

Pre-operative Serum Albumin Levels as a Marker of Post-operative Complications in Ovarian Masses Referred to a Tertiary Cancer Institute with Suspicion of Malignancy

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Abstract: ***Objective:** Hypo-albuminemia is a known risk factor for post-operative complications in Gynaecological patients. This study aims to evaluate the pre-operative albumin levels as a marker of post-operative complications in patients undergoing surgery for ovarian masses who were referred to our tertiary Cancer Institute with suspicion of malignancy. **Methods:** This is a prospective study which includes 40 patients with Ovarian masses with suspicion of malignancy. They underwent surgery in a Gynaecologic –Oncology units at The Gujrat Cancer Research Institute, Ahmedabad from January 2016 to August 2016. Hypo-albuminemia was defined as pre-operative serum albumin level less than 3.5mg/dl . Surgical complications were graded as per the Clavien Dindo Classification. **Results:** The incidence of pre-operative hypo-albuminemia in the entire cohort was 30% . Low albumin is associated with mild complications in 30% cases & severe complications in 15% cases .Hypo-albuminemia both pre-operative & even falling levels in post-operative period are an important predictive marker for severe post-operative complications after adjusting established prognostic markers like age, tumor stage & performance status. **Conclusion:** Pre-operative albumin level can be used as independent marker for predicting severe post-operative complications& even falling levels in post-operative period have a bearing on the final surgical outcome. Low albumin levels were associated with mild complications in benign disease whereas severe complications were seen in 3 patients with malignant histology. Surgical time & turn around time of frozen section report does add to morbidity in benign disease. Hence albumin levels may be included in future clinical trials as a valuable marker. However, further study is needed to delineate whether nutritional supplementation may reduce infection.*

Keywords: Low serum albumin, Ovarian masses, Post-operative complications, Clavien Dindo Classification

1. Introduction

Surgery is the cornerstone of therapy in women presenting with ovarian masses with suspicion of malignancy . Extensive surgery has been associated with adverse events & major post-operative morbidity to the tune of 30 to 60%. Surgical stress during major surgery may have a bearing on the final outcome & early quantification of this stress response would be helpful to allow prompt interventions for a better outcome . Surgical interventions trigger metabolic stress responses of varying magnitude which contributes to complication rate, delayed recovery & even increased hospital stay. The pre-operative nutritional status of the patient is a critical factor having bearing on the clinical outcome including infection & surgical efficacy. Several markers have an impact on the post-operative morbidity like age, surgical complexity, nutritional status & serum markers like albumin . A simple test based on objective values could help us to better classify morbidity risks in a uniform & standardized way independent of clinical & structural heterogeneity. Albumin the most important plasma protein in humans comprises 60% of the total serum proteins. It plays an important role in maintaining plasma colloid osmotic pressure & serves as a transport medium for drugs, metabolites & anti-oxidative agents. Low albumin levels

indicate inflammatory process & are a marker for post-operative complications & survival in cancer patients. Degree of malnutrition can be quantified by pre-operative serum albumin levels in patients scheduled for surgery. Malnutrition occurs upto 20% in Gynecology patients with maximum incidence in ovarian cancers. The present study aims to evaluate the role of pre-operative serum albumin levels as a marker for post-operative complications in patients under-going surgery for ovarian masses with suspicion of malignancy.

2. Materials & Methods

This is a prospective study of 40 patients who were treated by a Gynaecologic- Oncology unit of The Gujrat Cancer Institute, Ahmedabad. These patients underwent upfront surgery for ovarian masses with suspicion The present study aims to evaluate the role of pre-operative serum albumin levels as a marker for post-operative complications in patients under-going surgery for ovarian masses with suspicion of malignancy .of malignancy between January 2016 to August 2016.

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Inclusion criteria

- 1) Clinically mobile ovarian mass
- 2) Pre-operative Serum CA125 levels less than 500u/ml
- 3) Ascites <500ml
- 4) Radiologically (USG/CT) mass not adherent to bowel/bladder
- 5) No disease in upper abdomen
- 6) Peritoneal thickening <4mm on CT scan

Serum albumin was done as part of pre-operative work up and repeated on Day3 &Day5 in the post-operative period. Surgery was performed by a team of Gynaecologic Oncologists. Serum albumin levels between 3.5 to 5mg were considered as normal. Hypo-albuminemia was defined as levels less than 3.5mg/dl .Post-operative complications were noted until the patients were discharged from hospital or post-operative death occurred during hospital stay & complications were classified as per the Clavien Dindo Classification

3. Results

Patient profile

Forty patients were enrolled for surgery for ovarian masses with suspicion of malignancy from January 2016 to August 2016 . Mean age of the population under study was 39.5 years (range 12-75 years) . Twenty three patients (57.5%) were from urban background. Thirty three patients were vegetarians (80%) Five patients (12%) had history of infertility & 4 patients were unmarried. Twelve patients were postmenopausal, 27 were premenopausal &1 patient was pre-menarchal. Average BMI of the study population was 21.8 (Range18-32).Co-morbidities in the form of diabetes, hypertension & hypothyroidism were present in 2,6 & 2 patients respectively in the study population Twelve patients (30%) had pre-operative ascites with average CA125 levels 225u/ml (Range 100-440u/ml). CA125 levels were normal in 12 cases (30%).Out of 40 patients, final histology was malignant in 24 cases, 8 cases had benign histology & remaining 8 cases had pseudo-tumors of ovary presenting as ovarian masses.

Clinical profile of women with ovarian masses undergoing surgery (n=40)

Table1

| Variable | Number (%) |
|--------------------------------|----------------|
| Age-median(range)yrs | 39.5(12-75yrs) |
| Menstrual status- Premenarchal | 01(2.5) |
| Premenopausal | 27(67.5) |
| Postmenopausal | 12(30) |
| Vegeterians | 32(80) |
| BMI | 21.8(18-32) |
| Co-morbidities | |
| Diabetes | 2(5) |
| Hypertension | 6(15) |
| Hypothyroidism | 2(5) |
| Ascites <500ml | 08(20) |
| >500ml | 04(10) |
| CA125<35 | 12(30) |
| Albumin <3.5mg | 12(30) |
| >3.5mg | 28(70) |

Histology of ovarian masses and complications associated with them as per Clavien Dindo Classification

Of all the 40 patients, final histopathology was malignant in 24 cases. Out of 24 patients with malignant tumors, lymph node dissection along -with complete tumor de-bulking without macroscopic disease was achieved in 20 (83%) patients.4 patients had advanced disease at the time of presentation

Malignant tumors

If all the post-operative complications were graded as per the Clavien Dindo Classification, 12 patients(50%)out of total 24 patients with malignant histology had no complications. Four patients (16.5%) had Grade 1 complications in the form of fever & post-operative wound discharge & were managed conservatively. Four patients had Grade 2 complications in the form of post-operative anaemia requiring blood transfusion. Two patients had sepsis with burst abdomen which were sutured immediately. One patient with Malignant Yolk Sac Tumor had a thrombus in the subclavian vein which was managed with anti-coagulants in ICU.

Table 3: Malignant tumors (n=24)

| Diagnosis | Number (%) | Complications (CDC) |
|------------------------------|------------|-------------------------------------------------------------------------------------------------------|
| Serous cyst-adenocarcinoma | 9(22.5) | Fever with discharge (G1)-2 patients. Blood transfusion (G2)-2 patients |
| Mucinous cyst-adenocarcinoma | 3(7.5) | Post-operative wound discharge (G1) -2 patients |
| Fibroma/Thecoma | 4(10) | Minor wound gaps re-sutured under local anaesthesia(G3a)-2 patients, Blood transfusion (G2)-1 patient |
| Adult Granulosa cell tumor | 4(10) | Burst abdomen (G3b) with sepsis (4b)-2 patients Blood transfusion(G2)-1 patient |
| Germ cell tumor | 4(10) | Thrombus in subclavian vein (G4a)-1 patient |

Benign Tumors

Of the total 40 patients 8 had benign disease in final histopathology .If all complications were graded as per Clavien Dindo Classification, 4 patients (50%) had an uneventful post-operative period. Two patients (25%) had grade 1complications in the form of post-operative fever which was managed with antibiotics.Two patients (25%) had Grade3a complications in the form of minor wound gaps which were sutured under local anaesthesia .

Table 3: Benign tumors (n=8)

| Diagnosis | Number (%) | Complications (CDC) |
|----------------------|------------|---------------------------------------------------------------------|
| Serous cystadenoma | 3(7.5) | Post-operative fever(G1)-2 patients |
| Mucinous cystadenoma | 5(12.5) | Minor wound gaps(G3a) re-sutured under local anaesthesia-2 patients |

Pseudo-tumors of the ovary-

Of the total 40 patients, 8 had pseudo-tumors of the ovary presenting as ovarian mass. Two patients (25%) with pseudo-tumor had Grade 1 complications in the form of discharge from wound site & were managed conservatively. One patient with Xantho- granulomatous disease of ovary was given blood transfusion for post-operative anaemia (Grade 2)

Pseudo-tumors of ovary (n=8)

| Diagnosis | Number (%) | Complications (CDC) |
|------------------------------|------------|--------------------------------------------|
| Endometriosis | 5(12.5) | Wound discharge(G1)-2 patients |
| Tuberculosis | 2(5) | |
| Xantho-granulomatous Disease | 1(2.5) | Blood transfusion for anaemia(G2)-1patient |

Association of Pre-operative albumin levels & clinico-pathological parameters

Mean pre-operative albumin was 3.56 mg/dl in the study population. Mean D3&D5 post-operative albumin was 3.24mg/dl & 3.42mg/dl respectively. Pre-operative low serum albumin was observed in 12 patients (30%).

Eight patients (20%) had falling serum albumin levels in the post-operative period. Out of these 8 patients 3 had benign disease, 4 malignant tumors & 1 patient had pseudo-tumor of ovary .All 8 patients had post-operative complications adding to their morbidity & hospital stay.

BMI of the patients also had a direct bearing on pre-operative serum albumin levels. The higher the BMI the higher was the pre-operative serum albumin levels. Four patients (10%) with BMI>25kg/m2 had mean albumin levels of 3.63mg/dl & 36 patients (90%) with BMI <25kg/m2 had mean pre-operative albumin levels of 3.4mg/dl.

Albumin levels were not affected by patients age, grade & histology of tumor. Patients with low albumin levels had 5 times more chances of severe post-operative complications compared to those with normal albumin

4. Discussion

Malnutrition frequently co-exists in patients with chronic diseases & may itself be associated with adverse outcomes. It has been suggested that 20% of patients with ovarian masses die of malnutrition rather than the mass itself. Albumin is an objective parameter often used in clinical studies to measure long-standing malnutrition. Donato etal. defined nutritional status in patients with ovarian cancer as adequate versus poor on the basis of pre-operative serum albumin levels during preceeding 3 to 4 months. This study evaluated serum albumin kinetics as a response marker for surgical stress & predictor of adverse post-operative outcomes. Pre-operative low albumin is an independent marker not only for post-operative complications but also for overall survival in ovarian masses .In this study low serum albumin was associated with 4 times more incidence of mild complications like post-operative fever, anaemia & wound discharge compared to those with normal albumin levels. Similarly the incidence of severe complications in the form of sepsis & burst abdomen were 4 times more common in patients with low pre-op albumin levels.It was observed that patients with falling levels of albumin in post-operative period had more complications , longer hospital stay & more chances of re-suturing .BMI of the patients also had a bearing on albumin levels. The more the BMI of the patients ,the more were pre-operative serum albumin levels. The surgical time & the turn around time of frozen section report

added to morbidity especially in benign diseases. Study by Uppal etal[6] in 2110 patients supported the fact that patients with low albumin levels have 6 times more severe complications & more likely to die within first 30 days of surgery. Obermeir etal [12] retriated a significant rise of wound complications (64%vs14%) , septicemia (46%vs8%) & anastomotic leaks(18%vs0) in patients with hypo-albuminemia .Low serum albumin levels quantify the degree of malnutrition, cancer cachexia & reflect chronic inflammatory activity. Wantebbe et al demonstrated correlation between rapid turnover protein levels & inflammation related markers in ovarian cancer patients. According to European Society for Clinical Nutrition & Metabolism low serum albumin is an established marker for malnutrition. ESPEN [10] recommends parenteral & enteral support for 5 to 10 days in under-nourished patients prior to surgery. In Ovarian cancer, Geisler etal [5] showed an improvement of serum pre-albumin with pre-operative TPN. With regards to operative morbidity albumin levels are a better prognostic marker than anthropometric markers of nutritional status. Hypo-albuminemia has been proved to be an independent negative prognostic factor for overall survival & has been reported in various other cancers also like breast, gastric, colo-rectal & endometrium. Asher etal studied the median survival of ovarian cancer patients by pre-operative albumin levels .Patients with albumin less than 2.5mg/dl showed impaired median survival of 4.8 months compared to patients with albumin>3.5mg/dl with 43.2 months of survival. Martin etal, revealed falling albumin levels (<2mg/dl) in post-operative period are associated with increased morbidity, longer ICU stay& higher re-operation rates.

5. Limitations

Main limitation of this study is the small size of study population. Another limiting factor is optimal cut off values for low serum albumin levels which still remains unclear.

6. Conclusion

Hypo-albuminemia is a risk factor for post-operative complications in patients with Ovarian masses. Even falling levels of serum albumin in post-operative period has a bearing on the final surgical outcome. Falling serum albumin levels indicate the magnitude of surgical stress which has a positive impact on post-operative complications. All patients with benign histology had mild complications which were managed conservatively. However 3 patients with malignant histology had severe complications like burst abdomen, sepsis & thrombus in one of the major vessels which affected the final outcome. Surgical time & turn around time does add to morbidity especially in benign diseases. Serum albumin is a relatively low cost test which should be utilized more frequently as a prognostic tool to detect malnutrition & risk of adverse surgical outcomes. The impact of pre-operative nutrition in patients suffering malnutrition & its impact on post-operative outcome as well as prognosis in patients with Primary ovarian tumor needs to be further elucidated.

7. Compliance with Ethical Standards

The authors declare no conflict of interests.

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