**Early Postoperative Serum Albumin Predicts survival after Curative Nephrectomy of Kidney cancer: a Retrospective Study**

**Abstract**

**Background**: Previous studies showed albumin-related systemic inflammation was associated with long-term prognosis of cancer, but early postoperative level of serum albumin hasn’t been well documented as a prognostic factor of renal cell cancer. **Methods**: We retrospectively included patients hospitalized for kidney cancer, from January 2009 to May 2014. First the receiver operating characteristic (ROC) analysis was used to define the best cutoff of early postoperative level of serum albumin in distinguishing the prognosis, by which survival analysis was performed. **Results**: Totally 329 patients were included. The median follow-up was 54.8 months. Patients with early postoperative serum albumin < 32g/L had significantly shorter recurrence-free survival (RFS, median, 49.1 versus 56.5 months, P = 0.001) and OS (median, 52.2 versus 57.0 months, P = 0.049) than patients with early postoperative serum albumin ≥ 32g/L. Adjusted by age, BMI, tumor stage, postoperative hemoglobin and preoperative albumin, globulin and hemoglobin, the multivariate Cox regression showed early postoperative serum albumin < 32g/L was an independent prognostic factor associated with shortened RFS (HR = 3.60, 95%CI，1.05-12.42, P = 0.042) and shortened OS (HR = 9.95, 95%CI, 1.81-54.80, P = 0.008). **Conclusion**: Early postoperative serum albumin < 32g/L is an independent prognostic factor leading to unfavorable RFS and OS. Prospective trials and further researches in more confined patients are needed.

**Keywords**: kidney cancer; survival; hypoalbuminemia; radical resection

**Background**

Kidney cancer is one of the most common malignancy in urogenital system [1]. The most important treatment is surgical resection, but postoperative recurrence is common especially for stage Ⅱ and above. Although many risk factors has been reported, the prognostic prediction remains difficult [2, 3]. In recent years, researchers found some new prognostic factors that have potential to be intervened [4-7].

Several studies reported early postoperative neutrophil-to-lymphocyte ratio may be a long-term prognostic factor of some cancers, including pancreatic cancer, prostate cancer and bladder cancer [8-10]. This association may result from the potential anti-tumor effect of acute inflammation. Albumin is commonly used to evaluate nutrition status, but recent studies showed that albumin also participates in the inflammatory/stress reaction [11]. McMillan and colleges found serum albumin was positively correlated to C-reaction protein in 40 patients of lung or gastrointestinal cancer [12]. Bozzetti and colleges for the first time reported the phenomenon of frequent hypoalbuminemia status in early period after extensive surgery [13]. In our previous data, the serum albumin declined inferior to 35g/L in over 50% patients (P < 0.05), and then always recovered to preoperative level in 2 weeks. Some researchers found early postoperative hypoalbuminemia was associated with preoperative serum albumin, age and extent of surgery [14]. Other studies showed postoperative hypoalbuminemia may lead to unfavorable short-term prognosis, such as acute kidney injury [15, 16], unbalanced substances metabolism [17-19] and surgical site infection [20, 21]. Findings above implied that albumin may participate in immune-inflammatory reaction [11, 22].

Recent studies revealed albumin-related systemic inflammation was associated with long-term prognosis of advanced gastrointestinal cancer [11, 12, 23]. Cai and colleges found that hypoalbuminemia in 3 to 5 weeks after initiation of tyrosine kinase inhibitors was independently associated with significantly shortened progression-free survival and overall survival (OS) in advanced kidney cancer. Furthermore, when combined with the Memorial Sloan-Kettering Cancer Center (MSKCC) risk model, it would improve the efficiency in predicting recurrence-free survival (RFS) and OS [24]. This retrospective study aimed to explore the potential association between early postoperative hypoalbuminemia with long-term prognosis after resection of kidney cancer.

**Patients and Methods**

*Study population*

In this retrospective single-center study, we reviewed the electronic medical records of inpatients who were admitted for kidney cancer between January 2009 and May 2014 in the Department of Urology of West China Hospital, Sichuan University, China. All patients had undergone kidney cancer curative surgery. Patients for inclusion should be over 18 year-old and had pathologic diagnosis of kidney cancer and negative surgical margins. Negative surgical margin was defined as on evidence of either macroscopic residues on surgical report or microscopic residues on histopathological report. Patients would be excluded if they had incomplete resection, history of other life-threatening diseases within 5 years before or after surgery, adjuvant or neoadjuvant treatment, and distant metastasis except adrenal gland. The study conforms to the Declaration of Helsinki and is approved by the Ethics Committee of West China Hospital.

*Objectives*

We primarily aimed to assess the prognostic value of early postoperative hypoalbuminemia for recurrence-free survival (RFS) and OS in curative resection of kidney cancer. And then we tried to find out the best cutoff point of early postoperative serum albumin in predicting the prognosis of kidney cancer. RFS was defined as the date of surgery to date of recurrence, and OS was measured from the date of surgery to the date of death. For patients without recurrence or death, the survival time censored at the date of last follow-up. To distinguishing some confounding factors, the subgroup analyses would be performed.

*Data collection*

All data were obtained from medical records. The follow-up project were guided by the National Comprehensive Cancer Network (NCCN) clinical practice guidelines in kidney cancer [25]. Data were collected by two well-trained researchers. The discrepancies would be resolve by consensus of all authors. Data for collection included demographic characteristics, date and type of surgery, clinical-pathological TNM stage near the surgery, histopathological characteristics, date of recurrence and/or death if available or date of the last follow-up. TNM stage referred to the tumor size (T), local lymph node involved (N) and remote metastasis (M), and was assessed according to imaging studies, surgical record and hitopathological reports. TNM stage and anatomic stage/prognostic groups were also guided by the NCCN guidelines in kidney cancer, 2018 [25]. Cancer recurrence was defined as unequivocal radiology or biopsy evidence of emerging tumor lesions in local or distant place. Besides, we primarily collected the serum albumin, globulin and hemoglobin of the preoperative and postoperative laboratory test nearest to surgery respectively.

*Statistics*

All statistical analyses were carried out in Stata 14.0 (Stata Corp, College Station, Texas, USA). First the receiver operating characteristic (ROC) analysis was performed to find the best cutoff point of postoperative serum albumin in distinguishing the postoperative prognosis. By this cutoff point, we would divide these patients into two groups, and then survival curves would be made using the Kaplan-Meier method and compared using the logrank test. Including gender, age, body mass index (BMI), stage, type of surgery and pathological pattern, the patient and disease characteristics of the both groups would be compared and tested one by one. Data of fourfold or R×C table employed Chi-square test; data of abnormal distribution took median as the average and employed Wilcoxon rank-sum test; data of normal distribution took mean as the average and employed t-test [26]. A factor would be admitted into the multivariate Cox regression analysis if it was showed statistical difference in the both groups. Hazard ratio (HR) was adopted as the measurement. That P value < 0.05 was considered to indicate statistical significance.

**Results**

*Patients and disease characteristics*

Totally 694 patients were available in the database, of which 329 patients were agreed to the inclusion criteria. Among them, 64% of these patients were male, and the median age at surgery was 56 (range, 22-84) year. The median follow-up was 54.8 (range, 5.2-96.4) months. Means of preoperative and postoperative serum albumin are 42.2g/L and 34.1g/L (P = 0.000) respectively. ROC analyses showed the best cutoff points of postoperative serum albumin were 32g/L (AUC = 0.71) in predicting recurrence (Figure 1a) and 31g/L (AUC = 0.80) in predicting death (Figure 1b) respectively. We adopted 32g/L as the cutoff point for grouping comparisons. A total of 99 patients had serum albumin < 32g/L, and 230 patients had serum albumin ≥ 32g/L. The patient characteristics and laboratory test results of the both groups are presented in Table 1. Age, BMI, tumor stage, postoperative hemoglobin and preoperative albumin, globulin and hemoglobin had statistical differences (Table 1).

*Survival analysis*

No patient got lost in follow-up. The means of the follow-up in both groups were similar [58.5 (albumin < 32g/L) versus 59.9 (albumin ≥ 32g/L) months, P > 0.05]. During follow-up, 30 patients (30.3%) had recurrence and 24 patients (24.2%) didn’t survive in group of postoperative serum albumin < 32g/L, and only 20 patients (8.7%) had recurrence and 8 patients (3.5%) didn’t survive in group of postoperative serum albumin ≥ 32g/L. The median RFS of patients with postoperative serum albumin < 32g/L was significantly shorter than that of patients with postoperative serum albumin ≥ 32g/L (49.1 versus 56.5 months, P = 0.001). Meanwhile, the median OS of patients with postoperative serum albumin < 32g/L was also significantly shorter than that of patients with postoperative serum albumin ≥ 32g/L (52.2 versus 57.0 months, P = 0.049). The grouping survival curves are showed in Figure 2, and the logrank tests reveal the differences are significant (P = 0.000) for both RFS (Figure 2a) and OS (Figure 2b).

*Multivariate Cox regression*

According to difference tests, the age, BMI, tumor stage, postoperative hemoglobin and preoperative albumin, globulin and hemoglobin were admitted in the multivariate Cox regression analysis. Early postoperative serum albumin < 32g/L was showed to have independent impact on the shorten RFS (HR = 3.60, 95%CI，1.05-12.42, P = 0.042) and OS (HR = 9.95, 95%CI, 1.81-54.80, P = 0.008). Besides, tumor stage was also an independent prognostic factor (Table 2). Therefore the subgroup analysis was performed according to the tumor stage.

*Subgroup analysis* *admitting stage Ⅱ and Ⅲ*

The survival curves of patients grouped by tumor stage and relevant logrank tests showed significant differences between stage Ⅰ and stage Ⅱ, and stage Ⅲ and stage Ⅳ for both RFS and OS, rather than comparison of stage Ⅱ and Ⅲ. Furthermore, after excluding patients of stage Ⅰ and stage Ⅳ, the two groups had very similar TNM stage distributions (P = 0.995). Survival analysis and logrank test still showed that patients with postoperative serum albumin < 32g/L had significantly shorter RFS (P = 0.036) and shorter OS (P = 0.012) than that of patients with postoperative serum albumin ≥ 32g/L. The subsequent multivariate Cox regression analysis also showed early postoperative serum albumin < 32g/L was an independent prognostic factor associated with shortened RFS (HR = 6.76, 95%CI, 1.07-42.60, P = 0.042) and OS (HR = 26.92, 95%CI, 1.52-477.30, P = 0.025).

*Subgroup analysis based on other factors*

Histopathological type of RCC is an important prognostic factor. Clear cell renal cell carcinoma (ccRCC) is the most common histopathological type of kidney cancer. There were 88 (89%) and 214 (93%) cases in groups of postoperative serum albumin < 32g/L and ≥ 32g/L respectively. Survival analysis and logrank test showed ccRCC patients with postoperative serum albumin < 32g/L had significantly shorter RFS (P = 0.00) and shorter OS (P = 0.00) than that of patients with postoperative serum albumin ≥ 32g/L .

Surgery pattern is another important factor driving prognosis, especially regarding to partial or radical nephrectomy. In total, 224 and 105 patients received radical and partial nephrectomy respectively. Logrank test still showed that patients receiving radical nephrectomy with postoperative serum albumin < 32g/L had significantly shorter RFS (P = 0.00) and shorter OS (P = 0.00) than that of patients with postoperative serum albumin ≥ 32g/L. However, patient receiving partial nephrectomy with postoperative serum albumin < 32g/L had no significantly different RFS (P = 0.15) or OS (P = 0.76) compared with patients with postoperative serum albumin ≥ 32g/L.

**Discussion**

Despite radical resection of kidney cancer, local recurrence or distant metastasis still happens commonly [27-29]. Except those acknowledged prognostic factors, such as tumor state, pathological type and surgery status, some other potential prognostic factors deserve further elucidation [2, 3, 30, 31]. In this retrospective study we reported for the first time that early postoperative serum albumin is another long-term prognostic factor after radical resection of kidney cancer.

To prevent confounding factors as much as possible, we excluded patients who had incomplete resection of tumor, other life-threatening diseases, and adjuvant and/or neoadjuvant treatment. Besides, we had to exclude patients without blood proteins and cells test postoperatively near surgery, but it probably wouldn’t produce bias because no exact guideline ordered whether to have a laboratory test early after surgery without any indication. In our medical center, all radical surgeries of kidney cancer were performed by well-trained clinicians. To ensure enough length of follow-up, we only included patients who underwent surgery before May 2014. About 42% of the included patients had a follow-up over 5 years, and 94% of the included patients had a follow-up over 3 years. The median follow-up was near 5 years, and no patients got lost in follow-up.

All patients who had repeated serum protein tests showed their serum albumin recovered back near to preoperative level. Decrease of serum albumin may primarily result from exudation into extravascular space and attenuation by perioperative bleeding and fluid transfusion [11, 32]. We do found the significant decrease of hemoglobin early after surgery simultaneously, however, the postoperative serum albumin still significantly decreased compared with the serum albumin regulated by hemoglobin (34.1 versus 37.0g/L, P = 0.00), in which the regulated serum albumin ÷ preoperative albumin = postoperative hemoglobin ÷ preoperative hemoglobin. This decrease is regarded as extravascular exudation. When admitted only postoperative serum albumin and extravascular exudation in Cox regression, the results showed postoperative serum albumin has close association with RFS (HR = 0.85, P = 0.000) and OS (HR = 0.82, P = 0.000) rather than extravascular exudation with RFS (HR = 1.00, P = 0.113) and OS (HR = 0.99, P = 0.116).

Under the situation of all patients who have undergone pathologically complete resection of kidney cancer, we have admitted other universally accepted prognostic factors before survival analysis, including gender, age, nutrition status (BMI), tumor stage, pathological type, Fuhrman grade and type of surgery. Survival analysis showed patients who had early postoperative serum albumin < 32g/L had significantly shortened RFS and OS. Although patients in the group of lower postoperative albumin had elder age, lower BMI and more stage Ⅲ cancer and some other laboratory items were different, the multivariate Cox regression analysis has admitted all these factors, and the results still showed that early postoperative serum albumin < 32g/L is an independent risk factor for shortened RFS and OS. The positive results were obtained even when patients were confined in stage Ⅱ and Ⅲ. On the other hand, logrank test didn’t showed significant differences in RFS (P = 0.360) and OS (P = 0.814) between stage Ⅱ and stage Ⅲ in our patients. The subgroup analysis showedthe association between postoperative serum albumin and long-term prognosis based on patients of ccRC and radical nephrectomy rather than partial nephrectomy. However, only 26 patients with postoperative serum albumin < 32g/L received partial nephrectomy, the negative result may be constricted by the limit sample size.

Limited by the potential retrospective bias, the prognostic value of early postoperative serum albumin needs more high-quality studies for further elucidation. Allow for its good category power (AUC = 0.71-0.8), the early postoperative serum albumin deserves more attentions in predicting prognosis after radical resection of kidney cancer, especially combined with other prognostic factors. However, the mechanisms underlying the association remain unclear. Besides, it deserves further exploration whether transfusion of albumin lead to decrease recurrence and death after resection of kidney cancer.

**Conclusion**

In patients after curative resection of kidney cancer, this retrospective study revealed the early postoperative serum albumin < 32g/L is an independent risk factor associated with shortened RFS and shortened OS. Prospective trials and further researches in more confined patients are needed.

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