四川大学学报（医学版） 2020，51（4）：573－577
J Sichuan Univ（Med Sci Edi） doi: 10.12182/20200760106

预后营养指数预测小细胞肺癌预后的临床应用研究*

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【摘要】 **目的** 探讨预后营养指数（prognostic nutritional index, PNI）预测小细胞肺癌（small cell lung cancer, SCLC）患者预后的价值。**方法** 回顾性收集2017年1月−2018年1月经病理初次确诊，符合本研究纳入、排除标准的SCLC患者临床资料，计算PNI值，根据中位数分为高PNI、低PNI，分析其对SCLC总生存（overall survival, OS）的影响，并分析影响SCLC预后的因素。**结果** 共纳入105例患者，根据PNI中位数（48.68）分为高PNI和低PNI两组，其中位生存时间分别为25.1个月和14.2个月，1年生存率分别为82.5%和65.3%，2年生存率分别为49.7%和28.4%，差异有统计学意义（P<0.05）。单因素分析示：性别、ECOG PS评分、临床分期和PNI均与患者的中位OS时间相关（P<0.05）。多因素分析示：PNI〔优势比（odds ratio, OR）=0.331，95%置信区间0.189～0.580〕和性别（OR=1.897，95%置信区间1.051～3.423）为影响SCLC患者预后的独立因素。**结论** 低PNI患者的预后一般较差，PNI计算简便、临床易获取，值得临床推广。

【关键词】 肺癌 小细胞 PNI 预后

The Clinical Value of PNI in Assessing the Prognosis of Small Cell Lung Cancer

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【**Abstract**】 **Objective** To evaluate the clinical value of prognostic nutritional index (PNI) in assessing the prognosis of small cell lung cancer (SCLC) patients. **Methods** The clinical data of SCLC patients who were initial diagnosed by pathology and conformed to the conditions of this study from January 2017 to January 2018 were retrospectively collected. The PNI values were calculated and divided into high PNI and low PNI groups according to the median value. The potential prognostic factors for SCLC patients were analyzed. **Results** One hundred and five patients were divided into high-PNI and low-PNI groups according to the PNI median (48.68). The median survival time was 25.1 months and 14.2 months respectively. The one-year survival rates were 82.5% and 65.3% respectively and the two-year survival rates were 49.7% and 28.4% respectively, the differences were all statistically significant (P<0.05). Univariate analysis showed that gender, ECOG PS score, clinical stage and PNI were correlated with overall survival (OS) (P<0.05). Multivariate analysis showed that PNI (odds ratio (OR)=0.331, 95% confidence interval: 0.189-0.580) and gender (OR=1.897, 95% confidence interval: 1.051-3.423) were independent prognostic factors for SCLC patients. **Conclusion** Low PNI patients generally symbolize poor prognosis, PNI calculation is simple and easy to obtain, worthy of clinical promotion.

【**Key words**】 Lung cancer Small cell PNI Prognosis

近年来，肺癌仍是引起肿瘤性死亡的主要原因。在美国，每年约155 870例患者死于肺癌[1]。其中小细胞肺癌（small cell lung cancer, SCLC）约占肺癌患者的15%～20%[2]，因侵袭能力强、恶性程度高，预后往往较差。局限期SCLC患者的中位生存期为15～20个月，广泛期SCLC患者的中位生存期仅9～12个月[3]。近期一项研究发现接受一线化疗（铂类+依托泊苷或伊立替康）的广泛期SCLC患者的中位总生存期（overall survival, OS）为10.3个月，中位无进展生存期为4.3个月[4]。目前SCLC的治疗以化疗为主，对于局限期的SCLC可以同步放疗，推荐预防性颅脑放射来预防颅脑转移的发生[5]。尽管化疗初始反应比较明显，但大多数SCLC患者在疾病早期出现远处转移及治疗过程中耐药性迅速出现，因此预后较差[5-6]。化疗前对SCLC预后的评估可以为患者制定合理的治疗方案，从而避免不必要的化疗毒副作用。

影响SCLC预后的因素很多，肿瘤TNM分期是影响预后的重要因素[7]，临床因素〔如年龄、性别、吸烟指数、体力状况评分（performance status, PS）评分等〕和肿瘤因素（如肿瘤大小、细胞分化程度、有无胸膜转移及远处转移、血清肿瘤标志物的水平等）均参与了肿瘤的发展和恶化，影响患者的预后[8-9]。

* 国家自然科学基金面上项目（No. 81670024）和国家自然科学青年基金项目（No. 81801961）资助

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越来越多的研究表明营养和免疫状态与恶性肿瘤患者的远期生存率密切相关[10]。预后营养指数(prognostic nutritional index, PNI)根据血清白蛋白水平和淋巴细胞计数计算得来,而白蛋白及淋巴细胞均与患者的营养和免疫状态相关。最初PNI用来评估术前患者的免疫状况、手术风险及术后并发症的发生等[11-12]。近年来研究表明,高PNI是各种癌症类型中有利的预后因素[13-14]。但PNI在评估SCLC预后方面的研究相对较少,本研究主要探讨PNI在SCLC患者预后评估中的应用价值。

1 材料与方法

1.1 研究对象

回顾性分析本院自2017年1月–2018年1月收治的SCLC患者。纳入标准:①年龄≥18岁;②经病理或细胞学初次确诊的SCLC;③具有化疗前1周内血清白蛋白及淋巴细胞计数的资料;④具有完整的临床资料数据;⑤确诊后于本院行放化疗者。排除标准:①合并其他系统肿瘤者;②具有血液系统疾病或免疫系统疾病者;③近期输血者;④临床资料不完整者。本研究资料收集遵循知情同意原则。

1.2 资料收集

从电子病历中收集患者的一般资料,包括年龄、性别、吸烟状况、肿瘤分期、有无胸腔积液、有无咯血、是否放疗及治疗前1周内血清白蛋白水平及外周血淋巴细胞计数。PNI计算方法:PNI= 血清白蛋白(g/L)+5×外周血淋巴细胞计数(10^9 L^{-1})[15]。根据经修改的退伍军人管理肺癌组(the Modified Veterans Administration Lung Cancer Group, VALG)分期系统[16]确定癌症阶段,将患者分为局限期和广泛期。局限期疾病(limited-stage disease, LD)定义为限制于具有/不具有局部淋巴结转移(包括同侧和对侧肝门、锁骨上和纵隔淋巴结)的一侧胸腔的肿瘤以及同侧胸腔积液。广泛期疾病(extensive-stage disease, ED)定义为超出上述范围的任何肿瘤。

1.3 随访

通过电话进行随访,详细记录随访情况。OS为从病理或细胞学确诊至患者死亡或随访截止日期(2018年1月)的时间,以月为单位计算。本组病例失访3例,死于其他疾病者2例,最后纳入本研究者105例。

1.4 统计学方法

连续性变量的比较用t检验或方差分析,计数资料间的比较用卡方检验;Kaplan-Meier法绘制生存曲线,Cox比例风险模型进行单因素和多因素分析;$P<0.05$为差异有统计学意义。

2 结果

2.1 一般临床资料

见表1。符合纳入及排除标准的研究对象共105例,年龄40~82岁(中位年龄62岁)。其中女性患者32例(30.48%),男性患者73例(69.52%),男女比例为2.28∶1。吸烟指数(smoking index, SI)≥400的患者60例(57.14%),

表 1 105例SCLC患者的PNI与临床病理特征的关系

Table 1 Relationship between clinicopathological characteristics and PNI in 105 patients with SCLC

Characteristic	*n*	PNI	*P*
Age/yr.			0.326
≥62	62	48.18±6.43	
<62	43	49.40±5.98	
Gender			0.002
Male	73	47.59±6.62	
Female	32	51.18±4.50	
Smoking index*			0.517
≥400	60	48.34±6.64	
<400	45	49.14±5.14	
Hemoptysis			0.830
Yes	22	48.42±5.21	
No	83	48.75±6.52	
Thoracalgia			0.213
Yes	18	47.01±6.41	
No	87	49.03±6.20	
Pleural effusion			0.024
Yes	17	45.56±6.92	
No	88	49.29±5.97	
CEA/(ng/mL)			0.399
≥13	12	49.80±4.49	
<13	93	48.54±6.45	
NSE/(ng/mL)			0.298
≥51	25	47.54±6.25	
<51	80	49.04±6.25	
ECOG PS			0.003
0-1	23	49.62±6.08	
2-3	82	45.36±5.82	
Clinical stage			0.000
Limitation	40	52.16±4.53	
Extensive	65	46.54±6.23	

CEA: Carcinoembryonic antigen; NSE: Neuron-specific enolase; ECOG PS: Eastern Cooperative Oncology Group performance status. *Smoking index≥400 for the people at high risk of lung cancer[17]

咯血患者22例(20.95%), 胸痛患者18例(17.14%), 胸腔积液患者17例(16.19%), 癌胚抗原(carcinoembryonic antigen, CEA)≥13 ng/mL(正常值为3.5 ~ 5.0 ng/mL)的患者12例(11.43%), 神经元特异性烯醇化酶(neuron-specific enolase, NSE)≥51 ng/mL(正常值为< 12.5 ng/mL)的患者25例(23.81%)。按美国东部肿瘤协作组评分(Eastern Cooperative Oncology Group performance status, ECOG PS)为0 ~ 1分患者23例(21.90%)。所有患者中处于局限期的40例(38.10%), 广泛期65例(61.90%)。105例患者至少接受2次系统化疗, 化疗方案为EP方案(依托泊苷+顺铂), 有胸腔积液者行胸腔闭式引流, 必要时给予胸腔注射铂类药物治疗, 其他辅助对症支持治疗。

2.2　PNI与临床病理特征的关系

见表1。105例患者PNI的中位数为48.68, PNI与患者性别、有无胸腔积液、ECOG PS评分、临床分期有关(P< 0.05), 女性、无胸腔积液、ECOG PS评分0 ~ 1分、临床分期为局限期的患者PNI更高; 而年龄、吸烟状况、有无胸痛、有无咯血、CEA、NSE水平等与PNI无关(P> 0.05)。

2.3　PNI与SCLC预后的关系

根据PNI中位数(48.68)分为High-PNI和Low-PNI组, High-PNI组59例, Low-PNI组46例。至随访结束后, 105例患者中有75例(71.43%)死亡。所有患者的中位生存时间为19.6个月。生存分析显示(图1)High-PNI组和Low-PNI组1年生存率分别为82.5%和65.3%, 2年生存率分别为49.7%和28.4%, 差异均有统计学意义(P= 0.000)。Cox单因素分析显示(表2), 女性中位总生存时间高于男性, ECOG PS评分中0 ~ 1分的中位总生存时间高于2 ~ 3分, 临床分期中局限期的中位总生存时间高于广泛期, High-PNI组中位总生存时间高于Low-PNI组, 差异均有统计学意义(P< 0.05)。年龄、吸烟指数、咯血、胸痛、胸腔积液、CEA水平、NSE水平对中位总生存时间无影响(P>

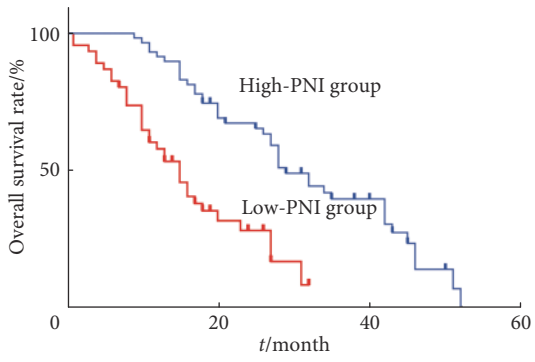

图 1　High-PNI和Low-PNI组SCLC患者的Kaplan-Meier曲线

Fig 1　Kaplan-Meier curves of SCLC patients in the high-PNI and low-PNI groups

表 2　105例SCLC患者OS的影响因素的单因素分析

Table 2　Univariate analysis of prognostic factors of OS in 105 patients with SCLC

Characteristic	Median OS/month	P
Age/yr.		0.308
≥62	18.2	
<62	24.1	
Gender		0.001
Male	18.5	
Female	27.3	
Smoking index		0.133
≥400	19.7	
<400	24.2	
Hemoptysis		0.706
Yes	19.6	
No	19.3	
Thoracalgia		0.133
Yes	15.2	
No	20.7	
Pleural effusion		0.058
Yes	11.6	
No	19.8	
CEA/(ng/mL)		0.286
≥13	24.1	
<13	18.9	
NSE/(ng/mL)		0.053
≥51	16.8	
<51	20.2	
ECOG PS		0.020
0-1	20.5	
2-3	15.6	
Clinical stage		0.001
Limitation	26.2	
Extensive	17.7	
PNI		0.000
High-PNI (≥48.68)	27.1	
Low-PNI (<48.68)	14.2	

0.05)。由表3可见, Cox多因素分析〔赋值情况: Low-PNI= 0, High-PNI= 1; 女性= 0, 男性= 1; ECOG PS (0-1)= 0, ECOG PS (2-3)= 1; 临床分期局限期= 0, 广泛期= 1〕显示, PNI〔优势比(odds ratio, OR)= 0.331, 95%置信区间0.189 ~ 0.580〕和性别(OR= 1.897, 95%置信区间1.051 ~ 3.423)是影响SCLC预后生存的独立影响因素(P< 0.05)。

表 3 多因素分析预后影响因素

Table 3 Multivariate analysis of prognostic factors

Characteristic	β	*SE*	Wald χ^2	*OR*	95% *CI*	*P*
PNI	−1.105	0.029	14.905	0.331	0.189-0.580	0.000
Gender	0.640	0.305	4.515	1.897	1.051-3.423	0.034
ECOG PS	0.058	0.309	0.035	1.060	0.578-1.942	0.851
Clinical stage	0.287	0.287	1.077	1.333	0.775-2.292	0.299

β: Partial regression coefficient; *SE*: Standard error; *OR*: Odds ratio; *CI*: Confidence interval. *Y*: Longer median OS=0, shorter median OS=1. *X*: Low-PNI=0, high-PNI=1; Female=0, male=1; ECOG PS (0-1)=0, ECOG PS (2-3)=1; Clinical stage (limitation)=0, clinical stage (extensive)=1

3 讨论

本研究结果显示，由血清白蛋白和淋巴细胞总数计算的PNI是SCLC独立预后指标，高PNI较低PNI的预后好。该结果与先前对PNI与食管癌[18]、胃癌[19]、结肠癌[20]、胰腺癌[21]等恶性肿瘤预后关系的研究结果一致。PNI最初被ONODERA等[22]用于评估消化系统疾病患者的营养和免疫状况，主要作为营养状况的指标。营养不良是癌症患者的常见问题，与并发症的风险增加和抗癌治疗耐受性降低有关。免疫功能受损、伤口愈合延迟和病情延长恢复是营养不良发病率增加的主要原因。不同于消化系统营养不良的主要原因(营养摄取减少)，肺癌患者营养不良常与副肿瘤综合征的代谢紊乱[23]和临床症状、心理素质等相关，包括疼痛、气短、抑郁或严重的身体和心理社会症状、严重疲劳。因此，基线营养状况很重要，营养不良可能是治疗预后差的一个重要原因。

血清白蛋白水平已被证明是各种患者人群营养不良的良好指标[24]，据相关研究表明：治疗前低白蛋白血症是不同恶性疾病预后的独立预测因子[25]。另一方面，淋巴细胞在各种恶性肿瘤细胞介导的免疫反应中起着重要作用，通过引发细胞毒性免疫应答和抑制肿瘤细胞增殖、侵袭和迁移等在肿瘤预防方面发挥重要作用，其也被证明可以预测临床预后[26]。现在普遍认为营养是免疫反应的重要决定因素；此外，免疫应答受损已被证明与低胆固醇相关[27]，这就意味着营养不良和免疫功能受损一起促进肿瘤发展。

本研究还探讨了临床病理变量与PNI之间的联系，以排除潜在的偏倚。结果显示男性、胸腔积液、ECOG PS评分差、广泛分期的SCLC患者PNI更低。不同PNI组的OS差异可能由选择偏倚来解释，因为高PNI组包括更多的局限期患者，其生存期比广泛期患者好，并且接受更多的治疗。单因素变量分析显示性别、ECOG PS、临床分期及PNI值与SCLC患者的OS相关，与既往文献一致[28]，而年龄、吸烟指数等与OS无关($P>0.05$)，这与前期学者[29]的研究不一致，这可能与本研究的样本量不够大有关。多因素分析发现性别和PNI是SCLC患者预后的独立因素，而ECOG PS评分和临床分期在多因素分析中无统计学意义。

PNI是一种易于获得和可重复的参数，因此临床实用。但是需要注意几个问题，PNI可能是肿瘤负荷的非特异性标志物，因此其他非肿瘤情况(如自身免疫和感染疾病和类固醇使用)可能是混杂因素。在本研究中，我们排除了这类患者，Cox多因素分析结果表明PNI是SCLC中独立预后影响因素。这一结论是否可以扩展到具有上述情况的SCLC患者尚待阐明。由于本研究为回顾性研究，样本量相对较少，结论有待于大样本量前瞻性研究进一步证实。

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（2019 – 09 – 23收稿, 2020 – 02 – 06修回）

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