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心脏瓣膜病

·专题报道·

混合性心脏瓣膜病相关年龄校正合并症指数的构建及其对患者预后的预测价值

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［摘　要］ **目的**：构建混合性心脏瓣膜病（MVHD）相关年龄校正合并症指数（MVACI）模型，明确其在MVHD患者预后预测中的价值。**方法**：纳入China-VHD研究中4080例中重度MVHD患者。以2年全因死亡率为主要终点，基于多因素Cox回归分析中$P<0.05$的年龄和合并症变量构建MVACI模型。绘制限制性立方样条曲线评估MVACI评分与2年全因死亡率的关系。以受试者操作特征（ROC）曲线分析约登指数最大点为阈值对患者进行分层，构建Kaplan-Meier曲线，采用Log-rank检验进行比较。通过单因素和多因素Cox比例风险模型计算风险比（HR）及95%置信区间（CI），评估MVACI评分与死亡率之间的关联。采用配对ROC曲线比较MVACI评分与欧洲心脏手术风险评估系统Ⅱ（EuroSCORE Ⅱ）或年龄校正Charlson合并症指数（ACCI）预测2年临床结局的区分度的优劣性，校准曲线评估这些模型的校准度；并采用Bootstrap方法进行内部验证。根据病因、治疗策略和疾病严重程度对患者进行亚组分析。**结果**：多因素分析确定与患者2年全因死亡率独立相关的合并症/年龄变量，包括肺动脉高压、心肌病、心力衰竭、低体重、贫血、低蛋白血症、肾功能不全、恶性肿瘤、纽约心脏协会（NYHA）心功能分级和年龄。基于这些变量构建的MVACI模型评分与MVHD患者全因死亡风险独立相关（均$P<0.01$），且具有较好的区分度［曲线下面积（AUC）=0.777，95%*CI*：0.755~0.799］和校准度（Brier评分为0.062），其预测价值明显优于EuroSCORE Ⅱ或ACCI（均$P<0.01$）。内部验证结果显示，MVACI模型对中重度MVHD患者2年全因死亡风险的预测概率与实际概率基本一致，且对不同时间点全因死亡风险预测的AUC均在0.750以上，对不良事件预测的AUC在0.630以上。亚组分析结果证实，无论患者病因、治疗方案和MVHD分期如何，MVACI评分均具有较高的预后预测价值。**结论**：基于年龄和合并症变量构建的MVACI模型可用于MVHD患者的死亡风险预测和危险分层，该评分算法简单，便于临床应用。

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［关键词］ 混合性心脏瓣膜病;年龄校正合并症指数;年龄;合并症;预后;预测
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Construction of a mixed valvular heart disease-related age-adjusted comorbidity index and its predictive value for patient prognosis

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［**Abstract**］ **Objective**: To create a mixed valvular heart disease (MVHD)-related age-adjusted comorbidity index (MVACI) model for predicting mortality risk of patients with MVHD. **Methods**: A total of 4080 patients with moderate or severe MVHD in the China-VHD study were included. The primary endpoint was 2-year all-cause mortality. A MVACI model prediction model was constructed based on the mortality risk factors identified by univariate and multivariate Cox regression analysis. Restricted cubic splines were used to assess the relationship between MVACI scores and 2-year all-cause mortality. The optimal threshold, determined by the maximum Youden index from receiver operator characteristic (ROC) curve analysis, was used to stratify patients. Kaplan-Meier method was used to calculate 2-year all-cause mortality and compared using the Log-rank test. Univariate and multivariate Cox proportional hazards models were employed to calculate hazard ratios (HR) and 95% confidence intervals (CI), evaluating the association between MVACI scores and mortality. Paired ROC curves were used to compare the discriminative ability of MVACI scores with the European System for Cardiac Operative Risk Evaluation Ⅱ (EuroSCORE Ⅱ) or the age-adjusted Charlson comorbidity index (ACCI) in predicting 2-year clinical outcomes, while calibration curves assessed the calibration of these models. Internal validation was performed using the Bootstrap method. Subgroup analyses were conducted based on etiology, treatment strategies, and disease severity. **Results**: Multivariate analysis identified the following variables independently associated with 2-year all-cause mortality in patients: pulmonary hypertension, myocardiopathy, heart failure, low body weight (body mass index <18.5 kg/m^2), anaemia, hypoalbuminemia, renal insufficiency, cancer, New York Heart Association (NYHA) class and age. The score was independently associated with the risk of all-cause mortality, and exhibited good discrimination (AUC=0.777, 95%*CI*: 0.755–0.799) and calibration (Brier score 0.062), with significantly better predictive performance than EuroSCORE Ⅱ or ACCI (both adjusted P<0.01). The internal validation showed that the MVACI model's predicted probability of 2-year all-cause mortality was generally consistent with the actual probability. The AUCs for predicting all-cause mortality risk were all above 0.750, and those for predicting adverse events were all above 0.630. The prognostic value of the score remained consistent in patients regardless of their etiology,

therapeutic option, and disease severity. **Conclusions**: The MVACI was constructed in this study based on age and comorbidities, and can be used for mortality risk prediction and risk stratification of MVHD patients. It is a simple algorithmic index and easy to use.

[**Key words**] Mixed valvular heart disease; Age-adjusted comorbidity index; Age; Comorbidity; Prognosis; Prediction

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[**缩略语**] 混合性心脏瓣膜病(mixed valvular heart disease,MVHD);心脏瓣膜病(valvular heart diseases,VHD);Charlson合并症指数(Charlson comorbidity index,CCI);年龄校正CCI(age-adjusted CCI,ACCI);MVHD相关年龄校正合并症指数(MVHD age-adjusted comorbidity index,MVACI);左心室射血分数(left ventricular ejection fraction,LVEF);估计肾小球滤过率(estimated glomerular filtration rate,eGFR);限制性立方样条(restricted cubic spline,RCS);受试者操作特征曲线(receiver operator characteristic curve,ROC曲线);风险比(hazard ratio,HR);置信区间(confidence interval,CI);欧洲心脏手术风险评估系统Ⅱ(European System for Cardiac Operative Risk Evaluation Ⅱ,EuroSCOREⅡ);纽约心脏协会(New York Heart Association,NYHA);曲线下面积(area under the curve,AUC)

随着人口老龄化进程的加剧,MVHD的患病率持续上升[1]。欧洲VHD调查结果显示,20.2%的原发性VHD患者和16.8%接受介入治疗的VHD患者为MVHD[2]。在一项包含62.3万例接受瓣膜手术患者的美国胸科医生协会数据库中,双瓣膜手术比例高达11%[3]。瑞典全国性研究也显示MVHD占VHD患者的11%[4]。中国VHD(以下称China-VHD)研究结果提示,MVHD在VHD患者中占39.3%,在原发性VHD中占37.5%,以二尖瓣反流联合三尖瓣反流最为普遍(占原发性VHD的16.3%),其中混合性主动脉瓣疾病和混合性二尖瓣疾病分别占2.3%和1.3%[5]。

MVHD的病因复杂多样,临床表现异质性强,且常伴有多种合并症,因此,预测患者死亡和不良事件等临床结局面临重大挑战。研究表明,年龄和合并症是决定MVHD患者是否接受手术干预的关键影响因素[6-7],且患者的存活率与年龄密切相关[8]。2008年,Koppie等[9]首次基于患者年龄、合并症的种类和严重程度进行量化评分构建ACCI,可预测膀胱癌根治术后患者死亡的风险。之后的研究显示,ACCI或CCI与VHD患者的预后也密切相关,但研究对象主要集中在单一瓣膜病患者[10-15],ACCI对MVHD患者预后的影响尚不明确。基于此,本研究拟构建针对中重度MVHD患者的ACCI预测模型(MVACI模型),并探讨其对患者2年全因死亡风险的预测价值。

1 对象与方法

1.1 对 象

China-VHD研究是一项针对成人(≥18岁)中重度VHD患者的全国多中心前瞻性队列研究(NCT03484806)。数据收集和质量控制见文献[16]。China-VHD研究纳入4690例中重度MVHD患者,本研究剔除其中数据缺失的患者610例(血清白蛋白缺失484例、血红蛋白缺失427例、体重指数缺失118例、丙氨酸转氨酶缺失470例、LVEF缺失1例、肌酐缺失423例),最终共纳入4080例MVHD患者。

1.2 MVHD的诊断

所有患者均采用标准超声系统进行全面的经胸二维和多普勒超声心动图检查,超声心动图测量和质量控制见文献[16]。通过双平面改良Simpson法计算LVEF以评估左心室收缩功能。存在两个或两个以上心脏瓣膜中度以上狭窄或反流者,以及同一瓣膜同时存在狭窄和反流病变者,即为MVHD[1, 17],包括混合性主动脉瓣疾病、混合性二尖瓣疾病、混合性三尖瓣疾病和多瓣膜心脏病。疾病严重程度(中度或重度)的诊断参

考《2014年美国心脏病学会（ACC）/美国心脏协会（AHA）瓣膜病指南》中的标准[18]。存在至少一个瓣膜严重狭窄或反流病变者为重度MVHD。

1.3 合并症的诊断

回顾患者的临床病史、实验室检验和临床检查资料确定合并症情况。LVEF为40%~49%和LVEF低于40%患者分别诊断为射血分数中间值的心力衰竭和射血分数降低的心力衰竭[19-21]。使用简化肾脏病膳食改良试验方程[22]估计基线eGFR，评估患者的肾功能，eGFR低于60 mL/（min·1.73 m^2）诊断为肾功能不全[23]。丙氨酸转氨酶高于150 U/L或总胆红素大于51.3 μmol/L诊断为中重度肝功能不全；体重指数低于18.5 kg/m^2诊断为低体重；血清白蛋白低于35 g/L诊断为低白蛋白血症；血红蛋白男性低于130 g/L或女性低于120 g/L诊断为贫血[24]。肺动脉收缩压不低于40 mmHg（1 mmHg=0.133 kPa）或平均肺动脉压不低于25 mmHg诊断为肺动脉高压。

1.4 随访及研究终点

China-VHD研究的临床随访数据通过患者门诊就诊、住院记录或电话随访获得。每六个月随访一次，持续两年。本研究的主要终点是2年全因死亡率，次要终点包括2年不良事件（如卒中、心功能不全、再住院、瓣膜再次干预、心肌梗死、血栓栓塞、心脏压塞、人工瓣膜血栓、心律失常、肾功能不全、大出血、严重感染和呼吸衰竭等）、2年因心力衰竭再次住院或门诊就诊、18个月全因死亡、18个月不良事件、1年全因死亡率、1年不良事件、6个月全因死亡率、6个月不良事件。每个医疗中心的调查人员对死亡和不良事件进行审查和核实。

1.5 MVACI模型的构建和评估

通过单因素和多因素Cox回归分析评估与MVHD队列人群2年全因死亡独立相关的年龄和合并症变量。将单因素分析P<0.05的变量纳入多因素分析模型，然后将多因素Cox回归分析中P<0.05的变量纳入MVACI模型构建。根据各变量的回归系数进行不同权重分配。各变量权重得分整数之和即为MVACI评分。

绘制RCS曲线评估MVACI评分与2年全因死亡率的关系。以ROC曲线分析的约登指数最大点为阈值对患者进行分层，构建Kaplan-Meier曲线，采用Log-rank检验进行比较。通过单因素和多因素Cox比例风险模型计算*HR*值及95%*CI*，评估MVACI评分与死亡率之间的关联。其中多因素校正分析的协变量为新型抗心力衰竭药物、起搏器植入、既往瓣膜干预、住院期瓣膜干预、心房颤动、血管紧张素转换酶抑制剂/血管紧张素受体拮抗剂、吸烟（包括既往吸烟和当前吸烟），以及未纳入MVACI模型但ACCI模型中包含的变量（如心肌梗死、中重度肝功能不全、慢性阻塞性肺疾病、周围血管病、脑血管疾病、消化性溃疡和糖尿病）。

采用ROC曲线评估MVACI模型的区分度，并使用配对ROC曲线比较该模型与ACCI模型及EuroSCORE Ⅱ模型对MVHD患者2年临床结局的区分度。采用校准曲线评估MVACI、ACCI和EuroSCORE Ⅱ这三种模型的校准度，并采用Bootstrap方法进行MVACI模型的内部验证。

最后，根据常见病因（风湿性、退行性以及功能性MVHD）、临床治疗策略和疾病严重程度对MVHD患者进行亚组分析。

1.6 China-VHD数据库中EuroSCORE Ⅱ模型和ACCI模型的评分方法

参照文献[25]中的方法进行EuroSCORE Ⅱ评分。由于China-VHD数据库中手术紧急状态（包括住院期常规手术、非择期住院期手术和急诊手术等）变量缺失，故删除该变量。ACCI模型计分方式参考文献[26-27]。其中，痴呆或阿尔茨海默病、类风湿或结缔组织疾病、偏瘫、肝脏疾病（轻度）、糖尿病伴终末器官损伤（视网膜病变）、艾滋病等变量因China-VHD数据库中缺失予以删除；实体瘤、白血病、淋巴瘤、转移性实体瘤均归类为恶性肿瘤，赋2分。项目累加得分之和为ACCI总分。

1.7 统计学方法

使用R语言4.0.2和SAS 9.4软件进行统计分析。分类变量以百分比（%）表示，采用χ^2检验或Fisher精确检验；连续变量以均数±标准差（$\bar{x}\pm s$）表示，采用Student's t检验。双侧P<0.05为差异具有统计学意义。

2 结 果

2.1 中重度MVHD患者基线特征

4080例中重度MVHD患者年龄为（63±13）岁，2116例（51.9%）为男性。心功能不全（NYHA Ⅲ/Ⅳ级，50.9%）、高血压（40.2%）、肺动脉高压

(59.4%)、贫血(35.3%)、心房颤动(39.8%)、冠心病(23.3%)、肾功能不全(26.5%)、低白蛋白血症(19.3%)、糖尿病(13.8%)和高脂血症(10.3%)等合并症的患病率较高,而脑血管疾病(9.4%)、心肌梗死(6.6%)、心肌病(8.2%)、低体重(8.8%)、主动脉疾病(6.5%)、慢性阻塞性肺疾病(6.3%)、心脏畸形(5.2%)、中重度肝功能不全(5.3%)、周围血管病(2.5%)、消化性溃疡(1.9%)、恶性肿瘤(1.7%)和感染性心内膜炎(1.4%)的患病率较低。患者LVEF为(52±13)%,其中568例(13.9%)患者的LVEF为40%~49%,810例(19.9%)患者的LVEF低于40%。住院期间共有1687例(41.3%)患者接受了瓣膜干预手术。研究人群的基线特征见附表1。

2.2 构建MVACI模型

经过单因素和多因素Cox回归分析(附表2和附表3),最终确定与患者2年全因死亡率独立相关的合并症/年龄变量为肺动脉高压、心肌病、心力衰竭、低体重、贫血、低蛋白血症、肾功能不全、恶性肿瘤、NYHA心功能分级(Ⅲ/Ⅳ级)。根据各变量回归系数进行不同权重分配,其中肺动脉高压的回归系数最小,权重分配为1分,其他变量的权重得分为其对应回归系数除以最小回归系数之商,结果以四舍五入的方式记录,MVACI模型中各合并症的评分方法见表1,加权整数之和(范围0~22分)估计随访死亡风险。经MVACI评分计算器(https://www.wjx.cn/vm/rkyV2n7.aspx#)计算,本研究队列的MVACI评分为6.73±4.03。

2.3 MVACI评分可预测中重度MVHD患者预后

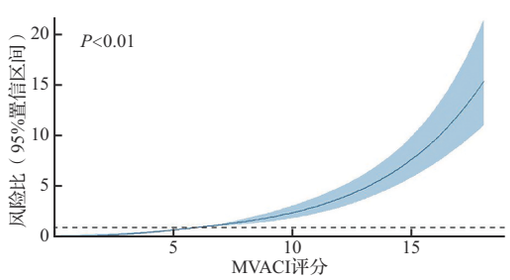
4080例中重度MVHD患者中,438例(13.0%)在2年随访期内死亡,总队列1、2年累积存活率分别为96.1%、94.9%。RCS曲线显示MVACI评分与中重度MVHD患者2年全因死亡率呈单调递增趋势(图1)。作为连续性变量,单因素分析结果显示MVACI评分与MVHD患者的全因死亡率相关,经多因素校正后,MVACI评分仍是MVHD患者全因死亡率的独立预测因子(表2)。通过约登指数确定的MVACI评分最佳阈值为8。以阈值8为分界点,将MVACI评分作为分类变量进行考察,Kaplan-Meier曲线显示MVACI评分8分及以上患者2年全因死亡的风险显著高于MVACI评分低于8分的患者(表2、图2)。结果提示,本研究构建的MVACI模型可用于MVHD患者预后预测。

表1 MVACI模型及评分方法

Table 1 Scoring method of the MVACI model

合并症变量		回归系数	计分值
肺动脉高压		0.248 02	1
心肌病		0.330 33	1
心力衰竭	LVEF为40%~49%	0.355 55	1
	LVEF低于40%	0.283 37	1
低体重		0.488 60	2
贫血		0.471 61	2
低白蛋白血症		0.398 94	2
肾功能不全		0.458 34	2
恶性肿瘤		0.580 49	2
NYHA心功能分级	Ⅲ级	0.723 71	3
	Ⅳ级	1.307 16	5
年龄(岁)	60~<70	0.636 30	3
	70~<80	0.854 70	3
	≥80	1.212 44	5

MVACI:混合性心脏瓣膜病相关年龄校正合并症指数;LVEF:左心室射血分数;NYHA:纽约心脏协会.



MVACI:混合性心脏瓣膜病相关年龄校正合并症指数.

图1 中重度混合性心脏瓣膜病患者2年全因死亡风险随MVACI评分变化的曲线(基于限制性立方样条)

Figure 1 Restricted cubic spline curve for the associations between MVACI scores and 2-year all-cause mortality in patients with moderate to severe mixed valvular heart diseases

2.4 MVACI模型预测MVHD患者预后的区分度和校准度较好

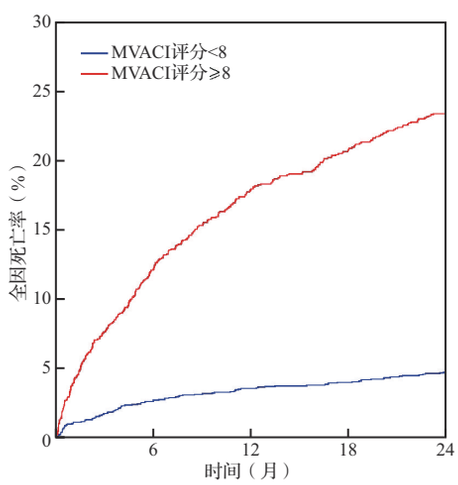
ROC曲线分析结果显示,MVACI模型具有良好的区分度(AUC=0.777,95%*CI*:0.755~0.799),且其对中重度MVHD患者2年全因死亡风险的预测价值显著优于EuroSCORE Ⅱ模型(AUC=0.667,95%*CI*:0.640~0.694,*P*<0.01)和ACCI模型(AUC=0.662,95%*CI*:0.635~0.689,*P*<0.01)。MVACI、EuroSCORE Ⅱ和ACCI三种模型的校准度Brier值均低于0.25,其中MVACI模型的校准度(Brier=0.062,95%*CI*:0.058~0.066)高于EuroSCORE Ⅱ模型(Brier=0.067,95%*CI*:0.063~0.071)和ACCI模

表2 MVACI评分与中重度混合性心脏瓣膜病患者全因死亡风险的相关性

Table 2 Association between MVACI scores and risk of all-cause mortality in patients with moderate to severe mixed valvular heart diseases

全因死亡		*HR*(95%*CI*)	校正后*HR*(95%*CI*)[#]
2年全因死亡	MVACI(每增加1分)	1.279(1.250~1.309)[**]	1.226(1.195~1.258)[**]
	MVACI≥8(相比<8)	5.430(4.354~6.772)[**]	3.429(2.718~4.327)[**]
18个月全因死亡	MVACI(每增加1分)	1.280(1.250~1.312)[**]	1.228(1.194~1.261)[**]
	MVACI≥8(相比<8)	5.578(4.398~7.075)[**]	3.501(2.726~4.496)[**]
1年全因死亡	MVACI(每增加1分)	1.273(1.241~1.307)[**]	1.224(1.189~1.260)[**]
	MVACI≥8(相比<8)	5.367(4.173~6.903)[**]	3.406(2.611~4.441)[**]
6个月全因死亡	MVACI(每增加1分)	1.264(1.226~1.304)[**]	1.224(1.182~1.268)[**]
	MVACI≥8(相比<8)	4.770(3.554~6.403)[**]	3.127(2.287~4.275)[**]
住院期全因死亡	MVACI(每增加1分)	1.242(1.146~1.346)[**]	1.262(1.151~1.385)[**]
	MVACI≥8(相比<8)	3.598(1.721~7.525)[**]	3.316(1.483~7.416)[**]

[**]*P*<0.01. [#]校正新型抗心力衰竭药物、起搏器植入、既往瓣膜手术干预、住院期瓣膜干预、心房颤动、血管紧张素转换酶抑制剂/血管紧张素受体拮抗剂、吸烟(包括既往吸烟和当前吸烟)、周围血管病、脑血管疾病、消化性溃疡、糖尿病、心肌梗死、中重度肝功能不全、慢性阻塞性肺疾病等因素. MVACI:混合性心脏瓣膜病相关年龄校正合并症指数；HR:风险比；CI:置信区间.



MVACI:混合性心脏瓣膜病相关年龄校正合并症指数.

图2 中重度混合性心脏瓣膜病患者中MVACI评分与2年全因死亡率的关系(Kaplan-Meier曲线)

Figure 2 Correlation between MVACI scores and 2-year all-cause mortality in patients with moderate to severe mixed valvular heart diseases (Kaplan-Meier curves)

型(Brier=0.065，95%*CI*：0.061~0.069)。见图3和表3。对于次要临床结局的预测，MVACI模型也均显示出优于EuroSCORE Ⅱ模型和ACCI模型的趋势(表3)。

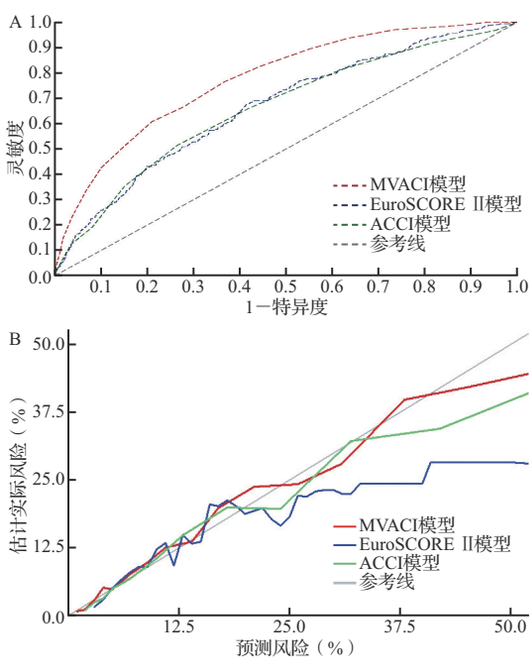
进一步采用Bootstrap法进行内部验证发现，MVACI模型对中重度MVHD患者2年全因死亡风险的预测概率与实际观察到的概率较为一致(图4)，且该模型对随访过程中不同时间点全因死亡风险预测的AUC均在0.750以上，对不良事件预测的AUC均在0.630以上(表4)。

以上结果提示，MVACI模型具有良好的区分度和校准度。

2.5 MVACI评分可预测在不同亚组中重度MVHD患者预后

根据病因进行亚组分析结果显示，无论作为连续变量还是分类变量，MVACI评分在风湿性MVHD、退行性MVHD和功能性MVHD患者中均具有预测价值(校正后*P*<0.01)，见图5和附表4~6。

根据临床治疗策略和MVHD严重程度对患者进行亚组分析：无论MVHD患者的临床治疗策略和MVHD分期如何，MVACI评分均是



A:受试者操作特征曲线；B:校准曲线. MVACI:混合性心脏瓣膜病相关年龄校正合并症指数；EuroSCORE Ⅱ:欧洲心脏手术风险评估系统Ⅱ；ACCI:年龄校正Charlson合并症指数.

图3 三种模型对中重度混合性心脏瓣膜病患者2年全因死亡风险的区分度和校准度

Figure 3 Discrimination and calibration of the MVACI, EuroSCORE Ⅱ, and ACCI models for 2-year all-cause mortality risk in patients with moderate to severe mixed valvular heart diseases

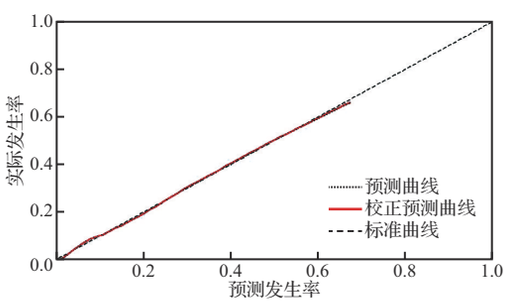
表3 三种模型预测中重度混合性心脏瓣膜病患者临床结局的曲线下面积比较

Table 3 Comparison of predictive values with MVACI, EuroSCORE Ⅱ, and ACCI models in patients with moderate to severe mixed valvular heart diseases

[AUC(95%*CI*)]

临床结局	MVACI模型	EuroSCORE Ⅱ模型	ACCI模型
2年全因死亡	0.777(0.755~0.799)$^{**\#\#\triangle\triangle}$	0.667(0.640~0.694)**	0.662(0.635~0.689)**
2年不良事件	0.634(0.611~0.656)$^{**\#\#}$	0.575(0.551~0.598)**	0.613(0.590~0.636)**
2年因心力衰竭就诊或再住院	0.704(0.674~0.733)$^{**\#\#\triangle\triangle}$	0.621(0.588~0.655)**	0.628(0.595~0.661)**
18个月全因死亡	0.780(0.756~0.803)$^{**\#\#\triangle\triangle}$	0.670(0.642~0.698)**	0.664(0.635~0.693)**
18个月不良事件	0.638(0.615~0.662)$^{**\#\#\triangle}$	0.578(0.553~0.603)**	0.609(0.585~0.633)**
1年全因死亡	0.772(0.747~0.798)$^{**\#\#\triangle\triangle}$	0.670(0.639~0.700)**	0.66(0.633~0.694)**
1年不良事件	0.638(0.615~0.662)$^{**\#\#\triangle}$	0.578(0.553~0.603)**	0.609(0.585~0.633)**
6个月全因死亡	0.762(0.732~0.793)$^{**\#\#\triangle\triangle}$	0.676(0.641~0.712)**	0.651(0.613~0.688)**
6个月不良事件	0.638(0.615~0.662)$^{**\#\#\triangle}$	0.578(0.553~0.603)**	0.609(0.585~0.633)**

零假设的差异，$^{**}P$<0.01. 配对ROC曲线的差异，与EuroSCORE Ⅱ模型比较，$^{\#\#}P$<0.01；与ACCI模型比较，$^{\triangle}P$<0.05，$^{\triangle\triangle}P$<0.01. MVACI：混合性心脏瓣膜病相关年龄校正合并症指数；EuroSCORE Ⅱ：欧洲心脏手术风险评估系统Ⅱ；ACCI：年龄校正Charlson合并症指数；AUC：曲线下面积；CI：置信区间.



MVACI：混合性心脏瓣膜病相关年龄校正合并症指数.

图4 MVACI模型预测中重度混合性心脏瓣膜病患者2年全因死亡风险的校准曲线(Bootstrap法内部验证)

Figure 4 Calibration curve of MVACI model predicting 2-year all-cause mortality in patients with moderate to severe mixed valvular heart diseases (internal validation by Bootstrap method)

表4 MVACI模型对中重度混合性心脏瓣膜病患者临床结局预测效果的内部验证结果(Bootstrap法)

Table 4 Internal validation of the MVACI model for prediction of the clinical outcomes of patients with moderate to severe mixed valvular heart diseases (Bootstrap method)

临床结局	AUC	95%*CI*
2年全因死亡	0.777	0.755~0.795
2年不良事件	0.634	0.611~0.658
18个月全因死亡	0.780	0.760~0.801
18个月不良事件	0.639	0.613~0.667
1年全因死亡	0.773	0.748~0.797
1年不良事件	0.639	0.613~0.667
6个月全因死亡	0.763	0.729~0.789
6个月不良事件	0.639	0.613~0.667

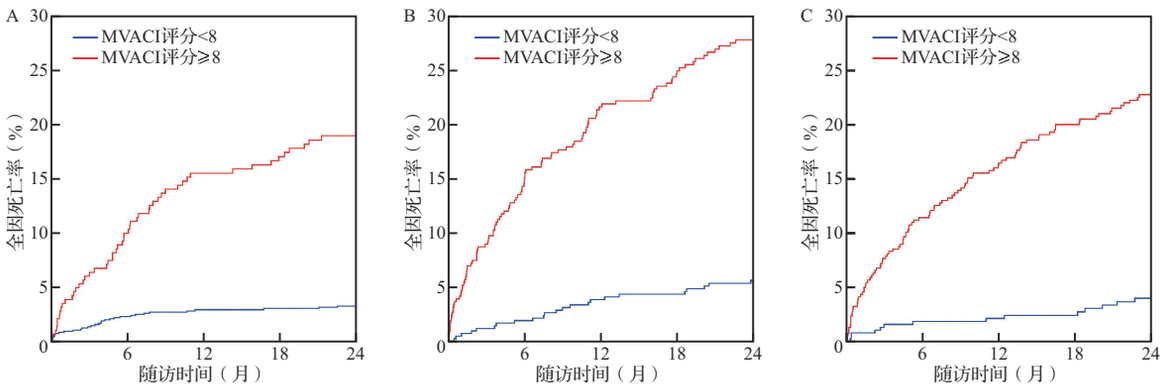
MVACI：混合性心脏瓣膜病相关年龄校正合并症指数；AUC：曲线下面积；CI：置信区间.

2年死亡的独立预测因子，其对各亚组患者的次要终点事件也具有一定的预测价值(校正后P<0.01)，见图6~7和附表7~10。

结果提示，在不同病因、临床治疗策略及MVHD分期的患者中，MVACI评分均展现出较好的预后预测价值。

3 讨 论

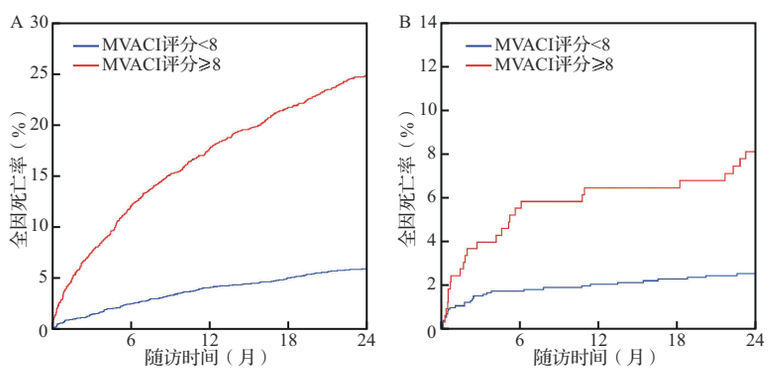
目前有关MVHD患者预后风险模型的研究有限，构建一种简易实用的MVHD预后模型具有重要临床意义。研究显示，合并症负担与高危主动脉瓣狭窄患者临床预后密切相关[28]。年龄和合并症是决定MVHD患者是否接受手术干预的关键影响因素[6]。此外，2021 ESC/EACTS瓣膜病管理指南[29]中强调了衰弱、营养不良、认知功能损害和器官功能损害等对VHD患者预后的重要性。研究显示，单一VHD患者合并低白蛋白血症或贫血[30]、营养不良[31-32]、低体重[32]、肺动脉高压[29, 33-34]、心肌病[35-36]时预后均较差。但上述VHD患者预后相关危险因素是否影响MVHD患者的临床结局不明确。基于此，本研究通过多因素回归分析发现肺动脉高压、心肌病、心力衰竭、低体重、贫血、低白蛋白血症、肾功能不全、恶性肿瘤、NYHA心功能分级(Ⅲ/Ⅳ级)和年龄与MVHD患



A：风湿性MVHD；B：退行性MVHD；C：功能性MVHD. MVHD：混合性心脏瓣膜病；MVACI：MVHD相关年龄校正合并症指数.

图5 不同病因中重度MVHD患者中MVACI评分与患者2年全因死亡率的关系（Kaplan-Meier曲线）

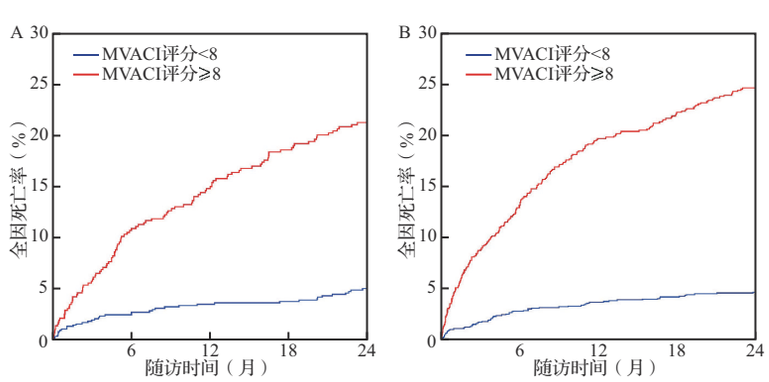
Figure 5 Correlation between MVACI scores and 2-year all-cause mortality in moderate to severe MVHD patients with different etiologies (Kaplan-Meier curves)



A：接受药物治疗的MVHD患者；B：接受瓣膜干预的MVHD患者. MVHD：混合性心脏瓣膜病；MVACI：MVHD相关年龄校正合并症指数.

图6 不同治疗策略中重度MVHD患者中MVACI评分与患者2年全因死亡率的关系（Kaplan-Meier曲线）

Figure 6 Correlation between MVACI scores and 2-year all-cause mortality in moderate to severe MVHD patients received different medical treatments (Kaplan-Meier curves)



A：中度MVHD；B：重度MVHD. MVHD：混合性心脏瓣膜病；MVACI：MVHD相关年龄校正合并症指数.

图7 不同严重程度中重度MVHD患者中MVACI评分与患者2年全因死亡率的关系（Kaplan-Meier曲线）

Figure 7 Correlation between MVACI scores and 2-year all-cause mortality in patients with moderate MVHD and severe MVHD (Kaplan-Meier curves)

者的2年全因死亡率独立相关。本研究基于上述危险因素构建MVACI模型，结果表明MVACI评分不管是作为连续变量还是分类变量进行危险分层对MVHD患者预后均有预测价值。且该模型具有较好的区分度和校准度，对患者预后的预测价值显著优于EuroSCORE Ⅱ或ACCI模型。MVACI模型还具有以下优势：①与ACCI模型比较，拓展了低体重、贫血、低白蛋白血症等营养不良、衰弱指标，以及心肌病、肺动脉高压等MVHD相关死亡危险因素，剔除了与MVHD患者预后无关变量（心肌梗死、中重度肝功能不全、慢性阻塞性肺疾病、周围血管病、脑血管疾病、消化性溃疡和糖尿病），对MVHD患者预后的预测具有特异性。②模型参数为临床常见合并症，并根据各变量权重大小进行赋分，相比依赖于计算机计算的EuroSCORE Ⅱ模型，计算方法简单且易于实施。③在确定临床干预方案之前即可预估MVHD患者的死亡风险。因

此,MVACI模型可对MVHD患者进行危险分层且使用简便,能在日常临床实践中广泛使用。

考虑到不同病因MVHD患者临床结局的差异[37-39],本研究对MVHD临床常见病因如风湿性、退行性和功能性MVHD患者进行亚组分析,结果显示MVACI在不同病因MVHD患者预后的预测价值中一致。另外,Saijo等[14]报道,无论二尖瓣狭窄患者治疗策略如何,合并症较多者的预后较合并症较少者差。与既往研究类似,本文资料显示,接受药物治疗或瓣膜干预患者中MVACI评分较高者2年全因死亡率均高于MVACI评分较低者。此外,年龄[40]、合并症[41-45]与不同分期的单一VHD患者(包括中度主动脉瓣狭窄[41-42]、中度LVEF保留的主动脉瓣反流[43]和重度主动脉瓣狭窄[44-45]患者)的全因死亡及不良事件密切相关。类似于单一VHD患者,本研究发现基于年龄和合并症构建的MVACI模型对中度MVHD和重度MVHD患者死亡风险均有预测价值,高合并症指数的中重度MVHD患者的死亡风险显著增加。因此,MVHD患者应加强合并症管理,可能有助于降低患者死亡风险。

本研究尚存在一定局限性。首先,本研究基于一项观察性China-VHD队列研究,EuroSCORE Ⅱ和ACCI模型中部分变量因缺失而予以删除或替代,故不能排除EuroSCORE Ⅱ、ACCI模型对MVHD患者临床结局的预测价值被低估。其次,由于数据的可及性,本研究没有进行外部验证。此外,尽管高龄MVHD患者同时合并低体重、肾功能不全、贫血和低白蛋白血症等并发症时可能增加患者死亡风险,但本研究基于传统的建模方式,并未发现变量之间存在双重交互作用。未来可尝试利用机器学习这类新型建模方式,以揭示模型中各变量之间的交互作用,进一步优化模型。

综上,本研究首次构建并验证了MVACI模型,证实其具有良好的区分度和校准度,对全因死亡率的预测价值显著优于EuroSCORE Ⅱ或ACCI模型。此外,MVACI评分计算方法简便,且在不同病因、临床治疗策略及MVHD分期的患者中均展现出较高的预测价值。

本文附表见电子版。

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Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the Fuwai Hospital, Chinese Academy of Medical Sciences (2017-968), and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The participant has signed an informed consent form

利益冲突 所有作者均声明不存在利益冲突

Conflict of Interests The authors declare that there is no conflict of interests

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