

亚太结直肠癌风险评分系统在我国北方无症状人群筛查中的应用

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摘要: [目的] 评价亚太结直肠癌筛查评分系统(APCS)在我国北方无症状人群筛查中的应用价值。[方法] 采取整群抽样的方法,选取河南省 40~74 岁城市户籍无症状人群进行癌症危险因素调查和结肠镜检查,应用 APCS 计算每位研究对象患进展期肿瘤的危险分值,绘制受试者工作特征(ROC)曲线,并计算曲线下面积(AUC)和 95%可信区间(95%CI),并采用 Logistic 回归分析计算不同危险分层中患结直肠癌进展期肿瘤的 OR 值及 95%CI。[结果] 共纳入无症状人群 7 454 例,接受结肠镜检查前评分,平均年龄(55.01±7.91)岁,进展期肿瘤检出率为 1.50%。APCS 分值范围为 0~7 分,预测的一致性较好($P=0.886$),区分能力一般(AUC 为 0.628,95%CI: 0.579~0.678),但优于仅基于年龄变量的预测模型。以低风险组(0~1 分)为对照组,中风险组(2~3 分)和高风险组(4~7 分)发生进展期肿瘤的风险分别为低风险组的 1.97 倍(95%CI: 0.83~4.65)和 4.07 倍(95%CI: 1.76~9.42)。[结论] 基于年龄、性别、一级亲属结直肠癌家族史和吸烟构建的 APCS 是确定中国北方无症状人群进展期肿瘤风险的有用工具。

关键词: 亚太结直肠癌筛查评分系统;高危人群;筛查

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Application of Asia-Pacific Colorectal Screening Score in Screening Asymptomatic Population in Northern China

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Abstract: [Purpose] To evaluate the application value of Asia-Pacific Colorectal Screening Score (APCS) in asymptomatic population screening in northern China. [Methods] A cluster sampling method was used to select the asymptomatic residents of 40~74 years old in Henan Province to investigate the risk factors and colonoscopy. A receiver operating characteristic(ROC) analysis was performed to calculate the area under the curve(AUC) and 95% confidence interval(95%CI) according to the APCS scoring system for each subject. Logistic regression analysis was used to calculate the odds ratio(OR) and 95% CI of advanced neoplasm in groups of different risks collected. [Results] Totally, there were 7 454 subjects with mean age of (55.01±7.91) years old, and the detection rate of advanced neoplasm was 1.50%. The APCS scores ranged from 0 to 7 and the predictions were consistent($P=0.886$). The distinguishing ability was moderate(AUC=0.628, 95%CI: 0.579~0.678), but better than the prediction model based on age only. Taking the average risk group(0~1 points) as control, the risk of developing advanced neoplasm in the moderate risk group(2~3 points) and the high risk group(4~7 points) were 1.97-fold(95%CI: 0.83~4.65) and 4.07-fold(95%CI: 1.76~9.42) respectively. [Conclusion] The APCS scoring system based on age, sex, family history of colorectal cancer in a first-degree relatives and smoking is a useful tool to determine the risk of advanced neoplasm in asymptomatic people in northern China.

Key words: Asia-Pacific Colorectal Screening Score; high risk population; screening

我国结直肠癌发病率逐年升高。肿瘤登记数据

显示,2016 年结直肠癌发病率和死亡率分别位列恶性肿瘤发病和死亡的第 3 位和第 4 位^[1]。开展人群结肠镜筛查,实现结直肠癌及其癌前病变的早期发现、早期诊断和早期干预是减轻结直肠癌疾病负担的

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有效方法^[2]。但是由于结肠镜检查费用高,对医师技术水平要求高,依从性低等特点,降低了结肠镜的筛查效果,因此利用结直肠癌的危险因素设计预测结直肠癌风险的评估模型,实现对人群进行结直肠癌危险分层,对于结直肠癌的预防与控制,降低结直肠癌带来的疾病负担意义重大^[2]。

2011年,Yeoh等^[3]在亚洲11个城市的2752例结肠镜筛查人群中建立了亚太结直肠癌筛查评分系统(Asia-Pacific Colorectal Screening Score,APCS)模型,该模型共纳入了4个变量(年龄、性别、一级亲属结直肠癌家族史和吸烟),模型对结直肠癌和高级别腺瘤预测效果c-统计值为0.66(内部验证后为0.64)。2014年新的亚太结直肠癌筛查共识意见中指出,APCS能够预测无症状的亚洲人群患结直肠肿瘤的风险^[4]。目前APCS在我国内地结直肠癌筛查中的应用研究很少,适用价值仍有待进一步验证。本研究通过对河南省多个城市地区结肠镜筛查人群数据进行分析,来探讨APCS在我国北方结直肠癌人群筛查中的应用价值。

1 资料与方法

1.1 研究对象

研究对象来源于河南省城市癌症早诊早治项目^[5],2013年10月至2019年10月以郑州市、驻马店市、安阳市、洛阳市、南阳市、焦作市、濮阳市和新乡市为研究地区,以区为单位选取社区,在选择的社区招募年龄为40~74岁、在本地居住3年及以上的居民为调查对象。共招募7454名参与结肠镜筛查的无症状人群为研究对象。排除标准:无法配合完成问卷填写;已确诊为恶性肿瘤或其他严重疾病的患者。本研究通过中国医学科学院肿瘤医院伦理委员会的批准(批号:CH-PRE-004),所有研究对象均签署了知情同意书。

1.2 方法

1.2.1 问卷调查

所有研究对象均被告知调查目的,在签署知情同意后参与调查,由经过培训的调查员统一发放危险因素调查问卷并进行调查,填写后的调查问卷经审核后录入到项目组开发的项目平台。问卷调查在结肠镜检查前实施,危险因素调查问卷调查内容包

括个人基本信息、饮食习惯、生活环境和习惯、心理和情绪、疾病既往史和癌症家族史以及女性的生理和生育史信息。

1.2.2 筛查方法及结果判定

检查前1~2d,筛查对象开始进无渣半流质饮食。检查当日,上午进行检查的筛查对象禁早餐,下午进行检查者禁午餐,所有筛查对象于检查前4~5h口服硫酸镁离子泻剂或复方聚乙二醇电解质散,以及2L温开水进行肠道准备。结肠镜操作者均为具有多年操作经验的主治医师或副主任医师。一旦在结肠镜下发现息肉,应取组织活检,并送病理检查。由高年资(3年及以上)医师出具检查报告。

采用项目组开发的结直肠癌筛查结果记录表和病理诊断表对结肠镜检查情况和病理结果进行记录。结直肠癌筛查结果记录表主要记录息肉数量、部位、大小、形状和颜色等情况;结直肠癌病理诊断表主要记录活检部位和病理诊断等。其中,本研究中的进展期肿瘤定义为进展期腺瘤(绒毛状腺瘤或管状绒毛状腺瘤或直径 ≥ 10 mm的其他腺瘤或腺上皮高级别上皮内瘤变)或者结直肠癌。

1.2.3 质量控制

调查人员接受统一的专业培训。负责结肠镜检查 and 病理诊断的医师由中国医学科学院肿瘤医院和河南省肿瘤医院联合组织,进行统一的技术培训,统一标准和治疗规范,并建立现场数据质量控制和集中多轮验证。问卷填写完成后,必须经质控员确认完整无误后方可录入数据库。项目平台本身建立了质量控制程序,以避免错误填写、遗漏填写和逻辑错误。

1.3 统计学处理

采用城市癌症早诊早治项目组研发的在线数据库进行数据收集和汇总,应用SAS 9.4软件对数据进行统计分析。计数资料采用频数和百分位数(%)表示,不同组间的差异性比较采用 χ^2 检验。根据APCS为每位筛查对象评分,绘制ROC曲线,并计算AUC和95%可信区间(confidence interval,CI)。模型拟合优度采用Hosmer-Lemeshow方法检验,并采用K折交叉验证和非参数Bootstrap方法进行验证。根据APCS评分共划分为3个危险分层:低风险组(0~1分)、中风险组(2~3分)、高风险组(4~7分)^[3],并采用Logistic回归分析计算OR值及95%CI。双侧检验,检验水准 $\alpha=0.05$ 。

2 结果

2.1 基本情况

接受结肠镜筛查的 7 454 名调查对象年龄为(55.01±7.91)岁,男性占 46.35%(3 455/7 454),具有结直肠癌一级亲属家族史占 21.33%(1 590/7 454),吸烟者占 39.91%(2 975/7 454)。共检出进展期肿瘤 112 例(包括进展期腺瘤 95 例和结直肠癌 17 例),检出率为 1.50%(Table 1)。

2.2 APCS 模型效能评价

根据 APCS 为每位筛查对象评分,0~7 分所占比例分别为 10.22%、3.66%、38.53%、9.97%、28.63%、3.15%、5.73%和 0.11%,0~7 分组进展期肿瘤累积检出率分别为 0.66%、0.37%、1.08%、1.35%、2.11%、1.70%、3.75%和 0.00%(Table 2)。根据每个研究对象患进展期肿瘤的危险分值,绘制进展期肿瘤 APCS 的 ROC 曲线,相应的 AUC 为 0.628(95%CI: 0.579~0.678),高于仅基于年龄变量(AUC=0.592, 95%CI:0.539~0.644),说明此预测模型区分度良好(Figure 1)。模型拟合优度 Hosmer-Lemeshow 检验结果和校准曲线显示, $\chi^2=1.15$, $P=0.886$,说明预测值与观察值无显著差别,模型拟合优度良好(Figure 2)。

Table 1 Basic information of colorectal cancer screening population

Factor	No. of subjects	Advanced neoplasm		χ^2	P	APCS score
		No	Yes			
Total	7454	7342(98.50%)	112(1.50%)			
Age(years old)						
40~49	2077(27.86%)	2054(98.89%)	23(1.11%)			0
50~69	5166(69.31%)	5079(98.32%)	87(1.68%)	3.78	0.151	2
≥70	211(2.83%)	209(99.05%)	2(0.95%)			3
Gender						
Female	3999(53.65%)	3959(99.00%)	40(1.00%)	14.71	<0.001	0
Male	3455(46.35%)	3383(97.92%)	72(2.08%)			1
Family history of colorectal cancer in a first-degree relative						
Absent	5864(78.67%)	5787(98.69%)	77(1.31%)	6.67	0.010	0
Present	1590(21.33%)	1555(97.80%)	35(2.20%)			2
Smoking						
Never	4479(60.09%)	4434(99.00%)	45(1.00%)	18.80	<0.001	0
Current or ex	2975(39.91%)	2908(97.75%)	67(2.25%)			1

Note: APCS: Asia-Pacific Colorectal Screening Score

Table 2 Distribution of number of subjects for each score category in the screening population

Score	No. of subjects	No. of subjects with advanced neoplasia
0	762(10.22%)	5(0.66%)
1	273(3.66%)	1(0.37%)
2	2872(38.53%)	31(1.08%)
3	743(9.97%)	10(1.35%)
4	2134(28.63%)	45(2.11%)
5	235(3.15%)	4(1.70%)
6	427(5.73%)	16(3.75%)
7	8(0.11%)	0
Total	7454(100.00%)	112(1.50%)

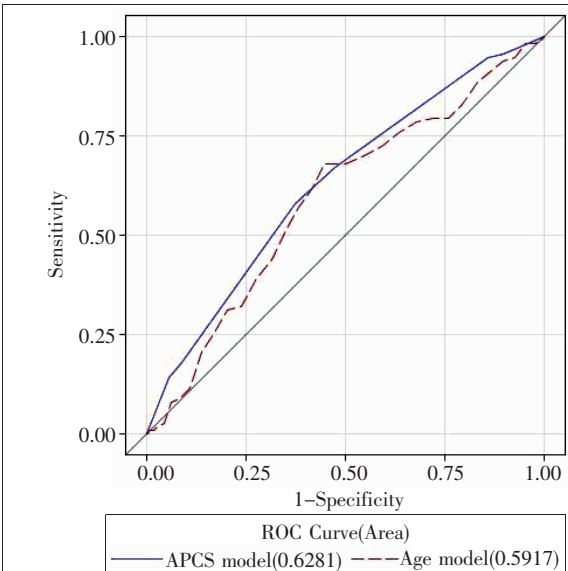


Figure 1 ROC curve of APCS model and age model in predicting colorectal advanced neoplasia

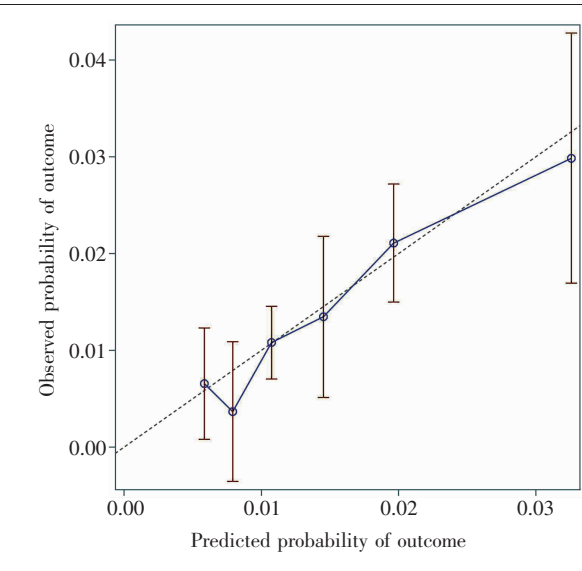


Figure 2 Calibration curve of APCS model

采用 K 折交叉验证和非参数 Bootstrap 方法进行验证,校正后的 AUC 分别为 0.603 和 0.620,说明预测模型比较稳定。

根据 APCS 将研究对象分为低风险组 (0~1 分)、中风险组 (2~3 分) 和高风险组 (4~7 分),三组分别占总人群的 13.89%、48.50% 和 37.62%,进展期肿瘤累积检出率分别为 0.58% (0.21%~1.26%)、1.13% (0.82%~1.54%) 和 2.32% (1.79%~2.95%)。以低风险组为对照组,中风险组和高风险组发生进展期肿瘤的风险分别为低风险组的 1.97 倍 (95%CI: 0.83~4.65) 和 4.07 倍 (95%CI: 1.76~9.42) (Table 3)。

3 讨论

多项研究已证实,对高危人群进行结直肠癌筛查可以提高生存率^[6-8],并且是符合成本效果的^[9-10]。结肠镜检查^[11]通过早期发现结直肠癌或通过切除腺瘤性息肉已被证明可显著减少结直肠癌死亡率^[12]。来自美国^[13]、英国^[14]和欧洲^[15-16]的国际指南,以及亚太地区共识均建议对一般风险人群进行结直肠癌筛查的年龄为 50 岁及以上^[17]。

众所周知,结肠镜筛查需要占用大量医疗资源,除了需要相关设备和必要的基础设施外,受过训练的医务人员操作水平对筛查效果的提升尤为重要^[18]。因此由于资源有限,结肠镜筛查限制了其在非发达地区的广泛开展^[19-20]。其次,结肠镜检查有发生穿孔、出血或与麻醉有关的并发症的风险^[21-22]。虽然中国结直肠癌发病率逐年增加,但是对于个人来说终生发病风险仅 5%^[23]。这意味着大多数接受结肠镜筛查的研究对象将面临此类侵入性手术并发症的潜在风险,但不会从中受益^[24]。使用结直肠癌风险预测模型对人群风险分层可以平衡收益和风险,最大程度地减少潜在的事故。此外,相关宣传不足、人群缺乏防癌意识以及筛查依从性差^[25-30]等其他一些因素也成为了实施结直肠癌筛查的障碍。与西方发达国家不同的是,中国人口基数大、结直肠癌筛查资源分

配不足等,因此我国不能照搬西方国家的筛查指南。

以往研究显示,亚洲人群中进展期肿瘤的检出率在 3%~12% 之间^[31-33],美国人群中进展期肿瘤的检出率为 9.4%^[34]。而本研究中进展期肿瘤检出率仅为 1.50%,检出率偏低。根据国际癌症研究署 (IARC) 发布的研究数据显示,我国 2020 年结直肠癌发病率为 23.9/10 万,远低于美国的 25.6/10 万以及日本的 38.5/10 万^[35]。以上结果提示,进展期肿瘤检出情况与结直肠癌流行情况是一致的,这意味着我们国家进展期肿瘤流行情况有自己的特点,并且与发达国家不同。

Yeoh 等^[3]于 2011 年在亚洲 11 所城市建立了 APCS 模型,该模型随后于 2016 年在结肠镜筛查人群中进行了外部验证^[23,36]。Wong 等^[37]于 2014 年对 APCS 模型进行了改良,增加了体质指数和糖尿病两个变量,并在 5 220 名中国香港人群中进行了构建和验证,模型构建和内部验证对进展期肿瘤的 c-统计值均为 0.62,随后又于 2016 年在中国香港地区结肠镜筛查人群中进行了外部验证^[38]。APCS 模型在我们的结直肠癌筛查人群中的预测效果 AUC 为 0.628,介于 APCS 模型和改良后的 APCS 模型之间,且预测例数与实际进展期肿瘤例数没有统计学差异 ($P>0.05$),说明该模型具有一定的预测效果且比较稳定。

研究内容显示,APCS 模型应用到城市社区筛查人群时,预测效果有所下降。一般来说,所建立的预测模型经内部或外部验证后,预测效果会下降^[2]。Peng 等^[39]两个德国队列中比较了 17 种结直肠癌风险预测模型的预测效果,结果发现大部分预测模型对结直肠癌的预测准确性低于原始研究,表明结直肠癌风险预测模型应根据目标人群进行优化。另外,用于构建 APCS 模型的研究人群中男女性别比较高 (1.22),而本研究中用于外部验证的筛查人群中男女性别比较低 (0.85),而我国男性结直肠癌发病率高于女性^[1],男女性结直肠癌发病危险因素存在差异^[40],这可能是导致预测效果降低的原因之一。

本研究发现,相对于低风险 (0~1 分) 人群,中风险 (2~3 分) 和高风险 (4~7 分) 人群发展为进展期肿瘤的 OR 值分别为 1.97 (95%CI: 0.83~4.65) 和 4.07 (95%CI: 1.76~9.42)。Chiu

Table 3 Detection rate and evaluation of colorectal advanced neoplasia by risk tier

Risk tier	No. of subjects	Advanced neoplasm			OR(95%CI)
		Predicted	Cases	Detection rate (95%CI)	
Low risk(0~1)	1035(13.89%)	6	6	0.58(0.21~1.26)	1
Moderate risk(2~3)	3615(48.50%)	41	41	1.13(0.82~1.54)	1.97(0.83~4.65)
High risk(4~7)	2804(37.62%)	65	65	2.32(1.79~2.95)	4.07(1.76~9.42)

等^[23]将 APCS 模型应用到亚太地区一项结直肠癌筛查研究中,发现相对于低风险(0~1 分)人群,中风险(2~3 分)和高风险(4~7 分)人群发展为进展期肿瘤的 OR 值分别为 4.5(95%CI:2.1~9.6)和 9.6(95% CI:4.5~20.5)。Li 等^[36]将 APCS 模型应用到北京地区开展的一项 1 010 人参与的结直肠癌筛查研究中,结果显示相对于低风险人群,中风险和高风险人群发展为进展期腺瘤的 OR 值分别为 1.85 (95% CI:0.53~6.42)和 6.14(95%CI:1.81~20.84)。与我们的研究结果基本一致。

本研究验证了 APCS 对于中国本土人群结直肠癌风险预测能力,证实了其在我国结直肠癌人群筛查中的应用科学性价值。因其简单易行,极具人群中应用推广的实践应用价值。

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