ORIGINAL RESEARCH

Five-year mortality and morbidity impact of prolonged versus brief ICU stay: a propensity score matched cohort study

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ABSTRACT

Purpose Long-term outcomes of critical illness may be affected by duration of critical illness and intensive care. We aimed to investigate differences in mortality and morbidity after short (<8 days) and prolonged (≥8 days) intensive care unit (ICU) stay.

Methods Former EPaNIC-trial patients were included in this preplanned prospective cohort, 5-year follow-up study. Mortality was assessed in all. For morbidity analyses, all long-stay and—for feasibility—a random sample (30%) of short-stay survivors were contacted. Primary outcomes were total and post-28-day 5-year mortality. Secondary outcomes comprised handgrip strength (HGF, %pred), 6-minute-walking distance (6MWD, %pred) and SF-36 Physical Function score (PF SF-36). One-to-one propensity-score matching of short-stay and long-stay patients was performed for nutritional strategy, demographics, comorbidities, illness severity and admission diagnosis. Multivariable regression analyses were performed to explore ICU factors possibly explaining any post-ICU observed outcome differences.

Results After matching, total and post-28-day 5-year mortality were higher for long-stayers (48.2% (95%CI: 43.9% to 52.6%) and 40.8% (95%CI: 36.4% to 45.1%)) versus short-stayers (36.2% (95%CI: 32.4% to 40.0%) and 29.7% (95%CI: 26.0% to 33.5%), p<0.001). ICU risk factors comprised hypoglycaemia, use of corticosteroids, neuromuscular blocking agents, benzodiazepines, mechanical ventilation, new dialysis and the occurrence of new infection, whereas clonidine could be protective. Among 276 long-stay and 398 short-stay 5-year survivors, HGF, 6MWD and PF SF-36 were significantly lower in long-stayers (matched subset HGF: 83% (95%CI: 60% to 100%) versus 87% (95%CI: 73% to 103%), p=0.020; 6MWD: 85% (95%CI: 69% to 101%) versus 94% (95%CI: 76% to 105%), p=0.005; PF SF-36: 65 (95%CI: 35 to 90) versus 75 (95%CI: 55 to 90), p=0.002).

Conclusion Longer duration of intensive care is associated with excess 5-year mortality and morbidity, partially explained by potentially modifiable ICU factors.

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Key messages

What is the key question?

► Does duration of critical illness and its treatments contribute to the long-term burden of critical illness, including increased morbidity and mortality rates?

What is the bottom line?

► Prolonged duration of intensive care (≥8 days) as compared with a brief intensive care unit (ICU) stay (<8 days) is associated with excess 5-year mortality and morbidity, which may be partially explained by potentially modifiable ICU factors.

Why read on?

► This large observational study provides new insights into the 'legacy' of critical illness and suggests that part of this legacy may be preventable.

INTRODUCTION

Critical illness can be defined as any acute, life-threatening condition requiring vital organ support in an intensive care unit (ICU) to avoid imminent death. While survival of the acute phase of critical illness has improved in the past decades,[1] critical illness is associated with increased long-term mortality and morbidity,[2–4] implicating major socioeconomic impact.[2 4] It is debated whether this so-called legacy of critical illness is due to the critical illness itself and related ICU treatments and events, or rather to a frail premorbid constitution of these patients, predisposing them to ICU admission, and to the type and severity of illness necessitating ICU stay.[5]

Several studies underlined the importance of the premorbid functional and health status, including age,[2 6–9] comorbidities,[6 9] frailty,[10] pre-ICU disabilities and functional trajectory,[11 12] as risk factors for increased long-term mortality and morbidity. In addition, type and severity of illness on ICU admission[9 13] predict outcomes. In contrast, it is challenging to quantify the actual contribution of critical illness and its treatments to long-term outcomes. This is because first, capturing the complex premorbid status and inherent susceptibility to ICU admission is virtually impossible and second, critically ill patients are fundamentally

different from other hospitalised patients due to the severity of illness. Hence, the ideal control population is hard to define. Unravelling attributable mortality and morbidity of critical illness and its treatment is nonetheless crucial to guide the development of treatments to reduce this late burden of mortality and morbidity.

We hypothesised that prolonged ICU stay, arbitrarily defined as ICU stay of 8 days or longer, and associated treatments contribute to the long-term burden. We compared 5-year outcomes of patients with prolonged ICU stay to those with short ICU stay (<8 days). By introducing another ICU population as a reference, we tried to adjust for the susceptibility for ICU admission and the overall severity of illness. To determine the excess 5-year burden associated with prolonged ICU stay, we matched short-stayers and long-stayers for randomisation to early or late parenteral nutrition (PN), demographics, comorbidities, type and severity of illness on ICU admission, hence rendering a group of patients comparable on ICU admission. We further explored which interventions and treatments related to prolonged ICU stay could possibly explain any role of prolonged ICU stay on 5-year outcomes.

METHODS

Study population

This is a preplanned prospective observational 5-year follow-up study of patients included in the EPaNIC trial,[14] an investigator-initiated randomised controlled trial conducted in seven medical/surgical ICUs from the University Hospitals Leuven and Jessa Hospitals, examining early (≤48 hour) versus late (>7 days) parenteral supplementation of deficient enteral nutrition. Study design, methodology, eligibility and primary outcomes have been reported.[14] In-ICU, standardised rehabilitation protocols were applied;[15] however, dose and duration of treatments sessions were not registered. Five-year mortality data were collected for all EPaNIC patients (N=4640). From June 2012 onwards, 5-year survivors previously admitted to the Leuven Hospitals were invited to a follow-up clinic and recruited for the long-term morbidity follow-up study. All long-stay patients and, for feasibility purposes, a random subset of short-stay patients were eligible. The cut-off for defining prolonged ICU stay at 8 days was based on the 75th percentile of duration of ICU stay. The subset of short-stay patients was a random, computer-generated sample (3/10). To reduce selection bias, sampling was weighed within admission diagnostic categories to obtain a similar distribution as among long-stayers. Patients with pre-ICU neuromuscular disorders, unable to walk without assistance prior to ICU or other disabilities present before follow-up potentially confounding morbidity endpoints, refusing participation or not contactable were excluded (online supplementary table 1). Home visits were proposed to patients unable or declining a hospital visit. In parallel, as a healthy reference, individuals never admitted to the ICU were recruited from primary care givers' practices and outpatient clinics.

Outcomes

Primary endpoints were 5-year all-cause mortality and post-28-day 5-year mortality (further referred to as 'postacute phase 5-year mortality'), with day 0 defined as time of randomisation. This distinction was made as early (≤28 days) mortality, in contrast with postacute phase mortality, is more impacted by illness severity.[16] The cut-off at >28 days was defined by a fixed time point, on the 75th percentile of duration of hospitalisation. Mortality data were collected from the national registry and for foreigners, by hospital records or phone contacts.

Secondary endpoints comprised three distinct measures of clinical status including evaluation of muscle strength with handgrip strength (HGF, %pred), exercise capacity with 6-minute-walking distance (6-MWD, %pred) and physical functioning with the Physical Function score of the SF-36 quality-of-life measure (PF SF-36, range 0–100 with higher values indicating better scores) as well as additional physical and functional evaluations (details online supplement).

Statistics

Propensity score matching

To compare 5-year outcomes between short-stay and long-stay patients, subsets of patients with short and prolonged ICU stay, matched for randomisation to early or late PN, baseline risk factors (age, gender, body mass index (BMI) and nutritional risk score), comorbidities (diabetes, malignancy and preadmission dialysis), type of illness (cardiac surgery, emergency admission to surgical ICU, elective admission to surgical ICU and medical ICU), presence or absence of sepsis and severity of illness (Acute Physiology And Chronic Health Evaluation: APACHE II) were selected. Matching was based on propensity scores obtained by logistic regression and using one-to-one nearest neighbour matching without replacement with prolonged ICU stay as the dependent variable. A calliper of 0.2 was used and satisfactory matching was obtained as indicated by an absolute standardised difference in means ≤0.1 for all variables. The distribution of propensity scores is provided in online supplementary figure 1. Three matched sets of short-stayers and long-stayers were created, respectively, for comparison of the total and postacute phase 5-year mortality as well as for morbidity analyses. Indeed, for each of these outcomes, the available patient population was different (see figure 1) and as such, we attempted optimal bias reduction in all analyses. For morbidity outcomes, patients were referenced to 50 controls, matched for demographics including age, sex and BMI (see online supplementary file). Outcomes of matched short-stay and long-stay patients were compared with Mann-Whitney U, χ^2 and Fisher exact test as appropriate. For completeness, also comparisons of outcomes between short-stayers and long-stayers of the total patient samples for which mortality and morbidity data were available are provided. Differences were considered significant when two-sided p values were 0.05 or less. For time-to-event analyses, comparisons for patients with short and prolonged ICU stay were performed with the log-rank test and visualised with Kaplan-Meier plots. Effect size was calculated with univariable Cox-proportional hazard regression analyses. Imputation for 6MWD was performed when not missing at random (details online supplementary file 1). No further imputation for missing data was performed.

Exploratory analyses of factors possibly explaining the association of prolonged ICU stay with 5-year outcomes

To explore which characteristics of the prolonged ICU stay may explain its possible adverse association with total, postacute phase 5-year mortality and with the three distinct measures of clinical status at 5 years, univariable and multivariable regression analyses were performed on all available data. These analyses included potentially modifiable ICU factors, such as treatments and exposures, which may be amendable to intervention. Multivariable models were performed backward, probability to enter 0.05, removal 0.2. For time-to-event data, a Cox-regression model was applied. For each of the morbidity outcomes, linear

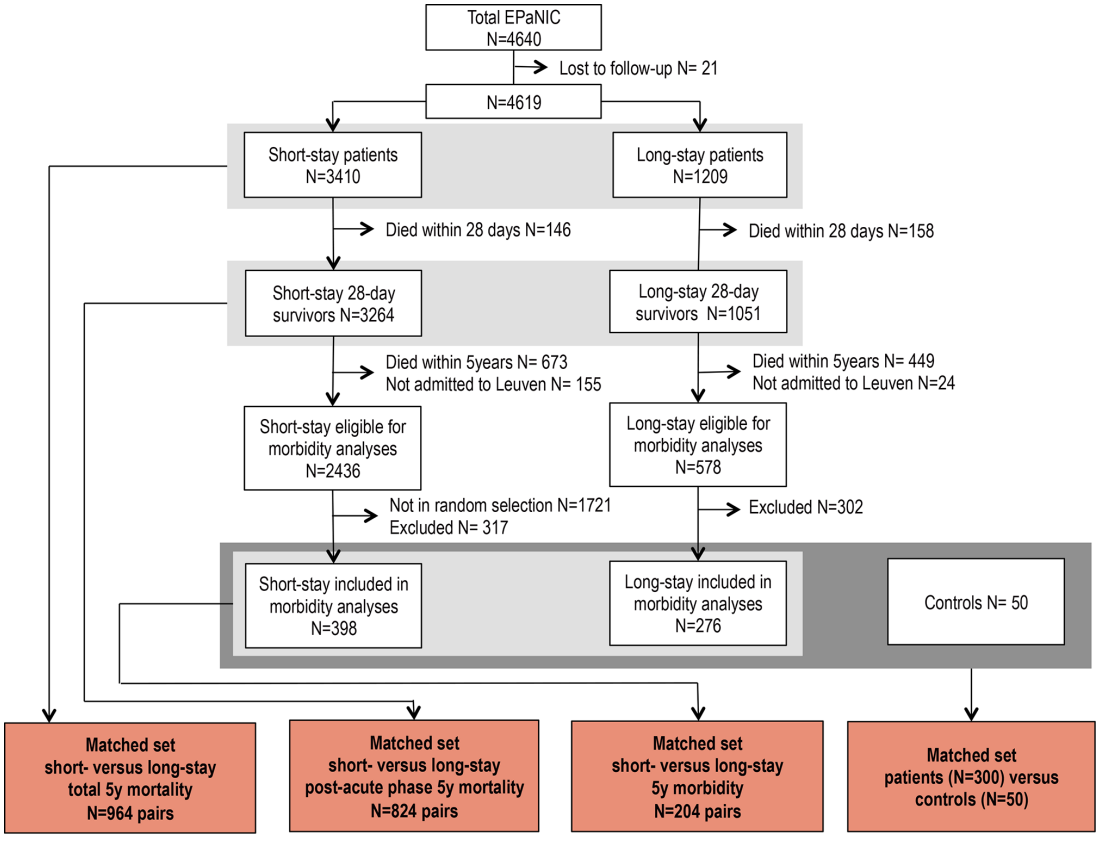

Figure 1 Flow chart of patients and controls and matched subsets for long-term mortality and morbidity analyses.

regression models were applied, if necessary after appropriate transformation. Further details on these analyses are reported in the online supplementary file.

First, multivariable models were built, introducing prolonged ICU stay along with baseline risk factors (randomisation, comorbidities, type and severity of illness) that showed a p value ≤0.2 with the outcome in univariable regression analyses. The 16 admission categories were grouped into four main categories for these analyses as done previously.[17] Next, another set of multivariable models were created in which prolonged ICU stay was replaced by ICU interventions and events that showed a p value ≤0.2 in univariable analyses with the outcome studied. Continuous ICU variables were dichotomised on median values for the total population to provide sufficient overlap between short-stay and long-stay patients. Liver dysfunction was defined as bilirubin >3 mg/dL.[14] Prior to entering these variables, colinearity was checked and judged problematic in case of variation inflation factor >5 or tolerance <0.2. Accuracy of these factors to discriminate prolonged ICU stay was evaluated with receiver operating characteristic curve and c-statistic.

Bootstrapping (n=1000) was performed on the final multivariable models to obtain robust estimators of the CIs for each of the regression coefficients.

Sensitivity analyses

To validate our definition of prolonged ICU stay, we evaluated the optimal cut-off for ICU stay to predict total 5-year mortality, based on martingale residual plots with local regression lines.[18]

At each step of the Cox-regression analyses, the proportional hazard assumption was checked for each variable retained in the model and sensitivity analyses were performed by adding the factors for which this assumption was violated as time-dependent covariates.

All analyses were performed with IBM SPSS V.24. Propensity score matching was performed with IBM SPSS V.24 with a custom SPSS application[19] and R V.3.2.1. Descriptive statistics included median and IQR for continuous variables and numbers and percentages for categorical variables.

RESULTS

Patient characteristics

Five-year mortality data were available for 4619/4640 EPaNIC patients (99.6%), among whom 3410 were short-stayers and 1209 were long-stayers (figure 1). We created 964 matched pairs of short-stayers and long-stayers, matching 79.7% of long-stayers and 28.2% of short-stayers. Of note, 4315/4619 patients survived the first 28 days of illness and were included in the postacute phase 5-year mortality analyses. Of these patients, 824 matched pairs were generated, matching 78.4% of long-stayers and 33.8% of short-stayers. For morbidity analyses, 674 of 3014 eligible patients, including 398 short-stayers and 276 long-stayers were recruited, as well as 50 controls. Reasons for exclusion are listed in online supplementary table 1. Characteristics of included and excluded patients are depicted in table 1 and online supplementary table 2. The subset of long-stayers included in the morbidity analyses was representative of the total population of long-stayers, whereas the subset of short-stayers included expectedly was sicker, had more comorbidities and less frequently were cardiac admissions as compared with the short-stayers not included. We matched 300 patients to 50 controls and created 204 pairs of short-stayers and long-stayers (representing 73.9% of evaluated long-stayers and 51.2% of

Table 1 Baseline characteristics and ICU factors in short-stay versus long-stay patients included in the matched mortality and morbidity analyses

	All cause 5-year mortality analyses			All cause postacute phase 5-year mortality analyses			Morbidity analyses		
	Matched population, N=1928			Matched population, N=1648			Matched population, N=408		
	Short-stay N=964	Long-stay N=964	P value	Short-stay N=824	Long-stay N=824	P value	Short-stay N=204	Long-stay N=204	P value
Baseline factors									
Age, median (IQR)	64.9 (53.5–74.3)	64.4 (53.6–74.8)	0.892	64.5 (54.3–73.5)	63.4 (51.7–74)	0.240	60.4 (50.7–68.2)	58.4 (49.1–70.1)	0.820
Sex, male, N (%)	608 (63.1)	605 (62.8)	0.888	531 (64.4)	518 (62.9)	0.506	145 (71.1)	140 (68.6)	0.590
BMI, median (IQR)	25 (22.5–28.1)	25.2 (22.6–28.9)	0.181	25.4 (22.8–28.6)	25.2 (22.6–28.9)	0.895	25.6 (23.2–28.3)	25.7 (22.8–29)	0.927
NRS ≥5, N (%)	269 (27.9)	265 (27.5)	0.839	217 (26.3)	211 (25.6)	0.736	40 (19.6)	41 (20.1)	0.901
Diabetes mellitus, N (%)	164 (17)	157 (16.3)	0.669	132 (16)	127 (15.4)	0.735	31 (15.2)	33 (16.2)	0.785
Malignancy, N (%)	220 (22.8)	222 (23)	0.914	175 (21.2)	181 (22)	0.719	28 (13.7)	34 (16.7)	0.408
Preadmission dialysis, N (%)	21 (2.2)	19 (2)	0.749	13 (1.6)	17 (2.1)	0.461	0	0	NA
Randomisation, late PN, N (%)	470 (48.8)	469 (48.7)	0.964	401 (48.7)	395 (47.9)	0.767	101 (49.5)	97 (47.5)	0.692
APACHE II, median (IQR)	31 (22–36)	30 (22–36)	0.930	30 (21–35)	29.5 (22–35)	0.773	28 (18–33)	27.5 (20–34)	0.588
Admission category, N (%)			0.811			0.802			0.968
Cardiac surgery	355 (36.8)	335 (34.8)		311 (37.7)	297 (36)		82 (40.2)	80 (39.2)	
Emergency SICU	429 (44.5)	442 (45.9)		363 (44.1)	383 (46.5)		102 (50)	103 (50.5)	
Elective SICU	53 (5.5)	53 (5.5)		51 (6.2)	48 (5.8)		9 (4.4)	8 (3.9)	
MICU	127 (13.2)	134 (13.9)		99 (12)	96 (11.7)		11 (5.4)	13 (6.4)	
Sepsis on admission, N (%)	334 (34.6)	365 (37.9)	0.142	286 (34.7)	289 (35.1)	0.877	50 (24.5)	53 (26)	0.732
ICU-related exposure variables									
Mean morning glycaemia >103 mg/dL	489 (51.3)	517 (53.6)	0.298	409 (50)	444 (53.9)	0.115	107 (52.5)	114 (55.9)	0.487
Mean insulin dose >43.43 U/d	462 (47.9)	679 (70.4)	<0.001	401 (48.7)	574 (69.7)	<0.001	102 (50)	155 (76)	<0.001
Hypoglycaemia during intervention*	26 (2.7)	50 (5.2)	0.005	18 (2.2)	36 (4.4)	0.013	1 (0.5)	8 (3.9)	0.037
Corticosteroids	339 (35.2)	476 (49.4)	<0.001	260 (31.6)	380 (46.1)	<0.001	69 (33.8)	84 (41.2)	0.125
NMBA	107 (11.1)	532 (55.2)	<0.001	61 (7.4)	448 (54.4)	<0.001	16 (7.8)	113 (55.4)	<0.001
Benzodiazepines >1 day	307 (31.8)	841 (87.2)	<0.001	267 (32.4)	712 (86.4)	<0.001	67 (32.8)	177 (86.8)	<0.001
Opioids >3 days	319 (33.1)	885 (91.8)	<0.001	277 (33.6)	759 (92.1)	<0.001	71 (34.8)	193 (94.6)	<0.001
Propofol >1 day	406 (42.1)	793 (82.3)	<0.001	360 (43.7)	681 (82.6)	<0.001	90 (44.1)	180 (88.2)	<0.001
Clonidine	26 (2.7)	185 (19.2)	<0.001	25 (3)	171 (20.8)	<0.001	4 (2)	53 (26)	<0.001
Ketamine	6 (0.6)	37 (3.8)	<0.001	5 (0.6)	31 (3.8)	<0.001	3 (1.5)	9 (4.4)	0.079
Mechanical ventilation >2 days	337 (35)	891 (92.4)	<0.001	276 (33.5)	763 (92.6)	<0.001	68 (33.3)	191 (93.6)	<0.001
Vasopressors/inotropes >2 days	319 (33.1)	799 (82.9)	<0.001	261 (31.7)	676 (82)	<0.001	67 (32.8)	162 (79.4)	<0.001
Bilirubin >3 mg/dL	151 (15.7)	290 (30.1)	<0.001	111 (13.5)	225 (27.3)	<0.001	21 (10.3)	57 (27.9)	<0.001
New dialysis	39 (4)	208 (21.6)	<0.001	13 (1.6)	157 (19.1)	<0.001	1 (0.5)	31 (15.2)	<0.001
New infection	84 (8.7)	736 (76.3)	<0.001	69 (8.4)	630 (76.5)	<0.001	13 (6.4)	157 (77)	<0.001

*Intervention involved early (within 48 hours) vs late (not within the first week) parenteral substitution of deficient enteral nutrition.
BMI, body mass index;ICU, intensive care unit; APACHE II, Acute Physiology And Chronic Health Evaluation; MICU, medical intensive care unit; NMBA, neuromuscular blocking agents; NRS, nutritional risk score; PN, parenteral nutrition; SICU, surgical intensive care unit.

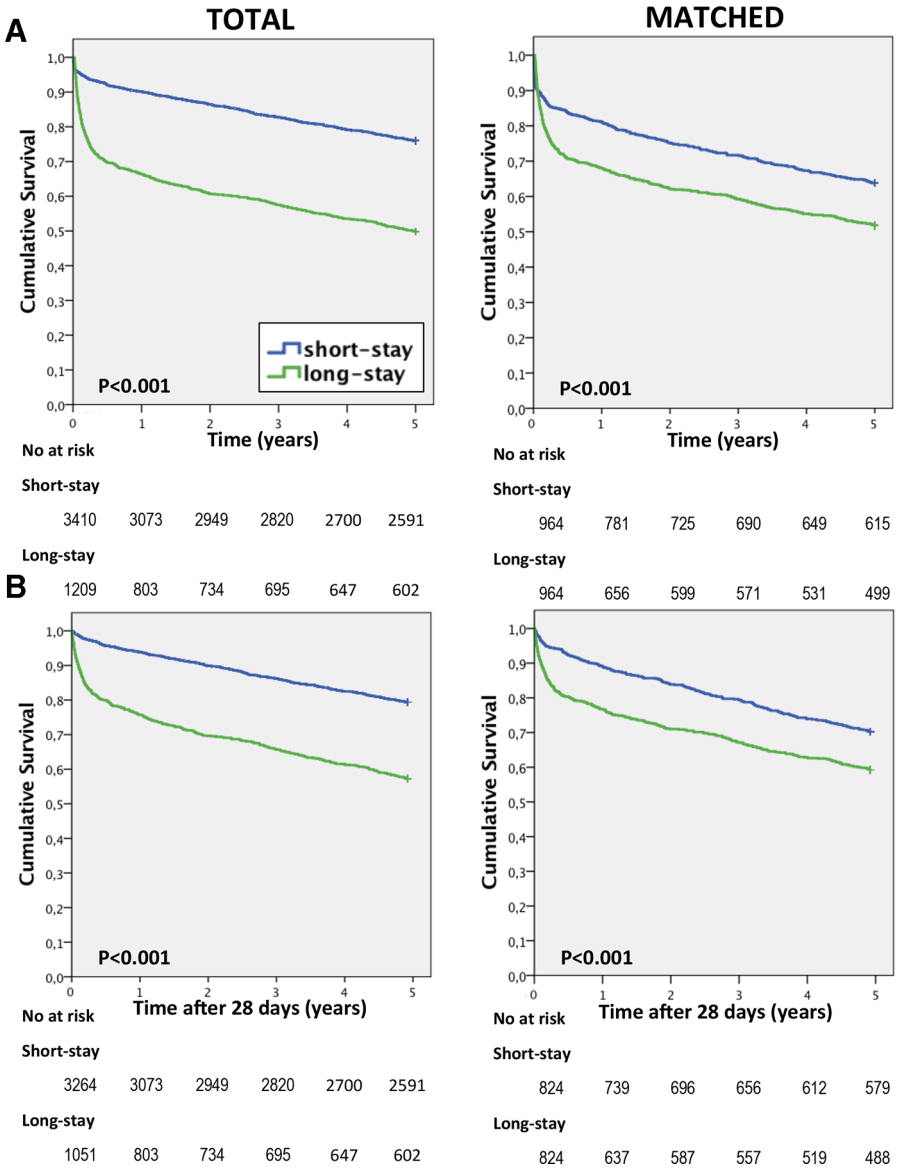

Figure 2 Kaplan-Meier survival curves for total (A) and postacute phase 5-year mortality (B) in the total and matched subset of patients with short (<8 days) and prolonged (≥8 days) ICU stay. restricted mean survival times for matched patients in the total 5-year mortality analyses are 1134 days (95% CI: 1084 to 1185 days) for long-stayers, 1353 days (1308–1398 days) for short-stayers, difference −219 days (95% CI: −287 to −151 days), p<0.001. restricted mean survival times for matched patients in the postacute phase 5-year mortality analyses are 1293 days (95% CI: 1243 to 1343 days) for long-stayers, 1503 days (95% CI: 1463 to 1543 days) for short-stayers, difference −209 days (95% CI: −274 to −146 days), p<0.001.

short-stayers). Patients with home visits were older, had more comorbidities and worse outcomes as compared with patients examined in the hospital (data not shown).

In both mortality endpoints analyses and in the morbidity analyses, long-stay patients were younger, had a higher severity of illness, more frequently received early PN and had different admission diagnoses. Additional differences are highlighted in online supplementary table 3 and 4. No residual imbalances remained in the matched sets (table1 and online supplementary table 5).

Primary endpoints: total and postacute phase 5-year mortality

In the matched analysis, total 5-year mortality was higher in long-stayers as compared with short-stayers (48.2% (95%CI: 43.9% to 52.6%) versus 36.2% (95%CI: 32.4% to 40.0%), p<0.001), rate differences are reported in figure 2. As compared with short-stayers, long-stayers experienced a higher likelihood of death during the 5-year follow-up (HR: 1.447 (95%CI: 1.286 to 1.697), p<0.001)(figure 2). The ICU exposures and events explored to explain the this line is incorrectly split and should continue with 'detrimental impact…'

detrimental impact of prolonged ICU stay on outcomes were highly discriminative for prolonged ICU stay (AUC=0.968, online supplementary figure 2). Multivariable analyses adjusting for potential confounders showed that new dialysis (1.528 (95%CI: 1.232 to 1.919), p<0.001), new infection (1.207 (95%CI: 1.050 to 1.417), p=0.015), any use of corticosteroids (1.534 (95%CI: 1.334 to 1.771), p<0.001), benzodiazepines >1 day (1.195 (95%CI: 1.026 to 1.382), p=0.024), hypoglycaemia (1.361 (95%CI: 1.019 to 1.774), p=0.042), mechanical ventilation >2 days (1.210 (95%CI: 1.029 to 1.416), p=0.019) and any use of neuromuscular blocking agents (1.222 (95%CI: 1.051 to 1.446), p=0.014) explained the excess 5-year mortality,

Table 2 Multivariable Cox-regression analyses for total 5-year mortality and postacute phase 5-year mortality

	5-year mortality		Postacute phase 5-year mortality	
	HR (95%BCaCI)	P value	HR (95%BCaCI)	P value
Baseline factors and prolonged ICU stay				
Age	1.038 (1.036 to 1.048)	0.001	1.042 (1.036 to 1.048)	0.001
BMI other than 25–40	1.262 (1.161 to 1.483)	0.001	1.319 (1.138 to 1.541)	0.001
NRS ≥5	1.193 (1.013 to 1.408)	0.008	1.208 (1.028 to 1.392)	0.014
Diabetes mellitus	1.245 (1.062 to 1.507)	0.001	1.262 (1.072 to 1.499)	0.004
Malignancy	1.641 (1.599 to 2.241)	0.001	1.895 (1.642 to 2.219)	0.001
Preadmission dialysis	2.454 (2.082 to 4.207)	0.001	2.861 (2.018 to 3.922)	0.001
APACHE II	1.031 (1.007 to 1.026)	0.001	1.017 (1.007 to 1.027)	0.001
Admission category (relative to cardiac surgery)				
Emergency SICU	1.439 (1.231 to 1.968)	0.001	1.590 (1.292 to 1.973)	<0.001
Elective SICU	3.296 (2.853 to 4.456)	0.001	3.600 (2.854 to 4.501)	<0.001
MICU	2.344 (1.919 to 3.129)	0.001	2.527 (1.999 to 3.269)	<0.001
Sepsis on admission	1.106 (0.901 to 1.252)	0.162	NA	NA
ICU stay, prolonged	1.596 (1.563 to 2.142)	0.001	1.851 (1.577 to 2.167)	0.001
Baseline factors and ICU factors				
Age	1.042 (1.036 to 1.048)	0.001	1.046 (1.040 to 1.053)	0.001
BMI other than 25–40	1.248 (1.109 to 1.427)	0.002	1.297 (1.112 to 1.525)	0.001
NRS ≥5	1.165 (1.014 to 1.332)	0.036	1.182 (1.009 to 1.383)	0.042
Diabetes mellitus	1.278 (1.094 to 1.497)	0.003	1.320 (1.127 to 1.578)	0.001
Malignancy	1.767 (1.543 to 2.004)	0.001	2.030 (1.740 to 2.416)	0.001
Preadmission dialysis	2.702 (1.914 to 3.777)	0.001	2.987 (2.034 to 4.146)	0.001
APACHE II	1.013 (1.003 to 1.023)	0.007	NA	NA
Admission category (relative to cardiac surgery)				
Emergency SICU	1.572 (1.298 to 1.856)	0.001	1.741 (1.432 to 2.091)	0.001
Elective SICU	3.314 (2.742 to 4.101)	0.001	3.675 (2.960 to 4.521)	0.001
MICU	2.527 (1.985 to 3.178)	0.001	2.683 (2.127 to 3.434)	0.001
Mean insulin dose >43.43 U/day	0.918 (0.813 to 1.053)	0.158	0.899 (0.788 to 1.027)	0.117
Hypoglycaemia during intervention*	1.361 (1.019 to 1.774)	0.042	1.235 (0.864 to 1.763)	0.222
Corticosteroids	1.534 (1.334 to 1.771)	0.001	1.698 (1.400 to 2.069)	0.001
NMBA	1.222 (1.051 to 1.446)	0.014	NA	NA
Benzodiazepines >1 day	1.195 (1.026 to 1.382)	0.024	1.194 (1.004 to 1.402)	0.034
Propofol >1 day	NA	NA	1.141 (0.980 to 1.314)	0.087
Clonidine	0.792 (0.637 to 0.985)	0.051	NA	NA
Mechanical ventilation > 2 days	1.210 (1.029 to 1.416)	0.019	NA	NA
Vasopressors/inotropes > 2 days	NA	NA	1.119 (0.952 to 1.286)	0.144
Bilirubin >3 mg/dl	1.166 (0.986 to 1.387)	0.069	NA	NA
New dialysis	1.528 (1.232 to 1.919)	0.001	1.472 (1.143 to 1.914)	0.002
New infection	1.207 (1.050 to 1.417)	0.015	1.429 (1.202 to 1.685)	0.001

*Intervention involved early (within 48 hours) vs late (not within the first week) parenteral substitution of deficient enteral nutrition.
BCa, bias-corrected accelerated CIs obtained by bootstrap sample procedure (n=1000); BMI, body mass index;ICU, intensive care unit; APACHE II, Acute Physiology And Chronic Health Evaluation; MICU, medical intensive care unit; NA, not applicable; NMBA, neuromuscular blocking agents; NRS, nutritional risk score; PN, parenteral nutrition; SICU, surgical intensive care unit.

whereas clonidine use was associated with improved outcome (0.792 (95%CI: 0.637 to 0.985), p=0.051)(table 2).

Postacute phase 5-year mortality in matched patients was higher in long-stayers as compared with short-stayers (40.8% (95%CI: 36.4% to 45.1%) versus 29.7% (95%CI: 26.0% to 33.5%), p<0.001). Long-stayers experienced a higher likelihood of late death than short-stayers (1.556 (95%CI: 1.320 to 1.834), p<0.001) (figure 2). This was possibly explained by the use of new dialysis (1.472 (95%CI: 1.143 to 1.914), p=0.002), occurrence of new infection (1.429 (95%CI: 1.202 to 1.685), p=0.001), any use of corticosteroids (1.698 (95%CI: 1.400 to 2.069), p<0.001) and use of benzodiazepines >1 day (1.194 (95%CI: 1.004 to 1.402), p=0.034)(table 2).

Sensitivity analyses accounting for the change over time of HR for those variables in which the proportional hazard assumption was violated, implicating that the association of these variables

with mortality changed within the 5-year observation period, did not alter these conclusions (data not shown). Posthoc analyses of the optimal cut-off to define short-stay and long-stay patients suggest a break-point at 6–8 days, supporting the a priori selected cut-off of 8 days (online supplementary figure 3).

Secondary outcomes: 5-year morbidity

To evaluate how prolonged ICU stay associates with long-term morbidity, 5-year survivors were evaluated at a mean 5.5±0.2 years following ICU admission.

In the matched subset, long-stayers demonstrated more impairment in muscle strength, more activity limitation and worse self-reported PF. This is demonstrated by lower handgrip strength: 83% (95%CI: 60% to 100%) versus 87% (95%CI: 73% to 103%), p=0.019, 6-MWD: 85% (95%CI: 69% to 101%) versus 94% (95%CI: 76% to 105%), p=0.005 and PF SF-36: 65 (95%CI: 35 to 90) versus 75 (95%CI: 55 to 90), p=0.002 (figure 3, online supplementary table 6). No difference in Medical Research Council (MRC) sum score was present in the matched subset, which is not unexpected given the ceiling effect of this test.[7] Hand-held dynamometry indicated lower hip and ankle strength, and inspiratory muscle strength was reduced in matched long-stayer as compared with short-stayers. Long-stayers performed worse in daily life activities and rated their overall physical health inferior as compared with short-stayers (online supplementary table 6).

Multivariable regression analyses identified benzodiazepines (HGF and PF SF-36), vasopressors (PF SF-36) and opioids (6-MWD) as ICU exposure variables, possibly explaining increased morbidity 5 years following ICU admission in long-stayers (online supplementary table 7). Former ICU patients performed worse on all measured outcomes as compared with controls who never experienced critical illness (online supplementary table 6, figure 3).

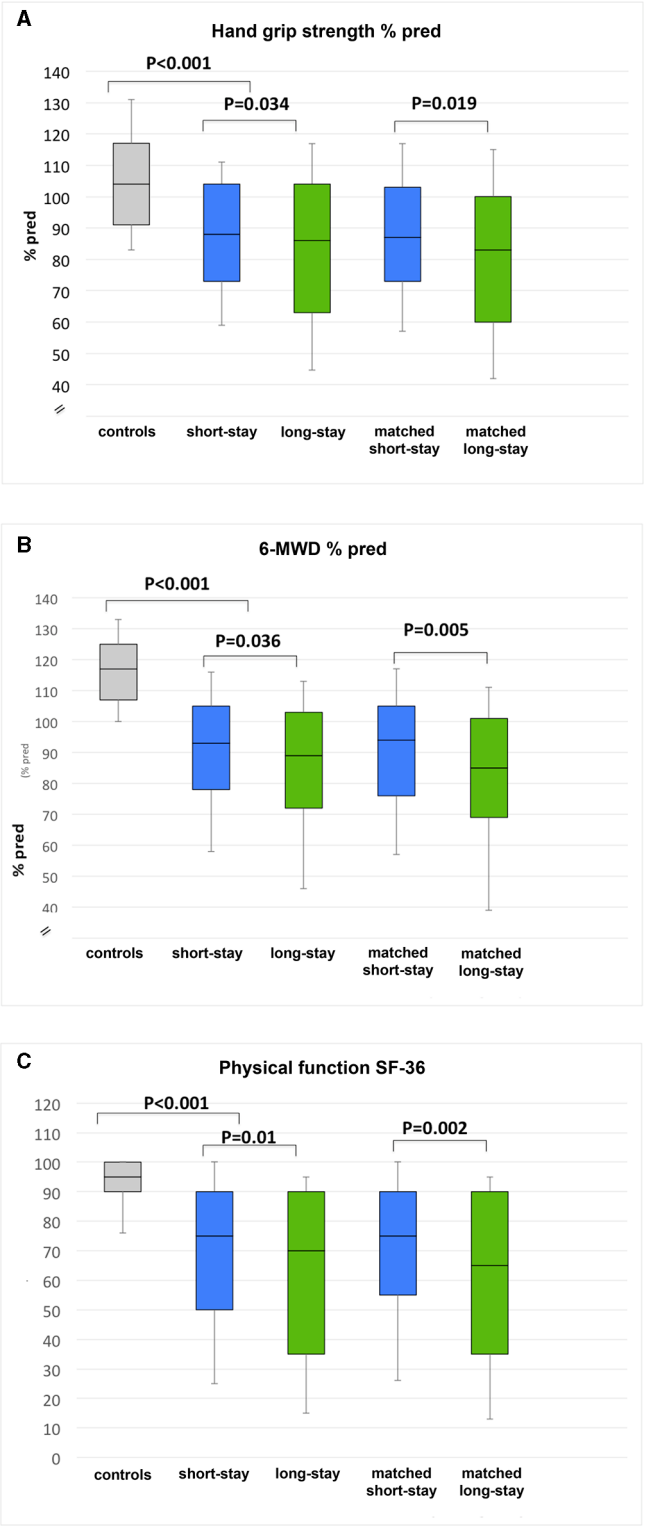

Figure 3 Boxplots of morbidity for short-stay and long-stay patients referenced to controls. (A) Handgrip strength as percentage predicted. (B) 6-minute-walk distance as percentage predicted. (C) Physical function of the short form 36 questionnaire. whiskers represent percentiles 10 and 90. comparisons were performed with Mann-Whitney U test.

DISCUSSION

In this follow-up study of former EPaNIC patients, total and postacute phase 5-year mortality was higher among long-stayers as compared with short-stayers. Increased mortality could not be entirely explained by differences in demographics, comorbidities, type and severity of illness. Furthermore, long-stayers who did survive 5 years as compared with short-stayers had worse functional status, including decreased muscle strength, activity limitation and reduced PF, again not entirely explained by differences on ICU admission. Former ICU patients clearly performed worse than matched controls. These data support that prolonged critical illness and associated exposure to the ICU environment itself may contribute to long-term mortality and morbidity, and hence, to the so-called legacy of critical illness.

As compared with short-stayers who were comparable to long-stayers on ICU admission following careful matching, long-stay patients had an absolute 44.7% and 55.6% increase in, respectively, total and postacute phase 5-year mortality. Furthermore, in those who did survive 5 years, prolonged ICU stay as compared with short ICU stay increased the burden of morbidity, not explained by the aforementioned baseline confounders. Importantly, we consistently identified across both mortality endpoints, several ICU-related exposures that could possibly explain the excess long-term mortality, independent from comorbidities, severity and type of illness on ICU admission. These included new dialysis and infection, and any treatment with corticosteroids or >1 day of benzodiazepines. Several ICU exposures were identified possibly explaining the association of prolonged ICU stay with long-term morbidity, including the use of benzodiazepine, vasopressors and opioids. As several of these factors may be modifiable, the excess mortality and morbidity

in prolonged ICU stay may be, to a certain extent, amendable. These findings should be considered hypothesis-generating and need further confirmation.

Our findings, demonstrating high total and postacute phase 5-year mortality in patients with prolonged ICU stay, are consistent with previously reported high 5-year mortality in critically ill patients as compared with hospitalised controls,[4] further increasing with longer ICU stay.[20 21] Our 5-year morbidity data also align with other work indicating reduced PF, and quality of life in specific subpopulations of mainly ARDS survivors as compared with healthy peers or reference values.[2 6] In these studies, duration of ICU stay,[7] or indicators hereof such as prolonged mechanical ventilation[8] and duration of immobilisation were identified as risk factors. Our study further advances current literature by studying morbidity in a general and heterogeneous population of critically ill patients. Our data do not contradict nor refute the importance of premorbid factors on outcomes, but extend on this knowledge by the comparison of matched short-stayers and long-stayers, indicating that about one out of three 5-year deaths in prolonged ICU stay and a small but consistent reduction in physical outcomes including handgrip strength, 6-MWD and PF SF-36, are incremental to any baseline risk. The identification of exposures during ICU stay that may explain these adverse long-term outcomes, further offers the opportunity to avert poor outcomes rather than resigning on the poor prognostic value of prolonged ICU stay.

Our study has several strengths. First, it is to date and to the best of our knowledge, the largest study on long-term mortality and morbidity following critical illness in a general population. Second, we used a population previously included in a randomised trial, from which baseline and ICU characteristics were carefully and prospectively documented. Third, although we cannot definitely prove the causal relationship between prolonged ICU stay and the observed burden, by comparing this long ICU-stay population with matched, hence comparable, short ICU-stayers, this appears to be the best possible attempt disentangling this issue. We chose this propensity score matching method, and accordingly prospectively recruited short-stayers and long-stayers, because it more effectively reduces bias than multivariable regression analysis.[22–24] As the long-stayers who remained unmatched had higher severity of illness and even worse outcomes than those who were matched (data not shown), propensity score matching represents a conservative approach to assess the long-term burden of prolonged critical illness.

Our study has some limitations. First, we chose to define prolonged ICU stay from day 8 onwards, coinciding with the 75th percentile of ICU stay. Different cut-offs, such as >10[16 21] or >14 days[25] were previously used. Posthoc analyses of the relationship between duration of ICU stay and mortality supported our choice as we found a breaking point after 6–8 days. Second, consistent with other reports,[13] we pragmatically defined postacute phase mortality from day 28 onwards, a fixed time point. Persistent critical illness, defined as the time point beyond which illness severity and diagnosis on admission cease to have additional predictive value on outcome,[16] likely is individually variable. Nevertheless, we found that 'postacute phase' mortality appeared no longer to dependent on illness severity on admission or admission diagnosis such as sepsis. Therefore, this time point appeared to be a sensible cut-off within our population.

Third, though we attempted to adjust for premorbid factors, comorbidities that were not assessed may cause residual confounding in the propensity analyses. This may lead to overestimation of attributable morbidity and mortality of long-stayers. Fourth, we did not include SF-36 data and Barthel-index on ICU admission in the matching as these data may have been flawed by being collected posthoc.[26] Nevertheless, our data indicate that prior to admission, if anything, long-stayers had better premorbid PF than short-stayers. Fifth, during EPaNIC, dexmedetomidine was not available on the Belgian market but has currently largely replaced and expanded the use of clonidine. Sixth, some identified ICU exposures may be unavoidable in specific situations. Hence, attributable mortality and morbidity of prolonged ICU stay may not be entirely preventable. Seventh, for feasibility purposes, only 30% of short-stayers were contacted for the morbidity follow-up. The short-stayers included were a computer-generated sample, randomly selected to match with the diagnostic categories of the long-stayers and consequently included less cardiac patients, were sicker and had more comorbidities than short-stayers who were not included, whereas the long-stayers included were representative for all long-stayers. Finally, external validity may be limited by the exclusion criteria of the randomised trial from which all patients were drawn. Nevertheless, the trial population does reflect a severely ill patient group (mean APACHE 23±10) and general population. Of note, other post-ICU cohort studies have also built on clinical trial populations.[7 27–30] Morbidity analyses evidently were limited to survivors and additional exclusion criteria, including disabilities potentially confounding morbidity endpoints were applied in the follow-up study, which may have introduced selection bias.

In conclusion, 5-year mortality and morbidity was higher among long-stayers than among short-stayers, a difference that was supplementary to any baseline premorbid vulnerability for ICU admission, and to type and severity of illness necessitating critical care. Identified ICU-related exposures may offer opportunities to reduce the long-term burden of prolonged ICU stay.

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Contributors Study concept and design: GH and GVdB. Acquisition of data: GH, HVM, PM, YD, AW, JG, JD and PW. Analysis and interpretation of data: GH, NVA and GVdB. Drafting of the manuscript: GH, NVA and GVdB. Critical revision of the manuscript for important intellectual content: GH, NVA, PM, HVM, YD, AW, JG, MPC, JD, RG, PW and GVdB. Statistical analysis: GH, NVA and GVdB. Obtained funding: GH, NVA and GVdB. Administrative, technical support: PW. Study supervision: GH, HVM, PW and GVdB.

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