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Clinical variables as indicative factors for endoscopy in adolescents with esophageal atresia

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ABSTRACT

Introduction: Gastro-esophageal reflux disease (GERD) occurs frequently in patients operated for esophageal atresia (EA). Longstanding esophagitis may lead to dysphagia, strictures, columnar metaplasia, and dysplasia with an increased risk of adenocarcinoma. Are clinical factors and non-invasive assessments reliable indicators for follow-up with endoscopy?

Material and method: A follow-up study with inclusion of EA adolescents in Norway born between 1996 and 2002 was conducted. Clinical assessment with pH monitoring, endoscopy with biopsies, along with interviews and questionnaires regarding gastroesophageal reflux disease (GERD) and dysphagia were performed.

Results: We examined 68 EA adolescents. 62% reported GERD by interview, 22% by questionnaire. 85% reported dysphagia by interview, 71% by questionnaire. 24-hour pH monitoring detected pathological reflux index (RI) (>7%) in 7/59 (12%). By endoscopy with biopsy 62 (92%) had histologic esophagitis, of whom 3 (4%) had severe esophagitis. Gastric metaplasia was diagnosed in twelve (18%) adolescents, intestinal metaplasia in only one (1.5%). None had dysplasia or carcinoma. Dysphagia and GERD were statistically correlated to esophagitis and metaplasia, but none of the questionnaires or interviews alone were good screening instruments with high combined sensitivity and specificity. A compound variable made by simply taking the mean of rescaled RI and dysphagia by interview showed to be the best predictor of metaplasia (85% sensitivity, 67% specificity).

Conclusion: The questionnaires and interviews used in the present study were not good screening instruments alone. However, combining dysphagia score by interview and RI may be helpful in assessing which patients need endoscopy with biopsy at each individual follow-up examination.

Level of Evidence: Level II prognostic study

1. Introduction

Dysphagia, gastroesophageal reflux disease (GERD), esophagitis and esophageal stenosis represent long-term problems in esophageal atresia and may complicate the clinical course in childhood and adolescence [1]. Gastroesophageal reflux (GER), the usually symptomless movement of gastric contents into the esopha-

Abbreviations: AUC, area under curve; CI, confidence interval; EAC, esophageal adenocarcinoma; EA, esophageal atresia; EAT-10, eating assessment tool; EoE, eosinophil esophagitis; ERNICA, European reference network for rare inherited and congenital anomalies; ESPGHAN, the European society for pediatric gastroenterology hepatology and nutrition; GE, gastroesophageal; GER, gastroesophageal reflux; GERD, gastroesophageal reflux disease; ISFET, ion-sensitive field-effect transistor; LOFHS, length of first hospital stay; MMS, medical measurement system; pH, potential of hydrogen; REK, regional ethical committee; RI, reflux index; ROC, receiver operating characteristic curve; SDS-BMI, standard deviation score body mass index; SDS-HFA, standard deviation score height for age; SPSS, statistical package for the social sciences; TEF, tracheoesophageal fistula; VACTERL, vertebra, anal, cardiac, trachea, esophagus, renal/radial, limb.

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gus, is a normal physiologic process occurring several times per day in healthy individuals. GERD on the other hand, is present when the reflux of gastric contents causes troublesome symptoms or complications, and is a frequent condition in EA patients [2–5].

Long-term exposure to GER may lead to histologically verifiable esophagitis, which has a reported prevalence ranging from 25% to 90% in EA patients [6,7]. Differences in observed prevalence of esophagitis may be due to varying definitions and heterogeneous age groups at assessment. longstanding and uncontrolled esophagitis may lead to esophageal strictures, columnar metaplasia, dysplasia, and even adenocarcinoma [3,8,9]. However, previous studies in both children and adults with EA report a lack of consistent relationship between symptoms of GERD, esophagitis and columnar metaplasia [8–12]. Thus, “alarm” symptoms and factors indicating need for follow-up and endoscopy are still missing.

Eosinophilic esophagitis (EoE) is assumed to be an allergen/immune-mediated inflammation causing dysphagia and symptoms resembling GERD due to loss of esophageal wall compliance and dysfunction [10,11]. It has been speculated that EA patients are at increased risk of developing EoE, with reported prevalence rates of 10–18%, compared to a prevalence of only 0.03% in a healthy population [12–16]. There is however, still much uncertainty and a high variability in estimates of EoE in children [17].

In this descriptive cross-sectional study we report the prevalence of histologic esophagitis, columnar metaplasia, EoE and clinical factors in EA adolescents.

Moreover, we evaluated whether histological esophagitis and metaplasia could be suspected or identified by clinical factors and non-invasive assessments such as questionnaires and a semi-structured interviews.

2. Material and methods

2.1. Patients

All children born in Norway with EA between January 1996 and December 2002 were retrospectively selected from medical registers at the three tertiary university hospitals.

2.2. Study design

A descriptive cross-sectional study of EA adolescents and their parents was conducted between June 2015 and September 2018. Clinical assessment and endoscopy were performed by a pediatric surgeon, a pediatric nurse, a physiotherapist, a dietician, a radiologist and an experienced gastrointestinal endoscopist.

Exclusion criteria included non-Norwegian speaking, genetic syndromes and diagnoses associated with growth disorder, or mental retardation leaving the EA adolescent/mother unable to undergo per protocol assessment with physical tests, interview and questionnaires presented in this- and previous papers [18–20].

2.3. Demographics and clinical data

Data retrieved from medical records included:

Baseline characteristics (Table 1). VACTERL (vertebral defects, anorectal malformation, cardiac defects, tracheoesophageal fistula, renal anomalies, and limb abnormalities) association was defined as having ≥ 3 of the characteristic abnormalities [21].

Esophageal atresia was classified according to Gross‘ classification [22].

Surgery related variables and age (Table 1).

2.4. Growth

Weight and height were measured with calculation of standard deviation score for body mass index (SDS-BMI) and standard deviation score height-for age (SDS-HFA) according to Norwegian reference data [23].

2.5. Dysphagia

Dysphagia was registered by a semi-structured interview and by modified EAT-10 questionnaire.

During a semi-structured interview the adolescent was asked if he or she could relate to any of the following; swallowing difficulties, difficulties with food boluses, needing regular fluid intake during meals, food stuck in the esophagus, cough during swallowing, regurgitation of food, or increased time spent on meals (> 30 min). Each registered symptom generated 1 point score and dysphagia was registered as present with ≥ 1 point, with a maximum score of 7.

The EAT-10 questionnaire is a direct-scoring screening tool for symptoms of dysphagia [24]. Each of the 10 question is scored from 0 (no problem) to 4 (severe problem). Dysphagia was registered as present with a total score of ≥ 3. The Norwegian version of the EAT-10 questionnaire was chosen, a version slightly modified from the original validated tool (Supplementary Table 1).

2.6. GERD

GERD was assessed by a validated Norwegian questionnaire, a semi-structured interview and 24-hour pH monitoring.

The validated Norwegian GERD questionnaire is developed for a pediatric population 7–16 years of age. The questionnaire consists of 5 questions focusing on symptoms during the last week, with each question generating a different set of points according to symptom discrimination. Questions and corresponding scores; regurgitation/vomiting (3 points), nausea (2 points), retrosternal pain (2 points), odynophagia (2 points) and acid regurgitation (1 point) [25]. A positive score of ≥ 3 points (with a maximum score of 10 points) is found to be symptom discriminative.

During semi-structured interview the adolescents were asked if they experienced weekly symptoms of GERD (Table 2). Each registered symptom generated 1 point score with a maximum of 7 points, and GERD was registered with ≥1 point.

2.7. 24-hour esophageal pH monitoring

24-hour pH monitoring was performed with acid reducing drugs discontinued minimum 1 week prior to admission. With the patient awake the pH-probe was inserted trans-nasally and by X-ray illumination the pH sensor was located approximately 2 vertebral bodies above the diaphragm [26]. The ESPGHAN/NASPGHAN 2009 guidelines were used as cut off for Reflux Index (RI, defined as the percentage of time of pH <4) [2]. Acid exposure to the esophagus was considered normal with RI <3%, intermediate between 3%–7%, and abnormal >7% [2]. The Medtronic pH 400 Digitrapper® with antimony sensor technology was used for the first 40 adolescents. Due to renewal of department pH-equipment the latter 19 adolescents were examined with the Ohmega Medical Measurement Systems (MMS), using ISFET (Ion-Sensitive Field-Effect Transistor) catheters measuring both pH and impedance.

GERD at follow-up was registered as present if the participants had an abnormal RI (>7%), reported reflux symptoms during semi-structured interview (≥1 point), or had a positive score of ≥ 3 on the validated GERD questionnaire according to ESPGHAN guidelines [3].

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Table 1
Demographics and clinical data.

Demographic data	Participants n=68	Non-participants n=34	
Gender, male; n (%)	40 (59)	20 (59)	p= 1.00
Gestational age; weeks (median, range)	38 (31–42)	39 (27–42)	p= 0.200
Prematurity (<37 weeks GA); n (%)	24 (35)	7 (21)	p= 0.131
Birth weight; grams, median (range)	2800 (1300–4600)	2872 (495–4020)	p= 0.795
Birth weight <2500 grams; n (%)	21 (31)	8 (24)	p= 0.992
Clinical data			
Type of atresia			p= 0.668
Gross A; n (%)	3 (4)	2 (6)	
Gross C; n (%)	58 (86)	28 (82)	
Gross D; n (%)	4 (6)	1 (3)	
Gross E; n (%)	3 (4)	2 (6)	
Gross F; n (%)	0	1 (3)	
Cardiac anomaly requiring surgery; n (%)	4 (6)	4 (12)	p= 0.199
VACTERL; n (%)	14 (21)	4 (12)	p= 0.275
Right sided Thoracotomy; n (%)	65 (96)	31 (91)	p= 0.377
Number of days on ventilator; days, median (range)	2 (1–43)		
LOFHS (length of first hospital stay); days, median (range)	22 (8–264)	20 (11–140)	p= 0.532
Complications			
Anastomotic leak; n (%)	3 (4)	NA	
Anastomotic dilatation; n (%)	30 (44)	NA	
≥3 anastomotic dilatations needed; n (%)	26 (38)	NA	
Total number of dilatations needed; median (range)	5 (1–108)	NA	
Re-do surgery (esophagus/TEF); n (%)	7 (10)	NA	
Fundoplication; n (%)	9 (13)	NA	
Previous gastrostomy; n (%)	12 (18)	NA	

NA= non-applicable

2.8. Endoscopy

Endoscopies were performed under general anesthesia with flexible Olympus® 180 and 190 series gastroscope. According to standard endoscopy protocols the gastroesophageal (GE) junction was identified at the level of the top of the proximal gastric folds, followed by a close inspection of the distal esophagus and the cardia region of the stomach to look for cardia patency, breaks in the esophageal mucosa, macroscopic esophagitis or signs of metaplastic transformation. Abnormal findings were photographed and recorded. Macroscopic esophagitis with mucosal breaks was graded and scored (A, B, C, and D) according to the Los Angeles classification [27,28].

Two to four biopsies were taken from the distal and proximal esophagus, 1- and 6 cm above the GE junction, respectively. Additional biopsies were taken from areas with macroscopic changes in the esophageal mucosa, including suspected metaplastic changes, according to standard protocols and with caution and special attention in patients with long-gap EA and possible pull-up of gastric mucosa [29].

2.9. Histology

The biopsies were fixated in formalin and underwent routine processing. Paraffin-embedded sections were stained with hematoxylin and eosin. The slides were reviewed by two pathologists (HMR and KG), with assessment of mucosal type and architecture, epithelial changes, and the presence and number and type of inflammatory cells.

Esophagitis: Inflammation in the squamous mucosa was graded as mild if there were few inflammatory cells in the epithelium and/or lamina propria, and mild or no thickening of the basal zone, papillary elongation, and intercellular edema, moderate if there was a moderate increase in inflammatory cells, and mild to moderate thickening of the basal zone, papillary elongation, and/or intercellular edema, and severe if there was a marked infiltration of inflammatory cells and marked thickening of the basal zone, papillary elongation, intercellular edema, and/or erosions or ulceration.

EoE: Possible EoE was suggested if characteristic features were present in mid-esophagus and/or distal biopsies, including a peak count of at least 15 eosinophils per high power field (x 400 magnification) [13,30].

Metaplasia: Any presence of columnar mucosa in distal esophageal biopsies was considered as metaplastic. Thus, gastric-type mucosa without goblet cells was classified as gastric metaplasia and columnar mucosa with goblet cells was classified as intestinal metaplasia.

2.10. Statistics

All analyses were performed by SPSS version 25 (SPSS, Chicago, IL).

Symmetric continuous variables are presented as means with standard deviation (SD), and skewed variables as median (range, percentiles). The strength of associations between normally distributed continuous variables was measured using Pearson's correlation coefficient, and Spearman's correlation coefficient elsewhere. Categorical variables are reported as proportions and percentages. Parametric (*t*-test) or non-parametric (Mann-Whitney) group comparisons were performed. ROC (Receiver Operating Curve) curves were used to find the optimal cut-off value for interview, questionnaires and clinical tests by balancing sensitivity and specificity at the maximum Youden index. We chose a 5% statistical significance level.

2.11. Ethics

After written and verbal information participants and parents (adolescents <18 years of age) signed the consent. The study was approved by the Regional Ethical Committee (REK) in Norway, reg.no: 2014/1224, and Data protection officer, reg. no: 2014/9344.

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Table 2
Results at follow-up.

	n=68	
Weight; kg, median (range)	58 (33–111)	
SDS-BMI; median (range)	−0.03 (−3.91 – 3.10)	
Undernourished (SDS-BMI <−2); n (%)	2 (3)	
Height; cm, median (range)	167 (138–185)	
SDS-HFA; median (range)	−0.6 (−4.6 – 1.8)	
Stunted (SDS-HFA <−2); n (%)	10 (15)	
GERD symptoms by semi-structured interview (≥ 1 point); n (%)	**42 (62)**	
Regurgitation of acidic stomach content; n (%)	27 (40)	
Heartburn; n (%)	26 (38)	
Night cough; n (%)	9 (13)	
Erosion of teeth (molars); n (%)	9 (13)	
Hoarseness; n (%)	8 (12)	
GERD symptoms by questionnaire (≥3 points); n (%)	**15 (22)**	
Nausea; n (%)	13 (19)	
Retrosternal pain; n (%)	11 (16)	
Regurgitation/vomiting; n (%)	10 (15)	
Acid regurgitation; n (%)	9 (13)	
Pain when swallowing; n (%)	2 (3)	
Dysphagia by semi-structured interview (≥1 point); n (%)	**58 (85)**	
Delayed swallowing; n (%)	48 (71)	
Difficulties with food boluses; n (%)	41 (60)	
Increased time (>30 min) spent on meals; n (%)	23 (34)	
Regurgitation of food; n (%)	22 (32)	
Food stuck in the esophagus; n (%)	15 (22)	
Regular fluid intake during meals; n (%)	14 (21)	
Cough during swallowing; n (%)	5 (7)	
Dysphagia by questionnaire (≥3 points); n (%)	**48 (71)**	
It feels like the food gets stuck in my throat; n (%)	44 (65)	
Fluid is needed to swallow boluses; n (%)	40 (59)	
Swallowing boluses is difficult; n (%)	38 (56)	
Eating is time consuming; n (%)	34 (50)	
Swallowing pills is difficult; n (%)	32 (47)	
I think it is difficult for me to eat as much as my healthy peers; n (%)	18 (26)	
Swallowing is painful; n (%)	13 (19)	
I cough when I eat; n (%)	11 (16)	
I avoid eating with friends because of dysphagia; n (%)	6 (9)	
Swallowing fluid is difficult; n (%)	1 (1.5)	
24-hour pH monitoring results		
Abnormal RI (>7%); n (%)	7/59 (12)	
Intermediate RI (3–7%); n (%)	14/59 (24)	
Normal RI (<3%); n (%)	38/59 (64)	
Endoscopy and histology	**n=67**	
	1 cm*	6 cm*
Macroscopic esophagitis		
Grade A; n (%)	15 (22)	3 (4)
Grade B; n (%)	12 (18)	1 (1.5)
Grade C; n (%)	1 (1.5)	0
Histologic esophagitis, non-specific		
Mild; n (%)	44 (67)	41 (61)
Moderate; n (%)	15 (22)	12 (18)
Severe; n (%)	3 (4)	2 (3)
Eosinophilic esophagitis; n (%)	5 (7)	3 (4)
Columnar metaplasia		
Gastric; n (%)	12 (18)	3 (4)
Intestinal; n (%)	1 (1.5)	0

* Biopsy site above the GE junction

3. Results

3.1. Patients

We identified 125 consecutive EA patients born in Norway between 1996 and 2002. Of the 102 eligible 68 (67%) EA adolescents, aged 16 (13–20) years, were finally included in the analysis (Fig. 1).

3.2. Demographics and clinical data

Demographic and clinical data are listed in Table 1. There were no statistical differences in baseline data between participants ($n = 68$) and non-participants ($n = 34$). One patient with EA type C had been re-operated with colonic interposition due to long-gap atresia and complications. The biopsies harvested from this patient were exclusively taken from the colon and showed only mild inflammation. These biopsies were not representative for this study and are hence omitted from analysis.

3.3. GERD

GERD was registered in 63% by semi-structured interview and in 22% by questionnaire (Table 2), with the corresponding median scores of 2 (range 1–6) and 5 (range 3–8), respectively. In adolescents with GERD as scored by interview and questionnaire 24–29% had histologic esophagitis or metaplasia by endoscopy. Table 3b presents the adequacy and usefulness of screening for histologic esophagitis and metaplasia by GERD interview and ques-

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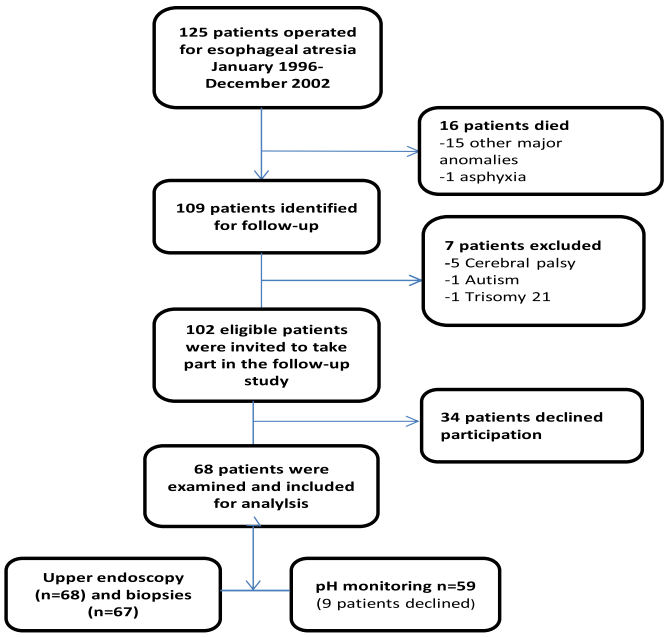

Fig. 1. Patients.

tionnaire, presented by positive predictive value, sensitivity and specificity.

3.4. Dysphagia

Dysphagia was reported by 58 (85%) by interview, with a median score of 3 (range 1–5). By EAT-10 questionnaire 48 (71%) reported dysphagia with a median score of 6.5 (range 3–29) (Table 2). Table 3b presents the screening results showing dysphagia interview and questionnaire having a high sensitivity for metaplasia and histologic esophagitis, but low specificity.

3.5. Endoscopic findings

In 67/68 (98%) of adolescents no anastomotic stricture was observed and in 10 (15%) of them it was proven to be challenging to identify the exact location of the anastomosis. One adolescent - who reported dysphagia symptoms during the interview and scored six points on the modified EAT-10 questionnaire - was diagnosed with an anastomotic stricture (8 mm in diameter) which was successfully treated by endoscope and 15 mm balloon dilatation. Twenty-eight (41%) adolescents were diagnosed with macroscopic esophagitis at 1 cm above the gastroesophageal (GE) junction; in four (14%) of them we also observed macroscopic esophagitis at 6 cm (Table 2).

3.6. Histological esophagitis

Histological esophagitis was identified at 1 cm above the GE junction in 62 (92%) adolescents, which was considered severe in 3 (4%), moderate in 15 (22%) and mild in 44 (66%) of the patients (Table 2).

3.7. Metaplasia

Columnar metaplasia without goblet cells (gastric metaplasia) was diagnosed in 12 (18%) adolescents, and one adolescent (1.5%), 14 years of age, had biopsies with intestinal metaplasia without dysplasia (Table 2). Of the 12 adolescents with gastric metaplasia, two were born with EA type A and 10 with type C according to Gross' classification.

Intestinal metaplastic changes were identified in the distal esophagus in an adolescent with EA type A with a complicated postoperative course with anastomotic leak, persistent stenosis with repeated esophageal dilatations, and finally resection of stenosis.

3.8. Eosinophilic esophagitis

The possibility of EoE was raised 1 cm above the GE junction in only five (7%) adolescents, all with EA type C according to Gross' classification (Table 2). Four of the patients (80%) had macroscopic esophagitis 1 cm above the GE junction, and two patients (40%) also at 6 cm. All five had histologic esophagitis at 1 and 6 cm above the GE junction, and 2/5 (40%) had gastric metaplasia at 6 cm. No statistical correlation was found between EoE, GERD and dysphagia by questionnaires or interview.

3.9. Clinical factors and questionnaires assessing histological esophagitis and metaplasia

3.9.1. Histologic esophagitis

The most important clinical factor related to histological esophagitis was dysphagia with symptom prevalence of 89% by questionnaire and 83% by interview (Table 3b). Dysphagia by questionnaire and previous anti-reflux surgery both had a significant positive correlation to histologic esophagitis, $p = 0.009$ and $p = 0.037$, respectively (Table 3).

The fact that more than 80% of patients with histologic esophagitis reported dysphagia at interview and by questionnaire may indicate that symptoms of dysphagia are more related to esophagitis than questions and interviews targeting reflux (Tables 3 and 3b). Analyzing the different items in the GERD and dysphagia questionnaires and interviews, only one specific item from GERD questionnaire targeting acid regurgitation correlated statistically to esophagitis ($p = 0.015$), none of the questionnaires or interviews alone were good screening instruments with high combined sensitivity and specificity (Table 3b).

3.10. Metaplasia

All 13 adolescents diagnosed with columnar metaplasia reported dysphagia by interview ($p = 0.014$) (Table 3). Metaplasia was found to correlate to re-do esophageal surgery ($p = 0.007$), anti-reflux surgery ($p = 0.003$) and pathological RI (>7%) ($p = 0.033$) (Table 3), to gestational age ($p< 0.001$), type of EA ($p = 0.002$) (EA type A>C) and anastomotic leak ($p< 0.001$) (not presented in table). Furthermore, scores on single items on acid regurgitation and on time consuming meals at both interviews and questionnaires were correlated to metaplasia. However, questionnaires and interviews alone were not good screening tools for metaplasia as evaluated by sensitivity and specificity.

ROC curves were implemented to visualize and evaluate the test accuracy of questionnaires, interview and clinical tests for the identification of metaplasia (Supplementary 2). An optimal cut-off was chosen where the Youden index = sensitivity + specificity – 1, was maximal. As the pH monitoring score had a low sensitivity (23%) but a high specificity (91%), whereas on the other hand dysphagia interview had a high sensitivity (100%) and low specificity (17%) (Table 3b), we combined the two measures to get a better balance between sensitivity and specificity.

The pH monitoring score was rescaled by the factor 6/20 (= total range of the dysphagia scores/total range of the observed pH monitoring score). The mean of this new rescaled score and the dysphagia score formed a new compound variable, merged

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Table 3
GERD, pH monitoring, Dysphagia and secondary surgical interventions in relation to esophageal macroscopic and histologic changes.

	All n=67 n (%)	Macroscopic esophagitis n=28 (41)	Histologic esophagitis (moderate and severe) n=18 (27)	Eosinophilic esophagitis n=5 (7)	Columnar metaplasia n=13 (19)	24-hour pH (RI>7%) n=7 (12)
GERD interview	42/67 (63)	22 (78) .289* p=0.017	12 (67)	3 (60)	10 (77) .245* p=0.045	6 (86)
GERD questionnaire	15/67 (22)	9 (32)	4 (22)	0	4 (31)	2 (29)
24-hour pH monitoring (RI>7%) (n=59)	7/59 (12)	5 (18) .259* p=0.048	3 (17)	1 (20)	3 (23) .280* p=0.033	
Anti-reflux surgery	9/67 (13)	8 (29) .379** p=0.001	5 (28) .255* p=0.037	1 (20)	5 (38) .360** p=0.003	2 (29)
Dysphagia questionnaire	48/67 (72)	18 (64)	16 (89) .321** p=0.009	4 (80)	10 (77)	4 (57)
Dysphagia interview	58/67 (87)	27 (96) .263* p=0.030	15 (83)	5 (100)	13 (100) .298* p=0.014	5 (71)
Re-do esophageal/TOF surgery	7/67 (10)	7 (25) .405** p=0.001	3 (17)	1 (20)	4 (31) .326** p=0.007	3 (43)
Esophageal dilatations (yes/no)	30/67 (45)	18 (64)	9 (50)	1 (20)	11 (85) .393** p<0.001	3 (43)
Recurrent (≥ 3) esophageal strictures	26/67 (39)	14 (50) .316** p=0.009	6 (33)	1 (20)	10 (77) .461** p<0.001	2 (29)

* X^2 test

Table 3b
Screening for histologic esophagitis and columnar metaplasia using positive predictive value, sensitivity and specificity.

	Histologic esophagitis (n=18)			Columnar metaplasia (n=13)		
	Positive predictive value	Sensitivity	Specificity	Positive predictive value	Sensitivity	Specificity
GERD by interview (n=42)	12 (29%)	67%	51%	10 (24%)	77%	46%
GERD by questionnaire (n=15)	4 (27%)	22%	69%	4 (27%)	31%	96%
Dysphagia by interview (n=58)	15 (26%)	83%	18%	13 (22%)	100%	17%
Dysphagia by questionnaire (n=48)	16 (33%)	89%	39%	10 (21%)	77%	35%
24-hour pH monitoring (RI>7%) (n=7)	3 (43%)	17%	90%	3 (43%)	23%	91%
Anti-reflux surgery (n=9)	5 (56%)	28%	92%	5 (56%)	38%	93%
Recurrent (≥3) esophageal strictures (n=26)	6 (23%)	33%	84%	10 (38%)	77%	76%

score = (score dysphagia + 6·score of pH/20)/2. This resulted in an acceptable value for the area under curve (AUC) of the ROC curve = 0.809. Maximal Youden index gave an optimal cutoff at a merged score = 1.975 with sensitivity 0.846 and specificity 0.667 (Fig. 2+ Supplementary Table 3). A patient with a merged score > 1.975 thus should be referred for endoscopy. In our study population using a cut-off at 1.975, 11 of 13 (85%) patients with metaplasia would have been referred for endoscopy. By choosing a cut-off at 1.5 (higher sensitivity, lower specificity) all patients with metaplasia would be subjected to endoscopy, but the 'number needed to treat' would increase by 15 patients (Supplementary 3). Still, about one third (35%) of the patients would have been spared the endoscopy.

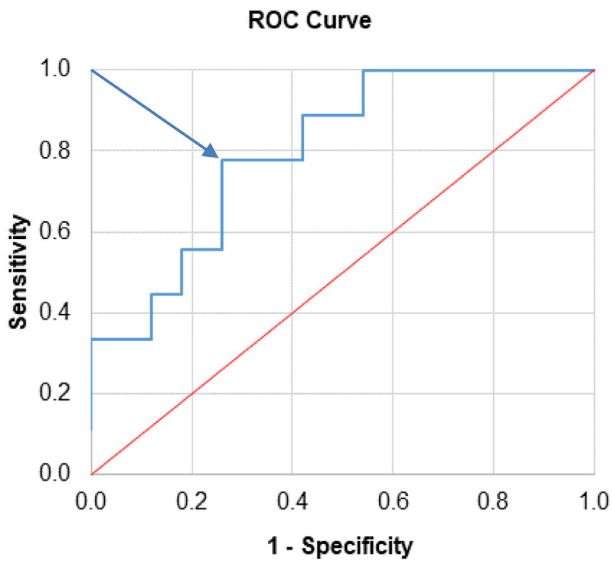

Fig. 2. Dysphagia by interview merged with rescaled reflux index vs. columnar metaplasia in 68 patients. AUC=0.809 (95% CI 0.692 –0.926). Optimal cut-off = 1.975 at sensitivity 0.846 and specificity 0.667. Nine patients did not have a pH measurement but participated still with their dysphagia score.

4. Discussion

Development of columnar metaplasia and esophageal cancer are rare complications in EA patients [9], but are main reasons for the recent recognition of necessary long-term follow-up [3,30]. However, the indications and timeline for endoscopy as part of the surveillance have not been established. In our study we evaluated whether EA adolescents with high risk of histological esophagitis and metaplasia could be suspected or identified by clinical factors and non-invasive assessments. Our results show that a history of redo surgery and esophageal dilatations, abnormal RI and the results of interviews regarding GERD and dysphagia were significantly correlated to the presence of metaplasia. No single factor is

a good screening tool, but combining RI and the scores on dysphagia interview at follow-up is a good risk indicator for metaplasia and thus an indication to perform endoscopy.

Histological esophagitis was identified in 93% of our patients, with 26% classified as severe or moderate. This is in accordance with reported prevalence between 24.8% and 90.5% in a systematic review including 285 EA patients [31], and within the range of 5–36% reported in other studies [32]. The discrepancy between macroscopic and histologic esophagitis in our study population was quite large, 41% vs. 92%. A discrepancy is also confirmed by previous studies, proving that histologic esophagitis may be present despite normal endoscopic appearance of the esophageal mucosa [33]. Due to the high prevalence of histologic esophagitis in our study, we recommend biopsies to be harvested despite the lack of macroscopic esophagitis during endoscopy.

Columnar metaplasia was diagnosed in 13 (19%) patients, compared to the prevalence of 1.3% in the general adult population [34], and a variable prevalence of 5–40.9% among EA patients [4,32]. In a meta-analysis from Connor et al. [31], five referred studies reported the prevalence of metaplasia in EA patients to be 1.1%−11.3% and the pooled estimated prevalence of metaplasia with 306 patients to be 6.4%, the majority being adults. The great variation in prevalence of metaplasia is explained by differences in the definition, i.e. the metaplasia being gastric metaplasia with or without intestinal metaplasia, and whether an overall prevalence or prevalence from an endoscopic surveillance program is reported [35].

The prevalence of columnar metaplasia in our study may seem high, but only one patient (1.5%) had intestinal metaplasia. Intestinal metaplasia has the greatest risk of dysplasia and malignant transformation, while the malignant potential in gastric metaplasia is still debated [36]. Although no dysplasia was present in our patients, both dysplasia and metaplasia may be precursors of esophageal adenocarcinoma (EAC). However, among 221 EA patients with metaplasia only 49 were intestinal, and the mean detection age was 38.5 years for intestinal and 9.5 years for gastric metaplasia [35]. Among 13 reported cases of esophageal cancer in EA patients only 4 were adenocarcinomas [35]. In a study from Vergouwe et al. [37], the prevalence of intestinal metaplasia in EA patients was 4-fold and the prevalence of esophageal squamous cell carcinoma 108-fold higher compared to the general population.

Eosinophilic esophagitis was registered in 7% of our patients. This is in accordance with the findings of Lardenois et al. [38] and Pedersen et al. [13], who reported 6/63 (9.5%) and 6/59 (10.2%) EoE in EA adolescents and 10 years old, respectively. The prevalence of EoE in the Norwegian population is unknown, but a study from Australia reports 364-fold enrichment of EoE in EA patients compared to a prevalence of 0.05% in the general pediatric population [39]. Only 5 patients makes it difficult to study the relationship between EoE and symptoms in our patients, but Krishnan et al. [39] reported a relationship between EoE and common long-term EA complaints such as dysphagia and anastomotic strictures. Food impaction being an important symptom in EoE is in accordance with a recent meta-analysis [11], and all patients in our study diagnosed with EoE reported dysphagia by interview.

Abnormal RI was identified in 12% of our EA adolescents. The reported prevalence of GER varies from 5.9% to 66.7% mostly because of the different definitions of GER [4]. The gold standard for evaluation of GER and diagnosing GERD is pH monitoring, but the use of pH monitoring as a screening tool to identify patients needing endoscopy is debatable. Lupu et al. [40] reporting a perfect parallel between pH monitoring scores and macroscopic esophagitis, stated that endoscopy is not necessary because pH monitoring scores are sufficient to diagnose GERD and the grade of macroscopic esophagitis. In accordance with Lupu et al., the abnormal pH in our study was statistically correlated to both presence of macroscopic esophagitis and to metaplasia, and pH monitoring results are factors to be considered as indicators for endoscopy to identify patients with metaplasia.

GERD as scored by interview and questionnaire was registered in 63% and 22%, respectively in our study. We have no national reference data for GERD, but in a national prevalence questionnaire study in 0–17 year old French children, 6% had GERD [41]. Pedersen et al. [13] applying GERD interviews in 7–13 year old EA patients reported a prevalence of 55.9% which is in the same level as our GERD interview results. A systematic review of long-term EA problems found an overall estimated GERD prevalence of 40.2% (with histological esophagitis) to 56.5% (without histological esophagitis) with variance in criteria and size of the study population [31], which may indicate that the true prevalence of GERD in our study is more like the results from the Interview (63%). The prevalence of GERD as found by the questionnaires in our study may be underreported.

In our study symptoms of dysphagia by questionnaire and interview were reported by 72 and 87%, respectively, which is in accordance with a prevalence ranging from 18.2 to 84.2% in a recent review [31].

Follow-up studies in EA patients have registered both GERD and dysphagia with simple yes or no categories which is a very open and unspecified way of asking for complex, multifactorial symptoms. Furthermore the different ways of recording GERD and dysphagia also makes it difficult to compare results between studies.

The reason for the lower prevalence as scored by questionnaires compared to interviews in our study both for GERD and dysphagia, may be that the questionnaires are not good instruments for perception of complaints and the fact that a questionnaire for healthy children is not appropriate for EA children. Filling out the questionnaire the EA patient does not necessarily relate the questions to clinical symptoms. On the contrary, during interview questions are explained to the patient and improve the understanding which may explain the difference in positive answers between interview and questionnaires. Eagerness to please the surgeon or the interviewer may also affect the answers. In our study the GERD interview was superior to the questionnaire in disclosing metaplasia which is confirmed by the statistical correlation between the GERD interview score and metaplasia (Table 3).

The diagnosis of GERD is based on symptomatic grounds and not on clinical investigations [2]. Even though the ESPGHAN and ERNICA guidelines highlight the importance of exploring dysphagia at follow up in EA patients, the awareness and knowledge of the many etiological mechanisms involved in dysphagia are poor among pediatric surgeons [3,30,42]. The finding that dysphagia and acid reflux are the strongest predictors of columnar metaplasia suggests that long-term acid exposure and disturbed passage caused by stricture or dysmotility are triggers of mucosal metaplastic changes.

The recommendations in recent guidelines are mainly based on expert opinions and include three routine endoscopies in EA children, i.e. after discontinuation of acid suppression, before the age of ten and one at transition to adulthood [3]. Follow-up visits are, however, more frequent than the visits for endoscopy, and assessing reported symptoms will determine whether to perform additional endoscopies with biopsies. Thus, we think a logical way of analysing our data is to interpret the usefulness of the symptoms and questions as tools to identify the risk of metaplasia and the need for endoscopy. For this purpose we assessed sensitivity and specificity of the variables and questions, and performed ROC and AUC analysis [43]. ROC curve analysis based on combining pH monitoring and the dysphagia interview score provided a cut-off with a high predictive power of the presence of columnar metaplasia. An important issue regarding the ideal cut-off is the 'number needed to treat'. The question is whether to increase the num-

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ber of patients examined (higher sensitivity, lower specificity) or to avoid unnecessary clinical examinations resulting in missing individuals with metaplasia, see considerations in the result section.

We recommend follow up of all EA adolescents with clinical interviews and pH monitoring prior to transitional age, to identify individuals for endoscopic evaluation. This is in consensus with recommendations in ESPGHAN and ERNICA guidelines [3,30].

Additional and lager studies utilizing clinical variables to identify and establish an indication for screening are needed.

4.1. Strengths and limitations

Strengths of the present study was that we were able to identify all EA patients born in Norway 1996–2002 and to include 67% of the eligible with clinical examination, endoscopy, esophageal biopsies and standardized questionnaires. This is the first nationwide follow-up study of adolescent EA patients in Norway regarding symptoms of GERD, dysphagia, pH and endoscopic findings. The gathered information has given us a more thorough understanding of the long-term esophageal pathophysiology that takes place in EA patients and how to use 'less invasive' investigative clinical tools during follow-up.

A limitation to our study was that 34 (33%) EA adolescents declined participation and follow-up, hence we are lacking valuable clinical information and current state of health regarding all eligible patients. Through contact with several of the 34 declining participants our impression was that some had less clinical complaints and did not feel any need to participate, and some were 'fed-up' with hospital and doctors after years of follow-up. Different pH-measurement systems and electrodes (antimony vs. ISFET) was used during the study period due to renewal of department equipment. As a consequence, and a possible limitation to our study, the interchangeable results between old and new equipment could be debated. According to Hemmink et al. [44] catheters with ISFET technology are more accurate than classical antimony catheters, this leads us to believe that our pH-measurement results are not exaggerated because the majority of the EA adolescents were examined with the latter.

For the detection of GERD we used the validated Norwegian GERD questionnaire developed for a pediatric population 7–16 years of age, even though a large part of our EA adolescents were older than 16 years of age. This specific questionnaire was chosen because so far we do not have any good Norwegian questionnaires detecting GERD in EA adolescents, and this questionnaire was the only one suitable for our study population.

Nine adolescents refused pH monitoring due to bad experiences during previous examinations, four of whom had columnar metaplasia without goblet cells (gastric metaplasia) in esophageal biopsies. Nine missing pH monitoring results is a statistical limitation to our study, but omitting the adolescents with only dysphagia score gave a modest change in the ROC-curve (Supplementary Table 4).

5. Conclusion

Our results support the observation that the prevalence of columnar metaplasia in EA adolescents is high compared to the normal population. Even though there are still few papers on the long-term consequences of having EA in terms of developing metaplasia, dysplasia and cancer, the documentation of increased risk of malignant transformation at a relatively young age seems alarming and is the basis for the discussions on the relevance for offering EA adolescents and adults an endoscopic surveillance program. However, with the low prevalence of intestinal metaplasia in our cohort, and the lack of reported benefits of endoscopic follow-up programs for adolescents, most EA without specific symptoms may probably wait until young adulthood before starting active surveillance.

In our study we have demonstrated that combining a structured dysphagia interview and 24-hour pH monitoring is helpful in identifying EA patients who should adhere to surveillance programs for metaplasia. The accuracy of clinical variables, alone and in combination, in monitoring dysphagic patients should be assessed on a larger scale.

Declaration of Competing Interest

None.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jpedsurg.2022.10.003.

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