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·论 著·

# C反应蛋白/白蛋白比值在胃黏膜相关淋巴组织淋巴瘤中的预后预测价值

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［摘要］ **目的** 探讨C反应蛋白与白蛋白比值（C-creative protein/albumin ratio, CAR）预测胃黏膜相关淋巴组织（MALT）淋巴瘤患者预后的价值。**方法** 纳入2004年1月至2020年6月在复旦大学附属中山医院初诊的胃MALT淋巴瘤患者，计算其CAR。通过X-tile软件获取最佳CAR临界值，将患者分为低CAR组和高CAR组。收集两组患者的基线数据及生存资料。应用Cox分析和Kaplan-Meier法分析CAR在胃MALT淋巴瘤的预后预测意义。**结果** CAR的最佳临界值为0.05。与低CAR组（CAR＜0.05，$n$＝66）相比，高CAR组（CAR≥0.05，$n$＝27）中高龄（70岁以上）、贫血患者更多，C反应蛋白水平、$\beta_2$-微球蛋白水平更高，白蛋白水平更低（$P$＜0.05）。Cox多因素分析示IgG为患者预后的独立预测因素（HR＝0.528, 95%CI 0.304～0.915, $P$＝0.023）。低CAR组中位总生存期（overall survival，OS）长于高CAR组（172.8个月 *vs* 112.7个月，$P$＝0.020）。不同MALT-IPI评分组患者OS差异无统计学意义；CAR联合MALT-IPI评分2分患者OS明显短于0分和1分患者（$P$＜0.05）。**结论** 高CAR组患者预后更差，CAR可用于评估胃MALT淋巴瘤患者预后。

［关键词］ 胃黏膜相关淋巴组织淋巴瘤；C反应蛋白/白蛋白比值；生存；MALT淋巴瘤国际预后指数

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## Prognostic value of the C-reactive protein/albumin ratio in gastric mucosa-associated lymphoid tissue lymphoma

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［**Abstract**］ **Objective** To investigate the prognostic value of C-reactive protein/albumin ratio (CAR) in gastric mucosa-associated lymphoid tissue (MALT) lymphoma. **Methods** The patients with gastric MALT lymphoma initially diagnosed in Zhongshan Hospital, Fudan University from January 2004 to June 2020 were included, and CAR values were calculated. These patients were divided into a low-CAR group ($n$＝66) and a high-CAR group ($n$＝27) according to the optimal CAR cut-off value obtained by X-tile software. The baseline indicators and survival states between the two groups were collected. The Cox regression analysis and Kaplan-Meier method were used to assess the prognostic significance of CAR in gastric MALT lymphoma. **Results** The optimal cut-off value of CAR was 0.05. Compared with the low-CAR group (CAR＜0.05, $n$＝66), the high-CAR group (CAR≥0.05, $n$＝27) had more patients older than 70 years old, higher anemia rate, higher C-reactive protein and $\beta_2$-microglobulin levels, and lower albumin level ($P$＜0.05). Multivariate Cox analysis showed that IgG was an independent predictive factor (HR＝0.528, 95%CI 0.304-0.915, $P$＝0.023). The median overall survival (OS) time was longer in the low-CAR group than that in the high-CAR group (172.8 months *vs* 112.7 months, $P$＝0.020). There was no significant difference in OS among different MALT-IPI score groups; the OS of patients with CAR combined with MALT-IPI score 2 was significantly worsen than patients with score 0 or 1 ($P$＜0.05). **Conclusions** The prognosis of patients in high CAR group was worsen. The CAR can be used as an indicator for predicting the prognosis of gastric MALT lymphoma.

［**Key Words**］ gastric mucosa-associated lymphoid tissue lymphoma; C-reactive protein/albumin ratio; survival; MALT lymphoma international prognostic index

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黏膜相关淋巴组织（mucosa-associated lymphoid tissue, MALT）淋巴瘤是边缘区淋巴瘤（marginal zone lymphoma，MZL）的最常见亚型[1]，其中胃是最常见的受累部位[2]。胃MALT淋巴瘤在原发胃淋巴瘤中约占38%，仅次于胃弥漫大B细胞淋巴瘤[3]。慢性炎症刺激和自身免疫疾病是MALT淋巴瘤发病的两大重要因素[4]。而幽门螺旋杆菌（*Helicobacter pylori*，*H. pylori*）感染是胃MALT淋巴瘤的重要致病因素[5]。

基于营养状况和（或）炎症反应的多种评分体系，如中性粒细胞/淋巴细胞比值、淋巴细胞/单核细胞比值、血小板/淋巴细胞比值、Glasgow预后评分已用于多种肿瘤患者的预后评估[6-8]。C反应蛋白（C-creative protein, CRP）/白蛋白（albumin, ALB）比值（CAR）能同时反映肿瘤患者的炎症及营养状况[9-10]。已有研究发现高CAR值与鼻咽癌[11]、胃癌[12]等多种实体瘤患者不良预后相关。目前，CAR与淋巴瘤关系的研究较少。本研究旨在探讨CAR应用于胃MALT淋巴瘤患者预后评估的价值。

## 1　资料与方法

1.1　*一般资料*　纳入2004年1月至2020年6月在复旦大学附属中山医院初诊的胃MALT淋巴瘤患者。纳入标准：年龄≥18岁；经胃镜活检或手术后病理检查证实为胃MALT淋巴瘤。胃MALT淋巴瘤诊断参照2016年WHO造血和淋巴组织肿瘤分类（第4版）标准。排除标准：病理发生组织学转化（如向弥漫大B细胞淋巴瘤转化）；初诊时合并其他恶性肿瘤；合并可能影响CRP水平的其他疾病，如急慢性炎症、风湿性疾病等。共纳入93例患者，男性60例、女性33例，年龄23～83岁，平均年龄（58.9±12.3）岁。

1.2　*治疗方法*　根据B细胞淋巴瘤NCCN指南推荐，对患者进行抗*H. pylori*治疗、局部治疗、系统性治疗。3例患者无治疗指征，定期随访。38例患者仅接受抗*H. pylori*治疗。39例患者接受靶向治疗和（或）全身化疗，其中部分患者接受抗*H. pylori*治疗。6例患者外科手术或内镜黏膜下剥离术（endoscopic submucosal dissection，ESD）后达完全缓解（CR），持续观察随访直至末次随访。7例患者接受局部放疗。

1.3　*基线指标及分组*　收集入组患者初诊入院后基线资料，包括性别、年龄、症状、结外受累部位，血红蛋白、血小板、白细胞、淋巴细胞、中性粒细胞、CRP、ALB、乳酸脱氢酶（LDH）、免疫球蛋白、$\beta_2$微球蛋白（$\beta_2$-microglobulin, $\beta_2$-MG）、血清铁蛋白（serum ferritin, SF）等实验室检查结果，影像学检查结果（全身增强CT或PET-CT），病理检查结果。临床分期采用胃肠道淋巴瘤Lugano分期系统，分为Ⅰ期、Ⅱ期、ⅡE期和Ⅳ期[13]。预后评分采用MALT国际预后指数（MALT international prognostic index, MALT-IPI）。计算患者CAR，用X-tile软件获得CAR的最佳临界值。根据该临界值将患者分为高CAR组与低CAR组。

1.4　*结局指标*　分别于初诊后1年、3年、5年随访患者生存情况，随访截止时间为患者死亡或末次随访的时间，末次随访时间为2022年6月30日。总生存期（overall survival, OS）指从疾病确诊至患者死亡或观察截止的时间。无进展生存期（progression-free survival, PFS）指从疾病确诊至发生进展或因任何原因死亡的时间。最终疗效指疾病首次进展前的疗效，若无进展，则根据最后1次随访时的状态来评估。患者治疗后达到CR或部分缓解（partial remission, PR），为疗效良好，否则为疗效不佳。

1.5　*统计学处理*　采用SPSS 23.0软件进行统计学分析。计量资料符合正态分布时用$\bar{x}\pm s$表示，两组间比较采用$t$检验；不符合正态分布时用$M(P_{25}, P_{75})$表示，组间比较采用非参数检验。计数资料以$n$(%)表示，组间比较采用$\chi^2$检验。采用Kaplan-Meier法绘制生存曲线。采用Cox风险模型分析生存影响因素。检验水准（$\alpha$）为0.05。

## 2　结　果

2.1　*低CAR组与高CAR组间基线指标比较*　CAR最佳临界值为0.05，CAR≥0.05者27例（高CAR组）、CAR＜0.05者66例（低CAR组）。结果（表1）显示：与低CAR组患者相比，高CAR组≥70岁、贫血患者更多，国际预后指数（IPI）评分更高，$\beta_2$-MG水平更高（$P$＜0.05）。

**表 1 高、低 CAR 组患者的临床、实验室指标比较**

**Table 1 Comparison of clinical and laboratory indicators between high and low CAR groups**

| Indicator | Low-CAR group ($n$=66) | High-CAR group ($n$=27) | $\chi^2/t/U$ value | $P$ value |
|---|---|---|---|---|
| Age $n$(%) | | | 4.763 | 0.029 |
| ≥70 years | 9(13.64) | 9(33.33) | | |
| <70 years | 57(86.36) | 18(66.67) | | |
| Sex $n$(%) | | | 2.923 | 0.087 |
| Male | 39(59.09) | 21(77.78) | | |
| Female | 27(40.91) | 6(22.22) | | |
| Hb/(g•L$^{-1}$) | 130.42±18.83 | 123.70±23.52 | -1.450 | 0.150 |
| WBC/($\times10^9$•L$^{-1}$) | 5.41±1.46 | 5.64±1.86 | 0.643 | 0.522 |
| N/($\times10^9$•L$^{-1}$) | 3.40±1.14 | 3.55±1.42 | 0.542 | 0.589 |
| L/($\times10^9$•L$^{-1}$) | 1.48±0.63 | 1.55±0.56 | 0.477 | 0.635 |
| PLT/($\times10^9$•L$^{-1}$) | 216.18±70.75 | 206.26±60.51 | -0.639 | 0.525 |
| ALB/(g•L$^{-1}$) | 43.64±4.10 | 39.22±4.07 | -4.722 | <0.001 |
| GLB/(g•L$^{-1}$) | 25.86±4.04 | 26.67±4.85 | 0.819 | 0.415 |
| LDH/(U•L$^{-1}$) | 175.05±29.08 | 181.44±37.19 | 0.886 | 0.378 |
| IgG/(g•L$^{-1}$) | 11.85(10.26, 13.70) | 11.04(10.05, 12.84) | 0.849 | 0.396 |
| $\beta_2$-MG/(mg•L$^{-1}$) | 1.94(1.63, 2.33) | 2.83(2.25, 3.49) | 3.575 | <0.001 |
| CRP/(mg•L$^{-1}$) | 0.60(0.40, 1) | 5.40(2.70, 11.50) | 7.499 | <0.001 |
| SF/(ng•mL$^{-1}$) | 116.95(33.57, 241.35) | 77.50(24.30, 188.45) | 0.678 | 0.498 |
| Symptom B $n$(%) | 10(15.15) | 5(18.51) | 0.008 | 0.928 |
| Anemia $n$(%) | 8(12.12) | 9(33.33) | 4.439 | 0.035 |
| Lymph nodes involvement $n$(%) | 33(50.00) | 18(66.67) | 2.149 | 0.143 |
| Ki-67* $n$(%) | | | 0.105 | 0.746 |
| ≥30% | 11(18.33) | 3(12.50) | | |
| <30% | 49(81.67) | 21(87.50) | | |
| Lugano stage $n$(%) | | | -1.378 | 0.168 |
| Stage Ⅰ | 27(40.91) | 8(29.63) | | |
| Stage Ⅱ＋ⅡE | 24(36.36) | 9(33.33) | | |
| Stage Ⅳ | 15(22.73) | 10(37.04) | | |
| MALT-IPI score $n$(%) | | | -2.289 | 0.022 |
| 0 | 39(59.09) | 10(37.04) | | |
| 1 | 27(40.91) | 14(51.85) | | |
| 2 | 0 | 3(11.11) | | |
| Final efficacy $n$(%) | | | 0.043 | 0.836 |
| CR＋PR | 45(68.18) | 19(70.37) | | |
| PD＋SD | 21(31.82) | 8(29.63) | | |

CAR: C-reactive protein/albumin ratio; Hb: hemoglobin; WBC: leukocyte; N: neutrophil; L: lymphocyte; PLT: platelet; ALB: albumin; GLB: globulin; LDH: lactate dehydrogenase; IgG: immunoglobulin G; $\beta_2$-MG: $\beta_2$ microglobulin; CRP: C-reative protein; SF: serum ferritin; CR: complete remission; PR: partial remission; PD: progressive disease; SD: stable disease. *84 patients underwent detection of Ki-67.

2.2 胃 MALT 淋巴瘤患者预后的影响因素分析 单因素 Cox 生存分析结果（表 2）显示：最终疗效、ALB 水平、IgG 水平、CAR 与胃 MALT 淋巴瘤患者预后相关。多因素 Cox 生存分析结果显示，IgG 为胃 MALT 淋巴瘤患者预后独立预测因素（HR＝0.528, 95%CI 0.304～0.915, $P$＝0.023）。

2.3 低 CAR 组与高 CAR 组间生存比较 高 CAR 组中位 OS 112.7 个月、中位 PFS 96.5 个月；低 CAR 组中位 OS 172.8 个月，中位 PFS 152.8 个月。截至随访终点，低 CAR 组除 3 例（4.5%）失访外均存活，高 CAR 组中有 6 例（22.2%）死亡。结果（图 1、表 3）显示：低 CAR 组患者 OS 高于高 CAR 组（$P$=0.020），两组间 PFS 差异无统计学意义（$P$=0.446）；随着随访时间延长，两组生存差异更明显。

**表 2　胃 MALT 淋巴瘤单因素 Cox 生存分析**

**Figure 2　Univariate Cox analysis of gastric MALT lymphoma**

| Variable | HR (95% CI) | *P* value |
|---|---|---|
| Age (≥70 years *vs* <70 years) | 0.970 (0.111-8.462) | 0.978 |
| Sex (Male *vs* Female) | 0.282 (0.033-2.431) | 0.250 |
| Ki-67 (≥30% *vs* <30%) | 2.560 (0.258-25.429) | 0.422 |
| Anemia | 2.709 (0.484-15.169) | 0.257 |
| Symptom B | 2.743 (0.491-15.334) | 0.250 |
| Lugano stage (Stage Ⅰ *vs* [Ⅱ+ⅡE]) | 0.386 (0.078-1.920) | 0.245 |
| MALT-IPI score (≥1 *vs* <1) | 1.873 (0.479-7.321) | 0.367 |
| MALT-IPI score (2 *vs* <2) | 1.873 (0.479-7.321) | 0.367 |
| Final efficacy ([CR+PR] *vs* [PD+SD]) | 0.027 (0.003-0.266) | 0.002 |
| CAR(≥0.05 *vs* <0.05) | 0.118 (0.014-1.013) | 0.049 |
| Hb | 0.984 (0.950-1.020) | 0.386 |
| WBC | 1.268 (0.758-2.123) | 0.366 |
| N | 1.664 (0.915-3.027) | 0.095 |
| L | 0.836 (0.239-2.921) | 0.779 |
| PLT | 0.997 (0.985-1.008) | 0.560 |
| ALB | 0.676 (0.494-0.924) | 0.014 |
| GLB | 0.936 (0.782-1.119) | 0.468 |
| LDH | 0.991 (0.963-1.021) | 0.557 |
| IgG | 0.634 (0.427-0.944) | 0.025 |
| β2-MG | 1.427 (0.677-3.006) | 0.350 |
| CRP | 0.988 (0.889-1.085) | 0.799 |
| SF | 1.000 (0.994-1.006) | 0.905 |

CR: complete remission; PR: partial remission; PD: progressive disease; SD: stable disease; CAR: C-reactive protein/albumin ratio; Hb: hemoglobin; WBC: leukocyte; N: neutrophil; L: lymphocyte; PLT: platelet; ALB: albumin; GLB: globulin; LDH: lactate dehydrogenase; IgG: immunoglobulin G; $\beta_2$-MG: $\beta_2$-microglobulin; CRP: C-reative protein; SF: serum ferritin.

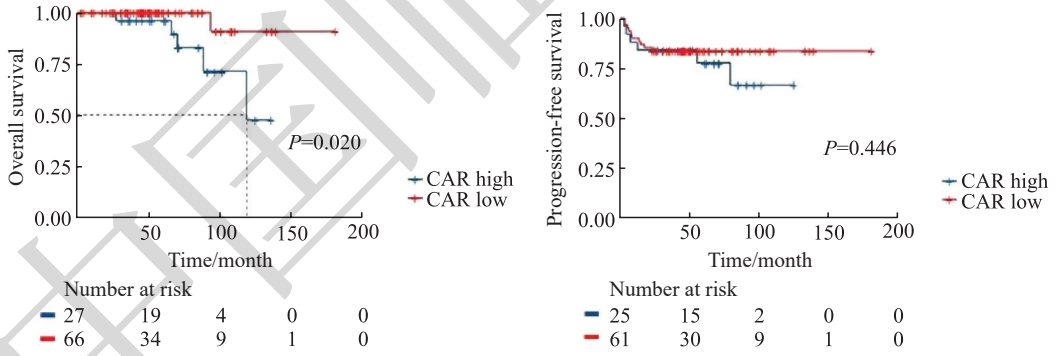


**图 1　Kaplan-Meier 曲线分析低 CAR 组和高 CAR 组患者生存**

**Figure 1　Kaplan-Meier survival analysis of patients in high and low CAR groups**

CAR: C-reactive protein/albumin ratio.

**表 3　低 CAR 组与高 CAR 组生存比较**

**Table 3　Comparison of survival between high and low CAR groups**

%

| Group | OS rate | | | PFS rate | | |
|---|---|---|---|---|---|---|
| | 1 year | 3 years | 5 years | 1 year | 3 years | 5 years |
| High CAR | 100.0 | 96.2 | 89.7 | 88.0 | 84.0 | 77.5 |
| Low CAR | 100.0 | 100.0 | 100.0 | 92.0 | 83.6 | 83.6 |

CAR: C-reactive protein/albumin ratio; OS: overall survival; PFS: progression-free survival.

2.4　不同 CAR 联合 MALT-IPI 评分组患者 OS 比较　不同 MALT-IPI 评分组患者 OS 差异无统计学意义（*P*=0.358，图 2A）。将高 CAR 记为 1 分，低 CAR 记为 0 分，并与 MALT-IPI 评分相加，得出 CAR 联合 MALT-IPI 评分，结果（图 2B）显示，联合评分 2 分组预后明显差于 0 分组（*P*=0.021）和 1 分组（*P*=0.049）。

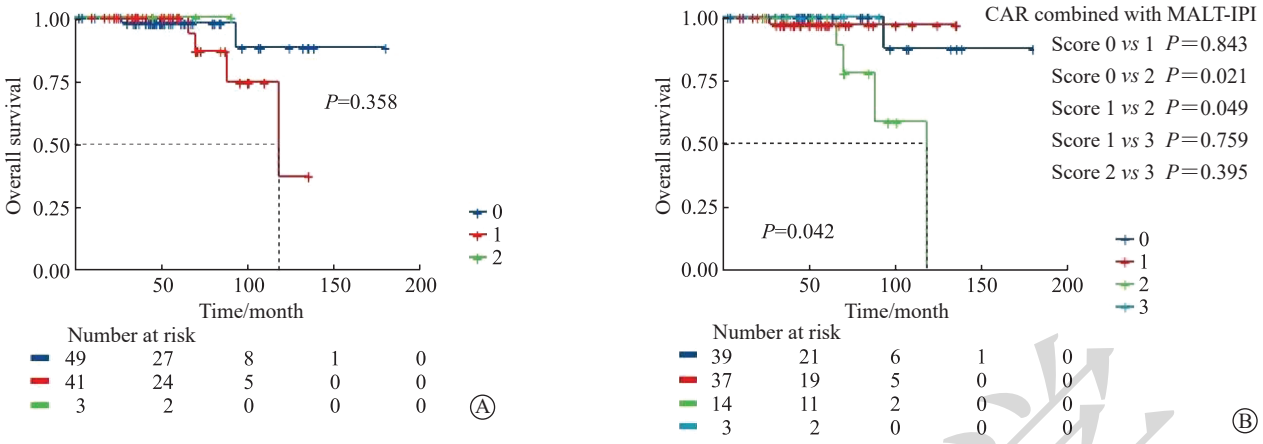


**图 2 Kaplan-Meier 曲线分析不同 CAR 联合 MALT-IPI 评分组患者生存**

**Figure 2 Kaplan Meier survival analysis of patients in different CAR combined with MALT-IPI scoring groups**

A: MALT-IPI only; B: CAR combined with MALT-IPI. High CAR as 1 point, low CAR as 0 point.

## 3 讨 论

炎症与肿瘤发生、预后的关系已获得广泛关注，如乙肝病毒感染与肝细胞癌，*H. pylori* 感染与胃腺癌、胃 MALT 淋巴瘤，慢性食管炎、食管腺上皮化生和食管癌[13-14]等。对于分期局限的胃 MALT 患者，如存在 *H. pylori* 感染，约 75% 在控制感染后获得持续的疾病缓解[15]。CRP 是临床上常用的炎症指标[16]，可用于评估多种实体肿瘤患者的预后[17-18]。国内有学者发现，基线血清 CRP 水平在评估结外 NK/T 细胞淋巴瘤（鼻型）患者预后方面有重要意义[19]。Troppan 等[20]发现，初诊时血清 CRP 水平高是弥漫性大 B 细胞淋巴瘤患者预后的独立危险因素，同时可提高修订后的国际预后指数（R-IPI）的预测水平。Adams 等[21]发现，治疗前 CRP 水平升高与弥漫性大 B 细胞淋巴瘤患者的无进展生存率和总生存率降低显著相关。

ALB 主要在肝脏合成，占血浆总蛋白的 50%，为临床评估患者营养状况的常用指标。血清 ALB 降低与多种肿瘤患者的总生存时间缩短有关[22-23]。肿瘤患者因炎症状态及慢性消耗可发生血清 ALB 水平降低。在血液系统恶性肿瘤中，ALB 已被纳入多个预后评分系统，如晚期霍奇金淋巴瘤国际预后评分（IPS）[24]、多发性骨髓瘤国际分期系统（ISS）[25]。

在鼻咽癌[11]、胃肠道恶性肿瘤[12]、肺癌[26]、和生殖系统肿瘤[27]等实体肿瘤中，CAR 为很好的预后预测指标。目前 CAR 在血液系统肿瘤中的预后预测价值尚不明确。国内外研究[11-12,26-28]显示，CAR 对实体肿瘤患者预后的预测价值的截断值波动于 0.03～0.68。本研究应用 X-tile 软件分析得出的 CAR 的最佳截断值为 0.05。本研究发现，低 CAR 组与高 CAR 组之间年龄、贫血患者比例、CRP、ALB 水平、$\beta_2$-MG 水平差异均有统计学意义，且高 CAR 组 OS 明显短于低 CAR 组（$P$=0.020），与实体肿瘤研究[17, 26]结果一致。两组患者间 OS 率、PFS 率在随访 1 年时相近，这与胃 MALT 淋巴瘤属于惰性淋巴瘤，患者总体生存时间均较长有关；随着随访时间延长，高 CAR 组 OS 率、PFS 率下降更明显。

IPI 评分为评估非霍奇金淋巴瘤患者预后最常用的指标，并不适用于惰性的 MALT 淋巴瘤[29]。对于 MALT 淋巴瘤患者，临床常使用基于临床分期、年龄、LDH 的 MALT-IPI 评分评估预后[30]，但临床分期需要依据实验室检查、骨髓穿刺及活检、全身影像学检查等判断。本研究将 MALT-IPI 评分与 CAR 相联合，结果显示联合评分为 2 分患者的 OS 更短，且评估效果优于单独 MALT-IPI 评分。

综上所述，胃 MALT 淋巴瘤患者中，CAR≥0.05 组 OS 更短，CAR 联合 MALT-IPI 评分可提高 MALT-IPI 单独应用的预后评估效果，且 CAR 值计算方便，有代替 MALT-IPI 用于该类患者的预后评

估的潜在价值。但是，由于本研究多因素Cox分析未发现CAR对患者预后的影响，同时本研究为单中心研究、纳入病例数有限，因此结论有待扩大样本量的多中心研究证实。

**伦理声明** 本研究经医院伦理委员会审批（B2017-033R），患者知情并签署知情同意书。

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