·论 著·

联合检测LDHA和PD-L1在晚期胃癌PD-1抑制剂疗效预测及预后评估中的价值

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［**摘要**］ **背景与目的：**胃癌对程序性死亡［蛋白］-1（programmed death-1，PD-1）抑制剂的应答率较低，建立有用的疗效预测方法筛选胃癌PD-1抑制剂治疗优势人群对改善患者预后有重要意义。本研究旨在探讨联合检测乳酸脱氢酶A（lactate dehydrogenase，LDHA）和程序性死亡［蛋白］配体-1（programmed death ligand-1，PD-L1）表达对接受PD-1抑制剂治疗胃癌患者的疗效预测和预后评估价值。**方法：**回顾性分析皖南医学院第一附属医院2020年1月—2022年3月接受PD-1抑制剂治疗的50例晚期胃癌患者的临床病理学资料，采用多因素logistic回归分析影响胃癌PD-1抑制剂疗效的独立危险因素，利用受试者工作特征（receiver operating characteristic，ROC）曲线分析联合检测LDHA和PD-L1对胃癌PD-1抑制剂疗效的预测价值，应用Kaplan-Meier法对患者进行生存分析。**结果：**LDHA低表达组和高表达组胃癌患者的客观缓解率（objective response rate，ORR）分别为59%和10%，疾病控制率（disease control rate，DCR）分别为83%和29%，差异有统计学意义（$P<0.001$）。多因素logistic回归分析结果显示，PD-L1阳性联合分数（combined positive score，CPS）＜5、LDHA高表达是胃癌PD-1抑制剂疗效不佳的独立危险因素（$P<0.05$）。ROC曲线分析结果提示LDHA联合PD-L1具有较好的胃癌PD-1抑制剂疗效预测价值［曲线下面积（area under curve，AUC）为0.951］。Kaplan-Meier生存分析显示，LDHA低表达合并PD-L1 CPS≥5的胃癌患者在接受PD-1抑制剂治疗后具有更长的总生存期（overall survival，OS，$P=0.003$）和无进展生存期（progression-free survival，PFS，$P<0.001$）。**结论：**LDHA低表达、PD-L1 CPS≥5与胃癌PD-1抑制剂的疗效呈正相关，LDHA低表达合并PD-L1 CPS≥5的胃癌患者接受PD-1抑制剂治疗可显著延长OS和PFS，联合检测LDHA和PD-L1对晚期胃癌患者PD-1抑制剂的疗效预测和预后评估有一定的临床应用价值。

［**关键词**］胃肿瘤；免疫检查点抑制剂；免疫治疗；疗效；预后

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The value of combined detection of LDHA and PD-L1 in predicting the efficacy and prognosis of advanced gastric cancer patients treated with PD-1 inhibitor

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［**Abstract**］ **Background and purpose:** The response rate of gastric cancer patients to programmed death-1 (PD-1) inhibitor is relatively low. Establishing a useful efficacy prediction method to screen the superior gastric cancer patients receiving anti-

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PD-1 therapy could improve the prognosis of patients. This study aimed to explore the value of combined detection of lactate dehydrogenase (LDHA) and programmed death ligand-1 (PD-L1) expressions in predicting the efficacy and prognosis of gastric cancer patients treated with PD-1 inhibitor. **Methods:** The clinicopathological data of 50 advanced gastric cancer patients treated with PD-1 inhibitor in The First Affiliated Hospital of Wannan Medical College from January 2020 to March 2022 were retrospectively analyzed. The independent risk factors affecting the efficacy of PD-1 inhibitor were analyzed by multivariate logistic regression. The value of combined detection of LDHA and PD-L1 in predicting the efficacy of PD-1 inhibitors in gastric cancer was analyzed by receiver operating characteristic (ROC) curve analysis. Gastric cancer patient survival was analyzed by Kaplan-Meier method. **Results:** The objective response rate (ORR) of gastric cancer patients receiving PD-1 inhibitor therapy in LDHA low and high expression groups were 59% and 10%, respectively. The disease control rate (DCR) in LDHA low and high expression groups were 83% and 29%, respectively. The difference was statistically significant ($P<0.001$). Multivariate logistic regression analysis showed that PD-L1 combined positive score (CPS)<5 and LDHA high expression were independent risk factors affecting the efficacy of PD-1 inhibitor in gastric cancer ($P<0.05$). ROC curve analysis showed that combined detection of LDHA and PD-L1 had good predictive value for the efficacy of PD-1 inhibitor in gastric cancer ［area under curve (AUC) was 0.951］. Kaplan-Meier survival analysis showed that gastric cancer patients with low LDHA expression and PD-L1 CPS≥5 had longer overall survival (OS, $P=0.003$) and progression-free survival (PFS, $P<0.001$) after receiving PD-1 inhibitor therapy. **Conclusion:** Low LDHA expression and PD-L1 CPS≥5 were positively correlated with the efficacy of PD-1 inhibitor in gastric cancer. Gastric cancer patients with low LDHA expression and PD-L1 CPS≥5 significantly had prolonged OS and PFS after receiving PD-1 therapy. Therefore, the combined detection of LDHA and PD-L1 expressions has good value in predicting the efficacy and evaluating prognosis of advanced gastric cancer patients treated with PD-1 inhibitor.

［**Key words**］ Stomach neoplasms; Immune checkpoint inhibitors; Immunotherapy; Efficacy; Prognosis

胃癌严重威胁人类健康，目前高居肿瘤相关死亡病因的第3位[1]。中国大多数胃癌患者确诊时已处于进展期，预后较差。晚期胃癌的治疗手段匮乏，传统化疗效果有限，与靶向和免疫药物的联合治疗日益受到关注，包括程序性死亡［蛋白］-1（programmed death-1，PD-1）和程序性死亡［蛋白］配体-1（programmed death ligand-1，PD-L1）单抗在内的免疫检查点抑制剂（immune checkpoint inhibitor，ICI）已广泛用于多种晚期肿瘤患者的治疗[2]。继KEYNOTE-059和ATTRACTION-2研究证实ICI单药在胃癌三线治疗中具有显著获益后，CheckMate 649和ATTRACTION-4临床试验[3-4]进一步奠定了PD-1抑制剂联合化疗用于PD-L1阳性联合分数（combined positive score，CPS）≥5、人表皮生长因子受体2（human epidermal growth factor receptor 2，HER2）阴性晚期胃癌一线治疗的新标准。

然而，KEYNOTE-062研究[5]表明，在PD-L1 CPS≥1的晚期胃癌意向性治疗人群中，帕博利珠单抗联合化疗组的总生存期（Overall survival，OS）和无进展生存期（Progress-free survival，PFS）并不显著优于单纯化疗组。因此，在真实世界中如何筛选胃癌免疫治疗优势人群仍值得思考，此外PD-L1单一指标并不能很好地预测胃癌ICI的疗效，多指标联合预测才有可能达到更好的预测效能[6]。

乳酸脱氢酶A（lactate dehydrogenase，LDHA）是糖酵解过程中催化乳酸生成的关键酶，在多种肿瘤中高表达或异常激活，能够调节细胞活性氧产生，抑制细胞凋亡，并促进肿瘤进展[7]。LDHA在胃癌中表达升高，与患者的不良预后存在显著相关性[8]。肿瘤细胞糖酵解产生大量乳酸形成酸性免疫抑制微环境，可影响ICI的疗效[9]。LDHA在胃癌免疫治疗效果预测和预后评估中的价值目前仍不清楚。本研究收集接受PD-1抑制剂治疗的晚期胃癌患者的临床病理学资料，分析LDHA表达水平与患者PD-1抑制剂治疗效果和预后的相关性，旨在为胃癌免疫治疗效果预测和预后评估提供新思路。

1 资料和方法

1.1 临床资料

回顾性分析2020年1月—2022年3月在皖南医

学院第一附属医院接受PD-1抑制剂治疗的50例晚期胃癌患者的临床病理学资料，其中男性40例，女性10例，中位年龄67岁。纳入标准：① 经组织病理学检查确诊为胃腺癌；② 初次PD-1抑制剂治疗前影像学评估为病灶不可切除；③ 接受了4个周期及以上的PD-1抑制剂治疗，且疗效可评价；④ 免疫治疗前均已在病理科检测PD-L1表达情况；⑤ 所有患者均签署知情同意书并接受随访。排除标准：① 非腺癌患者；② 具有严重系统性疾病不能耐受化疗或免疫治疗患者；③ 具有严重自身免疫性疾病；④ 合并精神性疾病，不能配合随访患者。本研究经皖南医学院第一附属医院伦理委员会批准。

1.2 免疫组织化学（immunohistochemistry，IHC）

在病理科收集患者免疫治疗前的胃癌组织蜡块，切片后用血清封闭30 min，4 ℃温育一抗过夜，室温温育二抗30 min。滴加辣根过氧化物酶溶液，室温温育30 min。经DAB显色，苏木精复染，梯度乙醇脱水，二甲苯浸泡，滴加中性树胶后用盖玻片封片，最后在显微镜下观察并拍照。PD-L1 CPS从患者病理学检查报告中获取，LDHA的IHC评分通过染色强度和阳性细胞比例评分乘积计算。染色强度评分标准为0分（阴性）、1分（弱阳性）、2分（中等强度）和3分（强阳性）。阳性细胞比例的评分标准为1分（＜10%）、2分（10%～49%）、3分（50%～69%）和4分（≥70%）。以LDHA的IHC评分中位数作为LDHA高表达和低表达的截断值。《中国临床肿瘤学会（CSCO）胃癌诊疗指南2022》[10]推荐免疫治疗联合化疗用于HER2阴性晚期胃癌PD-L1 CPS≥5患者的一线治疗（Ⅰ级推荐、1A类证据），本研究选择PD-L1 CPS=5作为截断值。

1.3 疗效评价

胃癌患者接受PD-1抑制剂治疗4个周期后按照实体瘤疗效评价标准（Response Evaluation Criteria in Solid Tumors，RECIST）1.1版进行疗效评价[3-5]，分为完全缓解（complete response，CR）、部分缓解（partial response，PR）、疾病稳定（stable disease，SD）和疾病进展（progressive disease，PD），并计算客观缓解率（objective response rate，ORR）和疾病控制率（disease control rate，DCR）。PD-1抑制剂应答组为CR和PR总和，无应答组为PD和SD总和。绘制LDHA、PD-L1及LDHA联合PD-L1的受试者工作特征（receiver operating characteristic，ROC）曲线，计算曲线下面积（area under curve，AUC），评估联合检测LDHA和PD-L1对PD-1抑制剂在胃癌中的疗效预测价值。

1.4 随访

通过查阅患者住院及门诊病历、微信、电话等方式随访。随访信息包括患者一般情况、疾病控制情况及生存或死亡时间等。随访时间从患者首次接受PD-1抑制剂治疗开始至2022年5月截止。OS是指从患者首次接受PD-1抑制剂治疗开始至患者死亡、失访或末次随访时间，PFS是指从患者首次接受PD-1抑制剂治疗开始至肿瘤进展时间。

1.5 统计学处理

采用SPSS 24.0软件对数据进行分析，利用GraphPad 7.0.0软件绘制生存曲线。对计数资料采用χ^2检验或Fisher确切概率法，对正态分布的两组计量资料比较采用独立样本t检验。通过多因素logistic回归分析影响胃癌PD-1抑制剂疗效的独立危险因素，采用ROC曲线评估联合检测LDHA和PD-L1对PD-1抑制剂在胃癌中的疗效预测价值。采用Kaplan-Meier法和log-rank检验进行生存分析。P＜0.05为差异有统计学意义。

2 结　果

2.1 LDHA表达与患者临床病理学变量及PD–1抑制剂疗效的相关性

在皖南医学院第一附属医院病理科收集胃癌患者的组织蜡块，采用IHC检测LDHA表达，并收集患者的临床病理学资料，比较LDHA表达水平与患者临床病理学资料及PD-1抑制剂疗效之间的相关性。结果显示，LDHA低表达患者对PD-1抑制剂的应答率比高表达患者更高

（P＜0.001，表1），LDHA低表达患者的ORR为59%（17/29），DCR为83%（24/29），LDHA高表达患者的ORR为10%（2/21），DCR为29%（6/21）。

表1 LDHA表达水平与胃癌患者临床病理资料的相关性

Tab. 1 Correlation between LDHA expression and clinicopathological features of gastric cancer patients

Characteristic	LDHA low expression	LDHA high expression	χ^2 value	P value
Gender			0.021	0.886
Female	6	4		
Male	23	17		
Age/year			0.618	0.432
＜60	8	8		
≥60	21	13		
Tumor location			0.019	0.890
Down	16	12		
Upper/middle	13	9		
ECOG performance score			0.069	0.793
0-1	19	13		
≥2	10	8		
HER2 expression			0.114	0.735
Negative	27	19		
Positive	2	2		
Metastasis sites			0.618	0.432
≤2	21	13		
＞2	8	8		
PD-L1 CPS			1.439	0.230
≥5	10	4		
＜5	19	17		
PD-1 inhibitor response				
PD	5	15	16.811	＜0.001
SD	7	4		
PR	17	2		

2.2 胃癌PD-1抑制剂疗效与患者临床病理学变量的相关性

影响胃癌PD-1抑制剂疗效的单因素分析显示，一线免疫治疗（P=0.007）、PD-L1 CPS≥5（P＜0.001）、LDHA低表达（P＜0.001）的患者PD-1抑制剂应答率更高（表2）。将单因素分析中差异有统计学意义的变量纳入多因素logistic回归分析结果显示，PD-L1 CPS＜5（P=0.011）、LDHA高表达（P=0.006）是胃癌PD-1抑制剂疗效不佳的独立危险因素（表3）。IHC结果显示，LDHA表达在PD-1抑制剂疗效差的胃癌患者中显著升高（图1）。

表2 胃癌PD-1抑制剂疗效与患者临床病理学资料的相关性

Tab. 2 Correlation between the efficacy of PD-1 inhibitor and clinicopathological features of gastric cancer patients

Characteristic	Responder	Non-responder	χ^2 value	*P* value
Gender			0.764	0.382
Female	5	5		
Male	14	26		
Age/year			3.701	0.054
＜60	3	13		
≥60	16	18		
Tumor location			2.401	0.121
Down	8	20		
Upper/middle	11	11		
ECOG performance score			0.496	0.481
0-1	11	21		
≥2	8	10		
HER2 expression			0.312	0.577
Negative	18	28		
Positive	1	3		
Metastasis sites			3.701	0.054
≤2	16	18		
＞2	3	13		
Immunotherapy line			7.371	0.007
First-line	7	2		
Second-line and above	12	29		
PD-L1 CPS			13.585	＜0.001
≥5	11	3		
＜5	8	28		
LDHA expression			12.462	＜0.001
Low	17	12		
High	2	19		

表3 影响胃癌PD-1抑制剂疗效的多因素logistic回归分析

Tab. 3 Multivariable logistic regression analysis of the efficacy of PD-1 inhibitor in gastric cancer patients

Characteristic	OR	95% CI	*P* value
Immunotherapy line (second and above)	19.757	0.945-413.003	0.054
PD-L1 CPS<5	24.180	2.049-285.278	0.011
LDHA high expression	44.987	2.916-693.960	0.006

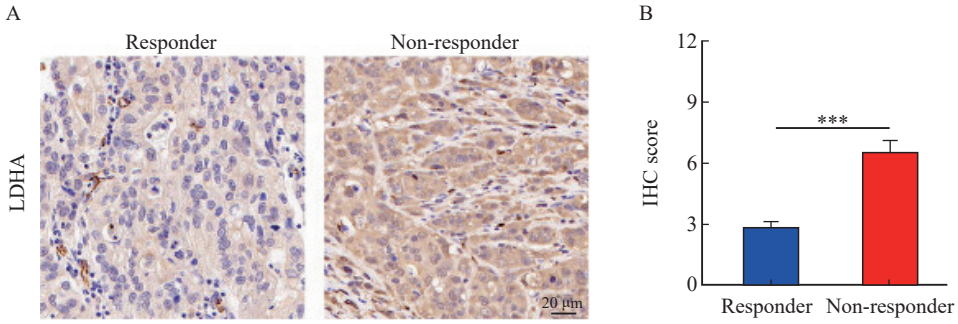

图1 LDHA表达与胃癌PD-1抑制剂疗效负相关

Fig. 1 LDHA expression is negatively correlated with the efficacy of PD-1 inhibitor in gastric cancer

A: Representative IHC photographs of LDHA expression in tumor tissues from responders and non-responders. B: IHC scores of LDHA in tumor tissues from responders and non-responders. ***: $P<0.001$, compared with responder.

2.3 联合检测LDHA和PD-L1对胃癌PD-1抑制剂疗效的预测价值

利用ROC曲线的AUC分别评估LDHA和PD-L1对胃癌PD-1抑制剂疗效的预测价值，结果显示，LDHA的AUC为0.857（95% CI: 0.757～0.958，图2A），PD-L1的AUC为0.772（95% CI: 0.622～0.923，图2B）。联合检测LDHA和PD-L1的AUC为0.951（95% CI: 0.890～1.000，图2C），表明联合检测LDHA和PD-L1对胃癌PD-1抑制剂疗效的预测价值更好。

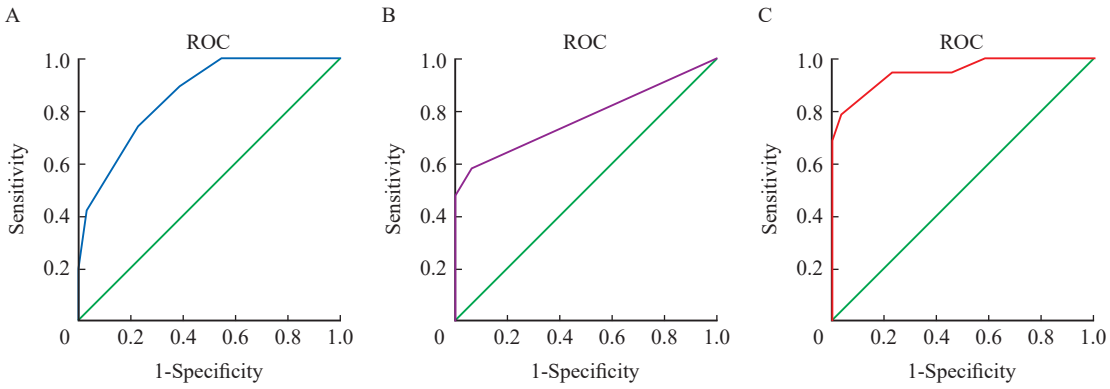

图2 LDHA、PD-L1及LDHA联合PD-L1预测胃癌PD-1抑制剂疗效的ROC曲线分析

Fig. 2 ROC curve analyses of LDHA, PD-L1 and the combination of LDHA and PD-L1 in predicting the efficacy of PD-1 inhibitor in gastric cancer patients

A: ROC curve of LDHA in predicting the efficacy of PD-1 inhibitor in gastric cancer patients; B: ROC curve of PD-L1 in predicting the efficacy of PD-1 inhibitor in gastric cancer patients; C: ROC curve of the combination of LDHA and PD-L1 in predicting the efficacy of PD-1 inhibitor in gastric cancer patients.

2.4 联合检测LDHA和PD-L1与接受PD-1抑制剂胃癌患者预后的相关性

对接受PD-1抑制剂治疗的50例胃癌患者进行随访，Kaplan-Meier生存曲线显示，胃癌组织中LDHA高表达较低表达的患者具有更短的OS（$P=0007$，图3A）和PFS（$P<0.001$，图4A），PD-L1 CPS≥5较PD-L1 CPS<5的患者OS（$P=0.002$，图3B）和PFS（$P=0.003$，图4B）显著延长，并且LDHA低表达合并PD-L1 CPS≥5的胃癌患者具有更长的OS（$P=0.003$，图3C）和PFS（$P<0.001$，图4C）。单因素生存分析结果显示，肿瘤转移部位数目>2、PD-L1 CPS<5、LDHA高表达是接受PD-1抑制剂治疗胃癌患者OS和PFS的危险因素（表4）。上述结果表明，联合检测LDHA和PD-L1对接受PD-1抑制剂治疗的晚期胃癌患者有较好的预后评估价值。

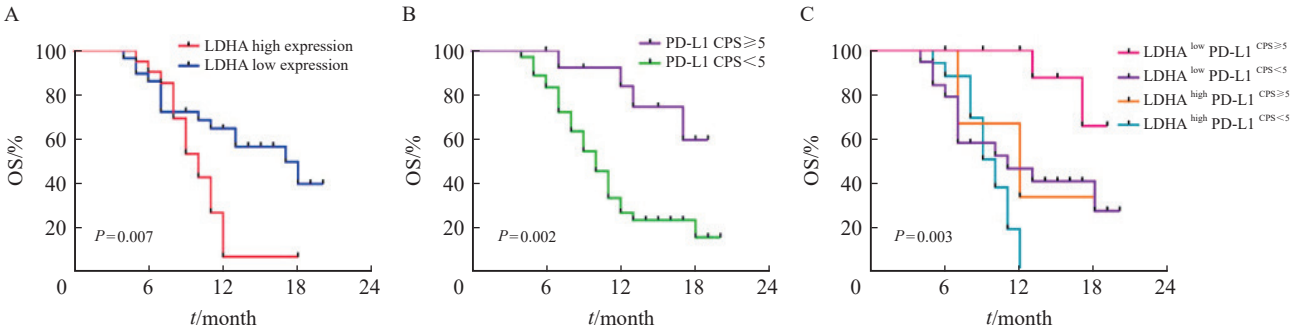

图3　LDHA和PD-L1对接受PD-1抑制剂胃癌患者OS的Kaplan-Meier生存曲线分析

Fig. 3　Kaplan-Meier curve analyses of LDHA, PD-L1, the combination of LDHA and PD-L1 in predicting the OS of gastric cancer patients treated with PD-1 inhibitor

A: Kaplan-Meier curve analysis of the correlation between LDHA expression and the OS of gastric cancer patients treated with PD-1 inhibitor; B: Kaplan-Meier curve analysis of the correlation between PD-L1 expression and the OS of gastric cancer patients treated with PD-1 inhibitor; C: Kaplan-Meier survival curves showing the effect of the combination of LDHA and PD-L1 on OS of gastric cancer patients treated with PD-1 inhibitor.

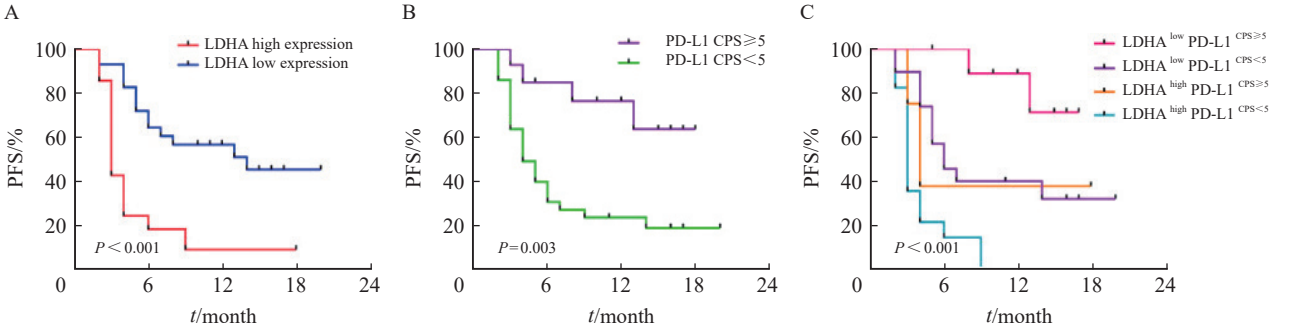

图4　LDHA和PD-L1对接受PD-1抑制剂胃癌患者PFS的Kaplan-Meier生存曲线分析

Fig. 4　Kaplan-Meier curve analyses of LDHA, PD-L1, the combination of LDHA and PD-L1 in predicting the PFS of gastric cancer patients treated with PD-1 inhibitor

A: Kaplan-Meier curve analysis of the correlation between LDHA expression and the PFS of gastric cancer patients treated with PD-1 inhibitor; B: Kaplan-Meier curve analysis of the correlation between PD-L1 expression and the PFS of gastric cancer patients treated with PD-1 inhibitor; C: Kaplan-Meier survival curves showing the effect of the combination of LDHA and PD-L1 on PFS of gastric cancer patients treated with PD-1 inhibitor.

表4　接受PD-1抑制剂治疗的胃癌患者OS和PFS的单因素分析

Tab. 4　Univariate analysis of OS and PFS of gastric cancer patients treated with PD-1 inhibitor

Characteristic	OS		PFS	
	Log-rank	*P* value	Log-rank	*P* value
Gender (male *vs* female)	0.085	0.770	0.060	0.806
Age (≥60 years *vs* <60 years)	1.914	0.167	3.063	0.080
Tumor location (upper/middle *vs* down)	1.034	0.309	0.847	0.357
ECOG performance score (≥2 *vs* <2)	1.302	0.254	0.894	0.344
HER2 expression (positive *vs* negative)	0.173	0.677	0.079	0.778
Metastasis sites (>2 *vs* ≤2)	5.195	0.023	5.744	0.017
Immunotherapy line (first *vs* second and above)	1.994	0.158	2.597	0.107
PD-L1 CPS (<5 *vs* ≥5)	9.334	0.002	9.004	0.003
LDHA expression (high *vs* low)	7.265	0.007	14.913	<0.001

3 讨 论

代谢重编程是恶性肿瘤的基本特征之一，肿瘤细胞通过代谢重塑实现快速增殖的能量供应和生物大分子的高效合成，调节肿瘤免疫微环境，逃避免疫杀伤和抵抗治疗等[11-13]。葡萄糖是肿瘤细胞最依赖的能量来源，也是T细胞等免疫细胞活化、分化、发挥功能所必需的重要能量物质。肿瘤细胞优先利用有氧糖酵解（Warburg效应）方式快速生成腺苷三磷酸，以适应乏氧的肿瘤微环境，还会限制正常组织对葡萄糖的消耗，增加自身利用率[14]。肿瘤细胞与免疫细胞竞争性利用葡萄糖等营养物质，能够改变T细胞和自然杀伤（natural killer，NK）细胞的分化和表型，影响免疫细胞的代谢模式[15]。肿瘤对葡萄糖的竞争性摄取能抑制肿瘤微环境中T细胞的活化和分泌IFN-γ的能力，进而影响T细胞对肿瘤细胞的杀伤作用[16]。

乳酸是细胞糖酵解的终产物，由丙酮酸在LDHA的催化下生成[17]。肿瘤微环境中较高的乳酸含量会抑制免疫细胞功能，导致免疫逃逸，促进肿瘤的发生、发展。肿瘤细胞分泌乳酸能够抑制T细胞和NK细胞的活化，导致肿瘤细胞免疫逃逸[18]；乳酸能够促进巨噬细胞向M2型极化，进而调节肿瘤的免疫逃逸[19]。

目前认为PD-L1高表达、Epstein-Barr病毒早期RNA（Epstein-Barr virus early RNA，EBER）表达阳性、高度微卫星不稳定（microsatellite instability-high，MSI-H）的胃癌患者是免疫治疗的优势人群[20-21]。但在真实世界中此类人群较少，预测价值有限。本研究纳入的患者EBER表达均为阴性，遗憾的是大多数患者未进行MSI检测，其中1例MSI-H患者，经三线免疫治疗后达到PR。既往研究表明，恶性黑色素瘤患者的血清LDH活性与PD-1抑制剂的疗效呈负相关[22]，LDH高表达也预示着小细胞肺癌患者对纳武利尤单抗的低应答率[23]。LDHA是肿瘤细胞中主要表达的LDH。在非小细胞肺癌中，LDHA抑制剂能够提高帕博丽珠单抗的应答率[24]。另外，LDHA抑制剂能够活化$CD8^+$ T淋巴细胞和NK细胞，提高乳腺癌对PD-1抑制剂的应答率[9, 25]。本研究发现，LDHA低表达胃癌患者对PD-1抑制剂的应答率较高，ORR和DCR较LDHA高表达患者明显提高。因此，LDHA表达水平可能具有预测胃癌PD-1抑制剂疗效的应用价值。

KEYNOTE-059研究[26-27]结果显示，随着PD-L1表达水平升高，患者经免疫治疗后中位OS逐渐延长。本研究纳入的PD-L1表达阳性患者大多为CPS≥10，中位OS和PFS较PD-L1表达阴性患者显著延长。同时本研究也探索了LDHA和PD-L1表达水平对接受PD-1抑制剂治疗的胃癌患者生存期的预测价值，发现LDHA高表达合并PD-L1 CPS＜5的胃癌患者在接受PD-1抑制剂治疗后的生存期更短。

综上所述，联合检测LDHA和PD-L1表达对胃癌PD-1抑制剂疗效预测和预后评估具有一定的应用价值，可能为胃癌免疫治疗效果预测和预后判断提供新方法。但本研究也存在一定局限性：首先，本研究为回顾性研究，所有患者在PD-1抑制剂治疗前均已在病理科检测了PD-L1表达，在接受免疫治疗的患者选择上可能存在一定偏倚；其次，本研究中所有患者均为PD-1抑制剂联合化疗，但PD-1抑制剂的药物选择及化疗方案并未完全统一，可能对结果产生一定影响；最后，本研究为单中心研究，样本量小，仍需要前瞻性多中心临床研究进一步证实。

利益冲突声明：所有作者均声明不存在利益冲突。

［参 考 文 献］

［1］ SUNG H, FERLAY J, SIEGEL R L, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries［J］. CA Cancer J Clin, 2021, 71(3): 209–249.

［2］ BAGCHI S, YUAN R, ENGLEMAN E G. Immune checkpoint inhibitors for the treatment of cancer: clinical impact and mechanisms of response and resistance［J］. Annu Rev Pathol, 2021, 16: 223–249.

［3］ JANJIGIAN Y Y, SHITARA K, MOEHLER M, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal

adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial [J]. Lancet, 2021, 398(10294): 27-40.

[4] KANG Y K, CHEN L T, RYU M H, et al. Nivolumab plus chemotherapy versus placebo plus chemotherapy in patients with HER2-negative, untreated, unresectable advanced or recurrent gastric or gastro-oesophageal junction cancer (ATTRACTION-4): a randomised, multicentre, double-blind, placebo-controlled, phase 3 trial [J]. Lancet Oncol, 2022, 23(2): 234-247.

[5] SHITARA K, VAN CUTSEM E, BANG Y J, et al. Efficacy and safety of pembrolizumab or pembrolizumab plus chemotherapy *vs* chemotherapy alone for patients with first-line, advanced gastric cancer: the KEYNOTE-062 phase 3 randomized clinical trial [J]. JAMA Oncol, 2020, 6(10): 1571-1580.

[6] SMYTH E C, NILSSON M, GRABSCH H I, et al. Gastric cancer [J]. Lancet, 2020, 396(10251): 635-648.

[7] LIU Y, GUO J Z, LIU Y, et al. Nuclear lactate dehydrogenase A senses ROS to produce α-hydroxybutyrate for HPV-induced cervical tumor growth [J]. Nat Commun, 2018, 9(1): 4429.

[8] SUN X R, SUN Z, ZHU Z, et al. Clinicopathological significance and prognostic value of lactate dehydrogenase A expression in gastric cancer patients [J]. PLoS One, 2014, 9(3): e91068.

[9] GONG Y, JI P, YANG Y S, et al. Metabolic-pathway-based subtyping of triple-negative breast cancer reveals potential therapeutic targets [J]. Cell Metab, 2021, 33(1): 51-64.e9.

[10] 中国临床肿瘤学会指南工作委员会. 中国临床肿瘤学会（CSCO）胃癌诊疗指南2022 [M]. 北京: 人民卫生出版社, 2022.
Guidelines Working Committee of the Chinese Clinical Oncology Society. Chinese Society of Clinical Oncology (CSCO) guidelines for the diagnosis and treatment of gastric cancer 2022 [M]. Beijing: People's Health Publishing House, 2022.

[11] DEY P, KIMMELMAN A C, DEPINHO R A. Metabolic codependencies in the tumor microenvironment [J]. Cancer Discov, 2021, 11(5): 1067-1081.

[12] MARTÍNEZ-REYES I, CHANDEL N S. Cancer metabolism: looking forward [J]. Nat Rev Cancer, 2021, 21(10): 669-680.

[13] LI X Y, WENES M, ROMERO P, et al. Navigating metabolic pathways to enhance antitumour immunity and immunotherapy [J]. Nat Rev Clin Oncol, 2019, 16(7): 425-441.

[14] VAUPEL P, SCHMIDBERGER H, MAYER A. The Warburg effect: essential part of metabolic reprogramming and central contributor to cancer progression [J]. Int J Radiat Biol, 2019, 95(7): 912-919.

[15] MA E H, VERWAY M J, JOHNSON R M, et al. Metabolic profiling using stable isotope tracing reveals distinct patterns of glucose utilization by physiologically activated $CD8^+$ T cells [J]. Immunity, 2019, 51(5): 856-870.e5.

[16] KAYMAK I, WILLIAMS K S, CANTOR J R, et al. Immunometabolic interplay in the tumor microenvironment [J]. Cancer Cell, 2021, 39(1): 28-37.

[17] JIANG W N, QIAO L, ZUO D, et al. Aberrant lactate dehydrogenase A signaling contributes metabolic signatures in pancreatic cancer [J]. Ann Transl Med, 2021, 9(4): 358.

[18] BRAND A, SINGER K, KOEHL G E, et al. LDHA-associated lactic acid production blunts tumor immunosurveillance by T and NK cells [J]. Cell Metab, 2016, 24(5): 657-671.

[19] ZHANG A K, XU Y Z, XU H S, et al. Lactate-induced M2 polarization of tumor-associated macrophages promotes the invasion of pituitary adenoma by secreting CCL17 [J]. Theranostics, 2021, 11(8): 3839-3852.

[20] MIZRAHI J, PANT S. Immunotherapy in gastrointestinal malignancies [J]. Adv Exp Med Biol, 2020, 1244: 93-106.

[21] CHAO J, FUCHS C S, SHITARA K, et al. Assessment of pembrolizumab therapy for the treatment of microsatellite instability-high gastric or gastroesophageal junction cancer among patients in the KEYNOTE-059, KEYNOTE-061, and KEYNOTE-062 clinical trials [J]. JAMA Oncol, 2021, 7(6): 895-902.

[22] WAGNER N B, FORSCHNER A, LEITER U, et al. S100B and LDH as early prognostic markers for response and overall survival in melanoma patients treated with anti-PD-1 or combined anti-PD-1 plus anti-CTLA-4 antibodies [J]. Br J Cancer, 2018, 119(3): 339-346.

[23] DAHER S, LAWRENCE Y R, DUDNIK E, et al. Nivolumab in non-small cell lung cancer: real world long-term survival results and blood-based efficacy biomarkers [J]. Front Oncol, 2021, 11: 625668.

[24] QIAO T Y, XIONG Y L, FENG Y B, et al. Inhibition of LDH-a by oxamate enhances the efficacy of anti-PD-1 treatment in an NSCLC humanized mouse model [J]. Front Oncol, 2021, 11: 632364.

[25] ZHANG Y X, ZHAO Y Y, SHEN J Z, et al. Nanoenabled modulation of acidic tumor microenvironment reverses anergy of infiltrating T cells and potentiates anti-PD-1 therapy [J]. Nano Lett, 2019, 19(5): 2774-2783.

[26] FUCHS C S, DOI T, JANG R W, et al. Safety and efficacy of pembrolizumab monotherapy in patients with previously treated advanced gastric and gastroesophageal junction cancer: phase 2 clinical KEYNOTE-059 trial [J]. JAMA Oncol, 2018, 4(5): e180013.

[27] BANG Y J, KANG Y K, CATENACCI D V, et al. Pembrolizumab alone or in combination with chemotherapy as first-line therapy for patients with advanced gastric or gastroesophageal junction adenocarcinoma: results from the phase Ⅱ nonrandomized KEYNOTE-059 study [J]. Gastric Cancer, 2019, 22(4): 828-837.

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