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Dysphagia Post-Extubation Affects Long-Term Mortality in Mixed Adult ICU Patients—Data From a Large Prospective Observational Study With Systematic Dysphagia Screening

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OBJECTIVES: Data on long-term effects of post-extubation dysphagia is lacking. We investigate mid- and long-term clinical outcomes in a large sample of ICU patients with systematic dysphagia screening.

DESIGN: Outcome analysis with a follow-up of 6 years or death (whichever occurred earlier) of ICU patients from a prospective observational trial (Dysphagia in Mechanically Ventilated ICU Patients study) with systematic dysphagia screening.

SETTING: ICU of a tertiary care academic center.

PATIENTS: Nine-hundred thirty-three mixed medical-surgical ICU patients (median age, 66 yr; interquartile range [IQR], 54–74, Acute Physiology and Chronic Health Evaluation II score 19 [IQR, 14–24], 71% male).

INTERVENTIONS: ICU patients were followed up for a mean follow-up period of 1,731 ± 772 days (4.7 ± 2.1 yr). Primary outcome measures were 180-day and 360-day all-cause mortality in ICU patients with versus without dysphagia.

MEASUREMENTS AND MAIN RESULTS: Two-hundred seventy-three patients died (29.3%) during the observational interval ($n = 76$ lost to follow-up). In dysphagia screening positive versus negative ICU patients, mortality at 180 days was 16% versus 5.8% (excess mortality 10.2%), whereas mortality at 360 days was 25% versus 9.1% (excess mortality 15.9%). Adjustment for confounders in a Cox model revealed a significant association of dysphagia with all-cause mortality in a time-dependent manner. The risk of death in ICU patients with versus without post-extubation dysphagia declined from about 2.5 times higher to about equal risk for both groups over the first year (i.e., 1.03 yr) post-ICU admission (at 360 d: hazard ratio [HR], 1.03; 95% CI, 0.42–3.70). The mean mortality HR for the first year post-ICU admission was HR 2.09 (95% CI, 1.34–3.24; $p = 0.0009$).

CONCLUSIONS: Long-term follow-up of a large cohort of medical-surgical adult ICU patients systematically screened for dysphagia showed that dysphagia is associated with increased hazards for death for up to 1 year after ICU admission. Our data underline effects of post-extubation dysphagia on long-term clinical outcomes in affected critically ill patients.

KEY WORDS: critical illness; deglutition disorder; long-term outcomes; mortality; post-extubation dysphagia; swallowing dysfunction

Dysphagia is a highly prevalent but likely underdiagnosed comorbidity post mechanical ventilation in critically ill patients and affects about 12% of extubated mixed medical-surgical ICU patients (18% of all emergency admissions) (1). Respective occurence rates may even be higher in

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selected adult ICU patients with baseline neurologic disease and/or prolonged mechanical ventilation (2, 3). Importantly, dysphagia on the ICU contributes to morbidity and short-term mortality (1, 4–6).

Despite its obvious relevance for daily clinical practice (4, 6, 7) and its feasibility for systematic bedside assessment (e.g., by trained ICU nurses [8]), dysphagia post-extubation is not systematically screened for in many ICUs (9, 10). Despite the fact that awareness for post-extubation dysphagia (PED) has likely risen in the past few years, it appears that its awareness can still be increased (11). Since undetected and/or untreated dysphagia is associated with malnutrition, increased risk for aspiration/pneumonia, prolonged ICU and hospital stay, decreased quality of life, and increased healthcare costs, dysphagia comes at a high cost for both affected individuals and society (4, 6–8, 12).

While several small investigations hinted toward potential risk factors for dysphagia (3, 5, 13, 14), a recently published larger analysis compromising 933 ICU patients identified some partly modifiable risk factors for development of dysphagia such as duration of mechanical ventilation (2). While identification of potential risk factors provides the basis for the development of preventive and/or therapeutic strategies, the evidence for current therapeutic strategies remains limited (4, 6, 15).

Dysphagia-associated mortality accounts for an excess short-term mortality of about 9%, as recently shown in 1,304 mixed medical-surgical ICU patients with systematic dysphagia screening (1). Importantly, PED diagnosed on the ICU is not limited to the ICU. Data show that 83% of the patients diagnosed with dysphagia in the ICU still have dysphagia at ICU discharge and more than 60% of affected patients have dysphagia at hospital discharge several days later (1).

Thus, ICU-acquired dysphagia likely has long-term adverse effects. In light of paucity of respective data, we embarked to investigate the impact of PED on long-term mortality in a large population of mixed medical-surgical adult critically ill patients with systematic dysphagia screening.

METHODS

Long-term follow-up data of 933 mixed medical-surgical (defined using the Acute Physiology and Chronic Health Evaluation [APACHE] IV diagnostic criteria) adult ICU patients post systematic dysphagia screening (1) were analyzed in a post hoc fashion (**Fig. 1**). Patients were included in the "Dysphagia in Mechanically Ventilated ICU Patients (DYnAMICS)" study (1) (ClinicalTrials.gov, NCT number 02333201), which was performed between April 2015 and October 2015 in a greater than 900-bed tertiary care academic center (Department of Intensive Care Medicine of the Inselspital, Bern University Hospital, University of Bern, Switzerland, the sole provider for adult intensive care in this center).

The study was performed in accordance with the Declaration of Helsinki and approved by the Kantonale Ethikkommission, Bern, Switzerland (No. 314/2014 and 2021-01363; approved August 09, 2021).

Systematic Assessment of Post-Extubation Dysphagia

In "DYnAMICS" (1), all ICU patients were systematically screened for PED within 3 hours from extubation following a prespecified two-step bedside screening algorithm ("Bernese ICU Dysphagia algorithm" [11]). In brief, prerequisites for extubation were stable gas exchange/hemodynamics with moderate pressure support and positive end-expiratory pressure, responsive to commands, and presumed ability to protect the airway (1).

In the standardized two-step "Bernese ICU Dysphagia algorithm" (11), an initial bedside screening was performed within 3 hours of extubation by trained ICU nurses unless any of the following exclusion criteria were met: 1) patients dying/on comfort therapy and/or 2) patients with recent esophageal injury and/or esophageal surgery (as reported elsewhere [1, 2]). After an initial check for exclusion criteria and readiness to attempt swallowing (with a reassessment performed after 3 hr, if necessary), dysphagia was screened for using a water swallow test consisting of three consecutive teaspoons of water, followed by drinking of one-half a glass of water (1). Failure in two screenings triggered referral to examination by a clinical expert (trained dysphagia specialist). In cases of overt severe dysphagia, the water swallow test could be replaced by a clinical examination performed by a dysphagia specialist (1).

Outcome Assessment

Outcome data (mortality) of individual ICU patients included in DYnAMICS (1) were censored in 2021 and

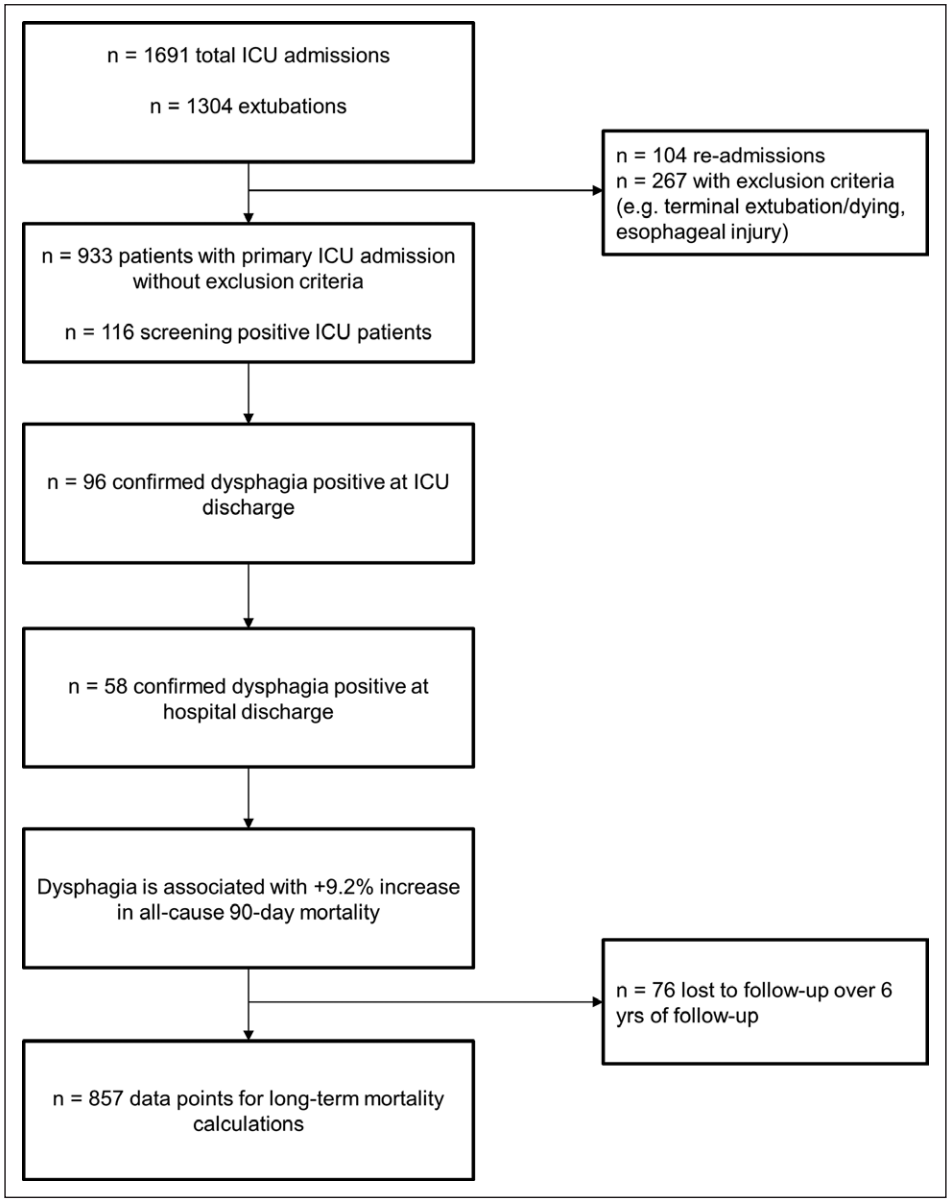

Figure 1. Study flowchart.

extracted electronically from official death registries. Automated data extraction was performed by the Insel Data Coordination Laboratory, Bern, Switzerland.

Statistical Analyses

R Version 4.1.0 (2021-05-18, R core Team) was used for statistical analysis. Continuous variables were presented as median and interquartile ranges and categorical variables as numbers and percentages. Between-group differences were tested with Wilcoxon rank-sum test and Pearson chi-square test.

Time-to-event analyses were performed with follow-up beginning on the date of ICU admission and ending on the date of death or after 6 years, whichever occurred earlier. Kaplan-Meier estimates and log-rank tests were performed for survival analyses to compare survival curves in patients with versus without dysphagia post mechanical ventilation.

Relationship between survival and variables were evaluated with univariate and multivariate Cox regressions. Variable selection was based on our previous publications (1, 2). To test for proportional hazard (PH) assumption (16), scaled Schoenfeld residuals were plotted against time and tested for nonzero slope.

The effect of previously identified risk factors (2) on survival were investigated with the following variables tested for significance in univariate Cox regression: dysphagia, age, APACHE II score, emergency at admission, baseline neurologic disease (APACHE IV diagnostic groups: neurologic patient), days on mechanical ventilation, gender, body mass index, days on renal replacement therapy, and ICU length of stay.

Variables with significant coefficients entered a multivariate Cox regression model (17). The model included six variables: dysphagia, age, APACHE II score, emergency at admission, baseline neurologic disease, and ICU length of stay. Due to strong evidence of non-PHs (global $p = 0.000025$), the multivariate Cox regression model was extended and allowed for time-dependence for the following variables: dysphagia and emergency at admission (18). Survival probability estimates for patients screened with versus without dysphagia were computed keeping the other covariates fixed at their mean value (or proportion where covariates were categorical).

For further investigation of the effect of dysphagia on mortality, time was divided into two periods upon visual inspection of the residuals. To determine the time limits of those periods, two-knots linear splines were fitted to Schoenfeld residuals. Intersection of the linear spline with hazard ratio (HR) of 1 was chosen as the predicted timepoint of change for the effect of dysphagia. To provide insight into differences in the early and late mortality rates in patients with and without dysphagia, we performed a landmark survival analysis with a landmark set at the predicted timepoint of change of the first year after ICU admission and compared it against the following 5 years.

RESULTS

Baseline clinical characteristics of the study population with long-term outcome data are presented in **Table 1**, with further details outlined elsewhere (1). Corresponding survival probabilities with respective CI and *p* values using Kaplan-Meier estimates (**Supplemental Digital Content—Table 1**, http://links.lww.com/CCX/B8) and Cox regression estimates after adjustment for confounders (**Supplemental Digital Content—Table 2**, http://links.lww.com/CCX/B8) are stated in the **Supplemental Digital Content** (http://links.lww.com/CCX/B8). In short, excess all-cause mortality for each timepoint was significant up to 5 years of follow-up, ranging from 10.2% at 180 days post-ICU admission ($p < 0.001$) up to 15.9% increased all-cause mortality at 360 days post-ICU admission ($p = 0.009$). After censoring in 2021, 273 patients died (29%) within the subsequent 6 years of follow-up, 584 were alive, and $n = 76$ lost to follow-up. Kaplan-Meier survival estimates for the 6-year follow-up period are given for dysphagia screening negative ($n = 817$) and dysphagia screening positive patients ($n = 116$) (**Fig. 2**). We observe time-dependency of HR for dysphagia

TABLE 1.
Patient Characteristics

Variable	Overall, *n* = 933[a]	Yes, *n* = 116[a]	No, *n* = 817[a]	*p*[b]
Age	65.00 (54.00–73.00)	64.50 (49.75–77.00)	65.00 (55.00–73.00)	0.83
Gender (male)	666 (71%)	80 (69%)	586 (72%)	0.54
Body mass index[c]	26.23 (23.69–29.38)	25.74 (23.51–27.80)	26.30 (23.74–29.39)	0.070
Emergency admission	525 (56%)	96 (83%)	429 (53%)	< 0.001
APACHE II score[d]	17.00 (13.00–23.00)	21.00 (17.00–25.00)	17.00 (13.00–22.00)	< 0.001
APACHE IV diagnostic group (neurologic)	147 (16%)	47 (41%)	100 (12%)	< 0.001
Patients on renal replacement therapy	47 (5.0%)	12 (10%)	35 (4.3%)	0.005
Days on renal replacement therapy[e]	0.00 (0.00–0.00)	7.02 (5.54–11.20)	3.7 (1.03–7.86)	0.069
Days on invasive mechanical ventilation	0.70 (0.48–1.25)	1.24 (0.64–3.25)	0.67 (0.48–1.07)	< 0.001
Days in ICU (length of stay)	0.98 (0.80–2.22)	2.92 (1.65–5.94)	0.93 (0.79–1.83)	< 0.001
All-cause mortality (180 d)	66 (7.1%)	19 (16%)	47 (5.8%)	< 0.001
All-cause mortality (1 yr)	103 (11%)	29 (25%)	74 (9.1%)	< 0.001
All-cause mortality (2 yr)	144 (15%)	32 (28%)	112 (14%)	< 0.001
All-cause mortality (3 yr)	179 (19%)	34 (29%)	145 (18%)	0.003
All-cause mortality (4 yr)	205 (22%)	37 (32%)	168 (21%)	0.006
All-cause mortality (5 yr)	237 (25%)	41 (35%)	196 (24%)	0.009
All-cause mortality (6 yr)	273 (29%)	42 (36%)	231 (28%)	0.079

APACHE = Acute Physiology and Chronic Health Evaluation.
[a]Median (interquartile range) or frequency (%).
[b]Wilcoxon rank-sum test; Pearson χ^2 test.
[c]Overall missing data in $n = 54$ ($n = 8$ in dysphagia yes, $n = 46$ in dysphagia no).
[d]Overall missing data in $n = 32$ ($n = 4$ in dysphagia yes, $n = 28$ in dysphagia no).
[e]For $n = 47$ out of 933 pts ($n = 12$ dysphagia screening positive, $n = 35$ screening negative).

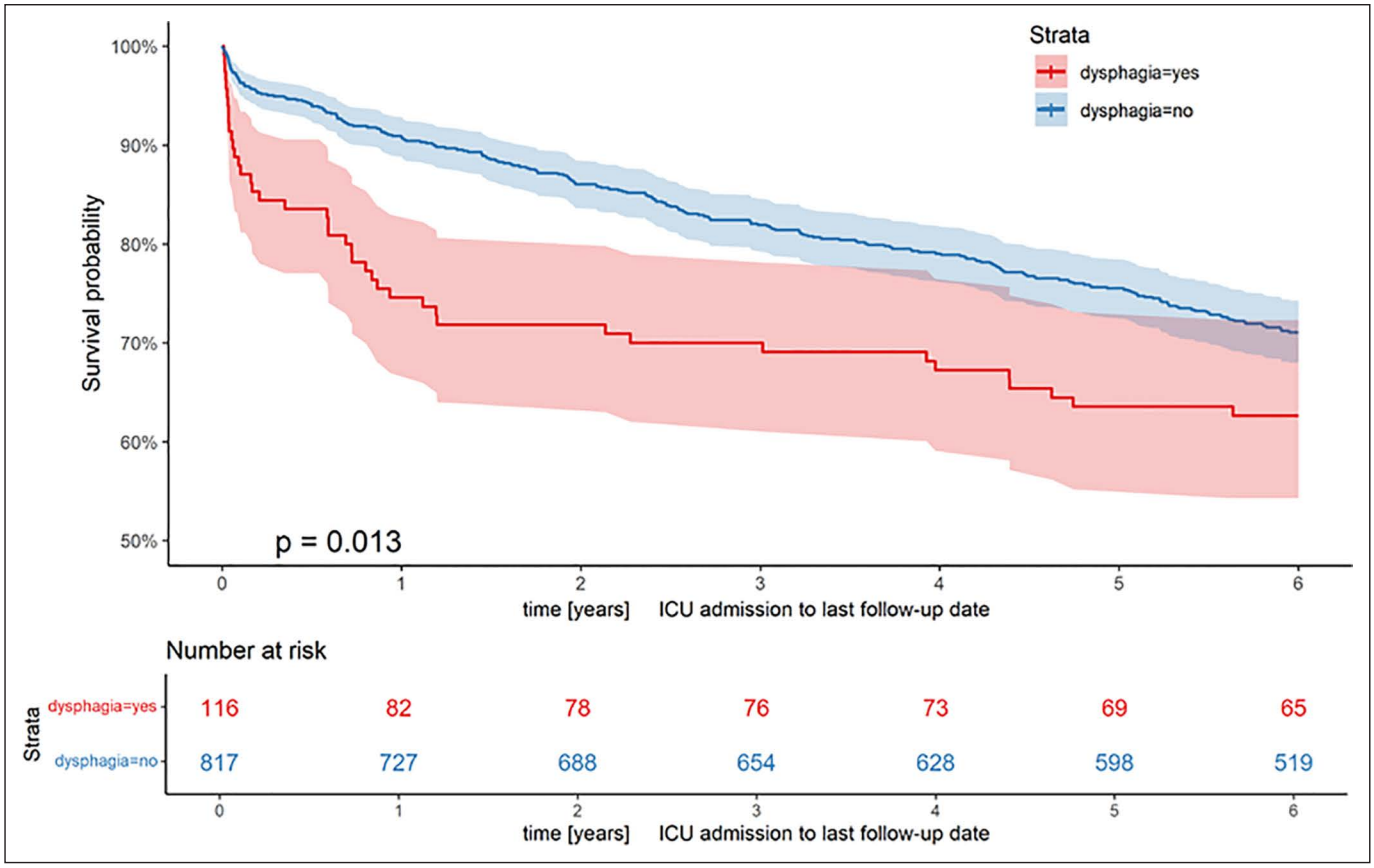

Figure 2. Kaplan-Meier survival estimates. Six-yr survival function of all-cause mortality inpatient groups with and without dysphagia. Numbers of patients at risk are shown below. Log-rank *p* value is indicated.

(**Supplemental Digital Content—Fig. 1**, http://links.lww.com/CCX/B8). The effect varies over time, showing increased HR for dysphagia within 360 days after ICU admission. Effects on mortality seem most pronounced during the first year (Fig. 2), which triggered a follow-up landmark analysis: splitting the effect for dysphagia on all-cause mortality into two time periods with linear splines (**Supplemental Digital Content—Fig. 2**, http://links.lww.com/CCX/B8) predicted a strong positive HR for the first period, which was declining with a slope of -0.92 ± 0.29 per year ($p = 0.0019$). The effect of dysphagia in the second period showed no significant slope (coefficient, 0.046; $p = 0.84$) (**Fig. 3**).

In univariate Cox regression (**Supplemental Digital Content—Table 3**, http://links.lww.com/CCX/B8), ICU length of stay (HR = 1.02, $p = 0.019$), age (HR = 1.04, $p < 0.001$), admission status (i.e., APACHE IV admission category: emergency vs elective, HR [emergency] = 2.29, $p < 0.001$ and neurologic vs non-neurologic disease, HR [neurologic disease] =1.37, $p = 0.039$), baseline disease severity (APACHE II, HR = 1.09, $p < 0.001$), days on mechanical ventilation (HR = 1.03, $p = 0.013$), and dysphagia status (HR [yes] = 1.51, $p = 0.013$) were associated with increased all-cause mortality.

In the multivariate time-dependent Cox regression model (**Table 2**), dysphagia, admission entry type (i.e., APACHE IV admission category), age, and baseline disease severity (i.e., APACHE II score) remained associated with all-cause mortality.

DISCUSSION

Here, we observe that dysphagia has substantial effects on long-term mortality, with an excess all-cause mortality of 10.4% at 180 days and 15.9% at 360 days post-ICU admission. Our data add to previous data showing that dysphagia after mechanical ventilation affects not only short-term (1) but also long-term all-cause mortality. This seems important as data on dysphagia-induced effects on long-term clinical outcomes in nonselected, mixed ICU patients (with systematic dysphagia screening) are currently missing.

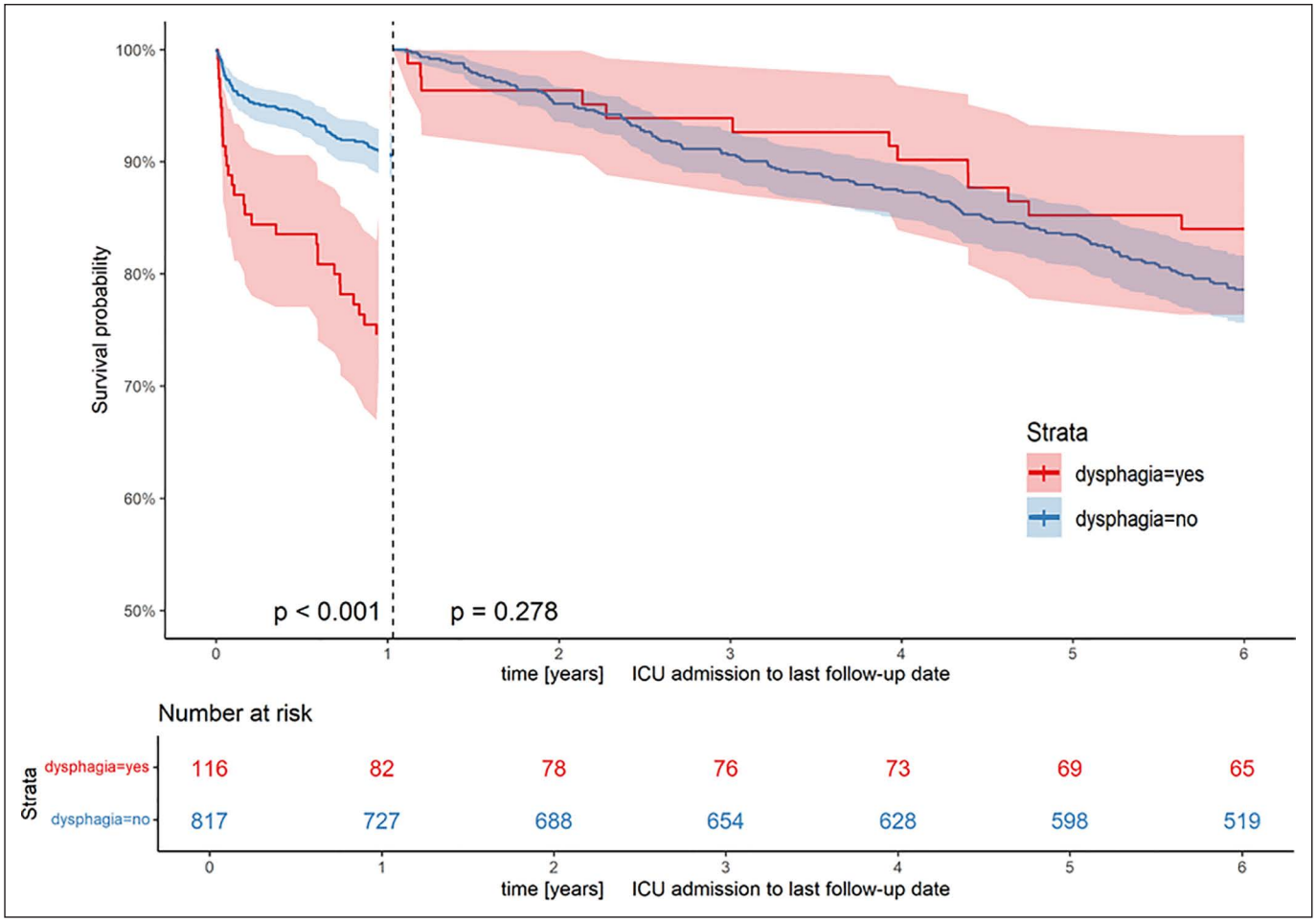

Figure 3. Landmark analysis. Survival functions are shown for patient groups with and without dysphagia for the first 1.03 yr after ICU admission. Numbers of patients at risk are shown below each graph.

As mentioned, previous studies showed that PED affects short-term mortality (1). In particular, patients with baseline neurologic conditions, emergency admissions, and/or increased duration of mechanical ventilation are affected (2). Here, we confirm these data and show that PED has substantial and long-lasting effects on mortality, with highest risks in these respective ICU subpopulations.

A striking observation is that the mortality effect of dysphagia remains for about 1 year of follow-up and declines later. This may underline that dysphagia awareness and early recognition by systematic screening and diagnosing seems important, complemented by long-term follow-up using multidisciplinary approaches (11) in an effort to reduce morbidity (and mortality) from PED in this time interval.

Strengths of our analysis include the fact that systematic dysphagia screening was applied using a structured screening algorithm performed in a large sample of mixed nonselected (i.e., medical-surgical) adult ICU patients. Second, regarding data quality, we used data from a prospective observational study and mortality data were extracted in an automated fashion from official registries. Third, we assume that our findings underestimate the true effects on mortality since some patients required direct tracheostomy and some additional ICU patients discharged alive while still intubated (no decannulation/no extubation, which would have triggered systematic dysphagia screening according to our institutional protocol). Respective patients were not included in the analysis (1). Fourth, we are able to present long-term follow-up data with a maximum follow-up period of 6 years.

A number of important limitations apply that deserve discussion. First, due to the observational character of the study, no cause-effect relationships can be established. Second, as dysphagia-specific mortality is considered hard to correctly assess,

TABLE 2.
Time-Dependent Multivariate Cox Regression for Survival Time Since ICU Admission

Variables	Multivariate Time-Dependent Cox Model				Schoenfeld Proportional Hazard Test
	Coefficient	Hazard Ratio (95% CI)	*p*	Wald	
Age (per 1 yr increase)	0.03	1.03 (1.02–1.04)	**0.00**	5.95	0.05
Dysphagia (screening positive)	0.53	1.7 (1.08–2.66)	**0.02**	2.31	0.16
Emergency admission (yes)	1.33	3,78 (2.31–6.16)	**0.00**	5.33	0.82
APACHE II score (per 1 increase)	0.05	1.05 (1.03–1.07)	**0.00**	4.77	0.85
APACHE IV admission diagnostic groups (neurologic)	0.06	1.06 (0.77–1.46)	0.72	0.36	0.28
Days in ICU (per 1 increase)	0.01	1.01 (0.98–1.04)	0.53	0.62	0.26
Days on invasive mechanical ventilation (per 1 increase)	0.02	1.02 (0.98–1.05)	0.38	0.87	0.17
Time: Emergency admission (yes)	–0.25	0.78 (0.67–0.9)	**0.00**	–3.31	0.41
Time: Dysphagia (screening positive)	–0.35	0.71 (0.56–0.89)	**0.00**	–2.98	0.10
				Global[a]	0.30

APACHE = Acute Physiology and Chronic Health Evaluation.
[a]Schoenfeld's global test to test the proportional hazards assumption in the Cox proportional hazards model.
Bold indicates $p < 0.05$.

we report effects on all-cause, rather than disease-specific, mortality. It thus seems important that our results be interpreted with caution in this regard. Third, although widely accepted as pragmatic bedside screening tool for dysphagia post-extubation, the implemented screening algorithm is not yet formally validated (11).

INTERPRETATION

Following systematic dysphagia screening in a prospective observational study including a large cohort of mixed adult ICU patients, we observed that dysphagia had substantial effects on long-term mortality. Our data indicate that the hazards for death are increased for up to 1 year after ICU admission. This underlines the clinical relevance of PED not only in the early but also in the phase after critical illness.

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Dr. Zuercher is the guarantor of the article and takes responsibility for the integrity of the work as a whole, from inception to publication. Drs. Zuercher and Schefold developed the research strategy and drafted the article with Drs. Pfortmueller and Waskowski. Dr. Moser performed all statistical analyses. All authors helped to finalize the article, revised it for important intellectual content, and approved the final version for publication. All authors meet the criteria for authorship as recommended by the International Committee of Medical Journal Editors.

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