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

Online supplement

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Methods

Outcomes

Secondary endpoints comprised three distinct measures of clinical status reported to be impaired in survivors up to years following ICU admission, [1-4] including evaluation of muscle strength with handgrip strength (HGF, %pred), [5] exercise capacity with 6-minute-walk distance (6-MWD, %pred), [6] indicative for activity limitation 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). [7, 8]
To further characterize physical and functional limitations, additional measurements were performed. These comprised global assessment of muscle strength with the MRC sum score (range 0-60, higher values indicating higher strength), isometric muscle strength with hand held dynamometry for the same muscle groups as included in the MRC evaluation, maximal inspiratory pressure, the physical and mental component score of the SF-36, representing the respective health summaries of the questionnaire (PCS and MCS, range 0-100 with higher values indicating better scores) and the Barthel-index, a scale to measure performance in daily life activities (range 0-20, lower values indicating more disability). [9]

1. Handgrip strength

Handgrip strength was measured with a hydraulic handgrip dynamometer (Jamar Preston, Jackson, Michigan, USA) as previously described. [10] The dynamometer was regularly calibrated. Measurements were performed by the same four experienced physiotherapists (TVH, SV, TVA, HVM). Measurements were standardly performed on the right side. In case of focal or regional problems for certain muscle groups, evaluation was performed on the contralateral side. Care was taken to perform measurements with the elbow in 90 degrees flexion. Handgrip strength was determined as the highest of 3 attempts. Values were expressed as percent of predicted values for sex and age.[5]

2. 6-minute walk distance

The 6-minute walking distance (6MWD) was performed in a 30-meter corridor or on the side-walk during home visits, according to the ATS guidelines. [11] Results were expressed as percent predicted. [6] For patients unable to perform the test due to physical limitations, a zero value was imputed as performed in earlier work. [12, 13]

3. Quality of life questionnaire

The quality of life was assessed with The Medical Outcomes Report – Short Form 36 (SF36) questionnaire. [7, 8] The SF-36 includes 8 scores, consisting of multiple items, that assess 8 domains, including physical and social functioning, physical and emotional role, mental health, pain, vitality and general health. In addition, 2 summary scores, physical component summary (PCS) and mental component summary (MCS) are calculated. Scores range from 0 – 100 with lower scores indicating more disability and higher scores indicating less disability.

4. Medical Research Council sum score

MRC sum score was measured as described earlier. [10] Six muscle groups were evaluated (abduction of the shoulder, flexion of the elbow, extension of the wrist, flexion of the hip, extension of the knee and dorsal flexion of the foot) bilaterally and scored between 0 and 5 (0= no visible/palpable contraction, 1= visible/palpable contraction without movement of the limb, 2= movement of the limb but not against gravity, 3= movement against gravity (almost full passive range of motion) but not against resistance, 4= movement against gravity and resistance, arbitrarily judged to be submaximal for sex and age, 5= normal). Measurements were performed by one of four physiotherapists (TVH, SV, TVA, HVM) who were extensively trained before the start of the study.

5. Hand held dynamometry

Isometric muscle force was measured using a hand held dynamometry (CompuFet 2; Biometrics, Almere, The Netherlands) that was connected to a laptop as previously described. [14] The same muscle groups involved in the MRC sum score were evaluated. Measurements were performed by the same four experienced physiotherapists (TVH, SV, TVA, HVM). Measurements were standardly performed on the right side. In case of

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focal or regional problems for certain muscle groups, evaluation was performed on the contralateral side. Values were expressed as percent of predicted values for sex and age.[15]

6. Maximal Inspiratory Pressure

We measured maximal static inspiratory pressure (MIP) according to the ATS guidelines.[16] Measurements were performed by the same four experienced physiotherapists (TVH, SV, TVA, HVM), specifically trained for this by the pulmonary function technicians. We used a mouthpiece that incorporated a small leak to prevent glottis closure during the inspiratory manoeuvre. Pressures were measured with the Micro Medical respiratory pressure meter, CareFusion® using Puma PC software. The patient was asked to perform a maximal inspiratory manoeuvre starting from functional residual capacity. Maximal static inspiratory pressure was determined as the mouth pressure measure at the side port of a mouthpiece, maintained for 1 second. The best of 3 consecutive measurements was recorded.

7. Activities of daily living

The Barthel Index was used to assess independence during 10 daily life activities, including presence or absence of faecal and urinary incontinence, need of help with grooming, toilet use, feeding, transfers, walking, dressing, climbing stairs and bathing. Higher scores indicate higher level of independence, with a maximum score of 20.[9]

Statistics

1. Total and post- acute phase five-year mortality

Propensity score matching

To compare total and post-acute phase five-year mortality between short-and long-stay patients, we selected a subset of patients with short and prolonged ICU stay matched for randomization to early or late PN, baseline risk factors (age, gender, BMI, nutritional risk score), co-morbidities (diabetes, malignancy, pre-admission dialysis), type of illness (cardiac surgery, emergency admission to surgical ICU, elective admission to surgical ICU, medical ICU and sepsis upon admission), presence or absence of sepsis and severity of illness (APACHE II). 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 evaluated based on an absolute standardized difference in means less than or equal to 0·1 for all variables.
Comparisons between short and long-stayers were made in the matched population, and for completeness, also in the total population. Total and post-acute phase five-year mortality for short-and long-stayers were reported as proportions and compared by Chi-square statistics. For time-to-event analyses, comparisons for patients with short and prolonged ICU stay were performed with the log-rank test and visualized with Kaplan-Meier plots. Effect size was calculated with univariable Cox-proportional hazard regression analyses.

Exploratory analyses of factors explaining effects of prolonged ICU stay on total and post-acute phase five-year mortality

To further explore which characteristics of the prolonged ICU stay may explain its possible adverse association with mortality, multivariable Cox proportional hazards analyses were performed in the total EPaNIC population with backward models, likelihood ratio, probability to enter 0·05, removal 0·2.
First, multivariable Cox regression models were built, introducing prolonged ICU stay along with baseline risk factors (randomization, co-morbidities, 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.[12] Next, another set of multivariable Cox regression 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 dichotomized on median values for the total population to provide sufficient overlap between short-and long-stay patients. Liver dysfunction was defined as bilirubin >3mg/dl.[17] Prior to entering these variables, co-linearity 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 (ROC) curve and c-statistic.
Bootstrapping (n=1000) was performed on the final multivariable models to obtain robust estimators of the

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confidence intervals 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 and post-acute phase five-year mortality, based on martingale residual plots with LOcal regrESSion (LOESS) lines.[18]

At each step of the cox regression analyses, the proportional hazard assumption was checked for each variable retained in the model with use of log-minus-log (LML) plots for categorical variables, partial residuals (PR) plots for continuous variables and, if unclear, by entering the variable as a time-dependent covariate. At each step of the multivariable Cox regression analyses, sensitivity analyses were performed by adding the factors for which this assumption were violated as time-dependent covariates.

2. Five-year morbidity

Propensity score matching

Short-and long-stay patients
To compare five-year morbidity between short-and long-stay patients we selected a subset of patients with short and prolonged ICU stay, matched for randomization, baseline risk factors, including co-morbidities, type and severity of illness. Matching for demographics, co-morbidities and severity of illness upon admission was performed as described above. Post-hoc, ICU admission quality of life data (SF-36 questionnaire) and performance in daily life activities (Barthel index) were collected at the five-year follow-up visit as supplementary information on the pre-morbid status. These data were not used in the matching procedure as recollection of pre-morbid state may have been flawed by the post-ICU trajectory.[19] For completeness, also comparisons of outcomes between short-and long-stay patients in the total sample for which morbidity data were available were provided.

Patients and controls
Morbidity outcomes of the former ICU patients were further referenced to controls in a subset matched for demographics including age, sex and BMI, and for completeness, also in the total population of patients and controls. To obtain satisfactory matching, repeated one-to-one nearest neighbour matching without replacement was performed based on propensity scores obtained by logistic regression with patients versus controls as dependent variable and age as covariate. This procedure was repeated as long as satisfactory matching for all 50 controls was obtained within the remaining patient population. This resulted in a 1:6 matching (50 controls and 300 patients). Final balance for each of the covariates was checked by chi-square and Mann-Whitney U test before examining any results.

Exploratory analyses of factors explaining effects of prolonged ICU stay on five-year morbidity

To further explore which characteristics of the prolonged ICU stay may explain any possible adverse association on the secondary outcomes, linear regression models were performed in the subset of five-year EPaNIC survivors who were evaluated at five years, with backward models, probability for enter 0·05, removal 0·2.
First, multivariable regression models were built, introducing prolonged ICU stay along with baseline risk factors (randomization, co-morbidities, 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.[12] Next, another set of multivariable regression 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. In order to obtain adequate model fit, the 6 MWD data were transformed to power 2 and the PF-SF36 were reversed (100 minus actual value) and subsequently transformed to power 0·54.
Bootstrapping (n=1000) was performed on the final multivariable models to obtain robust estimators of the confidence intervals for each of the regression coefficients.

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Supplementary figure 1: Distribution of propensity scores of unmatched and matched subsets of EPaNIC patients, for five year mortality, post-acute five year mortality and five year morbidity analysis.

Supplementary figure 2: Receiver operating characteristic (ROC) curve, generated from the binary logistic regression analyses with prolonged ICU stay as the dependent variable and ICU-related exposure variables as the independent variables. Area under the curve=0·968.
These ICU-related exposure variables included: age, sex (male versus female), BMI NRS (≥5 versus <5), Diabetes mellitus Malignancy, Pre-admission dialysis, Randomization (late versus early PN), APACHE II, Admission categories (cardiac surgery, emergency surgery, elective surgery, MICU), sepsis upon admission
Abbreviations: BMI: body mass index; NRS: nutritional risk score; PN: parenteral nutrition APACHE II: Acute Physiology And Chronic Health Evaluation; MICU: Medical Intensive Care Unit

Supplementary figure 3: Plot of martingale residuals versus duration of ICU stay. Martingale residuals were calculated form univariable Cox-proportional hazard analyses of total five-year mortality with ICU stay as the independent variable. LOESS lines (in red) indicate a breaking point around six to eight days. The right panel provides details of the main area of interest from the left panel. The bleu lines represent the actually applied cut-off to define long-stayers.

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Suppl. Table 1: Reasons for exclusion from morbidity analyses within eligible patients$

	Short-stay eligible N= 2436	Long-stay eligible N=578
Short stay not in random selection	1721	NA
Died after five years, before planned testing	6	12
Lost to follow-up/ living abroad	42	51
Time window passed	14	8
Language barrier	0	2
Pre-existent (pre-ICU) neuromuscular disorder[$]	18	25
Unable to walk without assistance prior to ICU	2	3
Cardiac assist device*	1	0
Pulmonary resection (pneumonectomy)*	6	10
Psychiatric disease*	8	11
Dementia*	4	1
Vegetative state*	0	2
Hospitalized/Rehabilitation center/Nursing home*	17	20
Refusal:		
Good health	17	8
Poor health	15	20
Old age	8	2
Practical	23	24
Other follow-up programs	67	34
Emotional reasons	12	7
Not interested	35	32
No reason	22	30

[$]Pre-ICU neuromuscular disorders were excluded by manual chart review of the medical history performed by study nurses, and when in doubt, discussed with the PI.
*present before follow-up evaluation
Abbreviations: ICU: intensive care unit; NA: not applicable

Suppl. Table 2: Characteristics of eligible patients according to inclusion status

	Short-stay eligible patients N=2436			Long-stay eligible patients N=578		
	Included N=398	Not included N=2038	*P*-value	Included N=276	Not included N=302	*P*-value
Baseline factors						
Age	61.4 (50.8-70.3)	66.3 (55.7-74.2)	<0.001	58.1 (48.4-68.8)	57.1 (43.8-69.7)	0.514
Gender, male	252 (63.3)	1309 (64.2)	0.728	198 (71.7)	178 (58.9)	0.001
BMI	25.6 (23-28.4)	26 (23.5-29.3)	0.009	25.8 (22.9-29.4)	25.2 (22.4-28.4)	0.206
NRS >5	69 (17.3)	204 (10.0)	<0.001	60 (10.4)	80 (13.8)	0.183
Diabetes mellitus	57 (14.3)	330 (16.2)	0.350	42 (15.2)	36 (11.9)	0.247
Malignancy	65 (16.3)	234 (11.5)	0.007	41 (14.9)	40 (13.2)	0.578
Preadmission dialysis	3 (0.8)	19 (0.9)	1	0	2 (0.7)	0.500
Randomisation, late PN	222 (55.8)	1014 (49.8)	0.028	122 (44.2)	147 (48.7)	0.282
APACHE II	19.5 (14-32)	16 (13-21)	<0.001	30 (22.9-29.4)	31 (24-36)	0.558
Admission category			<0.001			0.109
Cardiac surgery	203 (51.0)	1732 (85)		98 (35.5)	80 (26.5)	
Elective SICU	36 (9.0)	52 (2.6)		8 (2.8)	7 (2.3)	
Emergent SICU	144 (36.2)	201 (9.9)		139 (50.4)	178 (58.9)	
MICU	15 (3.8)	53 (2.6)		31 (11.2)	37 (12.3)	
Sepsis on admission	62 (15.6)	165 (8.1)	<0.001	114 (41.3)	138 (45.7)	0.288
ICU stay, days	3 (1-5)	2 (1-3)	<0.001	15 (11-25)	15 (11-23)	0.674

Continuous variables are expressed as median (IQR), dichotomous variables are expressed as numbers (percentages)
Abbreviations: BMI: body mass index; NRS: nutritional risk score; PN: parenteral nutrition; APACHE II: Acute Physiology And Chronic Health Evaluation; SICU: Surgical Intensive Care Unit; MICU: Medical Intensive Care Unit

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Suppl. Table 3: Baseline characteristics and ICU factors of the total population of short- versus long-stay patients included in the mortality and morbidity analyses									
	All cause five-year mortality analyses			**All cause post-acute phase five-year mortality analyses**			**Morbidity analyses**		
	Total population N= 4619			Total population N= 4315			Total population N= 674		
	Short-stay N=3410	Long-stay N=1209	*P*-value	Short-stay N= 3264	Long-stay N= 1051	*P*-value	Short-stay N=398	Long-stay N=276	*P*-value
Baseline factors									
Age, median (IQR)	67·1 (56·6-75·1)	64·5 (53·9-74·5)	<0·001	66·8 (56·5-74·8)	63·7 (53·3-73·9)	<0·001	61·4 (50·8-70·3)	58·1 (48·4-68·8)	0·052
Sex, male (%)	2187 (64·1)	774 (64)	0·943	2093 (64·1)	677 (64·4)	0·864	252 (63·3)	198 (71·7)	0·022
BMI, median (IQR)	25·9 (23·2-29·1)	25·3 (22·6-28·9)	0·002	25·9 (23·3-29·1)	25·3 (22·7-29)	0·003	25·6 (23-28·4)	25·8 (22·9-29·4)	0·419
NRS ≥ 5 (%)	471 (13·8)	385 (31·8)	<0·001	422 (12·9)	315 (30)	<0·001	69 (17·3)	60 (21·7)	0·153
Diabetes mellitus (%)	602 (17·7)	204 (16·9)	0·539	570 (17·5)	166 (15·8)	0·211	57 (14·3)	42 (15·2)	0·747
Malignancy (%)	603 (17·7)	288 (23·8)	<0·001	564 (17·3)	241 (22·9)	<0·001	65 (16·3)	41 (14·9)	0·605
Pre-admission dialysis (%)	46 (1·3)	23 (1·9)	0·173	40 (1·2)	18 (1·7)	0·233	3 (0·8)	0	0·273
Randomization, late PN (%)	1748 (51·3)	570 (47·1)	0·014	1678 (51·4)	488 (46·4)	0·005	222 (55·8)	122 (44·2)	0·003
APACHE II, median (IQR)	17 (13-26)	32 (25-38)	<0·001	17 (13-24)	32 (24-37)	<0·001	19·5 (14-32)	30 (23-36·8)	<0·001
Admission category (%)			<0·001			<0·001			<0·001
Cardiac surgery	2463 (72·2)	347 (28·7)		2413 (73·9)	313 (29·8)		203 (51)	98 (35·5)	
Emergency SICU	552 (16·2)	607 (50·2)		493 (15·1)	543 (51·7)		144 (36·2)	139 (50·4)	
Elective SICU	222 (6·5)	54 (4·5)		217 (6·6)	49 (4·7)		36 (9)	8 (2·9)	
MICU	173 (5·1)	201 (16·6)		141 (4·3)	146 (13·9)		15 (3·8)	31 (11·2)	
Sepsis upon admission (%)	423 (12·4)	586 (48·5)	<0·001	360 (11·0)	492 (46·8)	<0·001	62 (15·6)	114 (41·3)	<0·001
ICU-related exposure variables									
	Short-stay N=3410	Long-stay N=1209	p-value	Short-stay N= 3264	Long-stay N= 1051	p-value	Short-stay N=398	Long-stay N=276	p-value
Mean morning glycaemia > 103 mg/dl	1658 (49)	629 (52)	0·075	1587 (49)	541 (51·5)	0·171	202 (50·8)	153 (55·4)	0·231
Mean insulin dose >43·43 U/d	1451 (42·6)	855 (70·7)	<0·001	1382 (42·3)	741 (70·5)	<0·001	170 (42·7)	216 (78·3)	<0·001
Hypoglycaemia during intervention[a]	60 (1·8)	66 (5·5)	<0·001	50 (1·5)	51 (4·9)	<0·001	4 (1)	9 (3·3)	0·036
Corticosteroids	531 (15·6)	621 (51·4)	<0·001	460 (14·1)	525 (50)	<0·001	99 (24·9)	124 (44·9)	<0·001
NMBA	214 (6·3)	673 (55·7)	<0·001	159 (4·9)	578 (55)	<0·001	28 (7)	157 (56·9)	<0·001
Benzodiazepines > 1 day	719 (21·1)	1062 (87·8)	<0·001	646 (19·8)	922 (87·7)	<0·001	103 (25·9)	244 (88·4)	<0·001
Opioids > 3 days	729 (21·4)	1102 (91·1)	<0·001	669 (20·5)	969 (92·2)	<0·001	113 (28·4)	261 (94·6)	<0·001
Propofol > 1 day	1005 (29·5)	973 (80·5)	<0·001	952 (29·2)	858 (81·6)	<0·001	139 (34·9)	243 (88)	<0·001
Clonidine	60 (1·8)	245 (20·3)	<0·001	57 (1·7)	227 (21·6)	<0·001	9 (2·3)	79 (28·6)	<0·001
Ketamine	9 (0·3)	50 (4·1)	<0·001	8 (0·2)	48 (4·6)	<0·001	3 (0·8)	9 (3·3)	0·019
Mechanical ventilation > 2 days	632 (18·5)	1130 (93·5)	<0·001	553 (16·9)	978 (93·1)	<0·001	100 (25·1)	261 (94·6)	<0·001
Vasopressors/ inotropes> 2 days	805 (23·6)	1002 (82·9)	<0·001	731 (22·4)	868 (82·6)	<0·001	102 (25·6)	224 (81·2)	<0·001
Bilirubin>3 mg/dl	244 (7·2)	389 (32·2)	<0·001	207 (6·4)	317 (30·2)	<0·001	36 (9·1)	84 (30·4)	<0·001
New dialysis	54 (1·6)	304 (25·1)	<0·001	20 (0·6)	242 (23)	<0·001	2 (0·5)	55 (19·9)	<0·001
New infection	229 (6·7)	897 (74·2)	<0·001	199 (6·1)	790 (75·2)	<0·001	24 (6)	206 (74·6)	<0·001

Abbreviations: BMI: body mass index; NRS: nutritional risk score; PN: parenteral nutrition; APACHE II: Acute Physiology And Chronic Health Evaluation; SICU: Surgical Intensive Care Unit; MICU: Medical Intensive Care Unit; NMBA: neuromuscular blocking agents

[a]Intervention involved early (within 48h) versus late (not within the first week) parenteral substitution of deficient enteral nutrition

Suppl. Table 4: Post-hoc pre-morbid status in short- versus long-stay patients for total and matched population included in the morbidity analyses

	Matched population N= 408			Total population N= 674		
	Short-stay N=204	Long-stay N=204	*P*-value	Short-stay N=398	Long-stay N=276	*P*-value
PF SF 36, median (IQR)	70 (30-100)	85·0 (45·5-100)	0·100	75 (40-95)	85 (45-100)	0·016
PCS, median (IQR)	43·1 (31·9-56·0)	48·4 (34·7-57·9)	0·029	44·6 (33·8-55·6)	49·6 (35·4-57·9)	0·005
MCS, median (IQR)	52·4 (43·4-58·0)	51·6 (42·8-57·7)	0·659	52·7 (44·1-57·9)	51·7 (41·1-57·6)	0·155

Abbreviations: PF SF-36: physical function of the 36-item short form health survey; PCS: physical component score; MCS: mental component score

Suppl. Table 5: Demographics of patients and controls in morbidity analyses

	Matched population N= 350			Total population N= 724		
	Patients N=300	Controls N=50	*P*-value	Patients N= 674	Controls N= 50	*P*-value
Age	62 (58-68)	61 (57-66)	0·218	65 (55-75)	61 (57-66)	0·058
Sex, male (%)	205 (68·3)	35 (70)	0·814	450 (66·77)	35 (70)	0·639
BMI	27·3 (24·0-30·8)	26·4(23·7-29·3)	0·282	26·8 (23·8-30·0)	26·4 (23·7-29·3)	0·653

Abbreviations: BMI: body mass index

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Suppl. Table 6: Morbidity analyses in five-year survivors and controls

	Matched population N= 350			Total population N= 724			Matched population N= 408			Total population N= 674		
	Patients N= 300	Controls N= 50	*P*-value	Patients N= 674	Controls N= 50	*P*-value	Short-stay patients N= 204	Long-stay patients N= 204	*P*-value	Short-stay patients N= 398	Long-stay patients N= 276	*P*-value
Strength												
MRC sum score	60(58-60)	60(60-60)	<0·001	60(58-60)	60(60-60)	<0·001	60(57-60)	60(57-60)	0·254	60(58-60)	60(58-60)	0·049
HGF (%pred)	89(73-104)	104(91-117)	<0·001	87(70-104)	104(91-117)	<0·001	87(73-103)	83(60-100)	0·020	88 (73-104)	86 (63-104)	0·035
HHD (%pred)												
Shoulder	91(76-106)	98(86-119)	0·006	89(74-106)	98(86-119)	0·001	88(75-102)	85(65-104)	0·250	91(77-108)	88(68-105)	0·007
Elbow	84(72-97)	101(87-116)	<0·001	84(71-99)	101(87-116)	<0·001	83(71-97)	79(64-97)	0·148	86(73-100)	82(66-97)	0·003
Wrist	97(84-115)	109(93-122)	0·004	98(82-115)	109(93-122)	0·004	97(81-112)	94(77-111)	0·126	99(84-116)	96(79-112)	0·004
Hip	144(123-171)	165(134-183)	0·006	143(120-168)	165(134-183)	0·001	146(119-170)	134(110-157)	0·001	149(125-174)	135(113-158)	<0·001
Knee	52(43-60)	65(53-74)	<0·001	52(42-62)	65(53-74)	<0·001	50(42-62)	49(38-59)	0·083	53(44-64)	51(39-59)	0·002
Ankle	72(60-85)	91(74-108)	<0·001	73(59-86)	91(74-108)	<0·001	72(58-86)	67(52-79)	0·004	75(61-90)	68(54-81)	<0·001
MIP (%pred)	90(71-11)	104(85-124)	0·004	90(69-111)	104(85-124)	0·001	92(71-115)	87(64-105)	0·021	91(71-113)	88(65-105)	0·077
Exercise capacity												
6MWD (%pred)	95(79-107)	117(107-125)	<0·001	92(75-104)	117(107-125)	<0·001	94(76-105)	85(69-101)	0·005	93(78-105)	89(72-103)	0·036
Quality of life												
PF SF-36	75 (50-90)	95 (90-100)	<0·001	75 (45-90)	95 (90-100)	<0·001	75(55-90)	65 (35-90)	0·002	75 (50-90)	70 (35-90)	0·010
PCS	48(37-55)	55(51-58)	<0·001	46(35-54)	55(51-58)	<0·001	47(38-55)	43(32-52)	0·003	47(37-55)	45 (33-52)	0·013
MCS	55(49-59)	58(53-60)	0·049	55(46-59)	58(53-60)	0·046	56(48-60)	54(45-59)	0·053	55(47-59)	54(45-59)	0·206
ADL												
Barthel index	20 (19-20)	20 (20-20)	0·020	20 (19-20)	20 (20-20)	0·006	20 (19-20)	20 (18-20)	<0·001	20 (19-20)	20 (18-20)	0·001

Abbreviations: MRC: Medical Research Council; HGF: hand grip force; HHD: hand held dynamometry; MIP: maximal inspiratory pressure; PF SF-36: physical function of the 36-item short form health survey; PCS: physical component score; MCS: mental component score; ADL: activities of daily living

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Suppl. Table 7: Multivariable analyses of hand-grip strength (% predicted), 6MWD (% predicted) and PF SF36 in five-year survivors

	Hand-grip strength		**6-MWD** b		**PF SF36** c	
	Unstandardized coefficients (B) (95% BCa confidence intervals) a	*P*-value	Unstandardized coefficients (B) (95% BCa confidence intervals) a	*P*-value	Unstandardized coefficients (B) (95% BCa confidence intervals) a	*P*-value
Models with baseline factors and prolonged ICU stay						
Age	NA	NA	NA	NA	0.068 (0.051-0.085)	0.001
Sex. male	14.098 (10.081-18.018)	0.001	984.794 (341.928-1620.014)	0.006	-1.195 (-1.715 to -0.672)	0.001
BMI other than 25-40	-4.554 (-8.181 to -0.538)	0.022	NA	NA	-0.412 (-0.909-0.102)	0.114
NRS≥5	-3.598 (-9.045 to 1.999)	0.187	NA	NA	NA	NA
Diabetes mellitus	-8.526 (-14.343 to -3.101)	0.006	-2024.754 (-2903.779 to -1124.245)	0.001	1.233 (0.491-1.980)	0.001
Malignancy	NA	NA	NA	NA	0.715 (0.126-1.358)	0.023
Admission category - emergent surgery	NA	NA	NA	NA	0.391 (-0.100-0.904)	0.131
ICU stay. prolonged	-6.272 (-9.940 to -2.702)	0.002	-913.743 (-1566.921 to -260.837)	0.005	0.923 (0.447-1.426)	0.002
Models with baseline factors and ICU factors						
Age	NA	NA	NA	NA	0.066 (0.050-0.083)	0.001
Sex. male	13.830 (9.696-17.971)	0.001	946.598 (311.847-1568.265)	0.007	-1.128 (-1.623 to -0.609)	0.001
BMI other than 25-40	-4.694 (-8.268 to -0.704)	0.017	NA	NA	-0.426 (-0.922 -0.082)	0.108
NRS≥5	-3.636 (-9.157 to 1.660)	0.177	NA	NA	NA	NA
Diabetes mellitus	-9.177 (-15.038 to -3.807)	0.003	-2005.767(-2928.841 to -1090.329)	0.001	1.359 (0.623-2.083)	0.001
Malignancy	NA	NA	NA	NA	0.732 (0.151 -1.351)	0.008
Admission category. emergent surgery	NA	NA	NA	NA	0.355 (-0.159-0.857)	0.176
Hypoglycemia	NA	NA	-1764.531 (-3289.553 to -96.186)	0.028	NA	NA
Mean morning glycaemia > 103 mg/dl	2.991 (-0.334-6.782)	0.112	NA	NA	-0.471 (-0.929-0.047)	0.069
NMBA	NA	NA	-692.840 (-1485.853 – 121.982)	0.071	NA	NA
Benzodiazepines > 1day	-8.225 (-11.912 to -5.013)	0.001	NA	NA	0.572 (-0.004-1.118)	0.050
Opiates > 3 days	NA	NA	-743.458 (-1412.271 to -76.979)	0.031	NA	NA
Clonidine	5.055 (-1.318 -11.993)	0.118	NA	NA	NA	NA
Vasopressors/inotropes > 2 days	NA	NA	NA	NA	0.557 (-0.038 - 1.129)	0.052

Abbreviations: NRS: nutritional risk score; BMI: body mass index; APACHE II: Acute Physiology And Chronic Health Evaluation; BCa: bias-corrected accelerated confidence intervals obtained by bootstrap sample procedure (n=1000). bValues were transformed to power 2. cValues were reversed (100 minus PF-SF-36) and subsequently transformed to power 0·54.

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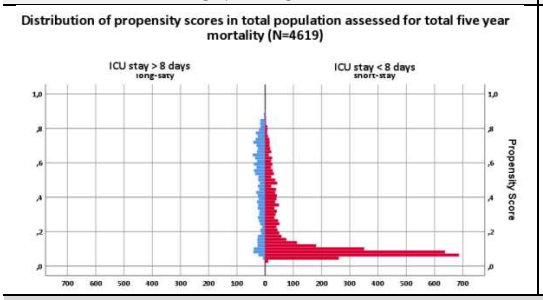
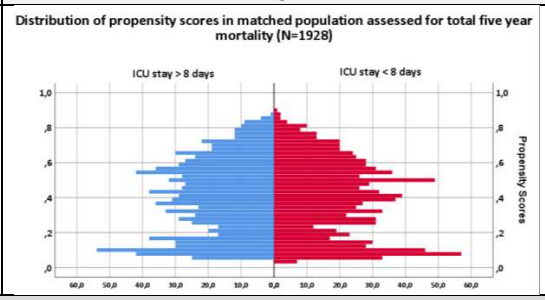
Supplemental figure 1

Total five year mortality population

UNMATCHED

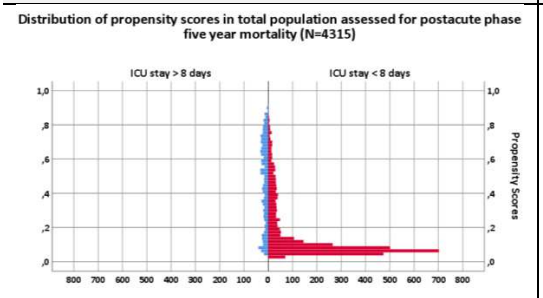


MATCHED

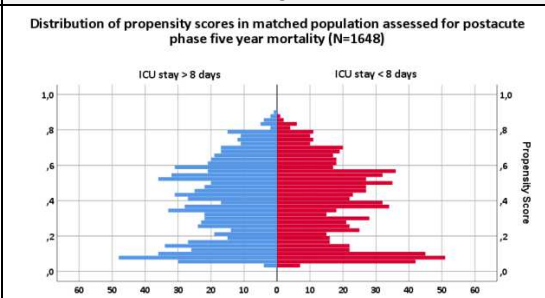


Post 28-days five year mortality

UNMATCHED

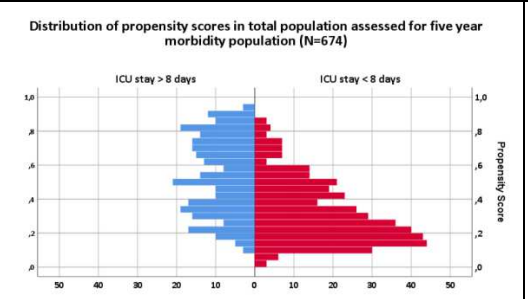


MATCHED



Five year morbidity

UNMATCHED



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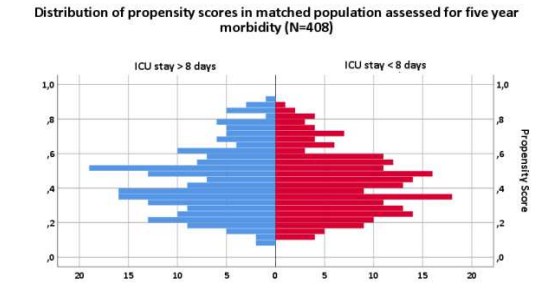

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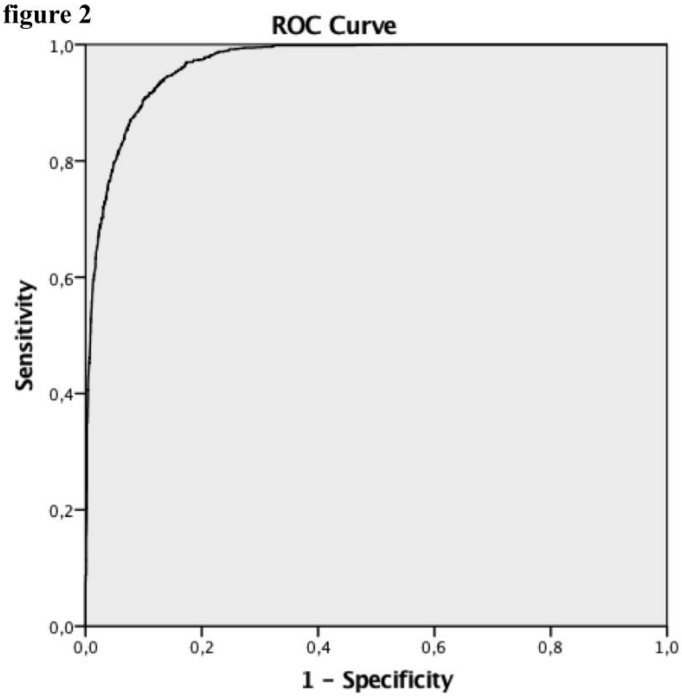
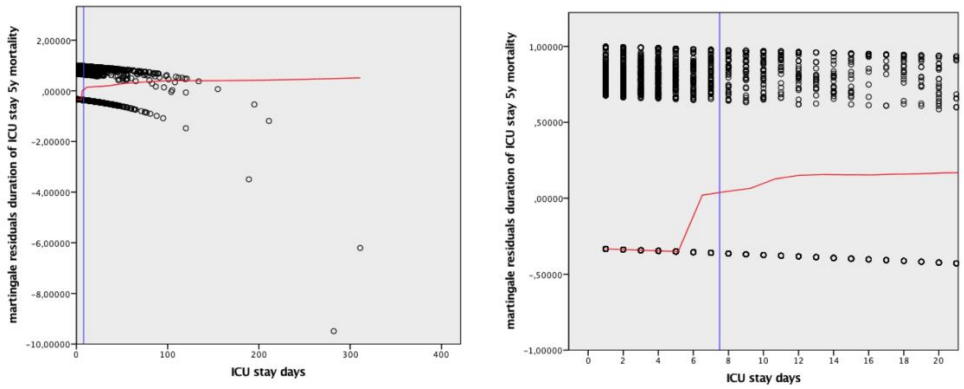
Supplemental figure 2



Supplemental figure 3



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