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Frailty trajectories in ICU survivors: A comparison between the clinical frailty scale and the Tilburg frailty Indicator and association with 1 year mortality

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ABSTRACT

Purpose: To test the agreement of the Clinical Frailty Scale (CFS) and the Tilburg Frailty Indicator (TFI), their association with 3, 6 months and 1-year mortality and the trajectory of frailty in a mixed population of ICU survivors.

Material and methods: This is a prospective, multicenter, longitudinal study on ICU survivors ≥18 years old with an ICU stay >72 h. For each patient, sociodemographic and clinical data were collected. Frailty was assessed during ICU stay and at 3, 6, 12 months after ICU discharge, through both CFS and TFI.

Results: 124 patients with a mean age of 66 years old were enrolled. The baseline prevalence of frailty was 15.3% by CFS and 44.4% by TFI. Baseline CFS and TFI correlated but showed low agreement (Cohen's K = 0.23, $p < 0.001$). Baseline CFS score, but not TFI, was significantly associated to 1 year mortality. Moreover, CFS score during the follow-up was independently associated 1-year mortality (OR = 1.43; 95% CI: 1.18–1.73).

Conclusions: CFS and TFI identify different populations of frail ICU survivors. Frail patients before ICU according to CFS have a significantly higher mortality after ICU discharge. The CFS during follow-up is an independent negative prognostic factor of long-term mortality in the ICU population.

1. Background

The admission to an Intensive Care Unit (ICU) is a stressful event and can increase the risk of long-term adverse outcomes, disability and death [1]. Moreover, the increased life expectancy over the last decades has led to a large number of older patients admissions [2,3] and of frail long-term ICU survivors [4,5].

Frailty is defined as a condition of vulnerability to negative outcomes (e.g. falls, disability, hospitalization, institutionalization, death) and is increasingly investigated in the ICU setting [6]. Advanced age per se does not imply the presence of frailty [7]. Increased evidences have been reported on frailty in younger adults [8-10] with a consequent negative impact on their prognosis [11]. The early detection of frailty among patients admitted to ICU and the analysis of the trajectories of frailty after ICU discharge may therefore provide a more precise risk stratification and care-planning [12-14].

Abbreviations: ICU, intensive care unit; CFS, clinical frailty scale; TFI, Tilburg Frailty indicator; BMI, Body mass index; SAPS II, Simplified acute physiology score; SOFA, sequential organ failure assessment.

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Despite the large number of tools available for the screening of frailty, only a few of them might be suitable for routine utilization in the ICU setting. Specifically, the Clinical Frailty Scale (CFS) and the Tilburg Frailty Indicator (TFI) are widely used and demonstrate high reliability in clinical practice [7,15]. The CFS is validated in the ICU setting on older patients, is easier to collect and widely adopted, but it may miss some aspects linked to frailty, not including any psychological or social items [16]. On the other hand, the TFI is a self-report screening questionnaire that integrates physical, psychological and social domains [17,18] and has been used also in the non-elderly population [19]. The multidimensional approach of TFI may therefore potentially be useful to assess aspects of frailty not evaluated by CFS, which is more focused on the clinical characteristics of the patient [20].

Considering the differences in the items used to evaluate frailty, we hypothesized that TFI and CFS may identify different populations of frail ICU patients and that the two tools may have different association with mortality during the 1th year follow up after ICU discharge. To test these hypotheses, we compared the TFI and CFS scores collected from a mixed population of ICU survivors during ICU stay and at 3, 6 and 12 months after ICU discharge. We also evaluated the trajectories of frailty the effect of frailty assessed by the two indices on 1-year mortality.

2. Methods

2.1. Study population

This is a multicenter prospective cohort study conducted between March 2017 and July 2018 (ICU enrollment: March 2017 – July 2017; follow-up: June 2017–July 2018) on ICU survivors admitted to three ICUs in Italy (Ferrara, Ravenna and Mantova). In each participating center, one physician who contributed to the study protocol was responsible for patient data collection and follow up (MD for Ferrara, GZ for Ravenna, and AB for Mantova). All patients admitted to these ICUs were considered for enrollment in the study. Inclusion criteria were: age $\geq$ 18, Italian mother-tongue, ICU admission and ICU stay >72 h. Patients were excluded from the study in case of pre-ICU diagnosis of severe cognitive impairment, ICU readmission during the study period, death during ICU stay, intensive care treatment withdrawal or diagnosis of delirium. The Institutional Ethical Committee of Ferrara (CE-AVEC), coordinating center of the present study, approved the study protocol (CE number 161297). Moreover, Ethical approval was obtained for each participating research centerand each patient gave the informed consent to the study participation.

2.2. Measures

Frailty was assessed with two different tools, i.e. the CFS [16] and the TFI [17]. The CFS is filled in by the physician after a brief interview with the patients and measures the overall level of frailty of the individual, ranging between 1 (very fit) and 9 (terminally ill). The TFI is indeed a self-administered screening questionnaire and ranges between 0 (non-frail) and 15 (extremely frail). While CFS is a 9-items tool, TFI consists of two main parts: the first section (part A) assesses the determinants of frailty (10 questions), the second one (part B) consists in a multidimensional evaluation on physical, psychological, and social status of the patient (15 questions). For both instruments, higher scores are indicative of more severe frailty. A cut-off of 5 was used to define the presence of frailty according to both scales [17,21]. Frailty was assessed at baseline (during ICU stay but referring to 1 month prior to hospitalization) and at 3, 6 and 12-month follow-up (see *data collection* and *Follow-up)*.

2.3. Data collection

For each participant, sociodemographic and clinical data were collected from hospital medical records. In particular: age, sex, Body Mass Index (BMI), main pre-admission comorbidities (arterial hypertension, chronic heart failure, coronary heart disease, chronic obstructive pulmonary disease, chronic kidney failure, diabetes, obesity), type of ICU admission (medical or surgical admission or trauma) and hospital medical treatment (e.g., vasoactive amines, mechanical ventilation). Clinical gravity scores (SAPS II and SOFA score) were assessed after 24 h from ICU admission using the Margherita-PROSAFE software (GiViTI, Italy). The date of ICU discharge and the length of stay were also collected. During ICU stay, as soon as the patient was conscious and capable of carrying out the interview, both CFS and TFI were obtained by a trained researcher (MD in Ferrara, GZ in Ravenna, and EB in Mantova). The order of administration was randomly selected using sealed envelopes previously prepared by a research coordinator who did not participate in the questionnaire administration. For both instruments and for the measurement at baseline the patient was asked to consider her/his status to 1 month before hospitalization. As concerns the TFI, which is a self-reported questionnaire, the physician facilitated the question to the patient if the latter was not able to directly read and fill the form.

2.4. Follow-up

Patient status (alive or dead) was assessed via hospital database at 3, 6 and 12 months after ICU discharge. Through a telephone interview, a new evaluation of frailty according to both CFS and TFI was performed for every patient who survived at each time point. For each center, the examiners were the same that performed the frailty evaluation at baseline. For the follow-up frailty evaluation, the patients were asked to refer to their current state to minimize recall biases and the examiners were asked to not check previous frailty data to avoid a prejudice bias.

2.5. Statistical analysis

Continuous variables were summarized as mean and standard deviation (SD), when normally distributed, otherwise median and interquartile range were used. Categorical variables were described using absolute and relative frequencies. Normality in distribution was assessed by means of visual inspection of histograms and Shapiro-Wilk test. The correlation between CFS and TFI was assessed using the Spearman's correlation coefficient and the Cohen's Kappa coefficient was used to determine the level of agreement between the two frailty groups.

Frail and non-frail groups at baseline, according to both CFS and TFI scales, were compared with respect to continuous variables using the Student's *t*-test for normally distributed variables or with the Wilcoxon-Mann-Whitney test otherwise. The association between frailty and categorical variables was assessed with the Pearson's $\chi 2$ test. Factors statistically associated with frailty were included in a multiple logistic regression model, with frailty as the dependent variable; the model was simplified using a backward stepwise selection method (p for removal >0.05). Results were reported as Odds Ratio (OR) and 95% Confidence Interval (95% CI).

Alluvial plots were used to describe variation in frailty status and mortality occurrence during the 1-year follow-up. In addition, linear mixed effects models were fitted to estimate CFS and TFI trajectories during the follow-up according to different groups, i.e. by sex, age classes and baseline frailty. Moreover, a sensitivity analysis was conducted in the subgroup of patients alive at 12 months to assess robustness of findings.

Univariate Cox regression models were used to assess the association between 1-year mortality and each other variable. TFI and CFS scores were considered both at baseline and during follow-up; in the second case they were included as time varying variables as their value could change between follow-ups.

A multiple Cox regression model was performed using clinically relevant factors (Age, SAPSII and SOFA score) to assess whether CFS and TFI remained significant predictors after the adjustment for other

factors. SOFA score was excluded from the model for the presence of collinearity with SAPSII.

Sample size was calculated on the primary outcome, i.e. on the accordance between the TFI and CFS scores. Assuming a prevalence of frailty ranging between 10% and 50% according to both the scores and that the TFI identifies a higher prevalence than CFS of about 25% (e.g. 40% vs 15%), with a power $\geq$ 80% and a significance level of 0.05, 124 patients are sufficient to identify a Cohen'kappa of 0.2 as statistically significant.

Statistical analyses were conducted with Stata statistical software 15.1 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC) and statistical significance was set for $p < 0.05$. Alluvial plots were created using the `ggalluvial` package of R statistical software (R Core Team (2022). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

3. Results

We enrolled 124 patients (Fig. 1) and their baseline characteristics are reported in Table 1. Fifty-nine percent was >65 years old, with an overall mean age of 66 years, and the 67.7% of the sample was male. More than three-quarters of the participants (83.9%) reported comorbidities, 52.4% had arterial hypertension and 21.8% diabetes. One-year mortality after ICU discharge was 24.3%.

3.1. Frailty population at baseline, CFS

The prevalence of frailty at baseline was 15.3% ($n = 19$) according to the CFS. Sociodemographic and clinical characteristics of the participants according to the presence of frailty at baseline are shown in Table 1. Advanced age (74 vs 64 years old, $p < 0.001$) and the number of medications chronically taken (5 vs 3 drugs, $p = 0.005$) were higher among individuals with frailty, while marital status was more common in non-frail patients (47.4% vs 80.5%, $p = 0.003$). Frail participants were more likely female (57.9% vs 27.6%, $p = 0.009$) and reported a higher prevalence of arterial hypertension (73.7% vs 48.6%, $p = 0.044$), chronic obstructive pulmonary disease (26.3% vs 8.6%, $p = 0.040$), and need of respiratory support longer than 24 h (92.3% vs 51.6%, $p = 0.006$). In the multivariable analysis, the factors associated with a greater likelihood of being frail at baseline according to CFS were age (OR = 1.09; 95%CI: 11.02–1.16) and female sex (OR = 3.31; 95%CI: 1.04–10.50). Marital status was protective (OR 0.33; 95% CI [0.10–1.06]), but the association was not significant ($p = 0.062$).

3.2. Frailty population at baseline, TFI

The baseline prevalence of frailty was 44.4% ($n = 55$) according to TFI. The frail population was characterized by higher age (69 vs 63 years old, $p = 0.011$), a higher number of chronic medications (4 vs 2 drugs, $p = 0.004$) and a lower frequency of married people (58.2% vs 88.4%, $p < 0.001$). The frail population at baseline had a higher prevalence of comorbidities (94.6% vs 72.4%, p = 0.004), and chronic kidney failure (18.2% vs 5.8%, $p = 0.030$). In multivariable analysis the number of

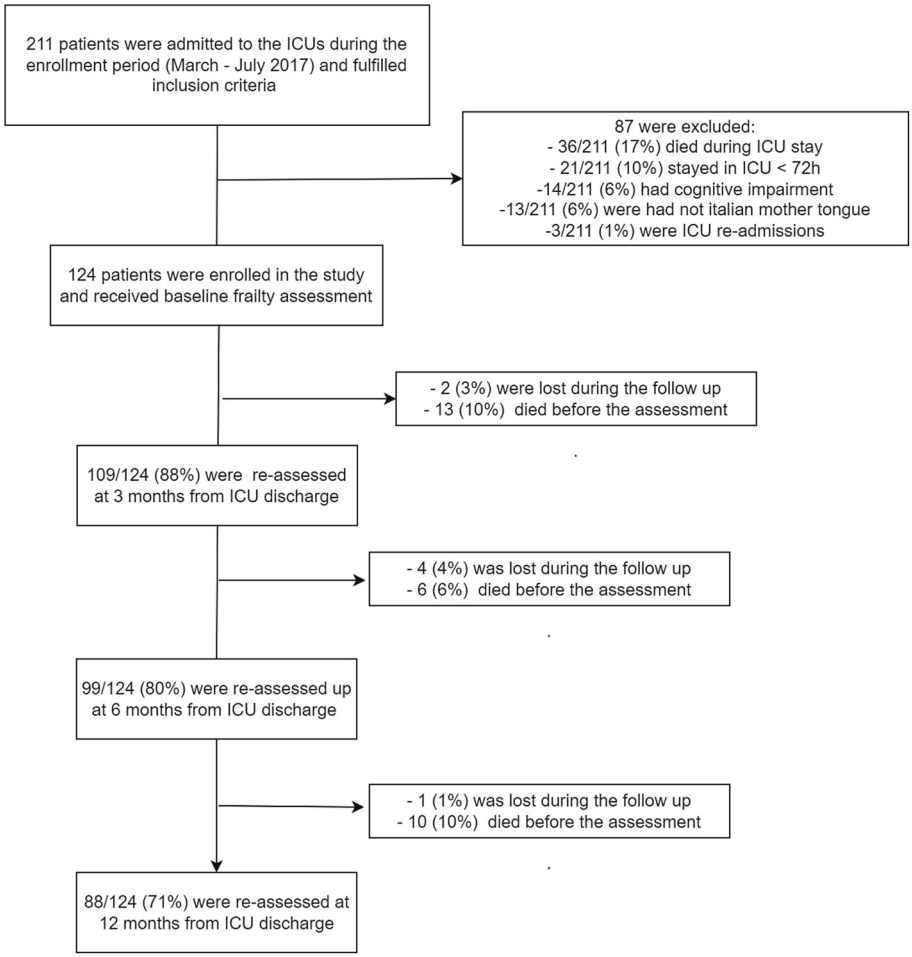

Fig. 1. Flowchart of the study with enrollment times and follow up.

Table 1
Factors associated with the presence of frailty at baseline according to CFS and TFI scores.

	CFS			TFI		
	Non-frail *N* = 105	Frail N = 19	p	Non-frail *N* = 69	Frail N = 55	p
Sex F, n (%)	29 (27.6)	11 (57.9)	**0.009**	18 (26.1)	22 (40.0)	0.100
Age (years), mean ± SD	64.0 ± 13.7	74.0 ± 6.7	**<0.001**	62.9 ± 14.4	68.9 ± 11.0	**0.011**
Married status, n (%)	84 (80.0)	9 (47.4)	**0.003**	61 (88.4)	32 (58.2)	**<0.001**
BMI (Kg/m^2), mean ± SD	28.2 ± 6.3	26.6 ± 6.3	0.333	27.5 ± 5.6	28.5 ± 7.1	0.389
Previous hospitalizations, n (%)	42 (40.0)	8 (42.1)	0.863	23 (33.3)	27 (49.1)	0.076
Admissions in ICU, n (%)	10 (9.5)	3 (15.8)	0.419	4 (5.8)	9 (16.4)	0.056
Number of drugs, median [IQR]	3 [1–5]	5 [4–8]	**0.005**	2 [1–4]	4 [2–7]	**0.004**
Comorbidity, n (%)	86 (81.9)	18 (94.7)	0.306	52 (72.4)	52 (94.6)	**0.004**
Arterial hypertension, n (%)	51 (48.6)	14 (73.7)	**0.044**	33 (47.8)	32 (58.2)	0.251
CODP, n (%)	9 (8.6)	5 (26.3)	**0.040**	5 (7.2)	9 (16.4)	0.111
CKD, n (%)	11 (10.5)	3 (15.8)	0.449	4 (5.8)	10 (18.2)	**0.030**
CHF/CHD, n (%)	13 (12.4)	5 (26.3)	0.151	8 (11.6)	10 (18.2)	0.301
Diabetes, n (%)	21 (20.0)	6 (31.6)	0.363	14 (20.3)	13 (23.6)	0.654
Obesity, n (%)	15 (14.3)	2 (10.5)	1.00	7 (10.1)	10 (18.2)	0.196
Type of admission, n (%)*			0.741			0.164
Medical admission, n (%)	24 (26.4)	5 (35.7)		16 (28.1)	13 (27.1)	
Surgery, n (%)	63 (69.2)	9 (64.3)		37 (64.9)	35 (72.9)	
Trauma, n (%)	4 (4.4)	0		4 (7.0)	0	
SAPSII, mean ± SD*	36.4 ± 13.6	39.8 ± 13.4	0.352	36.7 ± 14.7	37.1 ± 12.1	0.853
SOFA Score, mean ± SD*	5.6 ± 3.4	6.9 ± 2.6	0.159	5.9 ± 3.5	5.6 ± 3.0	0.638
Mechanical ventilation > 24 h, n (%)*	48 (51.6)	12 (92.3)	**0.006**	33 (55.0)	27 (58.7)	0.704
ICU LOS (days), median [IQR]*	6 [4–9]	7 [4–11]	0.496	6 [4–9.5]	7 [3.5–11]	0.475

Notes: CFS = Clinical Frailty Scale; TFI = Tilburg Frailty Indicator; BMI = Body Mass Index; CODP = Chronic Obstructive Pulmonary Disease; CKD = Chronic Kidney Disease; CHF = Chronic Heart Failure; CHD = Coronary Heart Disease; SAPSII = Simplified Acute Physiology Score II; SOFA Score = Sequential Organ Failure Assessment Score; ICU = Intensive Care Unit; LOS = Length of Stay. *Variable with missing data: SAPSII available in 115/124 patients, SOFA available in 108/124 patients, MV available in 106/124 patients, ICU LOS available in 108/124 patients, type of admission available in 105/124 patients.

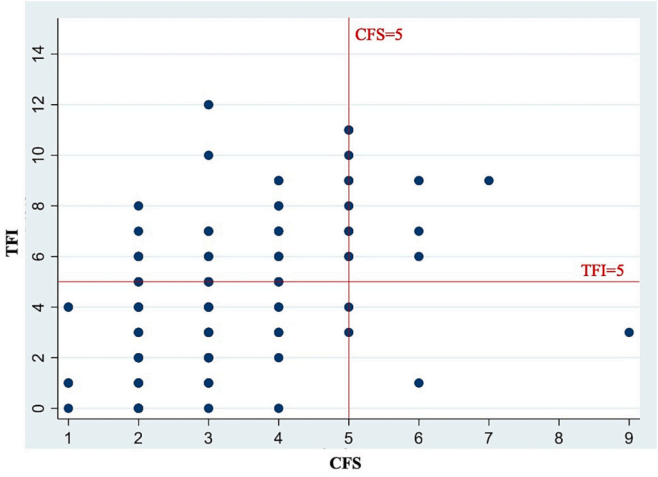

Fig. 2. Relation between Tilburg frailty indicator and Clinical Frailty Score at baseline.

comorbidities (OR = 9.46; 95%CI: 2.18–41.07) was independently associated with frailty based on TFI, whereas the married status resulted a protective factor (OR = 0.13; 95%CI: 0.04–0.37).

3.3. Trajectories of frailty and comparison between the scales

The baseline value of CFS and TFI showed a significant correlation at the baseline (Spearman's Rho = 0.51, $p < 0.05$, Fig. 2) but low agreement (Cohen's K = 0.23, $p < 0.001$). Fig. 3 shows the trajectories of frailty during the follow up. While a large proportion of individuals reported only a transient frailty condition according to TFI, patients that returned to a non-frailty status during the follow-up (graphically represented as orange streams ending in the green bar) were extremely rare using CFS. Moreover, among non-frail patients by CFS, the number of new frails and deceased individuals increased during the follow-up, mostly in the first 6 months after discharge (Fig. 3). No significant difference in the variation of the TFI score during follow up was observed between age classes ($p = 0.169$), but older patients reported a significant increase in the CFS score during follow up, as compared to patients <65 years ($p = 0.033$) (Supplementary material, Table 1).

3.4. Frailty scores and mortality

When comparing mortality rates among the frail population assessed with the two scales, patients classified as frail at baseline according to the CFS had a significantly higher mortality at 6 months compared to those non-frail (13 (12.6%) vs 6 (40.0%), $p = 0.016$, Table 2).

Considering CFS and TFI scores, in the unadjusted model (Table 3), patients who reported a higher CFS at baseline (HR = 1.30; 95%CI: 1.07–1.58) and during the follow-up (HR = 1.41; 95%CI: 1.19–1.67), or a higher TFI during the follow-up (HR = 1.15; 95%CI: 1.01–1.29) showed a major risk to die in the year after ICU discharge. Other factors associated with a higher risk of 1-year mortality after ICU discharge were the need of respiratory support longer than 24 h (HR = 2.53; 95% CI: 1.02–6.24), and a higher value of SAPS II (HR = 1.04; 95%CI: 1.02–1.07) and SOFA score (HR = 1.15; 95%CI: 1.02–1.30).

In the multivariable analysis adjusted for age and SAPS II score (Table 4), a higher CFS score during the follow-up remained significantly associated with a greater risk of 1-year mortality after ICU discharge. Every 1-point increase in CFS value resulted in a 43% increased risk to die (HR = 1.43; 95%CI: 1.18–1.73). On the other hand, a higher TFI score during the follow-up failed to reach the statistical significance (HR = 1.14; 95%CI: 0.98–1.31).

The Kaplan-Meier one-year survival estimates based on baseline frailty according to CFS and TFI are reported in the Supplemental Material, as Fig. S1 and Fig. S2, respectively. The analysis did not show difference in mortality among frail and non-frail patients at baseline classified using TFI and CFS.

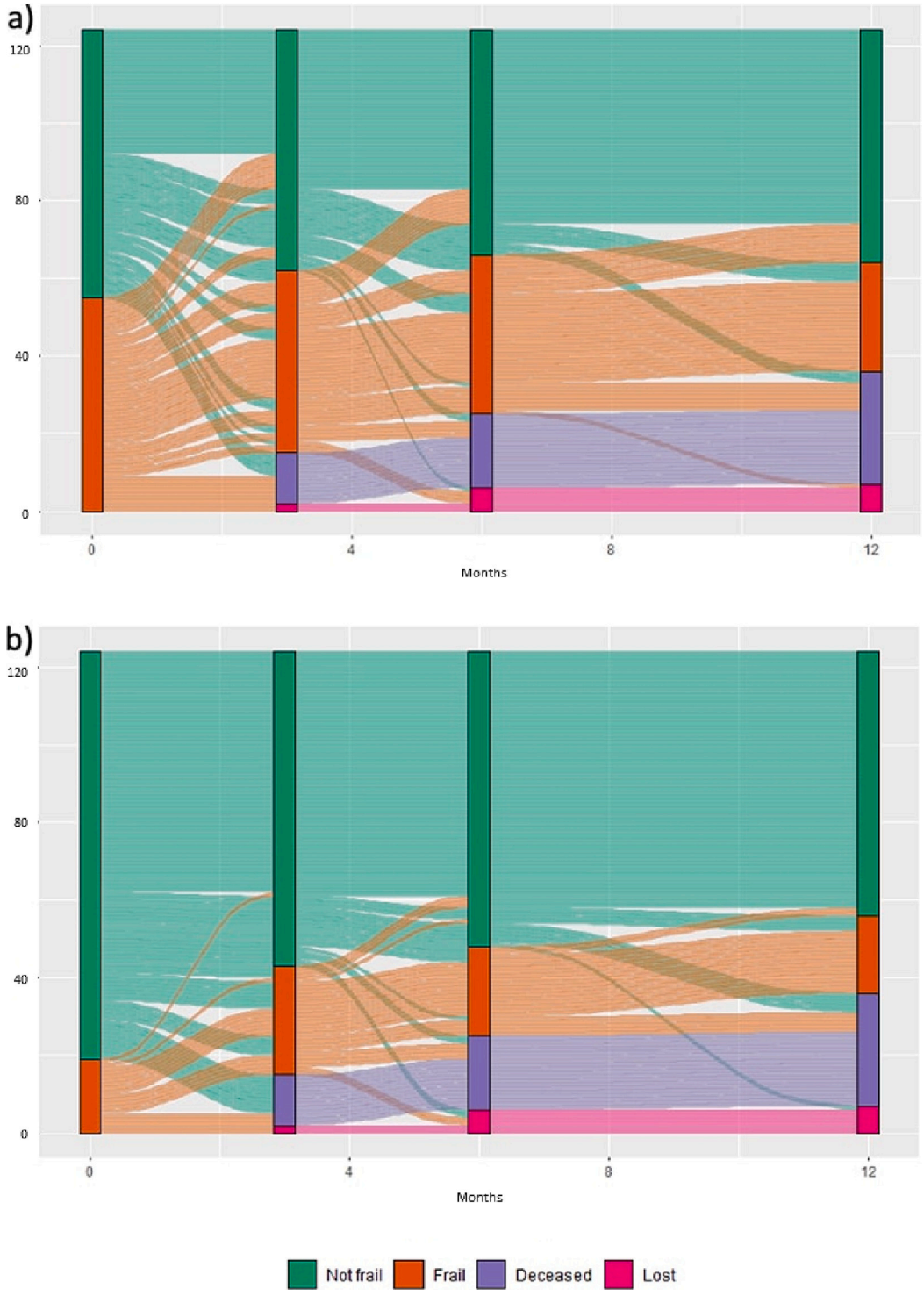

Fig. 3. Frailty trajectories according to TFI (a) e CFS (b) during 1 year after ICU discharge. X-axis = time (months); y-axis = sample (N).

4. Discussion

The Clinical frailty scale and the Tilburg frailty indicator identify two distinct populations of frail ICU survivors with different long-term prognosis. Patients classified as frail according to the CFS reported a higher likelihood to remain frail or die in the year after the critical illness, as compared to individuals assessed as frail by TFI, which were characterized often by a transient frailty status. Frailty patients at ICU admission according to CFS were at higher risk of death in the 6 months after hospital discharge while a higher CFS score during the follow-up was associated to an increased risk of death at 1-year from ICU discharge, independently from age and disease gravity at ICU admission. Finally, the trajectories analysis showed that patients non-frail at baseline according to CFS had high risk of becoming frail and die after ICU stay, while frailty identified at baseline by TFI was often only a transient condition.

The TFI and CFS showed a different prevalence of frailty at baseline in our population. In particular, TFI identified as frail almost half of the participants (44.4%), while only 15.3% of the sample was defined as frail according to the CFS. A systematic review including 10 studies

Table 2
Baseline frailty and mortality.

	CFS			TFI		
	Non-Frail	Frail	p-value	Non-frail	Frail	p-value
Deaths, 3 months, n (%)	10 (9.5)	3 (17.7)	0.389	6 (8.7)	7 (13.2)	0.423
Deaths, 6 months, n (%)	13 (12.6)	6 (40.0)	**0.016**	10 (14.9)	9 (17.7)	0.690
Deaths, 12 months, n (%)	23 (22.6)	6 (40.0)	0.197	16 (23.9)	13 (26.0)	0.793

Note: CFS = Clinical Frailty Scale; TFI = Tilburg Frailty Indicator.

Table 3
Factors associated with the 1-year mortality, unadjusted model.

	HR (95% CI)	p-value
Sex F	0.85 (0.38–1.91)	0.691
Age	1.03 (1.00–1.06)	0.081
Married status	0.93 (0.39–2.21)	0.867
BMI	1.01 (0.95–1.08)	0.694
Hospitalization in the last year	0.73 (0.35–1.55)	0.413
Admissions in ICU in the last year	0.59 (0.15–2.27)	0.443
Number of drugs	1.04 (0.93–1.15)	0.519
Comorbidity	1.73 (0.51–5.86)	0.376
Arterial hypertension	1.29 (0.62–2.69)	0.495
CODP	1.31 (0.44–3.91)	0.623
CKD	1.28 (0.44–3.73)	0.649
CHF/CHD	1.23 (0.48–3.15)	0.662
Diabetes	1.47 (0.64–3.34)	0.361
Obesity	1.28 (0.50–3.29)	0.607
SAPSII	1.04 (1.02–1.07)	**0.001**
SOFA Score	1.15 (1.02–1.30)	**0.018**
Mechanical ventilation > 24 h	2.53 (1.02–6.24)	**0.045**
Presence of frailty at baseline (CFS)	2.02 (0.80–5.10)	0.135
Baseline CFS score	1.30 (1.07–1.58)	**0.009**
CFS score during follow-up	1.41 (1.19–1.67)	**<0.001**
Presence of frailty at baseline (TFI)	1.11 (0.54–2.29)	0.782
Baseline TFI score	1.05 (0.92–1.20)	0.437
TFI score during follow-up	1.15 (1.01–1.29)	**0.029**

Notes: CFS = Clinical Frailty Scale; TFI = Tilburg Frailty Indicator; BMI = Body Mass Index; ICU = Intensive Care Unit; CODP = Chronic Obstructive Pulmonary Disease; CKD = Chronic Kidney Disease; CHF = Chronic Heart Failure; CHD = Coronary Heart Disease; SAPS II = Simplified Acute Physiology Score II; SOFA Score = Sequential Organ Failure Assessment Score; HR = Hazard Ratio; CI = Confidence Interval. *Baseline CFS/TFI frailty: HR of frail vs non-frail patients based on the score value at baseline; baseline CFS/TFI score: HR for a 1-point increase of the score at baseline; CFS/TFI score: HR for a 1-point increase of the scores during the follow-up.

assessing baseline frailty (using the CFS in seven studies, a frailty index in four, and the frailty physical phenotype in two) in patients older than 18 years of age admitted to ICU reported a pooled prevalence of frailty of 30% (95% CI 29–32%) [22]. Other authors using CFS in ICU setting reported a prevalence of 23% in patients aged ≥65y [23], and of 32.8% in patients aged 50y or more [24]. Therefore, despite the prevalence of frailty according to TFI in our study seems to be very high, also the proportion of patients classified at baseline as frail according to CFS was lower than expected.

The moderate correlation (Spearman $R = 0.51$) between the indexes and their low concordance (Cohen's K = 0.23) suggest that TFI and CFS identify two distinct populations of frail patients. The multidimensional approach of TFI captures a higher number of patients compared to CFS, which evaluates only the clinical aspects combining the presence of both physical disability and underlying chronic diseases [16,17].

The association of the CFS score at baseline - but not of the TFI - with a greater likelihood of short and 1-year mortality after ICU discharge is in agreement with other studies [21,25-28], and suggests that CFS may be more suitable than TFI for the critically ill patients. Nevertheless, the studies conducted until now focused generally only on elderly patients

Table 4
Factors associated with the 1-year mortality, model adjusted for age and SAPSII.

	CFS		TFI	
	HR (95%CI)	p-value	HR (95%CI)	p-value
Baseline frailty	2.01 (0.73–5.56)	0.178	0.94 (0.40–2.23)	0.895
Age	1.01 (0.98–1.05)	0.478	1.02 (0.98–1.06)	0.302
SAPS II	1.04 (1.01–1.07)	0.008	1.04 (1.01–1.07)	0.006
Baseline score	1.26 (0.99–1.61)	0.062	1.03 (0.87–1.22)	0.724
Age	1.01 (0.97–1.05)	0.656	1.02 (0.98–1.06)	0.340
SAPS II	1.04 (1.01–1.07)	0.009	1.04 (1.01–1.07)	0.007
Follow UP score	1.43 (1.18–1.73)	**<0.001**	1.14 (0.98–1.32)	0.085
Age	1.00 (0.96–1.04)	0.873	1.01 (0.97–1.04)	0.754
SAPS II	1.04 (1.01–1.07)	0.013	1.03 (1.00–1.07)	0.033

Notes: CFS = Clinical Frailty Scale; TFI = Tilburg Frailty Indicator; BMI = Body Mass Index; ICU = Intensive Care Unit; CODP = Chronic Obstructive Pulmonary Disease; CKD = Chronic Kidney Disease; CHF = Chronic Heart Failure; CHD = Coronary Heart Disease; SAPS II = Simplified Acute Physiology Score II; SOFA Score = Sequential Organ Failure Assessment Score; HR = Hazard Ratio; CI = Confidence Interval. Baseline frailty: HR of frail vs non-frail patients based on the score value at baseline; baseline score: HR for a 1 point increase of the score at baseline; Follow Up score: HR for a 1 point increase of the score recorded during the follow-up.

[21,29-31], despite TFI has been used also in younger patients [9]. Instead, the multidimensional approach of TFI could make it more suitable for patients admitted to other contexts, such as medical wards, being able to detect some nuances of frailty to which attention should be paid to avoid worsening. Moreover, beside from the content of the two instruments, the form of the TFI may expose the frailty quantification to a perception bias, since, while the CFS is determined by a trained physician after a targeted interview, the TFI might easily be altered by false self-perception of aging, quality of life and/or disabilities [32,33].

While the dichotomic presence/absence of frailty at baseline was not associated to 1-year mortality as also shown by the Kaplan-Meier analysis, the CFS and TFI scores at ICU admission significantly increased the risk of death in the unadjusted analysis. These results underline the presence of a *continuum* of risk, meaning that a single cutoff to identify frail/non-frail patients is probably incapable of providing a real advantage in assessing the long-term risk in the ICU population.

Moreover, this was confirmed by the significant association of the CFS value during follow up - but not of being classified as frail/non-frail - with the 1-year mortality. This result was still significant when adjusting also for disease gravity (SAPS II) and age, meaning that the frailty score can detect survivors at high risk of death in the first year after ICU discharge and that their risk is independent from age, which is classically associated to frailty itself, and disease severity.

When assessing the trajectories of frailty according to the two indexes, patients classified as frail by the TFI at ICU admission often saw a reversal of the frailty status during the follow-up. Since it is unlikely that ICU admission decreased frailty, this can be explained by the impact of ICU on the assessment of frailty using the TFI, especially on the psychological component of the TFI, which may be influenced by the experience of ICU. On the other side, patients described as non-frail by the CFS had a higher risk of becoming frail during the follow up, confirming the results of Launey et al. [13] who found that 32.9% of their >65-year-old patients non-frail at ICU admission were frail at six months [13].

These findings have a significant clinical impact, since frailty is associated with a higher risk of disability, institutionalization, hospitalization and death, with a consequent increase in public health costs [34-37]. Not only the qualitative assessment, but the quantification of frailty using the CFS both at ICU entrance and after ICU discharge may allow the identification of individuals more exposed to adverse outcomes with the possibility of nutritional and rehabilitation implementation strategies during and after ICU stay [38]. Moreover, the evaluation of frailty at ICU admission may allow a careful stratification

of the patient' risk and decide on the most appropriate therapeutic interventions, sharing the prospective goals of care with the families [39,40].

The major strength of our study is its prospective design, with standardized evaluations of frailty status during the 1 year of follow-up after ICU stay. To our knowledge this is the first study analyzing and comparing trajectories of frailty assessed by the Clinical Frailty Scale and the Tilburg Frailty Indicator during the first year after ICU discharge. Moreover, the multicenter design should allow generalizing our results. The second major strength is that the study was to evaluate the entire ICU population, not limiting our analysis to elderly patients, as previously done by the other studies on frailty trajectories. [12-14].

The study has some limitations. First, frailty status was assessed after ICU admission. The researcher asked the patient to consider their status 1 month before hospitalization, but we cannot exclude any recall bias. This bias could be of value especially for TFI, which requires the response of the patient, while CFS presupposes that the assessor recognizes frailty based on any information collected. Second, individuals with severe cognitive impairment were excluded because we could not administer them the TFI questionnaire, and this could be a source of selection bias. Third, we evaluated only ICU survivors and therefore no information can be derived on the impact of frailty on short-term mortality. Forth, the assessments were performed in each study center by a single researcher. The three researchers participated in the study design and concorded the way to administer the instruments. Finally, considering that the primary outcome was the concordance between the two instruments, the results concerning mortality at 1-year should be considered exploratory.

5. Conclusions

CFS and TFI identify two distinct populations of ICU survivors and compared to the TFI, CFS is more useful to predict long-term outcomes. Patients discharged from the ICU, also if not previously classified as frail by the CFS, have a major risk to become frail or die in the 1 year after ICU discharge, while the frail status evaluated at ICU admission using the TFI is often transient. Finally, the CFS score during the follow-up is associated with 1-year mortality independently from age and disease severity at ICU admission.

Ethics approval and consent to participate

The Institutional Ethical Committee of Ferrara (CE-AVEC), coordinating center of the present study, approved the study protocol (CE number 161297). Moreover, Ethical approval was obtained for each participating research center. And each patient gave the informed consent to the study participation.

Consent for publication

Not applicable.

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Authors' contributions

SS, SV CAV and FR participated to study conception and design; FR, EM, GS, AB, MD, GZ and RS contributed to data collection and analysis; CAV, GS, SS, SV, FR, MC and RL contributed to the interpretation of the data; FR and GS drafted the manuscript; all authors approved the submitted paper.

Declaration of Competing Interest

The authors declare that they have no competing interests.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2023.154398.

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