

· 论著 ·

胃癌患者术前血清GINS4、PD-1水平与临床病理特征及预后的相关性

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摘要 目的 探讨胃癌患者术前血清GINS复合物4 (GINS4)、PD-1水平与临床病理特征及预后的关系。方法 选取我院2016年8月至2018年8月治疗的95例胃癌患者, 并根据患者生存情况分为生存组和死亡组; 选取同期95例健康体检者作为对照组。采用酶联免疫吸附试验 (ELISA) 检测术前血清PD-1水平。采用实时定量PCR检测术前血清GINS4 mRNA水平; 采用Kaplan-Meier法分析胃癌患者术前血清GINS4 mRNA、PD-1水平与5年生存率的关系; 采用Cox回归分析胃癌预后的影响因素。结果 胃癌组血清GINS4 mRNA、PD-1水平显著高于对照组 ($P < 0.05$)。组织低分化、TNM分期 III~IV期、有淋巴结转移胃癌患者血清GINS4 mRNA、PD-1水平显著高于组织中/高分化、TNM分期 I~II期和无淋巴结转移患者 ($P < 0.05$)。死亡组血清GINS4 mRNA、PD-1水平及TNM分期 III~IV期、有淋巴结转移患者比例显著高于生存组 ($P < 0.05$)。Kaplan-Meier法分析结果显示, 胃癌患者血清中GINS4 mRNA高表达、PD-1高表达患者5年生存率低于GINS4 mRNA低表达、PD-1低表达患者 ($P < 0.05$)。GINS4 mRNA、PD-1水平是胃癌患者死亡的独立危险因素 ($P < 0.05$)。结论 胃癌患者血清GINS4 mRNA、PD-1水平升高, 二者与组织分化程度、TNM分期、淋巴结转移及预后密切相关。

关键词 胃癌; GINS复合物4; PD-1; 临床病理特征; 预后

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Correlations between preoperative serum levels of GINS4 and PD-1 and clinicopathological characteristics and prognosis in patients with gastric cancer

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Abstract Objective To analyze the expression levels of serum GINS complex 4 (GINS4) and PD-1 in patients with gastric cancer before surgery and to explore the relationship between these two factors and the clinicopathological characteristics and prognosis of these patients. **Methods** A total of 95 patients with gastric cancer treated at the First People's Hospital of Nanyang between August 2016 and August 2018 were included in this study. The patients were followed-up for 5 years and divided into survival and death groups based on their survival at the end of the follow-up. A total of 95 healthy individuals in the same period were selected as the control group. The serum PD-1 levels before surgery were measured using an enzyme-linked immunosorbent assay (ELISA). The level of serum GINS4 mRNA before surgery was detected with real-time quantitative PCR. The relationship between serum GINS4 mRNA and PD-1 levels prior to surgery and the 5-year survival rate in the patients with gastric cancer were analyzed using the Kaplan-Meier method. Cox regression was used to analyze the factors affecting gastric cancer prognosis. **Results** The serum levels of GINS4 mRNA and PD-1 were significantly higher in the patients with gastric cancer than in the healthy controls ($P < 0.05$). The serum levels of GINS4 mRNA and PD-1 in patients with poorly differentiated tissues in TNM stages III and IV, and lymph node metastasis were significantly higher than those in patients with moderately/highly differentiated tissues, in TNM stage II, and no lymph node metastasis ($P < 0.05$). The serum levels of GINS4 mRNA and PD-1, proportion of patients with TNM stages III and IV, and the proportion of patients with lymph node metastasis in the death group were significantly higher than those in the survival group ($P < 0.05$). According to the results of Kaplan-Meier analysis, the 5-year survival rate of patients with gastric cancer with high serum expression levels of GINS4 mRNA and PD-1 was lower than that of patients with low expression levels of GINS4 mRNA and PD-1 ($P < 0.05$). GINS4 mRNA and PD-1 levels were independent risk factors for death in patients

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with gastric cancer ($P < 0.05$). **Conclusion** The expression levels of serum GINS4 mRNA and PD-1 in patients with gastric cancer were higher than those of the controls, which were related to tissue differentiation, TNM staging, lymph node metastasis, and prognosis.

Keywords gastric cancer; GINS complex 4; PD-1; clinicopathological characteristics; prognosis

胃癌是全球常见的癌症和癌症相关死亡原因^[1]。由于胃癌患者确诊时常为晚期,因此预后较差,晚期患者总体5年生存率 $<30\%$ ^[2-3]。目前,胃癌的确诊主要依赖于病理活检和胃镜,然而胃镜检查费用昂贵,且给患者带来较大痛苦,患者依从性低^[1]。因此,阐明胃癌发生和进展的分子机制对探索早期诊断和治疗的新靶点有重要意义。GINS复合体是一种包含4种不同蛋白质的异四聚体结构。其中,GINS复合物4(GINS complex 4, GINS4)与胃癌的发生发展密切相关^[1-4]。PD-1有PD-L1和PD-L2 2种配体。其中,PD-L1广泛表达于非造血细胞、免疫细胞和各种肿瘤内,PD-1与PD-L1相互作用可抑制T淋巴细胞增殖、存活及免疫效应^[5]。研究^[6]显示,阻断PD-1与PD-L1之间的相互作用可能增强内源性抗肿瘤免疫能力。JIN等^[7]研究发现PD-1/PD-L1与GINS4均为食管鳞状细胞癌的免疫相关预后基因,可以提高免疫治疗的效率。本研究主要探讨血清GINS4 mRNA、PD-1水平与胃癌患者临床病理特征及预后的关系,旨在为胃癌治疗提供依据。

1 材料与方法

1.1 一般资料

选取本院2016年8月至2018年8月治疗的95例胃癌患者,作为胃癌组。患者年龄35~81岁,平均年龄为 (60.24 ± 9.74) 岁;选取同期95例体检健康者,作为对照组,年龄36~79岁,平均年龄 (60.38 ± 9.41) 岁。患者均已签署知情同意书,本研究获南阳市第一人民医院临床医学伦理委员会审批通过。

纳入标准:(1)符合《中华医学会胃癌临床诊疗指南(2021版)》标准^[8],经术后病理诊断确诊为胃癌;(2)认知功能正常,沟通无障碍,可进行术后随访;(3)入组前未接受免疫治疗、放化疗等相关治疗。排除标准:(1)合并心脑血管疾病、传染性疾病、感染性疾病、自身免疫性疾病;(2)妊娠或哺乳期;(3)合并其他类型恶性肿瘤。脱落标准:患者进入临床试

验后,因失访或主动撤回知情同意书而未完成最终临床试验。

1.2 方法

1.2.1 临床病理资料收集:收集胃癌患者年龄、性别、肿瘤直径、浸润深度、病理类型、组织分化程度、TNM分期、淋巴结转移等资料。

1.2.2 血清GINS4 mRNA、PD-1水平检测:采集胃癌患者术前及健康体检者体检时外周静脉血3 mL, 3 000 r/min离心10 min收集上层血清(离心半径10 cm),保存于 $-80\text{ }^{\circ}\text{C}$ 冰箱。采用酶联免疫吸附试验(enzyme linked immunosorbent assay, ELISA)检测血清PD-1水平(试剂盒购自北京凯诗源生物科技有限公司)。采用实时定量PCR检测血清GINS4 mRNA水平, RNA提取试剂盒(北京伊塔生物科技有限公司)提取血清总RNA,紫外分光光度计检测合格[光密度(optical density, OD)₂₆₀/OD₂₈₀为1.8~2.0]后采用RNA反转录试剂盒(北京康瑞纳生物科技有限公司)反转录为cDNA,实时定量PCR反应条件:95 $^{\circ}\text{C}$ 预变性30 s;95 $^{\circ}\text{C}$ 变性10 s,60 $^{\circ}\text{C}$ 退火60 s,72 $^{\circ}\text{C}$ 延伸10 s,共45个循环。实时定量PCR反应体系:模板cDNA 2 μL , SYBR Premix Ex TaqTM II(日本TaKaRa公司) 10 μL , ROX Reference Dye(江西艾博因生物科技有限公司) 0.4 μL , 正反向引物各0.4 μL , ddH₂O补至25 μL 。所有操作均采用ABI 7500型qRT-PCR仪,反应结束后采用 $2^{-\Delta\Delta\text{Ct}}$ 法计算。GINS4 mRNA正向引物序列为5'-CTGTAGACCAGCACTGATGTG-3',反向引物序列为5'-CTAGACATGAGAGCTGCGTCG-3'; GAPDH正向引物序列为5'-GGACGTAGCTAGAGTCGTACG-3',反向引物序列为5'-GCCGACCTGTGAGACTGTAC-3'。

1.2.3 随访:所有胃癌患者术后进行为期5年的随访,平均每6个月随访1次,随访的主要方式为电话结合复查,随访时间截至2023年8月,根据随访截止时胃癌患者的生存情况分为生存组(46例)和死亡组(49例)。

1.3 统计学分析

采用SPSS 25.0软件进行统计分析。计量资料符合正态分布,以 $\bar{x} \pm s$ 表示,2组比较采用独立样本t检验,3组比较采用单因素方差分析;计数资料以率(%)表示,采用 χ^2 检验比较;采用Kaplan-Meier法分析胃癌患者血清GINS4 mRNA、PD-1水平与5年生存率的关系;采用Cox回归分析胃癌预后的影响因素。 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 对照组与胃癌组血清GINS4 mRNA、PD-1水平比较

对照组血清GINS4 mRNA (1.02 ± 0.22)、PD-1

($502.21 \text{ ng/L} \pm 60.14 \text{ ng/L}$)水平显著低于胃癌组($2.34 \pm 0.38, 659.72 \text{ ng/L} \pm 93.98 \text{ ng/L}$),差异有统计学意义(t 分别为29.523和14.795, P 均 < 0.001)。

2.2 血清GINS4 mRNA、PD-1水平与胃癌患者临床病理特征的关系

不同年龄、性别、肿瘤直径、浸润深度、病理类型胃癌患者血清GINS4 mRNA、PD-1水平比较,差异无统计学意义($P > 0.05$)。组织低分化、TNM分期Ⅲ~Ⅳ期、有淋巴结转移胃癌患者血清GINS4 mRNA、PD-1水平显著高于组织中/高分化、TNM分期Ⅰ~Ⅱ期、无淋巴结转移患者($P < 0.05$)。见表1。

2.3 血清GINS4 mRNA、PD-1水平及临床病理参数与胃癌预后的关系

表1 血清GINS4 mRNA、PD-1水平与胃癌患者临床病理特征的关系($\bar{x} \pm s$)

Tab.1 Relationship between serum levels of GINS4 mRNA and PD-1 and clinicopathological characteristics of patients with gastric cancer ($\bar{x} \pm s$)

Clinicopathological characteristics	<i>n</i>	GINS4 mRNA	<i>t</i>	<i>P</i>	PD-1 (ng/L)	<i>t</i>	<i>P</i>
Age			0.253	0.801		1.160	0.249
<60 years	49	2.33 ± 0.37			647.21 ± 88.63		
≥ 60 years	46	2.35 ± 0.40			669.60 ± 99.49		
Sex			0.768	0.445		0.094	0.925
Male	52	2.32 ± 0.37			658.89 ± 88.67		
Female	43	2.38 ± 0.39			660.73 ± 101.08		
Tumor diameter			0.382	0.704		1.401	0.164
<5 cm	45	2.36 ± 0.45			673.89 ± 89.71		
≥ 5 cm	50	2.33 ± 0.31			646.97 ± 96.78		
Depth of infiltration			0.128	0.899		0.433	0.666
Mucosa and submucosa	43	2.34 ± 0.34			664.33 ± 85.46		
Muscle layer and serosal layer	52	2.35 ± 0.41			655.91 ± 101.15		
Degree of tissues differentiation			3.825	< 0.001		3.138	0.002
Moderate/high differentiation	41	2.19 ± 0.28			626.97 ± 87.84		
Poor differentiation	54	2.47 ± 0.40			685.95 ± 92.84		
Pathological type			0.828	0.440		0.041	0.960
Signet ring cell carcinoma	10	2.48 ± 0.48			663.50 ± 96.25		
Adenocarcinoma	75	2.33 ± 0.35			658.33 ± 97.07		
Mucinous carcinoma	10	2.28 ± 0.49			666.39 ± 73.67		
TNM staging			3.898	< 0.001		2.702	0.008
Stage I - II	46	2.20 ± 0.37			633.69 ± 89.33		
Stage III - IV	49	2.48 ± 0.33			684.16 ± 92.50		
Lymph node metastasis			3.886	< 0.001		2.938	0.004
No	50	2.21 ± 0.36			633.88 ± 89.00		
Yes	45	2.49 ± 0.34			688.44 ± 91.91		

生存组与死亡组年龄、性别、肿瘤直径、浸润深度、组织分化程度、病理类型比较,差异无统计学意义($P > 0.05$)。死亡组血清GINS4 mRNA、PD-1水平及

TNM分期Ⅲ~Ⅳ期、有淋巴结转移患者比例显著高于生存组($P < 0.05$)。见表2。

2.4 胃癌患者血清GINS4 mRNA、PD-1水平与5年生

表2 GINS4 mRNA、PD-1水平及临床病理特征与胃癌预后的关系

Tab.2 Relationship between GINS4 mRNA levels, PD-1 levels, clinicopathological characteristics and gastric cancer prognosis

Clinicopathological characteristics	n	Survival group (n = 46)	Death group (n = 49)	χ^2/t	P
Age [n (%)]				1.254	0.263
<60 years	49	21 (45.65)	28 (57.14)		
≥60 years	46	25 (54.35)	21 (42.86)		
Sex [n (%)]				0.005	0.941
Male	52	25 (54.35)	27 (55.10)		
Female	43	21 (45.65)	22 (44.90)		
Tumor diameter [n (%)]				0.007	0.931
<5 cm	45	22 (47.83)	23 (46.94)		
≥5 cm	50	24 (52.17)	26 (53.06)		
Depth of infiltration [n (%)]				0.236	0.627
Mucosa and submucosa	43	22 (47.83)	21 (42.86)		
Muscle layer and serosal layer	52	24 (52.17)	28 (57.14)		
Degree of tissues differentiation [n (%)]				0.125	0.724
Moderate/high differentiation	41	19 (41.30)	22 (44.90)		
Poor differentiation	54	27 (58.70)	27 (55.10)		
Pathological type [n (%)]				1.035	0.414
Signet ring cell carcinoma	10	5 (10.87)	5 (10.20)		
Adenocarcinoma	75	36 (78.26)	39 (79.60)		
Mucinous carcinoma	10	5 (10.87)	5 (10.20)		
TNM staging [n (%)]				47.213	<0.001
Stage I - II	46	39 (84.78)	7 (14.29)		
Stage III - IV	49	7 (15.22)	42 (85.71)		
Lymph node metastasis [n (%)]				32.146	<0.001
No	50	38 (82.61)	12 (24.49)		
Yes	45	8 (17.39)	37 (75.51)		
GINS4 mRNA	95	2.18 ± 0.35	2.50 ± 0.33	4.587	<0.001
PD-1 (ng/L)	95	623.25 ± 87.44	693.82 ± 88.49	3.907	<0.001

存率的关系

以胃癌患者血清GINS4 mRNA (2.36)、PD-1 (658.44 ng/L) 水平中位数为界,将胃癌患者分为GINS4 mRNA低表达47例、GINS4 mRNA高表达48例;PD-1低表达46例、PD-1高表达49例。采用Kaplan-Meier法分析胃癌患者血清GINS4 mRNA、PD-1水平与5年生存率的关系,结果显示,胃癌患者血清中GINS4 mRNA高表达患者5年生存率(14/48, 29.17%)低于GINS4 mRNA低表达患者(32/47, 68.09%),差异有统计学意义

($\chi^2=14.402, P < 0.05$);胃癌患者血清中PD-1高表达患者5年生存率(16/49, 32.65%)低于PD-1低表达患者(30/46, 65.22%),差异有统计学意义($\chi^2=10.074, P < 0.05$)。见图1。

2.5 影响胃癌患者预后的Cox危险因素分析

以胃癌患者是否死亡作为因变量,GINS4 mRNA、PD-1、TNM分期、淋巴结转移为自变量进行多因素Cox回归分析,结果显示,GINS4 mRNA、PD-1是胃癌患者死亡的独立危险因素($P < 0.05$)。见表3。

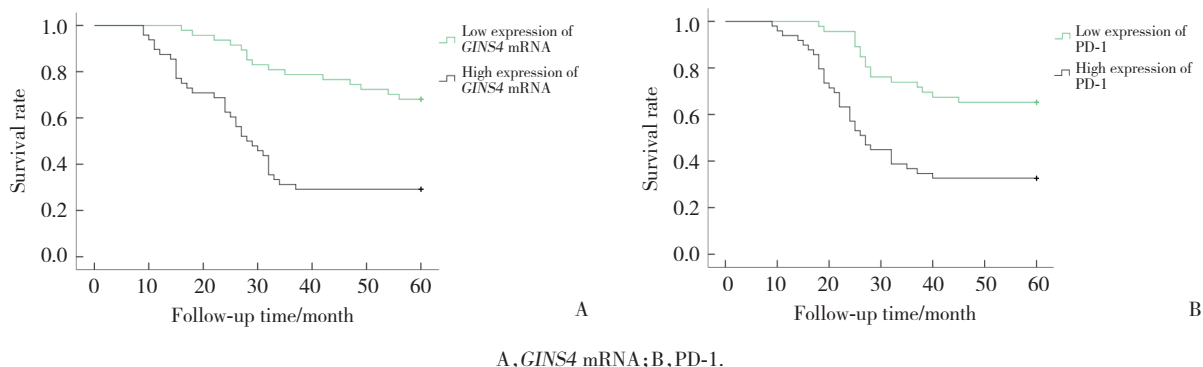


图1 胃癌患者血清GINS4 mRNA和PD-1水平与5年生存率的关系

Fig.1 Relationship between serum levels of GINS4 mRNA and PD-1 and 5-year survival rate in patients with gastric cancer

表3 影响胃癌患者预后的Cox回归分析

Tab.3 Cox regression analysis of the prognosis of patients with gastric cancer

Influencing factor	B	SE	Wald χ^2	HR	95%CI	P
GINS4 mRNA level	1.014	0.286	12.574	2.757	1.574-4.829	<0.001
PD-1 level	0.965	0.303	10.145	2.625	1.449-4.754	0.001
TNM staging	0.071	0.185	0.149	1.074	0.747-1.543	0.700
Lymph node metastasis	0.199	0.182	1.194	1.220	0.854-1.743	0.275

3 讨论

胃癌患者死亡率高,多数患者确诊时已为晚期,不适合手术治疗^[9]。免疫治疗目前已成为胃癌等多种癌症的可行性治疗选择,但仍缺乏治疗靶点^[10]。

GINS复合物是一种复制解旋酶,对DNA复制至关重要,其作用是在移动复制叉之前解锁双链DNA^[11]。SHAN等^[12]研究显示,GINS复合物2在胃癌中表达增加,可通过促进细胞增殖、迁移等发挥促癌作用。PD-1作为细胞穿膜受体之一,参与免疫反应中T细胞的活化^[13]。研究^[14]显示,上调PD-1及其配体PD-L1表达,可使该通路产生的干扰素、免疫激活蛋白等表达上调,增强免疫细胞的抗胃癌作用。QIN等^[15]研究显示,抗尿激酶型纤溶酶原激活物受体和抗PD-1的组合通过多种机制显著抑制胃癌生长并延长生存期。

本研究中胃癌患者血清GINS4 mRNA、PD-1水平显著高于正常人群,提示GINS4、PD-1在胃癌的发生发展中可能发挥促癌基因作用,二者高表达可能通过相关机制促进胃癌进展。此外,GINS4 mRNA、PD-1表达升高与组织低分化、TNM分期增加、淋巴

结转移有关,推测GINS4 mRNA参与胃癌的主要机制可能是调控胃癌细胞的增殖、迁移和凋亡。而血清PD-1表达增加提示患者机体免疫应激反应增加,推测血清PD-1与其配体PD-L1结合增加,二者结合后通过一系列作用降低T细胞活化水平,抑制机体免疫防御,促进胃癌进展。

本研究结果显示,GINS4 mRNA、PD-1表达水平是影响胃癌患者5年内死亡的危险因素。GINS4 mRNA、PD-1高表达可能促进胃癌患者的不良预后,GINS4 mRNA、PD-1可能是评估胃癌恶性生物学行为及不良预后的潜力指标。

综上所述,胃癌患者血清GINS4 mRNA、PD-1水平平均升高,且与患者组织低分化、TNM分期增加、淋巴结转移及较低的5年生存率有关。血清GINS4 mRNA、PD-1高表达是胃癌患者死亡的危险因素,监测二者表达水平可能有利于评估胃癌患者预后,降低死亡率。

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