Association between reduced preoperative serum albumin and prognosis in patients with adrenocortical carcinoma after primary resection: A retrospective study

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Research article

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Abstract

Purpose

To assess the correlation between preoperative serum albumin level and prognosis in patients with adrenocortical carcinoma after primary surgery.

Methods

We reviewed medical information of 71 included patients with diagnosis of ACC who underwent primary resection. Univariate and multivariate analysis were performed using Cox's proportional hazards model. Survival analysis was conducted by Kaplan–Meier method with log-rank test. Receiver operating characteristic (ROC) curve and Jordan index were generated to explore cut-off value for serum albumin. Statistical significance was defined as $P < 0.05$.

Results

Among included patients, 33 patients (46.5%) relapsed at the end of follow-up, while 39 patients (54.9%) died. The median OS of overall included patients was 17 (range 1–104) months and median RFS was 10 (range 0–104) months. In univariate analysis, the albumin significantly associated with OS and RFS (HR:0.491, 95%CI: 0.260–0.930, P = 0.029 and HR:0.383, 95%CI: 0.192–0.766, P = 0.007, respectively). In multivariate analysis, the albumin level as an independent prognostic factor of OS was confirmed(HR:0.351, 95%CI: 0.126–0.982, P = 0.046). Meanwhile, the present

results indicates the trend that albumin might be an independent predictor of RFS (

HR:0.423, 95%CI: 0.176–1.018, P = 0.055)

Conclusion

The preoperative serum albumin level is significantly correlated to prognosis of patients with ACC after primary resection. Reduced preoperative albumin level was proven to be a risk factor of clinical outcomes for ACC. Appropriate nutritional intervention prior to surgery may be beneficial to improve the prognosis of ACC patients.

Introduction

Adrenocortical carcinoma (ACC) is a rare and aggressive malignancy with an overall incidence of 1–2 cases/million per year[1]. Due to obscure presentation, the diagnosis of ACC is often delayed and the treatment encounters much difficulty caused by disease progression. Even worse, the rarity of ACC makes clinical researches uneasy and therapeutic options limited. Complete resection considered as the only treatment of ACC is unsuitable for advanced tumor that are common in this disease[2]. Furthermore, adjuvant therapies,including mitotane and chemo/radiotherapy, have never been evaluated in large randomized trials[3, 4]. Given the complexity of this rare malignancy, current treatment of ACC remains challenging and consequently the prognostic assessment is becoming increasingly crucial.

Malnutrition is correlated to many post-operative complications and poor clinical outcome in various cancers[5]. Thus, various nutritional markers such as transferrin, total protein and serum albumin have been taken into consideration for prognostic evaluation in cancer patients. In all, serum albumin as an objective, quantifiable and potentially recoverable parameter has been widely used to assess the nutritional status and prognosis in both benign and malignant diseases[6].

Thus, serum albumin maybe an important prognostic marker used to prognostic evaluation for ACC. Here, we aim to investigate the association of preoperative serum albumin with prognosis in patients with ACC after primary resection.

Methods

Patients and Study protocol

There were 90 patients with ACC after primary resection at the West China Hospital between January 2009 and January 2019, and their data were collected retrospectively (Supplementary Fig. 1). The patients included in this study must had to meet the following criteria: pathological diagnosis of ACC, available perioperative medical records and laboratory results, no previous treatment for any other tumor

The primary outcome was overall survival (OS) calculated as the time from first operation to death caused by any reason or last follow-up, while the secondary outcome was recurrence-free survival (RFS) defined as the time from first surgery to recurrence or last follow-up. Recurrence was determined by the radiological discovery of a neoplastic lesion after primary resection during the follow-up. Besides, follow-up was determined as the time from initial operation to death or last contact with patient.

Statistical analysis

All statistical analyses were performed by using SPSS 23.0. Median and ranges or mean value and standard deviation were calculated for continuous data. Rates or proportions were calculated for categorical data. The correlation between serum albumin level and clinicopathological variables were analyzed using Pearson’s test. Survival rates were computed using Kaplan–Meier curves and compared with log-rank test. Cox’s proportional hazards model was used for univariate and multivariate analysis.

Receiver operating characteristic (ROC) curve and Jordan index were generated to explore optimal cut-off value for albumin. All P values were two-sided and statistical significance was defined as $P < 0.05$.

Results

Patients and Prognostic Factors

After exclusion of 19 patients, information of 71 patients were collected and reviewed (Supplementary material). Among them, 46 patients (64.8%) were diagnosed at stage I/II, whilst 25 patients (35.2%) diagnosed at stage III/IV. At the end of the follow-up period, tumor recurrence occurred in 33 patients (46.5%), while 39 patients (54.9%) died. The clinicopathological characteristics and their association with preoperative albumin were showed in Table 1. The median OS of overall included patients was 17 (range 1–104) months and median RFS was 10 (range 0–104) months.

Table 1
Clinicopathological characteristics of the included patients and their association with serum albumin.

Patients	**N = 71**	**P-value**
Gender[n (%)]		
Male	30(42.3)	0.153
Female	41(57.7)	
Age(years)[median(range)]	44(2–79)	**0.024**
Function[n (%)]		
No	41(57.7)	0.977
Yes	30(42.3)	
Comorbidities [n (%)]		
No	43(60.6)	0.823
Yes	28(39.4)	
Diameter of tumor [n (%)]		
≤ 8.8 cm	36(50.7)	0.081
8.8 cm	35(49.3)	
Tumor stage[n (%)]		
I/II	46(64.8)	0.288
III/IV	25(35.2)	
Modus operandi [n (%)]		
Laparoscopy	23(32.4)	0.405
Open	48(67.6)	
Post-recurrence adjuvant treatment [n (%)]		
No	54(76.1)	0.103
Yes	17(23.9)	
Recurrence [n (%)]		
No	38(53.5)	**0.008**
Yes	33(46.5)	
Death [n (%)]		

Patients	N = 71	P-value
Survival	32(45.1)	**0.001**
Died	39(54.9)	
Ki67 index (%)[median(range)]	10(0–90)	0.600
Albumin (g/L)(Mean ± deviation)	40.6 ± 5.1	
Globulin (g/L)(Mean ± deviation)	27.6 ± 5.3	0.087
Hemoglobin (g/L)(Mean ± deviation)	130.2 ± 21.4	**0.001**

Univariate and multivariate prognostic analysis

ROC curve was plotted and Jordan index calculated to evaluate the optimal cutoff value (Fig. 1). In this study, ROC curve with AUC of 0.687 for predicting recurrence and 0.731 for death were generated, and the optimal cutoff value of albumin at lower than or equal to 39 g/L was confirmed (Supplementary material). In univariate analysis, the albumin significantly associated with OS and RFS (HR:0.491, 95%CI: 0.260–0.930, P = 0.029 and HR:0.383, 95%CI: 0.192–0.766, P = 0.007, respectively). In multivariate analysis, the albumin as an independent prognostic factor of OS was confirmed (HR:0.351, 95%CI: 0.126–0.982, P = 0.046). Meanwhile, the present results indicates the trend that albumin might be an independent predictor of RFS (HR:0.423, 95%CI: 0.176–1.018, P = 0.055)(Showed in Table 2 and Table 3).

Table 2
Cox univariate analysis of the OS and RFS with dichotomous serum albumin level.

Variables	OS			RFS		
	HR	95%CI	P-value	HR	95%CI	P-value
Gender	1.721	0.869–3.410	0.119	1.462	0.717–2.981	0.296
Age	0.997	0.977–1.019	0.813	0.995	0.974–1.016	0.638
Function	0.687	0.357–1.324	0.262	1.059	0.530–2.118	0.870
Comorbidities	0.759	0.394–1.461	0.409	1.082	0.542–2.162	0.823
Diameter of tumor	1.345	0.717–2.525	0.356	1.027	0.517–2.039	0.940
Tumor stage	1.424	0.742–2.730	0.288	1.384	0.678–2.825	0.372
Modus operandi	1.849	0.899–3.803	0.095	0.925	0.459–1.867	0.829
Post-recurrence adjuvant treatment	1.118	0.572–2.185	0.745			
Recurrence	1.769	0.922–3.394	0.086			
Ki67 index	1.034	1.011–1.057	**0.004**	1.024	0.999–1.050	0.059
Albumin	0.491	0.260–0.930	**0.029**	0.383	0.192–0.766	**0.007**
Globulin	0.994	0.940–1.052	0.846	0.989	0.929–1.054	0.741
Hemoglobin	0.992	0.978–1.006	0.257	0.974	0.955–0.992	**0.006**

Bold figures indicate statistical significance at P 0.05.

OS overall survival, RFS recurrence-free survival, HR hazard ratio, CI confidence interval.

Table 3
Cox multivariate analysis of the OS and RFS with dichotomous serum albumin level.

Variables	OS			RFS		
	HR	95%CI	P-value	HR	95%CI	P-value
Gender	2.210	0.792–6.163	0.130	1.272	0.545–2.970	0.578
Age	0.987	0.958–1.018	0.411	0.991	0.965–1.017	0.493
Function	0.770	0.325–1.823	0.551	0.883	0.385–2.024	0.768
Comorbidities	0.561	0.228–1.384	0.210	0.951	0.413–2.192	0.906
Diameter of tumor	1.333	0.564–3.154	0.512	0.938	0.375–2.344	0.891
Tumor stage	0.664	0.271–1.626	0.370	1.079	0.408–2.858	0.878
Modus operandi	1.664	0.575–4.820	0.348	0.773	0.279–2.143	0.621
Post-recurrence adjuvant treatment	0.540	0.186–1.567	0.257			
Recurrence	2.437	0.910–6.526	0.076			
Ki67 index	1.043	1.015–1.072	**0.003**	1.024	0.998–1.052	0.074
Albumin	0.351	0.126–0.982	**0.046**	0.423	0.176–1.018	0.055
Globulin	0.999	0.919–1.087	0.987	0.971	0.902–1.045	0.430
Hemoglobin	1.013	0.993–1.034	0.196	0.985	0.962–1.008	0.196

Bold figures indicate statistical significance at P 0.05.

OS overall survival, RFS recurrence-free survival, HR hazard ratio, CI confidence interval.

Discussion

ACC is considered as a rare tumor with few effective regimen and poor prognosis[7]. Although this heterogeneous and aggressive malignancy captured increasing focus gradually, the treatment and prognostic evaluation of ACC is still a challenge for clinicians worldwide. Due to the absence of

randomized controlled trials, so far, radical resection represents the only potential curative treatment and no chemo/radiotherapy or other adjuvant therapies could show long-term benefit for patients with ACC[8]. Besides, limited medications in adjuvant setting are still comprised of obsolete agents with substantial side effects, and the clinical outcomes remains dismal.

In order to evaluate the prognosis precisely and hereby constitute the basic treatment decisions for ACC patients, many prognostic studies have been performed and several predictors developed[9]. Out of these, resection status, tumor stage and grade are regarded as most predictive factor of ACC[8]. However, the amount of studies in prognosis is very small and current markers are characterized by intrinsic limitations which might reduce their utility in ACC[10, 11]. Consequently, exploiting a common parameter rather than searching for biomarkers in vivo may be more valuable for this rare malignancy to provide rapid application in prognostic evaluation and patients stratification.

As a common biochemical marker in assessment of nutritional status, serum albumin level has demonstrated prognostic value in several benign or malignant disease[12, 13]. In line with previous studies, our study indicates that the preoperative albumin level is a potential prognostic factor for ACC, which appears to be not only accessible but affordable. Specifically, patients with higher albumin level may have a better prognosis, by comparison, those with lower albumin suffered remarkable reduction in RFS and OS (Fig. 2). Unexpectedly, serum albumin did not demonstrate statistical significance as prognostic marker for RFS in Cox multivariate analysis(HR:0.423, 95%CI: 0.176–1.018, P = 0.055). However, it have shown an conspicuous tendency associated with RFS, and the Kaplan-Meier curves of RFS were significantly different (P = 0.0041), indicating that albumin might be a prognostic indicator for RFS (Table 3)(Fig. 2A).

We also noticed that the cutoff value of albumin (39 g/L) in this study is higher than previous studies[5, 14]. For this discrepancy, we hold the opinion that the number of patients with adrenal incidentaloma who accepted early operation is increasing. Although the preoperative diagnosis was histopathologically modified as ACC after primary resection, these patients possessed excellent nutritional performance which may influence ultimate findings. Additionally, this distinction may reflect the enormous heterogeneity and aggressiveness of ACC which might rapidly worsen nutritional status of patients, highlighting the importance of preoperative nutritional intervention.

The concrete mechanism underlying the association between serum albumin and prognosis in many malignancies remains unclear now. Maybe the malnutrition characterized by hypoalbuminemia tends to incur more postoperative complications, increasing the mortality and morbidity in some degree. On the other hand, the serum albumin with short half-life is prone to be impacted by several disorders such as diabetes mellitus, hepatic insufficiency, chronic kidney disease and hypercortisolism, which may have adverse effects on prognosis of ACC. Particularly, it is reported that in ACC patients cortisol-secretion significantly increase the risk of poor outcomes, including recurrence and death, and should be deemed as a negative prognostic factor[15]. Moreover, many cytokines from systemic inflammatory response related to tumor progression may inhibit the albumin synthesis and accelerate albumin loss to interstitial

space[16, 17]. In fact, there are various ways to evaluate the nutritional status, such as body mass index (BMI), weight loss, arm circumference and food-intake[18]. However, these measurements based on prospective studies with subjective and qualitative properties are subjective and impracticable for this retrospective study[19].

Resection remains the primary treatment for solid tumors in recent years. Despite the perioperative preparation and surgical procedures progress in recent years, surgery remains a substantially invasive therapy with potential risk to provoke complications, sometime seriously. As above-mentioned, patients with inferior nutritional performance maybe liable to invite serious complications and poor clinical outcomes. Thus, as other malignancies, adequate perioperative nutrient supplementation might be conducive to decrease postoperative complications and improve prognosis for ACC patients[20].

This study has several limitations. Due to the retrospective design, the bias from unmeasured confounding variables is inevitable. Meanwhile, given the heterogeneity of ACC, patients with lower albumin level maybe suffered more aggressive tumor and their condition may deteriorate faster. Additionally, statistical power in present study was impacted by small sample size since the rarity of ACC. Thus, it is indispensable to perform retrospective investigations to facilitate the data accumulation and provide high-level evidence for this rare malignancy.

Conclusion

Preoperative serum albumin level is significantly correlated to prognosis of patients with ACC after primary resection. As an independent prognostic factor for OS, the lower level of preoperative serum albumin was proven to be an risk predictor for clinical outcomes. Appropriate nutritional repletion and correction of malnutrition prior to the surgery would be beneficial to improve the prognosis of ACC patients.

Declarations

Funding

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Competing interests

The authors declare no conflict of interest.

Ethics approval and consent to participate

This article does not contain any studies with human or animal trials. Institution review board of West China Hospital had approved this study.

Consent for publication

All patients included in this study provided informed consent for use and publication of their data.

Acknowledgments

All named authors meet the ICMJE criteria for authorship in this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Data availability

The datasets analyzed during the current study are available from the corresponding author on reasonable request. We thank the participants of the study.

Authors' contributions

Fuxun Zhang: project development, data collection, data analysis, manuscript writing; Zhihong Liu: project development, data analysis; Jiayu Liang: data collection; Shengzhuo Liu: data collection; Kan Wu: data collection; Fan Zhang: data collection; Chuan Zhou: data collection; Yiping Lu: project development, data analysis; Yuchun Zhu:project development, data analysis; Xianding Wang: project development, data analysis, manuscript correction, manuscript editing.

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Figures

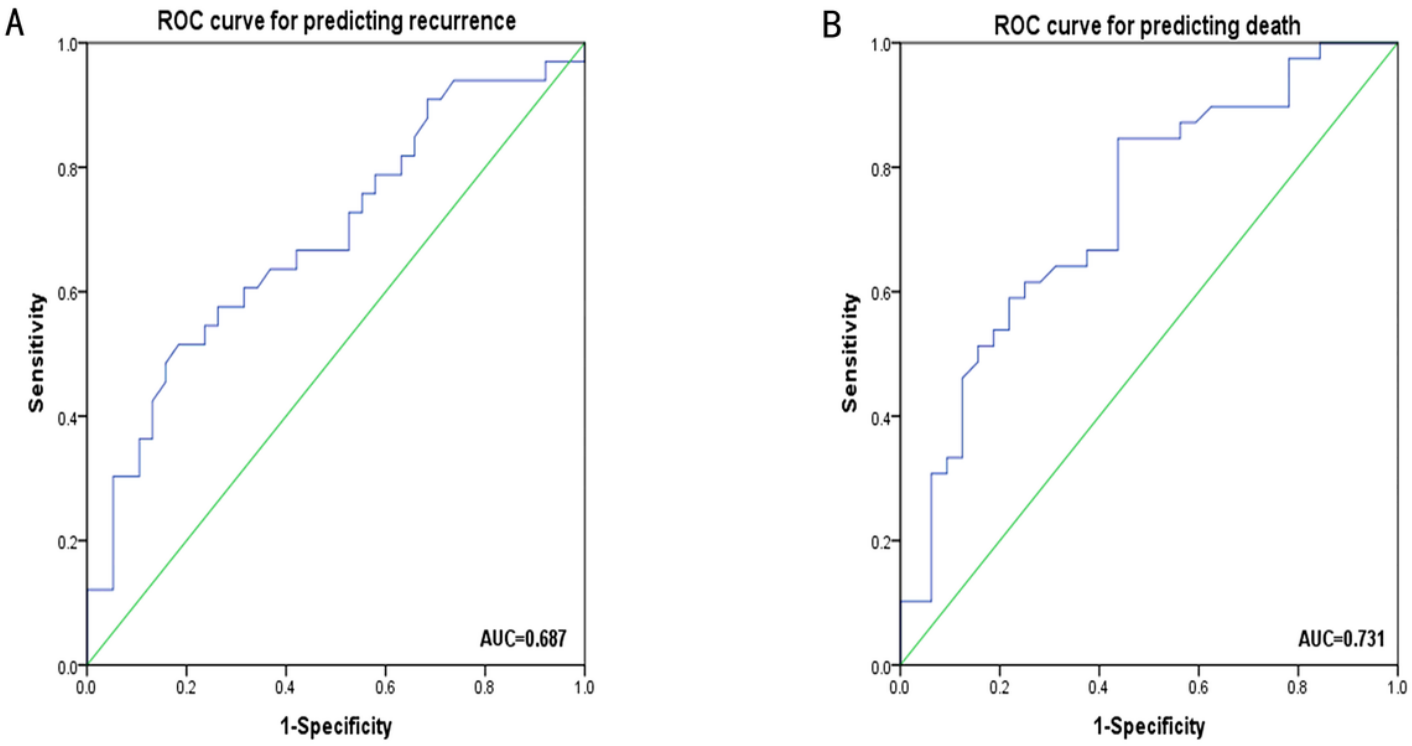

Figure 1

ROC1TG

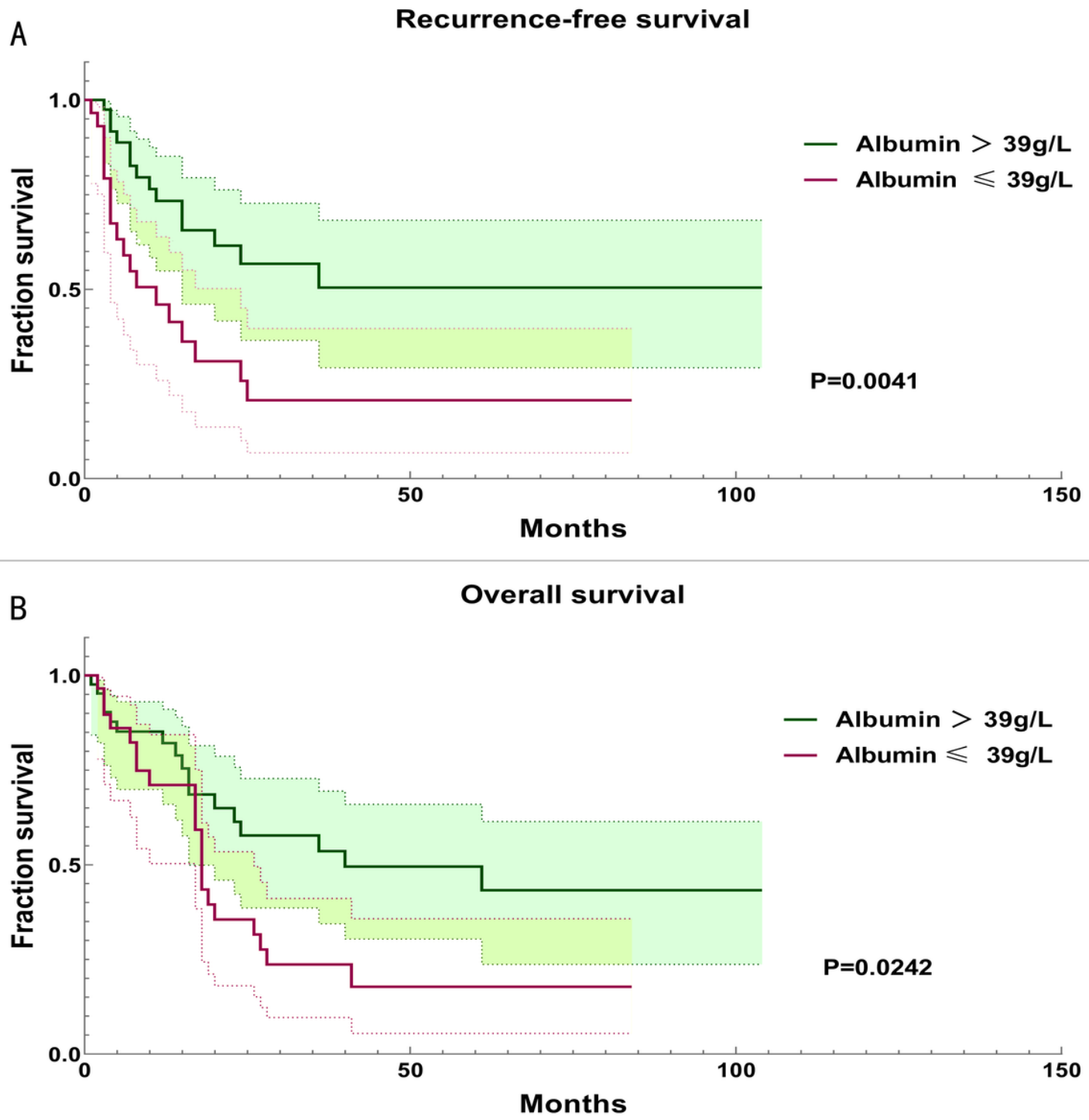

Figure 2

Survivalcurve

Supplementary Files

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- flowchartTG.tif