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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Sablerolles RSG, Lafeber M, van Kempen JAL, et al. Association between Clinical Frailty Scale score and hospital mortality in adult patients with COVID-19 (COMET): an international, multicentre, retrospective, observational cohort study. *Lancet Healthy Longev* 2021; published online Feb 9. https://doi.org/10.1016/S2666-7568(21)00006-4.

Supplemental table 1 Analysis comparing patients with and without a CFS

	CFS Sample Total (n=2434)	Non-CFS sample Total (n=3102)	p-value
Age (years)	67 [55-77]	69 [58-78]	<0·0001
<65 years	1096 (45%)	1222 (39%)	<0·0001
65-75 years	589 (24%)	774 (25%)	
>75 years	749 (31%)	1106 (36%)	
Male gender	1480 (61%)	1947 (63%)	0·13
Concomitant drugs			
Blood pressure-lowering drugs	1136 (47%)	1665 (54%)	<0·0001
Antiplatelet drugs	405 (17%)	699 (23%)	<0·0001
Oral anticoagulants	272 (11%)	373 (12%)	0·33
Glucose-lowering drugs	437 (18%)	636 (21%)	0·018
Antipsychotics and cholinesterase inhibitors	143 (6%)	136 (4%)	0·013
Number of drug classes	3 [1-7]	5 [2-9]	<0·0001
Clinical outcome			
Hospital mortality	456 (19%)	653 (21%)	0·032
ICU admission	616 (25%)	700 (23%)	0·13

Displayed values are median [interquartile range] and n (%), p-values are estimated using Mann Whitney U test and chi-square test for continuous and categorical variables where necessary.

Supplemental Table 2 Baseline characteristics of the total sample for patients <65 and ≥65 years, separately

	<65 years Total (n=1096)	≥65 years Total (n=1338)	p-value
Age (years)	53 [45-60]	76 [71-83]	NA
< 65 years	1096		NA
65-75 years		589	
>75 years		749	
Male gender	700 (64%)	780 (58%)	0.0050
Concomitant drugs			
Blood pressure-lowering drugs	285 (26%)	851 (64%)	<0·0001
Antiplatelet drugs	81 (7%)	324 (24%)	<0·0001
Oral anticoagulants	32 (3%)	240 (18%)	<0·0001
Glucose-lowering drugs	130 (12%)	307 (23%)	<0·0001
Antipsychotics and cholinesterase inhibitors	25 (2%)	118 (9%)	<0·0001
Number of drug classes	1 [1-4]	5 [2-9]	<0·0001
Clinical Frailty Score			<0·0001
1 Very fit	184 (17%)	69 (5%)	
2 Well	419 (38%)	258 (19%)	
3 Managing well	189 (17%)	258 (19%)	
4 Vulnerable	125 (11%)	241 (18%)	
5 Mildly frail	54 (5%)	144 (11%)	
6 Moderately frail	37 (3%)	145 (11%)	
7 Severely frail	47 (4%)	147 (11%)	
8 Very severely frail	37 (3%)	62 (5%)	
9 Terminally ill	4 (1%)	14 (1%)	
Clinical outcome			
Hospital mortality	53 (5%)	403 (30%)	<0·0001
ICU admission	290 (26%)	326 (24%)	0·26

Displayed values are median [interquartile range] and n (%). P-values are based on Mann-Whitney U test for continuous variables, and Fisher's exact test for categorical variables. NA are p-values that are non-informative and are therefore omitted from the table.

Supplemental Table 3 Baseline characteristics of the total sample for each CFS category, separately

Clinical Frailty Scale	***Fit [CFS 1-3]***	***Mildly frail [CFS 4-5]***	***Frail [CFS 6-9]***	
	(n=1377)	**(n=564)**	**(n=493)**	**p-value**
Age (years)	62 [51-72]	73 [60-81]	75 [65-84]	<0·0001
<65 years	792 (57%)	179 (32%)	125 (25%)	<0·0001
65-75 years	330 (24%)	136 (24%)	123 (25%)	
>75 years	255 (18%)	249 (44%)	245 (50%)	
Male gender	853 (62%)	329 (58%)	298 (60%)	0·33
Concomitant drugs				
Blood pressure-lowering drugs	537 (39%)	304 (54%)	295 (60%)	<0·0001
Antiplatelet drugs	179 (13%)	122 (22%)	104 (21%)	<0·0001
Oral anticoagulants	116 (8%)	72 (13%)	84 (17%)	<0·0001
Glucose-lowering drugs	198 (14%)	131 (23%)	108 (22%)	<0·0001
Antipsychotics and cholinesterase inhibitors	37 (2%)	37 (7%)	69 (14%)	<0·0001
Number of drug classes	2 [1-6]	5 [1-8]	5 [2-9]	<0·0001
Clinical outcome				
Hospital mortality	142 (10%)	132 (23%)	182 (37%)	<0·0001
ICU admission	353 (26%)	104 (18%)	159 (32%)	<0·0001

Displayed values are median [interquartile range] and n (%). P-values are based on one-way ANOVA for continuous variables and Fisher's exact test for categorical variables.

Supplemental Table 4 Binary logistic regression presenting all the estimates (Odds Ratios) and 95% Confidence intervals with hospital mortality as the outcome

Hospital mortality	**Model IV** **Total sample**	**Model IV** **<65 years**	**Model IV** **≥65 Years**
Mildly frail [CFS4-5]; ref is Fit[CFS1-3]	**1·54 (1·16-2·06)**	1·08 (0·48-2·39)	**1·64 (1·20-2·25)**
Frail [CFS6-9]; ref is Fit[CFS1-3]	**2·71 (2·04-3·60)**	**2·22 (1·08-4·57)**	**2·90 (2·12-3·97)**
Male	**2·04 (1·59-2·63)**	**2·01 (1·00-4·04)**	**2·04 (1·56-2·67)**
Age	**2·00 (1·80-2·24)**	**1·85 (1·24-2·75)**	**1·74 (1·46-2·08)**
Polypharmacy	**1·05 (1·01-1·09)**	**1·15 (1·06-1·26)**	1·02 (0·98-1·06)
Blood pressure-lowering drugs	1·14 (0·86-1·51)	0·54 (0·25-1·17)	1·26 (0·92-1·71)
Antiplatelet drugs	1·02 (0·75-1·39)	0·67 (0·24-1·91)	1·13 (0·81-1·56)
Oral anticoagulants	1·04 (0·74-1·39)	1·59 (0·50-5·96)	1·05 (0·74-1·49)
Glucose-lowering drugs	0·99 (0·74-1·34)	1·32 (0·60-2·90)	0·90 (0·66-1·24)
Cholinesterase inhibitors	1·44 (0·96-2·16)	2·72 (0·86-8·57)	1·30 (0·85-2·00)
N	2367	1069	1298
Nagelkerke R-square	0·3	0·15	0·16
-2 Loglikelihood	-1837·85	-367·68	-1449·07
Chi-square (df, p-value)	482·00 (10, <0·001)	54·09 (10, <0·001)	159·11 (10, <0·001)

Note: Bold values are significant at 5% alpha level.

Supplemental Table 5 Binary logistic regression presenting all the estimates (Odds Ratios) and 95% Confidence intervals with ICU admission as the outcome

ICU admission	Model IV Total sample	Model IV <65 years	Model IV ≥65 Years
Mildly frail [CFS4-5]; ref is Fit[CFS1-3]	**0·71 (0·55-0·92)**	0·93 (0·63-1·38)	**0·66 (0·47-0·93)**
Frail [CFS6-9]; ref is Fit[CFS1-3]	**1·54 (1·21-1·97)**	**2·96 (1·98-4·43)**	1·27 (0·92-1·75)
Male; ref is female	**2·03 (1·65-2·48)**	**2·06 (1·50-2·83)**	**1·75 (1·33-2·31)**
Age	1·00 (0·94-1·08)	**1·47 (1·25-1·72)**	**0·56 (0·46-0·68)**
Polypharmacy	0·98 (0·95-1·01)	1·00 (0·94-1·06)	0·97 (0·93-1·01)
Blood pressure-lowering drugs	**1·35 (1·06-1·71)**	0·95 (0·64-1·40)	**1·50 (1·10-2·06)**
Antiplatelet drugs	**0·72 (0·54-0·97)**	0·87 (0·50-1·53)	**0·69 (0·48-0·99)**
Oral anticoagulants	**0·60 (0·42-0·86)**	0·56 (0·23-1·36)	0·70 (0·47-1·04)
Glucose-lowering drugs	1·02 (0·78-1·34)	1·07 (0·67-1·72)	0·86 (0·61-1·20)
Cholinesterase inhibitors	0·63 (0·39-1·00)	0·92 (0·34-2·46)	0·70 (0·40-1·22)
N	2418	1091	1327
Nagelkerke R-square	0·06	0·11	0·11
-2 Loglikelihood	-12646·23	-1175·15	-1381·33
Chi-square (df, p-value)	98·20 (10, <0·001)	88·34 (10, <0·001)	98·34 (10, <0·001)

Note: Bold values are significant at 5% alpha level.

Supplemental Table 6 Binary regression analysis using CFS as a continuous variable

			Clinical frailty score	
Study endpoint		***No. of events***	***OR (95%CI) Per 1 increase Clinical Frailty Score (n=2434)***	***p-value***
Hospital mortality				
	I	456	1·44 (1·37 - 1·52)	<0·0001
	II		1·30 (1·22 - 1·37)	<0·0001
	III		1·28 (1·21 - 1·36)	<0·0001
	IV		1·27 (1·20 - 1·35)	<0·0001
Intensive care admission				
	I	616	1·08 (1·04 - 1·13)	<0·0001
	II		1·11 (1·05 - 1·16)	<0·0001
	III		1·12 (1·06 - 1·17)	<0·0001
	IV		1·12 (1·07 - 1·18)	<0·0001

Model
I: Crude
II: Adjusted for sex, age
III: II + additional adjustment for number of drugs
IV: III + additional adjustment for blood pressure-lowering drugs, antiplatelet drugs, oral anticoagulants, glucose-lowering drugs, antipsychotics, and cholinesterase inhibitors
**Estimates are Odds Ratios (OR) and their respective 95% Confidence Intervals (95% CI)*

Supplemental Table 7 Binary logistic regression analysis when including BMI as an additional covariate in the extended model IV

Outcome	**Hospital mortality**			**ICU admission**		
Sample	**Total**	**<65 years**	**≥65 Years**	**Total**	**<65 years**	**≥65 Years**
Model	**IV**	**IV**	**IV**	**IV**	**IV**	**IV**
Mildly frail [CFS4-5]; ref is Fit [CFS1-3]	**1·56 (1·13-2·15)**	1·13 (0·84-2·65)	**1·69 (1·19-2·42)**	0·65 (0·50-0·86)	0·80 (0·52-1·22)	**0·63 (0·43-0·92)**
Frail [CFS6-9]; ref is Fit [CFS1-3]	**2·43-1·74-3·38)**	2·13 (0·92-4·92)	**2·62 (1·82-3·79)**	**1·66 (1·26-2·19)**	**2·92 (1·80-4·73)**	**1·45 (1·01-2·08)**
Male; ref is female	**2·97 (1·64-2·94)**	1·86 (0·87-3·98)	**2·24 (1·64-3·06)**	**2·09 (1·67-2·62)**	**2·14 (1·51-3·04)**	**1·81 (1·32-2·47)**
Age	**1·87 (1·65-2·13)**	**1·85 (1·19-2·87)**	**1·52 (1·23-1·88)**	1·00 (0·92-1·08)	**1·48 (1·25-1·76)**	**0·51 (0·40-0·64)**
Pre-obesity; ref is normal	**1·66 (1·20-2·28)**	2·00 (0·89-4·47)	**1·54 (1·08-2·19)**	**1·70 (1·32-2·18)**	**1·92 (1·21-2·81)**	1·25 (0·89-1·77)
Obesity; ref is normal	**1·57 (1·13-2·19)**	1·51 (0·64-3·55)	**1·54 (1·07-2·22)**	**1·51 (1·17-1·96)**	**1·98 (1·34-2·92)**	0·98 (0·68-1·43)
Polypharmacy	**1·06 (1·02-1·10)**	**1·17 (1·06-1·29)**	1·03 (0·99-1·08)	0·98 (0·95-1·03)	1·00 (0·94-1·07)	0·98 (0·94-1·03)
Blood pressure-lowering drugs	1·06 (0·77-1·46)	0·49 (0·21-1·16)	1·19 (0·93-1·69)	1·24 (0·95-1·62)	0·84 (0·55-1·28)	**1·51 (1·06-2·16)**
Antiplatelet drugs	0·99 (0·70-1·40)	0·57 (0·18-1·82)	1·14 (0·79-1·65)	0·73 (0·53-1·01)	0·74 (0·41-1·37)	0·74 (0·50-1·10)
Oral anticoagulants	1·07 (0·74-1·56)	1·81 (0·54-6·06)	1·09 (0·73-1·62)	0·56 (0·38-0·82)	0·44 (0·17-1·15)	0·70 (0·54-1·16)
Glucose-lowering drugs	1·00 (0·72-1·39)	1·55 (0·67-3·61)	0·84 (0·58-1·21)	0·92 (0·69-1·24)	0·94 (0·57-1·57)	0·79 (0·54-1·16)
Cholinesterase inhibitors	1·49 (0·93-2·38)	2·87 (0·81-10·18)	1·30 (0·79-2·15)	0·69 -0·41-1·16)	1·11 (0·39-3·18)	0·70 (0·37-1·30)
N	1882	858	1024	1929	877	1052
Nagelkerke R-square	0·26	0·19	0·14	0·08	0·14	0·13
-2 Loglikelihood	-1445·38	-301·94	-1117·76	-2161·41	-976·18	-1108·73
Chi-square (df, p-value)	**317·49 (12, <0·001)**	**56·74 (12, <0·001)**	**100·89 (12, <0·001)**	**110·69 (12, <0·001)**	**88·23 (12, <0·001)**	**95·89 (12, <0·001)**

Note: Bold values are significant at 5% alpha level.

Supplemental Table 8 Binary logistic regression for the association between CFS and hospital mortality stratified for whether the patient was admitted at the ICU during the COVID-19 hospitalisation

Outcome	**Hospital mortality**	
Stratification	**ICU admission**	**No ICU admission**
Model	**IV**	**IV**
Mildly frail [CFS4-5]; ref is Fit [CFS1-3]	1·33 (0·78-2·27)	**1·90 (1·31-2·75)**
Frail [CFS6-9]; ref is Fit [CFS1-3]	**1·81 (1·14-2·87)**	**3·23 (2·22-4·72)**
Male	**1·84 (1·14-2·96)**	**1·86 (1·37-2·54)**
Age	**1·80 (1·49-2·17)**	**2·47 (2·11-2·90)**
Polypharmacy	1·05 (0·99-1·12)	1·05 (1·00-1·10)
Blood pressure-lowering drugs	0·85 (0·53-1·37)	1·28 (0·88-1·86)
Antiplatelet drugs	0·97 (0·54-1·75)	1·13 (0·78-1·65)
Oral anticoagulants	1·19 (0·62-2·30)	1·03 (0·68-1·55)
Glucose-lowering drugs	1·15 (0·68-1·95)	0·95 (0·65-1·38)
Cholinesterase inhibitors	1·94 (0·72-5·22)	1·45 (0·91-2·29)
N	570	1781
Nagelkerke R-square	0·19	0·38
-2 Loglikelihood	-603·77	-1127·63
Chi-square (df, p-value)	80·34 (10, <0·001)	448·52 (10, <0·001)

Note: Bold values are significant at 5% alpha level.

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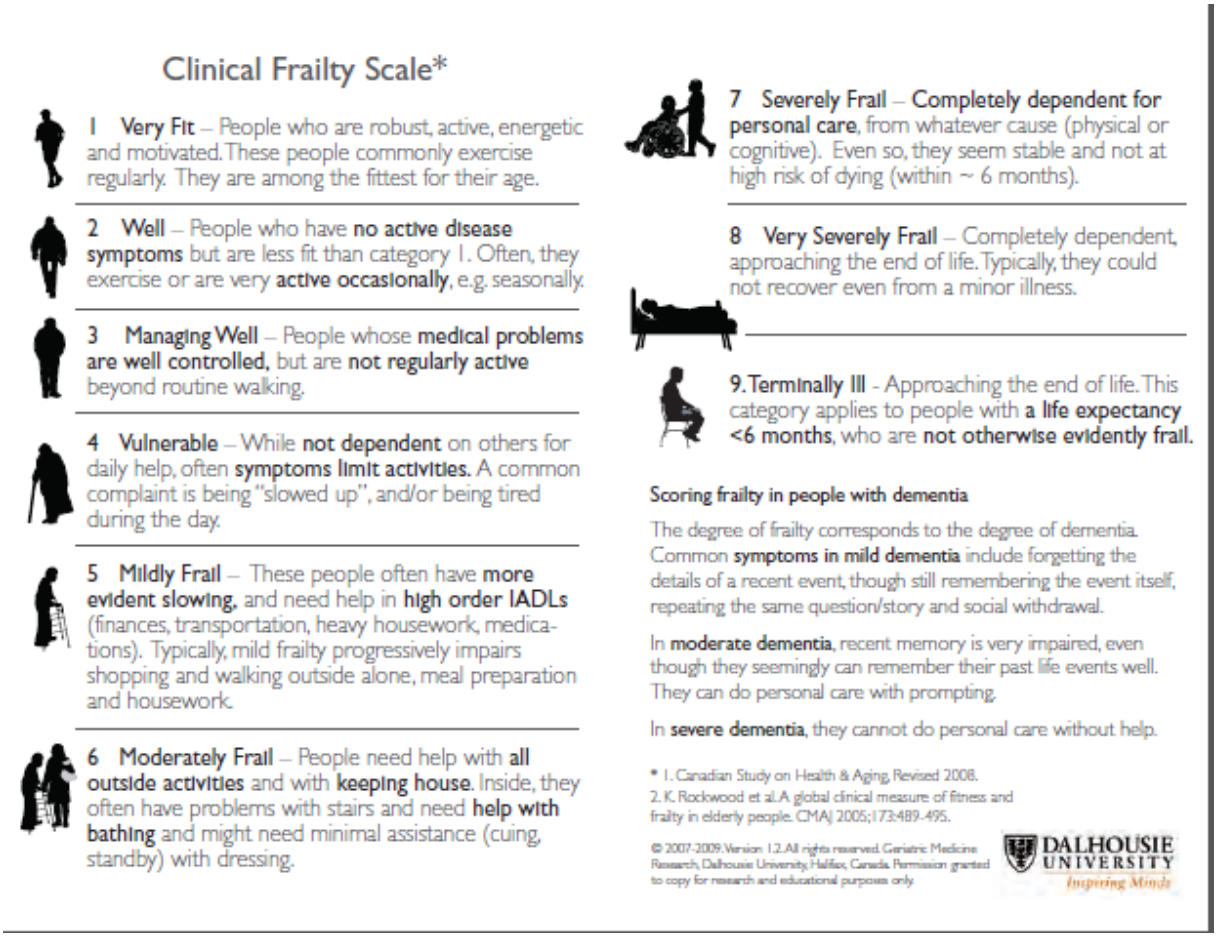
Supplemental file 2 Background of CFS categories



Clinical Frailty Scale*

1 **Very Fit** – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.

2 **Well** – People who have **no active disease symptoms** but are less fit than category 1. Often, they exercise or are very **active occasionally**, e.g. seasonally.

3 **Managing Well** – People whose **medical problems are well controlled,** but are **not regularly active** beyond routine walking.

4 **Vulnerable** – While **not dependent** on others for daily help, often **symptoms limit activities.** A common complaint is being "slowed up", and/or being tired during the day.

5 **Mildly Frail** – These people often have **more evident slowing,** and need help in **high order IADLs** (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.

6 **Moderately Frail** – People need help with **all outside activities** and with **keeping house**. Inside, they often have problems with stairs and need **help with bathing** and might need minimal assistance (cuing, standby) with dressing.

7 **Severely Frail** – **Completely dependent for personal care**, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).

8 **Very Severely Frail** – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.

9. **Terminally Ill** - Approaching the end of life. This category applies to people with **a life expectancy <6 months**, who are **not otherwise evidently frail.**

Scoring frailty in people with dementia

The degree of frailty corresponds to the degree of dementia. Common **symptoms in mild dementia** include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In **moderate dementia**, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.

In **severe dementia**, they cannot do personal care without help.

* 1. Canadian Study on Health & Aging, Revised 2008.
2. K. Rockwood et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489-495.

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