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

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ABSTRACT:

Purpose: To assess the association between respiratory muscle weakness (RMW) at intensive care unit (ICU)-discharge and 5-year mortality and morbidity, independent from confounders including peripheral muscle strength.

Methods: Secondary analysis of the prospective 5-year follow-up of the EPaNIC cohort (clinicaltrials.gov:NCT00512122), limited to 366 patients screened for respiratory and peripheral muscle strength in the ICU with maximal inspiratory pressure (MIP) after removal of the artificial airway, and the Medical-Research-Council (MRC) sum-score. Respiratory muscle weakness was defined as an absolute value of MIP<30 cmH₂O. Associations between RMW at (or closest to) ICU discharge and all-cause 5-year mortality, and key measures of 5-year physical function, comprising respiratory muscle strength (MIP), hand-grip strength (HGF), six-minute-walk-distance (6MWD), and physical function of the SF-36 quality-of-life questionnaire (PF-SF-36), were assessed with Cox-proportional hazards and linear regression models, adjusted for confounders including peripheral muscle strength.

Results: RMW was present in 136/366 (37.2%) patients at ICU discharge. RMW was not independently associated with 5-year mortality [hazard ratio with 95% confidence interval: 1.273 (0.751-1.943),p=0.352]. Among 156 5-year survivors, those with, as compared to those without RMW demonstrated worse physical function [MIP(absolute value, cmH₂O):62(42-77) versus 94(78-109),p<0.001; HGF(%pred):67(44-87) versus 96(68-110),p<0.001; 6MWD(%pred):87(74-102) versus 99(80-111),p=0.009; PF-SF36(score): 55(30-80) versus 80(55-95),p<0.001]. Associations between RMW and morbidity endpoints remained significant after adjustment for confounders [effect size with 95% confidence interval: MIP: -23.858(-32.097 to -15.027),p=0.001; HGF: -18.591(-30.941 to -5.744),p=0.001; 6MWD (transformed): -1587.007(-3073.763 to -179.253),p=0.034; PF-SF36 (transformed):1.176(0.144-2.270),p= 0.036].

Conclusions: Respiratory muscle weakness at ICU discharge is independently associated with 5-year morbidity but not 5-year mortality.

Word count: 246

KEY MESSAGE:

What is the key question? Does ICU-acquired respiratory muscle weakness during critical illness impact long-term outcome, independently from confounders including peripheral muscle weakness?

What is the bottom line? Respiratory muscle weakness at ICU discharge independently associates with reduced peripheral and respiratory muscle strength, physical function, and quality-of-life at 5-years post-ICU, but does not independently increase the 5-year mortality risk.

Why read on? In a large population of adult critically ill patients (mortality N=366, morbidity N=156) prospectively assessed for peripheral and respiratory muscle strength on the ICU, we illustrate that respiratory muscle weakness acquired in the ICU contributes to the legacy of critical illness, and could therefore hold potential as a target to improve long-term prognosis in ICU-survivors.

KEYWORDS: critical care, respiratory muscles, pulmonary rehabilitation

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INTRODUCTION

Respiratory muscle weakness (RMW), in particular diaphragm dysfunction, is a frequent complication of critical illness, occurring in over 60% of patients requiring mechanical ventilation[1-3]. Risk factors include higher age, infection, systemic inflammation, illness severity, mechanical ventilation- both over and under-assistance, and certain drugs such as sedatives[1-5]. RMW often co-occurs and shares common features with peripheral muscle weakness acquired in the intensive care unit (ICU), labeled as ICU-acquired weakness (ICUAW). Both are associated with increased ICU and hospital mortality[6]. However, recent research revealed that RMW is more frequent than ICUAW, risk factors do not completely overlap, and short-term impact on morbidity differs. Whereas RMW contributes to weaning failure, increased ICU mortality[3, 7, 8] and early readmission[1, 6], ICUAW predominantly affects the duration of mechanical ventilation, ICU-, and hospital stay[6, 9]. As such, RMW and ICUAW may be considered separate, though overlapping, entities[1, 10]. In contrast to ICUAW, of which we and others recently described the impact on long-term outcomes[11, 12], studies of RMW and its associated outcomes beyond the index hospitalisation, when patients have overcome the major short-term risks of RMW, are scarce. Current evidence is confined to two case series with follow-up periods of respectively 1 and 2 years that revealed conflicting results[10, 13]. Identifying a possible relationship between respiratory muscle weakness in the ICU and the legacy of critical illness is highly relevant as preventive strategies for the long-term, multidimensional limitations reported for survivors of critical illness, are lacking. Respiratory muscle strength training in ICU survivors may hold promise in improving the long-term outcomes of critically ill patients.

We hypothesized that RMW in critically ill patients, as assessed by the maximal inspiratory pressure (MIP) after removal of (or without) artificial airway at (or closest to) ICU discharge, associates with 5-year mortality and morbidity, independent of confounders, including peripheral muscle strength. To this aim, we investigated the 5-year outcomes of a subgroup of the post-EPaNIC prospective follow-up cohort[14], who received systematic in-ICU respiratory and peripheral muscle strength testing.

METHODS

Ethics

The study protocol and informed consents of EPaNIC and its long-term follow-up were approved by the Ethical Committee Research UZ/KU Leuven(ML4190).

Study design and patient population

This is a secondary analysis of the prospective 5-year follow-up study of EPaNIC patients. Study design and methods of the EPaNIC trial and the EPaNIC follow-up study (clinicaltrials.gov:NCT00512122) have been published previously[14, 15] and are summarized in the online supplement. We here focus on those patients who were systematically screened in the ICU for respiratory and peripheral muscle strength. This screening was performed for long-stay patients (ICU stay ≥ 8 days). Additionally, a random set of short-stayers (ICU stay < 8 days) were tested on the ward on day 8 ± 1 . The last evaluations performed in the ICU closest to ICU discharge, or on day 8 ± 1 on the ward are further referred to as values 'at ICU discharge'.

Measurement of respiratory muscle strength and diagnosis of respiratory muscle weakness

In patients without an artificial airway, MIP was measured according to the ATS guidelines[16] as described earlier[9]. Contra-indications included flail chest, pneumothorax, hemodynamic instability, intracranial hypertension, respiratory distress, or high flow oxygen therapy. A mouthpiece, incorporating a small leak to prevent glottic closure during the forceful inspiration was used. Measurements were performed with the Micro Medical respiratory pressure meter, CareFusion® with Puma PC software. The patients were instructed to perform a maximal inspiratory maneuver starting from FRC. Maximal static inspiratory pressure was determined as the pressure maintained for 1 second. The best of 3 consecutive measurements was recorded. RMW was defined as an absolute value of MIP < 30 cmH₂O [13, 17].

Outcomes

The primary endpoint was all-cause 5-year mortality. Secondary endpoints included respiratory muscle strength (MIP, cmH₂O) at 5-years follow-up as well as 3 key measures of physical function frequently compromised in ICU survivors, amounting to the so-called legacy of critical illness. These comprise hand-grip strength (HGF, %predicted), 6-minute-walk-distance (6MWD, %predicted), and the physical function domain of the SF-36 quality-of-life questionnaire (PF SF-36, range 0-100, higher values indicating better scores). Additionally, the associations between RMW and other 5-year morbidity outcomes were explored, including peripheral muscle strength (MRC-sum score and hand-held dynamometry), Barthel index (indicating the degree of physical independence), and the Physical and Mental Component Score (PCS and MCS) of the SF-36.

Statistics

Descriptive statistics included median and interquartile ranges for continuous variables and numbers and percentages for categorical variables. Continuous data were compared with the Mann-Whitney-U test, categorical variables with the Chi-square or Fisher-exact test, as appropriate. As this was a secondary analysis, sample size was not modifiable, however, it was estimated that the sample size was sufficient for the primary endpoint (details online supplement). Bootstrap resampling (N=1000) was performed to obtain more robust estimates of effect sizes (denoted as bias-corrected and accelerated confidence intervals, BcaCI). Analyses were performed with SPSS version 26 (IBM corporation) and R version 3.6.1. Two-sided p-values ≤0.05 were considered statistically significant.

Primary endpoint: 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 [18]. Potential confounders comprised demographic variables,

comorbidities, and ICU treatments and events, particularly including peripheral muscle strength. To identify the latter, the MRC sum-score at ICU discharge was dichotomised at 55, according to recent findings concerning its association with long-term outcomes [11]. Further details on the search strategy, confounders identified and modelling are provided in the online supplement.

Secondary endpoints: 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 the Mann-Whitney-U test. The association between RMW at ICU discharge and respiratory muscle strength at 5 years, as well as the three 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 (see online supplement for further details).

Exploratory analyses

As the cut-off for MIP to define RMW has not been validated for long-term outcomes, we assessed the functional form of the relationship between MIP at ICU discharge and the primary and secondary outcomes through a LOESS-smoother on the Martingale residuals plot[19] for survival analyses and on the scatter plots for linear regression analyses. If appropriate, analyses were repeated with alternative modelling of MIP.

Sensitivity analyses

Multiple sensitivity analyses were performed. This involved restricting 5-year mortality analyses to hospital survivors. Also, the proportional hazard assumption was checked for each variable in each of the Cox-regression models with the Schoenfeld residuals test. Where appropriate, sensitivity analyses were performed by adding factors for which the assumption was violated as time-dependent covariates. For both 5-year mortality and morbidity, sensitivity analyses also involved adjusting for

MRC at ICU discharge as a continuous variable as well as dichotomized for the previously defined cut-off of 48.

RESULTS

Patient cohorts and characteristics

The patient cohort with both peripheral and respiratory muscle strength assessment at ICU discharge consisted of 368 patients (Figure 1). Five-year mortality data were available for 366 patients. Among 246 survivors, 156 (63.4%) were evaluated for 5-year morbidity. For the 5-year mortality cohort, the median age was 60(50-72) years, duration of mechanical ventilation 4 (2-10) days, and ICU-stay 10 (3-17) days. For the 5-year morbidity cohort, the median age was 60 (51-70) years, duration of mechanical ventilation 3 (1-9) days, and ICU-stay 8 (2-15) days. Further details are provided in Table 1 and Supplemental Table 1. RMW was present in 136/366 (37.2%) patients at ICU discharge. Patients with RMW were older, more likely to be female, to have a high nutritional risk score, and to suffer from diabetes. Patients with RMW were sicker upon admission and were longer exposed to corticosteroids and benzodiazepines, more frequently acquired a new infection in the ICU, and had a longer duration of mechanical ventilation and ICU stay. Interestingly, the incidence of sepsis upon admission was not significantly different for patients with and those without RMW.

Five-year mortality analyses

Total 5-year mortality in the studied cohort was 104/366 (28.4%), involving 51/136 (37.5%) of patients with RMW and 53/230 (23.0%) patients without RMW. As mortality data were obtained from the national registry, no information on cause of death was available. Time-to-death was significantly different for patients with versus those without RMW [Log-Rank $p=0.002$], the former experiencing a higher event rate (Supplementary Figure 1). However, when adjusted for confounders, RMW was not associated with 5-year mortality [HR: 1.273 (95% BcaCI: 0.751-1.943), $p=0.352$](Table 2).

Five-year morbidity analyses

Five-year survivors with RMW at ICU discharge had worse 5-year morbidity outcomes than those without RMW [MIP (absolute value): 62 (42-77) cmH₂O versus 94 (78-109) cmH₂O, $p < 0.001$; HGF (%pred): 67% (44%-87%) versus 96% (68%-110%), $p < 0.001$; 6MWD (%pred): 87% (74%-102%) versus 99% (80%-111%), $p = 0.009$; PF-SF36: 55 (30-80) versus 80 (55-95), $p < 0.001$]. Further exploratory analyses showed that patients with RMW also scored worse for all other 5-year morbidity endpoints, including MRC sum-score, hand-held dynamometry, Barthel index and quality-of-life questionnaires (Supplementary Figure 2). Adjusted for confounders, RMW remained independently associated with all secondary endpoints [MIP (absolute value, cmH₂O): B: -23.858 (95%BcaCI: -32.097 to -15.027), $p = 0.001$; HGF (%pred): B: -18.591 (95% BcaCI: -30.941 to -5.744, $p = 0.001$; 6MWD(%pred, transformed) B: -1587.007 (95%BcaCI: -3073.763 to -179.253) $p = 0.034$; PF SF-36 (transformed with higher transformed values indicating lower scores): B: 1.176 (95% BcaCI: (0.144-2.270), $p = 0.036$] (Table 2). Additional information on rehabilitation trajectory, working and living conditions is provided in Supplementary Table 3.

Exploratory analyses

Martingale residual plots and scatter plots did not support a clear cut-off at 30 cmH₂O for MIP at ICU discharge, for prediction of the studied long-term endpoints (Supplementary Figure 3). Re-analyses with both MIP as a continuous variable and with MIP at a cut-off of 45 cmH₂O, possibly suggested by the plots as a better cut-off, did not alter the conclusions (Supplementary Table 2).

Sensitivity analyses

RMW at ICU discharge was not independently associated with 5-year mortality, neither when the analysis was restricted to hospital survivors, nor when MRC was modelled as a continuous variable or when dichotomised at 48. Also, the addition of time-dependent covariates to the survival model for those factors violating the proportional hazard assumption did not alter the conclusion

(Supplementary Table 2). For the morbidity endpoints, alternative modelling strategies for the MRC sum-score did not affect the conclusions (Supplementary Table 2).

DISCUSSION

In this patient cohort of mixed adult critically ill patients, systematically screened for respiratory and peripheral muscle strength at ICU discharge and prospectively followed, we demonstrated that RMW at ICU discharge was independently associated with lower respiratory muscle strength at 5 years follow-up. Furthermore, RMW at ICU discharge independently associated with key morbidity outcomes that characterize the post-intensive care syndrome[11, 12, 14, 20-23], comprising handgrip strength, 6-minute walk distance, and the physical function component of the SF-36 quality-of-life questionnaire. Importantly, these analyses were adjusted for confounders, including peripheral muscle strength at ICU discharge. In contrast, RMW at ICU discharge did not independently associate with 5-year mortality.

The incidence of RMW in this mixed cohort of critically ill patients, as assessed by a volitional maximal inspiratory pressure maneuver in cooperative patients without artificial airway at ICU discharge, was 37.2%. Previous research reported diaphragm dysfunction in 64% of patients upon ICU admission, strongly associated with the presence of sepsis and with illness severity [3]. At the start of the weaning process, the incidence of RMW ranged between 54% and 63%[1, 17], with severe diaphragm dysfunction present in 31%[10]. In patients with peripheral weakness, up to 80% also suffer from diaphragm dysfunction[7]. The lower incidence of RMW in our study may have several explanations. First, factors contributing to RMW may improve over time. Indeed, in contrast to the findings upon ICU admission[3] or up to a week prior to successful extubation[24], we and others who assessed RMW at a later stage in the ICU[1, 13] found no association between sepsis and RMW. Second, by measuring RMW after removal of the artificial airway at ICU discharge, we evidently eliminated the sickest patients from this analysis, including those who were never weaned or were not cooperative after weaning. As such, we likely excluded patients with severe RMW and poor short-term outcomes. This

allowed us to focus on the long-term impact of RMW, studying only patients who overcame the major short-term risks.

The detrimental short-term impact of RMW has been well documented[6]. This includes increased ICU and hospital mortality rates[1, 3, 6], possibly linked with longer duration of mechanical ventilation[25], later weaning[24] and increased risk of weaning failure[1, 2, 13]. The combination of respiratory and peripheral muscle weakness in particular associates with poor outcomes[17]. Data on the impact of RMW beyond the acute timeframe are scarce. We demonstrated increased 5-year mortality in patients with RMW (37.5%) at ICU discharge as compared to patients without RMW (23.0%). However, when adjusted for baseline characteristics, illness severity, co-morbidities, ICU exposures, and peripheral muscle strength at ICU discharge, the risk of death within 5 years was not increased in patients with RMW. These data were confirmed in all sensitivity analyses, including the scrutinized analysis limited to hospital survivors. Previous data obtained from 124 patients suggested that 1-year mortality was significantly increased in patients with RMW (31% versus 7%) at the time of successful extubation[13]. However, 21% of patients with RMW experienced extubation failure, and 47.6% of deaths occurred on the ICU. The difference in mortality after hospital discharge for those with, and those without RMW, was not statistically significant. Saccheri recently showed that 2-year mortality was not different between patients with and those without diaphragmatic dysfunction at the start of the weaning process (36% versus 29%)[10]. These data were confirmed when analyses were limited to hospital survivors. Survival at 2 years was worse for patients suffering from both ICUAW and RMW (36%), though the patient sample was too small to allow adjustment for confounders. Our study extended the follow-up time window and suggests that, if patients with RMW overcome the acute challenges, long-term survival is not independently affected by RMW.

We subsequently evaluated the association between RMW at ICU discharge and 5-year morbidity. We demonstrated that, among 5-year survivors, RMW was independently associated with reduced inspiratory muscle strength, but also with peripheral muscle weakness as assessed with handgrip

strength, poor physical function as assessed with six-minute-walk-distance, and low quality-of-life as assessed with PF-SF-36. These findings are novel, as data on the association between RMW at ICU discharge and morbidity beyond the index hospitalization are virtually absent. Saccheri recently found no association between RMW in critically ill patients and the quality-of-life assessed in 40 survivors at 2 years follow-up[10]. In light of the data we here present, the lack of effect in the aforementioned paper may be due to a lack of power. The finding of an independent relationship between RMW at ICU discharge and typical features of the long-term legacy of critical illness may have important consequences as, currently, strategies to prevent or cure this long-term burden of critical illness are lacking[26, 27]. Respiratory muscle training has demonstrated multiple positive effects when performed in various patient populations, including patients with COPD, chronic heart or kidney disease, as well as in healthy volunteers and athletes. These benefits surpass mere improvement of respiratory muscle strength and include improved submaximal and maximal exercise capacity, functional capacity, and quality-of-life[28-32]. Several mechanisms have been proposed to explain such beneficial effects [28, 33, 34], which are relevant at both strenuous and submaximal exercise effort, and reversible by inspiratory muscle training, in the aforementioned patient populations [35]. The role for inspiratory muscle training as an intervention to specifically reduce the long-term burden of critical illness therefore deserves consideration and further evaluation through randomised clinical trials.

Our study has several strengths. To the best of our knowledge, this is the largest dataset on the association between respiratory muscle weakness in critically ill patients and long-term outcomes. By focusing on RMW at ICU discharge, in contrast to previous studies, we dissociated the outcomes of interest from the acute risks of RMW. Furthermore, the dataset is unique, as we have concomitant information on peripheral muscle strength, well-known to contribute to the long-term sequelae of critical illness, which allowed us to assess the independent effect of RMW. Finally, this is the first study to assess the association between RMW at ICU-discharge and morbidity at five years post-ICU, a time-window of follow-up far exceeding currently available perspectives. This study also has several

limitations. First, we measured respiratory muscle strength with the maximal inspiratory pressure, rather than with transdiaphragmatic (or transtracheal) twitch pressure generated in response to bilateral magnetic phrenic nerve stimulation (BAMPS), which is considered to be the golden standard in critically ill patients[3, 25, 36]. MIP is a simple screening measure of global inspiratory muscle strength, not limited to evaluation of the diaphragm. MIP correlates with twitch tracheal pressure[7, 37] and several researchers have demonstrated its clinical relevance in the ICU setting[6, 13, 17, 24, 37]. MIP requires consciousness and cooperation, while BAMPS is not dependent on patient effort. As we performed measurements at ICU discharge and after removal of the endotracheal tube aiming to study post-acute phase impact of RMW, conscious cooperation was a reasonable inclusion criterion, and MIP was considered a suitable measure for our research purpose. Additionally, while MIP can be easily performed at the bedside, BAMPS is a time-consuming and technically challenging procedure, requiring expensive equipment that is only available in a few ICUs worldwide[16, 36, 38]. Second, although we adjusted our analyses for confounders identified through a systematic literature search, we cannot exclude unmeasured confounding. Consequently, as this is an observational study, we cannot draw causal conclusions. Third, morbidity endpoints are subject to selection bias, as not all survivors were evaluated. Fourth, as no systematic evaluations at intermediate time points were made, no conclusions can be drawn with regard to differential recovery trajectories of respiratory muscle strength. Fifth, as maximal expiratory pressure (MEP) was not a pre-specified outcome in our study, we cannot draw any conclusions on a potential association of expiratory muscle weakness with long-term outcomes. However, recent data could not define an independent effect of MEP when MIP was taken into account with regard to short-term outcomes[39]. Finally, all patients were included in the EPaNIC trial, possibly limiting generalisability.

We conclude that RMW at discharge from the ICU did not independently associate with 5-year mortality. However, RMW at ICU discharge was associated with peripheral and respiratory muscle strength, physical function, and quality-of-life in 5-year survivors, independent of baseline characteristics, comorbidities, illness severity, ICU exposures, and peripheral muscle strength. As

inspiratory muscle training has the potential to improve respiratory muscle strength as well as other outcomes, our findings suggest that inspiratory muscle training is an attractive and promising intervention that should be investigated in ICU survivors in randomised studies with the aim to improve long-term outcomes of critical illness.

DECLARATIONS

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Availability of data: Data sharing is considered under the format of collaborative projects. Proposals can be directed to the senior authors (GH, GVdB).

Conflicts of interest: The authors have no conflict of interest to declare

Ethics approval: The study protocol and informed consents of EPaNIC and its long-term follow-up were approved by the Ethical Committee Research UZ/KU Leuven (ML4190).

Author contributions: GH and GVdB designed the study and planned the statistical analysis; data was acquired by GH, PM, YD, AW, JG, MPC; NVA, GVdB and GH analysed and interpreted the data, and drafted the manuscript; critical revision of manuscript content was done by all authors, funding was obtained by MPC, JG, GH, NVA, and GVdB; administrative and technical support was provided by PJW.

ONLINE SUPPLEMENT

Supplementary methods, Supplementary Table 1-3, Supplementary figure 1-3

FIGURES AND TABLES

Figure 1. Patient flow chart for the 5-year mortality and morbidity analyses. The patient cohort is composed of EPaNIC patients in whom MIP was measured in the ICU as part of a systematic screening protocol in long-stay, cooperative patients without (after removal of the) artificial airway and in a random sample of short-stay patients on the ward. The same cohort was also systematically screened for peripheral muscle strength with the MRC-sum score. Abbreviations: *EPaNIC*: Early versus late Parenteral Nutrition in Critically ill adults; *MIP*: Maximal Inspiratory Pressure; *MRC*: Medical Research Council; *RMW*: Respiratory Muscle Weakness.

Table 1: Baseline characteristics, indicators of muscle strength in the ICU, and ICU factors of patients included in the five year mortality and morbidity analyses								
	5-year mortality				5-year morbidity			
	Total population (N=366)	RMW at ICU discharge (N=136)	No RMW at ICU discharge (N=230)	P-value	Total population (N=156)	RMW at ICU discharge (N=56)	No RMW at ICU discharge (N=100)	P-value
Baseline factors								
Age on admission	60 (50-72)	67 (55-76)	58 (47-69)	<0.001	60 (51-70)	61 (52-73)	60 (50-67)	0.203
Gender, male	222 (60.7)	70 (51.5)	152 (66.1)	0.006	97 (62.2)	27 (48.2)	70 (70)	0.007
NRS>5	95 (26.0)	49 (36.0)	46 (20.0)	0.001	30 (19.2)	11 (19.6)	19 (19.0)	0.922
BMI	25.1 (23.0-29.0)	25.0 (22.8-30.4)	25.2 (23.0-28.1)	0.474	25.4 (23.3-28.4)	25.6 (23.4-31.9)	25.2 (23.2-27.7)	0.190
Diabetes mellitus	58 (15.8)	30 (22.1)	28 (12.2)	0.012	24 (15.4)	12 (21.4)	12 (12.0)	0.117
Malignancy	87 (23.8)	35 (25.7)	52 (22.6)	0.497	30 (19.2)	11 (19.6)	19 (19.0)	0.922
Pre-admission dialysis	3 (0.8)	2 (1.5)	1 (0.4)	0.558	0 (0)	0(0)	0(0)	NA
Randomisation, late PN	191 (52.2)	75 (55.1)	116 (50.4)	0.383	83 (53.2)	35 (62.5)	48 (48.0)	0.082
APACHE II	30 (19-36)	33 (22-38)	27 (17-34)	<0.001	27 (17-35)	30 (18-36)	26 (16-34)	0.128
Admission category				0.305				0.801
Cardiac surgery	133 (36.3)	47 (34.6)	86 (37.4)		77 (49.4)	25 (44.6)	52 (52.0)	
Emergency SICU	149 (40.7)	61 (44.9)	88 (38.3)		52 (33.3)	20 (35.7)	32 (32.0)	
Elective SICU	20 (5.5)	4 (2.9)	16 (7.0)		6 (3.8)	2 (3.6)	4 (4.0)	
MICU	64 (17.5)	24 (17.6)	40 (17.4)		21 (13.5)	9 (16.1)	12 (12.0)	
Sepsis upon admission	141 (38.5)	59 (43.4)	82 (35.7)	0.142	47 (30.1)	19 (33.9)	28 (28.0)	0.439

Table 1 continued: Baseline characteristics, indicators of muscle strength in the ICU, and ICU factors of patients included in the five year mortality and morbidity analyses								
	5-year mortality				5-year morbidity			
	Total population (N=366)	RMW at ICU discharge (N=136)	No RMW at ICU discharge (N=230)	P-value	Total population (N=156)	RMW at ICU discharge (N=56)	No RMW at ICU discharge (N=100)	P-value
Muscle strength at ICU discharge								
MIP (absolute value in cmH ₂ O)	35 (25-49)	21 (17-26)	45 (37-58)	<0.001	38 (23-51)	21 (17-25)	46 (38-59)	<0.001
Timing of MIP	9 (8-15)	12 (8-19)	8 (8-14)	0.001	8 (8-15)	12 (8-19)	8 (8-11)	<0.001
MRC-sum score	54 (48-58)	50 (47-54)	56 (50-58)	<0.001	55 (49-58)	50 (47-54)	58 (52-59)	<0.001
Timing of MRC-sum score	9 (8-16)	12 (8-19)	8 (8-14)	<0.001	8 (8-15)	12 (8-19)	8 (8-11)	<0.001
ICU-related variables								
Corticosteroids, days	0 (0-5)	0 (0-8)	0 (0-4)	0.071	0 (0-4)	0 (0-8)	0 (0-2)	0.028
NMBA, days	0 (0-1)	0 (0-1)	0 (0-1)	0.293	0 (0-1)	0 (0-1)	0 (0-0)	0.269
New infection	157 (42.9)	78 (57.4)	79 (34.3)	<0.001	61 (39.1)	36 (64.3)	25 (25.0)	<0.001
Benzodiazepines, days	3 (0-8)	4 (1-10)	2 (0-7)	0.002	1 (0-7)	5 (0-12)	1 (0-6)	0.008
Mechanically ventilated	350 (95.6)	131 (96.3)	219 (95.2)	0.617	154 (98.7)	55 (98.2)	99 (99.0)	0.676
Mechanical ventilation, days	4 (2-10)	6 (2-13)	3 (1-8)	<0.001	3 (1-9)	6 (2-14)	2 (1-7)	0.001
ICU stay, days	10 (3-17)	13 (6-20)	8 (2-15)	<0.001	8 (2-15)	13 (6-22)	4 (1-11)	<0.001
Continuous variables are reported with median and interquartile range, dichotomous variables are reported with number and percentage. P-values reflect differences between patient with and without RMW. Abbreviations: <i>BMI</i> : body mass index, <i>NRS</i> : nutritional risk score, <i>PN</i> : parenteral nutrition, <i>APACHE II</i> : Acute Physiology And Chronic Health Evaluation, <i>SICU</i> : Surgical Intensive Care Unit, <i>MICU</i> : Medical Intensive Care Unit, <i>NMBA</i> : neuromuscular blocking agents, <i>MRC</i> : Medical Research Council, <i>MIP</i> : maximal inspiratory pressure								

Table 2. Association between RMW at ICU discharge and 5-year outcomes		
All-cause five-year mortality	HR (95% BCa CI)^f	P-value
RMW at ICU discharge, unadjusted	1.837 (1.242-2.689)	0.002
RMW at ICU discharge, adjusted ^a	1.273 (0.751-1.943)	0.352
Five-year morbidity	B (95% BCa CI)^f	P-value
MIP at 5-year follow-up (cmH₂O)		
RMW at ICU discharge, unadjusted	-31.285 (-39.911 to -22.972)	0.001
RMW at ICU discharge, adjusted ^b	-23.858 (-32.097 to -15.027)	0.001
Hand-grip strength at 5-year follow-up (%pred)		
RMW at ICU discharge, Unadjusted	-24.595 (-33.407 to -15.349)	0.001
RMW at ICU discharge, adjusted ^c	-18.591 (-30.941 to -5.744)	0.001
6-MWD at 5-year follow-up (%pred)^g		
RMW at ICU discharge, unadjusted	-2134.881 (-3575.090 to -739.109)	0.004
RMW at ICU discharge, adjusted ^d	-1587.007 (-3073.763 to -179.253)	0.034
PF SF-36 at 5-year follow-up^g		
RMW at ICU discharge, unadjusted	2.078 (1.107-3.005)	0.001
RMW at ICU discharge, adjusted ^e	1.176 (0.144-2.270)	0.036
^a HR were calculated by multivariable Cox regression analyses correcting for a priori defined confounders including: 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. Days of in-ICU treatment with benzodiazepines and duration of mechanical ventilation were eliminated from the mortality model due to collinearity with ICU length-of stay.		
^{b-e} B-estimates were calculated by multivariable linear regression analyses correcting for a priori defined confounders including, for MIP ^b : age, gender, BMI, diabetes mellitus, malignancy, preadmission dialysis, duration of treatment with benzodiazepines, duration of mechanical ventilation, maximal SOFA score, ICU length of stay, MRC sum-score≤55; HGF ^c : age, gender, BMI, diabetes mellitus, malignancy, preadmission dialysis, duration of treatment with sedatives ie benzodiazepines, duration of mechanical ventilation, maximal SOFA score, ICU length of stay, MRC sum-score≤55; 6-MWD ^d : age, gender, diabetes mellitus, malignancy, preadmission dialysis, duration of treatment with opioids, duration of mechanical ventilation, hypoglycaemia, length of ICU stay, MRC sum-score≤55; PF SF-36 ^e : age, gender, diabetes mellitus, malignancy, preadmission dialysis, duration of treatment with inotropics/vasopressors, duration of treatment with benzodiazepines, duration of mechanical ventilation, length of ICU stay, MRC sum-score≤55. In these models ^{b,c,d,e} , duration of in-ICU treatment with sedatives was eliminated due to collinearity with ICU length-of stay.		
^f BCa: bias-corrected accelerated confidence intervals, obtained by bootstrap resample procedure (N=1000), MIP: Maximal Inspiratory Pressure, 6MWD: 6-minute-walk-distance, PF SF-36: Physical function component of the SF-36 quality of life questionnaire, HR: hazard ratio, MRC: Medical Research Council		
^g 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 to obtain adequate model fit (with higher transformed values corresponding to lower values of PF SF-36)		

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* Reasons for exclusion involved: rehab/nursing facility: N=1, pulmonary resection: N=1, dementia: N=1, neuromuscular disease: N=1, exceeded time window: N=1;

† Reasons for exclusion involved: rehab/nursing facility: N=3, pulmonary resection: N=2, psychiatric disease: N=1, neuromuscular disease: N=4
Abbreviations: *MIP*: maximal inspiratory pressure, *MRC*: Medical Research Council, *RMW*: respiratory muscle weakness.

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].

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

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-insufficiency*)) 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*))

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(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)

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 $<30\text{cmH}_2\text{O}$. 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 $<30\text{cmH}_2\text{O}$. *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.

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.

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 ₂ O	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
<i>Maximal inspiratory pressure (cmH₂O)</i>		
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 ₂ O	-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
<i>Hand-grip strength (% pred)</i>		
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 ₂ O	-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
<i>6-minute walk distance (%pred, transformed)^c</i>		
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 ₂ O	-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

Continued Supplementary Table 2. Exploratory analyses and sensitivity analyses		
Five-year morbidity analyses	B (95%BcaCI) ^a	P-value
<i>PF-SF-36 (score, transformed)^c</i>		
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 ₂ O	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: <i>MIP</i> : maximal inspiratory pressure; <i>RMW</i> : respiratory muscle weakness defined as an absolute value of MIP<30 cmH ₂ O		

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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A. **B.**

A **B** **C** **D** **E**