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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

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1 **Risk factors for dysphagia in ICU patients following invasive mechanical ventilation**

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3 Patrick Zuercher MD, Noëlle V. Schenk, Céline Moret MD, David Berger MD, Roman

4 Abegglen, Joerg C. Schefold MD

5

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

7 Switzerland

8

✉ 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](https://orcid.org/0000-0003-0331-4577)

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1

2 **Abbreviation List**

3 ICU Intensive Care Unit

4 DYnAMICS Dysphagia in Mechanically Ventilated ICU Patients

5 IQR Interquartile Range

6 OR Odds Ratio

7 APACHE Acute Physiology And Chronic Health Evaluation

8 BMI Bod Mass Index

9 COPD Chronic Obstructive Pulmonary Disease

10 CVA Cerebrovascular Accident

11 NYHA New York Heart Association

12 SOFA Sequential Organ Failure Assessment

13 KEK Kantonale Ethikkommission (regional ethics committee)

14 WST Water Swallow Test

15 SAPS Simplified Acute Physiology Score

16 TISS-28 Therapeutic Intervention Scoring System (TISS)-28 points

17 RRT Renal Replacement Therapy

18 OOB Out-Of-Bag Error

19 GAM Generalized Additive Model

20 LRT Likelihood Ratio Test

21 PC(A) Principal Component (Analysis)

22 AUROC Area Under the Receiver Operating Characteristics

23 AIC Akaike Information Criterion

24 FEES Flexible Endoscopic Evaluation of Swallowing

25 VFSS Videofluoroscopic Swallowing Study

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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

- 1 dysphagia, systematic screening for dysphagia is recommended in respective critically ill
- 2 patients.
- 3 **Clinical Trial Registration:** clinicaltrials.gov (NCT 02333201)

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1 Introduction

2 Data from mixed adult ICU patients show that post-extubation dysphagia is commonly
3 observed on the ICU, mostly persists until hospital discharge, and is an independent predictor
4 of 28- and 90-day mortality after adjustment for typical confounders (excess 90-day mortality
5 9.2%)¹.

6 Available data on risk factors leading to post-extubation dysphagia are conflicting. In
7 smaller heterogeneous patient cohorts, investigating mostly patients post-dysphagia-
8 associated complications (e.g. aspiration-induced pneumonia), duration of intubation was
9 often proposed²⁻¹⁴. Further, in respective earlier studies with mostly limited sample sizes,
10 advanced age^{3,5,10,13}, sepsis^{13,15}, perioperative trans-oesophageal echocardiography^{5,11},
11 previous stroke^{2,11} or tracheostomy¹⁶, and presence of gastroesophageal reflux^{4,17} were
12 proposed associated with development of dysphagia. Despite these observations, Acute
13 Physiology and Chronic Health Evaluation (APACHE)-II scores^{4,16,18,19}, Body Mass Index
14 (BMI)^{4,16,18}, gender^{2,4,5,12,16,18,20,21}, specific comorbidities such as diabetes^{2,5,8,9,13,22},
15 hypertension^{2,5,13,23}, COPD^{5,8,9,22}, pre-existing renal dysfunction^{2,5,13}, myocardial
16 infarction^{2,5,8,9,13}, heart failure^{8,9,13,24}, preoperative/ history of cerebrovascular accidents
17 (CVA)^{2,5,8,23,24}, NYHA >2^{2,23}, smoking^{2,13}, SOFA scores^{4,8,9,18,24} and/or endotracheal tube
18 size^{8,9,20,24} were refuted in most investigations. Moreover, investigations on specific drugs/
19 medications, e.g. analgesia, and/or vasoactive medication are scarce and show
20 contradictory findings^{2,13}. Importantly, as stated above, data on risk factors in critically ill
21 patients mostly derive from smaller studies, analyzing mostly selective patient cohorts,
22 without systematic screening for dysphagia and often including patients with clinically overt
23 dysphagia-associated complications¹⁴.

24 Identification of potentially modifiable risk factors leading to development of post-
25 extubation dysphagia seems pivotal¹⁴. The risk for dysphagia could ideally be reduced or its
26 course modified, resulting in improved clinical outcomes. Importantly, screening for

1 dysphagia is not yet considered standard of care in most ICUs^{25,26}, likely due to restraints in
2 resources. Further, identification of risk factors for dysphagia may provide the basis for risk-
3 based (i.e. targeted) screening approaches. As post-extubation dysphagia appears an under-
4 recognized health care problem^{14,25} with considerable impact on clinical outcomes¹, we
5 embarked to identify risk factors for post-extubation dysphagia in a large cohort of mixed
6 medical-surgical adult ICU patients.

1 **Methods**

2 Patients and analysis design

3 Post-hoc analysis of data collected in the prospective observational study (“Dysphagia in
4 Mechanically Ventilated ICU Patients, DYnAMICS”) performed from April 2015 until
5 October 2015 in a 900+ bed tertiary care academic medical centre (Inselspital, Bern
6 University Hospital, University of Bern, Switzerland)¹. The centre treats all medical and
7 surgical critically ill patients in our institution and is the sole provider for adult intensive care
8 in our University Hospital. In DYnAMICS¹, a mixed medical/surgical patient cohort (defined
9 using the APACHE IV diagnostic criteria) were systematically screened for dysphagia using
10 the two-step Bernese ICU Dysphagia algorithm^{1,14,27,28}. In brief, in this standardized two-step
11 approach, an initial bedside screening was performed within 3 hours of extubation by trained
12 ICU nurses unless any of the following exclusion criteria were met: 1) patients dying/on
13 comfort therapy and/or 2) patients with recent oesophageal injury and/or esophageal surgery¹.
14 All patients extubated or decannulated after invasive mechanical ventilation were included.
15 Prerequisite for extubation were stable gas exchange/hemodynamics with moderate pressure
16 support and positive end-expiratory pressure, responsive to commands, and presumed ability
17 to protect the airway¹. The study was performed in accordance with the “Declaration of
18 Helsinki” and approved by the Kantonale Ethikkommission, KEK, Bern, Switzerland (KEK
19 Nr. 314/2014).

20

21 Dysphagia diagnosis

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

1 (physiotherapist or speech language therapist) and patients were followed-up until hospital
2 discharge. WST could be replaced by specialist examinations on clinical indications (e.g. in
3 cases of overt severe dysphagia). Full details are given elsewhere¹.

4

5 Assessment of disease severity, and ICU resource use

6 For assessment of disease severity, baseline Acute Physiology and Chronic Health Evaluation
7 (APACHE)-II scores³¹ and Simplified Acute Physiology Score (SAPS)-II scores³² were
8 recorded. ICU resource use was assessed by analysis of the sum of Therapeutic Intervention
9 Scoring System (TISS)-28 points (recorded once per shift over ICU stay)^{33,34}. Days on
10 (invasive) mechanical ventilation, need for gastric tube feeding, days on antibiotics/
11 antimicrobials, days on vasopressors and sedatives, and need for renal replacement therapy
12 (RRT) were recorded¹.

1 Statistical Analyses

2 In accordance to current recommendations in medical research^{35,36}, missing values were
3 imputed with multiple imputation, using a random forest algorithm³⁷. Missing values were
4 replaced with the mean of 50 independent imputations. Variables with a per-variable
5 imputation error (out-of-bag error, OOB) exceeding 0.2 (20%) were excluded. The
6 recommendations for purposeful variable selection were followed³⁸⁻⁴⁰, see detailed description
7 in Supplement (e-Appendix E1). In brief, a Generalized Additive Model (GAM) was used, as
8 this model does not rely on the linearity assumption that applies to logistic models^{41,42}. The
9 need for smoothing splines for each variable was checked individually using likelihood ratio
10 tests (LRT). $p < 0.2$ was used as threshold from simple to multiple regression. In order to avoid
11 multi-collinearity, representative variables were selected with Principal Component Analysis
12 (PCA)⁴³ and concurvity was assessed⁴⁴. PCA visualizes associations between multiple
13 variables and is used to reduce dimensionality by cluster formation, addressing multi-
14 collinearity. Multi-collinearity was considered inherent for parts of the data (e.g. invasive
15 mechanical ventilation typically paralleled by gastric tube placement). Per cluster of
16 correlated variables, a representative of each group was selected based on clinical criteria with
17 other members excluded. The adequacy of the resulting model was assessed using Area Under
18 the Receiver Operating Characteristics (AUROC) and Hosmer-Lemeshow tests. The final
19 model was validated using k-fold cross-validation (k = 500 iterations, test set of 5 %).
20 Sensitivity analyses, A) When limiting the dataset to shorter length of mechanical ventilation,
21 we chose the day where the model predicted an OR of 1 (at 4.85 days). Changes in the model
22 when limiting the dataset to this threshold were tested, and B) the robustness of respective
23 odds ratios (OR) against swaps of representative variables were measured, in an effort to
24 investigate the behaviour of all individual group members to confirm grouping and C)
25 APACHE II was replaced with SAPS II scores and D) elective patients were excluded. All
26 statistical analyses were performed using R, version 3.6.1⁴⁵, and Rstudio version 1.2.5001⁴⁶.

1 **Results**

2 Patient demographics

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

8 Outlier detection and missing value imputation

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

13 Variable selection

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

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

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

7
8 The resulting final model refuted concurvity >0.8 (data not shown, final model in Table 3,
9 AUROC 0.88, AIC 583.84, Hosmer-Lemeshow test proving no significant difference between
10 observed and predicted values). Although LRT indicated better fitness and AIC was lower in
11 the full model (Table 2B), the final model was kept, based lower risk of co-linearity. Cross-
12 validation reported an accuracy of 0.86, with a false-positive rate of 0.03 and a false-negative
13 rate of 0.11 with an accuracy of $>70\%$ for 499 of 500 predictions (e-Figure 3).

14 15 Risk factors for dysphagia on the ICU

16 In the final model (Table 3), the following risk factors for dysphagia were identified: baseline
17 neurologic disease (OR 4.45, 95%-CI: 2.74-7.24, $p<0.01$), emergency admission (OR 2.04,
18 95%-CI: 0.99-1.07, $p<0.01$), days on invasive mechanical ventilation (OR 1.19, 95%-CI:
19 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
20 (OR 1.03, 95%-CI: 0.99-1.07, $p<0.01$). Of note, when APACHE II was replaced by SAPS II
21 score, SAPS-II score was not a risk factor ($p=0.06$) (e-Table 1C). CIs for ORs cross 1 for
22 emergency admission, days on RRT and APACHE II, because they correspond to Wald type
23 CI approximations. Exact CIs were only available pointwise, as shown in e-Figure 4. Per
24 stepwise increase in BMI, the risk for dysphagia declined by 6% (OR 0.94, 95%CI: 0.9-0.99,
25 $p=0.01$). Days on mechanical ventilation, days on RRT, APACHE II score and age were fitted
26 with non-linear smoothed functions. The OR followed a flat humpbacked-shaped curve with a

1 peak at 4.85 days (regarding days on mechanical ventilation) and 12.1 days (regarding days
2 on RRT), respectively (e-Figures 4A, 4B). The first day of mechanical ventilation increased
3 the risk by 98%, with a moderate decrease in the ensuing days: at 4.85 days, the OR was 1,
4 with a potential decrease/ saturation thereafter (note 95%-CI, n=56 after day 5) (e-Figure 4A).
5 47 patients, i.e. about 5% of the total cohort of patients, were treated with RRT. During the
6 first 5 days, patients on RRT had an increased risk for dysphagia per additional RRT day by
7 20-25%. During the ensuing days, the additional risk potentially decreased with each day of
8 additional therapy (e-Figure 4B). However, this was accompanied by a large reduction in
9 sample size of RRT treated patients. Regarding APACHE II scores, it appeared that the OR
10 within the 0.25-0.5-quantile (14-18) was rather high at about 12% for each additional score
11 point (e-Figure 4C). The non-linear relationship of age with respective logits is indicated, two
12 age groups of opposite risk with increasing age were identified (e-Figure 4D). When BMI was
13 classified according to the WHO grading system, dysphagia incidence moderately increased
14 from obesity class II on (lower sample size at extreme ends; data not shown).

15

16 Sensitivity analysis

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

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

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

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

1 Discussion

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

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

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

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

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

15 Our analysis has several limitations that deserve discussion. First, our findings result
16 from a post-hoc analysis of a larger monocentric study¹ and the assessment was not stratified
17 to accommodate various specific underlying diseases. Although a considerable number of
18 ICU patients was systematically screened for post-extubation dysphagia, our data await
19 confirmation in additional centres. Nevertheless, we are convinced that the cohort under
20 investigation reflects a typical population of (mixed) medical-surgical ICU patients post
21 mechanical ventilation. Second, assessment for dysphagia was confirmed by dysphagia
22 specialists using clinical measures⁴⁹, which should ideally have been confirmed by
23 instrumental techniques to improve specificity (e.g. by flexible endoscopic evaluation of
24 swallowing (FEES) or videofluoroscopic swallowing studies (VFSS)). However, we used a
25 feasible two-step dysphagia algorithm (the Bernese ICU dysphagia algorithm) as a pragmatic
26 and rapidly available bedside tool for dysphagia assessment in the ICU¹⁴. Third, due to study

1 design, we present associations rather than cause-effect relationships and we are unable to
2 conclude on underlying pathomechanisms leading to dysphagia. Fourth, initial disease
3 severity was higher in patients diagnosed with dysphagia (Table 1) and one might
4 theoretically argue that dysphagia could simply be a consequence of increased disease
5 severity. After adjustment, however, only moderate or no effects of disease severity (reflected
6 by clinical scores) were observed. Fifth, data collinearity was tested and variables selected
7 integrating both mathematical and medical considerations. Collinearities may be inherent in
8 comprehensive data and could be considered typical in this clinical scenario. Sixth,
9 confidence intervals for odds ratios crossed or touched 1 in some parameters. This occurred in
10 the context of approximated confidence intervals, since exact confidence intervals were only
11 available pointwise (e-Figure 5). Methods for exact simultaneous confidence interval
12 calculation are not yet available for the applied nonparametric method⁴¹. Seventh, patients
13 were not assessed for baseline swallowing disorder prior to ICU admission. Eighth, the 3-hour
14 time limit for the first dysphagia assessment (with a repeat assessment if required) could be
15 viewed as somewhat arbitrary. However, an early structured risk assessment was deliberately
16 aimed for. Ninth, disease severity scores were assessed at admission and not on a daily basis.
17 Although longitudinal risk modeling might have been favorable, most ICU severity scores are
18 not validated for such an approach. Tenth, and importantly, we were unable to identify clearly
19 modifiable risk factors. Nevertheless, our data underline that e.g. duration of mechanical
20 ventilation should be kept as short as possible, e.g. using dedicated sedation protocols.

21

22 **Interpretation**

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

- 1 mechanical ventilation should be considered at risk for dysphagia, systematic screening for
- 2 dysphagia is recommended in respective critically ill patients.
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23

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1 **Table Legends**

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

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

6
7 Median and 25-75th IQRs are given. APACHE II scores given for first 24 hours
8 on the ICU. Between group p-values refer to Fisher's exact test ^A or Mann-
9 Whitney-U-Test ^B. Significant p-values are shown in bold. Means are reported
10 for cumulative Midazolam dose, and maximum and means are reported for
11 Days on RRT (IQR = 0 due to a low number of RRT-treated patients). ¹mean
12 = 21.7 mg, ²mean = 18.8 mg; ³max = 24.8 d, mean = 0.2 d; ⁴max = 24.2 d,
13 mean = 0.6 d; ⁵max = 24.8 d, mean = 0.2 d. More information on baseline
14 demographics is given elsewhere¹.

15
16 **Table 2 Regression models for Dysphagia Risk Factors.**

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

23
24 AIC and AUROC are given (both models). Results of candidate risk factors for
25 dysphagia after invasive mechanical ventilation analyzed using purposeful
26 variable selection ³⁸. ORs indicate mean values. Smoothed splines were used

1 for fitting, in cases where the logit did not increase linearly with increasing
 2 values (tested with LRT). In (A): Age, APACHE II score, cumulative Propofol
 3 dose, cumulative Midazolam dose, days on gastric tube, days on invasive
 4 mech. ventilation, days on RRT, days in hospital and days in ICU. In (B): Age,
 5 APACHE II score, cumulative Midazolam dose, days on gastric tube, days on
 6 invasive mech. ventilation, days on RRT, days in hospital and days in ICU. In
 7 (C): Age, days on gastric tube, cumulative Midazolam dose, days on RRT. The
 8 ORs are mean values over the whole range. Nonlinear OR relationships are
 9 shown in e-Figure 5. (A) Simple logistic GAM, using a significance level of
 10 0.2. (B) Multiple logistic GAM, including all candidate risk factors from (A) if
 11 $p < 0.2$. (C) Multiple logistic GAM, including all candidate risk factors from
 12 (B) with $p < 0.05$ as well as age, gender, BMI. Significant p-values given in
 13 bold.

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

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

22
 23 Significant variables are identified risk factors by the GAM logistic model.
 24 Variables were selected with purposeful variable selection³⁸ and representative
 25 variables were chosen for each cross-correlated group of variables. Positive
 26 ORs indicate enhanced dysphagia risk with increasing values of the respective

1 variable or presence of the variable category given in brackets. Smoothed
2 splines were used for fitting in cases where the logit did not increase linearly
3 with increasing values (tested with LRT), which applied to Age, APACHE II
4 score, days on invasive mechanical ventilation, days on RRT. Respective ORs
5 are mean values over whole range. Significant p-values given in bold. AIC =
6 584, AUROC = 0.88. ¹ n=47 RRT treated patients.

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1 **Figure Legend**

2

3 **Figure 1 Principal Components Analysis.**

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

8

9 PCA of the correlated cluster of variables days on RRT, days in hospital,
10 cumulative Midazolam dose, days on ICU, days on gastric tube, days on
11 invasive mechanical ventilation, cumulative Midazolam dose and APACHE II
12 score. PCs 1 to 4 (A-C) are shown on horizontal and vertical axes. Based on
13 PC 1 to 3 (explaining 70.25% of the variance), three groups of swappable
14 variables were identified: (1) days on RRT, days in hospital and cumulative
15 Midazolam dose, (2) days in ICU, days on gastric tube, days on invasive
16 mechanical ventilation and cumulative Propofol dose and (3) APACHE II
17 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.

Variables	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		
	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 [†] (admission until completed screening)	1.1 (1-1.23)	0.03	4.79

