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Architectural Patterns are a Relevant Morphologic Grading System for Clear Cell Renal Cell Carcinoma Prognosis Assessment

Comparisons With WHO/ISUP Grade and Integrated Staging Systems

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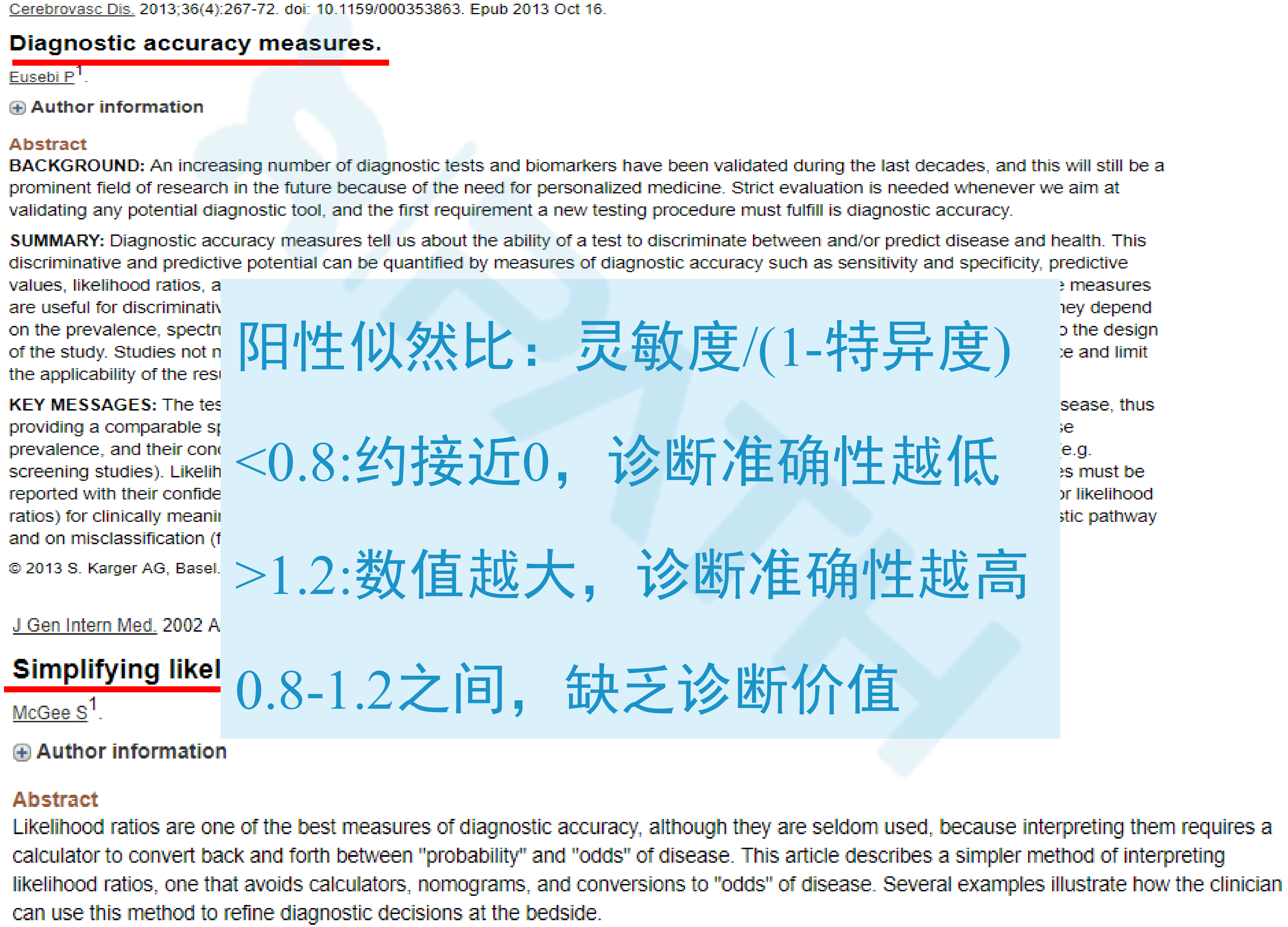
汇报者：吴建锋

关键词

- ccRCC
- LR+：阳性似然比
- DFS：从手术日期至首次复发，或死于其他疾病
- CSS：从手术日期至患者死于ccRCC
- Fuhrman分级、ISUP/WHO分级
- 整合分期系统：Leibovich prognosis score、SSIGN、UISS

LR+



Cerebrovasc Dis. 2013;36(4):267-72. doi: 10.1159/000353863. Epub 2013 Oct 16.

Diagnostic accuracy measures.

Eusebi P[1].

⊕ Author information

Abstract

BACKGROUND: An increasing number of diagnostic tests and biomarkers have been validated during the last decades, and this will still be a prominent field of research in the future because of the need for personalized medicine. Strict evaluation is needed whenever we aim at validating any potential diagnostic tool, and the first requirement a new testing procedure must fulfill is diagnostic accuracy.

SUMMARY: Diagnostic accuracy measures tell us about the ability of a test to discriminate between and/or predict disease and health. This discriminative and predictive potential can be quantified by measures of diagnostic accuracy such as sensitivity and specificity, predictive
values, likelihood ratios, a … measures
are useful for discriminativ … hey depend
on the prevalence, spectr … o the design
of the study. Studies not n … e and limit
the applicability of the resu

KEY MESSAGES: The tes … sease, thus
providing a comparable sp … se
prevalence, and their cond … e.g.
screening studies). Likelih … es must be
reported with their confide … or likelihood
ratios) for clinically meani … stic pathway
and on misclassification (f

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J Gen Intern Med. 2002 A

Simplifying likel

McGee S[1].

⊕ Author information

Abstract

Likelihood ratios are one of the best measures of diagnostic accuracy, although they are seldom used, because interpreting them requires a calculator to convert back and forth between "probability" and "odds" of disease. This article describes a simpler method of interpreting likelihood ratios, one that avoids calculators, nomograms, and conversions to "odds" of disease. Several examples illustrate how the clinician can use this method to refine diagnostic decisions at the bedside.

阳性似然比：灵敏度/(1-特异度)

<0.8:约接近0，诊断准确性越低

>1.2:数值越大，诊断准确性越高

0.8-1.2之间，缺乏诊断价值

肾细胞癌分级系统

分级	Fuhrman分级	ISUP/WHO分级
1级	细胞核小, 类似成熟的淋巴细胞, 染色质↑, 无核仁, 染色质结构不清	细胞核无核仁/不明显(400×)
2级	核染色质呈细颗粒状, 核仁不明显	核仁明显(400×); 核仁不明显/可见(100×)
3级	可见核仁	核仁明显(100×)
4级	具有多形性核, 核染色质↑, 有1个或多个大核仁	伴横纹肌/肉瘤样分化or瘤巨细胞or具有块状染色质的显著多形细胞核

摘自张静教授《ISUP肾细胞癌共识》授课幻灯

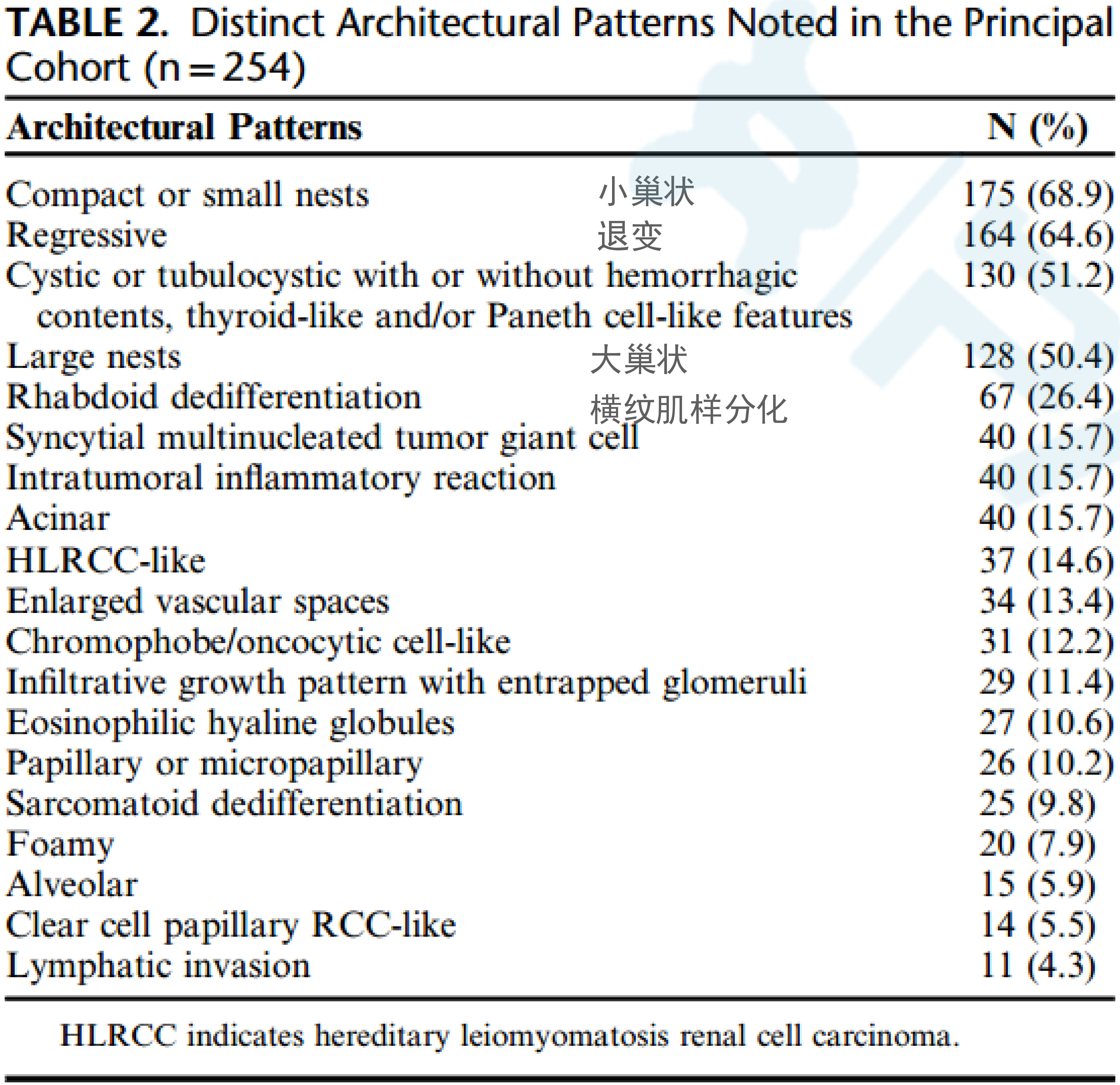
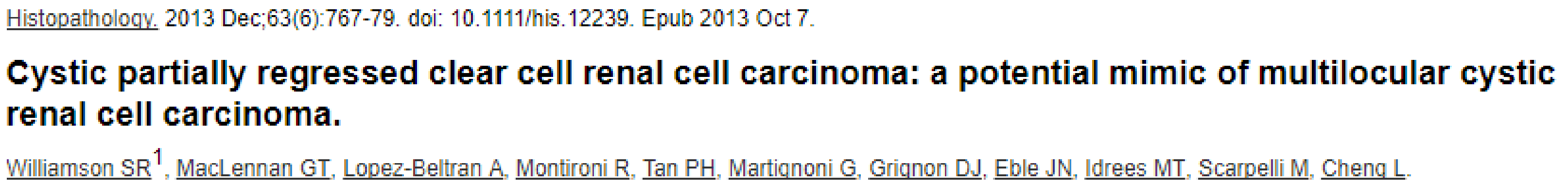


TABLE 2. Distinct Architectural Patterns Noted in the Principal Cohort (n = 254)

Architectural Patterns	N (%)
Compact or small nests 小巢状	175 (68.9)
Regressive 退变	164 (64.6)
Cystic or tubulocystic with or without hemorrhagic contents, thyroid-like and/or Paneth cell-like features	130 (51.2)
Large nests 大巢状	128 (50.4)
Rhabdoid dedifferentiation 横纹肌样分化	67 (26.4)
Syncytial multinucleated tumor giant cell	40 (15.7)
Intratumoral inflammatory reaction	40 (15.7)
Acinar	40 (15.7)
HLRCC-like	37 (14.6)
Enlarged vascular spaces	34 (13.4)
Chromophobe/oncocytic cell-like	31 (12.2)
Infiltrative growth pattern with entrapped glomeruli	29 (11.4)
Eosinophilic hyaline globules	27 (10.6)
Papillary or micropapillary	26 (10.2)
Sarcomatoid dedifferentiation	25 (9.8)
Foamy	20 (7.9)
Alveolar	15 (5.9)
Clear cell papillary RCC-like	14 (5.5)
Lymphatic invasion	11 (4.3)

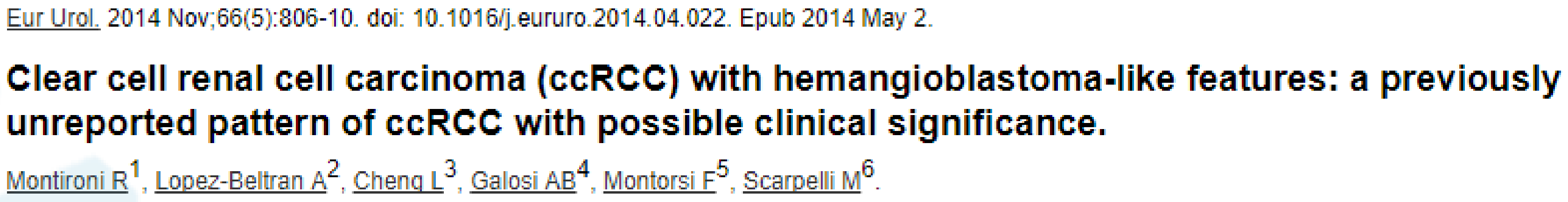
HLRCC indicates hereditary leiomyomatosis renal cell carcinoma.



Histopathology. 2013 Dec;63(6):767-79. doi: 10.1111/his.12239. Epub 2013 Oct 7.

Cystic partially regressed clear cell renal cell carcinoma: a potential mimic of multilocular cystic renal cell carcinoma.

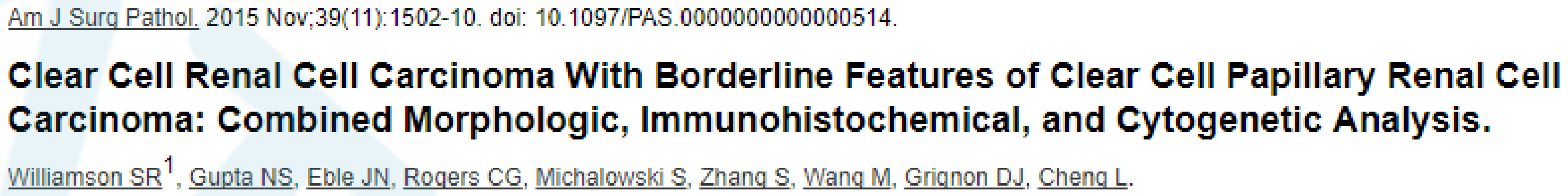
Williamson SR[1], MacLennan GT, Lopez-Beltran A, Montironi R, Tan PH, Martignoni G, Grignon DJ, Eble JN, Idrees MT, Scarpelli M, Cheng L.



Eur Urol. 2014 Nov;66(5):806-10. doi: 10.1016/j.eururo.2014.04.022. Epub 2014 May 2.

Clear cell renal cell carcinoma (ccRCC) with hemangioblastoma-like features: a previously unreported pattern of ccRCC with possible clinical significance.

Montironi R[1], Lopez-Beltran A[2], Cheng L[3], Galosi AB[4], Montorsi F[5], Scarpelli M[6].



Am J Surg Pathol. 2015 Nov;39(11):1502-10. doi: 10.1097/PAS.0000000000000514.

Clear Cell Renal Cell Carcinoma With Borderline Features of Clear Cell Papillary Renal Cell Carcinoma: Combined Morphologic, Immunohistochemical, and Cytogenetic Analysis.

Williamson SR[1], Gupta NS, Eble JN, Rogers CG, Michalowski S, Zhang S, Wang M, Grignon DJ, Cheng L.

⋮

形态

肾细胞癌分级系统

分级	Fuhrman分级	ISUP/WHO分级
1级	细胞核小, 类似成熟的淋巴细胞, 染色质↑, 无核仁, 染色质结构不清	细胞核无核仁/不明显(400×)
2级	核染色质呈细颗粒状, 核仁不明显	核仁明显(400×); 核仁不明显/可见(100×)
3级	可见核仁	核仁明显(100×)
4级	具有多形性核, 核染色质↑, 有1个或多个大核仁	伴横纹肌/肉瘤样分化or瘤巨细胞or具有块状染色质的显著多形细胞核

缺陷

研究目的

确立一种新的基于形态学分级系统，并在2个大型回顾性研究队列中验证该分级系统对ccRCC预测预后的能力

MATERIALS AND METHODS

病例来源

	研究队列组	验证队列组
例数	254	252
病例来源	圣路易斯医院 1998.01.01至2014.12.31	Institut Mutualiste Montsouris 2007.01.01至2012.12.31
诊断	由同一名泌尿病理专家（Jérôme Verine）回顾病理诊断	
入组条件	诊断为ccRCC并接受肾脏局部或全切且未接受新辅助化疗的患者； 至少有完整的18个月随访资料，或随访早期（<12个月）即发生转移	

详细临床资料见研究结果

数据收集

临床数据
01

年龄、性别、Patard症状分级、ECOG体力状态评分、淋巴结状态、远处转移情况

形态学数据
02

WHO/ISUP分级、镜下可见的肿瘤坏死、肿瘤大小、2017版TNM分期、SSIGN（分期、大小、分级、坏死）、UISS（加州大学洛杉矶分校整合分期系统）、 Leibovich prognosis score

研究过程

- 确定ccRCC的形态学分类（Jérôme Verine）
- 利用统计学方法根据不同形态学将ccRCC分为4个级别
- 在研究队列中用统计学方法分析新分级相比WHO/ISUP分级的优势
- 在验证队列中验证该分级系统对预测预后的价值
- 对比3级分类与4级分类的预测预后价值
- 由2名非泌尿专科病理医生（D.C.、M.N.）重新阅片分级，判断其可重复性

RESULTS

研究结果

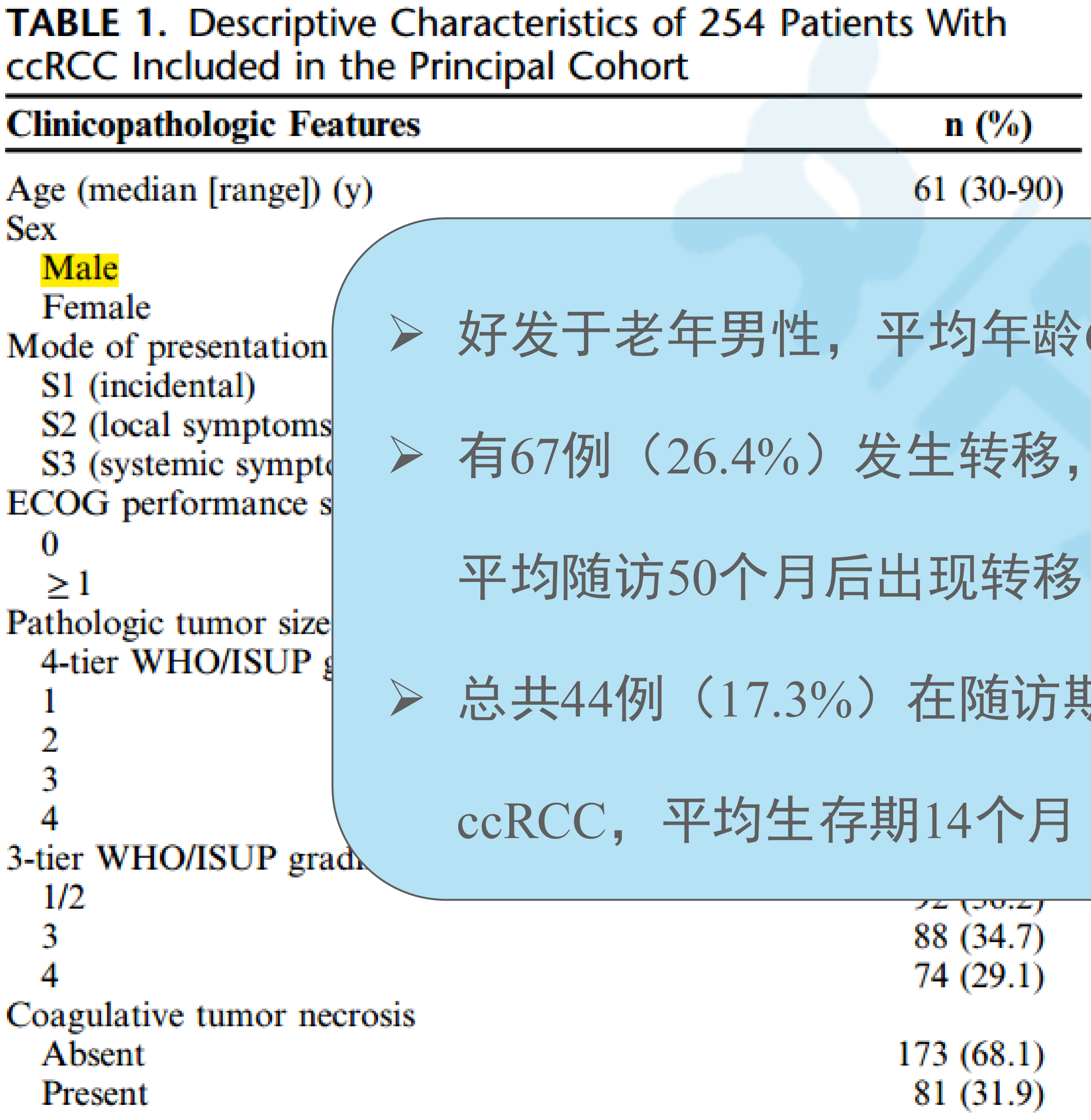


TABLE 1. Descriptive Characteristics of 254 Patients With ccRCC Included in the Principal Cohort

Clinicopathologic Features	n (%)
Age (median [range]) (y)	61 (30-90)
Sex	
Male	
Female	
Mode of presentation	
S1 (incidental)	
S2 (local symptoms	
S3 (systemic sympt	
ECOG performance s	
0	
≥ 1	
Pathologic tumor size	
4-tier WHO/ISUP g	
1	
2	
3	
4	
3-tier WHO/ISUP grad	
1/2	92 (36.2)
3	88 (34.7)
4	74 (29.1)
Coagulative tumor necrosis	
Absent	173 (68.1)
Present	81 (31.9)

- 好发于老年男性，平均年龄61岁，男：女=7:3
- 有67例（26.4%）发生转移，其中32例诊断时就发生转移，35例在平均随访50个月后出现转移
- 总共44例（17.3%）在随访期间死亡。其中35例（13.8%）死于ccRCC，平均生存期14个月

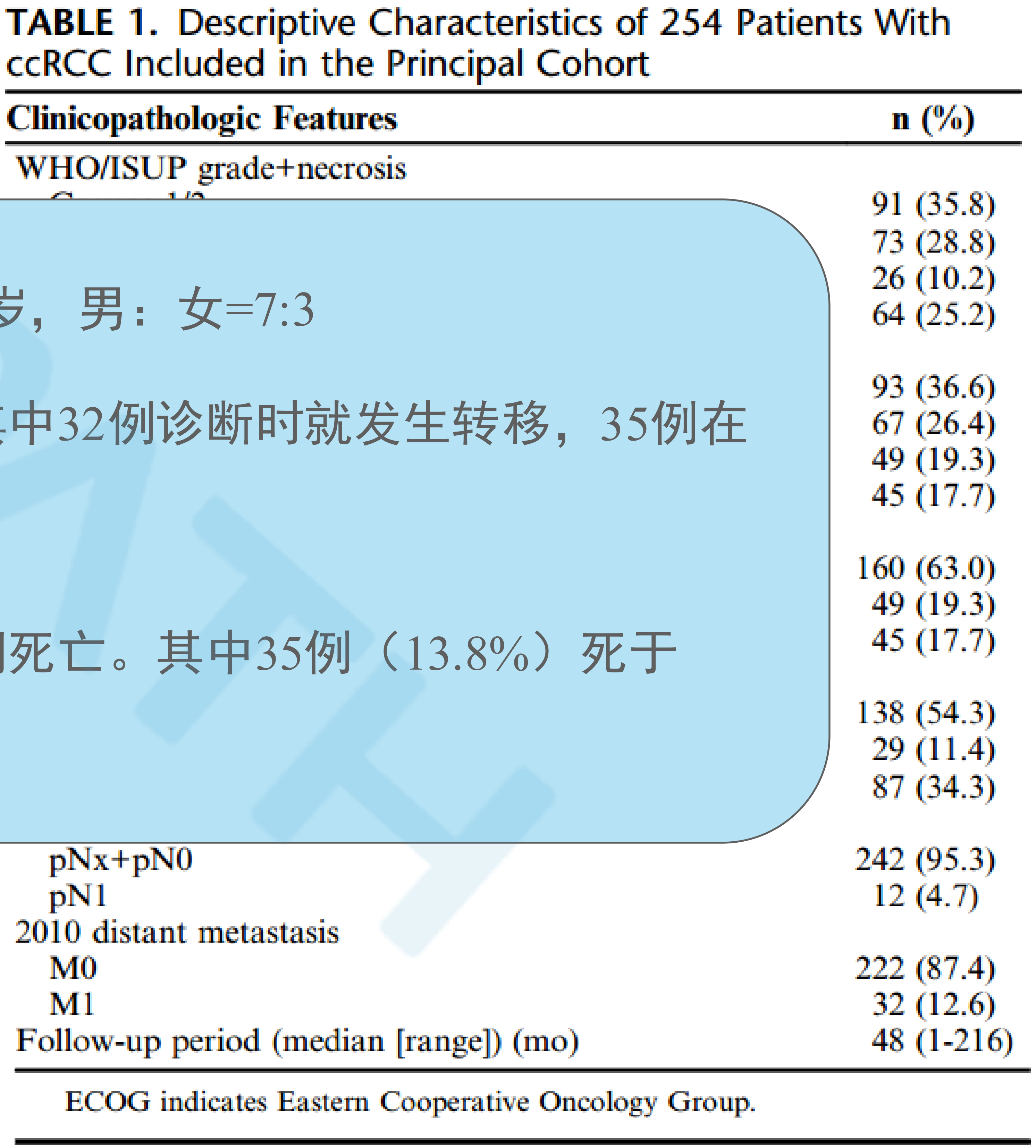


TABLE 1. Descriptive Characteristics of 254 Patients With ccRCC Included in the Principal Cohort

Clinicopathologic Features	n (%)
WHO/ISUP grade+necrosis	
	91 (35.8)
	73 (28.8)
	26 (10.2)
	64 (25.2)
	93 (36.6)
	67 (26.4)
	49 (19.3)
	45 (17.7)
	160 (63.0)
	49 (19.3)
	45 (17.7)
	138 (54.3)
	29 (11.4)
	87 (34.3)
pNx+pN0	242 (95.3)
pN1	12 (4.7)
2010 distant metastasis	
M0	222 (87.4)
M1	32 (12.6)
Follow-up period (median [range]) (mo)	48 (1-216)

ECOG indicates Eastern Cooperative Oncology Group.

研究结果

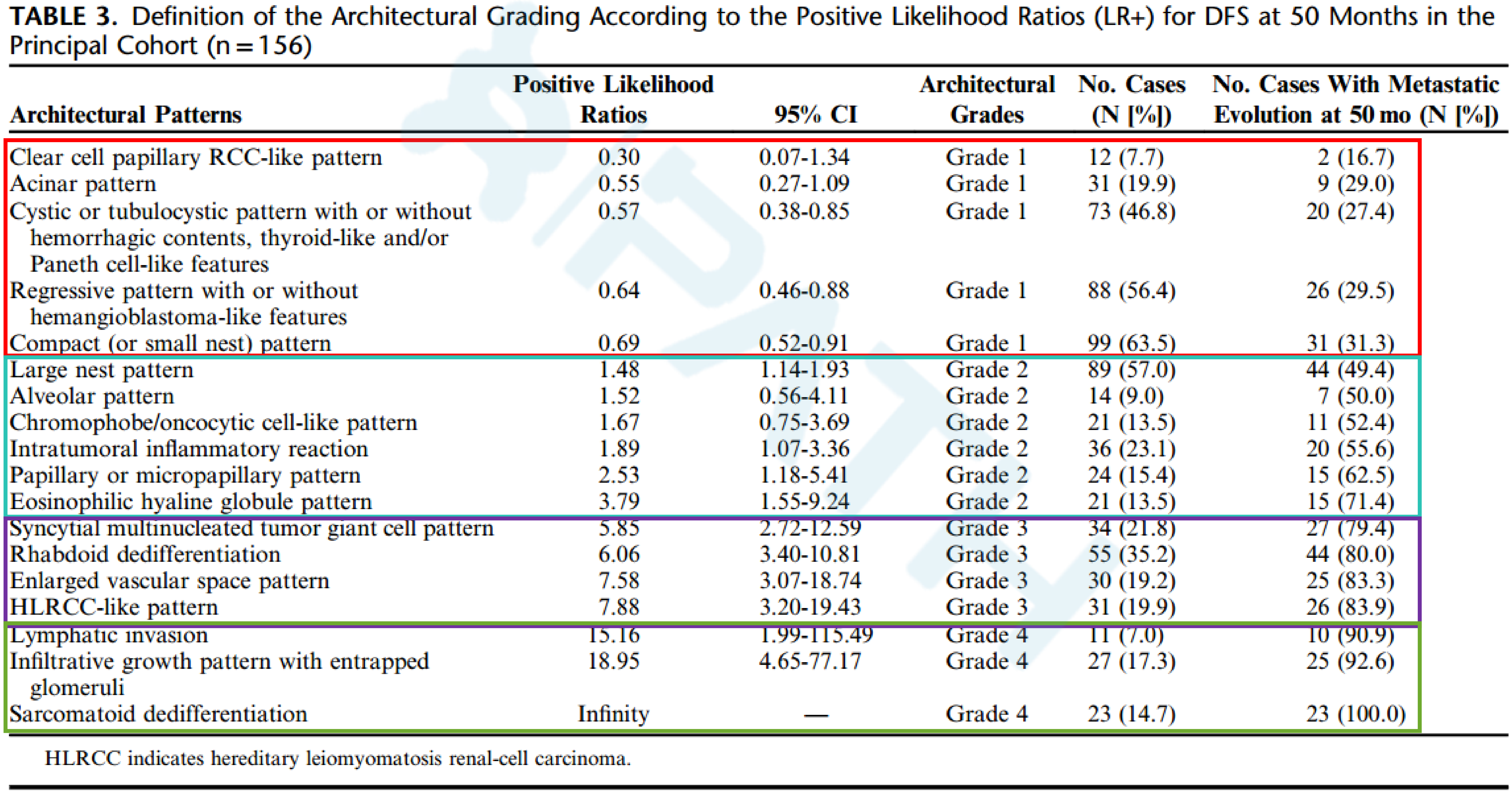


TABLE 3. Definition of the Architectural Grading According to the Positive Likelihood Ratios (LR+) for DFS at 50 Months in the Principal Cohort (n = 156)

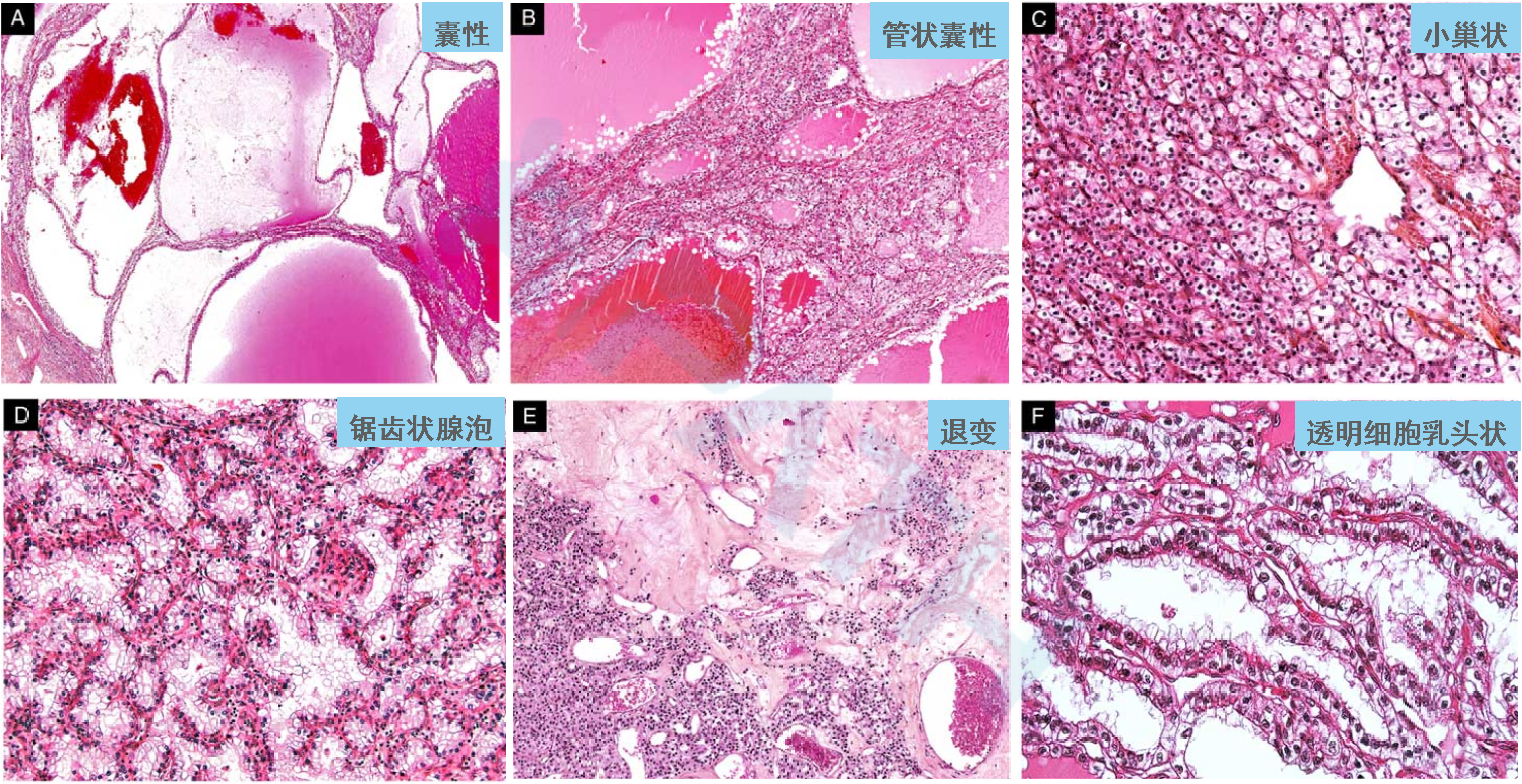
Architectural Patterns	Positive Likelihood Ratios	95% CI	Architectural Grades	No. Cases (N [%])	No. Cases With Metastatic Evolution at 50 mo (N [%])
Clear cell papillary RCC-like pattern	0.30	0.07-1.34	Grade 1	12 (7.7)	2 (16.7)
Acinar pattern	0.55	0.27-1.09	Grade 1	31 (19.9)	9 (29.0)
Cystic or tubulocystic pattern with or without hemorrhagic contents, thyroid-like and/or Paneth cell-like features	0.57	0.38-0.85	Grade 1	73 (46.8)	20 (27.4)
Regressive pattern with or without hemangioblastoma-like features	0.64	0.46-0.88	Grade 1	88 (56.4)	26 (29.5)
Compact (or small nest) pattern	0.69	0.52-0.91	Grade 1	99 (63.5)	31 (31.3)
Large nest pattern	1.48	1.14-1.93	Grade 2	89 (57.0)	44 (49.4)
Alveolar pattern	1.52	0.56-4.11	Grade 2	14 (9.0)	7 (50.0)
Chromophobe/oncocytic cell-like pattern	1.67	0.75-3.69	Grade 2	21 (13.5)	11 (52.4)
Intratumoral inflammatory reaction	1.89	1.07-3.36	Grade 2	36 (23.1)	20 (55.6)
Papillary or micropapillary pattern	2.53	1.18-5.41	Grade 2	24 (15.4)	15 (62.5)
Eosinophilic hyaline globule pattern	3.79	1.55-9.24	Grade 2	21 (13.5)	15 (71.4)
Syncytial multinucleated tumor giant cell pattern	5.85	2.72-12.59	Grade 3	34 (21.8)	27 (79.4)
Rhabdoid dedifferentiation	6.06	3.40-10.81	Grade 3	55 (35.2)	44 (80.0)
Enlarged vascular space pattern	7.58	3.07-18.74	Grade 3	30 (19.2)	25 (83.3)
HLRCC-like pattern	7.88	3.20-19.43	Grade 3	31 (19.9)	26 (83.9)
Lymphatic invasion	15.16	1.99-115.49	Grade 4	11 (7.0)	10 (90.9)
Infiltrative growth pattern with entrapped glomeruli	18.95	4.65-77.17	Grade 4	27 (17.3)	25 (92.6)
Sarcomatoid dedifferentiation	Infinity	—	Grade 4	23 (14.7)	23 (100.0)

HLRCC indicates hereditary leiomyomatosis renal-cell carcinoma.

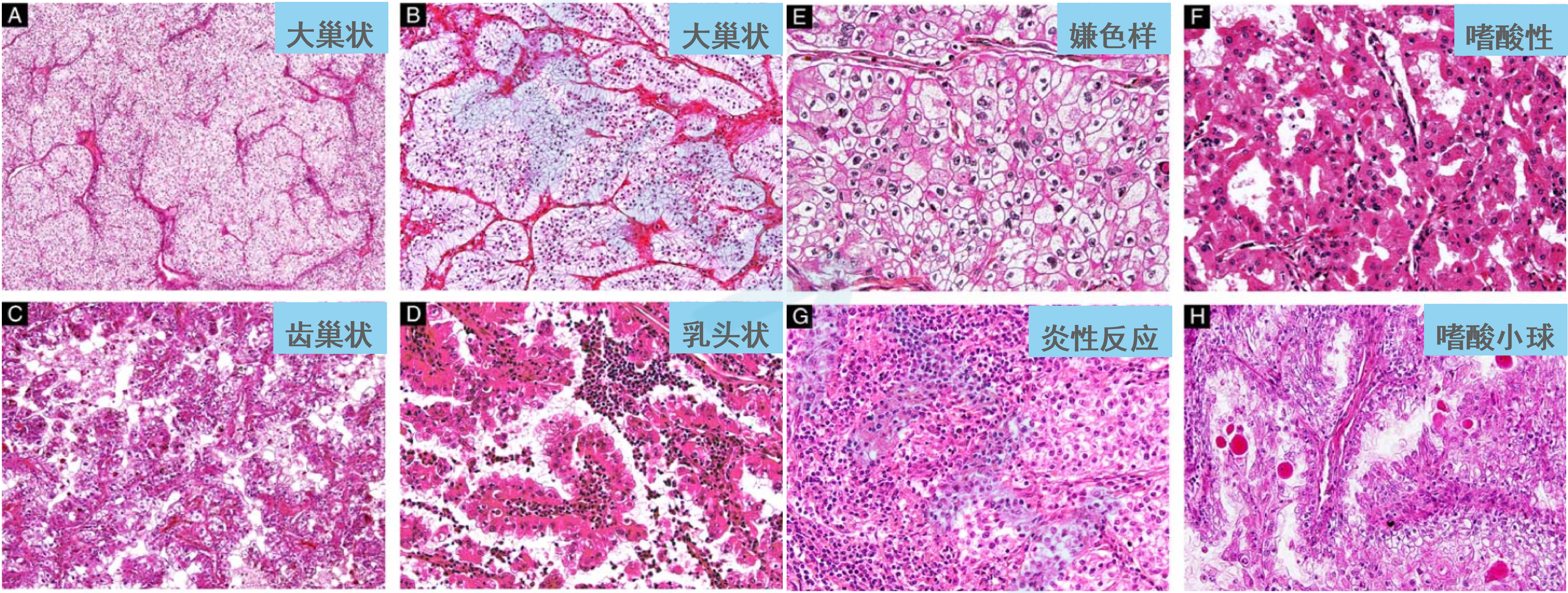
研究结果

分级	转移潜能	LR+	形态特征
1级	无	LR+≤0.8	大囊，微囊，管状囊性，巢状，腺泡状，透明细胞乳头状肾细胞癌样，退变
2级	低	1.2≤LR+<5	大巢状，乳头或微乳头，嫌色/嗜酸细胞样，胞浆内嗜酸性小球，瘤内炎症反应
3级	中	5≤LR+<10	横纹肌样，多核巨细胞，扩张的血管腔，遗传性平滑肌瘤病RCC样
4级	高	LR+≥10	肉瘤样，侵犯正常肾小球，脉管侵犯

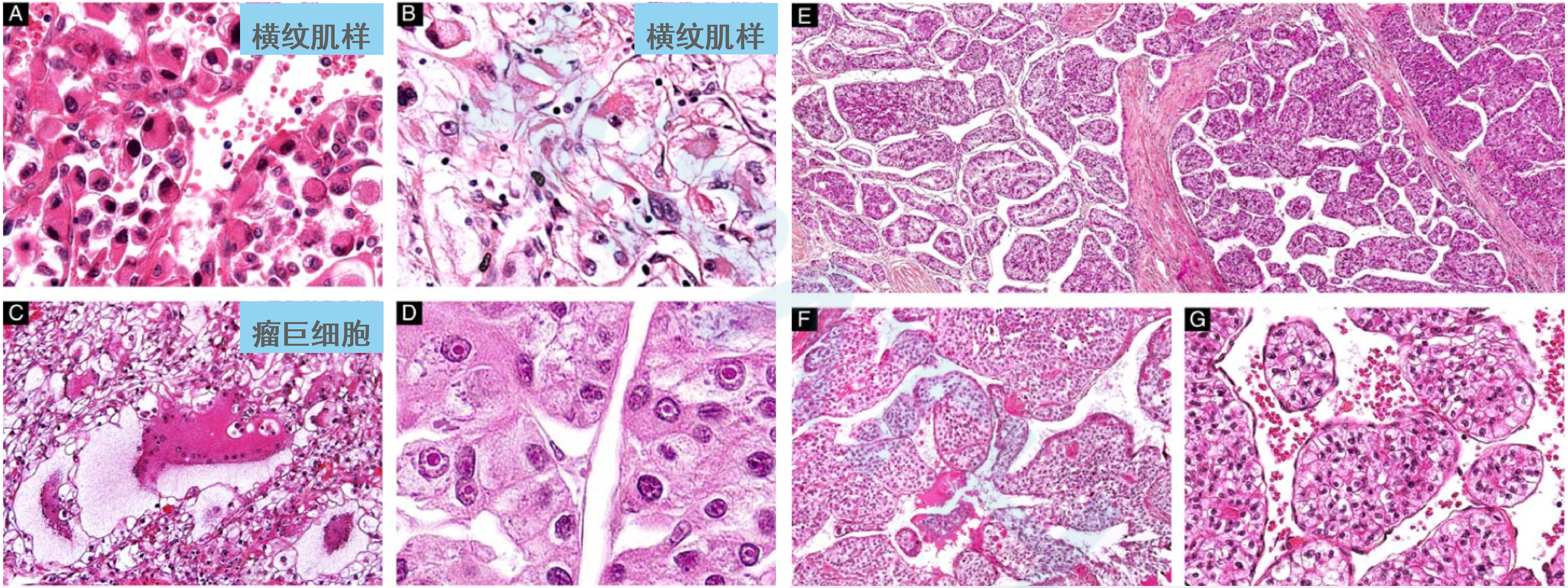
基于形态学的分级系统


A
囊性
B
管状囊性
C
小巢状
D
锯齿状腺泡
E
退变
F
透明细胞乳头状

Grade 1


A
大巢状
B
大巢状
E
嫌色样
F
嗜酸性
C
齿巢状
D
乳头状
G
炎性反应
H
嗜酸小球

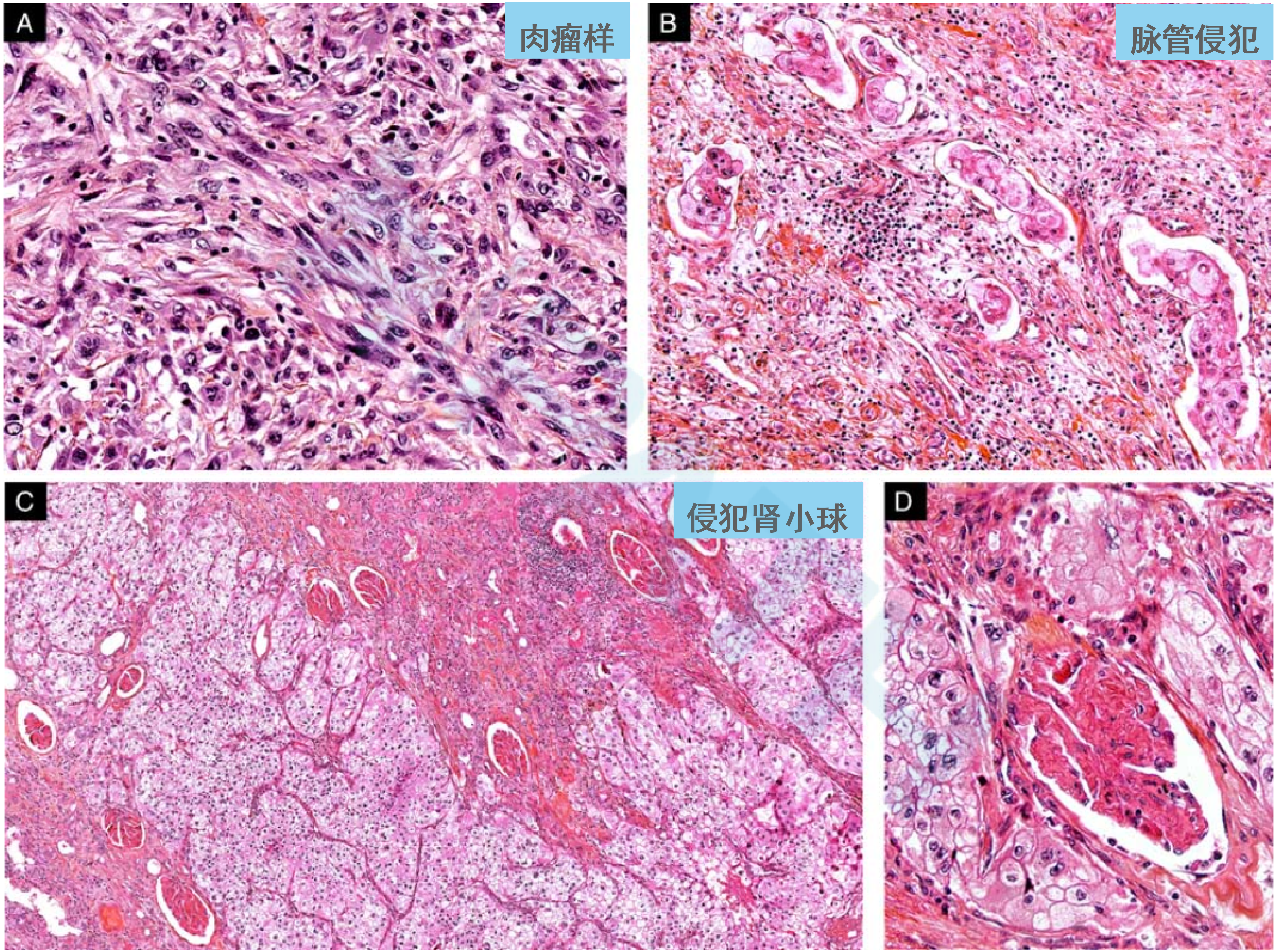
Grade 2


A
横纹肌样
B
横纹肌样
E
C
瘤巨细胞
D
F
G

遗传性平滑肌瘤病相关

扩张的血管腔

Grade 3



肉瘤样

脉管侵犯

侵犯肾小球

Grade 4

研究结果

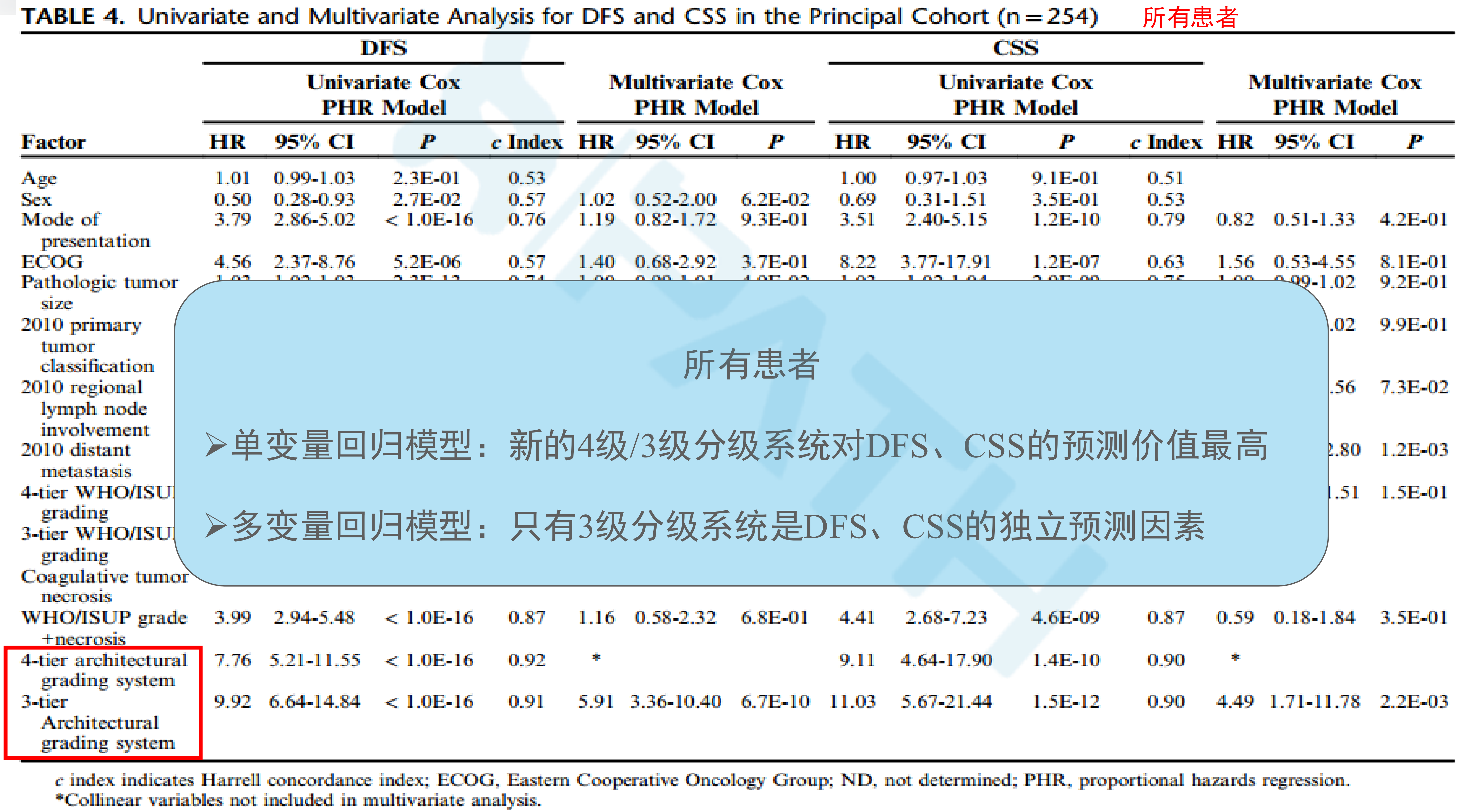


TABLE 4. Univariate and Multivariate Analysis for DFS and CSS in the Principal Cohort (n = 254)

所有患者

	DFS							CSS						
	Univariate Cox PHR Model				Multivariate Cox PHR Model			Univariate Cox PHR Model				Multivariate Cox PHR Model		
Factor	**HR**	**95% CI**	***P***	***c* Index**	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	***c* Index**	**HR**	**95% CI**	***P***
Age	1.01	0.99-1.03	2.3E-01	0.53				1.00	0.97-1.03	9.1E-01	0.51			
Sex	0.50	0.28-0.93	2.7E-02	0.57	1.02	0.52-2.00	6.2E-02	0.69	0.31-1.51	3.5E-01	0.53			
Mode of presentation	3.79	2.86-5.02	< 1.0E-16	0.76	1.19	0.82-1.72	9.3E-01	3.51	2.40-5.15	1.2E-10	0.79	0.82	0.51-1.33	4.2E-01
ECOG	4.56	2.37-8.76	5.2E-06	0.57	1.40	0.68-2.92	3.7E-01	8.22	3.77-17.91	1.2E-07	0.63	1.56	0.53-4.55	8.1E-01
Pathologic tumor size	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	9.2E-01
2010 primary tumor classification	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	9.9E-01
2010 regional lymph node involvement	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	7.3E-02
2010 distant metastasis	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	1.2E-03
4-tier WHO/ISUP grading	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	1.5E-01
3-tier WHO/ISUP grading	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]		
Coagulative tumor necrosis	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]		
WHO/ISUP grade +necrosis	3.99	2.94-5.48	< 1.0E-16	0.87	1.16	0.58-2.32	6.8E-01	4.41	2.68-7.23	4.6E-09	0.87	0.59	0.18-1.84	3.5E-01
4-tier architectural grading system	7.76	5.21-11.55	< 1.0E-16	0.92	*			9.11	4.64-17.90	1.4E-10	0.90	*		
3-tier Architectural grading system	9.92	6.64-14.84	< 1.0E-16	0.91	5.91	3.36-10.40	6.7E-10	11.03	5.67-21.44	1.5E-12	0.90	4.49	1.71-11.78	2.2E-03

c index indicates Harrell concordance index; ECOG, Eastern Cooperative Oncology Group; ND, not determined; PHR, proportional hazards regression.
*Collinear variables not included in multivariate analysis.

所有患者

- ➢单变量回归模型：新的4级/3级分级系统对DFS、CSS的预测价值最高
- ➢多变量回归模型：只有3级分级系统是DFS、CSS的独立预测因素

研究结果

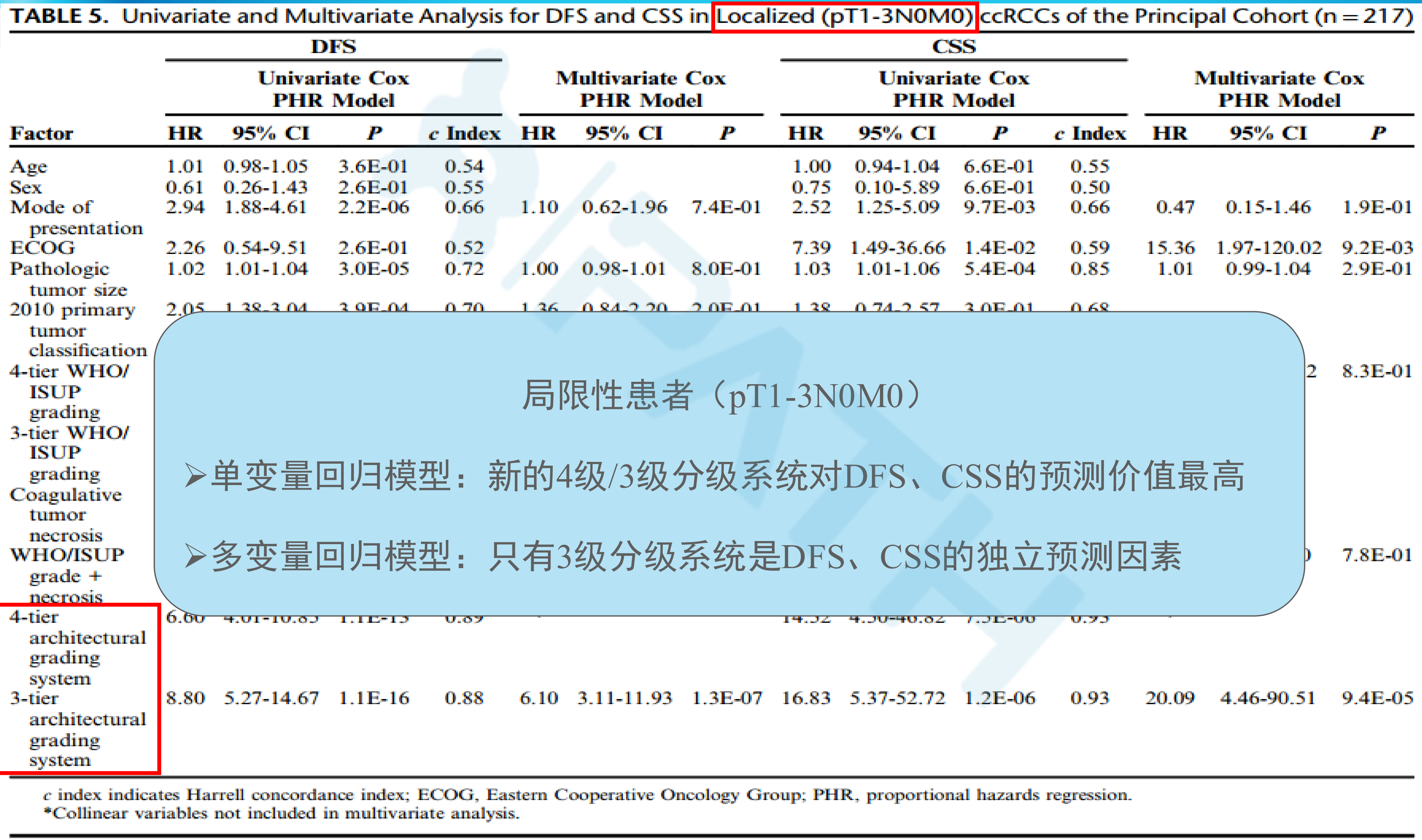


TABLE 5. Univariate and Multivariate Analysis for DFS and CSS in Localized (pT1-3N0M0) ccRCCs of the Principal Cohort (n = 217)

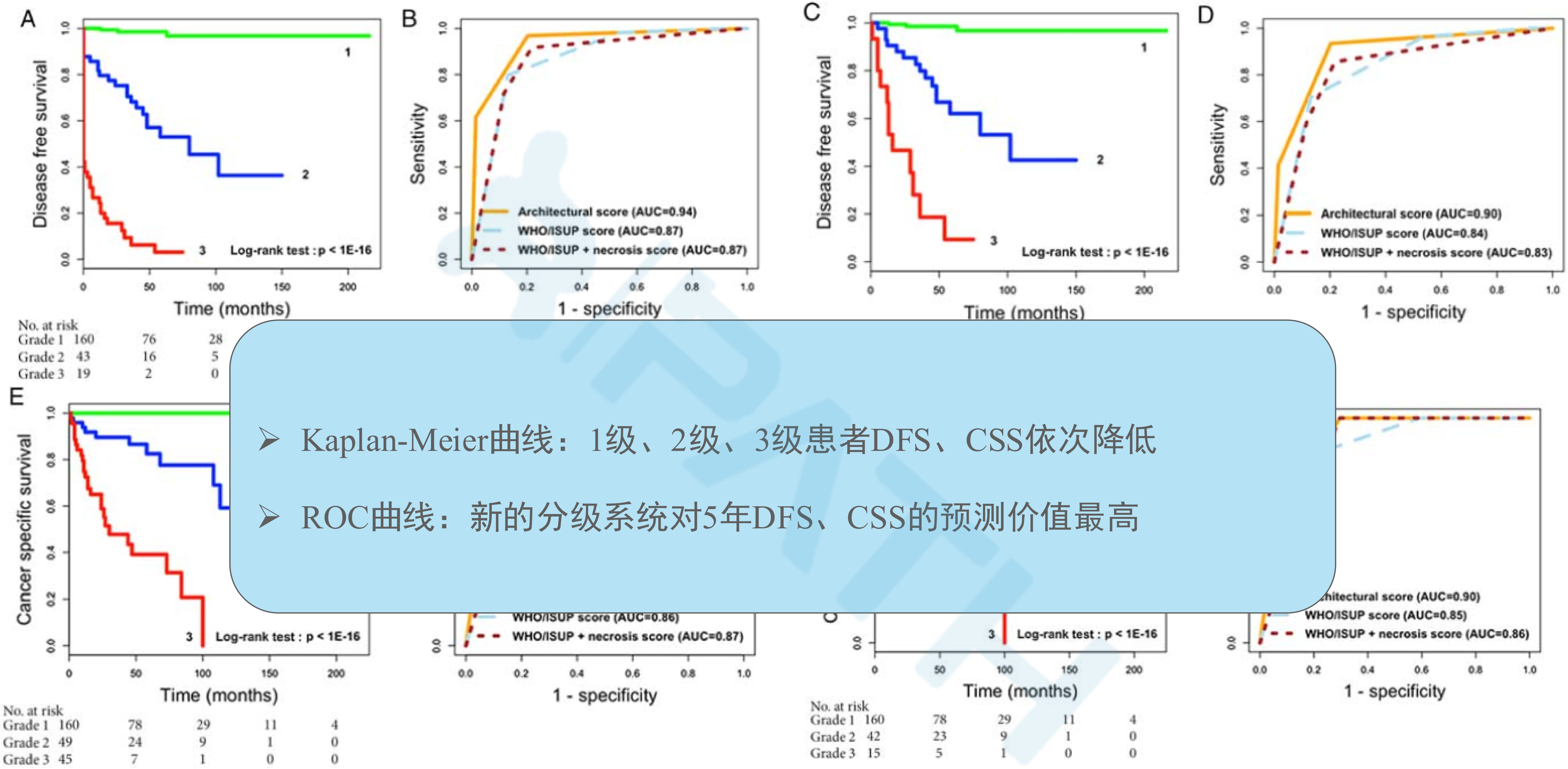
	DFS							CSS						
	Univariate Cox PHR Model				Multivariate Cox PHR Model			Univariate Cox PHR Model				Multivariate Cox PHR Model		
Factor	HR	95% CI	*P*	*c* Index	HR	95% CI	*P*	HR	95% CI	*P*	*c* Index	HR	95% CI	*P*
Age	1.01	0.98-1.05	3.6E-01	0.54				1.00	0.94-1.04	6.6E-01	0.55			
Sex	0.61	0.26-1.43	2.6E-01	0.55				0.75	0.10-5.89	6.6E-01	0.50			
Mode of presentation	2.94	1.88-4.61	2.2E-06	0.66	1.10	0.62-1.96	7.4E-01	2.52	1.25-5.09	9.7E-03	0.66	0.47	0.15-1.46	1.9E-01
ECOG	2.26	0.54-9.51	2.6E-01	0.52				7.39	1.49-36.66	1.4E-02	0.59	15.36	1.97-120.02	9.2E-03
Pathologic tumor size	1.02	1.01-1.04	3.0E-05	0.72	1.00	0.98-1.01	8.0E-01	1.03	1.01-1.06	5.4E-04	0.85	1.01	0.99-1.04	2.9E-01
2010 primary tumor classification	2.05	1.38-3.04	3.9E-04	0.70	1.36	0.84-2.20	2.0E-01	1.38	0.74-2.57	3.0E-01	0.68	[illegible]	[illegible]	[illegible]
4-tier WHO/ ISUP grading	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	8.3E-01
3-tier WHO/ ISUP grading	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	
Coagulative tumor necrosis	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	
WHO/ISUP grade + necrosis	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	7.8E-01
4-tier architectural grading system	6.60	4.01-10.85	1.1E-13	0.89	*			14.32	4.50-46.82	7.5E-06	0.93	*		
3-tier architectural grading system	8.80	5.27-14.67	1.1E-16	0.88	6.10	3.11-11.93	1.3E-07	16.83	5.37-52.72	1.2E-06	0.93	20.09	4.46-90.51	9.4E-05

c index indicates Harrell concordance index; ECOG, Eastern Cooperative Oncology Group; PHR, proportional hazards regression.
*Collinear variables not included in multivariate analysis.

局限性患者（pT1-3N0M0）

➢单变量回归模型：新的4级/3级分级系统对DFS、CSS的预测价值最高

➢多变量回归模型：只有3级分级系统是DFS、CSS的独立预测因素

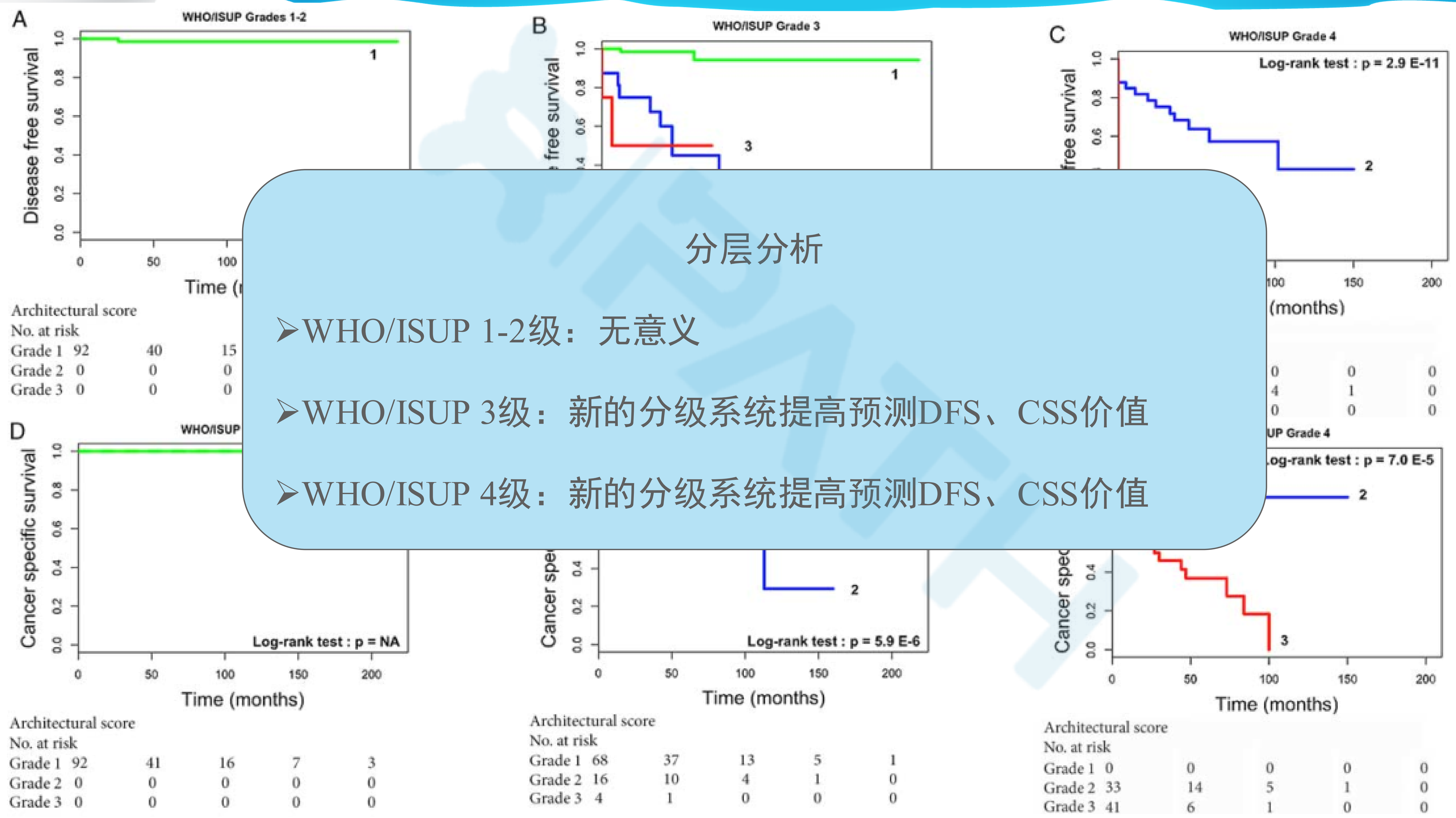


- Kaplan-Meier曲线：1级、2级、3级患者DFS、CSS依次降低
- ROC曲线：新的分级系统对5年DFS、CSS的预测价值最高

研究队列组

局限性（pT1-3N0M0）

研究结果



分层分析

- ➢WHO/ISUP 1-2级：无意义
- ➢WHO/ISUP 3级：新的分级系统提高预测DFS、CSS价值
- ➢WHO/ISUP 4级：新的分级系统提高预测DFS、CSS价值

研究队列与验证队列

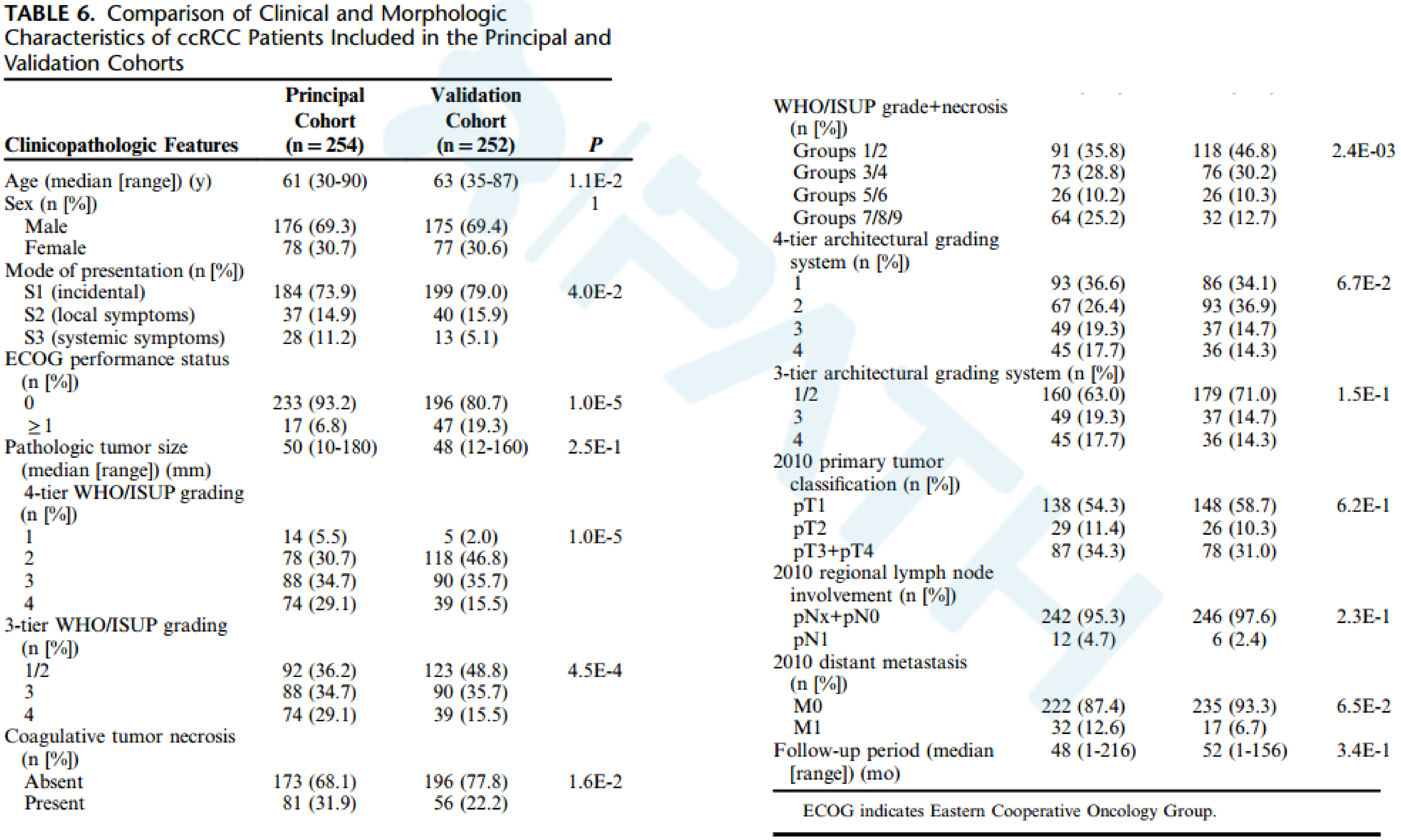


TABLE 6. Comparison of Clinical and Morphologic Characteristics of ccRCC Patients Included in the Principal and Validation Cohorts

Clinicopathologic Features	Principal Cohort (n = 254)	Validation Cohort (n = 252)	*P*
Age (median [range]) (y)	61 (30-90)	63 (35-87)	1.1E-2
Sex (n [%])			1
Male	176 (69.3)	175 (69.4)	
Female	78 (30.7)	77 (30.6)	
Mode of presentation (n [%])			
S1 (incidental)	184 (73.9)	199 (79.0)	4.0E-2
S2 (local symptoms)	37 (14.9)	40 (15.9)	
S3 (systemic symptoms)	28 (11.2)	13 (5.1)	
ECOG performance status (n [%])			
0	233 (93.2)	196 (80.7)	1.0E-5
≥1	17 (6.8)	47 (19.3)	
Pathologic tumor size (median [range]) (mm)	50 (10-180)	48 (12-160)	2.5E-1
4-tier WHO/ISUP grading (n [%])			
1	14 (5.5)	5 (2.0)	1.0E-5
2	78 (30.7)	118 (46.8)	
3	88 (34.7)	90 (35.7)	
4	74 (29.1)	39 (15.5)	
3-tier WHO/ISUP grading (n [%])			
1/2	92 (36.2)	123 (48.8)	4.5E-4
3	88 (34.7)	90 (35.7)	
4	74 (29.1)	39 (15.5)	
Coagulative tumor necrosis (n [%])			
Absent	173 (68.1)	196 (77.8)	1.6E-2
Present	81 (31.9)	56 (22.2)	
WHO/ISUP grade+necrosis (n [%])			
Groups 1/2	91 (35.8)	118 (46.8)	2.4E-03
Groups 3/4	73 (28.8)	76 (30.2)	
Groups 5/6	26 (10.2)	26 (10.3)	
Groups 7/8/9	64 (25.2)	32 (12.7)	
4-tier architectural grading system (n [%])			
1	93 (36.6)	86 (34.1)	6.7E-2
2	67 (26.4)	93 (36.9)	
3	49 (19.3)	37 (14.7)	
4	45 (17.7)	36 (14.3)	
3-tier architectural grading system (n [%])			
1/2	160 (63.0)	179 (71.0)	1.5E-1
3	49 (19.3)	37 (14.7)	
4	45 (17.7)	36 (14.3)	
2010 primary tumor classification (n [%])			
pT1	138 (54.3)	148 (58.7)	6.2E-1
pT2	29 (11.4)	26 (10.3)	
pT3+pT4	87 (34.3)	78 (31.0)	
2010 regional lymph node involvement (n [%])			
pNx+pN0	242 (95.3)	246 (97.6)	2.3E-1
pN1	12 (4.7)	6 (2.4)	
2010 distant metastasis (n [%])			
M0	222 (87.4)	235 (93.3)	6.5E-2
M1	32 (12.6)	17 (6.7)	
Follow-up period (median [range]) (mo)	48 (1-216)	52 (1-156)	3.4E-1

ECOG indicates Eastern Cooperative Oncology Group.

研究结果——验证

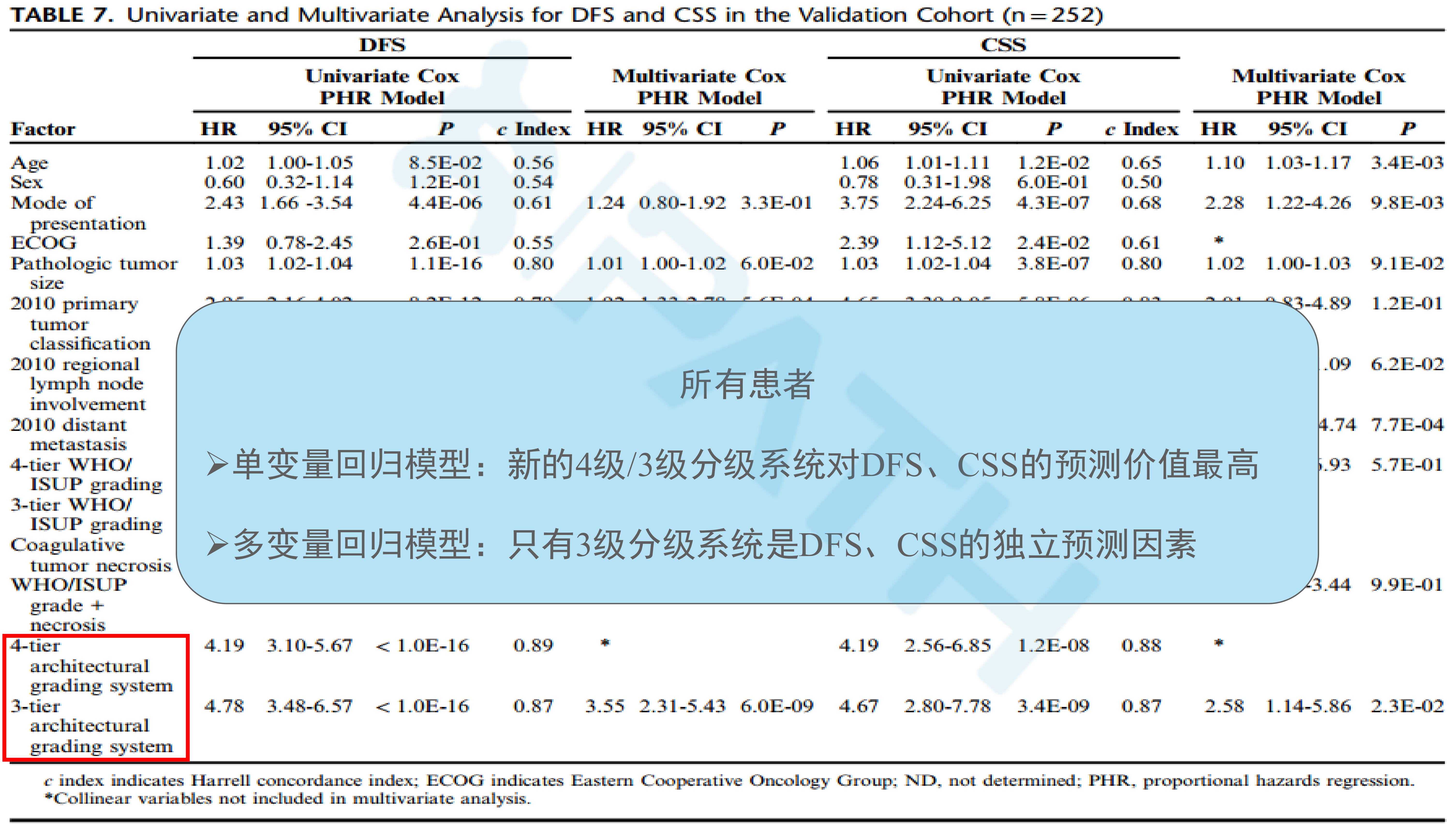


TABLE 7. Univariate and Multivariate Analysis for DFS and CSS in the Validation Cohort (n = 252)

	DFS							CSS						
	Univariate Cox PHR Model				Multivariate Cox PHR Model			Univariate Cox PHR Model				Multivariate Cox PHR Model		
Factor	HR	95% CI	*P*	*c* Index	HR	95% CI	*P*	HR	95% CI	*P*	*c* Index	HR	95% CI	*P*
Age	1.02	1.00-1.05	8.5E-02	0.56				1.06	1.01-1.11	1.2E-02	0.65	1.10	1.03-1.17	3.4E-03
Sex	0.60	0.32-1.14	1.2E-01	0.54				0.78	0.31-1.98	6.0E-01	0.50			
Mode of presentation	2.43	1.66 -3.54	4.4E-06	0.61	1.24	0.80-1.92	3.3E-01	3.75	2.24-6.25	4.3E-07	0.68	2.28	1.22-4.26	9.8E-03
ECOG	1.39	0.78-2.45	2.6E-01	0.55				2.39	1.12-5.12	2.4E-02	0.61	*		
Pathologic tumor size	1.03	1.02-1.04	1.1E-16	0.80	1.01	1.00-1.02	6.0E-02	1.03	1.02-1.04	3.8E-07	0.80	1.02	1.00-1.03	9.1E-02
2010 primary tumor classification													0.83-4.89	1.2E-01
2010 regional lymph node involvement													.09	6.2E-02
2010 distant metastasis													4.74	7.7E-04
4-tier WHO/ISUP grading													.93	5.7E-01
3-tier WHO/ISUP grading														
Coagulative tumor necrosis														
WHO/ISUP grade + necrosis													3.44	9.9E-01
4-tier architectural grading system	4.19	3.10-5.67	< 1.0E-16	0.89	*			4.19	2.56-6.85	1.2E-08	0.88	*		
3-tier architectural grading system	4.78	3.48-6.57	< 1.0E-16	0.87	3.55	2.31-5.43	6.0E-09	4.67	2.80-7.78	3.4E-09	0.87	2.58	1.14-5.86	2.3E-02

c index indicates Harrell concordance index; ECOG indicates Eastern Cooperative Oncology Group; ND, not determined; PHR, proportional hazards regression.
*Collinear variables not included in multivariate analysis.

所有患者

- ➢单变量回归模型：新的4级/3级分级系统对DFS、CSS的预测价值最高
- ➢多变量回归模型：只有3级分级系统是DFS、CSS的独立预测因素

研究结果——验证

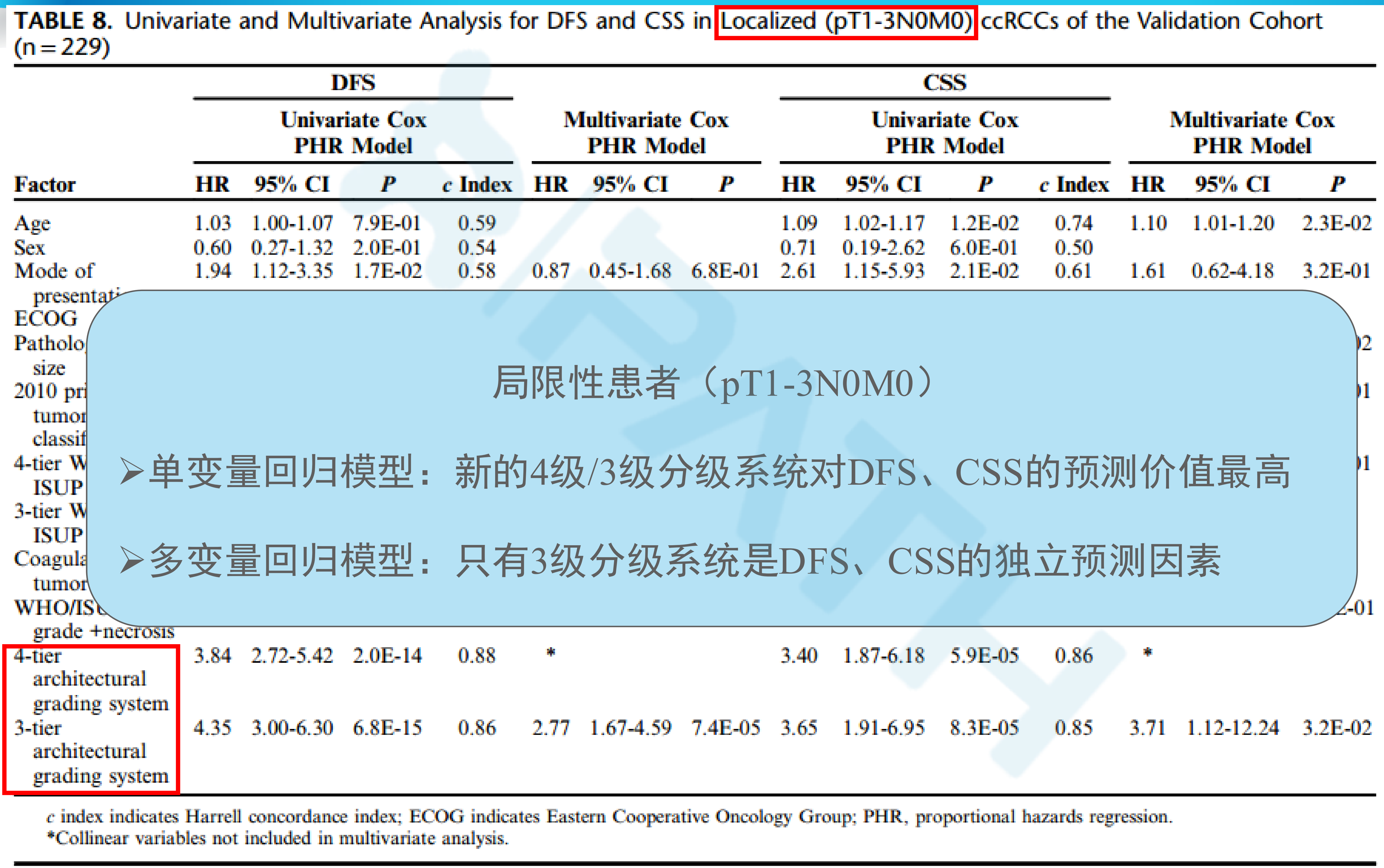


TABLE 8. Univariate and Multivariate Analysis for DFS and CSS in Localized (pT1-3N0M0) ccRCCs of the Validation Cohort (n = 229)

	DFS							CSS						
	Univariate Cox PHR Model				Multivariate Cox PHR Model			Univariate Cox PHR Model				Multivariate Cox PHR Model		
Factor	**HR**	**95% CI**	***P***	***c* Index**	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	***c* Index**	**HR**	**95% CI**	***P***
Age	1.03	1.00-1.07	7.9E-01	0.59				1.09	1.02-1.17	1.2E-02	0.74	1.10	1.01-1.20	2.3E-02
Sex	0.60	0.27-1.32	2.0E-01	0.54				0.71	0.19-2.62	6.0E-01	0.50			
Mode of presentati	1.94	1.12-3.35	1.7E-02	0.58	0.87	0.45-1.68	6.8E-01	2.61	1.15-5.93	2.1E-02	0.61	1.61	0.62-4.18	3.2E-01
ECOG														
Patholo size														2
2010 pri tumor classif														1
4-tier W ISUP														1
3-tier W ISUP														
Coagula tumor														
WHO/IS grade +necrosis														-01
4-tier architectural grading system	3.84	2.72-5.42	2.0E-14	0.88	*			3.40	1.87-6.18	5.9E-05	0.86	*		
3-tier architectural grading system	4.35	3.00-6.30	6.8E-15	0.86	2.77	1.67-4.59	7.4E-05	3.65	1.91-6.95	8.3E-05	0.85	3.71	1.12-12.24	3.2E-02

c index indicates Harrell concordance index; ECOG indicates Eastern Cooperative Oncology Group; PHR, proportional hazards regression.
*Collinear variables not included in multivariate analysis.

局限性患者（pT1-3N0M0）

- ➢单变量回归模型：新的4级/3级分级系统对DFS、CSS的预测价值最高
- ➢多变量回归模型：只有3级分级系统是DFS、CSS的独立预测因素

研究结果

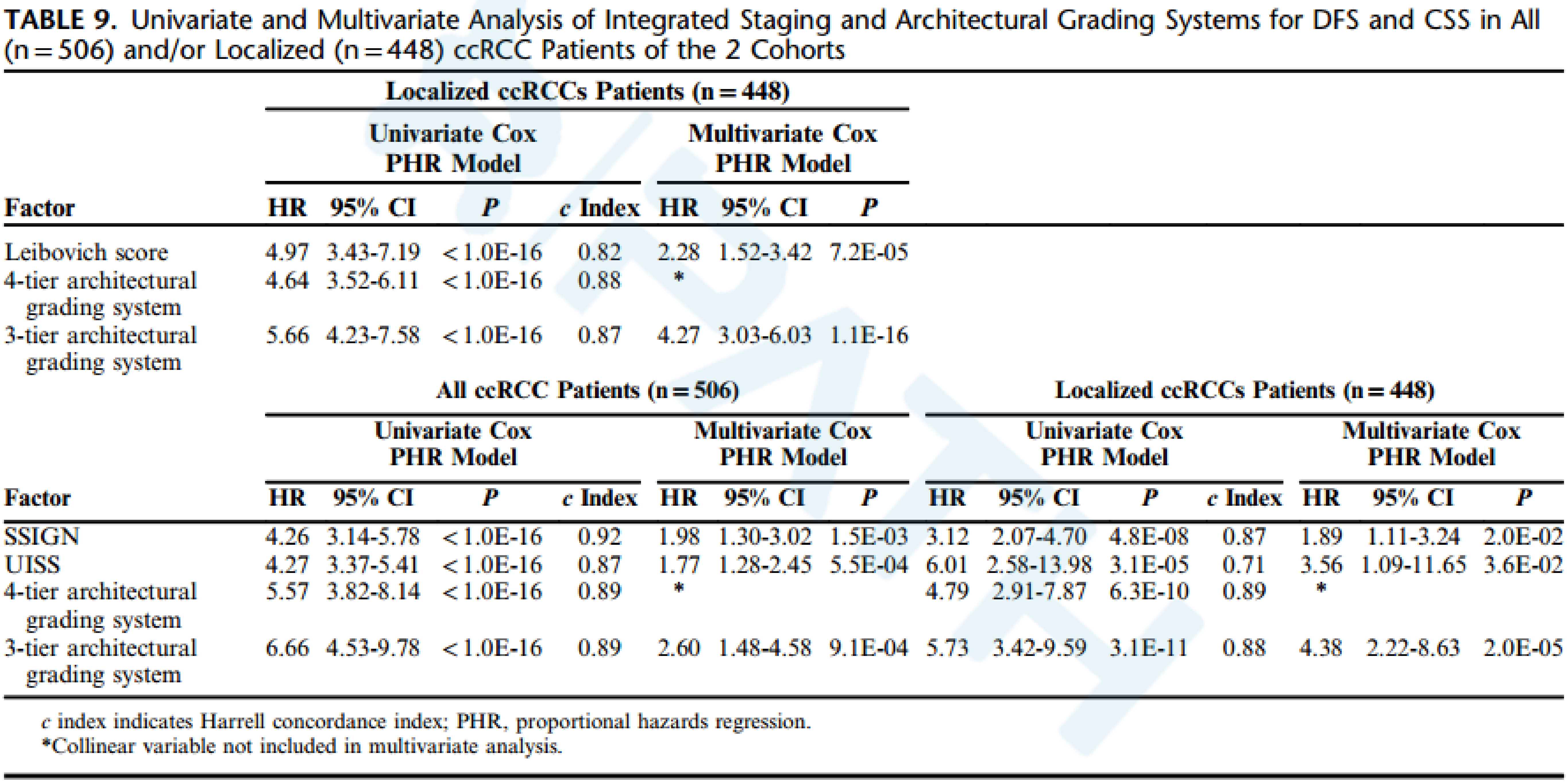


TABLE 9. Univariate and Multivariate Analysis of Integrated Staging and Architectural Grading Systems for DFS and CSS in All (n = 506) and/or Localized (n = 448) ccRCC Patients of the 2 Cohorts

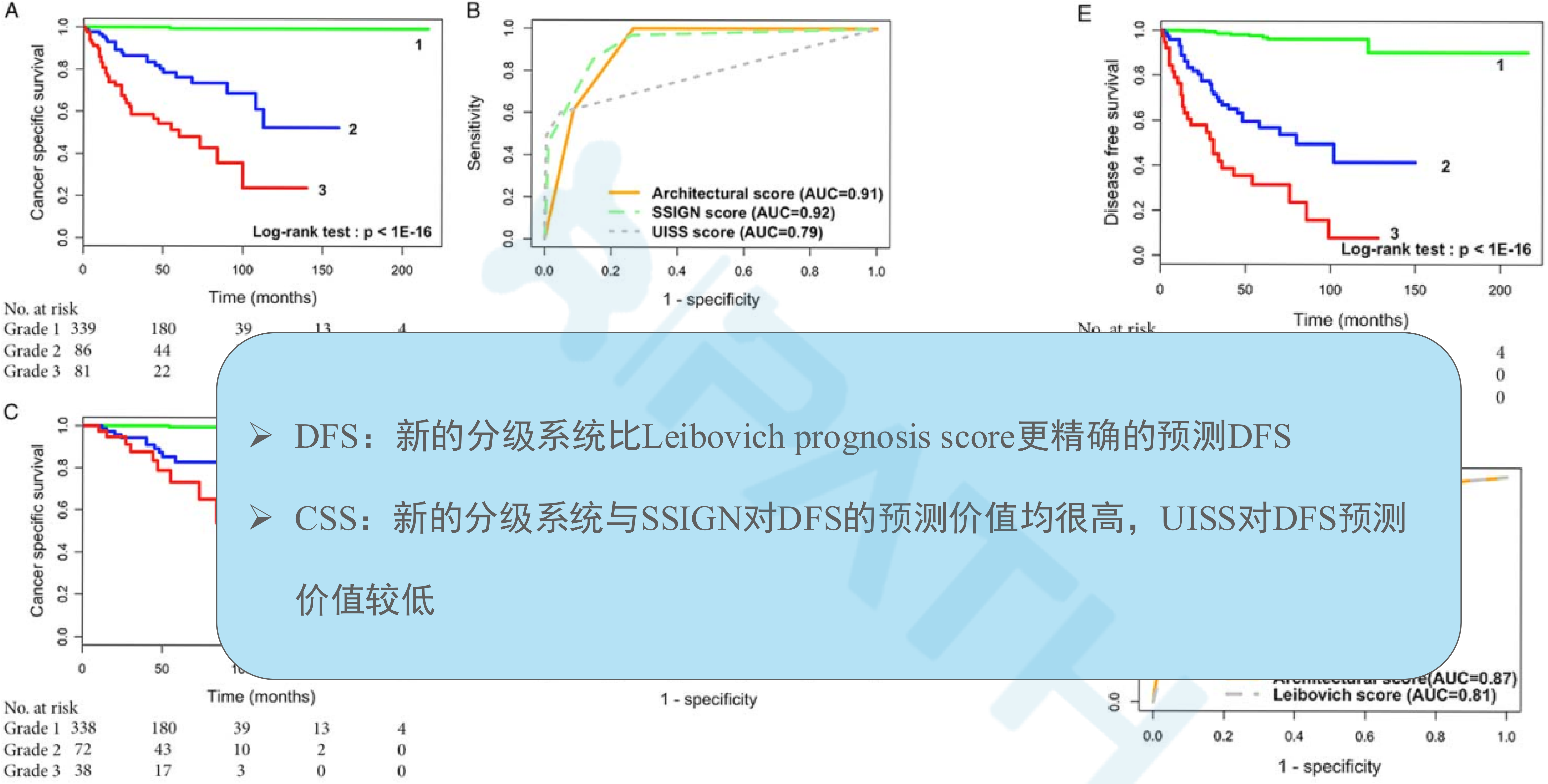
DFS

	Localized ccRCCs Patients (n = 448)						
	Univariate Cox PHR Model				Multivariate Cox PHR Model		
Factor	**HR**	**95% CI**	***P***	***c* Index**	**HR**	**95% CI**	***P***
Leibovich score	4.97	3.43-7.19	< 1.0E-16	0.82	2.28	1.52-3.42	7.2E-05
4-tier architectural grading system	4.64	3.52-6.11	< 1.0E-16	0.88	*		
3-tier architectural grading system	5.66	4.23-7.58	< 1.0E-16	0.87	4.27	3.03-6.03	1.1E-16

CSS

	All ccRCC Patients (n = 506)							Localized ccRCCs Patients (n = 448)						
	Univariate Cox PHR Model				Multivariate Cox PHR Model			Univariate Cox PHR Model				Multivariate Cox PHR Model		
Factor	**HR**	**95% CI**	***P***	***c* Index**	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	***c* Index**	**HR**	**95% CI**	***P***
SSIGN	4.26	3.14-5.78	< 1.0E-16	0.92	1.98	1.30-3.02	1.5E-03	3.12	2.07-4.70	4.8E-08	0.87	1.89	1.11-3.24	2.0E-02
UISS	4.27	3.37-5.41	< 1.0E-16	0.87	1.77	1.28-2.45	5.5E-04	6.01	2.58-13.98	3.1E-05	0.71	3.56	1.09-11.65	3.6E-02
4-tier architectural grading system	5.57	3.82-8.14	< 1.0E-16	0.89	*			4.79	2.91-7.87	6.3E-10	0.89	*		
3-tier architectural grading system	6.66	4.53-9.78	< 1.0E-16	0.89	2.60	1.48-4.58	9.1E-04	5.73	3.42-9.59	3.1E-11	0.88	4.38	2.22-8.63	2.0E-05

c index indicates Harrell concordance index; PHR, proportional hazards regression.
*Collinear variable not included in multivariate analysis.



- ➢ DFS：新的分级系统比Leibovich prognosis score更精确的预测DFS
- ➢ CSS：新的分级系统与SSIGN对DFS的预测价值均很高，UISS对DFS预测价值较低

FIGURE 7. Predicted survival and ROC curves in the 2 (principal and validation) cohorts. Kaplan-Meier estimates of CSS according to the architectural score in all patients (A), and in the localized (pT1-3N0M0) ccRCC subgroup (C). AUC for the architectural score and the SSIGN and UISS model groups in predicting 5-year CSS in all patients (B), and in the localized ccRCC subgroup (D). E, Kaplan-Meier estimates of DFS according to the architectural score in the localized ccRCC subgroup. F, AUC for the architectural score and the Leibovich model groups in predicting 5-year DFS in the localized ccRCC subgroup.

研究结果

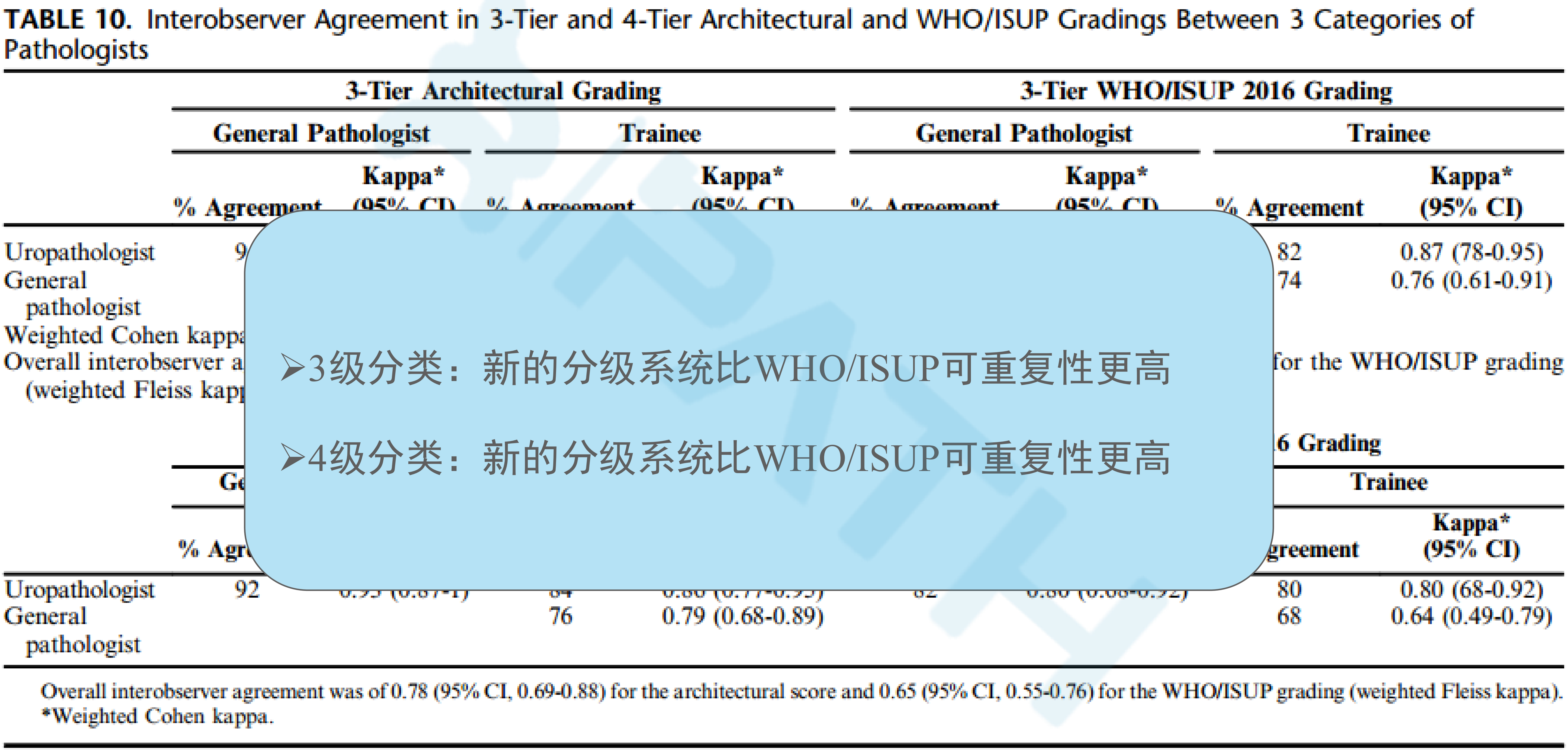


TABLE 10. Interobserver Agreement in 3-Tier and 4-Tier Architectural and WHO/ISUP Gradings Between 3 Categories of Pathologists

	3-Tier Architectural Grading				3-Tier WHO/ISUP 2016 Grading			
	General Pathologist		Trainee		General Pathologist		Trainee	
	% Agreement	Kappa* (95% CI)	% Agreement	Kappa* (95% CI)	% Agreement	Kappa* (95% CI)	% Agreement	Kappa* (95% CI)
Uropathologist	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	82	0.87 (78-0.95)
General pathologist	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	74	0.76 (0.61-0.91)

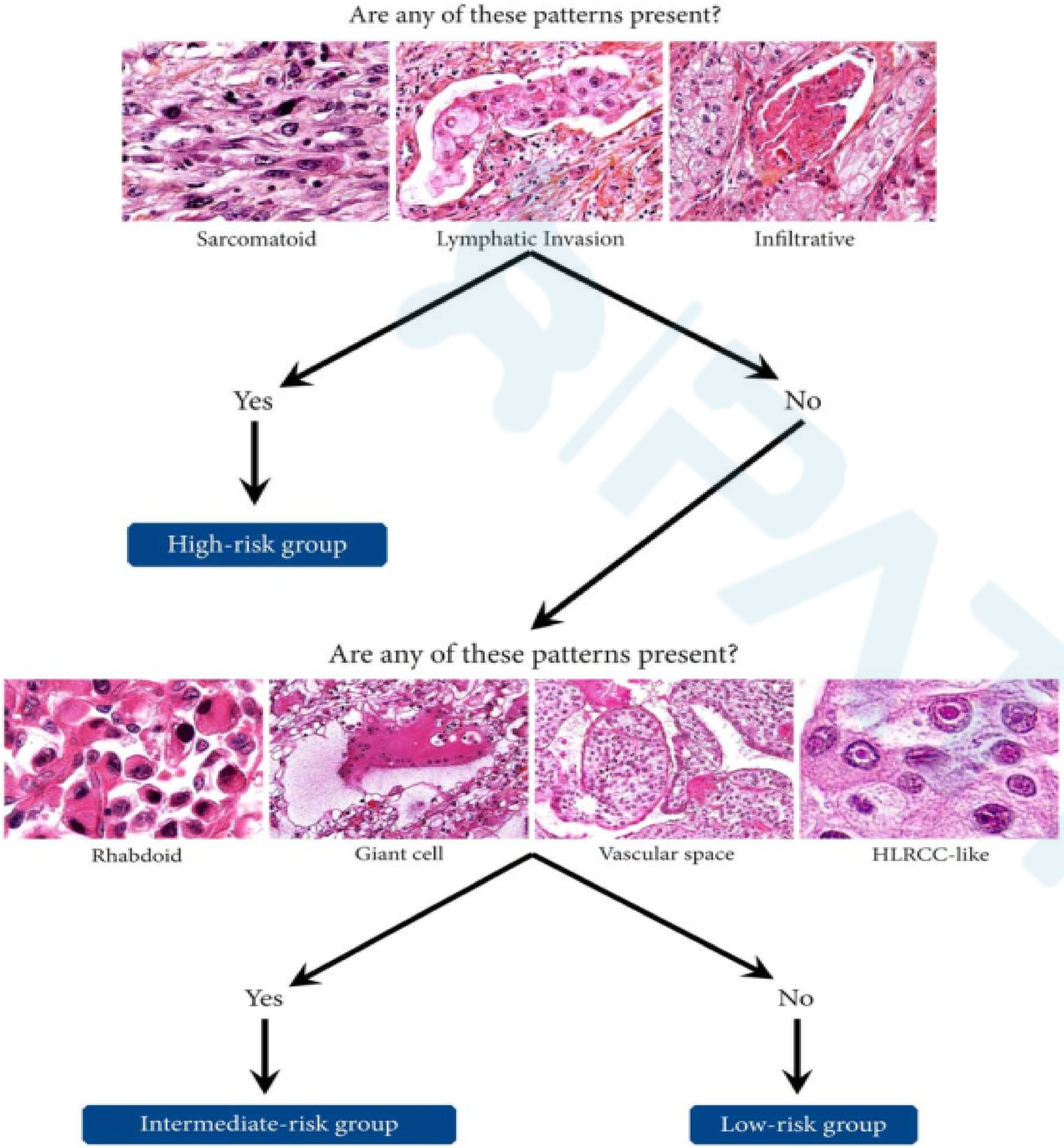
Weighted Cohen kappa [illegible]
Overall interobserver a[illegible] for the WHO/ISUP grading (weighted Fleiss kap[illegible]

	[illegible]				[illegible]6 Grading			
	Ge[illegible]		[illegible]		[illegible]		Trainee	
	% Agr[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]greement	Kappa* (95% CI)
Uropathologist	92	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	80	0.80 (68-0.92)
General pathologist			76	0.79 (0.68-0.89)			68	0.64 (0.49-0.79)

Overall interobserver agreement was of 0.78 (95% CI, 0.69-0.88) for the architectural score and 0.65 (95% CI, 0.55-0.76) for the WHO/ISUP grading (weighted Fleiss kappa).
*Weighted Cohen kappa.

- ➢3级分类：新的分级系统比WHO/ISUP可重复性更高
- ➢4级分类：新的分级系统比WHO/ISUP可重复性更高

分级思路



Are any of these patterns present?

Sarcomatoid

Lymphatic Invasion

Infiltrative

Yes

High-risk group

No

Are any of these patterns present?

Rhabdoid

Giant cell

Vascular space

HLRCC-like

Yes

Intermediate-risk group

No

Low-risk group

DISCUSSION

DISCUSSION

- 基于肿瘤形态特征的新的分级系统在预测DFS与CSS方面均优于目前其他的分级系统
- 该评分系统仅应用1种形态学资料，但在DFS与CSS的预测评分中优于目前的整合评分系统，如Leibovich prognosis score, SSIGN, UISS
- 之前的研究表明WHO/ISUP结合肿瘤坏死情况可提高预测预后价值，但本分级系统结合肿瘤坏死情况后对预测预后无显著提高

DISCUSSION

- 本研究指出，横纹肌样分化的预后与肉瘤样分化的预后有明显差异，应将两者分为不同的级别，但目前WHO/ISUP将两者同时归为4级；在之前的其他研究中同样认为两者在预后方面有明显差异
- WHO/ISUP分级中的3级病例有很大一部分在本分级系统中被降级为1/2级，说明原有分级系统对患者预后的预测方面存在偏倚

DISCUSSION

- 观察肿瘤的形态特征比单纯观察核仁是否显著具有更高的可重复性，并且在其他肿瘤的预后预测中已有应用(*Am J Surg Pathol.* 2010;34:1155–1162)
- 该分级系统可在HE下进行评估，省去其他耗时的技术环节，非泌尿专科病理医生也能轻松掌握

局限性

- 回顾性研究在研究设计上具有本身的缺陷
- 本评分系统均基于手术标本，对于活检标本的分级比较局限，但这点是所有其他分级系统的通病
- 本研究并未囊括所有ccRCC的形态特征
- 还需要更多的病例验证本分级系统的可靠性

总结

我们的分级系统比WHO/ISUP

分级系统好用！！！

THANK YOU

Any questions?

Q&A