·论著·

基于SEER数据库的小肠腺癌患者预后的危险因素分析及预测模型构建

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摘要 目的 基于监测、流行病学和最终结果（SEER）数据库探讨影响小肠腺癌（SBA）患者预后的危险因素，构建SBA生存风险模型并评价临床预测价值。**方法** 分析SEER数据库纳入的2 639例SBA患者临床信息及预后资料。以总生存期（OS）和疾病特异性生存期（DSS）作为预后预测指标。将患者按7 ∶ 3比例随机分为训练组和验证组。利用单因素和多因素Cox回归分析训练组患者影响预后的危险因素，构建预后预测模型，绘制受试者操作特征曲线；由验证组进行预后预测模型验证，绘制临床决策曲线。**结果** SBA患者年龄（$P < 0.01$）、肿瘤部位（$P = 0.018$）、大小（$P = 0.042$）、T分期（$P < 0.01$）、阳性淋巴结检出率（$P < 0.01$）、肿瘤单发灶（$P < 0.01$）、继发肝脏转移（$P < 0.01$）是影响OS的独立危险因素；年龄（$P < 0.01$）、肿瘤大小（$P = 0.022$）、T分期（$P < 0.01$）、阳性淋巴结检出率（$P < 0.01$）、肿瘤单发灶（$P < 0.01$）、继发肝脏转移（$P < 0.01$）是影响DSS的独立危险因素。成功建立预后预测模型，验证结果显示校准的预测曲线与实际曲线具有一致性。**结论** 年龄、肿瘤大小、T分期、阳性淋巴结检出率、肿瘤单发灶、继发肝脏转移是影响SBA患者OS和DSS的独立危险因素；除此之外，肿瘤部位也是影响SBA患者OS的独立危险因素。建立的预后预测模型具有良好预测价值，能有效评估SBA患者预后，可为患者提供合理的治疗建议。

关键词 小肠腺癌；总生存期；疾病特异性生存期；预后预测模型
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Prognostic risk factor analysis and prognosis prediction model construction for patients with small bowel adenocarcinoma based on the SEER database

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Abstract Objective To explore the risk factors affecting the prognosis of patients with small bowel adenocarcinoma（SBA），construct the SBA survival risk model，and evaluate the clinical predictive value. **Methods** Clinical information and prognosis data of 2 639 patients included in the surveillance，epidemiology，and end results（SEER）database were retrospectively analyzed. Overall survival（OS）and disease specific survival（DSS）were used as prognostic indicators. The training group and validation group were randomized at a 7 ∶ 3 ratio using univariate and multivariate Cox regression analysis. Prognostic factors affecting SBA survival were screened，and a prognostic prediction model was constructed. The receiver operation characteristic curve，model validation by validation group，and clinical decision curve. **Results** Age（$P < 0.01$），tumor site（$P = 0.018$），size（$P = 0.042$），T stage（$P < 0.01$），detection rate of positive lymph nodes（$P < 0.01$），single tumor focus（$P < 0.01$），and secondary liver metastasis（$P < 0.01$）were independent risk factors affecting prognosis of OS in patients with SBA；age（$P < 0.01$），tumor size（$P = 0.022$），T stage（$P < 0.01$），detection rate of positive lymph nodes（$P < 0.01$），single tumor focus（$P < 0.01$），and secondary liver metastasis（$P < 0.01$）were independent risk factors affecting the prognosis of DSS in patients with SBA. The nomogram，survival risk assessment model，and calibration prediction curve were consistent with the actual curve. **Conclusion** Age，tumor size，T stage，detection rate of positive lymph nodes，single tumor focus，and secondary liver metastasis were independent risk factors for OS and DSS in patients with SBA. Tumor site was also an independent risk factor for OS in SBA patients. The established prognostic prediction model has good predictive value，can effectively evaluate the prognosis of SBA patients，and can provide reasonable treatment advice for patients.

Keywords small bowel adenocarcinoma；overall survival；disease specific survival；prognostic prediction model

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虽然小肠约占消化道总长度（8~9 m）的75%和黏膜表面积的90%，但临床上小肠肿瘤（small bowel tumor，SBT）较为少见，发生率仅占消化系统肿瘤的3.4%[1]。SBT包括小肠腺癌（small intestinal adenocarcinoma，SBA）、间质瘤、神经内分泌肿瘤、淋巴瘤等，其中SBA是最常见的类型之一，约占40%[2-3]。SBA初发症状不明显，确诊时多已进展至晚期，且预后较差。已有研究[4-5]发现，饮食结构、某些肠道炎症性疾病（克罗恩病、乳糜泻）、遗传易感性疾病［家族性腺瘤性息肉病（familial adenomatous polyposis，FAP）、林奇综合征（Lynch syndromes，LS）、波伊茨–耶格综合征（Peutz-Jeghers syndrome，PJS）和青少年息肉病综合征］均可能是SBA的致病因素。研究[5-6]发现微卫星不稳定（microsatellite instability，MSI）在SBA发展过程中起重要作用，主要可能为*MMR*、*hMLH1*基因突变所致。

美国国家癌症研究所的监测、流行病学和最终结果（surveillance，epidemiology，and end results，SEER）数据库是临床常用的公共数据库之一，收纳乳腺、消化系统、生殖系统等9类肿瘤患者的人口统计学、原发肿瘤部位、肿瘤形态、分期、诊断阶段以及生存状态随访等临床数据。本研究收集SEER数据库中SBA患者的临床资料，分析影响SBA预后的危险因素，进而构建预后预测模型，旨在为SBA患者提供合理的治疗建议及预后评估提供参考。

1　材料与方法

1.1　临床资料来源

从SEER数据库（https://seer.cancer.gov/）中提取2010年至2018年病理诊断为SBA的2 639例患者信息。纳入标准：（1）2010年至2018年诊断为小肠恶性肿瘤并行手术的患者；（2）病理明确为原发SBA（ICD-O-3：8140/3）；（3）年龄>18岁；（4）临床资料完整。排除标准：（1）其他病理类型的SBT；（2）未明确生存时间及生存状态；（3）合并其他恶性肿瘤。

1.2　资料收集及分组

记录纳入患者的各项指标，包括年龄、性别、肿瘤部位、肿瘤大小、T分期、N分期、阳性淋巴结检出率、肿瘤单发灶、继发肝脏转移等，以总生存期（overall survival，OS）和疾病特异性生存期（disease specific survival，DSS）作为预后评估指标。将入选患者按7 ： 3比例随机分为训练组和验证组。

1.3　统计学分析

采用R4.1.1软件进行数据分析，对于不符合正态分布的计量资料采用$M(P_{25}\sim P_{75})$表示。计数资料采用率（%）表示，组间比较采用χ^2检验或Fisher确切概率法。从训练组中筛选有统计学意义（$P<0.05$）的指标进行单因素和多因素Cox分析来筛选影响SBA患者预后的危险因素，进而构建SBA患者预后预测模型。根据预测模型绘制受试者操作特征（receiver operating characteristic，ROC）曲线，在验证组进行模型验证并绘制临床决策曲线。$P<0.05$为差异有统计学意义。

2　结果

2.1　患者临床指标分析

共纳入2 639例，其中男1 454例（55.10%），女1 185例（44.90%）；年龄20~84岁，中位年龄65岁；生存时间1~107个月，中位生存时间15个月。训练组与验证组患者各项临床指标比较差异均无统计学意义（均$P>0.05$），见表1。

2.2　患者OS的单因素及多因素分析

单因素分析结果显示，患者年龄、性别、人种、肿瘤位置、肿瘤大小、肿瘤T分期、N分期、淋巴结阳性检出率、肿瘤单发灶、肝脏转移均与OS相关（均$P<0.05$），见表2。

将单因素分析有统计学意义（$P<0.05$）指标纳入多因素分析。结果显示，年龄（$P<0.01$）、肿瘤部位（$P=0.018$）、肿瘤大小（$P=0.042$）、T分期（$P<0.01$）、阳性淋巴结检出率（$P<0.01$）、肿瘤单发灶（$P<0.01$）和肝脏转移（$P<0.01$）是SBA患者OS的独立影响因素，见表2。

2.3　患者DSS的单因素及多因素分析

单因素分析结果显示，年龄、性别、肿瘤位置、肿瘤大小、肿瘤T分期、N分期、淋巴结阳性检出率、肿瘤单发灶、肝脏转移均与DSS相关（均$P<0.05$），见表3。

将单因素分析有统计学意义（$P<0.05$）的指标纳入多因素分析。结果显示，年龄（$P<0.01$）、肿瘤大小（$P=0.022$）、T分期（$P<0.01$）、阳性淋巴结检出率（$P<0.01$）、肿瘤单发灶（$P<0.01$）和肝脏转移（$P<0.01$）是SBA患者DSS的独立影响因素，见表3。

表1　SBA 患者各项临床指标分析

Tab.1　Analysis of the clinical indicators in patients with SBA

Item	Total	Training group (n = 1 847)	Validation group (n = 792)	P
Age (year)	65 (20–84)	64 (20–84)	66 (22–84)	0.087
Survival time (month)	15 (1–107)	16 (1–107)	15 (1–106)	0.978
Sex				0.501
Female	1 185 (44.90)	821 (44.45)	364 (45.96)	
Male	1 454 (55.10)	1 026 (55.55)	428 (54.04)	
Tumor site				0.361
Duodenum	1 541 (58.39)	1 079 (58.42)	462 (58.33)	
Ileum	313 (11.86)	230 (12.45)	83 (10.48)	
Jejunum	451 (17.09)	314 (17.00)	137 (17.30)	
Other	334 (12.66)	224 (12.12)	110 (13.89)	
Race				0.810
Melanoderm	557 (21.11)	393 (21.28)	164 (20.71)	
Caucasian	1 870 (70.86)	1 309 (70.87)	561 (70.83)	
Asians and Latinos	198 (7.50)	134 (7.26)	64 (8.08)	
Other	14 (0.53)	11 (0.60)	3 (0.38)	
Tumor size				0.250
≤2 cm	265 (10.04)	184 (10.00)	81 (10.22)	
>2–5 cm	1 125 (42.63)	804 (43.53)	321 (40.53)	
>5 cm	578 (21.90)	409 (22.14)	169 (21.34)	
Other	671 (25.43)	450 (24.36)	221 (27.90)	
T stage				0.103
$T_{1/2}$	411 (15.58)	285 (15.43)	126 (15.91)	
T_3	814 (30.85)	563 (30.48)	251 (31.69)	
T_4	1 013 (38.39)	734 (39.74)	279 (35.23)	
Other	401 (15.18)	265 (14.35)	136 (17.17)	
N stage				0.700
N_0	1 328 (50.32)	934 (50.57)	394 (49.75)	
N_1	726 (27.51)	503 (27.23)	223 (28.16)	
N_2	390 (14.78)	279 (15.10)	111 (14.01)	
Other	195 (7.39)	131 (7.10)	64 (8.08)	
Detection rate of positive lymph nodes				0.165
≤30%	1 265 (47.93)	888 (48.08)	377 (47.60)	
>30%	351 (13.30)	246 (13.32)	105 (13.26)	
Not detected	946 (35.85)	668 (36.17)	278 (35.10)	
Other	77 (2.92)	45 (2.43)	32 (4.04)	
Single tumor focus				0.199
No	230 (8.72)	170 (9.20)	60 (7.58)	
Yes	2 409 (91.28)	1 677 (90.8)	732 (92.42)	
Secondary liver metastasis				0.930
No	2 197 (83.25)	1 539 (83.32)	658 (83.08)	
Yes	442 (16.75)	308 (16.68)	134 (16.92)	

2.4　SBA患者预后预测模型建立及验证

基于年龄、肿瘤位置、肿瘤大小、T分期、阳性淋巴结检出率、肿瘤单发灶、肝脏转移等OS预后的独立危险因素建立关于OS的列线图（图1A）。基于年龄、肿瘤大小、T分期、阳性淋巴结检出率、肿瘤单发灶、继发肝脏转移等DSS预后的独立危险因素建

表2　SBA患者OS单因素及多因素分析

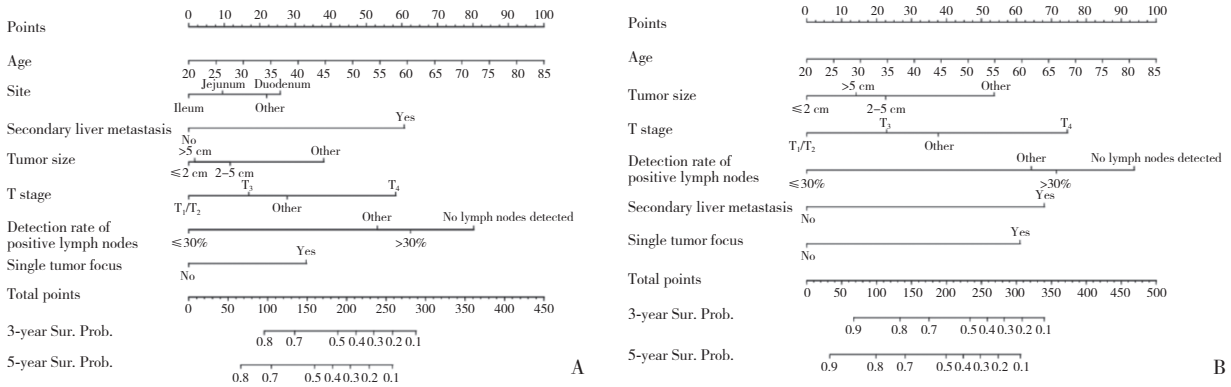
Tab.2　Univariate and multifactor analysis of OS in patients with SBA

Item	Univariate analysis			Multifactor analysis		
	HR	95%*CI*	*P*	*HR*	95%*CI*	*P*
Age	1.021	1.016–1.026	<0.001	1.019	1.013–1.024	<0.001
Sex	1.159	1.026–1.310	0.018	1.118	0.988–1.265	0.076
Female	1	–	–	1	–	–
Male	1.159	1.026–1.310	<0.001	1.094	0.966–1.239	0.158
Tumor site	0.856	0.807–0.908	<0.001	0.934	0.882–0.988	0.018
Duodenum	1	–	–	1	–	–
Ileum	0.489	0.395–0.606	<0.001	0.752	0.602–0.940	0.031
Jejunum	0.553	0.462–0.662	<0.001	0.812	0.673–0.982	0.031
Other	0.845	0.702–1.018	0.076	0.960	0.795–1.160	0.674
Race	0.930	0.866–0.999	0.045	0.965	0.920–1.013	0.148
Melanoderm	1	–	–	1	–	–
Caucasian	0.894	0.692–1.155	0.391	0.918	0.707–1.192	0.521
Asians and Latinos	0.877	0.759–1.014	0.077	0.893	0.769–1.036	0.136
Other	0.247	0.061–0.993	0.049	0.455	0.113–1.837	0.268
Tumor size	1.390	1.302–1.485	<0.001	1.072	1.002–1.147	0.042
≤2 cm	1	–	–	1	–	–
>2–5 cm	1.190	0.942–1.503	0.144	1.118	0.880–1.420	0.362
>5 cm	0.981	0.758–1.269	0.882	0.995	0.763–1.297	0.972
Other	2.632	2.073–3.340	<0.001	1.562	1.212–2.014	0.001
T stage	1.535	1.428–1.651	<0.001	1.223	1.142–1.308	<0.001
$T_{1/2}$	1	–	–	1	–	–
T_3	0.775	0.630–0.952	0.015	1.171	0.935–1.467	0.169
T_4	1.506	1.248–1.816	<0.001	1.956	1.594–2.400	<0.001
Other	2.783	2.239–3.459	<0.001	1.418	1.125–1.787	0.003
N stage	1.231	1.156–1.311	<0.001	1.031	0.970–1.096	0.320
N_0	1	–	–	1	–	–
N_1	1.280	1.110–1.476	<0.001	1.270	1.086–1.485	0.003
N_2	1.284	1.079–1.527	0.005	1.142	0.904–1.441	0.264
Other	2.261	1.807–2.828	<0.001	0.910	0.718–1.151	0.431
Detection rate of positive lymph nodes	1.805	1.698–1.918	<0.001	1.494	1.391–1.604	<0.001
≤30%	1	–	–	1	–	–
>30%	2.388	1.986–2.872	<0.001	1.983	1.585–2.483	<0.001
Not detected	3.942	3.429–4.532	<0.001	2.728	2.287–3.253	<0.001
Other	2.812	1.934–4.087	<0.001	1.788	1.207–2.649	0.004
Single tumor focus	0.282	0.244–0.326	<0.001	2.046	1.749–2.393	<0.001
No	1	–	–	1	–	–
Yes	3.547	3.068–4.101	<0.001	2.039	1.740–2.389	<0.001
Secondary liver metastasis	0.602	0.482–0.751	<0.001	0.663	0.530–0.829	<0.001
No	1	–	–	1	–	–
Yes	1.660	1.330–2.075	<0.001	1.497	1.196–1.874	<0.001

表3　SBA患者DSS单因素分析及多因素分析

Tab.3　Univariate and multifactor analysis of DSS in patients with SBA

Item	Univariate analysis			Multifactor analysis		
	HR	95%*CI*	*P*	*HR*	95%*CI*	*P*
Age	1.018	1.012–1.023	<0.001	1.015	1.010–1.021	<0.001
Sex	1.156	1.017–1.315	0.027	1.101	0.967–1.254	0.145
Female	1	–	–	1	–	–
Male	1.156	1.017–1.315	0.027	1.069	0.939–1.220	0.315
Tumor site	0.874	0.822–0.929	<0.001	0.950	0.895–1.008	0.088
Duodenum	1	–	–	1	–	–
Ileum	0.503	0.402–0.630	<0.001	0.795	0.629–1.005	0.055
Jejunum	0.588	0.488–0.708	<0.001	0.872	0.717–1.060	0.170
Other	0.876	0.722–1.065	0.184	1.008	0.827–1.227	0.941
Race	0.979	0.932–1.030	0.417			
Melanoderm	1	–	–			
Caucasian	0.932	0.710–1.224	0.612			
Asians and Latinos	0.931	0.797–1.087	0.365			
Other	0.288	0.072–1.158	0.080			
Tumor size	1.431	1.335–1.533	<0.001	1.087	1.012–1.167	0.022
≤2 cm	1	–	–	1	–	–
>2–5 cm	1.382	1.064–1.797	0.016	1.255	0.960–1.640	0.097
>5 cm	1.179	0.887–1.568	0.257	1.160	0.866–1.553	0.319
Other	3.081	2.358–4.026	<0.001	1.786	1.346–2.368	<0.001
T stage	1.630	1.509–1.761	<0.001	1.262	1.174–1.357	<0.001
$T_{1/2}$	1	–	–	1	–	–
T_3	0.850	0.676–1.067	0.161	1.242	0.970–1.590	0.086
T_4	1.781	1.448–2.191	<0.001	2.228	1.780–2.788	<0.001
Other	3.200	2.524–4.057	<0.001	1.533	1.194–1.969	<0.001
N stage	1.266	1.185–1.352	<0.001	1.044	0.980–1.113	0.186
N_0	1	–	–	1	–	–
N_1	1.326	1.140–1.542	<0.001	1.283	1.088–1.512	0.003
N_2	1.402	1.171–1.678	<0.001	1.203	0.945–1.532	0.134
Other	2.361	1.867–2.987	<0.001	0.910	0.711–1.164	0.451
Detection rate of positive lymph nodes	1.836	1.721–1.958	<0.001	1.499	1.389–1.616	<0.001
≤30%	1	–	–	1	–	–
>30%	2.596	2.140–3.149	<0.001	2.064	1.632–2.610	<0.001
Not detected	4.113	3.545–4.772	<0.001	2.934	2.436–3.535	<0.001
Other	3.044	2.064–4.489	<0.001	1.932	1.285–2.904	0.002
Single tumor focus	3.737	3.213–4.347	<0.001	2.096	1.781–2.467	<0.001
No	1	–	–	1	–	–
Yes	3.737	3.213–4.347	<0.001	2.100	1.781–2.475	<0.001
Secondary liver metastasis	0.456	0.350–0.594	<0.001	0.508	0.390–0.663	<0.001
No	1	–	–	1	–	–
Yes	2.192	1.684–2.854	<0.001	1.943	1.489–2.534	<0.001



A, OS; B, DSS.

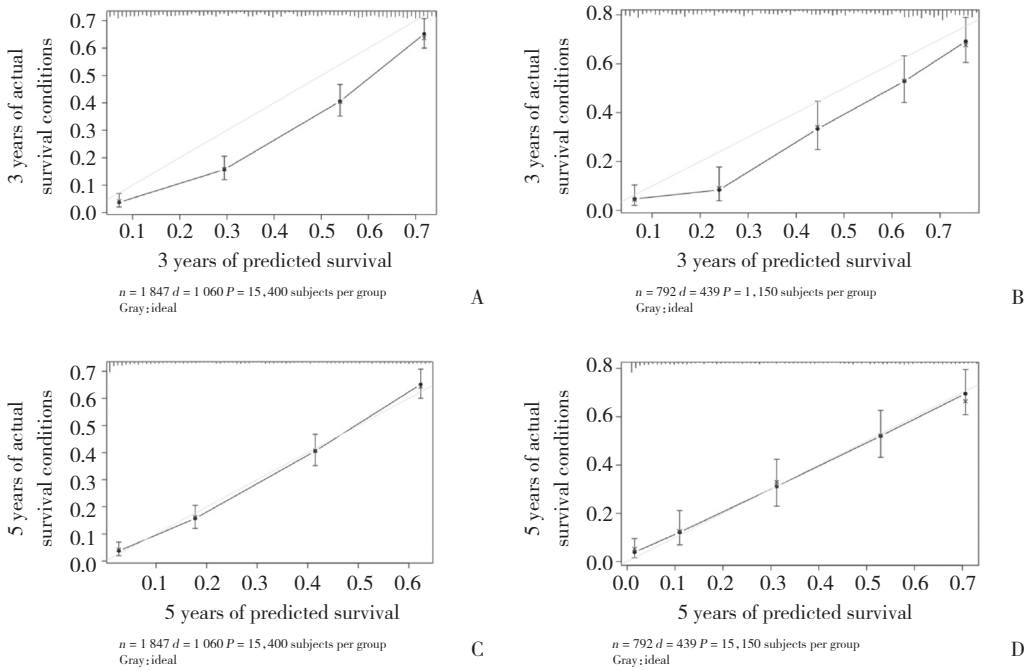
图1　SBA患者OS、DSS的列线图

Fig.1　The nomograms of OS and DSS of SBA patients

立了关于DSS的列线图(图1B)。验证组对模型进行验证的结果显示,校准曲线检验结果显示拟合良好(图2、3),3年、5年ROC曲线显示模型可信度良好(图4、5),可见模型预测值与实测值基本一致,预测能力较好。临床预测决策曲线分析(decision curve analysis,DCA)显示模型具有良好应用价值,见图6。

3　讨论

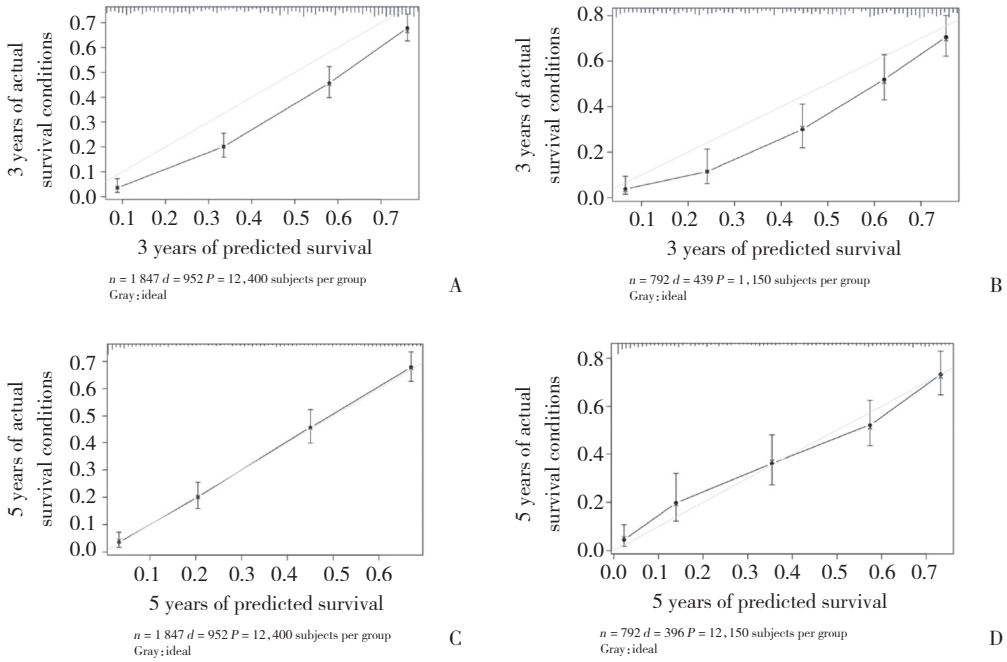
SBA临床上较少见,初始症状多不明显,慢性病程常有隐匿性消化道出血及贫血症状[7]。手术切除为SBA唯一根治性治疗方式。对于Ⅰ~Ⅲ期患者,优先选择根治性手术切除+区域性淋巴结清扫;对于Ⅳ期及不可根治性切除患者,可采用姑息性手术和化疗,目前使用的化疗方案有5-FU+亚叶酸+奥沙利铂(FOLFOX方案)、奥沙利铂联合卡培他滨方案(CAPEOX方案,又称XELOX方案)以及5-FU联合伊立替康方案等。已有研究[8-9]显示,采用辅助化疗的晚期SBA患者的OS明显延长。



A, B, 3-year calibration curve of OS in the training group and validation group; C, D, 5-year calibration curve of OS in the training group and validation group.

图2　SBA患者OS的3年及5年校准曲线验证

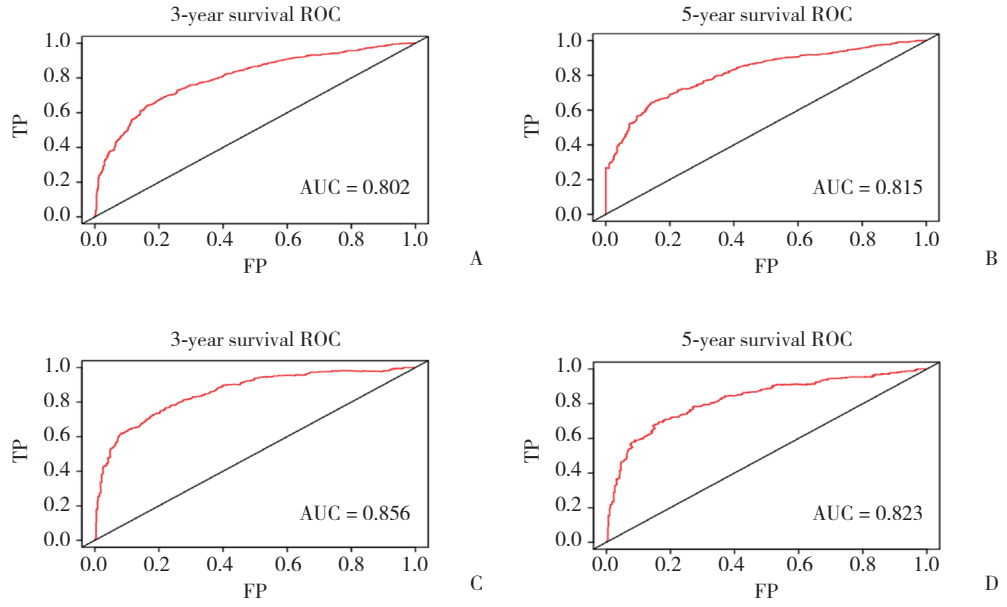
Fig.2　Calibration curve validation curve of SBA patients' OS in 3 and 5 years



A, B, 3-year calibration curve of DSS in the training group and validation group; C, D, 5-year calibration curve of DSS in the training group and validation group.

图3　SBA患者DSS的3年及5年校准曲线验证

Fig.3　Calibration curve validation curve of SBA patients' DSS in 3 and 5 years



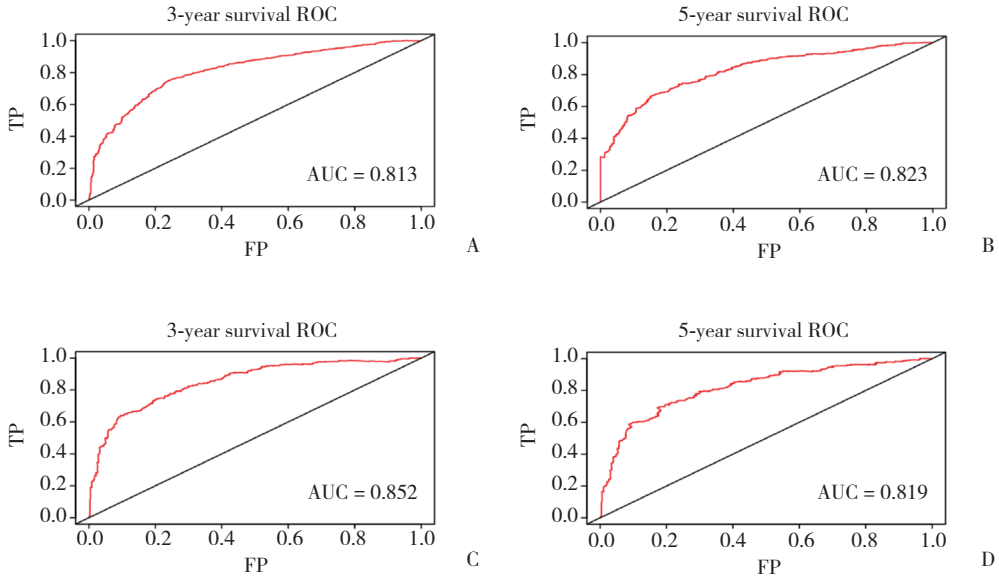
A, B, the ROC curves of the training group; C, D, the ROC curves of the validation group. TP, true positive rate; FP, false positive rate.

图4　SBA患者OS的3年、5年ROC曲线

Fig.4　3-year and 5-year ROC curves of OS for patients with SBA

BILIMORIA等[3]研究发现SBA患者平均年龄为66岁，且男女比例约为1.3 ： 1；本研究患者平均年龄为65岁，男女比例为1.2 ： 1，与之相近。本研究结果显示，年龄、T分期、阳性淋巴结检出率与继发肝脏转移为影响SBA预后的危险因素，与HUFFMAN等[10-12]的研究结论一致。但GU等[11]研究发现N分期同样是影响预后危险因素，本研究中N分期未被纳入，其原因可能是样本量较小所致。

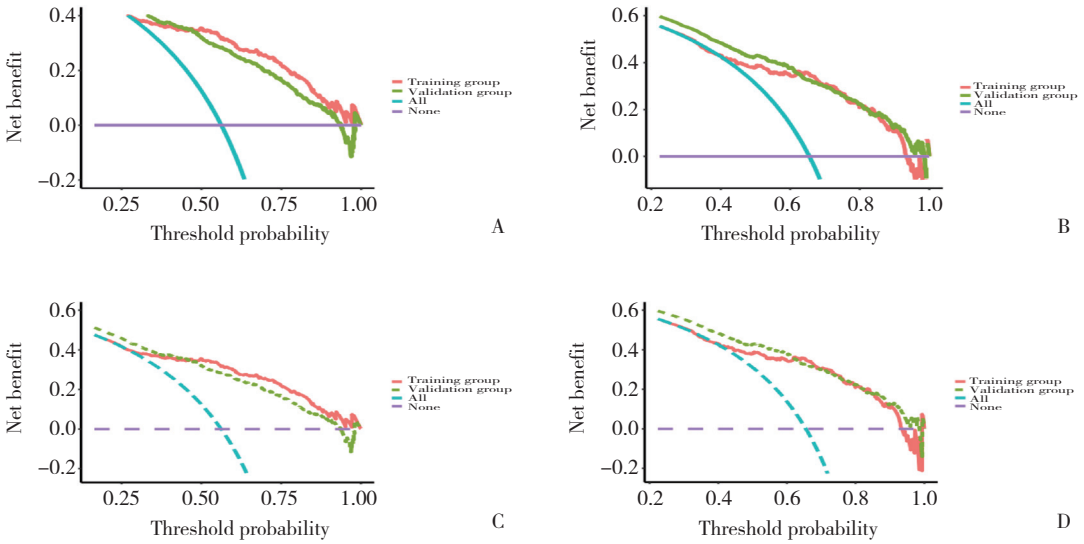
本研究结果显示，SBA原发位置位于十二指肠占58.39%，位于空肠、回肠分别占17.09%和11.86%，



A, B, the ROC curves of the training group; C, D, the ROC curves of the validation group. TP, true positive rate; FP, false positive rate.

图5　SBA患者DSS的3年、5年ROC曲线

Fig.5　3-year and 5-year ROC curves of DSS for patients with SBA



A, B, the 3-year and 5-year DCA curves for OS in SBA patients; C, D, the 3-year and 5-year DCA curves for DSS in SBA patients.

图6　SBA患者OS与DSS的临床预测DCA

Fig.6　Decision curve analysis of OS and DSS in patients with SBA

与已有研究[13-17]指出的SBA最常见于十二指肠(50%~55%),其次为空肠(16%~30%)及回肠(13%~20%)的结论一致。HOWE等[18]研究表明,与空、回肠腺癌患者相比,十二指肠腺癌患者预后更差。与本研究结论一致。另外,本研究发现SBA伴远处转移者预后更差,与国外相关研究[19-20]结果相似。有研究[21]推荐检测>9个淋巴结对SBA患者预后具有预测效果。肝脏是SBA最易远处转移的器官,伴肝脏转移的SBA患者较无远处转移患者预后差,与焦若男等[22]研究结论一致。

本研究中,患者3年、5年OS和DSS的验证曲线在训练组及验证组中表现出显著相关性,表明建立的预后预测模型具有良好的预测价值。3年与5年生存的DCA曲线分析显示训练组及验证组在死亡风险方面具有显著的正净收益,表明列线图在预测3年、5年的OS和DSS方面具有良好的临床价值,与以往研

究[14,23]结果一致。

本研究不足之处:(1)构建的列线图中,TNM分期对患者的预后影响未能得到完整体现;(2)N分期未被纳入到多因素分析中;(3)肿瘤直径>5 cm评分小于肿瘤直径为>2~5 cm评分;(4)阳性淋巴结未检者在列线图中评分高于其他项,考虑可能是纳入样本量相对较少所致。

综上所述,年龄、肿瘤大小、T分期、阳性淋巴结检出率、肿瘤单发灶、继发肝脏转移是影响SBA患者OS和DSS的独立危险因素;肿瘤部位也是影响SBA患者OS的独立危险因素。本研究建立的列线图具有良好的预测价值,可对患者预后进行准确评估,同时也可以为SBA患者提供合理的治疗建议。

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