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·临床研究·

# 胆管癌患者血清肿瘤型 M2 丙酮酸激酶水平变化及临床意义

王金[1]，赵一洁[2]，尚培中[1]，孙永杰[3]，贾国洪[1]，李晓武[1]

（中国人民解放军第二五一医院 1. 普通外科 3. 心胸外科，河北 张家口 075000；2. 河北北方学院图书馆，河北 张家口 075000）

**摘 要**

**背景与目的：**胆管癌临床起病隐匿，早期诊断困难，患者确诊时大多数已属晚期，并失去了根治性治疗的机会。因此，寻找一种新的生物标志物用于胆管癌早期诊断或评估治疗及预后具有极为重要的意义。肿瘤型 M2 丙酮酸激酶（TuM2-PK）是近年来发现的一种肿瘤标志物，可能与多种肿瘤相关。因此，本研究探讨胆管癌患者血清 TuM2-PK 水平的变化及其在胆管癌诊断中的价值。

**方法：**比较 54 例胆管癌患者、32 例胆管结石患者及 25 例健康体检者血清 TuM2-PK 水平；以 TuM2-PK>15 U/mL 为阳性判定标准，分析胆管癌患者血清 TuM2-PK 阳性率与临床参数的关系。采用 ROC 曲线分析血清 TuM2-PK 水平对胆管癌的诊断效能，并与 CA19-9 比较。最后分别比较胆管癌患者、胆管结石患者以及胆管癌患者中根治性手术、姑息性手术患者手术前后血清 TuM2-PK 水平的变化。

**结果：**胆管癌患者血清 TuM2-PK 水平明显高于胆管结石患者及健康人群（均 $P<0.05$），而后两者间差异无统计学意义（$P>0.05$）；胆管癌患者血清 TuM2-PK 阳性率与肿瘤分化程度、淋巴结转移、临床 TNM 分期明显有关（均 $P<0.05$）。血清 TuM2-PK 诊断胆管癌的 AUC 值为 0.781，灵敏度为 84.81%、特异度为 80.00%；血清 CA19-9 诊断胆管癌的灵敏度为 79.63%、特异度为 84.00%；两者联合检测的敏感度增高，但特异度降低。胆管癌患者术后血清 TuM2-PK 水平较术前明显降低（$P<0.05$），胆管结石患者手术前后血清 TuM2-PK 水平无明显差异（$P>0.05$）；胆管癌患者中，行根治性手术患者术后血清 TuM2-PK 水平较术前明显降低（$P<0.05$），姑息性手术患者无明显变化（$P>0.05$）。

**结论：**胆管癌患血清 TuM2-PK 水平升高，其水平与肿瘤的进展及治疗效果密切相关，对于胆管癌的早期诊断以及治疗效果与预后的判断有一定价值。

**关键词** 胆管肿瘤 / 诊断；丙酮酸激酶；生物标记，肿瘤

**中图分类号：**R735.8

# Changes in serum level of tumor type M2 pyruvate kinase in patients with cholangiocarcinoma and its clinical significance

WANG Jin[1], ZHAO Yijie[2], SHANG Peizhong[1], SUN Yongjie[3], JIA Guohong[1], LI Xiaowu[1]

*(1. Department of General Surgery 3. Department of Cardiothoracic Surgery, the 251st Hospital of PLA, Zhangjiakou, Hebei 075000, China; 2. Library of Hebei North University, Zhangjiakou, Hebei 075000, China)*

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**作者简介：**王金，中国人民解放军第二五一医院主治医师，主要从事普通外科方面的研究。

**通信作者：**尚培中，Email: spz251@163.com

**Abstract**

**Background and Aims:** Cholangiocarcinoma is insidious in its clinical onset, its early detection is difficult, and many patients are at an advanced stage at the time of diagnosis, thus lose the chance of radical treatment. Therefore, the search for a new biomarker for early diagnosis and prediction of treatment efficacy and prognosis of cholangiocarcinoma is of great importance. The tumor type M2 pyruvate kinase (TuM2-PK) To investigate the value of serum tumor type M2 pyruvate kinase is a tumor biomarker discovered in recent years, and may be associated with a variety of tumors. This study was conducted to investigate the change in serum TuM2-PK level in cholangiocarcinoma patients and its diagnostic value for cholangiocarcinoma.

**Methods:** The serum TuM2-PK levels in 54 patients with cholangiocarcinoma, 32 patients with bile duct stones and 25 subjects undergoing health maintenance examination were compared. Using TuM2-PK>15 U/mL as the positive standard, the relations of positive rate of the serum TuM2-PK with clinical factors of the cholangiocarcinoma patients were analyzed. The diagnostic efficacy of the serum TuM2-PK level for cholangiocarcinoma was determined by using ROC curve analysis, which was compared with that of CA19-9. Finally, the pre- and postoperative changes in serum TuM2-PK level in cholangiocarcinoma patients and patients with bile duct stones as well as in cholangiocarcinoma patients undergoing radical operation or palliative operation were respectively compared.

**Results:** The serum TuM2-PK level in cholangiocarcinoma patients was significantly higher than that in patients with bile duct stones or healthy individuals (both $P<0.05$), while it showed no significant difference between the latter two groups ($P>0.05$). The positive rate of TuM2-PK in the cholangiocarcinoma patients was significantly associated with the degree of tumor differentiation, lymph node metastasis and clinical TNM stage (all $P<0.05$). The AUC value of serum TuM2-PK for diagnosis of cholangiocarcinoma was 0.781, with a sensitivity of 84.81% and a specificity of 80.00%, and the sensitivity and specificity of serum CA19-9 for diagnosis of cholangiocarcinoma were 79.63% and 84.00. The sensitivity was increased but the specificity was decreased by their combined examination. The serum TuM2-PK level was significantly reduced after surgery than that before surgery in cholangiocarcinoma patients ($P<0.05$), but showed no significant difference in patients with bile duct stones before and after surgery ($P>0.05$); in cholangiocarcinoma patients, the serum TuM2-PK level was significantly reduced after surgery than that before surgery in cases undergoing radical surgery ($P<0.05$), but showed no significant change in those undergoing palliative surgery before and after surgery ($P>0.05$).

**Conclusion:** The serum TuM2-PK level is increased in cholangiocarcinoma patients, and its level is closely related to the tumor progression and treatment efficacy. So, it has certain value in early diagnosis and estimation of treatment effect and prognosis for cholangiocarcinoma.

**Key words** Bile Duct Neoplasms/diag; Pyruvate Kinase; Biomarkers, Tumor

**CLC number:** R735.8

胆管癌起源于胆管上皮细胞，是严重危害人类健康的主要恶性肿瘤之一[1]。胆管癌起病隐匿，由于缺乏早期特异性及检查费用昂贵，因此胆管癌的早期诊断仍然是一大难题[2]。在全球范围内，胆管癌的发病率及病死率均呈上升趋势[3]。胆管癌的治疗以手术切除为首选方法，但手术切除率低，复发率高，术后生存率低[4-6]，预后差。血清糖类抗原CA19-9（界点>129 U/mL）在本病诊断中有一些价值，但仍缺乏明确的血清肿瘤标志物[7]。已有研究表明，膜联蛋白A1（annexin A1）[8]、肝细胞生长因子（HGF）与其受体（C-Met）蛋白[9]、有丝分裂调控酶polo样激酶1（PLK1）和aurora A[10]、X连锁凋亡抑制蛋白（XIAP）[11]在胆管癌患者血清中高表达。随着血清肿瘤标志物研究的深入，相关种类逐渐被发现，敏感性、特异性的提升，在胆管癌诊治过程中，血清肿瘤标志物将会成为起决定性作用的成分之一[12]。血清肿瘤型M2丙酮酸激酶（tumor M2 pyruvate kinase，

TuM2-PK）在胆汁中有较高灵敏度和特异度，可能会成为胆管癌新的肿瘤标志物，帮助诊断及判断预后[13]。近年来TuM2-PK在胃癌[14-16]、胰腺癌[17]、肺癌[18-19]及结直肠癌[20-21]恶性肿瘤标志物中的研究越来越多，已有研究发现TuM2-PK在胆管癌组织中高表达[22]，本研究旨在探讨血清TuM2-PK在胆管癌诊断中的价值，为其临床应用提供依据。

## 1 资料与方法

### 1.1 一般资料

选取2012年9月—2017年10月在中国人民解放军第二五一医院普通外科收治的54例胆管癌患者，其中，男31例，女23例；年龄38~82岁，中位年龄62岁，年龄>60岁者29例，年龄≤60岁者25例；经病理医师证实均为胆管腺癌，其中肿瘤≤2 cm者25例，肿瘤>2 cm者29例；上段胆管癌24例，中下段胆管癌30例；有神经侵犯者22例，无神经侵犯者32例；低分化腺癌34例，高中分化腺癌20例；有淋巴结转移者25例，无淋巴结转移者29例；I~II期38例，III~IV期16例。54例患者均行手术治疗，术前均未行放疗、化疗或免疫治疗等辅助治疗，其中根治性手术43例（肝门部胆管癌根治19例，根治性胰十二指肠切除术24例），姑息性手术11例（胆肠吻合6例，胆管T管引流术5例）。随机抽选同期住院胆管结石患者32例，男18例，女14例；年龄38~72岁。随机抽选同期行健康体检者25例为对照组，男15例，女10例；年龄36~75岁，均无肿瘤家族史。3组性别及年龄比例比较差异无统计学意义（均$P$>0.05）。

### 1.2 标本采集

因胆管癌术后平均住院时间为12 d，胆管结石术后平均住院时间为5 d，胆管癌组分别于术前及术后10 d清晨空腹静脉抽血约5 mL，胆管结石组分别于术前及术后3 d清晨空腹静脉抽血约5 mL，对照组抽取清晨空腹静脉血约5 mL，将静脉血置于抗凝管内，摇匀后经离心机3 500 $r$/min离心15 min后分离出血清，标记后存储于-80 ℃冰箱备用。

### 1.3 试剂与仪器

TuM2-PK采用酶联免疫吸附试验（ELISA）检测，人M2-PK ELISA试剂盒购自武汉伊莱瑞特生物科技股份有限公司，仪器为DNM-9602酶标分析仪（北京朗普新技术有限公司），严格按试剂说明书进行操作，以TuM2-PK>15 U/mL判断为阳性结果[23-25]。CA19-9采用化学发光法检测，仪器为美国贝克曼公司的XDI800，以CA19-9>37 U/mL判断为阳性结果。

### 1.4 统计学处理

采用SPSS 17.0软件进行统计分析，计量资料用均数±标准差（$\bar{x}\pm s$）表示，计数资料以例和百分率表示，组间计量资料比较采用$t$检验，组间计数资料的比较采用$\chi^2$检验，$P$<0.05为差异有统计学意义。

## 2 结 果

### 2.1 不同患者血清 TuM2-PK 水平比较分析

胆管癌患者血清TuM2-PK明显高于胆管结石患者和健康对照者，差异有统计学意义（均$P$<0.05）；胆管结石患者与健康对照者间TuM2-PK水平差异无统计学意义（$P$>0.05）（表1）。

表1 各组血清 TuM2-PK 水平比较（$\bar{x}\pm s$）

Table 1 Comparison of the serum TuM2-PK levels among groups ($\bar{x}\pm s$)

| 组别 | $n$ | M2-PK（U/mL） |
|---|---|---|
| 胆管癌组 | 54 | 20.38±5.71 |
| 胆管结石组 | 32 | 15.63±3.86[1)] |
| 健康对照组 | 25 | 12.88±4.21[1)] |

注：1) 与胆管癌组比较，$P$<0.05

Note: 1) $P$<0.05 *vs.* cholangiocarcinoma group

### 2.2 不同临床病理参数与胆管癌患者血清 TuM2-PK 阳性率的关系

胆管癌患者血清TuM2-PK阳性率与肿瘤的分化程度、淋巴结转移和TNM分期密切有关（均$P$<0.05），而与性别、年龄、肿瘤大小、肿瘤位置及有无神经侵犯无关（均$P$>0.05）（表2）。

表 2　不同临床病理参数与胆管癌患者血清 TuM2–PK 阳性率的关系 [*n*（%）]

**Table 2　The relations of different clinicopathologic parameters with the positive rate of serum TuM2-PK in of cholangiocarcinoma patients [*n* (%)]**

| 临床病理参数 | *n* | 阳性 | 阴性 | $\chi^2$ | *P* |
|---|---|---|---|---|---|
| 性别 | | | | | |
| 男 | 31 | 22（70.97） | 9（29.03） | 1.208 | 0.272 |
| 女 | 23 | 13（56.52） | 10（43.48） | | |
| 年龄（岁） | | | | | |
| ＞60 | 29 | 19（65.52） | 10（34.48） | 0.014 | 0.907 |
| ≤60 | 25 | 16（64.00） | 9（36.00） | | |
| 肿瘤大小（cm） | | | | | |
| ≤2 | 25 | 15（60.00） | 10（40.00） | 0.473 | 0.492 |
| ＞2 | 29 | 20（68.97） | 9（31.03） | | |
| 肿瘤位置 | | | | | |
| 上段 | 24 | 17（70.83） | 7（29.17） | 0.686 | 0.407 |
| 中、下段 | 30 | 18（60.00） | 12（40.00） | | |
| 神经侵犯 | | | | | |
| 有 | 22 | 16（72.73） | 6（27.27） | 1.019 | 0.313 |
| 无 | 32 | 19（59.38） | 13（40.62） | | |
| 分化程度 | | | | | |
| 高、中分化 | 20 | 8（40.00） | 12（60.00） | 8.577 | 0.003 |
| 低分化 | 34 | 27（79.41） | 7（20.59） | | |
| 淋巴结转移 | | | | | |
| 有 | 25 | 20（80.00） | 5（20.00） | 4.707 | 0.030 |
| 无 | 29 | 15（51.72） | 14（48.28） | | |
| TNM 分期 | | | | | |
| I~II | 38 | 21（52.63） | 17（44.73） | 5.131 | 0.024 |
| III~IV | 16 | 14（87.50） | 2（12.50） | | |

### 2.3　胆管癌患者血清 TuM2-PK 与 CA19-9 表达水平真实性与预测值分析

ROC曲线分析结果显示，血清TuM2-PK的曲线下面积值（AUC）为0.781（>0.5），且对于诊断胆管癌具有显著的意义（*P*=0.037）（图1）。血清TuM2-PK诊断胆管癌的灵敏度为84.81%（35/54）、特异度为80.00%（20/25）、阳性预测值为87.50%（35/40）；血清CA19-9诊断胆管癌的灵敏度为79.63%（43/54）、特异度为84.00%（21/25）、阳性预测值为91.49%（43/47），血清TuM2-PK与CA19-9联合检测（两者任有一项为阳性计为阳性，同时为阴性计为阴性）灵敏度为96.91%、特异度为67.93%（表3–4）。与CA19-9检测相比，TuM2-PK检测胆管癌结果的灵敏度较高，特异度较低，差异有统计学意义（*P*<0.05）；与CA19-9单独检测相比，TuM2-PK+CA19-9的检测结果敏感度增高，但特异度降低。

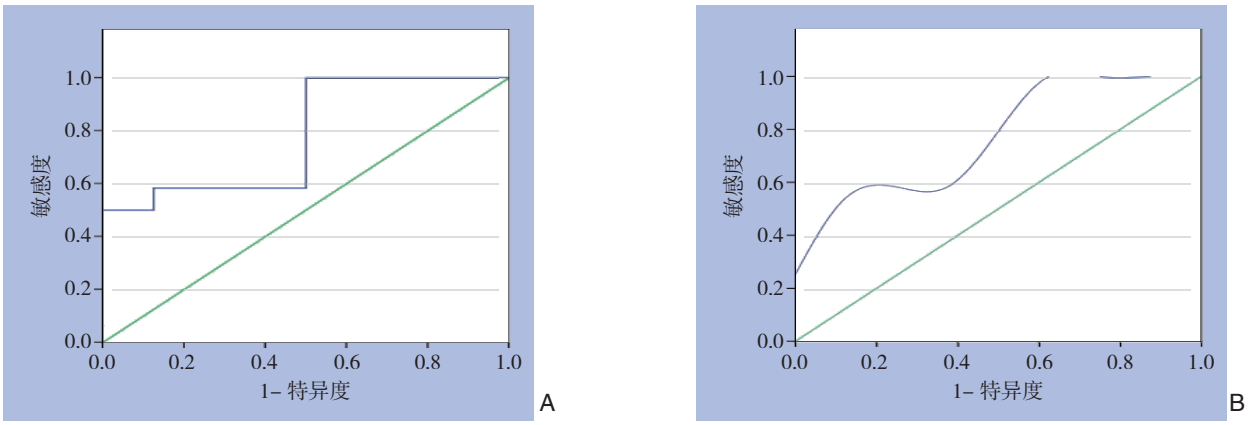


图 1　血清 TuM2-PK 诊断胆管癌的 ROC 曲线　A：原始 ROC 曲线；B：调节后的 ROC 曲线

**Figure 1　ROC curve of serum TuM2-PK for diagnosis of cholangiocarcinoma**　A: Original ROC curve; B: Optimal ROC curve

表 3　胆管癌患者血清 TuM2-PK 与 CA19-9 诊断效能比较

**Table 3　Comparison of diagnostic efficiencies of serum TuM2-PK and CA19-9**

| 组别 | *n* | TuM2-PK | | CA192-9 | |
|---|---|---|---|---|---|
| | | 阳性 | 阴性 | 阳性 | 阴性 |
| 胆管癌组 | 54 | 35 | 19 | 43 | 9 |
| 健康对照组 | 25 | 5 | 20 | 4 | 21 |
| 合计 | 79 | 40 | 39 | 47 | 30 |

表 4　血清 TuM2-PK 与 CA19-9 单独及联合检测结果比较

**Table 4　Comparison of results of lone and combined examination of serum TuM2-PK and CA19-9**

| 项目 | 灵敏度 | 特异度 |
|---|---|---|
| TuM2-PK | 84.81 | 80.00 |
| CA19-9 | 79.63 | 84.00 |
| TuM2-PK+CA19-9 | 96.91 | 67.93 |

### 2.4 胆管癌组及胆管良性病变组手术前后血清TuM2-PK水平变化

胆管癌组患者术前血清TuM2-PK水平为（20.38±5.71）U/mL，术后为（14.19±4.53）U/mL，差异有统计学意义（$P<0.05$）；胆管结石组患者术前血清TuM2-PK水平为（15.63±3.86）U/mL，术后为（14.45±3.23）U/mL，差异无统计学意义（$P>0.05$）。

### 2.5 根治性手术与姑息性手术者手术前后血清TuM2-PK水平变化

胆管癌患者中，根治性手术组患者术后血清TuM2-PK含量低于术前[（20.03±6.31）U/mL *vs.*（13.24±3.81）U/mL，$P<0.05$]；姑息性手术组患者手术前后血清TuM2-PK含量的差异无统计学意义[（20.09±5.63）U/mL *vs.*（20.09±5.63）U/mL，$P>0.05$]。

## 3 讨 论

M2-PK是丙酮酸激酶的一种同工酶,在肿瘤组织中以与磷酸化丙酮酸低亲和力的二聚体形式优先表达,故又称为肿瘤型M2-PK[21]。研究报道M2-PK能够促进恶性肿瘤细胞的侵袭和转移，包括肝癌[26]、胃癌[27]、胰腺癌[28]、结直肠癌[29]等消化系肿瘤，并且指出M2-PK可作为预测癌症患者不良预后的独立因素。柴浩等[22]发现M2-PK在胆管癌组织中的表达明显高于癌旁组织,提示其在胆管癌的发生发展中发挥重要作用。

本研究发现，TuM2-PK在胆管癌患者血清水平明显高于胆管结石患者与健康对照者，胆管结石患者血清TuM2-PK水平虽然高于健康对照者，但差异无统计学意义（$P>0.05$），这说明确定好TuM2-PK的医学决定水平可用于区别胆管的恶性病变、良性病变及健康组织，这与Li等[30]报道的在胆管癌患者血清中TuM2-PK水平明显高于正常者及良性疾病患者的结果一致。

胆管癌患者TuM2-PK水平的表达与癌细胞的分化程度、肿瘤是否有淋巴结转移及临床病理TNM分期密切有关，而与患者性别、年龄、肿瘤大小、肿瘤位置及有无神经侵犯无关。癌细胞分化程度越低，血清中TuM2-PK阳性率水平就越高，有淋巴转移的患者比未发生淋巴转移的患者血清中TuM2-PK阳性率水平高。在临床病理TNM分期中，III~IV期患者血清中TuM2-PK阳性率水平显著高于I~II期患者。这些结果都明确表明了胆管癌患者血清TuM2-PK水平变化随着癌细胞生物状态的改变而改变，一定程度上反映了肿瘤的发生、发展。

本研究发现，血清TuM2-PK诊断胆管癌的灵敏度高于CA19-9，但特异度低于CA19-9，这表明TuM2-PK相对于CA19-9在临床诊断胆管癌方面具有更高的检出率。目前肿瘤标志物的联合检测是研究的一大热点，在肿瘤预防、诊断和预后中肿瘤标志物将会占有很重要的地位[31]。有研究表明，对于胃癌患者[14, 16, 32]，肺癌患者[18-19]，结肠癌患者[33]通过TuM2-PK与其它肿瘤标志物联合检测，能够进一步提高诊断的灵敏度与特异度。本研究亦发现，通过血清TuM2-PK与CA19-9联合检测，灵敏度为96.91%、特异度为67.93%，灵敏度均明显高于单纯TuM2-PK或CA19-9检查，但特异度降低，可能在提高误诊率，降低漏诊率的同时，会增加患者的医疗成本。

本研究中的54例胆管癌患者手术后血清TuM2-PK水平明显低于手术前，其中肿瘤切除的患者术后血清TuM2-PK明显降低，但肿瘤未切除的姑息性手术患者手术前后血清TuM2-PK的差别不明显，考虑由于肿瘤仍存在，导致血清TuM2-PK水平无明显改变。由此笔者推测血清TuM2-PK可作为胆管癌术前诊断、术后效果及肿瘤转移复发的评价指标。

目前，手术切除仍是治疗胆管癌的首要方法，化疗药物敏感性差，且临床药物治疗过程中易出现抗药性[34]，如何从分子水平上对胆管癌的发生、发展情况进行分析，并采取有效的基因靶向治疗则是肿瘤化疗的新方向[35]。在胃癌的研究中发现，缺氧诱导因子（HIF-1α、HIF-2α）均可调控TuM2-PK的表达[36]，二烯丙基二硫可能通过靶向TuM2-PK抑制胃癌细胞能量代谢[37]，let-7a是通过调控PKM2的表达水平从而抑制胃癌细胞生长[38]，笔者认为TuM2-PK作为肿瘤治疗的新靶点，为抗肿瘤的药物研发、肿瘤的预后提供了新策略。

本次研究选取样本较小，对照组选取随机，可能不能反映真实情况，但是目前国内外对TuM2-PK在胆管癌血清中的表达报道较少，本次研究获取了一定的试验数据，如能加大样本量，进行多中心前瞻性大规模的病例对照研究，取得更为精确和可信的数据值，将有助于提高TuM2-PK的临

 

床应用价值。

胆管癌患者血清TuM2-PK水平可在一定程度上代表癌细胞的生物学状态，反映了胆管癌的发生、发展。血清TuM2-PK检测能够作为临床早期诊断胆管癌，判断临床分析，评估治疗预后的重要指标，与CA19-9联合检测能够进一步提高胆管癌的临床检出率。

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