

doi: 10.13241/j.cnki.pmb.2022.08.029

血清白介素 8 基因多态性与食管鳞癌根治术后的相关性分析*

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摘要 目的:探讨与分析血清白细胞介素 8(IL-8)基因多态性与食管鳞癌(ESCC)根治术后的相关性。**方法:**2017 年 8 月到 2020 年 6 月选择在本院诊治的食管鳞癌患者 98 例作为研究对象,检测血清 IL-8 表达水平。所有患者都给予根治手术治疗,随访患者的预后并进行相关性分析。**结果:**所有患者术后随访到 2021 年 7 月,平均随访时间为 25.69±2.58 个月,死亡 28 例,死亡率为 28.6%(死亡组)。两组血清 IL-8 表达水平表达具有差异($P<0.05$)。所有患者的基因型频率均符合 Hardy-Weinberg 这一平衡法则,表明本文所选取的样本均具有群体代表性。IL-8 基因启动子 rs4073A/T 的 AA 基因型较死亡组高,TT 基因型较死亡组低,两组 A、T 等位基因频率分布对比有差异($P<0.05$)。直线相关性分析显示:IL-8 基因启动子 rs4073A/T 的 AA 基因型、A 等位基因、血清 IL-8 表达水平与预后死亡率存在相关性($P<0.05$)。多因素 logistic 回归分析显示:IL-8 基因启动子 rs4073A/T 的 AA 基因型、A 等位基因、血清 IL-8 表达水平为导致患者随访死亡的主要因素(OR=2.051, 3.094, $P<0.05$)。**结论:**食管鳞癌根治术后患者依然存在一定的死亡率,患者死亡与血清 IL-8 基因多态性存在相关性,同时多伴随有 IL-8 的高表达。IL-8 基因启动子 rs4073A/T 的 AA 基因型、A 等位基因、血清 IL-8 表达水平为导致患者死亡的主要因素。

关键词:食管鳞癌;根治手术;白介素 8;基因多态性;相关性

中图分类号:R735.1 文献标识码:A 文章编号:1673-6273(2022)08-1539-04

Correlation Analysis between Serum Interleukin-8 Gene Polymorphism and Radical Resection of Esophageal Squamous Cell Carcinoma*

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ABSTRACT Objective: To explore and analyze the correlation between serum IL-8 gene polymorphism and ESCC after radical resection. **Methods:** From August 2017 to June 2020, 98 cases of patients with esophageal squamous cell carcinoma diagnosed and treated in our hospital were selected as the research object, and the serum IL-8 expression level were detected. All patients were treated with radical surgery, and the prognosis of the patients were followed up and given correlation analysis. **Results:** All patients were followed up to July 2021. The average follow-up time were 25.69±2.58 months. There were 28 deaths and the mortality rate were 28.6% (death group). The expression level of serum IL-8 in the death group were higher than that in the survival group ($P<0.05$). The genotype frequencies of all patients were conformed to the Hardy-Weinberg equilibrium rule, which confirmed that the samples were representative of the population. The AA genotype of the IL-8 gene promoter rs4073A/T were higher than that of the death group($P<0.05$), and the TT genotype were lower than that of the death group ($P<0.05$). There were also statistical differences in the frequency distribution of A and T alleles compared between the two groups ($P<0.05$). Linear correlation analysis showed that the AA genotype and A allele of IL-8 gene promoter rs4073A/T, expression level of serum IL-8 were correlated with prognosis and mortality($P<0.05$). Multivariate logistic regression analysis showed that the AA genotype and A allele of IL-8 gene promoter rs4073A/T, expression level of serum IL-8 were the main factors lead to followed-up death (OR=2.051, 3.094, $P<0.05$). **Conclusion:** Patients with esophageal squamous cell carcinoma still have certain mortality rate after radical resection. There are correlation between the death of patients and the polymorphism of serum IL-8 gene. It is also often accompanied by high expression of IL-8. The AA genotype and A allele of IL-8 gene promoter rs4073A/T, expression level of serum IL-8 are The main factor lead to the death of patients.

Key words: Esophageal squamous cell carcinoma; Radical surgery; Interleukin-8; Gene polymorphism; Correlation

Chinese Library Classification(CLC): R735.1 **Document code:** A

Article ID: 1673-6273(2022)08-1539-04

* 基金项目:陕西省科技厅面上项目(2018JM7113)

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(收稿日期:2021-09-03 接受日期:2021-09-26)

前言

由于社会经济发展、饮食习惯改变等多种因素,食管癌的发生率逐年增加。我国是食管癌大国,年新发食管癌病例接近50万例,年死亡病例在40万例左右^[1,2]。食管鳞癌(Esophageal squamous carcinoma, ESCC)为食管癌的主要类型,早期患者经过根治手术治疗后,5年生存率在80.0%以上^[3]。但大多食管鳞癌患者在就诊时多为晚期,该类患者5年生存率为20.0%左右,为此加强早期诊治具有重要价值^[4,5]。当前食管鳞癌的发病机制尚不明确,相关学者认为食管鳞癌的发生是环境和基因交互作用的结果^[6]。白细胞介素8(Interleukin-8, IL-8)是趋化因子家族的重要成员之一,由巨噬细胞等分泌而成,其可介导中性粒细胞参与机体的炎性反应^[7,8]。相对于正常人,肿瘤患者组织与血浆中IL-8呈现高表达状况,可促进上皮细胞的迁移、侵袭和增殖^[9]。IL-8在调节机体组织细胞稳态与机体免疫调节方面发挥着重要的作用,还具有很强的刺激血管生成的作用^[10]。有研究表明:IL-8基因的多态性增加了黄种人食管鳞癌的发生风险,但并不增加白种人食管鳞癌的发生风险,提示食管鳞癌的易感性与遗传背景、种族存在一定的相关性^[11,12]。本文探讨与分析了血清IL-8基因多态性与食管鳞癌根治术后的相关性,旨在从基因水平上评估IL-8在食管鳞癌的发生与发展中的作用。

1 资料与方法

1.1 一般资料

2017年8月到2020年6月选择在本院诊治的食管鳞癌患者98例作为研究对象。

纳入标准:病理学诊断为食管鳞癌;具有根治手术指征;无放疗化疗治疗史;临床与调查资料完整;所有患者均无血缘关系;患者知情并签署同意书;经医院伦理委员会批准。

排除标准:患有血液系统疾病的患者;合并其他自身免疫性疾病;合并有传染性疾病或接触史的患者;合并其他恶性肿瘤的患者。

1.2 手术方法

所有患者都给予食管鳞癌根治手术治疗,术前进行常规备皮,给予气管麻醉并建立人工气胸。于右侧腋部第7肋间建立胸腔镜观察孔,明确病灶部位。做3个操作孔于腋前线第3肋

间、腋后线第6肋间,然后在胸腔组织内置入手术器械,并将纵膈胸膜切开,切除气管食管沟内淋巴结及其周边疏松组织,游离食管并进行淋巴结清扫。切除周边受累组织,然后进行止血、留置引流管、吸痰、关闭气胸等操作。

1.3 血清IL-8基因多态性检测

采集所有患者禁食8h后的空腹静脉血3-5 mL,不抗凝,3000 rpm离心10 min,取上层血清并放置于医用冰箱备用。采用酶联免疫法(检测试剂盒购自上海生工公司)检测血清IL-8表达水平,严格按照试剂盒的说明书进行操作,提取外周血基因组DNA,根据GenBank中IL-8基因核苷酸序列资料及软件Primer Premier 5.0设计引物。IL-8序列如下:上游:5'-AA-CATCGGCTGTCTATTATAATC-3';下游:5'-AAATAACACG-TACGATACTGAAG-3'。PCR扩增条件:94℃ 3 min,然后94℃ 30 s,48℃ 55 s,72℃ 45 s,共30个循环,最后72℃延伸10 min。PCR反应体系均为25 μL,含2× Tag PCR Masterix 12.5 μL,1 μL上下游引物,1.5 μL DNA模板,Taq DNA聚合酶(依据不同体系进行调整)。取12 μL PCR扩增产物,并加入1 μL限制性内切酶,37℃水浴3 h,经琼脂糖凝胶电泳分离,进行紫外凝胶成像并记录结果。

1.4 随访调查

所有患者在术后采用电话随访、门诊复查、微信随访的方式进行调查,末次随访时间为2021年7月,统计患者的生存与死亡情况。

1.5 统计方法

使用SPSS23.00进行分析,计数资料采用n/%表示,计量资料采用($\bar{x} \pm s$)表示,t检验与卡方 χ^2 分析,采用直线相关分析,用(OR)及其95%可信区间(CI)表示相对风险度,采用多因素logistic回归分析,均为双侧检验,检验水准为 $\alpha=0.05$ 。

2 结果

2.1 术后随访情况

所有患者术后随访到2021年7月,平均随访时间为25.69±2.58个月,死亡28例,死亡率为28.6%(死亡组),生存70例为生存组。

2.2 病理特征对比分析

两组临床分期、组织学分化等病理特征对比无差异($P>0.05$),但血清IL-8表达水平表达具有差异($P<0.05$)。见表1。

表1 两组病理特征对比分析

Table 1 Comparative analysis of pathological features between the two groups

Groups	n	Gender (male/female)	Age (years)	Body mass index (kg/m ²)	Location of tumor (upper segment/middle segment/lower segment)	Clinical Stage (Stage i / ii A)	Histological differentiation (highly/moderately/poorly differentiated)	IL-8
Death group	28	16/12	43.22± 2.87	22.87± 1.48	8/8/12	19/9	17/8/3	24.83± 1.48
Survival group	70	40/30	43.67± 3.18	22.44± 2.18	19/19/32	47/23	50/12/8	5.69± 0.68
t/χ^2		0.000	0.414	0.467	0.066	0.005	1.625	29.472
P		1.000	0.642	0.614	0.968	0.944	0.444	0.000

2.3 血清 IL-8 基因多态性对比

所有患者的基因型频率均符合 Hardy-Weinberg 平衡法则,表明本文所选取的样本均具有群体代表性。IL-8 基因启动

子 rs4073A/T 的 AA 基因型较死亡组高,TT 基因型较死亡组低,两组 A、T 等位基因频率分布对比有差异($P<0.05$)。见表 2。

表 2 两组血清 IL-8 基因启动子 rs4073A/T 基因型与等位基因频率分布对比(n)

Table 2 Frequency distribution of rs4073A/T genotype and allele of IL-8 gene promoter in serum of two groups (n)

Groups	n	Genotype			Allele frequency	
		AA	AT	TT	A	T
Death group	28	12(42.9%)	12(42.9%)	4(14.3%)	22(78.6%)	6(21.4%)
Survival group	70	9(12.9%)	28(40.0%)	33(47.1%)	26(37.1%)	44(62.9%)
χ^2			14.159			13.736
P			<0.001			<0.001

2.4 直线相关性分析

在 98 例患者中,直线相关性分析显示 IL-8 基因启动子

rs4073A/T 的 AA 基因型、A 等位基因、血清 IL-8 表达水平与预后死亡率存在相关性($P<0.05$)。见表 3。

表 3 血清 IL-8 基因多态性与食管鳞癌根治术后的相关性(n=98)

Table 3 Association of serum IL-8 gene polymorphism with esophageal squamous cell carcinoma after radical resection (n=98)

Indicators	r	P
AA genotype	0.533	0.003
A allele	0.622	0.000
Serum IL-8 expression	0.574	0.002

2.5 影响因素分析

将患者随访调查死亡作为因变量,多因素 logistic 回归分析显示 IL-8 基因启动子 rs4073A/T 的 AA 基因型、A 等位基

因、血清 IL-8 表达水平为导致患者随访死亡的主要因素(OR=2.051,3.094, $P<0.05$)。见表 4。

表 4 影响食管鳞癌根治术后患者预后死亡危险因素的多因素分析(n=18)

Table 4 Multivariate analysis of risk factors affecting prognosis and death of patients with esophageal squamous cell carcinoma after radical resection (n=18)

Indicators	β	SE	Wald χ^2	P	OR	95%CI
AA genotype	0.294	0.824	3.445	0.041	2.051	1.633-6.496
A allele	0.563	0.815	4.853	0.026	3.094	1.443-7.194
Serum IL-8 expression	0.613	0.563	5.683	0.012	4.853	2.472-9.714

3 讨论

食管鳞癌是一种组织病变,该癌症具有较高致残率与死亡率^[13]。当患者发病后,会对其生活质量产生明显的负面影响,需加强早期诊治^[14]。临床研究显示,食管癌的预后与临床分期存在相关性,分期越早,预后越好;但仍有部分早期食管癌患者行根治手术后出现局部复发转移等情况,导致预后变差^[15]。随着医学技术的发展,食管鳞癌根治手术微创性治疗逐渐增加。本研究显示:所有患者术后随访到 2021 年 7 月,平均随访时间为 25.69± 2.58 个月,死亡 28 例,死亡率为 28.6%(死亡组)。这一结果与 Yin Q^[16]等人的结果一致,分析其原因可知:胸腔镜联合食管癌根治术在实施时,能够最大限度的维持患者胸廓的完整

性,未撑开肋骨。通过切断胸壁的组织间肌肉,减少对肺组织通气功能的损害。同时其在胸腔镜引导下进行手术,可降低胸、腹腔组织在空气内暴露时间,明显提升手术清晰度,减少术后对周边组织、神经的损伤,促进患者术后康复^[17,18]。

研究显示,食管鳞癌是一种多基因遗传病,是遗传、环境等共同作用产生的结果^[19,20]。本研究显示,两组临床分期、组织学分化等病理特征对比无差异,但血清 IL-8 表达水平表达具有差异,且死亡组的血清 IL-8 表达水平较生存组高。这一结果与 Wu J 等人^[21]的结果具有一致性。从机制上分析可知,IL-8 基因定位于 4 号染色体 q12-q21 部位,包含 3 个内含子和 4 个外显子。IL-8 可作用于肥大细胞、T 淋巴细胞、等效应细胞,是一个重要的炎症递质和免疫调节因子,可促使机体发生大量的炎症

因子。经细菌脂多糖刺激中性粒细胞产生 IL-8,进而促进炎症反应进程、刺激毛细血管形成、调节机体免疫功能等多种工程, 密切参与肿瘤、免疫性疾病的发生发展^[22,23];本研究显示,所有患者的基因型频率均符合 Hardy-Weinberg 平衡法则,表明本文所选取的样本均具有群体代表性。IL-8 基因启动子 rs4073A/T 的 AA 基因型较死亡组高,TT 基因型较死亡组低,两组 A、T 等位基因频率分布对比有差异。食管鳞癌根治术后随访死亡患者 IL-8 基因启动子 rs4073A/T 基因型 AA、AT 和 TT 频率分别为 42.9%、42.9%和 14.3%,等位基因 A、T 频率分别为 78.6%和 21.4%。这一结果与 Huang Z 等人^[11]的结果具有相似性。进一步分析原因可知:IL-8 对中性粒细胞具有特殊的趋化、激活和脱颗粒效应,可参与脓毒症、消化道炎症等病理过程,与肿瘤等息息相关^[24,25]。IL-8 的启动子区域存在基因多态性位点,其中 rs4073A/T 可影响 IL-8 启动子区转录活性,同时是诱发各种恶性肿瘤的危险因素^[26,27]。

当前食管鳞癌的发病率逐年升高,根治性手术是目前的主要治疗手段。目前对行食管鳞癌根治术患者预后的预测主要通过检测血清肿瘤标志物水平进行判断,但预测的准确性有待提高^[28,29]。本研究直线相关性分析显示:IL-8 基因启动子 rs4073A/T 的 AA 基因型、A 等位基因、血清 IL-8 表达水平与预后死亡率存在相关性;多因素 logistic 回归分析显示 IL-8 基因启动子 rs4073A/T 的 AA 基因型、A 等位基因、血清 IL-8 表达水平为导致患者随访死亡的主要因素(OR=2.051, 3.094, $P < 0.05$)。这一结果与 Rodrigues ISS^[30]以及 Deng Y^[31]等人的结果具有相似性。从机制上分析,IL-8 可与某些生长因子受体结合蛋白结合,作用于 T 细胞信号转导,从而在免疫调节中发挥作用,可导致机体炎症状态的发生。特别是 IL-8 基因启动子 rs4073A/T 的 AA 基因型、A 等位基因频率增加,降低其与淋巴细胞表面受体的黏附力以及免疫抑制作用降低,同时增强效应 T 细胞、B 细胞的免疫功能,导致记忆或效应 T 细胞分泌增多,从而导致患者的恶化^[32,33]。不过本研究存在一定的不足,在本文中,仅探究了基因多态性与疾病之间的相关性,因此将在后续的研究中进行 IL-8 基因的具体功能及其发病机制的研究。

总之,食管鳞癌根治术后患者依然存在一定的死亡率,患者死亡与血清 IL-8 基因多态性存在相关性,同时多伴随有 IL-8 的高表达。IL-8 基因启动子 rs4073A/T 的 AA 基因型、A 等位基因、血清 IL-8 表达水平为导致患者死亡的主要因素。

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(上接第 1542 页)

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