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Preoperative Neutrophil-to-lymphocyte Ratio Predicts Long-term Survival in Patients Undergoing Total Laryngectomy With Advanced Laryngeal Squamous Cell Carcinoma

A Single-center Retrospective Study

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Abstract: There is increasing evidence that the neutrophil-to-lymphocyte ratio (NLR) is a stage-independent predictor of poor outcome in patients with cancer. The purpose of this study was to investigate the association between cancer-specific survival (CSS), overall survival (OS), and the preoperative NLR in patients with advanced laryngeal squamous cell carcinoma (LSCC) undergoing total laryngectomy (TL).

All patients with a new diagnosis of advanced laryngeal cancer (stages III and IV) presenting at the Department of Head and Neck Oncology, Sun Yat-sen University Cancer Center between January 1990 and July 2010 (n = 420) were included. To evaluate the independent prognostic relevance of the NLR, univariate and multivariate Cox regression models were used. CSS and OS were estimated using the Kaplan-Meier method.

Four-hundred twenty patients were enrolled in this study. Patients with an NLR ≥2.59 showed a significantly lower CSS ($P = .014$) and OS ($P = .032$) than patients with an NLR <2.59. The Cox proportional multivariate hazard model showed that a higher preoperative NLR was independently correlated with a poor CSS and OS, with hazard ratios of 1.42 (95% confidence interval [CI] 1.06–1.91, $P = .018$) and 1.31 (95% CI 1.00–1.71, $P = .046$), respectively.

The NLR may be an independent prognostic marker for CSS and OS in patients with advanced LSCC undergoing TL.

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Abbreviations: AUC = area under the curve, CIs = confidence intervals, CSS = cancer-specific survival, HRs = hazard ratios, LSCC = laryngeal squamous cell carcinoma, NLR = neutrophil-to-lymphocyte ratio, OS = overall survival, ROC = receiver operating characteristic, SYSUCC = Sun Yat-sen University Cancer Center, TL = total laryngectomy.

INTRODUCTION

Laryngeal cancer is one of the most common cancers of the respiratory system, with almost 10,000 and 2630 new cases diagnosed in men and women, respectively, in the United States in 2014. It is estimated that about 3610 Americans will die of laryngeal squamous cell carcinoma (LSCC) this year.[1] This review of data from the National Cancer Data Base analysis confirms the previously identified trend toward a decreasing 5-year survival among patients with laryngeal cancer in the recent years (from 57.1% to 51.9%).[2]

Total laryngectomy (TL) with or without lymph node dissection of the neck region is still the standard treatment for advanced laryngeal cancer (stages III and IV), although larynx preservation is a viable alternative.[3] There is deep interest in the interpretation of prognostic and predictive biomarkers that will improve clinical outcomes for patients classified with stages III and IV laryngeal cancer. The most commonly used predictor for LSCC is the TNM classification system, but the effect of these measures may be limited. In addition, over the past 2 decades, many studies have been conducted to identify novel biomarkers characterizing patients with a poor prognosis,[4–6] but the application of these biomarkers in routine clinical practice is limited because of inherent shortages such as the expense, lack of standardization, regional availability, and need for further validation. Thus, a clinically useful parameter to predict survival that can be measured and repeated without difficulty is needed.

Recent data have shown that inflammation is a critical component of tumor progression, and it is associated with a poor prognosis in various tumors, as an oncogenic change induces an inflammatory microenvironment that promotes the development of tumours.[7–11]Studies have shown that a high level of neutrophils is associated with angiogenesis, which plays an important role in the growth and metastasis of malignancy. Furthermore, DNA damage and tumor metastasis suppress lymphocyte activity through the upregulation of cytokines that counteract the antitumor immune response.[7,12]

Markers of inflammation such as the neutrophil-to-lymphocyte ratio (NLR) have been evaluated in various types of cancer, including colorectal cancer, breast cancer, small-cell lung cancer, and large B-cell lymphoma, as a prognostic indicator.[13–16] NLR was shown to be increased in laryngeal carcinoma compared with that in benign laryngeal lesions, precancerous laryngeal lesions, and a healthy control group.[17,18] However, to our knowledge, the prognostic significance of NLR in patients with advanced LSCC is unclear.

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We hypothesized that inflammation is associated with the LSCC prognosis and that NLR may be a good indicator of the inflammatory process. Therefore, in this retrospective study, the association between NLR and the prognosis of patients with LSCC who underwent TL was evaluated.

METHODS

The institutional review board of the Sun Yat-sen University Cancer Center (SYSUCC) (Guangdong, China) approved the study, and all procedures were performed in accordance with the Declaration of Helsinki.

Patient Selection

A retrospective study was conducted using a primary cohort of consecutive patients undergoing TL as first curative treatment option for advanced LSCC between January 1990 and July 2010 at the SYSUCC. Inclusion criteria were the following: TL as first curative treatment option, histopathologically proven LSCC, no history of anticancer therapy, no history of other malignancies, and no distant metastasis. Exclusion criteria were as follows: tumors of uncertain origin or probable metastatic laryngeal tumor, mixed type of primary laryngeal cancer confirmed histopathologically, perioperative mortality, and a history of inflammatory disease or active concomitant infection. Four hundred twenty-five patients with LSCC were included. Five patients had incomplete preoperative laboratory data so 420 patients with LSCC were finally included in the present study (Supplementary Figure 1, http://links.lww.com/MD/A680). Patients were followed up every 3 months during the first 2 years, and every 6 months thereafter until death by telephone.

Study Variables

All of the clinicopathological data were retrieved from patients' medical records at the SYSUCC. Clinicopathological parameters included histologically confirmed LSCC, age, sex, smoking status, drinking status, neck dissection, tumor subsite, T stage, N stage, TNM stage, and pathological differentiation. The conventional TNM staging system for laryngeal cancer established by the Union for International Cancer Control and the American Joint Committee on Cancer was used.[19] Laboratory data, including the neutrophil and lymphocyte counts, were obtained by preoperative examination. Cancer-specific survival (CSS) was defined as the time in months from the date of the surgery until death because of intercurrent disease. Overall survival (OS) was defined as the time in months from the date of surgery until death because of any cause within the follow-up period.

Statistical Analysis

Optimal cutoff values for the NLR were determined using receiver-operating characteristic (ROC) curves. These curves were used to select cutoff scores for dichotomizing the NLR based on the score with the maximum area under the ROC curve and maximum sensitivity and specificity. The NLR was calculated from the differential counts by dividing the neutrophil number by the lymphocyte number. The NLR values were categorized into 2 groups: <2.59 and ≥ 2.59. Survival curves were calculated using the Kaplan–Meier method and compared using the log-rank test. Multivariate analysis was performed with the Cox proportional hazards model to test independent significance while adjusting for covariates; data are presented as hazard ratios (HRs) and 95% confidence intervals (CIs). Variables that were shown to be significant in the univariate analysis were evaluated in the multivariate Cox proportional hazard model. All analyses were performed using IBM SPSS statistics software, version 20.0 (SPSS, Inc, Chicago, IL). P values <0.05 in the 2-tailed test were considered significant.

RESULTS

Patients' Characteristics and Outcomes

Four hundred twenty patients with LSCC undergoing TL were included in our study. The median observation period (from the day of surgery to the final date) for the entire study population was 62.28 months. Baseline characteristics of the study population are shown in Table 1. The present study included 413 men (98.3%) and 7 women (1.7 %) with a median age of 60 ± 9.1 years (range 33–84 years). The majority of patients were current or ex-smokers (n = 383, 91.2%), and 159 (37.9%) had a history of alcohol intake. The site of the primary tumor was almost distributed between the glottis (206 [49.0%]) and supraglottic larynx (198 [47.1%]). One hundred ninety-nine patients (47.4%) underwent neck dissection. Of them, 256 (61.0%) had a T3 in tumor stage, and 164 (39.0%) had a T4 in tumor stage. One hundred forty-three patients (34.0%) had lymph node metastasis.

For the NLR, a cutoff of 2.59 was generated according to the ROC analysis in the training set for CSS (sensitivity 55.8%, specificity 58.8%, area under the curve [AUC] 0.57, 95% CI 0.52–0.63, $P = 0.028$; Figure 1A) and OS (sensitivity 56.6%, specificity 63.6%, AUC 0.61, 95% CI 0.55–0.66, $P = 0.028$; Figure 1B).

Univariate and Multivariate Analysis of Prognostic Factors

The estimated 5-year CSS of the 420 patients was 59.3%, and the 5-year OS was 58.0% (Figure 2).

Results of the Cox regression hazards model for predictors of CSS are shown in Table 2. In univariate analyses, age, a

TABLE 1. Patients' Clinicopathological Characteristics

Characteristics	Values
Age, y*	60 ± 9.1 (33–84)
Sex (male/female)	413 (98.3)/7 (1.7)
Smoking (no/yes)	37 (8.8)/383 (91.2)
Drinking (no/yes)	261 (62.1)/159 (37.9)
Neck dissection (no/yes)	221 (52.6)/199 (47.4)
Tumor subsite (supraglottic/glottic/subglottic)	198 (47.1)/206 (49.0)/16 (3.8)
T stage (T3/T4)	256 (61.0)/164 (39.0)
N stage (N0/N1–3)	277 (66.0)/143 (34.0)
†TNM stages (III/IV)	220 (52.4)/200 (47.6)
Pathological type (highly/moderately /poorly)	147 (35.0)/186 (44.3)/87 (20.7)
NLR ($<2.59/\geq 2.59$)	218 (51.9)/202 (48.1)

Values in parentheses are percentages unless indicated otherwise. N = node, NLR = neutrophil-to-lymphocyte ratio, T = tumor.

* Value is the median (range).

† According to the 7th American Joint Committee on Cancer staging system.

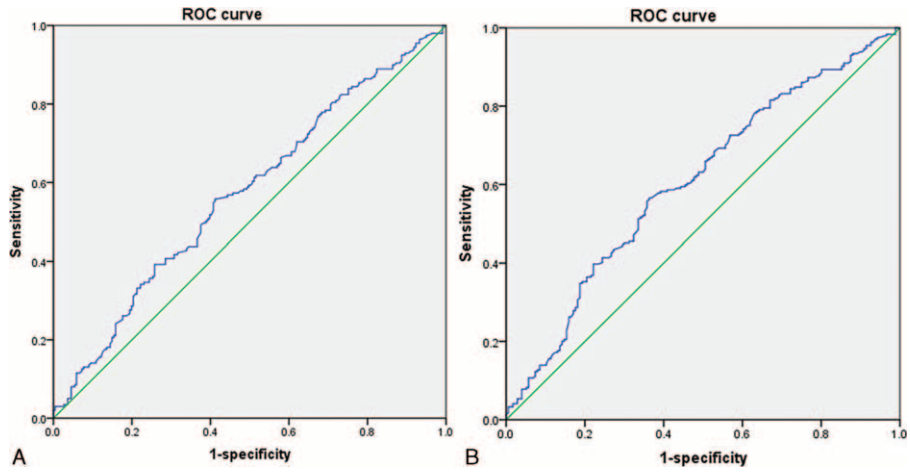

FIGURE 1. (A) ROC analysis based on NLR for cancer-specific survival. In this model, sensitivity was 55.8% and specificity was 58.8%. The AUC was 0.57 (95% CI 0.52–0.63, $P = 0.028$). (B) ROC analysis based on NLR for overall survival. In this model, sensitivity was 56.6% and specificity was 63.6%. The AUC was 0.61 (95% CI 0.55–0.66, $P = .028$). AUC = area under the curve, CI = confidence interval, NLR = neutrophil-to-lymphocyte ratio, ROC = receiver operating characteristics.

history of alcohol intake, neck dissection, the tumor subsite, T stage, N stage, TNM stage, pathological differentiation, and the NLR were significant predictors of CSS. In multivariate analysis, a high NLR (HR 1.42 [95% CI 1.06–1.91], $P = 0.018$), age, a history of alcohol intake, and N stage remained significant independent predictors of CSS. As shown in Figure 3A, the 5-year CSS rates of the patients with an NLR $\geq$2.59 (54.0%) were significantly lower ($P = 0.014$, log-rank test) than those of patients with an NLR <2.59 (64.3%).

In Table 3, factors associated with poor OS were age, a history of alcohol intake, neck dissection, the tumor subsite, T stage, N stage, TNM stage, pathological differentiation, and the NLR at any time. The NLR (HR 1.31, 95% CI 1.00–1.71, $P = 0.046$), age, a history of alcohol intake, and N stage were included in the multivariate analysis. As shown in Figure 3B, the 5-year OS rates of the patients with an NLR $\geq$2.59 (52.8%) were significantly lower ($P = 0.032$, log-rank test) than those of patients with an NLR <2.59 (63.0%).

DISCUSSION

Recently, numerous studies have shown that the pretreatment NLR is a predictor of clinical outcome in various malignancies.[20] Nevertheless, the prognostic significance of the NLR with other clinical factors in patients with LSCC was first reviewed in this study. In our study, the preoperative NLR was an independent prognostic factor for reduced CSS and OS in patients with LSCC who underwent TL. Therefore, it could be used to estimate tumor prognosis at the beginning of treatment.

NLR and Cancer

The NLR is now routinely measured as part of the cancer work-up, as it is easily calculated from the white blood cell count and is universally available. However, the clinical relevance of the NLR is complicated because it represents a combination of factors related to both inflammation and host

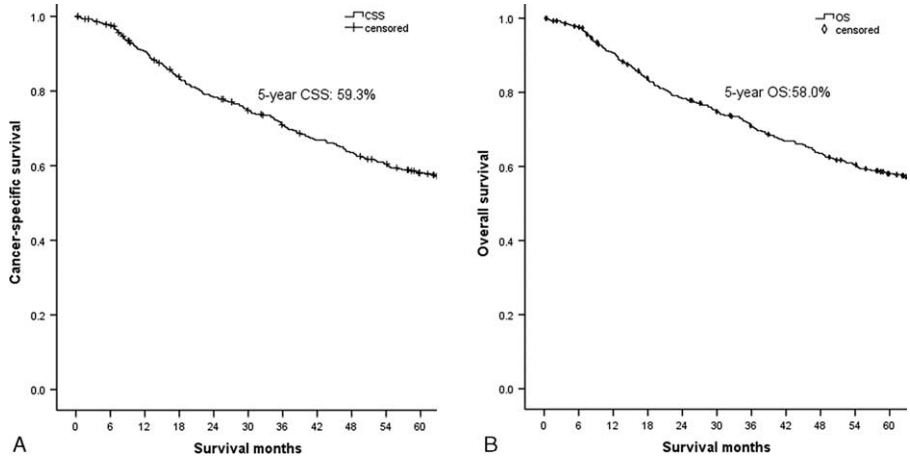

FIGURE 2. (A) The estimated 5-year CSS of the 420 patients was 59.3%, and (B) the 5-year OS of these patients was 58.0%. CSS = cancer-specific survival, OS = overall survival.

TABLE 2. Cox Regression Analyses for Cancer-specific Survival in Laryngeal Squamous Cell Carcinoma

	Univariate		Multivariate	
Characteristics	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Age, y				
<60	1.00	0.001	1.00	0.001
≥60	1.61 (1.21–2.15)		1.65 (1.23–2.21)	
Sex				
Female	1.00	0.934	nd	nd
Male	1.05 (0.34–3.28)			
Smoking				
No	1.00	0.672	nd	nd
Yes	1.12 (0.67–1.86)			
Drinking				
No	1.00	0.019	1.00	0.037
Yes	1.40 (1.06–1.86)		1.36 (1.02–1.83)	
Neck dissection				
No	1.00	0.002		NS
Yes	1.57 (1.18–2.09)			
Tumor subsite				
Supraglottic	1.00	0.005		NS
Glottic	0.63 (0.47–0.84)			
Subglottic	0.55 (0.24–1.25)			
T stage				
T3	1.00	0.034		NS
T4	1.36 (1.02–1.81)			
N stage				
N0	1.00	<0.001	1.00	<0.001
N1–3	2.24 (1.68–2.98)		2.30 (1.51–3.50)	
*TNM stage				
III	1.00	0.004		NS
IV	1.52 (1.14–2.01)			
Histological type				
Highly	1.00	0.012		NS
Moderately	0.99 (0.72–1.36)			
Poorly	1.62 (1.12–2.33)			
NLR				
<2.59	1.00	0.015	1.00	0.018
≥2.59	1.42 (1.07–1.88)		1.42 (1.06–1.91)	

CI = confidence interval, HR = hazard ratio, N = node, nd = not done, NLR = neutrophil-to-lymphocyte ratio, NS = not significant, T = tumor.

* According to the 7th American Joint Committee on Cancer staging system.

TABLE 3. Cox Regression Analyses for Overall Survival of Laryngeal Squamous Cell Carcinoma

	Univariate		Multivariate	
Characteristics	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Age, y				
<60	1.00	<0.001	1.00	<0.001
≥60	1.88 (1.44–2.44)		1.89 (1.45–2.47)	
Sex				
Female	1.00	0.860	nd	nd
Male	1.09 (0.41–2.94)			
Smoking				
No	1.00	0.842	nd	nd
Yes	1.05 (0.67–1.63)			
Drinking				
No	1.00	0.014	1.00	0.046
Yes	1.38 (1.07–1.79)		1.31 (1.00–1.71)	
Neck dissection				
No	1.00	0.001		NS
Yes	1.55 (1.19–2.02)			
Tumor subsite				
Supraglottic	1.00	0.002		NS
Glottic	0.63 (0.49–0.82)			
Subglottic	0.56 (0.26–1.21)			
T stage				
T3	1.00	0.006		NS
T4	1.44 (1.11–1.87)			
N stage				
N0	1.00	<0.001	1.00	<0.001
N1–3	2.07 (1.59–2.71)		2.01 (1.36–2.97)	
*TNM stage				
III	1.00	<0.001		NS
IV	1.59 (1.23–2.07)			
Histological type				
Highly	1.00	0.006		NS
Moderately	0.91 (0.68–1.21)			
Poorly	1.54 (1.10–2.16)			
NLR				
<2.59	1.00	0.032	1.00	0.046
≥2.59	1.32 (1.02–1.71)		1.31 (1.00–1.71)	

CI = confidence interval, HR = hazard ratio, nd = not done, N = node, NLR = neutrophil-to-lymphocyte ratio, NS = not significant, T = tumor.

* According to the 7th American Joint Committee on Cancer staging system.

immunity. Recent studies have confirmed a link between the local inflammatory microenvironment that is favorable for tumor growth and metastasis of a tumor, and systemic responses induced by the tumor. Moreover, lymphocytopenia indicates a generalized state of immunodepression.[7,21]

The rationale of the NLR is to compare the host's inflammatory response (ie, the neutrophils) to cancer with the host's immune response (ie, the lymphocytes). A high NLR means an increased neutrophil count and/or a decreased lymphocyte count. High levels of neutrophil infiltration, in response to an altered balance of proversus anti-inflammatory cytokines, can be associated with cytotoxicity, angiostasis, and tumor regression.[7,22] Neutrophil subpopulations can repress T-cell proliferation by integrin Mac-1 and hydrogen peroxide.[23] In contrast, the lymphocyte has a crucial role in tumor defense by inducing cytotoxic cell death and inhibiting tumor cell proliferation and migration. A decreased lymphocyte count results in suppression of the body's immune response. The NLR may remain stable with respect to various physiological, pathological, and physical factors, although the absolute neutrophil and lymphocyte counts may be affected by these factors. The NLR may be superior to the leukocyte subtype, and high NLR values resulting from cancer-related inflammation have been shown to negatively affect the cancer prognosis.[24]

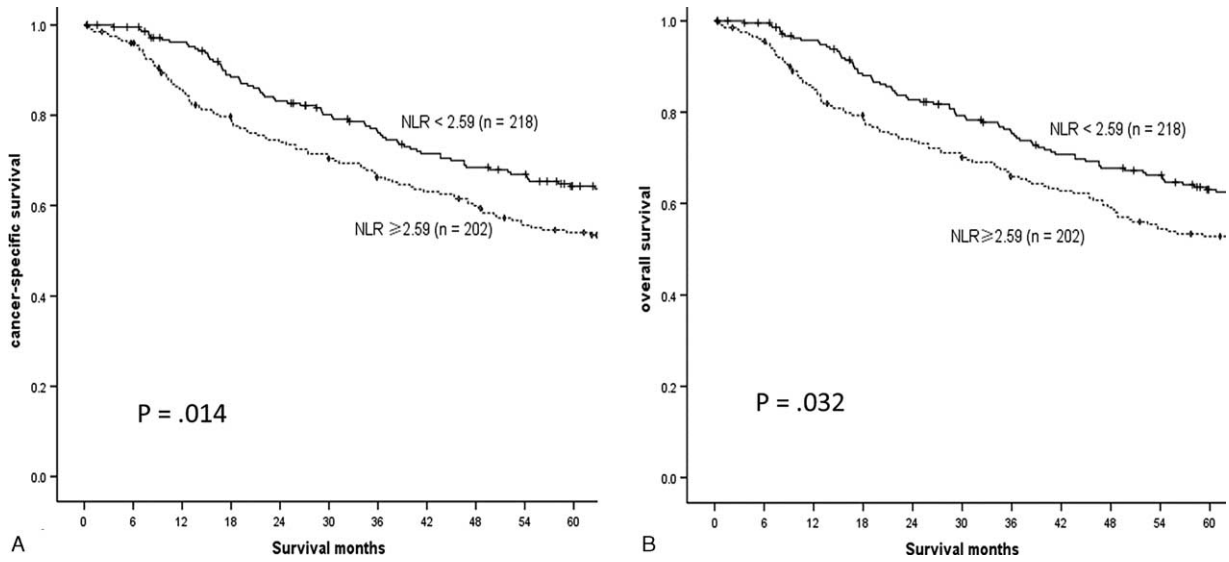

FIGURE 3. The NLR was significantly related to the (A) 5-year CSS ($P = 0.014$) and (B) OS ($P = 0.032$). CSS = cancer-specific survival, OS = overall survival, NLR = neutrophil-to-lymphocyte ratio.

NLR and Laryngeal Cancer

The presence of an elevated preoperative NLR has been validated as a marker of inflammation, and it has been shown to have a relationship with laryngeal cancer.[17,18] Neutrophils in a developing laryngeal neoplasm may produce an array of cytokines/chemokines such as cell-killing mediators, tumor necrosis factor-α, and interleukins, necessary for effector cell recruitment, activation, and response.[22,25,26] In contrast, decreased numbers of lymphocytes may suppress lymphokine-activated killer cells.[27] The adaptive immune cells such as B-lymphocytes, $CD4^+$ helper T-lymphocytes, and CD8+ cytotoxic T-lymphocytes, and the number of $CD4^+$ helper lymphocytes may decrease, and CD8+ suppressor lymphocytes may increase due to a disturbed inflammatory response, which modulates cancer development via cytokine-mediated lysis of tumor cells or establishes a proinflammatory state in the tumor microenvironment; thus, immunosuppression may be a result of this.[28–30] These may be the possible mechanisms for decreased survival in patients with LSCC so the recognition of the NLR as a key component of tumor growth is important when using cancer therapies to decrease laryngeal carcinoma cell proliferation and metastasis in patients.

There are several limitations in the present study. First, this was a retrospective analysis based on only 420 eligible patients. Although we did record detailed data, a prospective study would enable a better evaluation of prognostic factors in patients with LSCC. Hence, these analyses need to be validated in a larger cohort of patients. Second, numerous articles have reported on using different cutoff levels of the NLR by various methods that need to be verified. Various cutoff values were used to report a correlation between the NLR and survival in dozens of studies,[10,31–34] but additional details were not provided for LSCC. We determined that an NLR of 2.59 was the best cutoff value for distinguishing between patients with a poor prognosis and those with a better prognosis; therefore, further prospective, randomized studies with larger samples are needed to evaluate cutoff values and confirm our results. Third, there is increasing evidence that other inflammatory markers such as the C-reactive protein level is associated with poor survival in patients with various malignancies.[35,36] The NLR may be assessed together with other inflammatory markers in patients with LSCC, and this needs further research and summarization.[37]

In conclusion, our research firstly demonstrated that preoperative NLR ≥2.59 was an independent prognostic factor for long-term CSS and OS in patients with LSCC. Further prospective, randomized studies with larger samples are needed to evaluate cutoff values and confirm our results.

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