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## 血清NSE、SCCA及CEA在肺癌早期诊断和预后预测中的应用价值研究\*

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**摘要 目的:** 研究血清神经元特异性烯醇化酶(NSE)、鳞状细胞癌抗原(SCCA)及癌胚抗原(CEA)在肺癌早期诊断和预后预测中的应用价值。**方法:** 选择我院2013年1月~2017年1月收治的110例肺癌患者(肺癌组)及同期96例肺部良性疾病患者(肺良性病组)和85例门诊健康体检者(对照组)。比较各组血清NSE、SCCA及CEA水平,采用受试者工作特征(ROC)曲线分析以上指标对肺癌的诊断价值。**结果:** 肺癌组血清NSE、SCCA、CEA水平高于肺良性病组及对照组,肺良性病组血清NSE、SCCA、CEA水平高于对照组( $P<0.05$ )。肺癌III+IV组血清NSE、SCCA及CEA水平高于I+II组( $P<0.05$ )。小细胞肺癌组血清NSE水平高于鳞癌组、腺癌组,鳞癌组血清SCCA水平高于腺癌组及小细胞肺癌组,腺癌组血清CEA水平高于鳞癌组及小细胞肺癌组( $P<0.05$ )。NSE $<16.0\mu\text{g/L}$ 者平均无疾病进展生存期(PFS)长于NSE $\geq 16.0\mu\text{g/L}$ , SCCA $<1.5\mu\text{g/L}$ 者平均PFS长于SCCA $\geq 1.5\mu\text{g/L}$ , CEA $<5.0\mu\text{g/L}$ 平均PFS长于CEA $\geq 5.0\mu\text{g/L}$  ( $P<0.05$ )。NSE、SCCA和CEA及三者联合诊断肺癌的ROC曲线下面积分别为0.880、0.651、0.830及0.937, NSE+SCCA+CEA联合诊断的曲线下面积高于单个指标单独诊断( $P<0.05$ )。**结论:** 血清NSE、SCCA及CEA对肺癌的诊断有重要的参考价值,且有利于肺癌的分期、分型及预后评价。

**关键词:** 肺癌; 神经元特异性烯醇化酶; 鳞状细胞癌抗原; 癌胚抗原; 预后预测

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## Application Value of Serum NSE, SCCA and CEA for the Early Diagnosis and Prognostic Prediction of Lung Cancer\*

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**ABSTRACT Objective:** To investigate the application value of serum neuron-specific enolase (NSE), squamous cell carcinoma antigen (SCCA) and carcinoembryonic antigen (CEA) in the early diagnosis and prognosis prediction of lung cancer. **Methods:** 110 cases of patients with lung cancer (lung cancer group) admitted to our hospital from January 2013 to January 2017, and 96 patients with benign pulmonary diseases (benign lung disease group) and 85 outpatient health examinations (control group). Serum levels of NSE, SCCA and CEA of each group were compared, and the diagnostic value of the above indicators for lung cancer was analyzed using the ROC curve. **Results:** Serum levels of NSE, SCCA and CEA in lung cancer group were higher than those in benign lung disease group and control group, and serum levels of NSE, SCCA and CEA in benign lung disease group were higher than those in control group ( $P<0.05$ ). Serum NSE, SCCA and CEA levels in lung cancer III+IV group were higher than those in group I+II ( $P<0.05$ ). Serum level of NSE in the small cell lung cancer group was higher than that in the squamous cell carcinoma group and adenocarcinoma group, serum level of SCCA in the squamous cell carcinoma group was higher than that in the adenocarcinoma group and small cell lung cancer group, serum level of CEA in the adenocarcinoma group was higher than that in the squamous cell carcinoma group and urine lung cancer group ( $P<0.05$ ). Mean progression-free survival (PFS) of patients with NSE $<16.0\mu\text{g/L}$  was longer than that of patients with NSE $\geq 16.0\mu\text{g/L}$ , the average PFS of SCCA $<1.5\mu\text{g/L}$  was longer than that of SCCA $\geq 1.5\mu\text{g/L}$ , and the average PFS of CEA $<5.0\mu\text{g/L}$  was longer than that of CEA $\geq 5.0\mu\text{g/L}$  ( $P<0.05$ ). The area under the ROC curve of NSE, SCCA, CEA and the three combined diagnosis of lung cancer respectively was 0.880, 0.651, 0.830, 0.937. The area under the curve of NSE+SCCA+CEA combined diagnosis is higher than the single indicator alone. **Conclusion:** Serum NSE, SCCA and CEA have important reference value for the diagnosis of lung cancer, and it is conducive to the staging, classification and prognostic evaluation of lung cancer.

**Key words:** Lung cancer; Neuron-specific enolase; Squamous cell carcinoma antigen; Carcinoembryonic antigen; Prognostic prediction

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## 前言

肺癌为临床常见恶性肿瘤,具有发病率及病死率高等特点,是威胁机体生命的主要疾病之一<sup>[1]</sup>。相关研究报道<sup>[2,3]</sup>肺癌预后和临床分期有良好相关性,0期肺癌患者术后5年生生存率可高达90%,随着临床分期的增加生存率相应下降,但早期肺癌患者缺乏特异性表现,多数患者就诊时已进展至晚期,错失最佳诊疗机会。尽早诊治能够减轻肺癌的危害,延长生存期,改善患者预后。肿瘤发生为多阶段的长期过程,在肿瘤形成早期,血液中肿瘤特异蛋白或者基因改变,有助于早期诊断,既往研究显示肺癌发生和多种肿瘤标志物的异常表达有关<sup>[4-6]</sup>。

神经元特异性烯醇化酶(NSE)、鳞状细胞癌抗原(SCCA)、癌胚抗原(CEA)为临床已知的肺癌血清肿瘤标志物,和瘤体负荷、病灶扩散及复发紧密相关<sup>[7]</sup>。其中,NSE为非小细胞肺癌的最特异、最敏感标志物之一,SCCA为鳞状上皮癌的重要标志物,CEA为临床最广泛的肿瘤相关抗原,对肺癌的诊断价值已得到临床证实<sup>[8,9]</sup>。尽管以上肿瘤标志物各具优势,但均有一定的局限性<sup>[10]</sup>。本研究旨在分析血清NSE、SCCA及CEA在肺癌早期诊断和预后预测中的应用价值。

## 1 资料与方法

### 1.1 一般资料

选择我院2013年1月~2017年1月收治的110例肺癌患者,入选标准<sup>[11]</sup>:经活体组织病理检查学确诊为原发性肺癌;预计生存时间在3个月以上;临床资料完整。排除标准:入组前4周进行抗肿瘤治疗;全身系统明显病变。110例肺癌患者中,男68例,女42例;年龄37~70岁,平均(57.43±8.64)岁;鳞癌61

例,腺癌33例,小细胞肺癌16例;TNM分期:I~II期63例,III~IV期47例。同期选择96例肺脓肿、肺结核及肺炎等肺部良性疾病患者,男55例,女42例;年龄33~68岁,平均(55.96±9.75)岁。另收集85例门诊健康体检者作为对照组,均排除其他疾病,影像学及血液生化资料无明显异常者,男49例,女36例;年龄35~67岁,平均(56.84±8.03)岁。三组一般资料比较差异无统计学意义( $P>0.05$ )。

### 1.2 方法

1.2.1 指标检测 采集各组外周血4 mL,常规分离血清离心后放置于-20℃低温箱中保存待检。采用化学发光仪检测各组血清NSE、SCCA及CEA水平。

1.2.2 随访 所有肺癌患者均以电话、门诊等方式进行1年随访,入组日期即为随访起始日期,至随访结束、失访或者死亡为截止日期,计算疾病无进展生存期(PFS);随机化至患者出现肿瘤进展或者死亡时间。

### 1.3 统计学分析

数据处理选用SPSS18.0软件包,计量资料用( $\bar{x} \pm s$ )表示,两组间选用独立样本t检验,多组间采用方差分析,计数资料用[(例)%]表示,用 $\chi^2$ 检验比较,采用Log-rank检验分析并比较疾病无进展生存期,受试者工作特征(ROC)曲线分析各指标在肺癌中的诊断效能,以 $P<0.05$ 为差异有统计学意义。

## 2 结果

### 2.1 各组血清NSE、SCCA、CEA水平比较

肺癌组血清NSE、SCCA、CEA水平高于肺良性病组及对照组,肺良性病组血清NSE、SCCA、CEA水平高于对照组,差异有统计学意义( $P<0.05$ ),见表1。

表1 各组血清NSE、SCCA、CEA水平比较( $\bar{x} \pm s$ )Table 1 Comparison of the serum levels of NSE, SCCA and CEA between different groups( $\bar{x} \pm s$ )

| Groups                    | n   | NSE( $\mu\text{g/L}$ )   | SCCA( $\mu\text{g/L}$ )  | CEA( $\mu\text{g/L}$ )   |
|---------------------------|-----|--------------------------|--------------------------|--------------------------|
| Control group             | 85  | 3.75±0.33 <sup>▲</sup>   | 1.29±0.17 <sup>▲</sup>   | 2.55±0.31 <sup>▲</sup>   |
| Benign lung disease group | 96  | 4.81±0.65 <sup>#</sup>   | 1.85±0.26 <sup>#</sup>   | 3.27±0.49 <sup>#</sup>   |
| Lung cancer group         | 110 | 18.63±3.19 <sup>#▲</sup> | 10.31±1.53 <sup>#▲</sup> | 20.11±3.16 <sup>#▲</sup> |

Note: Compared with the control group, <sup>#</sup> $P<0.05$ ; Compared with the benign lung disease group, <sup>▲</sup> $P<0.05$ .

### 2.2 不同临床分期肺癌患者血清NSE、SCCA及CEA水平比较

III+IV组血清NSE、SCCA及CEA水平高于I+II组,差异有统计学意义( $P<0.05$ ),见表2。

表2 不同临床分期肺癌患者血清NSE、SCCA及CEA水平的比较( $\bar{x} \pm s$ )Table 2 Comparison of the serum levels of NSE, SCCA and CEA between lung cancer patients with different clinical stages( $\bar{x} \pm s$ )

| Groups | n  | NSE( $\mu\text{g/L}$ )  | SCCA( $\mu\text{g/L}$ ) | CEA( $\mu\text{g/L}$ )  |
|--------|----|-------------------------|-------------------------|-------------------------|
| I+II   | 63 | 12.04±2.25              | 4.02±1.65               | 11.43±1.98              |
| III+IV | 47 | 27.46±4.45 <sup>▲</sup> | 18.74±1.36 <sup>▲</sup> | 31.74±4.74 <sup>▲</sup> |

Note: Compared with the I+II, <sup>▲</sup> $P<0.05$ .

### 2.3 不同分型肺癌患者血清NSE、SCCA及CEA水平比较

鳞癌组及腺癌组血清NSE水平比较差异无统计学意义

( $P>0.05$ ),腺癌组及小细胞肺癌组血清SCCA水平比较差异无统计学意义( $P>0.05$ );鳞癌组及小细胞肺癌组血清CEA水平比

较差异无统计学意义( $P>0.05$ );小细胞肺癌组血清 NSE 水平高于鳞癌组、腺癌组,鳞癌组血清 SCCA 水平高于腺癌组及小细胞肺癌组,腺癌组血清 CEA 水平高于鳞癌组及小细胞肺癌组,差异有统计学意义( $P<0.05$ ),见表 3。

表 3 肺癌组不同分型中血清 NSE、SCCA 及 CEA 水平比较( $\bar{x}\pm s$ )Table 3 Comparison of serum levels of NSE, SCCA and CEA in different classification of lung cancer group ( $\bar{x}\pm s$ )

| Groups                       | n  | NSE( $\mu\text{g/L}$ )         | SCCA( $\mu\text{g/L}$ )        | CEA( $\mu\text{g/L}$ )         |
|------------------------------|----|--------------------------------|--------------------------------|--------------------------------|
| Squamous carcinoma group     | 61 | 13.19 $\pm$ 1.01 <sup>c</sup>  | 28.02 $\pm$ 2.53 <sup>bc</sup> | 12.60 $\pm$ 1.77               |
| Adenocarcinoma group         | 33 | 12.58 $\pm$ 1.05 <sup>c</sup>  | 6.93 $\pm$ 0.18                | 37.33 $\pm$ 6.52 <sup>ac</sup> |
| Small cell lung cancer group | 16 | 51.84 $\pm$ 4.50 <sup>ab</sup> | 6.95 $\pm$ 0.36 <sup>a</sup>   | 13.21 $\pm$ 1.52               |

Note: Compared with the squamous carcinoma group, <sup>a</sup> $P<0.05$ ; Compared with the adenocarcinoma group, <sup>b</sup> $P<0.05$ ; Compared with the small cell lung cancer group p, <sup>c</sup> $P<0.05$

#### 2.4 不同肿瘤标志物水平肺癌患者的生存分析

NSE 的正常参考范围为 0~116.0  $\mu\text{g/L}$ 、SCCA 为 0~1.5  $\mu\text{g/L}$ 、CEA 为 0~5.0  $\mu\text{g/L}$ ,110 例肺癌患者 1 年有 30 例死亡,其中 NSE<16.0  $\mu\text{g/L}$  死亡 11 例,NSE $\geq$  16.0  $\mu\text{g/L}$  死亡

19 例;SCCA <1.5  $\mu\text{g/L}$  死亡 8 例,SCCA $\geq$  1.5  $\mu\text{g/L}$  死亡 22 例,CEA <5.0  $\mu\text{g/L}$  死亡 8 例,CEA $\geq$  5.0  $\mu\text{g/L}$  死亡 22 例,NSE、SCCA 及 CEA 不同水平组平均无疾病进展生存期比较差异均有统计学意义( $P<0.05$ ),见表 4 及图 1。

表 4 不同肿瘤标志物水平肺癌患者的生存分析

Table 4 Survival analysis of lung cancer patients with different levels of tumor markers

| Index                   | n  | Average PFS (month) | $\chi^2$ | P     |
|-------------------------|----|---------------------|----------|-------|
| NSE( $\mu\text{g/L}$ )  |    |                     |          |       |
| <16.0                   | 69 | 9.1                 | 14.439   | 0.000 |
| $\geq$ 16.0             | 41 | 11.0                |          |       |
| SCCA( $\mu\text{g/L}$ ) |    |                     |          |       |
| <1.5                    | 63 | 9.5                 | 7.460    | 0.006 |
| $\geq$ 1.5              | 47 | 11.2                |          |       |
| CEA( $\mu\text{g/L}$ )  |    |                     |          |       |
| <5.0                    | 57 | 9.2                 | 7.770    | 0.005 |
| $\geq$ 5.0              | 53 | 11.1                |          |       |

#### 2.5 血清 NSE、SCCA 及 CEA 对肺癌早期诊断的效能比较

根据 ROC 曲线分析,NSE 诊断肺癌的 ROC 曲线下面积为 0.880、SCCA 为 0.651、CEA 为 0.830,NSE+SCCA+CEA 联合诊断为 0.937,NSE+SCCA+CEA 联合诊断的曲线下面积高于单个指标,见表 5 及图 2。

### 3 讨论

肺癌是危及患者生命安全的常见恶性肿瘤之一,临床统计学报道,近年来其发病率呈上升趋势,尽管其治疗已取得较大进步,但 5 年生存率仍较低<sup>[12,13]</sup>。早期诊治是提高肺癌患者 5 年生存率的重要手段。目前肺癌的诊断主要依靠影像学、组织细胞学和病理学等,其中胸部 X 线、低剂量螺旋 CT 等影像学检查对胸部结构和肺内小病变的敏感性较差,容易导致误诊及漏诊<sup>[14,15]</sup>。既往研究认为<sup>[16,17]</sup>痰细胞学检查是肺癌的早期发现依据,但痰检阳性、影像学检查阴性的需采用其他诊断方法,以明确肿瘤位置。纤维支气管镜可获得细胞学及组织学标本,但取材及切皮检查均抽样检查,难以代表整体病变,容易延误诊断或漏诊,但其为有创操作,不利于患者耐受<sup>[18]</sup>。

近年来,有研究报道<sup>[19,20]</sup>血清肿瘤标志物的发现让肿瘤的筛查及早期诊断成为可能,其作为一种体外检查方法,具有定量客观、操作简便和动态监测等优势,现已成为恶性肿瘤早期诊断的重点。但由于肿瘤基因的复杂性,单一的肿瘤标志物难以满足临床诊断的理想要求,有选择性的联合多项标记物可增加癌症的诊断效能<sup>[21]</sup>。

NSE 为酸性蛋白酶,主要分布于神经内分泌细胞及神经元,在小细胞肺癌中有较高的特异性及敏感性,能够反映肿瘤的负荷量,用于肿瘤诊断、病情监测、疗效评估<sup>[22,23]</sup>。Molina R 等<sup>[24]</sup>研究报道,NSE 在非小细胞肺癌患者中的表达水平较高,和腺癌、鳞癌比较有明显差异。SCCA 为细胞结构蛋白,广泛分布于恶性病变的上皮细胞中,以鳞状细胞癌最为显著,其上升程度和肿瘤病情进展、分化程度及预后相关<sup>[25,26]</sup>。CEA 作为一种细胞黏附因子,在胚胎期表达,正常成年者不表达,分布于细胞膜上,进入机体液后随着肿瘤发生又可重新表达,在肿瘤发生发展及转移中有重要作用<sup>[27]</sup>。血清 CEA 的上升可能和相应染色体基因发生阻碍,导致机体中 CEA 重新活跃有关<sup>[28]</sup>。多个研究表明<sup>[29,30]</sup>,CEA 浓度和肺癌组织学类型有一定相关性,其

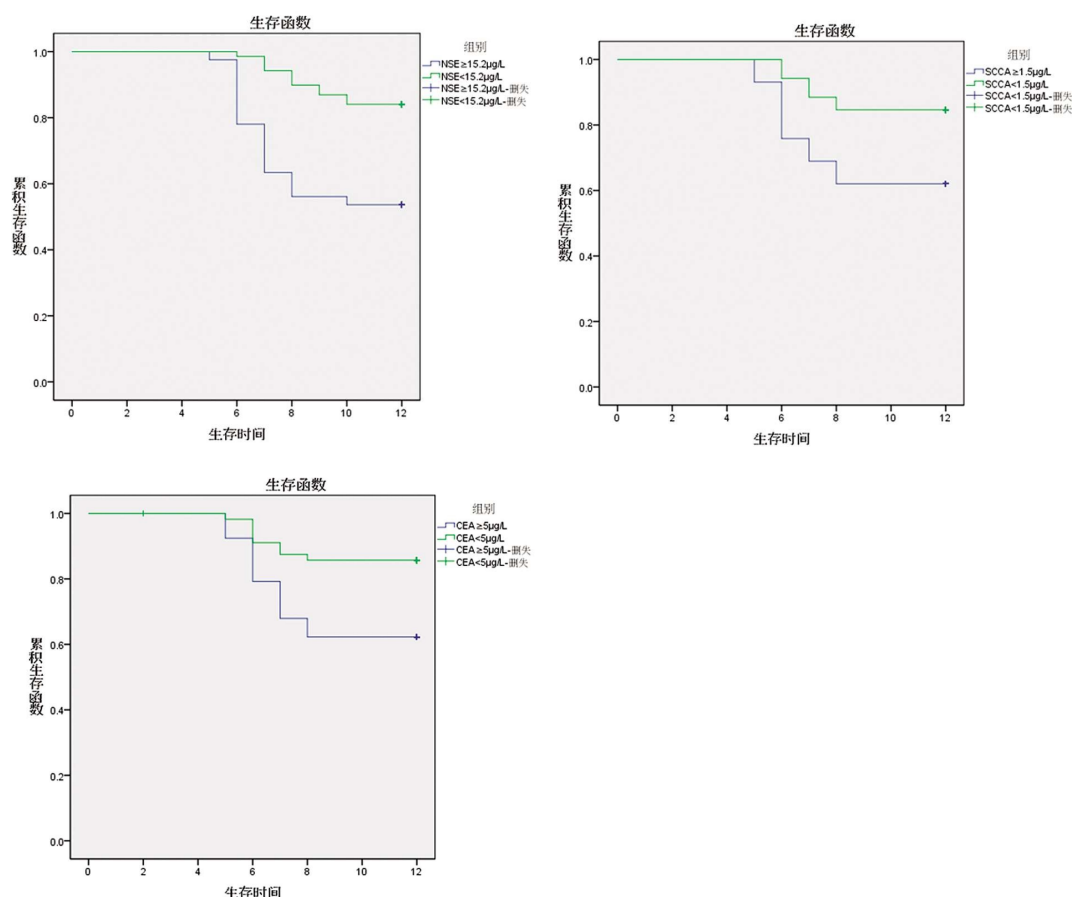


图 1 不同肿瘤标志物肺癌患者的生存曲线

Fig.1 Survival curves of lung cancer patients with different levels of tumor markers

表 5 血清 NSE、SCCA 及 CEA 对肺癌早期诊断的效能比较

Table 5 Diagnostic efficacy of serum NSE, SCCA and CEA for the early stage of lung cancer

| Index        | area  | SE    | sig   | 95%CI |       | cutoff | Sensitivity | specificity |
|--------------|-------|-------|-------|-------|-------|--------|-------------|-------------|
|              |       |       |       | Lower | limit |        |             |             |
| NSE          | 0.880 | 0.024 | 0.000 | 0.832 | 0.928 | 0.529  | 0.818       | 0.800       |
| SCCA         | 0.651 | 0.039 | 0.000 | 0.574 | 0.728 | 0.451  | 0.864       | 0.576       |
| CEA          | 0.830 | 0.029 | 0.000 | 0.773 | 0.887 | 0.605  | 0.718       | 0.835       |
| NSE+SCCA+CEA | 0.937 | 0.016 | 0.000 | 0.905 | 0.969 | 0.450  | 0.891       | 0.835       |

浓度增加能够间接说明肿瘤存在转移或者复发可能性。本研究结果显示肺癌组血清 NSE、SCCA 及 CEA 水平显著高于肺良性疾病组及对照组,随着临床分期的增加其浓度相应上升,提示在肺癌诊断中有一定价值。分析血清 NSE、SCCA 及 CEA 在不同分型肺癌中的表达,结果显示小细胞肺癌中血清 NSE 水平最高,鳞癌中血清 SCCA 水平最高,腺癌血清 CEA 水平最高,说明血清 NSE、SCCA 及 CEA 在肺癌分型鉴别中有一定的作用。进一步分析结果显示  $NSE \geq 16.0 \mu g/L$ 、 $SCCA \geq 1.5 \mu g/L$ 、 $CEA \geq 5.0 \mu g/L$  患者 1 年内病死率相对较高,提示其能一定程度的反映肺癌患者预后。ROC 曲线能够准确、客观的反映指标的特异性及敏感性,曲线下面积越大,其诊断准确性越高。本研究结果显示血清 NSE、SCCA 及 CEA 的 ROC 曲线下面积均大于 0.5,说明以上指标对肺癌患者预后有一定指导价值,但 NSE+SCCA+CEA 联合的 ROC 曲线下面积最高,提示指标联

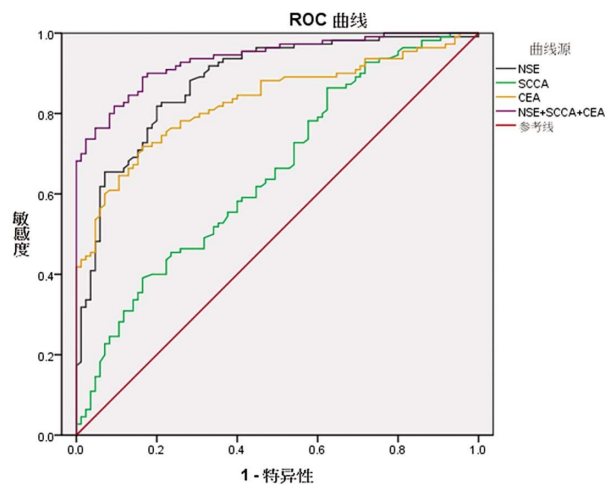


图 2 血清 NSE、SCCA 及 CEA 的 ROC 曲线

Fig.2 ROC curves of serum NSE, SCCA and CEA

合检测能够提高肺癌诊断的准确性。但本试验为回顾性研究,未事前确定明确的检验假设,样本量不足,结果有一定偏差。

综上所述,血清 NSE、SCCA 及 CEA 对肺癌的诊断有重要的参考价值,且有利于肺癌的分期、分型及预后评价。

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