



ICU discharge screening for prediction of new-onset physical disability—A multinational cohort study

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Background: Methods to identify patients at risk for incomplete physical recovery after intensive care unit (ICU) stay are lacking. Our aim was to develop a method for prediction of new-onset physical disability at ICU discharge.

Methods: Multinational prospective cohort study in 10 general ICUs in Sweden, Denmark, and the Netherlands. Adult patients with an ICU stay ≥ 12 hours were eligible for inclusion. Sixteen candidate predictors were analyzed with logistic regression for associations with the primary outcome; new-onset physical disability 3 months post-ICU, defined as a ≥ 10 score reduction in the Barthel Index (BI) compared to baseline.

Results: Of the 572 included patients, follow-up data are available on 78% of patients alive at follow-up. The incidence of new-onset physical disability was 19%. Univariable and multivariable modeling rendered one sole predictor for the outcome: physical status at ICU discharge, assessed with the five first items of the Chelsea critical care physical assessment tool (CPAx) (odds ratio 0.87, 95% confidence interval

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(CI) 0.81-0.93), a higher score indicating a lower risk, with an area under the receiver operating characteristics curve of 0.68 (95% CI 0.61-0.76). Negative predictive value for a low-risk group (CPAx score >18) was 0.88, and positive predictive value for a high-risk group (CPAx score ≤18) was 0.32.

Conclusion: The ICU discharge assessment described in this study had a moderate AUC but may be useful to rule out patients unlikely to need physical interventions post-ICU. For high-risk patients, research to determine post-ICU risk factors for an incomplete rehabilitation is mandated.

1 | INTRODUCTION

A significant proportion of intensive care unit (ICU) survivors suffer from new-onset physical disability with reduced ability to perform activities of daily living (ADL) after ICU stay.¹⁻³ This impacts the lives of millions of patients yearly,⁴ affecting their ability to return to work or other major activity.⁵ These problems can persist for months to years and affect health-related quality of life (HRQOL)^{6,7} as well as imply an economical burden for the individual and society.⁸

An increasing number of hospitals offer ICU follow-up. In lack of precise triage methods, the selection of patients for follow-up is often based on ICU length of stay (LOS).⁹⁻¹² ICU LOS has been associated with ICU-acquired weakness (ICUAW),¹³ but is poorly evaluated as a predictor of new-onset physical disability post-ICU. There is little research on risk factor-based triage for selection of patients at risk of incomplete physical recovery.

Identification of risk patients already at ICU discharge could enable early interventions, possibly improving long-term physical recovery. Further, triage might rule out patients without the need for follow-up, thereby concentrating follow-up resources to those with greater need. The aim of this study was to examine the potential predictors for poor physical outcome and develop a method for prediction of new-onset physical disability 3 months post-ICU.

2 | METHODS

We performed a multinational, prospective observational cohort study in 10 secondary and tertiary care hospitals in Sweden, Denmark, and the Netherlands, assessing risk factors for adverse physical and psychological outcome 3 months post-ICU. The psychological risk prediction study has been published previously.¹⁴ We adhered to the TRIPOD guidelines for reporting of multivariable prediction models.¹⁵ Ethical review boards in participating countries approved the study, which was performed in accordance with the 1964 Declaration of Helsinki and its later amendments. All participants gave informed consent. The study was registered at clinicaltrials.gov, NCT02679157.

Editorial Comment

Methods to identify patients at risk for incomplete physical recovery after intensive care unit (ICU) stay have not been available. This study developed an ICU discharge screening tool for prediction of new-onset physical disability. This model showed that physical function at ICU discharge was the single most important predictor. With a moderate predictive value, this model may first help to identify patients unlikely to need physical interventions post-ICU.

2.1 | Participants

Patients ≥18 years old with an ICU stay ≥12 hours (≥24 hours for patients admitted for planned elective post-operative observation) were eligible for inclusion for a maximum of 3.5 months. Inclusion dates varied between centers during January to April 2016. Exclusion criteria were conditions deemed to make reliable follow-up improbable: need of neurointensive care, documented dementia or substantial cognitive impairment, multiple limitations of treatment, no formal home address, or inability to communicate in the language of the study site. Patients admitted to the ICU solely for elective procedures were excluded.

2.2 | Outcome

The primary outcome was new-onset physical disability 3 months after ICU discharge. Caseness was defined as a Barthel Index (BI) reduction of ≥10 points compared to pre-ICU physical function. The BI is a 10-item questionnaire assessing the ability to perform ADL more or less independently. Total BI score ranges from 0 to 100, 100 indicating complete independency and 0 indicating total ADL dependency.¹⁶ A score reduction of 9.25 has been suggested as a minimal clinically important difference (MCID).¹⁷ For baseline assessment, patients or next-of-kin were asked in-ICU to estimate the patient's BI 2 weeks prior to hospitalization. Medical charts

were reviewed to validate the estimation if a clear response could not be obtained. The BI has been validated in the Netherlands¹⁸ and has been translated and adapted to Swedish and Danish settings.¹⁹⁻²¹

Secondary outcome was physical HRQOL assessed with the RAND-36, a 36-item validated questionnaire with scores ranging from 0 to 100, a higher score indicating better HRQOL.²² It consists of eight domains that can be divided into two component scores, the physical health component score (PCS) and the mental health component score.²³ We compared scores in the four physical domains as well as PCS between cases and non-cases.

Patients surviving 3 months post-ICU received and returned the outcome questionnaires by postal mail, consisting of the BI and RAND-36 for this study and two questionnaires assessing psychological symptoms for another study.¹⁴ Two weeks later, non-responders received a reminder phone call. A new set of questionnaires was sent to those not responding to the call.

2.3 | Risk factors

A literature search and an expert consensus discussion were performed to select potential risk factors for the primary outcome, considering the feasibility of risk factor assessment bedside by ICU clinicians (See Table S1 and risk factor categorization, Additional File 1). Data were collected in-ICU from medical charts, electronic patient data management systems, and patients and/or next-of-kin. Sixteen potential predictors were assessed:

1. *Pre-morbid risk factors*: age, sex, educational level, employment status, comorbidities assessed with the Charlson comorbidity index²⁴ and box 1 of the Simplified Acute Physiology Score III (SAPS III)²⁵ and pre-ICU physical function assessed with the BI.
2. *In-ICU risk factors*: severity of disease assessed with the Acute Physiology and Chronic Health Evaluation (APACHE) II, admission diagnosis (medical, surgical, or trauma), days with coma, severe sepsis, fractures, duration of invasive mechanical ventilation, and ICU LOS.
3. *ICU discharge risk factors*: Physical status at discharge assessed with the first five items of the Chelsea critical care physical assessment tool (CPAx). Each item generates a score from 0 to 5, a higher score indicating better function.²⁶ Evaluation was done bedside by the ICU nurse assessing the patient's respiratory function, ability to cough, roll within the bed, move from supine to sitting and dynamic sitting. The rationale for choosing only the first five items of the CPax was that these items were considered good descriptors of physical function, including core stability, a previously identified risk factor.²⁷ The last five items are more cumbersome to perform, requiring special equipment and several staff members, implying risk for missing data and reducing the feasibility of the screening method. To assess agreement between different CPax

observers, inter-rater reliability testing with Cohen's kappa was performed. Two nurses at each study site, blinded to each other's scoring, assessed five study participants. As the CPax was not translated into Swedish, Danish, and Dutch, we performed back-and-forward translations with bilingual collaborators.²⁸ Depressive symptoms at ICU discharge were assessed with a modified version of the 2-item patient health questionnaire (PHQ-2) rating symptoms during the past days.²⁹ Each question generates 0-3 points, a higher score indicating more frequent symptoms.

2.4 | Statistical methods

2.4.1 | Sample size

The targeted inclusion was 800 patients. With an expected loss to follow-up of 30% and 30% of patients having the primary outcome, this would render a case/predictor quotient of 10.5.³⁰

2.4.2 | Missing data

Outcome data missing due to non-response were managed with inverse probability weighting; a recommended strategy to minimize selection bias due to non-response which was applied to all subsequent analyses.³¹ The development of the weighted model has been described previously.¹⁴ Patients with a BI score reduction ≥ 10 compared to baseline despite missing items were considered cases. No imputation was made.

2.5 | Statistical analysis methods

Statistical analyses were performed with STATA, version 15 (StataCorp). Two-sided significance level was set to 0.05. Continuous data were summarized by their median and interquartile range (IQR) and categorical data with numbers and percentages. Comparisons of categorical variables were performed with the Fisher's exact test. The Mann-Whitney *U* test was used for comparison of continuous variables.

Associations between risk factors and the primary outcome were investigated with univariable logistic regression analysis. The relationship between the probability of the primary outcome and the continuous predictors (age, APACHE II score, ICU LOS, duration of mechanical ventilation, SAPS III box 1, Charlson comorbidity index, CPax score, and PHQ-2 score) was assessed visually with locally weighted scatterplot smoothing. Relationship for non-linear trends was tested by introducing the continuous predictors in logistic regression models by means of three-knot natural cubic splines. Variables were assessed with odds ratios and statistical significance with confidence intervals (CI) before selection and entry into the multivariable logistic regression model. After backward elimination,

total CPax score was the only predictor that remained significant ($P < .05$). See supplemental digital content for univariable analyses of predictors.

2.6 | The predictive model

We developed a prediction model for the probability of the primary outcome with the CPax total score as the only predictor. We defined a Bernoulli likelihood function whose individual contribution was

$$Y_i \sim \text{Bernoulli}(\pi_i)$$

with Y_i indicating the value of the binary outcome observed on the i th individual, and π_i its probability. Several models were tested but the model best fitting the data was a four-parameter symmetric logistic model. Probability was therefore modeled with a four-parameter symmetric logistic function.

$$\pi_i = \beta_0 + \beta_1 \frac{e^{\beta_2(x_i - \beta_4)}}{1 + e^{\beta_2(x_i - \beta_4)}}$$

where x_i indicates the predictor. The parameters indicate, respectively, the largest probability (β_0), range (β_1), slope (β_2), and midpoint (β_4) of the logistic function. The parameters and their standard errors were estimated by maximizing the likelihood function. The likelihood function was weighted by the inverse of the non-response probability. Using the logistic function in a likelihood-based model ensured that the predicted probability would decrease along with increasing values of the only predictor.

To assess the predictive value of the instrument, the area under the receiver operating characteristics curve (AUC) was used. Negative and positive predictive values (NPV and PPV) were calculated for risk groups of $<20\%$ and $\geq 20\%$ predicted risk of having the outcome. The distribution of cases and observed risks formed the base for the chosen cutoff. The observed risk for new-onset physical disability was plotted against predicted risk over 20% risk strata for calibration of the model. Bootstrapping in 500 samples was used for internal validation. A shrinkage factor of regression coefficients was calculated to adjust for possible overoptimism of the predictive model.

2.7 | Analysis of ICU length of stay as a predictor

As ICU LOS is the most commonly used criterion for ICU follow-up in many countries, we calculated the AUC for ICU LOS as a predictor for new-onset physical disability. We also calculated sensitivity, specificity, NPV, and PPV for patients with ICU LOS ≥ 72 hours, a common cutoff for ICU follow-up in Sweden as well as in the UK.^{10,12}

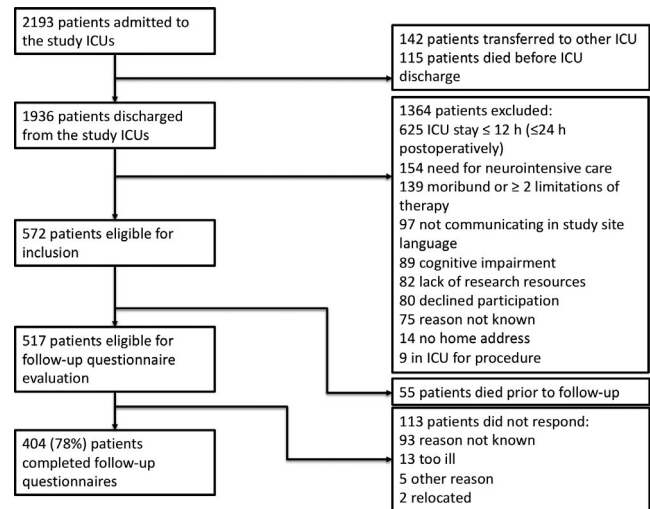


FIGURE 1 Flow chart of inclusion and exclusion

3 | RESULTS

Of the 2193 screened patients, 572 were included in the study. Seventy-eight percent ($n = 404$) of ICU survivors responded to the questionnaires (Figure 1). Of the included patients, 61% were men, median age was 65 years, and median APACHE II score was 18. Median duration of mechanical ventilation in patients receiving invasive ventilation (60%) was 50 hours and median ICU LOS was 62 hours (Table 1). Of the 404 patients, 19% ($n = 75$) reported new-onset physical disability 3 months after ICU discharge.

3.1 | Non-responders ($n = 168$)

Characteristics for responders and non-responders were similar except that non-responders had lower educational level and were more often admitted to hospital for acute reasons. Non-responders had lower pre-ICU physical function compared to responders. Other baseline characteristics did not differ between responders and non-responders (See Table S2, Additional File 2, for baseline characteristics for responders and non-responders).

3.2 | Missing data

In 12% of responders, one or more items were missing in the BI, the primary outcome questionnaire. Those with a score reduction ≥ 10 points despite some missing items were categorized as cases. Five percent of responders could not be defined unequivocally as case or non-case and were not included in the analyses. The number of participants in the final model analysis was 356. For a description of missing data, see Tables S3 and S4, Additional File 3.

TABLE 1 Patient characteristics by country and total population

Patient characteristic	Sweden n = 300	The Netherlands n = 166	Denmark n = 106	Total population n = 572
Age, y, median (IQR)	65 (49-74)	63 (56-71)	66 (59-73)	65 (53-73)
Male sex, n (%)	179 (60)	103 (62)	69 (65)	351 (61)
Somatic comorbidities (CCI score), median (IQR)	4 (1-5)	3 (2-5)	4 (2-6)	4 (2-5)
Pre-ICU physical function (BI score), mean (SD)	94 (18)	95 (15)	98 (9)	95 (16)
Severity of illness (APACHE II score), median (IQR)	18 (13-24)	16 (12-22)	21 (16-26)	18 (13-23)
Admission diagnosis, n (%)				
Medical	123 (41)	55 (33)	40 (38)	218 (38)
Surgical	156 (52)	92 (55)	53 (50)	301 (53)
Trauma	21 (7)	19 (11)	12 (11)	52 (9)
Mechanical ventilation, n (%)	153 (51)	143 (86)	47 (44)	343 (60)
Duration of mechanical ventilation (hours), median (IQR)	68 (19-174)	34 (8-118)	24 (12-101)	50 (13-137)
ICU LOS (h), median (IQR)	66 (27-142)	67 (43-188)	47 (22-99)	62 (30-140)

Note: Duration of mechanical ventilation calculated for mechanically ventilated patients only.

Abbreviations: APACHE, acute physiology and chronic health evaluation; BI, Barthel index; CCI, Charlson comorbidity index; ICU LOS, intensive care unit length of stay; IQR, interquartile range.

3.3 | Model development

Candidate predictors and univariable associations with the outcome are presented in Table 2. Six candidate predictors (severity of illness at admission (APACHE II score), educational level, duration of mechanical ventilation, ICU LOS, depressive symptoms, and physical status at ICU discharge) were deemed to be sufficiently associated with the outcome in the univariable analysis to be included in the multivariable logistic regression model (See Table S5, Additional File 4). After multivariable analysis with backward elimination, the only predictor that remained significantly associated with the outcome was physical status at ICU discharge, assessed with the CPaX (odds ratio (OR) 0.87 95% CI 0.81-0.93, $P < .001$), a higher score indicating a lower risk. The combination of predictors did not improve the model's predictive accuracy.

Based on the distribution of the data, the best-fitting model was a parametric model, which was used for the CPaX total score resulting in the predictive instrument (Figure 2). The predictive value of the final model assessed with the AUC was 0.68 (95% CI 0.61-0.76) (Figure 3). The PPV for a high-risk group with CPaX score ≤ 18 was 0.32 (95% CI 0.25-0.40). The NPV for a low-risk group with CPaX

score >18 was 0.88 (95% CI 0.83-0.91), implying that 88% of patients classified as low-risk would be without an adverse outcome at 3 months. The sensitivity for a CPaX score ≤ 18 was 73% and specificity was 60%. For calibration of the model, see Figure S1, Additional File 5.

3.4 | Internal validation

We performed internal validation in 500 bootstrap samples with a resulting AUC of 0.68 (95% CI 0.67-0.68). The shrinkage factor for the final model was 0.95, indicating minimal overoptimism.

3.5 | Secondary outcome

HRQOL was significantly lower for cases in all four physical domains as well as the PCS (See Table S6, Additional File 6). Median (IQR) PCS for cases was 30 (21-40) compared to 54 (38-76) for non-cases ($P < .001$) (See Figure S2, Additional File 7).

TABLE 2 Categorization of potential predictors for post-ICU new-onset physical disability (cases) and no physical disability (non-cases) and predictors' univariable association

Predictor	Categorization	Cases (n = 75)	Non-cases (n = 307)	Univariable association (P-value) ^a
Age, years, median (IQR)		67 (55-74)	64 (54-72)	.217
Male sex, n (%)		47 (63)	192 (63)	.881
Education level, n (%)	Elementary school	23 (31)	69 (22)	.116
	Senior high school	30 (40)	139 (45)	
	University/College	17 (23)	90 (29)	
Employment status pre-ICU, n (%)	Unemployed	3 (4)	9 (3)	.611
	Sick leave	5 (7)	36 (12)	
	Retired	41 (55)	156 (51)	
	Student	1 (1)	5 (2)	
	Employed	21 (28)	95 (31)	
Somatic comorbidities, median (IQR)		4 (2-5)	3 (2-5)	.263
Admission diagnosis, n (%)	Medical	29 (39)	110 (36)	.571
	Surgical	39(52)	172 (56)	
	Trauma	7 (9)	24 (8)	
Severity of illness at admission (APACHE II), median (IQR)		19 (15-24)	17 (13-22)	.074
SAPS III box 1, median (IQR)		20 (13-23)	18 (13-23)	.769
Physical function pre-ICU (BI), mean (SD)		95 (14)	96 (14)	.424
Fractures, n (%)		9 (12)	18 (6)	.423
Severe sepsis, n (%)		16 (21)	64 (21)	.930
Duration of coma, days, median (IQR)		0 (0-1)	0 (0-1)	.889
ICU LOS, hours, median (IQR)		65 (37-206)	51 (26-122)	.061
Duration of mechanical ventilation, hours, median (IQR)		46 (15-188)	42 (7-119)	.036
Depressive symptoms (PHQ-2), median (IQR)		1 (0-2)	0 (0-2)	.081
Physical status at ICU discharge (CPAx five first items), median (IQR)		16 (13-19)	20 (16-23)	.001

Note: Duration of mechanical ventilation calculated only for mechanically ventilated patients.

Abbreviations: APACHE, acute physiology and chronic health evaluation; CCI, Charlson comorbidity index; CPax, Chelsea critical care physical assessment tool; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; PHQ-2, patient health questionnaire-2; SAPS, simplified acute physiology score; SD, standard deviation.

^aP-values for the univariable association between the predictor and the outcome.

3.6 | CPax inter-rater reliability

The agreement between observers assessing the CPax items was moderate for cough, supine to sitting and moving within the bed, substantial for dynamic sitting, and almost perfect for respiratory function (See Table S7, Additional File 8).³²

3.7 | Analysis of ICU LOS as a predictor

The AUC for ICU LOS as a predictor for new-onset physical disability was 0.57 (95% CI 0.50-0.65). Using ICU LOS \geq 72 hours as a

single predictor detected as few as 48% (n = 36) of cases (sensitivity). Specificity was 59%, PPV was 22%, and NPV 82%.

4 | DISCUSSION

To our knowledge, this is the largest study aiming at developing an ICU discharge screening method for prediction of new-onset physical disability 3 months post-ICU. Physical function at ICU discharge was the single most important predictor, rendering an AUC of 0.68 (95% CI 0.61-0.76). The predictive accuracy was not as high as we would have hoped but better than ICU LOS (AUC 0.57, 95% CI 0.50-0.65), the current method for selection for ICU follow-up

1. Assess patient's physical status and score according to level achieved

Aspect of physicality	0 points	1 point	2 points	3 points	4 points	5 points
Respiratory function	Complete ventilator dependence. Mandatory breaths only. May be fully sedated/paralysed	Ventilator dependence. Mandatory breaths with some spontaneous effort	Spontaneously breathing with continuous invasive or non-invasive ventilator support	Spontaneously breathing with intermittent invasive or non-invasive ventilator support or continuous high flow oxygen (>15 l)	Receiving standard oxygen therapy (<15 l)	Self-ventilating with no oxygen therapy
Cough	Absent cough, may be fully sedated or paralysed	Cough stimulated on deep suctioning only	Weak ineffective voluntary cough, unable to clear secretions independently (e.g. requires deep suction)	Weak, partially effective voluntary cough, sometimes able to clear secretions (e.g. requires Yankauer suctioning)	Effective cough, clearing secretions with airways clearance techniques	Consistent effective, voluntary cough, clearing secretions independently
Moving within the bed (e.g. rolling)	Unable, may be fully sedated/paralysed	Initiates movement. Requires assistance of two or more people (maximal)	Initiates movement. Requires assistance of at least one person (moderate)	Initiates movement. Requires assistance of one person (minimal)	Independent in <3 seconds	Independent in <3 seconds
Supine to sitting on the edge of the bed	Dynamic. Unable/unstable	Initiates movement. Requires assistance of two or more people (maximal)	Initiates movement. Requires assistance of at least one person (moderate)	Initiates movement. Requires assistance of one person (minimal)	Independent in <3 seconds	Independent in <3 seconds
Dynamic sitting (i.e. when sitting on the edge of the bed/unsupported sitting)	Unable/unstable	Requires assistance of two or more people (maximal)	Requires assistance of at least one person (moderate)	Requires assistance of one person (minimal)	Independent with some dynamic sitting balance (i.e. able to alter trunk position within base of support)	Independent with full dynamic sitting balance (i.e. able to reach out of base of support)

2. Add total score from all five items and plot the score in the graph to obtain patient's probability of new-onset physical disability three months post-ICU

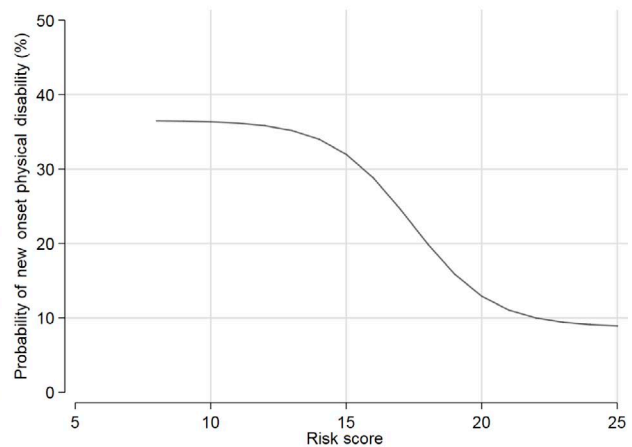


FIGURE 2 The screening method [Colour figure can be viewed at wileyonlinelibrary.com]

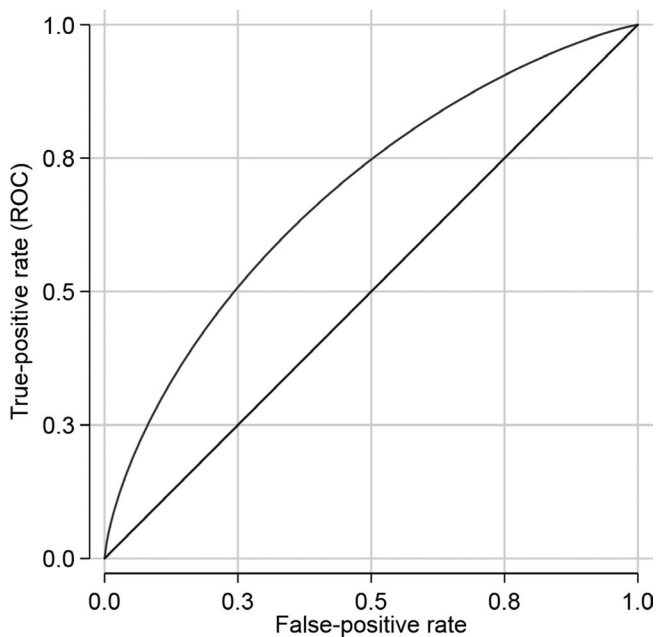


FIGURE 3 Receiver operating characteristics curve for the predictive value of the screening method

in several countries. Few earlier studies assess physical function at discharge as a predictor for later physical disability. Pre-ICU comorbidity assessed with the Charlson comorbidity index was not a risk factor for post-ICU adverse physical outcome in our study, but comorbidity has previously been described as a risk factor for mortality as well as reduced physical and mental HRQOL post-ICU.^{33,34} Prolonged bed rest has been associated with physical limitations after ICU stay in acute lung injury patients⁷ and ICU LOS >2 days was one of the several risk factors in another smaller study.²⁷ In our cohort, ICU LOS was associated with the outcome

in the univariable but not the multivariable analysis. A longer ICU stay implies longer bed rest and a greater burden of illness, factors that likely affect physical performance at discharge. Our interpretation is that multiple risk factors converge into poor physical function at ICU discharge, thereby making it a better predictor of long-term functional impairments than merely time spent in the ICU.

The NPV (0.88) was higher than the PPV, indicating that the greatest merit of the method may be to rule out patients not in need of follow-up, thereby reducing the number of ICU survivors considered for further ICU follow-up.

The prevalence of new-onset physical disability was lower than in previous studies, potentially due to the chosen caseness cutoff. Some studies used any reduction in physical function to classify physical disability,^{27,35} as opposed to BI score reduction ≥ 10 used in this study. A BI score reduction ≥ 10 implies going from independency to total dependency in activities such as feeding or dressing, and is close to the MCID for BI.

4.1 | Strengths and limitations

The prospective design, the inclusion of medical/surgical ICU patients from three countries, and a broad range of ICU LOS increase the generalizability of the results. The response rate of 78% is fairly high in an ICU survivor population. Potential selection bias due to non-response was handled with the weighted model, although we cannot completely rule out remaining bias.

More patients than expected were transferred to other ICUs or had an ICU LOS <12 hours, contributing to a smaller study size than projected. While retrospective reporting of the pre-ICU BI status is a limitation and carries the risk of recall bias, this type of reporting

has shown to have good validity.³⁶ In order to reduce potential recall bias, we performed a chart review for patients where a distinct history of physical status was lacking.

Another limitation is the use of only the first five items of the CPAx. In a previous study, core stability was predictive of a poor long-term functional status.²⁷ In a trade-off between completeness and user feasibility, we included only the first five items to assess physical function, of which dynamic sitting is one.

4.2 | Future perspectives

The predictive accuracy of the screening method is higher than for ICU LOS, the current triage method for ICU follow-up in many countries, also with regard to sensitivity, specificity, PPV, and NPV. In clinical practice, resources for ICU follow-up are limited. The suggested screening method may help direct resources to those more likely in need of post-ICU interventions. The simple screening at ICU discharge presented in this study could thereby reduce the number of patients included in follow-up.

We suggest further research of potential risk factors for incomplete physical recovery post-ICU, such as cognitive function at hospital discharge, or availability to rehabilitation. Such potential risk factors may also play a role in the trajectory of longer term recovery. The method needs external validation.

5 | CONCLUSIONS

We developed an ICU discharge screening method for individual risk prediction for new-onset physical disability 3 months post-ICU. The method has a moderate predictive value but may help to rule out patients unlikely to need physical interventions post-ICU. It has greater predictive accuracy than ICU LOS, the current selection criterion for follow-up in several countries. Further research of post-ICU risk factors for an incomplete recovery is warranted.

CONFLICT OF INTEREST

There is no conflict of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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