≥0.16

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摘要: 目的 探讨阳性淋巴结比率(LNR)对判断食管癌患者预后的价值。**方法** 选取2010年到2015年seer数据库中有完整临床病理资料的862例食管癌患者为研究对象, 应用X-tile软件选取LNR的最佳截断点, 在进行倾向性评分匹配(PSM)后, 运用单因素和多因素COX比例风险模型探讨LNR在食管癌患者预后中的价值。**结果** X-tile 3.6.1软件筛选出LNR的最佳截断点为LNR<0.16和LNR≥0.16。匹配前LNR<0.16和LNR≥0.16两组患者的被检淋巴结数、病理类型、T分期和M分期差异有统计学意义; 1∶1匹配后, 两组患者的临床资料和病理学指标差异均无统计学意义。匹配后的单因素和多因素COX回归分析结果显示, LNR、原发部位、M分期均是影响食管癌患者预后的独立危险因素, 其中尤以LNR最为显著(LNR<0.16 vs LNR≥0.16, HR=1.827, 95%CI: 1.140~2.929, P=0.000)。LNR<0.16组患者的中位生存时间为31个月(95%CI: 22.556~39.444), LNR≥0.16组为16个月(95%CI: 12.989~19.011), LNR<0.16组患者的预后显著优于LNR≥0.16组, 差异有显著统计学意义(Log Rank χ^2=27.392, P<0.0001)。LNR和N分期对评估预后的准确性分析显示, LNR的ROC曲线下面积为0.617(95%CI: 0.567~0.666), N分期的ROC曲线下面积为0.515(95%CI: 0.463~0.565), LNR预测预后的价值明显优于N分期(z=3.008, P=0.0026)。**结论** LNR≥0.16是食管癌患者预后的独立危险因素, 预后预测价值显著优于传统N分期。

关键词: seer数据库; 阳性淋巴结比率; 食管癌; 预后

Positive lymph node ratio ≥0.16 is an independent risk factor affecting the prognosis of patients with esophageal cancer

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Abstract: Objective To investigate the value of positive lymph node ratio (LNR) in predicting the prognosis of patients with esophageal cancer. **Methods** We retrieved the data of a total of 862 patients with esophageal cancer with complete clinical pathology data archived in SEER database in 2010 to 2015. The best cutoff point of LNR was selected using X-tile software. Univariate and multivariate COX proportional hazard models were used to assess the value of LNR in predicting the prognosis of patients after propensity score matching (PSM). **Results** The best cut-off point of LNR determined using X-tile 3.6.1 software was 0.16. The patients with LNR<0.16 and those with LNR≥0.16 showed significant differences in the number of positive lymph nodes, pathological type, T stage and M stage. After 1:1 propensity score matching, the two groups showed no significant difference in the clinical data or pathological parameters. Matched univariate and multivariate COX regression analyses showed that LNR, primary tumor site and M staging were all independent risk factors affecting the prognosis of patients, and among them LNR had the most significant predictive value (LNR<0.16 vs LNR≥0.16: HR=1.827, 95% CI: 1.140-2.929; P=0.000). The median survival time of patients with LNR<0.16 was 31 months (95%CI: 22.556-39.444 months), as compared with 16 months (95%CI: 12.989-19.011) in patient with LNR≥0.16 (Log Rank χ^2=27.392, P<0.0001). LNR had a better accuracy than N stage for assessing the patients' prognosis with an area under the ROC curve of 0.617 (95%CI: 0.567-0.666), as compared with 0.515 (95%CI: 0.463-0.565) of N stage (z=3.008, P=0.0026). **Conclusion** LNR≥0.16 is an independent risk factor affecting the prognosis of patients with esophageal cancer and has better prognostic value than N stage.

Keywords: SEER database; positive lymph node ratio; esophageal cancer; prognosis

据最新全球癌症负担状况报告显示, 食管癌发病率居第7位, 死亡率居第6位[1]。我国是食管癌发病大国, 据2019年国家癌症中心公布的最新数据, 我国食管癌发病率居第6位, 而死亡率高居第4位, 仅次于肺癌、肝

癌和胃癌[2]。淋巴结转移是影响食管癌患者预后的重要因素之一, 并且多项研究表明阳性淋巴结比率(LNR)在预测胃癌、直肠癌、甲状腺癌等多种肿瘤患者预后中更具优势[3-6]。然而之前的研究多集中在胃癌、直肠癌、甲状腺癌等肿瘤, 食管癌较少。尽管鲁建亮[3]涉及了对食管癌阳性淋巴结个数的研究, 但该研究以及之前所述的阳性淋巴结比率在其他肿瘤中的研究多是只用ROC进行的截断点选取, 或者直接参照其他肿瘤中阳性淋巴结比率的截断点, 前者没有考虑时序性, 后者不同肿瘤

又存在明显差异性。因此,本研究运用目前科学的PSM和X-tile统计学方法再加上更大的样本量进行研究分析,更加严谨科学。本研究分析862例食管癌患者的临床病理资料,旨在探讨LNR对食管癌患者预后的价值。

1 资料和方法

1.1 一般资料

提取seer数据库2010年1月1日~2015年12月31日被诊断为食管癌的患者为研究对象,随访截止日期为2016年12月31日。纳入和排除标准:筛选标准为患者年龄≤85岁,排除随访时间缺失、临床病理资料不明确、合并有其他肿瘤者且生存时间小于1个月者。共提取出862例符合要求的研究对象,其中男性716例,女性146例。患者组织学类型以ICD-O-3为分类标准。本文共纳入性别、年龄、肿瘤大小、被检淋巴结数、LNR(阳性淋巴结比率)(=淋巴结阳性个数/被检淋巴结个数)、原发部位、肿瘤分级、病理类型、T分期、N分期、M分期、人种等临床相关因素进行分析。

1.2 统计学方法

本文采用 R 3.6.1、X-tile 3.6.1、medcalc 和 SPSS 21.0统计学软件进行统计分析。其中X-tile 3.6.1用来选取连续型变量的最佳截断点;生存曲线的绘制采用R语言的survminer包进行绘制,倾向性评分匹配(PSM)以及图形的绘制采用R语言的nonrandom包和tableone包完成,其中卡钳值设置为0.02,以1:1进行匹配;使用SPSS 21.0进行单因素和多因素COX回归分析,使用medcalc软件对预后价值进行对比分析。$P<0.05$为显著性差异。

2 结果

2.1 最佳截断点的选择

使用X-tile 3.6.1软件筛选最佳截断点,其中LNR的最佳截断点为LNR<0.16和LNR≥0.16,年龄≤72岁和≥73岁,肿瘤大小为≤72 mm和≥73 mm,被检淋巴结数为≤8个和≥9个(图1为LNR最佳截断点的计算结果,其它略)。
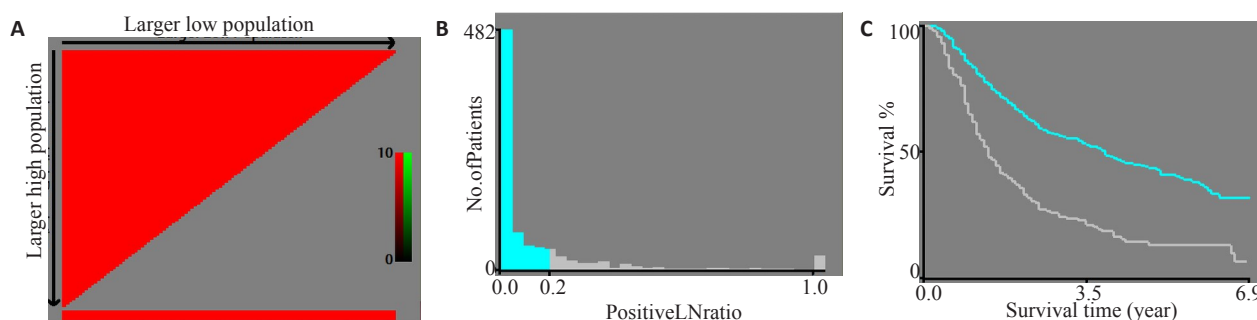

图1 LNR最佳截断点的选择

Fig.1 Selection of the best cut-off point for LNR. **A**: The colors of the plot represent the strength of correlation, ranging from low (dark, black) to high (green or red). An indirect correlation between a factor and the patients' survival is colored red, and a positive correlation colored green. **B**: Histogram showing the optimal cutoff point; **C**: Kaplan-Meier curve corresponding to the cutoff point.

2.2 LNR的PSM匹配结果

匹配前,LNR<0.16纳入674例,LNR≥0.16组纳入188例患者,倾向性评分曲线图显示两组评分分布差异大(图2),两组患者的被检淋巴结数、病理类型、T分期和M分期差异有统计学意义(表1);1:1匹配后,LNR<0.16组和LNR≥0.16组各纳入188例患者,单变量标准差散点图示各协变量对应点均落在虚线左侧,说明各变量达到均衡,匹配良好(图3),两组患者的临床资料和病理学指标差异均无统计学意义(表1)。

2.3 单因素和多因素cox回归分析

PSM评价后的单因素和多因素cox回归分析结果显示,LNR、原发部位、M分期均是影响食管癌患者预后的独立危险因素,其中尤以LNR最为显著(LNR<0.16 *vs* LNR≥0.16,HR=1.827,95%*CI*:1.140~2.929,P=0.000,表2)。

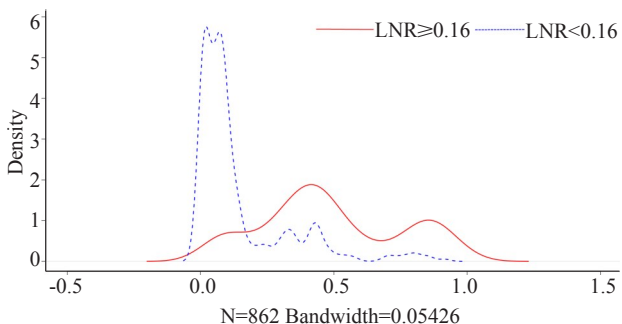**图2 匹配前倾向性评分密度曲线图**

Fig.2 Tendency score density curve before matching.

2.4 LNR对预后的影响及与N分期预后预测价值的对比

LNR<0.16组患者的中位生存时间为31个月(95%*CI*:22.556~39.444),LNR≥0.16 组 为 16 个 月 (95% *CI*:
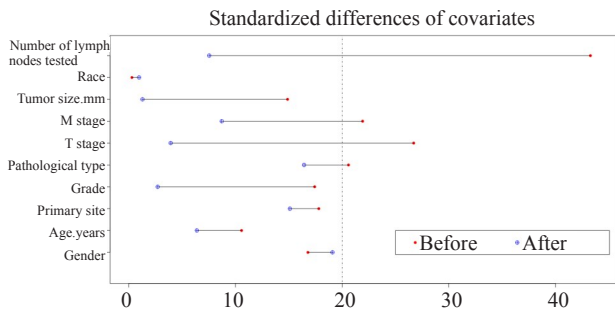
Standardized differences of covariates

图3 匹配后单变量标准差散点图
Fig.3 Univariate standard deviation scatter plot after matching.

12.989~19.011），LNR<0.16 组患者的预后显著优于 LNR≥0.16 组，差异有显著统计学意义（Log Rank χ^2= 27.392，P<0.0001），生存曲线见图4。LNR 和 N 分期对评估预后的准确性分析显示，LNR 的 ROC 曲线下面积为 0.617（95%CI：0.567~0.666），N 分期的 ROC 曲线下面积为 0.515（95%CI：0.463~0.565），LNR 预测与后的价值明显优于 N 分期，差异有统计学意义（Z=3.008，P= 0.0026，图5）。

表1 倾向性评分匹配前后两组患者临床资料的对比
Tab.1 Comparison of clinical data between the two groups before and after propensity score matching (PSM)

Variable	Before			After		
	LNR (n)		P	LNR (n)		P
	<0.16 (674)	≥0.16 (188)		<0.16 (188)	≥0.16 (188)	
Gender			0.067			0.089
Male	551	165		152	165	
Female	123	23		36	23	
Age (year)			0.232			0.643
≤72	604	162		166	162	
≥73	70	26		22	26	
Tumor size (mm)			0.079			1.000
≤72	563	146		147	146	
≥73	111	42		41	42	
Number of lymph nodes tested			<0.001			0.531
≤8	141	76		83	76	
≥9	533	112		105	112	
Primary site			0.160			0.266
Cervical esophagus	2	0				
Upper third of esophagus	9	3		2	3	
Middle third of esophagus	93	14		19	14	
Lower third of esophagus	525	152		157	152	
Abdominal esophagus	7	2		2	2	
Overlapping lesion of esophagus	22	12		3	12	
Thoracic esophagus	16	5		5	5	
Grade			0.094			0.314
I	30	8		5	8	
II	303	68		73	68	
III	333	107		109	107	
IV	8	5		1	5	
Pathological type			0.006			0.226
Squamous cell carcinoma	157	24		36	24	
Adenocarcinoma	456	147		138	147	
Others	61	17		14	17	
T stage			0.006			0.522
T1	64	12		8	12	
T2	121	19		21	19	
T3	451	138		146	138	
T4	38	19		13	19	
M stage			0.004			0.527
M0	656	174		178	174	
M1	18	14		10	14	
Race			0.992			0.927
White	598	167		165	167	
Black	35	10		13	10	
Asian	35	9		8	9	
Others	6	2		2	2	

表2　PSM评价后的单因素和多因素COX回归分析

Tab.2　Univariate and multivariate COX regression analysis after PSM evaluation

Variable	cases (*n*)	Univariate			Multivariate		
		P	HR	95%*CI*	*P*	HR	95%*CI*
Gender		0.131					
Male	317						
Female	59		0.750	0.517~1.089			
Age (year)		0.696					
≤72	328						
≥73	48		1.076	0.745~1.553			
Primary site		0.004			0.009		
Upper third of esophagus	5						
Middle third of esophagus	33		1.034	0.311~3.435		0.997	0.300~3.310
Lower third of esophagus	309		0.715	0.228~2.241		0.639	0.204~2.004
Abdominal esophagus	4		4.199	0.932~18.924		3.182	0.705~14.361
Overlapping lesion of esophagus	15		1.153	0.321~4.142		0.864	0.240~3.118
Thoracic esophagus	10		0.484	0.115~2.033		0.445	0.106~1.871
Grade		0.410					
I	13						
II	141		0.757	0.394~1.455			
IIII	216		0.821	0.432~1.560			
IV	6		1.531	0.522~4.489			
Pathological type		0.992					
Squamous cell carcinoma	60						
Adenocarcinoma	285		0.985	0.700~1.386			
Others	31		0.968	0.565~1.656			
T stage		0.089					
T1	20						
T2	40		0.788	0.384~1.619			
T3	284		1.129	0.614~2.074			
T4	32		1.649	0.807~3.372			
M stage		0.015			0.012	1.827	1.140~2.929
M0	352						
M1	24		1.792	1.121~2.865			
Tumor size (mm)		0.230					
≤72	293						
≥73	83		1.197	0.892~1.607			
Race		0.391					
White	332						
Black	23		1.471	0.930~2.327			
Asian	17		0.938	0.481~1.831			
Others	4		1.417	0.352~5.708			
LNR		0.000			0.000	1.827	1.140~2.929
<0.16	188						
≥0.16	188		1.917	1.490~2.465			
Number of lymph nodes tested		0.216					
≤8	159		0.854	0.665~1.097			
≥9	217						

3　讨论

食管癌的发病率和死亡率逐年攀升，70%左右的食管癌患者首诊即为晚期，丧失手术根治机会[7-8]。近20年来，晚期食管癌的治疗无明显进步，无标准的二线治疗方案，中位生存时间仍约10个月左右[9-10]。积极寻找影响食管癌患者预后的危险因素，提高患者生存率仍是临床上亟待解决的问题[11-12]。

目前临床普遍采用国际抗癌联盟（UICC）/美国癌症联合会（AJCC）联合制定的TNM分期系统进行淋巴结病理分期[13-14]。该方法是根据转移淋巴结数目进行分期，但并未考虑清扫淋巴结总数，当淋巴结清扫数目不足时则可能漏检已转移的淋巴结，因此在评估预后方面
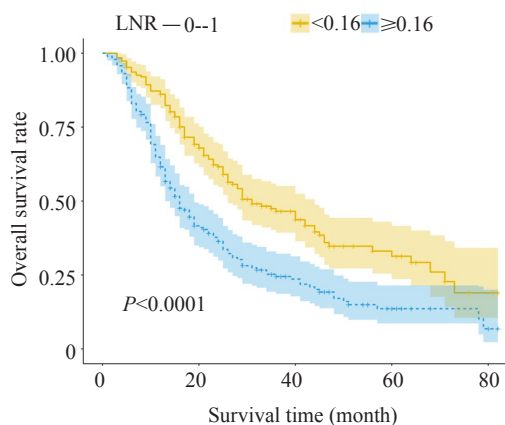
图4 两组患者的生存曲线
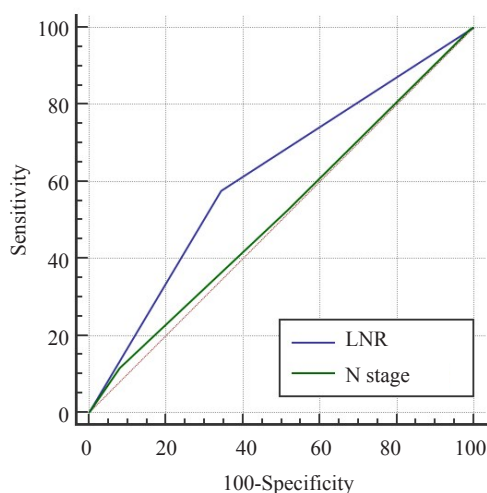Fig.4 Survival curves of the two groups of patients.

图5 LNR与N分期预后预测价值的对比
Fig.5 Comparison of the prognostic value of LNR and N staging.

存在一定的局限性。LNR即淋巴结转移阳性数占清扫淋巴结总数的百分率,其被认为在食管癌等多种肿瘤中评估患者预后方面的价值优于淋巴结转移状态,然而,目前对食管癌阳性淋巴结比率多是只用ROC进行的截断点选取,或者直接照搬其他肿瘤中阳性淋巴结比率的截断点,前者没有考虑时序性,后者不同肿瘤又存在明显差异性。因此,本研究运用目前科学的PSM和X-tile统计学方法再加上更大的样本量进行研究分析,更加严谨科学[15-17]。此外,鲁建亮[3]研究的为阳性淋巴结对数比,本文为阳性淋巴结比率,计算方法不一样,还有该学者对截断点的选取方法是间隔逐步分析法,也没有运用PSM法。因此研究内容基本不一致。本文的创新点即文章中所运用的统计学方法使结果更加合理科学,且研究结果也表明本文所选择的截断点的临床价值相比于N分期也更大。

X-tile的使用目的与ROC曲线相似,通过寻找最佳的截断点,从而参考某一截断点得出合理临床数据,但

其在统计分析时纳入了时间因素,因此结果更加合理、准确[18-20]。倾向性评分匹配是近年国内外广泛应用的统计学方法,是指特定研究对象在特定协变量条件下,接受某种处理的可能性[21-23]。倾向性评分匹配能够有效消除潜在混杂因素产生的潜在偏倚,倾向评分值调整后,除了处理因素和结局变量分布差异外,其它协变量都均衡可比,从而利用非随机分组数据研究试验因素和结局之间的关系,得出可信度更高的研究结果[24]。本文通过X-tile软件选择0.16为LNR最佳的截断点,使用倾向性评分匹配对LNR<0.16和LNR≥0.16两组患者进行筛选后各入组188例,匹配前两组患者的被检淋巴结数、病理类型、T分期和M分期差异有统计学意义,匹配后两组患者的临床资料和病理学指标差异均无统计学意义,说明消除混杂因素影响后LNR≥0.16确实是影响食管癌患者预后的独立危险因素。另外,LNR<0.16组患者的预后显著优于LNR≥0.16组,差异有显著统计学意义(Log Rank χ^2=27.392, P<0.0001);LNR ROC曲线下面积大于N分期,说明其预测预测价值明显优于AJCC 7版N分期,差异有统计学意义(z=3.008, P=0.0026)。该结论与国内外相关研究结果基本一致[25-28]。Wei C等[15]以496例食管癌根治性切除术患者为研究对象,单因素分析显示病变部位,肿瘤长度,肿瘤浸润深度,pN和LNR影响预后,多因素分析显示肿瘤浸润深度,pN和LNR是独立的危险因素;ROC分析表明与pN相比,LNR具有更好的预测价值(z=2.275, P=0.029)。Shao YJ等[29]回顾性分析916例食管癌根治性切除术患者的临床资料,Cox回归分析表明LNR是影响总生存率的独立危险因素,其认为基于LNR的改良分期系统具有很好的预后评价价值。赵芳[30]选择380例行根治术的胸段食管鳞癌患者,结果表明LNR为影响食管癌患者预后的独立预后因素,其评估预后的价值优于pN分期。

综上所述,LNR充分考虑了阳性淋巴结个数和被检淋巴结总数对食管癌患者预后的影响,是一种极具潜力的预后指标,LNR≥0.16是食管癌患者预后的独立危险因素,预后预测价值显著优于传统N分期,临床治疗决策制定时应重视该指标。

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