·临床研究·

性别对80岁以上高龄急性冠脉综合征患者长期预后的影响

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【摘 要】 **目的** 探讨性别对≥80岁高龄急性冠脉综合征(ACS)患者长期预后的影响。**方法** 连续入选解放军总医院心内科自2006年1月至2011年12月≥80岁行冠状动脉造影检查的ACS患者664例(女性占28.31%)。根据性别进行分组,对两组患者的临床资料结果进行比较分析,记录患者主要不良心脏事件(MACE),Kaplan-Meier生存曲线分析性别对高龄ACS患者长期生存率的影响。Cox多因素回归分析影响长期预后的独立危险因素。**结果** 随访周期13~79个月(中位数28个月)。女性患者高脂血症患病率、左室射血分数、体质量指数及空腹血糖水平高于男性患者($P<0.05$)。男性患者舒张压、血尿酸水平、吸烟史、慢性肾功能不全、陈旧性心肌梗死、脑卒中发病率高于女性患者($P<0.05$)。两组患者的ACS临床分型、用药方案及治疗策略未见显著差异($P>0.05$)。Kaplan-Meier生存曲线分析显示,两组患者长期生存率($P=0.619$)及无事件生存率($P=0.365$)均无显著差异。Cox多因素回归分析显示非高密度脂蛋白胆固醇(non-HDL-C)、收缩压水平是高龄ACS患者全因死亡(HR=1.73,95% CI:1.09~2.75,$P=0.019$;HR=0.98,95% CI:0.97~1.00,$P=0.015$)和MACE发生(HR=1.80,95% CI:1.22~2.63,$P=0.003$;HR=0.98,95% CI:0.97~0.99,$P=0.003$)的独立危险因素。**结论** 性别不是影响高龄ACS患者长期预后的危险因素,non-HDL-C和收缩压水平是该人群的全因死亡和MACE发生的独立危险因素。

【关键词】 急性冠脉综合征; 性别; 老年人,80以上; 预后; 危险因素
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Influence of gender on long-term prognosis of acute coronary syndrome in over-80-year-old patients

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【**Abstract**】 **Objective** To investigate the effect of gender on the long-term prognosis in the elderly acute coronary syndrome (ACS) patients over 80 years old. **Methods** All 664 consecutive ACS octogenarians (28.31% women) admitted and undergoing coronary angiography in our department from January 2006 to December 2011 were enrolled in this study. They were assigned into male and female groups. Clinical data were collected and compared between the 2 groups. The occurrence of major adverse cardiac events (MACE) was recorded. Kaplan-Meier survival analysis was performed for the effect of gender on long-term survival in the cohort. Cox multivariate regression analysis was carried out to study the independent predictors for long-term prognosis. **Results** The follow-up period ranged from 13 to 79 months (median 28 months). The women had higher hyperlipidemia incidence, larger left ventricular ejection fraction, higher body mass index, and elevated fasting blood glucose than the men ($P<0.05$). But diastolic blood pressure, serum uric acid, percentages of smoking history and previous myocardial infarction, and incidences of stroke and chronic renal failure were higher in the male than in the female groups ($P<0.05$). There were no significant differences in clinical classification of ACS, medicine and treatment strategies between the 2 groups ($P>0.05$). Kaplan-Meier survival analysis showed that no significant differences were observed in long-term survival ($P=0.619$) and event-free survival ($P=0.365$) between the 2 groups. Cox multivariate regression analysis revealed that non-high density lipoprotein cholesterol (non-HDL-C) and systolic blood pressure level were independent predictors for long-term all-cause mortality (HR=1.73, 95% CI: 1.09-2.75, $P=0.019$; HR=0.98, 95% CI: 0.97-1.00, $P=0.015$) and MACE (HR=1.80, 95% CI: 1.22-2.63, $P=0.003$; HR=0.98, 95% CI: 0.97-0.99, $P=0.003$). **Conclusion** Gender is not a risk factor for long-term prognosis in ACS octogenarians, but non-HDL-C and systolic blood pressure are independent predictors for long-term all-cause mortality and MACE.

【**Key words**】 acute coronary syndrome; gender; aged,80 and over; prognosis; clinical risk factors

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2014年中国心血管病报告显示,心血管病占居民疾病死亡构成的41%以上,为我国居民的首位死因。其中,冠心病患病率及死亡率均呈上升趋势。急性冠脉综合征(acute coronary syndrome, ACS)成为了导致患者死亡的主要疾病之一[1]。随着人口老龄化进程的加速[2],≥80岁心血管病的发病人数将持续增长,并且有研究显示≥80岁冠心病患者尽管接受了再血管化和强化的口服药物治疗,死亡率仍明显较<80岁者高[3]。目前针对≥80岁高龄ACS患者长期预后的大样本量研究较少,本研究连续入选2006年1月至2011年12月在解放军总医院住院并行冠状动脉造影(coronary artery angiography, CAG)检查的664例≥80岁ACS患者的临床资料、CAG结果,并对患者进行长期随访,探讨不同性别高龄ACS患者临床特点及性别对长期预后的影响。

1 对象与方法

1.1 研究对象

本研究入选解放军总医院自2006年1月至2011年12月因ACS在我院住院并行CAG检查的≥80岁的患者,共计664例。入选标准:经详细询问病史、体检、心电图及心肌酶学检查,诊断为ACS的患者。记录患者一般情况(性别、年龄、体质量指数、心率、血压等)、个人疾病史(高血压、糖尿病、高脂血症、慢性肾功能不全、脑卒中、陈旧性心肌梗死病史等)、冠心病的临床分型(急性ST段抬高型心肌梗死、急性非ST段抬高型心肌梗死、不稳定型心绞痛)以及患者的服药史。排除标准:恶性肿瘤、严重的心脏瓣膜病、原发性肺动脉高压、心力衰竭、严重的肝功能不全、代谢性疾病以及风湿免疫疾病。所有患者已签署研究知情同意书,伦理审查已通过。

1.2 血液生化指标的检测

采集患者外周血5 ml。采用罗氏公司COBAS全自动生化分析仪检测患者的空腹血糖、总胆固醇、甘油三酯、低密度脂蛋白胆固醇、高密度脂蛋白胆固醇、血尿酸、血肌酐,计算非高密度脂蛋白胆固醇(non-high density lipoprotein chlosterol, non-HDL-C)、估算的肾小球滤过率(estimated glomerular filtration rate, eGFR)。

1.3 CAG及狭窄程度的判断

全部患者入院后均行CAG检查,冠心病定义为≥1支病变的血管狭窄≥50%。冠状动脉狭窄程度采用Gensini评分的方法表示。根据患者的病变部位和狭窄程度进行计算。根据管腔直径的狭窄程度评分:狭窄1%~25%记为1分,狭窄26%~50%记为2分,狭窄51%~75%记为4分,狭窄76%~90%记为8分,管腔狭窄91%~99%记为16分,完全闭塞记为32分;根据病变部位计算倍数关系:左主干(left main, LM)×5,左前降支(left anterior descending, LAD)、左回旋支(left circumflex, LCX)近段×2.5, LAD中段×1.5,右冠状动脉(right coronary artery, RCA)近段×1,其余部位×1;冠状动脉狭窄的严重程度以计算的Gensini总分评估。

1.4 患者分组及随访

患者入院后根据性别分为男性和女性两组。根据患者CAG的结果,进行强化药物治疗、经皮冠状动脉介入术(percutaneous coronary intervention, PCI)及冠状动脉旁路移植术(coronary artery bypass graft, CABG)。患者出院后每12个月随访1次,记录患者主要不良心脏事件(major adverse cardiac events, MACE;包括死亡、急性心肌梗死、再血管化治疗)。

1.5 统计学处理

采用SPSS17.0统计分析软件进行分析。计量资料以均数±标准差表示,正态分布变量采用t检验,非正态分布变量采用Wilcoxon两样本检验。计数资料以百分率表示,组间比较采用卡方检验。生存分析采用Kaplan-Meier方法,Cox多因素回归分析长期预后的独立危险因素。以$P<0.05$为差异有统计学意义。

2 结 果

2.1 两组患者的一般资料比较

本研究详细记录了患者的一般情况和临床资料。结果显示,入组患者664例,男性476例,女性188例,其中654例(654/664, 98.49%)完成随访。两组患者的年龄、收缩压、心率、eGFR以及高血压、糖尿病患病率差异均无统计学意义($P>0.05$)。女性患者左室射血分数、高脂血症患病率、血脂水平、体质量指数及空腹血糖水平高于男性患者

($P<0.05$)。男性患者舒张压、血尿酸水平、吸烟史、慢性肾功能不全及陈旧性心肌梗死、脑卒中发病率高于女性患者($P<0.05$;表1)。

两组患者的ACS临床分型中,急性ST段抬高型心肌梗死、急性非ST段抬高型心肌梗死和不稳定型心绞痛的比例差异均无统计学意义($P>0.05$),冠脉病变狭窄程度Gensini评分差异无统计学意义($P>0.05$),患者的临床用药方案及治疗策略的选择差异均无统计学意义($P>0.05$;表2)。

2.2 性别对长期预后的影响

患者的随访周期是13~79个月(中位数28个月)。在全部随访期间,男性组患者全因死亡64例(13.45%),MACE发生率19.96%,其中心源性死亡62例(13.03%),靶血管重建20例(4.20%),急性心肌梗死13例(2.73%)。女性组患者MACE发生率16.49%,其中心源性死亡22例(11.70%),靶血管重建8例(4.26%),急性心肌梗死1例(0.53%)。两组患者间MACE发生率、死亡率、靶血管重建及急性心肌梗死发生率差异均无统计学意义($P>0.05$;表3)。Kaplan-Meier生存曲线分析显示,两组患者长期生存率($P=0.619$;图1A)及无事件存活率($P=0.365$;图1B)差异均无统计学意义。性别对长期预后无显著影响。

2.3 长期预后独立危险因素

Cox多因素回归分析显示non-HDL-C、左室射血分数、eGFR、心率及收缩压是全因死亡的独立危险因素($P<0.05$;表4),而non-HDL-C、收缩压和Gensini评分是MACE发生的独立危险因素($P<0.05$;表4)。non-HDL-C、收缩压水平是全因死亡(HR=1.73,95% CI:1.09~2.75,$P=0.019$;HR=0.98,95% CI:0.97~1.00,$P=0.015$)和MACE发生(HR=1.80,95% CI:1.22~2.63,$P=0.003$;HR=0.98,95% CI:0.97~0.99,$P=0.003$)共同的独立预测因子。

表1 两组患者基线临床资料比较

Table 1 Comparison of the baseline clinical characteristics between the two groups

Item	Male ($n=476$)	Female ($n=188$)	P value
General conditions			
Age(years, $\bar{x}\pm s$)	81.91±2.19	81.75±1.99	0.3760
BMI(kg/m^2, $\bar{x}\pm s$)	24.38±3.14	25.02±3.83	0.0270
HR(beats/min, $\bar{x}\pm s$)	74.36±13.85	75.85±14.18	0.2210
SBP(mmHg, $\bar{x}\pm s$)	138.03±22.05	134.45±20.91	0.0560
DBP(mmHg, $\bar{x}\pm s$)	72.05±12.07	69.81±12.09	0.0320
LVEF(%, $\bar{x}\pm s$)	54.84±10.02	57.11±8.99	0.0070
Risk factors[n(%)]			
Hypertension	360(75.63)	153(81.38)	0.4470
DM	156(32.77)	76(40.43)	0.1330
Hyperlipidemia	95(19.96)	56(29.79)	0.0170
Previous MI	96(20.17)	24(12.77)	0.0430
Previous stroke	110(23.11)	28(14.89)	0.0360
CRF	68(14.29)	10(5.32)	0.0020
Smoking	155(32.56)	9(4.79)	<0.0001
Baseline blood feature			
TG(mmol/L, $\bar{x}\pm s$)	1.31±0.73	1.73±0.80	<0.0001
TC(mmol/L, $\bar{x}\pm s$)	3.95±0.92	4.53±0.99	<0.0001
HDL-C(mmol/L, $\bar{x}\pm s$)	1.13±0.34	1.20±0.39	0.0210
LDL-C(mmol/L, $\bar{x}\pm s$)	2.24±0.78	2.63±0.91	<0.0001
Non-HDL-C(mmol/L, $\bar{x}\pm s$)	2.84±0.91	3.35±1.01	<0.0001
FBG(mmol/L, $\bar{x}\pm s$)	6.78±4.58	8.17±3.98	0.0004
SUA (μmol/L, $\bar{x}\pm s$)	367.3±163.2	328.8±110.8	0.0030
eGFR [ml/(min·1.73m^2), $\bar{x}\pm s$]	74.04±38.86	77.08±37.42	0.3800

BMI: body mass index; HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; LVEF: left ventricular ejection fraction; DM: diabetes mellitus; MI: myocardial infarction; CRF: chronic renal failure; TG: triglycerides; TC: total cholesterol; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; non-HDL-C: non high density lipoprotein cholesterol; FBG: fasting blood glucose; SUA: serum uric acid; eGFR: estimated glomerular filtration rate. 1mmHg=0.133kPa

表2 两组患者ACS分型及治疗方法比较

Table 2 Comparison of the ACS clinical type and treatment strategy between the two groups

Item	Male (n=476)	Female (n=188)	P value
ACS type[n(%)]			
STEMI	57(11.97)	16(8.51)	0.225
NSTEMI	30(6.30)	11(5.85)	0.833
UAP	389(81.72)	161(85.64)	0.618
Gensini score($\bar{x}\pm s$)	54.92±43.91	51.02±39.42	0.289
Treatment strategy			
PCI[n(%)]	299(62.82)	114(60.64)	0.749
Number of stents ($\bar{x}\pm s$)	1.23±0.97	1.24±0.77	0.921
CABG[n(%)]	21(4.41)	4(2.13)	0.172
Intensive medicine[n(%)]	156(32.77)	70(37.23)	0.375
Cardiovascular medication[n(%)]			
Aspirin	457(96.01)	187(99.47)	0.683
Clopidogrel	449(94.33)	185(98.40)	0.628
Beta-blocker	292(61.34)	125(66.49)	0.451
ACEI/ARB	255(53.57)	109(57.98)	0.490
Statin	439(92.23)	177(94.15)	0.817

ACS: acute coronary syndrome; STEMI: ST-segment elevation myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction; UAP: unstable angina pectoris; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker

表3 两组患者长期预后的比较

Table 3 Comparison of the long term outcomes between the two groups [n(%)]

Item	Male (n=476)	Female (n=188)	P value
Death	64(13.45)	22(11.70)	0.574
MACE	95(19.96)	31(16.49)	0.355
Cardiac death	62(13.03)	22(11.70)	0.666
MI	13(2.73)	1(0.53)	0.078
TVR	20(4.20)	8(4.26)	0.987

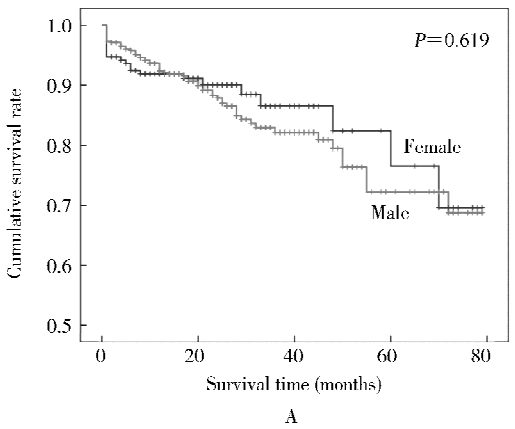
Follow-up period was 13-79 months. MACE: major adverse cardiac events; MI: myocardial infarction; TVR: target vessel revascularization

表4 长期预后的独立危险因素

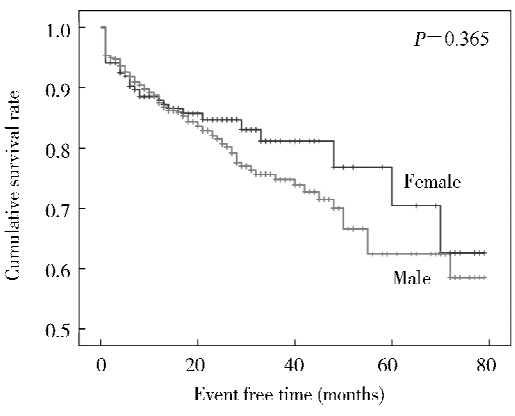
Table 4 Independent risk factors for long term outcomes

Risk factor	HR (95%CI)	P value
Death		
Non-HDL-C	1.73(1.09-2.75)	0.019
LVEF	0.97(0.95-0.99)	0.012
eGFR	0.98(0.96-0.99)	0.003
Heart rate	1.01(1.00-1.03)	0.046
SBP	0.98(0.97-1.00)	0.015
MACE		
Non-HDL-C	1.80(1.22-2.63)	0.003
SBP	0.98(0.97-0.99)	0.003
Gensini score	1.01(1.00-1.01)	0.009

HR: hazard ratio; CI: confidence interval; non-HDL-C: non high density lipoprotein cholesterol; LVEF: left ventricualr ejection fraction; eGFR: estimated glomerular filtration rate; SBP: systolic blood pressure; MACE: major adverse cardiac events



A



B

图1 Kaplan-Meier全因死亡及无事件生存曲线

Figure 1 Kaplan-Meier curves for all cause mortality and event free survival

There were no significant differences observed between male and female in survival rate curves for all cause mortality (A, P=0.619) and event-free survival (B, P=0.365)

3 讨 论

既往多数研究显示,冠心病的危险因素、临床表现、治疗方案及预后在男性和女性患者之间均有显著差异[4-6]。明确性别对冠心病的影响,有助于我们采取更好的预防和治疗措施,改善患者预后。对于冠心病整体人群,男性较女性冠心病发病早10~15年,在危险因素中,吸烟、高血压控制不佳、超重及肥胖对男性冠心病早发有更显著影响[7]。心肌梗死常是男性冠心病患者发病的首要表现,而且男性心肌梗死再发概率是女性的2倍[8]。而女性冠心病患者则合并症多、接受PCI治疗比例低、住院期间死亡率高[5,9,10]。近期也有研究提出尽管女性冠心病患者合并基础疾病较男性多,但两者长期预后并无差异[11,12]。然而,性别对≥80岁高龄ACS患者冠心病发病及长期预后的影响是否依然存在及其作用的强度尚不明确。

本研究首次入选较大规模的≥80岁行CAG证实的ACS人群,并进行了长期随访,结果显示对于≥80岁高龄ACS患者,高脂血症、体质量指数及空腹血糖升高成为女性患者冠心病的主要危险因素,而高血尿酸水平、吸烟史、慢性肾功能不全及陈旧性心肌梗死、脑卒中病史则是对男性冠心病患者影响更大的危险因素,女性左心收缩功能较男性好,本研究在中国高龄人群中得到与国外研究相似的结果[7,10,14],进而提示不同种族的高龄ACS患者的危险因素相似。1项纳入了8个欧洲国家共437例>80岁ACS患者的研究报道,该人群再血管化治疗比例<30%,但两性别间无显著差异(男性29.4%,女性21%)[14]。本研究显示我院≥80岁ACS患者的临床类型、冠状动脉病变狭窄程度及治疗策略选择,男、女性别间无明显差异,均有>60%的患者采取了PCI或CABG手术治疗,接受再血管化治疗比例明显高于上述欧洲研究。

Wenger[7]的研究显示性别对冠心病长期预后有影响,即便是在女性绝经后,与同龄女性相比,男性仍然是冠心病重要的危险因素,在全年龄段冠心病人群,男性冠心病死亡率较女性高,这种性别间的差异到两者>80岁才会逐渐消失[15]。Manfrini等[14]对欧洲437例(女性占50.1%)≥80岁高龄ACS患者的研究显示,住院期间死亡率两性间无显著差异(男性21%,女性21.1%)。本研究首次对600余例中国≥80岁ACS患者进行了长期随访,结果显示性别在长期死亡率及MACE发生率中均未见显著差异,对长期预后无影响。上述结果的产生,除了与随着年龄的增长不同性别间生理差异的减少有关,近年来女性接受药物、再血管化治疗比例较过去提高也是原因之一。

多项研究显示收缩压<100 mmHg(1 mmHg=0.133kPa)、Killip分级>2级、ST段抬高型心肌梗死、肾功能不全、糖尿病是冠心病患者死亡的独立危险因素[14,16,17]。本研究分析了影响高龄ACS长期预后的危险因素,结果显示,non-HDL-C、左室射血分数、eGFR、心率及收缩压是全因死亡的独立危险因素;评价血脂水平的non-HDL-C是高龄ACS患者全因死亡(HR=1.73,95% CI:1.09~2.75,P=0.019)及MACE发生(HR=1.80,95% CI:1.22~2.63,P=0.003)的独立危险因素。

non-HDL-C是指总胆固醇减去高密度脂蛋白胆固醇剩余部分,主要包括低密度脂蛋白胆固醇(low density lipoprotein cholesterol,LDL-C)、极低密度脂蛋白胆固醇、中密度脂蛋白胆固醇和脂蛋白a所含胆固醇。尽管LDL-C是公认的动脉粥样硬化发生、发展的关键因素,事实上富含脂质的极低密度脂蛋白胆固醇残粒、中密度脂蛋白胆固醇也均可以进入血管壁被巨噬细胞所吞噬,进而导致动脉粥样硬化。1项针对平均年龄61岁,CABG术后患者的研究显示,non-HDL-C每增加0.26 mmol/L,心脏事件发生危险增加4.9%,而LDL-C的增加与心脏事件的发生无明显相关性[18]。同样,另一项对年龄在40~64岁的4462例患者平均随访长达19年的研究也显示,无论男性还是女性,non-HDL-C的基线水平是对心血管疾病死亡的强预测因子,明显优于LDL-C[19]。Sinderman等[20]的一项荟萃分析显示non-HDL-C是比LDL-C更强的影响心血管疾病长期预后的危险因素。本研究首次提出non-HDL-C是高龄ACS患者全因死亡及MACE发生的独立危险因素,提示non-HDL-C可能是高龄ACS患者强化治疗的新靶点,特别是对于血脂水平控制不佳的高龄老年女性,会有更多获益。

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