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纤维化是否影响肝移植术后患者的生存：来自SEER数据库的证据

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摘　要

背景与目的：肝纤维化是否与肝细胞癌(HCC)有关，并对HCC患者肝移植术后生存有影响？这个问题仍存在争议。本研究旨在通过(SEER)数据库对肝纤维化的严重程度是否影响HCC患者肝移植术后总生存期(OS)的问题进行探索。方法：从SEER数据库中入组了2004年至2016年间共计1536例HCC患者。首先，对肝纤维化患者进行倾向评分匹配(propensity score matching, PSM)，然后通过使用Kaplan-Meier和Cox比例风险回归模型确定纤维化组的风险比(HR)及95%置信区间(CI)，比较纤维化和其他临床病理特征对生存结局的影响。同时通过建立基于多变量分析得出的列线图，校准、检验、预测其准确性。结果：纤维化评分高(5~6分)的患者比例大于纤维化评分低(0~4分)的患者(89.2% vs. 10.8%)。通过多变量Cox比例风险模型，纤维化评分是OS的独立预后因素[风险比(HR)：1.461，95%置信区间(CI)：1.191~1.792，P < 0.001]，且与其他肿瘤特征相比，纤维化与生存结局的相关性较高。将诊断年龄、纤维化评分、性别、种族、美国联合癌症委员会(AJCC) T分期、N分期、肿瘤大小、病理分级和甲胎蛋白(AFP)水平纳入多因素分析。综合这些因素的列线图对HCC患者的预后预测(C指数：0.601，95% CI：0.569~0.632)。结论：纤维化增加是HCC肝移植术后患者生存的独立危险因素。

关键词

肝癌，肝纤维化，预后，肝移植，SEER数据库

Does Fibrosis Influence Survival after Liver Transplantation? Evidence from the SEER Database

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Abstract

Background and Purpose: Whether liver fibrosis is associated with hepatocellular carcinoma (HCC) affects patients' survival after liver transplantation (LT) remains controversial. Using the US National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database, we explored whether the severity of liver fibrosis affected the overall survival (OS) after LT in patients with HCC. Methods: A total of 1536 HCC patients from the SEER database between 2004 and 2016 were enrolled. Propensity score matching was performed on patients with liver fibrosis. We then used Kaplan-Meier and Cox proportional hazards regression models to compare the effects of fibrosis and other clinicopathological characteristics on survival outcomes. We simultaneously established a nomogram based on multivariate analysis and then calibrated, tested, and predicted its accuracy. Results: The proportion of patients with a high fibrosis score (5~6 points, 89.2%) was greater than that of patients with a low fibrosis score (0~4 points, 10.8%). The fibrosis score was an independent prognostic factor for OS by a multivariate Cox proportional hazards model (hazard ratio [HR] 1.461, 95% confidence interval [CI] 1.191~1.792, P < 0.001) and was associated with a higher survival outcome than other tumor characteristics. Age at diagnosis, fibrosis score, gender, ethnicity, American Joint Cancer Committee tumor-node-metastasis stage, tumor size, case grade, and alpha-fetoprotein level were included in the multivariate analysis. A nomogram combining these factors predicted HCC patients' prognoses (C-index 0.601, 95% CI 0.569~0.632). Conclusion: Increased fibrosis was an independent risk factor for survival in patients with HCC after LT, as analyzed by prognostic nomograms that included fibrosis scores and other risk factors.

Keywords

Hepatocellular Carcinoma, Liver Fibrosis, Survival, Liver Transplantation, SEER Database

1. 前言

全球范围而言，肝癌在肿瘤发病率中排在第六位，在肿瘤相关死亡率中排第四位，世界卫生组织估计，2030 年将有 100 多万患者死于肝癌[1]。手术切除、消融、化疗和肝移植是主要的治愈性治疗方法[2] [3]，但由于其转移和复发的频率较高，HCC 的处理仍令人失望[4]。术后 5 年内携带 70%~100%的累积复发风险[5] [6] [7]。在绝大多数病例(70%~90%)中，由于各种病因导致，HCC 患者在晚期发生纤维化和肝硬化可能性大[8]。肝移植(LT)是一组伴有基础肝硬化的 HCC 患者的最佳治疗方式。然而，在所有接受过 LT 的患者中，8%~30%的患者 HCC 的复发是一个重大的临床问题[9] [10]。HCC 复发的主要机制可能与 LT 时肿瘤的亚临床肝外扩散和术中操作肝脏过程中恶性肿瘤细胞巢有关[11]。据报道，晚期复发(>5 年)的总生存率明显优于早期复发[12]。晚期复发似乎与侵袭性较低的肿瘤生物学和对局部治疗的较高反应性

相关[13]。然而，晚期复发的病理生物学尚不十分清楚，正如临床实践中的监测没有很好的标准化一样。HCC 是炎症相关癌症，慢性炎症可引起纤维化和肝硬化，最后导致肝癌发生[14]。纤维化是指肝内细胞外基质蛋白或纤维结缔组织的过度沉积，使肝实质的代谢和其他稳态功能受损，导致肝血流紊乱，建立炎症和致瘤环境[15] [16]。因此，肝纤维化可进展为肝硬化和肝细胞癌(HCC)。导致肝纤维化的典型慢性肝病包括病毒性肝炎、胆汁淤积性疾病、慢性酒精滥用、自身免疫性以及遗传性疾病。在几项纵向队列研究中一致认为纤维化程度与肝脏相关，同时也与肝外发病率和死亡率相关[17]。因此，有理由提出晚期肝纤维化更易导致肝移植术后复发的假设。故我们期望通过从 SEER 数据库中提取大量病例，探索肝纤维化对 HCC 肝移植术预后的影响。

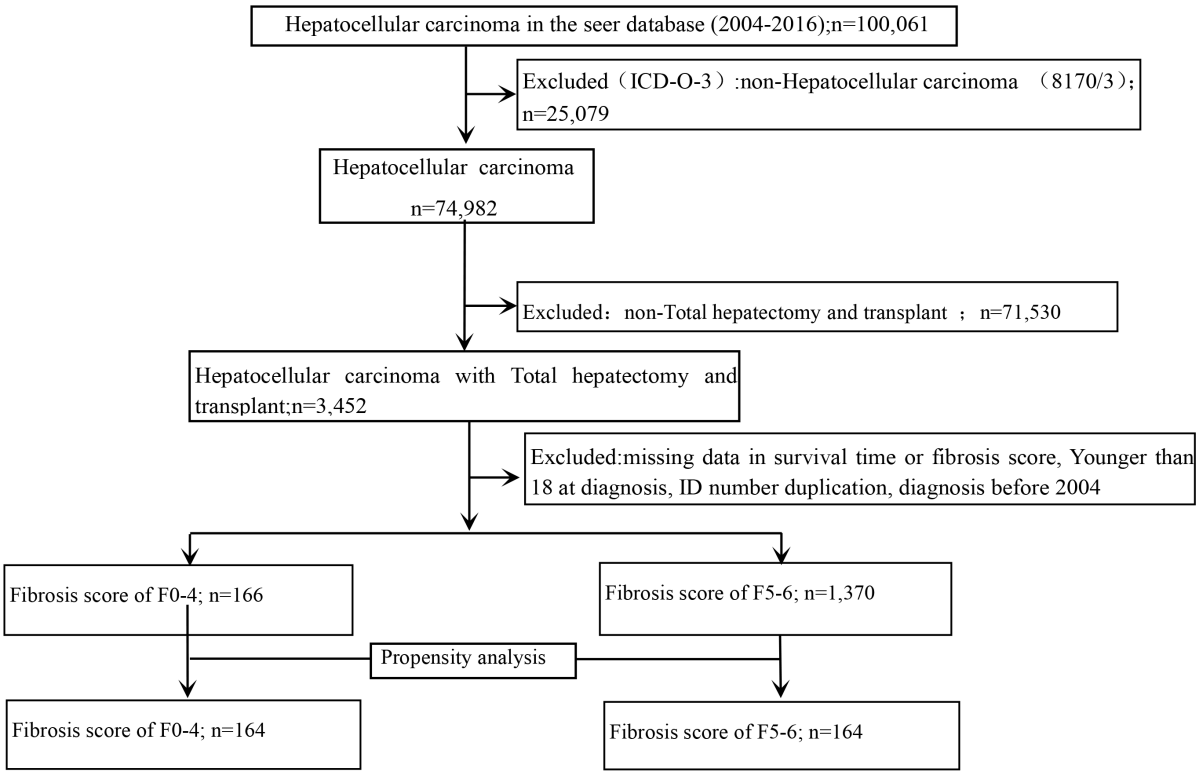


Figure 1. Flowchart for screening post-liver transplant patients with HCC in the SEER database
图 1. SEER 数据库中筛选肝移植后 HCC 患者的流程图

2. 资料和方法

2.1. 临床资料

通过查询 SEER-18 regs 研究数据(https://seer.cancer.gov/)，我们对 2004 年至 2016 年间诊断为 HCC 的患者进行了回顾性队列分析[国际肿瘤疾病分类(第 3 版，ICD-O-3)：HCC (8170/3)，形态学编码(C22.0)]。由于 SEER 数据是公开的以及本次研究是回顾性的，因此免除了伦理批准和知情同意等工作。本次研究患者的纤维化程度分为两类，分别为 F0-4 (代码 0，非至中度)和 F5-6 (代码 1，重度纤维化或肝硬化)，然后对这两个亚组患者的生存期作一个对比。按甲胎蛋白(AFP)水平分为 3 组，分别是阳性/升高(代码 10)、阴性/正常或在正常范围内(代码 20)或结果不明确。在肿瘤大小的分类中，由于 90%的患者 < 1 cm，故分为 3 组 ≤ 1 cm (代码 0-991)、>1 cm (代码 992-996)或不清楚。本分析最终选择了 1536 例符合所需标准的患者(图 1)。

2.2. 纳入标准和排除标准

本文患者的排除标准如下：(I) 年龄 < 18 岁，(II) 纤维化评分无效，(III) 非全肝切除和移植；(IV) 2004 年以前确诊的患者。

2.3. 观察指标

我们从 SEER 数据库中提取了相关患者的年龄、性别、AJCC TNM 分期、纤维化评分、AFP 水平、肿瘤大小、病理分级和生存期(月)等数据作为后续分析的基础。

2.4. 统计学处理

本文根据以下协变量进行倾向评分匹配(PSM)，以尽量减少选择偏倚并平衡纤维化评分为 F0-4 和 F5-6 两个亚组的基线协变量：性别、年龄、人种、诊断年份、纤维化评分(FS)、病理分级、甲胎蛋白(AFP)水平和肿瘤大小。为达到充分匹配，使用预设口径进行 1:1 最近邻匹配(在计算倾向评分 logit 的 0.02 标准差范围内)。随后我们通过标准软件(SPSS v19.0; IBM Corp., Armonk, NY, USA)对 SEER 数据进行统计分析。连续变量以平均值±标准差(SD)值来表示，并通过非配对 t 检验进行分析。而分类变量比较采用卡方或 Fisher 精确检验进行分析。Kaplan-Meier 法生成生存曲线(log-rank 检验)。通过多变量分析(Cox 比例风险模型)进一步检验单变量分析中显著影响生存期的因素。然后，利用多变量分析中的变量在 R 软件(http://www.R-project.org；rms 软件包；R Foundation for Statistical Computing, Vienna, China)中构建预后列线图。最后，为了验证预测的准确性我们进行了一致性指数(C-index)和校准曲线。统计学显著性设定为 $P < 0.05$。

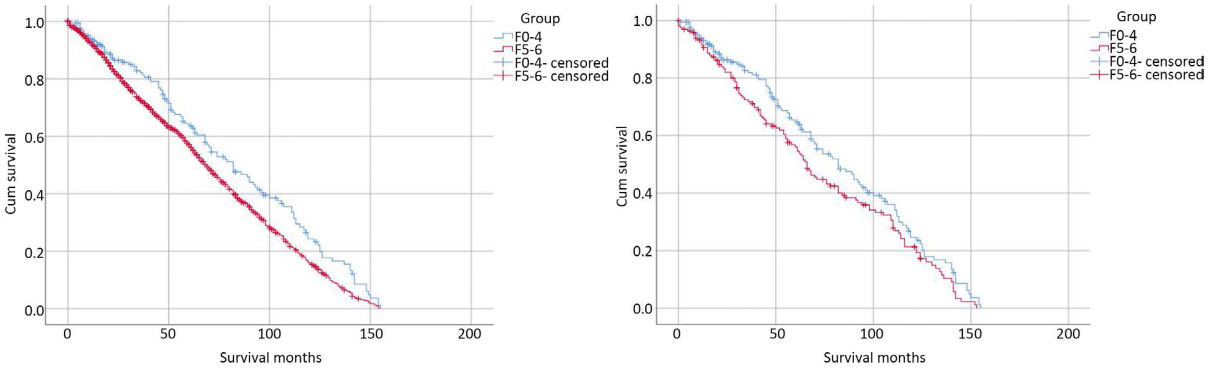
Table 1. The baseline characteristics of post-liver transplant patients with HCC of both types of fibrosis scores
表 1. 两种纤维化评分的 HCC 肝移植后患者的基线特征

Variables	Before PSM			After PSM		
	F0~4 (n = 166)	F5~6 (n = 1370)	P value	F0~4 (n = 164)	F5~6 (n = 164)	P value
Age at diagnosis (mean ± SD)	57.70 ± 7.28	57.89 ± 6.87	0.745	57.66 ± 7.31	59.44 ± 6.20	0.024
Sex, n			0.451			1.000
Male	134 (80.7%)	1,071 (78.2%)		132 (80.5%)	133 (81.1%)	
Female	32 (19.3%)	299 (21.8%)		32 (19.5%)	31 (18.9%)	
Race (White, Black, Other)			0.005			0.349
White	112 (67.5%)	1071 (78.6%)		111 (67.7%)	117 (71.3%)	
Black	19 (11.4%)	111 (8.1%)		19 (11.6%)	17 (10.4%)	
Other	35 (21.1%)	180 (13.2%)		34 (20.7%)	30 (18.3%)	
AJCC T, 7th ed., n			0.360			0.421
T1~T2	74 (44.6%)	691 (50.4%)		72 (43.9%)	83 (50.6%)	
T3~T4	4 (2.4%)	31 (2.3%)		4 (2.4%)	4 (2.4%)	
Unclear	88 (53.0%)	648 (47.3%)		88 (53.7%)	77 (47.0%)	

Continued

AJCC N, 7th ed., n			0.065		0.101
N0	73 (44.0%)	718 (52.4%)		73 (44.5%)	84 (51.2%)
N1	1 (0.6%)	4 (0.3%)		1 (0.6%)	1 (0.6%)
Unclear	92 (55.4%)	648 (47.3%)		90 (54.9%)	79 (48.2%)
AJCC M, 7th ed., n			0.268		0.135
M0	78 (47.0%)	718 (52.4%)		76 (46.3%)	87 (53.0%)
M1	0 (0.0%)	6 (0.4%)		0 (0.0%)	0 (0.0%)
Unclear	88 (53.0%)	646 (47.2%)		88 (53.7%)	77 (47.0%)
AFP, n			0.163		0.057
Positive/elevated	90 (54.2%)	668 (48.8%)		89 (54.3%)	78 (47.6%)
Negative	44 (26.5%)	464 (33.9%)		44 (26.8%)	61 (37.2%)
Unclear	32 (19.3%)	238 (17.4%)		31 (18.9%)	25 (15.2%)
Tumor size, n			0.366		1.000
≤1 cm	154 (92.8%)	1267 (92.5%)		152 (92.7%)	152 (92.7%)
>1 cm	1 (0.6%)	2 (0.1%)		1 (0.6%)	1 (0.6%)
Unclear	11 (6.6%)	101 (7.4%)		11 (6.7%)	11 (6.7%)
Grade, n			0.264		0.377
Well differentiated; Grade I	51 (30.7%)	332 (24.2%)		50 (30.5%)	42 (25.6%)
Moderately differentiated; Grade II	52 (31.3%)	526 (38.4%)		51 (31.1%)	69 (42.1%)
Poorly differentiated; Grade III	15 (9.0%)	100 (7.3%)		15 (9.1%)	14 (8.5%)
Undifferentiated; anaplastic; Grade IV	1 (0.6%)	6 (0.4%)		1 (0.6%)	1 (0.6%)
Unknown	47 (28.3%)	406 (29.6%)		47 (28.7%)	38 (23.2%)
Lymph involvement, n			0.775		0.808
No	151 (91.0%)	1266 (92.4%)		151 (92.1%)	150 (91.5%)
Yes	1 (0.6%)	9 (0.7%)		1 (0.6%)	1 (0.6%)
Unclear	14 (8.4%)	95 (6.9%)		12 (7.3%)	13 (7.9%)
Distant metastasis, n			0.614		/
No	155 (93.4%)	1271 (92.8%)		154 (93.9%)	152 (92.7%)
Yes	0 (0.0%)	8 (0.6%)		0 (0.0%)	1 (0.6%)
Unclear	11 (6.6%)	91 (6.6%)		10 (6.1%)	11 (6.7%)

PSM, Propensity Score Matching; AJCC, American Joint Cancer Committee; AFP, Alpha-Fetoprotein.



(a) (b)

Figure 2. Survival analysis curves for patients with two fibrosis scores before (a) and after (b) PSM，reflecting different prognoses. PSM, propensity score matching.
图 2. PSM 前(a)和 PSM 后(b)两种纤维化评分患者的生存分析曲线

3. 结果

3.1. 研究对象的基本情况

从 SEER 数据库中筛选出 2004 年至 2016 年间诊断为 HCC 且符合我们合格标准的总计 1536 例患者。随访间隔 0~155 (中位数，53)个月。纤维化评分为 F0~4 和 F5~6 的两个组，病例数分别为 166 例和 1370 例(图 1)。晚期纤维化者较早期患者白人比例更高(78.2% vs. 67.4%)，而两组的其他协变量平衡良好，基线时无显著差异(P 均 > 0.05；表 1)。为达到减少不同程度的肝纤维化患者基线水平差异的效果，我们使用 PSM 方法进行 1:1 配对(F0~4, 164; F5~6, 164)。基线结果显示，两组的协变量平衡良好，无显著差异(P 均 > 0.05；表 1)。

3.2. 纤维化进展与 HCC 患者肝移植后预后较差相关

匹配前，F0~4 (vs. F5~6)子集患者的累积 1 年、3 年和 5 年 OS 率(分别为 93.5%、82.1%和 63.6%vs. 91.8%、72.4%和 57.1%)。纤维化进展患者的预后明显更差(P = 0.002) (图 2(a))，中位 OS 明显降低(69 比 82 个月，P = 0.002)。1:1 PSM 后，1 年、3 年和 5 年累积 OS 率仍存在分歧(F0~4 分别为 93.4%、81.8%和 64.6%vs. F5~6 分别为 91.3%、71.8%和 56.0%)。在这些患者中，中位 OS 再次降低(66 vs. 82 个月，P = 0.053)，晚期纤维化/肝硬化患者的患者预后显著更差(P = 0.053) (图 2(b))。

匹配前患者的单变量 Cox 回归分析中(如表 2、表 3 所示)，将 P < 0.5 作为筛选条件，发现晚期纤维化/肝硬化(P = 0.003)、诊断年龄 > 60 岁(P < 0.001)、性别(P = 0.002)、T3~4 分期(P = 0.302)、N1 (P = 0.187)、肿瘤大小(P = 0.159)、种族(black P = 0.064; other P = 0.016)、AFP (Negative P = 0.496)、病理学分级(Grade I P = 0.051; Grade III P = 0.133)与 OS 相关并纳入多变量 Cox 回归分析中。我们发现晚期纤维化/肝硬化(HR: 1.461, 95% CI: 1.191~1.792; P < 0.001) [18]、诊断年龄 > 60 岁(HR: 1.383; 95% CI: 1.220~1.567; P < 0.001)、Race Other (HR: 0.834, 95% CI: 0.702~0.989; P = 0.037)、T3-4 分期(HR: 0.520; 95% CI: 0.328~0.825; P = 0.005)是死亡率增加的独立风险因素(如表 4 所示)。

3.3. 预后列线图的构建及内部验证

我们的预后列线图纳入 Cox 多变量分析的因素，预测生存期的 C 指数达到 0.601 (95% CI: 0.569~0.632) (图 3(a))。随后，我们也绘制了 1 年、3 年和 5 年生存概率的校准图(图 3(b))。因此，我们的列线图因素(即肝纤维化程度、诊断年龄、性别、人种、AJCC T 分期、AJCC N 分期、Pathological Grade、肿瘤大小和 AFP 水平)的整合为预测 HCC 患者肝移植术后的生存率提供了相对可靠的方法。

Table 2. Univariate analysis of prognostic factors for OS
表 2. OS 预后因素的单变量分析

Variables	Before PSM			After PSM		
	All patients	Survival time (months) median (95% CI)	P value	All patients	Survival time (months) median (95% CI)	P value
Group			**0.002**			0.053
F0~4	166	82 (67.731~96.269)		164	82 (66.397~97.603)	
F5~6	1370	69 (65.284~72.716)		164	66 (57.970~74.030)	
Age			<0.001			0.044
≤60	973	79 (74.673~83.327)		196	82 (64.906~99.094)	
>60	563	56 (49.586~62.414)		132	61 (50.962~71.038)	
Sex			0.002			0.364
Male	1205	72 (67.500~76.500)		265	78 (64.530–91.470)	
Female	331	60 (52.152~67.848)		63	68 (58.857–77.143)	
AJCC T, 7th ed.			<0.001			<0.001
T1~T2	765	46 (43.166~48.834)		155	47 (41.926~52.074)	
T3~T4	35	54 (44.367~63.633)		8	60 (47.118~72.882)	
Unclear	736	110 (107.186~112.814)	<0.001	165	116 (109.500~122.500)	<0.001
AJCC N, 7th ed.						
N0	791	46 (43.331~48.669)		157	/	
N1	5	/		2	/	
Unclear.	740	110 (107.180~112.820)	<0.001	169	/	<0.001
AJCC M, 7th ed						
M0	796	46 (43.290~48.710)		163	48 (43.079~52.921)	
M1	6	46 (7.079~84.921)		0	/	
Unclear	734	110 (107.187~112.813)		165	116 (109.500~122.500)	
Grade, n			0.006			0.031
Well differentiated; Grade I	383	72 (64.428~79.572)		92	/	
Moderately differentiated; Grade II	578	68 (62.454~73.546)		120	/	
Poorly differentiated; Grade III	115	91 (76.867~105.133)		29	/	
Undifferentiated; anaplastic; Grade IV	7	57		2	/	
Unknown	453	66 (60.917~71.083)		85	/	
AFP			0.086			0.138
Positive/elevated	758	70 (66.041~73.959)		167	70 (59.038~80.962)	
Negative	508	67 (60.709~73.291)		105	71 (58.040~83.960)	
Unclear	270	81 (64.346~97.654)		56	90 (60.854~119.146)	
Tumor size			<0.001			<0.001

Continued

≤1 cm	1421	74 (70.434~77.566)		304	79 (66.871~91.129)	
>1 cm	3	/		2	/	
Unclear	112	/		22	/	
Race (White, Black, Other)			0.005			0.007
White	1183	70 (65.701~74.299)		228	69 (59.566~78.434)	
Black	130	56 (44.243~67.757)		36	64 (38.543~89.457)	
Other	215	80 (67.866~92.134)		64	110 (98.320~121.680)	
Lymph involvement, n			<0.001			<0.001
No	1417	74 (70.393~77.607)		301	/	
Yes	10	79 (35.880~122.120)		2	/	
Unclear	109	7 (5.967~8.033)		25	/	
Distant metastasis, n			<0.001			
No	1426	74 (70.424~77.576)		306	/	<0.001
Yes	8	71 (18.836~123.164)		1	/	
Unclear	102	7 (5.998~8.002)		21	/	

OS, overall survival; PSM, propensity score matching; CI, confidence interval; AJCC, American Joint Cancer Committee; AFP, alpha-feto-protein

Table 3. Univariate analysis of factors predictive of patients' OS
表 3. 患者 OS 预测因素的单变量分析

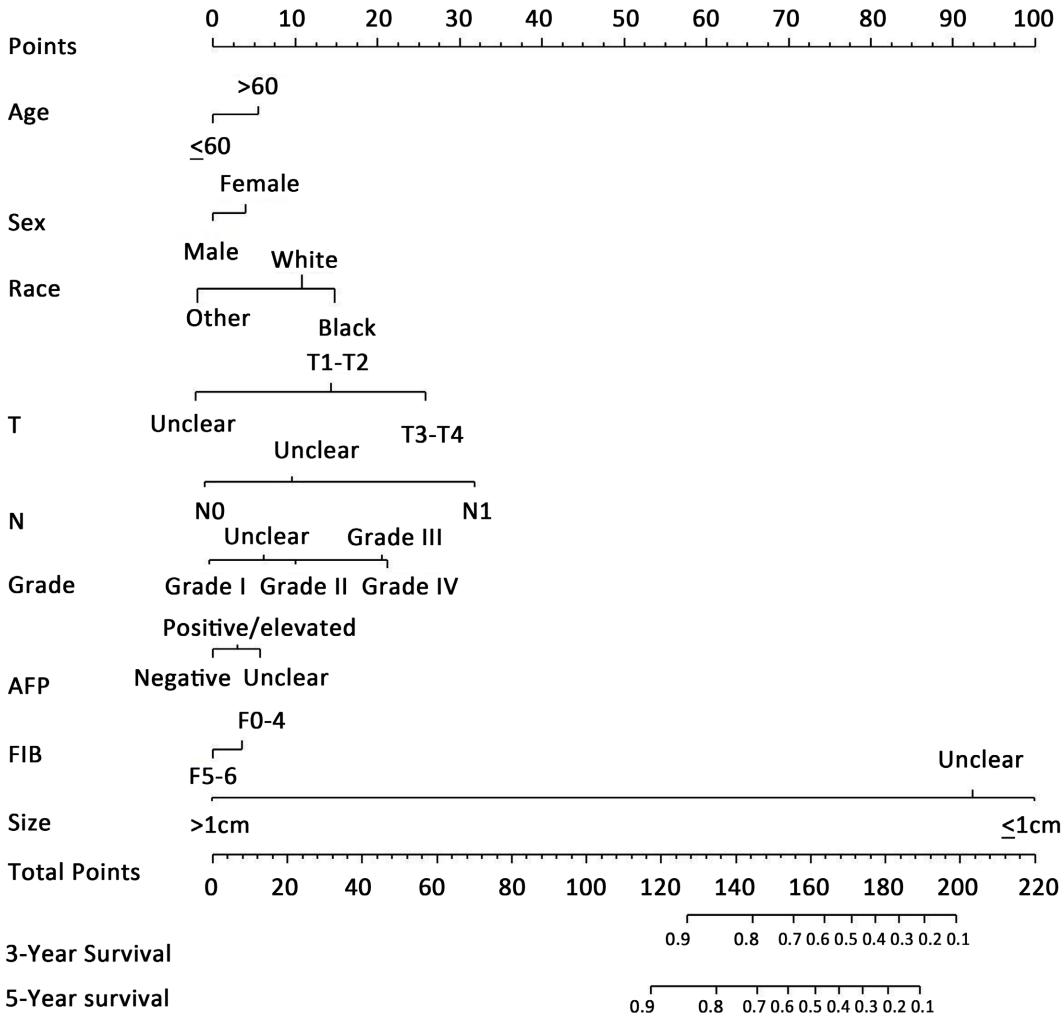
Variables	Before PSM		After PSM	
	HR (95% CI)	P value	HR (95% CI)	P value
Group, F5~6 (vs. F0~4)	1.340(1.104~1.626)	0.003	1.284(0.993~1.660)	0.057
Age at diagnosis, >60 (vs. ≤60)	1.433 (1.270~1.617)	<0.001	1.302 (1.004~1.689)	0.047
Sex, female (vs. male)	1.247 (1.083~1.437)	0.002	1.153 (0.844~1.574)	0.371
AJCC T, 7th ed., T3~4 (vs. T1□2)	0.791 (0.507~1.235)	0.302	0.777 (0.318~1.901)	0.581
AJCC N, 7th ed., N1 (vs. N0)	0.393 (0.098~1.574)	0.187	/	0.951
AJCC M, 7th ed., M1 (vs. M0)	0.965 (0.310~3.000)	0.950	/	/
Tumor size, >1 cm (vs. ≤1 cm)	0.442 (0.142~1.377)	0.159	0.377 (0.093~1.533)	0.173
Race Black(vs. White)	1.224 (0.988~1.515)	0.064	0.912 (0.582~1.428)	0.686
Race Other(vs. White)	0.817 (0.692~0.964)	0.016	0.593 (0.424~0.829)	0.002
AFP, Negative (vs. Positive/elevated)	1.046 (0.920~1.190)	0.493	0.976 (0.734~1.298)	0.868
Grade, Moderately differentiated; Grade II (vs. Well differentiated; Grade I)	1.159 (0.999~1.344)	0.051	1.422 (1.037~1.951)	0.029
Grade, Poorly differentiated; Grade III (vs. Well differentiated; Grade I)	0.819 (0.632~1.062)	0.133	0.731 (0.452~1.180)	0.199
Grade, Undifferentiated; anaplastic; Grade IV (vs. Well differentiated; Grade I)	0.754 (0.242~2.352)	0.627	/	0.952
Lymph involvement, Yes (vs. No)	0.714 (0.267~1.906)	0.501	/	0.954
Distant metastasis, Yes (vs. No)	1.166 (0.436~3.113)	0.760	1.000 (0.143~6.998)	1.000

OS, overall survival; PSM, propensity score matching; HR, hazard ratio; CI, confidence interval; AJCC, American Joint Cancer Committee; AFP, alpha-fetoprotein.

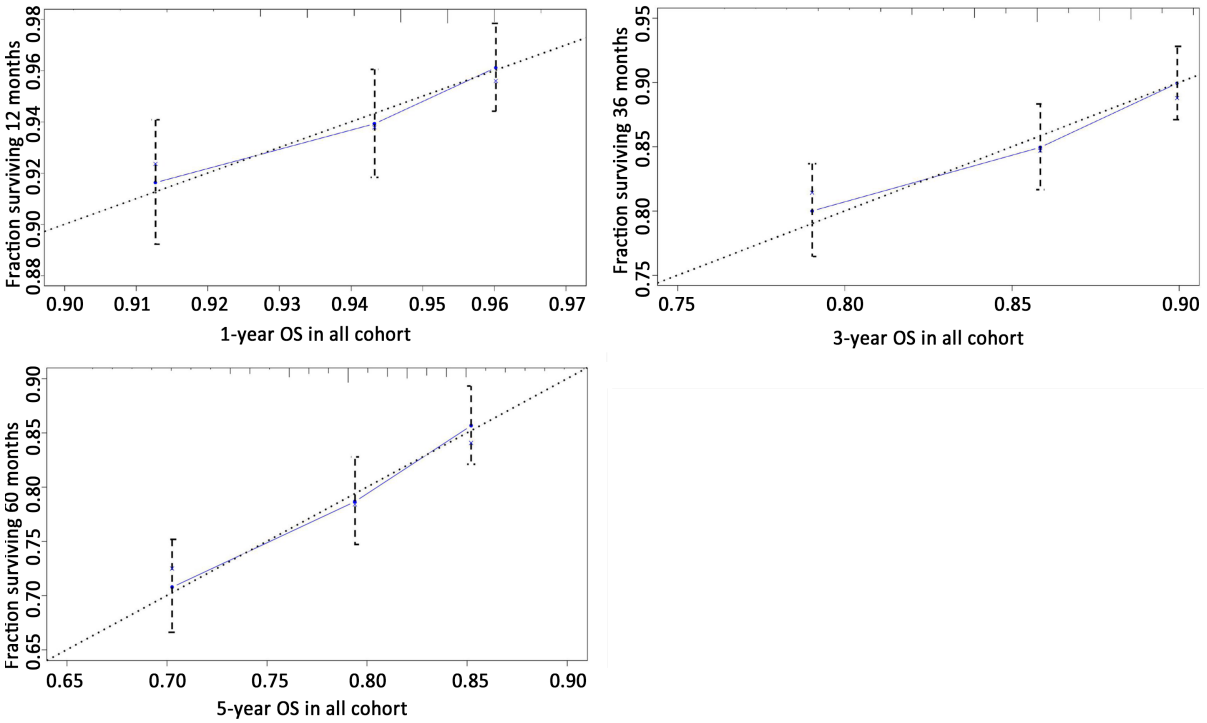
Table 4. Multivariate analysis of factors predictive of patients' OS
表 4. 患者 OS 预测因素的多变量分析

Variables	HR (95% CI)	P value
Fibrosis Score, F5~6 (vs. F0~4)	1.461 (1.191~1.792)	<0.001
Age at diagnosis, >60 (vs. ≤60)	1.383 (1.220~1.567)	<0.001
Race Black(vs. White)	0.883 (0.703~1.110)	0.288
Race Other(vs. White)	0.834 (0.702~0.989)	0.037
Sex, female (vs. male)	1.141 (0.988~1.317)	0.073
AJCC T, 7th ed., T3~4 (vs. T1~2)	0.520 (0.328~0.825)	0.005
AJCC N, 7th ed., N1 (vs. N0)	0.447 (0.111~1.799)	0.257
Tumor size, >1 cm (vs. ≤1 cm)	0.742 (0.236~2.332)	0.609
AFP, Negative (vs. Positive/elevated)	1.072 (0.940~1.222)	0.299
Grade, Moderately differentiated; Grade II (vs. Well differentiated; Grade I)	0.988 (0.850~1.150)	0.881
Grade, Poorly differentiated; Grade III (vs. Well differentiated; Grade I)	0.896 (0.686~1.170)	0.421
Grade, Undifferentiated; anaplastic; Grade IV(vs. Well differentiated; Grade I)	1.022(0.323~3.233)	0.970

HR, hazard ratio; CI, confidence interval; AJCC, American Joint Cancer Committee; AFP, alpha-fetoprotein.



(a)



(b)

Figure 3. Post-liver transplant patients with HCC survival nomogram (a) and calibration curves (b)
图 3. 肝移植后 HCC 患者生存列线图(a)和校准曲线(b)

4. 讨论

本研究的结果证明，晚期纤维化/肝硬化是 HCC 患者肝移植术后的生存期独立危险因素。相关信息被我们整合从而绘制成预后列线图。该预测模型在临床中具有一定的可信度。肝细胞癌(HCC)是最常见的原发性肝癌，是全球医生和患者面临的重大健康挑战。据世界卫生组织统计，未来十年内预计有超过 100 万患者死于肝癌[19]。肝移植(LT)是一组伴有基础肝硬化的 HCC 患者的最佳治疗方式。然而，随着全球不断尝试扩大 HCC 的 LT 适应症的趋势，移植后复发率的增加是不可避免的[20]。在所有接受过 LT 的患者中，8%~30%的患者 HCC 的复发是一个重大的临床问题[21] [22]。一些模型已经被开发用于预测肝移植后 HCC 复发。如米兰标准(0.63; 95%, 0.54~0.71)和 UCSF 标准(0.57; 95%, 0.47~0.66)。准确的模型可以预测肝移植后的肝细胞癌复发，有助于肝移植后的监测。然而，纤维化评分对预测肝移植后 HCC 预后的影响尚未得到充分探索[23] [24] [25] [26]。更好地理解纤维化在这种情况下所起的作用，并使用包括纤维化评分的列线图，可能对患者生存率产生更准确的预测。纤维化涉及异常伤口愈合反应的许多方面，最终导致肝组织瘢痕形成。单核细胞源性巨噬细胞表现出炎症表型，可激活星状细胞成为产生胶原的肌成纤维细胞[27] [28] [29]。肝星状细胞(HSC)的活化，意味着其从静息的维生素 A 储存表型转分化为增殖和产生胶原的肌成纤维细胞，是肝纤维化形成的核心[30]。但是，Noda 等人发现 HCC 患者是否存在肝纤维化与 OS 无明显相关(P = 0.1185) [31]。与此同时，Suh 等人也发现 OS 与纤维化程度无关(轻度 vs.重度；P = 0.267) [23]。有趣的是，在我们的研究中，晚期纤维化构成了肝移植术后 OS 的独立风险因素。本文的结局与 Zhang 等人最近的荟萃分析一致[32]，既往差异可能部分归因于患者入组标准的差异。本研究的优势在于通过在国家量表的代表性人群中进行充分的统计分析证实了结局。使用 SEER 的数据，我们能够调整一系列变量，包括纤维化评分(Ishak)、肿瘤大小、AFP 水平和 AJCC 肿瘤分期，并且在采集数

据时，我们进行了 PSM 以尽量减少选择偏倚。这样指定的患者在年龄、性别、AJCC TNM 分期、AFP 水平、肿瘤大小或血管浸润方面没有显著差异；因此，患者分布平衡良好。本研究存在一些潜在的局限性。首先，SEER 数据库仅提供纤维化评分的分类变量(0~4 vs 5~6)。如果有原始的纤维化评分信息，我们可以丰富分析内容，获得更令人信服的有关肝纤维化发现。其次，SEER 数据库缺乏与 HCC 病因学起源(例如，病毒性肝炎)、肝功能指数(包括 Child-Pugh 评分和凝血酶原时间/国际标准化比值、胆红素、肌酐、白蛋白)、门静脉高压程度或体能状态评分相关的任何记录。故在预测准确性方面，我们的列线图和其他常用系统(如 BCLC 分期、MESH、CLIP 评分)难以进行比较。第三，我们无法获得与术前(LT 前等待时间和 LRT 效果)或术后管理相关的数据；因此，在多变量分析中未分析辅助治疗的影响。第四，在 SEER 数据库中，关于 HCC 的合并症、复发和辅助化疗的信息不是开放数据。此外，由于 SEER 信息来自不同的医院，数据的准确性可能不可避免地存在错误，因为没有专业人员负责全面检查数据。但是，使用适当的统计程序开发了 SEER 质量改善方法，提供了评价 SEER 登记研究性能的措施。最后，本研究的回顾性性质使得很难避免其他混杂因素的偏倚，尽管我们实施了 PSM。通过多中心前瞻性招募进一步验证显然是必要的，以提高我们新的预后列线图的可靠性和准确性。

5. 结论

总的来说，很明显，晚期纤维化的 HCC 患者，肝移植术后的结局较差。我们已经成功地生成了一个列线图，这可以给临床工作提供一定的帮助。但是，我们希望获得更详细的数据或进行前瞻性研究，使临床预测模型更具有可靠性和准确性。

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