OncoTargets and Therapy

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ORIGINAL RESEARCH

Pretreatment Aspartate Aminotransferase-to-Alanine Aminotransferase (De Ritis) Ratio Predicts the Prognosis of Nonmetastatic Nasopharyngeal Carcinoma

This article was published in the following Dove Press journal:
OncoTargets and Therapy

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Background: The pretreatment aspartate aminotransferase-to-alanine aminotransferase (De Ritis) ratio is reportedly valuable in prognosis prediction of various malignancies. However, its value in the prognosis of nasopharyngeal carcinoma (NPC) has not yet been reported. This study aimed to evaluate the effect of the De Ritis ratio on the survival outcomes of patients with nonmetastatic NPC.

Methods: We retrospectively reviewed the medical data of 1023 patients with nonmetastatic NPC admitted between 2009 and 2013 at a single center. The Fine and Gray competing risk regression model was used to analyze the associations between the De Ritis ratio and the survival outcomes of cancer-specific survival (CSS) and progression-free survival (PFS) by using the subdistribution hazard ratio (SHR) and 95% confidence interval (CI) as size effects. The Cox proportional hazard model was used to evaluate the correlation between the De Ritis ratio and overall survival (OS) by using hazard ratio (HR) and 95% CI as size effects.

Results: Patients were divided into two groups in accordance with the pretreatment De Ritis ratio by using an optimal cutoff value of 1.65. Compared with the patients with low De Ritis ratio (< 1.65), those with elevated De Ritis ratio (≥ 1.65) had poorer prognosis with regard to CSS, PFS, and OS. Notably, multivariate analyses showed that high De Ritis ratio was independently associated with poor CSS (SHR = 1.64, 95% CI: 1.25–2.16), PFS (SHR = 1.69, 95% CI: 1.30–2.19), and OS (HR = 1.81, 95% CI: 1.39–2.40).

Conclusion: Pretreatment De Ritis ratio can be an independent prognostic predictor for patients with nonmetastatic NPC.

Keywords: aspartate aminotransferase-to-alanine aminotransferase ratio, nasopharyngeal carcinoma, prognosis, competing risk model

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Introduction

Nasopharyngeal carcinoma (NPC) is an epithelial carcinoma arising from the nasopharyngeal mucosal lining with a unique geographical and ethnic distribution pattern.[1] Worldwide, it is most prevalent in southern China with an incidence rate of 30 per 100,000 persons, in contrast to 0.4 per 100,000 persons in the US and Europe.[2] Over the past decade, the incidence of NPC has dramatically decreased, even in endemic regions, due to lifestyle and environmental changes, the enhanced understanding of risk factors, and the scale-up of population screening. Moreover, the mortality has been substantially reduced probably due to the improvement of radiotherapy (RT) technology and

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http://doi.org/10.2147/OTT.S232563

chemotherapy regimen. However, approximately 30% of patients with NPC will ultimately suffer distant metastasis and/or locoregional recurrence within a few years after treatment.[3] These high rates of treatment failure emphasize the need for the accurate risk stratification and the appropriate selection of treatment approaches of NPC. Currently, the prognosis of patients with NPC is primarily based on the Tumor-Node-Metastasis (TNM) staging system. However, extreme variation in clinical outcomes has been reported among patients with the same TNM stage who received similar treatment regimens.[4] This phenomenon suggests that the present staging system alone is far from a perfect predictive tool for prognosis and treatment efficacy. The possible explanation is that TNM staging only accounts for anatomical information and does not consider the biological heterogeneity of the tumor. Thus, identifying reliable prognostic factors for screening high-risk patients for complementing the existing staging system and tailored treatment is critical.

Aminotransaminases, including aspartate aminotransaminase (AST) and alanine aminotransaminase (ALT), are the most commonly requested panel for assessing the degree of hepatocellular damage in clinical practice. The ratio of the serum activities of AST and ALT was first reported by De Ritis in 1957 and has been known as the De Ritis ratio thereafter.[5] Over the past several decades, the De Ritis ratio has been widely used in the differentiation of various causes of liver diseases. At present, it has subsequently been shown to be a useful prognostic predictor in several types of malignant tumors, including hepatocellular carcinoma,[6] renal cell cancer,[7] prostate cancer,[8] and upper urinary tract urothelial carcinoma.[9] An elevated level of De Ritis ratio is hypothesized to be associated with increased anaerobic glycolysis, which is also termed as the "Warburg effect".[10] Given that glucose metabolism has a key role in the tumor progression and survival outcomes of NPC, we hypothesized that the De Ritis ratio may have a prognostic effect in patients with NPC.[11,12] However, to date, the prognostic significance of the De Ritis ratio in nonmetastatic NPC had not receive attention, leaving a major gap of evidence. To fill this knowledge gap, we performed this study to investigate the prognostic potential of the pretreatment De Ritis ratio on the oncological outcomes of patients with nonmetastatic NPC from a long-term perspective.

Materials and Methods

Patients and Data Selection

We retrospectively reviewed 1173 patients with nonmetastatic NPC who underwent intensity-modulated radiotherapy (IMRT) at the Affiliated Hospital of Guangdong Medical University from January 2009 to December 2013. The inclusion criteria were as follows: (1) histologically confirmed newly diagnosed NPC; (2) no evidence of metastasis or previous malignant disease; (3) without previous anticancer therapies or surgery; (4) available medical information and laboratory data; and (5) complete follow-up data. After exclusion of 150 patients because of age less than 18 years old (n = 8), chronic hepatitis (n = 29), liver cirrhosis (n = 7), severe fatty liver disease (n = 9), hepatitis B or C virus carriers (n = 42), liver function damage (n = 8), other tumors (n = 21), and infection or inflammatory disease (n = 26), we finally included 1023 patients. This study was approved by the ethics committee of the Affiliated Hospital of Guangdong Medical University. Written informed consent was waived because the study has a retrospective design, but patients' confidentiality was protected by the research institution and the researchers.

The following information was extracted from electronic medical records: demographic characteristics (sex, age, smoking status, and body mass index [BMI]), clinical data (pathological type, clinical stage, T stage, N stage, therapeutic regimen, and RT duration), and pretreatment laboratory measurements (EBV-DNA viral load, AST, and ALT). All baseline laboratory data were assessed within 1 month before any treatment. The serum AST and ALT levels were determined by colorimetric methods through an automatic analyzer. Upper levels of AST and ALT were ≥ 40 U/L and ≥ 35 U/L, respectively. The De Ritis ratio was calculated by dividing the serum AST level by the serum ALT level. All patients were staged in accordance to the Eighth Edition of the Union for International Cancer Control/American Joint Committee on Cancer TNM staging system through a combined assessment with magnetic resonance imaging, chest radiography, abdominal ultrasonography, whole-body bone scanning, and/or positron emission tomography-computed tomography. Patients who had smoked until the date of diagnosis or had stopped less than 1 year ago were defined as present smoking status.

Treatment

Patients with Stages I–IIA were treated with IMRT alone, whereas patients with Stages IIB–IVB were treated with concurrent chemoradiotherapy (CCRT) with or without neoadjuvant or adjuvant chemotherapies. The prescribed cumulative radiation doses were 68–74 Gy to the gross tumor volume, 60–66 Gy to positive nodal areas, and 52–56 Gy to negative nodal regions. The prescribed dose

is the minimum absorbed dose received by 95% of the planning target volume, respectively. CCRT was performed with 30 mg/m^2 cisplatin on day 1, and repeated every week during the period of RT. For patients who received adjuvant chemotherapy, the regimen of docetaxel (75 mg/m^2 intravenous on day 1) plus cisplatin (80 mg/m^2 intravenous on day 1) or cisplatin (80 mg/m^2 intravenous on day 1) plus 5-fluorouracil (1000 mg/m^2 continuously intravenous on days 1–5) or docetaxel (60 mg/m^2 intravenous on day 1) plus cisplatin (60 mg/m^2 intravenous on day 1) plus 5-fluorouracil (800 mg/m^2 intravenous on days 1–4) were repeated every 3 weeks for 2–4 cycles. For patients who underwent neoadjuvant chemotherapy, the abovementioned regimens were repeated every 3 weeks for 3 cycles. Patients with advanced malignancies did not receive chemotherapy due to patient refusal, old age, severe diabetes, heart disease, hepatic or renal function damage, or financial hardship. Dose modification during chemotherapy were conducted if absolute platelet count was < 25,000 cells/μL or absolute neutrophil count was < 500 cells/μL, and chemotherapy was stopped if grade 4 toxic effects developed.

Follow-Up

After finishing all treatment, patients were followed up every 3 months within the first 3 years, every 6 months for the following 2 years, and every year thereafter. The last follow-up date was December 31, 2018. Cancer-specific survival (CSS) was the primary endpoint of this study, and was defined as the time from initial diagnosis to death due to NPC in the absence of other causes. Progression-free survival (PFS) and overall survival (OS) were the secondary endpoints. PFS was defined as the time from the initial diagnosis to the first locoregional relapse and distant metastasis or censored at the last follow-up. OS was defined as the duration between the initial diagnosis and any-cause death or the last follow-up. Treatment-related toxicities were graded by the Common Terminology Criteria for Adverse Events version 4.0.[13]

Definition of Cutoff Values

To avoid a predetermined cutoff point, the most appropriate cutoff values of laboratory variables in this study were determined through a receiver operating characteristic (ROC) curve analysis using CSS as an endpoint. We determined 1.65 as the optimal cutoff value of the De Ritis ratio because it was closest to the point with the maximum sum of sensitivity (0.602) and specificity (0.628) in its prediction of CSS. Similarly, the cutoff value for AST, ALT, and EBV DNA was 35 U/L (sensitivity: 0.535; specificity: 0.557), 31 U/L (sensitivity: 0.610; specificity: 0.514), and 5.5 × 10^4/L (sensitivity: 0.520; specificity: 0.603), respectively.

Statistical Analysis

Baseline characteristics were compared by applying Chi-squared test, Fisher's exact test, or Wilcoxon rank sum test. The effect of De Ritis ratio on OS were calculated through the Kaplan–Meier (KM) method and the difference between groups was compared through the log–rank test. Univariate and multivariate survival analyses were conducted by utilizing the Cox proportional hazards regression model, in which hazard ratios (HRs) and 95% confidence intervals (CIs) were reported. In this study, we defined the noncancer specific death and death before tumor progression as competing events for CSS and PFS, respectively. The impacts of the De Ritis ratio on CSS and PFS were calculated by the cumulative incidence function (CIF) of the competing risk model, and the differences between groups were recognized by the Gray's test.[14] Univariate and multivariate analyses of CSS and PFS were performed by the Fine and Gray proportional subdistribution hazard model, of which size effects were estimated by subdistribution HR (SHR) and 95% CI.[15] All of the statistical analyses were performed with R software version 3.5.3. A two-sided *P* values less than 0.05 was regarded as statistically significant.

Results

Demographic Features

Baseline characteristics at the initial diagnosis are presented in Table 1. Overall, our study included 1023 patients, among whom 715 cases was male (69.9%), and the median age was 50 years old (range: 18–79 years old). More than half of the patients were absent of smoking status or their BMIs were less than 23. Most patients had pathologically confirmed nonkeratinized undifferentiated carcinoma. Among the patients, 403 (59.6%) had Stages III–IV malignancies, 458 patients (44.8%) had advanced T stages (Stage T3–T4), and 188 patients (18.4%) had no clinical nodal involvement (Stage N0). The baseline EBV-DNA viral load ranged from 0 copies/mL to 9.63 × 10^7 copies/mL with a median value of 5.11 × 10^4 copies/mL. A total of 105 patients (10.3%) received IMRT only, while 126 patients (12.3%) underwent CCRT only. Additional chemotherapies prior to or after IMRT

Table 1 Baseline Characteristics of Non-Metastatic Nasopharyngeal Carcinoma Patients (N = 1023)

Patients Characteristics	Total, n (%)	De Ritis Ratio		
		< 1.65, n (%)	≥ 1.65, n (%)	*P*
Age (years old)				0.161
≤ 45	355 (34.7)	244 (36.2)	111 (31.8)	
> 45	668 (65.3)	430 (63.8)	238 (68.2)	
Sex				0.394
Male	715 (69.9)	477 (70.8)	238 (68.2)	
Female	308 (30.1)	197 (29.2)	111 (31.8)	
Smoking status				0.726
Present	432 (42.2)	282 (41.8)	150 (43.0)	
Absent	591 (57.8)	392 (58.2)	199 (57.0)	
Body mass index				0.272
≤ 23	559 (54.6)	360 (53.4)	199 (57.0)	
> 23	464 (45.4)	314 (46.6)	150 (43.0)	
Histological type				0.415
NUC	914 (89.3)	606 (89.9)	308 (88.3)	
NDC	109 (10.7)	68 (10.1)	41 (11.7)	
Clinical stage				0.401
I	97 (9.5)	64 (9.5)	33 (9.5)	
II	207 (30.9)	207 (30.7)	109 (31.2)	
III	277 (39.6)	277 (41.1)	128 (36.7)	
IV	126 (20.0)	126 (18.7)	79 (22.6)	
T stage				0.015
T1	316 (30.9)	221 (32.8)	95 (27.2)	
T2	249 (24.3)	172 (25.5)	77 (22.1)	
T3	303 (29.6)	194 (28.8)	109 (31.2)	
T4	155 (15.2)	87 (12.9)	68 (19.5)	
N stage				0.204
N0	188 (18.4)	135 (20.0)	53 (15.2)	
N1	199 (19.5)	127 (18.8)	72 (20.6)	
N2	551 (53.9)	353 (52.4)	198 (56.7)	
N3	85 (8.2)	59 (8.8)	26 (7.5)	
EBV-DNA (copies/mL)				0.582
≤ 5.5×10^4	490 (47.9)	327 (48.5)	163 (46.7)	
> 5.5×10^4	533 (52.1)	347 (51.5)	186 (53.3)	
Therapeutic regimen				0.675
RT alone	105 (10.3)	69 (10.2)	36 (10.3)	
CCRT	126 (12.3)	83 (12.3)	43 (12.3)	
CCRT plus NACT	385 (37.6)	262 (38.9)	123 (35.2)	
CCRT plus ACT	407 (39.8)	260 (38.6)	147 (42.2)	
RT duration (weeks)				0.144
≤ 7	475 (46.4)	324 (48.1)	151 (43.3)	
> 7	548 (53.6)	350 (51.9)	198 (56.7)	
AST (U/L)				< 0.001
≤ 35	591 (57.8)	417 (61.9)	174 (49.9)	
> 35	432 (42.2)	257 (38.1)	185 (50.1)	

(*Continued*)

Table 1 (Continued).

Patients Characteristics	Total, n (%)	De Ritis Ratio		
		< 1.65, n (%)	≥ 1.65, n (%)	*P*
ALT (U/L)				< 0.001
≤ 31	505 (49.4)	292 (43.3)	212 (59.1)	
> 31	518 (50.6)	382 (56.7)	147 (40.9)	

Abbreviations: NUC, nonkeratinizing undifferentiated carcinoma; NDC, nonkeratinizing differentiated carcinoma; RT, radiotherapy; CCRT, concurrent radiotherapy; NACT, neoadjuvant chemotherapy; ACT, adjuvant chemotherapy; AST, aspartate aminotransaminase; ALT, alanine aminotransaminase.

were administered to 385 (37.6%) and 407 (39.8%) patients, respectively. The median RT duration was 7 weeks. The details of chemotherapy are listed in Supplementary Table 1.

Association Between the De Ritis Ratio and Clinicopathological Features

The patients were divided into two groups according to the optimal cut-off value of the De Ritis ratio (De Ritis ratio < 1.65, n = 674; De Ritis ratio ≥ 1.65, n = 349). As shown in Table 1, the clinicopathological characteristics of the two groups were compared. The patients with elevated De Ritis ratio had significantly higher AJCC T classifications ($P = 0.015$), elevated serum AST levels ($P < 0.001$), and lower serum ALT levels ($P < 0.001$). However, the De Ritis ratio was not significantly related to age, sex, smoking status, BMI, histological type, clinical stage, N stage, EBV-DNA viral load, therapeutic regimen, and RT duration in patients with NPC ($P > 0.05$).

Correlation Between the De Ritis Ratio and Prognosis

The median follow-up time of all patients was 46 months (range: 1–102 months). The 5-year CSS, PFS, and OS of the entire cohort were 75.6%, 74.9%, and 65.8%, respectively. The 5-year CSS, PFS, and OS rates of patients with low (< 1.65) versus elevated (≥ 1.65) De Ritis ratio levels were 79.6% vs 68.9% ($P < 0.001$, Figure 1A), 79.4% vs 65.7% ($P < 0.001$, Figure 1B), and 72.5% vs 60.5% ($P < 0.001$, Figure 1C), respectively.

We further evaluated the survival outcomes of patients with different De Ritis ratio in different subgroups (Table 2). After stratification by T stage, patients with elevated De Ritis levels also had worse 5-year CSS, PFS, and OS than patients with low De Ritis ratio. With regard to the patients who only received RT, the 5-year rates of CSS, PFS, and OS were much higher in patients with low De Ritis ratio levels than those with elevated De Ritis ratio levels.

Univariate analyses indicated that patients with NPC with elevated De Ritis ratios before treatment had poor CSS (SHR = 1.71, 95% CI: 1.32–2.23, Table 3), PFS (SHR = 1.75, 95% CI: 1.35–2.19, Table 3), and OS (HR = 2.02, 95% CI: 1.66–3.11, Table 4). Moreover, multivariate analyses suggested that the De Ritis ratio was an independent prognostic factor for CSS (SHR = 1.64, 95% CI: 1.25–2.16, Table 3), PFS (SHR = 1.69, 95% CI: 1.30–2.19, Table 3), and OS (HR = 1.81, 95% CI: 1.39–2.40, Table 4). The results of univariate and multivariate analyses of pretreatment De Ritis ratio and

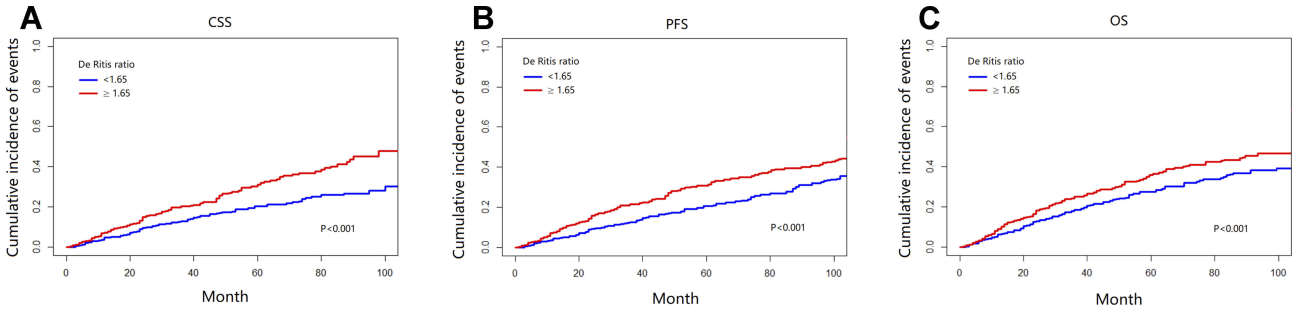

Figure 1 Cumulative incidence of cancer-specific death (**A**), progression-related death (**B**), and all-cause death (**C**) in patients with pretreatment De Ritis ratio ≥ 1.65 or < 1.65. We defined the cancer-specific death as the targeted event for cancer-specific survival, progression related death for progression-free survival, and all-cause death for overall survival. The cumulative incidence function considering competing risk was used to obtain the curves of cancer-specific death and progression-related death, while the Kaplan-Meier method was used to obtain the curve of all-cause death.

Table 2 Comparison of the Impact of De Ritis Ratio on Prognosis in Different Subgroups

Category	n	5-Year CSS (%)	*P* value	5-Year PFS (%)	*P* Value	5-year OS (%)	*P* Value
T1-2			< 0.001		< 0.001		< 0.001
De Ritis ratio < 1.65	393	88.0		87.6		80.1	
De Ritis ratio ≥ 1.65	172	75.7		73.3		68.7	
T3-4			0.003		0.002		< 0.001
De Ritis ratio < 1.65	281	71.3		72.2		66.4	
De Ritis ratio ≥ 1.65	177	62.6		62.9		53.5	
RT alone			0.012		0.016		0.023
De Ritis ratio < 1.65	69	84.1		84.5		77.4	
De Ritis ratio ≥ 1.65	36	73.4		73.9		68.2	

Notes: The 5-year CSS and PFS was calculated by the cumulative incidence function considering competing risk, while the 5-year OS was calculated by the Kaplan-Meier method.
Abbreviations: CSS, cancer-specific survival; PFS, progression-free survival; OS, overall survival; RT, radiotherapy.

other factors concerning survival outcomes for patients with NPC are showed in Tables 3 and 4.

Discussion

To our knowledge, this is the first study to explore the prognostic value of the pretreatment De Ritis ratio in patients with nonmetastatic NPC. The key findings of this study were as follows: (1) patients with NPC with elevated pretreatment De Ritis ratio (≥ 1.65) had unfavorable survival outcomes in terms of CSS, PFS, and OS; and (2) the De Ritis ratio rather than AST or ALT alone can be a significant independent predictor of cancer-specific death, progression-related death, and all-cause death. Furthermore, an elevated level of pretreatment De Ritis ratio was highly prominent among NPC patients with advanced T stages, indicating that these patients may benefit most from the evaluation of the pretreatment De Ritis ratio for clinical decision-making. Therefore, we believe that the De Ritis ratio might become a promising tool for the identification of patients with nonmetastatic NPC who have a high risk of poor survival outcomes.

To date, numerous studies have reported the effect of aminotransaminases on the prognosis of various cancers regardless of the presence of liver-specific disease.[16–18] In contrast to those of tissue biomarkers, the examinations of aminotransaminases are routine laboratory tests performed upon admission, with simple, noninvasive, and inexpensive operation. Moreover, they can be conveniently conducted in most hospitals. For the purposes of clinical practice, a predictive parameter would generally have great potential if it can be easily obtained at a low cost through routine measures. Nevertheless, although the single measures of AST or ALT are associated with the prognosis of patients with various cancer types, they are not perfect predictors because they are sensitive to various other nontumor-related factors, such as chronic hepatitis, coronary heart disease, renal function damage, and drugs.[19] By contrary, the De Ritis ratio reflects the combination of AST and ALT, and is stable because it has counteracted the effects of other factors.[20] Thus, all laboratory reports are recommended to include ALT and AST for the calculation of the De Ritis ratio, which provides valuable information for clinical decision.[21]

Generally, AST is widely expressed in various types of tissues, whereas ALT is enriched in liver tissues. The pathological processes of high proliferative status and tissue damage can increase the level of circulating AST but not that of ALT. In this context, the De Ritis (AST/ALT) ratio can serve as a potential biomarker. Initially, the association of the De Ritis ratio and cancer was primarily discussed in liver cancer or liver metastasis. Several recent studies have reported the prognostic value of the De Ritis ratio in several types of malignancies except for liver malignancies. For example, Lee et al[22] showed that elevated De Ritis ratio exceeding 1.5 is significantly associated with poor postoperative survival in patients with renal cell carcinoma (RCC). Moreover, Canat et al[23] demonstrated that an increased preoperative De Ritis ratio has a significant association with renal vein invasion and renal capsule infiltration but is not an independent prognostic marker in nonmetastatic RCC. Miyake et al[8] retrospectively analyzed 74 patients with metastatic prostate cancer and concluded that the assessment of the De Ritis ratio may provide useful prognostic, but not predictive, information. Ha et al[24] also reported that the De Ritis ratio might further improve the predictive accuracy for

Table 3 Univariate and Multivariate Analyses of Cancer-Specific Survival and Progression-Free Survival by Fine and Gray Proportional Sub-Distribution Hazard Model

Variables	Cancer-Specific Survival				Progression-Free Survival			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	SHR (95% CI)	*P* value	SHR (95% CI)	*P* value	SHR (95% CI)	*P* value	SHR (95% CI)	*P* value
Age (years old)								
≤ 45	1		1		1		1	
> 45	1.25 (1.09–1.31)	0.001	1.18 (1.07–1.29)	0.003	1.11 (1.05–1.45)	0.031	1.08 (1.02–1.24)	0.044
Sex								
Male	1		1		1		1	
Female	0.70 (0.51–0.96)	0.024	0.66 (0.51–0.95)	0.029	0.76 (0.55–0.90)	0.035	0.72 (0.58–0.98)	0.047
Smoking status								
Yes	1				1			
No	0.83 (0.55–1.24)	0.539			1.33 (0.97–1.82)	0.075		
Histological type								
NUC	1				1			
NDC	1.06 (0.74–1.56)	0.773			1.13 (0.84–1.67)	0.311		
T stage								
T1	1		1		1		1	
T2	1.65 (1.12–2.46)	0.012	1.55 (1.03–2.33)	0.035	1.73 (1.19–2.53)	0.005	1.63 (1.10–2.40)	0.014
T3	1.95 (1.33–2.87)	0.001	1.78 (1.25–2.81)	0.023	2.24 (1.54–3.27)	0.001	2.02 (1.30–2.86)	0.005
T4	2.25 (1.70–3.23)	< 0.001	2.08 (1.51–3.02)	0.006	2.68 (1.85–3.75)	< 0.001	2.35 (1.55–3.28)	0.002
N stage								
N0	1		1		1		1	
N1	1.56 (1.30–2.09)	0.008	1.49 (1.27–2.01)	0.025	1.50 (1.16–2.00)	0.012	1.42 (1.13–1.92)	0.030
N2	1.75 (1.49–2.51)	< 0.001	1.61 (1.40–2.33)	< 0.001	1.97 (1.45–2.77)	< 0.001	1.80 (1.32–2.56)	< 0.001
N3	2.24 (1.64–2.92)	< 0.001	2.08 (1.58–2.76)	< 0.001	2.69 (2.18–3.80)	< 0.001	2.41 (1.99–3.38)	< 0.001
EBV-DNA (copies/mL)								
≤ 5.5×10^4	1		1		1		1	
> 5.5×10^4	1.61 (1.30–2.28)	0.005	1.46 (1.11–1.95)	0.010	1.63 (1.24–2.89)	0.003	1.47 (1.08–2.54)	0.030
Therapeutic regimen								
RT alone	1				1			
CCRT	0.84 (0.57–1.25)	0.387			0.79 (0.55–1.13)	0.200		
CCRT plus NACT	0.63 (0.38–1.02)	0.059			0.70 (0.48–1.03)	0.068		
CCRT plus ACT	0.77 (0.50–1.17)	0.217			0.85 (0.63–1.17)	0.310		
RT duration (weeks)								
≤ 7	1				1			
> 7	0.93 (0.69–1.20)	0.450			0.95 (0.59–1.53)	0.834		
AST (U/L)								
≤ 35	1							
> 35	1.19 (1.04–1.44)	0.038			1.14 (0.95–1.41)	0.101		
ALT (U/L)								
≤ 31	1				1			
> 31	0.88 (0.54–1.35)	0.556			0.91 (0.59–1.30)	0.487		
De Ritis ratio								
≤ 1.65	1		1		1		1	
> 1.65	1.71 (1.32–2.23)	< 0.001	1.64 (1.25–2.16)	< 0.001	1.75 (1.35–2.25)	< 0.001	1.69 (1.30–2.19)	< 0.001

Abbreviations: SHR, sub-distribution hazard ratio; CI, confidence interval; NUC, nonkeratinizing undifferentiated carcinoma; NDC, nonkeratinizing differentiated carcinoma; RT, radiotherapy; CCRT, concurrent radiotherapy; NACT, neoadjuvant chemotherapy; ACT, adjuvant chemotherapy.

Table 4 Univariate and Multivariate Analyses of Overall Survival by Cox Proportion Hazard Regression

Variables	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age (years old)						
≤ 45	1			1		
> 45	1.27	1.15–1.51	0.011	1.14	1.08–1.49	0.027
Sex						
Male	1					
Female	0.75	0.60–0.86	0.002	0.66	0.50–0.95	0.030
Smoking status						
Present	1					
Absent	0.74	0.43–1.33	0.377			
Body mass index						
≤ 23	1					
> 23	1.32	0.92–1.89	0.256			
Histological type						
NUC	1					
NDC	1.20	0.77–1.75	0.442			
T stage						
T1	1			1		
T2	1.53	1.11–2.10	0.010	1.23	1.04–1.79	0.040
T3	1.73	1.24–2.40	0.001	1.61	1.15–2.44	0.004
T4	2.45	1.73–3.44	< 0.001	2.15	1.27–3.63	< 0.001
N stage						
N0	1			1		
N1	1.61	1.22–2.12	0.007	1.26	1.08–1.95	0.021
N2	1.87	1.31–2.68	0.001	1.69	1.20–2.38	0.003
N3	2.26	1.52–2.99	< 0.001	2.05	1.34–2.61	< 0.001
EBV-DNA (copies/mL)						
≤ 5.5×10^4	1			1		
> 5.5×10^4	1.45	1.15–1.82	0.001	1.37	1.07–1.76	0.013
Therapeutic regimen						
RT alone	1					
CCRT	0.65	0.35–1.31	0.469			
CCRT plus NACT	0.97	0.47–1.56	0.627			
CCRT plus ACT	1.15	0.76–1.33	0.237			
RT duration						
≤ 7	1					
> 7	0.64	0.31–1.14	0.099			
AST (U/L)						
≤ 35	1					
> 35	1.22	0.75–2.03	0.733			
ALT (U/L)						
≤ 31	1					
> 31	0.85	0.44–2.99	0.616			

(*Continued*)

Table 4 (Continued).

Variables	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
De Ritis ratio						
≤ 1.65	1			1		
> 1.65	2.02	1.66–3.11	< 0.001	1.81	1.39–2.40	< 0.001

Abbreviations: HR, hazard ratio; CI, confidence interval; NUC, nonkeratinizing undifferentiated carcinoma; NDC, nonkeratinizing differentiated carcinoma; RT, radiotherapy; CCRT, concurrent radiotherapy; NACT, neoadjuvant chemotherapy; ACT, adjuvant chemotherapy.

prognosis in bladder cancer. Takendaka et al[25] was the first to report the prognostic value of the De Ritis ratio in head and neck cancer. They found that a high De Ritis ratio is significantly related to poor prognosis among patients with Stage IVA. Thus, these patients can be considered as candidates for intensified treatment.

Oxidative phosphorylation (OXPHOS) and glycolysis are the two major energy-producing pathways in cells. Normal cells rely on OXPHOS for energy supply, whereas cancer cells favor a metabolic shift toward anaerobic glycolysis rather than OXPHOS even under the condition of sufficient oxygen. Moreover, the high rate of aerobic glycolysis not only renders cancer cells prone to resist hypoxia but also provides increased glycolytic intermediates for the biosynthesis of cellular building blocks, including nucleotides, amino acids, and lipids, to satisfy their rapid proliferation.[26] AST has a vital role in aerobic glycolysis through the malate-aspartate shuffle pathway. The pathological conditions associated with cancer progression, such as rapidly growing cancer tissues and normal tissue damage, can lead result in the higher activation of AST than that of ALT.[19] In vitro experiments have shown that decreased ALT level is more likely observed in more invasive cancer cells than in less invasive cancer cells, and more invasive cancer cells consume glucose to a greater extent.[27] Several oncogenes have been identified to promote the glycolysis of NPC cells, suggesting that glycolysis plays an important role in the progression of NPC.[28] Thus, the De Ritis ratio may reflect the metabolic alterations in this glucose-utilizing cancer. These alterations are possibly related to tumor progression and prognosis.

The strength of our study lies in the competing risk analysis used to address competing events. With the rapid aging of the population in China, the number of elderly patients with NPC is increasing with the increase in the incidence of concurrent comorbidities.[29] In our study, patients aged older than 45 years old accounted for approximately 2/3 of the entire cohort. These patients are vulnerable to competing events, such as death from noncancer diseases. Competing events, which are common in the medical literature, prevent the targeted events from occurring, indicating that patients suffering a competing event have an outcome risk of zero.[30] In the presence of competing events, traditional survival analyses, including the KM method and Cox regression model, often overestimate the true outcome risk because they treat competing events as independent censors and assume that the outcome risk of patients with competing events is the same as those of other patients in the cohort.[31] Instead, competing risk methods based on the CIF and subdistribution hazard model offer a suitable approach because they account for the informative nature of censoring and effectively discriminate the effects of risk factors on specific events.[32]

Several limitations of the present study should be acknowledged. First, the data were retrospectively retracted from medical records without a consistent clinical data collection and record-keeping. Second, this is a single-center study that lacks external validation for the further examination of the prognostic value of the De Ritis ratio. Third, the optimal cutoff of the De Ritis ratio also requires further validation. Fourth, due to undetected liver disease or drug interactions, the De Ritis ratio might have changed during the treatment course. Whether this dynamic change can predict prognosis remains uncertain. Future prospective studies are necessary to emphasize the prognostic value of this index and basic researches are also needed to uncover the underlying mechanisms of the De Ritis ratio.

Conclusion

This study was the first to investigate the effect of the pretreatment De Ritis ratio on survival outcomes in patients with nonmetastatic NPC. The results of this work showed that increased pretreatment De Ritis ratio was significantly

associated with poor CSS, PFS, and OS. Given the De Ritits ratio's advantages of simplicity, inexpensiveness, reproducibility, and easy application, it is considered useful in predicting the prognosis of patients with nonmetastatic NPC. Moreover, applying the pretreatment De Ritis ratio in counseling patients concerning expected outcomes and developing the optimal therapeutic strategy can be beneficial because it may provide more detailed prognostication.

Acknowledgments

This study was supported by Guangdong Province Science and Technology Development of Special Funding Support Project (No. 2016A020215151) and Zhanjiang Science and Technology Development Special Funds Competitive Allocation Project (No. 2018A01026). The funding agency had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Disclosure

The authors report no conflicts of interest in this work.

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