RESEARCH ARTICLE

Early postoperative decrease of albumin is an independent predictor of major complications after oncological esophagectomy: A multicenter study

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Abstract

Background and Objectives: Serum albumin perioperative decrease (Δ Alb) may reflect the magnitude of the physiological stress induced by surgery. Studies highlighted its value to predict adverse postoperative outcomes, but data in esophageal surgery are scant. This study aimed to investigate the role of Δ Alb to predict major complications after esophagectomy for cancer.

Methods: Multicenter retrospective study conducted in five high-volume centers, including consecutive patients undergoing an esophagectomy for cancer between 2006 and 2017. Patients were randomly assigned to a training ($n = 696$) and a validation ($n = 350$) cohort. Albumin decrease was calculated on postoperative day 1 and defined as Δ Alb. The primary endpoint was major complications according to Clavien classification.

Results: In the training cohort, esophagectomy induced a rapid drop of albumin. Cut-off of Δ Alb was established at 11 g/L and allowed to distinguish patients with adverse outcomes. On multivariable analysis, Δ Alb was identified as an independent predictor of major complications (OR, 1.06; 95% CI, 1.01–1.11; $p = .014$). Higher BMI and laparoscopy were associated with lower Δ Alb. Analysis of the validation cohort provided consistent findings.

Conclusions: Δ Alb appeared as a promising biomarker after oncological esophagectomy, allowing prediction of potential adverse outcomes.

KEYWORDS

cancer, biomarker, esophagus, surgical oncology

1 | INTRODUCTION

Esophageal cancer is the sixth most frequent cause of cancer-related mortality worldwide, with an increased incidence of adenocarcinoma in the Western world related to obesity and uncontrolled reflux disease.^{1,2} Surgery constitutes the cornerstone of curative treatment for non-metastatic lesions, combined with chemo/radiotherapy for locally advanced stages.^{3,4} Although minimally invasive esophagectomy (MIE) may improve short-term outcomes,^{5,6} esophagectomy remains associated with substantial rates of mortality and severe morbidity, which may compromise long-term survival.^{7,8} Early identification of postoperative complications is of utmost importance, as their systemic impact and subsequent risk of mortality may be reduced if they are promptly detected and treated, especially in elderly or frail patients.⁹ In this context, the identification of accurate biomarkers able to predict adverse outcomes early in the postoperative course is of high clinical relevance, as it may help to better anticipate patients' care and to improve their outcomes. Ideal candidate biomarkers need to fulfill the following criteria: performant, early indicative, easy to measure, and cost-effective.^{10,11}

Previous studies have suggested postoperative albumin drop (Δ Alb) as a marker of surgical stress, associated with the risk of postoperative complications after major abdominal surgery.^{12–16} It is already predictive within the first 6–24 h after surgery and was more robust than other inflammatory biomarkers currently used in daily practice, such as C-reactive protein, which reaches a postoperative peak between postoperative day (POD) 2 and 3.^{17,18} Albumin as an early predictor of postoperative complications after oncological esophagectomy was reported by Ryan et al. in 2007¹⁴; however, validation by a large-scale study was necessary to recommend its use in clinical practice.

This study aimed to investigate the value of Δ Alb to predict major complications after oncological esophagectomy.

2 | MATERIALS AND METHODS

2.1 | Design and cohorts

A multicenter retrospective study conducted in five high-volume University Hospitals was conducted: CHUV in Lausanne (Switzerland), CHU of Lille (France), St-James Hospital in Dublin (Ireland), Karolinska University Hospital of Stockholm (Sweden), and Amsterdam University Medical Centers (location AMC) of Amsterdam (Netherlands). Consecutive patients undergoing oncological esophageal resection between 2006 and 2017 were included. Each local Institutional Review Board (IRB) approved the study protocol.

2.2 | Selection of patients

Inclusion criteria were patients > 18 years undergoing esophagectomy during the study period. Non-oncological patients and

patients with missing preoperative or postoperative values of albumin were excluded. Data were retrieved from institutional databases and transmitted anonymously to the principal investigator for analyses. Collected data included demographics, surgical details, perioperative variables as well as short- and long-term outcomes.

2.3 | Biomarkers

Serum albumin concentration was measured in g/L, in preoperative blood samples taken <4 weeks before surgery, as well as postoperatively on POD 1–3. Its fluctuation was defined as Δ Alb and calculated on POD 1, as follows: (preoperative value of albumin – albumin value on POD 1). Timepoints were determined based on available prospective data,¹⁵ as well as to tailor a biomarker being indicative as early as possible. The absolute albumin value on POD 1 (g/L) was separately assessed as a categorical variable, with cutoffs determined at <20, 20–25, 25–30, and >30 g/L, based on previous data, suggesting a good correlation with adverse postoperative outcomes.¹⁴ Subgroup analysis was performed for a subset of patients with available values of white blood cell count (WBC) [G/L] and C-Reactive protein (CRP) (mg/L) on POD 3.

2.4 | Endpoints

The Clavien classification was used to grade postoperative complications. Minor complications, major complications, and mortality were defined as Grades I–II, III–IV, and V, respectively.¹⁹ Primary endpoint was major complications whereas secondary endpoints were overall complications, Comprehensive Complication Index (CCI),²⁰ and length of stay (LoS) calculated from the day of surgery.

2.5 | Statistical analyses

To obtain training and validation cohorts, patients were randomized in training and validation cohorts, according to a 2:1 ratio.²¹ To do so, we used the randomization system of statistical software. Training cohort was utilized to investigate the perioperative profile of albumin, to identify an optimal cut-off and to explore its predictive value. These findings were thereafter tested in the validation cohort. This approach displays the advantage to provide external validity, to avoid overparameterization and to reduce the risk of type-1 error.

According to their distribution, continuous variables were provided as median with interquartile range (IQR) or as mean with standard deviations ($\pm$ SD). Student's *t*-test was used for their comparison. Categorical data were displayed as frequencies with valid percentages and compared with χ^2 test. Receiver operating characteristic (ROC) curves were generated to calculate the area under the curve (AUC). The threshold was determined to obtain equal sensitivity and specificity. Multivariable analyses integrating potential confounding factors were performed by logistic regression.

TABLE 1 Cohorts and patients characteristics

	Training cohort (n = 696)	Validation cohort (n = 350)	p value
Age (years)	63 (57–69)	64 (58–70)	.483
Gender (female)	164 (24)	77 (22)	.587
ASA score (III–IV)	130 (19)	73 (21)	.400
Smoking	321 (47)	173 (51)	.298
BMI (Kg/m ²)	26 (22–29)	26 (23–29)	.675
Cancer type (ADC)	424 (61)	216 (62)	.966
Neoadjuvant therapy			
Chemotherapy	507 (73)	266 (77)	.172
Radiotherapy	347 (50)	193 (55)	.101
Surgery (Minimal invasive)			
Laparoscopy	268 (39)	132 (38)	.857
Thoracoscopy	94 (14)	63 (19)	.046
Surgery duration (min)	350 (290–410)	350 (290–410)	.660
Blood loss (ml)	350 (200–600)	350 (200–650)	.542

Note: Continuous variables are provided as median with interquartile range. Categorical variables are provided as frequencies with valid percentages.

Abbreviations: ADC, adenocarcinoma; ASA, American Society of Anesthesiologists; BMI, body mass index.

Variables with $p < .05$ in univariable analysis were further integrated and tested in multivariable analysis. Statistical significance was defined as a $p < .05$. IBM SPSS Statistics 25.0 was used to perform all analyses.

3 | RESULTS

3.1 | Patients, cohorts, and outcomes

A total of 1046 patients met the inclusion criteria and were attributed to either the training cohort ($n = 696$) or the validation cohort ($n = 350$). Patients' characteristics and the details of the surgery are provided in Table 1. These two cohorts were well balanced, displaying patients comparable for all variables, except for a higher rate of thoracoscopy in the validation cohort (19% vs. 14%, $p = .046$).

Altogether, minor, major, mortality, and overall complications were reported in 683 (65%), 363 (35%), 35 (3%), and 889 (85%) patients, respectively. Median CCI was 20.9 (8.7–33.7) and median LoS was 15 days (11–24). The outcomes of each cohort are detailed in Table 2.

3.2 | Albumin profile and ΔAlb

The perioperative profile of albumin is illustrated for the training (Figure 1A) and validation (Figure 1B) cohorts; albumin profiles were

TABLE 2 Outcomes

	Training cohort (n = 696)			Validation cohort (n = 350)			Whole cohort (n = 1046)		
	ΔAlb < 11 g/L	ΔAlb ≥ 11 g/L	p value	ΔAlb < 11 g/L	ΔAlb ≥ 11 g/L	p value	ΔAlb < 11 g/L	ΔAlb ≥ 11 g/L	p value
Complications (%)									
Minor	187 (62)	261 (66)	.281	91 (65)	144 (69)	.394	278 (63)	405 (67)	.163
Major	90 (30)	143 (36)	.081	43 (31)	87 (42)	.035	133 (30)	230 (38)	.007
Mortality	13 (4)	11 (3)	.272	4 (3)	7 (3)	.788	17 (4)	18 (3)	.442
Overall	243 (81)	342 (87)	.037	116 (82)	188 (90)	.037	359 (81)	530 (88)	.004
CCI	20.9 (8.7-32.2)	20.9 (8.7-33.7)	.379	20.9 (8.7-31.6)	22.6 (20.9-39.7)	.044	20.9 (8.7-31.5)	20.9 (8.7-34.6)	.058
Respiratory	141 (48)	203 (53)	.170	67 (49)	107 (53)	.434	208 (48)	310 (53)	.115
Anastomotic leak	29 (10)	44 (12)	.525	19 (14)	23 (12)	.547	48 (11)	67 (12)	.670
LoS, days	15 (10-22)	15 (11-25)	.261	16 (11-23)	16 (12-25)	.658	15 (10-22)	16 (11-25)	.230

Note: Continuous variables are provided as median with interquartile range. Categorical variables are provided as frequencies with valid percentages.

Abbreviations: CCI, comprehensive complication index; LoS, length of stay.

consistent in both cohorts. Esophagectomy triggered a prompt fall of albumin on POD 1, followed by a recovery phase. Patients who subsequently developed major complications showed a more rapid decrease in albumin.

Clustering of albumin levels per se on POD 1 did not statistically discriminate patients in terms of major complications rate (Figure 2).

The difference between preoperative and postoperative albumin values was measured on POD 1 (Δ Alb). Median Δ Alb showed a consistent value of 11 g/L (9–14) in all cohorts (training-, validation-, and whole-cohort). Patients with major complications showed higher Δ Alb in both training (12 vs. 11 g/L, $p = .022$) and validation (12 vs. 11 g/L, $p = .012$) cohorts (Figure 3).

3.3 | Δ Alb cut-off and its capacity to discriminate adverse outcomes

Using either technique to determine the ideal cut-off for major complications (either the median value or ROC curve for equal sensitivity/specificity), Δ Alb cut-off was consistently 11 g/L in both training and validation cohorts. We next sought to test whether this cut-off was able to distinguish patients who will develop adverse outcomes (Table 2). Δ Alb ≥ 11 g/L was associated with higher rates of overall complications in the training cohort (87 vs. 81%, $p = .037$). In the validation cohort, patients with Δ Alb ≥ 11 g/L showed increased major complications (42 vs. 31%, $p = .035$), a higher rate of overall complications (90 vs. 82%, $p = .037$) as well as higher CCI (22.6 vs. 20.9, $p = .044$). When merging the two cohorts, a difference was highlighted for major (38 vs. 30%, $p = .007$) and overall complications (88 vs. 81%, $p = .004$). Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of Δ Alb for major complications are summarized in Table S1.

FIGURE 2 Incidence of major complications for clusters of albumin value on POD 1. Columns illustrate incidences of major complications (Y-axis); patients were clustered based on their absolute value of serum albumin on POD 1 in [g/L] (X-axis): <20 g/L (blue), 20–25 g/L (orange), 26–30 g/L (green), and >30 g/L (gray). POD, postoperative day [Color figure can be viewed at wileyonlinelibrary.com]

3.4 | Predictors of major complications

A logistic regression model integrating multiple potential confounding factors was performed to identify independent predictors of major complications (Table 3). In the training cohort, ASA score (OR, 1.78; 95% CI, 1.26–2.52; $p = .001$) and Δ Alb (OR, 1.06; 95% CI, 1.01–1.11; $p = .014$) were identified as independent predictors of major complications. In the validation cohort, Δ Alb was the only factor independently associated with major complications (OR, 1.05; 95% CI, 1.00–1.11; $p = .041$). Of note, the absolute value of albumin POD 1 was not included in the multivariable analysis to avoid multicollinearity.

FIGURE 1 Perioperative profile of albumin. Perioperative profile of albumin: curves reflect median values of albumin [g/L] and bars represent interquartile range. Gray and orange curves indicate patients with and without major complications, respectively. A, Training cohort ($n = 696$). B, Validation cohort ($n = 350$) [Color figure can be viewed at wileyonlinelibrary.com]

FIGURE 3 Comparison of ΔAlb . ΔAlb , boxplots of perioperative albumin variation (ΔAlb). Gray and orange illustrate patients with and without major complications, respectively [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Multivariable analysis to identify independent predictors of major complications

	Training cohort (n = 696)						Validation cohort (n = 350)					
	Univariable			Multivariable			Univariable			Multivariable		
	OR	95% CI	p value	OR	95% CI	p value	OR	95% CI	p value	OR	95% CI	p value
Age, years	1.00	0.99–1.02	.684				1.01	0.98–1.03	0.591			
Gender (female)	0.59	0.41–0.85	.004	0.79	0.46–1.34	.383	0.98	0.58–1.65	0.932			
ASA score	1.29	1.03–1.63	.03	1.78	1.26–2.52	.001	1.09	0.79–1.50	0.588			
Smoking	0.71	0.51–0.97	.033	0.68	0.43–1.08	.104	1.15	0.74–1.78	0.537			
BMI, kg/m ²	0.98	0.95–1.01	.192				0.99	0.94–1.04	0.709			
Cancer type (ADC)	0.85	0.64–1.13	.257				0.871	0.59–1.28	0.483			
Neoadjuvant therapy												
Chemotherapy	0.83	0.58–1.17	.28				0.65	0.39–1.07	0.092			
Radiotherapy	1.14	0.83–1.57	.406				1.11	0.72–1.72	0.639			
Minimal invasive surgery												
Laparoscopy	0.65	0.46–0.9	.01	1.14	0.71–1.83	.587	0.62	0.39–0.98	0.042	0.68	0.43–1.09	.109
Thoracoscopy	1.19	0.76–1.88	.445				0.57	0.31–1.04	0.065			
Surgery duration, min	1.00	1.00–1.01	.019	1.00	1.00–1.00	.159	1.00	1.00–1.01	0.249			
Blood loss, ml	1.00	1.00–1.00	.213				1.00	1.00–1.00	0.072			
Preoperative Alb, g/L	0.98	0.95–1.00	.059				1.00	0.96–1.05	0.914			
ΔAlb , g/L	1.04	1.01–1.07	.023	1.06	1.01–1.11	.014	1.06	1.01–1.12	0.013	1.05	1.00–1.11	0.041

Abbreviations: ADC, adenocarcinoma; ASA, American Society of Anesthesiologists; BMI, body mass index; CI, confidential interval; HR, hazard ratio.

TABLE 4 Multivariable analysis to identify independent predictors of $\Delta\text{Alb} \geq 11$ g/L

	Training cohort (n = 696)						Validation cohort (n = 350)					
	Univariable			Multivariable			Univariable			Multivariable		
	OR	95% CI	p value	OR	95% CI	p value	OR	95% CI	p value	OR	95% CI	p value
Age, years	0.98	0.97–1.00	.035	0.99	0.97–1.01	.161	1.00	0.98–1.02	.803			
Gender (female)	0.61	0.42–0.88	.007	0.68	0.45–1.03	.067	0.56	0.33–0.97	.039	0.68	0.37–1.22	.196
ASA score	0.89	0.72–1.11	.311				1.03	0.75–1.41	.85			
Smoking	1.05	0.78–1.42	.75				1.36	0.88–2.10	.165			
BMI, kg/m ²	0.94	0.91–0.97	<.001	0.95	0.92–0.98	.003	0.94	0.89–0.98	.008	0.95	0.90–1.00	.038
Cancer type (ADC)	0.69	0.53–0.90	.007	0.85	0.63–1.15	.286	0.63	0.43–0.93	.018	0.76	0.50–1.16	.202
Neoadjuvant therapy												
Chemotherapy	0.93	0.66–1.31	.676				1.37	0.78–2.42	.271			
Radiotherapy	0.92	0.68–1.24	.569				2.69	0.30–24.29	.379			
Minimal invasive surgery												
Laparoscopy	0.57	0.42–0.77	<.001	0.58	0.40–0.83	.003	0.55	0.35–.85	.008	0.62	0.39–0.99	.046
Thoracoscopy	0.59	0.38–0.91	.017	0.75	0.44–1.28	.289	0.59	0.34–1.02	.058			

Abbreviations: ADC, adenocarcinoma; ASA, American Society of Anesthesiologists; BMI, body mass index; CI, confidential interval; HR, hazard ratio.

3.5 | Determinants of high ΔAlb

A multivariable analysis aimed to explore and understand which factors were associated with an $\Delta\text{Alb} \geq 11$ g/L. Results were consistent in both cohorts, identifying higher BMI and laparoscopy as protective factors (Table 4).

3.6 | The predictive value of other inflammatory biomarkers for major morbidity

A wider panel of commonly used inflammatory biomarkers (CRP, WBC) was available for a subset of 519 patients. Gender (OR, 0.49; 95% CI, 0.27–0.87; $p = .015$), ASA (OR, 1.44; 95% CI, 1.02–2.03; $p = .039$), smoking status (OR, 0.47; 95% CI, 0.28–0.78; $p = .003$), CRP on POD 3 (OR, 1.01; 95% CI, 1.00–1.01; $p < .001$), and ΔAlb (OR, 1.06; 95% CI, 1.00–1.11; $p = .035$) were significantly associated with major morbidity in the training cohort. However, in the validation cohort, only ΔAlb remained independently associated with major postoperative complications (OR, 1.08; 95% CI, 1.00–1.16; $p = .040$), outperforming all other variables including CRP and WBC values on POD 3 (Table S2).

4 | DISCUSSION

This study provided thorough and comprehensive data highlighting the role of albumin, particularly its early postoperative decrease (ΔAlb), to predict adverse postoperative outcomes in patients undergoing oncological esophageal resection.

As hypothesized, esophagectomy induced a rapid drop of albumin,^{9,10,12,12,17} which appeared more pronounced in patients who subsequently developed major complications (Figure 1). Present analyses established a cut-off of ΔAlb at 11 g/L. This cut-off appeared to be robust, regardless of the methodology (dichotomization according to median value or with ROC curve for equal sensitivity/specificity) and of the cohort. Interestingly, the cut-off and predictive values seem to vary according to the type of surgery. In a prospective study on major abdominal surgery, our group identified an ΔAlb of 10 g/L, calculated on POD 1 and predicting overall complications.¹² One of the most important results from this study comes from the multivariable analysis, which integrated multiple potential confounding factors, where ΔAlb was identified as an independent predictor of major complications in both cohorts, unlike other variables. This is likely explained by the fact that ΔAlb recapitulates the physiological stress intensity triggered by surgery, which is determined by several factors, such as the invasiveness of surgery and its duration, as well as the intrinsic characteristics of the patient. Therefore, ΔAlb outperforms these variables separately taken, when looking at complication prediction.

What factors determine the postoperative drop of albumin remains unclear. Laparoscopy and higher BMI appeared as protective factors, associated with lower decrease in albumin levels. Previous studies have also shown a reduction of albumin decrease on POD 1 after MIE compared to open resection, suggesting a blunted metabolic stress response with laparoscopy.²² The recently published MIRO study provides some further indirect evidence supporting this thesis, as a hybrid approach with a laparoscopic approach to the abdomen, and an open thoracotomy resulted in significantly lower rates of postoperative complications compared with open surgery.⁶

Previous studies support that capillary leak of albumin from plasma to adjacent tissues is the main source of albuminemia decrease, along with reduced hepatic production shifting to acute-phase proteins, such as CRP.¹⁷ Why a higher BMI impacts on albumin levels is unclear. A higher BMI was not associated with higher baseline levels and whether a high BMI, possibly in association with nonalcoholic fatty liver disease, blunts the postoperative switch between the acute phase response and generation of constitutive proteins, such as albumin, requires further study. BMI alone moreover does not fully reflect the nutritional status, and other surrogate parameters such as sarcopenia would be helpful, but were not available in the present study. Nonetheless, the present study was not designed to investigate the complex physiological mechanisms of albumin fall and thus we cannot speculate on this point.

In the only comparable study, Ryan et al. in 2007 investigated the postoperative hypoalbuminemia in patients undergoing esophagectomy, and used categorical levels on Day 1 rather than Δ Alb, and severe hypoalbuminemia was associated with increased risk of major complications.¹⁴ However, Δ Alb may be more informative since it is a dynamic value calculated as a difference between preoperative and postoperative values of albumin. Δ Alb as a biomarker of complication risk has an appealing rationale. These include its early indicative value, on POD 1, its ease to measure, reproducibility, and inexpensive cost. To date, Δ Alb has been reported to be associated with overall complications.^{10,12} This study highlighted its value for anticipating major adverse events, an important stake of postoperative course in major surgery.¹⁸

Several other biomarkers have been assessed for their capacity to predict postoperative complications; however, none of them has been widely implemented in daily clinical practice, as specific thresholds have yet to be validated. In addition, most of these biomarkers suffer from slow kinetics and are informative at a later time postoperatively (POD 2–4) compared with Δ Alb on Day 1. Serum CRP has been identified as a negative predictor of anastomotic leakage with the best diagnostic accuracy at POD 2, 3, and 6.²³ Published cut-offs for CRP show a wide range from >200 mg/ml on POD 2¹⁸ or >209 mg/ml on POD 2²³ to >111 mg/L on POD 4.²⁴ Thus, while CRP levels are commonly measured in daily practice, there is still no universally accepted threshold to detect postoperative complications. In the present study, CRP levels on POD 3 were predictive of major morbidity in the training, but not the validation cohort (Table S2). Although it was only available for a subset of patients, and more large-scale data might be helpful, its predictive value was less than Δ Alb in multivariable analysis. Previous studies have also identified hyperbilirubinemia as a risk factor for postoperative infectious complications,^{24,25} while serum angiotensin-converting enzyme 2 levels from POD 0–3 predicted postoperative pneumonia.²⁶ However, these biomarkers are not commonly used in current practice after esophageal surgery and were, thus, not analyzed in this cohort.

Limitations of this study are mainly related to its retrospective design. Parameters such as perioperative fluid management, a potential confounder of serum albumin concentration, is not available for this series. Inclusion of a relatively recent series of patients in reference centers aimed to limit heterogeneity of perioperative care protocols; however, precise and reliable information of fluid

perfusion is unfortunately difficult to obtain retrospectively. Moreover, (I) involved centers use clinical pathways that include goal-direct fluid therapies and (II) data have demonstrated that fluid minimally contributed to albumin decrease.^{12,15,17} The strengths of this study, however, include a multicenter design, including five high-volume centers, large sample size, and analysis of training and validation cohorts. Importantly, the design of the present study—with both a training and a validation cohort—precludes from a double (in the training cohort and thereafter in the validation cohort) type-1 error. In other words, these findings on Δ Alb are highly unlikely fortuitous. Another potential drawback might be the timing of postoperative albumin values. In this study, it was not available on POD 0 (4–6 h after the end of surgery) after esophageal resection. In liver surgery, where albumin is often measured on that timepoint, Δ Alb could be calculated on POD 0 and was more performant than on POD 1.¹³ Measuring albumin on POD 0 could be an option to optimize Δ Alb and enhance its performance, in esophageal surgery, as previous data from our institution have suggested.¹⁷

These findings provide a solid rationale to further investigate Δ Alb in esophageal surgery and understand how this marker may guide decision-making in the early and critical postoperative phase. Early identification of patients at increased risk allows tailored individual surveillance with early imaging or endoscopy, whereas Δ Alb may permit to select patients who would benefit from specific pharmaceutical measures, although such interventions have yet to be explored by randomized clinical trials. Of note, one can easily challenge a novel biomarker, such as Δ Alb, questioning its clinical contribution. The impact of Δ Alb in clinical practice is at least as important as any other markers, such as CRP, which are extensively used worldwide in daily routine, except that Δ Alb is informative even earlier.

In summary, Δ Alb > 11 g/L on POD 1 appeared as a valuable biomarker to predict major complications after esophagectomy. Further prospective trials are needed to define how precisely it may be integrated to guide postoperative management of patients undergoing surgery.

CONFLICTS OF INTERESTS

Mark I. van Berge Henegouwen: Researcher initiated grants Olympus and Stryker, consultant Mylan Medtronic and Johnson and Johnson. All fees paid to Institution and not related to present study. Guillaume Piessen: Relevant Financial Activities Outside the Submitted Work - AMGEN, ROCHE.

AUTHOR CONTRIBUTIONS

Study concept and design: Ismail Labgaa, Styliani Mantziari, Pierre Allemann, Martin Hübner, Nicolas Demartines, Markus Schäfer. *Acquisition of data:* Maxime Genety, Jessie A. Elliott, Satoshi Kamiya, Marianne C. Kalf, Michaël Winiker, Marguerite Messier. *Analysis and interpretation of data:* Ismail Labgaa, Styliani Mantziari, Jérôme Pasquier, Mark I. van Berge Henegouwen, Magnus Nilsson, John V. Reynolds, Guillaume Piessen, Markus Schäfer. *Drafting of the manuscript:* Ismail Labgaa, Styliani Mantziari, Markus Schäfer. *Critical revision of the manuscript for important intellectual content:* Ismail Labgaa, Styliani

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SYNOPSIS

This multicenter study investigated the early postoperative decrease of serum albumin (Δ Alb) as predictor of adverse outcomes after esophageal surgery. Δ Alb appeared as an independent predictor of major complications and as a promising biomarker in patients undergoing esophagectomy for cancer.

DATA AVAILABILITY STATEMENT

Data are available on request from the authors.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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