.55	0.80 (0.04, 1.55)	0.04
CRP				
<40	Reference		Reference	
≥40	0.02 (-0.62, 0.65)	0.95	0.04 (-0.54, 0.62)	0.90
CFS				
CFS 1 - 3	Reference		Reference	
CFS 4 - 5	0.62 (-0.05, 1.30)	0.07	1.16 (0.47, 1.85)	0.001
CFS 6 - 8	1.23 (0.24, 2.22)	0.01	1.52 (0.53, 2.50)	0.003

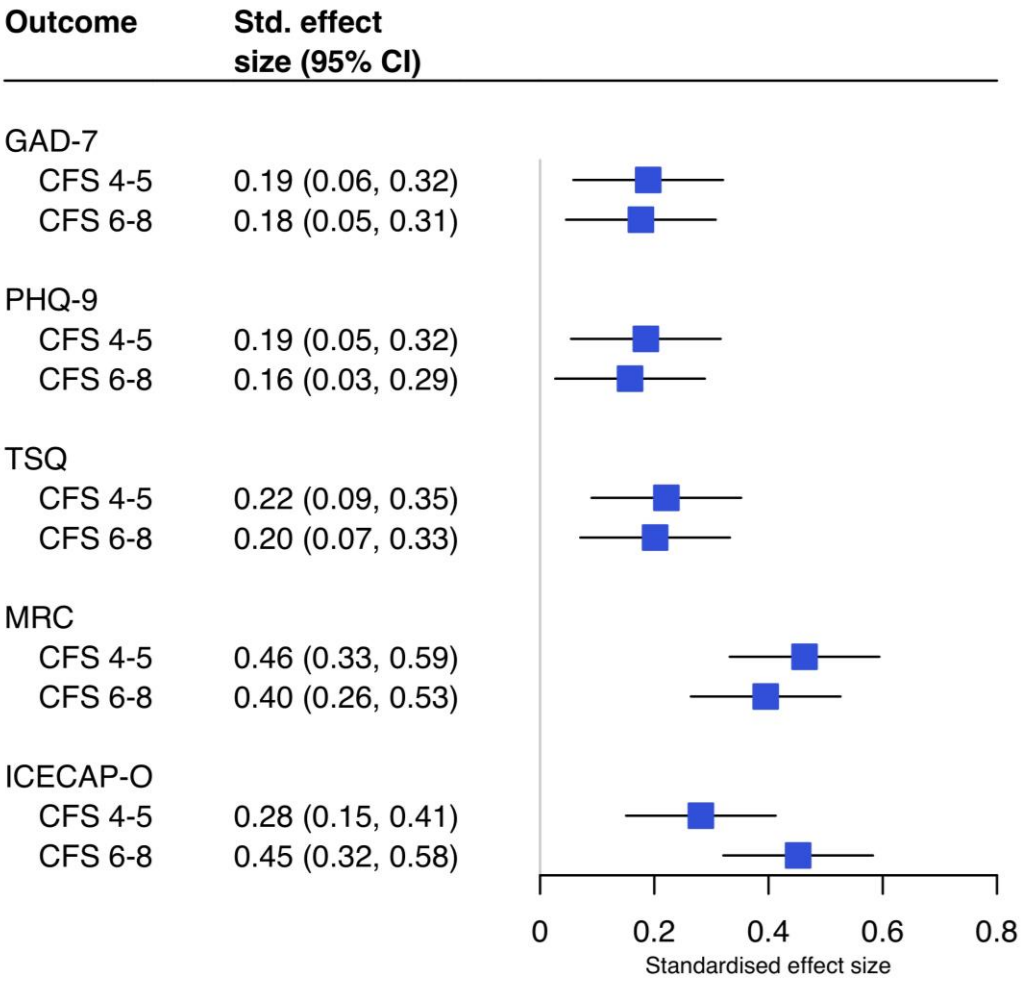
Table 5: The association between clinical characteristics and one year MRC Quality of Life, crude mean Difference (MD) and adjusted MD (aMD) are presented with associated p-values

	Crude Mean Difference (MD)		Adjusted MD (aMD)	
	MD (95%CI)	**p-value**	**aMD (95%CI)**	**p-value**
Age				
<65	Reference		Reference	
65-79	0.60 (0.29, 0.90)	<0.001	0.11 (-0.17, 0.39)	0.45
≥80	0.68 (0.23, 1.14)	0.003	0.01 (-0.41, 0.42)	0.98
Sex				
Female	Reference		Reference	
Male	-0.49 (-0.79, -0.20)	0.001	-0.30 (-0.55, -0.05)	0.02
Smoking				
Never smokers	Reference		Reference	
Ex-smokers	0.46 (0.17, 0.76)	0.002	0.21 (-0.04, 0.47)	0.10
Current smokers	0.60 (-0.08, 1.28)	0.08	0.15 (-0.44, 0.73)	0.62
Diabetes				
No	Reference		Reference	
Yes	0.49 (0.14, 0.83)	0.006	0.08 (-0.22, 0.38)	0.60
CAD				
No	Reference		Reference	
Yes	0.48 (0.09, 0.88)	0.017	0.07 (-0.28, 0.43)	0.69
eGFR				
≥60	Reference		Reference	
<60	0.70 (0.33, 1.07)	<0.001	0.32 (-0.01, 0.65)	0.06
CRP				
<40	Reference		Reference	
≥40	0.04 (-0.27, 0.35)	0.80	0.06 (-0.19, 0.31)	0.63
CFS				
CFS 1 - 3	Reference		Reference	
CFS 4 - 5	1.25 (0.97, 1.53)	<0.0001	1.06 (0.76, 1.36)	<0.0001
CFS 6 - 8	1.64 (1.21, 2.06	<0.0001	1.35 (0.90, 1.80)	<0.0001

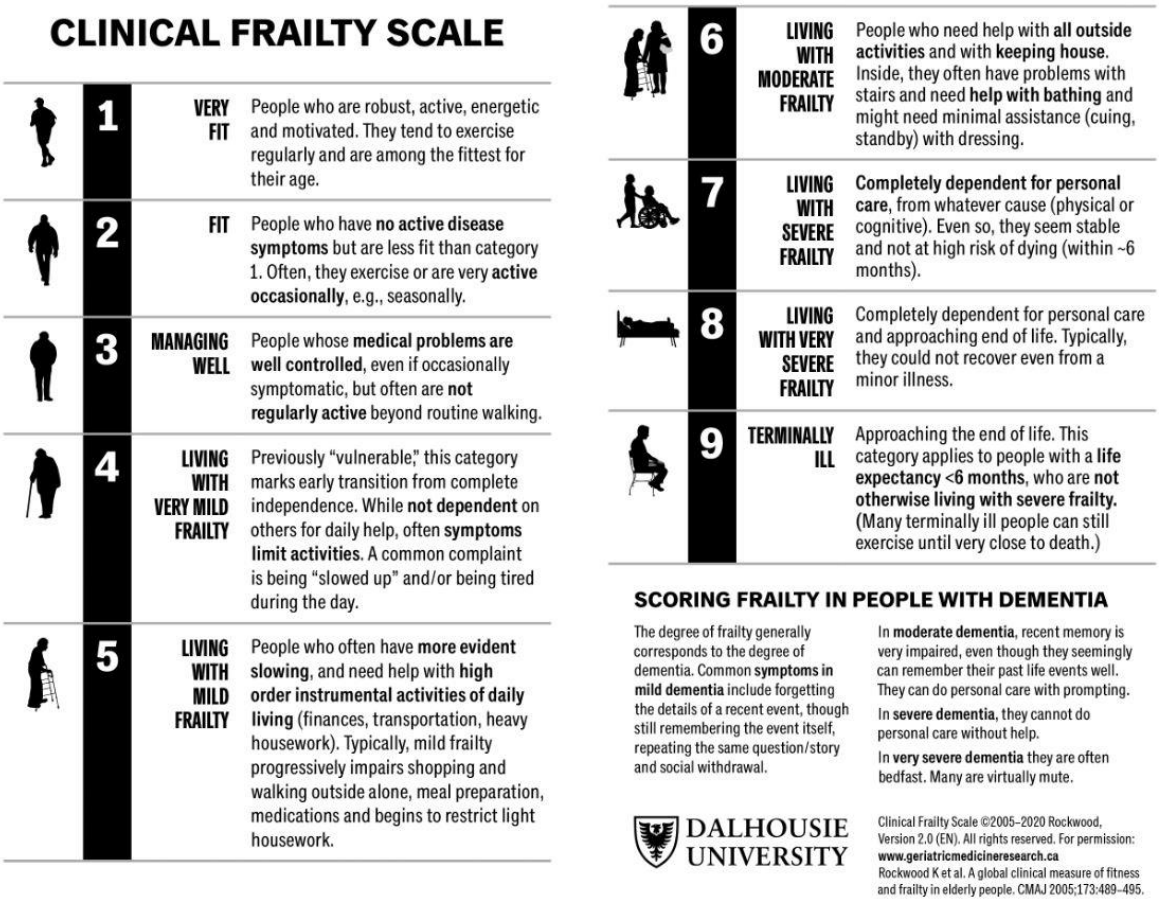
Table 6: The association between clinical characteristics and one year ICECAP-O, crude mean Difference (MD) and adjusted MD (aMD) are presented with associated p-values

	Crude Mean Difference (MD)		Adjusted MD (aMD)	
	MD (95%CI)	**p-value**	**aMD (95%CI)**	**p-value**
Age				
<65	Reference		Reference	
65-79	-0.23 (-1.12, 0.66)	0.61	0.58 (-0.29, 1.46)	0.19
≥80	-0.48 (-1.83, 0.88)	0.49	0.44 (-0.87, 1.74)	0.51
Sex				
Female	Reference		Reference	
Male	1.24 (0.40, 2.08)	0.004	0.51 (-0.28, 1.30)	0.21
Smoking				
Never smokers	Reference		Reference	
Ex-smokers	-0.34 (-1.19, 0.52)	0.44	-0.004 (-0.80, 0.79)	0.99
Current smokers	-1.66 (-3.65, 0.32)	0.10	-0.29 (-2.13, 1.54)	0.76
Diabetes				
No	Reference		Reference	
Yes	-1.09 (-2.09, -0.09)	0.03	-0.48 (-1.42, 0.45)	0.31
CAD				
No	Reference		Reference	
Yes	0.27 (-0.86, 1.40)	0.64	1.13 (0.03, 2.23)	0.04
eGFR				
≥60	Reference		Reference	
<60	-0.88 (-1.96, 0.19)	0.11	-0.80 (-1.84, 0.24)	0.13
CRP				
<40	Reference		Reference	
≥40	0.30 (-0.58, 1.19)	0.50	0.37 (-0.42, 1.16)	0.36
CFS				
CFS 1 - 3	Reference		Reference	
CFS 4 - 5	-1.96 (-2.83, -1.10)	<0.0001	-2.04 (-2.99, -1.09)	<0.0001
CFS 6 - 8	-4.61 (-5.86, -3.36)	<0.0001	-4.61 (-5.94, -3.27)	<0.0001

Figure 1: Adjusted standardised effect sizes with 95% confidence intervals for regressions of mental health outcomes on frailty (CFS 1-3 reference)



Supplementary Figure 1: Clinical Frailty Scale



Supplementary Table 1 – Comparison of the clinical symptoms scales and frailty

Clinical Frailty Scale (CFS)	Generalized Anxiety symptoms (GAD-7) None (n=148)	Mild (n=51)	Moderate or severe (n=25)
CFS 1-3	108 (71.5)	28 (18.5)	15 (9.9)
CFS 4-5	25 (52.1)	17 (35.4)	6 (12.5)
CFS 6-9	13 (61.9)	5 (23.8)	3 (14.3)
Missing	2	1	1

Clinical Frailty Scale (CFS)	Depression symptoms (PHQ-9) None (n=116)	Mild (n=645)	Moderate or severe (n=43)
CFS 1-3	92 (60.9)	39 (25.8)	20 (13.2)
CFS 4-5	16 (33.3)	17 (35.4)	15 (31.3)
CFS 6-9	6 (28.6)	9 (42.9)	6 (28.6)
Missing	2		2

Clinical Frailty Scale (CFS)	Trauma Screening Questionnaire Mean (SD)
CFS 1-3	1.40 (2.50)
CFS 4-5	2.46 (2.73)
CFS 6-9	2.26 (2.21)
Missing	

Clinical Frailty Scale (CFS)	ICE-CAP O Mean (SD)
CFS 1-3	17.02 (3.03)
CFS 4-5	14.41 (3.41)
CFS 6-9	13.62 (4.01)

Clinical Frailty Scale (CFS)	MRC Quality of Life Mean (SD)
CFS 1-3	1.85 (1.02)
CFS 4-5	3.08 (1.30)
CFS 6-9	3.26 (1.33)