

食管癌患者血清 β 2-MG、sCHE、PSGL-1的表达及其与纵隔镜术后肺部感染的关系

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Serum β 2-MG, sCHE, and PSGL-1 Expression in Patients with Esophageal Cancer and Their Association with Postoperative Lung Infection After Mediastinoscopy

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Abstract: Objective To investigate serum β 2-MG, sCHE, and PSGL-1 expression in patients with esophageal cancer and their relationship to lung infection after mediastinoscopy. **Methods** A total of 118 patients with esophageal cancer were selected and divided into infected and uninfected groups according to whether they developed lung infection after surgery. An automatic microbiological identification system was used to detect the pathogenic bacteria of lung infection. ELISA was used to detect the levels of β 2-MG, sCHE, and PSGL-1. Multivariate logistic regression was used to analyze the influencing factors of postoperative lung infection in patients with esophageal cancer. ROC curves were plotted to analyze the assessment value of serum β 2-MG, sCHE, and PSGL-1 on postoperative lung infection. **Results** Fifty-two strains of bacteria were isolated from the sputum of 38 patients with postoperative lung infections, and these included 35 (67.31%) Gram-negative, 14 (26.92%) Gram-positive, and 3 (5.77%) fungal strains. The difference in long-term smoking history between the infected and uninfected groups was statistically significant ($P < 0.05$). Serum β 2-MG and PSGL-1 levels were significantly higher and sCHE levels were significantly lower in the infected group than in the uninfected group ($P < 0.05$). Serum β 2-MG and PSGL-1 levels were sequentially higher ($P < 0.05$) and sCHE levels were sequentially lower ($P < 0.05$) in the mild, moderate, and severe lung infection groups. Long-term smoking history, β 2-MG, and PSGL-1 were risk factors affecting postoperative lung infection in patients with esophageal cancer ($P < 0.05$), and sCHE was a protective factor ($P < 0.05$). The AUCs of serum β 2-MG, sCHE, and PSGL-1 for assessing postoperative lung infections were 0.807, 0.845, and 0.800, respectively, and the AUC of the three combined factors for assessing postoperative lung infections was 0.954, which was superior to that assessed individually ($Z_{\text{combination vs. } \beta 2\text{-MG}} = 2.576$, $Z_{\text{combination vs. sCHE}} = 2.623$, $Z_{\text{combination vs. PSGL-1}} = 2.574$, all $P < 0.05$). **Conclusion** The serum levels of β 2-MG and PSGL-1 increase and the sCHE level decreases in patients with esophageal cancer and postoperative pulmonary infection, which are also related with lung infection. Combined testing can improve the evaluation value of postoperative pulmonary infection in patients.

Key words: Esophageal cancer; β 2-microglobulin; Cholinesterase; P-selectin glycoprotein ligand 1; Mediastinoscopy for esophageal cancer; Pulmonary infection

Funding: Joint Co-construction Project of Medical Science and Technology Tackling Program in Henan Province (No. LHGJ20230112)

Competing interests: The authors declare that they have no competing interests.

摘要: 目的 探究食管癌患者血清 β 2-MG、sCHE、PSGL-1表达及其与纵隔镜术后肺部感染的关系。**方法** 选取118例食管癌患者。根据患者术后是否发生肺部感染分为感染组和非感染组。全自动微生物鉴定系统检测肺部感染病原菌。ELISA检测 β 2-MG、sCHE、PSGL-1水平。多因素Logistic回归分析食管癌患者术后肺部感染的影响因素。绘制ROC曲线分析血清 β 2-MG、sCHE、PSGL-1对食管癌患者术后肺部感染的评估价值。

收稿日期: 2024-06-12; 修回日期: 2024-08-20
基金项目: 河南省医学科技攻关计划联合共建项目 (LHGJ20230112)

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管癌患者术后肺部感染的评估价值。

结果 38例术后肺部感染患者痰液中分离出52株菌株, 其中革兰氏阴性菌35株 (67.31%), 革兰氏阳性菌14株 (26.92%) 以及真菌3株 (5.77%)。感染组和未感染组长期吸烟史比较差异具有统计学意义 ($P < 0.05$)。感染组血清 β 2-MG、PSGL-1水平显著高于

未感染组 ($P<0.05$), sCHE水平显著低于未感染组 ($P<0.05$)。肺部感染轻度、中度和重度组血清 $\beta 2$ -MG、PSGL-1水平依次升高 ($P<0.05$), sCHE水平依次降低 ($P<0.05$)。长期吸烟史、 $\beta 2$ -MG和PSGL-1为影响食管癌患者术后肺部感染的危险因素 ($P<0.05$), sCHE为保护因素 ($P<0.05$)。血清 $\beta 2$ -MG、sCHE、PSGL-1评估食管癌患者术后肺部感染的AUC为0.807、0.845、0.800,三者联合评估食管癌患者术后肺部感染的AUC为0.954,三者联合优于单独评估 ($Z_{\text{联合 vs. } \beta 2\text{-MG}}=2.576$ 、 $Z_{\text{联合 vs. sCHE}}=2.623$ 、 $Z_{\text{联合 vs. PSGL-1}}=2.574$,均 $P<0.05$)。结论 食管癌术后肺部感染患者血清 $\beta 2$ -MG和PSGL-1水平显著升高, sCHE水平显著降低,还与肺部感染程度有关,联合检测可提高对患者术后肺部感染的评估价值。

关键词: 食管癌; $\beta 2$ 微球蛋白; 胆碱酯酶; P选择

糖素糖蛋白配体-1; 纵隔镜食管癌术; 肺部感染

中图分类号: R735.1

开放科学(资源服务)标识码(OSID):



0 引言

近年来食管癌发病率不断升高,其侵袭性强,死亡率也较高,食管癌早期症状不明显,容易被患者忽视,在确诊时往往已经是中晚期,中晚期已经出现进行性下咽困难,以致错过治疗的最佳时机,给患者家庭和生活带来沉重负担^[1-2]。纵隔镜食管癌术可避免开胸、能缓解患者术后疼痛,成为临床治疗食管癌的新方法,但由于该手术操作时间长,带来的手术创伤也较大,从而肺部感染风险加大^[3]。肺部感染是食管癌患者术后最常见的并发症,而且抗生素过度使用会提高病原菌耐药性,严重时引起肺部久治不愈,危及生命^[4]。因此在临床寻找与患者术后肺部感染有关的标志物对改善患者预后尤为重要。 $\beta 2$ 微球蛋白 ($\beta 2$ -microglobulin, $\beta 2$ -MG) 水平在出现癌细胞增加以及正常细胞发生破坏时会显著升高,还参与肿瘤患者肺部感染的进展过程^[5]。胆碱酯酶 (serum cholinesterase, sCHE) 是由肝脏细胞合成的水解酶,可反映肝脏的代谢以及合成功能,有研究发现其水平变化与肺部感染患者病情有关^[6]。P选择素糖蛋白配体-1 (P-selectin glycoprotein ligand-1, PSGL-1) 能激活下游趋化因子,促进其浸润肺泡间质组织,从而促进感染性疾病的进展^[7]。目前关于血清 $\beta 2$ -MG、sCHE、PSGL-1在食管癌患者术后肺部感染中的研究鲜有报道,因此本研究旨在探讨食管癌患者血清 $\beta 2$ -MG、sCHE、PSGL-1表达及其与纵隔镜食管癌术后肺部感染的关系。

1 资料与方法

1.1 一般资料

选取本院2021年8月至2023年8月收治的118例食管癌患者,其中男76例,女42例,根据患者术后是否发生肺部感染分为感染组和非感染组。纳入标准: (1) 符合食管癌诊断标准^[8],且经过临床确诊; (2) 均行纵隔镜食管癌术; (3) 符合肺部感染标准^[9]; (4) 资料完整; (5) 患者入组前未接受放疗或化疗; (6) 入组前未使用影响凝血系统的药物; (7) 患者及家属签署知情同意书。排除标准: (1) 合并其他恶性肿瘤患者; (2) 重要脏器功能障碍者; (3) 免疫系统疾病者; (4) 精神疾病者; (5) 入院前存在肺部感染者; (6) 其他部位感染者; (7) 存在吻合口瘘者。本研究经医院伦理委员会批准 (2020-07-017)。

1.2 方法

1.2.1 血清 $\beta 2$ -MG、sCHE和PSGL-1的检测 采集入选者术前静脉血 (空腹) 5 ml,分离血清后取上清液,采用ELISA检测 $\beta 2$ -MG、sCHE和PSGL-1水平,空白酶标板微孔中加入标准品和样品,两者均设置双孔检验,样品和标准孔中加入酶标记溶液,使用酶标仪 (Multiskan FC, 购自美国赛默飞世尔公司) 检测吸光度值 (波长450 nm),绘制标准品的标准曲线,然后计算血清 $\beta 2$ -MG、sCHE和PSGL-1的浓度。操作步骤严格按照说明书进行 (试剂盒购自武汉菲恩公司)。

1.2.2 病原菌的检测 患者术后3 d使用无菌0.9%氯化钠溶液漱口,采集3次痰液样本接种在培养基中,然后置于细菌培养仪 (BACT/ALERT 3D) 培养,使用全自动微生物鉴定系统 (型号VITEK2 COMPACT, 购自法国梅里埃公司) 对病原菌进行检测。

1.2.3 肺部感染判断^[9] 当以下5项中满足任意4项即可确诊: (1) $WBC \geq 1.2 \times 10^9/L$; (2) 体温保持在 $38.5^\circ C$ 以上; (3) 影像学检查显示肺内有浸润影和间质性改变等; (4) 临床症状存在咳嗽、发热以及胸痛等; (5) 听诊肺部时存在湿啰音。

1.2.4 肺部感染程度判断^[10] 肺部感染患者根据CURB-65评分进行分组,包含年龄 ≥ 65 岁、意识障碍、血尿素氮 >7 mmol/L、呼吸频率 ≥ 30 次/min、收缩压或舒张压 <90 mmHg或 ≤ 60 mmHg。满足其中一项为1分,分为轻度 (0~1分)、中度 (2~3分)、重度 (4~5分)。

1.3 统计学方法

使用SPSS 25.0软件处理数据。计量资料均经过Shapiro-Wilk正态性检验,符合正态分布的计量资料以 ($\bar{x} \pm s$) 表示,采用 t 检验;多组间比较采

用单因素方差分析,组间两两比较采用SNK-*q*检验;计数资料行 χ^2 检验,用*n*表示;食管癌患者术后肺部感染的影响因素采用多因素Logistic回归分析;绘制ROC曲线分析血清 β 2-MG、sCHE、PSGL-1对食管癌患者术后肺部感染的评估价值, $P<0.05$ 为差异有统计学意义。

2 结果

2.1 术后肺部感染病原菌分布情况

结果显示,38例术后肺部感染患者痰液中分离出52株菌株,其中革兰氏阴性菌35株(67.31%),革兰氏阳性菌14株(26.92%)以及真菌3株(5.77%),见表1。

表1 术后肺部感染病原菌分布情况
Table 1 Distribution of pathogenic bacteria in post-operative lung infections

Bacteria	Quantity (plants)	Proportions (%)
Gram-negative bacteria	35	67.31
<i>Klebsiella pneumoniae</i>	15	28.85
<i>Pseudomonas aeruginosa</i>	10	19.23
<i>Acinetobacter baumannii</i>	5	9.62
<i>Escherichia coli</i>	3	5.77
Other	2	3.85
Gram-positive bacteria	14	26.92
<i>Staphylococcus aureus</i>	6	11.54
Hemolytic <i>Staphylococcus</i>	4	7.69
<i>Enterococcus faecalis</i>	3	5.77
Other	1	1.92
Fungi	3	5.77
<i>Pseudomonas albicans</i>	3	5.77
Total	52	100.00

2.2 感染组和未感染组患者一般资料的比较

结果显示,感染组和未感染组长期吸烟史比较差异有统计学意义($P<0.05$),其他一般资料比较差异无统计学意义($P>0.05$),见表2。

2.3 感染组和未感染组患者血清 β 2-MG、sCHE、PSGL-1水平的比较

结果显示,感染组血清 β 2-MG和PSGL-1水平显著高于未感染组($P<0.05$),sCHE水平显著低于未感染组($P<0.05$),见表3。

2.4 不同感染程度患者血清 β 2-MG、sCHE和PSGL-1水平的比较

结果显示,轻度、中度和重度组血清 β 2-MG、PSGL-1水平依次升高($P<0.05$),sCHE水平依次降低($P<0.05$),见表4。

2.5 食管癌患者术后肺部感染的影响因素分析

结果显示,以食管癌患者术后是否发生肺部感染(否=0,是=1)作为因变量,以长期吸烟史

表2 感染组和未感染组患者一般资料的比较
Table 2 Comparison of general information of patients between infected and uninfected groups

General information	Infected group (n=38)	Uninfected group (n=80)	t/χ^2	<i>P</i>
Age(years)	63.12 $\pm$ 5.38	64.16 $\pm$ 5.37	0.982	0.328
Gender			0.038	0.845
Male	24(63.16)	52(65.00)		
Female	14(36.84)	28(35.00)		
BMI(kg/m ²)	22.89 $\pm$ 1.67	22.91 $\pm$ 1.68	0.068	0.952
Duration of disease(years)	7.81 $\pm$ 2.67	7.24 $\pm$ 2.64	1.092	0.277
Hypertension	9(23.68)	12(15.00)	1.328	0.249
Diabetes	12(31.58)	21(26.25)	0.363	0.547
Long history of smoking	20(52.63)	21(26.25)	7.908	0.005
Pathological type			0.301	0.583
Squamous carcinoma	32(84.21)	64(80.00)		
Adenocarcinoma	6(15.79)	16(20.00)		
Clinical staging			0.010	0.920
I	12(31.58)	26(32.50)		
II	26(68.42)	54(67.50)		
Tumour site			1.290	0.256
Upper/Middle segments	34(89.47)	65(81.25)		
Lower segments	4(10.53)	15(18.75)		
Surgical time(h)			0.420	0.517
$\leq$ 4	18(47.37)	43(53.75)		
$>$ 4	20(52.63)	37(46.25)		
Intraoperative haemorrhage(ml)			0.209	0.647
$\leq$ 500	29(76.32)	64(80.00)		
$>$ 500	9(23.68)	16(20.00)		

Note: BMI: body mass index.

表3 感染组和未感染组患者血清 β 2-MG、sCHE、PSGL-1水平的比较
Table 3 Comparison of serum β 2-MG, sCHE, and PSGL-1 levels of patients between infected and uninfected groups

Index	Uninfected group (n=80)	Infected group (n=38)	<i>t</i>	<i>P</i>
β 2-MG (μ g/L)	3.09 $\pm$ 0.86	4.60 $\pm$ 0.88	8.846	<0.001
sCHE (kU/L)	4.20 $\pm$ 0.89	2.96 $\pm$ 0.56	7.871	<0.001
PSGL-1 (U/ml)	254.68 $\pm$ 43.25	316.25 $\pm$ 44.50	7.159	<0.001

Notes: β 2-MG: β 2-microglobulin; sCHE: serum cholinesterase; PSGL-1: P-selectin glycoprotein ligand-1.

(是=1,否=0)、 β 2-MG、sCHE、PSGL-1(实测值)为自变量。多因素Logistic回归分析显示长期吸烟史、 β 2-MG和PSGL-1为影响食管癌患者术后肺部感染的危险因素($P<0.05$),sCHE为保护因素($P<0.05$),见表5。

2.6 血清 β 2-MG、sCHE和PSGL-1对食管癌患者术后肺部感染的评估价值

ROC曲线结果显示,血清 β 2-MG、sCHE、PS-

表 4 不同感染程度患者血清β2-MG、sCHE和PSGL-1水平的比较

Table 4 Comparison of serum β2-MG, sCHE, and PSGL-1 levels by degree of infection

Index	Light group (n=18)	Medium group (n=12)	Heavy group (n=8)	F	P
β2-MG (μg/L)	3.68±0.75	4.96±0.86 ^a	6.15±1.20 ^{ab}	22.686	<0.001
sCHE (kU/L)	3.54±0.64	2.74±0.53 ^a	2.03±0.41 ^{ab}	21.118	<0.001
PSGL-1 (U/ml)	286.54±40.21	320.74±46.37 ^a	376.38±51.37 ^{ab}	11.327	<0.001

Notes: a: $P<0.05$, compared with the light group; b: $P<0.05$, compared with the medium group.

表 5 食管癌患者术后肺部感染的影响因素分析

Table 5 Influencing factors of postoperative lung infection in patients with esophageal cancer

Factors	β	SE	Wald χ ²	P	OR	95%CI
Long history of smoking	1.275	0.245	27.086	<0.001	3.579	2.214-5.785
β2-MG	1.436	0.356	16.266	<0.001	4.203	2.092-8.445
sCHE	-0.667	0.301	4.917	0.027	0.513	0.284-0.925
PSGL-1	1.377	0.468	8.660	0.003	3.964	1.584-9.920

GL-1评估食管癌患者术后肺部感染的AUC分别为0.807、0.845、0.800，三者联合评估食管癌患者术后肺部感染的AUC为0.954，三者联合优于单独评估（ $Z_{\text{联合vs. } \beta 2\text{-MG}}=2.576$ 、 $Z_{\text{联合vs. sCHE}}=2.623$ 、 $Z_{\text{联合vs. PSGL-1}}=2.574$ ，均 $P<0.05$ ），见图1、表6。

3 讨论

食管癌好发于上消化道，患者早期症状不明显，可能有乏力、恶心等非特异性症状，而且随着老龄化加剧，其发病率不断升高^[11]。临床治疗以手术为主，然而肺部感染是术后发生率较高的并发症，因为手术带来的创伤以及疼痛等都会对呼吸道吞咽等产生影响，而且肺部防御机制较弱，从而增加肺部感染风险^[12]。本研究结果显示，革兰氏菌和真菌均能引起患者出现肺部感染，而且以肺炎克雷伯菌感染为主，这可能是因为该菌分布较为广泛，

表 6 血清β2-MG、sCHE、PSGL-1评估食管癌患者术后肺部感染的价值

Table 6 Value of serum β2-MG, sCHE, and PSGL-1 in assessing postoperative lung infection in patients with esophageal cancer

Factors	AUC	95%CI	Sensitivity (%)	Specificity (%)	Cut-off value
β2-MG	0.807	0.724-0.889	76.24	79.57	4.102 μg/L
sCHE	0.845	0.774-0.916	78.03	79.12	3.201 kU/L
PSGL-1	0.800	0.701-0.900	80.34	77.31	303.142 U/ml
Combination	0.954	0.913-0.996	96.26	75.27	-

Note: -: no content.

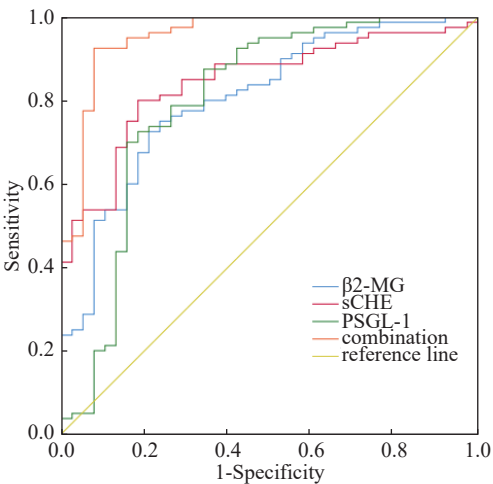


图 1 ROC曲线分析血清β2-MG、sCHE、PSGL-1对食管癌患者术后肺部感染的评估价值

Figure 1 Value of serum β2-MG, sCHE, and PSGL-1 in the assessment of postoperative lung infection in patients with esophageal cancer analyzed by ROC curve

还能在组织表面黏附，且与增加细菌耐药性有关^[13]。

β2-MG是一种单链多肽低分子蛋白质，主要由淋巴细胞分泌产生，以游离的形式存在于细胞外液中，也是非特异性的肿瘤标志物^[14]。正常情况下，β2-MG水平在机体正常时较低，然而在癌症患者血清中普遍升高，是因为癌症患者免疫系统被破坏，恶性肿瘤细胞快速增殖，加快合成β2-MG^[15]。β2-MG在弥漫性大B细胞淋巴瘤患者血清中显著升高，也证实癌细胞快速增加会导致大量释放β2-MG^[16]。有研究发现β2-MG在多发性骨髓瘤合并肺部感染患者血清中显著升高，可为治疗该病提供参考^[5]。还有研究发现，血清β2-MG在多发性骨髓瘤患者肺部感染中明显升高，化疗前检测其水平可预测肺部感染^[17]。本研究结果发现，感染组血清β2-MG水平显著升高，轻度、中度和重度感染组血清β2-MG水平依次升高，与已有研究结果相似，说明其参与食管癌患者术后肺部感染的进展，而且随着病情严重程度的增加，其水平也在不断升高。

sCHE主要由乙酰胆碱酯酶和丁酰胆碱酯酶组成，血清中主要以丁酰胆碱酯酶为主，能将神经递

质乙酰胆碱分解成为胆碱和乙酸来调节机体气道反应^[18]。sCHE主要在肝脏中分泌,可评估肝脏的功能状态,其活性在肝损伤时降低,对呼吸衰竭引起的肝损伤等可及时应答^[19]。当患者肺部发生感染后,细菌以及产生的内毒素激活中性粒细胞,导致蛋白质类多种物质增多,阻止肝脏合成sCHE,而且在感染时患者体内的血脂代谢功能受到限制,导致sCHE在血液中运载能力下降^[20]。还有研究发现血清sCHE在机械通气并发肺部感染患者中明显降低,其在一定程度上可反映病情严重程度,并且与患者预后有关^[21]。本研究结果发现,感染组血清sCHE水平显著降低,而且随着病情严重程度的增加,其水平不断降低,说明sCHE降低会对患者肺部感染产生影响。

PSGL-1大量分布在白细胞表面,是一种中性粒细胞调控相关因子,能募集下游的一种中性粒细胞酶,促进释放下游趋化因子,从而导致炎症反应的扩散^[22]。PSGL-1升高可激活下游炎症信号通路NF- κ B,促进炎症浸润肺泡支气管平滑肌细胞,最后促进支气管的狭窄等,致使病情进展^[23]。PSGL-1还是P-选择素配体,能与P-选择素结合促进血小板-白细胞聚集体形成,从而促进炎症反应升高^[24]。有研究发现PSGL-1在慢性阻塞性肺疾病患者血清中显著升高,还可对患者肺部感染进行诊断^[25]。还有研究发现血清PSGL-1在心外科ICU术后感染患者中明显升高,其表达水平与感染进展有关,可通过临床监测其水平变化来改善患者预后^[26]。本研究结果发现,感染组血清PSGL-1水平显著升高,而且随着病情严重程度的增加,其水平不断升高,说明PSGL-1可能在患者肺部感染时发挥重要作用。

本研究进一步发现,长期吸烟史、 β 2-MG和PSGL-1为影响食管癌患者术后肺部感染的危险因素,sCHE为保护因素,说明在临床检测其水平变化可有效评估患者的肺部感染情况;根据ROC曲线得知,血清 β 2-MG、sCHE、PSGL-1三者联合评估食管癌患者术后肺部感染的AUC为0.954,优于单独评估,说明三者联合检测可有效提高对食管癌患者术后肺部感染的评估价值,为临床医师优化治疗方案提供参考。

综上所述,食管癌术后肺部感染患者血清 β 2-MG、PSGL-1水平显著升高,sCHE水平显著降低,还与肺部感染程度有关,联合检测可提高对患者术后肺部感染的评估价值。本研究患者肺部感染的转归中有4例未见好转,其余均慢慢恢复,后续将扩大样本量进一步验证。

利益冲突声明:

所有作者均声明不存在利益冲突。

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