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The contribution of frailty, cognition, activity of daily life and comorbidities on outcome in acutely admitted patients over 80 years in European ICUs: the VIP2 study

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Abstract

Purpose: Premorbid conditions affect prognosis of acutely-ill aged patients. Several lines of evidence suggest geriatric syndromes need to be assessed but little is known on their relative effect on the 30-day survival after ICU admission. The primary aim of this study was to describe the prevalence of frailty, cognition decline and activity of daily life in addition to the presence of comorbidity and polypharmacy and to assess their influence on 30-day survival.

Methods: Prospective cohort study with 242 ICUs from 22 countries. Patients 80 years or above acutely admitted over a six months period to an ICU between May 2018 and May 2019 were included. In addition to common patients' characteristics and disease severity, we collected information on specific geriatric syndromes as potential predictive factors for 30-day survival, frailty (Clinical Frailty scale) with a CFS > 4 defining frail patients, cognitive impairment (informant questionnaire on cognitive decline in the elderly (IQCODE) with IQCODE ≥ 3.5 defining cognitive decline, and disability (measured the activity of daily life with the Katz index) with ADL ≤ 4 defining disability. A Principal Component Analysis to identify co-linearity between geriatric syndromes was performed and from this a multivariable model was built with all geriatric information or only one: CFS, IQCODE or ADL. Akaike's information criterion across imputations was used to evaluate the goodness of fit of our models.

Results: We included 3920 patients with a median age of 84 years (IQR: 81–87), 53.3% males). 80% received at least one organ support. The median ICU length of stay was 3.88 days (IQR: 1.83–8). The ICU and 30-day survival were 72.5% and 61.2% respectively. The geriatric conditions were median (IQR): CFS: 4 (3–6); IQCODE: 3.19 (3–3.69); ADL: 6 (4–6); Comorbidity and Polypharmacy score (CPS): 10 (7–14). CFS, ADL and IQCODE were closely correlated. The multivariable analysis identified predictors of 1-month mortality (HR; 95% CI): Age (per 1 year increase): 1.02 (1.–1.03, $p = 0.01$), ICU admission diagnosis, sequential organ failure assessment score (SOFA) (per point): 1.15 (1.14–1.17, $p < 0.0001$) and

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CFS (per point): 1.1 (1.05–1.15, $p < 0.001$). CFS remained an independent factor after inclusion of life-sustaining treatment limitation in the model.

Conclusion: We confirm that frailty assessment using the CFS is able to predict short-term mortality in elderly patients admitted to ICU. Other geriatric syndromes do not add improvement to the prediction model. Since CFS is easy to measure, it should be routinely collected for all elderly ICU patients in particular in connection to advance care plans, and should be used in decision making.

Keywords: Critical care, Outcome, Prediction, Elderly, Frailty, Cognitive functioning, Activities of daily living, Comorbidity

Introduction

The number of very old patients admitted to the intensive care unit (ICU) is rising, which parallels the increase in the proportion of elderly people in most developed countries [1]. In the past decade this has been identified as a potential health challenge because these patients aged 80 and above consume a disproportionally large part of the health care budget, while the mortality rates are consistently reported to be higher than in younger patients [2]. However, it is important to separate unplanned from planned ICU admissions, since the latter group has a much better outcome [3]. In unplanned admissions the overall 30-day mortality of ICU patients is approximately 40% [4]. Long-term mortality (6 months or 12 months) is most often 50% or above [5]. This high mortality translates into suffering in patients and relatives and moral distress in care-givers. It is, therefore, of utmost importance to better identify elderly patients with an expected good outcome including a post discharge acceptable quality of life.

Previous research has shown that age and severity of illness at admission only partly explain the chance of survival of elderly patients and traditional prognostic scoring systems are often inaccurate [6]. In the very old patients the ability to cope with severe stressors like critical illness seems to be more related with the geriatric syndromes, like frailty [4], cognitive decline [7, 8] and a reduced performance on the activity of daily life (ADL) scale in addition to comorbidity. However, the impact and relationship of this premorbid functioning on the outcome of acutely admitted elderly ICU patients have not been established [7, 8].

In this study, using the European Very elderly Intensive Patient (VIP) network, our primary aim was to document the prevalence of three common geriatric syndromes: frailty, cognitive impairment and disability in addition to the presence of comorbidity and polypharmacy, and to assess their influence on 30 days' survival.

Take-home message

In this prospective multinational study of 3920 very old intensive care patients (≥ 80 years), clinical frailty scale alone described geriatric syndromes. Cognition and activity of daily life did not add to the prediction model for 1-month survival after ICU admission.

Methods

Design and setting

This was a prospective observational study in 242 ICUs from 20 European countries, plus Turkey and Libya. The participating ICU characteristics were: mean number of beds: 15; mean number of ICU admission in year 2017: 955; percentage of patients 80 years of age or older admitted in 2017: 17%. Each participating ICU is listed in electronic supplement material (ESM1) and recruitment per country is presented in ESM2. The inclusion period was from May 2018 to May 2019. Most of the patients were included during the 2018–2019 winter season (ESM3). The 30-day follow-up ended on July 15 2019.

The study was coordinated through the health services resource and outcome (HSRO) section of the European society of intensive care medicine (ESICM). Each country had a national coordinator (NC) responsible for ICU recruitment and application for national or regional ethical and regulatory study approval. Institutional research ethic board approval was obtained from each study site. Five countries were allowed to recruit patients without prior written informed consent while others had to collect informed consent from patient or their legal representative [9]. Individual ICUs were asked to include consecutive patients for a 6-month period in the 1-year study period and were allowed to stop after 20 included patients. All patients were followed until 30 days after ICU admission. A dedicated web site (www.VIP2study.com) was set up to facilitate information about the study and study progress and to allow for data entry using an electronic case record form CRF (supplemental 1). The study is registered on ClinicalTrials.gov (ID: NCT03370692). There was no specific funding except an ESICM award received by HF.

Participants

Only emergency (acute) ICU admissions in patients ≥ 80 years of age were eligible. All reasons for acute ICU admissions were accepted.

Data collection

Data collection at admission

For each eligible patient, demographic data were collected: age, sex, place of living before admission to the hospital, and reason for admission according to a predefined list (ESM4).

Second, the study collected mandatory data on the patient's geriatric conditions prior to this hospital admission, including the clinical frailty scale (CFS) [10]. For the assessment of frailty, we defined the frailty level present before hospital admission and not affected by the acute illness. The information necessary to perform this assessment were given by patients or proxy or patient records, and the assessor's profession was reported. The Clinical Frailty Scale visual and with simple description were used with permission (ESM5) [10]. The scale is composed of 9 classes from very fit to terminally ill. Prefrail patients have a CFS of 4, while frail patients have a CFS of 5 or above. We also recorded Katz activities of daily living (Katz ADL) (ESM6) [11] with ADL score ≤ 4 defining disability. Short form of Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) [12] (ESM7) was used. The information to calculate the IQCODE was given by caregivers with intimate knowledge of the patient for the past 10 years. We defined cognitive decline as an IQCODE ≥ 3.5 [13]. Comorbidity and polypharmacy score (CPS) were calculated [14]. A CPS above 15 was considered as high.

Data collection of variables during ICU admission

Within the first 24 h of ICU admission the sequential organ failure assessment (SOFA) score was calculated [15]. The total SOFA score on admission was calculated using an online calculator in the eCRF. Length of ICU stay (LOS) was recorded as the number of hours between admission and discharge and latter converted to days in the analysis. Any period on non-invasive, invasive (with endotracheal intubation or tracheotomy) mechanical ventilation, use of vasoactive drugs and renal replacement therapy was registered with start (ICU day) and duration of the treatment (in hours).

Limitation of life sustaining therapies (LST) such as withholding or withdrawing life-supporting treatments was documented as performed and on which ICU day, or if not performed [16].

Outcome was measured as survival in the ICU and 30 days after ICU admission with information on the day of death after ICU admission. Information source for vital status at day 30 was documented.

The Case Record Form and database were hosted on a secure server located on the campus of Aarhus University, Denmark.

Bias

The ICUs were asked to include all acutely admitted, consecutive patients irrespective of the estimated duration of ICU stay.

Study size

We had no formal calculation in this purely observational study. We estimated a 30-day mortality of 40% in a similar population [17].

Statistical analysis

Baseline characteristics of patients were analyzed as frequencies and percentages for categorical variables and as medians and interquartile ranges (IQRs) for continuous variables.

Principal Component Analysis (PCA) was used to represent the variation present in the dataset and show association between geriatric and severity variables (age, SOFA score, CPS, IQ code, Katz's scale and clinical frailty scale). For visual analysis, two-dimensional projection of the sample was constructed having the axes (principal components, PC) as the factors. Each PC is a linear combination of the original variables (that retain some correlation among each other) and PCs are orthogonal to each other.

The crude overall survival at 30 days was estimated by the Kaplan–Meier method and compared using a log-rank test. We used multiple imputations for participants with missing data, using predictive mean matching for continuous variables, logistic regression for binary data, and polynomial regression for (unordered) categorical data. The cumulative baseline hazard was approximated by the Nelson-Aalen estimator and included in the imputation model. Five imputations were drawn.

Multivariable analyses were performed using the Cox proportional hazards model for overall survival at 30 days. All patients' characteristics listed in the CRF were included in our models including LST limitation. We used mean Akaike's information criterion (AIC) across imputations to evaluate the goodness of fit of our models. AIC = −2 Log likelihood + 2p, where p is the number of parameters [18]. Models with lower AIC are interpreted as models that best fit the data. Last, we included limitation decisions as a time-dependent variable to test whether geriatric parameters kept their prognostic value. Hazard ratio (HR) given by the Cox model

describe the relative risk of death based on comparison of event rates in different groups. HR gives the change in risk of death per each unit increase for continuous variables and for one specific category versus a reference category for categorical variables. HR > 1 suggests an increase in the risk of death, HR < 1 suggest a decrease in the risk of death. A Cox model was used to analyze treatment limitation as a time to event variable.

Adjusted survival curves were produced using an inverse probability-weighted Kaplan–Meier estimation [19]. Significance was tested using a Cox regression model weighted by the same weights (inverse probability-weighted Cox). Inter-rater variability for assessing Clinical Frailty Scale was analyzed with Med-Calc for Windows 15.0 (MedCalc Software, Ostend, Belgium) and presented as Weighted kappa [20]. All analyses were performed by AB with R software, version 3.2.2 (R Foundation for Statistical Computing) (packages FactorMineR and missMDA for PCA, MICE for multiple imputations, survival for survival analysis, ipw for inverse-probability weighting, rms for adjusted survival curves).

Results

Participants

We included 3920 patients (median age 84 years) from 22 countries and 242 ICUs. Most patients lived at home without help (72.8%,) or with care-givers (11.1%) before being admitted to the hospital. Admissions related to respiratory and/or circulatory failures and sepsis (as defined by sepsis 3 criteria) accounted for 63.2% of the total while emergency surgery represented 13.8% of the total admissions. The patients were severely ill as evidenced by a median SOFA score of 6 (IQR 4–9) (Table 1). Most patients had at least one organ support (Table 2). The median ICU LOS was 3.9 days (IQR: 1.83–8).

No difference was found in patients' characteristics in ICUs with a recruitment period above vs. below the median of 60 days (ESM8) ruling out possible bias due to different recruitment times. Recruitment per ICU was excellent (ESM9) but patients included in countries with no need for informed consent were sicker with a SOFA score almost two points higher (ESM10).

The geriatric syndromes (Tables 1, 3) were as follows: Median (IQR): CFS: 4 (3–6) with only 17 missing values. Information to assess CFS was given by the patient in 29.7% (1159/3901) and by the family in 51.7% (2016/3901). The professional assessor was an ICU physician (59.8%, 2335/3901), an ICU nurse (13.7%, 535/3901) or research staff (23.7%, 925/3901). CPS values were similar when measured by different assessors (ESM11). The CFS was measured by two different raters in 1924 individuals. The weighted Kappa was 0.85 (95%CI 0.84–0.87) which is excellent (ESM12).

Frailty (CFS ≥ 5) was present in 40.2% (1568/3903). IQCODE was 3.19 (3–3.69) with 940/3920 (24%) missing values. Patients with missing values of IQCODE were different from patients with documented IQCODE (ESM123). IQCODE above 3.5 indicating a cognitive decline was observed in 30.2%. Katz ADL was 6 (4–6) with 447/3920 (11.4%) missing values. An ADL of 4 or less, as a marker of functional decline was observed in 27.7% (962/3473). Comorbidity and polypharmacy score (CPS) was 10 (7–14) with 8/3920 (0.2%) missing values. A CPS above 15 was present in 17.7% (693/3912) of the patients.

Outcome data

LST limitations were documented in 34.4% (1332/3872) including withholding in 29.4% (1140/3872) of patients with a decision made at day 1 (IQR 1–4) and treatment withdrawal (with or without prior withholding) in 14% (545/3872) with a median decision time of 4 days (IQR 2–7) after ICU admission. Patients with LST limitation were frailer and more severely ill compared to patients with no LST limitation (Table 4). The multivariable analysis identified age, habitat, SOFA score, CPS and CFS as independent factors predicting decision to limit LST (Table 5).

The ICU and 30-day vital status were, respectively, available for 3900/3920 (99.9%) and 3841/3920 (99.4%) patients. The vital status was assessed by checking the hospital records (81.4%, 2780/3415), direct contact with the patient (12.3%, 420/3415) or checking a national registry (3.3%, 111/3415).

The overall proportion of patients surviving ICU was 72.5% (2828/3900). Survival after ICU admission was 96.3% at day one (95.7–96.9), 74.2% (72.8–75.6) at day 10, 65.9% (64.5–67.5) at day 20 and 61.2% (59.7–62.7) at day 30.

Predictive factors for 30-day survival

In our PCA analysis the first two PC explain as much as 56.79% of the total variation in the sample; the analysis was restricted to these first two dimensions. PC1 retained 39% of data variation and differentiates the individuals according to Katz ADL, Clinical Frailty Scale and IQCODE. Similarly, PC2 explained another 18% of variability in the original data and separates the individuals based on severity (SOFA) and age. Figure 1 represents the projection of variables on the factor-plane and shows correlation between the three geriatric syndromes IQ code, Katz ADL and Clinical Frailty Scale. Except for

Table 1 Patients characteristics

Variables	Categories	All	Survivors	Non survivors	*p*-value
	N	3920	2327	1514	
Age	Median (range) (IQR)	84 (range: 80–104) (81–87)	84 (range 80–104) (81–87)	84 (range 80–98) (82–87)	0.04
Gender	Male	2089 (53.3%)	1210 (52%)	836 (55.2%)	0.06
	Female	1831 (46.7%)	1117 (48%)	678 (44.8%)	
Place of living	Own home (including if with spouse)	2852 (72.8%)	1774 (76.3%)	1031 (68.1%)	< 0.0001
	Other home with family or caregivers	434 (11.1%)	228 (9.8%)	191 (12.6%)	
	Nursing home	210 (5.4%)	112 (4.8%)	96 (6.3%)	
	Hospital ward	361 (9.2%)	179 (7.7%)	174 (11.5%)	
	Other	35 (0.9%)	22 (0.9%)	11 (0.7%)	
	Unknown	27 (0.7%)	11 (0.5%)	11 (0.7%)	
Reason for admission	Respiratory failure	944 (24.1%)	583 (25.1%)	343 (22.7%)	< 0.0001
	Circulatory failure	541 (13.8%)	303 (13%)	228 (15.1%)	
	Combined respiratory/circulatory failure	449 (11.5%)	186 (8%)	253 (16.7%)	
	Sepsis (according to Sepsis3)	539 (13.8%)	287 (12.3%)	239 (15.8%)	
	Multitrauma without head injury	87 (2.2%)	58 (2.5%)	27 (1.8%)	
	Multitrauma with head injury	75 (1.9%)	35 (1.5%)	37 (2.4%)	
	Isolated head injury	71 (1.8%)	33 (1.4%)	38 (2.5%)	
	Intoxication	23 (0.6%)	17 (0.7%)	6 (0.4%)	
	Non-traumatic cerebral pathology	190 (4.8%)	103 (4.4%)	84 (5.5%)	
	Emergency surgery	541 (13.8%)	369 (15.9%)	163 (10.8%)	
	Other causes	459 (11.7%)	352 (15.1%)	96 (6.3%)	
SOFA	Median (range) (IQR)	6 (range: 0–20) (4–9)	5 (range 0–18) (3–8)	8 (range 0–20) (5–11)	< 0.0001
CFS	Median (range) (IQR)	4 (range: 1–9) (3–6)	4 (range 1–9) (3–5)	4 (range 1–9) (3-6)	< 0.0001
IQ Code	Median (range) (IQR)	3.19 (range: 1–5) (3–3.69)	3.19 (range 1–5) (3–3.56)	3.31 (range 1–5) (3–4)	< 0.0001
ADL (Katz)	Median (range) (IQR)	6 (range: 0–6) (4–6)	6 (range 0–6) (5–6)	6 (range 0–6) (3–6)	< 0.0001
Comorbidities	Median (range) (IQR)	4 (range: 0–20) (3–6)	4 (range 0–20) (3–5)	4 (range 0–20) (3–6)	0.013
Drugs taken daily	Median (range) (IQR)	6 (range: 0–26) (4–9)	6 (range 0–21) (4–9)	6 (range 0–26) (4–9)	0.17
CPS	Median (range) (IQR)	10 (range: 0–36) (7–14)	10 (range 0–36) (7–14)	11 (range 0–35) (7–14)	0.05

Vital status was assessed 1 month after ICU admission. 79 patients had no vital status reported at 1 month

SOFA sequential organ failure assessment, *CFS* clinical frailty scale, *IQCODE* informant questionnaire on cognitive decline in the elderly, *ADL* activity of daily living, *CPS* Co-morbidity and Polypharmacy score

CPS, each geriatric syndrome had impact on 1-month survival (Fig. 2).

The multivariable analysis identified the usual predictors of 30-day outcome (HR; 95% CI): Age (increase in risk of death per 1 year increase): 1.02 (1–1.03, $p = 0.01$), ICU admission diagnosis, SOFA (increase in risk of death per one-point increase): 1.15 (1.14–1.17, $p < 0.0001$) and CFS (increase in risk of death per one point increase): 1.1 (1.05–1.15, $p < 0.001$). The model including all geriatric parameters did not perform better than the model with CFS only (Table 6). The CPS was not independently associated with 30-day outcome. When including limitation decision as a time-dependent variable in the model, CFS still has a prognostic impact on survival with an increase in the risk of death per each unit increase of CFS of 1.08 (1.05–1.12, $p < 0.001$) (Table 7).

Discussion

In the ICU community there is a growing need for evidence and guidelines to ease the decision-making process for an informed ICU admission in the very old including ICU triage, and this should be supported by best available evidence [21]. In that perspective, this large prospective study of non-scheduled, acute ICU admissions provides important information.

We confirmed that 30-day survival is very low (61.2%) in unselected patients 80 years or older who are acutely admitted to the ICU. Age-related symptoms as frailty,

Table 2 ICU stay characteristics

Variables	Categories	All	Survivors	Non survivors	*p*-value
	N	3920	2327	1514	
Intubation	Yes	1953 (49.9%)	939 (40.4%)	974 (64.5%)	< 0.0001
Tracheostomy	Yes	264 (6.8%)	168 (7.2%)	90 (6%)	0.14
Non invasive ventilation	Yes	903 (23.1%)	547 (23.6%)	342 (22.6%)	0.51
Vaso active drugs	Yes	2329 (59.5%)	1169 (50.3%)	1114 (73.6%)	< 0.0001
Renal replacement therapy	Yes	429 (11%)	163 (7%)	259 (17.1%)	< 0.0001
Withholding of treatment	Yes	1140 (29.4%)	390 (16.9%)	738 (49.2%)	< 0.0001
Withdrawing of treatment	Yes	545 (14%)	27 (1.2%)	517 (34.4%)	< 0.0001
ICU LOS in days	Median (range) (IQR)	3.88 (0.04-30) (1.83-8)	3.67 (0.04-30) (1.92–7.71)	4 (0.04-30) (1.54–8.46)	0.75
ICU survival	Missing	13	10	3	
	Alive	2828 (72.5%)	2285 (98.6%)	471 (31.2%)	< 0.0001
30 days' survival	Missing	79			
	Alive	2346 (61.1%)			
Day of death	Median (range) (IQR)			7 (0–30)(3–14)	

Non-survivors are defined by 30-day mortality

Table 3 Scores assessed as categories

Variables	Categories	All	Survivors	Non survivors	*p*-value
CFS	Fit (CFS 1-3)	1544 (39.6%)	1011 (43.5%)	509 (33.9%)	< 0.0001
	Vulnerable (CFS 4)	791 (20.3%)	483 (20.8%)	287 (19.1%)	
	Frail (CFS 5-8)	1568 (40.2%)	830 (35.7%)	704 (46.9%)	
IQCODE categories	< 3	178 (6%)	125 (6.3%)	48 (5.1%)	< 0.0001
	3	709 (23.8%)	483 (24.5%)	212 (22.3%)	
	> 3–3.5	1194 (40.1%)	859 (43.6%)	316 (33.3%)	
	> 3.5	899 (30.2%)	505 (25.6%)	373 (39.3%)	
CPS categories	0–9	1697 (43.4%)	1024 (44%)	644 (42.6%)	0.12
	10–15	1522 (38.9%)	913 (39.3%)	575 (38.1%)	
	> 15	693 (17.7%)	389 (16.7%)	292 (19.3%)	
KATZ categories	0–4	962 (27.7%)	500 (22.6%)	441 (36.8%)	< 0.0001
	5	440 (12.7%)	295 (13.3%)	135 (11.3%)	
	6	2071 (59.6%)	1417 (64.1%)	623 (52%)	
SOFA categories	SOFA 0–5	1741 (44.5%)	1304 (56.2%)	410 (27.1%)	< 0.0001
	6–9	1286 (32.9%)	699 (30.1%)	555 (36.7%)	
	> 10	882 (22.6%)	317 (13.7%)	547 (36.2%)	

cognitive decline and disability were strongly associated with 30-day mortality and were more important than age alone. Comorbidity and polypharmacy, however, had no predictive value when measured as the CPS. Interestingly, the addition of cognitive impairment and disability to the prognostic analysis did not increase prognostic value compared with the model with frailty alone. The CFS was reported in 99.5% of the cases and the inter-rater reproducibility was very good confirming that this tool is robust and easy to use.

In a previous prospective study in Europe, frailty was found to be present in 46% of acute admitted elderly ICU patients [4] and was closely related to both ICU and 30-day mortality. In the present study, frailty remained independently associated with both ICU and 30 days mortality, and this strengthens its importance in pre-ICU assessment. Frailty affects several important body functions like the endocrine system, brain, muscular and immune function, all very important in the ICU context, and was recently discussed in a clinical review [22]. The link between frailty and health-related quality of life was documented in a prospective Canadian study [23]. Frail patients were found to report reduced quality of life both in the physical and mental subset of EuroQol Health

Table 4 Patient characteristics according to decision to limit life sustaining treatment: withholding and/or withdrawing

Variables	Categories	All	No limitation	Withdraw and/or withhold	*p*-value
	N	3920	2540	1332	
Age	Median (range) (IQR)	84 (range: 80–104) (IQR: 81–87)	83 (range 80–100) (IQR 81–86)	84 (range 80–99) (IQR 82-87)	< 0.0001
SOFA	Missing	11	3	6	
	Median (range) (IQR)	6 (range: 0–20) (IQR: 4–9)	6 (range 0–20) (IQR 3–9)	7 (range 0–19) (IQR 5–10)	< 0.0001
CFS	Missing	17	7	9	
	Median (range) (IQR)	4 (range: 1–9) (IQR: 3–6)	4 (range 1–9) (IQR 3–5)	4 (range 1–9) (IQR 3–6)	< 0.0001
IQ Code	Missing	940	504	416	
	Median (range) (IQR)	3.19 (range: 1–5) (IQR: 3–3.69)	3.19 (range 1–5) (IQR 3–3.57)	3.31 (range 1–5) (IQR 3.06–3.88)	< 0.0001
Katz	Missing	447	219	215	
	Median (range) (IQR)	6 (range: 0–6) (IQR: 4–6)	6 (range 0–6) (IQR 5–6)	6 (range 0–6) (IQR 4–6)	< 0.0001
Comorbidities	Missing	7	1	2	
	Median (range) (IQR)	4 (range: 0–20) (IQR: 3–6)	4 (range 0–20) (IQR 3–5)	4 (range 0–20) (IQR 3–6)	0.005
Drugs daily	Missing	8	1	2	
	Median (range) (IQR)	6 (range: 0–26) (IQR: 4–9)	6 (range 0–21) (IQR 4–8)	7 (range 0–26) (IQR 4–9)	< 0.0001
CPS	Missing	8	1	2	
	Median (range) (IQR)	10 (range: 0–36) (IQR: 7–14)	10 (range 0–36) (IQR 7–14)	11 (range 0–35) (IQR 8–5)	< 0.0001
ICU LOS in days (all patients alive/ dead)	Missing	11	3	1	
	Median (range) (IQR)	3.88 (range: 0.04–120) (IQR: 1.83–8)	3.96 (range 0.04–120) (IQR 1.96–8)	3.67 (range 0.04–85.5) (IQR 1.54–7.85)	0.03

N = 48 patients with missing information on LST limitation (WH/WD)

Table 5 Multivariate analysis of treatment limitation (Cox model analyzing treatment limitation as a time to event variable)

Variables	Categories	HR (95%CI)	*p*-value
Age	One-point increase	1.04 (95% CI 1.03–1.06)	< 0.00001
Habitat (ref = not home)	Own home	1.27 (95% CI 1.12–1.45)	0.0004
Gender (ref = male)	Female	1.08 (95% CI 0.97–1.21)	0.17
Reason for admission (ref = circulatory failure)	Combined respiratory/circulatory failure	0.9 (95% CI 0.7–1.11)	0.32
	Emergency surgery	0.67 (95% CI 0.5–0.83)	0.0003
	Multitrauma with head injury	0.92 (95% CI 0.–1.41)	0.70
	Multitrauma without head injury	0.77 (95% CI 0.–1.18)	0.23
	Other	0.8 (95% CI 0.6–0.97)	0.02
	Respiratory failure	1 (95% CI 0.8–1.19)	0.96
	Sepsis (according to Sepsis3)	0.92 (95% CI 0.75–1.12)	0.40
SOFA	One-point increase	1.07 (95% CI 1.05–1.09)	< 0.00001
CPS	One-point increase	1.01 (95% CI 1–1.02)	0.009
CFS	One-point increase	1.11 (95% CI 1.08–1.15)	< 0.00001

Questionnaire and in the SF-12. The use of the CFS has probably expanded lately, and different acute care settings find it useful to evaluate elderly patients in such a quick manner, even without patient contribution [24–26], making it of particular interest in the unresponsive or unconscious patient. There is also an emerging line of research trying to link frailty with delirium. Future studies are required to investigate the possible link between these two factors on ICU survival [27].

Cognitive decline has been found to affect mortality in many clinical settings [28, 29] and several methods are used to diagnose and assess the severity of cognitive decline and dementia. Most of these tests require active patient involvement and are, for obvious reasons, not

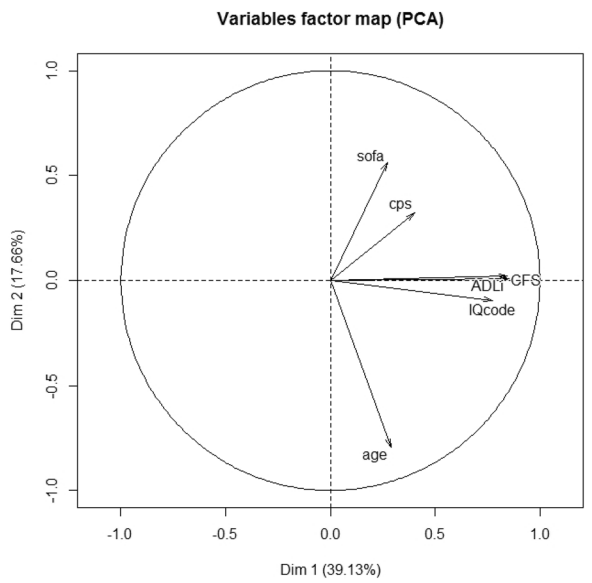

Fig. 1 Principal component analysis (PCA). Two-dimensional projection of the sample was constructed having the axes (principal components, PC) as the factors. Each PC is a linear combination of the original variables and PCs are orthogonal to each other. The angles between the vectors tell us how variables correlate with one another: when two vectors are close, forming a small angle, the two variables they represent are positively correlated. If they meet each other at 90 °, they are not likely to be correlated and when they diverge and form a large angle (close to 180 °), they are negatively correlated. The length of the vector shows how much weight a specific variable has on each principal component

applicable to patients who are acutely admitted to the ICU. Hence, we must rely on information from someone close to the patient in order to approach cognitive function if there is no clear evidence from patient records. The IQCODE was developed as a response to such demand [30] and has been used frequently as a simple screening tool based on information from caregivers. The IQCODE has been analyzed in a Cochrane review with regard to its accuracy in finding patients with dementia [13]. A threshold of 3.3 had 0.83 sensitivity and 0.80 specificity while a threshold of 3.5 had 0.82 sensitivity and 0.84 specificity. Studies where IQCODE has been applied prior to ICU admission are scarce. An early study of IQCODE compared with Modified Blessed Dementia Rating Scale (MBDRS) was performed in 130 ICU patients ≥ 65 years [31]. They found that an IQCODE > 3.3 was present in 31% of their patients. Using the same threshold, we found 44% having an IQCODE > 3.3, and the higher percentage probably mirrors the older age group in our study. With a threshold of 3.5; the prevalence of cognitive impairment was 30.2%. In a more recent study from Spain, ICU patients were prospectively studied with data on cognition (IQCODE), activity of daily life, comorbidity and a full geriatric assessment in addition to disease severity scores [32]. They found parameters related to quality of life and functional status to be independently correlated with mortality, but not cognitive decline. However, most of their patients had IQCODE values within the normal range. Although IQCODE did not increase the predictive value when added to frailty, it was shown to have impact on 30-day outcome. It is possible that other more specific measures on cognitive decline would have performed better, but such may be difficult to implement in an acute setting. Even the IQCODE proved the most difficult measure to obtain in our cohort with 24% missing data.

The CPS score is a simple score, which measures the impact of comorbidity by adding the number of comorbidities to the number of daily drugs [33]. Different thresholds have been used, but often a CPS score of < 8 has been considered to be categorized as minor, 8–14 as moderate and ≥ 15 as major comorbidity. In our cohort the median CPS value was 10, and 22% had a CPS ≥ 15. We have not found data from its previous use in ICU patients, but using the CPS in geriatric trauma (age ≥ 65 years), the investigators found CPS to predict mortality better than the more traditional Charlson Comorbidity Index (CCI) [34]. Other studies have found the CPS to predict hospital mortality and readmissions [35, 36] and to predict in hospital complications in older burn patients [37]. However, in our study this score had no impact on outcome prediction.

Our main aim was to document the impact from the clinical situation present before ICU admission on outcome in very old ICU patients. Such knowledge could support the important clinical decision of pre-ICU triage: *Will this patient benefit from being admitted to the ICU?* [21]. Despite associations between the geriatric syndromes and outcome, we will probably not be able to answer this important question just by using evaluation tools and measurement. Often the patient is admitted to the ICU in order to observe response to initial treatment. Important information related to survival can also be found during the first 48–72 h in the ICU. Hence the degree of organ dysfunction and vital organ support could be highly relevant due to what frequently is called the "in ICU triage". Such an evaluation, formal or informal, often leads to treatment being withheld and/or withdrawn. As a matter of fact, LST limitations occurred in 34.4% of the patients. Severity (SOFA) and also frailty were independent factors predicting decision to limit LST. In the Ethicus-2 study, LST limitations were documented in 13.1%, but the patients were younger (median 70 years) and age was found to be one of the determinants for EOL decision [38].

In our study, some form of organ support was given in 80% of all ICU admissions, most often as ventilator

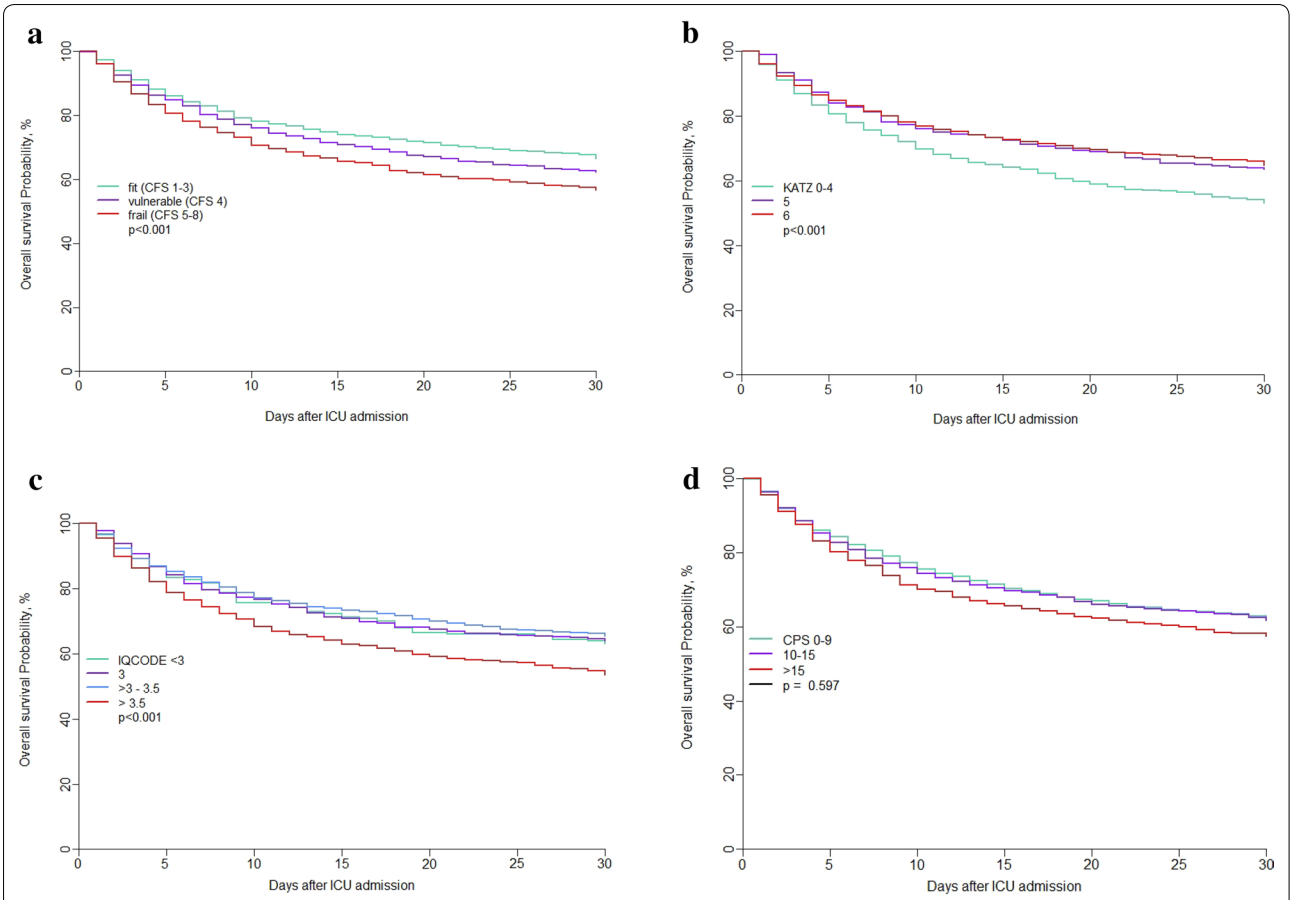

Fig. 2 Adjusted survival curves according to geriatric symptoms: Adjusted survival curves for geriatric variables were produced using an inverse probability-weighted Kaplan–Meier estimation [19]. Variables used to adjust the curves were age, gender, place of living, reason for ICU admission and SOFA score. Significance was tested using a Cox regression model weighted by the same weights (inverse probability-weighted Cox). **a** Survival curves according to CFS. **b** Survival curves according to Katz ADL. **c** Survival curves according to IQCODE. **d** Survival curves according to CPS

and cardiovascular support. This indicates that in most of the cases, there is no therapeutic limitation, and the very old ICU patients in our study were given active organ support when admitted to an ICU.

Strengths and limitations

The main strength of this study is the number of participants derived from several European countries, with different cultural and legal settings, and the prospective multicenter observation study design using the same definitions of the geriatric syndromes. Limitation of LST is common practice in most ICUs in Europe and contributes to the observed mortality. Patients with such decision differ from other patients (Table 4), but excluding those patients would introduce a bias to this "real life" observational study. When LST limitation was included in the multivariable model, CFS still has a prognostic impact on survival. The study was conducted within 1 year. Hence, we assume that trends in time do not influence the external validity. An unforeseen limitation was a huge delay in ethical and regulatory clearance in many countries caused by the General Data Protection Regulation (GDPR) introduced in all EU countries from May 2018. This made the actual recruitment period shorter for many ICUs. However, when comparing ICU with short versus long recruitment period, the patients' characteristics were very similar (see ESM 8). The estimated percentage of included patients to the potential candidates was 71.7% (ESM 9), but patients' characteristics were different in countries with a need for informed consent compared to patients enrolled in countries with no-informed consent (ESM10). This study did not focus on pre-ICU triage, and hence we cannot exclude some selection bias, in particular given the high number of patients living in their own home prior to admission. ICU triage has been the focus of other studies [39]. There is only scarce evidence of the inter-rater variability of the CFS between the caregiver and the patient when the

Table 6 Multivariable analysis (Cox regression analysis)

Variables	Categories	ALL covariates		CFS		Katz		IQ code	
		HR (95%CI)	*p*-value	HR (95%CI)	*p*-value	HR (95%CI)	*p*-value	HR (95%CI)	*p*-value
Age	One-point increase	1.02 (1–1.03)	0.01	1.02 (1.01–1.03)	0.006	1.02 (1.01–1.04)	0.002	1.02 (1.01–1.04)	0.003
Habitat (ref = not home)	Own home	1.01 (0.9–1.14)	0.83	1 (0.89–1.12)	0.96	0.98 (0.87–1.1)	0.73	0.95 (0.84–1.08)	0.43
Gender (ref = male)	Female	0.98 (0.88–1.09)	0.68	0.98 (0.88–1.09)	0.67	1 (0.9–1.11)	0.96	1.01 (0.91–1.13)	0.79
Reason for admission	Combined respiratory/circulatory failure	1.07 (0.89–1.29)	0.46	1.07 (0.89–1.29)	0.46	1.09 (0.91–1.31)	0.34	1.09 (0.91–1.31)	0.37
(Ref = circulatory failure)	Emergency surgery	0.64 (0.52–0.78)	< 0.0001	0.64 (0.52–0.78)	< 0.0001	0.64 (0.52–0.78)	< 0.0001	0.63 (0.51–0.77)	< 0.001
	Multitrauma w/wo head injury	1.16 (0.81–1.64)	0.41	1.15 (0.81–1.64)	0.42	1.12 (0.79-1.59)	0.51	1.09 (0.77–1.54)	0.63
	Multitrauma without head injury	0.86 (0.58–1.29)	0.46	0.87 (0.58–1.29)	0.48	0.83 (0.56–1.23)	0.35	0.78 (0.53–1.16)	0.23
	Other	0.81 (0.67–0.97)	0.025	0.81 (0.67–0.98)	0.03	0.8 (0.66–0.97)	0.02	0.79 (0.66–0.96)	0.016
	Respiratory failure	0.81 (0.69–0.96)	0.017	0.82 (0.69–0.97)	0.02	0.82 (0.69–0.98)	0.02	0.82 (0.69–0.98)	0.03
	Sepsis (according to Sepsis3)	0.71 (0.59–0.86)	0.0003	0.71 (0.59-0.86)	0.0003	0.72 (0.6-0.87)	0.0005	0.71 (0.59-0.86)	0.0004
SOFA	One-point increase	1.15 (1.14–1.17)	< 0.00001	1.15 (1.14–1.17)	< 0.00001	1.15 (1.14–1.17)	< 0.001	1.15 (1.14-1.17)	< 0.00001
CPS	One-point increase	1 (0.99–1.01)	0.75	1 (0.99–1.01)	0.74	1 (0.99–1.01)	0.65	1.01 (1-1.02)	0.28
CFS	One point increase	1.1 (1.05–1.15)	0.0001	1.12 (1.09–1.15)	< 0.00001				
Katz	One point increase	0.98 (0.94–1.02)	0.40			0.93 (0.9–0.95)	< 0.00001		
IQ code	One-point increase	1.03 (0.91–1.18)	0.63					1.18 (1.06–1.31)	0.0029
	Mean AIC across imputations	23,993.92		23,991.31		24,016.93		24,025.87	

HR gives the change in risk of death per each unit increase for continuous variables and for one specific category versus a reference category for categorical variables. HR > 1 suggests an increase in the risk of death, HR < 1 suggests a decrease in the risk of death

SOFA sequential organ failure assessment, *CFS* clinical frailty scale, *IQCODE* informant questionnaire on cognitive decline in the elderly, *ADL* activity of daily living, *CPS* Co-morbidity and Polypharmacy score

AIC Akaike's information criterion. AIC was used across imputations to evaluate the goodness of fit of our models. AIC = − 2 Log likelihood + 2p, where p is the number of parameters

CFS is performed at the same time. However, one study concluded that CFS scores can be reliably assigned retrospectively [40] and another study, comparing CFS using different assessors, concluded that "CFS scores can be generated using medical chart review and can be reliably completed by ICU clinicians and research staff" [41]. Inter-rater was excellent in our study with a weighted kappa above 0.8. The IQCODE was missing in 24% and was based on informant data collected in a life-threatening situation suggesting that it is not a good tool for critically ill patients.

Another limitation is the lack of other explanatory variables like individual socio-economic status, education and the absence of delirium evaluation on admission and during the ICU stay. We focused on mortality but other outcomes such as long-term ventilation, chronic critical illness and cognitive dysfunction which are patient-relevant outcomes should also be assessed in future studies.

Conclusions

We found that Clinical frailty scale alone was an independent prognostic factor for 1-month survival after ICU admission. Adding other geriatric syndromes and

Table 7 Multivariable analysis including life-sustaining treatment limitation

Variables	Categories	HR (95%CI)	*p*-value
Age	One-point increase	1 (0.99–1.02)	0.79
Habitat (ref = not home)	Own home	0.96 (0.85–1.08)	0.47
Gender (ref = male)	Female	0.94 (0.84–1.04)	0.24
Reason for admission (ref = circulatory failure)	Combined respiratory/circulatory failure	1.13 (0.94–1.36)	0.19
	Emergency surgery	0.68 (0.56–0.84)	0.0003
	Multitrauma w/wo head injury	1.21 (0.85–1.73)	0.28
	Multitrauma without head injury	0.91 (0.61–1.36)	0.64
	Other	0.88 (0.73–1.06)	0.18
	Respiratory failure	0.82 (0.69–0.97)	0.021
	Sepsis (according to Sepsis3)	0.67 (0.55–0.81)	0.0003
SOFA	One-point increase	1.16 (1.14–1.17)	< 0.0001
CPS	One-point increase	0.99 (0.98–1)	0.05
CFS	One-point increase	1.08 (1.05–1.12)	< 0.0001
Withholding or withdrawal	Yes vs no	4.25 (3.8–4.74)	< 0.0001

scores did not improve the model. This is an important finding suggesting that collection of only one score is feasible in circumstances of rapid processing of the decision making to admit or refuse an old patient in ICU. Predicting the future, look at the past! [42].

Electronic supplementary material
The online version of this article (https://doi.org/10.1007/s00134-019-05853-1) contains supplementary material, which is available to authorized users.

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Author contributions
BG, DDL, HF designed the study; AB performed the statistical analysis; JF run the database and the eCRF; BG, DDL, HF, AB drafted the manuscript; AM provided geriatric expertise in designing the protocol. All other authors were country coordinators and validated the manuscript.

Compliance with ethical standards

Conflicts of interest
Joerg C. Schefold declares that the Dept. of Intensive Care Medicine Bern has/had research and/or development/consulting contracts with (full disclosure): Orion Corporation, Abbott Nutrition International, B. Braun Medical AG, CSEM SA, Edwards Lifesciences Services GmbH/SA, Kenta Biotech Ltd, Maquet Critical Care AB, Omnicare Clinical Research AG, and Nestlé. Educational grants were received from Fresenius Kabi; GSK; MSD; Lilly; Baxter; Astellas; AstraZeneca; B. Braun Medical AG, CSL Behring, Maquet, Novartis, Covidien, Nycomed, Pierre Fabre Pharma (Roba Pharma); Pfizer, Orion Pharma. The money went into departmental funds. No personal financial gain applies. All other authors do not have any conflict of interest to declare related to this manuscript.

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