· 临床研究 ·

沙库巴曲缬沙坦治疗老年心力衰竭患者的预后列线图建立及验证

白盼盼[1],李春霞[2],卜星彭[1,2],郭梅凤[1],任建辉[1],罗天娥[1],陈还珍[1,3]*

([1] 山西医科大学公共卫生学院,太原 030012;[2] 山西白求恩医院综合医疗科,太原 030032;[3] 山西医科大学第一医院心血管内科,太原 030001)

【摘 要】 目的 对沙库巴曲缬沙坦治疗的心力衰竭(HF)患者建立列线图并验证,准确预测其 1 年内 HF 再入院的风险。**方法** 回顾性分析 2018 年 6 月至 2021 年 12 月山西医科大学第一医院 HF 患者的病历资料,对最小绝对收缩和选择算子回归筛选的变量进行多因素 Cox 回归分析,并建立列线图。使用一致性指数、受试者工作特征(ROC)曲线和校准曲线评估列线图的预测准确性。采用 SPSS 26.0、R 4.1.3 软件进行数据分析。根据数据类型,组间比较分别采用 t 检验、Mann-Whitney U 检验及 χ^2 检验。**结果** 多因素 Cox 回归分析示白细胞(*HR* = 1.125,95% *CI* 1.016~1.245;*P* = 0.023)、血清总胆固醇(*HR* = 1.522,95% *CI* 1.080~2.144;*P* = 0.016)、甘油三酯(*HR* = 1.619,95% *CI* 1.109~2.363;*P* = 0.013)和高密度脂蛋白胆固醇(*HR* = 0.273,95% *CI* 0.125~0.598;*P* = 0.001)是 HF 患者的预后预测因子,以此建立列线图模型。训练集 *C-index* 为 0.749(0.678~0.820),6 个月曲线下面积(AUC) = 0.821(0.700~0.893),12 个月 AUC = 0.771(0.575~0.836);测试集 *C-index* 为 0.851(0.641~0.809),6 个月 AUC = 0.851(0.692~0.940),12 个月 AUC = 0.847(0.679~0.995),提示模型具有中等预测价值,校准图呈现出较好的一致性。**结论** 基于临床电子病历,本研究得出白细胞、血清总胆固醇、甘油三酯和高密度脂蛋白胆固醇是沙库巴曲缬沙坦治疗 HF 患者的预后影响因素,构建的列线图具有良好的预测价值和临床实用性,利于评估患者短期预后。

【关键词】 沙库巴曲缬沙坦;心力衰竭;预后;列线图

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Development and validation of a prognostic nomogram for elderly heart failure patients receiving sakubatril/valsartan treatment

Bai Panpan[1], Li Chunxia[2], Bu Xingpeng[1,2], Guo Meifeng[1], Ren Jianhui[1], Luo Tian′e[1], Chen Huanzhen[1,3]*

([1]School of Public Health, Shanxi Medical University, Taiyuan 030012, China; [2]Department of General Medicine, Shanxi Bethune Hospital, Taiyuan 030032, China; [3]Department of Cardiology, First Hospital of Shanxi Medical University, Taiyuan 030001, China)

【Abstract】 Objective To draw and validate a predictive nomogram for 1-year readmission for patients with heart failure (HF) receiving sakubatril/valsartan treatment. **Methods** A retrospective study was conducted on the medical records of HF patients at the First Hospital of Shanxi Medical University from June 2018 to December 2021. Cox multifactor analysis was performed on variables screened by least absolute shrinkage and selection operator regression analysis, and then a nomogram was plotted based on obtained results. The prediction ability was evaluated using the concordance index (C-index), receiver operating characteristic (ROC) curve and calibration curve. SPSS statistics 26.0 and R 4.1.3 software were used for statistical analysis. Data comparison between two groups was performed using student′s t test, Mann-Whitney U test or *Chi-sqaure* test depending on data type. **Results** Multivariate Cox regression analysis showed that white blood cell count (*HR* = 1.125, 95% *CI* 1.016-1.245; *P* = 0.023), levels of total cholesterol (*HR* = 1.522, 95% *CI* 1.080-2.144; *P* = 0.016), triglyceride (*HR* = 1.619, 95% *CI* 1.109-2.363; *P* = 0.013) and high-density lipoprotein cholesterol (*HR* = 0.273, 95% *CI* 0.125-0.598; *P* = 0.001) were prognostic factors in HF patients, and then a nomogram model was build based on these indicators. The C-index value of the training set was 0.749 (0.678-0.820), with area under the ROC curve (AUC) of 0.821 (0.700-0.893) and 0.771 (0.575-0.836) for 6 and 12 months respectively. And the C-index value of the testing set was 0.851 (0.641-0.809), with AUC of 0.851 (0.692-0.940) and 0.847 (0.679-0.995) for 6 and 12 months respectively. These results suggested that the model had moderate predictive value, and the calibration curves indicated the model had good consistency. **Conclusion** Based on clinical electronic medical records, white blood cell count, total cholesterol, triglyceride and high-density lipoprotein cholesterol levels are prognostic factors in HF patients after sakubatril/valsartan treatment ($P<0.05$). Our nomogram has good predictive value and clinical utility, and is helpful for the assessment of short-term prognosis.

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通信作者: 陈还珍, E-mail: chenhz2001@sina.cn

【Key words】 sakubatril/valsartan; heart failure; prognosis; nomogram
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Corresponding author: *Chen Huanzhen*, *E-mail*: *chenhz2001@sina.cn*

心力衰竭(heart failure,HF)是一个发病率和病死率高的公共卫生问题[1],约一半患者确诊后1年内至少入院1次[2]。《慢性心力衰竭加重患者的综合管理中国专家共识2022》[3]指出需采取措施减少再入院,沙库巴曲缬沙坦是我国食品药品监督管理总局批准的第1个新型双效血管紧张素受体脑啡肽酶抑制剂(angiotensin receptor neprilysin inhibitor, ARNI),尽管证实其可降低心血管死亡率和HF住院率[4],但缺乏在中国人群的临床实践研究中的预后模型,故及时准确地预测该类患者的预后对临床医师和患者至关重要。列线图(nomogram)是将患者个体情况以图形方式描绘临床事件发生概率[5],故本研究对ARNI治疗的老年患者建立1年内HF再入院的列线图,为患者精细化管理和个体化治疗提供依据。

1 对象与方法

1.1 研究对象

回顾性分析2018年6月至2021年12月山西医科大学第一医院收治的HF患者的临床资料,诊断标准见指南[6]。纳入标准:年龄≥60岁、确诊后长期服用ARNI、基本资料完整。排除标准:收缩压<90mmHg(1 mmHg=0.133 kPa)、恶性肿瘤、严重肝肾功能器官等疾病、资料缺失、生存时间不足1 d或入院原因不明确。本研究通过山西医科大学第一医院伦理委员会审核批准伦理审查号[2020]伦审字(K071)号,患者知情同意豁免。

1.2 方法

收集患者的基线资料和实验室检查指标。基线资料包括性别、年龄、心率、血压、病史、住院天数、用药情况、美国纽约心脏病学会(New York Heart Association,NYHA)分级等;实验室指标包括白细胞(white blood cell, WBC)、血红蛋白(hemoglobin, Hb)、谷丙转氨酶(alamine aminotransferase, ALT)、谷草转氨酶(aspartate transaminase, AST)、空腹血糖(fasting blood glucose, FBG)、血清总胆固醇(total cholesterol, TC)、甘油三酯(triglyceride, TG)、高密度脂蛋白胆固醇(high-density lipoprotein cholesterol, HDL-C)、低密度脂蛋白胆固醇(low-density lipoprotein cholesterol, LDL-C)、血肌酐(creatinine, Cr)、N端-B型钠尿肽前体(N-terminal pro-B-type natriuretic peptide, NT-proBNP)、左心室舒张末期内径(left ventricular end-diastolic dimension, LVEDD)、左心室射血分数(left ventricular ejection fraction, LVEF)等。

本研究所有信息均从病历系统获取,主要终点为1年内HF再次入院。若患者在本院再入院,可从病历系统获取;若在他院再入院,则经电话回访记录相关信息。研究截止至患者发生结局或固定日期(2021年12月1日),至截止日期仍存活的患者作截尾处理,排除失访或缺失病历。由于慢病患者会反复住院,本研究只分析首次HF再入院患者。

1.3 统计学处理

采用SPSS 26.0、R 4.1.3进行统计学分析。符合正态分布的计量资料以均数±标准差($\bar{x}\pm s$)表示,组间比较采用t检验;不符合正态分布的计量资料使用中位数(四分位数间距)[$M(Q_1, Q_3)$]表示,组间比较采用Mann-Whitney U检验。计数资料以例数(百分率)表示,组间比较采用χ^2检验。将数据随机分为训练集和验证集,训练集用最小绝对收缩和选择算子(least absolute shrinkage and selection operator, LASSO)回归筛选变量,建立Cox回归列线图。一致性指数(C-index)、受试者工作特征(receiver operating characteristic, ROC)曲线和校准图评估模型精确性。$P<0.05$为差异有统计学意义。

2 结 果

2.1 训练集与测试集基线资料比较

本研究共收集患者195例,失访缺失患者18例,最终纳入患者177例,按7/3随机分为训练集和测试集,训练集124例中52例(41.94%)再入院,测试集53例中25例(47.17%)再入院。训练集和测试集中再入院患者的TC、TG和LDL-C水平较未再入院患者高,HDL-C水平较低,差异均有统计学意义(均$P<0.05$)。且训练集2组患者吸烟、饮酒、Hb和Na差异均有统计学意义(均$P<0.05$);测试集2组的DBP、LVEDD、LVEF、NYHA分级和HF类型差异均有统计学意义(均$P<0.05$;表1)。

2.2 LASSO回归分析筛选变量

将29个变量(性别、吸烟、饮酒、NYHA分级、年龄、心率、收缩压、舒张压、体质量、身高、体质量指数、LVEDD、LVEF、WBC、Hb、ALT、AST、K、Na、Cl、空腹血糖、TC、TG、HDL-C、LDL-C、Cr、NT-proBNP、日剂量、住院天数)进行LASSO回归,变量赋值见表2。选择十折交叉验证的最优λ值,lambda.min=0.07,确定7个变量(K、Na、WBC、AST、TC、TG、HDL-C),详见图1。

表 1 训练集与测试集一般临床资料比较

Table 1 General clinical information of training set and test set

Item	Training set			Test set (n=53)		
	No readmission (n=72)	Readmission (n=52)	P value	No readmission (n=28)	Readmission (n=25)	P value
Male[n(%)]	48(66.7)	27(51.9)	0.097	20(71.4)	19(76.0)	0.706
Smoking[n(%)]	34(47.2)	14(26.9)	0.004	13(46.4)	6(24.0)	0.089
Alcohol drinking[n(%)]	20(27.8)	6(11.5)	0.028	6(21.4)	3(12.0)	0.298
Hypertension[n(%)]	51(70.8)	33(63.5)	0.386	21(75.0)	19(76.0)	0.933
Coronary heart disease [n(%)]	46(63.9)	29(55.8)	0.970	11(39.3)	13(52.0)	0.353
Diabetes mellitus[n(%)]	23(31.9)	18(34.6)	0.755	7(25.0)	9(36.0)	0.384
NYHA classification[n(%)]			0.226			0.025
Ⅰ	0(0.0)	2(3.8)		1(3.6)	1(4.0)	
Ⅱ	16(22.2)	8(15.4)		11(39.3)	2(8.0)	
Ⅲ	37(51.4)	29(55.8)		12(42.9)	20(80.0)	
Ⅳ	19(26.4)	13(25.0)		4(14.3)	2(8.0)	
Type of heart failure[n(%)]			0.274			0.007
HFrEF	22(30.6)	17(32.7)		6(21.4)	16(64.0)	
HFmrEF	32(44.4)	28(53.8)		11(39.3)	4(16.0)	
HFpEF	18(25.0)	7(13.5)		11(39.3)	5(20.0)	
Combination of drugs[n(%)]						
ACEI/ARB	69(95.8)	51(98.1)	0.855	24(85.7)	24(96.0)	0.419
Beta-blockers	58(80.6)	43(82.7)	0.763	18(64.3)	17(68.0)	0.776
Diuretics	41(56.9)	30(57.7)	0.934	10(35.7)	9(36.0)	0.983
Age(years, $\bar{x}\pm s$)	69.69±7.03	72.54±8.66	0.054	71.89±8.90	73.72±9.38	0.470
HR(beats/min, $\bar{x}\pm s$)	79.36±14.43	79.73±14.63	0.895	81.39±16.93	75.18±12.15	0.129
SBP(mmHg, $\bar{x}\pm s$)	128.19±19.85	130.90±21.69	0.472	127.18±16.69	129.48±19.41	0.645
DBP(mmHg, $\bar{x}\pm s$)	76.47±11.42	75.91±13.28	0.806	73.82±9.23	79.08±9.37	0.045
Body mass(kg, $\bar{x}\pm s$)	69.22±11.21	68.15±12.36	0.619	65.04±10.03	68.60±12.00	0.245
Body height(m, $\bar{x}\pm s$)	1.66±0.09	1.66±0.09	0.878	1.67±0.06	1.69±0.08	0.536
BMI(kg/m^2, $\bar{x}\pm s$)	25.15±3.56	24.83±4.05	0.635	23.15±2.74	24.07±3.42	0.282
LVEDD(mm, $\bar{x}\pm s$)	56.57±7.91	56.44±6.61	0.925	53.50±7.71	58.60±9.19	0.033
LVEF(%, $\bar{x}\pm s$)	42.32±11.30	41.04±8.51	0.493	46.00±11.38	37.24±12.84	0.011
WBC(×10^9/L, $\bar{x}\pm s$)	6.62±1.93	6.73±2.99	0.815	6.68±2.65	6.74±2.09	0.927
Hb(g/L, $\bar{x}\pm s$)	135.53±16.70	126.08±17.20	0.003	133.64±20.08	125.08±18.49	0.114
ALT[U/L, $M(Q_1, Q_3)$]	27(16,43)	23(14,37)	0.086	25(14,43)	22(15,43)	0.830
AST[U/L, $M(Q_1, Q_3)$]	27(18,37)	23(17,34)	1.195	29(18,37)	23(21,37)	0.950
K(mmol/L, $\bar{x}\pm s$)	4.15±0.46	3.97±0.55	0.052	4.07±0.54	4.07±0.64	0.997
Na(mmol/L, $\bar{x}\pm s$)	139.44±4.17	137.35±5.94	0.022	140.07±2.85	138.44±4.17	0.100
Cl(mmol/L, $\bar{x}\pm s$)	102.03±4.13	102.49±3.53	0.515	102.47±4.07	102.78±3.82	0.781
FBG(mmol/L, $\bar{x}\pm s$)	6.21±2.30	6.48±2.45	0.528	6.13±2.32	5.78±1.44	0.524
TC(mmol/L, $\bar{x}\pm s$)	3.88±0.98	4.59±1.08	<0.001	3.72±0.96	4.69±0.85	<0.001
HDL-C(mmol/L, $\bar{x}\pm s$)	1.21±0.40	0.93±0.28	<0.001	1.28±0.45	0.84±0.23	<0.001
TG(mmol/L, $\bar{x}\pm s$)	1.34±0.61	1.80±1.06	0.006	1.36±0.70	1.81±0.77	0.033
LDL-C(mmol/L, $\bar{x}\pm s$)	2.32±0.80	2.88±0.78	<0.001	2.34±0.74	2.89±0.75	0.009
Cr(μmol/L, $\bar{x}\pm s$)	94.42±39.06	93.54±33.86	0.896	84.10±30.89	116.36±76.14	0.057
NT-proBNP[pg/ml, $M(Q_1, Q_3)$]	1 453.02(920.30,3 661.01)	1 754.00(906.27,3 282.42)	0.964	1 677.31(999.72,3 464.98)	2 306(1 303.14,4 502.75)	0.219
Daily dose(mg, $\bar{x}\pm s$)	102.43±56.63	88.94±47.33	0.164	90.18±51.97	107.00±56.61	0.265
Days in hospital(d, $\bar{x}\pm s$)	11.10±4.22	11.27±4.36	0.826	10.93±3.35	12.52±6.76	0.294
Survival time[d, $M(Q_1, Q_3)$]	250(188,323)	201(69,468)	0.121	279(156,322)	188(71,338)	0.176

NYHA: New York Heart Association; HFrEF: heart failure with reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction; HFmrEF: heart failure with mid-range ejection fraction; ACEI/ARB: angiotensin converting enzyme inhibitors/angiotensin receptor blockers; HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; LVEDD: left ventricular end diastolic diameter; LVEF: left ventricular end diastolic dimension; WBC:white blood cell; Hb: hemoglobin; ALT: alanine transaminase; AST: aspartate aminotransferase; FBG: fasting blood glucose; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; TG: triglyceride; LDL-C: low-density lipoprotein cholesterol; Cr: creatinine; NT-proBNP: N-terminal pro-B-type natriuretic peptide. 1 mmHg=0.133 kPa.

表 2 变量赋值表

Table 2 Variable assignment table

Variable	Variable naming	Variable type	Value assignment
Readmission	Status	categorisation	No=0, Yes=1
NYHA classification	NYHA	categorisation	Ⅰ=1,Ⅱ=2,Ⅲ=3,Ⅳ=4
Gender	Gender	categorisation	Male=1, Female=2
Alcohol drinking	Drinking	categorisation	No=0, Yes=1
Smoking	Smoking	categorisation	No=0, Yes=1

NYHA: New York Heart Association.

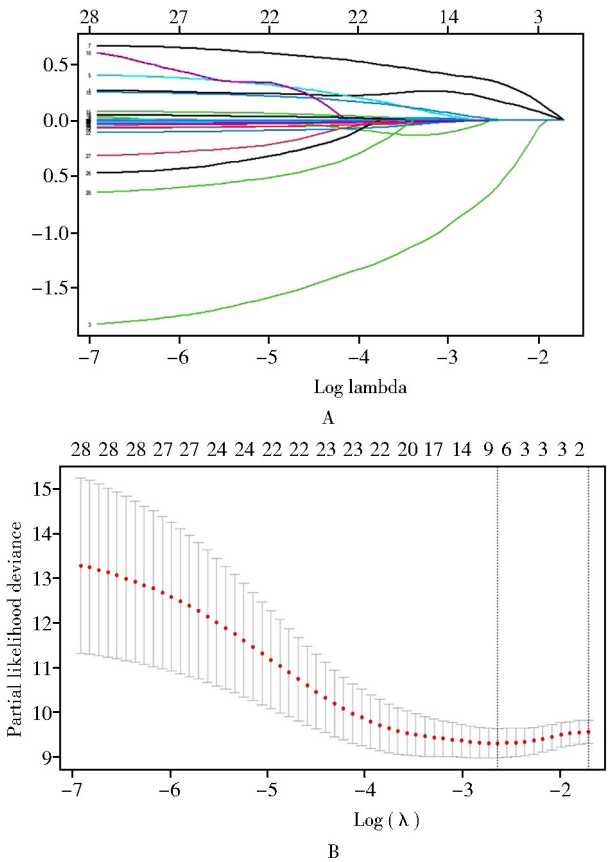


图 1 LASSO 变量选择过程图

Figure 1 LASSO variable selection process diagram

LASSO: least absolute shrinkage and selection operator.
A: regression coefficient compression plot; B: λ Iterative graph.

2.3 基于 Cox 回归的列线图

将 LASSO 筛选的变量进行多因素 Cox 分析，结果显示 WBC、TC、TG 和 HDL-C 是 HF 再入院的影响因素（P <0.05；图 2，图 3）。

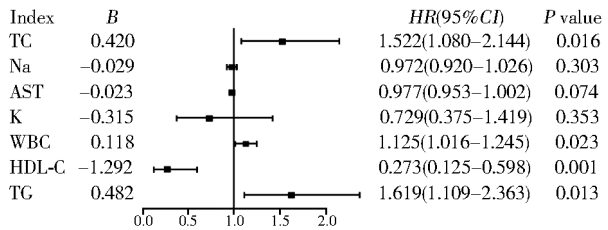


图 2 Cox 多因素分析森林图

Figure 2 Cox multifactor analyses forest plots

TC: total cholesterol; AST: aspartate aminotransferase; WBC: white blood cell; HDL-C: high-density lipoprotein cholesterol; TG: triglyceride.

2.4 模型评价（C 指数、ROC 曲线、校准图）

训练集 *C-index* 为 0.749（0.678～0.820），6 个月 ROC 曲线下面积（area under the curve，AUC）= 0.821（0.700～0.893），12 个月 AUC = 0.771（0.575～0.836）；测试集 *C-index* 为 0.851（0.641～0.809），6 个月 AUC = 0.851（0.692～0.940），12 个月 AUC = 0.847（0.679～0.995）。校准图 x 轴和 y 轴分别代表预测和实际的总生存期，黑色虚线是预测值，红色实线是实际值，图示两条线总体上较贴近，可作辅助参考。详见图 4，图 5。

3 讨 论

HF 影响全球 6 400 多万人[7]，我国现有 1 370 多万例患者，年发病率达 1.3%[8]。改善治疗方法可降低住院率，但同时增加了再住院人数[9]。有 27%的患者在出院后 6 个月内再入院，35%的患者在 12 个月内再入院[10]。考虑到患者的生存情况，发现患者的预后因素并应用生存预测模型在临床上至关重要。因此，本研究在“大数据+健康中国”背景下，基于临床电子病历建立预测 ARNI 治疗 HF 患者的预后列线图，尽早为预后差的患者改善治疗效果，为临床决策提供参考依据。

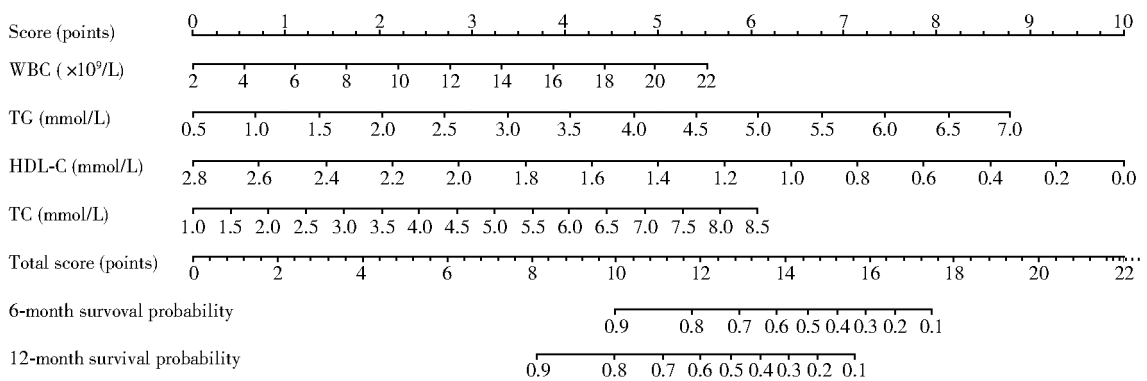


图 3 基于 Cox 回归的列线图模型

Figure 3 Cox regression-based nomogram model

TC: total cholesterol; WBC: white blood cell; HDL-C: high-density lipoprotein cholesterol; TG: triglyceride.

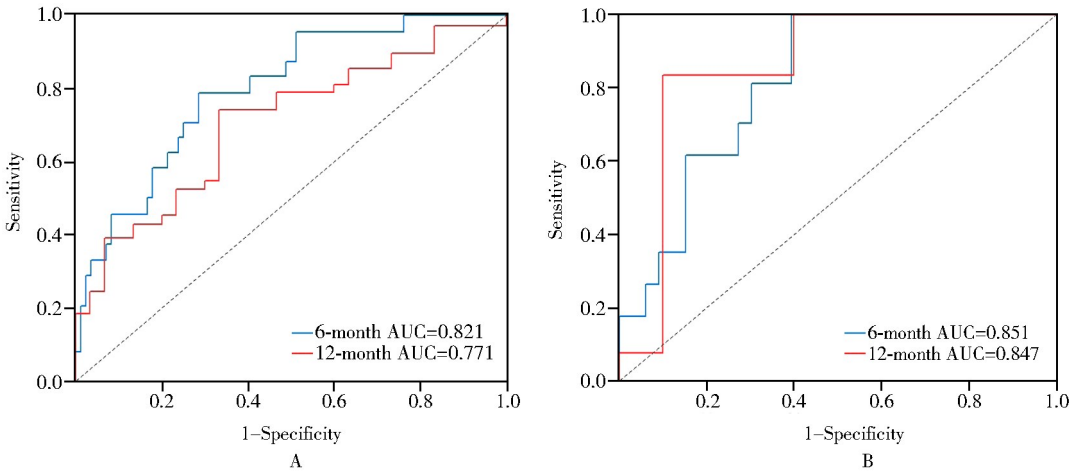


图 4 列线图模型的 ROC 曲线

Figure 4 Receiver operating characteristic curve of nomogram model

A: training set; B: test set. ROC: receiver operating characteristic; AUC: area under the curve.

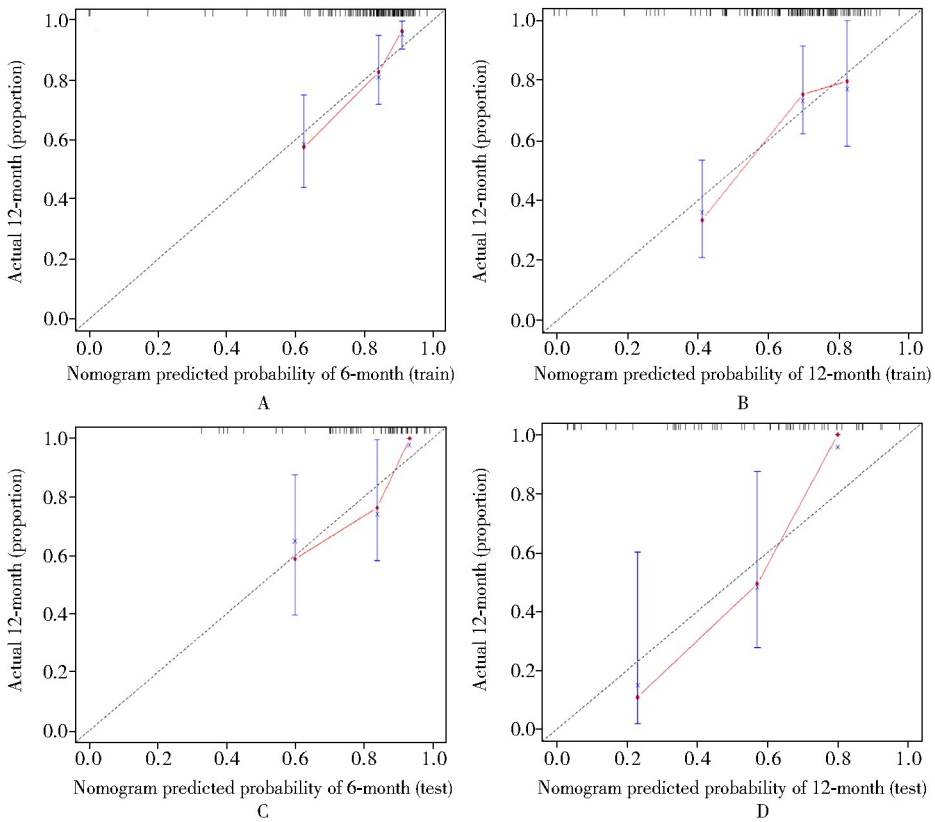


图 5 列线图模型校准曲线

Figure 5 Calibration curve of nomogram model

A and B: training set June and December calibration curves; C and D: testing set June and December calibration curves.

多因素 Cox 回归示 TC、TG、HDL-C、WBC 是患者再入院的影响因素。研究示高水平 TC 和 TG 是心血管病的危险因素[11],高甘油三酯血症可能通过增加缺血性心肌病的风险增加 HF 风险[12],与本研究结果一致。有学者发现 TC 与心血管病呈 U 型关联[13],也有人提出高水平 TC 利于改善 HF 预后[14],建议治疗 HF 同时关注炎症和血脂水平。本研究 HDL-C 是保护因素,与 Emmens 等[15]研究结果一致。HDL-C 在 HF 中起兴奋-收缩耦合、改善能量稳态、抗炎、抗氧化和神经激素激活的作用[16]。也有研究显示,高 WBC 患者易再入院,可能与感染致机体免疫力下降有关[17],与本研究结果一致。减少

HF再入院的推荐策略是出院后随访[18],提高药物依从性也可降低住院和死亡风险[19]。鉴于ARNI在患者中体现成本效益[20],故医务人员应嘱咐患者出院后按时服药、复诊。

本研究结果与大多研究结果相似,但本研究目的和统计方法不同,以往研究仅探索HF影响因素或评价ARNI疗效,未建立预测模型。训练集用于建模,测试集用于内部验证,*C-index*、AUC均大于70%,校准图预测值与实际值基本吻合。列线图在显示影响因素的同时对变量预后风险进行赋值,未来可引入医疗系统,搭建风险预测平台,为ARNI治疗HF这一特定老年人群的短期预后提供参考依据。然而,本研究是一项单中心回顾性分析,结果可能有偏差,病历中缺少饮食、药物依从性、心脏植入式电子设备、社会经济、暴露空气污染等项目,有待后续纳入多因素进行研究。

综上,本研究明确了ARNI治疗HF患者的1年内HF再入院的预后影响因素,成功构建患者短期预后模型,模型具有较好的预测性和临床应用价值。实际应用需多中心大样本及前瞻性的预测研究验证,并探索纳入其他变量进一步提高模型的预测准确性和推广价值。

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