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Low Preoperative Serum Albumin Levels Are Associated With Impaired Outcome After Cytoreductive Surgery and Perioperative Intraperitoneal Chemotherapy for Peritoneal Surface Malignancies

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Abstract

Preoperative hypoalbuminemia is known to be associated with postoperative morbidity and mortality, as well as with poor survival after gastrointestinal cancer surgery. However, limited data exist regarding the prognostic significance of hypoalbuminemia in patients with peritoneal metastases undergoing cytoreductive surgery, combined with perioperative intraperitoneal chemotherapy. We performed a systematic literature review of the previously published studies addressing the potential association between preoperative albumin levels and overall surgical outcomes after the performance of cytoreductive surgery and perioperative intraperitoneal chemotherapy for peritoneal surface malignancies. Our research yielded a total of nine retrospective studies which met our inclusion criteria, and despite their heterogeneity; and we can conclude that preoperatively low albumin levels are associated with greater likelihood of overall and major morbidity, as well as less favorable oncological outcome after the performance of cytoreductive surgery and perioperative intraperitoneal chemotherapy.

Keywords: Albumin; Cytoreductive surgery; Intraperitoneal chemotherapy; HIPEC; Nutrition; Cancer; Peritoneal malignancy

Introduction

Cytoreductive surgery (CRS) combined with perioperative intraperitoneal chemotherapy (PIC) is considered a promising treatment option in appropriately selected patients with peritoneal metastatic disease and primary peritoneal malignancies [1, 2]. CRS aims to achieve complete macroscopic removal of the visible cancerous deposits within the abdominal cavity (complete cytoreduction), while the administration of PIC is used to achieve microscopic disease clearance, targeting the intra-abdominally circulating cancer cells and cancerous lesions of few cell lines depth [3]. Due to the nature of the operation, which usually requires multi-visceral resections, and the adverse effects of the intraperitoneal chemotherapy, this combined procedure carries considerable postoperative morbidity and mortality, even in high-volume centers [4]. In order to improve the postoperative outcome and the oncological benefit of this complex procedure, several key areas for improvement have been identified over the last years. These include the recognition of the role mentorship and senior supervision to overcome the procedure's steep learning curve [5-7], the rationalization of patient selection criteria for CRS and PIC [8, 9], the improvement of imaging techniques used to guide the operative decision-making [10], along with efforts to reduce the toxicity of the intraperitoneal chemotherapy and optimize the postoperative care of these patients [11-13].

Interestingly, there is a relative lack of studies focusing on the impact of malnutrition on postoperative morbidity and mortality, as well as the survival after CRS and PIC. The latter is of great importance given the widely accepted value of optimizing the patients' nutrition status prior to any major abdominal procedure, which has been shown to be inversely correlated with overall complication rates and length of hospitalization [14, 15]. Moreover, particularly in patients undergoing major abdominal oncological operation, preoperative malnutrition has been strongly associated with poorer survival [16, 17]. Therefore, it is reasonable to assume that preoperative detection of patients at nutritional risk and enhanced nutritional support could help to achieve a reduction of morbidity and mortality after CRS and PIC, and potentially improve the oncological outcomes of the procedure. Under this notion, the preoperative evaluation of widely available malnutrition markers, with serum albumin being the traditional laboratory reference test [18] could be of value in the planning of
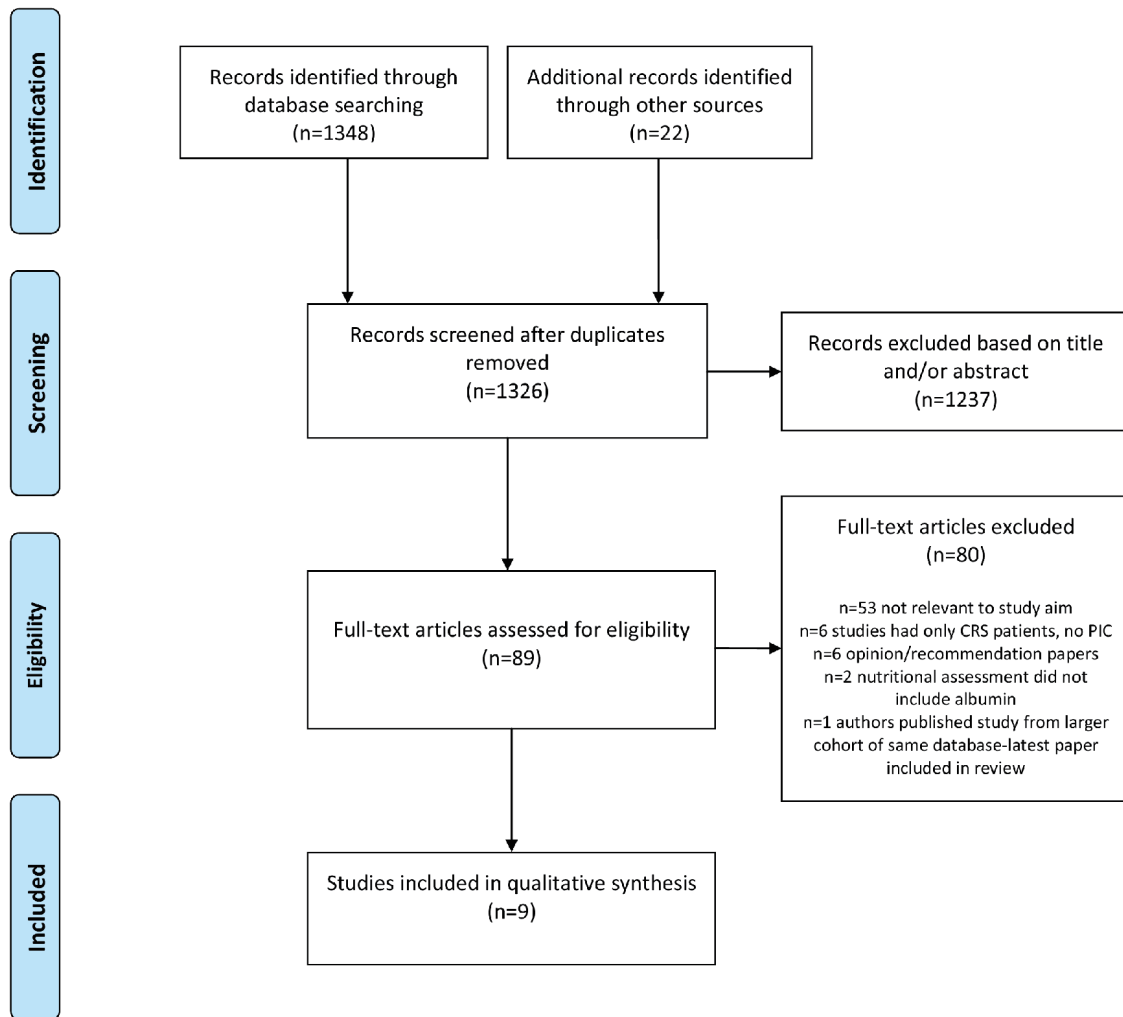
Figure 1. Flowchart of the systematic review.

a holistic treatment plan. To address this question, we have performed a systematic review of the literature of the studies examining an association of preoperative albumin levels with the occurrence of postoperative morbidity and mortality, as well as survival after CRS and PIC for peritoneal surface malignancies.

Methods

We performed a systematic review of the studies indexed in Pub-Med database until August 2020, using the search terms ("albumin" AND "cytoreductive surgery") and ("albumin" AND "intraperitoneal chemotherapy"), in accordance to PRISMA guidelines. Citations of articles retrieved at the initial literature search were manually searched to identify further relevant studies meeting the purpose and selection criteria of this systematic review. We excluded studies referring to pediatric population, as well as studies where CRS was performed but not followed by PIC. Also, we excluded studies published in other than English

language as well as case reports and case series.

Results

A total of nine studies [19-27], all retrospective in nature, met our inclusion criteria (Fig. 1). Six out of the nine included studies included patients with peritoneal disease arising from two or more primary origins [19-23, 25], while two studies used as study population patients of older age groups, who had undergone CRS and PIC [20, 25]. Despite the significant heterogeneity in terms of primary malignancies, extent of peritoneal disease and differences in patient selection and treatment protocols, the main two clinical questions of our systematic review, association of albumin levels with postoperative morbidity/mortality and survival after CRS and PIC, could be answered in a clear manner.

With respect to the potential value of preoperative serum albumin as a prognostic factor of survival after CRS and PIC, seven of the studies addressed this point [19, 21, 23-27]. In

five of those studies, preoperatively lower albumin levels, as defined in each study by the authors, were strongly associated with poorer survival rates [19, 21, 23, 24, 26, 27], while Votanopoulos and co-workers [25] did not demonstrate any relevant prognostic significance of preoperative albumin in their cohort of patients after CRS and PIC. The key features of the included studies (study population, origin of peritoneal disease, postoperative morbidity and mortality, as well as survival outcomes) and information regarding the correlations of preoperative serum albumin levels with the operative and oncological outcome are presented in detailed manner in Table 1 [19-27].

Discussion

Serum albumin has traditionally been considered as a classical laboratory marker reflecting surgical patients' nutritional status, despite the fact that its levels can be influenced by a variety of factors (i.e., acute illness, chronic inflammatory response, and liver pathologies, etc) [28, 29]. However, the low cost of the relevant laboratory essays and the wide availability of this examination as a basic paraclinical parameter, has led to its disseminated use as a nutritional marker in the general surgery practice [30]. The latter is of great importance in surgical oncology, as apart from the surgical stress and the subsequent catabolic cascade, the operable patients can frequently be in preclinical stages of cancer-related cachexia with evolving skeletal muscle depletion [31, 32]. Therefore, preoperative serum albumin levels have been highlighted by numerous previous studies in the field of surgical oncology as an important marker of perioperative morbidity and survival after surgery for gastrointestinal malignancies [33, 34].

Taking into consideration the greater magnitude of cancer burden in cases of peritoneal metastatic disease, which very frequently can present with symptoms of gastrointestinal intolerance and poor oral intake, the importance of adequate nutritional status is a key feature for the success of a major procedure as CRS and PIC. Previous studies in patients with peritoneal malignancy undergoing CRS and PIC have clearly demonstrated the postoperative occurrence of prolonged ileus, which prohibits early oral nutrition; even early enteral nutrition has been shown not to be well tolerated in the immediate postoperative phase, requiring frequently the postoperative administration of parenteral nutrition [35]. Furthermore, the major stress assault from this extensive surgical procedure results in a significant drop of postoperative serum albumin levels, indicating the extent of the post-surgical inflammatory response and the initiation of a catabolic response [36]. As a result, it is evident that patients scheduled for CRS and PIC need to be nutritionally optimized before embarking for surgery with a structured specialist nutritional assessment and supplementation as required, and serum albumin should be included as a baseline laboratory marker in the nutrition enhancement pathway.

Although the above-mentioned seem reasonable, very few studies [19-27] have previously assessed the usefulness of preoperative albumin levels as a marker of post-CRS and PIC morbidity and/or survival outcomes. Our study is the first in the literature to review in a systematic manner the available evidence of this topic. Despite their heterogeneity with regards to primary cancer origin, extent of peritoneal metastatic disease and different albumin cut-off values, the overall qualitative conclusion from our review study is that preoperatively low albumin levels are associated with an increase in postoperative morbidity, especially grade III/IV complications, and have a prognostic value as a marker of survival post CRS and PIC. As presented in the Table 1 summarizing the relevant findings of the included studies, there is no universal agreement to define a cut-off value of serum albumin value as a predictor of expected postoperative morbidity and/or mortality. However, the majority of included studies define hypoalbuminemia when serum albumin value was lower than 3.5 g/dL, and therefore this value potentially could be a starting point for future prospectively conducted studies, as a target to reach before proceeding with CRS and PIC. Considering the known limitations of albumin as the sole laboratory marker of nutritional status, effort should be made towards the formation of nutritional risk stratification scoring systems, combining laboratory markers (albumin, pre-albumin, electrolytes and minerals, etc.) with anthropometric nutritional assessments (body mass index (BMI), skinfold thickness, mid-arm muscle circumference, etc.), existing validated nutritional risk tools (MUST, SNAQ, MNA-SF, etc.) and perhaps imaging techniques, such as estimation of skeletal mass via the standard preoperative computed tomography. We believe that preoperative enhanced nutrition should be considered as a standard parameter of the preoperative assessment and patient optimization before CRS with PIC, and serum albumin levels should be assessed as a standard parameter in the preoperative workup of these patients.

Conflict of Interest

None to declare.

Author Contributions

CS, AM, JG and AME equally contributed to the performance of literature review and drafting of the manuscript; US and HY contributed to the critical revision of the manuscript, which all listed co-authors approve in its final format.

Data Availability

The authors declare that data supporting the findings of this

Table 1. Detailed Presentation of the Studies' Key Features and the Significance of Preoperative Serum Albumin Levels With Respect to the Surgical and Oncological Outcome

Authors	PSM origin and study sample	Postoperative morbidity and mortality (entire cohort)	Survival (entire cohort)	Significance of hypoalbuminemia
Graziosi et al, 2016 [19]	N = 64 pts with PM of various primary origins (34.4% colorectal, 32.8% gastric, 14.1% ovarian and 10.9% other origin)	5.1% major postoperative morbidity (grades III/IV) 5.1% postoperative mortality	Median follow-up was 26.5 months (range 4 - 120 months) 5-year OS was 55 % for entire cohort	With 3.8 g/dL as preoperative albumin cut-off value, 5-year OS of 70% vs. a 5- year OS of 38% in the high vs. low albumin group. Preoperative albumin level was identified as an independent prognostic factor for OS in multivariate analysis. No data regarding albumin as predictor of postoperative morbidity/mortality.
Cascales-Campos et al, 2016 [20]	N = 85 pts (> 75 years) with PM of various primary origins (42% colorectal, 31% ovarian, 20% appendiceal-PMP, 7% other origin)	43.5% overall morbidity (grades I - IV) 23.5% and 14.4% minor (grades I/II) and major (grades III/IV) morbidity 5.1% 90-day mortality (2/5 of the deceased died of complications not related to CRS and PIC)	No survival data	Preoperative albumin level <3 g/dL was associated with overall morbidity (grades I - IV) in univariate analysis. Preoperative albumin level <3.5 g/dL was associated with major morbidity (grades III/IV) in multivariate analysis. No survival data.
Huang et al, 2016 [21]	N = 591 pts with PM of various primary origins (31.3% appendiceal 23.4% colorectal, 29.3% PMP, 11.5% mesothelioma, ovarian 4.7%)	41.8% overall major morbidity (grades III/IV) 0.8% post-operative mortality	62.2 months median OS	Preoperative albumin was 3.7 ± 0.55 g/dL for entire cohort; albumin value of 3.5 g/dL used as cut-off of hypoalbuminemia. Hypoalbuminemic group had statistically significant higher PCI than the normoalbuminemic one. N.S. differences in mortality between normo- and hypoalbuminemic groups (2 vs. 3 pts). Hypoalbuminemic group had statistically significant higher rates of major morbidity (grades III/IV), as well as LOS, ICU and HDU hospitalization duration (twice median stay). In multivariate analysis, preoperative serum albumin <3.5 g/dL was an independent prognostic factor for a poor perioperative outcome (grades III - V - 1.5-fold risk of a poor perioperative outcome when preoperative serum albumin <3.5g/dL)). Hypoalbuminemic group had statistically significant poorer OS (49.3 months (32.0 -66.6) vs. 65.8 months (48.5 - 83.1)).
Peters et al, 2015 [22]	N = 1,085 pts with PM of various primary origins	44% and 37% overall and major morbidity 1.8% postoperative mortality overall 30-day DSM rate of 37.4%	No survival data	Preoperative albumin <3 g/dL and weight loss were the only preoperative factors significantly associated with DSM in the multivariate model. No survival data.

Table 1. Detailed Presentation of the Studies' Key Features and the Significance of Preoperative Serum Albumin Levels With Respect to the Surgical and Onco-logical Outcome - *(continued)*

Authors	PSM origin and study sample	Postoperative morbidity and mortality (entire cohort)	Survival (entire cohort)	Significance of hypoalbuminemia
Winer et al, 2013 [23]	N = 67 pts with PM of appendiceal (AP, n = 37) or colorectal origin (CRC, n = 30) with signet cell histology	22% vs. 29% major morbidity (grade III/IV) in the CRC vs. AP group 5.4% vs. 6.7% 60-day mortality for AP vs. CRC group	Median follow-up of CRC and AP groups was 4.4 and 4.1 years, respectively PFS and OS were 9 and 12 months in CRC and 12 and 21 months in AP pts	In univariate analysis, preoperative albumin level < 3.5 g/dL was significant predictor of poor survival in the CRC group and marginally in the AP group. Preoperative albumin was not independent survival predictor in multivariate analysis in any of the groups. No data regarding albumin as predictor of postoperative morbidity/mortality.
Votanopoulos et al, 2013 [24]	N =13 pts with PM from rectal primary; N = 204 pts with PM from colonic primary	30-day mortality for colon and rectal group was 5.7% and 0%, respectively Overall morbidity for the colon and rectal groups was 51% and 46 %, respectively	Median follow-up was 40.1 and 88.1 months for rectal and colonic group, respectively Median survival was 14.6 months for the rectal group and 17.3 months for the colon group 3-year survival was 28.2% and 25.1 % for the rectal and colon groups, respectively	In univariate analysis, preoperative albumin level was not statistically significant in predicting survival in the pts groups. Albumin was not independent survival predictor in multivariate analysis in any of the groups. No data regarding albumin as predictor of postoperative morbidity/mortality.
Votanopoulos et al, 2013 [25]	N = 81 patients (> 70 years) with PM of various primary origins (39.5% appendiceal, 24.7% colorectal, 12.3% mesothelioma, 9.9% ovarian, 7.4% gastric, 6.2% other primaries)	Minor morbidity (grade I/II) was 28 %, while major morbidity (grade III/IV) was 38 % 13.6% 30-day mortality for the entire cohort 27.4% 90-day mortality for the entire cohort	Median follow-up was 48.1 months Median survival stratified by primary cancer: 31.8 months for appendiceal, 41.5 months for mesothelioma, 54 months for ovarian, 13.2 months for colonic, and 7.6 months for gastric	Average albumin level of the entire cohort was 3.6 g/dL, while for patients with complications was 3.7 g/dL; average albumin level of those patients who suffered mortality was 3.2 g/dL. Preoperative albumin was a significant predictor of survival in both univariate and multivariate analysis in absence of complications. Mortality risk was reduced by 40% for each additional gram of albumin.
Deraco et al, 2012 [26]	N = 56 pts with PM from recurrent ovarian cancer	5.3% procedure-related mortality Overall DSM rate of 26.3%	23.1 months median follow-up time Median OS and PFS were 25.7 and 10.8 months, respectively 5-year OS and PFS were 23% and 7%, respectively	Preoperative serum albumin (cut-off for hypoalbuminemia was 3.5 g/dL) was identified as independent prognostic factor of PFS and OS in multivariate analysis. No data regarding albumin as predictor of postoperative morbidity/mortality.
Banaste et al, 2018 [27]	N = 214 patients with PM from colorectal primary	50% major postoperative complication rate No mortality data	Median follow-up was 24 months (range 0 - 82 months) Median OS and PFS were 58.9 and 13 months, respectively 3- and 5-year OS were 63% and 46%, respectively 3- and 5-year PFS survival were 17% and 14%, respectively	Preoperative serum albumin (cut-off for hypoalbuminemia was 3.5 g/dL) was identified as independent prognostic factor of PFS and OS in multivariate analysis. Hypoalbuminemia was not a predictor of postoperative morbidity.

OS: overall survival; PFS: progression-free survival; DFS: disease-free survival; DSM: death and serious morbidity; PM: peritoneal metastases; PSM: peritoneal surface malignancies; PMP: pseudomyxoma peritonei; LOS: length of stay; ICU: intensive care unit; HDU: high dependency unit; N.S.: non-significant; pts: patients.

study are available within the article.

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