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Inflammatory markers and clinical factors which affecting the survival in metastatic renal cell carcinoma

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Abstract

Objective: According to metastatic renal cell carcinoma treatment protocol, after the use of tyrosine kinase inhibitors (TKI) has been achieved significant improvements for the treatment of metastatic renal cell carcinoma (mRCC). In this study, we aimed to investigate the effect of neutrophil-to-lymphocyte ratio (NLR) and prognostic nutritional index (PNI) on survival in patients with mRCC treated with sunitinib or pazopanib.

Material and Methods: Medical data for 38 patients with mRCC were reviewed retrospectively. NLR and PNI values were dichotomized based on receiver operating characteristic (ROC) curve analysis (cut-off values: 3 and 46, respectively). Univariate and multivariate analyses were performed to identify prognostic factors for progression free survival (PFS) and overall survival (OS) using a Cox proportional hazards model.

Results: Median PFS and OS were 12 and 27 months, respectively. Median PFS was 10 months in patients with NLR ⩾ 3 while 14 months in patients with NLR <3 (p: 0.008). Median OS was 18 months in patients with NLR ⩾3 while 31 months in patients with NLR <3 (p: 0.003). In patients with PNI ⩾ 46, PFS was 21 months and OS was 47 months whereas in patients with PNI < 46, PFS was 8 months and OS was 13 months (p values were <0.001, <0.001 respectively). In multivariate analysis, PNI was the independent risk factor for both PFS and OS, while NLR was the independent risk factor for OS only.

Conclusion: In patients with mRCC that using sunitinib or pazopanib, NLR and PNI values can be used as easily accessible prognostic markers.

Keywords: Renal cell carcinoma, Tyrosine kinase inhibitors, Neutrophil-to-lymphocyte ratio, Prognostic nutritional index.

Introduction

Renal cell carcinoma (RCC) is an aggressive malignancy with a 40% recurrence risk after nephrectomy for localized tumor, with a 5-year survival rate below 20% in advanced stage. Today, despite the increase in early detection of small renal masses, up to 20% of the patients with RCC apply to health centers in the metastatic phase (1). In clinical studies with tyrosine kinase inhibitors (TKI) such as sunitinib, pazopanib, sorafenib; prolonged progression-free survival (PFS) and overall survival (OS) have been obtained in patients with metastatic renal cell carcinoma (mRCC). New prognostic and predictive markers are needed for these agents that cause significant changes in mRCC management (2).The relationship between cancer development and inflammation has increased interest in the prognostic significance of inflammatory markers (3). The neutrophil-to-lymphocyte ratio (NLR), an index formed by dividing absolute neutrophil count into absolute lymphocyte count, is an inflammatory marker that has attracted researchers' attention due to its potential prognostic effect and has been identified as an independent prognostic factor in many types of cancer (4,5). Although a relationship between increased NLR and poor prognosis was demonstrated in patients with RCC (6); data on its role in patients with mRCC treated with sunitinib or pazopanib are insufficient. The Prognostic Nutritional Index (PNI), which is calculated using serum albumin concentration and total lymphocyte count in peripheral blood, was first used to obtain an idea about the immune nutritional status and surgical risk in patients undergoing gastrointestinal surgery (7). However, it was found that preop nutritional and immunological status was not only associated with postoperative complications but also associated with prognosis in malignancy patients, and currently PNI is used prognostically in various types of cancer (8-10). However, the prognostic role of PNI in mRCC patients using tyrosine kinase inhibitors has not been fully established. In this study, we aimed to evaluate the effects of NLR and PNI and also clinicopathological factors on progression-free

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survival (PFS) and overall survival (OS) in mRCC patients treated with sunitinib or pazopanib.

Materials and Methods

Study Design and Population

We evaluated data of 64 patients with mRCC treated in the medical oncology department between January 2014 and December 2018. The data were obtained retrospectively from medical records, laboratory results and patient files. This study included patients who were treated with tyrosine kinase inhibitors (TKI) such as sunitinib or pazopanib for mRCC, Eastern Cooperative Oncology Group (ECOG) performance score ⩽2, over 18 years of age and with clear cell subtype.

Demographic data including age and gender, interferon use, risk groups according to Memorial Sloan Kettering Cancer Center (MSKCC) risk criteria, surgical status were recorded from patient files. Complete blood count, serum calcium, albumin, LDH levels of all patients were recorded within a week before the TKI treatment. Patients with chronic diseases such as chronic heart failure, liver cirrhosis, systemic lupus erythematous, myeloproliferative disease and those with secondary malignancy were excluded. 26 patients were excluded from the final analysis for the following reasons: other type of tyrosine kinase inhibitor therapy (n = 9), no survival outcome data (n = 13), concomitant chronic disease or secondary malignancy (n = 4). Ethics committee approval was obtained from the ethics committee of University of Health Sciences-Adana Health Practice and Research Center. All the procedures were performed according to the 1964 Helsinki declaration.

Treatment Regimens

38 patients who used sunitinib (sutent; pfizer) or pazopanib (votrient; novartis) treatment were included in the study. Sunitinib was administered 50 mg once daily on 28 consecutive days of a given 6-week cycle and pazopanib was administered continuously 800 mg once daily. During the treatment of TKI according to the severity, treatment interruption or dose reduction for side effect management was performed according to the standard guidelines. Treatment continued until unacceptable adverse events were observed, disease progression was detected on imaging, or death occurred. Disease progression was assessed using the modified Response Evaluation Criteria in Solid Tumors version 1.1. (11).

Statistical analyses

PFS was considered as the time from the onset of TKI treatment to disease progression in imaging or death from any cause. OS was considered as the time from the first day of treatment to last follow up or death. NLR was calculated dividing the neutrophil counts by lymphocyte counts. PNI was calculated with the formula '(10 × albumin (g/L) + (0.005 × total lymphocyte count)'. The most sensitive and specific cut-off values for NLR and PNI were determined by using receiver operating characteristic (ROC) curve analysis.

The association between survivals and clinical and laboratory variables was evaluated using univariable Cox regression analysis, followed by multivariable analysis using the Cox proportional hazards model. The log rank test was used to determine differences between groups. Kaplan-Meier curves were used to estimate the time to event distribution. All analyses were performed using the SPSS statistical software package (SPSS statistics 21.0) and $p< 0.05$ was considered as statistically significant.

Results

A total of 38 patients, including 10 males and 28 females, were included in the study and the median age was 59 (range 38-76). The ECOG performance score was 0-1 in 25 patients, and 2 in 13 patients. All patients were from the clear cell subtype and the number of patients with Fuhrman grade 1, 2, 3 and 4 were 2, 2, 9, and 25, respectively.

According to the Memorial Sloan Kettering Cancer Center (MSKCC) index, 5 patients were in favorable, 20 patients were intermediate and 13 patients were in poor risk group. 25 patients received sunitinib therapy while 13 patients received pazopanib therapy. In response to the first treatment, 11 (28.9%) patients developed progression, 10 (26.3%) patients had partial response, and 17 patients had stable disease (44.8%). While 11 patients had a single metastatic focus, 27 patients had multiple foci of metastatic lesions. Metastasectomy was performed in 5 patients with a single metastatic focus. Twenty-eight patients underwent radical nephrectomy. The relationship of the clinical and demographic data of the patients with survival is shown in Table 1.

The median follow-up time was 20 months. Median PFS and OS were 12 and 27 months, respectively. ROC analysis was performed to determine cut off values for NLR and PNI and the results were shown in Table 2. Median PFS was 10 months in patients with NLR ⩾3 and 14 months in patients with NLR <3 (p: 0.008). Median OS was 18 months in patients with NLR ⩾3, and 31 months in patients with NLR <3 (p: 0.003). In patients with PNI ⩾46, PFS was 21 months and OS was 47 months; in patients with PNI <46, PFS was 8 months and OS was 13 months (p values <0.001, <0.001, respectively). Independent risk factors for survival were evaluated by Cox regression analysis and for this purpose, the number of metastatic fields, ECOG performance status, MSKCC index, and NLR and PNI values were included in this analysis (Table 3 and 4).

ECOG performance status, number of metastatic fields and MSKCC index were determined as independent risk factors for PFS and OS. Cox regression analysis showed that pretreatment NLR value was not an independent risk factor for PFS [HR: 1.282 (0.808-1.816 95% CI), p: 0.147] but it was an independent risk factor for OS [HR: 1.632 (1.112-2.442 95% CI), p: 0.034]. As important finding of our results, the low PNI was determined as an independent risk factor for shorter PFS and OS [HR: 1.934 (1.244-2.978 %95 CI), p: 0.033; HR: 1.568 (1.030-2.466 %95 CI), p: 0.044, respectively].

Table 1. Clinical and demographic data of patients

	n (%)	PFS Median, months	p value	OS Median, months	p value
Age					
Median(range)	59 (38-76)				
Gender					
Female	14 (36.8)	13	0.95	37	0.75
Male	24 (63.2)	12		22	
ECOG					
0-1	25 (65.8)	34	**<0.001**	50	**<0.001**
≥ 2	13 (34.2)	6		11	
MSKCC index			**<0.001**		**<0.001**
Favorable	5 (13.2)	21		NR	
Intermediate	20 (52.6)	16		29	
Poor	13 (34.2)	4		11	
Nephrectomy			0.34		0.56
Yes	28 (73.7)	15		30	
No	10 (26.3)	9		20	
Number of Metastatic Site			**0.004**		**0.002**
1	11 (28.9)	21		55	
≥ 2	27 (71.1)	7		15	
Use of INF-α			0.5		0.66
Yes	15 (39.5)	10		31	
No	23 (60.5)	14		24	
Sunitinib	25 (65.8)	12	0.9	26	0.95
Pazopanib	13 (34.2)	13		28	
Status					
Alive	11 (28.9)				
Death	27 (71.1)				
Overall	38 (100)	12			27

PFS: Progression-free survival, OS: Overall survival, ECOG: Eastern Cooperative Oncology Group, MSKCC: Memorial Sloan Kettering Cancer Center index

Table 2. ROC analysis results for NLR and PNI

	Cut off Value	AUC	95% CI for AUC Lower Bound	Bound Upper	Sensitivity	Specificity	p value
NLR	3	0.724	0.55	0.89	70.4	72.2	0.032
PNI	46	0.779	0.62	0.94	82	77.8	0.008

CI: Confidence interval, NLR: Neutrophil-to-lymphocyte ratio, PNI: Prognostic nutritional index

Table 3. Univariate and Multivariate Analysis of Potential Prognostic Factors for Progression-Free Survival

Parameters	Univariate		Multivariate	
	HR (95% CI)	p value	HR (95% CI)	p value
ECOG performance score	1.626 (1.124-2.348)	<0.001	1.354 (1.046-2.128)	**0.005**
Number of metastatic site (0-1 vs ≥ 2)	1.650 (1.154-2.455)	0.004	1.432 (1.054-2.122)	**0.035**
MSKCC index				
Favorable		Ref		
Intermediate	1.642 (1.104-2.450)	0.001	1.268 (1.116-2.096)	**0.044**
Poor	3.454 (1.760-5.870)	<0.001	2.876 (1.136-3.986)	**0.001**
NLR	1.764 (1.242-2.432)	0.008	1.282 (0.808-1.816)	0.147
PNI	2.450 (2.052-3.985)	<0.001	1.934 (1.244-2.978)	**0.033**

HR: Hazard ratio, CI: Confidence interval, ECOG: Eastern Cooperative Oncology Group, MSKCC: Memorial Sloan Kettering Cancer Center, NLR: Neutrophil-to-lymphocyte ratio, PNI: Prognostic nutritional index

Tablo 4. Univariate and Multivariate Analysis of Potential Prognostic Factors for Overall Survival

Parameters	Univariate HR (95% CI)	p value	Multivariate HR (95% CI)	p value
ECOG performance score	2.154 (1.348-3.246)	<0.001	2.114 (1.264-3.175)	**0.006**
Number of metastatic site (0-1 vs ≥ 2)	1.856 (1.124-2.774)	0.002	1.356 (1.084-2.243)	**0.038**
MSKCC index				
Favorable		Ref		
Intermediate	1.784 (1.108-2.789)	0.001	1.456 (1.008-2.564)	**0.013**
Poor	4.876 (1.986-8.142)	<0.001	3.468 (1.126-7.168)	**<0.001**
NLR	1.936 (1.237-2.652)	0.003	1.632 (1.112-2.442)	**0.034**
PNI	2.875 (1.984-3.964)	<0.001	1.568 (1.030-2.466)	**0.044**

HR: Hazard ratio, CI: Confidence interval, ECOG: Eastern Cooperative Oncology Group, MSKCC: Memorial Sloan Kettering Cancer Center, NLR: Neutrophil-to-lymphocyte ratio, PNI: Prognostic nutritional index

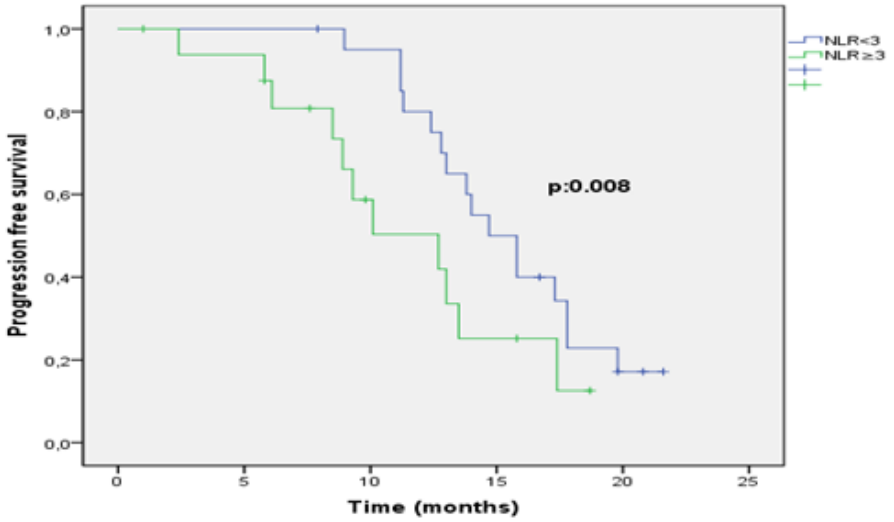

Figure 1a. Progression free survival times according to NLR

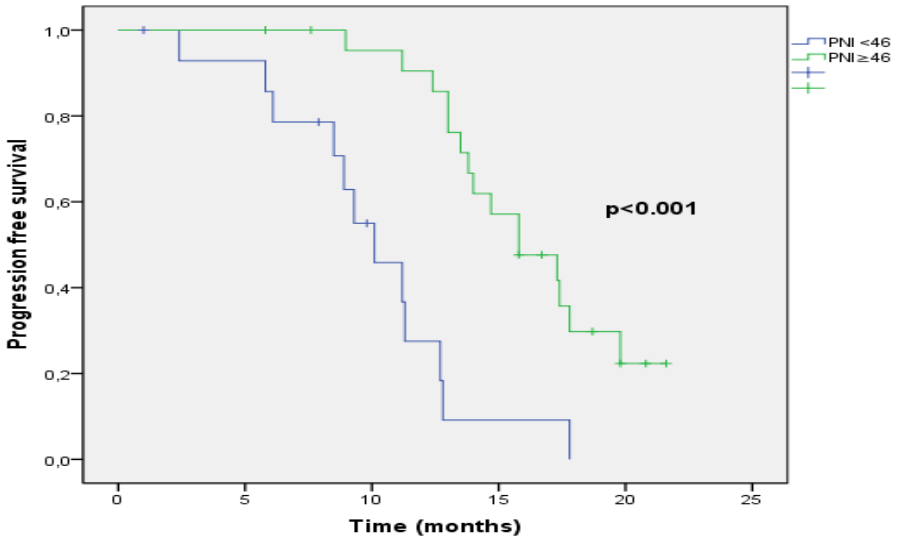

Figure 1b. Progression free survival times according to PNI

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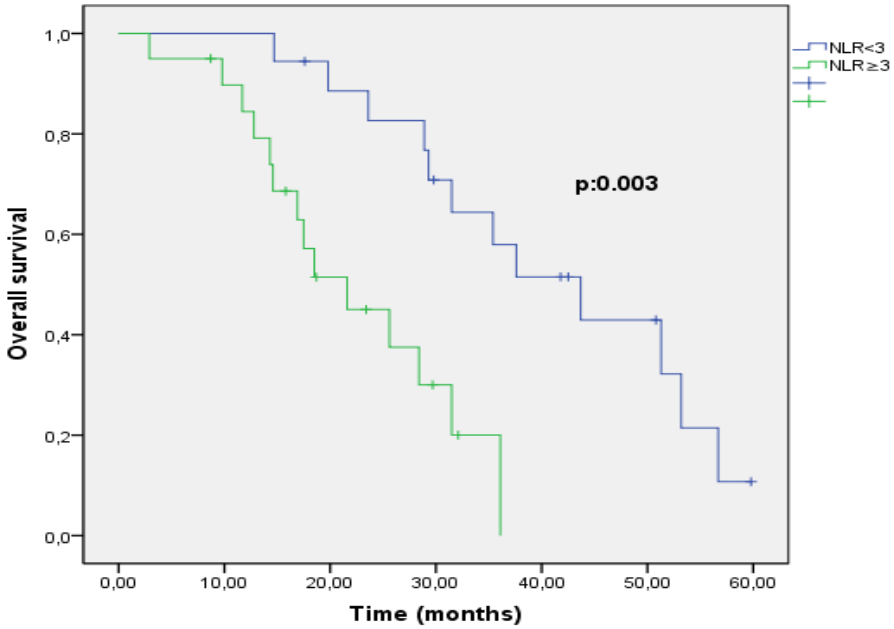

Figure 2a. Overall survival times according to NLR

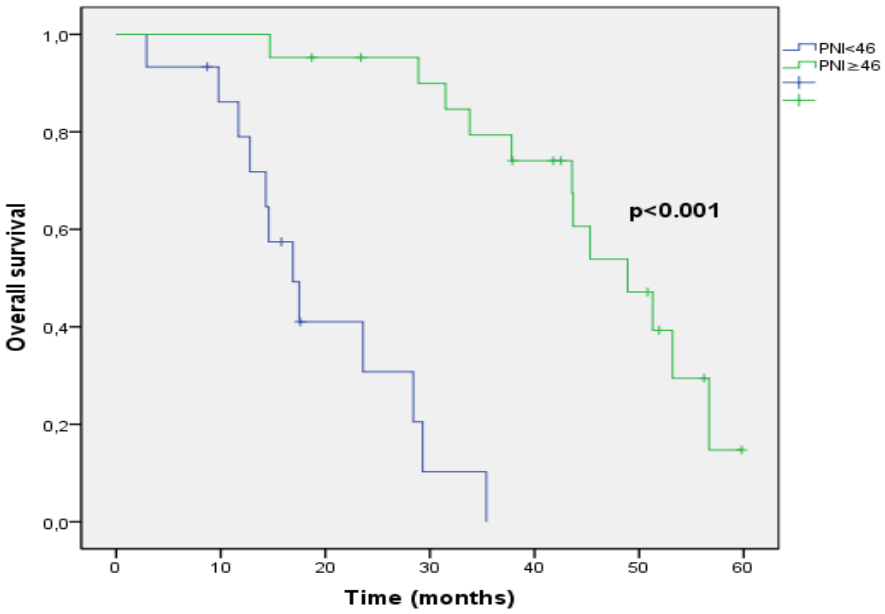

Figure 2a. Overall survival times according to PNI

Discussion

RCC is the most common cancer of the kidney, and about half of the patients with RCC eventually move on to the metastatic stage, where 5-year survival is quite low. In the literature it was showed that significant advances have been achieved in mRCC management by proving the therapeutic effects of TKIs such as sunitinib, pazopanib sorafenib that increase PFS and OS in patients with mRCC (12). However, new prognostic clinical markers are needed for these targeted agents. We evaluated the clinicopathological results of 38 patients with mRCC who used sunitinib or pazopanib as primary care targeted therapy, and found that NLR was an independent prognostic marker for OS and PNI was an independent prognostic marker for PFS and OS in our study. In our study, we analyzed the factors affecting PFS and OS in patients using sunitinib or pazopanib as a first-line tyrosine kinase inhibitor with or without previous history of using INF-α. Similar survivals have been demonstrated in the use of both agents in patients with mRCC, and there has been an overall survival expectancy of 22.9 to 26.4 months (13, 14) and is consistent with our study. The relationship between tumor development and inflammation has been evaluated for many years, and tumor-promoting inflammation is now considered as an important step in the cancer development (15,16). It is also known that tumor progression is not only related to the biological structure of the tumor, but also it is associated

with acute phase proteins such as albumin, C-reactive protein, and serum levels of components that make up the inflammatory response such as lymphocyte, platelet, white blood cells, etc. (17). Similarly, neutrophils are inflammatory markers known to be the main component of the tumor microenvironment, which are produced in response to cytokines with increased release due to aggressive tumor biology and tumor load (18,19). Recently, various combinations of these factors have been investigated quite frequently as inflammatory markers in determining the prognosis of various cancers. High NLR value before treatment has been shown to be an independent risk factor for short survival in many types of cancer such as gastric cancer (20), ovarian cancer (21), pancreatic cancer (22). In a study conducted by Keizman D et al. (23) in patients with mRCC receiving sunitinib, the cut off value 3 for NLR was found to be an independent risk factor for PFS and OS. In our study, in which the same cut off value was taken for NLR, the high NLR value was prognostic for short PFS and OS, but it was only an independent risk factor for OS. NLR was not determined as an independent risk factor for PFS, and this may be related with the limited number of patients included in the study. PNI, calculated by serum albumin level and total lymphocyte count in peripheral blood, gives an idea about the nutritional and immunological status of patients and can be used as a prognostic marker for survival rates (24). Albumin is frequently used as an indicator of nutritional status, and studies have proven that its low concentration is an independent indicator of long-term outcomes in various types of cancer, such as breast (25), colorectal (26), and hepatocellular cancer (27). Lymphocytes are an important component of cell-mediated immunity, which plays an important role in defending against cancer. Low lymphocyte count may be associated with inability to defend against cancer by causing weakness in immunological response (28). In addition, tumor-infiltrating lymphocytes are an important component of the anti-tumor response and more tumor-infiltrating lymphocytes are associated with stronger antitumor response and better survival (29-31). All these findings brought to mind the idea that PNI can be used as a prognostic marker for survival in cancer patients, and this theory has been supported by a growing number of recent studies (32, 33). In our study, PNI level was significantly associated with OS and PFS in univariate and multivariate analyzes, and longer survival was achieved in patients with high PNI level. In the non-inferiority study, it has been proven that pazopanib and sunitinib are equally effective in the treatment of mRCC. Also in this study, MSKCC index and performance status were determined as factors that were affecting the survival (34). When we evaluated patients receiving sunitinib and pazopanib as a single group and made their survival analysis, MSKCC index and ECOG performance status were determined as independent factors affecting survival in accordance with the literature.

The fact that the study was retrospective, single-centered and with a small sample size may have caused bias in the analysis of the results, and this is the major limitation of our study. The other limitation was the inability to form a homogenous group in terms of the use of INF-α and the relationship between dynamic changes of the inflammatory markers and the survival during the treatment

Conclusion

After the use of TKI in the treatment of mRCC, and there has been a need for markers to predict the treatment response. Our study showed that PNI was an independent prognostic marker for PFS and OS and NLR was an independent prognostic marker only for OS in mRCC patients using sunitinib or pazopanib. While the NLR value reflects the only inflammatory state but the PNI value also shows the nutritional state, and the fact that the nutritional state is an important prognostic factor for mRCC may have caused this condition.

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Author's contiributions: All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Mahmut Buyuksimsek and Ali Ogul. The first draft of the manuscript was written by Mahmut Buyuksimsek and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Conceptualization: Mahmut Buyuksimsek, Methodology: Ali Ogul; Formal analysis and investigation: Mahmut Buyuksimsek; Writing - original draft preparation: Mahmut Buyuksimsek; Writing - review and editing: Mahmut Buyuksimsek; Supervision: Ali Ogul.

Ethical issues: Author declare, originality and ethical approval of research. The study was conducted under defined rules by the Local Ethics Commission guidelines and audits.

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