Five-year impact of ICU-acquired neuromuscular complications: a prospective, observational study

Nathalie Van Aerde, MD[1]; Philippe Meersseman, MD[2]; Yves Debaveye MD, PhD[1,3]; Alexander Wilmer, MD, PhD[2]; Jan Gunst MD, PhD[1,3]; Michael P. Casaer, MD, PhD[1,3]; Frans Bruyninckx, MD[4]; Pieter J. Wouters, MSc[1,3]; Rik Gosselink, PT, PhD[5]; Greet Van den Berghe, MD, PhD[1,3]*; Greet Hermans, MD, PhD[1,2]*

[1]Laboratory of Intensive Care Medicine, Department of Cellular and Molecular Medicine, KU Leuven, Herestraat 49, B-3000 Leuven, Belgium;

[2]Medical Intensive Care Unit, Department of General Internal Medicine, University Hospitals Leuven, Herestraat 49, B-3000 Leuven, Belgium;

[3]Department of Intensive Care Medicine, University Hospitals Leuven, Herestraat 49, B-3000 Leuven, Belgium;

[4]Department of Physical Medicine and Rehabilitation, University Hospitals Leuven, Herestraat 49, B-3000 Leuven, Belgium;

[5]Department of Rehabilitation Sciences, KU Leuven, Herestraat 49, B-3000 Leuven, Belgium;

*Equally contributed

Corresponding author

Greet Hermans, MD, PhD, Medical Intensive Care Unit, Department of General Internal Medicine, UZ Leuven, Herestraat 49, B-3000 Leuven, Belgium Tel: +32-16-344275, Fax: +32-16-344230, Email: greet.hermans@uzleuven.be, ORCID: 0000-0001-5340-1500

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Neuromuscular complications of critical illness are independently associated with 5-year morbidity and mortality. MRC-sum score at ICU discharge, even if only slightly reduced, may impact long-term mortality, strength, functional capacity and physical function, whereas reduced CMAP after 1 week in ICU only related to long-term mortality.

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ICU-acquired neuromuscular dysfunctions independently associate with 5-year morbidity and mortality.

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ABSTRACT:

Purpose: To assess the independent association between ICU-acquired neuromuscular complications and 5-year mortality and morbidity. To explore the optimal threshold of the Medical-Research-Council (MRC) sum-score, assessing weakness, for prediction of 5-year outcomes.

Methods: Sub-analyses of a prospective, 5-year follow-up study including 883 EPaNIC patients (**E**arly **Pa**renteral **N**utrition in **I**ntensive **C**are) (Clinicaltrials.gov:NCT00512122), systematically screened in-ICU for neuromuscular complications with MRC-sum-score ('MRC-cohort',N=600), electrophysiology on day 8±1 to quantify compound muscle action potential ('CMAP-cohort',N=689), or both ('MRC&CMAP-cohort',N=415). Associations between ICU-acquired neuromuscular complications and 5-year mortality, hand-grip strength (HGF,%predicted), six-minute-walk-distance (6-MWD,%predicted) and physical function of the SF-36 quality-of-life questionnaire (PF-SF-36) at 5-years, were assessed with Cox-regression and linear regression, adjusted for confounders. The optimal threshold for MRC at ICU-discharge to predict 5-year outcomes was determined by martingale residual plots (survival) and scatterplots (morbidity).

Results: Both lower MRC-sum-score at ICU-discharge, indicating less strength [HR,per-point-increase:0.946(95%CI:0.928-0.968),p=0.001], and abnormal CMAP, indicating nerve/muscle dysfunction [HR:1.568(95%CI:1.165-2.186),p=0.004], independently associated with increased 5-year mortality. In the MRC&CMAP-cohort, MRC [HR:0.956(95%CI:0.934-0.980),p=0.001] but not CMAP [HR:1.478(95%CI:0.875-2.838),p=0.088] independently associated with 5-year mortality. Among 205 survivors, low MRC independently associated with low HGF [0.866(95%CI:0.237-1.527),p=0.004], low 6-MWD [105.1(95%CI:12.1-212.9),p=0.043] and low PF-SF-36 [-0.119(95%CI:-0.186 to-0.057),p=0.002], whereas abnormal CMAP did not correlate with these morbidity endpoints. Exploratory analyses suggested that MRC≤55 best predicted poor long-term morbidity and mortality. Both MRC≤55 and abnormal CMAP independently associated with 5-year mortality.

Conclusions: ICU-acquired neuromuscular complications may impact 5-year morbidity and mortality. MRC-sum-score, even if slightly reduced, may affect long-term mortality, strength, functional capacity and physical function, whereas abnormal CMAP only related to long-term mortality.

Key words: muscle weakness, paresis, electrophysiology, critical care outcomes

WORD COUNT 250

INTRODUCTION

ICU-acquired weakness (ICUAW), as diagnosed by a Medical-Research-Council (MRC) sum-score <48, and electrophysiological signs of neuromuscular dysfunction often occur during critical illness and are associated with in-ICU morbidity and up to 1-year mortality[1, 2]. In particular, weakness persisting until ICU discharge and reduced compound muscle action potential (CMAP) on screening electrophysiology after 1 week of intensive care strongly and independently associate with 1-year mortality[3, 4]. Beyond this time-frame, few data suggest that, for ARDS patients, the association between weakness at hospital discharge and mortality attenuates over time and loses significance by 5 years[5]. Regarding long-term morbidity, ICU survivors report reduced physical function and quality of life, imposing a burden on patients, their families and on society[2, 6-8]. ICU-acquired neuromuscular dysfunctions presumably contribute to this so-called 'legacy of critical illness' or 'post-intensive care syndrome'[9-11], though clear evidence of an independent relationship with long-term outcomes is lacking. Indeed, complaints of persisting weakness and disabilities were documented in 5-year ARDS survivors, but weakness could not be objectified[6]. Quantifying the degree to which in-ICU neuromuscular abnormalities contribute to long-term adverse outcomes could be important for risk stratification and for targeting strategies to prevent or reduce such long-term burden of critical illnesses.

We investigated a large cohort of former general ICU patients, who received systematic in-ICU clinical and electrophysiological neuromuscular screening, 5 years after ICU admission. We hypothesized that muscle strength at ICU discharge, as assessed by the MRC sum-score and abnormal CMAP on electrophysiological screening after 1 week in ICU continue to independently associate with 5-year mortality (primary outcome) and morbidity (secondary outcome). We further aimed to explore the optimal threshold of the MRC-sum score at ICU discharge, for predicting 5-year morbidity and mortality.

METHODS

Ethics

The study protocol and informed consent forms were approved by the Leuven University Hospital Ethics Committee (ML4190). Patients gave separate informed consent for the five-year morbidity evaluations.

Study design and participants

This was a sub-analysis of a prospective 5-year follow-up study, involving 883 EPaNIC (Clinical trials.gov:NCT00512122) patients who received systematic neuromuscular evaluation in the ICU. The EPaNIC trial was a large, randomised controlled trial (RCT) performed in 7 medical/surgical ICUs of the University Hospitals Leuven and Jessa Hospitals Hasselt, comparing early (≤48 hours) with late (>8days) parenteral supplementation of insufficient enteral nutrition in critically ill patients[12]. In the Leuven ICUs, as part of EPaNIC and to investigate effects of the intervention on neuromuscular outcomes, 730 patients received electrophysiological screening weekly from day 8±1 onwards[4]. In 698 of these patients, CMAP evaluation was technically feasible. Furthermore, 600 patients were clinically evaluated for weakness with the MRC-sum score from day 8 onwards, 3-times weekly from awakening until ICU discharge or death[3, 13]. For both electrophysiology and strength assessment, we included long-stayers at risk for neuromuscular complications, as well as a randomly selected subgroup of short-stayers who were assessed on the ward at day 8±1. Further details on CMAP assessment and evaluation criteria are provided in the online supplement.

As part of the prospective post-EPaNIC follow-up study, 5-year mortality was assessed for all EPaNIC patients, whereas 5-year morbidity was assessed for survivors during hospital or home visits from June 2012 onwards[14]. Exclusion criteria included the inability to walk without assistance prior to ICU admission, pre-existing neuromuscular disease, other pre-ICU disabilities potentially confounding the morbidity endpoints, and refusal for participation[14]. Hence, for the following sub-analyses involving patients with in-ICU neuromuscular evaluation, we define three populations, comprising the 'MRC-

cohort', the 'CMAP-cohort', and the overlapping cohort who received both assessments, further referred to as 'MRC&CMAP-cohort' (Figure 1).

Outcomes

To investigate long-term outcomes in relation to ICU-acquired neuromuscular dysfunctions, we defined all-cause 5-year mortality, obtained from the national registry, as the primary endpoint. We further assessed the association of ICU-acquired neuromuscular dysfunctions with 5-year morbidity, with three distinct measures of physical function as secondary endpoints. These included hand-grip strength (HGF, %predicted), six-minute-walk-distance (6-MWD, %predicted), and the physical function of the SF-36 quality-of-life questionnaire (PF SF-36, range 0-100, higher values indicating better scores) at 5-years follow-up. Other outcomes comprised evaluation of peripheral strength with the MRC-sum score and hand-held dynamometry of the muscle groups involved in the MRC-sum score, as well as respiratory muscle strength, assessed by maximal inspiratory pressure[15]. Additionally, we assessed the Physical and Mental Component Score (PCS and MCS) of the SF-36[16, 17] and Barthel-index[18, 19] (range 0-20, higher scores indicating higher degree of physical independence).

Additional exploratory analyses involved the assessment of linearity between the MRC-sum score and the primary outcomes and, if appropriate, identification of the optimal threshold for the MRC-sum score to predict 5-year outcomes.

Statistics

Descriptive statistics included median and interquartile ranges for continuous variables and numbers and percentages for categorical variables. Continuous data were compared with Mann-Whitney-U test and categorical variables with Chi-square test or Fisher-exact test, as appropriate.

Study of the independent association between ICU-acquired neuromuscular dysfunctions and 5-year mortality

We explored in unadjusted analyses, whether last MRC at (or close to) ICU discharge (further referred to as 'MRC at ICU discharge') and abnormal CMAP on day 8±1 in ICU were associated with 5-year mortality in respectively the MRC- and CMAP-cohorts. Hazard ratios for both predictors were calculated with univariable Cox-regression analyses. MRC-sum score was entered as a continuous variable[5]. For CMAP, data were visualised with Kaplan-Meier plots. If a univariable association was present between MRC or abnormal CMAP and 5-year mortality, adjusted hazard ratios were calculated for the cohort(s) of interest by adding literature-based, a priori defined confounders to the models[20]. Potential confounders included demographics, comorbidities and ICU treatments and events. Details on the search strategy, confounders identified, check of collinearity, and bootstrapping are provided in the online supplement.

If both predictors showed an independent association with five-year mortality, the added value of the combined information of MRC and CMAP was assessed within the MRC&CMAP-cohort.

Study of the independent association between ICU-acquired neuromuscular dysfunctions and 5-year morbidity

The association between the MRC-sum score at ICU discharge and CMAP on ICU day 8±1 with the morbidity endpoints was explored in unadjusted analyses. For the MRC-sum score, we performed linear regression analyses. If necessary, the morbidity endpoints were transformed to obtain adequate model fit (see online supplement)[14]. For CMAP, outcomes for patients with normal and abnormal values were compared with Mann-Whitney-U or Fisher-exact test, as appropriate. If a univariable association was demonstrated for either of the three distinct measures of physical function, multivariable models were constructed for each of the cohorts of interest by introducing literature-based, a priori defined confounders, as covariates (see online supplement for search strategy, confounders identified, and modelling).

If appropriate, further analyses on the MRC&CMAP-cohort were performed to explore any additional information provided by the combination of data.

Exploratory analyses for defining the optimal threshold of MRC-sum score at ICU discharge for prediction of 5-year outcomes

Linearity of the relationship between MRC-sum score and 5-year outcomes was assessed (see online supplement) and if appropriate, multivariable analyses were repeated with MRC as a binary factor.

Sensitivity analyses

The proportional hazard assumption was checked for each variable in each of the Cox-regression models with the Schoenfeld residuals test. If appropriate, sensitivity analyses were performed by adding all factors for which the assumption was violated as time-dependent co-variates.

Analyses were performed with SPSS version 25 (IBM corporation) and R version 3.6.1.

Two-sided p-values ≤0.05 were considered statistically significant.

RESULTS

Patient cohorts and characteristics

MRC-sum scores at ICU discharge were obtained for 600 patients. Four of these were lost to follow-up and lack 5-year mortality data. Five-year morbidity was assessed in 205 of these patients (Figure 1). Of the 730 patients with electrophysiological screening on ICU day 8±1, 698 patients had available CMAPs. Within this CMAP-cohort, 5 patients were lost to follow-up and lack 5-year survival data and 184 received 5-year morbidity assessment. The overlapping cohort, with both MRC and CMAP assessment, consisted of 415 patients, of whom 3 were lost to follow-up and 134 were assessed for 5-year morbidity. Baseline and ICU characteristics of these 3 cohorts are provided in Table 1 and Supplementary Table1.

Primary outcome: 5-year mortality analyses

Within the MRC-cohort, 231/596(38.8%) died during the 5-year follow-up (Supplementary Table 1). MRC at ICU discharge was significantly lower in non-survivors [48(43-54)] than in survivors [54(48-58)],p<0.001. Lower MRC was independently associated with higher 5-year mortality [HR per-point-increase:0.946(95%CI:0.928-0.968),p=0.001](Table 2). In the CMAP-cohort, 328/693(47.3%) deaths occurred within 5 years (Supplementary Table 1). Patients with abnormal CMAP on ICU day 8±1 had higher 5-year mortality as compared to patients with normal CMAP [281/523(53.7%) versus 47/170(27.6%),p<0.001](Figure 2) and abnormal CMAP was independently associated with increased 5-year mortality [HR:1.568(95%CI:1.165-2.186),p=0.004](Table 2). When combining the clinical and electrophysiological information in the MRC&CMAP-cohort, low MRC remained independently associated with worse 5-year survival [HR:0.956(95%CI:0.934-0.980),p=0.001], whereas for abnormal CMAP, this relationship was no longer significant [HR:1.478(95%CI:0.875-2.838),p=0.088].

Secondary outcomes: 5-year morbidity analyses

Within the MRC-cohort, MRC at ICU discharge was significantly and independently associated with with hand-grip strength [0.866(95%CI:0.237-1.527),p=0.004], 6-MWD [105.1(95%CI:12.1-212.9),p=0.043] and PF SF-36 [-0.119(95%CI-0.186to-0.057),p=0.002] (Table 3). MRC at ICU discharge was also associated with most of the other morbidity outcomes (Supplementary Table 2). No univariable association was found between abnormal CMAP on ICU day 8±1 and any of the 5-year morbidity endpoints, except for hip strength and Barthel index (Supplementary Table2).

Exploratory analyses

Assessment of the linearity of the relationship between MRC at ICU discharge and 5-year mortality and morbidity suggested an optimal threshold of MRC≤55 for predicting 5-year mortality as well as 5-year hand-grip strength and 6-MWD (Supplementary Figure 1). Within the MRC-cohort, MRC was ≤55 in 401/596(67.3%) and >55 in 195/596(32.7%) patients. 5-year mortality was higher in patients with MRC≤55 as compared to patients with MRC>55 [187/401(46.6%) versus 44/195(22.6%),p<0.001] and

MRC≤55 independently associated with increased 5-year mortality [HR:1.584(95%CI:1.106-2.266),p=0.014] (Figure 2 and Supplementary Table 3). Combining this clinical and electrophysiological information indicated that both MRC≤55 and abnormal CMAP provided additional predictive information with respect to 5-year mortality (Figure 2 and Supplementary Table3).

Reassessment of morbidity revealed that patients with MRC≤55 at ICU discharge had worse outcomes for all 5-year morbidity endpoints (Supplemental Figure 2 & Supplementary Table2). Indeed, patients with MRC≤55 had a 25% (or 7kg), 11% and 25-point reduction in respectively median hand-grip force, 6-MWD and PF SF-36. These associations remained significant when adjusted for confounders (Table 3). Readmission rate was not different (Supplementary Table4).

Sensitivity analyses

The proportional hazard assumption was violated for MRC, indicating that the association of MRC at ICU discharge per point decrease with 5-year mortality attenuated over time (Supplemental Table 5). However, linear modelling of MRC may not have been optimal as indicated by the Martingale residual plot. Indeed, the association of MRC≤55 with mortality persisted throughout the 5-year observation period. The effect of abnormal CMAP on ICU day 8±1 on 5-year mortality also remained constant during the 5-year period.

DISCUSSION

The primary outcome of this 5-year follow-up study of patients systematically screened in ICU for neuromuscular dysfunctions showed that both more pronounced loss of strength, as measured with the MRC-sum score at ICU discharge, as well as abnormal CMAP assessed after 1 week of intensive care were independently associated with higher 5-year mortality. Secondary outcomes showed that, among survivors, more pronounced loss of strength at ICU discharge but not abnormal CMAP assessed after 1 week of intensive care independently associated with poor 5-year morbidity. Furthermore, exploratory analyses indicated that even mildly reduced strength (MRC≤55) may identify patients with

247 worse long-term outcomes. These data support that neuromuscular complications of critical illness
248 impact long-term survival as well as physical function.

249 Neuromuscular complications of critical illness, diagnosed clinically or with electrophysiology, relate
250 with mortality in the acute hospitalization phase[3, 21-24], up to 90 days[25], and 1 year[3, 4]. Beyond
251 this time frame, few data are available. We found a 4.4% decrease in the risk of death within 5 years
252 per point increase in MRC-sum score. This is remarkably similar to the findings of Dinglas et al. in ARDS
253 patients[5] and extends these findings to a general ICU population. While in the acute setting MRC<48
254 is a well-validated cut-off, differentiating populations with distinct clinical outcomes[3, 21, 26], Dinglas
255 et al. showed that the effect of MRC<48 at hospital discharge on 5-year mortality attenuated over time
256 and was no longer significant at 5 years[5]. Our study provides additional exploratory data indicating
257 that dichotomizing patients at an MRC of 55 at ICU discharge best describes the relationship between
258 strength and 5-year mortality. This cut-off indeed defined a group of patients in whom the increased
259 mortality risk persisted throughout the 5-year follow-up period. Hence, our data suggest that even a
260 slightly submaximal MRC-sum score is prognostically detrimental. We also further extend on our
261 previous data, indicating that CMAP on day 8±1 independently related with increased 1-year mortality,
262 and expand these findings up to 5-years follow-up. The excess mortality in patients with abnormal
263 CMAP is in the same order of magnitude as for patients with MRC≤55 and therefore provides similar
264 prognostic information if MRC is not available. Moreover, and similar to the findings at 1 year[4], both
265 MRC and CMAP provided complementary information on 5-year mortality. These data suggest that
266 neuromuscular complications of critical illness are a major contributor to the increased long-term
267 mortality in critically ill patients and stress the relevance of both clinical as well as simple
268 electrophysiological evaluation.

269 We further demonstrated an independent relationship between strength at ICU discharge and 5-year
270 morbidity, including persisting weakness, reduced functional capacity and physical function. These
271 findings are consistent with the widely accepted paradigm that ICUAW contributes to long-term

disabilities. Recent studies showed that 6 months following ICU discharge, ICUAW independently related with physical function[27] and physical limitations persisted up to 1 year in patients with ICUAW[28]. Previous work identified age, comorbidities and number of organ failures as risk factors for an episode of strength decline during 5 years following ARDS[8]. Nevertheless, recovery of the MRC-sum score above the generally accepted threshold defining ICUAW mostly occurs within 12 to 24 months[11, 29-31]. In the small percentage of patients with persisting weakness following ICU discharge, unadjusted analyses showed a correlation with activity limitation and reduced physical function up to 2 years[29]. The MRC cut-off of 48 may be insufficient to capture subtle changes in strength after the acute phase of critical illness and we show that strength at ICU discharge, even if mildly reduced, remains independently associated with morbidity up to five years post-ICU. Indeed, patients with MRC≤55, compared to MRC>55 at ICU discharge, exhibited reductions in hand-grip force, 6-MWD and PF SF-36, exceeding minimal important clinical differences (MICD respectively 5-6.5kg[32], 3-5%[33], and 5 point reduction[16, 34], respectively.

Unexpectedly and in contrast with the mortality data, we could not confirm an independent relationship between CMAP on day 8 and 5-year morbidity outcomes. In-ICU electrophysiological abnormalities are related with short-term morbidity, including prolonged duration of mechanical ventilation, ICU and hospital stay and physical impairments prior to hospital discharge[4, 22, 23, 35]. Data on the relationship between electrophysiological abnormalities and long-term outcomes are confined to small case series, describing delayed rehabilitation, disability and persistent motor handicap months to years following ICU admission in patients with abnormal electrophysiology in the ICU[35-38]. In this large series, we could not confirm a 5-year functional impact of electrophysiological abnormalities 8±1 days following ICU admission. A first explanation could be our focus on abnormal CMAPs 8 days following ICU admission, as based on our previous findings[4]. It remains to be explored whether other electrophysiological characteristics or different timing relate with the 5-year morbidity. Though we cannot exclude lack of power, these findings confirm that electrophysiological information and strength assessment are not commutable[4, 23, 39]. These data underscore the need to unravel

differential pathophysiological mechanisms involved in the clinical and electrophysiological phenotypes of neuromuscular involvement during critical illness and to explore the hypothesis that reduced CMAP may be an epiphenomenon, marking other non-neuromuscular derangements, causally associated with increased mortality.

This study has several strengths. To the best of our knowledge, this is the largest, prospective 5-year mortality and morbidity follow-up study in patients systematically assessed for neuromuscular complications of critical illness with clinical and electrophysiological screening in ICU. As patients were enrolled in an RCT, data were of high quality. This study has potential limitations. First, given the unpredictable nature of ICU admission, we do not have baseline strength measurements and, for feasibility purposes, no admission electrophysiology was performed. Second, also for practical reasons, electrophysiology did not include direct muscle stimulation to differentiate between critical illness polyneuropathy and myopathy. As myopathy may recover faster and more complete than neuropathy[38, 40-42], we cannot exclude a differential impact of both entities on 5-year outcomes. Third, as mortality data were collected from the national registry, we could not provide information on the cause of death. Fourth, obviously, morbidity analyses were limited to survivors and we excluded patients with disabilities potentially confounding morbidity endpoints, which may have introduced selection bias. Fifth, according to recent guidelines[20], we adjusted analyses for confounders identified through a systematic literature search. We cannot exclude unmeasured confounding. Sixth, as this is a single observational study, no definite causal conclusion can be drawn and the MRC threshold should be further validated. Finally, generalizability may be limited due to study of an RCT population. Also, subgroup analyses (eg sepsis and SICU patients) would be interesting for further studies.

We conclude that the impact of neuromuscular complications of critical illness extends well beyond the acute phase and associates with 5-year outcomes, confirming the long-standing hypothesis of its role in the legacy of critical illness. We demonstrated that poor strength at ICU discharge

independently associated with 5-year mortality and morbidity. Furthermore, even mildly reduced strength at ICU discharge (MRC≤55) independently related with worse 5-year outcomes. Reduced CMAP documented after 1 week of intensive care independently associated with worse 5-year mortality but not morbidity. Our findings are important as they describe the population, which should be targeted in future studies, attempting to reduce the burden of critical illness. Meanwhile, our data underscore that lower strength at ICU discharge, even if only mildly reduced, and CMAP on D8, may provide guidance for clinicians towards prognosis and may assist in targeting post-ICU services.

AUTHOR CONTRIBUTIONS

Study concept and design: Hermans, Van den Berghe.

Acquisition of data: Hermans, Meersseman, Bruyninckx, Debaveye, Wilmer, Gunst, Wouters

Analysis and interpretation of data: Van Aerde, Van den Berghe, Hermans.

Drafting of the manuscript: Van Aerde, Van den Berghe, Hermans.

Critical revision of the manuscript for important intellectual content: Van Aerde, Meersseman, Bruyninckx, Debaveye, Wilmer, Gunst, Casaer, Gosselink, Wouters, Van den Berghe, Hermans.

Statistical analysis: Hermans, Van Aerde, Van den Berghe.

Obtained funding: Hermans, Van Aerde, Van den Berghe.

Administrative, technical support: Wouters.

Study supervision: Hermans, Wouters, Van den Berghe.

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Fig. 1 Patient flow-chart for the 5-year mortality and morbidity analyses. The first cohort, labeled as 'MRC-cohort', is composed of EPaNIC patients in whom last in-ICU MRC-sum score was available, based on 3 times weekly screening. The second cohort consists of patients who underwent screening electrophysiological testing in ICU on D8±1 and in whom CMAP was evaluable. This cohort is further referred to as 'CMAP-cohort'. The third cohort is the overlapping population who received both MRC-sum scores and electrophysiological screening in ICU, labeled as the 'MRC&CMAP cohort'.

Fig. 2 Kaplan-Meier survival plots depicting the proportion of patients alive up to 5 years following ICU admission according to (A) MRC-sum score at (or close to) ICU discharge ≤55 or not (Log-rank test $p<0.001$) (B) CMAP D8±1 normal or abnormal (Log-rank test $p<0.001$) and (C) the combined information of MRC-sum score at ICU discharge ≤55 or not and CMAP D8±1 normal or abnormal (Log-rank test –as compared to normal CMAP and MRC-sum score at ICU discharge >55: for MRC>55 & abnormal CMAP: $p=0.003$; for MRC≤55 and normal CMAP: $p=0.029$; for MRC≤55 and abnormal CMAP: $p<0.001$). *MRC:* Medical-Research-Council, *CMAP:* compound muscle action potential, *D:* day.

Table 1. Baseline characteristics, indicators of neuromuscular dysfunction in ICU and ICU factors of patients included in the five year mortality and morbidity analyses

	MRC-cohort		CMAP-cohort		MRC&CMAP-cohort	
	5-year mortality N=596	5-year morbidity N = 205	5-year mortality N= 693	5-year morbidity N = 184	5-year mortality N=412	5-year morbidity N=134
Baseline factors						
Age, median (IQR)	63.4 (52.7-73.1)	60.0 (51.2-70.1)	64.1 (53.8-74.2)	59.7 (51.0-71.0)	63.6 (53.3-73.4)	59.7 (51.2-71.3)
Gender, male (%)	352 (59.1)	128 (62.4)	439 (63.3)	119 (64.7)	245 (59.5)	85 (63.4)
BMI, median (IQR)	25.0 (22.8-28.5)	25.4 (23.1-29.4)	25.3 (22.8-29.1)	25.6 (23.3-29.4)	25.0 (22.9-28.7)	24.8 (23.1-29.7)
NRS ≥5 (%)	174 (29.2)	39 (19.0)	206 (29.7)	37 (20.1)	123 (29.9)	26 (19.4)
Diabetes mellitus (%)	95 (15.9)	29 (14.1)	121 (17.5)	30 (16.3)	66 (16.0)	19 (14.2)
Malignancy (%)	162 (27.2)	38 (18.5)	173 (25.0)	28 (15.2)	108 (26.2)	24 (17.9)
Pre-admission dialysis (%)	6 (1.0)	0 (0)	11 (1.6)	0 (0)	6 (1.5)	0 (0)
Randomisation, late PN (%)	303 (50.8)	109 (53.2)	349 (50.4)	92 (50.0)	213 (51.7)	72 (53.7)
APACHE II, median (IQR)	31 (20-37)	27 (17-35)	32 (24-38)	30 (20-37)	33 (23-38)	29 (18-38)
Admission category (%)						
Cardiac surgery	202 (33.9)	99 (48.3)	196 (28.3)	72 (39.1)	129 (31.3)	58 (43.3)
Emergency SICU	256 (43.0)	75 (36.6)	329 (47.5)	82 (44.6)	192 (46.6)	54 (40.3)
Elective SICU	35 (5.9)	7 (3.4)	28 (4.0)	5 (2.7)	22 (5.3)	5 (3.7)
MICU	103 (17.3)	24 (11.7)	140 (20.2)	25 (13.6)	69 (16.7)	17 (12.7)
Sepsis upon admission (%)	261 (43.8)	71 (34.6)	335 (48.3)	73 (39.7)	197 (47.8)	55 (41.0)
Indicators of neuromuscular function in the ICU						
MRC-sum score at ICU discharge	51 (47-57)	54 (48-58)	50 (46-56)	51 (47-56)	50 (46-56)	52 (47-56)
Abnormal CMAP D8±1, N (%)	300/412 (72.8)	87/134 (64.9)	523 (75.5)	121 (65.8)	300 (72.8)	87 (64.9)
ICU-related exposure variables						
Corticosteroids, days, median (IQR)	0 (0-7)	0 (0-3.5)	0 (0-9)	0 (0-6)	0 (0-10)	0 (0-6)
NMBA, days, median (IQR)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)
New infection (%)	306 (51.3)	85 (41.5)	445 (64.2)	107 (58.2)	252 (61.2)	72 (53.7)
Benzodiazepines, days, median (IQR)	4 (1-11)	3 (0-9)	6 (2-13)	5 (1-10)	6 (2-14)	5 (1-10)
Mechanical ventilation, days, median (IQR)	6 (2-14)	4 (1-11)	9 (5-17)	7 (3-14)	8 (4-17)	7 (2-13)
ICU stay, days, median (IQR)	12 (4-21)	9 (2-18)	14 (9-23)	12 (8-20)	14 (9-25)	12 (6-20)

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, *MRC:* Medical Research Council, *CMAP:* compound muscle action potential, *D:* day.

Table 2. Primary outcomes: Association between indicators of neuromuscular dysfunction in ICU and 5-year mortality		
	HR (95% Bca CI) [b]	***P*-value**
MRC-cohort		
MRC-sum score at ICU discharge, continuous variable		
Unadjusted		
MRC-sum score at ICU discharge (per point increase)	0.930 (0.915-0.945)	0.001
Adjusted [a]		
MRC-sum score at ICU discharge (per point increase)	0.946 (0.928-0.968)	0.001
CMAP-cohort		
Unadjusted		
Abnormal CMAP on day 8±1	2.406 (1.782-3.330)	0.001
Adjusted [a]		
Abnormal CMAP on day 8±1	1.568 (1.165-2.186)	0.004
MRC&CMAP-cohort		
MRC-sum score at ICU discharge, continuous variable		
Unadjusted		
MRC-sum score at ICU discharge (per point increase)	0.945 (0.926-0.967)	0.001
Abnormal CMAP on day 8±1	1.866 (1.214-3.320)	0.007
Adjusted [a]		
MRC-sum score at ICU discharge (per point increase)	0.956 (0.934-0.980)	0.001
Abnormal CMAP on day 8±1	1.478 (0.875-2.838)	0.088

[a] HR were calculated by multivariable Cox regression analyses correcting for a priori defined confounders including: age, diabetes mellitus, malignancy, preadmission dialysis, admission APACHE II-score, sepsis upon admission, ICU length-of-stay, days of in-ICU treatment with corticosteroids and neuromuscular blocking agents, and acquisition of new infection in ICU. Days of in-ICU treatment with benzodiazepines and duration of mechanical ventilation were eliminated from the model due to collinearity with ICU length-of stay; [b] BCa: bias-corrected accelerated confidence intervals, obtained by bootstrap resample procedure (n=1000).

Abbreviations: *MRC:* Medical Research Council, *CMAP:* Compound Muscle Action Potential, *HR:* hazard ratio

Table 3. Secondary outcomes: Association between indicators of neuromuscular dysfunction in ICU and primary outcomes of 5-year morbidity						
	Hand-grip strength (%pred)		**6-MWD (%pred)** [c]		**PF SF-36** [c]	
	B (95% Bca CI) [b]	*P*-value	B (95% Bca CI) [b]	*P*-value	B (95% Bca CI) [b]	*P*-value
COHORT 1: MRC-cohort						
MRC-sum score at ICU discharge, continuous variable						
Unadjusted						
MRC-sum score at ICU discharge (per point increase)	1.116 (0.526 - 1.714)	0.001	102.6 (-1.6 - 213.1)	0.051	-0.144 (-0.212 to -0.073)	0.001
Adjusted [a]						
MRC-sum score at ICU discharge (per point increase)	0.866 (0.237 - 1.527)	0.004	105.1 (12.1 - 212.9)	0.043	-0.119 (-0.186 to -0.057)	0.002
MRC-sum score at ICU discharge, dichotomous (exploratory analyses)						
Unadjusted						
MRC-sum score at ICU discharge ≤55	-16.441 (-24.386 to -7.925)	0.001	-1618 (-2898.4 to -303.6)	0.013	1.700 (0.765 - 2.634)	0.002
Adjusted [a]						
MRC-sum score at ICU discharge ≤55	-14.674 (-23.284 to -5.092)	0.002	-1648.2 (-2978.7 to -290.9)	0.023	1.464 (0.306 - 2.570)	0.007
COHORT 2: CMAP-cohort						
Unadjusted						
Abnormal CMAP on day 8±1	-5.921 (-14.009 - 2.483)	0.163	-171.6 (-1563.2 – 1132.0)	0.804	0.718 (-0.309 - 1.806)	0.168

[a] Regression coefficients were calculated with multivariable linear regression analyses, correcting for a priori defined confounders including: (1) for hand grip strength: demographics (age, gender, BMI), comorbidities (diabetes mellitus, malignancy, preadmission dialysis) and ICU features (maximal SOFA score, ICU length-of-stay), days of benzodiazepine treatment in ICU was omitted due to collinearity with ICU length-of-stay (2) for 6-MWD: demographics (age, gender), comorbidities (diabetes mellitus, malignancy, preadmission dialysis) and ICU features (in-ICU hypoglycaemia and ICU length-of-stay). Days of in-ICU opioid treatment was omitted due to collinearity with ICU length-of-stay (3) for PF SF-36: demographics (age, gender), comorbidities (diabetes mellitus, malignancy) and ICU features (duration of treatment with inotropics and/or vasopressors and ICU length-of-stay). Duration of in-ICU treatment with benzodiazepines was omitted due to collinearity with duration of ICU stay. Preadmission dialysis was dropped from analysis as no patients in the studied cohorts received dialysis prior to admission[b] *BCa* bias-corrected accelerated confidence intervals, obtained by bootstrap resampling procedure (n=1000) [c] In order to obtain adequate model fit, the 6-MWD data were transformed to power 2 and PF SF-36 scores were reversed (100 minus actual value) and subsequently transformed to power 0.54.

Abbreviations: *MRC*: Medical Research Council, *CMAP:* Compound Muscle Action Potential, *6-MWD:* six minute walk distance, *PF SF-36:* Physical Function domain of the SF-36 quality of life questionnaire.