



Pre-operative serum albumin is associated with post-operative complication rate and overall survival in patients with epithelial ovarian cancer undergoing cytoreductive surgery



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HIGHLIGHTS

- Hypoalbuminemia is a risk factor for severe postoperative complications.
- Hypoalbuminemia is a risk factor for impaired overall survival.
- Albumin levels should be incorporated in pre-operative workup.

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ABSTRACT

Objective. Hypoalbuminemia has been reported as a risk factor for post-operative complications and unfavorable survival in cancer patients. We aimed to evaluate the predictive value of preoperative serum albumin levels on post-operative complication rate and the impact on overall survival (OS) in patients with epithelial ovarian cancer (EOC) undergoing primary cytoreductive surgery.

Methods. The present retrospective study included 604 consecutive patients with EOC who underwent primary cytoreductive surgery at two tertiary cancer centers specialized in gynecologic oncology. Hypoalbuminemia was defined as a pre-operative serum albumin level ≤ 35 g/L. Post-operative surgical complications were graded according to the Clavien–Dindo-Classification (CDC). Fisher-test was used to investigate the predictive value of hypoalbuminemia on the rate of severe post-operative complications. Survival analyses were calculated using log-rank test and Cox regression models.

Results. The incidence of pre-operative hypoalbuminemia in the entire cohort was 16.4%. Hypoalbuminemia was a predictive factor for severe post-operative complications (CDC 3–5) (OR 3.65, (CI95% 1.59–8.39); $p = 0.002$). Furthermore, median overall survival time of patients with hypoalbuminemia was 24 months compared to 83 months in patients with normal albumin ($p < 0.001$), respectively. Hypoalbuminemia was independently associated with shortened overall survival (HR 2.2 (95% CI 1.6–3.0); $p < 0.001$) even after adjusting established prognostic factors such as age, tumor stage, performance status, and post-operative residual disease.

Conclusion. Pre-operative hypoalbuminemia can be used as both an independent predictive factor for severe post-operative complications and as prognostic parameter regarding overall survival in EOC patients. Therefore, albumin levels may be incorporated into future clinical trials as stratification factor.

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1. Introduction

Cytoreductive surgery is one of the mainstays in the treatment of women with epithelial ovarian cancer (EOC). Surgical outcome

significantly impacts patients' survival [1–4]. However, extensive surgery may be associated with considerable adverse events, and major post-operative morbidity has been reported to occur in 33% to 64% [5]. Several factors associated with peri-operative morbidity like age, performance status, surgical complexity, nutritional status and serum markers (e.g., prealbumin and albumin) have been described with heterogeneous results [6–9]. Many of these factors are difficult to standardize and classification is based on individual clinical judgment. A simple test based on objective values could help to better classify morbidity

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risks in a uniform, standardized way, independent of clinical and structural heterogeneity.

Albumin is the most abundant plasma protein in humans, comprising for 50%–65% of the measured total serum protein [10]. It plays a key role in maintaining colloid osmotic pressure, as well as acting as a transport vehicle for intrinsic metabolites, drugs, and anti-oxidative agents [11]. Low serum albumin reflects inflammatory activity and has been reported as a risk factor of post-operative complications and survival in various cancer types [9,12–15]. Furthermore, serum albumin level has been described to be a crucial parameter of malnutrition [16] and has also been reported to be an indicator of malnutrition in gynecologic patients [17]. Malnutrition at the time of cancer diagnosis occurs in about 20% of gynecologic cancer patients [18] with its highest prevalence in ovarian cancer (67%) [17]. Thus, the pre-operative evaluation of ovarian cancer patients in regard to radical surgery with a significant risk for severe post-operative complications seems to be of particular importance.

The present study focused on two major aims: the first aim was to evaluate the predictive role of pre-operative serum albumin levels on post-operative complications categorized by Clavien–Dindo–Classification (CDC). The second aim was to elucidate the prognostic association between pre-operative serum albumin levels and overall survival (OS) in patients with epithelial ovarian cancer undergoing primary cytoreductive surgery independent of peri-mortality.

2. Patients and methods

We reviewed data on 604 consecutive patients with primary epithelial ovarian, primary peritoneal, and fallopian cancer (EOC) who underwent cytoreductive surgery at two academic partner centers (Kliniken Essen-Mitte (KEM), Essen–Germany and Medical University of Vienna (AKH), Vienna–Austria). Patients treated with pre-operative chemotherapy and patients with borderline tumors or non-epithelial ovarian neoplasms were excluded. Pre-operative serum albumin was part of the routine pre-operative check-up in both centers and all patients with available serum albumin values were included. All patients gave informed consent for documentation of clinical data in the associated clinical tumor registries for clinical research and quality assurance. Surgery was performed by a dedicated surgical team specialized on gynecologic oncology. Surgical complexity scoring (SCS) system was based upon complexity and number of surgical procedures performed as reported previously [6]. Platinum-based chemotherapy was the recommended stage adapted after surgery according to standard guidelines [19,20].

We defined the cut-off for hypoalbuminemia as previously reported [21]. In clinical practice a value of serum albumin ≤ 35 g/L is generally considered as hypoalbuminemia. Serum albumin was assessed according to the bromocresol green technique [22] (Roche Diagnostics COBAS Integra Albumin Gen.2; Indianapolis, USA). Serum albumin concentrations between 35 and 52 g/L were considered as normal. For 309 patients treated at KEM post-operative complications were recorded and classified according to the Clavien–Dindo–Classification [23] including at least the period until patient's discharge or post-operative death after surgery. The scoring grades complication in eight categories depending on severity (0: no complications, and 5: death; Table 1–S–Supplementary). We further categorized complications into mild (CDC 0–2) and severe (CDC 3–5), the latter representing those grades with serious clinical consequences. In patients who experienced more than one complication the highest CDC was noted.

3. Statistics

Descriptive statistics such as mean, median, frequencies, and percentages were used to summarize the data: frequency (%) by categorical variables; median/range by ordinal variables and age; mean (standard deviation = SD) by metric variables. The relationship

between complication and albumin was assessed by the Fisher–exact-test. For univariate and multivariate analyses, albumin levels were labeled as “hypoalbuminemia” and “normal albumin” to create a categorical variable. In order to evaluate independent risk factors for complication (“mild”: CDC 0–2; “severe” CDC 3–5) binary logistic regression was used, incorporating all well-established parameters. The overall presence of interaction between risk factors and event was evaluated by the Wald test. To rule out a potential bias regarding prognostic value of hypoalbuminemia on OS patients, who died within 30 days after surgery, were excluded from this survival analysis to distinguish between those patients in whom albumin could have a prognostic value independent from peri-operative complications and those in whom albumin could predict complications with fatal outcome. However, a sensitivity analysis with all patients including those who died peri-operatively was also performed. Uni- and multivariable survival analyses were performed using Kaplan–Meier and Cox proportional hazard models, respectively. Multiple logistic regression was conducted to analyse the association of variable with OS adjusting for potential confounding variables. Tests were two-sided at the 0.05 level. Statistical analysis was performed using SPSS version 20.0 (IBM Corporation, New York, USA).

4. Results

4.1. Patient's characteristics

A total of 604 consecutive patients with EOC were included in the present series. Three hundred and nine (51.2%), and 295 (48.8%) patients were enrolled from the Departments of Gynecology and Gynecological Oncology at the KEM and AKH, respectively. Patient's characteristics are shown in Table 1. Mean pre-operative serum albumin level was 41 g/L (SD 6 g/L). Low pre-operative serum albumin ≤ 35 g/L, was observed in 99 (16.4%) patients. Four hundred seventy-two (78.1%) patients had advanced disease (FIGO III–IV). For the entire study group lymph node dissection was performed in 382 (63.2%) patients, of whom 217 (56.8%) showed metastatic lymph node involvement. In 362 (59.9%) patients a complete tumor debulking without any macroscopic residual disease was achieved. Detailed information regarding peri- and post-operative status (e.g., surgical procedure) was available for 309 patients treated at KEM and is given in Table 2–S–Supplementary.

4.2. Association of pre-operative albumin level and clinico-pathological parameters

Significant differences between patients with hypoalbuminemia compared to patients with normal albumin levels were detected in terms of performance stage (ECOG > 0: 21.2% versus 13.5%), ascites (ascites > 500 mL: 58.6% versus 26.5%), and advanced FIGO-stage (FIGO III–IV: 88.9% versus 76.0%; Table 2). Hypoalbuminemia was associated with more advanced disease (stage or ascites volume) and poorer performance status. These associations between hypoalbuminemia and well known prognostic factors made it necessary to adjust univariate analyses and perform multivariate analyses. No differences with respect to albumin level were detected regarding patient's age, grading and histology.

4.3. Association of pre-serum albumin and post-operative complication (CDC)

If all grades of complications were considered we could not detect a significant difference between patients with low as compared to normal albumin levels (OR 2.40 [95% CI 0.55–10.51], $p = 0.40$, Table 3). In the total cohort mild and severe complications had been observed in 74.8% (231/309) and 25.2% (78/309) of patients, respectively. Patients with hypoalbuminemia experienced severe complications in 52.0% of

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