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Research Article

Postoperative Decrease of Serum Albumin is an Early Predictor of Complications After Major Abdominal Surgery: A Prospective Cohort Study

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The present study was presented at the *103rd Congress of Swiss Surgery* (June 2016, Lugano, Switzerland) and will be presented at the Clinical Congress of the American College of Surgeons (October 2016, Washington, DC, USA).

Key words: Biomarker; albumin; major surgery; postoperative complications; stress response

Word count: 3106

ABSTRACT

Objective: To test postoperative serum albumin drop (ΔAlb) as a marker of surgical stress response and early predictor of clinical outcomes.

Design: Prospective cohort study (NCT02356484). Albumin was prospectively measured in 138 patients undergoing major abdominal surgery. Blood samples were collected before surgery and on postoperative days 0, 1, 2, and 3. ΔAlb was compared to the *Modified Estimation of Physiologic Ability and Surgical Stress* (mE-PASS) score and correlated to the performances of C-reactive protein (CRP), procalcitonin (PCT), and lactate (LCT). Postoperative outcomes were postoperative complications according to both Clavien classification and Comprehensive Complication Index (CCI), and length of hospital stay (LoS).

Setting: Division of abdominal surgery in a European tertiary center.

Participants: Adult patients undergoing elective major abdominal surgery, with a duration ≥2h. Patients on immunosuppressive or antibiotic treatments before surgery were excluded.

Results: The level of serum albumin rapidly dropped after surgery. ΔAlb correlated to the mE-PASS score (r=0.275, p=0.01) and to CRP increase (r=0.536, p<0.001). ΔAlb also correlated to overall complications (r=0.485, p<0.001), CCI (r=0.383, p<0.001) and LoS (r=0.468, p<0.001). A ΔAlb ≥10 g/L yielded a sensitivity of 77.1% and a specificity of 67.2% (AUC: 78.3%) to predict complications. Patients with ΔAlb ≥ 10g/l on POD 1 showed a 3 fold increased risk of overall postoperative complications.

Conclusion: ΔAlb correlated to the extent of surgery and to other biological stress markers. ΔAlb ≥10 g/L on POD 1 appears to be a promising early predictor of postoperative complications.

STRENGHTS AND LIMITATIONS OF THE STUDY

- The present study has a prospective design and offers a head-to-head comparison with biomarkers currently used in clinical practice (C-Reactive Protein and Procalcitonin).
- Albumin drop was thoroughly assessed by analyzing its correlation with a comprehensive panel of surrogate markers for surgical trauma and validated scores for outcomes.
- Serum albumin is a biomarker with ideal properties for this setting: easy to measure and to interpret, readily available, early modified after surgery, can be repeated for monitoring, and associated with low costs.
- This study involved a single center and included a training cohort, without validation cohort.

INTRODUCTION

Abdominal surgery is among the most frequently performed elective surgery [1]. Although surgical and perioperative improvements reduced postoperative mortality over the last decades, postoperative morbidity has remained high [2]. Postoperative complications cause a substantial financial burden, while the current context stresses the urgency to contain health care expenditures [2].

The magnitude of metabolic stress response recapitulates the extent of surgery [3 4] and presumably contributes to the risk of developing postoperative complications [5 6]. Early identification of patients at risk may improve outcomes, since measures to attenuate the overshooting surgical stress response and to reduce morbidity exist [7].

Although C-reactive protein (CRP) and procalcitonin (PCT) have been suggested as predictors for adverse outcomes in colorectal surgery, they both display the critical limitation of a slow kinetics [8 9]. Serum albumin (Alb) is an acute phase protein with immediate response to metabolic stress [3 10]. Preliminary data suggested that Alb level rapidly dropped after surgery and correlated to outcomes in esophageal [11], oral cancer [12], abdominal [3], pancreatic [13], liver resection[14]/transplant [15] and cardiac [16] surgeries. However, prospective validation is missing and Alb is not used to assess surgical stress or to predict outcomes.

This study aimed to test the hypotheses that early postoperative albumin drop (I) reflects the magnitude of surgical trauma, (II) correlates to established markers of metabolic stress, and (III) predicts postoperative complications.

METHODS

Study design and patient groups

This prospective study was conducted at the Department of Visceral Surgery of the University Hospital of Lausanne Switzerland (CHUV) between February and December 2015 (NCT02356484). The study was approved by the Institutional Review Board (N°367/15) and all patients provided written consent prior to surgery. Inclusion criteria were age >18 years, and elective major abdominal surgery - defined as an operative procedure with duration ≥2h [17], whereas patients on immunosuppressive or antibiotic treatments before surgery were excluded.

Demographics, comorbidities, surgical details and clinical outcomes were prospectively collected and anonymized in a computerized protected database. The sample size was similar to comparable studies in the field [18].

Extent of surgery

The amplitude of surgical stress was measured by the *Modified Estimation of Physiologic Ability and Surgical Stress* (mE-PASS). Briefly, mE-PASS score encompasses 7 items (6 preoperative variables and the surgical procedure). It predicts the in-hospital mortality and the 30-day mortality rates, respectively [19]. Type of surgery, operative time, and surgical approach (open *vs*. laparoscopic) were recorded. Conversions from laparoscopy to laparotomy were counted as laparoscopic cases. Anesthesiologists and surgeons jointly estimated blood loss by measuring the volume of aspirated fluid and soaked gauzes.

Biological markers

Serum levels of albumin, CRP, PCT and lactate (LCT) were perioperatively measured in a fasting state, following standardized institutional guidelines. Blood samples were drawn the day before surgery, the day of surgery (4-6 hours after the end of the operation) and on the first, second and third postoperative day. As baseline values tend to show large variations especially for

albumin [3 10], we considered that a dynamic value (difference between two time-points) might be more informative than a snapshot value. Several values based on pre- and post-operative concentrations, were thus calculated for each marker (i.e., Δ Max: Maximal difference between the pre- and post-operative values; Δ POD 0: Difference of concentration on POD -1 and POD 0; Δ POD 1: Difference of concentration on POD -1 and POD 1).

Outcome measures

Complications were graded with the Clavien classification within 30 postoperative days, accounting grade I/II events as minor complications and grade III-V as major complications [20]. Every complication was documented. Global morbidity for each patient was quantified by the Comprehensive Complication Index (CCI) on a scale from 0 to 100 [21]. Length of stay (LoS) was considered as the duration from the day of surgery until discharge.

Statistical analysis

Continuous variables were presented as mean with standard deviation (SD) or median value with interquartile range (IQR) depending on the normality of the distribution and compared using Student's *t* test and Mann-Whitney U test, whereas categorical variables were given as frequencies with percentages and compared with chi-square test. For statistical analyses, the following parameters were dichotomized: age (>60 years), body-mass index (>25 kg/m^2), operative time (>180 minutes), and blood loss (>200 ml). Spearman's and Pearson's tests were used to measure correlations of categorical and continuous variables, respectively. Receiver operating characteristic (ROC) curves were applied to obtain the area under the curve (AUC), and to determine ideal cut-offs. Logistic regression was applied to identify independent predictors; variables with significance < 0.1 were included in multivariable analyses. A p value <0.05 was considered to be statistically significant in all tests. Data analyses were generated using SPSS v20 statistical software (Chicago, IL).

RESULTS

Patients Characteristics, Details of Surgery, and Outcomes

During the study period, 155 consecutive patients undergoing major abdominal surgery were potentially eligible for inclusion, but 17 of them refused to participate. As a result, 138 patients were included in the study and had a complete follow-up. Demographics and surgical details are displayed in **Table 1**. Median mE-PASS score was 0.66 (IQR 0.45-0.96).

Overall, 60/138 patients (43%) experienced at least one complication, and one patient died after total gastrectomy and splenopancreatectomy due to cardiorespiratory arrest. Minor and major complications were observed in 35 and 25 patients, respectively. Patients showed a mean CCI of 13.2 (SD 18.5), and were discharged after a median LoS of 8 days (IQR 5-15 days).

Perioperative Profile of Biomarkers

The perioperative profile of albumin showed a rapid drop induced by surgery, followed by a plateau phase between POD 0 and POD 3 (**Supplementary Figure 1**). Lactate levels peaked in the first 4-6h after surgery and were back to baseline on POD1. Conversely, CRP and PCT showed slow kinetics reaching maximal values on POD 4 and 3, respectively. The mean maximal decrease of albumin was 11.3 g/L (± 5.6), which was similar to albumin drop on POD 1: 10.1 g/L (SD: 5.8). Further analyses were hence focused on ΔAlb on POD1.

Correlation of ΔAlb to surgical stress, biomarkers, and outcomes

ΔAlb on POD1 correlated to surgical stress (mE-PASS) ($r=0.275$, $p=0.01$) and to surrogates such as duration of surgery ($r=0.562$, $p<0.001$), blood loss ($r=0.391$, $p<0.001$), and surgical approach ($\rho=0.55$, $p<0.001$) (**Figure 1**).

ΔAlb on POD1 also correlated to maximal increases of CRP ($r=0.54$, $p<0.001$), PCT ($r=0.43$, $p<0.001$), and LCT ($r=0.25$, $p=0.02$). Furthermore, a positive and significant correlation was highlighted between ΔAlb on POD1 and ΔCRP on POD4 ($\rho=0.234$, $p=0.044$). ΔAlb on POD1 was

significantly associated with adverse outcomes, showing significant correlations with CCI (ρ=0.383, p<0.001) and LoS (ρ=0.468, p<0.001) (**Figure 2).**

The correlations of CRP, PCT, and LCT with surgical stress and outcomes were also tested and are detailed in **Supplementary Table 1**.

Predictive Value of Albumin Decrease

A ROC curve was used to determine the optimal cut-off of ΔAlb on POD1, settled at 10 g/L. The area under the curve (AUC) measured 78.3% (95% CI: 70-87%), giving a sensitivity of 77.1%, a specificity of 67.2%, a positive predictive value of 64.8%, and a negative predictive value of 79.6%, for overall complications (**Figure 3**). The respective ROC curves for POD1 values of ΔCRP, ΔPCT, and ΔLCT are provided in **Supplementary Figure 2**.

It was subsequently investigated whether this cut-off was able to discriminate and stratify patients' risk. Patients with an intense drop of Alb on POD 1 (ΔAlb POD1 ≥10 g/L) showed a higher mE-PASS (0.73 *vs.* 0.49, p=0.029) with higher rates of minor (36% *vs.* 15%, p=0.011), major (28% *vs.* 6%, p=0.002), and overall complications (64% *vs.* 20%, p<0.001). This resulted in a significantly higher CCI (20.9 *vs.* 0, p<0.001) and in a significantly longer LoS (13 *vs.* 4 days, p<0.001) (**Supplementary Table 2**).

Logistic regression with multivariable analysis identified open surgery (OR: 11.22; 95% IC: 2.74-46.05; p=0.001) and ΔAlb POD1≥ 10 g/L (OR: 3.29; 95% CI: 1.14-9.49; p=0.028) to be independently associated with overall complications (**Table 2**).

DISCUSSION

Surgery induced a rapid decrease of serum albumin in patients undergoing elective major abdominal procedures; and it remained stable for several postoperative days. The decrease in serum albumin correlated with (I) the extent of surgery (mE-PASS, blood loss, duration of surgery, and surgical approach), (II) the maximal amplitude of other stress markers, such as CRP, PCT and LCT and (III) was consistently associated with adverse outcomes (according to both Clavien classification, CCI, and LoS). A serum albumin decrease ≥ 10 g/L on POD 1 was independently associated with a 3-fold increased risk for postoperative complication.

The present study tested a panel of 4 biomarkers of which 2 are routinely used and served as benchmarks (CRP and PCT) and 2 are less established markers and deserved prospective investigations (Alb and LCT). The mE-PASS accurately recapitulates surgical stress, and was validated and used in abdominal surgery [19 22-25]. To our knowledge, there is no other validated and available score. One study endpoint was the CCI, which is a score summing each complication graded according to the Clavien classification. As a result, CCI avoids omitting minor complications, and is therefore more accurate than the Clavien classification alone [21]. Serum albumin showed the more consistent correlation with stress response and clinical outcomes. Alb and LCT both display some of the features for ideal markers: easy to measure and to interpret, readily available, can be repeated for monitoring and non-expensive. While Alb rapidly dropped after surgery and subsequently stabilized until POD 3, lactate showed a prompt increase followed by a fast return to baseline value, already on POD 1. It can be assumed that the timing of blood collection may have a more important impact on LCT than on Alb. As a consequence, Alb is more robust and easier to use in the clinical setting. Importantly, the selected markers were repeatedly measured, which allowed to capture their perioperative profiles and to further calculated differences of concentrations between various time-points. The latter was revealed to be pivotal and more informative than a single value.

Some limitations need to be addressed. The present analyses were focused on 4 markers that are readily available and easy to evaluate in clinical setting. This non-inclusive panel of markers could be perceived as a methodological shortcoming. Notwithstanding, integrating complex and costly markers such as cytokines would also be of clinically restraint relevance, given their low reproducibility, cost and complexity. In addition, blood collection on POD 0 typically occurred 4-6 hours after the end of surgery, which raises 2 concerns: (I) because of the variety of different postoperative scenarios (i.e. patients transferred to: ICU, intermediate care, ward, or staying in recovery room), any potential variability from the protocol cannot be excluded, and (II) it may also be argued that this delay is long enough to alter the discriminatory ability of certain markers, particularly lactate [26].

Available data on the predictive role of postoperative Alb are scarce; and most of these reports were retrospective studies [11-13 15 16]. Of note, each of the studies investigated only a single postoperative value of serum albumin. This represents a critical drawback as it cannot be discriminated whether the low postoperative concentration of serum albumin resulted from intense surgical stress or from low preoperative level, which is an acknowledged predictor of increased postoperative complication [27 28]. A prospective pilot study in abdominal surgery – conducted recently in our institution- showed consistent findings, with an increased risk of complication related to the amplitude of serum albumin postoperative drop [3]. Of note, the cohorts from this previous study (70 patients) and from the present one (138 patients) were strictly distinct. Postoperative lactate has been more thoroughly explored in liver surgery, with few reports in other surgical fields. In a recent landmark study, Vibert et al. demonstrated that a postoperative cut-off of arterial lactate > 3mmol/L at the end of surgery was an independent predictor of complications after elective hepatectomies [26]. Their conclusion correlates with the present findings since ΔLCT POD0 was correlated with mE-PASS ($p=0.039$), overall complication ($p<0.001$), CCI ($p=0.007$) and LoS ($p=0.008$) (**Figure 2**). Although both CRP and PCT are routinely used markers in clinical practice, they are typically contributive on POD 4 only. The present study design allowed to

confirm the ultimate advantage of Alb to be up-regulated within the early postoperative phase, illustrated by the correlation between ΔAlb on POD1 and ΔCRP on POD4 (ρ=0.234, p=0.044), highlighted in this study. In fact, ΔAlb on POD1 was even more performant than ΔCRP on POD4, illustrated by AUC of 0.78 and 0.75, respectively (Figure 3 and Supplementary 3D). Other candidate biomarkers have been explored to predict postoperative complications. Recently, Rettig et al. tested the predictive performance of IL-6 in a prospective cohort of 137 patients undergoing elective abdominal surgery [18]. Although a high level of IL-6 on POD1 was associated with increased risk of complication, one must consider its intrinsic limitations, such as high costs, precluding its routine use in clinical practice[29]. Furthermore, IL-6 on POD1 yielded an AUC of 0.67 while the present AUC of Alb on POD 1 reached 0.78.

How the monitoring of Alb in surgical patients can lead to better outcomes is key question. Measures to preoperatively attenuate the overshooting stress response to surgery have been extensively explored. Interestingly, successful attempts were reported with immunonutrition [30], enhanced recovery programs (ERAS) [31 32], or high-dose glucocorticoids [33]. Whether these options would be able to restrain the stress response, once triggered, in the early postoperative phase remains to be investigated. In this setting, albumin drop may facilitate to test whether these measures may also be beneficial in the early postoperative phase, by permitting to design clinical trials enriched for patients at higher risk.

In summary, early postoperative decrease of serum albumin correlated with the (I) extent of surgery, (II) its metabolic response, and with (III) adverse outcomes such as complications and length of hospital stay.

A decreased concentration of serum albumin ≥ 10g/l on POD 1 was associated with a 3-fold increased risk of overall postoperative complications; albumin decrease occurs rapidly after surgery, remains stable for several days. As it is easy to measure, it could be used to identify patients at risk.

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Table 1: Baseline characteristics of patients with and without postoperative complications.

			Pat. with complications (n=60)	Pat. without complications (n=78)	p-value
Demographics					
	Median age (years)		64 (50-73)	59 (51-69)	0.306
	Age ≥ 70 years		20 (51)	19 (49)	0.246
	Gender (male)		38 (63)	34 (44)	**0.021**
	Median BMI (kg/m^2)		24 (22-28)	26 (22-31)	**0.038**
	BMI ≥25 kg/m^2		27 (47)	46 (60)	0.128
Comorbidities					
	ASA (I-II)		36 (60)	52 (67)	0.419
	ECOG (0-1)		45 (75)	66 (85)	0.158
	Cirrhosis		2 (3)	1 (1)	0.413
	Heart disease		10 (17)	12 (16)	0.864
	Lung disease		8 (13)	7 (9)	0.415
	Diabetes		8 (13)	13 (17)	0.589
	History of surgery		33 (55)	42 (55)	0.958
	Cancer		45 (75)	54 (69)	0.456
Surgery					
	Type				
		Colorectal	14 (23)	17 (22)	0.840
		HPB	31 (52)	19 (24)	0.001
		Upper-GI	11 (18)	17 (22)	0.674
		Other	4 (7)	25 (32)	<0.001
	Approach				<0.001
		Open	50 (83)	29 (37)	
		Laparoscopy	10 (17)	49 (63)	
	Duration	Median (min)	271 (224-340)	154 (112-239)	<0.001
		≥ 180 min	46 (77)	33 (42)	<0.001
	Blood Loss	Median (mL)	300 (100-575)	90 (0-263)	0.002
		≥ 200 mL	40 (67)	24 (31)	<0.001
Median mE-PASS			0.77 (0.57-1.03)	0.49 (0.4-0.81)	0.12

BMI: Body mass index; ASA: American Association of Anesthesiologists physical status classification system; ECOG: Eastern Cooperative Oncology Group performance status; cancer: operative indication; HPB: Hepato-Pancreatico-Biliary surgery; Upper-GI: Upper-Gastrointestinal surgery; mE-PASS: Modified Estimation of Physiologic Ability and Surgical Stress; CCI: Comprehensive complication index; LoS: Length of stay. Other surgeries included pressurized intra-abdominal aerosol chemotherapy (17), endocrine operations

(4), complex abdominal wall operations (2), resections of retroperitoneal sarcomas (3), nephrectomy (1), and interrupted limb perfusions for melanoma (2).

Table 2: Logistic regression with uni- and multivariable analysis for predictors of postoperative complications.

	Overall postoperative complications					
	Univariable			Multivariable		
	HR	95% CI	p-value	HR	95% CI	p-value
Age> 70 years	1.55	0.74-3.27	0.247			
Gender (Female)	0.45	0.22-0.89	**0.022**	1.06	0.38-2.96	0.905
ASA I/II	1.33	0.66-2.68	0.42			
ECOG 0/1	1.83	0.79-4.28	0.161			
Cirrhosis	2.66	0.24-30	0.43			
Cancer	1.33	0.63-2.84	0.456			
Diabetes	0.77	0.3-2	0.59			
BMI>25 kg/m^2	0.59	0.3-1.17	0.129			
Approach (open)	8.49	3.72-19.18	**<0.001**	11.22	2.74-46.05	**0.001**
Duration ≥180 min	4.48	2.12-9.47	**<0.001**	0.47	0.11-1.94	0.297
Blood loss ≥200 mL	4.50	2.19-9.25	**<0.001**	1.68	0.57-4.99	0.350
ΔAlb POD1 ≥10 g/L	6.89	2.94-16.14	**<0.001**	3.29	1.14-9.49	**0.028**

ASA: American Association of Anesthesiologists physical status classification system; ECOG: Eastern Cooperative Oncology Group performance status; BMI: Body mass index; ΔAlb POD1: The difference between serum albumin concentration on POD -1 and POD 1 (g/L).

LEGENDS

Figure 1:

ΔAlb on POD1 correlates with the extent of surgery. ΔAlb on POD1 showed a significant correlation with (a) mE-PASS (r=0.275, p=0.01), (b) blood loss (r=0.391, p<0.001), and (c) duration of surgery (r=0.562, p<0.001).

Figure 2:

The postoperative decrease of Alb on POD 1 correlated with outcomes. ΔAlb on POD1 showed a significant correlation with CCI (Comprehensive complication index) (a), and with length of stay (LoS) (b).

Figure 3:

Receiver operating characteristic (ROC) curve to determine the optimal cut-off of ΔAlb on POD1 (blue line), showed an AUC of 0.78.

Supplementary Figure 1:

Mean perioperative concentration of serum albumin (vertical bars illustrate standard deviations).

Supplementary Figure 2:

ΔCRP (a), ΔPCT (b) and ΔLCT (c) on POD1 yielded AUC of 0.73, 0.63 and 0.64, respectively. The AUC of ΔCRP on POD4 was 0.75 (d).

Contributorship statement:

IL involved in study design, data collection, analysis and interpretation, review of the literature, drafting and critical revision of the manuscript. GRJ involved in study design, data collection, analysis and interpretation, review of the literature, critical revision of the manuscript. AK involved in data collection, analysis and interpretation, review of the literature, critical revision of the manuscript. SM involved in data collection, analysis and interpretation, review of the literature, critical revision of the manuscript. MS involved in study design, analysis and interpretation, critical revision of the manuscript. ND involved in study design, analysis and interpretation, critical revision of the manuscript. MH study design, analysis and interpretation, drafting and critical revision of the manuscript.

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Figure 1: The intensity of ΔAlb on POD1 Correlates with the Extent of Surgery

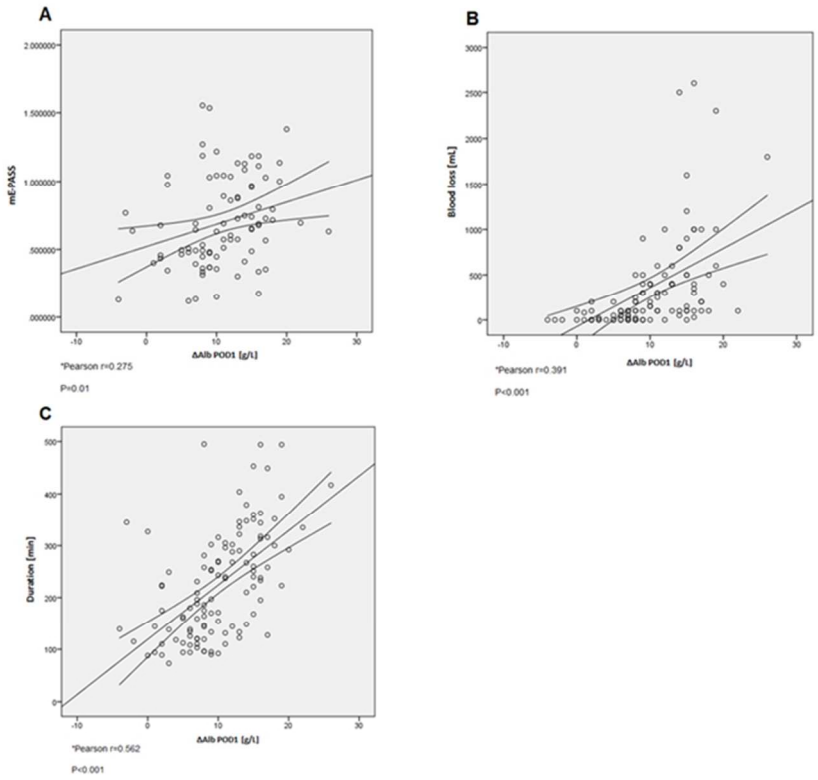

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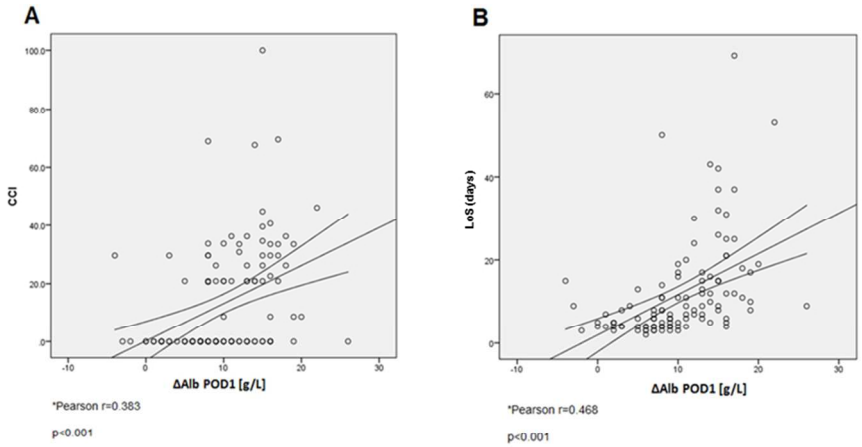
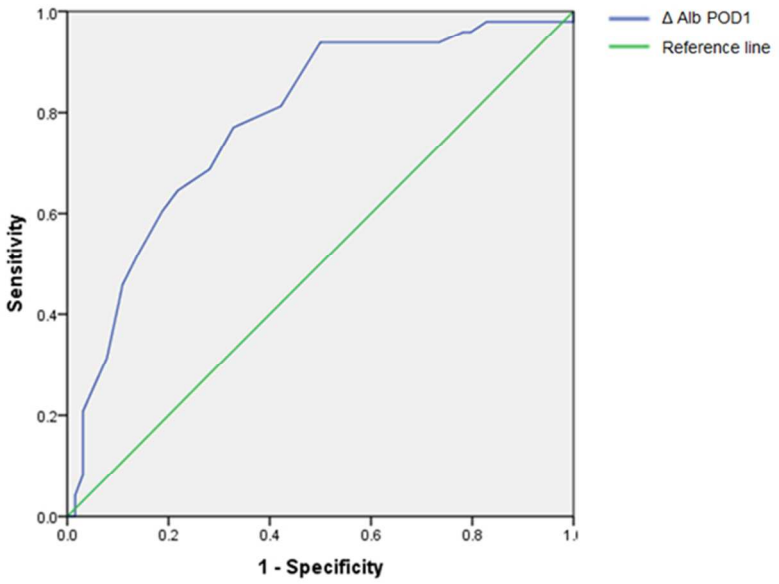
Figure 2: ΔAlb on POD1 Correlates with Complications (CCI) and Length of Stay (LoS)



254x190mm (96 x 96 DPI)

Figure 3: Receiver operating characteristic (ROC) curve of ΔAlb on POD1



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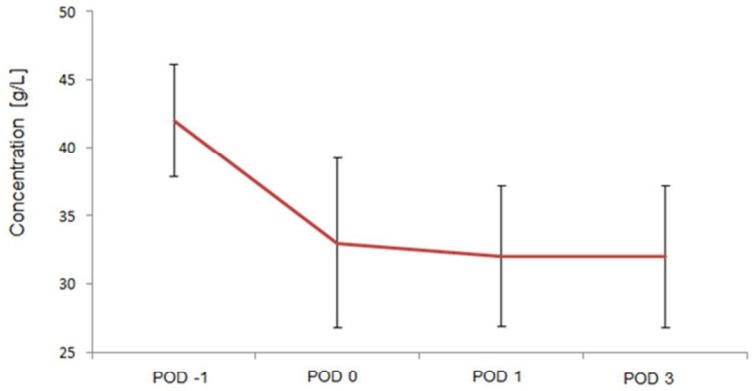
Supplementary Figure 1: Perioperative Kinetics of Serum Albumin (Alb)



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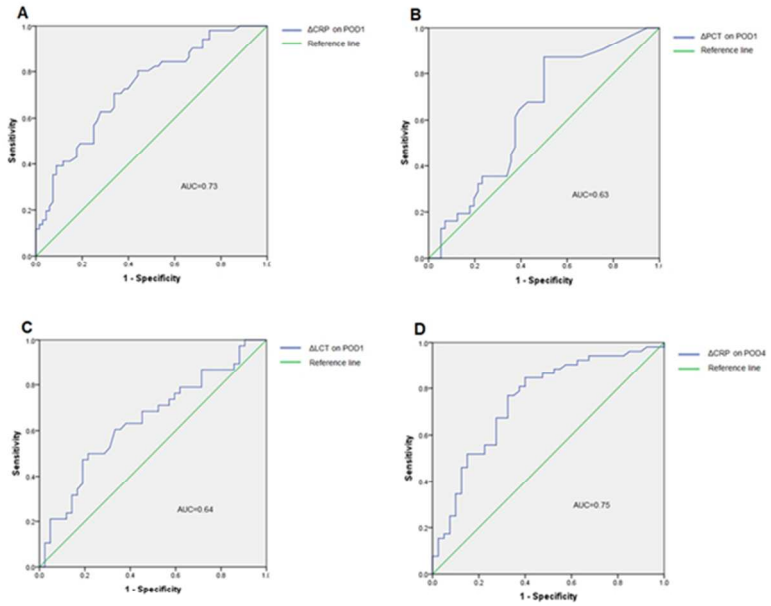
Supplementary Figure 2: Receiver operating characteristic (ROC) curves of other stress markers



190x254mm (96 x 96 DPI)

Supplementary Table 1: Correlations of the candidate biomarkers with outcomes.

		mE-PASS		Minor (I-II)		Major (III-V)		Overall complication		CCI		LoS	
		Pearson	p-value	Spearman	p-value	Spearman	p-value	Spearman	p-value	Pearson	p-value	Pearson	p-value
CRP	Δ Max	0.062	0.530	0.256	**0.003**	0.387	**<0.001**	0.534	**<0.001**	0.529	**<0.001**	0.484	**<0.001**
	Δ POD 0	0.052	0.693	0.070	0.566	0.049	0.686	0.098	0.417	0.231	0.052	0.381	**0.001**
	Δ POD 1	0.116	0.256	0.207	**0.024**	0.273	**0.003**	0.395	**<0.001**	0.469	**<0.001**	0.462	**<0.001**
Alb	Δ Max	0.323	**0.001**	0.264	**0.003**	0.345	**<0.001**	0.470	**<0.001**	0.373	**<0.001**	0.358	**<0.001**
	Δ POD 0	0.479	**<0.001**	0.298	**0.006**	0.194	0.077	0.420	**<0.001**	0.302	**0.005**	0.259	**0.018**
	Δ POD 1	0.275	**0.010**	0.228	**0.016**	0.372	**<0.001**	0.485	**<0.001**	0.383	**<0.001**	0.468	**<0.001**
PCT	Δ Max	-0.050	0.656	0.240	**0.016**	0.181	0.071	0.339	**0.001**	0.140	0.162	0.204	**0.040**
	Δ POD 0	0.017	0.906	0.171	0.204	0.076	0.570	0.211	0.112	0.015	0.909	0.168	0.206
	Δ POD 1	-0.010	0.933	0.135	0.216	0.150	0.165	0.220	**0.041**	-0.034	0.752	0.103	0.342
LCT	Δ Max	0.269	**0.013**	0.301	**0.003**	0.196	0.057	0.426	**<0.001**	0.317	**0.002**	0.327	**0.001**
	Δ POD 0	0.244	**0.039**	0.297	**0.007**	0.178	0.111	0.412	**<0.001**	0.299	**0.007**	0.292	**0.008**
	Δ POD 1	0.118	0.331	0.265	**0.018**	0.026	0.817	0.248	**0.026**	0.193	0.087	0.104	0.360

Complications are graded according to the Clavien classification (grade I to V); mE-PASS: Modified Estimation of Physiologic Ability and Surgical Stress; CCI: Comprehensive complication index; LoS: Length of stay; CRP: C-reactive protein; Alb: Serum albumin; PCT: Procalcitonin; LCT: Lactates; Δ Max: Maximal difference between the pre- and post-operative values; Δ POD 0: Difference of concentration on POD -1 and POD 0; Δ Pod 1: Difference of concentration on POD -1 and POD 1

Supplementary Table 2: Discriminatory ability of albumin decrease on POD1

	ΔAlb POD1		
	<10 g/L	**≥10 g/L**	**p-value**
Complications			
Minor (I-II)	8 (15)	21 (36)	**0.011**
Major (III-V)	3 (6)	16 (28)	**0.002**
Overall	11 (20)	37 (64)	**<0.001**
CCI	0	20.9 (0-33.5)	**<0.001**
LoS	4 (4-7)	13 (13-21)	**<0.001**

Complications are graded according to the Clavien classification (grade I to V); ΔAlb POD1: The difference between serum albumin concentration on POD -1 and POD 1 (g/L); mE-PASS: Modified Estimation of Physiologic Ability and Surgical Stress; CCI: Comprehensive complication index; LoS: Length of stay

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	5-6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, explain how loss to follow-up was addressed	Not applicable
		(*e*) Describe any sensitivity analyses	6

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	Not applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	16
		(c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	7-8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8
		(*b*) Report category boundaries when continuous variables were categorized	6
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Assessing Postoperative Decrease of Serum Albumin as an Early Predictor of Complications After Major Abdominal Surgery: A Prospective Cohort Study

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Research Article

Assessing Postoperative Decrease of Serum Albumin as an Early Predictor of Complications After Major Abdominal Surgery: A Prospective Cohort Study

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The present study was presented at the *103rd Congress of Swiss Surgery* (June 2016, Lugano, Switzerland) and at the Clinical Congress of the American College of Surgeons (October 2016, Washington, DC, USA).

Key words: Biomarker; albumin; major surgery; postoperative complications; stress response

Word count: 3106

ABSTRACT

Objective: To test postoperative serum albumin drop (ΔAlb) as a marker of surgical stress response and early predictor of clinical outcomes.

Design: Prospective cohort study (NCT02356484). Albumin was prospectively measured in 138 patients undergoing major abdominal surgery. Blood samples were collected before surgery and on postoperative days 0, 1, 2, and 3. ΔAlb was compared to the *Modified Estimation of Physiologic Ability and Surgical Stress* (mE-PASS) score and correlated to the performances of C-reactive protein (CRP), procalcitonin (PCT), and lactate (LCT). Postoperative outcomes were postoperative complications according to both Clavien classification and Comprehensive Complication Index (CCI), and length of hospital stay (LoS).

Setting: Department of abdominal surgery in a European tertiary center.

Participants: Adult patients undergoing elective major abdominal surgery, with anticipated duration ≥2h. Patients on immunosuppressive or antibiotic treatments before surgery were excluded.

Results: The level of serum albumin rapidly dropped after surgery. ΔAlb correlated to the mE-PASS score (r=0.275, p=0.01) and to CRP increase (r=0.536, p<0.001). ΔAlb also correlated to overall complications (r=0.485, p<0.001), CCI (r=0.383, p<0.001) and LoS (r=0.468, p<0.001). A ΔAlb ≥10 g/L yielded a sensitivity of 77.1% and a specificity of 67.2% (AUC: 78.3%) to predict complications. Patients with ΔAlb ≥ 10g/l on POD 1 showed a 3 fold increased risk of overall postoperative complications.

Conclusion: ΔAlb correlated to the extent of surgery and to other biological stress markers. ΔAlb ≥10 g/L on POD 1 appears to be a promising early predictor of postoperative complications.

STRENGHTS AND LIMITATIONS OF THE STUDY

- The present study has a prospective design and offers a head-to-head comparison with biomarkers currently used in clinical practice (C-Reactive Protein and Procalcitonin).
- Albumin drop was thoroughly assessed by analyzing its correlation with a comprehensive panel of surrogate markers for surgical trauma and validated scores for outcomes.
- The predictive value of combined biomarkers was not assessed in the present study.
- This study involved a single center and included a training cohort, without validation cohort.

INTRODUCTION

Abdominal surgery is among the most frequently performed elective surgery [1]. Although surgical and perioperative improvements have reduced postoperative mortality over the last decades, postoperative morbidity has remained high [2]. In addition to being troublesome experiences for patients, postoperative complications cause a substantial financial burden, while important efforts are currently pursued to reduce health care expenditures [2].

The magnitude of metabolic stress response recapitulates the extent of surgery [3 4] and presumably contributes to the risk of developing postoperative complications [5 6]. Early identification of patients at risk may improve outcomes, since measures to attenuate the surgical stress response and to reduce morbidity exist [7].

Although C-reactive protein (CRP) and procalcitonin (PCT) have been proposed as predictors for adverse outcomes in colorectal surgery, they both display the critical limitation of slow kinetics[8 9]. Conversely, serum albumin (Alb) is a maintenance protein that is rapidly downregulated by inflammatory signals [4 10]. Preliminary data suggested that Alb level rapidly dropped after surgery and correlated to outcomes in esophageal [11], oral cancer [12], abdominal [4], pancreatic [13], liver resection[14]/transplant[15] and cardiac [16] surgeries. However, prospective validation is missing and Alb is not used to assess surgical stress or to predict outcomes.

This study aimed to test the hypotheses that early postoperative albumin drop (I) reflects the magnitude of surgical trauma, (II) correlates to established markers of metabolic stress, and (III) predicts postoperative complications.

METHODS

Study design and patient groups

This prospective study was conducted at the Department for Visceral Surgery at the University Hospital of Lausanne Switzerland (CHUV) between February and December 2015 (NCT02356484). The study was approved by the Institutional Review Board (N°367/15) and all patients provided written consent prior to surgery. Inclusion criteria were age >18 years, and elective major abdominal surgery - defined as an operative procedure with anticipated duration ≥2h [17]. Perioperative care closely adhered to recently published enhanced recovery guidelines (http://erassociety.org.loopiadns.com/guidelines/list-of-guidelines). Standardized fluid administration was followed by advanced hemodynamic monitoring to avoid intraoperative fluid overload. According to the clinical care pathway, intravenous fluid was typically discontinued the morning after surgery.

Demographics, comorbidities, surgical details and clinical outcomes were prospectively collected and anonymized in a computerized protected database. A two-sample t-test was used to calculate sample size, with size effect of 0.8, power of 0.99 and significance level of 0.05. This determined a required number of 50 patients per group (i.e. with complication vs. without complication). Anticipating a complication rate of 40%, the final sample size for this study was n=125 patients. In order to adjust for 10% drop-out or missing data, final sample size resulted in n=138.

Extent of surgery

The amplitude of surgical stress was measured by the *Modified Estimation of Physiologic Ability and Surgical Stress* (mE-PASS). Briefly, mE-PASS score encompasses 7 items (6 preoperative variables and the surgical procedure). It predicts the in-hospital mortality and the 30-day mortality rates, respectively [18]. Type of surgery, operative time, and surgical approach (open *vs*. laparoscopic) were recorded. Conversions from laparoscopy to laparotomy were counted as

laparoscopic cases. Anesthesiologists and surgeons jointly estimated blood loss by measuring the volume of aspirated fluid and soaked gauzes.

Biological markers

Serum levels of albumin, CRP, PCT and lactate (LCT) were perioperatively measured in a fasting state, following standardized institutional guidelines. Blood samples were drawn the day before surgery, the day of surgery (4-6 hours after the end of the operation) and on the first, second and third postoperative day. As baseline values tend to show large variations especially for albumin [4 10], we considered that a dynamic value (difference between two time-points) might be more informative than a snapshot value. Several values based on pre- and post-operative concentrations, were thus calculated for each marker (i.e., Δ Max: Maximal difference between the pre- and post-operative values; Δ POD 0: Difference of concentration on POD -1 and POD 0; Δ POD 1: Difference of concentration on POD -1 and POD 1).

Outcome measures

Complications were graded with the Clavien classification within 30 postoperative days, accounting grade I/II events as minor complications and grade III-V as major complications [19]. Every complication was documented. Global morbidity for each patient was quantified by the Comprehensive Complication Index (CCI) on a scale from 0 to 100 [20]. Length of stay (LoS) was considered as the duration from the day of surgery until discharge.

Statistical analysis

Continuous variables were presented as mean with standard deviation (SD) or median value with interquartile range (IQR) depending on the normality of the distribution and compared using Student's *t* test and Mann-Whitney U test, whereas categorical variables were given as frequencies with percentages and compared with chi-square test. For statistical analyses, the following

parameters were dichotomized: age (≥70 years), body-mass index (≥25 kg/m^2), operative time (≥180 minutes), and blood loss (≥200 ml). Spearman's and Pearson's tests were used to measure correlations of categorical (ρ) and continuous (r) variables, respectively. Receiver operating characteristic (ROC) curves were applied to obtain the area under the curve (AUC), and to determine ideal cut-offs. Logistic regression was applied to identify independent predictors; variables with significance < 0.1 in univariable analyses were further included in multivariable analyses. A p value <0.05 was considered to be statistically significant in all tests. Data analyses were generated using SPSS v20 statistical software (Chicago, IL).

RESULTS

Patients Characteristics, Details of Surgery, and Outcomes

During the study period, 155 consecutive patients undergoing major abdominal surgery were potentially eligible for inclusion, but 17 of them refused to participate. As a result, 138 patients were included in the study and had a complete follow-up. Demographics and surgical details are displayed in **Table 1**. Median mE-PASS score was 0.66 (IQR 0.45-0.96).

Overall, 60/138 patients (43%) experienced at least one complication, and one patient died after total gastrectomy and splenopancreatectomy due to cardiorespiratory arrest. Minor and major complications were observed in 35 and 25 patients, respectively. Patients showed a mean CCI of 13.2 (SD 18.5), and were discharged after a median LoS of 8 days (IQR 5-15 days).

Perioperative Profile of Biomarkers

The perioperative profile of albumin showed a rapid drop induced by surgery, followed by a plateau phase between POD 0 and POD 3 (**Supplementary Figure 1**). Lactate levels peaked in the first 4-6h after surgery and were back to baseline on POD1. Conversely, CRP and PCT showed slow kinetics reaching maximal values on POD 4 and 3, respectively. The mean maximal decrease of albumin was 11.3 g/L (± 5.6), which was similar to albumin drop on POD 1: 10.1 g/L (SD: 5.8). Further analyses were hence focused on ΔAlb on POD1.

Correlation of ΔAlb to surgical stress, biomarkers, and outcomes

ΔAlb on POD1 correlated to surgical stress (mE-PASS) ($r=0.275$, $p=0.01$) and to surrogates such as duration of surgery ($r=0.562$, $p<0.001$), blood loss ($r=0.391$, $p<0.001$), and surgical approach ($\rho=0.55$, $p<0.001$) (**Figure 1**).

ΔAlb on POD1 also correlated to maximal increases of CRP ($r=0.54$, $p<0.001$), PCT ($r=0.43$, $p<0.001$), and LCT ($r=0.25$, $p=0.02$). Furthermore, a positive and significant correlation was highlighted between ΔAlb on POD1 and ΔCRP on POD4 ($\rho=0.234$, $p=0.044$). ΔAlb on POD1 was

significantly associated with adverse outcomes, showing significant correlations with CCI (ρ=0.383, p<0.001) and LoS (ρ=0.468, p<0.001) (**Figure 2).**

The correlations of CRP, PCT, and LCT with surgical stress and outcomes were also tested and are detailed in **Supplementary Table 1**.

Predictive Value of Albumin Decrease

A ROC curve was used to determine the optimal cut-off of ΔAlb on POD1, settled at 10 g/L. The area under the curve (AUC) measured 78.3% (95% CI: 70-87%), giving a sensitivity of 77.1%, a specificity of 67.2%, a positive predictive value of 64.8%, and a negative predictive value of 79.6%, for overall complications (**Figure 3**). The respective ROC curves for POD1 values of ΔCRP, ΔPCT, and ΔLCT are provided in **Supplementary Figure 2**.

It was subsequently investigated whether this cut-off was able to discriminate and stratify patients' risk. Patients with an intense drop of Alb on POD 1 (ΔAlb POD1 ≥10 g/L) showed a higher mE-PASS (0.73 *vs.* 0.49, p=0.029) with higher rates of minor (36% *vs.* 15%, p=0.011), major (28% *vs.* 6%, p=0.002), and overall complications (64% *vs.* 20%, p<0.001). This resulted in a significantly higher CCI (20.9 *vs.* 0, p<0.001) and in a significantly longer LoS (13 *vs.* 4 days, p<0.001) (**Supplementary Table 2**).

Logistic regression with multivariable analysis identified open surgery (OR: 11.22; 95% CI: 2.74-46.05; p=0.001) and ΔAlb POD1≥ 10 g/L (OR: 3.29; 95% CI: 1.14-9.49; p=0.028) to be independently associated with overall complications (**Table 2**).

DISCUSSION

Surgery induced a rapid decrease of serum albumin in patients undergoing elective major abdominal procedures; and it remained stable for several postoperative days. Although correlation coefficients were modest, the decrease in serum albumin significantly correlated with (I) the extent of surgery (mE-PASS, blood loss, duration of surgery, and surgical approach), (II) the maximal amplitude of other stress markers, such as CRP, PCT and LCT and (III) was consistently associated with adverse outcomes (according to both Clavien classification, CCI, and LoS). A serum albumin decrease ≥ 10 g/L on POD 1 was independently associated with a 3-fold increased risk for postoperative complication.

The present study tested a panel of 4 biomarkers of which 2 are routinely used and served as benchmarks (CRP and PCT) and 2 are less established markers and deserved prospective investigations (Alb and LCT). The mE-PASS accurately recapitulates surgical stress, and was validated and used in abdominal surgery [18 21-24]. To our knowledge, there is no other validated and available score. One study endpoint was the CCI, which is a score summing each complication graded according to the Clavien classification. As a result, CCI avoids omitting minor complications, and is therefore more accurate than the Clavien classification alone [20]. Serum albumin showed the more consistent correlation with stress response and clinical outcomes. Alb and LCT both display some of the features for ideal markers: easy to measure and to interpret, readily available, can be repeated for monitoring and non-expensive. While Alb rapidly dropped after surgery and subsequently stabilized until POD 3, lactate showed a prompt increase followed by a fast return to baseline value, already on POD 1. It can be assumed that the timing of blood collection may have a more important impact on LCT than on Alb. As a consequence, Alb is more robust and easier to use in clinical setting. Importantly, the selected markers were repeatedly measured, which allowed to capture their perioperative profiles and to further calculate differences of concentrations between various time-points. The latter was revealed to be pivotal and more informative than a single value.

The mechanisms of early postoperative albumin decrease combine altered metabolism, blood loss/dilution and most importantly redistribution into the third space, due to capillary leakage. The latter accounts for >75% of albumin decrease in the early postoperative phase and appears to be related to the magnitude of systemic inflammatory response[10 25 26]. Therefore, albumin decrease is certainly influenced by perioperative fluid management (liberal *vs.* restrictive) but it mainly reflects the extent of postsurgical stress response.

In multivariable analysis (table 2), 2 factors were independently associated with complications: approach and ΔAlb POD1 ≥10 g/L. The overlap of certain parameters of surgical stress may, in part, explain why they were not identified as independent predictor of complication. It may also suggest that serum albumin recapitulates these different parameters.

Some limitations need to be addressed. The present analyses were focused on 4 markers that are readily available and easy to evaluate in clinical setting. This non-inclusive panel of markers could be perceived as a methodological shortcoming. Notwithstanding, integrating more complex and costly markers would unlikely to be more informative given their poor reproducibility, cost and assay measurement complexity. Likewise, this study did not assess the predictive value of albumin drop combined with other biomarker and/or clinical variables. Although such a classifier may presumably improve sensitivity and specificity, it will also be more complex which could ultimately preclude its implementation in clinical practice. Blood collection on POD 0 occurred 4-6 hours after the end of surgery. This delay might be long enough to alter the discriminatory ability of certain markers, particularly lactate [27].

Available data on the predictive role of postoperative Alb are scarce; and most of these reports were retrospective studies [11-13 16 28]. Of note, each of the studies investigated only a single postoperative value of serum albumin. This represents a critical drawback as it cannot be discerned whether the low postoperative concentration of serum albumin resulted from intense surgical stress or from low preoperative level, which is an acknowledged predictor of increased postoperative complication [29 30]. A prospective pilot study in abdominal surgery – conducted

recently in our institution- showed consistent findings, with an increased risk of complication related to the amplitude of serum albumin postoperative drop [4]. Of note, the cohorts from this previous study (70 patients) and from the present one (138 patients) were strictly distinct. Postoperative lactate has been more thoroughly explored in liver surgery, with few reports in other surgical fields. In a recent landmark study, Vibert et al. demonstrated that a postoperative cut-off of arterial lactate > 3mmol/L at the end of surgery was an independent predictor of complications after elective hepatectomies [27]. Their conclusion correlates with the present findings since ΔLCT POD0 was correlated with mE-PASS (p=0.039), overall complication (p<0.001), CCI (p=0.007) and LoS (p=0.008) (**Figure 2**). Although both CRP and PCT are routinely used markers in clinical practice, they are typically contributive on POD 4 only. The present study design allowed to confirm the ultimate advantage of Alb to be up-regulated within the early postoperative phase, illustrated by the correlation between ΔAlb on POD1 and ΔCRP on POD4 (ρ=0.234, p=0.044), highlighted in this study. In fact, ΔAlb on POD1 was more sensitive than ΔCRP on POD4, illustrated by AUC of 0.78 and 0.75, respectively (Figure 3 and Supplementary 3D).

How the monitoring of Alb in surgical patients can lead to better outcomes is key question. Measures to preoperatively attenuate the stress response to surgery have been extensively explored. Interestingly, successful attempts were reported with immunonutrition [31], enhanced recovery programs (ERAS) [32 33], or high-dose glucocorticoids [34]. Whether these options would be able to restrain the stress response, once triggered, in the early postoperative phase remains to be investigated. In this setting, albumin drop may facilitate to test whether these measures may also be beneficial in the early postoperative phase, by permitting to design clinical trials enriched for patients at higher risk.

In summary, early postoperative decrease of serum albumin correlated with the (I) extent of surgery, (II) its metabolic response, and with (III) adverse outcomes such as complications and length of hospital stay. A decreased concentration of serum albumin ≥ 10g/l on POD 1 was associated with a 3-fold increased risk of overall postoperative complications; albumin

decrease occurs rapidly after surgery, remains stable for several days. As it is easy to measure, it could be used to identify patients at risk.

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Table 1: Baseline characteristics of patients with and without postoperative complications.

			Pat. with complications (n=60) n (%)	Pat. without complications (n=78) n (%)	p-value
Demographics					
	Median age (years)*		64 (50-73)	59 (51-69)	0.306
	Age ≥ 70 years		20 (51)	19 (49)	0.246
	Gender (male)		38 (63)	34 (44)	**0.021**
	Median BMI (kg/m^2)*		24 (22-28)	26 (22-31)	**0.038**
	BMI ≥25 kg/m^2		27 (47)	46 (60)	0.128
Comorbidities					
	ASA (I-II)		36 (60)	52 (67)	0.419
	ECOG (0-1)		45 (75)	66 (85)	0.158
	Cirrhosis		2 (3)	1 (1)	0.413
	Heart disease		10 (17)	12 (16)	0.864
	Lung disease		8 (13)	7 (9)	0.415
	Diabetes		8 (13)	13 (17)	0.589
	History of surgery		33 (55)	42 (55)	0.958
	Cancer		45 (75)	54 (69)	0.456
Surgery					
	Type				
		Colorectal	14 (23)	17 (22)	0.840
		HPB	31 (52)	19 (24)	0.001
		Upper-GI	11 (18)	17 (22)	0.674
		Other	4 (7)	25 (32)	<0.001
	Approach				<0.001
		Open	50 (83)	29 (37)	
		Laparoscopy	10 (17)	49 (63)	
	Duration	Median (min)*	271 (224-340)	154 (112-239)	<0.001
		≥ 180 min	46 (77)	33 (42)	<0.001
	Blood Loss	Median (mL)*	300 (100-575)	90 (0-263)	0.002
		≥ 200 mL	40 (67)	24 (31)	<0.001
Median mE-PASS*			0.77 (0.57-1.03)	0.49 (0.4-0.81)	0.12

BMI: Body mass index; ASA: American Association of Anesthesiologists physical status classification system; ECOG: Eastern Cooperative Oncology Group performance status; cancer: operative indication; HPB: Hepato-Pancreatico-Biliary surgery; Upper-GI: Upper-Gastrointestinal surgery; mE-PASS: Modified Estimation of Physiologic Ability and Surgical Stress; CCI: Comprehensive complication index; LoS: Length of stay. Other surgeries included pressurized intra-abdominal aerosol chemotherapy (17), endocrine operations (4), complex abdominal wall operations (2), resections of retroperitoneal sarcomas (3), nephrectomy (1), and interrupted limb perfusions for melanoma (2). * Median values (IQR)

Table 2: Logistic regression with uni- and multivariable analysis for predictors of postoperative complications.

	Overall postoperative complications					
	Univariable			Multivariable		
	OR	95% CI	p-value	OR	95% CI	p-value
Age≥ 70 years	1.55	0.74-3.27	0.247			
Gender (Female)	0.45	0.22-0.89	**0.022**	1.06	0.38-2.96	0.905
ASA I/II	1.33	0.66-2.68	0.42			
ECOG 0/1	1.83	0.79-4.28	0.161			
Cirrhosis	2.66	0.24-30	0.43			
Cancer	1.33	0.63-2.84	0.456			
Diabetes	0.77	0.3-2	0.59			
BMI≥25 kg/m^2	0.59	0.3-1.17	0.129			
Approach (open)	8.49	3.72-19.18	**<0.001**	11.22	2.74-46.05	**0.001**
Duration ≥180 min	4.48	2.12-9.47	**<0.001**	0.47	0.11-1.94	0.297
Blood loss ≥200 mL	4.50	2.19-9.25	**<0.001**	1.68	0.57-4.99	0.350
ΔAlb POD1 ≥10 g/L	6.89	2.94-16.14	**<0.001**	3.29	1.14-9.49	**0.028**

ASA: American Association of Anesthesiologists physical status classification system; ECOG: Eastern Cooperative Oncology Group performance status; BMI: Body mass index; ΔAlb POD1: The difference between serum albumin concentration on POD -1 and POD 1 (g/L). OR: odds ratio

LEGENDS

Figure 1:

ΔAlb on POD1 correlates with the extent of surgery. ΔAlb on POD1 showed a significant correlation with (a) mE-PASS (r=0.275, p=0.01), (b) blood loss (r=0.391, p<0.001), and (c) duration of surgery (r=0.562, p<0.001).

Figure 2:

The postoperative decrease of Alb on POD 1 correlated with outcomes. ΔAlb on POD1 showed a significant correlation with CCI (Comprehensive complication index) (a), and with length of stay (LoS) (b).

Figure 3:

Receiver operating characteristic (ROC) curve to determine the optimal cut-off of ΔAlb on POD1 (blue line), showed an AUC of 0.78.

Supplementary Figure 1:

Mean perioperative concentration of serum albumin (vertical bars illustrate standard deviations).

Supplementary Figure 2:

ΔCRP (a), ΔPCT (b) and ΔLCT (c) on POD1 yielded AUC of 0.73, 0.63 and 0.64, respectively. The AUC of ΔCRP on POD4 was 0.75 (d).

Contributorship statement:

IL involved in study design, data collection, analysis and interpretation, review of the literature, drafting and critical revision of the manuscript. GRJ involved in study design, data collection, analysis and interpretation, review of the literature, critical revision of the manuscript. AK involved in data collection, analysis and interpretation, review of the literature, critical revision of the manuscript. SM involved in data collection, analysis and interpretation, review of the literature, critical revision of the manuscript. MS involved in study design, analysis and interpretation, critical revision of the manuscript. ND involved in study design, analysis and interpretation, critical revision of the manuscript. MH study design, analysis and interpretation, drafting and critical revision of the manuscript.

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Data sharing statement: There is no additional data.

Figure 1: The Intensity of ΔAlb on POD1 Correlates With the Extent of Surgery

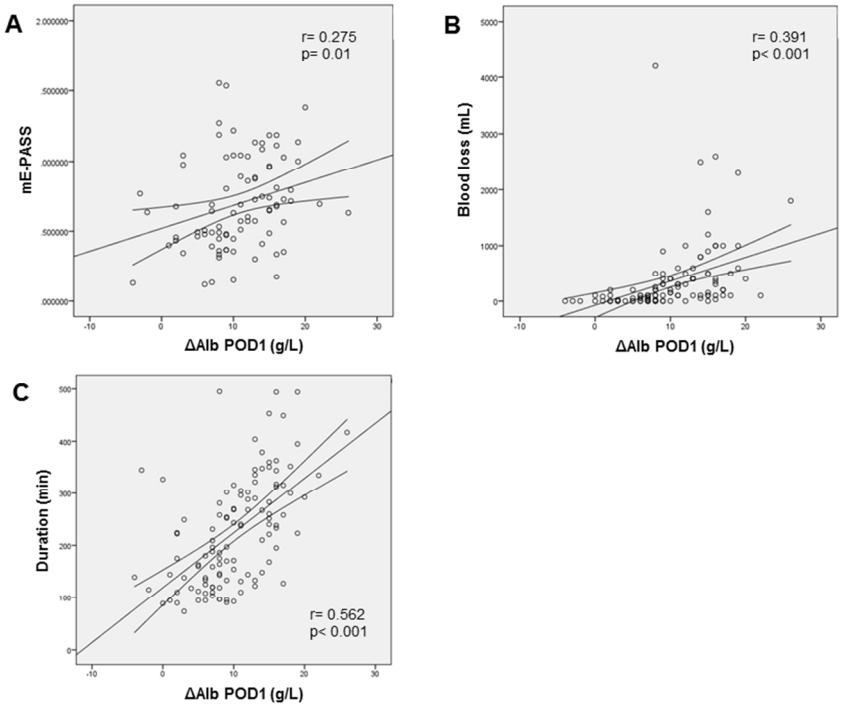


Figure 1

254x190mm (96 x 96 DPI)

Figure 2: ΔAlb on POD1 Correlates With Complications (CCI) and Length of Stay (LoS)

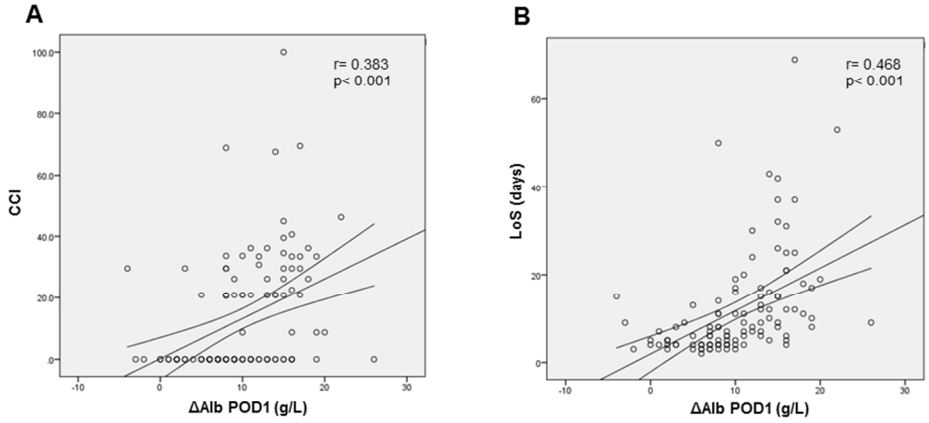
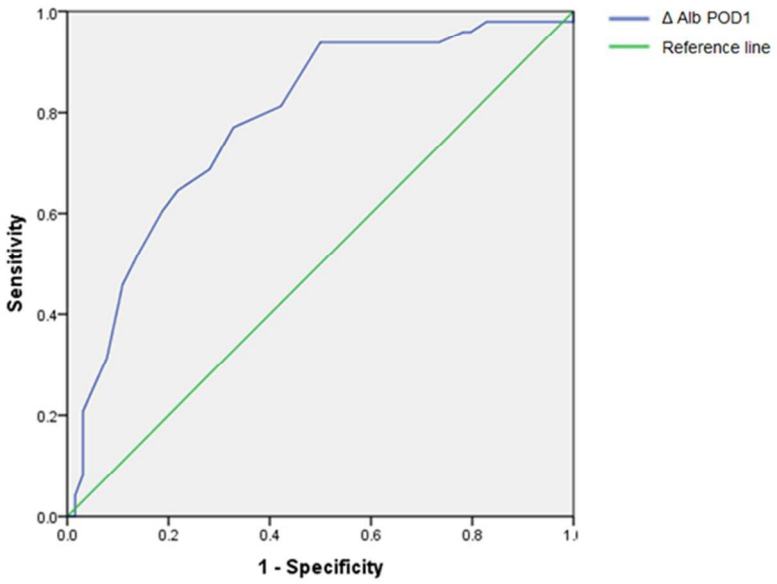


Figure 2

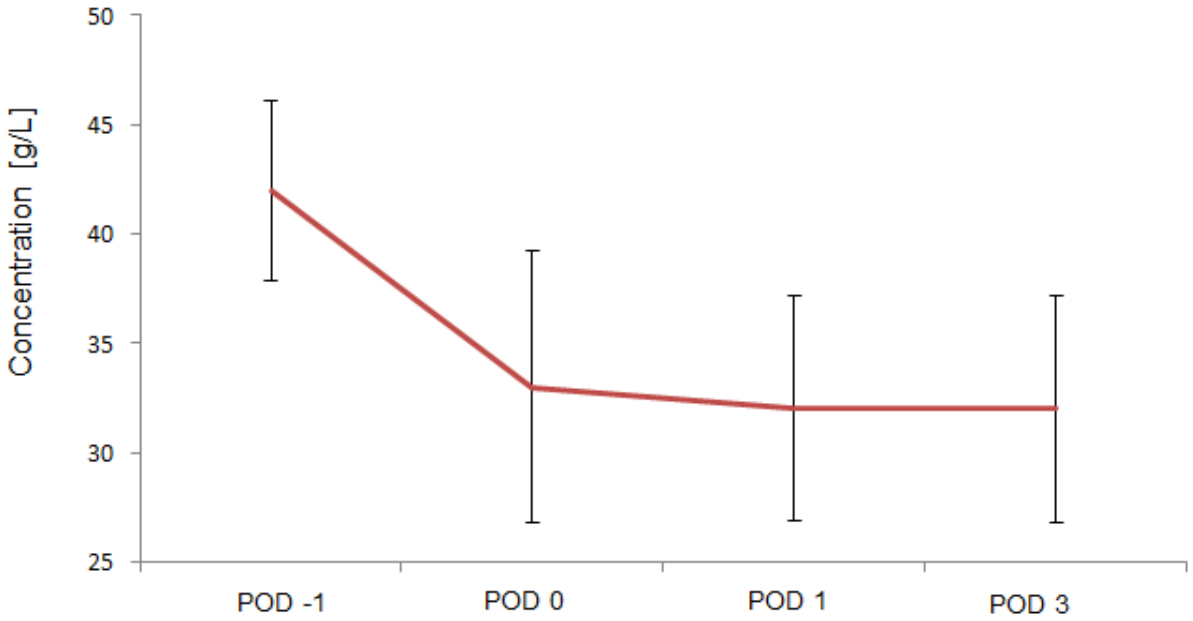
254x190mm (96 x 96 DPI)

Figure 3: Receiver operating characteristic (ROC) curve of ΔAlb on POD1

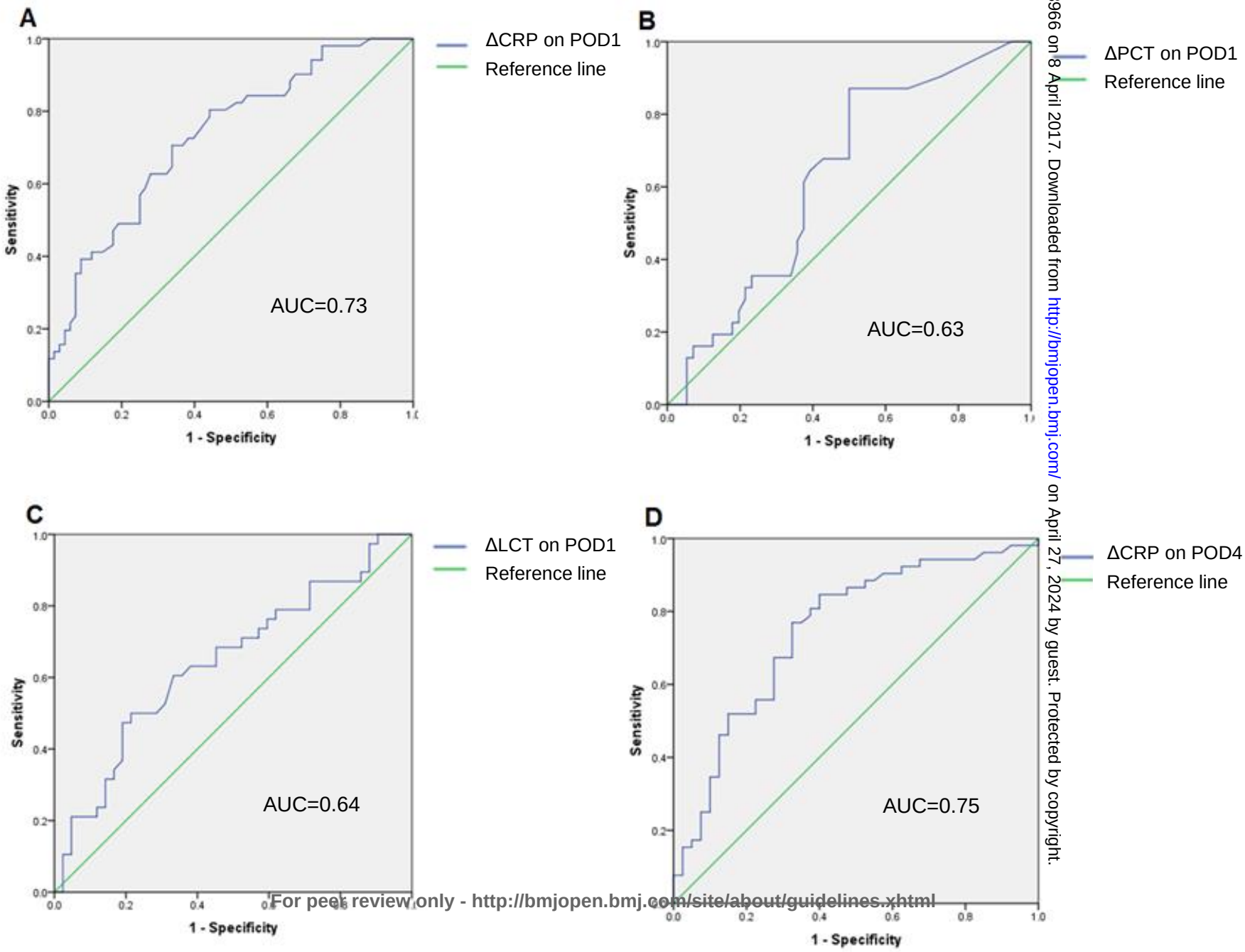


190x254mm (96 x 96 DPI)

Supplementary Figure 1: Perioperative Kinetics of Serum Albumin (Alb)



Supplementary Figure 2: Receiver operating characteristic (ROC) curves of other stress markers



Supplementary Table 1: Correlations of the candidate biomarkers with outcomes.

		mE-PASS		Minor (I-II)		Major (III-V)		Overall complication		CCI		LoS	
		Pearson	p-value	Spearman	p-value	Spearman	p-value	Spearman	p-value	Pearson	p-value	Pearson	p-value
CRP	Δ Max	0.062	0.530	0.256	**0.003**	0.387	**<0.001**	0.534	**<0.001**	0.529	**<0.001**	0.484	**<0.001**
	Δ POD 0	0.052	0.693	0.070	0.566	0.049	0.686	0.098	0.417	0.231	0.052	0.381	**0.001**
	Δ POD 1	0.116	0.256	0.207	**0.024**	0.273	**0.003**	0.395	**<0.001**	0.469	**<0.001**	0.462	**<0.001**
Alb	Δ Max	0.323	**0.001**	0.264	**0.003**	0.345	**<0.001**	0.470	**<0.001**	0.373	**<0.001**	0.358	**<0.001**
	Δ POD 0	0.479	**<0.001**	0.298	**0.006**	0.194	0.077	0.420	**<0.001**	0.302	**0.005**	0.259	**0.018**
	Δ POD 1	0.275	**0.010**	0.228	**0.016**	0.372	**<0.001**	0.485	**<0.001**	0.383	**<0.001**	0.468	**<0.001**
PCT	Δ Max	-0.050	0.656	0.240	**0.016**	0.181	0.071	0.339	**0.001**	0.140	0.162	0.204	**0.040**
	Δ POD 0	0.017	0.906	0.171	0.204	0.076	0.570	0.211	0.112	0.015	0.909	0.168	0.206
	Δ POD 1	-0.010	0.933	0.135	0.216	0.150	0.165	0.220	**0.041**	-0.034	0.752	0.103	0.342
LCT	Δ Max	0.269	**0.013**	0.301	**0.003**	0.196	0.057	0.426	**<0.001**	0.317	**0.002**	0.327	**0.001**
	Δ POD 0	0.244	**0.039**	0.297	**0.007**	0.178	0.111	0.412	**<0.001**	0.299	**0.007**	0.292	**0.008**
	Δ POD 1	0.118	0.331	0.265	**0.018**	0.026	0.817	0.248	**0.026**	0.193	0.087	0.104	0.360

Complications are graded according to the Clavien classification (grade I to V); mE-PASS: Modified Estimation of Physiologic Ability and Surgical Stress; CCI: Comprehensive complication index; LoS: Length of stay; CRP: C-reactive protein; Alb: Serum albumin; PCT: Procalcitonin; LCT: Lactates; Δ Max: Maximal difference between the pre- and post-operative values; Δ POD 0: Difference of concentration on POD -1 and POD 0; Δ Pod 1: Difference of concentration on POD -1 and POD 1

Supplementary Table 2: Discriminatory ability of albumin decrease on POD1

	ΔAlb POD1		
	<10 g/L	**≥10 g/L**	**p-value**
	n (%)	**n (%)**	
Complications			
Minor (I-II)	8 (15)	21 (36)	**0.011**
Major (III-V)	3 (6)	16 (28)	**0.002**
Overall	11 (20)	37 (64)	**<0.001**
CCI	0	20.9 (0-33.5)	**<0.001**
LoS	4 (4-7)	13 (13-21)	**<0.001**

Complications are graded according to the Clavien classification (grade I to V); ΔAlb POD1: The difference between serum albumin concentration on POD -1 and POD 1 (g/L); mE-PASS: Modified Estimation of Physiologic Ability and Surgical Stress; CCI: Comprehensive complication index; LoS: Length of stay

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	5-6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, explain how loss to follow-up was addressed	Not applicable
		(*e*) Describe any sensitivity analyses	6

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	Not applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	16
		(c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	7-8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8
		(*b*) Report category boundaries when continuous variables were categorized	6
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Assessing Postoperative Decrease of Serum Albumin as an Early Predictor of Complications After Major Abdominal Surgery: A Prospective Cohort Study in a Western Center

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Research Article

Assessing Postoperative Decrease of Serum Albumin as an Early Predictor of Complications After Major Abdominal Surgery: A Prospective Cohort Study in a Western Center

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The present study was presented at the *103rd Congress of Swiss Surgery* (June 2016, Lugano, Switzerland) and at the Clinical Congress of the American College of Surgeons (October 2016, Washington, DC, USA).

Key words: Biomarker; albumin; major surgery; postoperative complications; stress response

Word count: 3106

ABSTRACT

Objective: To test postoperative serum albumin drop (ΔAlb) as a marker of surgical stress response and early predictor of clinical outcomes.

Design: Prospective cohort study (NCT02356484). Albumin was prospectively measured in 138 patients undergoing major abdominal surgery. Blood samples were collected before surgery and on postoperative days 0, 1, 2, and 3. ΔAlb was compared to the *Modified Estimation of Physiologic Ability and Surgical Stress* (mE-PASS) score and correlated to the performances of C-reactive protein (CRP), procalcitonin (PCT), and lactate (LCT). Postoperative outcomes were postoperative complications according to both Clavien classification and Comprehensive Complication Index (CCI), and length of hospital stay (LoS).

Setting: Department of abdominal surgery in a European tertiary center.

Participants: Adult patients undergoing elective major abdominal surgery, with anticipated duration ≥2h. Patients on immunosuppressive or antibiotic treatments before surgery were excluded.

Results: The level of serum albumin rapidly dropped after surgery. ΔAlb correlated to the mE-PASS score (r=0.275, p=0.01) and to CRP increase (r=0.536, p<0.001). ΔAlb also correlated to overall complications (r=0.485, p<0.001), CCI (r=0.383, p<0.001) and LoS (r=0.468, p<0.001). A ΔAlb ≥10 g/L yielded a sensitivity of 77.1% and a specificity of 67.2% (AUC: 78.3%) to predict complications. Patients with ΔAlb ≥ 10g/l on POD 1 showed a 3 fold increased risk of overall postoperative complications.

Conclusion: ΔAlb correlated to the extent of surgery and to other biological stress markers. ΔAlb ≥10 g/L on POD 1 appears to be a promising early predictor of postoperative complications.

STRENGHTS AND LIMITATIONS OF THE STUDY

- The present study has a prospective design and offers a head-to-head comparison with biomarkers currently used in clinical practice (C-Reactive Protein and Procalcitonin).
- Albumin drop was thoroughly assessed by analyzing its correlation with a comprehensive panel of surrogate markers for surgical trauma and validated scores for outcomes.
- The predictive value of combined biomarkers was not assessed in the present study.
- This study involved a single center and included a training cohort, without validation cohort.

INTRODUCTION

Abdominal surgery is among the most frequently performed elective surgery [1]. Although surgical and perioperative improvements have reduced postoperative mortality over the last decades, postoperative morbidity has remained high [2]. In addition to the morbidity which patients are exposed to, postoperative complications pose a significant financial burden, while important efforts are currently pursued to reduce health care expenditures [2].

The magnitude of metabolic stress response mirrors the extent of surgery [3 4] and presumably contributes to the risk of developing postoperative complications [5 6]. Early identification of patients at risk may improve outcomes, since measures to attenuate the surgical stress response and to reduce morbidity exist [7].

Although C-reactive protein (CRP) and procalcitonin (PCT) have been proposed as predictors for adverse outcomes in colorectal surgery, they both display the critical limitation of slow kinetics[8 9]. Conversely, serum albumin (Alb) is a maintenance protein that is rapidly downregulated by inflammatory signals [4 10]. Preliminary data suggested that Alb level rapidly dropped after surgery and correlated to outcomes in esophageal [11], oral cancer [12], abdominal [4], pancreatic [13], liver resection[14]/transplant[15] and cardiac [16] surgeries. However, prospective validation is missing and Alb is not used to assess surgical stress or to predict outcomes.

This study aimed to test the hypotheses that early postoperative albumin drop (I) reflects the magnitude of surgical trauma, (II) correlates to established markers of metabolic stress, and (III) predicts postoperative complications.

METHODS

Study design and patient groups

This prospective study was conducted at the Department for Visceral Surgery at the University Hospital of Lausanne Switzerland (CHUV) between February and December 2015 (NCT02356484). The study was approved by the Institutional Review Board (N°367/15) and all patients provided written consent prior to surgery. Inclusion criteria were age >18 years, and elective major abdominal surgery - defined as an operative procedure with anticipated duration ≥2h [17]. Perioperative care closely adhered to recently published enhanced recovery guidelines (http://erassociety.org.loopiadns.com/guidelines/list-of-guidelines). Standardized fluid administration was followed by advanced hemodynamic monitoring to avoid intraoperative fluid overload. According to the clinical care pathway, intravenous fluid was typically discontinued the morning after surgery.

Demographics, comorbidities, surgical details and clinical outcomes were prospectively collected and anonymized in a computerized protected database. A two-sample t-test was used to calculate sample size, with size effect of 0.8, power of 0.99 and significance level of 0.05. This determined a required number of 50 patients per group (i.e. with complication vs. without complication). Anticipating a complication rate of 40%, the final sample size for this study was n=125 patients. In order to adjust for 10% drop-out or missing data, final sample size resulted in n=138.

Extent of surgery

The amplitude of surgical stress was measured by the *Modified Estimation of Physiologic Ability and Surgical Stress* (mE-PASS). Briefly, mE-PASS score encompasses 7 items (6 preoperative variables and the surgical procedure). It predicts the in-hospital mortality and the 30-day mortality rates, respectively [18]. Type of surgery, operative time, and surgical approach (open *vs*. laparoscopic) were recorded. Conversions from laparoscopy to laparotomy were counted as

laparoscopic cases. Anesthesiologists and surgeons jointly estimated blood loss by measuring the volume of aspirated fluid and soaked gauzes.

Biological markers

Serum levels of albumin, CRP, PCT and lactate (LCT) were perioperatively measured in a fasting state, following standardized institutional guidelines. Blood samples were drawn the day before surgery, the day of surgery (4-6 hours after the end of the operation) and on the first, second and third postoperative day. As baseline values tend to show large variations especially for albumin [4 10], we considered that a dynamic value (difference between two time-points) might be more informative than a snapshot value. Several values based on pre- and post-operative concentrations, were thus calculated for each marker (i.e., Δ Max: Maximal difference between the pre- and post-operative values; Δ POD 0: Difference of concentration on POD -1 and POD 0; Δ POD 1: Difference of concentration on POD -1 and POD 1).

Outcome measures

Complications were graded with the Clavien classification within 30 postoperative days, counting grade I/II events as minor complications and grade III-V as major complications [19]. Every complication was documented. Global morbidity for each patient was quantified by the Comprehensive Complication Index (CCI) on a scale from 0 to 100 [20], representing respectively no complication and postoperative death. Length of stay (LoS) was considered as the duration from the day of surgery until discharge.

Statistical analysis

Continuous variables were presented as mean with standard deviation (SD) or median value with interquartile range (IQR) depending on the normality of the distribution and compared using Student's *t* test and Mann-Whitney U test, whereas categorical variables were given as frequencies

with percentages and compared with chi-square test. For statistical analyses, the following parameters were dichotomized: age (≥70 years), body-mass index (≥25 kg/m^2), operative time (≥180 minutes), and blood loss (≥200 ml). Spearman's and Pearson's tests were used to measure correlations of categorical (ρ) and continuous (r) variables, respectively. Receiver operating characteristic (ROC) curves were applied to obtain the area under the curve (AUC), and to determine ideal cut-offs. Logistic regression was applied to identify independent predictors; variables with significance < 0.1 in univariable analyses were further included in multivariable analyses. A p value <0.05 was considered to be statistically significant in all tests. Data analyses were generated using SPSS v20 statistical software (Chicago, IL).

RESULTS

Patients Characteristics, Details of Surgery, and Outcomes

During the study period, 155 consecutive patients undergoing major abdominal surgery were potentially eligible for inclusion, but 17 of them refused to participate. As a result, 138 patients were included in the study and had a complete follow-up. Demographics and surgical details are displayed in **Table 1**. Median mE-PASS score was 0.66 (IQR 0.45-0.96).

Overall, 60/138 patients (43%) experienced at least one complication, and one patient died after total gastrectomy and splenopancreatectomy due to cardiorespiratory arrest. Minor and major complications were observed in 35 and 25 patients, respectively. Patients showed a mean CCI of 13.2 (SD 18.5), and were discharged after a median LoS of 8 days (IQR 5-15 days).

Perioperative Profile of Biomarkers

The perioperative profile of albumin showed a rapid drop induced by surgery, followed by a plateau phase between POD 0 and POD 3 (**Supplementary Figure 1**). Lactate levels peaked in the first 4-6h after surgery and were back to baseline on POD1. Conversely, CRP and PCT showed slow kinetics reaching maximal values on POD 4 and 3, respectively. The mean maximal decrease of albumin was 11.3 g/L (± 5.6), which was similar to albumin drop on POD 1: 10.1 g/L (SD: 5.8). Further analyses were hence focused on ΔAlb on POD1.

Correlation of ΔAlb to surgical stress, biomarkers, and outcomes

ΔAlb on POD1 correlated to surgical stress (mE-PASS) ($r=0.275$, $p=0.01$) and to surrogates such as duration of surgery ($r=0.562$, $p<0.001$), blood loss ($r=0.391$, $p<0.001$), and surgical approach ($\rho=0.55$, $p<0.001$) (**Figure 1**).

ΔAlb on POD1 also correlated to maximal increases of CRP ($r=0.54$, $p<0.001$), PCT ($r=0.43$, $p<0.001$), and LCT ($r=0.25$, $p=0.02$). Furthermore, a positive and significant correlation was highlighted between ΔAlb on POD1 and ΔCRP on POD4 ($\rho=0.234$, $p=0.044$). ΔAlb on POD1 was

significantly associated with adverse outcomes, showing significant correlations with CCI (ρ=0.383, p<0.001) and LoS (ρ=0.468, p<0.001) (**Figure 2).**

The correlations of CRP, PCT, and LCT with surgical stress and outcomes were also tested and are detailed in **Supplementary Table 1**.

Predictive Value of Albumin Decrease

A ROC curve was used to determine the optimal cut-off of ΔAlb on POD1, settled at 10 g/L. The area under the curve (AUC) measured 78.3% (95% CI: 70-87%), giving a sensitivity of 77.1%, a specificity of 67.2%, a positive predictive value of 64.8%, and a negative predictive value of 79.6%, for overall complications (**Figure 3**). The respective ROC curves for POD1 values of ΔCRP, ΔPCT, and ΔLCT are provided in **Supplementary Figure 2**.

It was subsequently investigated whether this cut-off was able to discriminate and stratify patients' risk. Patients with an intense drop of Alb on POD 1 (ΔAlb POD1 ≥10 g/L) showed a higher mE-PASS (0.73 *vs.* 0.49, p=0.029) with higher rates of minor (36% *vs.* 15%, p=0.011), major (28% *vs.* 6%, p=0.002), and overall complications (64% *vs.* 20%, p<0.001). This resulted in a significantly higher CCI (20.9 *vs.* 0, p<0.001) and in a significantly longer LoS (13 *vs.* 4 days, p<0.001) (**Supplementary Table 2**).

Logistic regression with multivariable analysis identified open surgery (OR: 11.22; 95% CI: 2.74-46.05; p=0.001) and ΔAlb POD1≥ 10 g/L (OR: 3.29; 95% CI: 1.14-9.49; p=0.028) to be independently associated with overall complications (**Table 2**).

DISCUSSION

Surgery induced a rapid decrease of serum albumin in patients undergoing elective major abdominal procedures; and it remained stable for several postoperative days. Although correlation coefficients were modest, the decrease in serum albumin significantly correlated with (I) the extent of surgery (mE-PASS, blood loss, duration of surgery, and surgical approach), (II) the maximal amplitude of other stress markers, such as CRP, PCT and LCT and (III) was consistently associated with adverse outcomes (according to both Clavien classification, CCI, and LoS). A serum albumin decrease ≥ 10 g/L on POD 1 was independently associated with a 3-fold increased risk for postoperative complication.

The present study tested a panel of 4 biomarkers of which 2 are routinely used and served as benchmarks (CRP and PCT) and 2 are less established markers and deserved prospective investigations (Alb and LCT). The mE-PASS accurately recapitulates surgical stress, and was validated and used in abdominal surgery [18 21-24]. To our knowledge, there is no other validated and available score. One study endpoint was the CCI, which is a score summing each complication graded according to the Clavien classification. As a result, CCI avoids omitting minor complications, and is therefore more accurate than the Clavien classification alone [20]. Serum albumin showed the more consistent correlation with stress response and clinical outcomes. Alb and LCT both display some of the features for ideal markers: easy to measure and to interpret, readily available, can be repeated for monitoring and non-expensive. While Alb rapidly dropped after surgery and subsequently stabilized until POD 3, lactate showed a prompt increase followed by a fast return to baseline value, already on POD 1. It can be assumed that the timing of blood collection may have a more important impact on LCT than on Alb. As a consequence, Alb is more robust and easier used in the clinical setting. Importantly, the selected markers were repeatedly measured, which allowed us to capture their perioperative profiles and to further calculate differences of concentrations between various time-points. The latter was revealed to be pivotal and more informative than a single value.

The mechanisms of early postoperative albumin decrease combine altered metabolism, blood loss/dilution and most importantly redistribution into the third space, due to capillary leakage. The latter accounts for >75% of albumin decrease in the early postoperative phase and appears to be related to the magnitude of systemic inflammatory response[10 25 26]. Therefore, albumin decrease is certainly influenced by perioperative fluid management (liberal *vs.* restrictive) but it mainly reflects the extent of postsurgical stress response.

In multivariable analysis (table 2), 2 factors were independently associated with complications: approach and ΔAlb POD1 ≥10 g/L. The overlap of certain parameters of surgical stress may, in part, explain why they were not identified as independent predictors of complications. It may also suggest that serum albumin mirrors these different parameters.

Some limitations need to be addressed. The present analyses were focused on 4 biomarkers that are readily available and easy to evaluate in the clinical setting. This non-inclusive panel of biomarkers could be perceived as a methodological shortcoming. Notwithstanding, integrating more complex and costly biomarkers would unlikely be more informative given their poor reproducibility, cost and assay measurement complexity. Likewise, this study did not assess the predictive value of albumin drop combined with other biomarker and/or clinical variables. Although such a classifier may presumably improve sensitivity and specificity, it will also be more complex which could ultimately preclude its implementation in clinical practice. Blood collection on POD 0 occurred 4-6 hours after the end of surgery. This delay might be long enough to alter the discriminatory ability of certain biomarkers, particularly lactate [27].

Available data on the predictive role of postoperative Alb are scarce; and most of these reports were retrospective studies [11-13 16 28]. Of note, each of the studies investigated only a single postoperative value of serum albumin. This represents a critical drawback as it cannot be discerned whether the low postoperative concentration of serum albumin resulted from intense surgical stress or from low preoperative level, which is an acknowledged predictor of increased postoperative complication [29 30]. A prospective pilot study in abdominal surgery – conducted

recently in our institution- showed consistent findings, with an increased risk of complication related to the amplitude of serum albumin postoperative drop [4]. Of note, the cohorts from this previous study (70 patients) and from the present one (138 patients) were strictly distinct. Postoperative lactate has been more thoroughly explored in liver surgery, with few reports in other surgical fields. In a recent landmark study, Vibert et al. demonstrated that a postoperative cut-off of arterial lactate > 3mmol/L at the end of surgery was an independent predictor of complications after elective hepatectomies [27]. Their conclusion correlates with the present findings since ΔLCT POD0 was correlated with mE-PASS (p=0.039), overall complication (p<0.001), CCI (p=0.007) and LoS (p=0.008) (**Figure 2**). Although both CRP and PCT are routinely used biomarkers in clinical practice, they are typically contributive on POD 4 only. The present study design allowed to confirm the ultimate advantage of Alb to be up-regulated within the early postoperative phase, illustrated by the correlation between ΔAlb on POD1 and ΔCRP on POD4 (ρ=0.234, p=0.044), highlighted in this study. In fact, ΔAlb on POD1 was more sensitive than ΔCRP on POD4, illustrated by AUC of 0.78 and 0.75, respectively (Figure 3 and Supplementary 3D).

How the monitoring of Alb in surgical patients can lead to better outcomes is a key question. Measures to preoperatively attenuate the stress response to surgery have been extensively explored. Interestingly, successful attempts were reported with immunonutrition [31], enhanced recovery programs (ERAS) [32 33], or high-dose glucocorticoids [34]. Whether these options would be able to restrain the stress response, once triggered, in the early postoperative phase remains to be investigated. In this setting, albumin drop may indicate whether these measures may be beneficial in the perioperative period by being incorporated into the design of clinical trials as a marker for patients at higher risk of perioperative complications.

In summary, early postoperative decrease of serum albumin correlated with the (I) extent of surgery, (II) its metabolic response, and with (III) adverse outcomes such as complications and length of hospital stay. A decreased concentration of serum albumin ≥ 10g/l on POD 1 was associated with a 3-fold increased risk of overall postoperative complications; albumin

decrease occurs rapidly after surgery and remains stable for several days. As it is easy to measure, it could be used to identify patients at risk.

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Table 1: Baseline characteristics of patients with and without postoperative complications.

			Pat. with complications (n=60) n (%)	Pat. without complications (n=78) n (%)	p-value
Demographics					
	Median age (years)*		64 (50-73)	59 (51-69)	0.306
	Age ≥ 70 years		20 (51)	19 (49)	0.246
	Gender (male)		38 (63)	34 (44)	**0.021**
	Median BMI (kg/m^2)*		24 (22-28)	26 (22-31)	**0.038**
	BMI ≥25 kg/m^2		27 (47)	46 (60)	0.128
Comorbidities					
	ASA (I-II)		36 (60)	52 (67)	0.419
	ECOG (0-1)		45 (75)	66 (85)	0.158
	Cirrhosis		2 (3)	1 (1)	0.413
	Heart disease		10 (17)	12 (16)	0.864
	Lung disease		8 (13)	7 (9)	0.415
	Diabetes		8 (13)	13 (17)	0.589
	History of surgery		33 (55)	42 (55)	0.958
	Cancer		45 (75)	54 (69)	0.456
Surgery					
	Type				
		Colorectal	14 (23)	17 (22)	0.840
		HPB	31 (52)	19 (24)	0.001
		Upper-GI	11 (18)	17 (22)	0.674
		Other	4 (7)	25 (32)	<0.001
	Approach				<0.001
		Open	50 (83)	29 (37)	
		Laparoscopy	10 (17)	49 (63)	
	Duration	Median (min)*	271 (224-340)	154 (112-239)	<0.001
		≥ 180 min	46 (77)	33 (42)	<0.001
	Blood Loss	Median (mL)*	300 (100-575)	90 (0-263)	0.002
		≥ 200 mL	40 (67)	24 (31)	<0.001
Median mE-PASS			0.77 (0.57-1.03)	0.49 (0.4-0.81)	0.12

BMI: Body mass index; ASA: American Association of Anesthesiologists physical status classification system; ECOG: Eastern Cooperative Oncology Group performance status; cancer: operative indication; HPB: Hepato-Pancreatico-Biliary surgery; Upper-GI: Upper-Gastrointestinal surgery; mE-PASS: Modified Estimation of Physiologic Ability and Surgical Stress; CCI: Comprehensive complication index; LoS: Length of stay. Other surgeries included pressurized intra-abdominal aerosol chemotherapy (17), endocrine operations (4), complex abdominal wall operations (2), resections of retroperitoneal sarcomas (3), nephrectomy (1), and interrupted limb perfusions for melanoma (2). * Median values (IQR)

Table 2: Logistic regression with uni- and multivariable analysis for predictors of postoperative complications.

	Overall postoperative complications					
	Univariable			Multivariable		
	OR	95% CI	p-value	OR	95% CI	p-value
Age≥ 70 years	1.55	0.74-3.27	0.247			
Gender (Female)	0.45	0.22-0.89	**0.022**	1.06	0.38-2.96	0.905
ASA I/II	1.33	0.66-2.68	0.42			
ECOG 0/1	1.83	0.79-4.28	0.161			
Cirrhosis	2.66	0.24-30	0.43			
Cancer	1.33	0.63-2.84	0.456			
Diabetes	0.77	0.3-2	0.59			
BMI≥25 kg/m^2	0.59	0.3-1.17	0.129			
Approach (open)	8.49	3.72-19.18	**<0.001**	11.22	2.74-46.05	**0.001**
Duration ≥180 min	4.48	2.12-9.47	**<0.001**	0.47	0.11-1.94	0.297
Blood loss ≥200 mL	4.50	2.19-9.25	**<0.001**	1.68	0.57-4.99	0.350
ΔAlb POD1 ≥10 g/L	6.89	2.94-16.14	**<0.001**	3.29	1.14-9.49	**0.028**

ASA: American Association of Anesthesiologists physical status classification system; ECOG: Eastern Cooperative Oncology Group performance status; BMI: Body mass index; ΔAlb POD1: The difference between serum albumin concentration on POD -1 and POD 1 (g/L). OR: odds ratio

LEGENDS

Figure 1:

ΔAlb on POD1 correlates with the extent of surgery. ΔAlb on POD1 showed a significant correlation with (a) mE-PASS (r=0.275, p=0.01), (b) blood loss (r=0.391, p<0.001), and (c) duration of surgery (r=0.562, p<0.001).

Figure 2:

The postoperative decrease of Alb on POD 1 correlated with outcomes. ΔAlb on POD1 showed a significant correlation with CCI (Comprehensive complication index) (a), and with length of stay (LoS) (b).

Figure 3:

Receiver operating characteristic (ROC) curve to determine the optimal cut-off of ΔAlb on POD1 (blue line), showed an AUC of 0.78.

Supplementary Figure 1:

Mean perioperative concentration of serum albumin (vertical bars illustrate standard deviations).

Supplementary Figure 2:

ΔCRP (a), ΔPCT (b) and ΔLCT (c) on POD1 yielded AUC of 0.73, 0.63 and 0.64, respectively. The AUC of ΔCRP on POD4 was 0.75 (d).

Contributorship statement:

IL involved in study design, data collection, analysis and interpretation, review of the literature, drafting and critical revision of the manuscript. GRJ involved in study design, data collection, analysis and interpretation, review of the literature, critical revision of the manuscript. AK involved in data collection, analysis and interpretation, review of the literature, critical revision of the manuscript. SM involved in data collection, analysis and interpretation, review of the literature, critical revision of the manuscript. MS involved in study design, analysis and interpretation, critical revision of the manuscript. ND involved in study design, analysis and interpretation, critical revision of the manuscript. MH study design, analysis and interpretation, drafting and critical revision of the manuscript.

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Data sharing statement: There is no additional data.

Figure 1: The Intensity of ΔAlb on POD1 Correlates With the Extent of Surgery

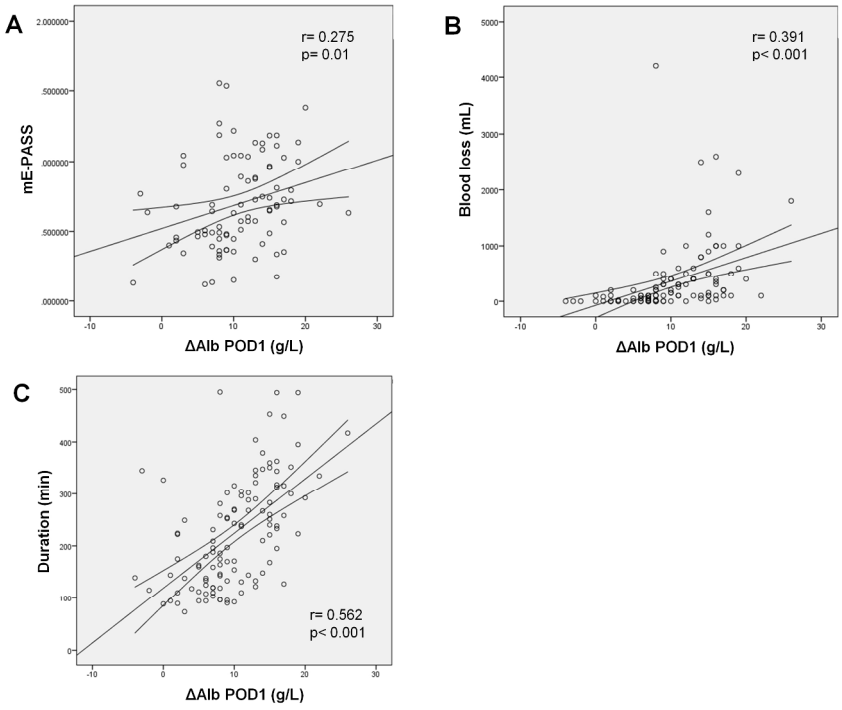


Figure 1

254x190mm (300 x 300 DPI)

Figure 2: ΔAlb on POD1 Correlates With Complications (CCI) and Length of Stay (LoS)

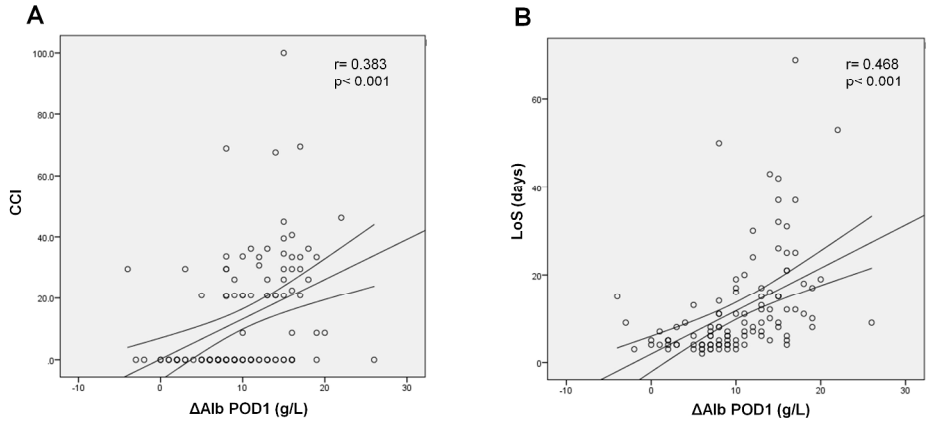


Figure 2

254x190mm (300 x 300 DPI)

Figure 3: Receiver operating characteristic (ROC) curve of ΔAlb on POD1

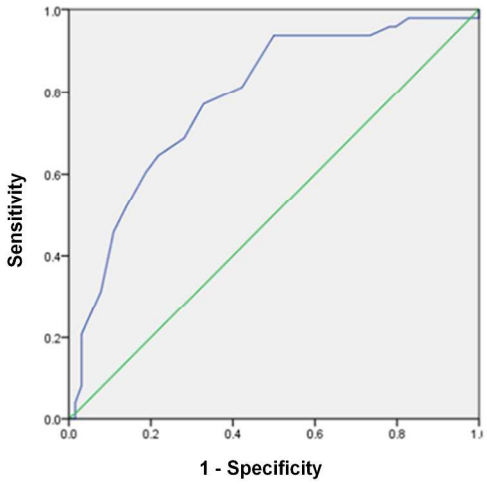
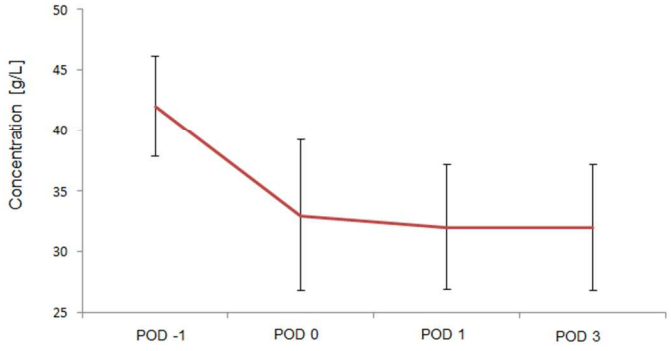


Figure 3

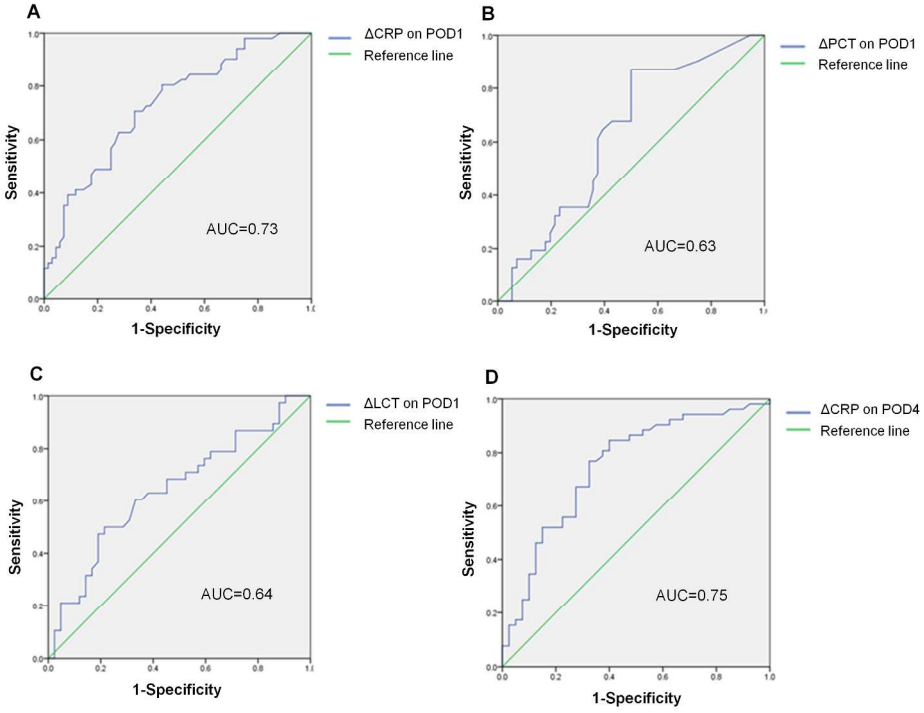
254x190mm (300 x 300 DPI)

Supplementary Figure 1: Perioperative Kinetics of Serum Albumin (Alb)



254x190mm (300 x 300 DPI)

Supplementary Figure 2: Receiver operating characteristic (ROC) curves of other stress markers



254x190mm (300 x 300 DPI)

Supplementary Table 1: Correlations of the candidate biomarkers with outcomes.

		mE-PASS		Minor (I-II)		Major (III-V)		Overall complication		CCI		LoS	
		Pearson	p-value	Spearman	p-value	Spearman	p-value	Spearman	p-value	Pearson	p-value	Pearson	p-value
CRP	Δ Max	0.062	0.530	0.256	**0.003**	0.387	**<0.001**	0.534	**<0.001**	0.529	**<0.001**	0.484	**<0.001**
	Δ POD 0	0.052	0.693	0.070	0.566	0.049	0.686	0.098	0.417	0.231	0.052	0.381	**0.001**
	Δ POD 1	0.116	0.256	0.207	**0.024**	0.273	**0.003**	0.395	**<0.001**	0.469	**<0.001**	0.462	**<0.001**
Alb	Δ Max	0.323	**0.001**	0.264	**0.003**	0.345	**<0.001**	0.470	**<0.001**	0.373	**<0.001**	0.358	**<0.001**
	Δ POD 0	0.479	**<0.001**	0.298	**0.006**	0.194	0.077	0.420	**<0.001**	0.302	**0.005**	0.259	**0.018**
	Δ POD 1	0.275	**0.010**	0.228	**0.016**	0.372	**<0.001**	0.485	**<0.001**	0.383	**<0.001**	0.468	**<0.001**
PCT	Δ Max	-0.050	0.656	0.240	**0.016**	0.181	0.071	0.339	**0.001**	0.140	0.162	0.204	**0.040**
	Δ POD 0	0.017	0.906	0.171	0.204	0.076	0.570	0.211	0.112	0.015	0.909	0.168	0.206
	Δ POD 1	-0.010	0.933	0.135	0.216	0.150	0.165	0.220	**0.041**	-0.034	0.752	0.103	0.342
LCT	Δ Max	0.269	**0.013**	0.301	**0.003**	0.196	0.057	0.426	**<0.001**	0.317	**0.002**	0.327	**0.001**
	Δ POD 0	0.244	**0.039**	0.297	**0.007**	0.178	0.111	0.412	**<0.001**	0.299	**0.007**	0.292	**0.008**
	Δ POD 1	0.118	0.331	0.265	**0.018**	0.026	0.817	0.248	**0.026**	0.193	0.087	0.104	0.360

Complications are graded according to the Clavien classification (grade I to V); mE-PASS: Modified Estimation of Physiologic Ability and Surgical Stress; CCI: Comprehensive complication index; LoS: Length of stay; CRP: C-reactive protein; Alb: Serum albumin; PCT: Procalcitonin; LCT: Lactates; Δ Max: Maximal difference between the pre- and post-operative values; Δ POD 0: Difference of concentration on POD -1 and POD 0; Δ Pod 1: Difference of concentration on POD -1 and POD 1

Supplementary Table 2: Discriminatory ability of albumin decrease on POD1

	ΔAlb POD1		
	<10 g/L	**≥10 g/L**	**p-value**
	n (%)	**n (%)**	
Complications			
Minor (I-II)	8 (15)	21 (36)	**0.011**
Major (III-V)	3 (6)	16 (28)	**0.002**
Overall	11 (20)	37 (64)	**<0.001**
CCI	0	20.9 (0-33.5)	**<0.001**
LoS	4 (4-7)	13 (13-21)	**<0.001**

Complications are graded according to the Clavien classification (grade I to V); ΔAlb POD1: The difference between serum albumin concentration on POD -1 and POD 1 (g/L); mE-PASS: Modified Estimation of Physiologic Ability and Surgical Stress; CCI: Comprehensive complication index; LoS: Length of stay

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	5-6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, explain how loss to follow-up was addressed	Not applicable
		(*e*) Describe any sensitivity analyses	6

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	Not applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	16
		(c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	7-8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8
		(*b*) Report category boundaries when continuous variables were categorized	6
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Is postoperative decrease of serum albumin an early predictor of complications after major abdominal surgery? A prospective cohort study in a European centre

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Research Article

Is postoperative decrease of serum albumin an early predictor of complications after major abdominal surgery? A prospective cohort study in a European centre

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The present study was presented at the *103rd Congress of Swiss Surgery* (June 2016, Lugano, Switzerland) and at the Clinical Congress of the American College of Surgeons (October 2016, Washington, DC, USA).

Key words: Biomarker; albumin; major surgery; postoperative complications; stress response

Word count: 3106

ABSTRACT

Objective: To test postoperative serum albumin drop (ΔAlb) as a marker of surgical stress response and early predictor of clinical outcomes.

Design: Prospective cohort study (NCT02356484). Albumin was prospectively measured in 138 patients undergoing major abdominal surgery. Blood samples were collected before surgery and on postoperative days 0, 1, 2, and 3. ΔAlb was compared to the *Modified Estimation of Physiologic Ability and Surgical Stress* (mE-PASS) score and correlated to the performances of C-reactive protein (CRP), procalcitonin (PCT), and lactate (LCT). Postoperative outcomes were postoperative complications according to both Clavien classification and Comprehensive Complication Index (CCI), and length of hospital stay (LoS).

Setting: Department of abdominal surgery in a European tertiary center.

Participants: Adult patients undergoing elective major abdominal surgery, with anticipated duration ≥2h. Patients on immunosuppressive or antibiotic treatments before surgery were excluded.

Results: The level of serum albumin rapidly dropped after surgery. ΔAlb correlated to the mE-PASS score (r=0.275, p=0.01) and to CRP increase (r=0.536, p<0.001). ΔAlb also correlated to overall complications (r=0.485, p<0.001), CCI (r=0.383, p<0.001) and LoS (r=0.468, p<0.001). A ΔAlb ≥10 g/L yielded a sensitivity of 77.1% and a specificity of 67.2% (AUC: 78.3%) to predict complications. Patients with ΔAlb ≥ 10g/l on POD 1 showed a 3 fold increased risk of overall postoperative complications.

Conclusion:

Early postoperative decrease of serum albumin correlated with the extent of surgery, its metabolic response, and with adverse outcomes such as complications and length of stay. A decreased concentration of serum albumin ≥ 10g/l on POD 1 was associated with a 3-fold increased risk of overall postoperative complications, and may thus be used to identify patients at risk.

STRENGHTS AND LIMITATIONS OF THE STUDY

- The present study has a prospective design and offers a head-to-head comparison with biomarkers currently used in clinical practice (C-Reactive Protein and Procalcitonin).
- Albumin drop was thoroughly assessed by analyzing its correlation with a comprehensive panel of surrogate markers for surgical trauma and validated scores for outcomes.
- The predictive value of combined biomarkers was not assessed in the present study.
- This study involved a single center and included a training cohort, without validation cohort.

INTRODUCTION

Abdominal surgery is among the most frequently performed elective surgery [1]. Although surgical and perioperative improvements have reduced postoperative mortality over the last decades, postoperative morbidity has remained high [2]. In addition to the morbidity which patients are exposed to, postoperative complications pose a significant financial burden, while important efforts are currently pursued to reduce health care expenditures [2].

The magnitude of metabolic stress response mirrors the extent of surgery [3 4] and presumably contributes to the risk of developing postoperative complications [5 6]. Early identification of patients at risk may improve outcomes, since measures to attenuate the surgical stress response and to reduce morbidity exist [7].

Although C-reactive protein (CRP) and procalcitonin (PCT) have been proposed as predictors for adverse outcomes in colorectal surgery, they both display the critical limitation of slow kinetics[8 9]. Conversely, serum albumin (Alb) is a maintenance protein that is rapidly downregulated by inflammatory signals [4 10]. Preliminary data suggested that Alb level rapidly dropped after surgery and correlated to outcomes in esophageal [11], oral cancer [12], abdominal [4], pancreatic [13], liver resection[14]/transplant[15] and cardiac [16] surgeries. However, prospective validation is missing and Alb is not used to assess surgical stress or to predict outcomes.

This study aimed to test the hypotheses that early postoperative albumin drop (I) reflects the magnitude of surgical trauma, (II) correlates to established markers of metabolic stress, and (III) predicts postoperative complications.

METHODS

Study design and patient groups

This prospective study was conducted at the Department for Visceral Surgery at the University Hospital of Lausanne Switzerland (CHUV) between February and December 2015 (NCT02356484). The study was approved by the Institutional Review Board (N°367/15) and all patients provided written consent prior to surgery. Inclusion criteria were age >18 years, and elective major abdominal surgery - defined as an operative procedure with anticipated duration ≥2h [17]. Perioperative care closely adhered to recently published enhanced recovery guidelines (http://erassociety.org.loopiadns.com/guidelines/list-of-guidelines). Standardized fluid administration was followed by advanced hemodynamic monitoring to avoid intraoperative fluid overload. According to the clinical care pathway, intravenous fluid was typically discontinued the morning after surgery.

Demographics, comorbidities, surgical details and clinical outcomes were prospectively collected and anonymized in a computerized protected database. A two-sample t-test was used to calculate sample size, with size effect of 0.8, power of 0.99 and significance level of 0.05. This determined a required number of 50 patients per group (i.e. with complication vs. without complication). Anticipating a complication rate of 40%, the final sample size for this study was n=125 patients. In order to adjust for 10% drop-out or missing data, final sample size resulted in n=138.

Extent of surgery

The amplitude of surgical stress was measured by the *Modified Estimation of Physiologic Ability and Surgical Stress* (mE-PASS). Briefly, mE-PASS score encompasses 7 items (6 preoperative variables and the surgical procedure). It predicts the in-hospital mortality and the 30-day mortality rates, respectively [18]. Type of surgery, operative time, and surgical approach (open *vs*. laparoscopic) were recorded. Conversions from laparoscopy to laparotomy were counted as

laparoscopic cases. Anesthesiologists and surgeons jointly estimated blood loss by measuring the volume of aspirated fluid and soaked gauzes.

Biological markers

Serum levels of albumin, CRP, PCT and lactate (LCT) were perioperatively measured in a fasting state, following standardized institutional guidelines. Blood samples were drawn the day before surgery, the day of surgery (4-6 hours after the end of the operation) and on the first, second and third postoperative day. As baseline values tend to show large variations especially for albumin [4 10], we considered that a dynamic value (difference between two time-points) might be more informative than a snapshot value. Several values based on pre- and post-operative concentrations, were thus calculated for each marker (i.e., Δ Max: Maximal difference between the pre- and post-operative values; Δ POD 0: Difference of concentration on POD -1 and POD 0; Δ POD 1: Difference of concentration on POD -1 and POD 1).

Outcome measures

Complications were graded with the Clavien classification within 30 postoperative days, counting grade I/II events as minor complications and grade III-V as major complications [19]. Every complication was documented. Global morbidity for each patient was quantified by the Comprehensive Complication Index (CCI) on a scale from 0 to 100 [20], representing respectively no complication and postoperative death. Length of stay (LoS) was considered as the duration from the day of surgery until discharge.

Statistical analysis

Continuous variables were presented as mean with standard deviation (SD) or median value with interquartile range (IQR) depending on the normality of the distribution and compared using Student's *t* test and Mann-Whitney U test, whereas categorical variables were given as frequencies

with percentages and compared with chi-square test. For statistical analyses, the following parameters were dichotomized: age (≥70 years), body-mass index (≥25 kg/m^2), operative time (≥180 minutes), and blood loss (≥200 ml). Spearman's and Pearson's tests were used to measure correlations of categorical (ρ) and continuous (r) variables, respectively. Receiver operating characteristic (ROC) curves were applied to obtain the area under the curve (AUC), and to determine ideal cut-offs. Logistic regression was applied to identify independent predictors; variables with significance < 0.1 in univariable analyses were further included in multivariable analyses. A p value <0.05 was considered to be statistically significant in all tests. Data analyses were generated using SPSS v20 statistical software (Chicago, IL).

RESULTS

Patients Characteristics, Details of Surgery, and Outcomes

During the study period, 155 consecutive patients undergoing major abdominal surgery were potentially eligible for inclusion, but 17 of them refused to participate. As a result, 138 patients were included in the study and had a complete follow-up. Demographics and surgical details are displayed in **Table 1**. Median mE-PASS score was 0.66 (IQR 0.45-0.96).

Overall, 60/138 patients (43%) experienced at least one complication, and one patient died after total gastrectomy and splenopancreatectomy due to cardiorespiratory arrest. Minor and major complications were observed in 35 and 25 patients, respectively. Patients showed a mean CCI of 13.2 (SD 18.5), and were discharged after a median LoS of 8 days (IQR 5-15 days).

Perioperative Profile of Biomarkers

The perioperative profile of albumin showed a rapid drop induced by surgery, followed by a plateau phase between POD 0 and POD 3 (**Supplementary Figure 1**). Lactate levels peaked in the first 4-6h after surgery and were back to baseline on POD1. Conversely, CRP and PCT showed slow kinetics reaching maximal values on POD 4 and 3, respectively. The mean maximal decrease of albumin was 11.3 g/L (± 5.6), which was similar to albumin drop on POD 1: 10.1 g/L (SD: 5.8). Further analyses were hence focused on ΔAlb on POD1.

Correlation of ΔAlb to surgical stress, biomarkers, and outcomes

ΔAlb on POD1 correlated to surgical stress (mE-PASS) ($r=0.275$, $p=0.01$) and to surrogates such as duration of surgery ($r=0.562$, $p<0.001$), blood loss ($r=0.391$, $p<0.001$), and surgical approach ($\rho=0.55$, $p<0.001$) (**Figure 1**).

ΔAlb on POD1 also correlated to maximal increases of CRP ($r=0.54$, $p<0.001$), PCT ($r=0.43$, $p<0.001$), and LCT ($r=0.25$, $p=0.02$). Furthermore, a positive and significant correlation was highlighted between ΔAlb on POD1 and ΔCRP on POD4 ($\rho=0.234$, $p=0.044$). ΔAlb on POD1 was

significantly associated with adverse outcomes, showing significant correlations with CCI (ρ=0.383, p<0.001) and LoS (ρ=0.468, p<0.001) (**Figure 2).**

The correlations of CRP, PCT, and LCT with surgical stress and outcomes were also tested and are detailed in **Supplementary Table 1**.

Predictive Value of Albumin Decrease

A ROC curve was used to determine the optimal cut-off of ΔAlb on POD1, settled at 10 g/L. The area under the curve (AUC) measured 78.3% (95% CI: 70-87%), giving a sensitivity of 77.1%, a specificity of 67.2%, a positive predictive value of 64.8%, and a negative predictive value of 79.6%, for overall complications (**Figure 3**). The respective ROC curves for POD1 values of ΔCRP, ΔPCT, and ΔLCT are provided in **Supplementary Figure 2**.

It was subsequently investigated whether this cut-off was able to discriminate and stratify patients' risk. Patients with an intense drop of Alb on POD 1 (ΔAlb POD1 ≥10 g/L) showed a higher mE-PASS (0.73 *vs.* 0.49, p=0.029) with higher rates of minor (36% *vs.* 15%, p=0.011), major (28% *vs.* 6%, p=0.002), and overall complications (64% *vs.* 20%, p<0.001). This resulted in a significantly higher CCI (20.9 *vs.* 0, p<0.001) and in a significantly longer LoS (13 *vs.* 4 days, p<0.001) (**Supplementary Table 2**).

Logistic regression with multivariable analysis identified open surgery (OR: 11.22; 95% CI: 2.74-46.05; p=0.001) and ΔAlb POD1≥ 10 g/L (OR: 3.29; 95% CI: 1.14-9.49; p=0.028) to be independently associated with overall complications (**Table 2**).

DISCUSSION

Surgery induced a rapid decrease of serum albumin in patients undergoing elective major abdominal procedures; and it remained stable for several postoperative days. Although correlation coefficients were modest, the decrease in serum albumin significantly correlated with (I) the extent of surgery (mE-PASS, blood loss, duration of surgery, and surgical approach), (II) the maximal amplitude of other stress markers, such as CRP, PCT and LCT and (III) was consistently associated with adverse outcomes (according to both Clavien classification, CCI, and LoS). A serum albumin decrease ≥ 10 g/L on POD 1 was independently associated with a 3-fold increased risk for postoperative complication.

The present study tested a panel of 4 biomarkers of which 2 are routinely used and served as benchmarks (CRP and PCT) and 2 are less established markers and deserved prospective investigations (Alb and LCT). The mE-PASS accurately recapitulates surgical stress, and was validated and used in abdominal surgery [18 21-24]. To our knowledge, there is no other validated and available score. One study endpoint was the CCI, which is a score summing each complication graded according to the Clavien classification. As a result, CCI avoids omitting minor complications, and is therefore more accurate than the Clavien classification alone [20]. Serum albumin showed the more consistent correlation with stress response and clinical outcomes. Alb and LCT both display some of the features for ideal markers: easy to measure and to interpret, readily available, can be repeated for monitoring and non-expensive. While Alb rapidly dropped after surgery and subsequently stabilized until POD 3, lactate showed a prompt increase followed by a fast return to baseline value, already on POD 1. It can be assumed that the timing of blood collection may have a more important impact on LCT than on Alb. As a consequence, Alb is more robust and easier used in the clinical setting. Importantly, the selected markers were repeatedly measured, which allowed us to capture their perioperative profiles and to further calculate differences of concentrations between various time-points. The latter was revealed to be pivotal and more informative than a single value.

The mechanisms of early postoperative albumin decrease combine altered metabolism, blood loss/dilution and most importantly redistribution into the third space, due to capillary leakage. The latter accounts for >75% of albumin decrease in the early postoperative phase and appears to be related to the magnitude of systemic inflammatory response[10 25 26]. Therefore, albumin decrease is certainly influenced by perioperative fluid management (liberal *vs.* restrictive) but it mainly reflects the extent of postsurgical stress response.

In multivariable analysis (table 2), 2 factors were independently associated with complications: approach and ΔAlb POD1 ≥10 g/L. The overlap of certain parameters of surgical stress may, in part, explain why they were not identified as independent predictors of complications. It may also suggest that serum albumin mirrors these different parameters.

Some limitations need to be addressed. The present analyses were focused on 4 biomarkers that are readily available and easy to evaluate in the clinical setting. This non-inclusive panel of biomarkers could be perceived as a methodological shortcoming. Notwithstanding, integrating more complex and costly biomarkers would unlikely be more informative given their poor reproducibility, cost and assay measurement complexity. Likewise, this study did not assess the predictive value of albumin drop combined with other biomarker and/or clinical variables. Although such a classifier may presumably improve sensitivity and specificity, it will also be more complex which could ultimately preclude its implementation in clinical practice. Blood collection on POD 0 occurred 4-6 hours after the end of surgery. This delay might be long enough to alter the discriminatory ability of certain biomarkers, particularly lactate [27]. Finally, the present findings need to be further validated with an independent cohort.

Available data on the predictive role of postoperative Alb are scarce; and most of these reports were retrospective studies [11-13 16 28]. Of note, each of the studies investigated only a single postoperative value of serum albumin. This represents a critical drawback as it cannot be discerned whether the low postoperative concentration of serum albumin resulted from intense surgical stress or from low preoperative level, which is an acknowledged predictor of increased

postoperative complication [29 30]. A prospective pilot study in abdominal surgery – conducted recently in our institution- showed consistent findings, with an increased risk of complication related to the amplitude of serum albumin postoperative drop [4]. Of note, the cohorts from this previous study (70 patients) and from the present one (138 patients) were strictly distinct. Postoperative lactate has been more thoroughly explored in liver surgery, with few reports in other surgical fields. In a recent landmark study, Vibert et al. demonstrated that a postoperative cut-off of arterial lactate > 3mmol/L at the end of surgery was an independent predictor of complications after elective hepatectomies [27]. Their conclusion correlates with the present findings since ΔLCT POD0 was correlated with mE-PASS (p=0.039), overall complication (p<0.001), CCI (p=0.007) and LoS (p=0.008) (**Figure 2**). Although both CRP and PCT are routinely used biomarkers in clinical practice, they are typically contributive on POD 4 only. The present study design allowed to confirm the ultimate advantage of Alb to be up-regulated within the early postoperative phase, illustrated by the correlation between ΔAlb on POD1 and ΔCRP on POD4 (ρ=0.234, p=0.044), highlighted in this study. In fact, ΔAlb on POD1 was more sensitive than ΔCRP on POD4, illustrated by AUC of 0.78 and 0.75, respectively (Figure 3 and Supplementary 3D).

How the monitoring of Alb in surgical patients can lead to better outcomes is a key question. Measures to preoperatively attenuate the stress response to surgery have been extensively explored. Interestingly, successful attempts were reported with immunonutrition [31], enhanced recovery programs (ERAS) [32 33], or high-dose glucocorticoids [34]. Whether these options would be able to restrain the stress response, once triggered, in the early postoperative phase remains to be investigated. In this setting, albumin drop may indicate whether these measures may be beneficial in the perioperative period by being incorporated into the design of clinical trials as a marker for patients at higher risk of perioperative complications.

In summary, early postoperative decrease of serum albumin correlated with the (I) extent of surgery, (II) its metabolic response, and with (III) adverse outcomes such as complications and length of hospital stay. A decreased concentration of serum albumin ≥ 10g/l on

POD 1 was associated with a 3-fold increased risk of overall postoperative complications; albumin decrease occurs rapidly after surgery and remains stable for several days. As it is easy to measure, it could be used to identify patients at risk.

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Table 1: Baseline characteristics of patients with and without postoperative complications.

		Pat. with complications (n=60) n (%)	Pat. without complications (n=78) n (%)	p-value
Demographics				
Median age (years)*		64 (50-73)	59 (51-69)	0.306
Age ≥ 70 years		20 (51)	19 (49)	0.246
Gender (male)		38 (63)	34 (44)	**0.021**
Median BMI (kg/m^2)*		24 (22-28)	26 (22-31)	**0.038**
BMI ≥25 kg/m^2		27 (47)	46 (60)	0.128
Comorbidities				
ASA (I-II)		36 (60)	52 (67)	0.419
ECOG (0-1)		45 (75)	66 (85)	0.158
Cirrhosis		2 (3)	1 (1)	0.413
Heart disease		10 (17)	12 (16)	0.864
Lung disease		8 (13)	7 (9)	0.415
Diabetes		8 (13)	13 (17)	0.589
History of surgery		33 (55)	42 (55)	0.958
Cancer		45 (75)	54 (69)	0.456
Surgery				
Type				
	Colorectal	14 (23)	17 (22)	0.840
	HPB	31 (52)	19 (24)	0.001
	Upper-GI	11 (18)	17 (22)	0.674
	Other	4 (7)	25 (32)	<0.001
Approach				<0.001
	Open	50 (83)	29 (37)	
	Laparoscopy	10 (17)	49 (63)	
Duration	Median (min)*	271 (224-340)	154 (112-239)	<0.001
	≥ 180 min	46 (77)	33 (42)	<0.001
Blood Loss	Median (mL)*	300 (100-575)	90 (0-263)	0.002
	≥ 200 mL	40 (67)	24 (31)	<0.001
Intravenous fluid (mL)		2500 (2000-4000)	1500 (1000-2500)	0.018
Median mE-PASS		0.77 (0.57-1.03)	0.49 (0.4-0.81)	0.12

BMI: Body mass index; ASA: American Association of Anesthesiologists physical status classification system; ECOG: Eastern Cooperative Oncology Group performance status; cancer: operative indication; HPB: Hepato-Pancreatico-Biliary surgery; Upper-GI: Upper-Gastrointestinal surgery; mE-PASS: Modified Estimation of Physiologic Ability and Surgical Stress; CCI: Comprehensive complication index; LoS: Length of stay. Other surgeries included pressurized intra-abdominal aerosol chemotherapy (17), endocrine operations (4), complex abdominal wall operations (2), resections of retroperitoneal sarcomas (3), nephrectomy (1), and interrupted limb perfusions for melanoma (2). * Median values (IQR)

Table 2: Logistic regression with uni- and multivariable analysis for predictors of postoperative complications.

	Overall postoperative complications					
	Univariable			Multivariable		
	OR	95% CI	p-value	OR	95% CI	p-value
Age≥ 70 years	1.55	0.74-3.27	0.247			
Gender (Female)	0.45	0.22-0.89	**0.022**	1.06	0.38-2.96	0.905
ASA I/II	1.33	0.66-2.68	0.42			
ECOG 0/1	1.83	0.79-4.28	0.161			
Cirrhosis	2.66	0.24-30	0.43			
Cancer	1.33	0.63-2.84	0.456			
Diabetes	0.77	0.3-2	0.59			
BMI≥25 kg/m^2	0.59	0.3-1.17	0.129			
Approach (open)	8.49	3.72-19.18	**<0.001**	11.22	2.74-46.05	**0.001**
Duration ≥180 min	4.48	2.12-9.47	**<0.001**	0.47	0.11-1.94	0.297
Blood loss ≥200 mL	4.50	2.19-9.25	**<0.001**	1.68	0.57-4.99	0.350
ΔAlb POD1 ≥10 g/L	6.89	2.94-16.14	**<0.001**	3.29	1.14-9.49	**0.028**

ASA: American Association of Anesthesiologists physical status classification system; ECOG: Eastern Cooperative Oncology Group performance status; BMI: Body mass index; ΔAlb POD1: The difference between serum albumin concentration on POD -1 and POD 1 (g/L). OR: odds ratio

LEGENDS

Figure 1:

ΔAlb on POD1 correlates with the extent of surgery. ΔAlb on POD1 showed a significant correlation with (a) mE-PASS (r=0.275, p=0.01), (b) blood loss (r=0.391, p<0.001), and (c) duration of surgery (r=0.562, p<0.001).

Figure 2:

The postoperative decrease of Alb on POD 1 correlated with outcomes. ΔAlb on POD1 showed a significant correlation with CCI (Comprehensive complication index) (a), and with length of stay (LoS) (b).

Figure 3:

Receiver operating characteristic (ROC) curve to determine the optimal cut-off of ΔAlb on POD1 (blue line), showed an AUC of 0.78.

Supplementary Figure 1:

Mean perioperative concentration of serum albumin (vertical bars illustrate standard deviations).

Supplementary Figure 2:

ΔCRP (a), ΔPCT (b) and ΔLCT (c) on POD1 yielded AUC of 0.73, 0.63 and 0.64, respectively. The AUC of ΔCRP on POD4 was 0.75 (d).

Contributorship statement:

IL involved in study design, data collection, analysis and interpretation, review of the literature, drafting and critical revision of the manuscript. GRJ involved in study design, data collection, analysis and interpretation, review of the literature, critical revision of the manuscript. AK involved in data collection, analysis and interpretation, review of the literature, critical revision of the manuscript. SM involved in data collection, analysis and interpretation, review of the literature, critical revision of the manuscript. MS involved in study design, analysis and interpretation, critical revision of the manuscript. ND involved in study design, analysis and interpretation, critical revision of the manuscript. MH study design, analysis and interpretation, drafting and critical revision of the manuscript.

Competing interests: There are no conflicts of interest relevant to the nature of this manuscript.

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Data sharing statement: There is no additional data.

Figure 1: The Intensity of ΔAlb on POD1 Correlates With the Extent of Surgery

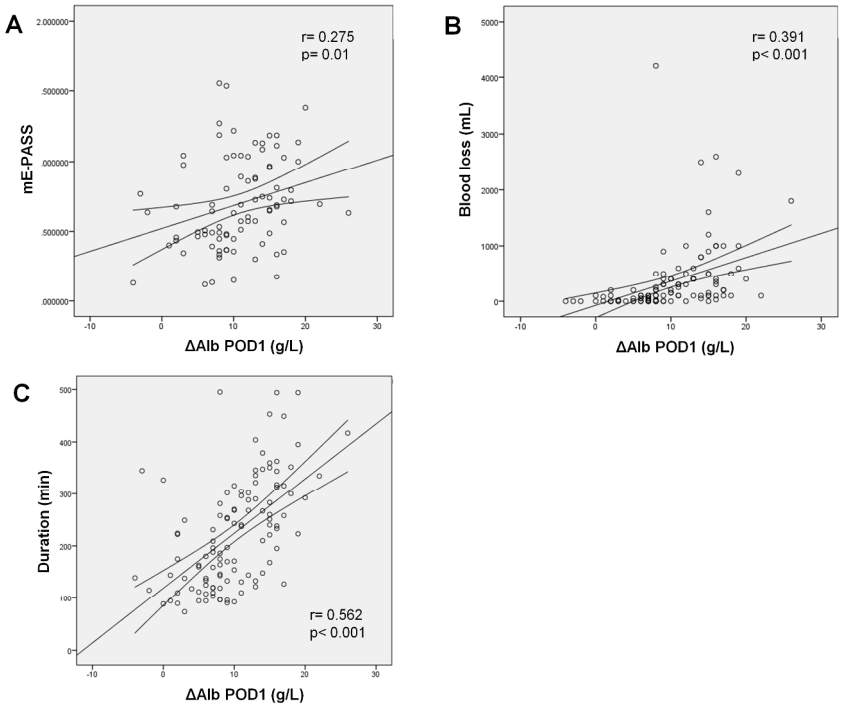


Figure 1

254x190mm (300 x 300 DPI)

Figure 2: ΔAlb on POD1 Correlates With Complications (CCI) and Length of Stay (LoS)

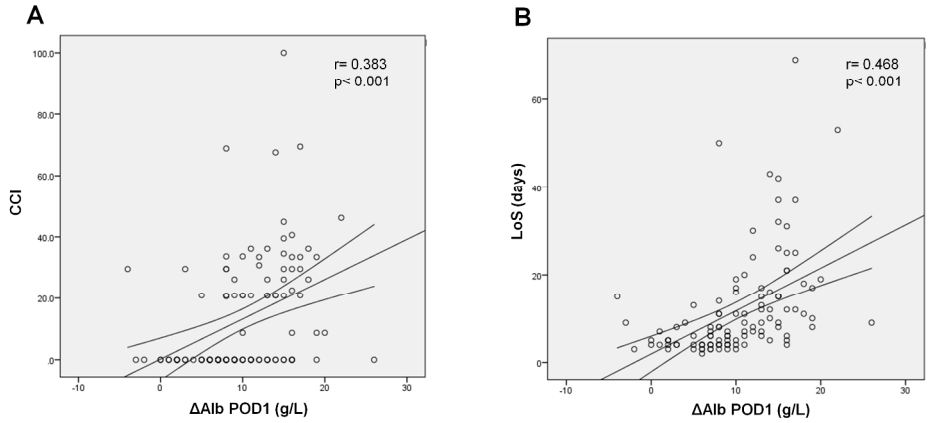


Figure 2

254x190mm (300 x 300 DPI)

Figure 3: Receiver operating characteristic (ROC) curve of ΔAlb on POD1

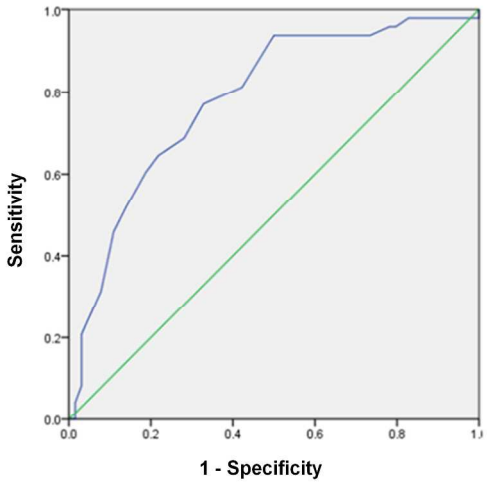
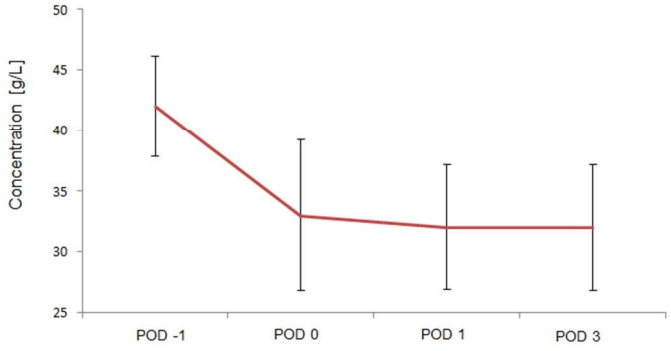


Figure 3

254x190mm (300 x 300 DPI)

Supplementary Figure 1: Perioperative Kinetics of Serum Albumin (Alb)



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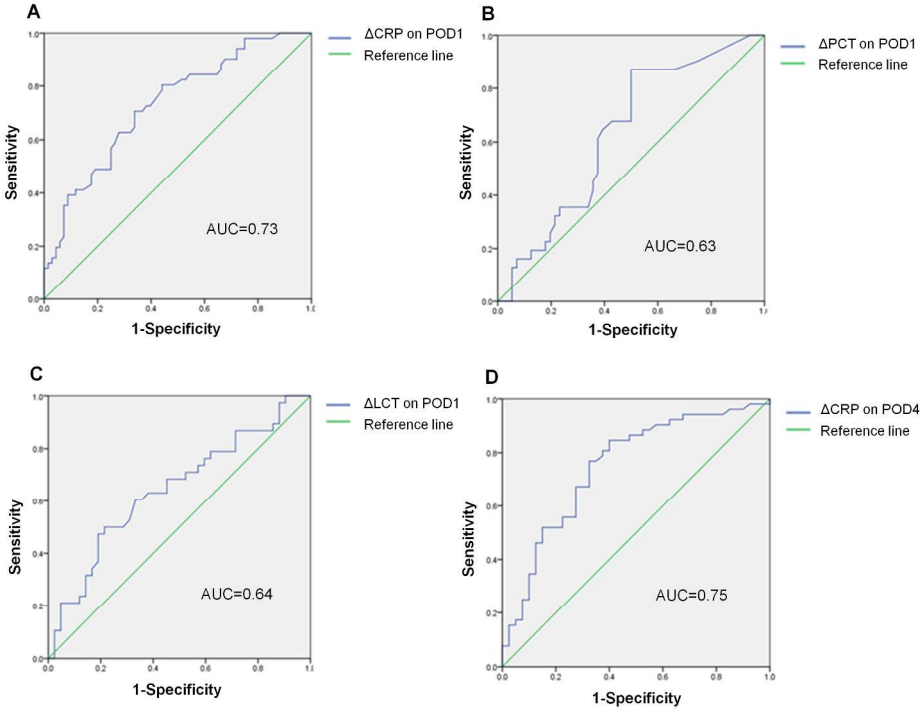
Supplementary Figure 2: Receiver operating characteristic (ROC) curves of other stress markers



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Supplementary Table 1: Correlations of the candidate biomarkers with outcomes.

		mE-PASS		Minor (I-II)		Major (III-V)		Overall complication		CCI		LoS	
		Pearson	p-value	Spearman	p-value	Spearman	p-value	Spearman	p-value	Pearson	p-value	Pearson	p-value
CRP	Δ Max	0.062	0.530	0.256	**0.003**	0.387	**<0.001**	0.534	**<0.001**	0.529	**<0.001**	0.484	**<0.001**
	Δ POD 0	0.052	0.693	0.070	0.566	0.049	0.686	0.098	0.417	0.231	0.052	0.381	**0.001**
	Δ POD 1	0.116	0.256	0.207	**0.024**	0.273	**0.003**	0.395	**<0.001**	0.469	**<0.001**	0.462	**<0.001**
Alb	Δ Max	0.323	**0.001**	0.264	**0.003**	0.345	**<0.001**	0.470	**<0.001**	0.373	**<0.001**	0.358	**<0.001**
	Δ POD 0	0.479	**<0.001**	0.298	**0.006**	0.194	0.077	0.420	**<0.001**	0.302	**0.005**	0.259	**0.018**
	Δ POD 1	0.275	**0.010**	0.228	**0.016**	0.372	**<0.001**	0.485	**<0.001**	0.383	**<0.001**	0.468	**<0.001**
PCT	Δ Max	-0.050	0.656	0.240	**0.016**	0.181	0.071	0.339	**0.001**	0.140	0.162	0.204	**0.040**
	Δ POD 0	0.017	0.906	0.171	0.204	0.076	0.570	0.211	0.112	0.015	0.909	0.168	0.206
	Δ POD 1	-0.010	0.933	0.135	0.216	0.150	0.165	0.220	**0.041**	-0.034	0.752	0.103	0.342
LCT	Δ Max	0.269	**0.013**	0.301	**0.003**	0.196	0.057	0.426	**<0.001**	0.317	**0.002**	0.327	**0.001**
	Δ POD 0	0.244	**0.039**	0.297	**0.007**	0.178	0.111	0.412	**<0.001**	0.299	**0.007**	0.292	**0.008**
	Δ POD 1	0.118	0.331	0.265	**0.018**	0.026	0.817	0.248	**0.026**	0.193	0.087	0.104	0.360

Complications are graded according to the Clavien classification (grade I to V); mE-PASS: Modified Estimation of Physiologic Ability and Surgical Stress; CCI: Comprehensive complication index; LoS: Length of stay; CRP: C-reactive protein; Alb: Serum albumin; PCT: Procalcitonin; LCT: Lactates; Δ Max: Maximal difference between the pre- and post-operative values; Δ POD 0: Difference of concentration on POD -1 and POD 0; Δ Pod 1: Difference of concentration on POD -1 and POD 1

Supplementary Table 2: Discriminatory ability of albumin decrease on POD1

	ΔAlb POD1		
	<10 g/L	**≥10 g/L**	**p-value**
	n (%)	**n (%)**	
Complications			
Minor (I-II)	8 (15)	21 (36)	**0.011**
Major (III-V)	3 (6)	16 (28)	**0.002**
Overall	11 (20)	37 (64)	**<0.001**
CCI	0	20.9 (0-33.5)	**<0.001**
LoS	4 (4-7)	13 (13-21)	**<0.001**

Complications are graded according to the Clavien classification (grade I to V); ΔAlb POD1: The difference between serum albumin concentration on POD -1 and POD 1 (g/L); mE-PASS: Modified Estimation of Physiologic Ability and Surgical Stress; CCI: Comprehensive complication index; LoS: Length of stay

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	5-6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, explain how loss to follow-up was addressed	Not applicable
		(*e*) Describe any sensitivity analyses	6

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	Not applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	16
		(c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	7-8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8
		(*b*) Report category boundaries when continuous variables were categorized	6
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.