

Appendix 1: Procedures for evaluation of each frailty index.

Clinical Frailty Scale ¹⁵

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 helping 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 around 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.)

Derby Frailty Index ²⁰

Frailty is suggested if one or more of the following criteria were met:

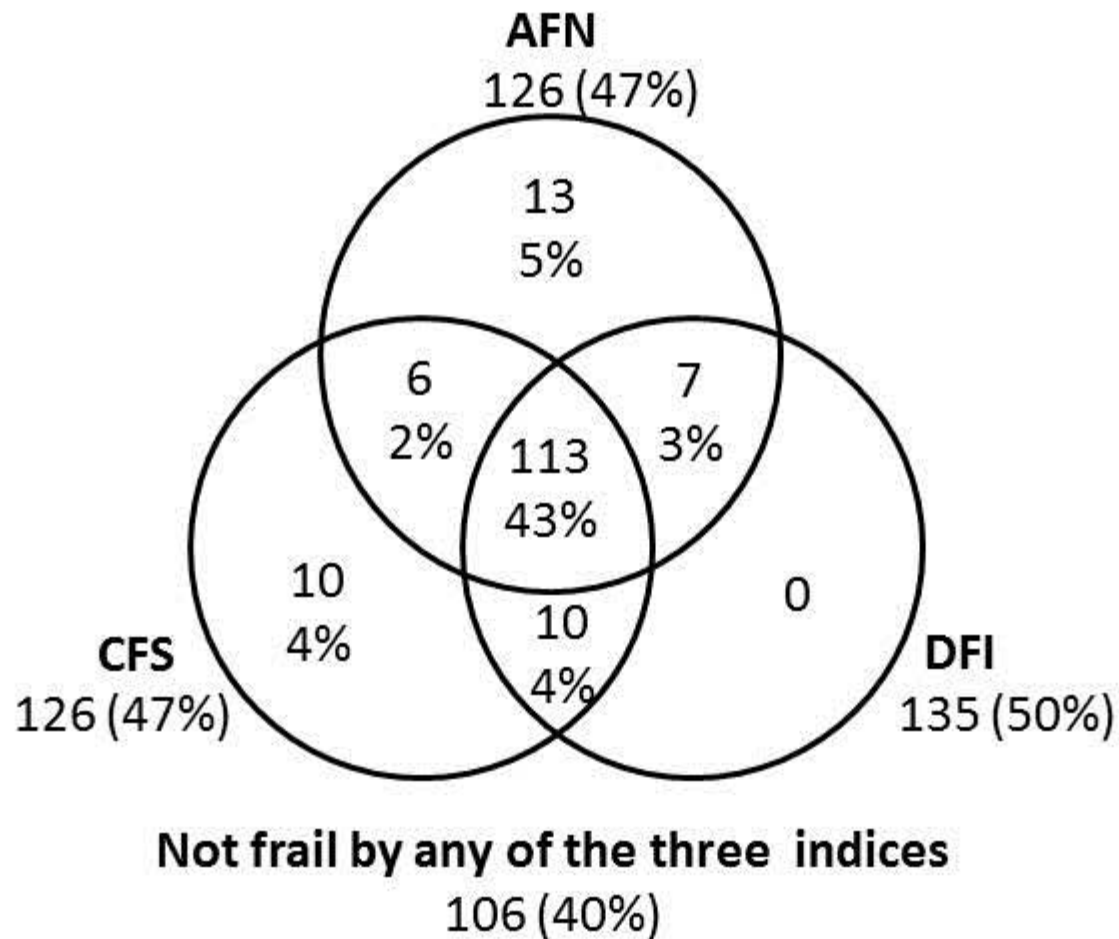
- >65 and a care home resident
- >75 with confusion, falls or reduced mobility
- >84 with >4 co-morbidities.

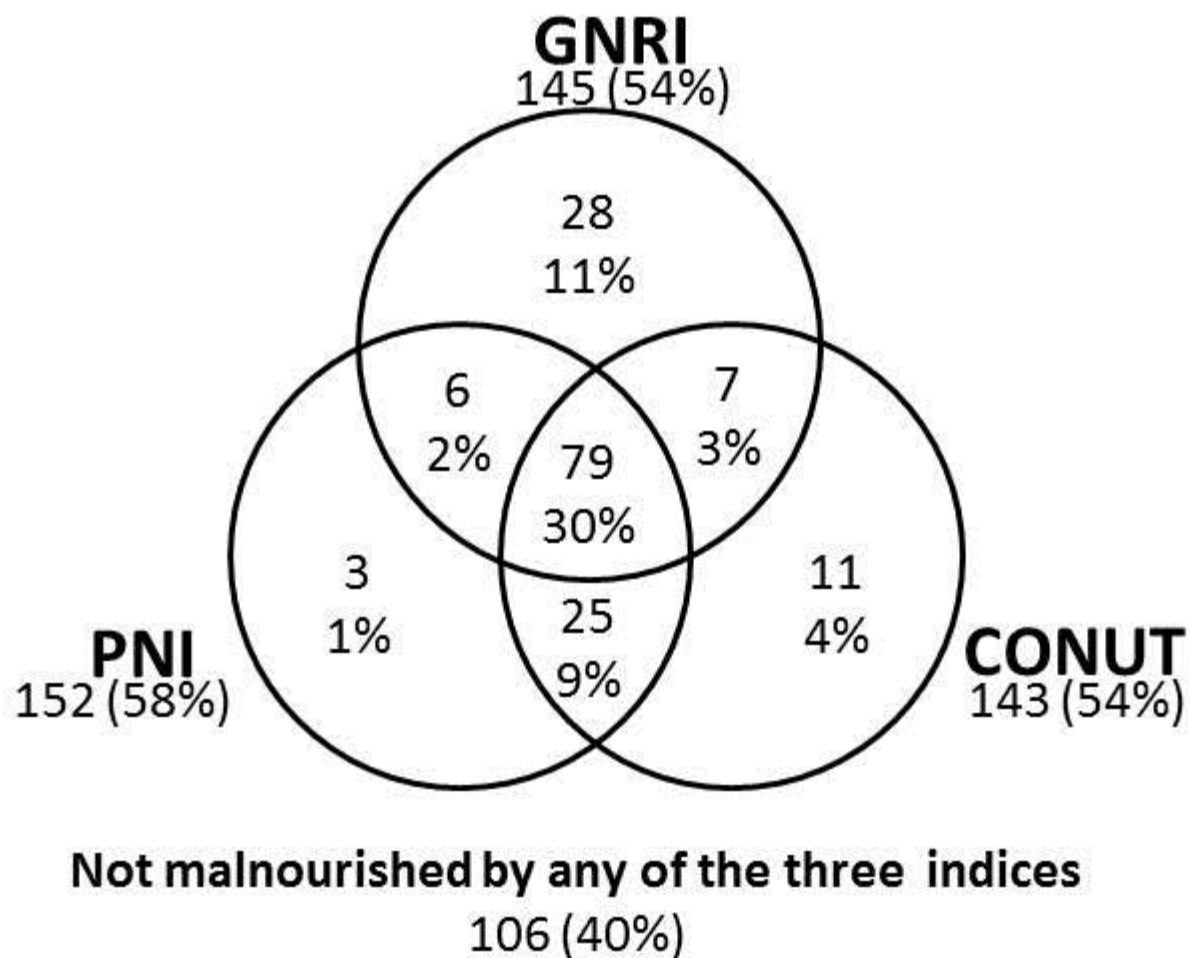
Acute frailty network (AFN) frailty definition ²¹

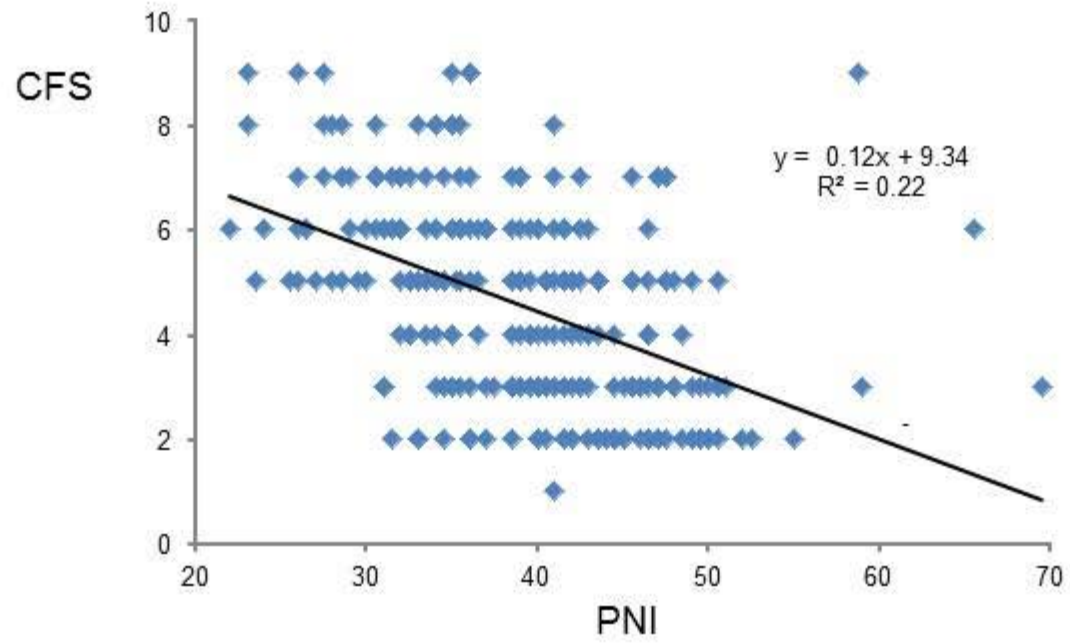
- people aged 85+ or
- people aged 65+ with one or more of the following presenting features:
 1. cognitive impairment (delirium or dementia)
 2. Care home residents (nursing or dementia)
 3. people with fragility fractures
 4. people with Parkinson's disease
 5. People with recurrent falls

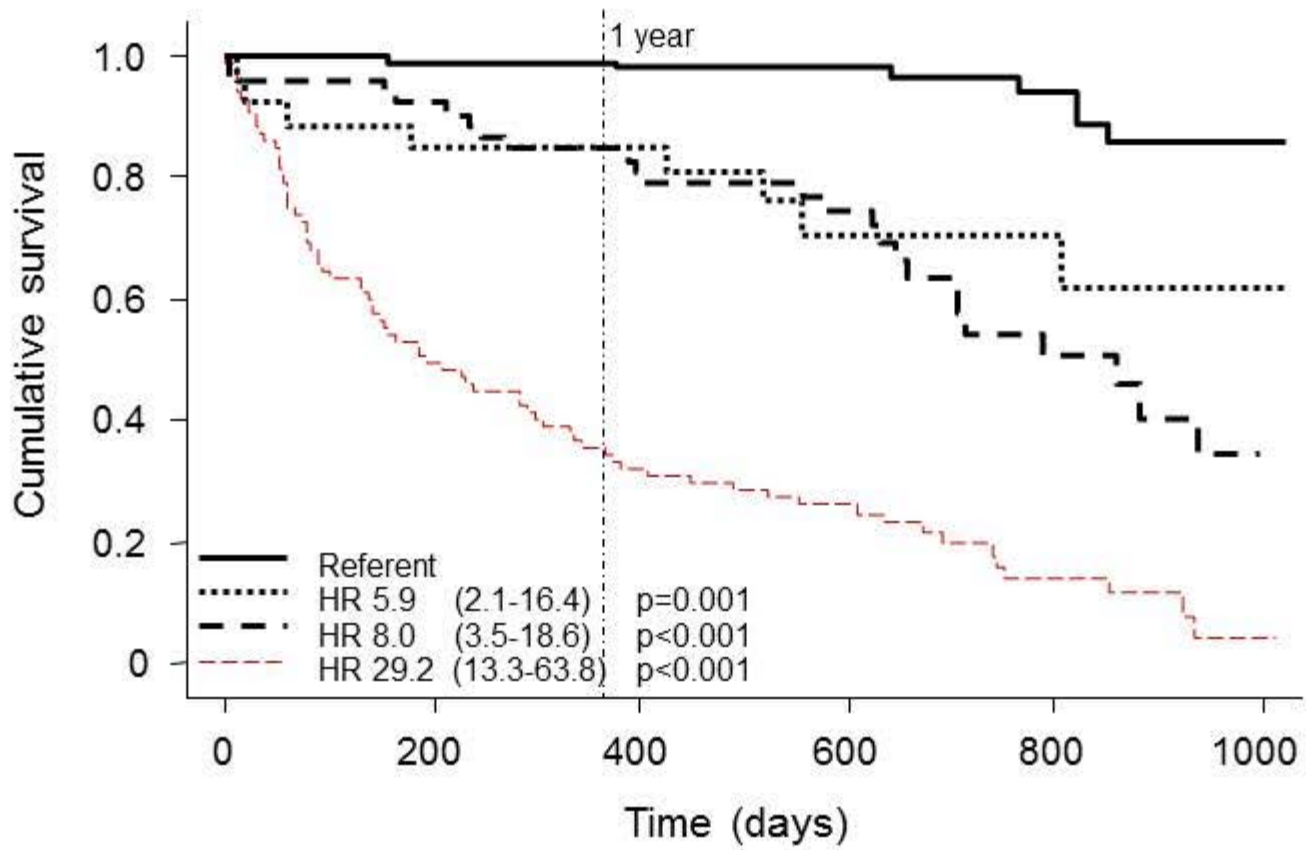
Appendix 2: Procedures for evaluation of each nutritional index.

Nutritional Indices	Degree of malnutrition			
	Normal	Mild	Moderate	Severe
<u>Controlling Nutritional Status (CONUT) score</u> ¹³				
Albumin, g/L (score)	≥35 (0)	30-34 (2)	25-29 (4)	<25 (6)
Cholesterol, mmol/L (score)	>4.65 (0)	3.62-4.65 (1)	2.59-3.61 (2)	<2.59 (3)
Total Lymphocyte count , x10 ⁹ /L (score)	≥1.60 (0)	1.20-1.59 (1)	0.80-1.19 (2)	<0.80 (3)
Overall score	0-1	2-4	5-8	9-12
<u>Geriatric Nutritional risk index (GNRI)</u> ¹⁴				
= 1.489 x serum albumin (g/L) + 41.7 x (body weight in kilograms / ideal body weight)	>98	92-98	82-91	<82
<u>Prognostic nutritional index (PNI)</u> ¹⁶				
= 10 x serum albumin (g/dL) + 0.005 x total lymphocyte count (mm ³)	>38	-	35-38	<35









Not malnourished & not frail	100	99	98	74	39	6	—
Malnourished & not frail	26	22	22	10	8	1
Not malnourished & frail	52	48	41	29	14	0	- - -
Malnourished & frail	86	43	28	18	6	1	- - -

Table 1: Baseline characteristics of study cohort

Variables	Total cohort (N=265)	Frail CFS >4 (N=139)	Not frail CFS ≤4 (N=126)	P value	Malnourished PNI ≤38 (N=113)	Not malnourished PNI >38 (N =152)	P value
Age (years)	80 (72-86)	85 (80-89)	73 (66-79)	<0.001	84 (77-89)	78 (69-84)	<0.001
Age >75 (years)	66.4%	87.8%	42.9%	<0.001	75.2%	59.9%	0.009
Men	61.9%	59.3%	65.9%	0.2	62.8%	61.2%	0.8
Nursing home resident	14%	26.6%	0	<0.001	27.4%	3.9%	<0.001
NYHA III-IV	74%	84.2%	62.7%	0.001	81.4%	68.4%	0.03
SBP (mmHg)	123 (109-140)	123 (109-140)	122 (109-139)	0.9	120 (107-138)	125 (110-141)	0.1
Heart rate (bpm)	83 (68-97)	82 (66-96)	84 (72-98)	0.4	83 (69-100)	82 (66-96)	0.5
QRS duration	108 (96-134)	110 (96-135)	107 (96-124)	0.4	106 (94-137)	110 (97-127)	0.3
Weight (kg)	78.0	72.8	84.1	<0.001	71	81.8	0.002
	(65-90.4)	(62-84.8)	(70.4-94.3)		(59.2-85.4)	(69.8-93)	
BMI (kg/m ²)	27.5	26.1	28.4	0.02	25.8	28.4	0.03
	(23.4-31.1)	(22.3-30.3)	(24.6-32.7)		(21.3-29.6)	(24.5-32.1)	
Comorbidities							
Atrial fibrillation	55.1%	66.9%	42.1%	<0.001	61.9%	50%	0.05
Hypertension	63%	69.1%	56.3%	0.03	64.6%	61.8%	0.6
IHD	43.4%	47.5%	38.9%	0.2	45.1%	42.1%	0.6
Valvular disease	32.1%	41%	22.2%	0.001	44.2%	23%	<0.001
Device therapy	18.5%	21.6%	15.9%	0.3	17.7%	19.7%	0.6
Diabetes Mellitus	35.5%	30.9%	40.5%	0.1	30.1%	39.5%	0.1
COPD	22.3%	24.5%	19.8%	0.4	23.9%	21.1%	0.6
Depression	17.4%	20.1%	14.3%	0.2	16.8%	17.8%	0.8
Falls	44.2%	72.7%	12.7%	<0.001	62.8%	30.3%	<0.001
Dementia	17.7%	33.1%	0.8%	<0.001	25.7%	11.8%	0.004
Charlson Score	8 (6-10)	9 (7-11)	7.5 (5-7)	0.001	8 (6-11)	8.5 (6-10)	0.6
Medications							
ACEi/ARB	64.2%	57.6%	71.4%	0.02	54%	71.7%	0.003
MRA	42.6%	38.1%	47.6%	0.1	42.5%	42.8%	0.9
Betablockers	74.7%	69.1%	81%	0.03	68.1%	79.6%	0.03
Loop diuretics	85.3%	89.2%	81%	0.06	87.6%	83.6%	0.4
Thiazide diuretics	2.3%	1.4%	3.2%	0.3	1.8%	2.6%	0.6
Digoxin	20.4%	23%	17.5%	0.3	21.2%	19.7%	0.8
Statin	54.3%	48.9%	60.3%	0.06	47.8%	59.2%	0.07
Laboratory variables							
NT Pro BNP (ng/L)	3633	3669	3537	0.8	4198	3322	0.1
	(2025-6407)	(1899-6579)	(2091-6097)		(2230-7966)	(1514-5600)	
Haemoglobin (g/dL)	12.4 (11.1-13.8)	11.8 (10.5-13)	13.4 (12-14.2)	<0.001	11.8 (10.5-13)	13.2 (11.6-14.1)	<0.001
Urea (mmol/L)	8.9 (6.4-13.2)	11.1 (7.3-16.2)	7.6 (5.8-10.9)	<0.001	11.7(7.1-17)	8 (6.1-11.6)	0.001
Creatinine (μmol/L)	105 (83-141)	118 (89-156)	98 (77-117)	0.008	115 (85-158)	100 (82-126)	0.06
Sodium (mmol/L)	138 (135-140)	137 (134-139)	138 (135-140)	0.1	137 (133-139)	138 (135-140)	0.008
Potassium (mmol/L)	4.2 (3.9-4.65)	4.3 (3.9-4.7)	4.2 (3.9-4.5)	0.05	4.3 (3.9-4.8)	4.2 (3.9-4.5)	0.1
Albumin (g/L)	33 (29-36)	30 (27-34)	35 (32-37)	<0.001	28 (26-30)	35 (34-37)	<0.001
Cholesterol (mmol/L)	4.0 (3.4-4.7)	3.9 (3.3-4.6)	4.2 (3.6-4.9)	0.2	3.9 (3.2-4.6)	4.1 (3.6-4.8)	0.1
Lymphocyte (x10 ⁹ /L)	1.2 (0.8-1.7)	1.0 (0.7-1.4)	1.5 (1.1-2.0)	<0.001	0.9 (0.6-1.2)	1.6(1.1-2.1)	<0.001

Values are presented as median (interquartile range) or percentage.

NYHA = New York Heart Association Class, SBP = Systolic blood pressure, IHD = Ischaemic heart disease, COPD = Chronic obstructive pulmonary disease, ACEi/ARB = Angiotensin-converting enzyme inhibitor or Angiotensin receptor blocker, MRA = Mineralocorticoids receptor antagonists, NTProBNP = N-terminal Pro Brain Natriuretic Peptide, Hb = Haemoglobin , CONUT = Controlling nutritional status, PNI = Prognostic nutritional Index, GNRI = Geriatric nutritional risk index, AFN = Acute frailty network frailty criteria, DFI = Derby frailty index, CFS = Clinical Frailty Scale

Table 2 Correlation coefficients for frailty and malnutrition indices

Indices	DFI	AFN	CFS	CONUT	GNRI
AFN	0.78				
CFS	0.70	0.61			
CONUT	0.46	0.40	0.50		
GNRI	-0.34	-0.30	-0.39	-0.58	
PNI	-0.43	-0.38	-0.47	-0.85	0.55

All p values < 0.001.

CONUT= Controlling nutritional index, GNRI = Geriatric Nutritional Risk Index, PNI = Prognostic Nutritional Index, AFN = Acute Frailty Network Frailty criteria, CFS = Clinical Frailty Scale, DFI = Derby Frailty Index

Table 3: Univariable predictors of mortality, multivariable analysis for malnutrition scores, multivariable analysis for frailty scores

Worse outcome per unitary increase	Univariate analysis			Malnutrition MV analysis			Frailty MV analysis		
	HR(95%CI)	Wald X ²	p-value	HR(95%CI)	Wald X ²	p-value	HR(95%CI)	Wald X ²	p-value
Age (yrs)	1.05(1.03-0.07)	23.04	<0.001						
Haemoglobin (g/dL)	0.85 (0.78-0.94)	11.16	0.001						
Atrial fibrillation* (yes vs no)	1.97 (1.32-2.92)	11.22	0.001						
Log NTProBNP	1.92 (1.16-3.16)	6.45	0.01						
Creatinine (μmol/L)	1.02 (1.01-1.05)	9.55	0.002						
Sodium (mmol/L)	0.95 (0.93-0.98)	8.76	0.003	0.96 (0.93-1.00)	4.49	0.03			
Recurrent Falls* (yes vs no)	4.89 (3.19-7.51)	52.71	<0.001	2.60 (1.60-4.24)	14.67	<0.001			
IHD* (yes vs no)	1.50 (1.03-2.17)	4.49	0.03						
CONUT score (increasing score)	1.42 (1.32-1.53)	91.39	<0.001	1.06 (0.89-1.27)	0.44	0.51**			
GNRI (decreasing score)	1.04 (1.03-1.06)	40.45	<0.001						
PNI (decreasing score)	1.14 (1.12-1.17)	88.36	<0.001	1.08 (1.01-1.16)	4.41	0.04**			

AFN* (frail vs not frail)	6.46 (3.90-10.70)	52.27	<0.001			
CFS (increasing score)	1.74 (1.57-1.93)	109.00	<0.001	1.56 (1.35-1.81)	35.76	<0.001
DFI* (frail vs not frail)	9.23 (5.43-15.69)	67.24	<0.001	2.58 (1.09-6.12)	4.62	0.03

For continuous variables, HR relate to the hazard associated per unitary increase in the variable except for creatinine where HR relates to the hazard associated per10 $\mu\text{mol/L}$ increase in creatinine. For categorical variables (*), HR quoted compares groups specified in brackets.

** As increasing CONUT score is highly correlated with decreasing PNI (correlation coefficient = 0.85, $p < 0.0001$), excluding either CONUT or PNI from the multivariable model would render the other variable statistically significant in predicting mortality.

HR = hazard ratio, CI= confidence interval, MV = multivariable, X²= chi-square, IHD = Ischaemic heart disease, CONUT= controlling nutritional index, GNRI = Geriatric Nutritional Risk Index, PNI = Prognostic Nutritional Index, AFN = Acute Frailty Network Frailty criteria, CFS = Clinical Frailty Scale, DFI = Derby Frailty Index

Table 4: Addition of frailty and malnutrition indices to base models improved model performance in predicting all-cause mortality

Discrimination		
Model	C-statistics	P-value (compared to base model)
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Malnutrition base model*	0.74	
+ CONUT score	0.80	<0.001
+ GNRI	0.78	0.001
+ PNI	0.81	<0.001
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Frailty base model**	0.68	
+ AFN	0.74	0.009
+ CFS	0.81	<0.001
+ DFI	0.76	0.004
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*Variables included in the malnutrition base model: age, sex, haemoglobin, atrial fibrillation, logNTProBNP, serum creatinine, serum sodium, recurrent falls and presence of ischaemic heart disease.

** Variables included in the frailty base model: sex, haemoglobin, atrial fibrillation, logNTProBNP, serum creatinine, serum sodium and presence of ischaemic heart disease. Age and recurrent falls were excluded as they are part of the DFI and AFN frailty criteria.

CONUT= controlling nutritional index, GNRI = Geriatric Nutritional Risk Index, PNI = Prognostic Nutritional Index, AFN = Acute Frailty Network Frailty criteria, CFS = Clinical Frailty Scale, DFI = Derby Frailty Index

Table 5: Multivariable analysis including Clinical frailty scale and prognostic nutrition index

	HR	95% CI	Wald X ²	P value
Worse outcome per unitary increase				
Clinical Frailty Scale (increasing score)	1.55	1.35-1.77	39.06	<0.001
Prognostic nutrition index (decreasing score)	1.09	1.06-1.12	27.98	<0.001
Creatinine (µmol/L)	1.03	1.00-1.05	4.67	0.03
Recurrent Falls* (yes vs no)	1.53	0.94-2.50	2.89	0.09
Sodium (mmol/L)	0.97	0.94-1.01	2.46	0.12
Log NTProBNP	1.45	0.88-2.40	2.16	0.14
Gender* (male vs female)	0.82	0.54-1.24	0.88	0.35
Atrial fibrillation* (yes vs no)	1.10	0.73-1.67	0.20	0.65
Haemoglobin (g/dL)	1.02	0.91-1.13	0.10	0.75
Ischaemic heart disease* (yes vs no)	1.06	0.70-1.60	0.07	0.79
Age (years)	0.99	0.97-1.02	0.01	0.93

c-statistic = 0.84.

For continuous variables, HR relate to the hazard associated per unitary increase in the variable except for creatinine where HR relates to the hazard associated per 10 µmol/L increase in creatinine. For categorical variables (*), HR quoted compares groups specified in brackets.

HR = hazard ratio, CI= confidence interval, X²= chi-square