· 论著 ·

术前营养相关指标对上尿路尿路上皮癌根治术后生存结局的预测价值

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[摘 要] **目的**:探讨术前营养相关指标与上尿路尿路上皮癌(upper tract urothelial carcinoma,UTUC)患者根治性肾输尿管切除术(radical nephroureterectomy,RNU)后生存结局的相关性,并比较不同营养评分体系的预测效能。**方法**:选择2007年1月至2021年4月在北京大学人民医院接受RNU治疗UTUC患者的病例资料进行回顾性分析,收集术前临床病理资料及实验室指标,计算老年营养风险指数(geriatric nutritional risk index,GNRI)、预后营养指数(prognostic nutritional index,PNI)、控制营养状态评分(controlling nutritional status,CONUT),以及甘油三酯-总胆固醇-体重指数(triglycerides-total cholesterol-body weight index,TCBI)。采用Cox比例风险模型进行单因素和多因素分析,单因素分析中$P<0.10$的变量通过向后逐步回归法(基于Akaike信息准则)筛选纳入多因素模型并构建列线图,以总生存期(overall survival,OS)和癌症特异性生存期(cancer-specific survival,CSS)为主要终点指标,采用Kaplan-Meier法绘制生存曲线并进行Log-rank检验,应用时间依赖性受试者工作特征曲线(time-dependent receiver operating characteristic curve,time-dependent ROC)评估各营养指标预测效能。**结果**:研究共纳入481例UTUC患者。多因素分析显示,OS的独立影响因素包括病理分期T3/T4期、N1/N2期、WHO/ISUP(World Health Organization/International Society of Urological Pathology)高级别、估算的肾小球滤过率(estimated glomerular filtration rate, eGFR)、输血、输尿管末端处理、GNRI及PNI($P<0.05$);CSS的独立影响因素包括病理分期T2~T4期、N1/N2期、术式(腹腔镜)、输血、GNRI及PNI($P<0.05$)。基于独立影响因素构建的列线图具有良好的校准度,GNRI<98组、PNI<52组患者OS和CSS明显缩短(Log-rank $P<0.05$)。60个月时,GNRI和PNI预测OS的曲线下面积(area under the curve,AUC)分别为0.623和0.632,预测CSS的AUC分别为0.632和0.645。时间依赖性ROC分析显示,GNRI和PNI两指标对CSS的预测效能较为稳定,对OS的预测能力随随访时间延长呈轻度增强趋势。**结论**:术前GNRI和PNI与UTUC患者RNU术后OS和CSS独立相关,在不同随访阶段均具有稳定的预测能力。

[关键词] 上尿路尿路上皮癌;术前营养;总生存期;癌症特异性生存期
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Comparison of preoperative nutritional scoring systems for predicting survival in upper tract urothelial carcinoma

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ABSTRACT **Objective**: To investigate the association between preoperative nutritional indicators and survival outcomes in patients with upper tract urothelial carcinoma (UTUC) undergoing radical nephroureterectomy (RNU), and to compare the predictive performance of different nutritional scoring systems. **Methods**: A retrospective analysis was conducted on UTUC patients who underwent RNU. Nutritional scores [geriatric nutritional risk index (GNRI), prognostic nutritional index (PNI), controlling nutritional status (CONUT), triglycerides-total cholesterol-body weight index (TCBI)] were calculated. Variables with $P<0.10$ in univariable Cox regression were entered into multivariable analysis using backward stepwise selection based on the Akaike Information Criterion (AIC) to identify independent

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predictors and construct a nomogram. Kaplan-Meier curves with log-rank tests and time-dependent ROC curves were applied for survival analysis. A two-sided $P<0.05$ was considered statistically significant. **Results**: A total of 481 UTUC patients were included. Multivariable analysis identified pathological T3/T4 stage, N1/N2 stage, high World Health Organization/International Society of Urological Pathology (WHO/ISUP) grade, estimated glomerular filtration rate (eGFR), blood transfusion, ureteral management, GNRI, and PNI as independent predictors of overall survival (OS) ($P<0.05$). Independent predictors of cancer-specific survival (CSS) included pathological T2 – T4 stage, N1/N2 stage, laparoscopic surgical approach, blood transfusion, GNRI, and PNI ($P<0.05$). The nomogram constructed based on these independent predictors demonstrated good calibration. Patients with GNRI < 98 or PNI < 52 had significantly shorter OS and CSS (Log-rank $P<0.05$). At the end of 60 months, the area under the curve (AUC) values of GNRI and PNI for predicting OS were 0.623 and 0.632, respectively, and for predicting CSS were 0.632 and 0.645, respectively. Time-dependent ROC analysis showed that both indicators had stable predictive performance for CSS, while their predictive ability for OS showed a mild increasing trend over the follow-up time. **Conclusion**: Preoperative GNRI and PNI are independently associated with OS and CSS in patients with UTUC after RNU, demonstrating stable predictive performance across different follow-up periods.

KEY WORDS Upper tract urothelial carcinoma; Preoperative nutrition; Overall survival; Cancer-specific survival

上尿路尿路上皮癌(upper tract urothelial carcinoma,UTUC)是一种起源于肾盂或输尿管尿路上皮组织的恶性肿瘤,约占所有尿路上皮癌的 5% ~ 10%[1]。对于局限性 UTUC,根治性肾输尿管切除术(radical nephroureterectomy,RNU)是当前标准的一线外科治疗方式。由于 UTUC 本身具有较强的侵袭性,其总体预后较膀胱尿路上皮癌更差,术后患者面临较高的疾病进展及死亡风险[2]。目前临床风险分层主要依赖肿瘤分期、分级及淋巴结状态等病理因素,但此类信息多需在术后方可明确,限制了其在术前治疗决策中的应用价值。因此,寻找能够在术前早期、便捷且可靠地预测 UTUC 患者复发及生存风险的生物学标志物,对于指导个体化治疗决策和优化随访策略具有重要的临床意义。

近年来,越来越多的研究证据表明,全身营养状态与肿瘤患者的治疗耐受性及长期预后密切相关[3-7]。老年营养风险指数(geriatric nutritional risk index,GNRI)基于血清白蛋白水平及实际体重与理想体重的比值评估患者的营养储备状况,已经在多种恶性肿瘤中被证实具有良好的预后预测价值[8]。在 UTUC 等泌尿系统肿瘤研究中,低 GNRI 水平与术后并发症发生率升高以及癌症特异性生存期(cancer-specific survival,CSS)和总生存期(overall survival,OS)缩短显著相关[4]。预后营养指数(prognostic nutritional index,PNI)结合血清白蛋白和外周血淋巴细胞计数,在其他肿瘤领域已被证明是预后危险因素[5,9],且在 UTUC 中低 PNI 水平与较差的 OS 和 CSS 之间的相关性亦有报道[10-11]。此外,控制营养状态评分(controlling nutritional status,CONUT)通过综合白蛋白、淋巴细胞计数及胆固醇水平评估营养及免疫状态,已被证实与多种恶性肿瘤预后显著相关[12-13]。甘油三酯-总胆固醇-体重指数(triglycerides-total cholesterol-body weight index,TCBI)主要反映脂质代谢与体重储备状态,其评估侧重与前述营养评分存在差异,在多种慢性疾病相关研究中显示出一定的预测价值[14-15],TCBI 可能从代谢层面覆盖更多风险信息。

目前,关于营养指标在 UTUC 预后评估中应用的现有研究存在一定局限性,多数既往研究仅关注单一营养指标,且在结局指标选择上不一致,难以对不同评分体系的预测效能进行直接比较和综合评价,尤其缺乏在同一 UTUC 患者队列中,系统比较多种常用营养指标在不同生存终点上预测能力的研究。因此,本研究以 OS 和 CSS 为主要结局指标,系统评估 GNRI、PNI、CONUT 及 TCBI 在同一人群中对 UTUC 预后的预测能力,旨在识别具有临床推广价值的术前营养评估工具。

1　资料与方法

1.1　一般资料

连续选择 2007 年 1 月至 2021 年 4 月在北京大学人民医院接受治疗的 UTUC 患者的病例资料进行回顾性分析。纳入标准:(1)成年 UTUC 患者;(2)接受根治性肾输尿管切除术;(3)术后组织病理学诊断为尿路上皮癌;(4)随访资料完整,术前检查资料完整。排除标准:(1)确诊即合并其他肿瘤者;(2)合并严重的心、肺、肝、肾功能障碍者;(3)合并慢性感染或自身免疫性疾病者。最终 481 例患者被纳入,本研究开始前已经北京大学人民医院医学伦理委员会审查批准(批件号:2023PHB194-001),所有研究程序均符合《赫尔辛基宣言》的要求。

1.2　手术及随访

根治性肾输尿管切除术根据入路不同分为腹腔

镜手术和开放手术,通常采用经腹膜后入路,切除范围涵盖患侧肾、全程输尿管以及输尿管膀胱开口周围的部分膀胱壁。对于术前评估提示肿瘤具有侵袭性特征、影像学检查发现可疑淋巴结转移,或术中探查见淋巴结肿大的患者,在根治性肾输尿管切除术的基础上同期行淋巴结清扫术。所有患者术前均完成血常规、尿常规、血生化、凝血功能、胸部 X 线片及心电图等常规检查,在确认无手术禁忌证后实施手术。术后第 3 个月进行第一次随访,术后两年内每半年随访一次,两年后每年随访一次,随访采用住院复查、门诊就诊及电话联系的方式。根治性手术后前两年内,每半年一次膀胱镜检查;两年后每年一次膀胱镜检查。每次随访均同步进行血液学、尿液分析以及计算机断层扫描(computed tomography, CT)或磁共振成像(magnetic resonance imaging, MRI)检查。对于临床怀疑存在肿瘤远处转移的患者,酌情增加全身性检查,如骨扫描或正电子发射计算机断层显像(positron emission tomography-computed tomography, PET-CT)。本研究的主要观察终点为 OS 与 CSS,其中,OS 定义为从手术日期至因任何原因死亡或末次随访日期的时间间隔;CSS 定义为从手术日期至明确因 UTUC 进展导致死亡或末次随访日期的时间间隔。

1.3 统计学分析

使用 R 4.3.2(R Foundation for Statistical Computing, Vienna, Austria)进行统计分析,对于患者的基线特征,分类变量以 n (%)表示,符合正态分布的连续变量以 $\bar{x} \pm s$ 表示。采用单因素和多因素 Cox 回归模型探索影响 OS、CSS 的独立危险因素,结果以风险比(hazard ratio, *HR*)及其 95% 置信区间(confidence interval, *CI*)表示。采用 Cox 比例风险模型进行单因素和多因素生存分析。首先对各个变量分别进行单因素 Cox 回归分析,将单因素分析中 $P<0.10$ 的变量以及临床认为重要的基线变量纳入多因素 Cox 回归模型,基于每个营养指标单独建立模型。多因素分析采用向后逐步回归法进行变量筛选,以赤池信息准则(Akaike Information Criterion, AIC)最小化作为变量保留和剔除的标准。采用 Kaplan-Meier 法绘制生存曲线,并使用 Log-rank 检验比较组间生存差异。应用时间依赖性受试者工作特征(receiver operating characteristic, ROC)曲线评估各营养指标对 OS 和 CSS 的预测效能,并计算曲线下面积(area under the curve, AUC)。基于多因素 Cox 回归模型筛选出的独立预后因素,构建列线图以可视化呈现预测模型,所有检验均为双侧检验,$P<0.05$ 认为差异有统计学意义。

2 结果

2.1 病例基本信息

共纳入 481 例 UTUC 患者,中位随访时间为 56 个月(范围:0.7 ~ 198.5 个月),随访期间癌症特异性死亡人数占总体死亡人数的 58.9%(96/163),患者男性 248 例(51.6%),女性 233 例(48.4%)。平均年龄为(66.6 ± 9.78)岁,年龄≥65 岁者共 289 例(60.1%)。肿瘤位于肾盂 227 例(47.2%),位于输尿管 192 例(39.9%),肾盂和输尿管同时发生 62 例(12.9%,表 1)。

表 1 UTUC 患者的临床资料

Table 1 Clinical characteristics of patients with UTUC

Indicator	Total (n = 481)
Age/years	66.55 ± 9.78
Gender	
Male	248 (51.6)
Female	233 (48.4)
Smoking	73 (15.2)
Previous bladder cancer	30 (6.2)
Concomitant bladder cancer	41 (8.5)
T	
Ta/T1	119 (24.7)
T2	121 (25.2)
T3/T4	241 (50.1)
N	
Nx/N0	464 (96.5)
N1/N2	17 (3.5)
Location	
Ureter	192 (39.9)
Renal pelvis	227 (47.2)
Ureter + Renal pelvis	62 (12.9)
Multifocality	112 (23.3)
WHO/ISUP grade	
Low grade	86 (17.9)
High grade	395 (82.1)
eGFR/[mL/(min · 1.73 m^2)]	64.44 ± 25.42
Surgical approach	
Open	39 (8.1)
Laparoscopic	442 (91.9)
Surgical access	
Transabdominal	80 (16.6)
Retroperitoneal	401 (83.4)
Distal ureter management	
Total laparoscopic	129 (26.8)
Bladder opening	321 (66.7)
Endoscopic-assisted	31 (6.4)
Lymph node dissection	88 (18.3)
Intravesical instillation	31 (6.4)
Blood transfusion	96 (20.0)

Data are n(%) or $\bar{x} \pm s$. UTUC, upper tract urothelial carcinoma; WHO/ISUP, World Health Organization/International Society of Urological Pathology; eGFR, estimated glomerular filtration rate.

2.2　Cox 回归分析

单因素和多因素 Cox 回归分析发现,病理分期 T3/T4 期、病理分期 N1/N2、WHO/ISUP 高级别、eGFR、输血、输尿管末端处理方式(打开膀胱及内镜辅助)、GNRI、PNI 是 UTUC 患者术后 OS 的独立危险因素($P<0.05$,表 2),病理分期 T2～T4 期、病理分期 N1/N2、术式、输血、GNRI、PNI 是术后 CSS 的独立危险因素($P<0.05$,表 3)。

表 2　影响 UTUC 术后 OS 的单因素和多因素 Cox 回归分析

Table 2　Univariate and multivariate Cox analysis of factors influencing OS after UTUC surgery

Variable	Univariate analysis			Multivariate analysis		
	HR	95%*CI*	*P*	*HR*	95%*CI*	*P*
Age/years	1.027	1.010－1.044	0.002	1.008	0.990－1.026	0.401
Gender[a]						
Male	Reference					
Female	0.863	0.636－1.172	0.346			
Smoking index (cigarettes · years)	1.000	0.999－1.000	0.334			
Previous bladder cancer[a]	1.779	1.045－3.026	0.034	1.396	0.806－2.420	0.234
Concomitant bladder cancer[a]	1.552	0.951－2.533	0.079	1.180	0.712－1.958	0.520
T[a]						
Ta/T1	Reference					
T2	2.250	1.235－4.102	0.008	1.681	0.908－3.112	0.098
T3/T4	4.906	2.907－8.278	<0.001	3.716	2.166－6.374	<0.001
N[a]						
Nx/N0	Reference					
N1/N2	3.298	1.783－6.098	<0.001	2.003	1.071－3.748	0.030
Location[a]						
Renal pelvis	Reference					
Ureter	1.022	0.734－1.422	0.899			
Ureter + renal pelvis	0.999	0.615－1.622	0.997			
Multiple *vs.* single[a]	0.967	0.669－1.396	0.857			
WHO/ISUP grade[a]						
Low grade	Reference					
High grade	2.399	1.467－3.923	<0.001	1.827	1.095－3.046	0.021
eGFR/[mL/(min · 1.73 m^2)]	0.985	0.978－0.991	<0.001	0.993	0.986－1.000	0.038
Surgical approach[a]						
Open	Reference					
Laparoscopic	0.571	0.363－0.898	0.015	0.687	0.431－1.096	0.115
Surgical access[a]						
Transabdominal	Reference					
Retroperitoneal	0.932	0.608－1.429	0.748			
Distal ureter management[a]						
Total laparoscopic	Reference					
Bladder opening	0.479	0.348－0.660	<0.001	0.574	0.412－0.798	<0.001
Endoscopic-assisted	0.431	0.214－0.867	0.018	0.465	0.228－0.950	0.036
Lymph node dissection[a]	0.983	0.640－1.509	0.937			
Intravesical instillation[a]	0.992	0.538－1.831	0.980			
Blood transfusion[a]	2.117	1.521－2.948	<0.001	1.807	1.275－2.562	<0.001
GNRI	0.969	0.953－0.985	<0.001	0.979	0.963－0.996	0.017
PNI	0.946	0.921－0.972	<0.001	0.969	0.941－0.997	0.032
CONUT	1.145	1.028－1.274	0.014	1.045	0.932－1.171	0.453
TCBI	1.000	0.999－1.001	0.899			

CI, confidence interval; *HR*, hazard ratio; UTUC, upper tract urothelial carcinoma; OS, overall survival; WHO/ISUP, World Health Organization/International Society of Urological Pathology; eGFR, estimated glomerular filtration rate; GNRI, geriatric nutritional risk index; PNI, prognostic nutritional index; CONUT, controlling nutritional status; TCBI, triglyceride-total cholestorol-body mass index. a, included in the regression model as a categorical variable; reference category as listed.

表 3 影响 UTUC 术后 CSS 的单因素和多因素 Cox 回归分析

Table 3 Univariate and multivariate Cox analysis of factors influencing CSS after UTUC surgery

Variable	Univariate analysis			Multivariate analysis		
	HR	95%*CI*	*P*	*HR*	95%*CI*	*P*
Age/years	1.009	0.989 – 1.030	0.376			
Gender[a]						
Male	Reference					
Female	0.806	0.541 – 1.200	0.288			
Smoking index (cigarettes × years)	0.999	0.998 – 1.000	0.081	0.999	0.998 – 1.000	0.104
Previous bladder cancer[a]	1.132	0.495 – 2.585	0.769			
Concomitant bladder cancer[a]	1.730	0.945 – 3.166	0.075	1.294	0.690 – 2.426	0.422
T[a]						
Ta/T1	Reference					
T2	6.232	1.826 – 21.266	0.003	4.159	1.194 – 14.484	0.025
T3/T4	16.667	5.259 – 52.828	<0.001	11.988	3.708 – 38.759	<0.001
N[a]						
Nx/N0	Reference					
N1/N2	4.867	2.523 – 9.386	<0.001	2.986	1.530 – 5.826	0.001
Location[a]						
Renal pelvis	Reference					
Ureter	1.184	0.770 – 1.822	0.441			
Ureter + renal pelvis	1.142	0.613 – 2.128	0.676			
Multiple *vs.* single[a]	1.137	0.722 – 1.791	0.580			
WHO/ISUP grade[a]						
Low grade	Reference					
High grade	3.554	1.644 – 7.682	0.001	1.838	0.831 – 4.063	0.133
eGFR/[mL/(min · 1.73 m^2)]	0.988	0.980 – 0.996	0.005	0.999	0.989 – 1.009	0.837
Surgical approach[a]						
Open	Reference					
Laparoscopic	0.475	0.269 – 0.839	0.010	0.515	0.287 – 0.925	0.026
Surgical access[a]						
Transabdominal	Reference					
Retroperitoneal	0.637	0.392 – 1.034	0.068	0.901	0.529 – 1.534	0.700
Distal ureter management[a]						
Total laparoscopic	Reference					
Bladder opening	0.509	0.334 – 0.777	0.002	0.646	0.416 – 1.005	0.053
Endoscopic-assisted	0.672	0.299 – 1.510	0.335	0.789	0.341 – 1.824	0.579
Lymph node dissection[a]	1.323	0.807 – 2.168	0.267			
Intravesical instillation[a]	0.913	0.400 – 2.087	0.829			
Blood transfusion[a]	2.024	1.309 – 3.131	0.002	1.835	1.169 – 2.880	0.008
GNRI	0.966	0.946 – 0.987	0.002	0.971	0.950 – 0.991	0.005
PNI	0.946	0.913 – 0.980	0.002	0.959	0.924 – 0.995	0.025
CONUT	1.165	1.017 – 1.335	0.027	1.122	0.974 – 1.292	0.110
TCBI	1.000	0.998 – 1.001	0.511			

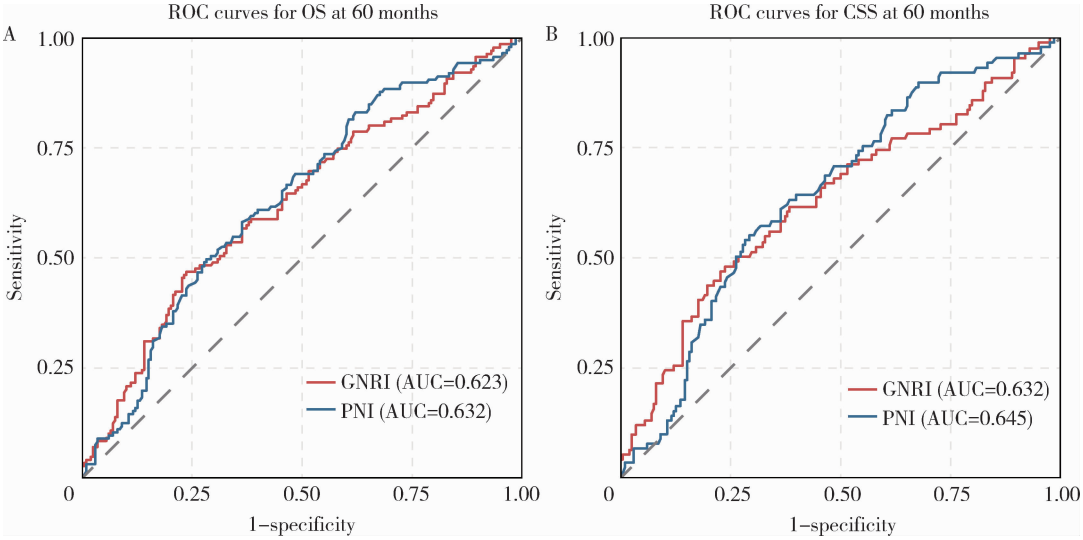
CI, confidence interval; *HR*, hazard ratio; UTUC, upper tract urothelial carcinoma; CSS, cancer-specific survival; WHO/ISUP, World Health Organization/International Society of Urological Pathology; eGFR, estimated glomerular filtration rate; GNRI, geriatric nutritional risk index; PNI, prognostic nutritional index; CONUT, controlling nutritional status; TCBI, triglyceride-total cholesterol-body mass index. a, included in the regression model as a categorical variable; reference category as listed.

2.3　GNRI 和 PNI 的 ROC 曲线

以 60 个月生存状态为结局,绘制 ROC 曲线(图 1),AUC 预测 OS,GNRI 为 0.623,PNI 为 0.632;AUC 预测 CSS,GNRI 为 0.632,PNI 为 0.645。

2.4　GNRI 和 PNI 的 Kaplan-Meier 生存曲线

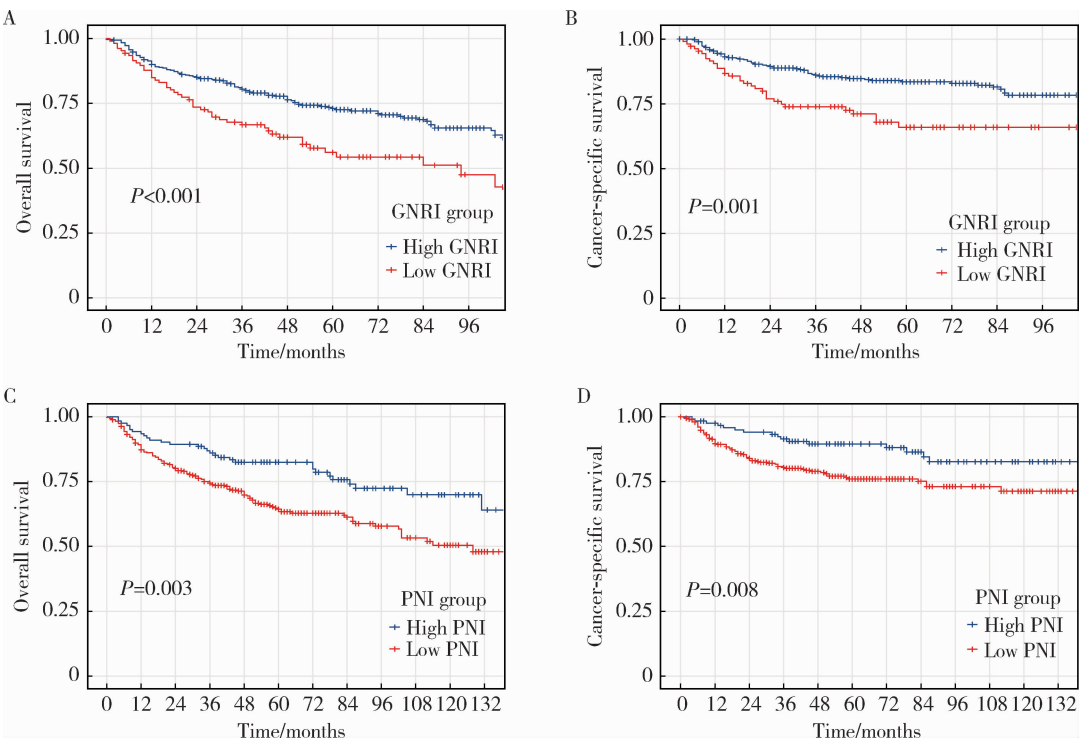
参考 GNRI 分级标准分为两组(≥98 *vs.* <98),另外参考 60 个月生存状态对 PNI 作 ROC 曲线得出最佳截断值,将 OS(≥51.25 *vs.* <51.25)和 CSS(≥51.82 *vs.* <51.82)生存数据各分为两组,分别作 Kaplan-Meier 生存曲线(图 2),Log-rank 检验提示两组间 OS 和 CSS 差异均有统计学意义($P<0.05$)。



GNRI, geriatric nutritional risk index; PNI, prognostic nutritional index; OS, overall survival; CSS, cancer-specific survival; ROC, receiver operating characteristic; AUC, area under the curve.

图 1　GNRI 和 PNI 预测 60 月 OS(A)和 CSS(B)生存情况的 ROC

Figure 1　ROC curves of GNRI and PNI in predicting OS (A) and CSS (B) survival at 60 months



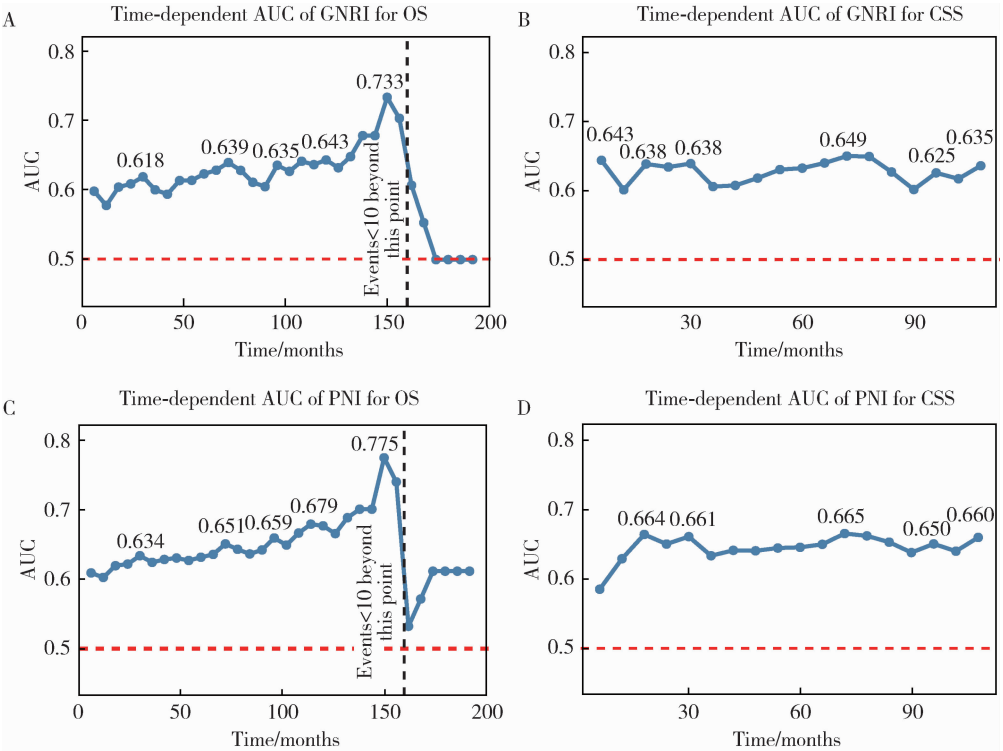
GNRI, geriatric nutritional risk index; PNI, prognostic nutritional index.

图 2　GNRI(A 和 B)和 PNI(C 和 D)二分类的生存曲线,风险集人数小于 10 截断

Figure 2　Kaplan-Meier survival curves for GNRI (A, B) and PNI (C, D) dichotomization, truncated when risk set size < 10

2.5 GNRI 和 PNI 的时间依赖性 ROC 线下面积

自术后 6 个月起每隔 6 个月，基于生存状态对 GNRI 和 PNI 绘制 ROC 曲线，其 AUC 变化趋势见图 3，预测 OS 时，GNRI 和 PNI 均在 30、72、96、150 个月达到阶段峰值；预测 CSS 时，GNRI 和 PNI 均在 18、30、72、96 个月达到阶段峰值。



GNRI, geriatric nutritional risk index; PNI, prognostic nutritional index; OS, overall survival; CSS, cancer-specific survival; AUC, area under the curve.

图 3 GNRI（A 和 B）和 PNI（C 和 D）预测生存 AUC 随时间变化曲线，AUC 阶段峰值标注

Figure 3 Time-dependent AUC curves for GNRI (A, C) and PNI (B, D) predicting survival, with stage peak AUC values marked

2.6 GNRI 和 PNI 的多因素列线图

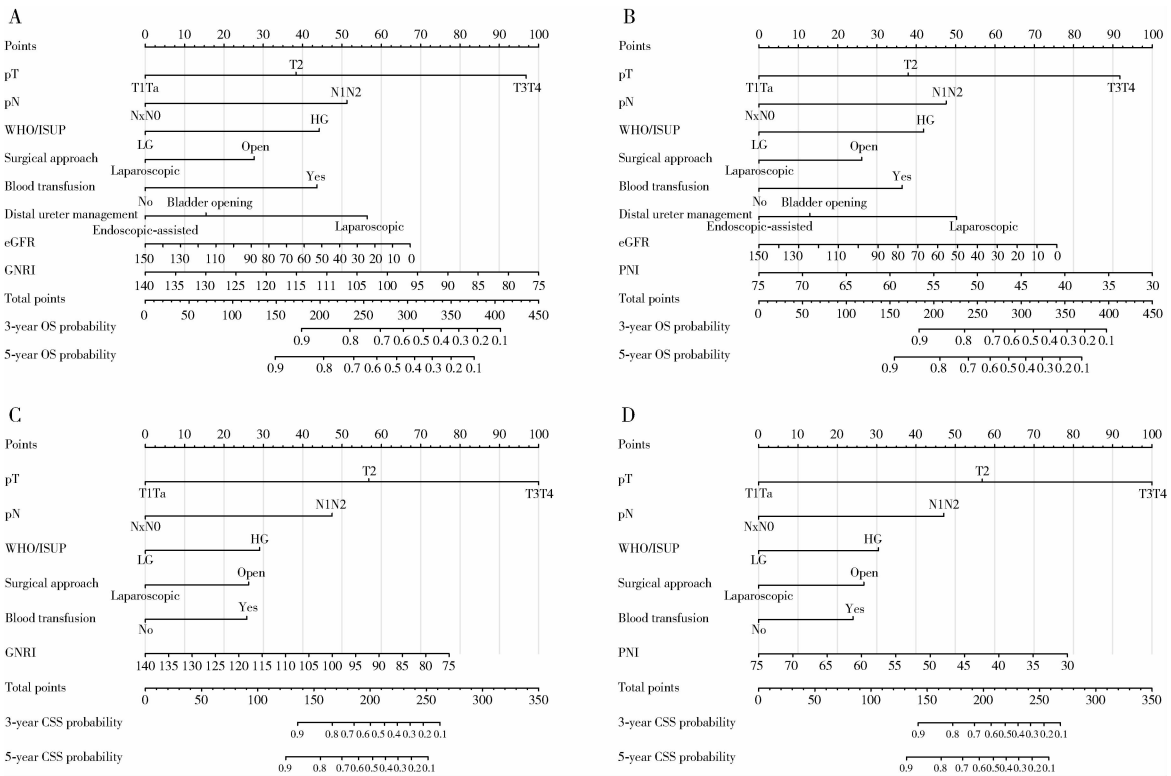
基于向后逐步回归法多因素 Cox 回归筛选出的预测因素，构建了整合术前营养指标（GNRI 与 PNI）的四种列线图见图 4，通过 500 次 Bootstrap 重抽样进行内部验证，基于 GNRI 和 PNI 构建的列线图在预测患者术后 3 年及 5 年 OS 和 CSS 时均表现出优异的校准度，经偏差校正后的预测概率与实际随访观察概率高度一致，未见显著的风险高估或低估现象。

3 讨论

本研究基于单中心回顾性 UTUC 根治性肾输尿管切除术患者队列，系统评估了多种临床病理特征及术前营养相关指标与患者预后的关系，结果显示，在校正肿瘤分期、淋巴结状态及肾功能等已知相关因素后，术前 GNRI 和 PNI 均为 UTUC 患者术后 OS 和 CSS 的独立危险因素，提示营养状态在 UTUC 预后评估中具有重要意义。GNRI 和 PNI 在临床工作中易于计算，数据来源客观可靠，在多因素模型和时间依赖的 ROC 曲线中表现出较为稳定的预测效能，可视化的列线表便于它们应用于临床风险分层。

本研究分别从 OS 和 CSS 两个结局指标维度评估了 GNRI 和 PNI 的时间依赖性预测能力，结果显示，两者对 CSS 的预测效能在整个随访期间保持相对稳定，对 OS 的预测效能则随随访时间延长呈轻度增强趋势。这一差异可能反映了两类结局在生物学基础上的不同，CSS 主要受肿瘤侵袭性及机体抗肿瘤免疫状态影响，术前营养状况在一定程度上已整合了肿瘤相关消耗与免疫储备水平，其对 CSS 的影响在疾病早期即已体现。相比之下，OS 除肿瘤因素外，还受感染、心血管事件及慢性肾功能进展等非肿瘤因素影响，营养不良可通过削弱免疫功能、降低抗感染能力影响整体生理状态，表现为对 OS 预测能力的时间累积效应。总体而言，GNRI 和 PNI 在不同时间节点均表现出相对稳定的预测能力，提示其在短期与长期风险分层中均具有潜在临床价值。在具体应用时，可结合患者年龄结构、炎症状态和基础疾病等情况选择更可靠的指标。

GNRI 最初是针对老年群体改良的营养风险指数,多项研究已经证实,GNRI 在中青年患者中同样具有适用性和预后预测价值。Qiu 等[16] 基于 NHANES(National Health and Nutrition Examination Survey)数据库对 3 253 名 40 岁及以上的癌症患者分析显示,GNRI 在 40~60 岁和 60 岁以上两个年龄组均表现出良好的稳定性和适用性。在 UTUC 和其他多种肿瘤的研究中[4,8,17-19],GNRI 也被证实在不同年龄层中与预后存在显著的相关性,这与本文研究结果一致。因此,GNRI 的应用不应严格受限于年龄,而应综合考虑体重、白蛋白等指标的可靠性来选择营养评估工具。



GNRI, geriatric nutritional risk index; PNI, prognostic nutritional index; OS, overall survival; CSS, cancer-specific survival; pT, pathological tumor stage; pN, pathological node stage; WHO/ISUP, World Health Organization/International Society of Urological Pathology; eGFR, estimated glomerular filtration rate; LG, low grade; HG, high grade.

图 4　GNRI 预测 OS(A)、PNI 预测 OS(B)、GNRI 预测 CSS(C)和 PNI 预测 CSS(D)的列线图

Figure 4　Nomograms for GNRI predicting OS (A), PNI predicting OS (B), GNRI predicting CSS (C) and PNI predicting CSS (D)

除 GNRI 和 PNI 外,本研究亦评估了 CONUT 和 TCBI 两个常用的营养评分,结果显示,CONUT 在单因素分析中与 OS 和 CSS 均存在显著相关性,提示其在一定程度上能够反映 UTUC 患者的整体营养及免疫状态;而 TCBI 在单因素及多因素分析中均未显示出显著的预测价值。在多因素模型中,CONUT 的独立预测效应未能保持,可能与其分级的形式以及各级病例数量不均的队列特征有关[8]。GNRI 和 PNI 以连续性评分形式被构建,白蛋白水平占据主导因素,反映患者更长期和相对稳定的营养状态,这可能是其在多因素分析中仍保持独立预测价值的重要原因。上述结果提示,不同营养评分在 UTUC 预后评估中的侧重点和稳定性存在差异,应结合具体人群和研究目的进行选择。对于高龄患者可优先考虑采用 GNRI 评估,而对于伴有明显炎症状态或体重数据可靠性存疑(如合并严重水肿)的患者,则更适合应用 PNI,二者均可作为术前营养评估的一线工具。

既往研究已证实,营养不良及免疫功能受损与多种实体肿瘤的不良结局密切相关[3-7]。Zheng 等[4] 报道,GNRI 可作为 UTUC 患者根治性手术后的独立预后指标;Zheng 等[5] 和 Xue 等[11] 分别报道 PNI 与 OS 和 CSS 显著相关。GNRI 基于血清白蛋白和体重指数,反映患者营养储备及消耗状态;PNI 结合白蛋白与外周血淋巴细胞计数,综合体现营养和免疫系统情况。白蛋白下降是肿瘤相关慢性炎症对机体影响的综合体现[20]。促炎因子可通过激活急性期反应,抑制肝白蛋白合成并促进全身蛋白分解代谢[21-23]。炎症信号可同时通过 STAT3 和 NF-κB 信号通路促进细胞增殖、血管生成及上皮-间质转

化,增强肿瘤侵袭与转移潜能[24]。针对尿路上皮癌的研究进一步验证了这一机制。尿路上皮癌细胞被证实可诱导或分泌白介素(interleukin,IL)-1、IL-6及肿瘤坏死因子(tumor necrosis factor,TNF)-α等促炎细胞因子,引发外周脂肪组织的褐变和骨骼肌异常分解,导致全身性恶病质[25],也可以直接刺激肝急性期蛋白质的合成,从而竞争性抑制白蛋白的生成[26]。同时,泌尿系统肿瘤微环境中的肿瘤相关巨噬细胞与调节性T细胞会构建免疫屏障,导致外周和局部抗肿瘤淋巴细胞的耗竭与功能障碍[27]。因此,低白蛋白水平既反映宿主营养储备不足,也提示炎症驱动的肿瘤生物学恶性特征。基于炎症与营养对癌症反应的交互作用,C反应蛋白和白蛋白比值等基于白蛋白的复合指标被引入肿瘤预后评估[28]。UTUC患者常伴有高龄、慢性肾功能损害及反复尿路感染等基础状态[29],可进一步加剧系统炎症反应及低白蛋白[30-31]。近期研究在临床队列中证实,低GNRI水平与UTUC患者组织学高分级和深层浸润显著相关[4]。GNRI和PNI同时整合了肿瘤负荷、慢性炎症及宿主储备功能等多重信息,使其在UTUC中的预后意义更为全面而敏感。

本研究存在一定局限性。首先,本研究为单中心回顾性分析,结局事件数相对有限,部分指标可能存在Ⅱ类误差、选择偏倚和信息偏倚风险,其结论需要多中心及前瞻性研究的进一步验证;其次,对于不同亚组患者,如年龄分层、合并基础疾病或不同肿瘤分期,可能存在不同的最佳预测模型,本研究尚未进行充分验证;再次,本研究仅基于术前单次指标评估营养状态,未能动态反映围手术期及随访过程中的变化情况;最后,本研究患者均未接受辅助治疗,尽管排除了辅助化疗作为主要混杂因素对生存结局的影响,也限制了将研究结论直接外推至接受辅助化疗的患者群体。未来研究可结合动态营养评估、细化患者分类分层,评估加入营养指标后是否可增强临床病理指标对预后预测的准确性,进一步优化UTUC患者的个体化风险评估。

综上所述,肿瘤病理T分期、N分期、输血以及术前营养状态与上尿路尿路上皮癌患者根治性肾输尿管切除术后的生存结局显著相关。校正病理分期、手术方式及肾功能后,GNRI和PNI仍是OS和CSS的独立预测因素,在不同随访阶段保持相对稳定的区分能力。作为简便、可重复的术前营养评估工具,GNRI和PNI可为UTUC患者的术前风险分层和个体化管理提供有价值的补充信息。

利益冲突 所有作者均声明不存在利益冲突。

作者贡献声明 郭泽菁:分析数据,撰写文章;孙长海、赖世聪:收集数据,撰写文章;高汉林:整理数据;杜依青、徐涛:指导研究,总体把关和审定论文,经费支持。所有作者均参与论文修改,并对最终文稿进行审读和确认。

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