Risk factors for dysphagia in ICU patients following invasive mechanical ventilation

Patrick Zuercher, MD, Noëlle V. Schenk, Céline Moret, MD, David Berger, MD, Roman Abegglen, Joerg C. Schefold, MD

PII: S0012-3692(20)31646-9

DOI: https://doi.org/10.1016/j.chest.2020.05.576

Reference: CHEST 3262

To appear in: *CHEST*

Received Date: 12 February 2020

Revised Date: 30 March 2020

Accepted Date: 6 May 2020

Please cite this article as: Zuercher P, Schenk NV, Moret C, Berger D, Abegglen R, Schefold JC, Risk factors for dysphagia in ICU patients following invasive mechanical ventilation, *CHEST* (2020), doi: https://doi.org/10.1016/j.chest.2020.05.576.

word count: abstract 259/300; main text 2972/3200

Risk factors for dysphagia in ICU patients following invasive mechanical ventilation

Patrick Zuercher MD, Noëlle V. Schenk, Céline Moret MD, David Berger MD, Roman Abegglen, Joerg C. Schefold MD

Dept. of Intensive Care Medicine, Inselspital, Bern University Hospital, University of Bern, Switzerland

✉ Dr. med. Patrick Zuercher, MD
Department of Intensive Care Medicine
Inselspital, Bern University Hospital
University of Bern
CH – 3010 Bern
Switzerland
Tel.: +41 31 632 6987
patrick.zuercher@insel.ch
ORCID 0000-0003-0331-4577

Running title:	Risk factors for dysphagia
Key words:	deglutition disorder, post-extubation dysphagia, swallowing dysfunction, ICU acquired swallowing dysfunction, critical illness, sepsis
Registry:	NCT02333201, clinicaltrials.gov
COI statement (full disclosure):	The Dept. of Intensive Care Medicine has/ had research & development/consulting contracts (full disclosure) with Orion Corporation, Abbott Nutrition International, B. Braun Medical AG, CSEM SA, Edwards Lifesciences Services GmbH/ SA, Kenta Biotech Ltd, Maquet Critical Care AB, Omnicare Clinical Research AG, and Nestlé. Educational grants have been received from Fresenius Kabi; GSK; MSD; Lilly; Baxter; Astellas; AstraZeneca; B. Braun Medical AG, CSL Behring, Maquet, Novartis, Covidien, Nycomed, Pierre Fabre Pharma (Roba Pharma); Pfizer, Orion Pharma. No personal financial gain resulted from respective development/ consulting contracts and/or grants.

Abbreviation List

ICU	Intensive Care Unit
DYnAMICS	Dysphagia in Mechanically Ventilated ICU Patients
IQR	Interquartile Range
OR	Odds Ratio
APACHE	Acute Physiology And Chronic Health Evaluation
BMI	Bod Mass Index
COPD	Chronic Obstructive Pulmonary Disease
CVA	Cerebrovascular Accident
NYHA	New York Heart Association
SOFA	Sequential Organ Failure Assessment
KEK	Kantonale Ethikkommission (regional ethics committee)
WST	Water Swallow Test
SAPS	Simplified Acute Physiology Score
TISS-28	Therapeutic Intervention Scoring System (TISS)-28 points
RRT	Renal Replacement Therapy
OOB	Out-Of-Bag Error
GAM	Generalized Additive Model
LRT	Likelihood Ratio Test
PC(A)	Principal Component (Analysis)
AUROC	Area Under the Receiver Operating Characteristics
AIC	Akaike Information Criterion
FEES	Flexible Endoscopic Evaluation of Swallowing
VFSS	Videofluoroscopic Swallowing Study

Abstract

Background: Dysphagia is common and independently predicts death in ICU patients. Risk factors for dysphagia are largely unknown with sparse data available from mostly small cohorts without systematic dysphagia screening.

Research Question: What are the key risk factors for dysphagia in ICU patients post invasive mechanical ventilation?

Study Design and Methods: Post-hoc analysis of data from a monocentric prospective observational study (*"DYnAMICS"*) using comprehensive statistical models to identify potential risk factors for post-extubation dysphagia. 933 primary admissions of adult medical-surgical ICU patients (median age 65 years [IQR 54-73], n=666 (71%) male) were investigated in a tertiary care academic centre. Patients received systematic bedside screening for dysphagia within 3 hours post extubation. Dysphagia screening positivity (n=116) was followed within 24 hours by a confirmatory exam.

Results: After adjustment for confounders, baseline neurological disease (OR 4.45, 95%-CI: 2.74-7.24, p<0.01), emergency admission (OR 2.04, 95%-CI: 1.15-3.59, p<0.01), days on mechanical ventilation (OR 1.19, 95%-CI: 1.06-1.34, p<0.01), days on renal replacement therapy (OR 1.1, 95%-CI: 1-1.23, p=0.03), and disease severity (APACHE II score within first 24 hours; OR 1.03, 95%-CI: 0.99-1.07, p<0.01) remained independent risk factors for dysphagia post extubation. Increased Body Mass Index reduced the risk for dysphagia (6% per step increase, OR 0.94, 95%-CI: 0.9-0.99, p=0.03).

Interpretation: In ICU patients, baseline neurological disease, emergency admission and duration of invasive mechanical ventilation appeared as prominent independent risk factors for dysphagia. As all ICU patients post mechanical ventilation should be considered at risk for

dysphagia, systematic screening for dysphagia is recommended in respective critically ill patients.

Clinical Trial Registration: clinicaltrials.gov (NCT 02333201)

Introduction

Data from mixed adult ICU patients show that post-extubation dysphagia is commonly observed on the ICU, mostly persists until hospital discharge, and is an independent predictor of 28- and 90-day mortality after adjustment for typical confounders (excess 90-day mortality 9.2%)[1].

Available data on risk factors leading to post-extubation dysphagia are conflicting. In smaller heterogeneous patient cohorts, investigating mostly patients post-dysphagia-associated complications (e.g. aspiration-induced pneumonia), duration of intubation was often proposed[2-14]. Further, in respective earlier studies with mostly limited sample sizes, advanced age[3,5,10,13], sepsis[13,15], perioperative trans-oesophageal echocardiography[5,11], previous stroke[2,11] or tracheostomy[16], and presence of gastroesophageal reflux[4,17] were proposed associated with development of dysphagia. Despite these observations, Acute Physiology and Chronic Health Evaluation (APACHE)-II scores[4,16,18,19], Body Mass Index (BMI)[4,16,18], gender[2,4,5,12,16,18,20,21], specific comorbidities such as diabetes[2,5,8,9,13,22], hypertension[2,5,13,23], COPD[5,8,9,22], pre-existing renal dysfunction[2,5,13], myocardial infarction[2,5,8,9,13], heart failure[8,9,13,24], preoperative/ history of cerebrovascular accidents (CVA)[2,5,8,23,24], NYHA >2[2,23], smoking[2,13], SOFA scores[4,8,9,18,24] and/or endotracheal tube size[8,9,20,24] were refuted in most investigations. Moreover, investigations on specific drugs/ medications, e.g. analgosedation, and/or vasoactive medication are scarce and show contradictory findings[2,13]. Importantly, as stated above, data on risk factors in critically ill patients mostly derive from smaller studies, analyzing mostly selective patient cohorts, without systematic screening for dysphagia and often including patients with clinically overt dysphagia-associated complications[14].

Identification of potentially modifiable risk factors leading to development of post-extubation dysphagia seems pivotal[14]. The risk for dysphagia could ideally be reduced or its course modified, resulting in improved clinical outcomes. Importantly, screening for

dysphagia is not yet considered standard of care in most ICUs[25,26], likely due to restraints in resources. Further, identification of risk factors for dysphagia may provide the basis for risk-based (i.e. targeted) screening approaches. As post-extubation dysphagia appears an under-recognized health care problem[14,25] with considerable impact on clinical outcomes[1], we embarked to identify risk factors for post-extubation dysphagia in a large cohort of mixed medical-surgical adult ICU patients.

Methods

Patients and analysis design

Post-hoc analysis of data collected in the prospective observational study ("Dysphagia in Mechanically Ventilated ICU Patients, DYnAMICS") performed from April 2015 until October 2015 in a 900+ bed tertiary care academic medical centre (Inselspital, Bern University Hospital, University of Bern, Switzerland)[1]. The centre treats all medical and surgical critically ill patients in our institution and is the sole provider for adult intensive care in our University Hospital. In DYnAMICS[1], a mixed medical/surgical patient cohort (defined using the APACHE IV diagnostic criteria) were systematically screened for dysphagia using the two-step Bernese ICU Dysphagia algorithm[1,14,27,28]. In brief, in this standardized two-step approach, 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 oesophageal injury and/or esophageal surgery[1]. All patients extubated or decannulated after invasive mechanical ventilation were included. Prerequisite 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]. The study was performed in accordance with the "Declaration of Helsinki" and approved by the Kantonale Ethikkommission, KEK, Bern, Switzerland (KEK Nr. 314/2014).

Dysphagia diagnosis

For screening and potential diagnosing of dysphagia, patients were checked for exclusion criteria and readiness to attempt swallowing (one re-assessment performed after 3 hours, if necessary)[1]. Water swallow tests (WST) consisted of consecutive swallowing of three teaspoons of water at room temperature followed by drinking half a glass of water, as suggested[29,30]. Failure in two screenings triggered an examination by a dysphagia specialist

(physiotherapist or speech language therapist) and patients were followed-up until hospital discharge. WST could be replaced by specialist examinations on clinical indications (e.g. in cases of overt severe dysphagia). Full details are given elsewhere[1].

Assessment of disease severity, and ICU resource use

For assessment of disease severity, baseline Acute Physiology and Chronic Health Evaluation (APACHE)-II scores[31] and Simplified Acute Physiology Score (SAPS)-II scores[32] were recorded. ICU resource use was assessed by analysis of the sum of Therapeutic Intervention Scoring System (TISS)-28 points (recorded once per shift over ICU stay)[33,34]. Days on (invasive) mechanical ventilation, need for gastric tube feeding, days on antibiotics/ antimicrobials, days on vasopressors and sedatives, and need for renal replacement therapy (RRT) were recorded[1].

Statistical Analyses

In accordance to current recommendations in medical research[35,36], missing values were imputed with multiple imputation, using a random forest algorithm[37]. Missing values were replaced with the mean of 50 independent imputations. Variables with a per-variable imputation error (out-of-bag error, OOB) exceeding 0.2 (20%) were excluded. The recommendations for purposeful variable selection were followed[38-40], see detailed description in Supplement (e-Appendix E1). In brief, a Generalized Additive Model (GAM) was used, as this model does not rely on the linearity assumption that applies to logistic models[41,42]. The need for smoothing splines for each variable was checked individually using likelihood ratio tests (LRT). $p<0.2$ was used as threshold from simple to multiple regression. In order to avoid multi-collinearity, representative variables were selected with Principal Component Analysis (PCA)[43] and concurvity was assessed[44] . PCA visualizes associations between multiple variables and is used to reduce dimensionality by cluster formation, addressing multi-collinearity. Multi-collinearity was considered inherent for parts of the data (e.g. invasive mechanical ventilation typically paralleled by gastric tube placement). Per cluster of correlated variables, a representative of each group was selected based on clinical criteria with other members excluded. The adequacy of the resulting model was assessed using Area Under the Receiver Operating Characteristics (AUROC) and Hosmer-Lemeshow tests. The final model was validated using k-fold cross-validation (k = 500 iterations, test set of 5 %). Sensitivity analyses, A) When limiting the dataset to shorter length of mechanical ventilation, we chose the day where the model predicted an OR of 1 (at 4.85 days). Changes in the model when limiting the dataset to this threshold were tested, and B) the robustness of respective odds ratios (OR) against swaps of representative variables were measured, in an effort to investigate the behaviour of all individual group members to confirm grouping and C) APACHE II was replaced with SAPS II scores and D) elective patients were excluded. All statistical analyses were performed using R, version 3.6.1[45], and Rstudio version 1.2.5001[46].

Results

Patient demographics

Data of a total of 1,304 patients were assessed (post-hoc analysis of prospectively collected data of the DYnAMICS study)[1]. After exclusion of patients for ICU-re-admissions (n=104) and exclusion criteria (n=267), 933 mixed medical-surgical adult ICU patients remained in the dataset. Characteristics of these 933 extubated study patients are given in Table 1.

Outlier detection and missing value imputation

No outliers were detected in the candidate risk factors. Six outliers were observed in three variables of the imputation dataset (e-Appendix E2, consisting of 58 variables). The overall mean OOB imputation error was 9.35%.

Variable selection

As the linearity assumption of the logistic model was not met (e-Figure 1), GAM models were used. Details on purposeful variable selection are given in Tables 2A (simple regression), 2B, and 2C (multiple regression). Comparison of the multiple regression models by LRT indicated selection of the full model ($p = 0.02$), although Akaike Information Criterion (AIC) indicated preference of the reduced model at delta AIC of 0.16 (Table 2). AIC estimates model quality based on goodness of fit (likelihood) and the simplicity of the model (number of parameters). As the full model was selected, no removal of variables as proposed by purposeful variable selection was necessary.

Days on gastric tube and days on ICU showed high concurvity (> 0.8, data not shown; model Table 2B). Clustering of the respective variables with days on invasive mechanical ventilation, cumulative neurotropic medication doses (Propofol and Midazolam), days on RRT until screening, days in hospital until screening and likely with APACHE-II score was identified (Figure 1, e-Appendix E2 and e-Figure 2). Based on the most relevant PCA axes

(PC 1-3, explained 70.25% of the variance, Figure 1), the correlated variables were classified into three groups of interchangeable variables: (1) days on RRT, days in hospital, and cumulative Midazolam dose, (2) days on invasive mechanical ventilation, days in ICU, days on gastric tube, and cumulative Propofol dose, and (3) APACHE-II score. In-group swapping of respective variables resulted in models with mostly low (<20%) changes in estimated ORs (exponentials of estimated coefficients) (see below).

The resulting final model refuted concurvity >0.8 (data not shown, final model in Table 3, AUROC 0.88, AIC 583.84, Hosmer-Lemeshow test proving no significant difference between observed and predicted values). Although LRT indicated better fitness and AIC was lower in the full model (Table 2B), the final model was kept, based lower risk of co-linearity. Cross-validation reported an accuracy of 0.86, with a false-positive rate of 0.03 and a false-negative rate of 0.11 with an accuracy of >70% for 499 of 500 predictions (e-Figure 3).

Risk factors for dysphagia on the ICU

In the final model (Table 3), the following risk factors for dysphagia were identified: baseline neurologic disease (OR 4.45, 95%-CI: 2.74-7.24, p<0.01), emergency admission (OR 2.04, 95%-CI: 0.99-1.07, p<0.01), days on invasive mechanical ventilation (OR 1.19, 95%-CI: 1.06-1.34, p<0.01), days on RRT (OR 1.1, 95%-CI: 1-1.23, p=0.03) and APACHE II score (OR 1.03, 95%-CI: 0.99-1.07, p<0.01). Of note, when APACHE II was replaced by SAPS II score, SAPS-II score was not a risk factor (p=0.06) (e-Table 1C). CIs for ORs cross 1 for emergency admission, days on RRT and APACHE II, because they correspond to Wald type CI approximations. Exact CIs were only available pointwise, as shown in e-Figure 4. Per stepwise increase in BMI, the risk for dysphagia declined by 6% (OR 0.94, 95%CI: 0.9-0.99, p=0.01). Days on mechanical ventilation, days on RRT, APACHE II score and age were fitted with non-linear smoothed functions. The OR followed a flat humpbacked-shaped curve with a

peak at 4.85 days (regarding days on mechanical ventilation) and 12.1 days (regarding days on RRT), respectively (e-Figures 4A, 4B). The first day of mechanical ventilation increased the risk by 98%, with a moderate decrease in the ensuing days: at 4.85 days, the OR was 1, with a potential decrease/ saturation thereafter (note 95%-CI, n=56 after day 5) (e-Figure 4A). 47 patients, i.e. about 5% of the total cohort of patients, were treated with RRT. During the first 5 days, patients on RRT had an increased risk for dysphagia per additional RRT day by 20-25%. During the ensuing days, the additional risk potentially decreased with each day of additional therapy (e-Figure 4B). However, this was accompanied by a large reduction in sample size of RRT treated patients. Regarding APACHE II scores, it appeared that the OR within the 0.25-0.5-quantile (14-18) was rather high at about 12% for each additional score point (e-Figure 4C). The non-linear relationship of age with respective logits is indicated, two age groups of opposite risk with increasing age were identified (e-Figure 4D). When BMI was classified according to the WHO grading system, dysphagia incidence moderately increased from obesity class II on (lower sample size at extreme ends; data not shown).

Sensitivity analysis

When the dataset was reduced to the first 4.85 days of mechanical ventilation (n=876, Table 1) (please note decrease in sample size after maximum risk at day 4.85, e-Figure 4), the model did not change substantially, except that days on RRT was no longer a risk factor (likely due to low number of RRT-treated patients) (e-Table 2). The OR for days on mechanical ventilation increased by 31% per day, likely due to absence of days with saturated risk. ORs for baseline neurological disease and emergency admission increased by 14% and 10% (e-Table 2). The sensitivity analysis may thus demonstrate that the final model (Table 3) likely predicts the risk in a conservative fashion.

In-group swapping of respective variables resulted in models without concurvity (<0.8) and low (<20%) changes in estimated ORs (exponentials of estimated coefficients) (e-Figure 5, e-

Table 1), except for swapping days on mechanical ventilation with days in ICU. This model was classified as unreliable and thus refuted. Swapping of RRT did result in slightly narrower confidence intervals (as expected due to a limited number of RRT-treated patients) with rather unchanged results.

When electively admitted patients were excluded from the analysis (n=525), no substantial changes in size and direction of ORs were observed, except the 3 risk factors with lowest ORs were not significant any more, likely due to the lower sample size (e-Table 1 D).

Discussion

When data from a large cohort of ICU patients was analysed in a post-hoc fashion, we observed that baseline neurological disease, emergency admission, and duration of mechanical ventilation were key independent risk factors for dysphagia post mechanical ventilation after adjustment for typical confounders. Interestingly, each step increase in BMI reduced the risk for dysphagia on the ICU by about 6%.

Earlier studies proposed a number of potential risk factors for post-extubation dysphagia. Despite that previously available data mostly derived from smaller studies, and often analyzed selective patient cohorts after clinically overt dysphagia-associated complications (e.g. aspiration), advanced age[3,5,10,13] and previous stroke[2,11] appeared among the most often proposed risk factors for dysphagia. In the present analysis, age did not appear a risk factor in both the unadjusted or adjusted analyses (Table 2). Further, we confirm findings from previous studies showing that the risk for post-extubation dysphagia appears not simply related to increased baseline disease severity [4,8,9,16,18,19,24], as we observed moderate or no effects, depending on the specific scores chosen (Table 2, e-Table 1C).

Despite observations that previously proposed risk factors for dysphagia post invasive mechanical ventilation included male gender[2,4,5,12,16,18,20,21], increased BMI[4,16,18], use of specific medications[2,13], and/or specific comorbidities[2,5,8,9,13,22], we observed that gender was not a risk factor for post-extubation dysphagia. Further, comorbidities (except baseline neurological disease), and/ or use of cumulative dose of specific drugs often used in the ICU setting in mechanically ventilated patients (e.g. Propofol, Midazolam, Table 2) appeared not as risk factors after adjustment. Interestingly, our data demonstrate that with each step increase in BMI, the risk declines by about 6%. This observation is intriguing and following exclusion of collider stratification[47,48] might remind of an obesity paradox. Nevertheless, this is speculative and should be investigated in subsequent studies.

Theoretically, duration of gastric tube presence might be associated with an increased risk for dysphagia. Our data show that patients with post-extubation dysphagia had longer tube feeding before screening measures (Table 1) and this was confirmed in multiple regression (e-Table 2). However, this seems not surprising, as presence and duration of gastric tubes is typically paralleled by mechanical ventilation (see PCA in Figure 1). The reason seems inherent, as intubated patients usually require a gastric feeding tube.

Further, days in hospital and/or days in the ICU before dysphagia screening differed considerably between patients with *vs.* without dysphagia (Table 1). Importantly, after adjustment, ICU- and/or hospital length of stay were not observed risk factors for dysphagia (Table 2B). Finally, prolonged duration of RRT consistently appeared as a risk factor for dysphagia after adjustment. One could argue that this would be explained by RRT being an indicator of disease severity, but PCA strongly suggests otherwise, showing a different clustering pattern. Given the limited number of patients on RRT, this may hint towards a rather strong effect.

Our analysis has several limitations that deserve discussion. First, our findings result from a post-hoc analysis of a larger monocentric study[1] and the assessment was not stratified to accommodate various specific underlying diseases. Although a considerable number of ICU patients was systematically screened for post-extubation dysphagia, our data await confirmation in additional centres. Nevertheless, we are convinced that the cohort under investigation reflects a typical population of (mixed) medical-surgical ICU patients post mechanical ventilation. Second, assessment for dysphagia was confirmed by dysphagia specialists using clinical measures[49], which should ideally have been confirmed by instrumental techniques to improve specificity (e.g. by flexible endoscopic evaluation of swallowing (FEES) or videofluoroscopic swallowing studies (VFSS)). However, we used a feasible two-step dysphagia algorithm (the Bernese ICU dysphagia algorithm) as a pragmatic and rapidly available bedside tool for dysphagia assessment in the ICU[14]. Third, due to study

design, we present associations rather than cause-effect relationships and we are unable to conclude on underlying pathomechanisms leading to dysphagia. Fourth, initial disease severity was higher in patients diagnosed with dysphagia (Table 1) and one might theoretically argue that dysphagia could simply be a consequence of increased disease severity. After adjustment, however, only moderate or no effects of disease severity (reflected by clinical scores) were observed. Fifth, data collinearity was tested and variables selected integrating both mathematical and medical considerations. Collinearities may be inherent in comprehensive data and could be considered typical in this clinical scenario. Sixth, confidence intervals for odds ratios crossed or touched 1 in some parameters. This occurred in the context of approximated confidence intervals, since exact confidence intervals were only available pointwise (e-Figure 5). Methods for exact simultaneous confidence interval calculation are not yet available for the applied nonparametric method[41]. Seventh, patients were not assessed for baseline swallowing disorder prior to ICU admission. Eighth, the 3-hour time limit for the first dysphagia assessment (with a repeat assessment if required) could be viewed as somewhat arbitrary. However, an early structured risk assessment was deliberately aimed for. Ninth, disease severity scores were assessed at admission and not on a daily basis. Although longitudinal risk modeling might have been favorable, most ICU severity scores are not validated for such an approach. Tenth, and importantly, we were unable to identify clearly modifiable risk factors. Nevertheless, our data underline that e.g. duration of mechanical ventilation should be kept as short as possible, e.g. using dedicated sedation protocols.

Interpretation

In ICU patients post mechanical ventilation, neurological disease at baseline, emergency admission, and duration of mechanical ventilation appeared as prominent independent risk factors for dysphagia after adjustment for typical confounders. An inverse correlation in the risk for dysphagia was observed for BMI, warranting further studies. As all ICU patients post

mechanical ventilation should be considered at risk for dysphagia, systematic screening for dysphagia is recommended in respective critically ill patients.

Acknowledgments

PZ, NVS and JCS drafted this manuscript. All other authors helped to draft the manuscript, and revised it for important intellectual content. All authors read and approved the final version. All authors meet the criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE).

Funding

No study-specific funding applied for this analysis. The DYnAMICS study was supported in part by funding from Nestec. Ltd, Vevey, Switzerland, as outlined in [1].

Conflict of interest statement

The authors report departmental grants (full disclosure): from Orion Pharma, Abbott Nutrition International, B. Braun Medical AG, CSEM AG, Edwards Lifesciences Services GmbH, Kenta Biotech Ltd, Maquet Critical Care AB, Omnicare Clinical Research AG, Nestle, Pierre Fabre Pharma AG, Pfizer, Bard Medica S.A., Abbott AG, Anandic Medical Systems, Pan Gas AG Healthcare, Bracco, Hamilton Medical AG, Fresenius Kabi, Getinge Group Maquet AG, Dräger AG, Teleflex Medical GmbH, Glaxo Smith Kline, Merck Sharp and Dohme AG, Eli Lilly and Company, Baxter, Astellas, Astra Zeneca, CSL Behring, Novartis, Covidien, and Nycomed outside the submitted work. The money was paid into departmental funds. No personal financial gain resulted. The DYnAMICS study [1] was supported, in part, by Nestec, Vevey, Switzerland. Financial support was also received from the institutional scientific fund (Department of Intensive Care Medicine, Bern, Switzerland).

References

1. Schefold JC, Berger D, Zurcher P, et al. Dysphagia in Mechanically Ventilated ICU Patients (DYnAMICS): A Prospective Observational Trial. *Crit Care Med.* 2017;45(12):2061-2069.
2. Barker J, Martino R, Reichardt B, Hickey EJ, Ralph-Edwards A. Incidence and impact of dysphagia in patients receiving prolonged endotracheal intubation after cardiac surgery. *Can J Surg.* 2009;52(2):119-124.
3. Bordon A, Bokhari R, Sperry J, Testa Dt, Feinstein A, Ghaemmaghami V. Swallowing dysfunction after prolonged intubation: analysis of risk factors in trauma patients. *Am J Surg.* 2011;202(6):679-682; discussion 682-673.
4. Brodsky MB, Gellar JE, Dinglas VD, et al. Duration of oral endotracheal intubation is associated with dysphagia symptoms in acute lung injury patients. *J Crit Care.* 2014;29(4):574-579.
5. Hogue CW, Jr., Lappas GD, Creswell LL, et al. Swallowing dysfunction after cardiac operations. Associated adverse outcomes and risk factors including intraoperative transesophageal echocardiography. *J Thorac Cardiovasc Surg.* 1995;110(2):517-522.
6. Kim MJ, Park YH, Park YS, Song YH. Associations Between Prolonged Intubation and Developing Post-extubation Dysphagia and Aspiration Pneumonia in Non-neurologic Critically Ill Patients. *Ann Rehabil Med.* 2015;39(5):763-771.
7. Kwok AM, Davis JW, Cagle KM, Sue LP, Kaups KL. Post-extubation dysphagia in trauma patients: it's hard to swallow. *Am J Surg.* 2013;206(6):924-927; discussion 927-928.
8. Macht M, Wimbish T, Bodine C, Moss M. ICU-acquired swallowing disorders. *Crit Care Med.* 2013;41(10):2396-2405.
9. Macht M, Wimbish T, Clark BJ, et al. Postextubation dysphagia is persistent and associated with poor outcomes in survivors of critical illness. *Crit Care.* 2011;15(5):R231.
10. Oliveira ACM, Friche AAL, Salomao MS, Bougo GC, Vicente LCC. Predictive factors for oropharyngeal dysphagia after prolonged orotracheal intubation. *Braz J Otorhinolaryngol.* 2017.
11. Rousou JA, Tighe DA, Garb JL, et al. Risk of dysphagia after transesophageal echocardiography during cardiac operations. *Ann Thorac Surg.* 2000;69(2):486-489; discussion 489-490.
12. Sassi FC, Medeiros GC, Zambon LS, Zilberstein B, Andrade CRF. Evaluation and classification of post-extubation dysphagia in critically ill patients. *Rev Col Bras Cir.* 2018;45(3):e1687.
13. Skoretz SA, Yau TM, Ivanov J, Granton JT, Martino R. Dysphagia and associated risk factors following extubation in cardiovascular surgical patients. *Dysphagia.* 2014;29(6):647-654.
14. Zuercher P, Moret CS, Dziewas R, Schefold JC. Dysphagia in the intensive care unit: epidemiology, mechanisms, and clinical management. *Crit Care.* 2019;23(1):103.
15. Zielske J, Bohne S, Axer H, Brunkhorst FM, Guntinas-Lichius O. [Dysphagia management of acute and long-term critically ill intensive care patients]. *Med Klin Intensivmed Notfmed.* 2014;109(7):516-525.
16. Zielske J, Bohne S, Brunkhorst FM, Axer H, Guntinas-Lichius O. Acute and long-term dysphagia in critically ill patients with severe sepsis: results of a prospective controlled observational study. *Eur Arch Otorhinolaryngol.* 2014;271(11):3085-3093.
17. Metheny NA, Clouse RE, Chang YH, Stewart BJ, Oliver DA, Kollef MH. Tracheobronchial aspiration of gastric contents in critically ill tube-fed patients: frequency, outcomes, and risk factors. *Crit Care Med.* 2006;34(4):1007-1015.
18. Brodsky MB, Huang M, Shanholtz C, et al. Recovery from Dysphagia Symptoms after Oral Endotracheal Intubation in Acute Respiratory Distress Syndrome Survivors. A 5-Year Longitudinal Study. *Ann Am Thorac Soc.* 2017;14(3):376-383.
19. El Solh A, Okada M, Bhat A, Pietrantoni C. Swallowing disorders post orotracheal intubation in the elderly. *Intensive care medicine.* 2003;29(9):1451-1455.
20. Elpern EH, Scott MG, Petro L, Ries MH. Pulmonary aspiration in mechanically ventilated patients with tracheostomies. *Chest.* 1994;105(2):563-566.

21. Omura K, Komine A, Yanagigawa M, Chiba N, Osada M. Frequency and outcome of post-extubation dysphagia using nurse-performed swallowing screening protocol. *Nurs Crit Care.* 2018.
22. Ajemian MS, Nirmul GB, Anderson MT, Zirlen DM, Kwasnik EM. Routine fiberoptic endoscopic evaluation of swallowing following prolonged intubation: implications for management. *Archives of surgery (Chicago, Ill. : 1960).* 2001;136(4):434-437.
23. Ferraris VA, Ferraris SP, Moritz DM, Welch S. Oropharyngeal dysphagia after cardiac operations. *Ann Thorac Surg.* 2001;71(6):1792-1795; discussion 1796.
24. Macht M, King CJ, Wimbish T, et al. Post-extubation dysphagia is associated with longer hospitalization in survivors of critical illness with neurologic impairment. *Crit Care.* 2013;17(3):R119.
25. Zuercher P, Moret C, Schefold JC. Dysphagia in the intensive care unit in Switzerland (DICE) - results of a national survey on the current standard of care. *Swiss medical weekly.* 2019;149:w20111.
26. Marian T, Dunser M, Citerio G, Kokofer A, Dziewas R. Are intensive care physicians aware of dysphagia? The MAD(ICU) survey results. *Intensive care medicine.* 2018;44(6):973-975.
27. Zuercher P, Dziewas R, Schefold JC. Dysphagia in the intensive care unit - a (multidisciplinary) call to action. *Intensive Care Med.* accepted 2020.
28. Zuercher P, Dziewas R, Schefold JC. Dysphagia in the intensive care unit: a (multidisciplinary) call to action. *Intensive Care Med.* 2020.
29. Perry L. Screening swallowing function of patients with acute stroke. Part one: Identification, implementation and initial evaluation of a screening tool for use by nurses. *J Clin Nurs.* 2001;10(4):463-473.
30. Brodsky MB, Suiter DM, Gonzalez-Fernandez M, et al. Screening Accuracy for Aspiration Using Bedside Water Swallow Tests: A Systematic Review and Meta-Analysis. *Chest.* 2016;150(1):148-163.
31. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med.* 1985;13(10):818-829.
32. Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. *JAMA.* 1993;270(24):2957-2963.
33. Miranda DR, de Rijk A, Schaufeli W. Simplified Therapeutic Intervention Scoring System: the TISS-28 items--results from a multicenter study. *Crit Care Med.* 1996;24(1):64-73.
34. Moreno R, Morais P. Validation of the simplified therapeutic intervention scoring system on an independent database. *Intensive Care Med.* 1997;23(6):640-644.
35. Pedersen AB, Mikkelsen EM, Cronin-Fenton D, et al. Missing data and multiple imputation in clinical epidemiological research. *Clinical epidemiology.* 2017;9:157-166.
36. Petersen I, Welch CA, Nazareth I, et al. Health indicator recording in UK primary care electronic health records: key implications for handling missing data. *Clinical epidemiology.* 2019;11:157-167.
37. Stekhoven DJ, Buhlmann P. MissForest--non-parametric missing value imputation for mixed-type data. *Bioinformatics.* 2012;28(1):112-118.
38. Bursac Z, Gauss CH, Williams DK, Hosmer DW. Purposeful selection of variables in logistic regression. *Source code for biology and medicine.* 2008;3:17.
39. Hosmer Jr DW, Lemeshow S, Sturdivant RX. *Applied logistic regression.* Vol 398: John Wiley & Sons; 2013.
40. Zhang Z. Model building strategy for logistic regression: purposeful selection. *Annals of translational medicine.* 2016;4(6):111.
41. *gam: Generalized Additive Models. R package version 1.16* [computer program]. 2018.
42. Hastie T, Tibshirani R. Generalized additive models for medical research. *Stat Methods Med Res.* 1995;4(3):187-196.
43. Zhang Z, Castello A. Principal components analysis in clinical studies. *Annals of translational medicine.* 2017;5(17):351.

44. Wood SN. Fast stable restricted maximum likelihood and marginal likelihood estimation of semiparametric generalized linear models. *Journal of the Royal Statistical Society: Series B (Statistical Methodology).* 2011;73(1):3-36.
45. *R: A language and environment for statistical computing* [computer program]. Vienna, Austria: R Foundation for Statistical Computing; 2019.
46. *RStudio: Integrated Development for R.* [computer program]. Boston, MA: RStudio Inc.; 2015.
47. Banack HR, Stokes A. The 'obesity paradox' may not be a paradox at all. *Int J Obes (Lond).* 2017;41(8):1162-1163.
48. Hernan MA, Hernandez-Diaz S, Robins JM. A structural approach to selection bias. *Epidemiology.* 2004;15(5):615-625.
49. Perren A, Zurcher P, Schefold JC. Clinical Approaches to Assess Post-extubation Dysphagia (PED) in the Critically Ill. *Dysphagia.* 2019;34(4):475-486.

Table Legends

Table 1 **Demographics of extubated ICU patients.**

APACHE = Acute Physiology and Chronic Health Evaluation, BMI = Body Mass Index, ICU = Intensive Care Unit, IQR = Interquartile range, RRT = renal replacement therapy, d = days.

Median and 25-75th IQRs are given. APACHE II scores given for first 24 hours on the ICU. Between group p-values refer to Fisher's exact test [A] or Mann-Whitney-U-Test [B]. Significant p-values are shown in bold. Means are reported for cumulative Midazolam dose, and maximum and means are reported for Days on RRT (IQR = 0 due to a low number of RRT-treated patients). [1]mean = 21.7 mg, [2]mean = 18.8 mg; [3]max = 24.8 d, mean = 0.2 d; [4]max = 24.2 d, mean = 0.6 d; [5]max = 24.8 d, mean = 0.2 d. More information on baseline demographics is given elsewhere[1].

Table 2 **Regression models for Dysphagia Risk Factors.**

AIC = Akaike information criterion, AUROC = Area Under the Receiver Operating Characteristics, BMI = Body Mass Index, APACHE = Acute Physiology and Chronic Health Evaluation, ICU = Intensive Care Unit, RRT = Renal Replacement Therapy (please note limited number of subjects receiving RRT), GAM = Generalised Additive Model, OR = Odds Ratio, CI = Confidence Interval, LRT = Likelihood Ratio Test, W = Wald test (F-value).

AIC and AUROC are given (both models). Results of candidate risk factors for dysphagia after invasive mechanical ventilation analyzed using purposeful variable selection [38]. ORs indicate mean values. Smoothed splines were used

for fitting, in cases where the logit did not increase linearly with increasing values (tested with LRT). In (A): Age, APACHE II score, cumulative Propofol dose, cumulative Midazolam dose, days on gastric tube, days on invasive mech. ventilation, days on RRT, days in hospital and days in ICU. In (B): Age, APACHE II score, cumulative Midazolam dose, days on gastric tube, days on invasive mech. ventilation, days on RRT, days in hospital and days in ICU. In (C): Age, days on gastric tube, cumulative Midazolam dose, days on RRT. The ORs are mean values over the whole range. Nonlinear OR relationships are shown in e-Figure 5. (A) Simple logistic GAM, using a significance level of 0.2. (B) Multiple logistic GAM, including all candidate risk factors from (A) if $p < 0.2$. (C) Multiple logistic GAM, including all candidate risk factors from (B) with $p < 0.05$ as well as age, gender, BMI. Significant p-values given in bold.

Table 3 **Final Multiple Regression Model for Risk Factors in post-extubation dysphagia.**

AIC = Akaike Information Criterion, APACHE = Acute Physiology and Chronic Health Evaluation, AUROC = Area Under the Receiver Operating Characteristics, BMI = Body Mass Index, CI = Confidence Interval GAM = Generalised Additive Model, OR = Odds Ratio, RRT = Renal Replacement Therapy.

Significant variables are identified risk factors by the GAM logistic model. Variables were selected with purposeful variable selection[38] and representative variables were chosen for each cross-correlated group of variables. Positive ORs indicate enhanced dysphagia risk with increasing values of the respective

variable or presence of the variable category given in brackets. Smoothed splines were used for fitting in cases where the logit did not increase linearly with increasing values (tested with LRT), which applied to Age, APACHE II score, days on invasive mechanical ventilation, days on RRT. Respective ORs are mean values over whole range. Significant p-values given in bold. AIC = 584, AUROC = 0.88. [1] n=47 RRT treated patients.

Figure Legend

Figure 1 **Principal Components Analysis.**

APACHE = Acute Physiology and Chronic Health Evaluation, BMI = Body Mass Index, Cum. = cumulative, D. = days, ICU = Intensive Care Unit, inv. = invasive, PC = Principal Component, PCA = Principal Components Analysis, RRT = Renal Replacement Therapy.

PCA of the correlated cluster of variables days on RRT, days in hospital, cumulative Midazolam dose, days on ICU, days on gastric tube, days on invasive mechanical ventilation, cumulative Midazolam dose and APACHE II score. PCs 1 to 4 (A-C) are shown on horizontal and vertical axes. Based on PC 1 to 3 (explaining 70.25% of the variance), three groups of swappable variables were identified: (1) days on RRT, days in hospital and cumulative Midazolam dose, (2) days in ICU, days on gastric tube, days on invasive mechanical ventilation and cumulative Propofol dose and (3) APACHE II score. The first member of each group was selected as representative variable.

Table 1. Demographics of extubated ICU patients.

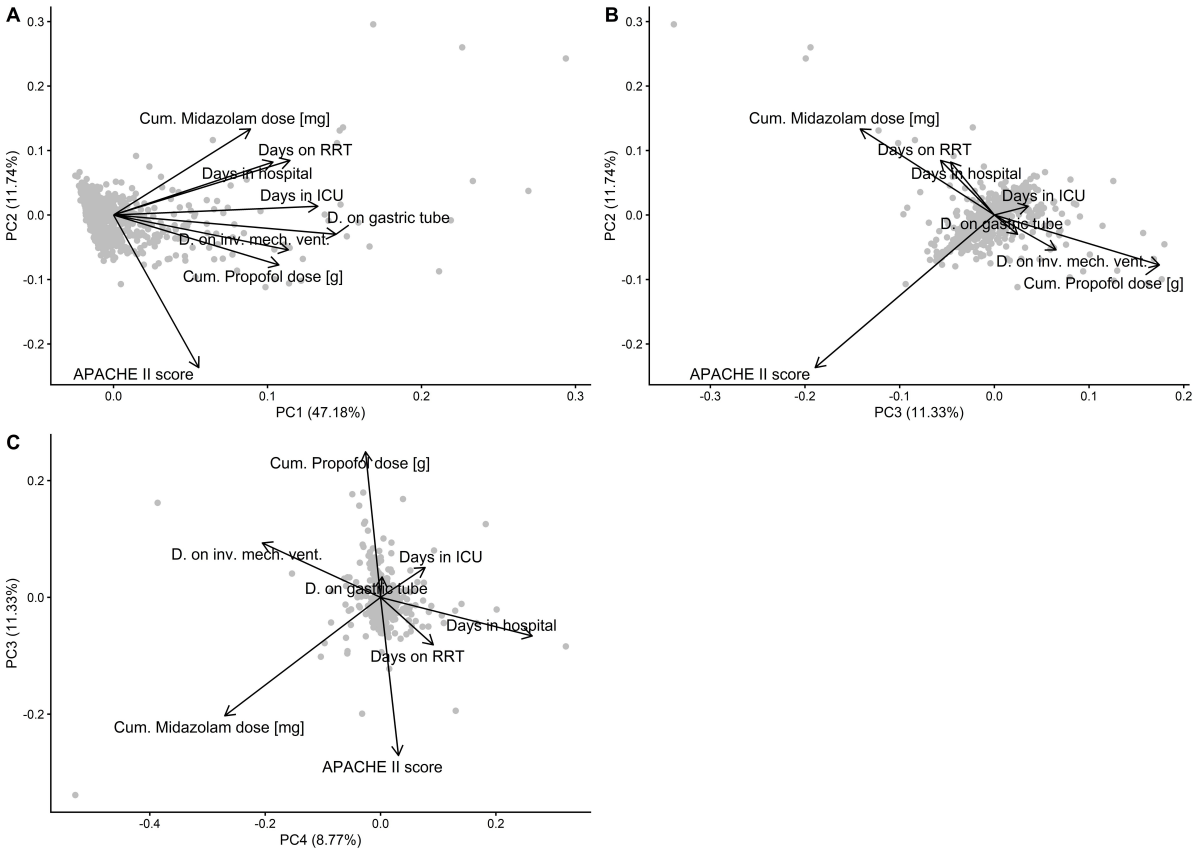
Variables	Total cohort, n = 933	Dysphagia screening positive, n = 116	Dysphagia screening negative, n = 817	between group p value
Age [years]	65 (54-73)	65 (50-77)	65 (55-73)	0.83 B
Gender [male n (%)]	666 (71)	80 (69)	586 (72)	0.58 A
BMI	26 (24-29)	26 (24-28)	26 (24-29)	0.10 B
APACHE II score	18 (14-24)	22 (18-26)	18 (14-23)	< 0.01 B
Admission type [emergency n (%)]	525 (56)	96 (83)	429 (53)	< 0.01 A
APACHE IV admission category: neurologic disease [yes n (%)]	147 (16)	47 (41)	100 (12)	< 0.01 A
Cumulative Propofol dose [g] (admission until completed screening)	1.1 (0.5-2.3)	1.6 (0.5-4.6)	1.1 (0.5-2.2)	0.01 B
Cumulative Midazolam dose [g] (admission until completed screening)	0 (0-6) [1]	1 (0-15)	0 (0-4) [2]	< 0.01 B
Days on gastric tube (admission until completed screening)	0.6 (0.4-1.2)	1.7 (0.7-3.7)	0.5 (0.3-1)	< 0.01 B
Days on invasive mechanical ventilation (admission until completed screening)	0.7 (0.5-1.2)	1.2 (0.6- 3.2)	0.7 (0.5-1.1)	< 0.01 B
Days on Renal Replacement Therapy (RRT) (admission until completed screening)	0 (0-0) [3]	0 (0-0) [4]	0 (0-0) [5]	< 0.01 B
Days in hospital (admission until completed screening)	1.9 (1.4-4.2)	2.9 (1.4-5.6)	1.9 (1.4-4)	< 0.01 B
Days in ICU (admission until completed screening)	0.7 (0.5-1.6)	1.8 (0.8-3.9)	0.6 (0.4-1.2)	< 0.01 B

Table 2. Regression Models for Dysphagia Risk Factors.

	Simple regression (A)			Multiple regression (B) p<0.2 in A AIC = 555.41, AUROC = 0.88			Multiple regression (C) p<0.05 in B AIC =555.25 , AUROC = 0.88		
Variables	**OR (95% CI)**	**p**	**W**	**OR (95% CI)**	**p**	**W**	**OR (95% CI)**	**p**	**W**
Age [years]	1 (0.99-1.01)	0.82	0.05	1 (0.99-1.02)	0.13	2.29	1 (0.99-1.02)	0.13	2.29
Gender (male)	0.88 (0.57-1.34)	0.54	0.38	1.22 (0.74-2)	0.61	0.26	1.32 (0.8 2.15)	0.77	0.08
BMI	0.96 (0.92-1)	0.06	3.56	0.95 (0.9-1)	0.23	1.47	0.95 (0.9-1)	0.23	1.45
APACHE II score	1.08 (1.04-1.11)	<0.01	20.43	1.03 (0.99-1.07)	<0.01	14.94	1.03 (0.99-1.07)	<0.01	14.31
Admission type (emergency)	4.34 (2.63-7.16)	<0.01	32.93	1.75 (0.95-3.2)	<0.01	14.29	1.87 (1.04-3.36)	<0.01	14.8
APACHE IV admission cat.: neurologic disease (yes)	4.88 (3.19-7.47)	<0.01	53.25	4.14 (2.48-6.91)	<0.01	33.77	4.01 (2.43-6.62)	<0.01	33
Cumulative Propofol dose [g] (admission until completed screening)	1.05 (1.02-1.09)	<0.01	10.14	1 (0.96-1.05)	<0.01	18.67	0.99 (0.95-1.03)	<0.01	12.6
Cumulative Midazolam dose [g] (admission until completed screening)	1 (1-1.01)	<0.01	9.89	1 (1-1)	<0.01	9.68	1 (1-1)	<0.01	18.62
Days on gastric tube (admission until completed screening)	1.3 (1.19-1.42)	<0.01	37.55	1.53 (1.12-2.09)	<0.01	39.83	1.31 (1.13-1.53)	<0.01	19.83
Days on invasive mech. ventilation (admission until completed screening)	1.28 (1.16-1.4)	<0.01	25.34	0.95 (0.75-1.21)	0.43	0.62	-	-	-
Days on RRT (admission until completed screening)	1.09 (1.01-1.19)	0.04	4.33	1.29 (1-1.66)	0.02	5.52	1.12 (0.93-1.36)	0.15	2.04
Days in hospital (admission until completed screening)	1.03 (1-1.06)	0.06	3.6	0.99 (0.94-1.04)	0.53	0.4	-	-	-
Days in ICU (admission until completed screening)	1.13 (1.06-1.2)	<0.01	16.71	0.97 (0.71-1.31)	0.78	0.08	-	-	-

Table 3. Final Multiple Regression Model for Risk Factors in post-extubation dysphagia.

Selected variables	OR (95% CI)	p-value	Wald
Age (years)	1 (0.99-1.02)	0.35	0.86
Gender (male)	1.29 (0.8-2.08)	0.98	0
BMI	0.94 (0.9-0.99)	0.01	6.6
APACHE II score	1.03 (0.99-1.07)	<0.01	9.2
Admission type (emergency)	2.04 (1.15-3.59)	<0.01	8.23
APACHE IV admission category: neurologic disease (yes)	4.45 (2.74-7.24)	<0.01	63.89
Days on invasive mechanical ventilation (admission until completed screening)	1.19 (1.06-1.34)	<0.01	14.75
Days on RRT [1] (admission until completed screening)	1.1 (1-1.23)	0.03	4.79


A
Cum. Midazolam dose [mg]
Days on RRT
Days in hospital
Days in ICU
D. on gastric tube
D. on inv. mech. vent.
Cum. Propofol dose [g]
APACHE II score
PC2 (11.74%)
PC1 (47.18%)
B
Cum. Midazolam dose [mg]
Days on RRT
Days in hospital
Days in ICU
D. on gastric tube
D. on inv. mech. vent.
Cum. Propofol dose [g]
APACHE II score
PC2 (11.74%)
PC3 (11.33%)
C
Cum. Propofol dose [g]
D. on inv. mech. vent.
Days in ICU
D. on gastric tube
Days in hospital
Days on RRT
Cum. Midazolam dose [mg]
APACHE II score
PC3 (11.33%)
PC4 (8.77%)