Assessment of the role of the Edinburgh dysphagia score in referral triage in a national service evaluation of the urgent suspected upper gastrointestinal cancer pathway

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DOI:
10.1111/apt.16811

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Funding declaration

Nothing to declare.

Conflicts of Interests:

No conflict of interest.

Author contributions:

Study concept and design was jointly conceived by UK, DK and NT. All co-authors participated in data collection. UK and NA analysed the data. UK and NT drafted manuscript and it was critically revised and approved by all authors.

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The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

Word count

Main document 2720

Summary

Background

The British Society of Gastroenterology has recommended the Edinburgh Dysphagia Score (EDS) to risk stratify dysphagia referrals during the endoscopy COVID recovery phase.

Aims

External validation of the diagnostic accuracy of EDS and exploration of potential changes to improve its diagnostic performance.

Methods

A prospective multicentre study of consecutive patients referred with dysphagia on an urgent suspected upper gastrointestinal (UGI) cancer pathway between May 2020 and February 2021. The sensitivity and negative predictive value (NPV) of EDS were calculated. Variables associated with UGI cancer were identified by forward stepwise logistic regression and a modified Cancer Dysphagia Score (CDS) developed.

Results

1301 patients were included from 19 endoscopy providers; 43% male; median age 62(IQR 51-73) years. 91(7%) UGI cancers were diagnosed, including 80 oesophageal, 10 gastric and one duodenal cancer. An EDS ≥3.5 had a sensitivity of 96.7(95% CI 90.7-99.3)% and a NPV of 99.3(97.8-99.8)%. Age, male sex, progressive dysphagia and unintentional weight loss >3kg were positively associated and acid reflux and localisation to the neck were negatively associated with UGI cancer. Dysphagia duration <6 months utilised in EDS was replaced with progressive dysphagia in CDS. CDS ≥5.5 had a sensitivity of 97.8(92.3-99.7)% and NPV of 99.5(98.1-99.9)%. Area under receiver operating curve was 0.83 for CDS, compared to 0.81 for EDS.

Conclusions

128 In a national cohort, the EDS has high sensitivity and NPV as a triage tool for UGI cancer. The CDS
129 offers even higher diagnostic accuracy. The EDS or CDS should be incorporated into urgent
130 suspected UGI cancer pathway.
131
132

Introduction

Around 16,000 patients are diagnosed with upper gastrointestinal (UGI) cancer each year in the UK.[1,2] UGI cancer often has a poor prognosis with only 17% and 21% surviving for 5 years after an oesophageal and gastric cancer diagnosis respectively.[3] In the UK, patients suspected of having UGI cancer are referred on an urgent suspected cancer two week wait (2WW) pathway, direct to endoscopy or an outpatient clinic. In 2018/19, 190,000 patients were referred on the UGI 2WW pathway in the UK[4], but only 3% were actually diagnosed with cancer.[5] Dysphagia is an important predictor of UGI cancer[6,7] and the National Institute for Health and Care Excellence (NICE) in the UK recommends that direct, open access UGI endoscopy should be offered to all patients with dysphagia within two weeks.[8] However, it has been reported that up to 15% of patients referred with dysphagia in the UK do not have actual difficulty swallowing and less than 10% are diagnosed with UGI cancer.[9] This results in significant pressures on endoscopy services to achieve these national waiting time targets and may delay UGI cancer diagnosis in patients investigated outside the 2WW pathway.

During the first wave of the COVID-19 pandemic in the UK in April 2019, the British Society of Gastroenterology (BSG) recommended that all 2WW referrals should be triaged by senior clinicians and the Edinburgh dysphagia score (EDS) used to prioritise patients with dysphagia for urgent endoscopy.[5] The EDS was devised in 2010 for risk stratification of patients with symptoms of dysphagia, with those with an EDS ≥3.5 at higher risk of oesophageal cancer.[10] Predictors of oesophageal cancer included age, sex, unintentional weight loss > 3kg, localisation to the neck, duration of symptoms and reflux symptoms. The EDS was further validated in a single centre study of 1775 patients and reported to have a sensitivity of 98.4% and negative predictive value of 98.0%.[11]

We conducted a national service evaluation of the UGI cancer 2WW referral pathway during the recovery phase of COVID-19 and prospectively validated EDS performance in a cohort of patients referred with dysphagia.

Methodology

Study population and data collection

This study included consecutive adult patients referred with symptoms of dysphagia on a 2WW UGI cancer pathway, to the 19 participating providers across the UK, between May 2020 and February 2021. All referrals were triaged on the telephone by consultant gastroenterologists, consultant UGI surgeons, nurse endoscopists or clinical nurse specialists in UGI cancer or endoscopy. A standardised anonymised data collection tool on a Microsoft Excel spreadsheet was used by all providers, which allowed automatic calculation of the EDS and included a decision aid to guide prioritisation of endoscopy or alternate investigations if no endoscopy capacity, based on the BSG recovery document.[5] Data on additional clinically relevant variables identified from a literature search were also collected.[11,12] Variables included patient demographics (age, sex, smoking status), symptoms (dysphagia or odynophagia, duration of dysphagia >6 months, localisation of dysphagia to neck, progressive or intermittent symptoms of dysphagia, unintentional weight loss >3kg and reflux symptoms). Data on triage decision details and investigation results was also recorded.

Referrals were triaged to one of the following pathways: EDS ≥3.5- 2WW endoscopy; EDS < 3.5 and patient age >55 years- urgent (non 2WW) endoscopy; EDS < 3.5 and patient age <55 years- routine endoscopy; and no investigation if no true dysphagia or other indication for investigations. Alternative investigations included CT scan and barium swallow.

Exclusion criteria included: patients not referred with symptoms of dysphagia, if investigations were declined by patients, if patients were not fit for any investigation, if patients did not have true dysphagia or other symptoms worthy investigation, if investigation results not available on 28th February 2021 and if a non-UGI cancer was diagnosed.

Aims

190 The primary aims of this study were to validate the diagnostic accuracy of EDS and to assess if
191 any amendments could potentially improve its diagnostic performance, using patient variables
192 associated with UGI cancer.
193
194 **Statistical analysis and development of cancer dysphagia score**
195 Statistical analysis was performed using *Stata Statistical Software Release 16*: StataCorpLLC.
196 Categorical variables were summarised as number and percentages and continuous variables as
197 median and interquartile range (IQR). The $\chi 2$ test was used to compare categorical variables and
198 the t-test or nonparametric test (Mann-Whitney U) were used to compare continuous variables
199 as appropriate. The sensitivity, specificity, positive predictive value (PPV) and negative predictive
200 value (NPV) of EDS at a cut off of ≥3.5 were calculated.
201
202 Univariable and multivariable logistic regression models explored the association of study
203 variables with an UGI cancer diagnosis. The dependent variable was the occurrence of UGI cancer
204 and the exploratory variables included age as a continuous variable and sex, unintentional weight
205 loss >3kg, localisation of dysphagia to neck, progressive dysphagia, presence of reflux symptoms,
206 history of smoking and duration of symptoms of <6months as categorical variables. The variables
207 with statistical significance on univariate analysis were included in multivariable analysis. Missing
208 data were treated as complete case analysis and any observation with a missing value for the
209 variable of interest was excluded and only complete observations were included in the logistic
210 regression analysis.
211
212 To develop a modified prediction model, candidate variables were selected using a forward
213 stepwise regression approach. Forward stepwise regression is a method of fitting regression
214 models in which the choice of predictive variables is carried out by an automatic procedure.
215 Starting with no variables in the model, the addition of each variable using a chosen model fit
216 criterion ($p<0.1$) is tested, adding the variable whose inclusion gives the most statistically
217 significant improvement of the fit, and repeating this process until none improves the model to
218 a statistically significant extent. The model was internally validated by bootstrap resampling,

219 which used 1000 random samples drawn with replacement from the original dataset.[13,14]
220 Regression coefficients of the selected variables from multivariable logistic regression analysis
221 were used to develop a scoring system following the methodology described by Sullivan et al.[15]
222 and explained in supplementary material 1.
223
224 Receiver operating characteristic (ROC) curves were produced for both the EDS and the modified
225 prediction model and the discriminative ability of both models was compared using the area
226 under receiver operating curve (AUC), equivalent to *c*-statistics. Calibration plots were produced
227 to examine the performance of the models, displaying observed probability by deciles of
228 predicted probability. LOWESS (Locally weighted scatterplot smoothing) function was used to
229 create a smooth line through the scatter plot to display relationship between expected and
230 observed probabilities and foresee trends. Calibration slope gradient and calibration in the large
231 (CITL) were reported. Calibration slope close to 1 and CITL close to 0 represent good calibration.
232
233 Subgroup analyses were performed to compare the sensitivity of both scoring systems at age cut
234 offs of 70 and 60 years.
235
236 **Patient and public involvement**
237 There was no patient and public involvement in this study.
238
239 **Ethics**
240 As determined by the national decision-making tool of the NHS Health Research Authority and
241 the Medical Research Council, this study was part of a service evaluation and did not require
242 ethics committee approval. Each participating provider attained local institutional approval prior
243 to data collection.
244

245 ## Results

246 ### Study subjects

247 A total of 1301 patients were included from 19 providers across the UK. A flow chart of the
248 patients included in the study is shown in Figure 1. 69% (n=910) of patients were triaged to 2WW
249 endoscopy, 20% (n=257) to urgent (non 2WW) endoscopy, 5% (n=66) to routine endoscopy, 2%
250 (n=25) to CT scan and 3% (n=43) to barium swallow.
251
252 91 (7%) patients were diagnosed with UGI cancer, including 80 oesophageal, 10 gastric and one
253 duodenal cancer. Prevalence of UGI cancer in the patients triaged to 2WW endoscopy and urgent
254 (non 2WW) endoscopy was 9.2% and 2.3% respectively. One cancer was diagnosed in patients
255 triaged to Barium swallow (2.3%) and no UGI cancer was diagnosed in patients triaged to routine
256 endoscopy or CT scan. The baseline characteristics and the symptoms of patients with and
257 without an UGI cancer diagnosis are shown in Table 1. Patients with UGI cancer were more
258 commonly male and reported more often progressive symptoms, a history of unintentional
259 weight loss, less commonly had symptoms localised to the neck or reflux symptoms and had a
260 higher median EDS.
261

262 ### The diagnostic accuracy of the Edinburgh Dysphagia Score

263 An EDS ≥3.5 had a sensitivity of 96.7(95% CI 90.7-99.3)%, a specificity of 32.6(30.0-35.4)%, a PPV
264 of 9.7(7.9-11.9)% and a NPV of 99.3(97.8-99.8)%. 3(3%) UGI cancers were diagnosed in patients
265 with an EDS <3.5 (one gastric cancer with EDS 2.5, two oesophageal cancers with EDS 1.5). The
266 AUC for EDS was 0.81(0.76-0.85).
267

268 ### Univariable and multivariable logistic regression analysis of factors associated with
269 UGI cancer and development of a new Cancer Dysphagia Score

270 The results of univariable and multivariable regression analysis of factors associated with UGI
271 cancer are shown in Table 2. Increasing age, sex, unintentional weight loss > 3kg, localisation of
272 dysphagia to neck, progressive symptoms and reflux symptoms were associated with UGI cancer
273 and retained in the prediction model. However, duration of dysphagia <6 months and history of
274 smoking were excluded in forward stepwise selection regression analysis. Weighted points were

assigned proportional to the regression coefficient values of selected variables to develop the cancer dysphagia score (CDS), as explained in supplementary material 1. This had strong discriminative ability on internal validation, as measured by AUC (0.83(95% CI 0.79-0.87)).

A CDS cut off of ≥5.5 had a sensitivity of 97.8(92.3-99.7)%, a specificity of 31.2(28.7-34.0)%, a PPV of 9.7(7.8-11.8)% and NPV of 99.5(98.1-99.9)%. Two (2.2%) oesophageal cancers were diagnosed in patients with a CDS <5.5. Both patients were female (age <50 years) and presented with more than 6 months history of dysphagia without weight loss (CDS 2.0). One patient had associated symptoms of chest pain. Both were triaged to urgent endoscopy which was performed within a month of triage.

Comparison between the Edinburgh Dysphagia Score and the Cancer Dysphagia Score

The variables and points allocated to each of the risk categories for both EDS and CDS are presented in Table 3 and a comparison of the ROC curves and AUC is shown in Figure 2. The AUC for the CDS (0.829) is higher than the AUC for EDS (0.805). Calibration plots are presented in Figure 3. Slope gradients of 1.00 and CITL of 0.00 represent excellent performance for both models. When applied to the overall cohort, the prevalence of UGI cancer in high and low risk categories based on the CDS and EDS is shown in Table 4. The CDS is more sensitive than the EDS with less cancers in the low risk group, but this difference is only based on one UGI cancer that is high risk on the CDS but low risk on the EDS.

On subgroup analyses, sensitivity and NPV of CDS ≥5.5 and EDS ≥3.5 were 100% at the age cut off ≥70 years. However, CDS was more sensitive than EDS in identifying UGI cancer patients in those less than 70 years of age (CDS 94.59% vs EDS 91.89%) and in those less than 60 years of age (CDS 86.67% vs EDS 80%).

Discussion

Given the relatively low diagnostic yield (3%) of the current 2WW UGI cancer referral pathway in the UK and the pressures on endoscopy units given the COVID 19 pandemic and addressing consequent waiting issues, the availability of an effective triage tool will be of great value in prioritising patients for endoscopy. In this multicentre, prospective study, we have shown that the EDS and the updated CDS are just such triage tools with very high sensitivities and negative predictive values. Applying the CDS to the 2WW referral population studied, up to 30% of dysphagia referrals could have been safely investigated more routinely.

The EDS was initially developed to triage patients with dysphagia into high and low risk groups.[10] The prevalence of cancer in this study was 10% and 14% in the derivation and validation cohorts, respectively, and the AUC for the EDS was reported to be 0.70 in the validation cohort. However, this study had a number of limitations including a relatively small sample size, being from a single provider and retrospective. Finally, data were extracted from the primary care referral forms for both the derivation and validation of the EDS rather than from direct contact with the patient. An audit of dysphagia referrals to a district general hospital reported that up to 15% of patients referred on a cancer pathway did not have true dysphagia and relying on data from referral forms may therefore have limitations.[9] The present study is the largest prospective multicentre study of the EDS in 2WW referrals. Senior clinicians collected information directly from patients using a structured data collection tool during telephone triage. 5% of patients referred on the 2WW pathway did not have true swallowing difficulties or had a brief episode with spontaneous resolution of symptoms and hence did not require any investigation. Unlike the study that developed EDS[10], in the present study the duration of symptoms was not found to be associated with UGI cancer, and a strong positive association was found between UGI and progressive dysphagia. A single provider study of 2000 patients with dysphagia has also reported a positive association of progressive symptoms with UGI cancer [11]. Progressive dysphagia increased the odds of having UGI cancer more than two-fold and was therefore selected as a predictor in the updated CDS. The AUC for the CDS was 0.83 (compared to 0.81 for the EDS), with small improvements in sensitivity and NPV compared with EDS.

331 According to NICE recommendations in the UK, 2WW endoscopy should be offered to patients
332 of any age over 18 referred with dysphagia to exclude cancer.[8] However, dysphagia is a
333 common symptom in the community with a prevalence of up to 16% in the general
334 population[16,17], and despite it being considered an important "alarm" feature, only 2%-8% of
335 those referred with dysphagia for investigation are diagnosed with UGI cancer.[18–20] We found
336 that the CDS, at a threshold of ≥5.5, clearly identified a much higher risk group of patients with
337 dysphagia with a prevalence of UGI cancer of 9.7%. Although both CDS and EDS were highly
338 sensitive to detect UGI cancers in elderly patients over 70 years of age, the sensitivity of CDS was
339 higher in identifying the higher risk patients in younger age groups. However, two female patients
340 (age <50 years) were mis-categorised as low risk by both CDS and EDS and were found to have
341 oesophageal cancer. It is important that although high risk patients with EDS ≥3.5 (or CDS ≥5.5)
342 as a smaller cohort with a higher prevalence of cancer can be investigated more urgently within
343 two weeks, as recommended by the BSG and NHS England, patients at lower risk (but not zero
344 risk) of UGI cancer are safety netted in primary care and their investigation pathway should be
345 reviewed if their symptoms and CDS get worse.[21]
346
347 Although urgent investigation pathways for dysphagia are focused on cancer detection, there are
348 important non-malignant causes of dysphagia including eosinophilic oesophagitis, benign
349 oesophageal strictures and achalasia, which can have a major impact on patients' quality of life.
350 Although effective treatments are available for these conditions, such patients may not be
351 categorised as higher risk on risk stratification systems and there is a risk of delayed diagnoses
352 for those not investigated on an urgent pathway.
353
354 This study has a number of limitations. The absence of long term follow up data limited the ability
355 to assess the outcomes for a small number of patients (5%) who were triaged to no investigations
356 due to the absence of true dysphagia or a brief episode of symptoms which had spontaneously
357 resolved. During the pandemic it was not possible to endoscope such patients with clinically an
358 extremely low risk of UGI cancer. These patients were consequently excluded from the analysis
359 but it is possible that some might have re-presented with similar symptoms at a later date and

360 been diagnosed with UGI cancer. Although a standardised data collection tool was used to
361 prospectively collect information, clinical judgment was required to interpret the information
362 provided on the telephone by the patient bringing a risk of information or measurement bias.
363 Progressive dysphagia was found to be a predictor of UGI cancer and was used in the
364 development of the CDS, but this information was based on a patient's perception of worsening
365 in their swallowing since the start of their symptoms, rather than a functional grading system to
366 assess the severity of dysphagia. We suggest that future studies should consider using a validated
367 dysphagia grading system for consistency in the interpretation of progressive dysphagia. The data
368 for this study was collected directly from the patients by experienced clinicians over the
369 telephone. This was an important process to prioritise scarce endoscopy resources during the
370 first wave of the COVID 19 pandemic in the UK.[5] It has not been possible in UK hospitals to
371 continue to provide the clinical time for telephone triage of all 2WW referrals, given the partial
372 recovery of endoscopy services and competing demands on clinical time. There are still
373 considerable endoscopy diagnostic backlogs due to COVID throughout the UK and resource
374 prioritisation is still important. It has been proposed that the EDS is used by primary care
375 practitioners in England to prioritise referrals with dysphagia [21]. However, as previously noted,
376 primary care practitioners may be less able to accurately recognise dysphagia and other
377 symptoms as experienced gastroenterological clinicians [9] and the EDS or CDS should be studied
378 when utilised in primary care prior to referral for endoscopy to ensure it performs as well in this
379 setting as it does in secondary care telephone triage. This study was carried out during the
380 COVID19 pandemic and it is possible that primary care practitioners had a lower threshold for
381 referral on the 2WW pathway, given difficulty accessing secondary care opinions through other
382 routes. However, the overall cancer rate was 7% and this is similar to historic cancer rates for
383 2WW UGI cancer referrals.[22] Finally, although the CDS showed a high sensitivity and
384 discriminative ability on internal validation, it has not been externally validated.
385

386 **Conclusion**

387 In a multi-centre prospective evaluation of patients referred on an urgent cancer pathway from
388 primary care with dysphagia, the EDS had a high sensitivity and NPV as a triage tool for UGI

389 cancer. The sensitivity and NPV can be improved further in the CDS. The CDS or EDS should be
390 incorporated into the 2WW UGI cancer pathway to prioritise those at highest risk of cancer.
391

392 **Acknowledgement**
393 We are grateful to the Clinical Services and Standards Committee of the BSG for their support
394 and help promoting this service evaluation. We are also grateful to Sara Brogden (Lead Non-
395 medical Endoscopist, University College London Hospitals NHS Foundation Trust, United
396 Kingdom), Samantha Horley (Endoscopy Nurse Practitioner, The Dudley Group NHS Foundation
397 Trust, United Kingdom), Suzanne Friday (Advanced Nurse Practitioner, Upper Gastrointestinal
398 Cancer Nurse, Croydon Health Services NHS Trust, United Kingdom) and Tracey Noakes (Upper
399 Gastrointestinal Cancer Nurse Specialist, James Paget University Hospitals NHS Foundation
400 Trust, United Kingdom) for their help in data collection.
401

402 **Funding declaration**
403 Nothing to declare.
404
405

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470 ## Tables

471

472 **Table 1 The demographic details and symptoms at triage of study patients, stratified**

473 **by a diagnosis of upper gastrointestinal cancer**

474

Variables	Total	Non-UGI cancer cohort	UGI cancer cohort	P-value
Number	1301	1210	91	
Age, median (IQR)	62 (51, 73)	62 (51, 73)	71 (61, 76)	<0.001
Male	554 (42.7%)	488 (40.4%)	66 (72.5%)	<0.001
History of smoking*	437 (34.9%)	399 (34.3%)	38 (42.7%)	0.11
Duration of dysphagia <6 months	908 (69.8%)	843 (69.7%)	65 (71.4%)	0.72
Dysphagia localised to neck	314 (24.1%)	305 (25.2%)	9 (9.9%)	<0.001
Progressive dysphagia**	577 (45.6%)	519 (44.1%)	58 (66.7%)	<0.001
Unintentional weight loss >3kg	377 (29.0%)	323 (26.8%)	54 (59.3%)	<0.001
Reflux symptoms	407 (31.3%)	391 (32.3%)	16 (17.6%)	0.003
Other associated symptoms				
Abdominal mass	2 (0.2%)	2 (0.2%)	0 (0.0%)	0.12

Chest pain	45 (3.5%)	38 (3.1%)	7 (7.7%)	
Dyspepsia	643 (49.4%)	603 (49.8%)	40 (43.4%)	
Globus	38 (2.9%)	38 (3.1%)	0 (0.0%)	
Haematemesis/melaena	4 (0.3%)	4 (0.3%)	0 (0.0%)	
Throat clearing/cough	17 (1.3%)	15 (1.2%)	2 (2.2%)	
EDS score	5 (3-6)	4 (2.5-6)	7 (6-8)	<0.001

*Data not available for 49 patients.

**Data not available for 30 patients.

UGI: upper gastrointestinal cancer, EDS: Edinburgh Dysphagia Score, IQR: Interquartile range.

480 **Table 2 Univariable and multivariable logistic regression analysis of factors**
481 **associated with a diagnosis of upper gastrointestinal cancer.**
482

Variables	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)**	**P-value***	**Regression coefficients**
Age	1.05 (1.03-1.06)	1.05 (1.03-1.06)	<0.001	0.04
Male	3.89 (2.42-6.25)	3.95 (2.36-6.58)	<0.001	1.40
History of smoking	1.43 (0.92-2.20)			
Unintentional weight loss >3kg	3.99 (2.58-6.19)	3.28 (2.02-5.31)	<0.001	1.22
Dysphagia localised to neck	0.33 (0.16-0.66)	0.26 (0.12-0.57)	0.001	-1.40
Duration of dysphagia <6 months	1.09 (0.68-1.75)			
Progressive dysphagia	2.54 (1.60-4.02)	2.30 (1.39-3.79)	0.001	0.83
Reflux	0.45 (0.26-0.78)	0.47 (0.25-0.88)	0.018	-0.73

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484 49 subjects were excluded from the regression analyses due to missing data.

485 *p value of adjusted odds ratio.

486 OR: odds ratio; CI: confidence interval.

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488 **Table 3 Variables and the points allocated to each of the risk category in Edinburgh**
489 **Dysphagia Score and Cancer Dysphagia Score.**
490

Variables	Edinburgh Dysphagia Score	Cancer Dysphagia Score
Age (years)		
<39	0	0
40-49	4	2
50-59	5	4
60-69	6	6
70-79	7	8
80-89	8	10
90-99	9	12
Sex		
Female	-1	0
Male	0	6
Unintentional weight loss >3kg		
No	0	0
Yes	2	5.5
Duration of symptoms ≥ 6 months		
No	0	Not included
Yes	-1.5	
Localisation of dysphagia to neck		
No	0	0
Yes	-2	-6
Acid reflux symptoms		
No	0	0
Yes	-1	-3
Progressive dysphagia		
No	Not included	0
Yes		3.5

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494 **Table 4 The prevalence of upper gastrointestinal cancer in the high and low risk**
495 **categories of the Cancer Dysphagia Score and the Edinburgh Dysphagia Score.**
496

Scoring system	Risk category	Number of patients	Number of cancers	Prevalence (95% Confidence interval)
Cancer dysphagia score (CDS)	High risk (CDS ≥5.5)	920	89	9.7% (7.9-11.8)
	Low risk (CDS <5.5)	381	2	0.5% (0.1-1.8)
Edinburgh dysphagia score (EDS)	High risk (EDS ≥3.5)	903	88	9.8% (7.9-11.9)
	Low risk (EDS <3.5)	398	3	0.8% (0.2-2.2)

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502 ## Figures
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505 **Figure 1 Flow chart of patients in the study.**

506 2WW: two week wait; UGI: upper gastrointestinal.

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509 **Figure 2 Comparison between receiver operating curves for the Edinburgh**
510 **Dysphagia Score and the Cancer Dysphagia Score.**
511 AUC: area under the curve, EDS: Edinburgh Dysphagia Score, CDS: Cancer Dysphagia Score

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514 **Figure 3 Calibration plots for the Edinburgh Dysphagia Score and the Cancer**
515 **Dysphagia Score.**
516 CITL: Calibration in the large, LOWESS: Locally weighted scatterplot smoothing

517

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519 # Supplementary material 1

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521 **Development of a new cancer dysphagia scoring system from the multivariable**
522 **logistic regression model**

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