

## RESEARCH PAPER

# Association of Pre-operative Serum Albumin Level with Post-operative Complications in Patients Undergoing Primary Cytoreductive Surgery for Epithelial Ovarian Carcinoma (EOC)

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## Abstract

**Background:** Epithelial ovarian carcinoma (EOC) is the most lethal of all the gynaecological malignancies. Primary cytoreductive surgery is one of the mainstays in the management of women with epithelial ovarian carcinoma. Because of the silent nature of the condition, most patients present in advanced stage of the disease and malnutrition is common in them. Thus, preoperative evaluation of serum albumin in patients with EOC in regards to primary cytoreductive surgery seems to be of particular importance.

**Objective:** The aim of this study was to evaluate the association between preoperative serum albumin level with postoperative complications up to 30-th postoperative day in patients with EOC underwent primary cytoreductive surgery.

**Methods:** This is a cross sectional study conducted on 60 patients with EOC who underwent primary cytoreductive surgery in the Gynaecological Oncology Department of NICRH, Mohakhali, Dhaka from March 2019 to February 2020. Hypoalbuminemia was defined as a serum albumin level <3.5g/dl. Postoperative complications were recorded up to 30th postoperative day. Data were analysed by Chi-squared test or the Fischer exact test as feasible and p-value was calculated. P-value <0.05 was considered statistically significant.

**Results:** The median age was 50 years (range: 21 to 68 years). Out of total 60 patients, 25(42%) had hypoalbuminemia (<3.5g/dl) and 35(58%) had normal albumin ( $\geq$ 3.5g/dl). The mean ( $\pm$ SD) albumin value was 3.18 ( $\pm$ 0.12) and 3.97 ( $\pm$ 0.36) g/dl in hypoalbuminemia and normal albumin group respectively. Patients with hypoalbuminemia suffered more complications compared to normoalbuminemic patients ( $p$  0.001) and longer duration of hospital stay ( $p$  0.039).

**Conclusion:** Preoperative hypoalbuminemia in patients with EOC who will undergo primary cytoreductive surgery is an important predictor of 30-day postoperative complications. Identification of this subset and preoperative optimization of nutritional status may improve surgical outcome.

**Keywords:** Hypoalbuminemia, Epithelial ovarian cancer Primary cytoreductive surgery, Postoperative complications.

## Introduction

Epithelial ovarian cancer (EOC) has the highest fatality-to-case ratio of all the gynaecological malignancies. According to GLOBOCAN 2020, worldwide 313,959 new cases were diagnosed and 207,252 new deaths were due to ovarian cancer and it was the third most common gynecological cancer<sup>1</sup>.

Ovarian cancer encompasses a heterogenous group of malignancies. Epithelial cancers are most common among women of all racial/ethnic groups, accounting for 90% of all cases.<sup>2</sup> Epithelial ovarian cancer rates are highest in women aged 55 to 64 years (median age 63 years), and deaths are highest in people aged 75 to 84 years (median age 71 years).<sup>3</sup>

Surgery is the primary treatment for epithelial ovarian cancer. It is used for staging and cytoreduction (debulking), but it is potentially curative in disease confined to the ovaries.<sup>4,5</sup> Primary cytoreductive surgery followed by adjuvant chemotherapy, if indicated, is the standard treatment for patients with epithelial ovarian carcinoma.<sup>6</sup> However, aggressive

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surgery is often associated with increased intraoperative and postoperative major complications and morbidity.<sup>7</sup> Several factors have been described as risk factors for increased postoperative complications: age, performance status, surgical aggressiveness, nutritional status, and serum albumin level.<sup>8,9</sup> Most of these factors cannot be measured with standardized quantitative methods.

Albumin is the major plasma protein in humans and has the major role in maintaining serum colloid osmotic pressure as well as acting as a transport vehicle for intrinsic metabolites, drugs, and anti-oxidative agents; it acts as a free-radical scavenger.<sup>10</sup> Preoperative low serum albumin level has been associated with increased postoperative major complications and morbidity for various types of oncological surgery.<sup>11-13</sup> Albumin level is also an indicator of malnutrition in patients. A significant percentage of patients with gynaecological malignancy have malnutrition (20%), but ovarian cancer patients have the highest prevalence of malnutrition (67%).<sup>14</sup> Thus, the preoperative evaluation of ovarian cancer patients in regard to radical surgery with a significant risk of severe postoperative complications seems to be of particular importance.

Most of the cases attend to us in advanced stages and malnutrition is much more common in such patients. Therefore, poor pre-operative nutritional status might be related to poor surgical outcome in patients with epithelial ovarian cancer. Protein deficient patients are at higher risk of post-operative complications and death, compared to well-nourished patients undergoing to similar surgeries. Hypoalbuminemia, as a marker of malnutrition and disease, is associated with higher risk of poor post-operative outcomes. Serum albumin is the most readily available parameter. Therefore, estimation of serum albumin level is standard before operation on epithelial ovarian cancer patients. The technique to measure is simple, cheap and widely available.

However, no study has been reported from our country until now to identify the relationship between preoperative serum albumin with post-operative complications in epithelial ovarian carcinoma. So, on the basis of this background, the present study has been designed to see the association between preoperative serum albumin level with post-operative morbidity and mortality in patients undergoing primary cytoreductive surgery for epithelial ovarian carcinoma. The results of this study are important in the sense of proposing an effective treatment.

## Materials and Methods

This cross-sectional study conducted in the Department of Gynaecological Oncology, National Institute of Cancer Research and Hospital (NICRH), Dhaka. The research work was done from March 2019 to February 2020. Study population was all diagnosed cases of epithelial ovarian cancer who underwent primary cytoreductive surgery in NICRH during the study period. Purposive sampling was done on the basis of inclusion and exclusion criteria. Inclusion criteria was women with Epithelial Ovarian Carcinoma (EOC) who were admitted for primary cytoreductive surgery in NICRH during the study period and Exclusion criteria were: 1) Women with non-epithelial ovarian cancer. 2) Patients who underwent interval debulking surgery following NACT. 3) Patients with icterus. 4) Patients with Chronic liver disease and renal disease.

Patients with a provisional diagnosis of epithelial ovarian carcinoma who were admitted in the Gynaecological Oncology Department of NICRH for primary cytoreductive surgery and met the eligibility criteria on the basis of inclusion and exclusion criteria were initially recruited as study population. Preoperative serum albumin level done in all patients. As all the previous studies were done after collecting data from past records, taking patients with very low albumin level may pose critical problems, that's why considering ethical issues, in this study we included patients only those whose albumin level is more than 2.8gm/dl but less than 3.5 gm/dl i.e., hypoalbuminemia.

The study design, objectives, and procedure were explained in details to the patients. Of them who gave their consent were recruited. After getting informed written consent, the patients were followed from immediate postoperative period up to 30-th day of operation. During the follow-up period any sign/symptoms of complications were recorded and subsequently it was confirmed by laboratory investigations. After discharge from the hospital, they were contacted at regular interval over telephone and advised to inform if any adverse effect would develop. All postoperative complications were documented in data collection sheet. When histopathology report became available, only those with a diagnosis of epithelial ovarian carcinoma were followed up to 30-th postoperative day and relevant data collected in the pre-tested data collection sheet.

All the data were compiled and sorted properly and analysis done using SPSS. Mean $\pm$ SD values were

used for continuous data, with discrete variables displayed as totals and frequencies. Chi-square and Fisher-exact tests were used for categorical data. Level of significance was calculated at  $p < 0.05$ .

Prior to the commencement of this study, the research protocol was approved by the Ethical Committee of NICRH. The aims and objectives of this study along with its procedure, risks and benefits of this study was explained to the patients in easily understandable local language and then informed written consent was taken from each of them.

## Results

A total number of 60 cases with the diagnosis of epithelial ovarian carcinoma who underwent primary cytoreductive surgery having preoperative serum albumin level were enrolled for the study. Patients were followed from the day of operation up to 30-th postoperative day to document any complications. The patients were categorized into hypoalbuminemia and normal albumin group according to a cut off value 3.5 g/dl.

Mean( $\pm$ SD) age of the patients was 53.68 ( $\pm$ 10.61) in hypoalbuminemia group and 45( $\pm$ 11.72) in normal albumin group. The mean( $\pm$ SD) albumin value was 3.18 ( $\pm$ 0.12) and 3.97( $\pm$ 0.36) g/dl in hypoalbuminemia and normal albumin group respectively. The mean( $\pm$ SD) BMI was 23.85( $\pm$ 2.70) and 24.31( $\pm$ 5.00) in hypoalbuminemia and normal albumin group respectively. Ascites was present in 12 (48%) patients in hypoalbuminemia group and 16 (45.71%) patients in normal albumin group. Number of patients in ASA Class 1,2,3 was 18(72%), 7(28%), 0(0%) in hypoalbuminemia group and 21(60.00%),12(34.28%), 2(0.16%) in normal albumin group. Diabetes, Hypertension and both were present in 5(20%), 6(24.00%), 3(12.00%) patients in hypoalbuminemia group and 11(31.42%), 10(28.57%) and 7(20.00%) patients in normal albumin group. (Table I).

In this study, the youngest and the oldest patients were 21 and 68 years respectively. The median age was 50 years. Majority, 34(56.7%) of the patients were in the age group 50-70 years, while 21(35.0%) and 5(8.3%) patients were in between 30-50 years and below 30 years of age respectively (Figure 1).

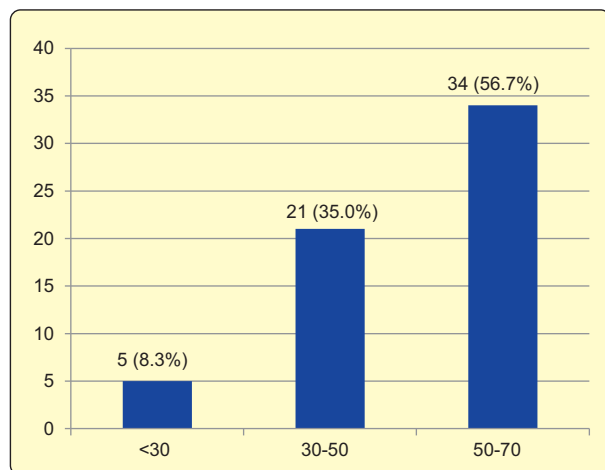
**Table I:** Baseline demographic and clinical features comparison between the hypoalbuminemia group and the normal albumin group (60).

Variables	Hypoalbuminemia (n=25)	Normal Albumin (n=35)	OR (Lower-Upper)	p-value
Age MeanSD	53.6810.61	4511.72	-	0.007
Albumin MeanSD	3.180.12	3.970.36	1.179(0.382-3.640)	0.503
BMI MeanSD	23.852.70	24.315.00	0.914(0.32-0.55)	0.534
Ascites N (%)	12(48%)	16(45.71%)	-	0.264
ASA Class N (%)	1 18(72.00%) 2 7(28.00%) 3 0(0%)	21(60.00%) 12(34.28%) 2(0.16%)	-	0.264
Comorbidity				
a. Diabetes (DM)	5(20.00%)	11(31.42%)	1.833(0.55-6.16)	0.247
b. Hypertension	6(24.00%)	10(28.57%)	1.267(0.391-4.101)	0.464
c. Diabetes with Hypertension	3(12.00%)	7(20.00%)	1.833(0.42-7.92)	0.325

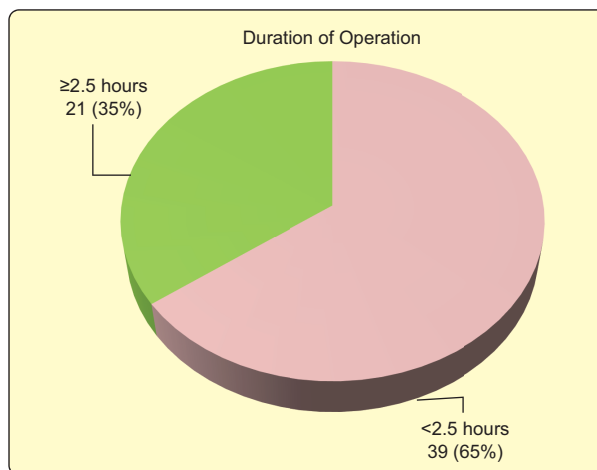
Values are presented as mean  $\pm$ SD, or number (%).

SD= Standard Deviation

ASA= American Society of Anaesthesiology.



**Figure 1:** Age distribution of the study subjects (n=60)



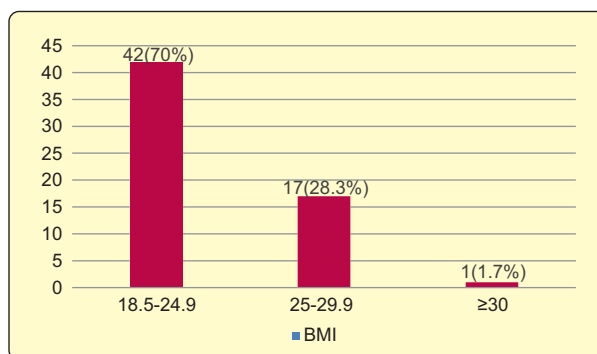
**Figure 2:** Distribution of study subjects according to Duration of Operation (n=60)

Bar diagram shows that 34(56.7%) patients were in the age group 50-70 years.

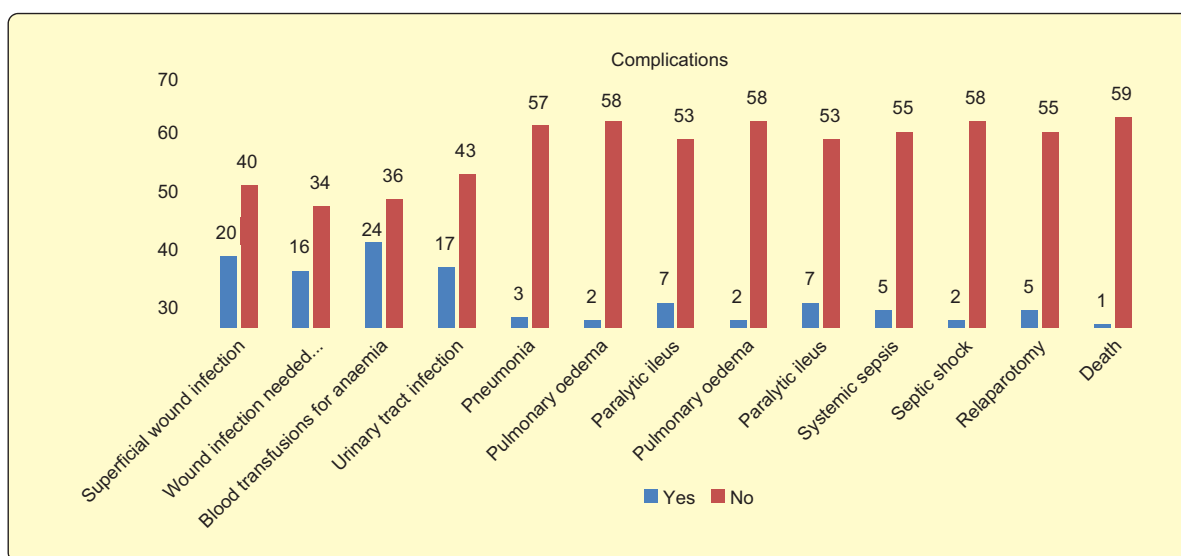
The duration of operation was ≥2.5 hours in 39(65%) patients and <2.5 hours in 21(35%) study subjects (Figure 2).

Most of the patients, 42(70%) had normal BMI (18.5-24.9), 17(28.3%) patients were overweight (25-29.9%) and only 1(1.7%) patient was obese (≥30) (Figure 3).

The most common complication was blood transfusion for anaemia in 24 patients followed by superficial wound infection (20) and deep wound infection needed secondary suturing (16) (Figure 4).



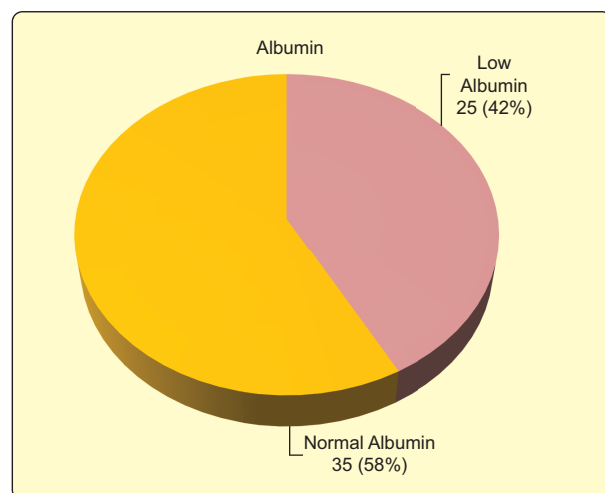
**Figure 3:** Distribution of study subjects according to BMI (n=60)



**Figure 4:** Distribution of study subjects according to types of postoperative complications (n=60)

Among the different types of postoperative complications, Blood transfusions for anaemia (24), Superficial wound infection (20) and Wound infection needed secondary suturing (16) were the top three

When postoperative complications were compared in relation to albumin category (Table V) only superficial wound infection was more in normal albumin group while other complications were more frequent in hypoalbuminemia group. Normal albumin was found in 35(58.3%) patients and hypoalbuminemia in 25(41.7%) patients (Figure 5).



**Figure 5:** Distribution of study subjects according to Albumin Category (n=60)

Majority of the patients 35(58%) had normal albumin level

Analysis revealed that all categories of complications had significant association with hypoalbuminemia group.

Overall, duration of hospital stay was shorter (5-10 days) in most of the patients (29) in normal albumin group (Table II) but longer (11-16 days) in

hypoalbuminemia group ( $p$  0.039). Association between number of postoperative complications and preoperative albumin level (Table III) showed a significant correlation. When two or more complications are compared, ( $p$  0.020), three or more complications compared, ( $p$  0.001) and four or more complications are compared, ( $p$  0.004).

Association among Ascites, Diabetes, Hypertension and Albumin group with complications was shown in Table-IV. In Binary Logistic Regression, we considered Complication scores as dependent variable which are distributed into two categories: one is “No Complication” and another is “One or More Complication”. We wanted to measure any relationship between Ascites, Diabetes, Hypertension and Albumin Level with complications scores. Analysis showed that the patients having Diabetes were 1.115 times more likely to turn out one or more complication than no complication ( $p=0.049$ ). On the other hand, Albumin group indicated that hypoalbuminemia was 2.077 times more likely to turn out one or more complication than no complication ( $p=0.038$ ).

Table-V showed that significant association between hypoalbuminemia and wound dehiscence that needed secondary suturing ( $p$  0.010), blood transfusion for anaemia (0.001), urinary tract infection (0.041) and paralytic ileus (0.002)

Data are expressed as frequency. Chi-squared test was done to compare between groups.  $p$  value  $<0.05$  was considered as expected level of significance.

Analysis shows significant correlation between low serum albumin level ( $<3.5g/dl$ ) and wound dehiscence in 11( $p$  0.010), Postoperative blood transfusion for anaemia in 16 ( $p$  0.001), Urinary tract infection in 10( $p$ -0.041) and paralytic ileus in 5 ( $p$  0.002) patients. Superficial wound infection in 11 ( $p$  0.71), Pneumonia in 1( $p$  0.36) did not show significant correlation.

**Table-II:** Association between Albumin group and Duration of Hospital Stay (n=60)

Duration of Hospital Stay (Days)	Hypoalbuminemia N=25	Normal albumin N=35	p-value
5-10	15	29	0.039
11-16	9	4	
17+	1	2	



**Table III:** Association between Albumin group and Number of Complications (n=60)

Parameter	Hypoalbuminemia	Normal Albumin	p-value	Odds ratio (OR)
	N=25	N=35		
One or More Complication	14	21	0.020	0.063(0.008- 0.516)
Two or more Complication	22	12	0.001	0.071(0.018-0.287)
Three or more Complications	13	5	0.004	0.154(0.045-0.526)

**Table IV:** Association of Ascites, Diabetes, Hypertension and Albumin group with complications (n=60) Variables in the Equation

Variables	B	S.E.	Wald statistic	df	Sig.(p)	OddsRatio
Ascites	-.702	.601	1.363	1	.243	0.0496
Diabetes	.109	.614	.032	1	.049	1.115
Hypertension	-2.022	1.552	1.697	1	.193	0.132
Albumin Level	.564	.970	.022	1	.038	2.077
Constant	1.030	.533	3.727	1	.054	2.801

a. Variable(s) entered on step 1: Ascites Diabetes, Hypertension, Albumin Level

Again, the patients having only Ascites or only Hypertension had no significant impact on omplication score

**Table V:** Association between Albumin group and Postoperative Complications (n=60)

Variables	Albumin Level		p-value
	Hypoalbuminemia < 3.5	Normal albumin ≥3.5	
Superficial wound infection	9(36%)	11(31.42%)	0.71
Wound dehiscence	11(44%)	5(14.28%)	0.010
Postoperative blood transfusions for anaemia	16(48%)	8(22.85%)	0.001
Urinary tract infection	10(40%)	7(20%)	0.041
Pneumonia	2(8%)	1(2.85%)	0.36
Pulmonary oedema	2(8%)	0(0%)	0.09
Paralytic ileus	5(20%)	2(5.71%)	0.002

### Discussion:

This is a cross sectional study done in NICRH, which is to our knowledge the first research work, so far, in our country to see the predictive value of preoperative serum albumin on postoperative complications in patients undergoing primary cytoreductive surgery with Epithelial Ovarian Carcinoma. Overall, the results demonstrated that preoperative hypoalbuminemia was significantly associated with postoperative complications.

Complications after any surgery are inherent. Though it can be minimized, can never be eliminated.<sup>15</sup> Many studies have shown that low preoperative serum albumin is a risk factor for postoperative complications. In various other studies, different types

of surgical procedures as a general or a specific type of surgical procedure has been considered in certain subclass of patients. This study analyzed the different aspects of primary cytoreductive surgery for epithelial ovarian cancer in relation to hypoalbuminemic and normal albumin cohort.

In the present study, out of total 60 patients, 25 (42%) had hypoalbuminemia (<3.5 g/dl) while 35 (58%) patients had normal albumin (≥3.5 g/dl). There is quite high percentage of patients having hypoalbuminemia in comparison to a study conducted by Uppal et al where they showed 13.3% of patients had low albumin level<sup>11</sup>. This might reflect the poor pre-existing nutritional status as the study conducted in a

government facility where most of the patients come from lower socio-economic class.

In our study, the mean albumin value of the hypoalbuminemia group was 3.18 g/dl, and the mean albumin value for the normal albumin group was 3.97 g/dl. This is almost similar to the findings documented by Kim J et al<sup>16</sup> where the mean albumin value of the hypoalbuminemia group was 3.05 g/dl, and the mean albumin value for the normal albumin group was 4.06 g/dl. The median age was 50 years (range: 21 to 68 years) and there was significant statistical difference ( $p=0.007$ ) between mean age of hypoalbuminemic and normal albumin group ( $53.68\pm 10.61$  vs.  $45\pm 11.72$ ). In a study also observed similar median age of 49 years but the range was more extreme (range: 13 to 85 years).<sup>16</sup>

In the present study, BMI was not significantly different between normal albumin and hypoalbuminemic patients. Similar findings also noted by Kim J et al.<sup>16</sup> Serum albumin level is a better indicator to detect protein-energy malnutrition than anthropomorphic markers of nutritional status.<sup>17</sup> Protein-energy malnutrition is not necessarily accompanied by lower body weight and it may not be clinically knowable, but it is related to adverse surgical outcomes.<sup>18</sup> Hypoalbuminemia is a well-known indicator of malnutrition, and an association between hypoalbuminemia, inflammation, and malignancy has been recently suggested.<sup>19</sup>

Cancer patients are prone to malnutrition due to cancer-induced increased metabolic rate, decreased nutritional intake, and cancer cachexia.<sup>20</sup> There may also be an increased whole protein turnover and subsequent body nitrogen loss.<sup>11</sup> Tumour necrosis factor-alpha is considered to be the main mediator of cancer cachexia as it is responsible for altered metabolic rates and it leads to decreased hepatic protein synthesis.<sup>21</sup> Albumin has a long half-life of 20 days, so the metabolic effects on its concentration reflect prolonged malnourishment, as in cancer patients. Although serum albumin concentration may also be influenced by other factors such as trauma and surgical stress, it is generally accepted to be a good marker for malnutrition in previous national cancer studies.<sup>22-23</sup>

When we compared the outcomes of surgery between hypoalbuminemic and normal albumin cohort, we found significant statistical differences in the complications between hypoalbuminemic and normal

albumin groups ( $p<0.05$ ). This study is concordant with the study conducted by Bhagvat VN et al.<sup>24</sup> Uppal et al. showed a six times elevated risk of major postoperative complications in the first 30 postoperative days for patients with preoperative hypoalbuminemia in their patient cohort, which consisted of 2110 gynaecologic oncology patients.<sup>11</sup> Kim J et al also showed in their study hypoalbuminemic patients were more likely to develop postoperative complications and increased length of hospital stay compared to non-hypoalbuminemic patients.<sup>16</sup> In our study, we have also seen increased duration of hospital stay ( $p=0.039$ ) and postoperative complications in patients with preoperative hypoalbuminemia.

Prolonged postoperative hospitalization in hypoalbuminemic patients may result from higher rates of postoperative complication and delayed recovery of bowel function. This may be because hypoalbuminemia causes swelling and oedema of the bowel<sup>25</sup> resulting in paralytic ileus.<sup>26</sup> We did not find any significant difference between the presence of ascites and ASA class in the two groups.

In the present study, out of various postoperative complications, infectious morbidity was significantly higher in hypoalbuminemia group ( $p<0.05$ ), e.g., wound dehiscence that needed secondary suturing (44% vs 14.28%), urinary tract infection (40% vs 20%). This finding is in accordance with that found by Sharma L et al.<sup>27</sup> Postoperative blood transfusions for anaemia (48% vs 22.85%) and paralytic ileus (20% vs 5.71%) was also statistically significant between hypoalbuminemic and normal albumin cohort. Pneumonia and pulmonary oedema were also greater in magnitude in hypoalbuminemia group though not statistically significant.

The mechanisms of increase in infectious aetiologies in hypoalbuminemia are multifactorial and likely to include impairment of tissue healing, decreased collagen synthesis and granuloma formation. The immune response in hypoalbuminemia is also compromised through impairment of macrophage activation and induction of macrophage apoptosis.<sup>28</sup> These factors together could explain the higher risk of surgical site infections and remote infections such as pneumonia in hypoalbuminemic patients.

In our study, hypoalbuminemia was strongly associated with higher number of postoperative complications than normal albumin group ( $p<0.05$ ). This is consistent with the observations in a study by

Uppal et al<sup>11</sup> who found according to multivariate analysis, the low albumin group had significantly higher odds of developing one or more post-operative complications (OR-2, CI: 1.47-2.73,  $p < 0.0001$ ), three or more complications (OR-4.1, CI: 2.31-7.1,  $p < 0.0001$ ).

In our study, there was one mortality within 30-th postoperative day and that was from hypoalbuminemic group.

Related other studies also showed higher rates of postoperative morbidities in hypoalbuminemic group. Hypoalbuminemia has been reported to be associated with greater risk of negative surgical outcome in non-gynaecologic surgery.<sup>22,29-30</sup> However, there is sparse literature addressing the effect of hypoalbuminemia on the risk of postoperative morbidity in patients who are undergoing gynaecologic cancer surgery.<sup>11</sup> The National Veterans Affairs Surgical Risk Study, from 54,215 major general surgery cases examining 30-day morbidity and mortality, found that serum albumin level was the strongest predictor of morbidity and mortality.<sup>22</sup> Similarly, hypoalbuminemia was found to be the predictor of poor surgical outcomes of colon cancer and it was the poor indicator of long-term survival after curative resection in 2,529 patients.<sup>31</sup> Uppal et al. reported that preoperative albumin levels  $< 3$  g/dL identify a population of patients at a very high-risk of experiencing perioperative morbidity after gynaecologic cancer surgery.<sup>11</sup>

Given the high incidence of postoperative complications in hypoalbuminemic patients, these patients should either be nutritionally supported or be considered with alternative treatment strategies that delay a potentially complicated surgery. In ovarian cancer patients with large volume of carcinomatosis, which generally induces a high catabolic state and decreased oral intake secondary to nausea and bloating, enteral feeding difficulty is common. Primary debulking surgery in this population may lead to high postoperative complication rate and a subsequent delay in installation of adjuvant chemotherapy, which affects the overall survival negatively. Recent randomized trial has demonstrated the non-inferiority of neoadjuvant chemotherapy followed by interval debulking compared with primary debulking surgery and this approach is plausible in this high-risk population.<sup>26</sup> In this study, patients having huge ascites, poor performance status, albumin level less than 2.5 g/dl poor resectability as evidenced by CT scan where optimum debulking would not be possible

were considered for neoadjuvant chemotherapy followed by interval debulking surgery.

### Conclusion:

After observing the results of the present study, it can be concluded that preoperative low serum albumin level can have an adverse effect on the immediate postoperative outcome of patients undergoing primary cytoreductive surgery for epithelial ovarian carcinoma. In this study there was higher frequency of postoperative complications like wound dehiscence, urinary tract infection, pneumonia, pulmonary oedema and paralytic ileus among hypoalbuminemia group than normal albumin group of patients.

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