Five-year outcome of respiratory muscle weakness at intensive care unit discharge: secondary analysis of a prospective cohort study

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SUPPLEMENTAL METHODS

EPaNIC and post-EPaNIC follow-up study

The EPaNIC trial (Clinical trials.gov: NCT00512122, N=4640) was a multicentre, randomised controlled trial (7 medical and surgical intensive care units) conducted at the University Hospitals Leuven and Jessa Hospitals Hasselt, comparing early (within 48 hours) with late (not before day 8) parenteral supplementation of insufficient enteral nutrition to reach caloric goals in adult critically ill patients [1]. Main exclusion criteria included age < 18 years, moribund state or DNR-coding, enrollment in other trial, short-bowel syndrome, home ventilation, diabetic coma, referred with nutritional regime, pregnant or lactating women, no central catheter, on oral nutrition, readmission, BMI<17 kg/m², nutritional risk score < 3, or refusal to participate. The study showed that late initiation of parenteral nutrition was associated with faster recovery and fewer complications [1]. The post-EPaNIC follow-up study prospectively assessed 5-year mortality in all, and 5-year morbidity in a subgroup of long-term surviving EPaNIC-patients through hospital or home visits from June 2012 onwards [1-4]. Recruitment for the 5-year morbidity follow-up focussed on patients with prolonged ICU-stay (≥8 days), and for feasibility purposes, a random sample (398/2436) of eligible short-stay patients was included, matched to the diagnostic category distribution of long-stayers. Exclusion criteria for the 5-year morbidity analysis involved pre-existing neuromuscular disease, other pre-ICU disabilities potentially confounding the morbidity endpoints, and patients refusing participation [3, 4].

Statistics

Primary outcome: explanatory modelling of the association between respiratory muscle weakness at ICU discharge *and all-cause 5-year mortality*

Crude 5-year mortality of patients with and without RMW was compared as a time-to event analysis with log-rank test and visualized with Kaplan-Meier plots. The effect size was estimated with Cox proportional hazard analyses, adjusting for a priori defined confounders, identified through a systematic literature search [5]. The search strategy and results are presented below. Prior to entering the variables as covariates to the models, collinearity was checked and judged problematic in case of variance inflation factor >5 or tolerance <0.2. Potential confounders comprised demographic variables, comorbidities, and ICU treatments and events, particularly including peripheral muscle strength. Potential confounders identified included age, BMI, diabetes mellitus, malignancy, preadmission dialysis, diagnostic category, APACHE II-score, sepsis upon admission, ICU length-of-stay, days of in-ICU treatment with corticosteroids and neuromuscular blocking agents, acquisition of new infection in ICU and MRC sum-score ≤ 55. MRC sum-score at ICU discharge was dichotomised at 55, according the recent findings with regard to long-term outcomes [4]. Of the pre-specified ICU-factors, days of in-ICU treatment with benzodiazepines and duration of mechanical ventilation were eliminated from the final model due to collinearity with ICU length-of stay.

Secondary outcomes: explanatory modelling of the association between respiratory muscle weakness at ICU discharge and 5-year morbidity

The association between 5-year morbidity outcomes and RMW at ICU discharge was explored with Mann-Whitney U test. The association between RMW at ICU discharge and respiratory muscle strength at 5 years as well as the 3 key measures of physical function, comprising hand-grip strength, 6-minute-walk-distance and the physical function domain of the SF-36, was further assessed by multivariable linear regression analyses, adjusted for confounders identified through a systematic literature search.
In order to enable the adjusted analyses through linear regression and obtain adequate model fit for 6-MWD and PF-SF-36, we performed Box-Cox based transformations [6, 7] as we did previously [4].

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This involved transformation of the 6-MWD to power 2. For PF-SF-36, data were reversed and subsequently transformed to power 0.54. Agreement with assumptions for linear regression (linearity, homoscedasticity, independence of errors and normal distribution of residuals) was assessed through normal probability plot, histogram of standardized residuals, scatter plot of the standardised residuals versus the standardised predicted values.
The search strategy and results for relevant confounders are presented below. Again, collinearity was checked and judged problematic if variance inflation factor >5 or tolerance <0.2. The following factors were identified as potential confounders, for MIP: age, gender, BMI, diabetes mellitus, malignancy, preadmission dialysis, duration of mechanical ventilation, maximal SOFA score, ICU length of stay, MRC sum-score ≤ 55; for HGF: age, gender, BMI, diabetes mellitus, malignancy, preadmission dialysis, duration of mechanical ventilation, maximal SOFA score, ICU length of stay, MRC sum-score ≤ 55; for 6-MWD: age, gender, diabetes mellitus, malignancy, preadmission dialysis, duration of mechanical ventilation, hypoglycaemia, length of ICU stay, MRC sum-score ≤ 55; for PF SF-36e: age, gender, diabetes mellitus, malignancy, preadmission dialysis, duration of treatment with inotropics/vasopressors, duration of mechanical ventilation, length of ICU stay, MRC sum-score ≤ 55. Duration of in-ICU treatment with sedatives (for MIP, HGF and PF-SF-36: duration of treatment with benzodiazepines; for 6MWD: duration of treatment with opioids) was eliminated from the final models due to collinearity with ICU length-of stay.

As this was a secondary analysis, sample size was not modifiable. However, we anticipated based on prior data, 40% of patients would have RMW. For the primary outcome, given a hazard ratio of 4.4 at 1-year [8], and assuming this difference would reduce to a HR of 2 at 5 years, with an overall 5-year mortality in critically ill patients of 30% [9], with type I error at 0.05 and power of 80% this would require a total sample size of 227 patients, which was covered by the available sample. As the number of deaths was 104, and 13 confounders were identified to be included in the Cox-regression analysis, the likelihood of problematic error was small [10]."

Search strategy to identify known confounders of the relationship between respiratory muscle weakness in ICU and 5-year mortality and morbidity.

The Medline database was searched through Ovid and PubMed platforms for full-text, human subject, English language original research journal articles (prospective as well as retrospective observational studies, randomized controlled trials) of patients admitted to an intensive care unit, reporting on the association between demographic factors, co-morbidities and ICU treatments and events with 5-year outcomes in relation to measures of respiratory muscle strength in the ICU. Systematic reviews and meta-analyses retrieved with the search were screened for referenced original research articles.
We used Mesh terms and additional exploded searches centering around key concepts 'critical illness', 'intensive care unit acquired respiratory muscle weakness/ventilator-induced diaphragm dysfunction', 'potential confounders' and 'mortality/morbidity outcomes'. All used Mesh terms and additional search terms (relevant entry terms based on the tree built on each Mesh-term, as well as recently introduced professional language not indexed in the Mesh-database including 'ventilator-induced diaphragm dysfunction') are listed below. We included papers published within the past 20 years (prior to January 2020). Due to limited available evidence on 5-year outcomes, we included studies with shorter follow-up after ICU-discharge and with measures of respiratory muscle weakness other than the MIP. A confounder was defined according to recent guidelines on causal inference studies, as a factor independently associated with both ICU-acquired respiratory muscle weakness, and with long-term outcome in ICU-patients[5]. For verification of the latter requirement, given sparsity of data in particular for 5-year morbidity, we extrapolated evidence from research on the adverse long-term outcome of prolonged mechanical ventilation and sepsis [11-14], and refer to previous work centering more specifically on the association of prolonged ICU-stay and ICUAW with

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long-term outcome [3, 4, 11, 12, 15, 16]. Final construction of the search string as presented below and article retrieval was conducted between the 4th and 10th of January 2020.

1. Five-year mortality

Pubmed search

(((“Critical Illness”[Mesh] OR “Critical Care”[Mesh] OR “Intensive Care Units"[Mesh] OR “Acute Disease”[Mesh] OR “Shock”[Mesh] OR “Systemic Inflammatory Response Syndrome”[Mesh] OR “Multiple organ failure”[Mesh] OR “Respiratory insufficiency”[Mesh] OR critical-illness* OR critical-care* OR intensive-care* OR acute-disease* OR *shock* OR Systemic-Inflammatory-Response-Syndrome* OR multiple-organ-failure* OR respiratory-insufficienc*)) AND (“Respiratory paralysis”[Mesh] OR respiratory-paralys* OR Respiratory-Muscle-Paralysis* OR Diaphragm-atrophy* OR Diaphragm-dysfunction* OR Diaphragm/pathology* OR Diaphragmatic-Paralysis* OR Diaphragm-paralysis* OR Respiratory-muscle-weakness* OR Respiratory-muscle-paresis* OR diaphragm-paresis* OR Ventilator-induced-diaphragmatic-dysfunction* OR Ventilator-induced-diaphragm* OR inspiratory-pressure* OR MIP* OR transtracheal-pressure*) AND (“Length of Stay”[Mesh] OR “Severity of illness index”[Mesh] OR “Simplified acute physiology score”[Mesh] OR “APACHE”[Mesh] OR “Artificial respiration”[Mesh] OR “Neuromuscular blocking agents”[Mesh] OR “Kidney, artificial”[Mesh] OR “Vasoconstrictor agents”[Mesh]OR “Comorbidity”[Mesh] OR “Body mass index”[Mesh] OR length-of-stay*or severity-of-illness-index* OR simplified-acute-physiology-score* OR SOFA-score* OR APACHE* OR comorbidit* OR multimorbidit* OR gender* OR age* OR body-mass-index* OR artificial-respiration* OR mechanical-ventilation* OR neuromuscular-blocking-agent* OR artificial-kidney* OR vasoconstrictor* OR vasopress* OR vasoactive-agonist* OR “Polyneuropathy”[Mesh] OR “Paresis”[Mesh] OR “Muscle weakness”[Mesh] OR “Muscle strength”[Mesh] OR polyneuropath* OR paresis* OR *muscle-weakness* OR muscle-strength* OR muscle-wasting*) AND (“Critical care outcomes”[Mesh] OR “Mortality”[Mesh] OR *mortality* OR critical-care-outcome*OR follow-up* OR survival* OR “Long Term Adverse Effects”[Mesh] OR Long-Term-Adverse-Effect*)))

Ovid search

(Critical Illness OR Critical Care OR Intensive Care Units OR Multiple organ failure) AND (Respiratory paralysis OR Diaphragm-atrophy OR Diaphragm-dysfunction OR Diaphragm/pathology OR Respiratory-muscle-weakness OR Ventilator-induced-diaphragmatic-dysfunction) AND (Critical care outcomes OR Mortality OR critical-care-outcome OR follow-up OR survival)

2. Five-year morbidity

Pubmed search

(((“Critical Illness”[Mesh] OR “Critical Care”[Mesh] OR “Intensive Care Units"[Mesh] OR “Acute Disease”[Mesh] OR “Shock”[Mesh] OR “Systemic Inflammatory Response Syndrome”[Mesh] OR “Multiple organ failure”[Mesh] OR critical-illness* OR critical-care* OR intensive-care* OR acute-disease* OR *shock* OR Systemic-Inflammatory-Response-Syndrome* OR multiple-organ-failure*)) AND (“Respiratory paralysis”[Mesh] OR respiratory-paralys* OR Respiratory-Muscle-Paralysis* OR Diaphragm-atrophy* OR Diaphragm-dysfunction* OR Diaphragm/pathology* OR Diaphragmatic-Paralysis* OR Diaphragm-paralysis* OR Respiratory-muscle-weakness* OR Respiratory-muscle-paresis* OR diaphragm-paresis* OR Ventilator-induced-diaphragmatic-dysfunction* OR Ventilator-induced-diaphragm* OR inspiratory-pressure* OR MIP* OR transtracheal-pressure*) AND (“Length of Stay”[Mesh] OR “Severity of illness index”[Mesh] OR “Simplified acute physiology score”[Mesh] OR

"APACHE"[Mesh] OR "Artificial respiration"[Mesh] OR "Neuromuscular blocking agents"[Mesh] OR "Kidney, artificial"[Mesh] OR "Vasoconstrictor agents"[Mesh]OR "Comorbidity"[Mesh] OR "Body mass index"[Mesh] OR length-of-stay*or severity-of-illness-index* OR simplified-acute-physiology-score* OR SOFA-score* OR APACHE* OR comorbidit* OR multimorbidit* OR gender* OR age* OR body-mass-index* OR artificial-respiration* OR mechanical-ventilation* OR neuromuscular-blocking-agent* OR artificial-kidney* OR vasoconstrictor* OR vasopress* OR vasoactive-agonist* OR "Polyneuropathy"[Mesh] OR "Paresis"[Mesh] OR "Muscle weakness"[Mesh] OR "Muscle strength"[Mesh] OR polyneuropath* OR paresis* OR *muscle-weakness* OR muscle-strength* OR muscle-wasting*) AND ("Morbidity"[Mesh] OR "Muscle strength"[Mesh] OR "Hand strength"[Mesh] OR "Pinch strength"[Mesh] OR "Walk test"[Mesh] OR "Activities of Daily Living"[Mesh] OR "Quality of life"[Mesh] OR morbidit* OR muscle-strength* OR hand-strength* OR pinch-strength* OR 6-min-walk-test*OR activities-of-daily-living* OR ADL* OR barthel-index* OR quality-of-life* or SF36* OR physical-component-score* OR "Respiratory paralysis"[Mesh] OR Respiratory-muscle-weakness* OR Respiratory-muscle-paresis* OR Diaphragm-dysfunction* OR inspiratory-pressure* OR MIP*)))

Ovid search

(Critical Illness OR Critical Care OR Intensive Care Units OR Multiple organ failure) AND (Respiratory paralysis OR Diaphragm-atrophy OR Diaphragm-dysfunction OR Diaphragm/pathology OR Respiratory-muscle-weakness OR Ventilator-induced-diaphragmatic-dysfunction) AND (Critical care outcomes OR OR Morbidity OR Muscle strength OR Walk test OR Quality of life OR Activities of Daily Living OR Respiratory-muscle-weakness OR MIP)

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Supplementary Figure 1. Kaplan-Meier survival plots with 95% confidence intervals depicting the proportion of patients alive up to 5 years following ICU admission according to the presence or absence of RMW at ICU discharge. RMW is defined as an absolute value of MIP <30cmH_2O. Effect size is expressed as Log-rank test and adjusted hazard ratio, correcting for potential confounders, was calculated with multivariable cox regression analysis. Abbreviations: *RMW*: Respiratory Muscle Weakness; *MIP*: Maximal Inspiratory Pressure.

Supplementary Figure 2. Morbidity outcomes at 5 years according to presence or absence of RMW at ICU discharge. RMW is defined as an absolute value of MIP <30cmH_2O. *Panel A:* maximal inspiratory pressure (MIP, cmH_2O), handgrip-strength (HGF, % predicted), 6-minute walk distance (6-MWD, % predicted) and Physical function of the SF-36 (PF-SF-36, range 0-100 with higher values indicating better scores). *Panel B:* measures of peripheral muscle strength: hand-held dynamometry (HHD) for shoulder abduction, elbow flexion, wrist extension, hip flexion, knee extension, ankle dorsiflexion (% predicted), Medical-Research-Council (MRC) sum-score, Barthel index (range 0-20, higher values indicating better scores), Physical (PCS) and Mental Component score (MCS) of the SF-36 questionnaire and. P-values were obtained by Mann-Whitney U tests. Abbreviations: *RMW:* Respiratory Muscle Weakness, *MIP:* Maximal Inspiratory Pressure, *HGF:* Handgrip-strength, *6MWD:* 6-minute walk distance, *PF-SF-36:* Physical function of the 36-item Short Form Health Survey, *HHD:* Hand-Held Dynamometry, *MRC:* Medical-Research-Council, *PCS:* Physical Component score, *MCS:* Mental Component score.

Supplementary Figure 3. Exploration of the linearity assumption for MIP at ICU discharge in relation with 5-year mortality and morbidity. *Panel A:* LOESS-smoother on the Martingale residuals plot for 5-year mortality by MIP at ICU discharge. Martingale residuals were calculated from the adjusted Cox-regression model for 5-year mortality, including MIP at ICU discharge as a continuous variable and all confounders as covariates; *Panel B:* LOESS-smoother on the scatter plot for MIP (absolute value, cmH_2O) at 5-year follow-up by MIP at ICU discharge; *Panel C:* LOESS-smoother on the scatter plot for hand grip strength at 5-year follow-up (% predicted) by MIP at ICU discharge; *Panel D:* LOESS-smoother on the scatter plot for transformed 6-MWD at 5-year follow-up by MIP at ICU discharge; *Panel E:* LOESS-smoother on the scatter plot for of transformed PF-SF36 at 5-year follow-up by MIP at ICU discharge. The following transformations were performed: the 6-MWD data were transformed to power 2 and the PF SF-36 were reversed (100 minus actual value) and subsequently transformed to power 0.54 (higher transformed values of PF-SF-36 correspond to lower actual values of PF SF-36). Abbreviations: *MIP:* Maximal Inspiratory Pressure, *HGF:* handgrip-strength, *6MWD:* 6-minute walk distance, *PF-SF-36:* Physical function of the 36-item Short Form Health Survey.

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Supplementary Table 1. Comparison of baseline and ICU-characteristics of eligible 5-year survivors included versus not-included in the five year morbidity analysis

	RMW at ICU discharge, included (N=56)	**RMW at ICU discharge, not included (N=23)**	***P*-value**	**No RMW at ICU discharge, included (N=100)**	**No RMW at ICU discharge, not included (N=67)**	***P*-value**
Baseline factors						
Age on admission	61 (52-73)	58 (40-76)	0.567	60 (50-67)	50 (37-63)	0.002
Gender, male	27 (48.2)	11 (47.8)	0.651	70 (70)	40 (59.7)	0.385
NRS>5	11 (19.6)	11 (47.8)	0.004	19 (19.0)	11 (16.4)	0.418
BMI	25.6 (23.4-31.9)	25.4 (21-29.4)	0.409	25.2 (23.2-27.7)	25 (23-29)	0.686
Diabetes mellitus	12 (21.4)	6 (26.1)	0.877	12 (12.0)	7 (10.4)	0.798
Malignancy	11 (19.6)	2 (8.7)	0.009	19 (19.0)	6 (9.0)	<0.001
Pre-admission dialysis	0(0)	1 (4.3)	0.336	0(0)	0 (0)	0.264
Randomisation, late PN	35 (62.5)	13 (56.5)	0.268	48 (48.0)	32 (47.8)	0.458
APACHE II	30 (18-36)	34 (25-37)	0.142	26 (16-34)	25 (14-33)	0.302
Admission category			0.449			<0.001
Cardiac surgery	25 (44.6)	6 (26.1)		52 (52.0)	23 (34.3)	
Emergency SICU	20 (35.7)	13 (56.5)		32 (32.0)	30 (44.8)	
Elective SICU	2 (3.6)	0 (0)		4 (4.0)	4 (6.0)	
MICU	9 (16.1)	4 (17.4)		12 (12.0)	10 (14.9)	
Sepsis upon admission	19 (33.9)	13 (56.5)	0.134	28 (28.0)	26 (38.8)	0.084
ICU factors						
Mechanically ventilated	55 (98.2)	22 (95.7)	0.607	99 (99.0)	63 (94.0)	0.040
Mechanical ventilation, days	6 (2-14)	8 (3-11)	0.914	2 (1-7)	3 (1-8)	0.491
ICU stay, days	13 (6-22)	12 (5-17)	0.593	4 (1-11)	9 (2-14)	0.083
Hospital stay, days	29 (19-59)	28 (15-40)	0.362	16 (10-30)	18 (10-36)	0.316

Continuous variables are reported with median and interquartile range, dichotomous variables are reported with number and percentage. *P*-values reflect differences between eligible patients included versus not included in the 5-year morbidity analyses. Eligible patients were those surviving at 5 years and not falling under the exclusion criteria.

Abbreviations: *RMW:* Respiratory Muscle Weakness, *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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Supplementary Table 2. Exploratory analyses and sensitivity analyses		
Five-year mortality analyses	**HR (95%CI)[a]**	**P-value**
MIP (absolute value) at ICU discharge as a continuous variable, HR per unit increase	0.991 (0.976-1.004)	0.240
MIP (absolute value) at ICU discharge, dichotomised at 45 cmH_2O	1.381 (0.770-2.980)	0.220
RMW at ICU discharge, analysis limited to hospital survivors	1.217 (0.624-2.300)	0.518
RMW at ICU discharge (model including MRC sum score at ICU discharge as a continuous variable)	1.162 (0.658-1.970)	0.569
RMW at ICU discharge (model including MRC sum score at ICU discharge, dichotomised at 48)	1.346 (0.811-2.136)	0.240
RMW at ICU discharge (model including time-dependent covariates for factors violating the proportional hazard assumption[b])	1.248 (0.785-1.984)	0.348
Five-year morbidity analyses	**B (95%BcaCI)[a]**	**P-value**
Maximal inspiratory pressure (cmH_2O)		
MIP (absolute value) at ICU discharge as a continuous variable	0.669 (0.389-0.975)	0.001
MIP (absolute value) at ICU discharge, dichotomised at 45 cmH_2O	-20.086 (-28.325 to -11.539)	0.001
RMW at ICU discharge (model including MRC sum-score at ICU discharge as a continuous variable)	-22.919 (-32.645 to -14.262)	0.001
RMW at ICU discharge (model including MRC sum-score at ICU discharge, dichotomised at 48)	-25.031 (-33.517 to -16.827)	0.001
Hand-grip strength (% pred)		
MIP (absolute value) at ICU discharge as a continuous variable	0.421 (0.200-0.676)	0.002
MIP (absolute value) at ICU discharge, dichotomised at 45 cmH_2O	-10.714 (-19.606 to -1.572)	0.020
RMW at ICU discharge (model including MRC sum-score at ICU discharge as a continuous variable)	-19.811 (-32.318 to -6.897)	0.001
RMW at ICU discharge (model including MRC sum-score at ICU discharge, dichotomised at 48)	-21.534 (-32.253 to -9.371)	0.001
6-minute walk distance (%pred, transformed) [c]		
MIP (absolute value) at ICU discharge as a continuous variable	78.778 (37.600-131.736)	0.001
MIP at ICU discharge, dichotomised at an absolute value of 45 cmH_20	-3464.1 (-5116.8 to -1959.9)	0.001
RMW at ICU discharge (model including MRC sum-score at ICU discharge as a continuous variable)	-1643.64 (-3395.4 to -106.2)	0.030
RMW at ICU discharge (model including MRC sum-score at ICU discharge, dichotomised at 48)	-1921.4 (-3282.3 to -651.2)	0.007

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Continued Supplementary Table 2. Exploratory analyses and sensitivity analyses		
Five-year morbidity analyses	**B (95%BcaCI)[a]**	**P-value**
PF-SF-36 (score, transformed) [c]		
MIP (absolute value) at ICU discharge as a continuous variable	-0.049 (-0.075 to -0.020)	0.001
MIP (absolute value) at ICU discharge, dichotomised at 45 cmH_2O	1.755 (0.649-2.768)	0.002
RMW at ICU discharge (model including MRC sum-score at ICU discharge as a continuous variable)	1.183 (-0.072 - 2.337)	0.046
RMW at ICU discharge (model including MRC sum-score at ICU discharge, dichotomised at 48)	1.324 (0.218-2.379)	0.015

[a] All models are adjusted for confounders;

[b] The proportional hazards assumption was violated for BMI and for ICU length of stay, adjusted hazard ratio is based on adjustment of the model by adding a time dependent factor for BMI and for ICU length of stay;

[c] The following transformations were performed: the 6-MWD data were transformed to power 2 and the PF-SF-36 were reversed (100 minus actual value) and subsequently transformed to power 0.54 (higher transformed values of PF-SF-36 correspond to lower actual values of PF-SF-36).

Abbreviations: *MIP*: maximal inspiratory pressure; *RMW*: respiratory muscle weakness defined as an absolute value of MIP<30 cmH_2O

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Supplementary Table 3. Rehabilitation trajectory, working and living conditions at 5-year follow-up

	RMW at ICU-discharge (N=56)	No RMW at ICU discharge (N=100)	P-value
Rehabilitation between hospital discharge and 5-year follow up visit			
Any physiotherapy	37 (66.1)	67 (67.0)	0.906
Any in-patient rehabilitation	15 (26.8)	14 (14.0)	0.049
Living conditions			
Living at home	56 (100)	98 (98.0)	0.567
Working conditions			
Fulltime job	4 (7.1)	17 (17.0)	0.277
Part-time job	2 (3.6)	7 (7.0)	
House wife	2 (3.6)	3 (3.0)	
Invalidity	12 (21.4)	11 (11.0)	
Student	0	1 (1.0)	
Retirement	33 (58.9)	60 (60.0)	
Temporarily at home	1 (1.8)	0	
Unemployed	2 (3.6)	1 (1.0)	
Working condition as compared to pre-ICU [a]			
Same work as before	15/32 (46.8)	26/55 (47.3)	0.967
Readmissions			
N of patients readmitted to the ICU (%)[b]	11 (19.6)	13 (13.0)	0.270

[a] Calculated after exclusion of patients retired prior to ICU admission

[b] Readmissions to the ICUs of the University hospitals of Leuven following hospital discharge

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REFERENCES

1. Casaer MP, Mesotten D, Hermans G, Wouters PJ, Schetz M, Meyfroidt G, Van Cromphaut S, Ingels C, Meersseman P, Muller J, Vlasselaers D, Debaveye Y, Desmet L, Dubois J, Van Assche A, Vanderheyden S, Wilmer A, Van den Berghe G, (2011) Early versus late parenteral nutrition in critically ill adults. N Engl J Med 365: 506-517
2. Hermans G, Casaer MP, Clerckx B, Güiza F, Vanhullebusch T, Derde S, Meersseman P, Derese I, Mesotten D, Wouters PJ, Van Cromphaut S, Debaveye Y, Gosselink R, Gunst J, Wilmer A, Van den Berghe G, Vanhorebeek I, (2013) Effect of tolerating macronutrient deficit on the development of intensive-care unit acquired weakness: a subanalysis of the EPaNIC trial. Lancet Respir Med 1: 621-629
3. Hermans G, Van Aerde N, Meersseman P, Van Mechelen H, Debaveye Y, Wilmer A, Gunst J, Casaer MP, Dubois J, Wouters P, (2019) Five-year mortality and morbidity impact of prolonged versus brief ICU stay: a propensity score matched cohort study. Thorax 74: 1037-1045
4. Van Aerde N, Meersseman P, Debaveye Y, Wilmer A, Gunst J, Casaer MP, Bruyninckx F, Wouters PJ, Gosselink R, Van den Berghe G, (2020) Five-year impact of ICU-acquired neuromuscular complications: a prospective, observational study. Intensive Care Med: 1-10
5. Lederer DJ, Bell SC, Branson RD, Chalmers JD, Marshall R, Maslove DM, Ost DE, Punjabi NM, Schatz M, Smyth AR, (2019) Control of confounding and reporting of results in causal inference studies. Guidance for authors from editors of respiratory, sleep, and critical care journals. Ann Am Thorac Soc 16: 22-28
6. Sakia RM, (1992) The Box-Cox transformation technique: a review. J R Stat Soc Series D 41: 169-178
7. Osborne J, (2010) Improving your data transformations: Applying the Box-Cox transformation. Practical Assessment, Research, and Evaluation 15: 12
8. Medrinal C, Prieur G, Frenoy É, Quesada AR, Poncet A, Bonnevie T, Gravier F-E, Lamia B, Contal O, (2016) Respiratory weakness after mechanical ventilation is associated with one-year mortality-a prospective study. Crit Care 20: 231
9. Hill AD, Fowler RA, Pinto R, Herridge MS, Cuthbertson BH, Scales DC, (2016) Long-term outcomes and healthcare utilization following critical illness--a population-based study. Crit Care 20: 76
10. Vittinghoff E, McCulloch CE, (2007) Relaxing the rule of ten events per variable in logistic and Cox regression. Am J Epidemiol 165: 710-718
11. Fan E, Dowdy DW, Colantuoni E, Mendez-Tellez PA, Sevransky JE, Shanholtz C, Himmelfarb CR, Desai SV, Ciesla N, Herridge MS, Pronovost PJ, Needham DM, (2014) Physical complications in acute lung injury survivors: a two-year longitudinal prospective study. Crit Care Med 42: 849-859
12. Needham DM, Wozniak AW, Hough CL, Morris PE, Dinglas VD, Jackson JC, Mendez-Tellez PA, Shanholtz C, Ely EW, Colantuoni E, Hopkins RO, Network NIoHNA, (2014) Risk factors for physical impairment after acute lung injury in a national, multicenter study. Am J Respir Crit Care Med 189: 1214-1224
13. Pfoh ER, Wozniak AW, Colantuoni E, Dinglas VD, Mendez-Tellez PA, Shanholtz C, Ciesla ND, Pronovost PJ, Needham DM, (2016) Physical declines occurring after hospital discharge in ARDS survivors: a 5-year longitudinal study. Intensive Care Med 42: 1557-1566
14. Iwashyna TJ, Ely EW, Smith DM, Langa KM, (2010) Long-term cognitive impairment and functional disability among survivors of severe sepsis. JAMA 304: 1787-1794
15. Dinglas VD, Friedman LA, Colantuoni E, Mendez-Tellez PA, Shanholtz CB, Ciesla ND, Pronovost PJ, Needham DM, (2017) Muscle weakness and 5-year survival in acute respiratory distress syndrome survivors. Crit Care Med 45: 446

16. Intiso D, Amoruso L, Zarrelli M, Pazienza L, Basciani M, Grimaldi G, Iarossi A, Di Rienzo F, (2011) Long-term functional outcome and health status of patients with critical illness polyneuromyopathy. Acta Neurol Scand 123: 211-219