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Prognostic Value of Albumin Levels before Therapy on Survival of Nasopharyngeal Carcinoma Patients

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Abstract: Nasopharyngeal cancer (NPC) is a type of cancer in Southeast Asia, with 30-80 cases annually per 10,000 population. Based on the data, about 80% of patients with advanced-stage are diagnosed first, while 20% develop metastases after therapy. A prognostic assessment is essential for the optimization of treatment. Malnutrition is one of the consequences of decreased response to treatment, quality of life, and survival. The patient's albumin determines nutrition. This study was a retrospective study to evaluate the ability of pre-therapy albumin levels to predict long-term mortality in 227 NPC patients at Dr. Sardjito Hospital. Univariate analysis identified albumin as a statistically significant predictive factor for survival (P 0.021). Albumin (ALB) < 3.50 was significantly associated with shorter survival. Median Overall Survival showed (OS) ± SE ALB < 3.50 vs. ALB 3.50: 9.40 ± 2.56 vs. 17.63 ± 1.51 months, P 0.021, Hazard Ratio (HR) 1.368; 95% CI (1.049–1.783). However, multivariate analysis showed low serum albumin levels before therapy on survival in NPC patients (P 0.778, HR 1.050, 95% CI (0.75–1.469). Treatment was identified as the only independent predictive factor for survival. Albumin before therapy was a potential predictive biomarker to evaluate survival in NPC patients but not an independent predictor.

Keywords: albumin; nasopharyngeal carcinoma; prognosis; survival

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is the most common malignancy in Southeast Asia, with the number of 30-80 cases per year per 10,000 population.[1] NPC is the most common type of cancer of the head and neck as well as the fifth most common sort of cancer in men in Indonesia. The prevalence of NPC in Indonesia is 6.6/100,000, with a passing rate of 4.3/100,000.[2] Roughly 80% of patients with progressed stages are analyzed at the primary time due to the covered-up tumor area, asymptomatic and non-specific symptoms.[3] One of the foremost common medicines for NPC is radiotherapy (RT). In recent years, advancements in demonstrative strategies, radiotherapy procedures, and chemotherapy regimens have provided significant survival benefits in locally advanced NPC patients.[4] However, more than 20% of patients with progressed illnesses will have metastases after treatment. Thus, it is critical to form an exact prognostic assessment to optimize treatment at the time of determination. Making an accurate prognostic evaluation at diagnosis is very important for optimizing therapy.[5] Current methods for assessing the prognosis of patients with NPC are mainly based on tumor-associated factors. The Tumor, Node and Metastatic (TNM) *staging* system, consisting of Tumour (T), Node (N) and Metastatic (M) classifications, is the most commonly used method for determining clinical therapeutic strategies and predicting treatment outcomes. In addition, some molecular biomarkers, such as plasma Epstein-Barr DNA viral load, are prognostic factors for overall survival and recurrence. However, high costs and technical requirements often limit their clinical application. As a result, novel low-cost prognostic biomarkers are urgently needed. However, it becomes increasingly clear

that the prognostic value of tumor-associated factors in disease progression is inadequate. Significant heterogeneity of treatment outcomes was observed for the existing predictive model of NPC. [3] Thus, the discovery of biological markers, which can predict metastatic risk and mortality to aid clinical decision-making, is still a major topic of translational research in NPC.

Malnutrition and cancer-associated inflammation are considered important host-related factors that can negatively affect cancer treatment outcomes, as they can promote tumor growth and metastasis by impairing the immune system and altering tumor cell biology in the tumor microenvironment.[6] Albumin is an important serum protein that describes the patient's nutritional status. Previous studies have shown that low serum albumin is an independent predictor of poor survival in several types of cancer, including gastrointestinal, lung, ovarian, and breast cancer.[7] In this study, the relationship between serum albumin levels before therapy and survival in nasopharyngeal cancer patients will be tested with different characteristics of patient subjects, where nasopharyngeal patients in the population at Dr. Sardjito Hospital mostly come with an advanced stage and poor performance status, as well as different therapeutic strategies.

MATERIAL AND METHOD

This study is a retrospective cohort study conducted at Dr. Sardjito Hospital from 2007 – 2016 using data from the clinical register of diagnosed and histologically proven NPC patients. This study was designed to determine prognostic factors, including albumin levels before starting therapy, that affect the 2-year survival of locally advanced NPC patients at Dr. Sardjito Hospital.

This study used survival analysis, where patient factors (age, sex), tumor factors (tumor size, location of affected cervical lymph nodes), therapeutic factors (type of therapy), and clinical factors (albumin levels before starting therapy) were independent variable and tested for its effect on the survival of NPC patients as the dependent variable to determine the factors that influenced the survival of NPC patients in Dr. Sardjito Hospital.

The research subjects were patients who met the criteria, including patients diagnosed with NPC for the first time, clinical stage III, IVA, and IVB based on The American Joint Committee on Cancer (AJCC) criteria, who received treatment at Dr. Sardjito Hospital in 2007-2016 and aged 18-70 years. Meanwhile, the exclusion criteria in this study were incomplete data, without therapy, ECOG 4 performance index, and other malignancies.

Overall, 227 patients were included in the analysis. Patient records/information were anonymized and not identified prior to analysis. This study wanted to determine the prognostic role of serum albumin levels before therapy on the 2-year survival of patients with locally advanced NPC at Dr. Sardjito Hospital.

Treatment

Before therapy, the patient underwent basic examinations such as a complete medical history, physical examination, hematological and biochemical profile, contrast Multislice Computed Tomography scan of the neck and nasopharynx, chest X-ray and abdominal ultrasound. A treatment plan was based on the standard protocol on tumor stage and general health. All patients were treated with continuous definitive radiotherapy (RT) with a daily fraction of 2.0 Gy and five fractions per week. The radiation dose was about 70 Gy. Patients received induction chemotherapy in three cycles of cisplatin with 5-fluorouracil or cisplatin, 5-fluorouracil and taxane every 28 days. The patient received adjuvant chemotherapy consisting of 4-6 cycles of cisplatin with 5-fluorouracil every 28 days. Patients receiving chemotherapy and radiotherapy were given cisplatin every week.

Data collection

Clinicopathological characteristics were recorded before starting treatment. Selected patients had serum chemistry analyses and total blood tallies. Blood tallies were performed employing a Sysmex XE-5000 robotized hematology analyzer (Sysmex, Kobe, Japan). Serum albumin was used as a mechanized immunoturbidimetric analyzer (7600-020; Hitachi High-Technologies, Tokyo, Japan). None of the patients had any hematological variations from the norm or were in dynamic disease.

Follow up

Nasopharyngeal carcinoma (NPC) patients who sought treatment at Dr. Sardjito Hospital from 2007 – 2016 were included as research subjects if he/she met the inclusion criteria and was not included in the exclusion criteria. The data were obtained through the hospital's clinical registration, including data on the patient's complete identity, clinical data, data on the findings and reports of the treatment being

followed as well as laboratory, radiological, and anatomical pathology examinations at the Tulip Installation of Dr. Sardjito Hospital and every 6 months after that. Median follow-up in this study included 29.46 months (27.11 - 31.81). The number of subjects who experienced loss to follow-up was 30.4%. The main outcome assessed was survival.

The patient's life status was determined based on medical record data. However, if the life status information from the medical record was incomplete, then the patient's life status information was obtained through interviews through face-to-face meetings at Dr. Sardjito Hospital, home visits, telephone interviews, or correspondence to the patient's address.

Statistical Analysis

The collected data was then analyzed using various statistical methods using SPSS computer software. NPC frequency data at Dr. Sardjito Hospital is presented in the form of proportions and then analyzed using the chi-squared method.

The limit value of serum albumin levels before treatment was determined using receiver operating characteristic (ROC) curve analysis. Based on the threshold value, it was divided into 2 groups, namely high and low.

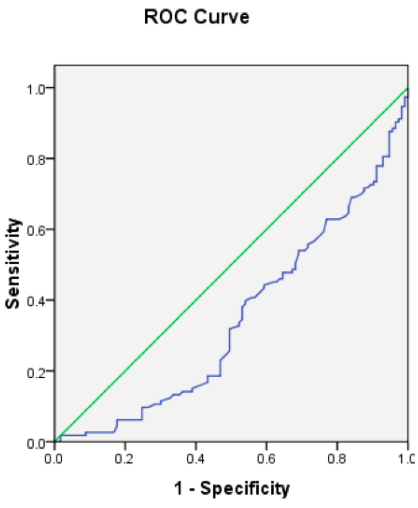
The Cox regression method included all independent variables in the bivariate analysis. All independent variables with $p < 0.05$ in bivariate analysis were then entered into multivariate analysis using the Cox regression time-independent method. In the results of multivariate analysis, the independent variable was considered related to the dependent variable if $p < 0.05$, and in the confidence interval, there was no zero. The strength of the relationship between the independent variable and the dependent variable was described by the magnitude of the hazard ratio (HR) value.

RESULT

The clinicopathological features of 227 patients, of whom 155 (68.3%) were male and 72 (31.7%) were female, are shown in Table 1. The median age at diagnosis was 49 years (range, 12–76). Disease staging was classified according to the International Union against Cancer/American Joint Committee on Cancer (UICC/AJCC) staging system for NPC 7th edition. [8]

Identifying The Optimal Cut-off Point Values for Defining High or Low Albumin

This study's cut-off point for serum albumin levels before starting therapy was 3.50. This cut-off point was used to divide patients into NPC patients with high and low serum albumin groups. This albumin limit was determined by the receiver operating characteristic (ROC) curve. The albumin threshold of 3.50 has a sensitivity of 44.2% and a specificity of 59.3% in determining 2-year survival in stage III-IVB NPC patients (Figure 1).



Coordinates of the Curve

Test Result Variable(s):Albumin

Positive if Greater Than or Equal To[a]	Sensitivity	1 - Specificity
3.2600	.540	.708
3.2750	.540	.699
3.2850	.540	.690
3.2950	.531	.690
3.3100	.504	.681
3.3250	.496	.681
3.3400	.487	.681
3.3600	.487	.673
3.3850	.478	.673
3.4100	.478	.664
3.4350	.478	.646
3.4550	.469	.646
3.4650	.460	.646
3.4750	.460	.637
3.4850	.451	.628
3.4950	.451	.619
3.5050	.442	.593
3.5200	.434	.593
3.5350	.416	.575
3.5450	.407	.566
3.5550	.407	.558
3.5650	.398	.540

Figure 1. Receiver Operating Curve (ROC) for Serum Albumin Levels

Table 1. Basic Characteristics of the Low Serum Albumin Group Compared to the Group with High Serum Albumin in NPC Patients at Dr. Sardjito Hospital

Variable	Low ALB group (ALB < 3.5 g/dL)	High ALB group (ALB *≥3.5 g/dL)*	No (%)	P-Value
Age, years				0.001
< 50	41 (39.9)	76 (61.3)	117 (51.5)	
≥ 50	62 (60.1)	48 (38.7)	110 (48.5)	
Gender				0.001
Male	82 (79.6)	73 (58.9)	155(68.3)	
Female	21 (20.4)	51 (41.1)	72 (31.7)	
T classification				0.889
T1-2	35 (33.3)	42 (34.4)	77 (33.9)	
T3-4	70 (66.7)	80 (65.6)	150 (66.1)	
N Classification				
N0-1	46 (42.6)	61 (51.3)	107 (47.1)	0.127
N2-3	62 (57.4)	58 (48.7)	120 (52.9)	
Stage				
I + II	7 (6.8)	9 (7.26)	16 (7.04)	0.892
III+IV	96 (93.2)	115 (92.74)	211 (92.96)	
Therapy				0.002
None	31 (29.5)	16 (13.1)	47 (20.7)	
Chemotherapy	38 (36.2)	44 (36.1)	82 (36.1)	
CCRT	30 (28.6)	39 (31.9)	69 (30.4)	
Neoadjuvant + RT	4 (3.8)	21 (17.3)	25 (11.0)	
RT	2 (1.9)	2 (1.6)	4 (1.8)	
BSA, kg/m2	1.44±0.17	1.48 ± 0.17		0.042
White blood cell count	13.18 ± 6.49	9.22 ± 5.31		0.013
Neutrophil	70.01 ± 14.86	66.19 ± 12.79		0.045
Lymphocyte	15.24 ± 8.20	20.53 ± 8.32		0.000

The Relationship of Serum Albumin Level before Therapy with Other Prognostic Factors

This study analyzed the relationship between serum albumin levels and other prognostic factors for survival, namely age, gender, tumor size, lymph node involvement, stage, therapy, body mass index, number and type of leukocytes using chi-square analysis. Based on the result of the analysis, it was found that there was a relationship between serum albumin levels with age (p 0.001) and gender (p 0.001). Low serum albumin levels were associated with advanced age and male gender (Table 1). Patients who received standard therapy with CCRT (concurrent chemotherapy with radiation) were given more than patients with high serum albumin levels (P 0.002). Low body mass index was significantly higher in patients with low serum albumin (P 0.042). Serum leukocyte levels were significantly higher in patients with low serum albumin levels (P 0.013), and the lymphocyte count was significantly lower in patients with low serum albumin levels (P 0.00).

Univariate Analysis of 2-Year Survival Prognostic Factors

Based on the univariate analysis in this study, serum albumin before therapy was found to be a significant prognostic factor for survival. Serum albumin < 3.50 was significantly associated with shorter survival (Median OS SE ALB < 3.50 vs ALB 3.50 : 9.40 2.56 vs 17.63 1.51 months, P 0.021, HR 1.368; 95% CI (1.049 – 1.783).

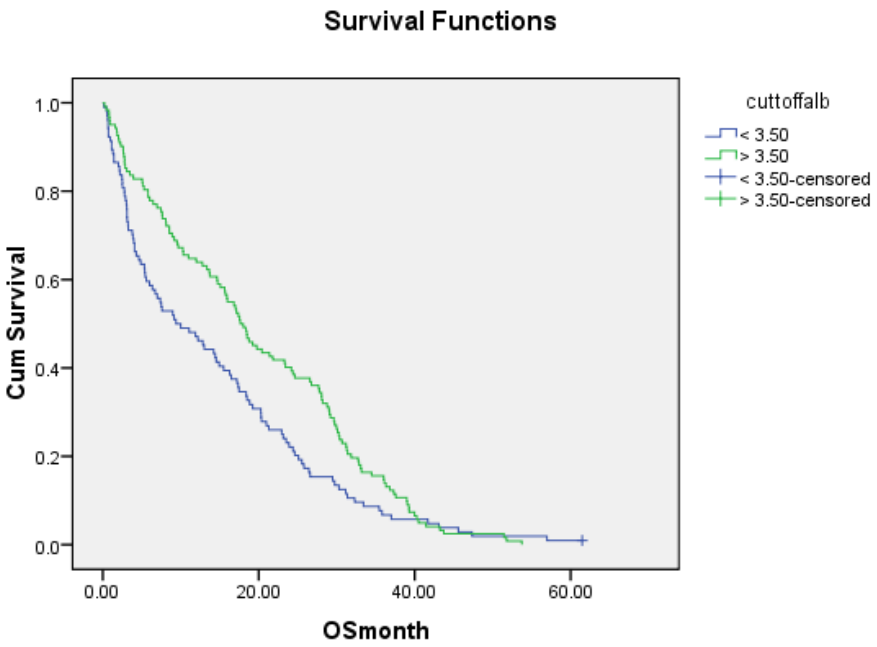


Figure 2. Kaplan-Meier Curve for Serum Albumin Levels and 2-year Survival

Based on the Kaplan-Meier curve, it was found that the survival curve for serum albumin levels before therapy did not coincide with each other and did not meet the proportional hazard assumption (Figure 2). The univariate analysis also found that the type of therapy was a prognostic factor in 2-year survival in stage III-IVB NPC patients. The Concurrent Chemotherapy with Radiation Therapy (CCRT) had significantly better survival than non-CCRT therapy.

Multivariate Analysis of 2-Year Survival Prognostic Factors

Based on the result of multivariate analysis with Cox regression in this study, it was found that the type of CCRT therapy showed a reduction in mortality with a 2-year survival hazard of HR 0.689 with 95% CI 0.577-0.822 and p 0.000. Meanwhile, serum albumin levels before therapy showed no difference in mortality (survival) with a 2-year survival hazard of HR 1.050 with 95% CI 0.750-1,469 and p 0.778. Multivariate analysis showed that serum albumin level was not an independent prognostic factor in 2-year survival in stage III-IVB NPC patients (Table 2).

Table 2. Multivariate Analysis of Prognostic Factors for 2-year Survival

Variable	5 Years OS	
	P-value	HR (95%CI)
Age (≥ 50 vs < years)	0.331	0.991 (0.975-1.008)
Gender (male vs. female)	0.190	1.254 (0.894-1.761)
T Classification (T3-4 vs. T1-2)	0.692	0.929 (0.645-1.338)
N Classification (N1-2 vs. N3)	0.220	1.219 (0.888-1.674)
Treatment (None, Chemotherapy, Neoadjuvant+ RT, CCRT, RT)	0.000	0.689 (0.577-0.822)
Albumin (≥ 3.5 g/dL vs < 3.5 g/dL)	0.778	1.050 (0.750-1.469)

DISCUSSION

This study showed that serum albumin level before therapy was a significant prognostic factor for mortality in NPC in univariate analysis but not in multivariate analysis after adjustment for other prognostic factors. Low serum albumin levels are associated clinically with advanced age, male gender, soft body mass index, high serum leukocyte count, and low lymphocyte count. Patients with low serum albumin before therapy had a worse survival than those with high serum albumin on univariate analysis. However, this result was influenced by the type of therapy in a multivariate analysis, where patients with low serum albumin levels received less gold standard therapy with CCRT. In contrast, patients with high serum albumin levels received more gold standard therapy with CCRT.

Previously, albumin is considered a predictive factor for poor survival in breast cancer[7] and colorectal cancer. [9] Albumin is the foremost inexhaustible serum protein. In adults, the ordinary albumin run is 3.5–5.0 g/dL; levels < 3.5 g/dL are called hypoalbuminemia.[10] Albumin is most frequently utilized to evaluate the wholesome status and is also a great calculation for anticipating cancer patients' forecasts. Over the final decade, an affiliation between albumin and expanded illness seriousness has appeared; high risk of disease progression and poor survival in some cancers.[11] A few instruments have been proposed to clarify albumin's anti-cancer impacts, counting its capacity to stabilize cell development and DNA replication. It equalizes different biochemical changes and maintains calcium and sex hormone homeostasis to ensure against sex hormone-induced cancer frequency and its antioxidant impacts against carcinogens.[12] In vitro, high albumin concentrations can hinder the multiplication or development of cancer cells (breast cancer cells). [13]

On the other hand, ailing health and irritation can smother albumin synthesis. As a portion of systemic aggravation in reaction to tumors, the tumor or encompassing cells discharged tall levels of proinflammatory cytokines and development variables, modifying metabolic homeostasis within the tumor microenvironment. For illustration, interleukin-6 invigorates the generation of acute-phase response proteins within the liver and balances albumin generation by hepatocytes. In differentiation, tumor rot calculation can restrain albumin translation and increment microvascular penetrability, driving expanded transcapillary albumin loss.[14]

This study showed a noteworthy affiliation between serum albumin levels and higher leukocyte and neutrophil checks, reliable with past breast cancer considerations. [7] It has been reported that high levels of peripheral neutrophils, actuated by related cytokines (i.e., interleukin-6 and tumor necrosis factor) or tumor-derived myeloid growth factor, may show a systemic incendiary reaction or tumor movement. It can be because neutrophils can deliver proangiogenic components to increase tumor aggressiveness, such as vascular endothelial growth factor.[15]

The systemic incendiary reaction may be a non-specific reaction auxiliary to tumor hypoxia and neighborhood tissue corruption or damage. Clinical proof proposes that a persistent fiery systemic response is associated with progressive nutritional decline, poor response to treatment and poor prognosis in cancer patients. [13] The intense stage C-Reaction Protein (CRP) is fundamentally synthesized and discharged into the systemic circulation by hepatocytes and is utilized as a non-specific marker of aggravation. Endlessly raised CRP levels have been related to destitute cancer survival, particularly in patients with the progressed disease.[16] A past ponders appeared that elevated CRP levels (>2.46 mg/L) were poor prognostic of survival in NPC. [16] The systemic inflammatory reaction was appraised using a specific combination of hematological components to make inflammation-based prognostic factors.[17] A high neutrophil to lymphocyte proportion has been related to destitute survival in NPC, while a high lymphocyte to monocyte ratio was reported as a significant predictor of favorable prognosis in NPC that has been detailed as a noteworthy indicator of favorable forecast in NPC.[18]

The researchers suspect that nutritional status and systemic inflammatory response are critical in NPC's advancement and metastasis. Low albumin in the serum would weaken cellular and humoral immunity, phagocytic functions, and other defense mechanisms in patients with cancer; low albumin may reflect immunological environments.[19] Useful pointers or other provocative components should be surveyed related to recently beginning treatment in NPC patients. Dietary appraisal, bolster, and anti-inflammatory therapy may be helpful choices in NPC. There are, as of now, a few continuous ponders exploring the capacity of anti-inflammatory treatments (e.g., headache medicine and other non-steroidal anti-inflammatory drugs) to avoid and treat lung, esophageal, stomach, colon, and bladder cancers.[20] Inflammatory therapy in NPC ought to be investigated.

Disease progression in cancer depends on the complex interactions between the tumor and the host immunological response. Low albumin provides biological information about a tumor’s potential outcome. Albumin may be ideal for assessing the tumor microenvironment for not only the nutritional status but also the patient’s status over a long period. Albumin levels have been reported to be associated with breast cancer risk and cancer mortality. Further research is necessary to establish the effect of low serum albumin on immunological features and the tumor microenvironment.[8]

There are a few confinements to this investigation. Other variables, such as CRP and other serum proteins, which are fundamental markers of cancer-associated aggravation, are not routinely measured in Dr. Sardjito Hospital's cancer center; in this manner, the predictive value of these factors cannot be assessed. In addition, serum albumin was evaluated at one point, sometimes at the recently beginning treatment. Changes in serum and whole blood natural chemistry after treatment and in reaction to a medicine and their relationship to survival are of extraordinary interest. They will be the subject of advanced investigation.

Despite these confinements, this consideration is very instructive. This finding recognized a collaborative relationship between serum albumin levels at recent treatment and mortality in NPC patients.

It was not noteworthy after multivariate examination since it was affected by the treatment given. It is suggested that albumin represents one of the clinical biomarkers that seem balanced to move forward. Since albumin can be inspected in regular clinical hone at a moderately fetched, as well as a basic prognostic calculation, it can anticipate and stratify effortlessly to help clinical decision-making in NPC patients.

CONCLUSION

Serum albumin level before therapy could represent a potential predictive biomarker, easy and inexpensive to evaluate the survival of NPC patients. However, serum albumin level was not an independent predictor factor.

CONFLICT OF INTEREST

There are no conflicts of interest declared by either of the contributors.

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