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·临床研究·

# miR-17-92 簇高表达与恶性肿瘤患者预后关系的 Meta 分析

全强,赵凤芝,赵建夫,胡鹏辉,苏嘉敏,徐萌(暨南大学附属第一医院 肿瘤科,广东 广州 510632)

[摘 要] **目的**:采用 Meta 分析评估 miR-17-92 簇高表达在肿瘤患者预后中的价值。**方法**:检索 Web of Science、PubMed、EMBASE 数据库从建库至 2015 年 10 月 1 日关于 miR-17-92 簇成员高表达与恶性肿瘤患者预后关系的英文文献,提取关键数据,计算合并风险比(hazard ratio,HR)及其 95% 置信区间(confidence interval,CI)。**结果**:共纳入 39 篇文献,包含 4 908 例患者。miR-17-92 簇的高表达与恶性肿瘤患者总生存率(HR=1.83,95% CI:1.58~2.12,$P$=0.000)低有关,并且 miR-17-92 簇高表达的肿瘤患者的无病生存率(HR=1.80,95% CI:1.43~2.26,$P$=0.000)、无进展生存率(HR=1.83,95% CI:1.11~3.02,$P$=0.018)及肿瘤特异性生存率(HR=1.59,95% CI:1.04~2.42,$P$=0.032)均降低;然而无复发生存率的合并风险比无统计学意义($P$=0.539)。**结论**:miR-17-92 簇高表达与恶性肿瘤患者的不良预后有关,有望成为新型肿瘤预后标志物。

[关键词] miR-17-92 簇;恶性肿瘤;生存率;预后;Meta 分析
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# Meta-analysis of relationship between high-expression of miR-17-92 cluster and prognosis of cancer patients

QUAN Qiang, ZHAO Fengzhi, ZHAO Jianfu, HU Penghui, SU Jiamin, XU Meng (Department of Oncology, The First Affiliated Hospital of Jinan University, Guangzhou 510632, Guangdong, China)

[**Abstract**] **Objective**: Value of high-expression of miR-17-92 cluster in evaluating prognosis of cancer patients was analyzed with Meta-analysis. **Methods**: English literatures on the relationship of high-expression of miR-17-92 cluster and the prognosis of cancer patients were retrieved from Web of Science, PubMed and EMBASE from construction of the data bases to Oct 1, 2015. Key data were extracted from the literatures, pooled hazard ratios (HRs) and corresponding 95% confidence interval (CI) were calculated. **Results**: Total of thirty-nine literatures was included, involving 4 908 patients. The high-expression of miR-17-92 cluster was associated with low overall survival rate of the patients with malignant tumor (HR=1.83, 95% CI: 1.58~2.12, $P$=0.000). Furthermore, disease-free survival rate (HR=1.80, 95% CI: 1.43~2.26, $P$=0.000), progression-free survival rate (HR=1.83, 95% CI: 1.11~3.02, $P$=0.018) and cancer-specific survival rate (HR=1.59, 95% CI: 1.04~2.42, $P$=0.032) in the cancer patients with high-expression of miR-17-92 cluster were all reduced. However, the pooled HRs for relapse- free survival rate was not statistically significant ($P$=0.539). **Conclusion**: The high-expression of miR-17-92 cluster was associated with poor prognosis of the patients with malignant tumor, and it could be expected as a new marker for prognosis of the cancer patients.

[**Key words**] miR-17-92 cluster; cancer; survival; prognosis rate; Meta-analysis
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恶性肿瘤是全世界最常见的病死原因之一,已成为主要的公共卫生问题[1]。因此,发现新的肿瘤标志物对恶性肿瘤患者的治疗及预后非常重要。微小 RNA(microRNA,miRNA 或 miR)的异常表达通过抑癌作用或促癌作用调节肿瘤细胞的增殖、分化、凋亡及转移等生物学行为[2-3],已成为重要的肿瘤标志物。miR-17-92 簇位于人类常染色体 13q31.3 基因座位上,*C13orf25* 基因第 3 个内含子区,是一种典型的含有多顺反子启动子的基因簇,其编码的成熟

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[作者简介] 全强(1989-),男,贵州省遵义市人,硕士生,住院医师,主要从事肿瘤分子诊治相关研究,E-mail:35098828@qq.com
[通信作者] 徐萌(XU Meng, corresponding author),E-mail:xumengjinan@yahoo.com
[优先发表] http://www.cnki.net/kcms/detail/31.1725.R.20160331.2039.018.html

microRNAs 包括 miR-17、miR-18a、miR-18b、miR-19a、miR-19b、miR-20 及 miR-92 等成员[4]。miR-17-92 簇的生物学功能已经被广泛研究,其高表达对肺癌、胃癌、结直肠癌、前列腺癌、乳腺癌等患者的预后不利,但仍存在争议,因此需应用 Meta 分析评估其预后价值。本研究旨在分析 miR-17-92 簇的高表达与恶性肿瘤患者生存率的关系,探讨 miR-17-92 簇作为恶性肿瘤预后标志物的作用。

## 1　材料与方法

### 1.1　文献检索

检索从建库至 2015 年 10 月 1 日 Web of Science、PubMed、EMBASE 英文数据库。英文检索词包括 miR-17、miR-18、miR-19、miR-20、miR-92 及 miR-17-92 cluster、cancer、malignancy、neoplasm、carcinoma、tumor 等。仔细阅读题目、摘要,辅助手工检索相关参考文献。

### 1.2　纳入标准及排除标准

纳入标准:( 1 )英文文献;( 2 )明确恶性肿瘤诊断;( 3 )涉及 miR-17-92 簇的高表达与恶性肿瘤患者预后的关系;( 4 )miR-17-92 簇为高低表达的二分类资料。排除标准:( 1 )读者来信、会议等非正式文献;( 2 )缺乏关键数据,如 HR、95% CI;( 3 )生存曲线信息不全者。

### 1.3　数据提取及转换

由 2 位研究人员独立提取重要资料,详见表 1,若 HR > 1,miR-17-92 簇的高表达对肿瘤患者预后不利。若原文缺乏 95% CI,利用 HR 和 P 值通过 Review Manager 5.2 软件算出;对于只提供生存曲线的文献,利用 Engauge Digitizer 4.1 软件提取数据,转换后纳入[5]。不确定资料交给资历更高的第三者进行分析。

### 1.4　质量评估

两名研究员采用 NOS( Newcastle-Ottawa Scale )量表队列研究评分项目对纳入文献质量进行独立评分[6],评分项目:①暴露组的代表性;②非暴露组的选择;③暴露组确认;④研究开始前结局未发生;⑤研究的设计或者分析的可比性;⑥结局的评估;⑦随访时间是否充分;⑧随访的完整性,其中第五项满分为 2 分,其余各项为 1 分,8 项满分为 9 分。评分结果显示,1 篇纳入文献为 5 分,其余文献均大于等于 6 分。总体纳入文献质量较高( 详见 NOS 质量评分附件,本文中未展示 )。

### 1.5　统计方法

采用 $I^2$ 检验和 $Q$ 检验分析异质性,$I^2 < 25\%$ 为轻度异质性,$25\% \leqslant I^2 < 50\%$ 为中度异质性,$I^2 \geqslant 50\%$ 为显著异质性。研究间 $I^2 < 50\%$ 或 $P > 0.10$ 时,采用固定效应模型;$I^2 \geqslant 50\%$ 或 $P \leqslant 0.10$ 时,采用随机效应模型;个别分析模型根据专业实际异质性决定。采用 Stata12.0 软件合并 HR,绘制森林图、漏斗图,利用 Egger's、Begg's 检验评估发表偏倚,双侧 $P$ 值 < 0.05 时有统计学意义。

## 2　结　果

### 2.1　文献筛选结果及纳入研究基本信息

初筛相关文献共 1573 篇,排除综述、病例报告、非临床研究等文献 1 487 篇。剩余 86 篇全文中,24 篇与生存率无关,16 篇缺乏关键数据,7 篇重复,最终纳入 39 篇[7-45]( 图 1 ),包含 68 个研究共 4 908 例患者,其基本信息见表 1,纳入研究涵盖鼻咽癌、口腔癌、食管癌、肺癌、胃癌、肝癌、胰腺癌、结肠癌、直肠癌、肾癌、前列腺癌、淋巴瘤、骨髓瘤;19 篇文献检测肿瘤组织中 miRNAs 表达量,9 篇采用石蜡包埋组织( FFPE )标本,12 篇文章利用血样;共 31 篇采用实时荧光定量 PCR ( quantitative real-time PCR,qRT-PCR )检测技术,其余研究采用原位杂交( in situ hybridization,ISH )、逆转录 PCR( reverse transcriptase-PCR,RT-PCR )、高通量测序( high-throughput sequencing,Hiseq )技术检测;26 篇文献采用多变量 Cox 比例风险模型,5 篇文献采用单变量 Cox 比例风险模型,8 篇文献采用乘积极限法。纳入的生存率指标包括总生存率( overall survival,OS )、无复发生存率( recurrent-free survival,RFS )、无进展生存率( progress free survival,PFS )、无病生存率( disease free survival,DFS )、肿瘤特异性生存率( cancer specific survival,CSS )。

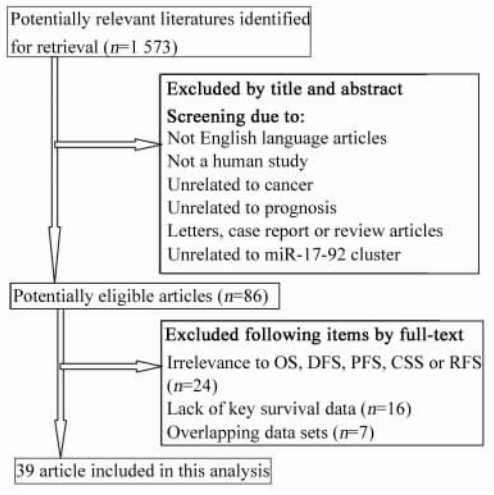


**图 1　文献筛选流程**

**Fig. 1　Flow diagram of article screening**

**表 1 所有纳入研究基本信息**

**Tab. 1 Essential characteristics of all included studies**

| Author/year | Nation | Cancer | Stage | miRNA | Case ($n$) | Follow-up ($t$/a) | Survival | Cutoff |
|---|---|---|---|---|---|---|---|---|
| XU et al. 2014[12] | China | ESCC | Ⅰ-Ⅳ | 17a/18a/19a | 105 | >4 | OS/PFS | 2 |
| | | | | 19b/20a/92a | | | OS | |
| CHEN et al. 2010[41] | China | ESCC | Ⅰ-Ⅲ | 92a | 65 | 5 | OS | 75$^{th}$%[a] |
| WANG et al. 2012[17] | China | GC | Ⅰ-Ⅳ | 17-5p/20a | 65 | 3 | OS | Median |
| KATADA 2008[35] | Japan | GC | LNM $n_1$-$n_4$ | 20b | 42 | >4 | OS | Mean |
| CHEN et al. 2015[42] | China | GC | Ⅰ-Ⅲ | 18a | 90 | >3 | OS | 3 scores |
| SU et al. 2014[19] | China | GC | T1-T4 | 18a | 82 | >5 | OS/CSS/DFS | 4.85 |
| XUE et al. 2015[11] | China | GC | Ⅰ-Ⅳ | 20b | 102 | >5 | OS | Mean |
| AYERBES et al. 2011[18] | Spain | GIC | Ⅰ-Ⅳ | 17 | 33 | >2 | OS/PFS | Mean |
| SU et al. 2015[20] | China | HCC | Ⅰ-Ⅳ | 92a | 90 | >5 | OS | Mean |
| CHEN et al. 2012[44] | China | HCC | Ⅰ-Ⅳ | 17-5p | 120 | >3 | OS/DFS | Median |
| DIAZ et al. 2008[40] | Spain | CC | Ⅰ-Ⅳ | 17-5p | 110 | >6 | OS/DFS | 4.35 |
| YU et al. 2012[10] | China | CC | Ⅰ-Ⅳ | 17/18a19a19b | 48 | >5 | OS | Median |
| ZHANG et al. 2013[8] | China | CC | Ⅱ | 20a-5p | 735 | >5 | DFS | Risk[e] |
| MA et al. 2012[27] | China | CRC | Ⅰ-Ⅳ | 17-5p | 425 | >5 | OS | Median |
| LI et al. 2015[32] | China | CRC | Ⅱ-Ⅲ | 17-3p | 175 | >2 | DFS | 1.613 |
| FANG et al. 2014[39] | China | CRC | Ⅰ-Ⅳ | 17 | 295 | 8 | OS | Score 7 |
| LIU et al. 2013[29] | China | CRC | Ⅰ-Ⅳ | 92a | 166 | >3 | OS | Mean |
| ZHOU et al. 2012[7] | China | CRC | Ⅰ-Ⅳ | 92a | 82 | >5 | OS | 2.4 fold |
| KE et al. 2015[34] | China | CRC | Ⅰ-Ⅳ | 92a | 158 | >4 | OS | Mean |
| WU et al. 2013[16] | China | CRC | DukesA-C | 18a | 45 | 6 | PFS | Median |
| YU et al. 2012[9] | Japan | PC | Ⅰ-Ⅳ | 17-5p | 80 | >6 | OS | 5.69 |
| MITANI et al. 2013[25] | USA | SACC | Ⅰ-Ⅳ | 17/20a/92a | 30 | >4 | OS | 2 |
| CHANG et al. 2013[45] | China | OSCC | Ⅰ-Ⅳ | 17a/20a | 98 | 7 | OS | 0.24[b] |
| XI et al. 2015[14] | China | T-LBL | Ⅰ-Ⅳ | 17/19 | 57 | 13 | OS | Median |
| SANFIORENZO et al. 2013[21] | France | NSCLC | Ⅰ-Ⅲ | 20a-5p | 52 | >5 | DFS | Mean |
| LIN et al. 2013[30] | China | NSCLC | Ⅰ-Ⅲ | 19a | 201 | >3 | OS | 2 fold |
| WU et al. 2014[15] | China | NSCLC | Ⅰ-Ⅲ | 19b | 155 | >3 | OS | Median |
| SAITO et al. 2012[22] | Japan/USA | NSCLC | Ⅰ-Ⅲ | 17 | 191/89 | >6 | RFS/CSS | Median |
| | Norway | | | | 37 | | CSS | |
| CHEN et al. 2012[43] | China | LC | Ⅰ-Ⅳ | 17-5p | 221 | >3 | OS | Median |
| GE et al. 2015[38] | China | chRCC | Ⅰ-Ⅳ | 19a | 58 | >5 | RFS | Median |
| LIN et al. 2014[31] | Australia | PCa | - | 20a | 100 | >5 | OS | Median |
| QIANG et al. 2014[23] | China | PCa | - | 20a | 34 | >10 | OS | Median |
| HE et al. 2013[36] | China | PCa | T2a-T4 | 19a | 20 | >8 | RFS | Mean |
| HAO et al. 2014[37] | China | myeloma | Ⅰ-Ⅲ | 19a | 103 | >3 | OS/PFS | Mean |
| XIE et al. 2014[13] | China | OC | Ⅰ-Ⅳ | 20a | 35 | >4 | OS | Median |
| MARCHINI et al. 2011[26] | Italy | OC | Ⅰ | 20a | 89 | >9 | OS/PFS | Median |
| SAHIBERG et al. 2014[33] | USA | BCa | Ⅰ-Ⅲ | 18b | 40 | >5 | OS/RFS | Median |
| NILSSON et al. 2012[24] | USA | BCa | Ⅰ-Ⅲ | 92a | 117 | >6 | RFS | Median |
| LUO et al. 2013[28] | China | NPC | Ⅰ-Ⅳ | 18a | 68 | >5 | OS | Mean |

ESCC: Esophageal squamous carcinoma; GC: Gastric carcinoma; GIC: Gastrointestinal cancer; HCC: Hepatocellular carcinoma; CC: Colon Cancer;CRC: Colorectal cancer; PC: Pancreatic cancer; OSCC: Oral squamous cell carcinoma;SACC: Salivary adenoid cystic carcinoma; T-LBL: T-cell lymphoblastic lymphoma;LC: Lung cancer; NSCLC: non-small cell lung cancer; chRCC: Chromophobe renal cell carcinoma; PCa: Prostate cancer; OC: Ovarian cancer; BCa: Breast cancer; NPC: Nasopharynx cancer;OS: Overall survival; DFS: Disease free survival; PFS: Progression free survival; CSS: Cancer specific survival; RFS: Recurrence or relapse free survival; 75$^{th}$%[a]: 75$^{th}$ percentiles of $2^{-\triangle\triangle Ct}$; 0.24[b]: multiple of change >0.24; Risk[e]: Risk score

2.2　miR-17-92 簇高表达与肿瘤患者 OS 的关系

共纳入 31 篇涉及 OS 研究的文献,包含 46 个研究及 3 455 例患者,研究间呈中度异质性,$I^2$ = 46.8%,$P$ = 0.000,鉴于肿瘤、样品来源及 miRNA 成员实际异质性,应用随机效应模型,合并风险比(HR = 1.83,95% CI:1.58 ~ 2.12,$P$ = 0.000)表明 miR-17-92 簇高表达的肿瘤患者 OS 较低(图 2)。根据肿瘤类型、miR-17-92 簇成员、样品、地域进一步进行亚组分析。

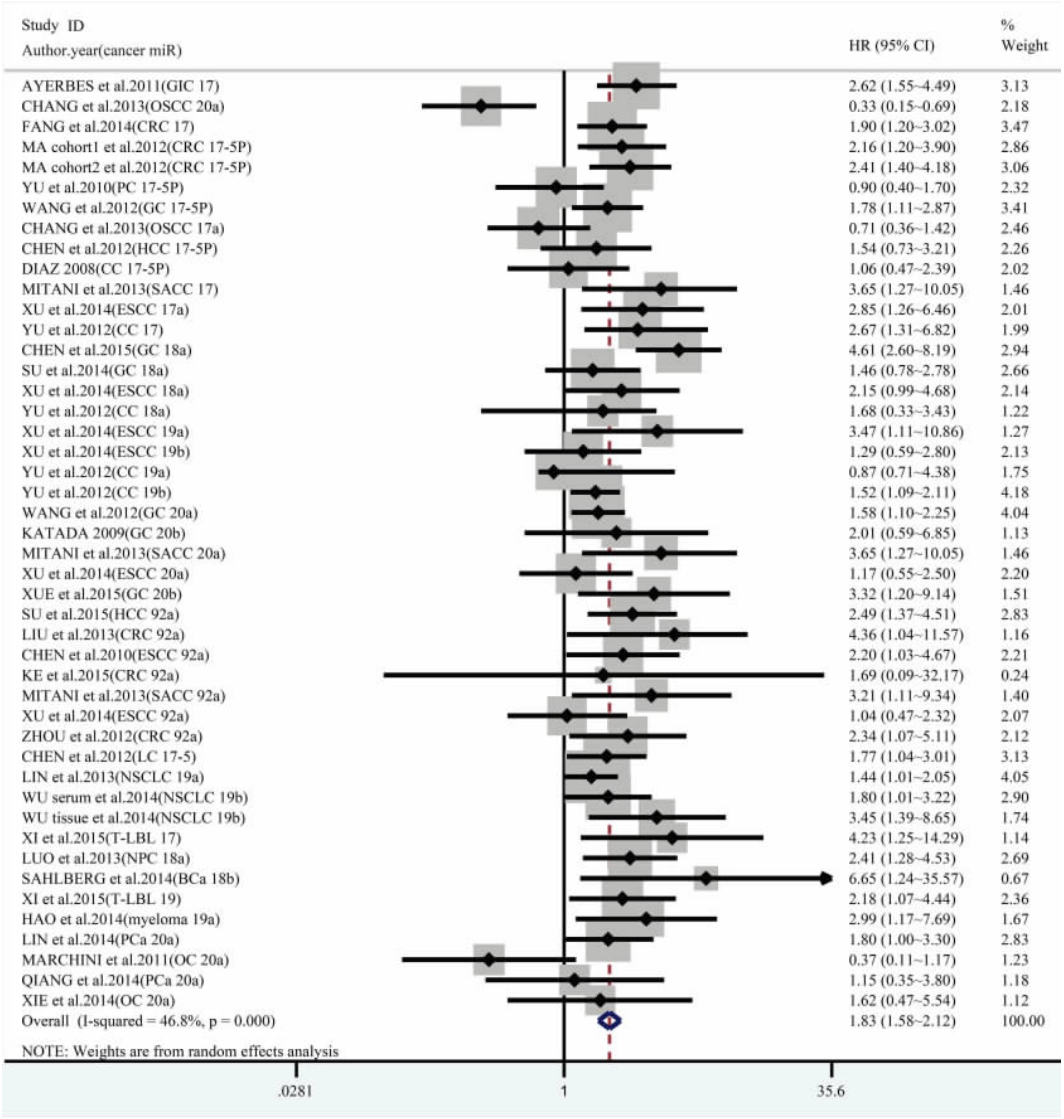


**图 2　miR-17-92 簇的高表达与恶性肿瘤患者 OS 关系的森林图**

**Fig. 2　Forest plot of the association between increased miR-17-92 cluster and OS of cancer patients**

在肿瘤类型亚组中,乳腺癌、肾癌、淋巴瘤等研究数量少,统一归类为其他肿瘤进行分析,消化系统肿瘤、肺癌及其他肿瘤 miR-17-92 簇高表达的肿瘤患者的 OS 均较低表达组低;在 miR-17-92 簇取样来源亚组中,新鲜组织、FFPE 组织和血样中 miR-17-92 簇高表达的肿瘤患者的 OS 均较低表达组低;亚洲人群和非亚组人群 miR-17-92 簇高表达肿瘤患者的 OS 同样低于低表达组;就 miR-17-92 簇单一成员表达异常对恶性肿瘤患者 OS 影响而言,在 miR-17-92 簇成员(miR-17,miR-18,miR-19,miR-20,miR-92)亚组中,每一成员高表达的恶性肿瘤患者的 OS 均低于低表达组。各亚组分析合并效应量详见表 2。

2.3　miR-17-92 簇的高表达与肿瘤患者 DFS/PFS/RFS/CSS 的关系

2.3.1　DFS　见图 3,共纳入 6 篇文献,包含 8 个研究及 1 274 例患者,异质性检验显示,$I^2$ = 0.0%,

$P=0.838$，采用固定效应模型，合并 HR = 1.80，95% CI：1.43-2.26，$P=0.000$；表明 miR-17-92 簇高表达肿瘤患者的 DFS 低。

**表 2 miR-17-92 簇的高表达与恶性肿瘤患者 OS 的亚组分析结果**

**Tab. 2 Results of subgroup analysis about association between increased miR-17-92 cluster and OS of cancer patients**

| Subgroup analysis | Number of study | Number of case | HR( 95% CI ) | *P* | Heterogeneity | |
|---|---|---|---|---|---|---|
| | | | | | $I^2$ | *P* |
| Global effect | 46 | 3 455 | 1.83 ( 1.58 ~ 2.12 )b | 0.000 | 46.80% | 0.000 |
| Origin of cancer | | | | | | |
| Digestive system | 33 | 2 352 | 1.81 ( 1.51 ~ 2.17 )[b] | 0.000 | 52.20% | 0.000 |
| Lung | 4 | 577 | 1.68 ( 1.31 ~ 2.17 )[a] | 0.000 | 6.10% | 0.363 |
| Other | 9 | 526 | 1.96 ( 1.30 ~ 2.96 )[b] | 0.001 | 41.90% | 0.008 |
| Sample | | | | | | |
| Tissue | 10 | 1 212 | 1.60 ( 1.25 ~ 2.04 )[b] | 0.000 | 51.60% | 0.001 |
| FFPE | 10 | 1 138 | 2.34 ( 1.94 ~ 2.84 )[a] | 0.000 | 36.20% | 0.118 |
| Blood | 26 | 1 105 | 1.71 ( 1.44 ~ 2.03 )[a] | 0.000 | 0.00% | 0.571 |
| Region | | | | | | |
| Asian | 37 | 2 895 | 1.80 ( 1.54 ~ 2.10 )[b] | 0.000 | 46.00% | 0.001 |
| Non-asian | 9 | 560 | 2.06 ( 1.29 ~ 3.29 )[b] | 0.000 | 52.80% | 0.031 |
| miRNAs component[c] | | | | | | |
| miR-17 | 14 | 1 350 | 1.86 ( 1.57 ~ 2.20 )[a] | 0.000 | 39.40% | 0.064 |
| miR-18 | 6 | 280 | 2.56 ( 1.89 ~ 3.47 )[a] | 0.000 | 44.30% | 0.110 |
| miR-19 | 9 | 564 | 1.64 ( 1.36 ~ 1.99 )[a] | 0.000 | 15.20% | 0.307 |
| miR-20 | 9 | 467 | 1.60 ( 1.25 ~ 2.04 )[a] | 0.000 | 32.50% | 0.158 |
| miR-92 | 7 | 696 | 2.21 ( 1.60 ~ 3.06 )[a] | 0.000 | 0.00% | 0.503 |

a：Fixed effects model；b：Random effects model；c：A subgroup representing high expression of microRNA membership among miR-17-92 cluster associated with OS of cancer patients

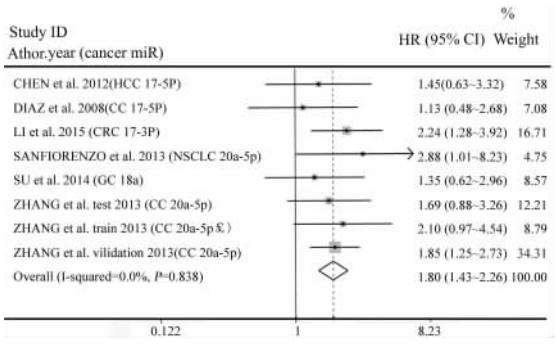


**图 3 miR-17-92 簇的高表达与恶性肿瘤患者 DFS 关系的森林图**

**Fig. 3 Forest plot of the association between increased miR-17-92 cluster and DFS of cancer patients**

2.3.2 PFS 见图 4，共纳入 5 篇文献，包含 6 个研究及 375 例患者，异质性检验显示，$I^2=57.2\%$，$P=0.039$，采用随机效应模型，合并 HR = 1.83，95% CI：1.11 ~ 3.02，$P=0.018$；表明 miR-17-92 簇高表达的恶性肿瘤患者的 PFS 低。

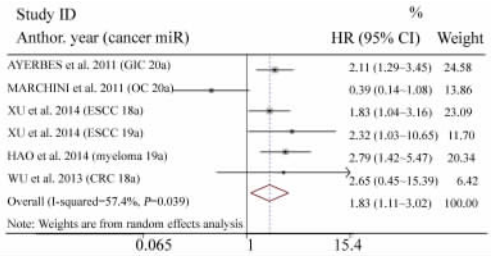


**图 4 miR-17-92 簇的高表达与恶性肿瘤患者 PFS 关系的森林图**

**Fig. 4 Forest plot of the association between increased miR-17-92 cluster and PFS of cancer patients**

2.3.3 RFS 见图 5，纳入 5 篇文献( 426 例患者 )，异质性检验显示，$I^2=68.2\%$，$P=0.013$，采用随机

效应模型,合并 HR = 1. 29,95% CI:0. 57 ~ 2. 94,$P$ = 0. 539,无统计学意义。

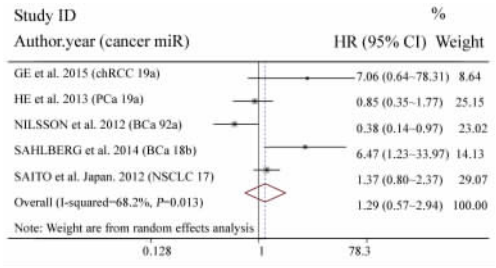


**图 5　miR-17-92 簇的高表达与恶性肿瘤患者 RFS 关系的森林图**

**Fig. 5　Forest plot of the association between increased miR-17-92 cluster and RFS of cancer patients**

2.3.4　CSS　见图 6,纳入 2 篇文献( 208 例患者 ),异质性检验显示,$I^2$ = 0. 0%,$P$ = 0. 556,采用固定效应模型,合并 HR = 1. 59,95% CI:1. 04 ~ 2. 42,$P$ = 0. 032;表明 miR-17-92 簇高表达的肿瘤患者的 CSS 低。

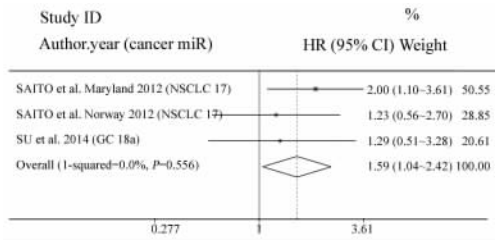


**图 6　miR-17-92 簇家族的高表达与恶性肿瘤患者 CSS 关系的森林图**

**Fig. 6　Forest plot of the association between increased miR-17-92 cluster and CSS of cancer patients**

2.4　发表偏倚

鉴于纳入研究数低于 10 时,发表偏倚检验的效能降低[46],因此只列出 miR-17-92 簇与肿瘤患者 OS 关系的漏斗图( 图 7 ),其基本对称,Egger's 检验$P$ = 0. 319,未见发表偏倚。

## 3　讨　论

最近 miR-17-92 簇已被广泛研究,其成员在肺癌[30]、肝癌[20]、结直肠癌[16, 39]、前列腺癌[23]等肿瘤中表达增高,但预后价值存在争议,因此,需采用 Meta 分析综合评估。本分析共纳入 39 篇文献,包含 68 个研究及 4 908 例患者,分析结果表明 miR-17-92 簇家族高表达组患者的生存结局较低表达组差。肿瘤类型、地域、组织来源及 miR-17-92 簇成员亚组分析均得到同样结果。

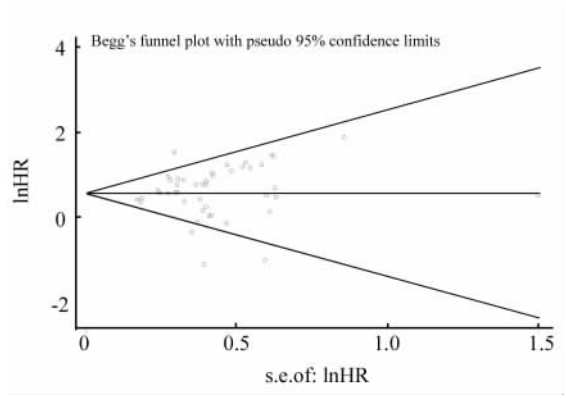


**图 7　miR-17-92 簇家族的高表达与恶性肿瘤患者 OS 关系的漏斗图**

**Fig. 7　Funnel plots of relationship between elevated miR-17-92 cluster and overall survival of cancer patients**

miR-17-92 簇在不同肿瘤中的致癌角色已被证实[47]。在肺癌、前列腺癌细胞中 Myc 基因扩增编码的 MYC 蛋白结合到 miR-17-92 簇编码基因对应的启动子区域,上调 miR-17-92 簇成员表达[48]。高表达的 miR-17 激活 P38/MAPK 通路,诱导热休克蛋白 27 磷酸化,促进肝癌细胞增殖、转移[45, 49],并能激活 Wnt/β-catenin 通路,促进结直肠癌进展[27];miR-18a 抑制 P53 表达,促进胃癌细胞增殖、侵袭转移[42],抑制 PIAS3 的表达,促进 STAT3 调控相关癌基因的表达及胃腺癌的进展[49];高表达的 miR-19 与肺癌的 TNM 分期及淋巴结转移有关[30],下调 TNF-α 的表达,促进食管癌细胞增殖,抗癌细胞凋亡[50];miR-20 靶向非受体型酪氨酸激酶 ABL2 促进前列腺癌细胞侵袭和转移[23];miR-92 抑制 PTEN 表达,激活 PTEN/PI3K/AKT 信号通路,促进直肠癌细胞侵袭转移[34],抑制 CDH1 的表达,降低 E 钙连蛋白水平,促进食管鳞癌细胞转移[41]。转染 miR-17-5P 的结直肠癌细胞中 PTEN 的表达量降低,并对奥沙利铂、伊立替康及氟尿嘧啶产生明显的耐药性[39]。miR-19 靶向 PTEN 调控乳腺癌细胞耐药相关蛋白( MRP-1, MDR-1, BCRP )表达[51]。综上所述,miR-17-92 簇成员以致癌的角色参与恶性肿瘤细胞的增殖、侵袭转移及耐药,促进恶性肿瘤的进展。本研究亦进一步证实了 miR-17-92 簇的致癌作用,并为其致癌角色提供临床循证医学证据。

Hayes 等[52]认为,HR < 1. 5 是弱的预后危险因素。本研究结果表明,miR-17-92 簇高表达对恶性肿

瘤患者有较高的危险性。对于 OS，miR-17-92 簇的高表达在消化系统肿瘤及肺癌患者中有独立的预后作用，亚洲人群、非亚洲人群亚组合并的 HR 均有明显危险性，提示 miR-17-92 簇高表达的致癌作用无人种地域特异性。能够更有效地预测肿瘤预后的 miR-17-92 簇成员个数还未知，在 miRNA-17-92 簇成员的亚组分析中，每一成员（miR-17/18/19/20/92）高表达均对恶性肿瘤患者的预后不利，它们都是独立的预后因子，进一步证实了 miR-17-92 簇高表达的危险性。高表达的 miR-17、miR-20、miR-19a/b 可以协同削弱 *PTEN* 编码的关键 mRNA 的作用，*PTEN* 表达的下调将增强 AKT/mTOR 信号，促进肿瘤发生[48]。因此推测，联合检测 miR-17/18/19/20/92 的表达量会增强生存预后预测效果，但需深入研究。

在纳入研究中，就临床应用而言，主要样品来源包括血标本、新鲜组织、石蜡包埋组织，目前还不清楚哪一种样品更好。亚组分析发现，三种样品来源 miR-17-92 簇高表达均有独立的预后危险性。Xi 等[53]认为甲醛不会改变 miRNAs 的稳定性，石蜡包埋组织中 miRNAs 和新鲜组织中的相关性很好。miRNAs 从肿瘤组织释放入血液，仍能抵抗 RNA 酶保持较好的稳定性[54]。3 种样品有各自的应用价值，石蜡包埋组织容易储存，便于回顾性观察研究使用；而新鲜肿瘤组织是最稳定的样本来源，可靠性高，便于术后立即检测研究。miRNAs 由组织细胞被动或主动释放入体液[55]，因此推测可以通过组织比血液更早检测到 miR-17-92 簇的异常表达。但对于不能手术切除中晚期肿瘤患者，血样的采集更便捷，也便于监测 miR-17-92 簇的表达水平。

本研究存在一些局限，大部分研究采用中位数及平均数作为 miR-17-92 簇高低表达分界值（cut-off），其余研究的分界值采用危险评分、相对倍数及具体表达量等（表 1）。分界值的不同会增加结果的异质性，同时将限制 miR-17-92 簇对恶性肿瘤患者预后预测的临床应用，合理的标准化分界值应被进一步临床研究确定；CSS 分析纳入文献数较少，该部分结果精确性欠佳，期待更多 miR-17-92 簇家族与 CSS 关系的研究。本研究初步分析了 miR-17-92 簇高表达与恶性肿瘤患者预后的关系，miR-17-92 簇在不同恶性肿瘤中的预后作用需进一步研究。

总之，miR-17-92 簇高表达肿瘤患者的生存率低。对于 OS，miR-17-92 簇高表达在消化道肿瘤及肺癌患者中有独立危险性；并且 miR-17-92 簇中每一成员高表达均有独立的危险性。miR-17-92 簇的高表达与恶性肿瘤患者的预后差有关，有望成为新型的肿瘤预后标志物，并为肿瘤分子靶向治疗提供新途径，但仍需更多高质量研究进一步证实。

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[本文编辑] 黄静怡

·读者·作者·编者·

## 《中国肿瘤生物治疗杂志》免收审稿费的通知

《中国肿瘤生物治疗杂志》本着竭诚为广大作者和读者服务的宗旨，加大力度努力宣传我国肿瘤生物治疗领域的科技成果，以推动我国肿瘤防治事业的发展，本刊从 2015 年 10 月开始取消稿件审理费用，欢迎肿瘤生物治疗领域基础和临床研究工作者积极踊跃投稿。

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