# 比较肝切除术vs.肝移植对治疗符合米兰标准的早期肝细胞癌的成本效用分析

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# 背景

- **肝细胞癌是**全球癌症死亡的第三大常见原因

- 对于具有较好肝功能的早期**肝细胞癌患者，有**两种治疗方法：
  - **Liver resection 肝切除**
  - **Cadaveric liver transplantation 肝移植**

- 哪种是最佳治疗方法仍然存在争议

- 目前仅有一个成本效用分析研究，且年份较早（发表于1998年）

# 研究目的

对于具有较好肝功能（即Child-Pugh A / B级代偿期肝硬化）且**符合米兰标准的早期肝细胞癌患者**

从长远来看，哪一种疗法具有成本效用， 来作为第一线疗法？

- **Liver resection (LR) 肝切除术**
- **Cadaveric liver transplantation (CLT)肝移植**

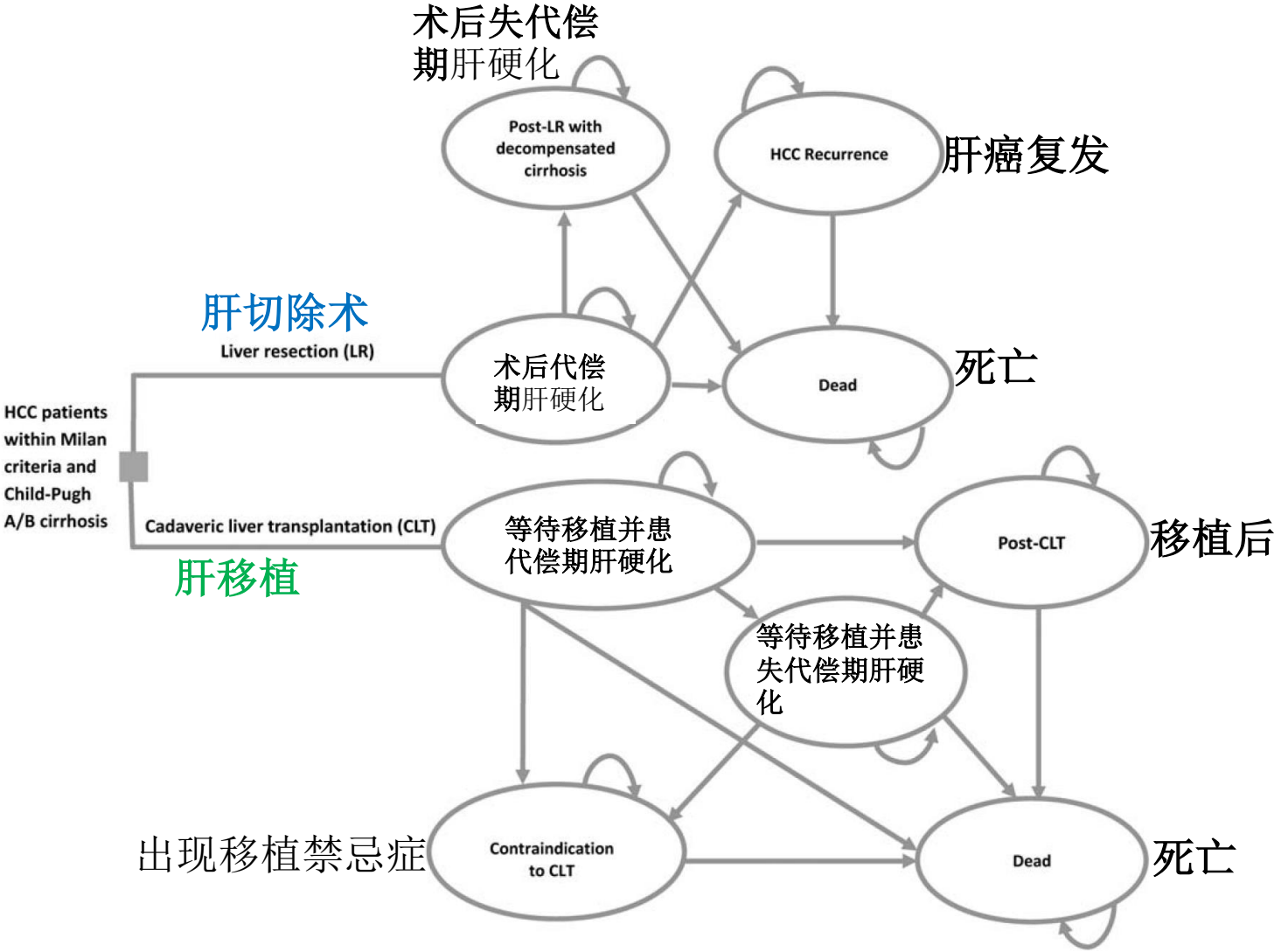
# 研究方法

- 马可夫队列模型
  - 时间范围：从LR治疗日期或放在CLT等待名单的注册日期开始到死亡
  - 周期时间：一个月

- 有效性(Effectiveness): 疗效和质量调整生命年 (QALYs)
  - 对新加坡中央医院的肝切除术患者数据库 (n=241)，美国器官采购和移植网络(OPTN)数据库(n=4381) 的分析结果
  - 文献综述

- 成本:
  - 从医疗体系的角度，选取了3个国家做为不同的成本情境
  - 与医疗资源的利用相关的直接医疗费用
  - 文献综述以及专家调研

# 总体模型结构


术后失代偿期肝硬化
Post-LR with decompensated cirrhosis
HCC Recurrence
肝癌复发
肝切除术
Liver resection (LR)
术后代偿期肝硬化
Dead
死亡
HCC patients within Milan criteria and Child-Pugh A/B cirrhosis
Cadaveric liver transplantation (CLT)
肝移植
等待移植并患代偿期肝硬化
Post-CLT
移植后
等待移植并患失代偿期肝硬化
出现移植禁忌症
Contraindication to CLT
Dead
死亡

# 模型参数：基础情境参数值和敏感性分析中的数值范围

**Table 1. Base Case Value and Sensitivity Range Extracted From Literature for Transition Probabilities**

| 参数 | | 基础情境参数值（文献范围的中位数，除非另外说明） | 敏感性分析使用的文献范围 |
|---|---|---|---|
| Background (all-cause) mortality[40] | 背景死亡率 | Age-specific | |
| Cirrhosis annual decompensation rate (%)[18-21] | 代偿期肝硬化的年度恶化率 | 11.8[18] | 3.9-12.5 |
| Derived monthly decompensation rate (%)* | | 0.98 | 0.32-1.04 |
| Decompensated cirrhosis-related 5-year cumulative survival (%)[19,20,22-24] | 失代偿期肝硬化相关的5年累积存活率 | 35 | 14-50.8 |
| Derived monthly mortality risk (%)† | | 1.73 | 1.12-3.22 |
| LR-related 30-day perioperative mortality (%)[25,26,31,35-39] | 肝切除后30天的围手术期死亡风险 | 2.2 | 0-5.3 |
| Post-LR 5-year cumulative recurrence rate (%)[25,27-31,#] | 肝切除术后5年肝癌累积复发率 | 62 | 42-78 |
| Derived monthly recurrence rate (%)‡ | | 1.60 | 0.90-2.49 |
| Annual mortality risk of recurrent HCC (%)[26,28,§,#] | 肝癌复发后的年死亡风险 | 30.1 | 23.6-38.7 |
| Derived monthly mortality risk (%)‡ | | 2.94 | 2.22-4.00 |
| Median waiting-list time to CLT (days)[7,**,††] | 50%的患者获得移植前的等待天数 (中位数) | 110** | 36-234 |
| Derived monthly probability of obtaining CLT (%)¶ | | 17.44 | 8.62-44.33 |
| 24 month dropout risk due to tumor progression (%)[41] | 2年内因肿瘤恶性发展而放弃移植的累积概率 | 53[41] | - |
| Monthly dropout risk due to tumor progression (%)†† | | - | 2.3-5.6 |
| Derived monthly dropout risk (%)‡ | | 3.10 | 2.3-5.6 |
| Annual mortality risk of HCC outside Milan (%)[44-47] | 不符合米兰标准的中晚期肝癌死亡率 | 44.2 | 33.8-51.0 |
| Derived monthly mortality risk (%)‡ | | 4.75 | 3.38-5.77 |
| CLT-related 30-day perioperative mortality (%)[35,**,††] | 移植30天的围手术期死亡率 | 3.2** | 0-9.88 |
| CLT-related 5-year cumulative survival (%)[3,5,7,8,25,35,**,††] | 移植相关的术后5年累积存活率 | 67.8** | 60-90 |
| Derived monthly mortality risk (%)† | | 0.65 | 0.18-0.85 |

# 模型参数– 成本数据 （以美国为例）

**Table 2. Base Case Value and Sensitivity Range for Costs**

| 参数 | 基础情境参数值（文献范围的中位数） | 敏感性分析的测试范围（基础情境参数值的50%到 200%） |
|---|---|---|
| **Costs in USA ($)** | | |
| One time cost of surgical treatments | 手术(一次性成本) | |
| LR cost* 肝切除术 | 25,086 | 12,543–50,172 |
| CLT cost[16,*] 肝移植 | 137,701 | 68,851–275,402 |
| TACE per session* 肝动脉栓塞化疗(每疗程) | 25,961 | 12,981–51,922 |
| Monthly follow-up cost | 随访 (每月成本) | |
| Compensated cirrhosis[16,*] 代偿期肝硬化 | 61 | 31-122 |
| Decompensated cirrhosis* 失代偿期肝硬化 | 1,519 | 760-3,038 |
| Post-CLT in Year 1* 肝移植后第1年 | 5,410† | 2,705-10,820 |
| Post-CLT in Year 2 and onwards* | 958 | 344-2,215 |
| HCC recurrence 肝切除但出现复发后 | 1,770‡ | 885-3,540 |
| Contraindication to CLT | 3,894‡ | 1,947-7,788 |

- 肝癌恶化出现移植禁忌症后

# 模型参数– 效用值数据

**Table 3. Base Case Value and Sensitivity Range Extracted From Literature for Utilities**

| 参数 | | 基础情境参数值（文献范围的中位数） | 敏感性分析的测试范围（文献范围） |
|---|---|---|---|
| Compensated cirrhosis* | 代偿期肝硬化 | 0.76 | 0.65-0.90 |
| Decompensated cirrhosis* | 失代偿期肝硬化 | 0.66 | 0.37-0.86 |
| Post-CLT in Year 1* | 肝移植后第1年 | 0.69 | 0.64-0.71 |
| Post-CLT in Year 2 and onwards* | 肝移植后第2+年 | 0.73 | 0.62-0.84 |
| Contraindication to CLT* | 出现移植禁忌症后 | 0.63 | 0.26-0.86 |
| HCC recurrence* | 肝切除但出现复发后 | 0.63 | 0.26-0.86 |

# 分析的结果 - 基础情境

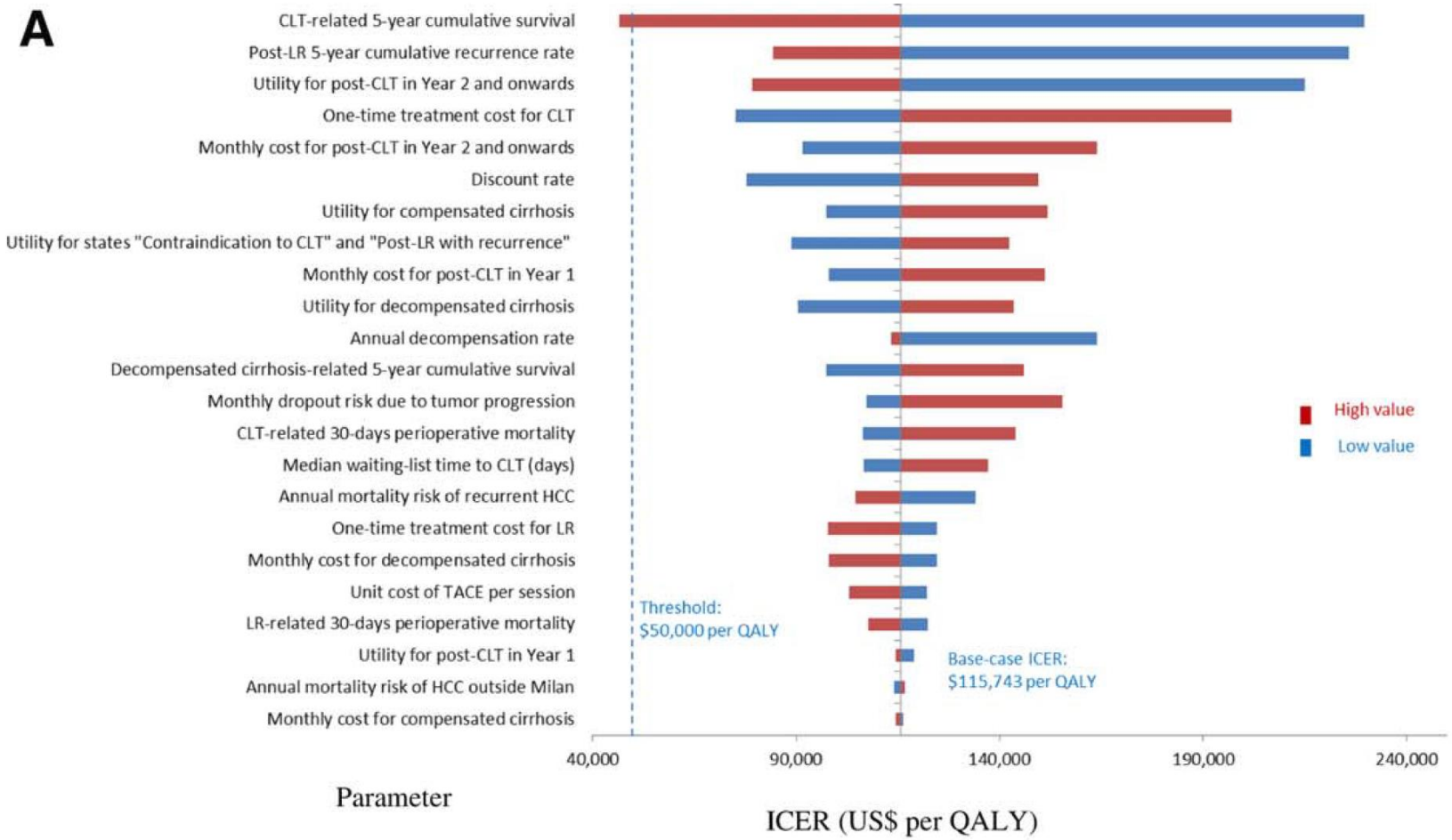
**Table 4. Incremental Cost-Effectiveness Ratios Comparing Liver Resection Versus Cadaveric Liver Transplantation in the Three Countries at the Base Case**

| | USA | | Switzerland | | Singapore | |
|---|---|---|---|---|---|---|
| **Various Costs** | **LR** | **CLT** | **LR** | **CLT** | **LR** | **CLT** |
| QALYs (years) | 3.9 | 5.3 | 3.9 | 5.3 | 3.9 | 5.3 |
| Incremental QALY gained (years) | – | 1.4 | – | 1.4 | – | 1.4 |
| Lifetime cost (US$) | 81,870 | 244,876 | 100,256 | 320,379 | 39,097 | 196,578 |
| Incremental cost (US$) | – | 163,005 | – | 220,122 | – | 157,481 |
| ICER (US$) | – | 115,743 | – | 156,300 | – | 111,821 |
| Cost-effectiveness threshold (US$) | 50,000 | | 51,507 | | 50,123 | |
| Is CLT cost-effective? | No | | No | | No | |

肝切除术产生了3.9个质量调整生命年（QALYs），而肝移植则多产生了1.4个QALYs。

肝移植相对于肝切除术的增量成本效益比（ICER）均高于所有三个国家的成本效益阈值。

# 分析结果 - 单维度敏感性分析 （美国）




- **增量成本效果比（ICER）最为敏感的参数：移植后的5年存活率**
- 当肝移植相关的5年累积生存率提高到87.6％或以上时，ICER将低于成本效益阈值。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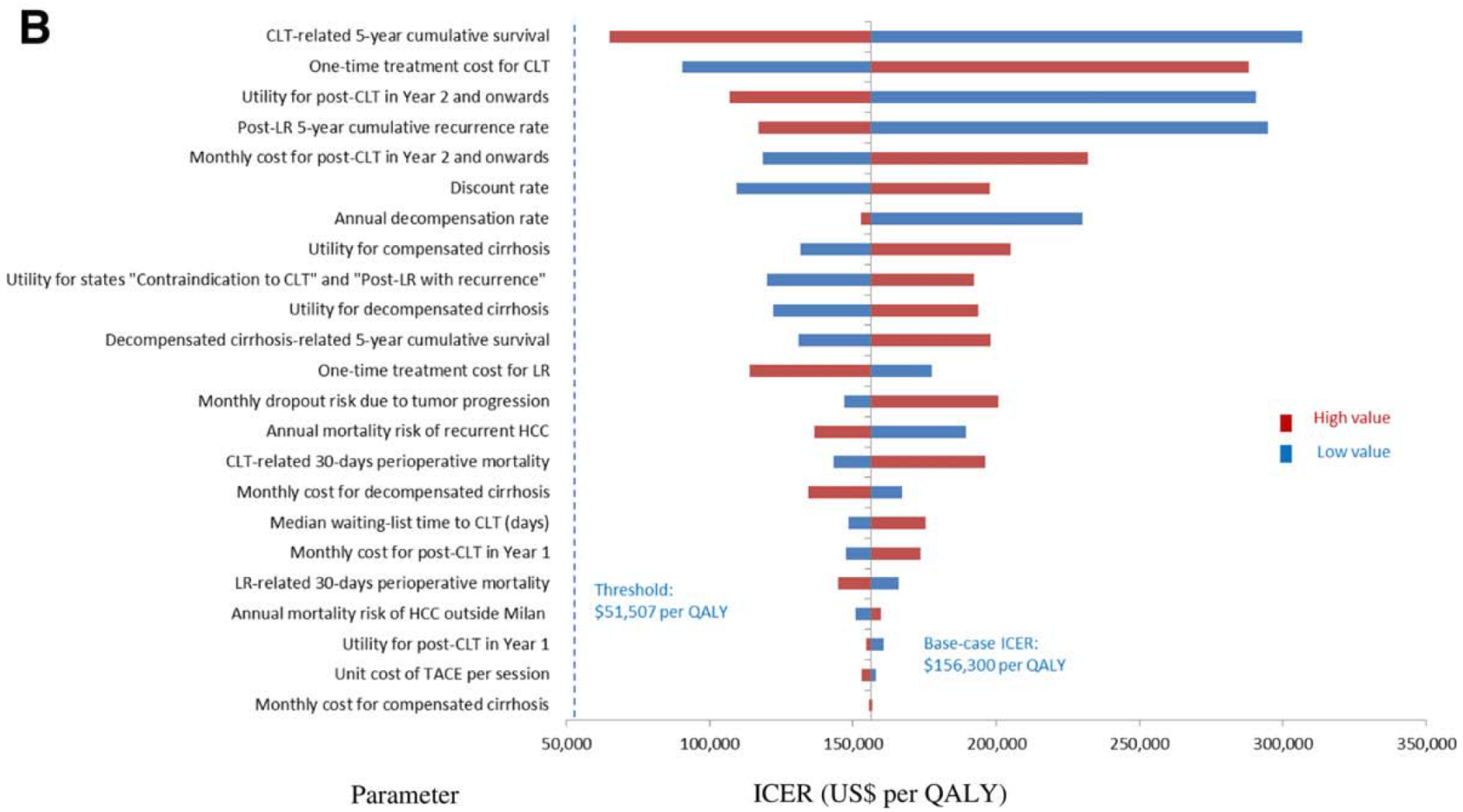
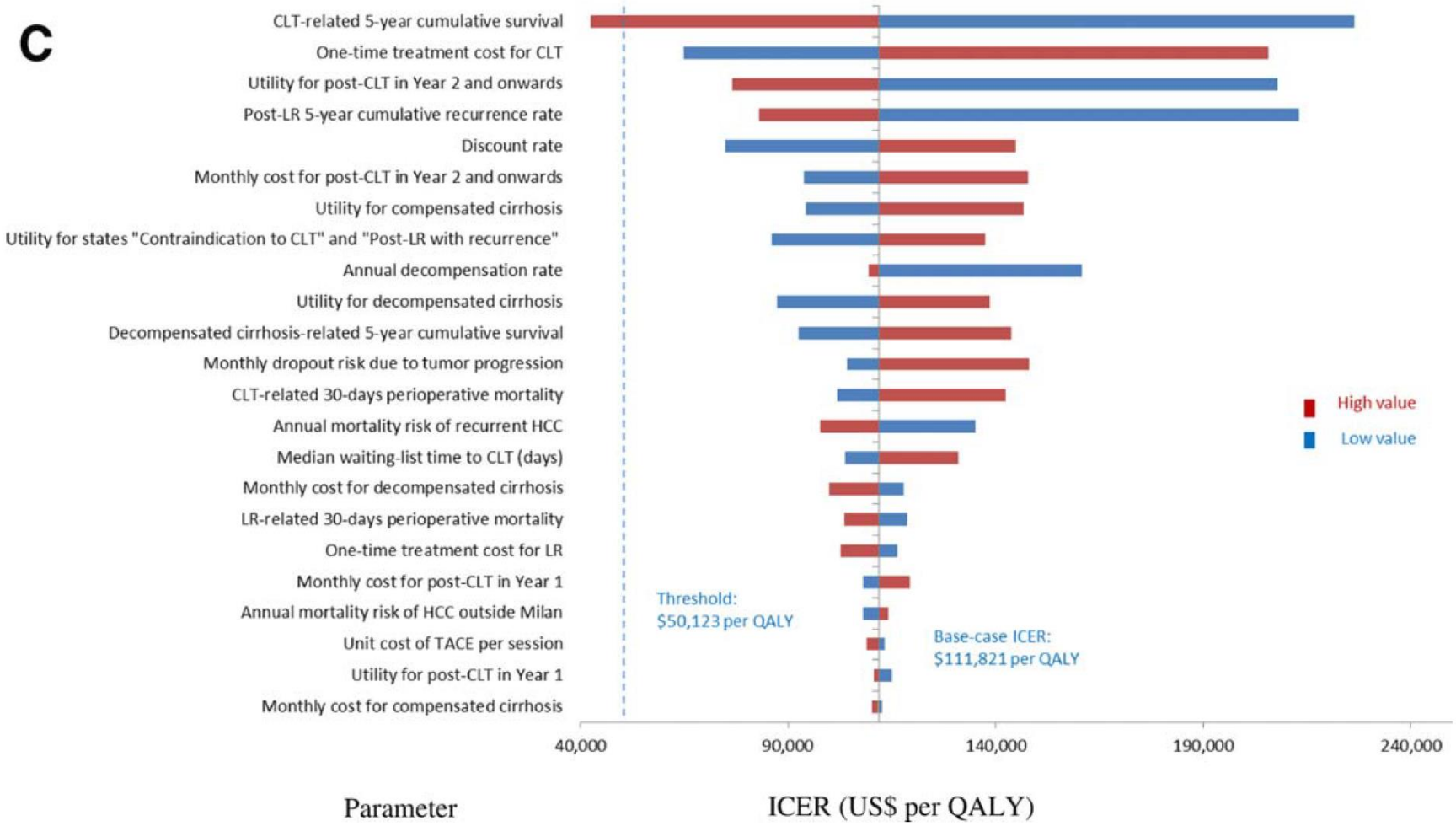
# 分析结果 - 单维度敏感性分析 （瑞士）




只要参数在范围内变化，**增量成本效果比（ICER）**始终高于成本效益阈值

# 分析结果 - 单维度敏感性分析 （新加坡）




- **增量成本效果比（ICER）最为敏感的参数：移植后的5年存活率**
- 当肝移植相关的5年累积生存率提高到84.9％或以上时，ICER将低于成本效益阈值。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# 情境分析： 假设在对肝切除最悲观的临床表现下的敏感性分析

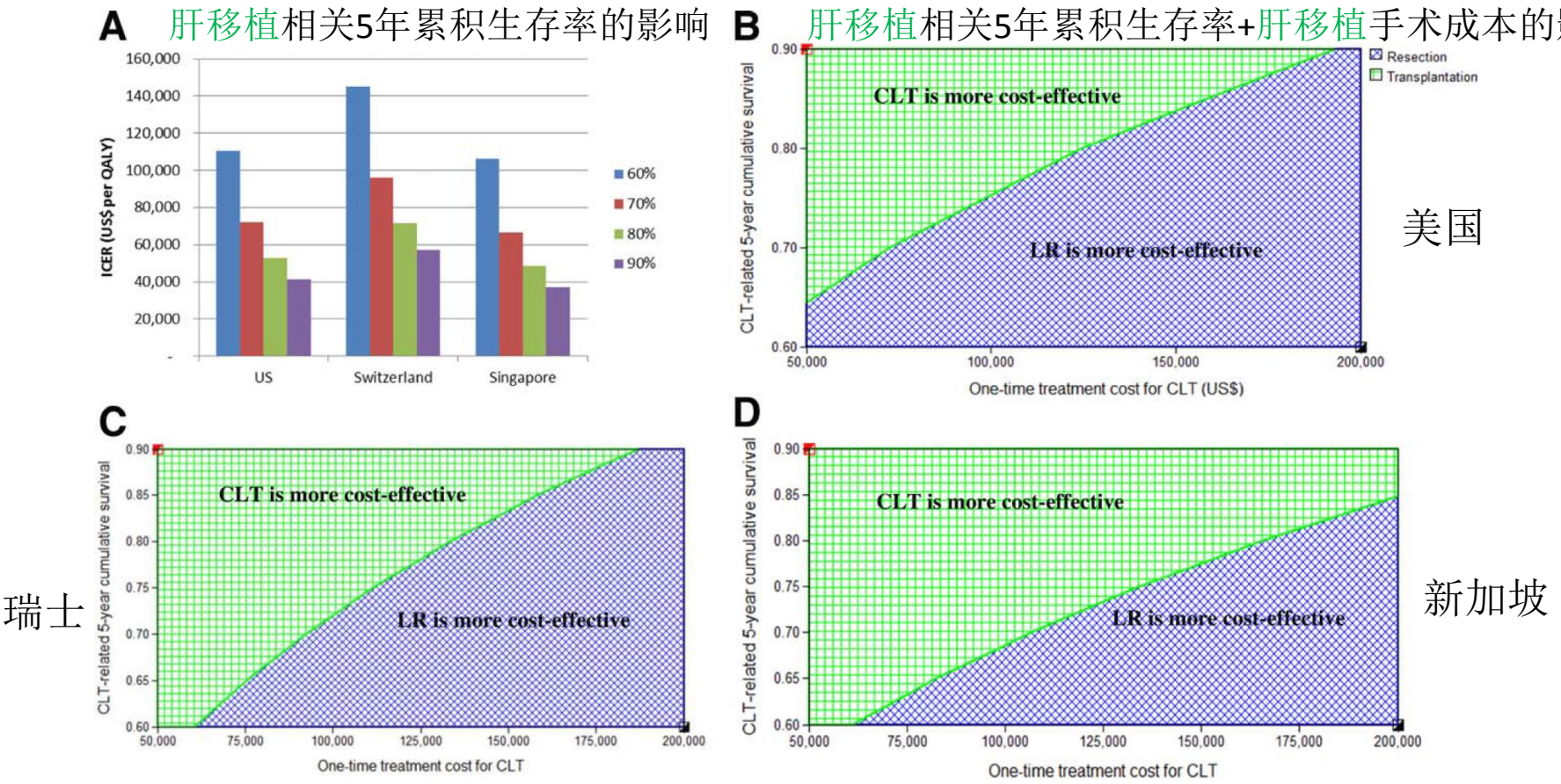


Fig. 3. Scenario analyses: the most pessimistic scenario for liver resection. (A) Impact of CLT-related 5-year cumulative survival on ICER. (B) USA: Combined impact of CLT-related 5-year cumulative survival and one-time treatment cost for CLT on ICER. (C) Switzerland: Combined impact of CLT-related 5-year cumulative survival and one-time treatment cost for CLT on ICER. (D) Singapore: Combined impact of CLT-related 5-year cumulative survival and one-time treatment cost for CLT on ICER.

# 结论

对于具有较好肝功能（即Child-Pugh A/B 级代偿期肝硬化）且**符合米兰标准的早期肝细胞癌患者来说，**在这3个国家里的绝大多数情况下，与选择等待接受肝移植(CLT)相比，立即接受肝切除(LR)是具有成本效用的。


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# 更多细节供参考...

Lim KC*, **Wang VW***, Siddiqui FJ, Shi LM, Chan SYE, Oh HC, Tan SB, Chow PKH. Cost-effectiveness analysis of liver resection versus transplantation for early hepatocellular carcinoma within the Milan criteria. Hepatology 2015;61:227-37. (*contributed equally to this work as **co-first authors**) (2016影响因子: 13.246)

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## Cost-Effectiveness Analysis of Liver Resection Versus Transplantation for Early Hepatocellular Carcinoma Within the Milan Criteria

Kheng Choon Lim,[1,2]* Vivian W. Wang,[3]* Fahad J. Siddiqui,[1,4] Luming Shi,[2,5] Edwin S.Y. Chan,[1,2,4] Hong Choon Oh,[3] Say Beng Tan,[1,2] and Pierce K.H. Chow[2,6,7]

**Both liver resection (LR) and cadaveric liver transplantation (CLT) are potentially curative treatments for patients with hepatocellular carcinoma (HCC) within the Milan criteria and with adequate liver function. Adopting either as a first-line therapy carries major cost and resource implications. The objective of this study was to estimate the rel-**

# Thank you

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# 建模中的主要假设

(1) HCC within the criteria stated above carry no additional specific short-term mortality rate in addition to that of the underlying cirrhosis.

(2) HCC patients face the risks of tumor spreading while waiting for LT. We assumed the probability of HCCs outgrowing the criteria for CLT to be constant over time.

(3) We only consider contra-indication due to tumor progression

(4) Once the HCC is outside Milan criteria, only palliative care with TACE would be given.

(5) Once a patient has recurrent HCC after resection, only palliative care with TACE would be given.

(6) During palliative care for HCC, we assumed that most patients would die from HCC rather than the underlying cirrhosis. Nevertheless, no HCC-specific mortality is reported in the literature, while only all-cause mortality was available for patients with recurrent HCC and patients with unresectable HCC treated by TACE.

(7) No recurrence state modeled in the CLT arm.


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