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Qualitative features of esophageal fluorescence angiography and anastomotic outcomes in children

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ABSTRACT

Background: Indocyanine green (ICG) is commonly used to assess perfusion, but quality defining features are lacking. We sought to establish qualitative features of esophageal ICG perfusion assessments, and develop an esophageal anastomotic scorecard to risk-stratify anastomotic outcomes.
Methods: Single institution, retrospective analysis of children with an intraoperative ICG perfusion assessment of an esophageal anastomosis. Qualitative perfusion features were defined and a perfusion score developed. Associations between perfusion and clinical features with poor anastomotic outcomes (PAO, leak or refractory stricture) were evaluated with logistic and time-to-event analyses. Combining significant features, we developed and tested an esophageal anastomotic scorecard to stratify PAO risk.
Results: From 2019 to 2021, 53 children (median age 7.4 months) underwent 55 esophageal anastomoses. Median (IQR) follow-up was 14 (10–19.9) months; mean (SD) perfusion score was 13.2 (3.4). Fifteen (27.3%) anastomoses experienced a PAO and had significantly lower mean perfusion scores (11.3 (3.3) vs 14.0 (3.2), $p = 0.007$). Unique ICG perfusion features, severe tension, and primary or rescue traction-induced esophageal lengthening [Foker] procedures were significantly associated with PAO on both logistic and Cox regression. The scorecard (range 0–7) included any Foker (+2), severe tension (+1), no arborization on either segment (+1), suture line hypoperfusion >twice expected width (+2), and segmental or global areas of hypoperfusion (+1). A scorecard cut-off >3 yielded a sensitivity of 73% and specificity of 93% (AUC 0.878 [95%CI 0.777 to 0.978]) in identifying a PAO.
Conclusions: A scoring system comprised of qualitative ICG perfusion features, tissue quality, and anastomotic tension can help risk-stratify esophageal anastomotic outcomes accurately.
Levels of Evidence: Diagnostic - II

1. Introduction

Repair of Esophageal Atresia (EA) is one of the most common esophageal procedures in infants and yet, it can be quite challenging. EA repairs can be complicated by leak or stricture in up to 23% and 42% of cases, respectively [1]. These rates are greater than for other gastrointestinal (GI) anastomoses presumably due to the lack of serosa, mesentery, and limited esophageal length [2,3]. Evidence suggests that tension, tissue quality, and perfusion are key factors in GI anastomotic healing [4,5]. These factors are assessed intraoperatively by surgeons in a subjective fashion and concerns exist regarding the reliability and accuracy of these assessments [6].

There is growing interest in Fluorescence Guided Surgery (FGS) with intraoperative near infra-red fluorescence (NIRF) imaging to evaluate tissue features with indocyanine green (ICG) [7–9]. Of particular interest has been the use of ICG to evaluate the perfusion of GI anastomoses in adults, but limited pediatric data exists [10,11]. One of the challenges with this technology is that most current NIRF systems lack the ability to quantify perfusion, and standardized definitions of what qualitatively represents satisfactory perfusion do not exist. Hence, although we accept these NIRF ICG systems visualize perfusion, the interpretation of the fluorescence as

Abbreviations: Anastomotic Scorecard, (ASC); Color segmented fluorescence, (CSF); Esophageal Atresia, (EA); Esophageal Anastomotic Perfusion, (EAP); Fluorescence Guided Surgery, (FGS); Gastrointestinal, (GI); Indocyanine Green, (ICG); Near Infrared Fluorescence, (NIRF); Poor Anastomotic Outcome, (PAO); SPY Portable Handheld Imager, (SPY-PHI).

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it relates to perfusion remains subjective with uncertain implications for healing, akin to the assessment of anastomotic tension and tissue quality.

To help address these issues, we sought to characterize and define qualitative esophageal NIRF ICG perfusion features, then evaluate the impact of those features as well as other clinical features such as anastomotic tension and tissue quality on esophageal anastomotic healing in children. We hypothesized that we could identify qualitative features indicative of the state of perfusion of an esophageal anastomosis, and then combine these features with tissue quality and anastomotic tension into an esophageal anastomotic scorecard that could stratify the risk of a poor anastomotic outcome (PAO) with a high degree of accuracy.

2. Methods

2.1. Study design

With Institutional Review Board (IRB) approval and adherence to the Health Insurance Portability and Accountability Act (HIPAA) standards, we conducted a single center, retrospective review of children who underwent an esophageal anastomosis, and had an intraoperative NIRF ICG perfusion assessment (SPY technology, Stryker, Kalamazoo, MI) consecutively from September 2019 to January 2021 at Boston Children's Hospital. Operations included primary EA repair, Foker repair (staged esophageal repair after traction-induced esophageal lengthening for long gap esophageal atresia), rescue Foker (patient's second or greater attempt at traction-induced esophageal lengthening), esophageal strictureplasty, segmental esophageal stricture resection, and esophageal replacement with a jejunal interposition [12–16]. Demographic, perioperative and follow-up data were abstracted from the electronic medical record. Exclusion criteria were adult age, lack of video recording of ICG angiography, or lack of an anastomosis (e.g. esophageal perfusion assessment done before the anastomosis).

Our primary outcome measure was the occurrence of a poor anastomotic outcome (PAO) defined as any anastomosis with either an anastomotic leak or development of a refractory anastomotic stricture. Leaks were defined as any extravasation of contrast from the anastomosis on postoperative fluoroscopic examination requiring intervention. Refractory anastomotic strictures were defined as those requiring advanced endoscopic therapies (stenting, esophageal vacuum assisted closure [e-VAC]), $\geq$6 dilations in the first 12 postoperative months, or need for resection of an anastomotic stricture [17–19].

2.2. Intraoperative perfusion assessments

The NIRF ICG anastomotic perfusion assessment was performed after completion of the esophageal anastomosis or repair. Each assessment was conducted in a standardized fashion: the room lights are turned off, the SPY-PHI (portable handheld imager, Stryker, Kalamazoo, MI) device in the Color-Segmented Fluorescence (CSF) mode is focused on the anastomosis via the thoracotomy incision, and the video recording is started. Weight-based dosing of ICG is given intravenously by the anesthesiologist at the surgeon's signal, and flushed with saline (according to the manufacturer's recommendations) [20]. When the lung first registers a signal in the CSF mode, the device is switched to the Spy Fluorescence mode (black and white) for the remainder of the assessment; the perfusion of the entire circumference of the anastomosis (both front and back walls) is assessed. The perfusion assessment takes less than two minutes to complete.

2.3. Qualitative evaluation of perfusion assessments and score development

The literature was searched for existing qualitative NIRF ICG perfusion assessment instruments in esophageal surgery by reviewing references in several systematic reviews about ICG in esophageal surgery published to date [21–23]. We found studies referencing speed until visual fluorescence and planning an esophagogastric anastomosis in a grossly fluorescent region [10,11,24–28]. However, no studies providing purely qualitative features as a means to grade the perfusion of an esophageal anastomosis were found. Perfusion assessment videos were reviewed to identify and define NIRF ICG fluorescence features that recurred in graded intensities or patterns. These features were revised after iterative discussions among authors to develop the Esophageal Anastomotic Perfusion (EAP) score (Table 1). This instrument consists of six perfusion features in total scored on an ordinal scale unless the item is dichotomous: four items evaluate each side of the anastomosis separately, and two items evaluate the anastomosis as a unit. Side-specific features include: strength of perfusion (degree of brightness), pattern of hypoperfusion (non-fluorescent areas), speed of perfusion (relative to the lung), visualization of vessel arborization (presence of discrete fluorescent vessel outlines on the wall of the esophagus). Unit features include visualization of the posterior wall, and anastomotic suture line hypoperfusion width (Fig. 1). Each anastomosis had one EAP score, which was a sum of all perfusion features for that anastomosis. Higher scores reflected better perfusion. The definition of "expected suture line hypoperfusion width" is the darkness or hypoperfusion width extending to the tissue immediately adjacent to the area of the esophagus where the suture passes through (bites) the tissue for approximation. "Fast" speed of perfusion occurs when the esophagus attains its fluorescence at the same speed or rate as the ipsilateral lung completely perfuses or fluoresces (a matter of seconds at maximum), while "slow" speed of perfusion was considered when the esophageal perfusion was evident several seconds after the peak ipsilateral lung fluoresces.

The four operative surgeons were trained to use the EAP scoring and example images of the different items were included with the scoring sheet. Fifty-one videos were independently scored by each of the four surgeons in a blinded fashion to establish inter-rater reliability. One of surgeons re-scored a random sample of 21 videos eight weeks later to establish intra-rater reliability. Scoring disagreements were resolved by consensus, and this consensus score was used for subsequent outcomes analyses.

2.4. Clinical determinants of anastomotic outcome

Additional clinical variables including anastomotic tension, type of anastomosis, operative approach, operative history, and patient demographics were abstracted from the medical record in order to evaluate their impact on anastomotic outcome. Anastomotic tension was graded based on the surgeon's perception as described in the operative note and consistent with the following working definitions. Mild tension was defined as the esophageal ends overlapping easily and not retracting significantly when the tips were cut. Moderate tension was defined as needing to cross the anastomotic sutures in a distributed tension technique in order to bring the esophageal ends together [14]. Severe tension was defined as requiring additional maneuvers to get the ends together, such as putting the patient in a flexed position or using instruments (e.g. kittner blunt dissector) to facilitate the back or front wall coming together (in addition to crossing sutures with distributed tension technique) or some combination thereof. Anastomoses being performed in a reoperative field, such as those that had undergone a

Table 1
Esophageal Anastomotic Perfusion (EAP) Scoring System.

EAP Score*	Upper (if vertical) or Screen Left (if horizontal) Segment	Lower (if vertical) or Screen Right (if horizontal) Segment.
Strength of Perfusion (Brightness/Intensity)	Robust (+2) Intermediate (+1) Weak (+0)	Robust (+2) Intermediate (+1) Weak (+0)
Extent of Hypoperfusion (Dark Areas)	None (+3) Patchy (+2) Segmental (+1) Global (+0)	None (+3) Patchy (+2) Segmental (+1) Global (+0)
Speed of Perfusion Uptake (Relative to Lung)	Fast (+2) Slow (+1) Cannot Tell (+0)	Fast (+2) Slow (+1) Cannot Tell (+0)
Vessel Arborization or Branching Evident?	Yes (+1) No (+0)	Yes (+1) No (+0)
Pouch Score (0–8)		
Ability to See Posterior Anastomotic Wall?	Yes (+1) No (+0)	
Width of Suture Line Darkness/Hypoperfusion?	Expected Suture Line Width (+2) Double the Expected Suture Line Width (+1) Greater than Double the Expected Suture Line Width (+0)	
Total Score (0–19)		

* This is the scoring system used for the NIRF ICG perfusion assessments after construction of the anastomosis. The first 4 features are assessed in a side or pouch specific way (UL, upper or screen left segment. LR, lower or screen right segment), thus providing a pouch score. All features were set to an ordinal scale, unless the feature was dichotomous (i.e. visualization of posterior wall). Greater scores indicate greater perfusion. EAP – Esophageal Anastomotic Perfusion.

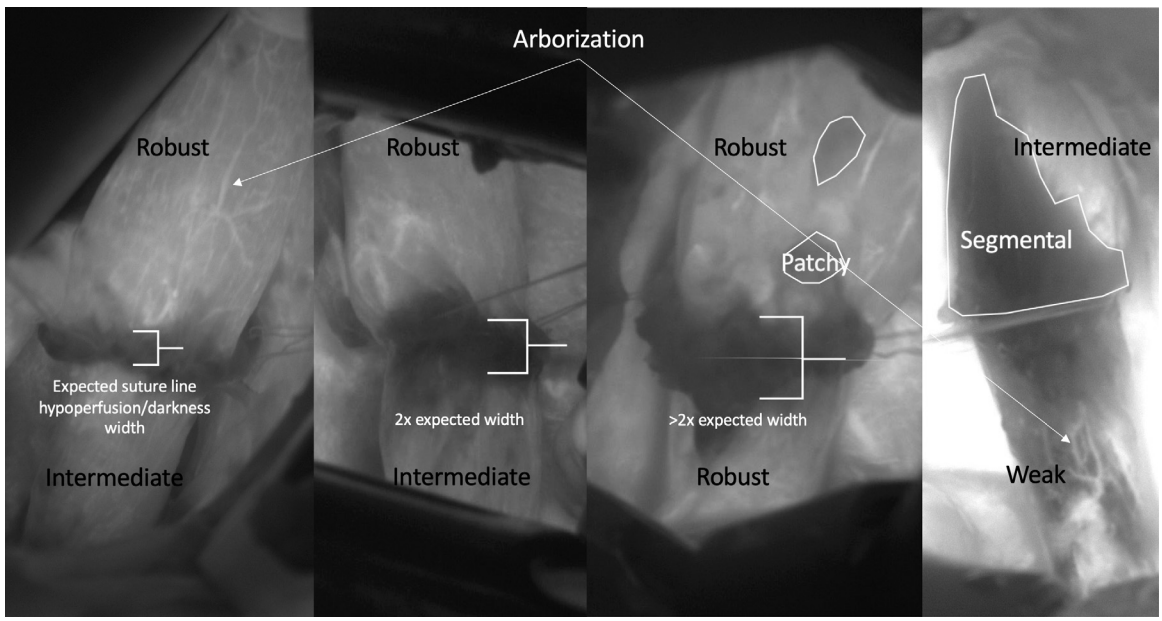


Fig. 1. Representative still frames from various indocyanine green (ICG) perfusion assessments. 4 separate NIRF ICG perfusion assessment still frames are shown with corresponding examples the various esophageal anastomotic perfusion (EAP) features listed. Speed and ability to see posterior wall were omitted. Extent of hypoperfusion examples are outlined in a transparent white.

rescue Foker process, were considered surrogates for poor tissue quality.

2.5. Statistical analysis

Inter-rater reliability and intra-rater reliability statistics were calculated with kappa coefficient and intra class coefficients. The associations between EAP features, EAP score, degree of anastomotic tension (mild, moderate, severe), and patient-level variables (operative indication, tissue quality, demographic features, etc.) with a PAO (leak or refractory stricture) were evaluated with univariate testing (using Student's *t*-test or the nonparametric Wilcoxon rank sum test depending on normality of continuous variables, or Fisher's exact test for categorical data) and multivariable logistic regression. Statistically significant ($p<0.05$) EAP features and clinical variables on univariate analysis were used to develop an anastomotic scorecard (ASC). Points were assigned to each independent predictor based on the regression coefficients (the log-odds ratios) from the multivariable logistic regression model, and the ASC score was calculated as the sum of the points for each patient. Model calibration was examined with Hosmer-Lemeshow goodness-of-fit test, with non-significant results interpreted as indicating good model fit to the data. The area under the curve (AUC) was evaluated using receiver operating characteristic (ROC) curve analysis to assess the level of discrimination of the predictive risk model to distinguish between patients with and without the PAO. The optimal cut-point for the multivariable risk score in predicting PAO was determine by maximizing Youden's J index (the sum of sensitivity and specificity). An internal bootstrap model validation was performed using 1000 bootstrap resamples, with the Brier

score and Somers' D statistics calculated. We then reanalyzed the data with a time to event Cox regression and log-rank testing to verify our findings and create Kaplan-Meier curves. Stata (version 16.1, StataCorp LLC, College Station, TX) was implemented for all statistical analyses. A two-tailed 5% alpha was considered statistically significant.

A total sample size of 55 procedures (15 with poor anastomotic outcome and 40 with good outcome) provided 80% power for detecting a clinically meaningful difference in esophageal anastomotic perfusion (EAP) score between procedures with a PAO versus no PAO (mean difference of 2.7 and pooled standard deviation of 3.25; minimum detectable standardized difference of 0.86), based on Student's *t*-test assuming a two-tailed 5% alpha [29]. Statistical power calculations were performed using G*Power software (University of Dusseldorf, Germany).

3. Results

During the study, 74 children underwent 77 procedures with an esophageal anastomosis or repair along with a NIRF-ICG assessment. Twenty-two procedure recordings were excluded due to missing (11) or poor quality (5) video, or lack of an anastomosis (6). 55 videos from 53 patients (median age at operation 7.4 months, interquartile range [IQR] 3.9–16.6 years) met inclusion criteria. Twenty-five patients were female and thirty were male. Fifty-two patients (94.6%) had a history of Esophageal Atresia (EA): sixteen (30.7%) were type A, three (5.9%) were type B, thirty-three (63.4%) were type C. The remaining three (5.4%) patients had a history of caustic ingestion. There were no adverse advents from ICG administration.

Mean (SD) EAP score was 13.2 (3.4), possible range 0 to 19. The rater agreement was good to excellent (inter-rater ICC 0.83, 95%CI 0.7,0.9; intra-rater ICC 0.93, 95%CI 0.8, 0.97). With a median (IQR) follow-up of 14 (10–19.9) months, 15 (27.3%) anastomoses had a poor anastomotic outcome (PAO), including 5 anastomotic leaks (5 treated with eVAC), 8 refractory strictures (3 were treated with stents, 5 had ≥6 dilations in the first year), 1 eVAC was placed in a shallow mucosal ulcer found post-op, and one underwent esophagectomy and jejunal interposition. One patient without a PAO died after an airway intervention to address severe tracheomalacia.

Procedures with PAO had significantly lower mean [SD] EAP scores compared to those which did not (11.3 [3.3] vs 14.0 [3.2], $p = 0.007$). Primary and reoperative traction esophageal lengthening procedures (Foker process) were more likely to experience a PAO, as were procedures with severe anastomotic tension (Table 2). Furthermore, increased anastomotic tension was associated with decreased mean [SD] EAP score (mild 14.7 [2.5], moderate 12.2 [3.8], severe tension 12.1 [3.3], $p = 0.023$). Esophago-jejunal (EJ) anastomoses (with microvascular augmentation) had greater mean EAP scores than esophago-esophageal anastomoses (15.9 [2.3] vs 12.7 [3.4], $p = 0.009$), and there were no PAO in the EJ anastomosis group. However, as individual operative approaches, mean [SD] EAP scores did not significantly differ between groups (primary anastomosis 12 [1.6], primary Foker 13.3 [4.1], rescue Foker 12.1 [3.5], stricture resection 12.8 [3.5], jejunal interposition 15.9 [2.3] $p = 0.099$).

Qualitative EAP features associated with PAO on univariate analysis were: presence of segmental or global areas of hypoperfusion (hypoperfusion subscore ≤4) ($p = 0.027$), lack of vessel arborization on both segments ($p = 0.011$), and suture line hypoperfusion width >twice the expected ($p = 0.001$) (Table 3).

The Anastomotic Scorecard (ASC, Table 4) was created by combining EAP features and clinical variables which were significant on univariate analysis. The point-value of each component was determined from the relative strengths of association each component had with PAO when combined into a multivariable logistic regression model. Primary or rescue Foker (+2), severe anastomotic tension (+1), lack of arborization on both segments (+1), suture line hypoperfusion >twice the expected width (+2), and presence of segmental or global areas of hypoperfusion (hypoperfusion ≤4) (+1), were included in the ASC model (ASC range 0–7, with greater values indicating greater risk of PAO). The ability of the ASC to identify an at-risk anastomosis was superior to the EAP score alone, with an optimal cut-point of >3 having a sensitivity of 73% (11/15), and specificity of 93% (37/40), with AUC 0.878 (95%CI 0.777 to 0.978) and an odds ratio of 33.9 (95%CI 6.57–175.1) for poor anastomotic outcome (good model fit to the data based on nonsignificant Hosmer-Lemeshow test $p = 0.226$; Fig. 2). Based on internal model validation with 1000 bootstrap resamples, the Brier score was 0.12 and Somers' D was 0.76, which provides evidence of good internal validity of the multivariable ASC risk score [30].

Table 2
Univariate analysis of clinical variables for poor anastomotic outcome.

Variable	Poor Anastomotic Outcome[a] ($n = 15$)	No Poor Anastomotic Outcome ($n = 40$)	*P* value[c]
Age at Repair (months)	6.2 (4.1, 12.8)	7.7 (3.9, 24.8)	0.539
Operative weight (kg)	6.0 (5.0, 9.9)	7.0 (5.2, 10.1)	0.657
Operative Approach			
Primary anastomosis	1 (12.5%)	7 (87.5%)	
Primary Foker	7 (41.2%)	10 (58.8%)	0.017
Rescue Foker	5 (62.5%)	3 (37.5%)	
Stricture resection	2 (15.4%)	11 (84.6%)	
Jejunal interposition	0 (0%)	9 (100%)	
Anastomosis Type			
End-to-end	13 (37.1%)	22 (62.9%)	0.110
Slide[b]	2 (14.3%)	12 (85.7%)	
Single Cheatle	0 (0%)	6 (100%)	
Prior Chest Operation			
No	3 (30%)	7 (70%)	0.999
Yes	12 (26.7%)	37 (73.3%)	
Anastomotic Tension			
Mild	3 (13.0%)	20 (87.0%)	
Moderate	6 (27.3%)	16 (72.7%)	0.023*
Severe	6 (60.0%)	4 (40%)	

[a] Two patients each had two procedures where ICG was used. For both patients, the first procedure resulted in a PAO and we used this event in our Kaplan-Meier analysis, giving $n = 53$.
[b] ref. [14].
[c] *P* values were calculated using Fisher's exact test or the Wilcoxon rank sum test, as appropriate.

Table 3
Univariate analysis of esophageal anastomotic perfusion features with poor anastomotic outcome (Combined feature score for both esophageal segments).

Perfusion feature	Poor Anastomotic Outcome (n = 15)	No Poor Anastomotic Outcome (n = 40)	P value[c]
Strength of Perfusion[a]			
Weak/Weak (0 + 0 = 0)	0 (0%)	1 (100%)	0.114
Intermediate/Weak (1 + 0 = 1)	2 (66.7%)	1 (33.3%)	
Intermediate/Intermediate (1 + 1 = 2)	6 (40%)	9 (60%)	
Robust/Intermediate (2 + 1 = 3)	5 (29.4%)	12 (70.6%)	
Robust/Robust (2 + 2 = 4)	2 (10.5%)	17 (89.5%)	
Extent of Hypoperfusion[a]			
Global/Global (0)	0 (0%)	0 (0%)	0.027[a]
Global/Segmental (1)	0 (0%)	0 (0%)	
Segmental/Segmental (2)	0 (0%)	0 (0%)	
Segmental/Patchy (3)	5 (55.6%)	4 (44.4%)	
Patchy/Patchy (4)	5 (35.7%)	9 (64.3%)	
None/Patchy (5)	5 (23.8%)	16 (76.2%)	
None/None (6)	0 (0%)	11 (100%)	
Speed of Perfusion Uptake[a,b]			
Cannot tell/Cannot tell (0)	2 (25%)	6 (75%)	0.999
Slow/Cannot tell (1)	0 (0%)	1 (100%)	
Slow/Slow (2)	5 (31.3%)	11 (68.8%)	
Fast/Slow (3)	2 (25%)	6 (75%)	
Fast/Fast (4)	6 (27.3%)	16 (72.7%)	
Vessel Arborization[a]			
Absent in both (0)	10 (52.6%)	9 (47.4%)	0.011*
Present in one (1)	3 (18.8%)	13 (81.3%)	
Present in both (2)	2 (10%)	18 (90%)	
Posterior Wall Visualization			
No (0)	0 (0%)	7 (100%)	0.171
Yes (1)	15 (31.3%)	33 (68.7%)	
Width of Suture Line Hypoperfusion			
>Twice expected (0)	7 (77.8%)	2 (22.2%)	0.001*
Twice expected (1)	6 (22.2%)	21 (77.8%)	
Expected (2)	2 (10.5%)	17 (89.5%)	

[a] EAP Score features that were assessed in a side specific manner (strength, extent of hypoperfusion, speed, arborization) were added together (both sides summed) such that each EAP feature had one score per anastomosis. This was done because the anastomosis heals as a unit and the outcome was not measured in such a way that maintains the side specificity. As such, there are multiple ways to get a score of 2 or 3 for strength [i.e. both sides intermediate 1 + 1 = 2 as well as one side being weak, while the other is robust 0 + 2 = 2], and 2, 3, 4 for extent of hypoperfusion and 2 of 3 for speed and 1 for arborization. Example combinations are shown followed by the corresponding summated score in parenthesis.

[b] Cannot tell for perfusion speed was an option for when the speed of perfusion was unable to be assessed relative to the speed with which the lung fluoresces. This has a value of 0, implying that slow perfusion is better than not being able to assess speed.

[c] P values were calculated using Fisher's exact test.

When excluding the nine jejunal interposition procedures, the EAP score components remain significant (global or segmental areas of hypoperfusion (hypoperfusion ≤4) $p = 0.044$, absence of vessel arborization on both sides $p = 0.044$, >twice suture line hypoperfusion width $p = 0.008$). The ASC retains its high accuracy with an AUC of 0.846 (95%CI: 0.724 to 0.968, $p<0.001$).

The time-to-event analysis using univariate Cox regression and log-rank testing on the entire cohort demonstrated the same clinical and EAP features are significantly associated with PAO. Primary Foker hazard ratio [HR] is 5.7 (95%CI: 1.15–28.2) $p = 0.033$, and rescue Foker HR = 14.5 (95%CI: 2.8–75.6) $p = 0.002$, and severe anastomotic tension HR = 8 (95%CI: 1.55–41.6) $p = 0.013$. The log-rank test p-values were significant for global or segmental areas of hypoperfusion (hypoperfusion ≤4) ($p = 0.048$), for absence of arborization on both sides ($p = 0.014$), and for greater than twice suture line hypoperfusion width ($p<0.001$). When using multivariable Cox regression analysis and log-rank testing to model the ASC, we similarly determined that a score >3 was highly indicative of a PAO with log-rank testing (log-rank = 37.1, $p<0.001$).

4. Discussion

This study defines qualitative NIRF ICG perfusion features of esophageal anastomoses and evaluates their impact on anastomotic outcome. Combining perfusion features with anastomotic tension and operative approach created a pragmatic scorecard to identify anastomoses at-risk of poor outcomes.

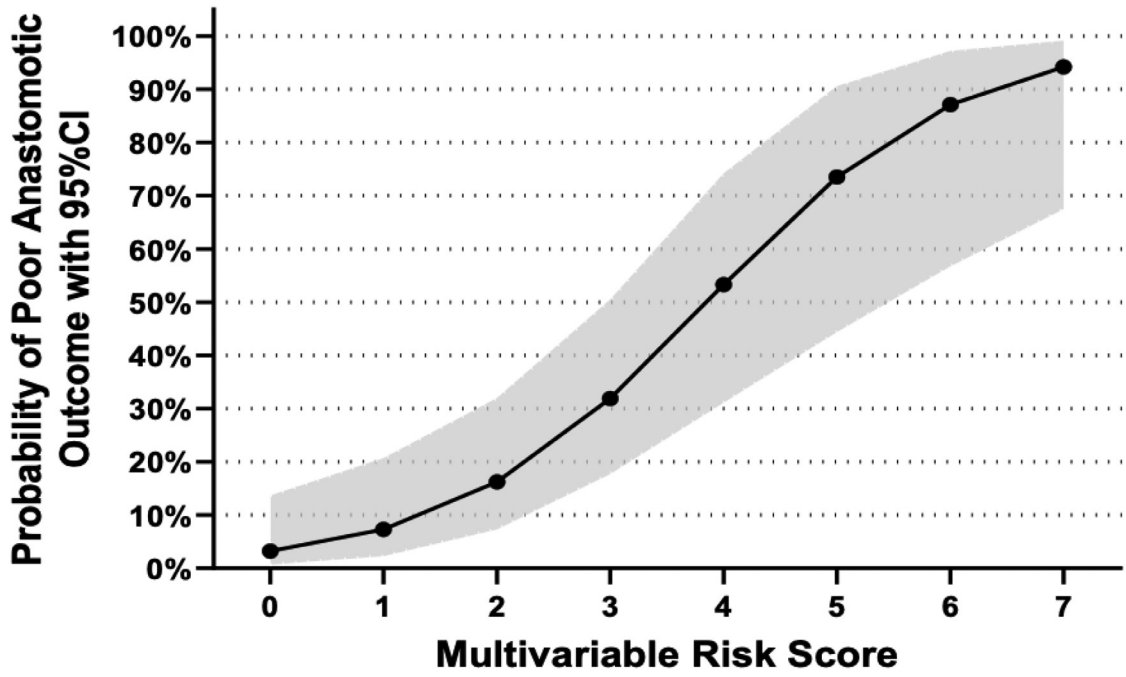
In adults, the use of intraoperative ICG perfusion assessments has been associated with improvements in anastomotic outcomes [11,23,31,32]. Such improvements are likely related to ICG perfusion assessments influencing intraoperative decisions such as: selecting the margin of bowel to resect, the optimal location for the anastomosis, etc. However, because we lack universal organ-specific definitions of what ICG features separate a “good” from a “poor” assessment, these intraoperative decisions are largely subjective and experience dependent. It may be easy to distinguish an outstanding perfusion assessment (vigorous, bright fluorescence) from an overtly concerning assessment (entirely dark on the monitor), it is more often that assessments are somewhere between. Knowing what to do with a “moderate” perfusion assessment can be difficult. Our study provides a valuable starting framework and common language for future studies that seek to better understand ICG fluorescent perfusion assessments.

Some studies have demonstrated that various quantitative ICG features (e.g. time to maximum fluorescence) correlate with outcome and provide some objectivity to the ICG perfusion assessments [33,25,34,35]. However, these quantitative assessments require special post-processing software, can be costly and hard to implement. Hence, the current ability of quantitative systems to impact intra-operative decision making is limited.

In order to identify and define the EAP features, we relied heavily on the underpinnings of esophageal anatomy. The esophagus that lacks a mesentery and serosa leading to a vascular arrangement that is effectively pushed one level deeper towards the lu-

Table 4
Anastomotic Scorecard (ASC).

Variable		Points[a]
Operative Approach: Primary or rescue Foker		+2
Severe anastomotic tension		+1
Global or segmental hypoperfusion		+1
Absence of arborization on both segments		+1
> twice expected suture line hypoperfusion width		+2
Risk Score	Probability of Poor Anastomotic Outcome	95% CI
0	3.2%	0.7% - 13.7%
1	7.3%	2.3% - 20.7%
2	16.2%	7.3% - 32.0%
3	31.9%	17.7% - 50.5%
4	53.3%	31.1% - 74.2%
5	73.5%	44.4% - 90.6%
6	87.1%	56.7% - 97.2%
7	94.2%	67.5% - 99.2%



[a] Points were determined based on rounding log-odds ratios from the multivariable logistic regression model. Risk score showing point values for the component variables and the increasing probabilities of PAO with increasing ASC score. The line represents the increasing probability of a poor anastomotic outcome – leak or refractory stricture – with increase ASC score. The shaded region represents the 95% confidence interval.

men relative to the rest of the GI tract [36–38]. The esophagus acquires vascular input from each compartment it descends across – cervical, thoracic, and abdominal – leading to a "segmental" organization of vessels [39,40]. But the esophagus itself is not segmented nor is the intramural vascular architecture (as in the liver). The main vessels, arising from or tributary to named arteries or veins, respectively, run in the interface of the muscularis externa and adventitia. These vessels give rise to circumferential and perforating branches. The circumferential branches distribute into the capillary plexus of the muscularis externa, while the perforating branches travel to the submucosal plexus, the mucosal longitudinal arterioles, and the subepithelial capillary network [37,38]. This redundancy allows the entirety of the esophagus to be mobilized without significant ischemia [41].

Given the unique anatomy of the esophageal vessels and the fluorescence kinetics of ICG, we expect to see outlines of the main vessels at the muscularis externa – adventitia interface from the outside as discrete, discernible tube-like structures (arborization) if there is normal vascular flow [42–47]. If there is compromised inflow, such that not enough blood is getting to the esophageal wall, or compromised outflow such that there is high enough backpressure to the flow of blood, we would expect to not see any arborization since the ICG is loitering and not flowing. Tension can also compromise blood supply. Longitudinal tension on the esophagus narrows the lumen of longitudinal vessels, increasing resistance to flow. All else being constant, less blood will flow through the vessels resulting in a net decrease in perfusion per unit time. Our results support these observations and provide clinical evidence that increasing tension is associated with decreased perfusion and worse anastomotic outcomes.

Common techniques of assessing anastomotic perfusion (palpation for turgor, warmth, inspection of color and response to pinprick) have not been shown to reliably correlate with anastomotic outcomes [6]. This is likely because other factors such as anastomotic tension, tissue quality, previous surgery, and nutritional status also play a role in anastomotic healing [2,3,48]. Our study results are in line with such observations, as the accuracy of our Anastomotic Scorecard (ASC) in identifying a PAO, which incorporates the perfusion assessment and clinical variables, is superior to the EAP assessment alone.

4.1. Implications for practice

Given the limited length of the esophagus, it is likely that surgeons may not be able to redo a poorly perfused esophageal anastomosis. This is particularly true in settings of EA. In our practice, if

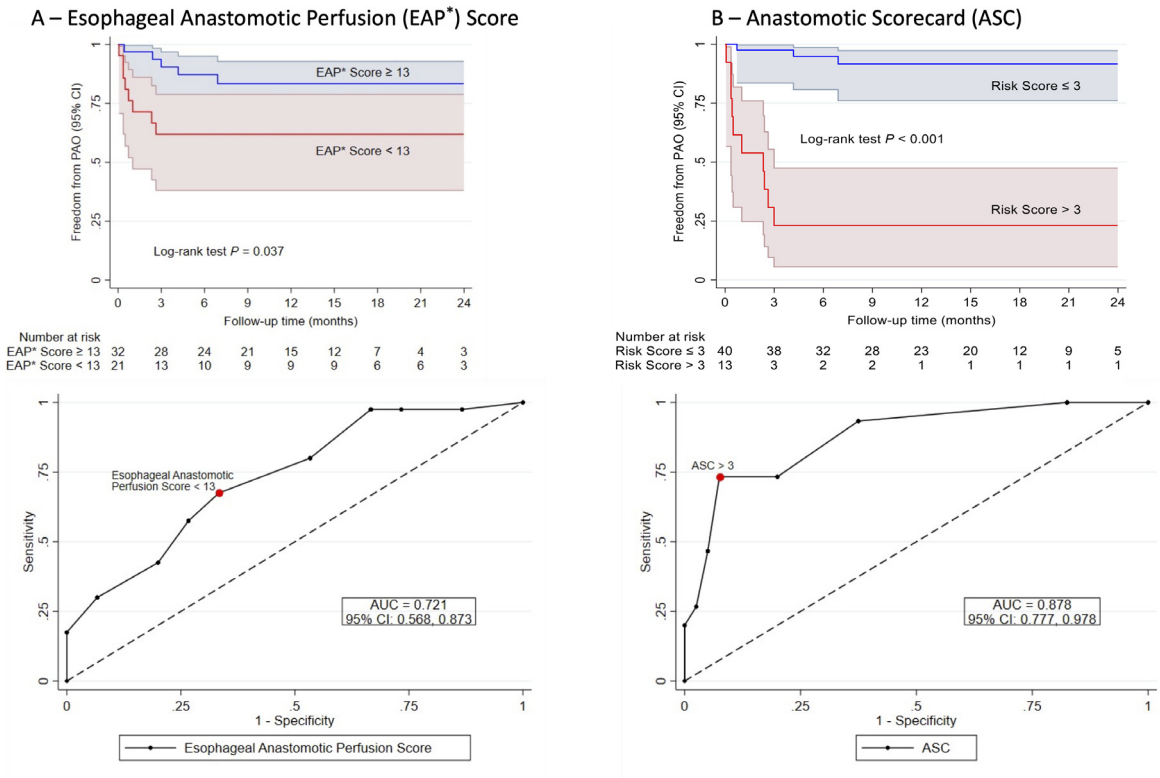


Fig. 2. Receiver Operating Characteristic (ROC) and Kaplan- Meier (KM) curves of the Esophageal Anastomotic Perfusion (EAP) Score and Anastomotic Scorecard (ASC).

concerning perfusion features are identified and revising the anastomosis is not possible, we consider certain adjuncts to mitigate the risk of a PAO. For example, using a pleural flap to cover a hypoperfused anastomosis or suture imbricating an isolated area of poor perfusion. A second look thoracotomy or a staged repair may be considered in unique circumstances, such as in cases with global hypoperfusion of one or both esophageal segments. The perceived PAO risk (ASC Score) may also influence the number, type, and criteria for removing pleural drains, or the need for and timing of a contrast esophagram. For high-risk anastomoses, we may elect to keep the child intubated or chemically paralyzed to minimize stress on the anastomosis. Conversely, anastomoses with favorable perfusion features may allow the patient to be treated with an enhanced recovery mindset. We recognize that these interventions are not yet evidence-based, however they do provide a way of utilizing fluorescence information beyond how much tissue to resect (i.e. decision of primary vs staged EA repair, type of esophageal traction process (external vs internal) in the setting of long-gap EA).

4.2. Limitations

Our study has some limitations. It is inherently subjective due to the qualitative nature of the variables, however the first aim of the study was to create a framework to help provide consistency and reproducibility to overcome such limitations. Factors such as distance between the camera and operative field, background illumination, camera angle can affect fluorescence interpretations in both qualitative studies such as ours and quantitative studies where a region of interest (ROI) needs to be selected by the user for the video analysis software to track [49,50]. This is particularly true of the “speed of perfusion” and “extent of suture line width hypoperfusion width” features, where the anchors are subjective visual assessments themselves (i.e. how quickly the lung perfuses, how far the hypoperfusion extends beyond where the suture passes through the esophagus). True quantification requires a spectrophotometer. It is certainly possible that qualitative and quantitative features may be complimentary in their perfusion assessment ability, yet this remains to be studied.

Our assessments were conducted with the SPY-PHI system via a thoracotomy or open incision. Future studies should examine the accuracy of ICG perfusion assessments in a minimally invasive setting.

The retrospective design of our study precluded prospective validation of our scoring system in a separate cohort (ideally, in a different patient population). Though our length of follow up is not long-term, our previous work has shown that most poor anastomotic outcomes occur within the first few months of the anastomosis [19]. The referral nature of our practice provides a complex patient population with a high proportion of patients undergoing the Foker process or re-operative thoracic surgery, which limits the generalizability of our results to other practice settings. There are inherent limitations with the subjective assessment of anastomotic tension. Esophageal gap length could theoretically be a more objective surrogate for anastomotic tension. However, a greater gap does not always mean greater anastomotic tension. The development of a surface tensiometer could be explored as a potential way to more objectively assess anastomotic tension.

Additionally, nine anastomoses (16%) of our cohort were supercharged esophagojejunal (EJ) anastomoses. This involves a microvascular anastomosis to bolster vascular inflow and outflow to the EJ anastomosis. This, and the aforementioned differences in vascular architecture between the esophagus and small bowel (i.e. presence of arborization), explain the greater average EAP scores for the EJ anastomoses when compared to esophagoesophageal anastomoses. However, even after removing these jejunal interposition patients from the main analysis, the results remained consistent. Thus, we felt compelled to include the esophagojejunal anastomoses in our study cohort for veracity, and because half of the anastomosis is the native esophagus. We acknowledge that there

could be a component of a learning curve in performing the ICG assessments and their interpretation. This study did not formally assess such learning curve, although this is an opportunity for further research. We attempted to mitigate this learning curve and potential variability by scoring all assessments in an asynchronous (at the end of the study period) and blinded fashion, directly from the video recordings. As demonstrated by our high intra-rater and inter-rater agreement statistics, there was overall minimal variation in scoring between surgeons.

Our definition of a poor anastomotic outcome was intentionally sensitive to include any variation of a less than ideal outcome for any patient. We included several patients that were able to retain their native esophagus or not need another operation in the long-term, despite having had a less than ideal early postoperative outcome.

We believe the framework and terminology described in this study is unique and sets the groundwork for future work in the area, not just as it pertains to esophageal surgery in children but more globally to the use of fluorescent guided surgery. Qualitative work as the one described in our study can be inherently subjective, but it's only a starting point. Future, more rigorous studies are needed to add to our understanding of ICG perfusion assessments.

5. Conclusions

We have developed and evaluated an Esophageal Anastomotic Scorecard (ASC), which combines clinical and qualitative perfusion factors and demonstrates a high degree of accuracy in identifying esophageal anastomoses at-risk of poor outcomes. Moreover, this study provides evidence of the deleterious effects of increased anastomotic tension, poor perfusion and poor tissue quality on esophageal anastomotic healing. The ability to accurately risk-stratify anastomotic outcomes may allow surgeons the opportunity to modify certain features and tailor intra- or postoperative interventions aimed at decreasing the risk or the impact of a poor anastomotic outcome. Prospective evaluation and external validation of our anastomotic scorecard (ASC) with longer term follow-up is needed.

Previous communication

An abstract of a portion of our work was accepted by and presented at the 102nd Annual Meeting of the New England Surgical Society, Mashantucket, Connecticut September 24–26, 2021.

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Declarations of Competing Interest

Dr. Zendejas is a consultant for Stryker Corp. Stryker Corp. had no role in the design, conduct, interpretation, or decision to publish this study.

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