Supplementary materials

Is frailty incremental to the 4C Mortality model for mortality risk prediction in hospitalized older individuals with COVID-19 disease?

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Supplement 1: Information about 4C mortality model

Comorbidities used in the model: chronic cardiac disease, chronic respiratory disease (excluding asthma), chronic renal disease (eGFR =< 30), liver disease (moderate to severe), dementia, chronic neurological conditions, connective tissue disease, diabetes, AIDS/HIV, malignancy, obesity (clinically defined)

Knight SR, Ho A, Pius R, Buchan I, Carson G, Drake TM, Dunning J, Fairfield CJ, Gamble C, Green CA, Gupta R. Risk stratification of patients admitted to hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: development and validation of the 4C Mortality Score. bmj. 2020 Sep 9;370. https://www.bmj.com/content/370/bmj.m3339

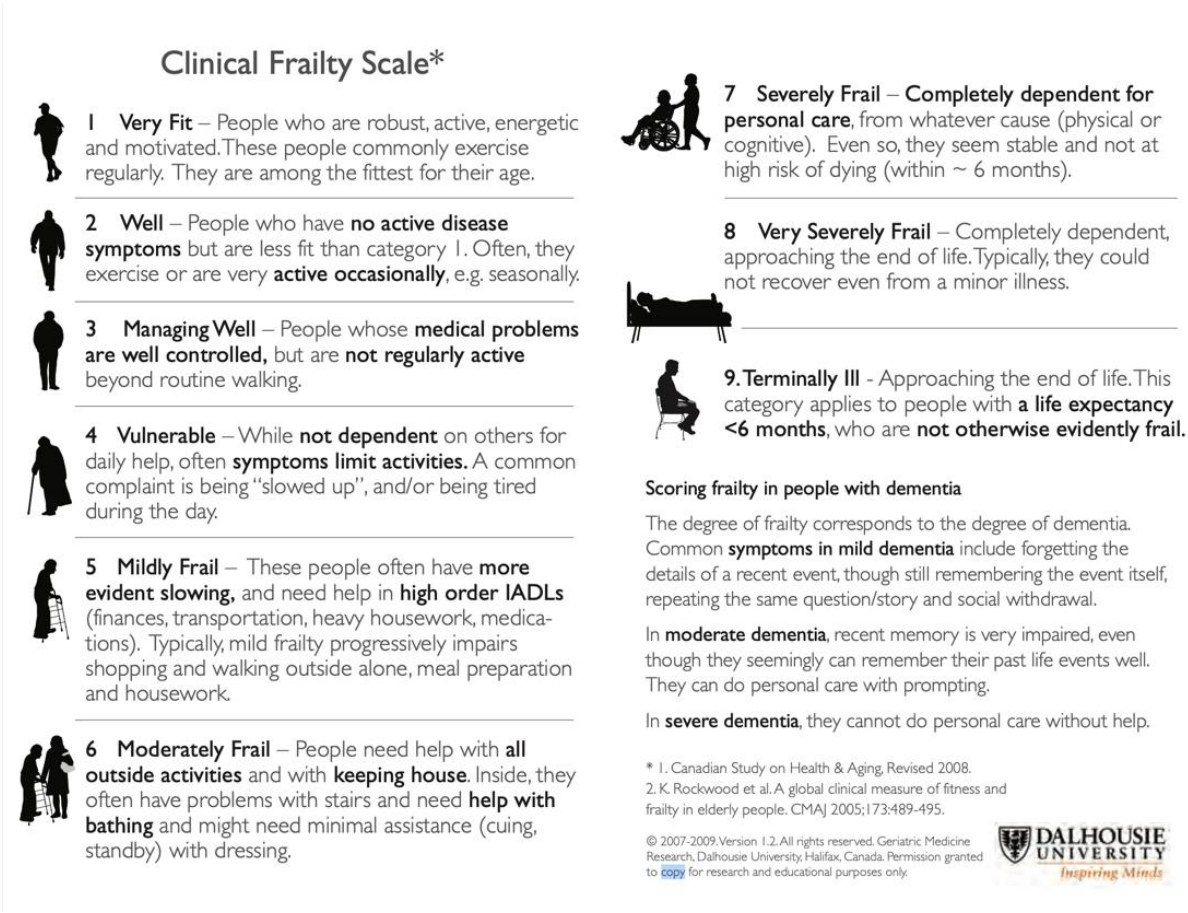
Table S1: Details coefficients and predictors of 4C mortality model

Level		**Penalised coefficient**
Intercept		-4.203
Age (years)	50-59	0.687
	60-69	1.337
	70-79	1.842
	≥80	2.252
Sex at birth	Male	0.172
Number of comorbidities*	1	0.300
	≥2	0.532
Respiratory rate (breaths/minute)	20-29	0.232
	≥30	0.649
Oxygen saturation on room air (%)	<92	0.577
Glasgow Coma Scale	<15	0.558
Urea (mmol/L)	7-14	0.439
	>14	1.011
CRP (mg/dL)	50-99	0.363
	≥100	0.74

Step 2: Details of Clinical Frailty Scale

The Clinical Frailty Scale (CFS) is a simple instrument to quantify degree of frailty measured from a scale of 1 to 9.

Reference: Rockwood K, Theou O. Using the Clinical Frailty Scale in Allocating Scarce Health Care Resources. Can Geriatr J. 2020 Sep 1;23(3):210-215. doi: 10.5770/cgj.23.463. PMID: 32904824; PMCID: PMC7458601.



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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Supplement 3: Comparison between derivation population for 4C Mortality model and study population

Table S2: Comparison between derivation population for 4C Mortality model and COVID-OLD population

Population characteristics	**4C Mortality model**	**COVID-OLD cohort**
Number of participants, N	35,463	3,067
Mortality, n (%)	11,426 (32)	960 (31)
Age, median (IQR)	73 (59 to 83)	79 (74 – 84)
Male, n (%)	20,722 (58)	1862 (61)
Malignant neoplasm, n (%)	3,312 (10)	605 (20)
Liver disease, n (%)	604 (2)	47 (2.0)
Obesity	3,414 (11)	654 (21)
Diabetes, n (%)	8,487 (26)	949 (31)
*Chronic kidney disease, n (%)	5,653 (17)	351 (11)
Respiratory rate (breaths/min)	22.0 (9.0)	21 (18 – 25)
Oxygen saturation (%)	94.0 (6.0)	93 (89 – 95)
Systolic blood pressure (mm Hg)	124.0 (33.0)	-
Diastolic blood pressure (mm Hg)	70.0 (19.0)	-
Temperature (C)	37.3 (1.5)	-
Heart rate (bpm)	90.0 (27.0)	-
Haemoglobin (g/L	129.0 (30.0)	-
White blood cell count (10^9/L)	7.4 (5.1)	-
Neutrophil count (10^9/L)	5.6 (4.6)	-
Lymphocyte count (10^9/L)	0.9 (0.7)	-
Potassium (mmol/L)	4.1 (0.8)	-
Urea (mmol/L)	7.0 (6.3)	9.0 (6.9 – 11.4)
Creatinine (µmol/L)	86.0 (53.0)	-
C reactive protein (mg/L)	84.9 (122.0)	74.0 (36.5 - 131.6)

COPD; Chronic obstructive pulmonary disease, IQR; interquartile range SD; standard deviation, NR; Not reported.

Supplement 4: Sample size calculations

Table S3: Required sample size based on pmsampsize, with shrinkage = 0.9

Parameters	Mortality fraction	c-statistic	Required sample size	Events per predictor
14	0.31	0.70	1127	25.2
14	0.31	0.65	2040	45.6
14	0.31	0.60	4667	104.3
15	0.31	0.70	1207	25.2
15	0.31	0.65	2186	45.6
15	0.31	0.60	5000	104.3
16	0.31	0.70	1288	25.2
16	0.31	0.65	2332	45.6
16	0.31	0.60	5334	104.4
17	0.31	0.70	1368	25.2
17	0.31	0.65	2477	45.6
17	0.31	0.60	5667	104.3

Supplement 5: Details of COVID-OLD cohort

Description of the cohort

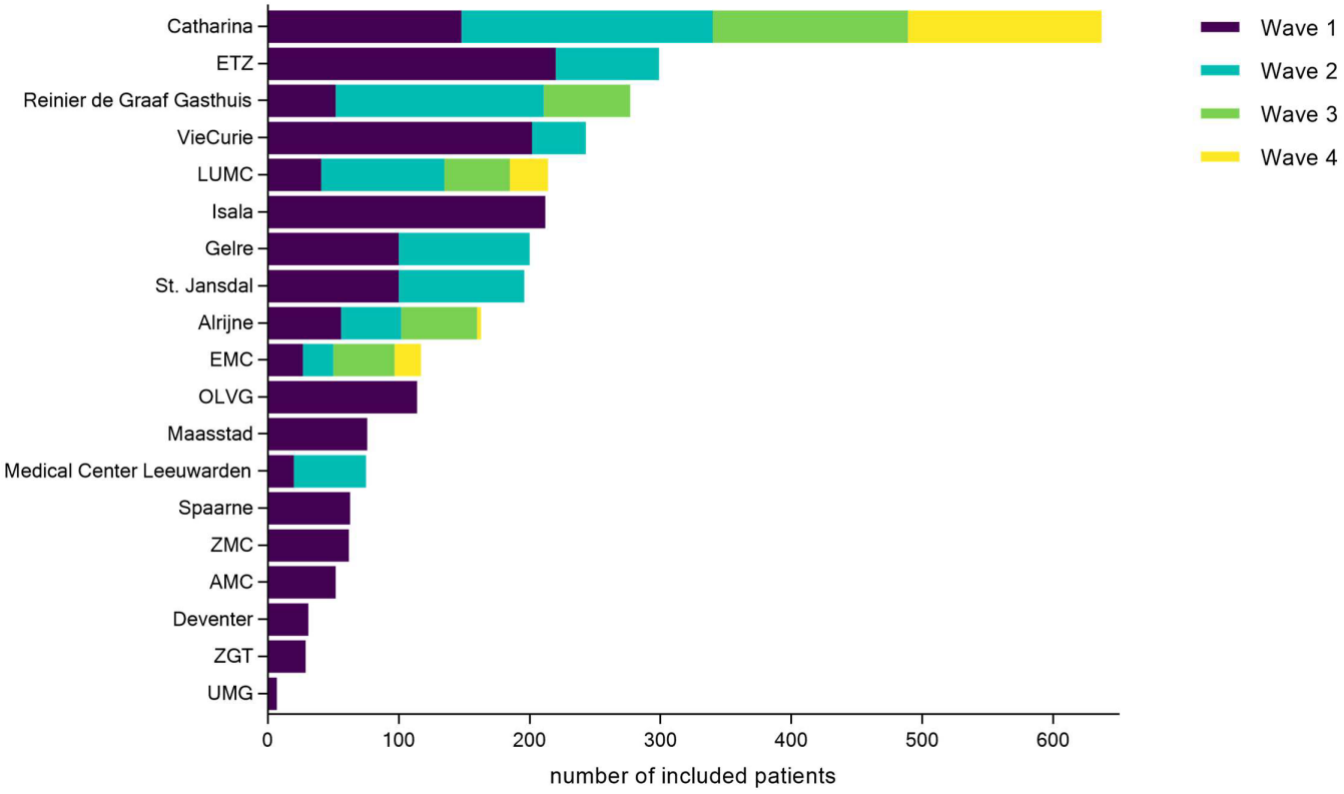
The COVID-OLD study, a multicenter retrospective cohort study in the Netherlands, included older people hospitalised for COVID-19 during the four pandemic waves between February 2020 and April 2022. The 19 participating hospitals are listed in table S4 and an overview of the number of inclusions per hospital and wave is provided in figure S1. The included hospitals in this study varied from peripheral hospitals to large teaching and academic medical centers. The flowchart with inclusions and exclusions is shown in Figure S2.

The Dutch vaccination program for COVID-19 started on 6 January 2021, shortly after the end of the second wave and well before the start of the third wave. In other words, all patients included in this study had the opportunity to be vaccinated in the third and fourth waves. The vaccination coverage of the first series of COVID-19 vaccinations in people aged 70 years and older ranged from 92 to 93% in the Netherlands.

Table S4. List of participating hospitals in the COVID-OLD study

Hospital	Location
Alrijne	Leiderdorp
Amsterdam University Medical Center	Amsterdam
Catharina Hospital	Eindhoven
Deventer Hospital	Deventer
Elisabeth-TweeSteden	Tilburg
Erasmus Medical Center	Rotterdam
Gelre	Apeldoorn and Zutphen
Isala	Zwolle
Leiden University Medical Center	Leiden
Maasstad Hospital	Rotterdam
Medical Center Leeuwarden	Leeuwarden
OLVG	Amsterdam
Reinier de Graaf	Delft
Spaarne	Haarlem
St. Jansdal	Harderwijk
University Medical Center Groningen	Groningen
VieCuri Medical Center	Venlo
Zaans Medical Center	Zaandam
ZGT	Almelo

Figure S1. Number of inclusions per hospital for each pandemic wave



Participant selection

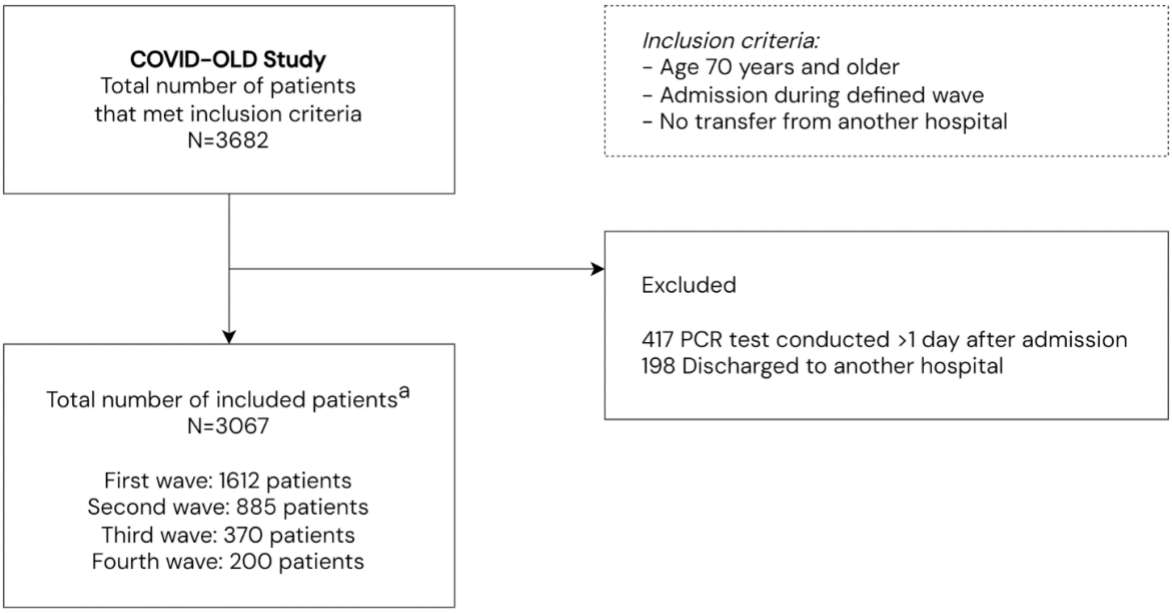
Older people, aged 70 years or older, were hospitalised for COVID-19 during one of four waves. In the first wave, both clinical diagnosis and reverse transcription polymerase chain reaction (RT-PCR) confirmed COVID-19 disease while in the second, third and fourth waves only RT-PCR were used for COVID-19 diagnosis.

- First wave: February 27th to May 15th, 2020
- Second wave: September 1st to December 31st, 2020
- Third wave: September 1st to December 31st, 2021
- Fourth wave: February 1st to April 30th, 2022

Inclusion criteria
Hospitalized during one of the four waves, age 70 years or older, not admitted via another hospital (because data could be missing).

Exclusion criteria
Discharged to another hospital (missing data, possibly missing the outcome of in-hospital mortality), no COVID-19 diagnosis >24 hrs after admission (because possibly no hospital treatment indication for COVID-19, especially important for later waves)
The exclusion of patients who acquired COVID-19 >1 day after admission was performed with the following rule in COVID-OLD: a PCR test conducted >24 hrs after admission because most of the admitted patients got a PCR test even if there was already a positive test at the GP. Patients admitted for other causes e.g. a planned cholecystectomy and had (by chance) a positive PRC test.

Figure S2. Flowchart of the COVID-OLD study



Details of the Predictor measurement

Table S5: Details of the Predictor measurement in the COVID-OLD cohort

Predictors		**Derivation settings**	**Definition and timing of measurement in COVID-OLD cohort**
Age	Measurement procedure/unit	Years	Years
	Timing	The day of presentation with COVID-19 at general practitioner	Registered the day of hospital admission for COVID-19 (24 hours)
Sex	Measurement procedure/unit	Male/Female at birth	Male/Female at birth
	Timing	The day of presentation with COVID-19 at general practitioner	Registered the day of hospital admission for COVID-19 (24 hours)
Chronic cardiac disease	Measurement procedure/unit	Defined using the Charlson Comorbidity Index	Extracted from case report forms under Heart failure
	Timing	The day of presentation with COVID-19 at general practitioner	Registered the day of hospital admission for COVID-19 (24 hours)
Chronic respiratory disease (excluding asthma)	Measurement procedure/unit	Defined using the Charlson Comorbidity Index	Extracted from case report forms under COPD
	Timing	The day of presentation with COVID-19 at general practitioner	Registered the day of hospital admission for COVID-19 (24 hours)
Chronic kidney disease	Measurement procedure/unit	Defined using the Charlson Comorbidity Index	Defined based on estimated GFR ≤60 using CKD-EPI Equations for Glomerular Filtration Rate (GFR) using age, sex, and serum creatinine
	Timing	The day of hospital admission for COVID-19 (24 hours)	Registered the day of hospital admission for COVID-19 (24 hours), with lookback window of entire lifetime
Mild to severe liver disease	Measurement procedure/unit	Defined using the Charlson Comorbidity Index (Severe = cirrhosis and portal hypertension with variceal bleeding history, moderate = cirrhosis and portal hypertension but no variceal bleeding history, mild = chronic hepatitis (or	Extracted from case report forms under liver disease

		cirrhosis without portal hypertension)	
	Timing	The day of hospital admission for COVID-19 (24 hours)	Registered the day of hospital admission for COVID-19 (24 hours), with lookback
Dementia	Measurement procedure/unit	Defined using the Charlson Comorbidity Index	Extracted from case report forms
	Timing	The day of hospital admission for COVID-19 (24 hours)	Registered the day of hospital admission for COVID-19 (24 hours), with lookback window of entire lifetime
Chronic neurological conditions	Measurement procedure/unit	Defined using the Charlson Comorbidity Index	Not registered in the cohort
	Timing	The day of hospital admission for COVID-19 (24 hours)	-
Connective tissue disease	Measurement procedure/unit	Defined using the Charlson Comorbidity Index	Extracted from case report forms
	Timing	The day of hospital admission for COVID-19 (24 hours)	Registered the day of hospital admission for COVID-19 (24 hours), with lookback window of entire lifetime
Diabetes mellitus	Measurement procedure/unit	Defined using the Charlson Comorbidity Index Uncomplicated, End-organ disease	Registered with medical history of Diabetes mellitus type 1 or type 2
	Timing	The day of hospital admission for COVID-19 (24 hours)	Registered the day of hospital admission for COVID-19 (24 hours), with lookback window of entire lifetime
HIV or AIDS	Measurement procedure/unit	Defined using the Charlson Comorbidity Index	Extracted from case report form under HIV and AIDS
	Timing	The day of hospital admission for COVID-19 (24 hours)	Registered the day of hospital admission for COVID-19 (24 hours), with lookback window of entire lifetime
Malignancy	Measurement procedure/unit	Defined using the Charlson Comorbidity Index Localized and metastatic	Extracted from case report form under history of malignancies
	Timing	The day of hospital admission for	Registered the day of hospital admission for COVID-19 (24 hours), with lookback window of entire lifetime

		COVID-19 (24 hours)	
Obesity	Measurement procedure/unit	Clinician defined (not further defined)	Computed based on BMI greater than 30 using weight and height
	Timing	The day of hospital admission for COVID-19 (24 hours)	Registered the day of hospital admission for COVID-19 (24 hours), with lookback window of entire lifetime
Respiratory rate	Measurement procedure/unit	Breaths per minute	Breaths per minute extracted from case report form
	Timing	The day of hospital admission for COVID-19 (24 hours)	Registered the day of hospital admission for COVID-19 (24 hours), with lookback window of entire lifetime
Oxygen saturation	Measurement procedure/unit	Peripheral oxygen saturation on room air in %	Peripheral oxygen saturation on room air in % extracted from case report form
	Timing	The day of hospital admission for COVID-19 (24 hours)	Registered the day of hospital admission for COVID-19 (24 hours), with lookback window of entire lifetime
Glasgow Coma Scale	Measurement procedure/unit	Score 15 or <15	Extracted from case report
	Timing	The day of hospital admission for COVID-19 (24 hours)	Registered the day of hospital admission for COVID-19 (24 hours), with lookback window of entire lifetime
Urea	Measurement procedure/unit	mmol/L	Mmol/L extracted from case report form
	Timing	The day of hospital admission for COVID-19 (24 hours)	Registered the day of hospital admission for COVID-19 (24 hours), with lookback window of entire lifetime
C-reactive protein	Measurement procedure/unit	mg/dL	Mg/dL extracted from case report form
	Timing	The day of hospital admission for COVID-19 (24 hours)	Registered the day of hospital admission for COVID-19 (24 hours), with lookback window of entire lifetime

Participant characteristics and missing predictors

In total, 3682 patients hospitalised for COVID-19 of the COVID-OLD cohort met the inclusion criteria (Appendix 1). We excluded 417 (11%) patients who acquired COVID-19 after admission and 198 (5%) patients discharged to another hospital for whom mortality follow-up was incomplete.

Total participants: 3067 (First wave: 1612, Second wave: 885, Third wave: 370, Fourth wave: 200)
PCR-confirmed: All waves, wave 1 (clinical diagnosis: 144, PCR-confirmed: 1468)

Table S6: Participant characteristics (binary) in the non-imputed dataset

Variables	**N (%)**	**Missing**
Sex	1861 (60.7)	2 (<1)
Mortality	960 (31.3)	-
Chronic cardiac disease	636 (20.8)	2 (<1)
Chronic kidney disease	343 (11.5)	88 (2.9)
COPD	607 (19.8)	2 (<1)
Chronic liver disease	47 (1.5)	5 (<1)
Dementia	252 (8.2)	2 (<1)
Connective tissue disease	74 (2.4)	3 (<1)
Diabetes	949 (31)	3 (<1)
HIV	2 (<1)	1 (<1)
Cancer	605 (19.7)	1 (<1)
Obesity (BMI)	573 (23.0)	579 (18.9)

Table S7: Participant characteristics (continuous) in non-imputed dataset

Variables	**Median (IQR)**	**Missing**
Age	79 [74 – 84]	-
Respiratory rate	21 [17 - 26]	154 (5.0)
Oxygen saturation	93 [89 - 96]	853 (27.8)
Urea	8.2 [6 - 12]	1548 (50.5)
CRP	73 [35 - 132]	108 (3.5)
CFS	4 [3 - 6]	705 (23.0)
BMI	26.2 [23.7-29.7]	579 (18.9)
leucocytes	6.9 [5.1-9.5]	113 (3.7)
Lymphocytes	0.86 [0.59-1.30]	450 (14.7)
Creatinine	95 [74-131]	86 (2.8)
LDH	310 [236-413.8]	477 (15.6)
Oxygen saturation (without oxygen support)	93.0 [89.3-96.0]	853 (27.8)

Table S8: Participant characteristics in non-imputed dataset stratified by mortality

Variables	Survivors (N=2107)	Missing (%)	Died (N=960)	Missing (%)
Sex	1203 (57.2)	1 (<1)	658 (68.6)	1 (<1)
Chronic cardiac disease	407 (19.3)	-	229 (23.9)	2 (<1)
Chronic kidney disease	179 (8.8)	62 (3)	164 (17.6)	26 (2.7)
COPD	421 (20)	1 (<1)	186 (19.4)	1 (<1)
Chronic liver disease	33 (1.5)	3 (<1)	14 (1)	2 (<1)
Dementia	166 (7.8)	1 (<1)	86 (9)	1 (<1)
Connective tissue disease	45 (2.1)	2 (<1)	29 (3)	1 (<1)
Diabetes	619 (29.4)	3 (<1)	330 (34.4)	-
HIV	2 (<1)	-	0 (0)	1 (<1)
Cancer	427 (20.3)	-	178 (18.6)	1 (<1)
Obesity (BMI)	387 (22.4)	376 (17.8)	186 (24.6)	203 (21.1)
Glasgow coma scale	425 (39.0)	1016 (48.2)	96 (32.8)	667 (69.5)
Age	78 [74 – 83]	-	80 [75 – 85]	-
Respiratory rate	20 [16 - 25]	105 (5)	23 [19 - 28]	49 (5.1)
Oxygen saturation	94 [91 - 97]	510 (24.2)	91 [86 - 95]	343 (35.7)
Urea	7.75 [5.80 – 11.0]	923 (44)	10.9 [7.55 – 15.95]	625 (65.1)
CRP	64.0 [30.35 - 119]	76 (3.6)	98.5 [51.0 - 160]	32 (3.3)
CFS	4 [3 – 6]	456 (21.6)	5 [3 – 6]	249 (25.9)

Supplement 6: Detailed results of the incremental predictive performance assessment

Apparent performance

Table S9: Apparent predictive performance of 4C Mortality model and clinical frailty scale

Apparent performance		**Scaled brier score**	**Discrimination**	**Calibration-in-the-large**	**Calibration slope**
Step 1	Original 4C Mortality model	0.026 [-0.009 to 0.058]	0.70 [0.68 to 0.72]	-0.59 [-0.67 to -0.50]	0.88 [0.77 to 0.98]
	4C Mortality model + CFS	0.041 [0.006 to 0.072]	0.71 [0.69 to 0.73]	-0.61 [-0.69 to -0.53]	0.90 [0.80 to 0.99]
Step 2	Recalibrated 4C Mortality model	0.09 [0.07 to 0.11]	0.70 [0.68 to 0.72]	0.00 [-0.08 to 0.08]	1.00 [0.88 to 1.12]
	Recalibrated 4C Mortality model + CFS	0.112 [0.091 to 0.136]	0.71 [0.69 to 0.73]	-0.03 [-0.11 to 0.05]	0.98 [0.87 to 0 1.09]
Step 3	Revised 4C Mortality model	0.22 [0.20 to 0.25]	0.79 [0.77 to 0.80]	0.00 [-0.09 to 0.09]	1.00 [0.91 to 1.08]
	Revised 4C Mortality model + CFS	0.24 [0.21 to 0.27]	0.80 [0.78 to 0.82]	0.00 [-0.09 to 0.09]	1.00 [0.92 to 1.08]

Coefficients in the incremental predictive performance assessment steps

Table S 10: Model coefficients for the different versions of 4C Mortality model and clinical frailty scale incremental assessment steps.

		Step 1		**Step 2**		**Step 3**	
Predictors		**Original 4C Mortality model**	**Original 4C Mortality model +CFS**	**Recalibrated 4C Mortality model**	**Recalibrated 4C Mortality model +CFS**	**Revised 4C Mortality model**	**Revised 4C Mortality model +CFS**
Intercept	**-**	-4.203		-4.284643		-3.3717	-3.25224
Age (years)	70-79	1.842		1.615018		-	-
	≥80	2.252		1.974495		0.3434	0.15157
Sex at birth	Male	0.172		0.1508052		0.2294	0.37560
Number of comorbidities*	1	0.300		0.2630322		0.3914	0.27566
	≥2	0.532		0.4664439		0.1645	-0.04705
Respiratory rate (breaths/minute)	20-29	0.232		0.2034116		0.3797	0.37119
	≥30	0.649		0.5690264		0.5222	0.53523
Oxygen saturation on room air (%)	<92	0.577		0.5058987		1.1733	1.20956

Glasgow Coma Scale	<15	0.558		0.48924		-1.0494	-1.06836
Urea (mmol/L)	7-14	0.439		0.3849039		1.4598	1.33599
	>14	1.011		0.8864187		1.8988	1.74434
CRP (mg/dL)	50-99	0.363		0.318269		0.2511	0.30664
	≥100	0.74		0.6488129		0.4429	0.58018
CFS		-	0.28526	-	0.33569	-	0.43857

Supplement 7: TRIPOD checklist

TRIPOD Checklist: Prediction Model Development

Section/Topic	Item	Checklist Item	Page
Title and abstract			
Title	1	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	5
Abstract	2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	5-6
Introduction			
Background and objectives	3a	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	7
	3b	Specify the objectives, including whether the study describes the development or validation of the model or both.	7
Methods			
Source of data	4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	8
	4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	Supplement 5
Participants	5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	8
	5b	Describe eligibility criteria for participants.	Supplement 5
	5c	Give details of treatments received, if relevant.	NA
Outcome	6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	8
	6b	Report any actions to blind assessment of the outcome to be predicted.	NA
Predictors	7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	8, Supplement 5
	7b	Report any actions to blind assessment of predictors for the outcome and other predictors.	NA
Sample size	8	Explain how the study size was arrived at.	Supplement 4
Missing data	9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	10, Supplement 5
Statistical analysis methods	10a	Describe how predictors were handled in the analyses.	9
	10b	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	9
	10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	9-10
Risk groups	11	Provide details on how risk groups were created, if done.	NA
Results			
Participants	13a	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	10, Supplement 5
	13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	10, Supplement 5
Model development	14a	Specify the number of participants and outcome events in each analysis.	Supplement 4
	14b	If done, report the unadjusted association between each candidate predictor and outcome.	NA
Model specification	15a	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	Supplement 6
	15b	Explain how to the use the prediction model.	NA
Model performance	16	Report performance measures (with CIs) for the prediction model.	11
Discussion			
Limitations	18	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	13
Interpretation	19b	Give an overall interpretation of the results, considering objectives, limitations, and results from similar studies, and other relevant evidence.	14
Implications	20	Discuss the potential clinical use of the model and implications for future research.	14
Other information			
Supplementary information	21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	14
Funding	22	Give the source of funding and the role of the funders for the present study.	14