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To find the role of postoperative fall in serum albumin as a predictor of outcome after major abdominal surgery

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Abstract
Introduction: Surgical interventions lead to well-understood metabolic, neuroendocrine, and immune responses, and the stress responses to surgery contribute to increased postoperative complications. Pro-inflammatory cytokines increased due to surgical injury, leads to changes of circulating acute phase proteins, such as albumin and C-reactive protein.
Aims and Objectives: To find the role of postoperative fall in serum albumin as a predictor of outcome after major abdominal surgery, perioperative levels of albumin, maximal fall in albumin in early postoperative period, postoperative albumin levels with type of approach and magnitude of surgery in terms of duration of surgery and estimated blood loss, grade of complications and length of hospital stay.
Material and Methods: The prospective cohort study was conducted from June 2018 – December 2019 in the Department of Surgery of a tertiary care hospital of the Armed Forces in which 150 patients who underwent routine elective major surgeries.
Results: Mean age of the patients was 52.33 ± 12.08 years. 68.67% of the patients were males and 31.33% were females. Maximum fall in serum albumin was observed on first post-operative day, which was higher in the patients who underwent open surgery (69.70%) than laparoscopic surgery (40.47%). Serum albumin levels were significantly lower on POD 1 in comparison to preoperative levels (p<0.0001). Maximum fall in serum hematocrit was observed on third post-operative day, which was higher in the patients who underwent open surgery (71.22%) than laparoscopic surgery (42.86%) (p<0.001). Complications were observed in 49.33% patients; and no deaths occurred. Mean duration of surgery was significantly higher in laparoscopic surgery as compared to open surgery (6.86 ± 0.76 vs 4.14 ± 1.42 hours, p<0.0001). Mean estimated blood loss (ml) was significantly lower in laparoscopic surgery than open surgery (255.68 ± 85.58 vs 472.58 ± 183.92, p<.0001). Mean value of maximum percentage of fall in serum hematocrit level was significantly lower in patients without complications as compared to those with complications (8.88 ± 6.27 vs 12.96 ± 5.3, p<.0001). Mean value of maximum percentage of fall in serum albumin was significantly lower in patients without complications than those with complications (11.41 ± 5.2 vs 20.83 ± 7.23, p<.0001).
Conclusion: It is concluded that maximum fall of serum albumin happens on first postoperative day and found to be significantly correlated with complications and important early predictor regarding patient outcome.

Keywords: Postoperative fall, serum albumin, predictor, abdominal surgery

Introduction

Surgical interventions lead to well-understood metabolic, neuroendocrine, and immune responses, and the stress responses to surgery contribute to increased postoperative complications [1]. Pro-inflammatory cytokines increased due to surgical injury, which leads to changes of circulating acute phase proteins, such as albumin and C-reactive protein (CRP) [2, 3]. A simple and reliable parameter representing surgical stress would be clinically important to identify patients at risk and plan perioperative care, an early knowledge of the complication helps in managing the same prudently [4].

Various parameters were noted to be helpful in early diagnosis of postoperative complications such as insulin resistance, interleukin-6, interleukin-10, and other cytokines used in clinical studies only [5]. Postoperative serum C-reactive protein (CRP) levels are widely used in clinical practice to assess postoperative inflammation. A major drawback of CRP as predictor for stress-related complications is the delayed kinetics [6].

Peak values are measured only at postoperative day 2 or 3, which may be too late for early preventive interventions.

Albumin is the most abundant protein in humans and widely used as nutritional marker and predictor for outcomes. In addition, albumin shows an immediate response to surgical stress and could therefore qualify to measure surgical stress and to predict a complicated postoperative course [7, 8]. This aspect has not yet been considered for clinical use. For example, preoperative hypoalbuminemia can predict surgical site infections [9]. Albumin is also a negative acute phase protein and decreases after surgery [10].

The aim of this study was to clarify whether the reduction of albumin level after surgery could be a predictor for short term complications following major abdominal surgeries.

Materials and Methods

The present prospective cohort study was conducted in the Department of Surgery of a tertiary care hospital of the Armed Forces during June 2018–December 2019. The study population comprised of the patients who underwent routine elective major surgeries at the hospital according to the following criteria.

Inclusion Criteria

1. All patients who underwent elective major abdominal surgeries (≥ 2 hours duration)
2. Age > 18 yrs

Exclusion Criteria

1. All emergency abdominal surgeries and re-explorations
2. Pregnant women
3. Patients on immunosuppressant or on antibiotics treatment immediately preceding surgery
4. Patients who received peri-operative albumin infusion

Methodology

Patients attending the hospital, admitted for elective major surgery and willing to consent to participate in the study were enrolled. They were explained about the study via patient information sheet and informed consent was taken from them. Patient demographics, co-morbidities, surgical details and various outcome measures were collected. 5 ml of the patient's blood was collected in EDTA and plain vial and sent to pathology department for testing. Serial monitoring of Serum albumin levels & Hematocrit on 4 preoperative day (in the morning), postoperative day 0 (4-6 hours after surgery), postoperative day 1 to 5 (in the morning) were done and recorded.

Outcome measures

1. Serum albumin levels & Hematocrit on preoperative day 1 (in the morning), postoperative day 0 (4-6 hours after surgery), postoperative day 1 to 5 (in the morning)
2. Type of surgical approach – laparoscopic or open and its correlation with maximal fall in albumin and haematocrit.
3. Magnitude of surgery in terms of duration of surgery and estimated blood loss and its correlation with maximal fall in albumin and haematocrit.
4. Postoperative complications as graded by Comprehensive Complication Index (CCI) and its correlation with albumin levels.
5. Postoperative length of hospital stay and its correlation with albumin levels.

Statistical analysis

At the end of the study, the data was collected and analysed statistically. Categorical variables were presented in number and percentage and continuous variables were presented as mean±SD and median. Quantitative variables were compared using Mann-Whitney Test between the two groups and Wilcoxon signed rank test was used for comparison between pre and post. Qualitative variables were correlated using Chi-Square test. Spearman rank correlation coefficient was used to assess the association of various parameters with each other. A p value of <0.05 was considered statistically significant. Statistical analysis was done by using Statistical Package for Social Sciences (SPSS) version 21.0.

Results

In the present study, mean age of the patients was 52.33±12.08 years. Majority of the patients, i.e. 40.67% belonged to the age group 51-60 years, followed by 22.67% patients >60 years of age, and 21.33% in 41-50 years age group. 68.67% of the patients were males and 31.33% were females. Mean BMI of the patients was 25.47 ± 3.81 kg/m^2. Majority of patients i.e. 58.67% were designated as ASA class grade 3 followed by 40% patients in grade 2 and only 2 patients 1.33% in grade 1. On ECOG performance scale, most of the patients i.e. 66% were found to be capable of only limited self-care, 32.67% patients were ambulatory and capable of all self-care, and 2 patients i.e. 1.33% were completely disabled.

Among the pre-existing comorbidities of study subjects, COPD and Perforation peritonitis (OPTD) were present in most of the patients (18.75% each), followed by Abdominal koch's in 12.50% patients. A total of 17.33% were diagnosed as having B/L inguinal hernia followed by CA gall bladder in 10% patients. In majority of patients i.e. 58.67%, laparoscopic surgery was performed and in 41.33% patients open surgery was done. Mean duration of surgery was 3.39 ± 1.25 hours, mean estimated blood loss was 304 ± 146.49 ml, and mean intraoperative IV fluids given were 1301.33 ± 333.98 ml.

Table 1: Hematocrit levels at different time intervals

Hematocrit levels (%)	Mean±SD	Median (IQR)	P value
Preoperative	36.14 ± 2.7	36(34 - 39)	
POD 0	32.81 ± 3.77	32(30 - 36)	<.0001
POD 1	32.66 ± 2.84	32(30 - 35)	<.0001
POD 2	33.49 ± 2.83	34(30.400 - 35.100)	<.0001
POD 3	34.13 ± 2.59	34(32 - 36)	<.0001
POD 4	35.15 ± 2.6	35(34 - 36)	<.0001
POD 5	35.79 ± 2.54	36(34 - 38)	0.115

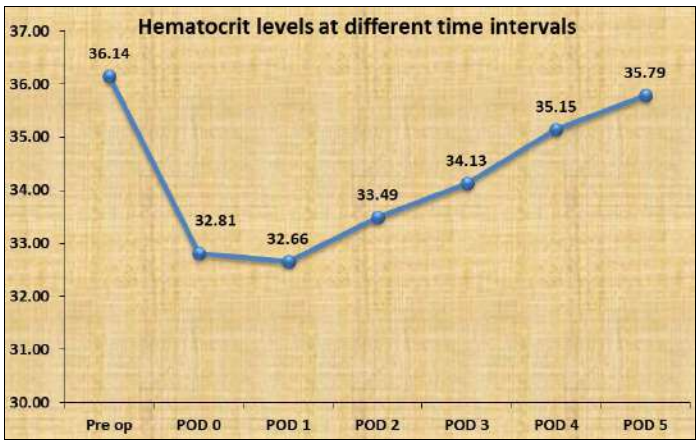

Fig 1: Hematocrit levels at different time intervals

Mean values of hematocrit levels at preoperative, POD 0, POD 1, POD 2, POD 3, POD 4, and POD 5 were 36.14%, 32.81%, 32.66%, 33.49%, 34.13%, 35.15%, and 35.79%, respectively. Hematocrit levels were significantly lower on POD 1, POD 2, POD 3, and POD 4 in comparison to preoperative levels (p<.0001). However, no significant difference was noted in the hematocrit levels on POD 5 in comparison to preoperative levels (P = 0.115).

Table 2: Serum albumin at different time intervals

Serum albumin(g/dl)	Mean ± Stdev	Median(IQR)	P value
Pre-op	3.22 ± 0.34	3.3(2.800 - 3.500)	
POD 0	2.78 ± 0.36	2.8(2.400 - 3)	<.0001
POD 1	2.74 ± 0.37	2.8(2.400 - 3)	<.0001
POD 2	2.86 ± 0.27	2.8(2.600 - 3)	<.0001
POD 3	2.94 ± 0.28	2.85(2.800 - 3.200)	<.0001
POD 4	3.03 ± 0.29	3(2.800 - 3.300)	<.0001
POD 5	3.09 ± 0.29	3(2.800 - 3.400)	<.0001

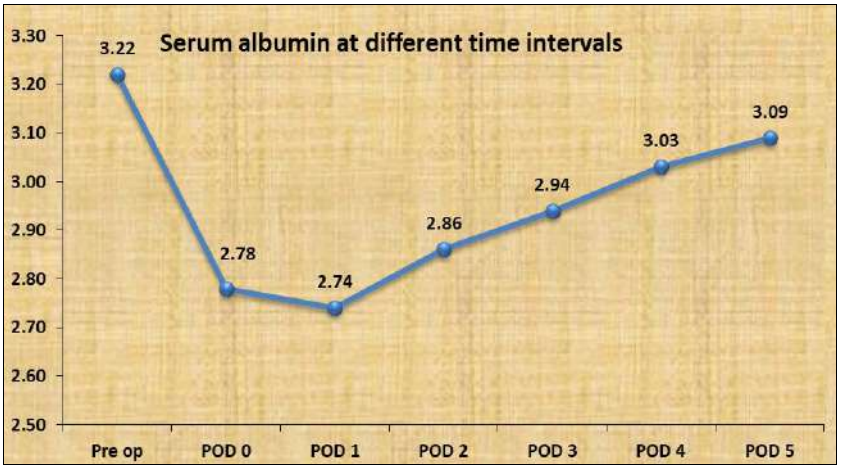

Fig 2: Serum albumin at different time intervals

Mean values of serum albumin levels at preoperative, POD 0, POD 1, POD 2, POD 3, POD 4, and POD 5 were 3.22, 2.78, 2.74, 2.86, 2.94, 3.03, and 3.09 g/dL respectively. Serum albumin levels were significantly lower on POD 1, POD 2, POD 3, POD 4, and POD 5 in comparison to preoperative levels (p<.0001).

In the present study, mean maximum percentage change in hematocrit levels and serum albumin were 11.92% and 18.44%, respectively. In most of the patients (55.33%), mean hematocrit levels was maximum at day 0, in 30.00% patients, values was maximum on day postoperative 1, and in 9.33% patients on day 3. In 8 patients, it was maximum on day 2. In 53.33% patients, mean serum albumin levels were maximum at day 0, in 34.67% patients, values was maximum on day postoperative 1, and in 12.00% patients on day 2. In 8 patients, it was maximum on day 2. No deaths were occurred in the present study. All the patients were discharged. In the present study, complications were observed in 74.67% patients.

Table 3: Association of hematocrit levels, serum albumin with type of surgery

Hematocrit levels and serum albumin	Lap(n=88)		Open(n=62)		P value
	Mean ± SD	Median(IQR)	Mean ± SD	Median(IQR)	
Hematocrit levels (%) (POD 5)	35.35 ± 2.18	36(34 - 38)	36.41 ± 2.88	36(34 - 38)	0.012
Max percentage change in hematocrit levels (%)	13.74 ± 4.07	15(10.256 - 16.667)	9.35 ± 6.89	10.53(5.882 - 12.500)	<.0001
Serum albumin (g/dl) (POD 5)	3.07 ± 0.31	3(2.800 - 3.400)	3.13 ± 0.27	3.05(3 - 3.400)	0.126
Max percentage change in serum albumin (%)	20.08 ± 7.16	20(14.286 - 28.571)	16.11 ± 8.39	15.15(13.333 - 21.429)	0.007

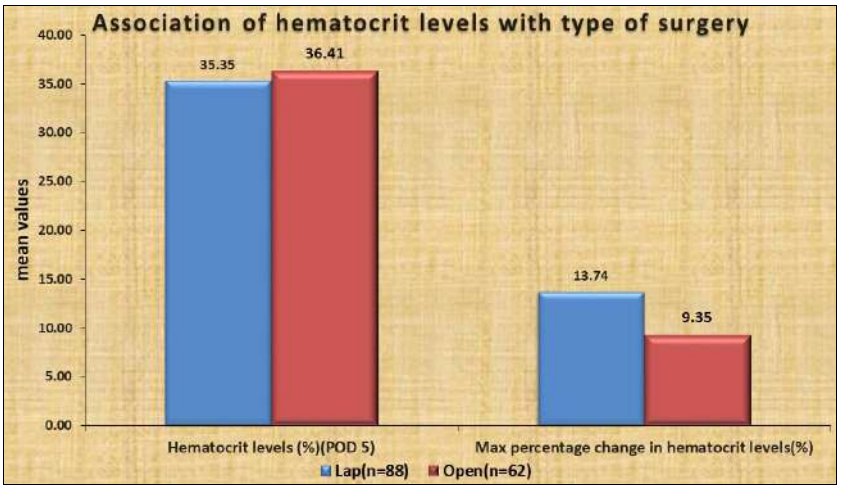

Fig 3(a): Association of hematocrit levels with type of surgery

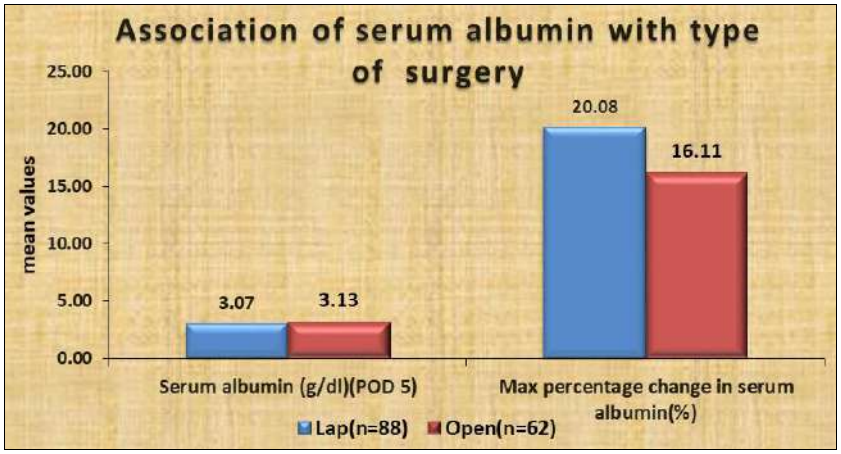

Fig 3(b): Association of serum albumin with type of surgery

Mean Hematocrit levels (%) (POD 5) were significantly lower in laparoscopic surgery as compared to that of open surgery (35.35 ± 2.18 vs 36.41 ± 2.88, P = 0.012). Mean max percentage change in hematocrit levels (%) was significantly higher in laparoscopic surgery than open surgery (13.74 ± 4.07 vs 9.35 ± 6.89, p<.0001). Mean serum albumin (g/dl) (POD 5) was comparable among laparoscopic surgery and open surgery (3.07 ± 0.31 vs 3.13 ± 0.27, P = 0.126). Mean max percentage change in serum albumin (%) was significantly higher in laparoscopic surgery than open surgery (20.08 ± 7.16 vs 16.11 ± 8.39, P=0.007).

There was a significant association of the day at which change in hematocrit levels was maximum and type of surgery. (p<0.05). At day 0, change in haematocrit was maximum with both Lap and open types of surgery but there was a significant difference on other days. The haematocrit change at Day 1 was seen in 38.64% patients with Lap Surgery and only 17.74% patients with open surgery; and on Day 3 it was seen in 5.68% patients with Lap Surgery and 14.52% patients with open surgery.

There was a significant association of the day at which change in serum albumin levels was maximum and type of surgery. (p<0.05). At day 0, change in serum albumin was maximum with both Lap and open types of surgery but there was a significant difference on other days. The serum albumin change at Day 1 was seen in 43.18% patients with Lap Surgery and only 22.58% patients with open surgery; and on Day 2 it was seen in 9.09% patients with Lap Surgery and 16.13% patients with open surgery.

Table 4: Association of duration of surgery, estimated blood loss with type of surgery

Duration of surgery and estimated blood loss	Lap(n=88)		Open(n=62)		P value
	Mean ± Stdev	Median(IQR)	Mean ± Stdev	Median(IQR)	
Duration of surgery(hours)	2.86 ± 0.76	3(2 - 3)	4.14 ± 1.42	4(3 - 5)	<.0001
Estimated blood loss(ml)	255.68 ± 85.58	200(200 - 300)	372.58 ± 183.92	400(300 - 400)	<.0001

Mean duration of surgery (hours) was significantly lower in laparoscopic surgery as compared to open surgery (2.86 ± 0.76 vs 4.14 ± 1.42, p<.0001). Mean estimated blood loss (ml) was significantly lower in laparoscopic surgery than open surgery (255.68 ± 85.58 vs 372.58 ± 183.92, p<.0001).

Mean max percentage fall in Hematocrit levels (%) was significantly lower in patients without complications as compared to those with complications (8.88 ± 6.27 vs 12.96 ± 5.3, p<.0001). Mean max percentage fall in serum albumin (%) was significantly lower in patients without complications than those with complications (11.41 ± 5.2 vs 20.83 ± 7.23, p<.0001).

There was a significant association of the day at which change in hematocrit levels was maximum with complications (p<0.05). At day 0, change in hematocrit levels was significantly more in the patients without complications (78.95%) than with complications (47.32%). The hematocrit levels change at Day 1 was seen in 13.16% patients without complications and only 35.71% patients with complications; on Day 2 it was seen in 7.89%patients without complications and 4.46% patients with complications; and on Day 3 it was seen in none of the patients without complications and 12.50% patients with complications.

There was a significant association of the day at which change in serum albumin levels was maximum with complications. (p<0.05). At day 0, change in serum albumin levels was significantly more in patients without complications (81.58%) than with complications (43.75%). The serum albumin levels change at Day 1 was seen in 10.53% patients without complications and only 42.86% patients with complications; and on Day 2 it was seen in 7.89%patients without complications and 13.39% patients with complications.

Mean max percentage change in Hematocrit levels (%) was comparable between patients with Grade 1 postop complications and Grade 2 postop complications (13.14 ± 5.37 vs 10.86 ± 4.08, P=0.194). Mean max percentage change in serum albumin(%)was comparable among patients with Grade 1 postop complications and those with Grade 2 postop complications (21.07 ± 7.39 vs 18.06 ± 4.47, P= 0.063).

There was no significant association of the day at which change in hematocrit levels was maximum with post op complications grade (p>0.05). At day 0, there was the highest change in haematocrit in both post op complications grade 1 and 2than other days. The haematocrit change at Day 1 was seen in 37.86% patients with post op complications grade 1 and only 11.11% patients with post op complications grade 2; and on Day 3 it was seen in 13.59%patients with post op complications grade 1 and none of the patients with post op complications grade 2.

There was a significant association of the day at which change in serum albumin levels was maximum with post op complications grade. (P<0.05). At day 0, change in serum albumin was seen in all patients with post op complications grade 2and in only

38.83% of Grade 1 complication patients. The serum albumin change at Day 1 was seen in 46.60% patients with post op complications grade 1 and none of the patients with post op complications grade 2; and on Day 2 it was seen in 14.56%patients with post op complications grade 1 and none of the patients with post op complications grade 2.

Table 5: Association of duration of surgery, estimated blood loss with post op complications grade

Duration of surgery and estimated blood loss	Grade 1(n=103)		Grade 2(n=9)		P value
	Mean ± SD	Median(IQR)	Mean ± SD	Median(IQR)	
Duration of surgery(hours)	3.33 ± 1.16	3(2.250 - 4)	6 ± 1.5	5(5 - 8)	<.0001
Estimated blood loss (ml)	284.47 ± 121.88	200(200 - 400)	700 ± 0	700(700 - 700)	<.0001

The mean duration of surgery in Grade 1 complication patients(3.33±1.16 hrs) was significantly less as compared to Grade 2 complication patients (6±1.5 hrs) with $p<0.0001$. The estimated blood loss in Grade 1 complication patients (284.47 ± 121.88 ml) was significantly less as compared to Grade 2 complication patients (700±0 ml) with $p<0.0001$.

Discussion

In the present study, in comparison to preoperative levels (3.56 ± 0.34 g/dL), serum albumin levels were significantly lower on post-operative days 0-5 with the lowest being on first post-operative day (2.60 ± 0.37 g/dL, $p<.0001$); which was observed in 53.33% of patients. The mean value of maximum fall in serum albumin has showed a significant association with post-operative complications i.e. fall in albumin was lower in patients without complications than those with complications ($p<.0001$). The mean value of maximum fall in albumin also showed significant association with type of surgery and blood loss during surgery i.e. the fall in albumin was significantly higher in the patients who underwent open surgeries than in laparoscopic surgeries, also fall in serum albumin was significantly higher in the patients who had more amount of blood loss. Also, a positive correlation was observed between maximum fall in serum albumin level and final clinical outcome after surgery.

In the present study, mean age of the patients was 52.33 years and majority i.e. 68.67% of the patients were males and only 31.33% were females. In a study done by Labgaa *et al*, median age was 61.5 years with 52.2% males and 47.8% females [11]. In Norberg *et al*, the mean age was 64 years, with M:F of 3:2 [12]. Most of the studies have elderly age groups as such patients undergo major surgeries mostly.

In this study, mean BMI of the patients was 25.47 ± 3.81 kg/m^2. In Norberg *et al*, the median BMI was 25 kg/m^2 [12]. In Li *et al*, the mean BMI was 23.4 ± 3.2 kg/m^2 [13].

In this study, the majority of patients (48%) were designated as ASA grade III followed by 40% patients in grade II and 12% in grade I. Even in Norberg *et al*, ASA status was grade 3 in majority of the patients followed by Grade 2 (Grade 3:2 ratio of 6:4) [12]. However, in Li *et al*, it was grade 2 in most of the patients [13].

On ECOG performance scale, most of the patients (66.00%) were found to be capable of all self-care and unable to carry out any activity, 32.67% patients could perform light/sedentary activities, and 2 patients (1.33%) were capable of only limited self-care.

Among the pre-existing comorbidities of study subjects, Hypertension, Ischemic heart diseases (16%) and Obesity (10.67%) were prime contributors. In Li *et al*, hypertension and COPD were the most common co-morbidities [13]. In Wang *et al*, hypertension and Diabetes were the most common co-morbidities [14]. Co-morbidities have been frequently seen in the age group of 50-60 years as was seen in our study and most of the studies; however, their effects on the complications and albumin fall were not individualized in the study.

Surgery causes an instant fall in the serum albumin levels among patients of major abdominal surgeries which may continue for upto 5 days. In our study, in comparison to preoperative levels (3.56 ± 0.34 g/dL), serum albumin levels were significantly lower on POD 0-5 with the lowest being on first post-operative day (2.60 ± 0.37 g/dL, $p<.0001$).

The fall in albumin levels can depend upon a number of surgery related factors. In our study, the mean value of maximum fall in serum albumin (%) showed significant association with post-op complications i.e. fall in albumin was higher in patients with complications than those without complications ($p<.0001$). The mean of maximum fall in albumin also showed significant association with type of surgery and blood loss during surgery i.e. the fall in albumin significantly higher in open surgery than laparoscopic surgery and the more the blood loss, the more was the fall in albumin and more are the associated post-operative complications.

Similar to our study, Labgaa *et al* found that the level of serum albumin rapidly dropped after surgery [11]. ΔAlb correlated to overall complications (r=0.485, $p<0.001$), and Length of stay (r=0.468, $p<0.001$). On multilinear regression they found that 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 ≥10 g/L on POD 1 showed a threefold increased risk of overall postoperative complications. Even in the study by Norberg *et al*, there was a significant fall in the albumin levels from 33.5 g/dL on Day 0 to 22.1 g/dL on Day 2 after major pancreatic surgery ($P<0.001$) [12]. In another study by Li *et al*, where a total of 533 Lung cancer patients were included, 52 experienced complications [13]. The ΔALB was significant in the patients with complications group than in the non-complication group ($P<0.001$) as seen in our study. ΔALB was observed an independent risk factor for complications (OR =2.268, 95% CI: 1.153–4.460).

Liu *et al* (2017) in their study also found that postoperative decrease in serum albumin (ΔALB)was an independent risk factor to predict complications (OR = 17.957, 95%CI: 6.073-53.095, $p < 0.001$). However, ΔALB showed no significant association with duration of surgery, intra-op blood loss and mode of surgical approach among surgery for gastric cancer patients specifically [15].

Based on the studies it can be seen that early postoperative albumin drop reflects the magnitude of surgical trauma and shows significant association with the mode of surgery (Lap/open), occurrence of complications and the amount of blood loss.

Conclusion

It is concluded that maximum fall of serum albumin happens on first postoperative day and found to be significantly correlated with complications and found to be important early predictor regarding patient outcome. The fall was also seen significantly more in open surgeries as compared to laparoscopic surgeries favouring minimal invasive surgeries and found to be correlated

well with amount of blood loss and adverse outcome.

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