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Nomogram Model Is Used to Predict the Individualized Prognosis of Gastric Cancer after D2 Radical Operation

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Abstract

Background and Purpose: At present, there is no prediction model for the prognosis of gastric cancer in Yan'an City. This study intends to build a personalized prediction model to predict the prognosis of gastric cancer in Yan'an City. Method: The patients who underwent gastric cancer surgery in YAUAH Gastrointestinal Surgery (705 cases) were collected retrospectively from January 1, 2010 to November 1, 2014. The COX proportional hazards regression model was used for multi-factor survival analysis, and the Nomogram model was constructed. Results: Multivariate analysis showed that age, tumor diameter, T stage, N stage, LODDS, and the number of chemotherapy were independent risk factors affecting overall survival (OS), and based on this, the Nomogram model was constructed. Conclusion: The Nomogram model constructed in this study can predict the 3-year and 5-year survival rates of gastric cancer patients, and has good clinical application prospects.

Keywords

Gastric Cancer, Survival Rate, Prognosis, Nomogram

Nomogram模型用于预测胃癌D2根治术后个体化预后

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摘　要

背景与目的：目前延安市尚未有针对胃癌患者预后的预测模型，本研究拟构建一种个体化预测模型预测延安市患者胃癌预后的列线图模型。方法：回顾性收集2010年1月1日至2014年11月1日在YAUAH胃肠外科(705例)行胃癌手术的患者。并采用COX比例风险回归模型进行多因素生存分析，并构建Nomogram模型。结果：多因素分析显示，年龄、肿瘤直径、T分期、N分期、LODDS和化疗次数是影响总生存率(OS)的独立危险因素，并依据此构建了Nomogram模型。结论：本研究构建的Nomogram模型能够预测胃癌患者3年、5年生存率，并有良好的临床应用前景。

关键词

胃癌，生存率，预后，列线图

1. 引言

胃癌是全球第五大恶性肿瘤，也是第三大癌症相关死亡原因，在东亚地区发病率尤其高[1]。世界上每年有近一半的胃癌新发病例发生在中国，但近 90%的胃癌患者在初次诊断时已进展或远处转移，特别是在非发达地区[2]。准确预测预后对选择治疗策略和有效的医患沟通是至关重要的。

根治性胃癌切除联合局部淋巴结切除术是治疗无远处转移胃癌唯一有效的方法[3]。GC 患者生存预测的准确性是术后治疗决策和监测的关键。近年来，淋巴结分期方法一直都是国际关注的热点，每个分期都有其各自的优势与局限性。目前，被广泛接受的淋巴结分期是美国癌症联合会(American Joint Committee on Cancer, AJCC)/国际抗癌联盟(Union for International Cancer Control, UICC)的N分期，pN 分期是胃癌独立预后因素[4]，但以 pN 作为基础的淋巴结分期的可靠性因其可导致淋巴结分期产生偏移而受到广泛质疑[5]。鉴于 pN 分期的局限性，相关学者提出了阳性淋巴结对数比率(log odds of positive lymph nodes, LODDS)分期，并且在肺癌[6]、乳腺癌[7]、胰腺癌[8]、食管癌[9]和结直肠癌[10]等几种癌症中，尤其是在根治术中淋巴结清扫不足的情况下，LODDS 分期与 AJCC-pN 分期相比，在患者的生存率方面显示出明显的优越性。

2. 材料与方法

2.1. 一般资料

收集 2010 年 1 月 1 日至 2014 年 11 月 1 日在 YAUAH 胃肠外科(705 例)行胃癌手术的患者。纳入标准：原发性胃癌；无合并恶性肿瘤；无术前化疗；无远处转移；R0 切除(无肉眼或显微镜下残留肿瘤)；无一个或多个缺失值。数据集中包括患者的人口统计学(年龄和性别)、病理特征(位置、直径、分化、组织学、浸润深度、转移淋巴结数目和检查淋巴结数目)、辅助化疗和随访数据(随访时间和生存率)。肿瘤的位置分为胃的上三分之一、中三分之一、下三分之一或超过胃体一半。胃食管交界处腺癌被归类为上三分之一胃癌。肿瘤大小定义为最大直径长度。分化程度分为高分化、中分化、低分化和其他。侵犯深

度分为粘膜下层、固有肌、浆膜下、浆膜下及邻近器官侵犯。转移淋巴结数目按(AJCC) TNM 第八版[11]分类(0, 1~2, 3~6, 7~15, ≥16)的淋巴结分组进行分类。LODDS 通过 log(pnod + 0.5)/(tnod-pnod + 0.5)估计(pnod：阳性淋巴结数；tnod：总淋巴结切除数) [5]，0.5 是为了避免无穷多个节点。LODDS 值按 X-tile 分为：LODDS < 0.70；−0.70 ≤ LODDS < 0.27；LODDS ≥ 0.27。辅助化疗分为无、1~5 次或≥6 次。从医院记录中收集随访数据。随访资料收集自手术时间至最后一次随访时间。

2.2. LODDS 的计算公式

阳性淋巴结对数比率(log odds of positive lymph nodes, LODDS)。定义为当淋巴结被获取时，阳性淋巴结数和阴性淋巴结比率的对数，其公式为 log(pnod + 0.5)/(tnod-pnod + 0.5) (pnod：阳性淋巴结数；tnod：总淋巴结切除数) [12]，分子和分母各加 0.5 的目的是为了避免出现被除数为 0 以及出现众多 LODDS 为 0 的情况。

2.3. 统计分析

YAUAH 患者(n = 705)评估其临床病理特征。被认为与临床相关或与结果呈单变量关系的变量将被纳入多变量 Cox 比例风险回归模型。多变量模型包括单变量分析 P < 0.2 的候选变量。在多元 Cox 回归模型中，变量采用反向逐步选择法。在确定预后因素的预测模型的基础上，构建了预测 3 年和 5 年总生存率的列线图。

3. 结果

3.1. 临床特征

训练集中患者的临床特征见表 1。在训练和验证数据集中，死亡率分别为 55.2%。在训练集中，LN 的平均数分别为 15。大多数病人接受了辅助化疗。中位生存期分别为 54 个月。中位随访期分别为 87 个月。

Table 1. Characteristics of patients of radical resection of GC in the dataset
表 1. 胃癌根治术患者的特征数据集

Characteristic	Training Dataset		P
	Status = 0 (n = 316)	Status = 1 (n = 389)	
Gender, No. (%)			0.23
Male	75 (23.7%)	77 (19.8%)	
Female	241 (76.3%)	312 (80.2%)	
Age, No. (%), years			<0.01
≤60	197 (62.3%)	180 (46.3%)	
>60	119 (37.7%)	209 (53.7%)	
Part, No. (%),			<0.01
Bottom	79 (25.0%)	84 (21.6%)	
Antrum	179 (56.6%)	178 (45.8%)	
Esophageal connection	50 (15.8%)	107 (27.5%)	
Multiple parts	8 (2.5%)	20 (5.1%)	

Continued

Differentiation, No. (%)			<0.01
High	6 (1.9%)	1 (0.3%)	
Middle	118 (37.3%)	107 (27.5%)	
Lox	173 (54.7%)	248 (63.8%)	
Other	19 (6.0%)	33 (8.5%)	
Organizationtype, No. (%)			0.04
Adenocarcinoma	277 (87.7%)	318 (81.7%)	
Other	39 (12.3%)	71 (18.3%)	
Borrmann, No. (%)			<0.01
I	46 (14.6%)	23 (5.9%)	
II	42 (13.3%)	19 (4.9%)	
III	233 (70.6%)	323 (83.0%)	
IV	5 (1.6%)	24 (6.2%)	
Size No. (%), cm			<0.01
≤4	144 (45.6%)	76 (19.5%)	
>4	172 (54.4%)	313 (80.5%)	
T-Stage, No. (%)			<0.01
1	61 (19.3%)	11 (2.8%)	
2	80 (25.3%)	44 (11.3%)	
3	88 (27.8%)	134 (34.4%)	
4a	83 (26.3%)	129 (33.2%)	
4b	4 (1.3%)	71 (18.3%)	
N-Stage No. (%)			<0.01
0	199 (63.0%)	86 (22.1%)	
1	41 (13.0%)	62 (15.9%)	
2	49 (15.5%)	97 (24.9%)	
3a	24 (7.6%)	106 (27.2%)	
3b	3 (0.9%)	38 (9.8%)	
LODDS, No. (%)			<0.01
LODDS1	216 (68.4%)	108 (27.8%)	
LODDS2	87 (27.5%)	179 (46.0%)	
LODDS3	13 (4.1%)	102 (26.2%)	
Chemotherapy No. (%)			<0.01
None	3 (0.9%)	70 (18.0%)	
1~5 times	170 (53.8%)	278 (71.5%)	
≥6 times	143 (45.3%)	41 (10.5%)	

3.2. 训练集单因素分析的独立预后因素

单因素分析显示性别与生存率无明显相关性(P = 0.286)。多因素分析显示，年龄、肿瘤直径、T 分期、N 分期、LODDS 和化疗次数是影响总生存率(OS)的独立危险因素(表 2)。

Table 2. Predictors for prognosis of patients following surgical
表 2. 术后患者预后的预测因素

Variable	β	Odds Ratio (95% CI)	P
Age	0.383	1.466 (1.196 to 1.798)	0.000
Size	0.295	1.343 (1.025 to 1.759)	0.033
T-stage			0.000
T2	0.406	1.500 (0.756 to 2.977)	0.246
T3	0.945	2.574 (1.320 to 5.019)	0.006
T4a	0.822	2.275 (1.173 to 4.412)	0.015
T4b	1.788	5.976 (2.946 to 12.123)	0.000
Chemotherapy			0.000
1~5	−1.151	0.316 (0.237 to 0.422)	0.000
≥6	−2.313	0.099 (0.066 to 0.149)	0.000
LODDS			0.009
LODDS2	0.368	1.445 (0.968 to 2.155)	0.071
LODDS3	0.740	2.097 (1.283 to 3.427)	0.003
N-stage			0.057
N1	0.167	1.181 (0.775 to 1.802)	0.439
N2	0.317	1.373 (0.859 to 2.192)	0.185
N3a	0.507	1.660 (1.000 to 2.755)	0.050
N3b	0.863	2.370 (1.294 to 4.339)	0.005

3.3. OS 的预后列线图

图 1 显示了数据集中 OS 所有重要独立因素的预后列线图。

4. 讨论

在本研究中，我们对 701 例胃癌根治术患者进行了评估，结果表明：1) LODDS 与(AJCC) pN 分期都是独立的预后因素；2) 建立了一个诺模图，并在预测胃癌患者的生存率方面表现良好。

本研究构建了延安地区胃癌患者预后的 Nomogram 模型。发现 LODDS 定量分析对淋巴结转移的胃癌患者的预后判断是有一定价值的，胃癌淋巴结转移对治疗决策和生存评估有很大的临床影响。(AJCC) pN 分期被广泛应用，但其一个主要缺陷是预后的准确性受淋巴结总数的影响[12]。最新的 AJCC 指南建议使用 D2 淋巴结切除术切除足够数量的淋巴结(不少于 16 个)；然而，并非所有机构都能达到这一标准。一些研究报告称，在美国[13]和中国[14] [15]，只有 29%和 60.2%的病例获得了≥16 个淋巴结。此外，在一些研究中，避免分期偏移的总淋巴结的最佳数目仍不清楚[16] [17]。因此，在淋巴结总数不足的情况下，可能出现分期偏移现象。在我们的研究中，我们根据训练组评估了独立的危险因素，包括年龄、肿瘤直

径、T 分期、pN 分期、LODDS 和化疗次数。正如 Antoni M. Szczepanik 所认为的，由于胃癌的异质性，可能无法通过单一的测量来预测疾病过程。与其他研究人员相比，本研究通过随访后，将患者术后化疗次数也纳入到了本研究的模型中，其对患者的预后更有意义。

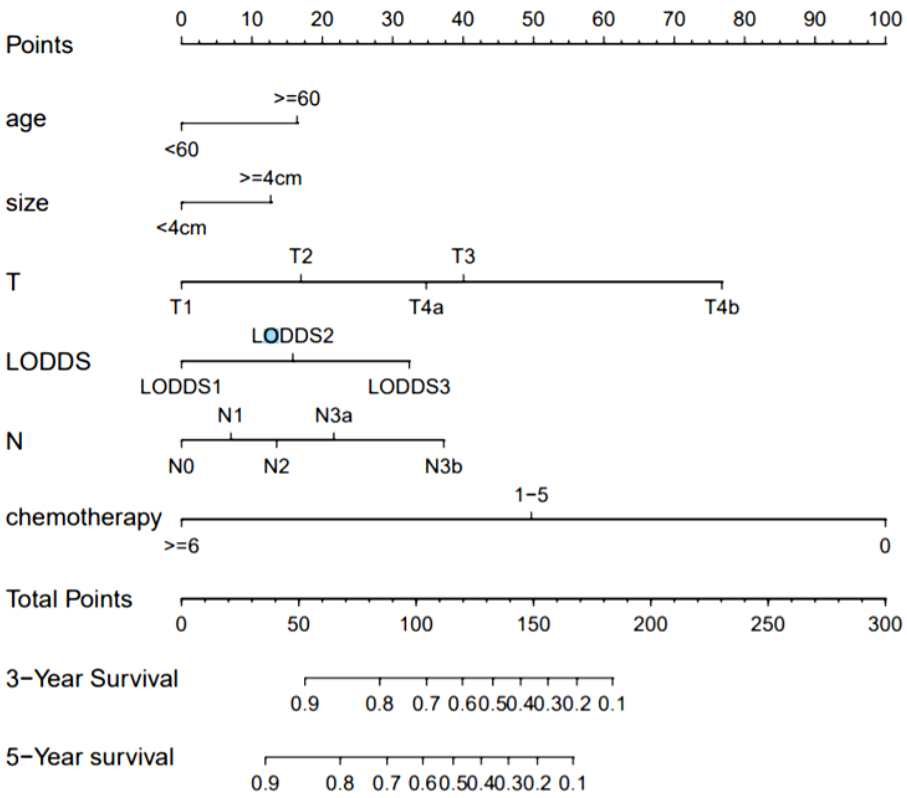

Figure 1. Prognostic nomogram of all important independent factors of OS in dataset
图 1. 集中 OS 所有重要独立因素的预后列线图

综上所述，目前的研究表明 LODDS 是胃癌根治术患者的一个有用的预后指标。本研究构建了延安地区胃癌根治术后的个体化预后预测模型，该 Nomogram 模型优于传统 TNM 分期，有着良好的应用前景。

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