·临床研究·

倾向性评分匹配法分析达格列净和沙库巴曲缬沙坦对心力衰竭预后的影响

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【摘 要】 目的 基于倾向性评分匹配法分析达格列净和沙库巴曲缬沙坦对心力衰竭患者预后的影响。**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收治的369例心力衰竭患者的临床资料,根据治疗方法不同将患者分为达格列净组和沙库巴曲缬沙坦组。倾向性评分匹配后比较2组患者的预后并分析其影响因素。采用SPSS 26.0和R Studio(4.1.2版本)进行数据分析。根据数据类型,组间比较分别采用 t 检验、秩和检验、χ^2 或 *Fisher* 精确概率法。采用Cox回归模型分析2组患者预后的影响因素并绘制Kaplan-Meier曲线。**结果** 倾向性评分匹配后每组70例,Kaplan-Meier曲线示2组患者出院后首次心力衰竭再住院情况差异无统计学意义($P=0.190$)。Cox多因素分析显示,达格列净组纽约心脏病学会(NYHA)分级($HR=6.923$,95%$CI=1.032\sim46.426$;$P=0.046$)、左室舒张末期内径(LVEDD)($HR=1.139$,95%$CI=1.004\sim1.293$;$P=0.044$)、标准化 Z 值的N端-B型钠尿肽前体(NT-proBNP)($HR=1.825$,95%$CI=1.075\sim3.097$;$P=0.026$)是影响心力衰竭患者预后的危险因素;饮酒($HR=0.086$,95%$CI=0.018\sim0.413$;$P=0.002$)和HDL-C($HR=0.012$,95%$CI=0.000\sim0.642$;$P=0.029$)是保护因素。沙库巴曲缬沙坦组吸烟($HR=14.376$,95%$CI=1.657\sim124.748$;$P=0.016$)是影响心力衰竭患者预后的危险因素;饮酒($HR=0.082$,95%$CI=0.012\sim0.578$;$P=0.012$)和血红蛋白($HR=0.953$,95%$CI=0.912\sim0.995$;$P=0.030$)是保护因素。**结论** 倾向性评分匹配后,达格列净组NYHA分级、LVEDD、标准化 Z 值的NT-proBNP、HDL-C和饮酒是患者预后的影响因素;沙库巴曲缬沙坦组吸烟、Hb和饮酒是患者预后的影响因素。达格列净和沙库巴曲缬沙坦对患者预后的影响无显著差异。

【关键词】 心力衰竭;达格列净;沙库巴曲缬沙坦;再入院;预后

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Influence of dapagliflozin and sacubitril/valsartan on prognosis of heart failure by propensity score matching

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【Abstract】 Objective To determine the effect of dapagliflozin and sacubitril/valsartan on prognosis of patients with heart failure based on propensity score matching. **Methods** Clinical data of 369 patients with heart failure diagnosed in the First Hospital of Shanxi Medical University from June 2018 to December 2021 were collected and analyzed retrospectively in this study. According to the treatment they received, the subjects were divided into dapagliflozin group and sacubitril/valsartan group. After propensity score matching, the prognosis of the two groups was compared and the influencing factors were analyzed. SPSS statistics 26.0 and R Studio (version 4.1.2) were used for data analysis. Data comparison between two groups was conducted using student's t test, rank sum test, *Chi*-square test or *Fisher* exact probability method depending on data type. Cox regression models were used to analyze the influencing factors for prognosis in two groups of patients, and Kaplan-Meier curves were plotted. **Results** There were 70 patients in each group after propensity score matching. Kaplan-Meier survival analysis showed no statistical difference in first heart failure rehospitalization after discharge between the two groups ($P=0.190$). Cox multivariate analysis showed that the New York Heart Association (NYHA) classification ($HR=6.923$, 95%$CI=1.032-46.426$; $P=0.046$), left ventricular end diastolic diameter (LVEDD) ($HR=1.139$, 95%$CI=1.004-1.293$; $P=0.044$) and Z score of N-terminal pro-B-type natriuretic peptide (NT-proBNP) ($HR=1.825$, 95%$CI=1.075-3.097$; $P=0.026$) were prognostic risk factors for patients with heart failure. Alcohol drinking ($HR=0.086$, 95%$CI=0.018$

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−0.413; P=0.002) and high-density lipoprotein cholesterol (HDL-C) (HR=0.012, 95%CI=0.000−0.642; P=0.029) were prognostic protective factors in the dapagliflozin group. For the sakubatril/valsartan group, smoking (HR=14.376, 95%CI=1.657−124.748; P=0.016) was a risk factor, while drinking (HR=0.082, 95%CI=0.012−0.578; P=0.012) and hemoglobin (Hb, HR=0.953, 95%CI=0.912−0.995; P=0.030) were protective factors. **Conclusion** After propensity score matching, NYHA classification, LVEDD, Z score of NT-proBNP, HDL-C and alcohol drinking are factors influencing the prognosis of patients with heart failure in the dapagliflozin group. Smoking, Hb and alcohol drinking are prognostic factors in the sakubatril/valsartan group. There is no significant difference in prognosis for heart failure in comparison of dapagliflozin and sakubatril/valsartan.

【Key words】 heart failure; dapagliflozin; sacubitril/valsartan; readmission; prognosis

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心力衰竭(heart failure,HF)是一个主要的临床和公共卫生问题,给全球造成沉重的经济负担[1]。美国心脏协会(American Heart Association,AHA)/美国心脏病学会(American College of Cardiology,ACC)/美国心力衰竭协会(Heart Failure Society of American,HFSA)联合发布《2022 年 AHA/ACC/HFSA 指南》[2]提出钠-葡萄糖协同转运蛋白 2(sodium-dependent glucose transporters 2,SGLT-2)抑制剂和血管紧张素受体脑啡肽酶抑制剂(angiotensin receptor neprilysin inhibitor,ARNI)是抗心力衰竭新药,现已有多项试验证实其可有效降低心血管死亡率和心力衰竭住院率[3,4]。鉴于二者对比的研究、尤其是在中国人群的临床研究较少,故本研究对应用达格列净和沙库巴曲缬沙坦的慢性心力衰竭患者的预后进行分析。

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 月于山西医科大学第一医院收治的 369 例射血分数减少的心力衰竭(heart failure with reduced ejection fraction,HFrEF)患者的临床资料,诊断标准参考《2022 年 AHA/ACC/HFSA 指南》[2]。根据心力衰竭用药将患者分为达格列净组和沙库巴曲缬沙坦组。达格列净组 118 例,男性 83 例,女性 35 例;年龄 32~84(61.03±11.30)岁。沙库巴曲缬沙坦组 251 例,男 182 例,女性 69 例;年龄 22~90(60.73±15.98)岁。

纳入标准:(1)年龄≥18 岁;(2)纽约心脏病学会(New York Heart Association,NYHA)分级Ⅱ~Ⅳ级;(3)左室射血分数(left ventricular ejection fraction,LVEF)<40%;(4)有心力衰竭症状和体征。

排除标准:(1)收缩压<90 mmHg(1 mmHg=0.133 kPa);(2)肾小球滤过率<30 ml/(min·1.73m^2);(3)血钾>5.2 mmol/L;(4)恶性肿瘤、肝肾功能衰竭及免疫性疾病;(5)1 型糖尿病、高渗性昏迷及乳酸酸中毒或糖尿病酮症酸中毒;(6)对治疗药物过敏或不耐受其副作用;(7)临床资料或终点信息不完整、生存时间不足 1 d、意外事故入院或入院原因不明确。

1.2 方法

所有患者均给予一般治疗及抗心力衰竭治疗。达格列净组在此基础上加达格列净,10 mg/次,1 次/d。沙库巴曲缬沙坦组在常规治疗基础上加沙库巴曲缬沙坦,起始剂量为 50 mg,2 次/d,之后根据血压酌情调整,最大剂量 200 mg,2 次/d。

1.3 终点事件

所有资料从病历系统中获取并进行回顾性分析,主要终点心力衰竭再入院,次要终点全因死亡。若患者在本院死亡或再入院,可从病历系统中获取;若在其他医院发生终点,则通过电话回访记录相关信息。研究停止至发生结局或截止日期(2021 年 12 月 1 日),至截止日仍存活的患者作截尾处理,失访或再入院信息不完整者全部排除。考虑到患者会反复住院,本研究只分析研究期间出院后首次心力衰竭再入院。

1.4 统计学处理

采用 SPSS 26.0 和 R Studio(4.1.2 版本)进行数据分析。删除缺失>20%的数据,缺失≤20%的数据采用均值填补法进行处理。设卡钳值为 0.2,用 1∶1最邻近匹配法对 2 组患者的基线资料及出院时临床检查进行倾向性评分匹配。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 检验或 *Fisher* 精确概率法。匹配后应用 Cox 回归模型分析 2 组 HF 患者预后的影响因素并绘制 Kaplan-Meier 曲线。P<0.05 为差异有统计学意义。

2 结 果

2.1 2组患者一般资料比较

最终纳入369例患者,达格列净组118例(31.98%),沙库巴曲缬沙坦组251例(68.02%)。倾向性评分匹配前,2组患者NAYH分级、LVEF及左室舒张末期内径(left ventricular end diastolic diameter,LVEDD)、空腹血糖(fasting blood glucose,FBG)、甘油三酯(triglyceride,TG)和N端-B型钠尿肽前体(N-terminal pro-B-type natriuretic peptide,NT-proBNP),差异均有统计学意义($P<0.05$;表1)。匹配后每组70例,组间差异无统计学意义($P>0.05$;表2),提示2组数据较为均衡。

2.2 2组患者终点事件分析

2组全因死亡共0例,心力衰竭再入院共64例,其中达格列净组35例(50.0%),沙库巴曲缬沙坦组29例(41.4%)。出院后6个月至1年内,2组再入院率均增加(图1),Kaplan-Meier曲线示预后差异无统计学意义($P=0.190$;图2)。

2.3 Cox多因素分析2组患者预后的影响因素

Cox回归分析示:达格列净组NYHA分级、LVEDD、标化Z值的NT-proBNP是危险因素;高密度脂蛋白胆固醇(high-density lippoprotein cholesterol,HDL-C)和饮酒是保护因素($P<0.05$)。沙库巴曲缬沙坦组吸烟是危险因素,Hb和饮酒是保护因素($P<0.05$;表3)。

表1 2组患者一般资料比较(匹配前)

Table 1 Comparison of baseline data between two groups (before matching)

Item	Dapagliflozin group($n=118$)	Sacubitril/valsartan group($n=251$)	$\chi^2/t/Z$	P value
Male[n(%)]	83(70.3)	182(72.5)	0.187	0.666
Age(years, $\bar{x}\pm s$)	61.03±11.30	60.73±15.98	0.210	0.852
HR(beats/min, $\bar{x}\pm s$)	76.94±13.27	80.04±15.68	−1.859	0.064
SBP(mmHg, $\bar{x}\pm s$)	130.13±20.63	127.65±18.71	1.148	0.252
DBP(mmHg, $\bar{x}\pm s$)	76.34±12.58	77.73±12.47	−0.997	0.319
Body mass(kg, $\bar{x}\pm s$)	72.45±13.17	71.98±14.93	0.288	0.773
Height(cm, $\bar{x}\pm s$)	167.67±7.81	167.83±7.94	−0.176	0.861
BMI(kg/m^2, $\bar{x}\pm s$)	25.68±3.68	25.40±4.23	0.623	0.534
Smoking[n(%)]	52(44.1)	108(43.0)	0.035	0.851
Alcohol drinking[n(%)]	31(26.3)	60(23.9)	0.242	0.623
Hypertension[n(%)]	97(82.2)	202(80.5)	0.155	0.693
Coronary heart disease[n(%)]	86(72.9)	189(75.3)	0.247	0.619
ACEI/ARB[n(%)]	103(87.3)	211(84.1)	0.658	0.417
Beta-blockers[n(%)]	91(77.1)	190(75.7)	0.089	0.765
Diuretics[n(%)]	25(21.2)	43(17.1)	0.878	0.349
NYHA classification[n(%)]			14.483	<0.001
Ⅱ	55(46.6)	72(28.7)		
Ⅲ	51(43.2)	123(49.0)		
Ⅳ	12(10.2)	56(22.3)		
LVEDD[mm, $M(Q_1, Q_3)$]	50.00(46.00,53.00)	58.00(52.00,65.00)	−8.399	<0.001
LVEF[%, $M(Q_1, Q_3)$]	28.00(23.00,35.00)	20.00(10.00,28.00)	10.102	<0.001
WBC($\times10^9$/L, $\bar{x}\pm s$)	6.89±2.28	6.95±2.65	−0.187	0.852
Hb(g/L, $\bar{x}\pm s$)	139.01±19.59	141.16±20.01	−0.925	0.356
FBG[mmol/L, $M(Q_1, Q_3)$]	8.17(6.38,9.41)	5.46(4.76,6.23)	8.554	<0.001
TC(mmol/L, $\bar{x}\pm s$)	4.10±1.33	3.97±1.13	0.976	0.330
HDL-C(mmol/L, $\bar{x}\pm s$)	0.99±0.25	0.98±0.25	0.366	0.714
TG[mmol/L,$M(Q_1, Q_3)$]	1.79(1.31,2.37)	1.32(1.00,1.79)	5.440	<0.001
LDL-C[mmol/L, $M(Q_1,Q_3)$]	2.54(1.94,3.44)	2.47(2.00,2.97)	1.210	0.226
Cr[μmol/L, $M(Q_1, Q_3)$]	79.00(65.83,105.15)	84.00(72.50,97.10)	−1.282	0.200
NT-proBNP[pg/ml, $M(Q_1, Q_3)$]	948.13(124.78,1032.19)	1432.50(470.49,3227.17)	−5.736	<0.001

HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; ACEI/ARB: angiotensin converting enzyme inhibitor/angiotensin receptor blocker; NYHA: New York Heart Association; LVEDD: left ventricular end diastolic diameter; LVEF: left ventricular ejection fraction; WBC: white blood cell; Hb: hemoglobin; 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 2 组患者一般资料比较(1∶1匹配后)

Table 2 Comparison of baseline data between two groups (after 1∶1 propensity score matching)

Item	Dapagliflozin group(n=70)	Sacubitril/valsartan group(n=70)	$\chi^2/t/Z$	P value
Male[n(%)]	51(72.9)	46(65.7)	0.839	0.360
Age(years, $\bar{x}\pm s$)	61.71±11.52	62.30±15.28	−0.256	0.798
HR(beats/min, $\bar{x}\pm s$)	76.10±13.49	76.47±13.23	−0.164	0.870
SBP(mmHg, $\bar{x}\pm s$)	128.83±20.81	131.21±18.69	0.534	0.477
DBP(mmHg, $\bar{x}\pm s$)	76.60±12.04	77.80±13.61	−0.592	0.581
Body mass(kg, $\bar{x}\pm s$)	73.33±13.93	72.04±12.46	0.581	0.562
Height(cm, $\bar{x}\pm s$)	168.38±8.13	1.67±7.87	0.934	0.352
BMI(kg/m^2, $\bar{x}\pm s$)	25.75±3.90	25.61±3.77	0.206	0.837
Smoking[n(%)]	33(47.1)	28(40.0)	0.726	0.394
Alcohol drinking[n(%)]	18(25.7)	19(27.1)	0.037	0.848
Hypertension[n(%)]	53(75.7)	49(70.0)	0.578	0.447
Coronary heart disease[n(%)]	48(68.6)	50(71.4)	0.136	0.712
ACEI/ARB[n(%)]	62(88.6)	67(95.7)	2.467	0.116
Beta-blockers[n(%)]	56(80.0)	53(75.7)	0.373	0.541
Diuretics[n(%)]	11(15.7)	15(21.4)	0.756	0.385
NYHA classification[n(%)]			0.482	0.786
Ⅱ	29(41.4)	25(35.7)		
Ⅲ	31(44.3)	34(48.6)		
Ⅳ	10(14.3)	11(15.7)		
LVEDD[mm, $M(Q_1, Q_3)$]	51.00(48.00,57.00)	51.00(48.00,58.00)	0.687	0.492
LVEF[%, $M(Q_1, Q_3)$]	26.00(18.00,31.00)	24.00(15.00,30.00)	0.217	0.828
WBC($\times10^9$/L, $\bar{x}\pm s$)	6.85±2.16	7.01±2.63	−0.536	0.706
Hb(g/L, $\bar{x}\pm s$)	137.80±19.91	140.07±18.05	−0.716	0.481
FBG[mmol/L, $M(Q_1, Q_3)$]	7.79(5.87,8.96)	6.20(5.16,9.99)	1.121	0.262
TC(mmol/L, $\bar{x}\pm s$)	3.82±1.12	3.94±1.35	−0.567	0.552
HDL-C(mmol/L, $\bar{x}\pm s$)	0.97±0.27	0.95±0.23	0.568	0.896
TG[mmol/L,$M(Q_1, Q_3)$]	1.51(1.18,2.16)	1.55(1.19,2.06)	1.892	0.058
LDL-C[mmol/L, $M(Q_1, Q_3)$]	2.39(1.85,3.07)	2.39(1.77,2.95)	0.709	0.479
Cr[μmol/L, $M(Q_1, Q_3)$]	81.20(66.00,105.15)	79.75(69.05,93.85)	1.876	0.061
NT-proBNP[pg/mL, $M(Q_1, Q_3)$]	1032.19(245.87,1421.50)	789.89(248.20,1815.35)	−1.676	0.094

HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; ACEI/ARB: angiotensin converting enzyme inhibitor/angiotensin receptor blocker; NYHA: New York Heart Association; LVEDD: left ventricular end diastolic diameter; LVEF: left ventricular ejection fraction; WBC: white blood cell; Hb: hemoglobin; 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.

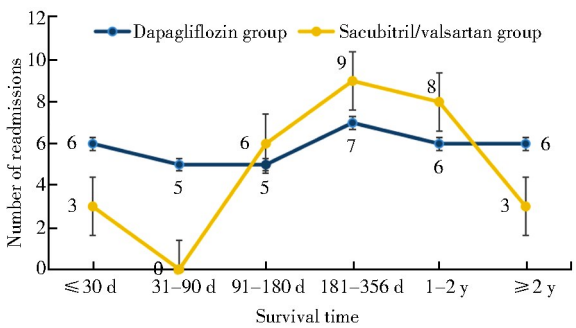

图 1 2 组患者终点事件比较

Figure 1 Comparison of endpoint events between two groups

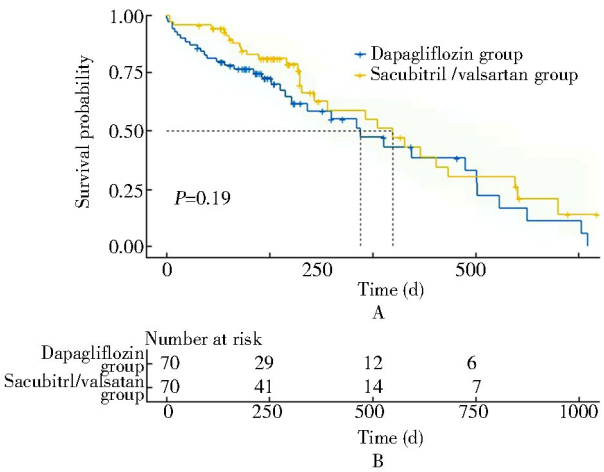

图 2 2 组患者 Kaplan-Meier 生存曲线

Figure 2 Kaplan-Meier survival curves of two groups

A: Kaplan-Meier survival curves for the two prognostic groups; B: the risk table, which refers to the number of people who did not have an outcome but may have an outcome. The two rows in figure B correspond to the two curves in figure A respectively.

2.4 亚组分析

Kaplan-Meier 曲线示沙库巴曲缬沙坦组女性、低体质量、NYHA Ⅲ/Ⅳ级预后较差($P<0.05$;图 3),达格列净组无显著差异。

表3 Cox多因素分析2组患者预后的影响因素

Table 3 Cox multivariate analysis on influencing factors of prognosis in both groups

Factor	Dapagliflozin group(n=70)			Sacubitril/valsartan group(n=70)		
	β	HR(95%CI)	P value	β	HR(95%CI)	Pvalue
Smoking	1.122	3.070(0.830-11.360)	0.093	2.666	14.376(1.657-124.748)	0.016
Alcohol drinking	-2.455	0.086(0.018-0.413)	0.002	-2.504	0.082(0.012-0.578)	0.012
NYHA classification	1.935	6.923(1.032-46.426)	0.046	1.128	3.880(0.206-13.752)	0.863
LVEDD	0.130	1.139(1.004-1.293)	0.044	0.034	1.067(0.625-1.545)	0.398
Hb	-0.003	0.997(0.974-1.021)	0.793	-0.048	0.953(0.912-0.995)	0.030
HDL-C	-4.384	0.012(0.000-0.642)	0.029	-1.297	0.059(0.014-1.355)	0.413
Z score(NT-proBNP)	0.602	1.825(1.075-3.097)	0.026	0.259	1.772(1.368-2.619)	0.493

NYHA: New York Heart Association; LVEDD: left ventricular end diastolic diameter; Hb: hemoglobin; HDL-C: high-density lipoprotein cholesterol; Z score(NT-proBNP): standardized Z score of N-terminal pro-B-type natriuretic peptide.

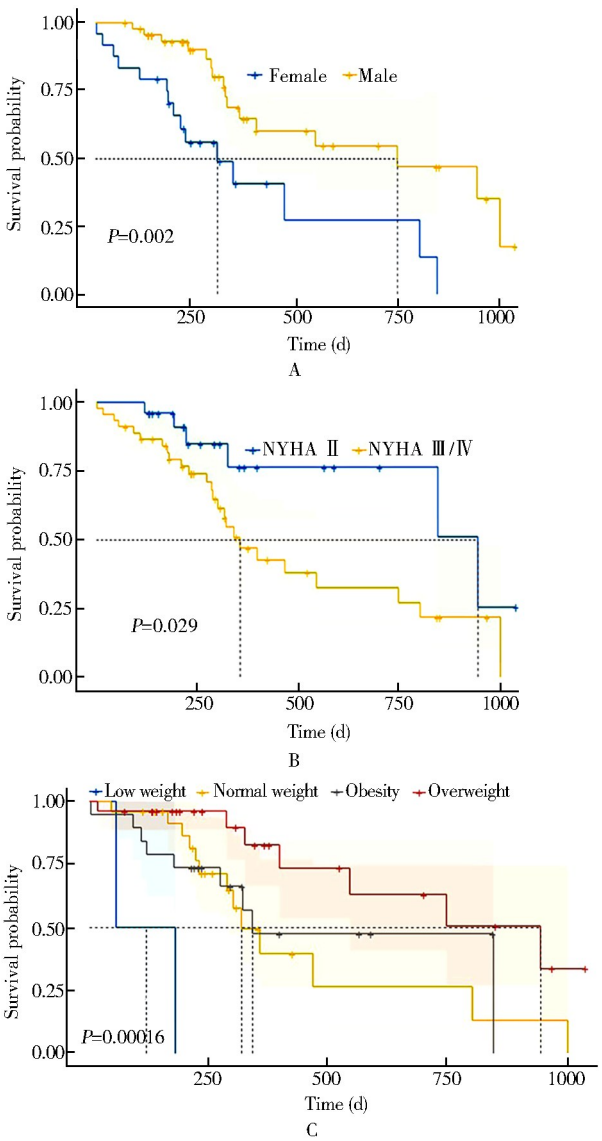

图3 沙库巴曲缬沙坦组Kaplan-Meier生存曲线

Figure 3 Kaplan-Meier survival curves of sacubitril/valsartan group

A: Kaplan-Meier survival curves for different genders; B: Kaplan-Meier survival curves for different NYHA classifications; C: Kaplan-Meier survival curves for different body mass index. NYHA: New York Heart Association.

3 讨 论

心力衰竭是许多心血管疾病的终末阶段,大约50%心力衰竭病例为HFrEF[5]。我国现有1 370多万心力衰竭患者[6],每年成本约54.2亿美元[1]。随着治疗的改进再住院人数也增加了[7],有27%患者在出院后6个月内再入院,35%患者1年内再入院。因此,再入院是心力衰竭患者的主要问题之一[8]。目前,达格列净和沙库巴曲缬沙坦均在医保药品中且体现成本效益[1,9],故本研究对应用这些药物的HFrEF患者匹配后进行预后分析,以期为患者制定预防策略,为临床决策提供诊疗新思路。

在2组患者基线资料和实验室指标均均衡的情况下,心力衰竭再入院情况无显著差异,与Teo等[10]研究结果一致。通过Cox多因素分析,达格列净组NYHA分级、LVEDD和标准化Z值的NT-proBNP是患者预后的危险因素,有研究表示这些指标与心力衰竭预后有关[11,12],与本研究结果基本一致。同时,Jackson等[13]发现HDL-C是保护因素,在心脏修复中发挥重要作用。矛盾的是,极高水平的HDL-C增加心血管风险,导致HDL-C与心血管疾病呈U型关系[14],这种关联目前仍存在争议。沙库巴曲缬沙坦组吸烟是预后危险因素,而Hb是保护因素,Lu等[15]和Sabah等[16]研究与本研究结果一致。本研究中2组结果均显示饮酒是心力衰竭预后的保护因素,饮酒既可引起心力衰竭,也可预防心力衰竭,取决于个人敏感性、酒精剂量、生活方式等[17]。在患者出院后6个月至1年内再入院率升高,表明出院后随访对预后至关重要,Morken等[18]也证实随访可降低再入院风险。

亚组分析示沙库巴曲缬沙坦组女性、低体质量、NYHA Ⅲ/Ⅳ级预后风险大。显然,NYHA Ⅲ/Ⅳ级身体耐受更差。本研究也证实存在“肥胖悖论”[19],但体质量指数没有提供脂肪分布的信息,并

不能完全准确衡量肥胖程度[20]。Hoang-Kim 等[21]还发现随访少于 1 年时,女性再入院率较高;随访超过 1 年时,男性再入院率较高。达格列净组内分析未显示显著差异,可能是样本不足或潜在机制影响。

综上,本研究基于临床真实数据,分析了达格列净组和沙库巴曲缬沙坦组患者的预后生存情况并确定了影响因素。虽得出有意义的结果,但本研究是小样本、单中心、回顾性分析,且病历中缺少社会经济地位[22]、药物依从性[23]、肌钙蛋白、生长分化因子[24]等数据,此外,还需考虑心力衰竭与体质量、脂肪之间的潜在机制及药物间相互作用的关系,因此结果的推广需通过多中心、大样本及前瞻性研究验证,并探索纳入其他因子以提高推广价值。

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