Systemic Inflammatory Response and the Noble and Underwood (Nun) Score as Early Predictors of Anastomotic Leakage after Esophageal Reconstructive Surgery

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Posted Date: 5 January 2024

doi: 10.20944/preprints202401.0456.v1

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Article

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Abstract: Anastomotic Leakage (AL) remains the main cause of post-esophagectomy morbidity and mortality. Early detection can avoid sepsis and reduce morbidity and mortality. This study evaluates the diagnostic accuracy of the NUn-score and its components as early detectors of AL. This single centre observational cohort study included all esophagectomies from 2010-2020. C-reactive Protein (CRP), Albumin (Alb) and White cell count (WCC) were analyzed and Nun-scores calculated. Area under the curves (AUC) were used to assess their predictive accuracy. Seventy-four of the 668 patients (11%) developed an AL. CRP and the NUn-score proved to be good diagnostic accuracy tests on POD2 (CRP AUC:0,859; Nun-score AUC:0,869) and POD4 (CRP AUC:0,924; Nun-score AUC:0,948). A 182mg/L CRP cut-off on POD4 yielded a 87% sensitivity, 88% specificity, a negative predictive value (NPV) of 98% and a positive predictive value (PPV) of 47,7%. A Nun score cut-off>10 resulted in 92% sensitivity, 95% specificity, 99% NPV and 68% PPV. Albumin and WCC have limited value in the detection of post-esophagectomy AL. Elevated CRP and a high NUn score on POD4 provide a high accuracy to predict AL after esophageal cancer surgery. Their high negative predictive value allows to select patients who can safely proceed with enhanced recovery protocols.

Keywords: NUn score; esophagectomy; anastomotic leakage; risk score; esophageal cancer; inflammatory biomarkers

1. Introduction

The incidence of esophageal (EC) is increasing, making it the 6th leading cause of cancer related mortality worldwide . The prognosis remains poor with 5 Year overall survival rates varying from 90% for stage 1 cancer to <10% for stage IV cancer patients. For locally advanced cancer, multimodality therapy followed by surgery has convincingly improved both local control and overall survival . Surgical resection and lymphadenectomy remain crucial in the treatment of non-metastatic esophageal cancer patients . However, the procedure is known for its potentially complicated postoperative course. Large benchmarking series report postoperative complications in more than 50% of cases, even in high volume centers. Pulmonary complications (15-25%), cardiac events (14-15%) and failure of the esophagogastric anastomosis (12-16%) remain the most important sources of both morbidity and mortality after esophagectomy . Considerable improvements in surgical technique and perioperative care have resulted in 90-day mortality rates after esophagectomy of less than 5% in experienced centers . However, the mortality of AL remains high, ranging from 7 to 17%. The severity of AL depends on the location of the anastomosis, the estimated surface and circumference of the defect, the extent of contamination, the degree of sepsis, and the time from occurrence to diagnosis and therapy . Early detection and management of an AL can prevent the development of a mediastinitis related sepsis and is critical to improving its outcome .

 doi:10.20944/preprints202401.0456.v1

Inflammatory biomarkers have previously been proposed as easy and cheap tests for early diagnosis of postoperative infectious complications after major surgery. C-reactive protein (CRP) is an acute phase protein produced in response to infection, tissue damage and ischemia. A low CRP on postoperative day (POD) 3 and 5 may rule out AL after esophagectomy . However, it can be difficult to distinguish the normal systemic inflammatory response to surgical stress from AL associated sepsis. Identifying a clinically relevant, easy to use scoring system may be helpful in the early diagnosis of AL, selecting patients for imaging, and tailoring AL management. Noble and Underwood introduced the NUn score, using acute phase markers white cell count (WCC), CRP and albumin (Alb) as a predictor of AL and major postoperative complications . The attempts to validate the score are limited and conflicting . We aimed to determine the diagnostic accuracy of these inflammatory response biomarkers and the combined NUn score as early predictors of post-esophagectomy AL.

2. Materials and Methods

The study protocol was approved by the institutional review board of the Ghent University Hospital (reference: B670201111232).

2.1. Surgery and Postoperative care:

Transthoracic (sub)total esophagectomy with 2 or 3-field lymphadenectomy and a right intrathoracic (Ivor Lewis, IL or Transhiatal, THE) or cervical esophagogastric anastomosis (McKeown, McK) was performed in all cases. All procedures were performed by 2 surgeons (PP&EVD). The surgical approach included open as well as hybrid minimally invasive procedures (introduced in 2013). Fully minimal invasive esophagectomy (MIE) was introduced in 2014. All patients received an intrathoracic end-to-side or end-to-end circular esophagogastric anastomosis using a Premium Plus EEA™ (Medtronic) stapler (25 or 28 mm), or a standardized cervical end-to-side hand sewn anastomosis. Patients recovered at the intensive care unit for 12-24h and were then discharged to a dedicated gastrointestinal surgery ward. A nasogastric tube was kept in place during a period of 2-3 days. A water-soluble contrast swallow was obtained on the third postoperative day as a routine screening before initiating oral intake. Patients suspected of AL received an emergency CT scan with oral contrast and/or upper endoscopy. Anastomotic leakage was treated conservatively, endoscopically, or surgically according to clinical presentation. Nutritional support was provided by a feeding jejunostomy. Since 2018 patients were treated according to an Enhanced Recovery After Surgery (ERAS) protocol.

2.2. Patient selection:

This cohort study was based on data gathered from a prospectively kept institutional database supplemented with data from the electronic patient records. Consecutive patients undergoing esophagectomy for cancer and fitting the criteria between January 2010 and December 2020 were included. Patients in whom the esophagus was replaced with the small bowel or the colon, or who underwent concurrent laryngectomy, were excluded.

2.3. Outcomes:

Individual collected data included demographics, American Society of Anesthesiologists (ASA) score, tumor characteristics, type of neoadjuvant therapy, surgical details, pathology reports, laboratory results, and postoperative morbidity and mortality until 90 days postoperatively. Pathological staging was based on the 7th AJCC TNM classification manual. Postoperative morbidity and mortality were classified using the European Complication Consensus Group (ECCG) platform and graded according to the Clavien Dindo classification . Anastomotic leakage was defined as a full thickness gastrointestinal defect involving the esophagus, anastomosis, staple line, or conduit irrespective of presentation or method of identification, according to the ECCG classification. Results

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are reported according to the Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE) guidelines .

2.4. Inflammatory biomarkers and the NUn score:

Acute phase markers were retrieved from the daily blood samples postoperatively, WCC was measured in cells x 10^3/µL (reference range 3.6-9.3 10^3/µL) and converted to 10^9/L for the NUn score calculation. Serum concentrations of Albumin were expressed in g/L (normal range 35-52 g/L) and CRP in mg/L (normal range < 0.5 mg/L). The NUn score was calculated according the original Noble formula: 11.3894 + (0.005 x CRP in mg/L) + (0.186 x WCC in 10^9/L) - (0.174 x albumin in g/L). Missing data were replaced using the last observation carried forward approach.

2.5. Statistical analysis:

All analyses were performed using IBM SPSS® version 28 for Windows® and Sigmaplot® version 13 for Windows®. Continuous data are summarized as means with standard deviations (SD), or as medians with interquartile ranges (IQR). Categorical data are reported using frequencies and percentages. Independent samples t test, Pearson chi square, Fisher's exact and Mann-Witney U tests are used to compare means and proportions. Significance of the different covariates in the prediction of AL were assessed using univariate analysis. Predictive accuracy of the biomarkers and the NUn score was assessed using receiver operating curve (ROC) analyses and the area under (AUC). Sensitivity, specificity, positive and negative predictive value are calculated for the determined cut off values of the biomarkers and the NUn score.

3. Results

3.1. Demographics of the study cohort:

Between January 2010 and December 2020, 668 esophagectomy patients were identified matching the inclusion criteria. Demographic data and their univariable association with AL are detailed in Table 1. Mean age was 64,0 ± 12,2 years (78,9%% male). Overall 74 patients (11,1%) experienced an anastomotic leak. The majority of patients were treated for an adenocarcinoma (67,5%). Univariable analysis could not identify statistically significant differences in demographics, comorbidities, neoadjuvant treatment regimens, histology or clinical staging between the patients with and without leakage, except for a higher percent of ASA 3 patients in the AL group. The surgical procedure, approach and conditions did however significantly influence the AL rate, with a significant higher AL rate in patients with a cervical anastomosis (McK 28% vs IL 10,9% vs THE 5,2%, p=0,010), after total minimally invasive surgery (16,8% vs 8,6% after both open and hybrid procedures, p=0,008) and when an emergency procedure was performed. AL was defined according to the ECCG guidelines, diagnosed on CT-scan and/or upper GI endoscopy and graded according to both the CD (17,6% gr 2; 1,4% gr 3a; 43,2% gr 3b; 27% gr 4a; 8,1% gr 4b and 2,7% gr 5) and ECCG grading system (18,9% type 1; 12,2% type 2 and 68,9% type 3).

Table 1. Baseline characteristics.

		All patients (n= 668)	*no AL (n= 594)*	*AL (n= 74)*	*P value*
Age, (y)	Mean ± SD	64,0 ± 12,2	64,8 ± 10,2	65,6 ± 8,9	0,508
BMI (kg/m²)	Mean ± SD	25,3 ± 4,6	25,2 ± 4,5	25,9 ± 4,9	0,252
ASA score, n (%)	1	27 (4,0%)	24 (4,1%)	3 (4,1%)	**0,036**
	2	286 (42,8%)	261 (43,9%)	25 (33,7%)	
	3	335 (50,1%)	292 (49,2%)	43 (58,1%)	
	4	4 (0,6%)	2 (0,3%)	2 (2,7%)	
Gender, n (%)	Male	527 (78,9%)	468 (78,8%)	59 (79,7%)	0,851

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	Female	141 (21,1%)	126 (21,2%)	15 (20,3%)	
Comorbidities, n (%)	Kidney disease	21 (3,1%)	19 (3,2%)	2 (2,7%)	0,818
	Cardiovascular disease	257 (38,5%)	226 (38,0%)	31 (41,9%)	0,522
	Pulmonary disease	161 (24,1%)	140 (23,6%)	21 (28,4%)	0,362
	Diabetes	88 (13,2%)	75 (12,6%)	13 (17,6%)	0,236
	Smoking	230 (34,4%)	200 (33,7%)	30 (40,5%)	0,241
	Corticosteroids	20 (3,0%)	16 (2,7%)	4 (5,4%)	0,197
Tumor Location, n (%)	proximal	17 (2,5%)	12 (2,0%)	5 (6,8%)	0,094
	mid	121 (18,1%)	110 (18,5%)	11 (14,9%)	
	distal	402 (60,2%)	357 (60,1%)	45 (60,8%)	
	GEJ	128 (19,2%)	115 (19,4%)	13 (17,6%)	
Neoadjuvant therapy, n (%)	none	179 (26,8%)	158 (26,6%)	21 (28,4%)	0,932
	Chemotherapy	97 (14,5%)	87 (14,6%)	10 (13,5%)	
	Radiochemotherapy	392 (58,7%)	349 (58,8%)	43 (58,1%)	
Histology, n (%)	Adeno Ca	451 (67,5%)	402 (67,7%)	49 (66,2%)	0,719
	Squamous cell Ca	200 (29,9%)	176 (29,6%)	24 (32,4%)	
	Other	17 (2,5%)	16 (2,7%)	1 (1,4%)	
cT-stage, n (%)*	Tx	8 (1,2%)	7 (1,2%)	1 (1,4%)	0,641
	T1	56 (8,4%)	49 (8,2%)	7 (9,5%)	
	T2	136 (20,4%)	118 (19,9%)	18 (24,3%)	
	T3	455 (68,1%)	407 (68,5%)	48 (64,9%)	
	T4	13 (1,9%)	13 (2,2%)	0 (0,0%)	
cN-stage, n (%)*	N0	227 (34,0%)	203 (34,2%)	24 (32,4%)	0,898
	N1	308 (46,1%)	276 (46,5%)	32 (43,2%)	
	N2	112 (16,8%)	97 (16,3%)	15 (20,3%)	
	N3	13 (1,9%)	11 (1,9%)	2 (2,7%)	
cM-stage, n (%)*	M0	625 (93,6%)	556 (93,6%)	69 (93,2%)	0,989
	M1	35 (5,2%)	31 (5,2%)	4 (5,4%)	
Procedure, n (%)	IL	586 (87,7%)	522 (87,9%)	64 (86,5%)	**0,010**
	McK	25 (3,7%)	18 (3,0%)	7 (9,5%)	
	THE	57 (8,5%)	54 (9,1%)	3 (4,1%)	
Approach, n (%)	Open	327 (49,0%)	299 (50,3%)	28 (37,8%)	**0,008**
	Hybride	139 (20,8%)	127 (21,4%)	12 (16,2%)	
	MIE	202 (30,2%)	168 (28,3%)	34 (45,9%)	
type of surgery, n (%)	Elective	608 (91,0%)	545 (91,8%)	63 (85,1%)	**<0,001**
	Emergency	5 (0,7%)	1 (0,2%)	4 (5,4%)	
	Salvage	55 (8,2%)	48 (8,1%)	7 (9,5%)	

SD, standard deviation; BMI, body mass index; ASA, American Society of Anesthesiologists; GEJ, gastro esophageal junction; IL, Ivor-Lewis; McK, McKeown; THE, transhiatal esophagectomy; * cTNM staging according to the AJCC 8th edition; Bold values state statistical significance.

3.2. Mean levels of inflammatory biomarkers and severity of the AL:

CRP was available in 642 and 613 patients on POD2 and 4, WCC was measured in 645 and 662 patients on both days and Albumin was available for 596 patients on POD2 and 615 on POD4. Missing data were replaced using the last observation carried forward approach. Nun scores were calculated for all but 5 patients on POD2 and 4 on POD4. Mean CRP, WCC and combined NUN scores were

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significantly higher in AL patients compared to the non-AL patients, and this significance was confirmed for al ECCG AL types. Mean Alb was significantly lower in the AL group. Mean CRP and WCC levels were higher in patients with a more sever ECCG grade of AL, specifically when type 1 AL were compared to type 2 and 3 AL. The significance was present for the evaluated biomarkers both on POD2 and POD4 (Figure 1). All biomarkers were identified as significant markers for any type of AL at POD2 and POD4 on univariate analysis including the NUn-score proposed by Noble (Table 2).

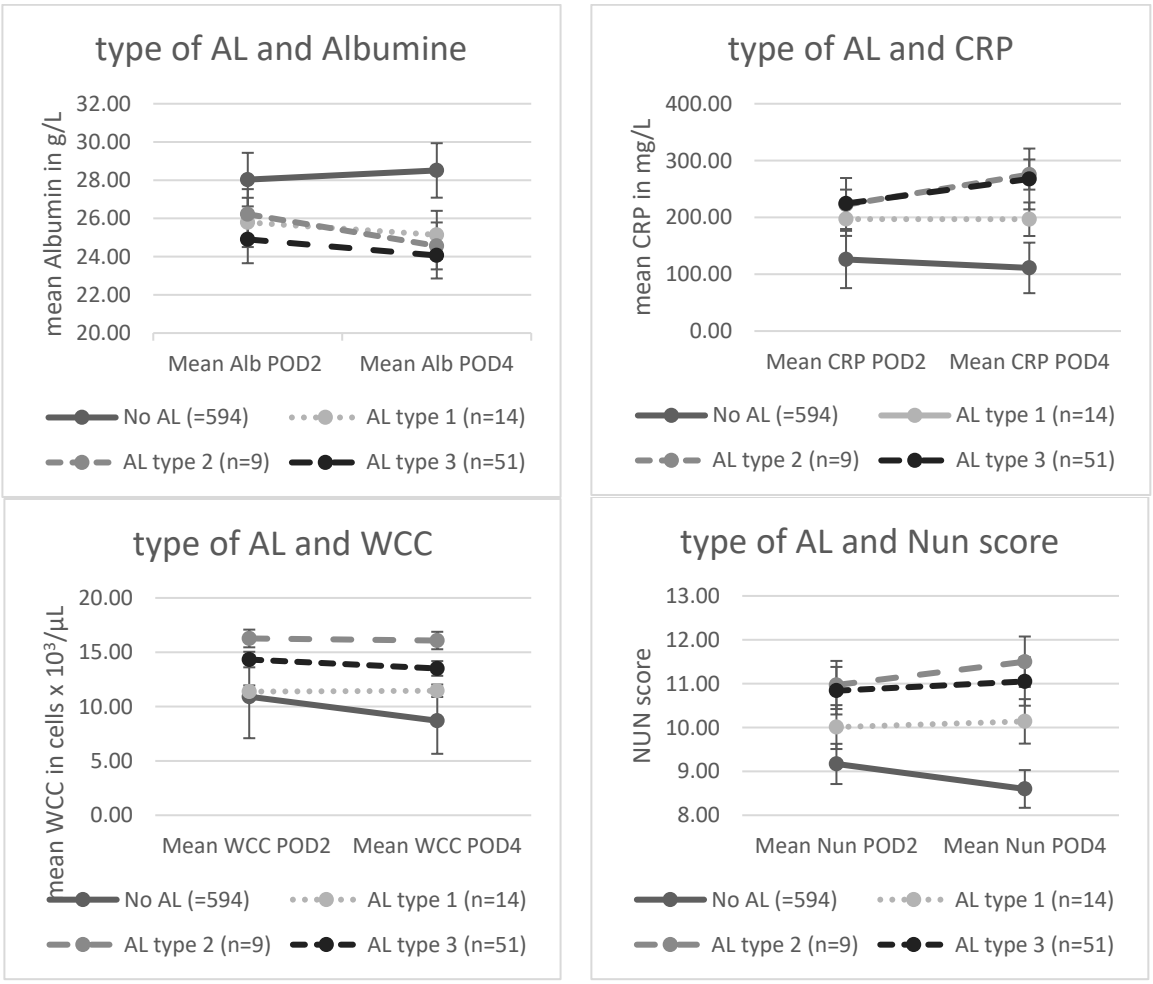

Figure 1. Mean levels of Albumin, CRP, WCC and Nun score on postoperative day 2 and 4 in patients with and without AL, stratified by ECCG type of AL (data displayed as means with standard deviation). (a) Correlation between mean Alb and type of AL, (b) Correlation between mean CRP and type of AL, (c) Correlation between mean WCC and type of AL, Correlation between mean NUn and type of A.

Table 2. univariate analysis of the mean biomarkers and Nun score on POD2 and 4 according to the ECCG type of AL.

	No AL (=594)	AL type 1 (n=14)	AL type 2 (n=9)	AL type 3 (n=51)	p value
Alb POD2 (mean ± SD)	28,0 (± 3,7)	25,8 (± 2,6)	26,2 (± 4,4)	24,9 (± 4,1)	<,001
Alb POD4 (mean ± SD)	28,5 (± 3,9)	25,1 (± 3,4)	24,6 (± 4,0)	24,1 (± 3,2)	<,001
CRP POD2 (mean ± SD)	125,9 (± 55,4)	197,0 (± 89,8)	222,3 (± 73,2)	224,4 (± 67,9)	<,001
CRP POD4 (mean ± SD)	111,1 (± 62,8)	196,8 (± 84,9)	275,4 (± 86,4)	267,6 (± 74,0)	<,001
WCC POD2 (mean ± SD)	10,9 (± 5,2)	11,4 (± 3,6)	16,3 (± 6,5)	14,3 (± 4,2)	<,001

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WCC POD4 (mean ± SD)	8,7 (± 2,9)	11,46 (± 3,7)	16,1 (± 5,7)	13,5 (± 4,5)	<,001
Nun POD2 (mean ± SD)	9,2 (± 1,2)	10,0 (± 0,8)	10,9 (± 1,4)	10,8 (± 1,0)	<,001
Nun POD4 (mean ± SD)	8,6 (± 1,0)	10,1 (± 1,2)	11,5 (± 0,8)	11,1 (± 0,9)	<,001

3.3. Optimal cut-off and predictive accuracy of Albumin:

Mean Albumin levels for patients with and without AL were 25.2 versus 28.0 g/L on POD2 (p<0.001) and 24.3 versus 28.5 g/L on POD4 (p<0,001). Figure 2 shows the ROC curve analyses of albumin, with a fair performance on POD2 (AUC 0.710, 95% CI: 0.646 – 0.774) and POD4 (AUC 0.799, 95% CI: 0.746 – 0.853). A POD4 albumin threshold of 26.5 g/L had the highest but still limited diagnostic accuracy, with a sensitivity of 80%, a specificity of 68%, a negative predictive value of 96% but a positive predictive value of only 24%.

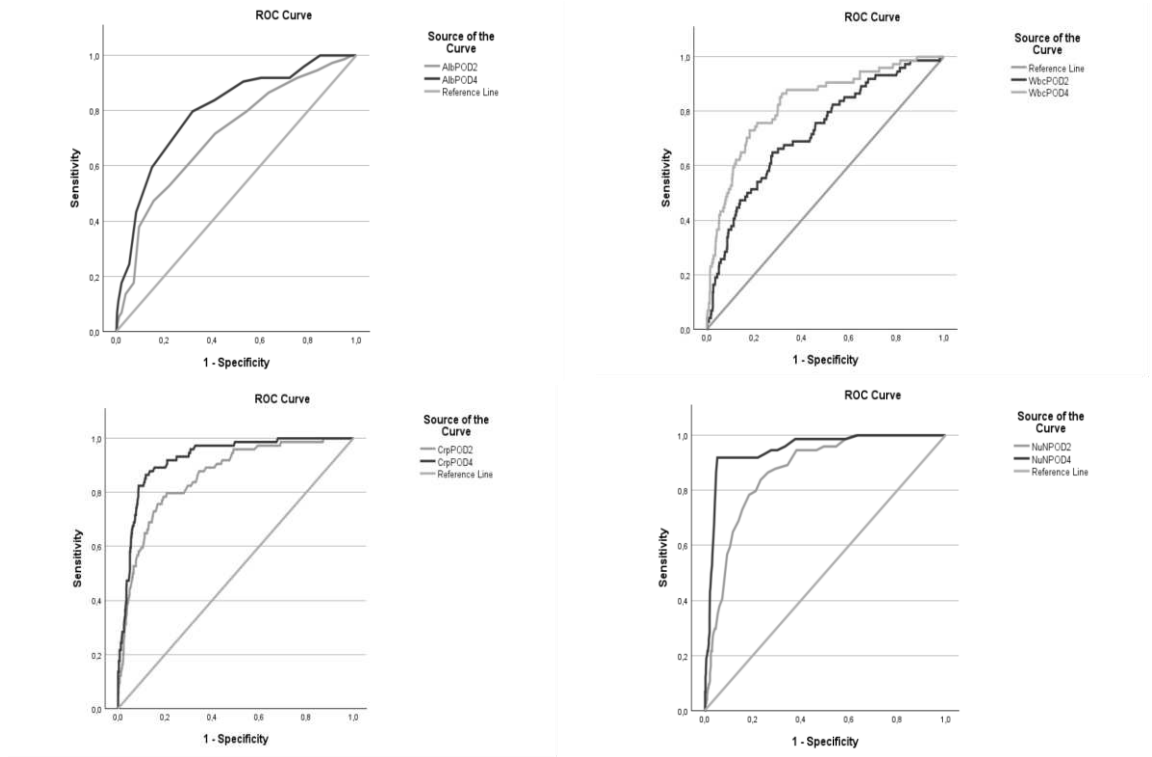

Figure 2. Receiver operating curve (ROC) for Albumin, C-reactive protein, White cell count and the Nun score on POD2 (light gray) and POD4 (dark grey) and their diagnostic accuracy in detecting AL. (a) ROC curve for Alb, (b) ROC curve for WCC, (c) ROC curve for CRP, (a) ROC curve for the Nun score.

3.4. Optimal cut-off and predictive accuracy of CRP:

The mean CRP levels for patients with and without AL was 218,9 versus 125,9 mg/L respectively on POD2 (p<0,001) and 255,2 mg/L versus 111,1 on POD4 (p<0,001). Figure 2 shows the ROC curve analyses of CRP, with a good performance on POD2 (AUC 0.859, 95% CI: 0.816 – 0.903) and an excellent performance on POD4 (AUC 0.924, 95% CI: 0.896 – 0.953). A POD4 CRP threshold of 181,5 mg/L had the highest diagnostic accuracy compared to all the other individual markers, with a sensitivity of 87%, a specificity of 88%, a negative predictive value of 98% and a positive predictive value of 48%.

3.5. Optimal cut-off and predictive accuracy of WCC:

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Mean WCC levels were significantly higher for patients with AL (14.0 and 13.4 x 10^3/µL on POD 2 and 4) compared to the those from patients without an AL (10.9 and 8.7 x 10^3/µL on POD2 and 4) (p<0,001). Figure 2 shows the ROC curve analyses of WCC, with a fair performance on POD2 (AUC 0.724 95% CI: 0.662 – 0.786) but a good performance on POD4 (AUC 0.829, 95% CI: 0.777 – 0.880). A POD4 WCC cut-off of 10.9 x 10^3/µL resulted in a sensitivity of 73%, a specificity of 82%, a negative predictive value of 96% and a positive predictive value of 33%.

3.6. Optimal cut-off and predictive accuracy of the NUn score:

Patients with AL presented a mean NUn score of 10.7 on POD2 and 10.9 on POD2 compared to a 9.2 and 8.6 score on POD 2 and 4 on the non-AL group (p<0,001). The presence of a NUn score>10 on POD4 as presented by Noble and Underwood who designed the score, was identified as a significant risk factor for AL both in univariate and multivariate analysis in this study group. Figure 2 shows the ROC curve analyses of the NUn score, with a good performance on POD2 (AUC 0.869, 95% CI: 0.833 – 0.905) and an excellent performance on POD4 (AUC 0.948, 95% CI: 0.923 – 0.972). This combined score presented an excellent performance on POD4 with an even higher AUC (AUC 0.948) than CRP on POD4 (AUC 0.924). A POD4 NUn score of >10 had the highest diagnostic accuracy compared to all the other individual markers, with a sensitivity of 92%, a specificity of 95%, a negative predictive value of 99% and a positive predictive value of 68% (Table 3).

Table 3. Threshold values for Alb, CRP, WCC and the Nun score and their diagnostic accuracy for AL .

variable		AUC	95% CI	p value	Cut-off	sens	spec	PPV	NPV	PLR	NLR
Alb	POD2	0,710	0,646 - 0,774	**< 0,001**	24,5	47,30%	84,40%	27,42%	92,78%	3,032	0,624
	POD4	0,799	0,746 - 0,853	**< 0,001**	26,5	79,70%	68,20%	23,79%	96,42%	2,506	0,298
CRP	POD2	0,859	0,816 - 0,903	**< 0,001**	165,5	79,70%	79,30%	32,42%	96,90%	3,850	0,256
	POD4	0,924	0,896 - 0,953	**< 0,001**	181,5	86,50%	88,20%	47,73%	98,13%	7,330	0,153
WCC	POD2	0,724	0,662 - 0,786	**< 0,001**	12,255	64,90%	72,30%	22,59%	94,30%	2,343	0,486
	POD4	0,829	0,777 - 0,880	**< 0,001**	10,885	73,00%	82,00%	33,57%	96,06%	4,056	0,329
Nun	POD2	0,869	0,833 - 0,905	**< 0,001**	9,75	83,80%	76,80%	31,03%	97,44%	3,612	0,211
	POD4	0,948	0,923 - 0,972	**< 0,001**	10,05	91,90%	94,70%	68,36%	98,95%	17,340	0,086

AUC, area under the curve; SE, standard error; CI, confidence interval; Sen, sensitivity; Spec, specificity; PPV, positive predictive value; NPV, negative predictive value; PLR, positive likelihood ratio; NLR, negative likelihood ratio.

4. Discussion

Failure of the esophagogastric anastomosis (12-16%) remain the most important source of prolonged hospital stay, increased risk for reoperation and stricture, short term reduced quality of live, increased costs and increased perioperative death . The effect of post esophagectomy AL on long term oncological and functional outcome is still under debate.

 doi:10.20944/preprints202401.0456.v1

The clinical presentation of AL is diverse and its severity ranges widely, mainly determined by the location and extent of the defect, the extent of the contamination and sepsis, and the time from onset to treatment . Early diagnosis and treatment helps to prevent subsequent sepsis and improves AL related outcome. This observational study demonstrates the clinical utility of both CRP and the NUN score in postoperative AL monitoring in esophagectomy patients. The high NPV and the rather low PPV, however suggest that their main value is not the early detection, but rather the early exclusion of an AL.

A postoperative drop in *albumin* (Alb) is thought to be a marker for surgical stress and low concentrations of Alb and prealbumin on POD4-6 are identified as potential risk factors for AL. Five studies evaluated post Alb in relation to AL but only Noble reported a significant association with a POD 5 cut-off <22,5 g/L with fair performance (AUC 0,742). Our analyses identified an equally fair performance for Alb with threshold values of <24,5 on POD2 (AUC 0,710) and <26,5 g/L on POD4 (AUC 0,799). Given the limited AUCs, the authors do not advocate Alb alone as a prediction of AL, however pre albumin, Alb in combined scores (Alb/CRP ratio, CART algorithm) and a perioperative Alb decrease of 11 g/L seem more promising as predictors .

Elevated *CRP* levels are the most common previously identified marker for post esophagectomy complications . CRP is an acute phase protein synthesized in the liver in response to endotoxins, and its levels commonly increase within 6h after the onset of the inflammation. It is a marker for acute inflammation with a high sensitivity but often low specificity for its inflammatory origin. CRP values have been studied from POD 1-10 with most studies focusing on POD 3-5. However the earlier the AL is suspected, the earlier adequate diagnosis and treatment can be performed. We therefor focused on POD 2-4, as POD1 CRP showed low diagnostic performance in previous literature. In this study mean CRP levels on POD2-4 were significantly higher in the AL group and proportionally correlated to the ECCG type of the AL. A finding consistent with Hagens's findings, however due to the small sample size in that cohort, they could not prove statistical significance . ROC curves were plotted to identify a CRP cut-off level of 165 mg/L on POD2 with good diagnostic performance (AUC 0.859) and cut-off level of 181 mg/L on POD4 with excellent performance on POD4 (AUC 0.924). Six other studies evaluated POD2 CRP with varying thresholds from 177-300 mg/L . All studies identified higher thresholds then ours on POD2, and with lower AUC's, except Ji who identified a cut-off of 177 mg/L on POD2 with a good performance (AUC 0,994, sens 90%, spec 95%) similar to the one identified in this study. Our POD4 cut-off of 181 mg/L was significantly higher than the cut-off level of 111 mg/L reported by Miki and 106 mg/L by Stuart , probably because they only included MIE patients, but in line with the threshold value of 177 mg/L published in a meta-analyses by Aiolfi . Based on the high AUC, the relevant sensitivity, specificity, low PPV but high NPV, we could identify POD2-4 CRP levels only to be useful in the exclusion and not in the diagnosis of an AL. Consistent with most other studies who identify CRP as a negative predictor for AL but not as a clinically useful diagnostic test.

Mean *WCC* levels were significantly different between the AL and the non-AL patients. However our study identified WCC on POD 2 to have only a fair diagnostic accuracy (AUC 0,724) while POD4 had a good diagnostic performance (AUC 0,829) on POD 4. The high NPV and low PPV again suggests clinically use as negative predictor instead of a diagnostic tool. Multiple studies evaluated WCC but only 3 reported cut-off values, however on POD 3 and 5 and with poor diagnostic accuracy, eliminating the possibility for comparison .

Noble combined CRP, Alb and white cell count in the NUn score, in an attempt to increase their accuracy as a AL predictor . Findlay and Paireder failed to validate the score, potentially because they included all AL, both symptomatic and asymptomatic compared to Noble who included only "leaks sufficient to cause symptoms" . Bundred however successfully validated the scores' cut-off value of 10 on POD4 for AL, however with a fair diagnostic accuracy (AUC 0,77) and again including "any symptomatic leak, confirmed by radiology or endoscopy" consistent to Noble's definition . Liesenfeld identified a sign difference between the mean NUn score of AL negative and positive patients (8.6 vs 9.1, p=0.006) but the optimal cut-off value recommended by Noble could not be confirmed as AL predictor. Mean NUn scores on POD2-4 were significantly different between both groups in our

cohort. The presence of a NUn score >10 on POD4 was identified as a significant risk factor for AL and the ROC curve analyses showed good performance on POD2 (AUC 0.869) and an excellent performance on POD4 (AUC 0.948), validating the score in this cohort. A POD4 NUn score of >10 had the highest diagnostic accuracy compared to all other markers, with a high sensitivity (92%) and specificity (95%). The NPV of 99% and PPV of 68% again suggest its main value in excluding AL rather than diagnosing them.

This study has multiple pitfalls, it is retrospective in nature but based on prospectively collected data. We included a heterogenic esophagectomy population including different procedures, approaches and types of surgery, all know to have an impact on the AL rate and potentially biasing the results. However we wanted to evaluate cheap and easily available tests and facilitate and standardize their clinical use in postoperative monitoring for all esophagectomy patients. EC cancer is a rare disease resulting in a limited amount of annual esophagectomies, nevertheless we present a large population for a single center observational study. Moreover this is the first study to validate the NUn-score for all ECCG types of AL.

5. Conclusions

CRP and the NUn score both show good diagnostic performance on POD2 and excellent performance on POD4. They are however only valuable for AL exclusion, which can be useful in algorithms for a safe and early discharge. There is no single test that can rule out AL but patients with a CRP <165 mg/L on POD2 are unlikely to develop an AL and can safely continue their ERAS protocol. Patients with a CRP <181 mg/dL and or a NUn score <10 on POD4 can safely be discharged when clinically possible. The value of CRP in the diagnosis of AL however is limited and other diagnostic tools are needed in case of AL suspicion.

Author Contributions: Conceptualization, Elke Van Daele, Hanne Vanommeslaeghe and Piet Pattyn; Data curation, Elke Van Daele, Hanne Vanommeslaeghe, Flo Decoster, Louise Beckers Perletti and Esther Beel; Formal analysis, Elke Van Daele and Wim Ceelen; Investigation, Flo Decoster, Louise Beckers Perletti and Esther Beel; Methodology, Elke Van Daele; Supervision, Yves Van Nieuwenhove, Wim Ceelen and Piet Pattyn; Writing – original draft, Elke Van Daele; Writing – review & editing, Hanne Vanommeslaeghe, Yves Van Nieuwenhove, Wim Ceelen and Piet Pattyn.

Institutional Review Board Statement: Ethical approval for the creation and maintenance of an observational prospective database for patients after esophageal resections was granted by the institutional Ethical committee of the Ghent University Hospital. Belgian registration number: B670201111232. Ethical approval for this retrospective data analysis was granted by the same Ethical committee of the Ghent University Hospital, registration number: BC-07939.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study for the inclusion in the institutional dataset. The authors received a statement from their ethical committee stating that no additional informed consent is required for this retrospective analyses.

Data Availability Statement: All relevant data are available within the paper. Additional data if needed can be obtained through the corresponding author after approval by the local ethical committee.

Acknowledgments: We thank our study and data nurses for their help in constructing and supporting our esophageal database.

Conflicts of Interest: The authors declare no conflict of interest.

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