肿瘤内科学专题 • 临床研究 •

术前外周血血小板/淋巴细胞比值和血小板相关指标对晚期下咽鳞癌的预后价值*

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[摘要] **目的:** 探讨术前外周血血小板(platelet, PLT)/淋巴细胞比值(platelet-to-lymphocyte ratio, PLR)和 PLT 相关指标[PLT 平均体积(mean platelet volume, MPV)、PLT 分布宽度(platelet distribution width, PDW)]对晚期(TNM Ⅲ/Ⅳ)下咽鳞癌患者长期预后的影响。**方法:** 回顾性分析 2003 年 1 月至 2012 年 12 月我院诊治的 176 例晚期下咽鳞癌患者临床资料。使用 X-tile 法分析术前血指标[PLR、PLT、MPV、PDW、MPV/PLT 计数(MPV to platelet count ratio, MPV/P)、PDW/PCT 计数(PDW to platelet count ratio, PDW/P)], 选取最佳截点(cut-off point)区分高、低两组。应用 Pearson 卡方检验或 Fisher 精确概率法对两组进行描述性分析, 采用单因素和多因素 Cox 回归模型分析两组患者的 PLR 及其它临床病理因素与 5 年总生存期(overall survival, OS)、5 年无病生存期(disease-free survival, DFS)的关系。**结果:** 随访时间至 2017 年 12 月 31 日, 平均随访时间(47.81 ± 30.48)月。X-tile 分析得出 5 年 OS 最佳截点: PLR 为 170.8, PLT 为 260×10^9/L, MPV 为 8.2fL, PDW 为 16.5%, MPV/P 为 0.036, PDW/P 为 0.0635; 5 年 DFS 最佳截点: PLR 为 139.6, PLT 为 271×10^9/L, MPV 为 11.1fL, PDW 为 16.5%, MPV/P 为 0.036, 和 PDW/P 为0.0635。纳入单因素及多因素 Cox 分析得出影响 5 年 OS 的独立危险因素有: 高 PLR(170.8)、高 PLT(260×10^9/L)、低 MPV(8.2fL)、T 分级、术后转移。影响 5 年 DFS 的独立危险因素有: 高 PLR(139.6)、高 PDW(11.1%)、T 分级、TNM 分期。**结论:** PLR 升高提示下咽鳞癌患者预后较差, 或可作为其长期预后(5 年 OS、DFS)评估指标。

[关键词] 下咽鳞癌; 外周血血小板/淋巴细胞比值; 血小板平均体积; 血小板分布宽度

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Prognostic Value of Preoperative Platelet-to-Lymphocyte Ratio and Platelet-Related Indexes in Advanced Hypopharyngeal Squamous Cell Carcinoma

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[**Abstract**] **Objective**: To investigate whether preoperative platelet-to-lymphocyte ratio (PLR) and platelet (PLT)-related indexes, mean platelet volume (MPV) and platelet distribution width (PDW), can be long-term prognostic indicators of patients with advanced (TNM Ⅲ/Ⅳ) hypopharyngeal squamous cell carcinoma (HPSCC). **Method**: Data of 176 HPSCC patients in our hospital from January 2003 to December 2012 were retrospectively studied. X-tile method was used to select best cut-off point for preoperative blood indexes [PLR, PLT, mean platelet volume (MPV), platelet distribution width (PDW), mean platelet volume to platelet count ratio (MPV/P), platelet distribution width to platelet count ratio (PDW/P)] to divide the patients into two groups (high and low). Pearson's chi-squared test or Fisher exact test were used to conduct a descriptive analysis. Univariate and multivariate analysis were conducted to evaluate the relationship between clinicopathological factors like PLR and 5-year overall survival (OS) and 5-year disease-free survival (DFS) of patients in two groups. **Result**: Follow up was around 47.81 months until 31 December 2017. According to X-tile method, the optimal cut-off points were 170.8 for PLR, 260×10^9/L for PLT, 8.2fL for MPV, 16.5% for PDW, 0.036 for MPV/P and 0.064 for PDW/P in 5-year OS analysis. In 5-year DFS analysis, the optimal cut-off points were 139.6 for PLR, 271×10^9/L for PLT, 11.1fL for MPV, and the rest were the same as those in the 5-year OS analysis. Univariate and multivariate analysis showed that the independent risk factors of 5-year OS were high PLR(>170.8), high PLT($>260\times10^9$/L), low MPV(≤8.2fL), tumor classification and postoperative metastasis; the independent risk factors of 5-year DFS were high PLR(>139.6), high PDW(>11.1%), tumor classification and TNM stage. **Conclusion**: The increase in PLR suggests that the prognosis of patients with HPSCC is poor, and it could be an indicator of long-term prognosis (5 – year OS and 5-year DFS).

[**Key words**] Hypopharyngeal squamous cell carcinoma; Platelet-to-lymphocyte ratio; Mean platelet volume; Platelet distribution width

头颈部鳞状细胞癌占全身恶性肿瘤的 10%,全球每年新发病例约 65 万例。尽管治疗模式及理念的不断进步,近 30 年来该病患者的 5 年生存率仍维持在 60% 左右[1]。下咽鳞癌是一种侵袭性高的头颈部鳞状细胞癌,发病位置隐匿且症状不典型,约 60% 患者就医时就被诊断为晚期。临床上,美国癌症联合会(American Joint Committee on Cancer, AJCC) TNM 分期系统依然是临床医生判断预后的主要手段,且目前尚无针对下咽鳞癌特异性高的生化指标来判断预后。近年来,随着系统性炎症的深入研究,人们发现外周血中的相关比值,如中性粒细胞/淋巴细胞比值(neutrophil-to-lymphocyte ratio, NLR)、血小板/淋巴细胞比值(platelet-to-lymphocyte ratio, PLR)、淋巴细胞/单核细胞比值(lymphocyte-to-monocyte ratio, LMR)等与机体炎症高度相关[2-3],且被应用于多种恶性肿瘤的预后判断。本研究拟在前期针对喉鳞癌预后研究基础上,探讨术前外周血 PLR 和血小板(platelet, PCT)相关指标[血小板平均体积(mean platelet volume, MPV)、血小板分布宽度(platelet distribution width, PDW)]对晚期(TNM Ⅲ/Ⅳ)下咽鳞癌患者长期预后的影响。

1 资料与方法

1.1 临床资料

自 2003 年 1 月至 2012 年 12 月共计 377 例在我院耳鼻喉科接受手术治疗的下咽鳞癌患者,经过纳入排除标准后,将 176 例晚期下咽鳞癌患者纳入本研究。入选患者需符合:(1)经病理检查确诊为晚期下咽鳞癌,即 AJCC TNM Ⅲ期或 IV 期(AJCC 7 版);(2)患者或其家属自愿签署知情同意书、临床信息授权及随访资料;(3)临床信息、随访资料相对完整。201 例排除病例包含:(1)病理不属于下咽鳞癌($n=2$);(2)慢性炎症包括胃炎、肝炎、肾炎及系统性炎症如梅毒等病变($n=40$);(4)有术前放化疗史($n=41$);(5)临床信息及随访缺失($n=76$);(6)伴有其他部位癌症($n=12$);(7)伴活动期免疫性、血液性疾病患者($n=1$);(8)长期服用抗凝药物史($n=4$);(9)TNM Ⅰ期或Ⅱ期($n=53$)。另外,收集我院眼科资料库随访的近视及白内障患者 250 例作为对照,年龄 38 ~ 85 岁,排除相关慢性炎症(包括胃炎、肝炎、肾炎)、系统性炎症(如梅毒)、伴活动期免疫性与血液性疾病患者,无长期抗凝药物使用史。

1.2 信息采集

入组下咽鳞癌患者均以手术为第一次治疗方式,回顾性收集自 2003 年 1 月至 2012 年 12 月患者的临床资料,包括年龄、性别、肿瘤原发部位、病理类型、分化程度、浸润深度、肿瘤最大直径、淋巴结转移情况。此外收集患者术前 2 周内的外周血常规指标,包括血小板计数、淋巴细胞计数、平均血小板体积、血小板分布宽度。我院下咽鳞癌手术患者住院前常规行喉镜、胃镜、腹部 B 超、颈/胸部 CT 等检查。相关外周血标本(血小板计数、淋巴细胞计数、PDW、

MPV)等均使用全自动血细胞分析仪器(Mindary BC-5500)进行计数分析。所有患者数据均受到复旦大学附属眼耳鼻喉科医院伦理委员会监督。

1.3　随访

本研究选择总生存期(overall survival, OS)和无病生存期(disease-free survival, DFS)作为预后分析。自第一次手术治疗为观察起点, OS 定义至随访终点存活时间段。DFS 定义为患者为第一次治疗至患者出现复发, 转移, 或在随访期内死亡时间段。所有患者术后前两年每 1 ~ 3 月定期我院复诊, 2 年后半年复查一次。本研究末次随访日期为 2017 年 12 月 30 日。

1.4　统计学方法

采用 SPSS 22.0 软件统计分析。将患者治疗一开始的外周血 PLR、血小板及其参数, 用 X-tile 软件分高低 2 组, 对分组的病人参数, 如临床病理、性别、年龄、发病部位、肿瘤大小、术后转移等关系采用 Pearson 卡方检验或 Fisher 精确概率法分析。应用单因素及多因素 Cox 回归模型分析长期预后(5 年 OS 及 DFS)的相关独立影响因素。检验水准 $\alpha = 0.05$, $P < 0.05$ 代表具有统计学差异。应用 Kaplan-Meier 法对相关独立影响因素计算生存率, 不同分组患者生存率的比较采用 log-rank 检验。

2　结　果

2.1　患者临床特征

176 例患者中, 男性 172 例, 女性 4 例; 年龄最小 38 岁, 最大 85 岁[平均(58.74 ± 9.91)岁]; 吸烟 138 人(78.4%), 饮酒 118 人(67%); 按下咽原发肿瘤部位分类: 梨状窝型 142 例(80.7%)、咽后壁型 23 例(13.1%)、环后型 11 例(6.3%)。TNM Ⅲ期 49 例, Ⅳ期 127 例, 伴淋巴结转移者 152 例, 其中淋巴结融合 67 例, 淋巴结数量≥3 个 97 例, 淋巴结外侵犯 84 例, 有血管癌栓 25 例, 颈部血管侵犯 56 例, 出现术后转移病人 95 例(表 1)。按原发灶手术方式: 全喉全下咽手术 24 例, 全喉部分下咽手术 117 例, 部分下咽手术 14 例, 部分喉部分下咽手术 21 例。平均随访时间是 47.81 ± 30.48 月(4 ~ 147 月)。总随访率为 80%。5 年总生存率为 29.5%, 术后复发及转移占 54%。

表 1　176 例晚期下咽鳞癌患者基本情况

Table 1. Demographic Data of 176 Patients with Hypopharyngeal Squamous Cell Carcinoma

Characteristic	Number(Ratio)
Gender	
Male/female	172 (97.7%)/4 (2.3%)
Age (years)	
<60/≥60	99 (56.3%)/77 (43.8%)
Hypertension	
No/Yes	130 (73.9%)/46 (26.1%)
Diabetes mellitus	
No/Yes	169 (96.0%)/7 (4%)
Smoking history	
No/Yes	38 (21.6%)/138 (78.4%)
Drinking history	
No/Yes	58 (33%)/118 (67%)
Tumor location	
Pyriform sinus/Post-cricoid/Posterior pharyngeal	142 (80.7%)/11 (6.3%)/23 (13.1%)
Differentiation grade	
Good and moderate/Poor	155 (88.1%)/21 (11.9%)
Platelet ($\bar{x} \pm s$, 10^9/L)	208.86 ± 61.12
Lymphocyte ($\bar{x} \pm s$, 10^9/L)	1.803 ± 0.486
Platelet-to-lymphocyte ratio($\bar{x} \pm s$)	123.74 ± 45.91
Mean platelet volume $\bar{x} \pm s$, fL	10.011 ± 1.31
Platelet distribution width ($\bar{x} \pm s$, %)	14.952 ± 2.4

(Table 1 continues on next page)

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Characteristic	Number(Ratio)
TNM stage	
Ⅲ/Ⅳ	49 (27.8%)/127 (72.2%)
Tumor classification	
T1/T2/T3/T4A/T4B	9 (5.1%)/37 (21%)/82 (46.6%)/46 (26.1%)/2 (1.1%)
Lymph node dissection	
No/Yes	10 (5.7%)/166 (94.5%)
Node classification	
N0/N1/N2a/N2b/N2c/N3	24 (13.6%)/41 (23.3%)/4 (2.3%)/79 (44.9%)/9 (5.1%)/19 (10.8%)
Vascular embolus	
No/Yes	151 (85.8%)/25 (14.2%)
Metastasis	
No/Yes	81 (46%)/95 (54%)
Follow-up time ($\bar{x} \pm s$, month)	47.81 ± 30.48

2.2 晚期下咽癌患者与健康对照组 PLR、MPV、PDW 比较

将 250 例对照组与本研究 176 例晚期下咽癌患者血液中 PLR、MPV、PDW 进行 t 检验，并得出如图 1A ~ C。从中发现晚期下咽鳞癌患者平均 PLR (123.7 ± 3.46) 及 PDW (14.95 ± 0.18) 均较健康对照组平均 PLR (108.6 ± 2.52) 及 PDW (11.77 ± 0.15) 升高，且二者差异有统计学意义 ($P < 0.001$)，进一步分析 MPV，发现晚期下咽鳞癌患者外周血平均 MPV (10.01 ± 0.099) 较健康对照组 MPV (10.54 ± 0.024) 降低，两者间差异有统计学意义 ($P < 0.05$)。

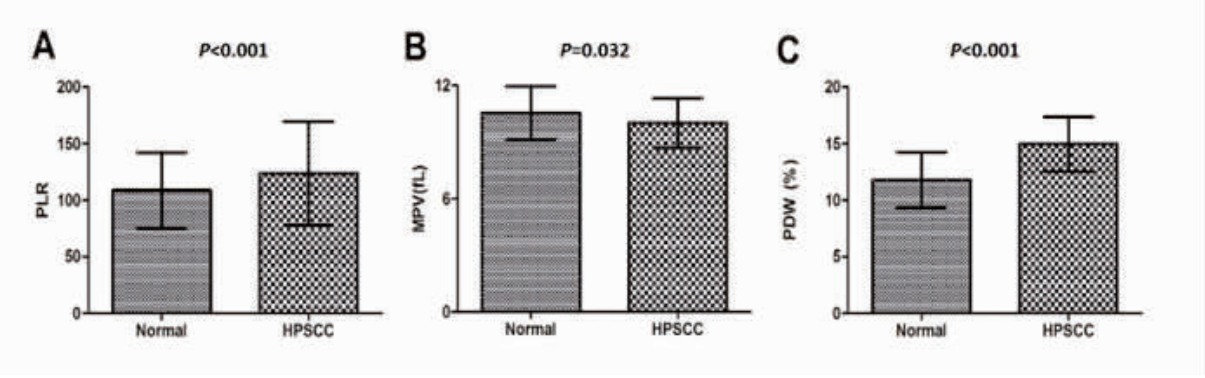

图 1 比较晚期下咽癌及健康对照组 PLR、MPV、PDW 分布

Figure 1. PLR, MPV, PDW Distribution in Advanced HPSCC and Healthy Controls

A: Compared with the healthy controls, advanced HPSCC patients exhibit higher PLR ($P < 0.001$); B: Compared with the healthy controls, advanced HPSCC patients exhibit lower MPV ($P = 0.032$); C: Compared with the healthy controls, advanced HPSCC patients exhibit higher PDW ($P < 0.001$). PLR: Platelet-to-lymphocyte ratio; MPV: Mean platelet volume; PDW: Platelet distribution width; HPSCC: Hypopharyngeal squamous cell carcinoma. PLR, MPV, and PDW in healthy controls and advanced HPSCC patients were analyzed through t-test.

2.3 X-tile 分组后的 PLR 和血小板相关参数与患者相关临床因素的关系

X-tile 软件 (Chicago, Rim 实验室) 查找外周血指标 PLR、PLT、MPV、PDW 的最佳截点，该截值点选择依据最高卡方值及最低 P 值。对 5 年 OS 分析中得出各截点：PLR 为 170.8，PLT 为 260×10^9/L，MPV 为 8.2fL，PDW 为 16.5%，血小板分布宽度/血小板计数 (mean platelet volume to plateler count ratio, MPV/P) 为 0.036，和血小板分布宽度/血小板计数 (platelet distribution width to platelet count ratio, PDW/P) 为 0.0634。对 5 年 DFS 分析中得出各截点：PLR 为 139.6，PLT 为 271×10^9/L，MPV 为 11.1fL，PDW 为 16.5%，MPV/P 为 0.036，PDW/P 为 0.0634，AUC 及 P 值分别列于表 2、表 3。依截点将 PLR、

MPV、PDW 分成高低 2 组，Pearson 或精确卡方检验对其可能影响下咽癌生存预后的临床危险因素如抽烟、喝酒、糖尿病、高血压、T 分级、N 分级以及病理提示的颈内静脉侵犯、癌栓、术后转移等进行组内探查，分析 OS 时，癌栓、饮酒史在高 PLR 组间差异有统计学意义（$P<0.05$），癌栓则在高 MPV 分组间差异有统计学意义（$P<0.05$；表 4）；分析无病生存期时，发现升高 PLR 与术后转移的发生相关，升高的 PDW 与较高肿瘤分期相关，差异具有统计学意义（$P<0.05$；表 5）；此临床意义提示癌栓可能影响总生存率，而高肿瘤分期及术后转移提示可能与无病生存期相关，为了探查生存时间与各组之间的关系，进一步验证发现，高 PLR 组在 OS 及 DFS 均有较差的平均总生存期，差异有统计学意义（$P<0.05$）。

表 2　5 年 OS 最佳 cut-off 值选择及其曲线下面积（AUC）

Table 2. Optimal Cut-off Points Chosen and Their AUCs in 5-year OS

Variable	AUC（%）	*P*	95% *CI*	Cut-off point	Sensitivity（%）	Specificity（%）
PLR	70.7	0.001	0.634 – 0.773	170.8	75.86	62.59
PLT	75.2	0.001	0.682 – 0.814	260	96.97	42.66
MPV	64.4	0.035	0.568 – 0.715	8.2	62.82	65.00
PDW	62.9	0.006	0.553 – 0.700	16.5	97.22	26.43

OS: Overall survival; AUC: Area under the curve; CI: Confidence interval; PLR: Platelet-to-lymphocyte ratio; PLT: Platelet; MPV: Mean platelet volume; PDW: Platelet distribution width.

表 3　5 年 DFS 最佳 cut-off 值选择及其曲线下面积（AUC）

Table 3. Optimal Cut-off Points Chosen and Their AUCs in 5-year DFS

Variable	AUC（%）	*P*	95% *CI*	Cut-off point	Sensitivity（%）	Specificity（%）
PLR	65.7	0.001	0.581 – 0.726	139.6	72.13	53.04
PLT	78.6	0.001	0.718 – 0.844	271	80.00	69.54
MPV	60.5	0.047	0.528 – 0.678	8.2	66.67	55.00
PDW	61.5	0.016	0.539 – 0.687	16.5	97.22	24.29

DFS: Disease-free survival; AUC: Area under the curve; CI: Confidence interval; PLR: Platelet-to-lymphocyte ratio; PLT: Platelet; MPV: Mean platelet volume; PDW: Platelet distribution width.

表 4　分析 5 年总生存期时 PLR、MPV 分组与各临床因素的关系

Table 4. Variables in Different PLR and MPV Groups When Doing 5-Year Overall Survival

Variable	PLR≤170.8 (*n*=147)	PLR>170.8 (*n*=29)	*P*	MPV≤8.2fL (*n*=20)	MPV>8.2fL (*n*=156)	*P*
Survival time (month)	47.32 ± 32.14	26.41 ± 21.53	0.001	31.80 ± 29.48	45.42 ± 31.58	0.065
Drinking history			0.049			0.836
No	53 (48.4)	5 (9.6)		7 (6.6)	51 (51.4)	
Yes	94 (98.6)	24 (19.4)		13 (13.4)	105 (104.6)	
PLT (10^9/L)			0.001			0.879
Lower event (≤260)	130 (119.4)	13 (23.6)		16 (16.3)	127 (126.8)	
Higher event (>260)	17 (27.6)	16 (5.4)		4 (3.8)	29 (28.3)	
PDW (%)			0.702			0.081
Lower event (≤16.5)	121 (120.3)	23 (23.7)		19 (15.9)	121 (124.1)	
Higher event (>16.5)	26 (26.7)	6 (5.3)		1 (4.1)	35 (31.9)	
PDW/P (% * 10^{-9}/L)			0.002			0.765
Lower event (≤0.064)	42 (49.3)	17 (9.7)		6 (6.6)	52 (51.4)	
Higher event (>0.064)	105 (97.7)	12 (19.3)		14 (13.4)	104 (104.6)	

(Table 4 continues on next page)

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Variable	PLR≤170.8 (*n* =147)	PLR >170.8 (*n* =29)	*P*	MPV≤8.2fL (*n* =20)	MPV >8.2fL (*n* =156)	*P*
TNM stage			0.065			0.406
Ⅲ	45 (40.9)	4 (8.1)		4 (5.6)	45 (43.4)	
Ⅳ	102 (106.1)	25 (20.9)		16 (14.4)	111 (112.6)	
Tumor classification			0.465			0.902
T1 – T2	40 (38.4)	6 (7.6)		5 (5.2)	41 (40.8)	
T3 – T4	107 (108.6)	23 (21.4)		15 (14.8)	115 (115.2)	
Node classification			0.979			0.715
N0	20 (20.0)	4 (4.0)		2 (2.7)	22 (21.3)	
N +	127 (34.2)	25 (6.8)		18 (17.3)	134 (134.7)	
Vascular embolus			0.024			0.032
No	130 (126.1)	21 (24.9)		14 (17.2)	137 (133.8)	
Yes	17 (20.9)	8 (4.1)		6 (2.8)	19 (22.2)	
Metastasis			0.155			0.423
No	82 (78.5)	12 (15.5)		9 (10.7)	85 (83.3)	
Yes	65 (68.5)	17 (13.5)		11 (9.3)	71 (72.7)	

t-test was used to analyze mean survival time; Pearson's chi-squared test or Fisher exact test were used to verify other clinical variables in different PLR and MPV groups when doing 5-year OS. Components of this table: Observed values (predicted values). PLR: Platelet-to-lymphocyte ratio; MPV: Mean platelet volume; PLT: Platelet; PDW: Platelet distribution width; PDW/P: Platelet distribution width to platelet count ratio.

表 5　分析 5 年无病生存期时 PLR、PDW 分组与各临床因素关系

Table 5. Variables in Different PLR and PDW Groups When Doing 5-Year Disease Free Survival

Variable	PLR≤139.6 (*n* =115)	PLR >139.6 (*n* =61)	*P*	PDW≤16.5% (*n* =144)	PDW >16.5% (*n* =32)	*P*
Survival time (month)	50.36 ±31.63	31.63 ±24.90	<0.001	47.05 ±33.10	31.50 ±20.81	0.008
Differentiation grade			0.724			0.622
Good and moderate	102 (01.3)	8 (7.3)		18 (17.2)	3 (3.8)	
Poor	13 (13.7)	53(53.7)		126 (126.8)	29 (28.2)	
PLT (10^9/L)			0.001			0.200
Lower event (≤271)	110 (98.7)	41 (52.3)		121 (123.5)	30 (27.5)	
Higher event (>271)	5 (16.3)	20 (8.7)		23 (20.5)	2 (4.5)	
MPV			0.033			0.001
Lower event (11.1)	86 (91.5)	54 (48.5)		125 (114.5)	15 (25.5)	
Higher event (11.1)	29 (23.5)	7 (12.5)		19 (29.5)	17 (6.5)	
MPV/P (fL * 10^{-9}/L)			0.001			0.061
Lower event (≤0.036)	12 (26.1)	28 (13.9)		37 (32.7)	3 (7.3)	
Higher event (>0.036)	103 (88.9)	33 (47.1)		107 (11.3)	29 (24.7)	
PDW/P (% * 10^{-9}/L)			0.001			0.001
Lower event (≤0.064)	24 (38.6)	35 (20.4)		56 (47.5)	2 (10.5)	
Higher event (>0.064)	91 (76.4)	26 (40.6)		88 (96.5)	30 (21.5)	
TNM stage			0.159			0.405
Ⅲ	36 (32)	13 (17)		43 (37.6)	3 (8.4)	
Ⅳ	79 (83)	48 (44)		101 (106.4)	29 (23.6)	
Tumor classification			0.075			0.015
T1 – T2	35 (30.1)	11 (15.9)		42 (36.6)	4 (9.4)	
T3 – T4	80 (84.9)	50 (45.1)		98 (103.4)	32 (26.6)	

(Table 5 continues on next page)

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Variable	PLR≤139.6 (*n* =115)	PLR >139.6 (*n* =61)	*P*	PDW≤16.5% (*n* =144)	PDW >16.5% (*n* =32)	*P*
Node classification			0.883			0.351
N0	16 (15.7)	8 (8.3)		18 (19.6)	6 (4.4)	
N +	99 (99.3)	53 (52.7)		126 (124.4)	26 (27.6)	
Vascular embolus			0.289			0.576
No	101 (98.7)	50 (52.3)		122 (123.5)	29 (27.5)	
Yes	14 (16.3)	11 (8.7)		22 (20.5)	3 (4.5)	
Metastasis			0.025			0.226
No	60 (52.9)	21 (28.1)		80 (76.9)	14 (17.1)	
Yes	55 (62.1)	40 (32.9)		64 (67.1)	18 (14.9)	

t-test was used to analyze mean survival time; Pearson's chi-squared test or Fisher exact test were used to verify other clinical variables in different PLR and PDW groups when doing 5-year DFS. Components of this table: Observed values (predicted values). PLR: Platelet to lymphocyte ratio; PDW: Platelet distribution width; PLT: Platelet; MPV: Mean platelet volume; MPV/P: Mean platelet volume to platelet count ratio; PDW/P: Platelet distribution width to platelet count ratio.

2.4　Kaplan-Meier 法进行单因素筛查、生存分析及 log-rank 检验

在 5 年 OS 中，对比低 PLR 组与高 MPV 组，术前高 PLR 组与低 MPV 组与长期 OS 的差异有统计学意义（$P<0.001$），其 5 年总生存率分别为 10.3%（高 PLR 组）、33.3%（低 PLR 组）；31.4%（高 MPV 组）、15.0%（低 MPV 组）（图 2A－B）；在 5 年 DFS 中，对比低 PLR 组与低 PDW 组，术前高 PLR 组与高 PDW 组与长期 DFS 的差异有统计学意义（$P<0.001$），其 5 年无病生存率分别为 14.8%（高 PLR 组）、32.2%（低 PLR 组）；10.3%（高 PDW 组）、33.9%（低 PDW 组）（图 2C－D），术后放化疗对 5 年 OS 及 DFS，差异无统计学意义（$P>0.05$）（图 3A－B）

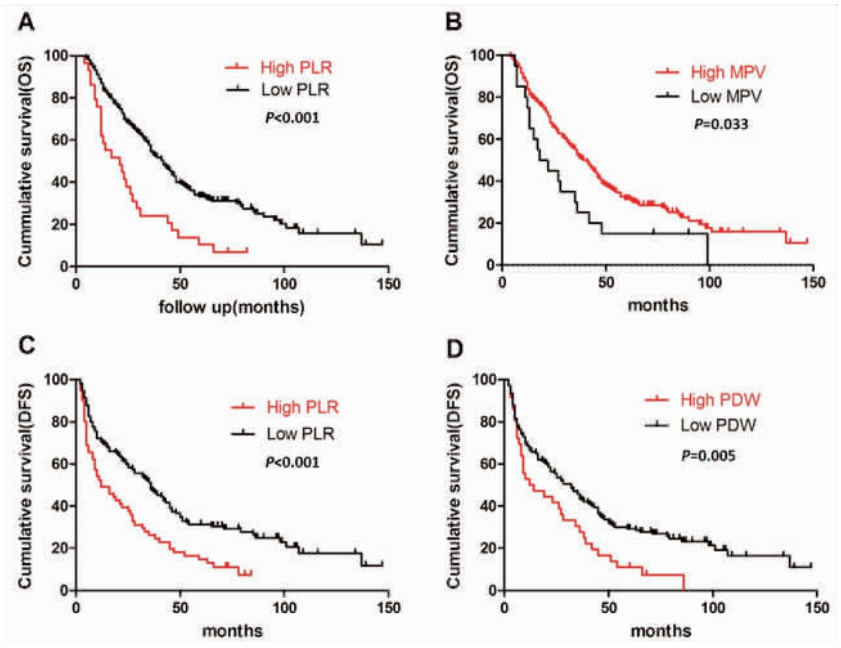

图 2　Kaplan-Meier 生存分析比较不同 PLR、MPV、PDW 组生存率

Figure 2. Cumulative Survival of Different PLR, MPV and PDW Groups Analyzed by Using Kaplan-Meier Method

Cumulative survival in different groups (PLR, MPV and PDW) were estimated by using Kaplan-Meier method, and log-rank test was used to evaluate corresponding differences. A: Compared to the lower PLR group, the higher PLR group indicates poor 5-year OS ($P<0.05$); B: Compared to the higher MPV group, the lower MPV group indicates poor 5-year OS ($P<0.05$); C: Compared to the lower PLR group, the higher PLR group indicates poor 5-year DFS ($P<0.001$); D: Compared to the lower PDW group, the higher PDW group indicates poor 5-year DFS ($P<0.01$). PLR: Platelet-to-lymphocyte ratio; MPV: Mean platelet volume; PDW: Platelet distribution width; OS: Overall survival; DFS: Disease free survival.

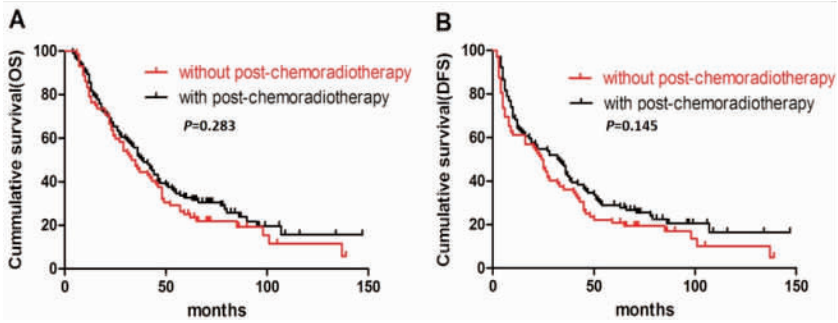

图 3 Kaplan-Meier 生存分析比较术后放化疗组和术后无放化疗生存率（OS，DFS）

Figure 3. Cumulative Survival of Patients with or without Postoperative Chemoradiotherapy Analyzed by Using Kaplan-Meier Method

Kaplan-Meier method was used to analyze cumulative survival (overall survival and disease free survival) of patients with or without postoperative chemoradiotherapy, and log-rank test was used evaluate corresponding differences. A: There is no statistically significant difference in the overall survival between patients with or without postoperative chemoradiotherapy ($P>0.05$). B: There is no statistically significant difference in the disease free survival between patients with or without postoperative chemoradiotherapy ($P>0.05$).

2.5 影响晚期下咽鳞癌患者 OS 及 DFS 的单因素及多因素 Cox 模型分析结果

将可能影响晚期下咽鳞癌预后的变量分别纳入 Cox 单因素分析，如年龄、肿瘤大小、肿瘤分期、TNM 分期、T 分级、N 分级、颈内静脉侵犯及相关外周血指标（PLR、PLT、MPV、PDW、MPV/P、PDW/P）等危险因素，得出影响 5 年 OS 的危险因素有：年龄、肿瘤直径、T 分级、手术切缘、颈静脉侵犯、术后转移等临床因素以及外周血指标（PLR、PLT、MPV、PDW、MPV/P、PDW/P）纳入 Cox 多因素回归分析模型分析，得出影响患者 5 年 OS 的独立危险因素为高 PLR 组、高 PLT 组、低 MPV 组、术后转移、T 分级（$P<0.05$）（表 6）。依据同样方法得出影响 5 年无病生存率的独立危险因素有高 PLR、高 PDW、T 分级、TNM 分期（$P<0.05$）（表 7）。

表 6 Cox 单因素及多因素分析（5 年 OS）

Table 6. Univariate and Multivariate Analysis of 5-Year OS

Variable	*OS*(*HR*)	*P*(95% *CI*)	*OS*(*HR*)	*P*(95% *CI*)
Age (year)		0.013		0.088
<60	1	(0.458 – 0.911)	1	(0.496 – 1.050)
≥60	0.646		0.721	
Maximum diameter of tumor (cm)		0.004		0.124
≤4	1	(1.176 – 2.342)	1	(0.918 – 2.034)
>4	1.659		1.366	
TNM stage (AJCC)		0.055	N/A	N/A
Ⅲ	1	(0.992 – 2.108)		
Ⅳ	1.446			
Tumor classification		<0.001		0.005
T1 – T2	1	(1967 – 4.881)	1	(1.252 – 3.551)
T3 – T4	3.098		2.108	
PLR		<0.001		0.026
Lower event (≤170.8)	1	(1504 – 3.545)	1	(1.072 – 2.963)
Higher event (>170.8)	2.309		1.783	
PLT (10^9/L)		<0.001		0.004
Lower event (≤260)	1	(1.948 – 4.442)	1	(1.407 – 6.230)
Higher event (>260)	2.941		2.961	

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Variable	*OS*(*HR*)	*P*(95% *CI*)	*OS*(*HR*)	*P*(95% *CI*)
PDW (%)		0.004		0.246
Lower event (≤16.5)	1	(1.211 – 2.752)	1	(0.823 – 2.142)
Higher event (>16.5)	1.826		1.328	
MPV (fL)		0.039		0.007
Lower event (≤8.2)	1	(0.359 – 0.973)	2.227	(0.252 – 0.800)
Higher event (>8.2)	0.591		1	
PDW/P(% $*10^{-9}$/L)		0.006		0.363
Lower event (≤0.0635)	1	(0.434 – 0.870)	1	(0.743 – 2.252)
Higher event (>0.0635)	0.614		1.293	
MPV/P (fL $*10^{-9}$/L)		0.004		0.432
Lower event (≤0.036)	1	(0.383 – 0.840)	1	(0.675 – 2.505)
Higher event (>0.036)	0.571		1.300	
Metastasis		0.001		0.001
No	1	(2.675 – 5.480)	1	(1.964 – 4.360)
Yes	3.829		2.926	
IJVI		0.039		0.074
No	1	(1.018 – 2.054)	1	(0.967 – 2.097)
Yes	1.446		1.424	
Surgical margin (cm)		0.025		0.438
≥0.5	1	(1.051 – 2.072)	1	(0.788 – 1.733)
<0.5	1.475		1.169	

Five-year OS was analyzed by the Cox model. OS: Overall survival; *CI*: Confidence interval; AJCC: American Joint Committee on Cancer; PLR: Platelet to lymphocyte ratio; PLT: Platelet; PDW: Platelet distribution width; MPV: Mean platelet volume; PDW/P: Platelet distribution width to platelet count ratio; MPV/P: Mean platelet volume to platelet count ratio; IJVI: Internal jugular vein invasion.

表 7　Cox 单因素及多因素分析 (5 年 DFS)

Table 7. Univariate and Multivariate Analysis of 5-Year DFS

Variable	DFS(*HR*)	*P*(95% *CI*)	DFS(*HR*)	*P*(95% *CI*)
Age (year)		0.002		0.004
<60	1	(0.416 – 0.822)	1.691	(0.602 – 1.521)
≥60	0.585		1	
Maximum diameter of tumor (cm)		0.027		0.709
≤4	1	(1.044 – 2.059)	1	(0.737 – 1.588)
>4	1.466		1.075	
TNM stage (AJCC)		0.045		0.023
Ⅲ	1	(1.099 – 2.135)	1	(1.066 – 2.340)
Ⅳ	1.468		1.579	
Tumor classification		<0.001		0.003
T1 – T2	1	(1.607 – 3.770)	1	(1.288 – 3.329)
T3 – T4	2.462		2.071	
PLR		0.001		0.028
Lower event (≤139.6)	1	(1.303 – 2.595)	1	(1.046 – 2.778)
Higher event (>139.6)	1.839		1.525	

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Variable	DFS(*HR*)	*P*(95% *CI*)	DFS(*HR*)	*P*(95% *CI*)
PLT (10^9/L)		0.297	N/A	N/A
Lower event (≤271)	1	(0.746 - 2.611)		
Higher event (>271)	1.396			
PDW (%)		0.007		0.006
Lower event (≤16.5)	1	(1.161 - 2.533)	1	(1.183 - 2.778)
Higher event (>16.5)	1.715		1.813	
MPV (fL)		0.540	N/A	N/A
Lower event (≤11.1)	1	(0.651 - 2.273)		
Higher event (>11.1)	1.216			
PDW/P (% * 10^{-9}/L)		0.001		0.056
Lower event (≤0.0635)	1	(0.405 - 0.807)	1	(0.425 - 1.012)
Higher event (>0.0635)	0.572		0.656	
MPV/P (fL * 10^{-9}/L)		0.002		0.610
Lower event (≤0.036)	1	(0.374 - 0.802)	1	(0.561 - 1.404)
Higher event (>0.036)	0.547		0.888	

Five-year DFS was analyzed by the Cox model. DFS: Disease Free Survival; *CI*: Confidence interval; AJCC: American Joint Committee on Cancer; PLR: Platelet to lymphocyte ratio; PLT: Platelet; PDW: Platelet distribution width; MPV: Mean platelet volume; PDW/P: Platelet distribution width to platelet count ratio; MPV/P: Mean platelet volume to platelet count ratio.

3 讨 论

下咽鳞癌是一种侵袭性高且症状隐匿的头颈部鳞癌,患者就诊时常被诊断为晚期(TNM III/IV)。尽管对晚期下咽鳞癌的治疗及理念不断改变[4],但不管是欧美提倡的高保喉率的同步放化疗或诱导化疗,还是中国抗癌协会临床肿瘤学协作专业委员会提倡以手术为主的综合治疗[5],远期总生存率并没有因此得到改善。目前 AJCC TNM 分期系统仍是指导临床医生判断肿瘤预后的重要参照,但仅通过解剖部位的分期在晚期肿瘤中仍存在局限性,尤其肿瘤的浸润、侵袭迁移、增殖信号传递、血管生成,均需要通过血液进行信号传递,因此有必要进一步深入探讨血液组分对肿瘤患者的影响,以补充临床上对晚期下咽鳞癌患者的总体认识。

随着肿瘤的深入研究,人们发现机体炎症、免疫反应都与肿瘤发生发展的相关,有研究者于 1968 年发现富含血小板能使 TA3 腹水瘤细胞发生转移,从而拓展了外周血细胞的认知[6]。近年来,IL-6 信号通路被证实在系统性炎症出现时能进一步上调外周血细胞[7],且准确性高[8],但 IL-6 检测费用高昂,不适宜推广应用。因此,目前研究多着重使用快速、便宜、易获取的相关外周血比值 NLR、PLR、LMR 等作为预测肿瘤预后的指标,并在肺癌[9-10]、结直肠癌[11]、食管癌[12]、乳腺癌[13],头颈鳞癌[14]等中证实与预后密切相关。

对于血小板促进肿瘤进展、炎症及免疫反应的的假说与机制主要体现如下方面[6]:1)血小板能覆盖肿瘤细胞表面逃逸 T 细胞或 NK 细胞的免疫打击;2)释放黏附分子,如选择素 P(P-selectin)、血管内皮生长因子等促进肿瘤在远处血管或内皮细胞进行桥接,实现循环中肿瘤细胞种植;3)血小板细胞因子 IL-6、IL-1、G-CSF 释放,促进血栓形成及血管重塑;4)肿瘤所处的炎症微环境能够聚集中性粒细胞、单核细胞等、同时肿瘤又促进炎症持续性的进展,导致肿瘤进一步发生侵袭转移[15]。淋巴细胞是机体参与免疫功能的重要细胞,能对抗外来感染及肿瘤侵犯,如果出现淋巴细胞减少,往往提示机体免疫变差,可导致肿瘤的发生发展,Liu 等[16]在鼻咽癌研究中发现出现淋巴细胞缺乏往往提示较差的预后。

血小板的相关参数包含血小板数量(total platelet count, TPC)和体积(platelet volume index, PVI),TPC 是由血小板在机体中生成及消耗中的动态平衡的总和,在恶性肿瘤细胞中 TPC 处于高生成及高消耗,然而 Seretis 等[17]在结肠癌研究中发现即使正常的血小板计数是也是可以掩盖患者高凝状态及促炎癌症表型。PVI 包含 MPV 和 PDW,主要用来推论血

小板的大小，近年来研究显示 MPV 能反映炎症前期及血栓前期的情况[18]；PDW 能说明血小板的异质性及活动度[19]。目前多数研究认为 MPV 较低的患者预后更差，这可能源于高炎症反应下血小板大量的消耗，尤其 MPV 容易受到血小板细胞肿胀的影响，因此选择 PDW 似乎更为直观准确[20]。Fu 等[21]对比喉良性肿物及正常空白对照发现 216 例喉癌患者中，外周血 MPV 是下调且 PDW 是上调的。但在 Eryilmaz 等[22]研究 96 例头颈肿瘤中却发现 MPV 升高才影响患者预后。目前在头颈部肿瘤中，PDW 肿瘤预后研究的仍少，Zhang 等[23]研究 241 例喉癌中发现高 PDW 组（>16.7%）有较差的预后；而 Xie 等[24]也发现高 PLT（$>266\times10^9$/L）和高 PDW 组（>16.3%）在鼻咽癌患者提示更差预后。此外，MPV/P 及 PDW/P 等比值也被应用于肿瘤预后[25]、栓塞[26]等回顾性研究中，这些结论均为本研究分析提供了基础与思路。

分析对照组及晚期下咽癌患者外周血 PLR、MPV、PDW 得出，PLR 及 PDW 可能是评估肿瘤发生发展预后的促进因素，而 MPV 则是拮抗因素。为了有效评价晚期下咽鳞癌患者术前外周血 PLR，血小板相关参数与各临床因素对 5 年生存期（OS、DFS）的相关性，我们使用 X-tile 作为截点选择工具[27]。X-tile 是芝加哥大学 Rim 实验室设计的一种可视化、与结果高度相关的截止点选择软件，目前已被应用在许多生化指标选择及回顾性研究中。本研究依照最高卡方值及最低的 P 值选择最佳截点，其优点在于此唯一值具备较好的评价能力。不过纳入分析后发现 5 年的 OS 和 DFS 两者截点稍有不同，其差异的原因可能在于晚期下咽鳞癌术后补充放化疗的应用，使得即使出现术后复发转移的患者也能有较长的总生存期。在分组后，用独立样本 t 检验分析总生存时间得出升高 PLR 有明显较差 OS 及 DFS（$P<0.05$），由于 PLR、MPV、PDW 组内样本数量上有所差距，因此在 F 检验后本研究进一步探讨组内差异性研究，发现在癌栓的变化可能是引起总生存期 OS 差异的危险因素，而术后转移及高肿瘤分期可能是影响 DFS 的危险因素，其余无明显统计学差异（$P>0.05$），说明分组后组内成分应是均衡的。

针对影响预后的独立危险因素分析发现，5 年的 OS 中，高 PLR（>170.8）和高 PLT（$>260\times10^9$/L）、低 MPV（<8.2fL）有较差的预后，而截止点不同的 5 年 DFS 分析中，高 PLR（>139.6）和高 PDW（>16.5%）则提示较差预后及肿瘤进展的可能，这些与目前头颈肿瘤外周血指标的相关文献报道是一致的。本研究进一步发现下咽鳞癌术后放化疗不能影响总体预后（$P>0.05$），反而因此侧面证实术前外周血指标具有提示预后的应用价值。

综上，外周血 PLR 升高是可以成为判断晚期下咽鳞癌长期预后（5 年 OS、DFS）共同的独立危险因素，但本研究仍仅是单一机构的回顾性研究，且 X-tile 选出唯一值容易出现样本量差异大的情况，同时本研究随访跨度较长，样本量仍偏少，因此需要多中心、大规模的前瞻性研究再进一步证实。

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学术不端：本文在初审、返修及出版前均通过中国知网（CNKI）科技期刊学术不端文献检测系统的学术不端检测。

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