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血清 PCT、CRP 与 sTREM-1 在肺癌患者术后肺部感染中表达及其诊断价值分析 *

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摘要 目的:探究血清降钙素原(PCT)、C-反应蛋白(CRP)与可溶性人髓系细胞触发受体-1(sTREM-1)在肺癌患者术后肺部感染中表达及其诊断价值。**方法:**选择 2016 年 2 月至 2019 年 10 月期间在我院行肺癌根治术的 420 例肺癌患者作为研究对象,根据术后患者是否发生肺部感染进一步划分为 380 例未感染组和 40 例感染组。感染组根据治疗结局进一步划分为 29 例治疗好转亚组与 11 例未好转亚组。采用酶联免疫吸附法检测各组的血清 PCT、CRP 与 sTREM-1 水平,采用受试者工作特征(ROC)曲线分析血清 PCT、CRP 和 sTREM-1 对肺癌患者术后肺部感染的预测价值。**结果:**与未感染组相比,感染组手术后血清 PCT、CRP 和 sTREM-1 水平均明显升高($P<0.05$)。与治疗好转亚组相比较,治疗未好转亚组手术后以及感染后血清 PCT、CRP 和 sTREM-1 水平均明显升高($P<0.05$)。ROC 曲线显示,PCT 的曲线下面积(AUC)为 0.713,最佳截断值为 1.23 ng/mL,灵敏度、特异度分别为 0.81、0.79,准确度为 0.82;CRP 的 AUC 为 0.752,最佳截断值为 36.07 mg/L,灵敏度、特异度分别为 0.83、0.81,准确度为 0.83;sTREM-1 的 AUC 为 0.792,最佳截断值为 20.58 pg/mL,灵敏度、特异度分别为 0.86、0.84,准确度为 0.85;PCT、CRP 联合 sTREM-1 预测肺癌患者术后肺部感染的 AUC 为 0.884,灵敏度、特异度分别为 0.89、0.91,准确度为 0.92。**结论:**肺癌根治术后肺部感染发生与患者血清 PCT、CRP 和 sTREM-1 水平相关,早期联合检测血清 PCT、CRP 和 sTREM-1 有助于预测肺癌根治术患者肺部感染发生风险,在肺癌根治术后肺部感染的预测和诊断中具有一定临床价值。

关键词:肺癌;肺部感染;降钙素原;C-反应蛋白;可溶性人髓系细胞触发受体 1

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Expression of Serum PCT, CRP and sTREM-1 in Patients with Lung Cancer and Its Diagnostic Value*

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ABSTRACT Objective: To investigate the expression and diagnostic value of serum Procalcitonin (PCT), C-reactive protein (CRP) and Soluble human myeloid cell trigger receptor-1 (strom-1) in postoperative pulmonary infection in patients with lung cancer. **Methods:** 420 cases of lung cancer patients who underwent radical resection of lung cancer in our hospital from February 2016 to October 2019 were selected as the study subjects. According to whether or not pulmonary infection occurred after the surgery, the patients were further divided into 380 cases of uninfected group and 40 cases of infected group. The infection group was further divided into 29 cases improved subgroup and 11 cases not improved subgroup according to treatment outcome. Serum PCT, CRP and sTREM-1 levels in each group were detected by ELISA, and the predictive value of PCT, CRP and sTREM-1 on postoperative pulmonary infection in lung cancer patients was analyzed by ROC curve. **Results:** Compared with the uninfected group, serum PCT, CRP and sTREM-1 levels in the infected group were significantly increased after surgery (all $P<0.05$). Serum PCT, CRP and sTREM-1 levels were significantly increased in the unimproved subgroup after surgery and after infection (all $P<0.05$). ROC curve shows that the AUC of PCT was 0.713, the best cutoff value was 1.23 ng/mL, the sensitivity and specificity were 0.81, 0.79, and the accuracy was 0.82. the AUC of CRP was 0.752, the best cutoff value was 36.07 mg/L, the sensitivity and specificity were 0.83, 0.81, and the accuracy was 0.83. the AUC of strom-1 was 0.792, the best cutoff value was 20.58 pg/mL, the sensitivity and specificity were 0.86, 0.84, respectively. The accuracy was 0.85, the AUC of PCT and CRP combined with srem-1 was 0.884, the sensitivity and specificity were 0.89 and 0.91 respectively, and the accuracy was 0.92. **Conclusion:** The occurrence of pulmonary infection after radical resection of lung cancer is related to serum PCT, CRP and sTREM-1 levels. Early combined detection of serum PCT, CRP and sTREM-1 can help predict the risk of pulmonary infection in patients

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undergoing radical resection of lung cancer, and has certain clinical value in the prediction and diagnosis of pulmonary infection after radical resection of lung cancer.

Key words: Lung cancer; Pulmonary infection; Procalcitonin; C-reactive protein; Soluble myeloid cells trigger receptor 1

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前言

2018 年肺癌的新发病例数和死亡病例数分别占癌症新发病例数和死亡病例数的 11.6% 和 18.4%，均排在恶性肿瘤榜首，是死亡率和发病率最高的恶性肿瘤，严重危害人们的生命健康^[1]。肺癌根治术是治疗肺癌患者的主要方式，但肺癌根治术患者由于手术造成身体机能下降，术后容易发生肺部感染，病情严重时会导致患者死亡^[2,3]，因此在手术前对患者进行合理评估以减少术后肺部感染的发生显得尤为必要。降钙素原(procalcitonin, PCT)是降钙素的前体蛋白分子，在健康人体内 PCT 含量极低，当人体出现炎症反应时 PCT 水平异常升高，是体内炎症反应的重要标志物分子^[4]。C-反应蛋白(C-reactive protein, CRP)主要由肝脏细胞分泌合成，机体在感染和受到创伤时会引起体内 CRP 水平急剧升高，在慢性阻塞性肺疾病和肺结核等肺部炎症疾病患者中均能够检测到血清 CRP 水平升高^[5,6]。可溶性人髓系细胞触发受体-1(soluble Triggering Receptor Expressed on Myelocytes-1, sTREM-1)能够抑制 T 淋巴细胞功能，造成机体的免疫功能损伤，同时与炎症反应的发生密切相关，在炎症性疾病的诊断和治疗中具有一定临床意义^[7]。本研究通过检测肺癌根治术后肺癌患者血清 PCT、CRP 和 sTREM-1 水平，旨在探讨其在术后肺部感染中的表达及其对术后肺部感染的诊断价值，现报道如下。

1 资料与方法

1.1 一般资料

选择 2016 年 2 月至 2019 年 10 月期间在我院行肺癌根治术的 420 例肺癌患者作为研究对象，纳入标准：(1)经病理学诊断确诊为肺癌；(2)无自身免疫性疾病；(3)适宜进行肺癌根治术；(4)入院前未接受过放化疗治疗。排除标准：(1)合并多种肿瘤；(2)存在全身性感染性疾病；(3)入院前 3 个月内接受过抗炎抗菌治疗；(4)肝肾功能障碍患者。根据术后患者是否发生肺部感染^[8]将肺癌患者进一步划分为 380 例未感染组和 40 例感染组，未感染组中男性 196 例，女性 184 例；年龄 45-76 岁，平均年龄(60.84±14.92)岁；TNM 分期 I 期 180 例，II 期 144 例，III 期 56 例；小细胞肺癌 40 例，非小细胞肺癌 152 例，中央型肺癌 96 例，周围型肺癌 92 例。感染组男性 22 例，女性 18 例；年龄 45-77 岁，平均年龄(61.28±15.18)岁；TNM 分期 I 期 19 例，II 期 15 例，III 期 6 例；小细胞肺癌 2 例，非小细胞肺癌 16 例，中央型肺癌 10 例，周围型肺癌 12 例。未感染组患者和感染组患者在性别、年龄、TNM 分期和肺癌类型等一般资料比较差异无统计学意义($P>0.05$)，具有可比性。根据感染组患者的治疗结局进一步划分为 29 例治疗好转亚组与 11 例治疗未好转亚组。研究开展前均与患者签署知情同意书，研究的开展经过医院伦理委员会批准。

1.2 血清 PCT、CRP 与 sTREM-1 水平检测

于手术前(T_0)、手术后 1d(T_1)、手术后 3d(T_2)、感染后 1d(T_3)和感染后 3d(T_4)分别采集患者的晨时空腹静脉血 3 mL，室温静置 1h 后 8000 r/min 离心 20 min，离心半径 12.5 cm，收集上清液至另一洁净离心管中，冻存于 -80℃ 待测。采用酶联免疫吸附法对血清 PCT、CRP 与 sTREM-1 水平进行检测，分别使用 PCT 检测试剂盒(上海晶抗生物工程有限公司)、CRP 检测试剂盒(上海钰博生物科技有限公司)以及 sTREM-1 检测试剂盒(上海恒渡生物科技有限公司)对血清 PCT、CRP 与 sTREM-1 水平进行检测，实验操作严格按照试剂盒说明书进行。

1.3 统计学分析

采用 SPSS20.0 统计学软件对临床数据进行分析。平均年龄、血清 PCT、CRP 和 sTREM-1 水平等计量资料采用平均值±标准差的方式来表示，两组间比较采用独立样本 t 检验。多组间比较采用方差分析。采用受试者工作特征(Receiver operating characteristic, ROC)曲线对血清 PCT、CRP 和 sTREM-1 对肺癌患者术后肺部感染的预测价值进行分析， $P<0.05$ 则表示差异具有统计学意义。

2 结果

2.1 未感染组和感染组手术前后血清 PCT、CRP 和 sTREM-1 水平比较

T_0 时，未感染组和感染组血清 PCT、CRP 和 sTREM-1 水平比较，组间差异均无统计学意义($P>0.05$)。 T_1 及 T_2 时，感染组血清 PCT、CRP 和 sTREM-1 水平均明显高于未感染组，组间差异具有统计学意义($P<0.05$)，见表 1。

2.2 治疗好转亚组和治疗未好转亚组各时间点血清 PCT、CRP 和 sTREM-1 水平比较

T_0 时，治疗好转亚组和治疗未好转亚组血清 PCT、CRP 和 sTREM-1 水平比较，组间差异均无统计学意义($P>0.05$)。 T_1 、 T_2 、 T_3 及 T_4 时，治疗未好转亚组血清 PCT、CRP 和 sTREM-1 水平均明显高于治疗好转亚组，组间差异具有统计学意义($P<0.05$)，见表 2。

2.3 血清 PCT、CRP 和 sTREM-1 对肺癌患者术后肺部感染的预测价值

采用 ROC 曲线评估血清 PCT、CRP 和 sTREM-1 对肺癌患者术后肺部感染的预测价值，结果显示 PCT 的曲线下面积(Area under curve, AUC)为 0.713, 95%CI: 0.602~0.824，最佳截断值为 1.23 ng/mL，灵敏度、特异度分别为 0.81、0.79，准确度为 0.82；CRP 的 AUC 为 0.752, 95%CI: 0.646~0.857，最佳截断值为 36.07 mg/L，灵敏度、特异度分别为 0.83、0.81，准确度为 0.83；sTREM-1 的 AUC 为 0.792, 95%CI: 0.694~0.889，最佳截断值为 20.58 pg/mL，灵敏度、特异度分别为 0.86、0.84，准确度为 0.85；PCT、CRP 联合 sTREM-1 预测肺癌患者术后肺部感染

的 AUC 为 0.884,95%CI:0.813~0.955,灵敏度、特异度分别为 0.89、0.91,准确度为 0.92,见图 1。

表 1 未感染组和感染组手术前后血清 PCT、CRP 和 sTREM-1 水平比较

Table 1 Comparison of serum PCT, CRP and sTREM-1 levels before and after surgery between the uninfected group and the infected group

Groups	n	Time	PCT(ng/mL)	CRP(mg/L)	sTREM-1(pg/mL)
Uninfected group	380	T ₀	0.30±0.05	11.78±1.93	7.86±1.29
		T ₁	0.76±0.12	20.18±3.31	12.75±2.09
		T ₂	0.71±0.12	25.69±4.21	13.06±2.14
		F	0.566	0.460	0.890
		P	0.575	0.648	0.379
Infected group	40	T ₀	0.31±0.05	12.14±1.84	8.05±1.22
		T ₁	2.49±0.38*	45.63±6.91*	37.86±5.74*
		T ₂	2.45±0.37*	60.71±9.20*	38.59±5.85*
		F	1.649	1.469	1.572
		P	0.101	0.144	0.118

Note: Compared with the uninfected group, * $P<0.05$.

表 2 治疗好转亚组和治疗未好转亚组各时间点血清 PCT、CRP 和 sTREM-1 水平比较

Table 2 Comparison of serum PCT, CRP and sTREM-1 levels at each time point between the improved subgroup with and the not improved subgroup

Groups	n	Time	PCT(ng/mL)	CRP(mg/L)	sTREM-1(pg/mL)
Improved subgroup	29	T ₀	0.30±0.04	12.01±1.69	8.01±1.13
		T ₁	2.41±0.34	42.38±5.97	33.49±4.72
		T ₂	2.29±0.32	53.17±7.63	31.27±4.40
		T ₃	2.36±0.33	56.71±7.99	34.71±4.89
		T ₄	2.38±0.34	58.74±8.27	36.59±5.15
		F	0.933	0.955	0.999
		P	0.357	0.346	0.324
Not improved subgroup	11	T ₀	0.31±0.05	12.48±1.71	8.16±1.12
		T ₁	2.70±0.37*	54.20±7.42*	49.38±6.76*
		T ₂	2.87±0.39*	77.95±10.68*	54.25±7.43*
		T ₃	3.35±0.46*	86.27±11.82*	68.39±9.37*
		T ₄	3.82±0.52*	98.71±13.52*	79.62±10.91*
		F	0.613	0.566	0.759
		P	0.544	0.575	0.452

Note: Compared with the improved subgroup, * $P<0.05$.

3 讨论

在恶性肿瘤当中,肺癌的发生率和死亡率最高,因此肺癌患者的治疗得到业界的广泛关注^[9]。肺癌根治术是肺癌的主要治疗手段,但术后肺部感染的发生率和死亡率均较高^[10,11]。因此在肺癌根治术前进行综合评估以减少术后肺部感染的发生显得尤为重要。

PCT 是降钙素的前体物质,与脓毒症及出血热等感染性疾病的发生及进展密切相关^[12,13]。PCT 一方面能够调节干扰素信号通路的活化,进而调节机体的免疫功能,如 He 等人^[14]的研究发现 PCT 能够抑制干扰素- γ 蛋白的表达,另一方面 PCT 受到信号转导与转录激活因子 3 (Signal transduction and

transcriptional activator 3, STAT3) 信号通路的调节,如 Ching 等人^[15]的研究发现 STAT3 能够抑制 PCT 的表达,进而抑制细菌感染。同时,PCT 表达上调会对组织细胞造成损伤,如 Wagner 等人^[16]的研究发现 PCT 会造成上皮细胞损伤,使其功能和增殖活性下降。本研究发现感染组及治疗未好转亚组血清 PCT 水平相较未感染组和治疗好转亚组有明显的升高,表明肺部感染会引起患者体内 PCT 水平的明显升高,同时血清 PCT 水平与肺部感染患者的转归相关。分析其原因可能是由于肺部感染会抑制 STAT3 信号通路,并且解除 STAT3 对 PCT 的抑制,导致患者体内 PCT 明显升高,进而抑制干扰素信号通路的活化,导致巨噬细胞免疫机能下降,促进肺部感染。同时 PCT 水平升高可能对肺部组织细胞造成损伤,导致肺部感染情况恶化^[17]。

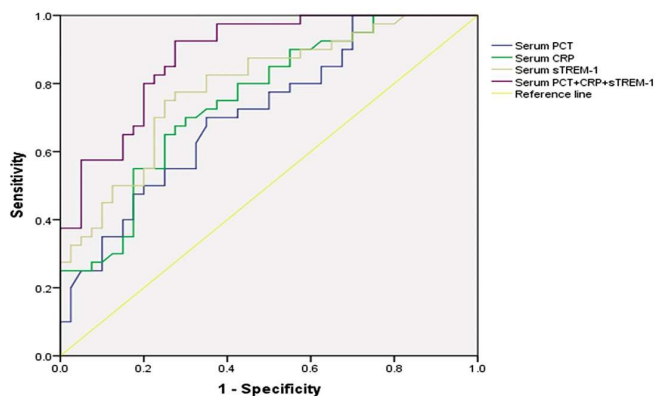


图1 血清 PCT、CRP 和 sTREM-1 对肺癌患者术后肺部感染的预测价值

Fig.1 The predictive value of serum PCT, CRP and sTREM-1 for postoperative pulmonary infection in patients with lung cancer

CRP 是一种炎症促进因子,与重症肺炎和肺纤维化等肺部炎症疾病发病密切相关^[18,19]。CRP 一方面能够调节细胞外信号调节激酶(Extracellular Signal Regulated Kinase, ERK)信号通路并参与细胞增殖和分裂。如 Zhang 等人^[20]的研究发现 CRP 能够抑制 ERK 信号通路,进而抑制细胞的上皮-间质转化。另一方面 CRP 蛋白的表达受到 Janus 激酶(Janus kinase, JAK)信号通路的调节,如 Febvre 等人^[21]的研究发现 JAK 信号通路的抑制会下调 CRP 蛋白的表达。本研究发现感染组及治疗未好转亚组血清 CRP 水平相较未感染组和治疗好转亚组有明显的升高,该结果表明肺部感染会引起患者体内 CRP 水平的明显升高,同时血清 CRP 水平与肺部感染患者的转归相关。分析其原因可能是由于肺部感染会激活 JAK 信号通路,进而上调 CRP 蛋白的表达,因此在肺部感染患者 CRP 水平明显升高,从而抑制 ERK 信号通路,进而抑制肺组织细胞增殖和代谢,使得损伤的肺部组织细胞无法及时进行自我修复而死亡,从而促进肺部感染的恶化^[22,23]。

sTREM-1 与炎症性疾病的发生发展密切相关,在风湿性关节炎和脓毒症等炎症疾病患者体内 sTREM-1 水平上调^[24,25]。sTREM-1 的表达受到核因子 κ B (nuclear factor κ B, NF- κ B)炎症信号通路的调控,而白介素-6(interleukin-6, IL-6)和 PCT 等炎症因子均是 NF- κ B 炎症信号通路的下游靶基因。如 Dong 等人^[26]的研究发现 NF- κ B 炎症信号通路的活化能够上调 sTREM-1 的表达。而 Derek 等人^[27]的研究发现 sTREM-1 的表达水平与 CRP、IL-6 和 PCT 等炎症因子的表达均呈正相关。同时 sTREM-1 参与免疫调节,如 Cui 等人^[28]的研究发现 sTREM-1 能够抑制 T 淋巴细胞的分化。本研究发现感染组及治疗未好转亚组血清 sTREM-1 水平相较未感染组和治疗好转亚组有明显的升高,该实验结果表明肺部感染会引起患者体内 sTREM-1 水平的明显升高,同时血清 sTREM-1 水平与肺部感染患者的转归相关。分析其原因可能是由于肺部感染会促进炎症反应的发生,导致 NF- κ B 炎症信号通路的活化,继而上调 sTREM-1 的表达,使得 sTREM-1 水平明显升高^[29]。同时 sTREM-1 水平升高会抑制机体的免疫功能,导致机体对外界病原微生物的抵抗力下降,使得患者肺部感染情况恶化^[30]。

结果还显示,血清 PCT、CRP 联合 sTREM-1 预测肺癌患者术后肺部感染的价值较高,明显优于血清 PCT、CRP、sTREM-1

单独预测的价值。提示早期检测肺癌根治术后患者血清 PCT、CRP、sTREM-1 水平,可作为临床预测术后肺部感染发生风险的重要手段。

综上所述,血清 PCT、CRP、sTREM-1 水平异常升高与肺癌根治术后肺部感染发生密切相关,早期联合检测有助于预测肺癌根治术后肺部感染发生风险,血清 PCT、CRP、sTREM-1 在肺癌根治术后肺部感染的预测和诊断中具有一定临床价值。

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