

doi: 10.3978/j.issn.2095-6959.2018.08.019

View this article at: <http://dx.doi.org/10.3978/j.issn.2095-6959.2018.08.019>

增殖性糖尿病视网膜病变对 2 型糖尿病患者无症状 冠状动脉粥样硬化性心脏病的识别

陆长峰¹, 周建博²

(首都医科大学附属北京同仁医院 1. 神经内科; 2. 内分泌科, 北京 100730)

[摘要] 目的: 探讨增殖性糖尿病视网膜病变(proliferative diabetic retinopathy, PDR)对于无症状冠状动脉粥样硬化性心脏病(coronary atherosclerotic heart disease, CHD)的早期识别作用。方法: 从北京同仁医院内分泌科选取351例2型糖尿病(T2 diabetes mellitus, T2DM)患者, 其中211例非糖尿病视网膜病变(non-diabetic retinopathy, NDR)和140例PDR。受试者均无已知CHD, 通过冠状动脉造影或冠状动脉CT诊断无症状性CHD。应用受试者工作特征曲线(receiver operating characteristic curve, ROC)和再分类指数评估PDR对无症状CHD的识别价值。结果: 基于英国糖尿病前瞻性研究(United Kingdom Prospective Diabetes Study, UKPDS)模型, 不合并PDR与合并PDR对无症状CHD的风险识别的曲线下面积(area under curve, AUC), 从0.583 (95% CI: 0.51~0.66)提高到0.697 (95% CI: 0.641~0.752)。加入PDR后, 对无症状CHD基本模型(8个传统的危险因素)识别的C统计值从0.746 (95% CI: 0.681~0.811)增加到0.762 (95% CI: 0.699~0.825, $P=0.73$), 净重新分类指数(net reclassification indexes, NRI)为5.9% (95% CI: 1.4%~10.2%, $P=0.017$), 绝对综合判别指数(integrated discrimination index, IDI)为0.004 ($P=0.02$)。结论: 与传统危险因素相比, PDR有助于识别T2DM患者的无症状CHD。

[关键词] 增殖型糖尿病视网膜病变; 无症状冠状动脉粥样硬化性心脏病; 2型糖尿病

Identification of proliferative diabetic retinopathy to asymptomatic coronary heart disease in type 2 diabetes mellitus individuals

LU Changfeng¹, ZHOU Jianbo²

(1. Department of Neurology; 2. Department of Endocrinology, Beijing Tongren Hospital, Capital Medical University, Beijing 100730, China)

Abstract **Objective:** To investigate the early identification of proliferative diabetic retinopathy (PDR) to coronary atherosclerotic heart disease (CHD). **Methods:** A total of 351 patients with type 2 diabetes mellitus (T2DM) individuals [211 non-diabetic retinopathy (NDR) and 140 proliferative diabetes mellitus (PDR)] were recruited

收稿日期 (Date of reception): 2018-05-07

通信作者 (Corresponding author): 周建博, Email: jianbo.zhou@foxmail.com

基金项目 (Foundation item): 北京市医院管理局青苗人才项目 (QML20170204)。This work was supported by the Beijing Municipal Administration of Hospital's Youth Project, China (QML20170204).

from one of the national diabetes mellitus center from China. CHD was newly diagnosed and defined by the evidences of coronary angiography or computed tomography coronary angiography. The area under curve (AUC) was performed. Discrimination and reclassification were also used to evaluate the value of addition of PDR to the base model. **Results:** In our present study, with the model estimating risk of asymptomatic CHD based on the United Kingdom Prospective Diabetes Study (UKPDS) engine, we found that the level of AUC was greatly improved from 0.583 (95% CI: 0.51–0.66) to 0.697 (95% CI: 0.641–0.752) between the models with PDR and without PDR. Besides, the C statistic was increased from 0.746 (95% CI: 0.681–0.811) to 0.762 (95% CI: 0.699–0.825; $P=0.73$) by the addition of PDR to a base model to identify asymptomatic CHD. There was a continuous net reclassification indexes (NRI) of 5.9% (95% CI: 1.4%–10.2%, $P=0.017$) for the asymptomatic CHD. The absolute integrated discrimination index (IDI) was 0.004 ($P=0.02$). **Conclusion:** Compared with the traditional risk factors, our results improved the identification of asymptomatic CHD, which further confirmed that PDR could identify cardiovascular risk stratification in Chinese diabetic individuals.

Keywords proliferative diabetic retinopathy; asymptomatic coronary heart disease; type 2 diabetes mellitus

冠状动脉粥样硬化性心脏病 (coronary heart disease, CHD) 是 2 型糖尿病 (T2 diabetes mellitus, T2DM) 患者的主要死亡原因^[1]。糖尿病患者 CHD 无症状这一事实使 CHD 早期识别成为一个挑战。传统 CHD 危险因素, 如血脂异常、高血压与无症状 CHD 无明显相关^[2-3]。目前不推荐对糖尿病患者进行无症状 CHD 的常规侵入性筛查。糖尿病视网膜病变 (diabetic retinopathy, DR) 是一种常见的慢性微血管并发症之一, 会促进 T2DM 的心血管事件发生和增加全因病死亡率^[4]。研究^[1]发现: 糖尿病病程和血糖控制的时间与 DR 的严重程度有关, 因此有理由推测, 糖尿病晚期表现, 如增殖性糖尿病视网膜病变 (proliferative diabetic retinopathy, PDR), 会增加 CHD 患病风险。既往研究^[5]表明: 不同阶段 DR 增加 T2DM 患者全因死亡风险, 这表明 PDR 患者有预测全因病死亡率风险效果, 包括心血管性死亡。然而, PDR 是否能识别无症状 CHD 尚不清楚。此外, 由于抗血管内皮生长因子 (vascular endothelial growth factor, VEGF) 抗体在 PDR 中广泛应用, 有证据表明抗 VEGF 药物可能增加 CHD 发生率^[6-7]。这种相关性是否在亚洲人中存在, 目前只有零星研究^[8]。人们仍然不太清楚患有 PDR 与亚洲人群无症状 CHD 的风险增加是否有关。本研究拟探讨 PDR 是否作为一个独立危险因素与无症状 CHD 发生相关, 并进一步与传统危险因素关联强度进行比较, 以明确 PDR 与 T2DM 患者无症状 CHD 有无关联。

1 对象与方法

1.1 对象

选取 2011 年 1 月至 2012 年 12 月期间糖化血红蛋白 (HbA1c) $\geq 7\%$ (53 mmol/mol) 的北京同仁医院住院患者。由于大多数糖尿病患者诊断后 10 年内发展为 DR, 纳入标准: 完成冠状动脉造影或冠状动脉 CT 扫描且符合糖尿病视网膜病变诊断标准的被纳入研究 (图 1); 病例组为糖尿病病程 ≥ 10 年增殖性糖尿病视网膜病变 (proliferative diabetic retinopathy, PDR) 患者, PDR 的诊断标准采用我国糖尿病视网膜病变临床诊疗指南 (2014 年)^[9]。对照组为糖尿病病程 ≥ 10 年但无糖尿病视网膜病变 (non-diabetic retinopathy, NDR) 患者。排除标准: 1) 糖尿病急性严重并发症患者如酮症酸中毒、糖尿病非酮症高渗性昏迷等; 2) 特殊类型的糖尿病、1 型糖尿病、妊娠糖尿病或糖尿病合并妊娠的患者; 3) 恶性肿瘤、胰腺疾病、严重心、脑血管疾病及其他合并慢性严重并发症的患者; 4) 慢性严重肾脏疾病, 血肌酐 (serum creatinine, SCr) $>132.6 \mu\text{mol/L}$ (1.5 mg/dL) 的患者; 5) 需要长期应用糖皮质激素、抗精神病药物或者类似药物治疗的患者; 6) 患有自身免疫性疾病、全身性疾病或其他各种原因引起的眼病患者。无症状 CHD 定义为冠脉造影或冠状动脉 CT 扫描检测显示冠脉 $\geq 75\%$ 狭窄, 同时无已知 CHD 史。PDR 经眼底照片分级确诊。本研究经首都医科大学附属北京同仁医院医学伦理委员会审核批准, 患者均签署知情同意书。

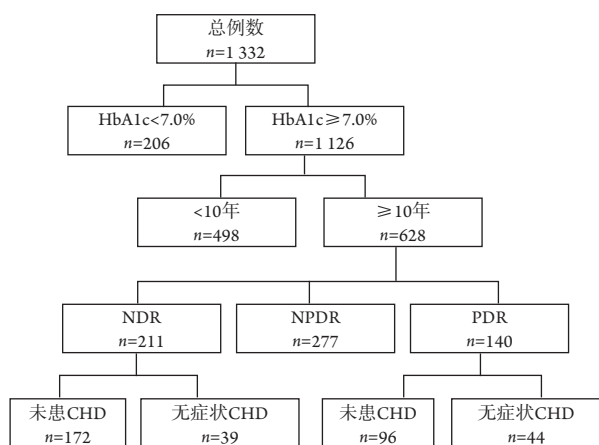


图1 病例对照组的纳入与排除流程图

Figure 1 Inclusion and exclusion flow chart of the case-control study

1.2 方法

对DR进行回顾性交叉横断面研究。无症状CHD和非CHD组间的差异基线特征被作为协变量, 包括年龄、性别、腰臀比(waist-to-hip

ratio, WHR)、收缩压(systolic blood pressure, SBP), SCr、空腹C肽(表1)。

1.3 统计学处理

HbA1c与糖尿病病程也作为构建基础模型的协变量。连续和分类变量分别采用t检验和卡方检验。校正后 $P < 0.05$ 为差异有统计学意义。Logistic回归确定基本模型纳入PDR前后与无症状CHD关系: 首先通过英国前瞻性糖尿病研究(United Kingdom Prospective Diabetes Study, UKPDS)采用的传统心血管危险因素构建的基本模型, 观察研究受者操作特征曲线下面积(area under curve, AUC)的变化^[10], 然后评估基本模型的识别效能, 将PDR纳入基本模型并计算模型识别效能变化。模型识别效能通过计算Harrell C评估^[11]、连续净重新分类指数(net reclassification indexes, NRI)和综合判别的改进(integrated discrimination index, IDI)进行评估^[12-13], 计算各参数的95% CI。分析采用Stata 11完成。

表1 病例对照组的基线特征

Table 1 Baseline characteristics of the case-control group

检查项目	PDR (n=140)	NDR (n=211)	P
性别(男/女)	66/73	111/100	NS
年龄/岁	61.1 ± 5.8	61.3 ± 4.6	NS
患病时间/年	14.8 ± 10.3	14.1 ± 10.3	NS
BMI/(kg·m ⁻²)	25.4 ± 3.80	26.3 ± 3.91	NS
WHR	0.93 ± 0.09	0.92 ± 0.07	NS
SCr	87.07 ± 43.70	84.87 ± 27.56	NS
UA	325.41 ± 75.64	322.53 ± 78.42	NS
FBG/(mmol·L ⁻¹)	7.55 ± 2.78	7.45 ± 2.60	NS
TG/(mmol·L ⁻¹)	2.31 ± 2.12	1.84 ± 1.06	0.007
TC/(mmol·L ⁻¹)	5.01 ± 1.31	4.65 ± 0.95	0.003
HDL (mmol·L ⁻¹)	1.14 ± 0.38	1.13 ± 0.33	NS
LDL-C (mmol·L ⁻¹)	3.12 ± 0.99	3.06 ± 0.83	NS
SBP/mmHg	143 ± 18.2	132 ± 16.6	<0.001
DBP/mmHg	84.35 ± 10.95	79.20 ± 8.92	<0.001
HbA1c/%	8.36 ± 2.02	8.33 ± 1.73	NS
UAER/(mg·24 h ⁻¹)	495.63 ± 1078.24	39.58 ± 166.37	<0.001
Fasting C-peptide	0.87 ± 0.61	1.05 ± 0.64	0.01

NS为差异无统计学意义。

NS is the difference without statistical significance.

1 mmHg=0.133 kPa.

2 结果

2.1 纳入研究特点

对1 332例糖尿病患者进行筛选, 其中1 126例HbA1c \geq 7%。根据本研究筛选标准, 211例NDR和140例PDR符合标准纳入本研究。NDR和PDR无症状CHD病例数和比例分别为39(18.5%)和44(31.5%)。NDR与PDR组间, 除血压、空腹C肽、尿蛋白、总胆固醇和三酰甘油外, 年龄、糖尿病病程、BMI、低密度脂蛋白胆固醇差异无统计学意义(表1)。经过对年龄, 性别, HbA1c, 糖尿病病程, WHR, SBP, SCr, 空腹C肽校正后, PDR组无症状CHD风险较对照组高1.16倍($P<0.01$)。

2.2 PDR对无症状CHD风险的识别

通过基于UKPDS建议的传统心血管危险因素建立的预估无症状CHD风险模型, 与不合并PDR组相比, PDR组AUC从0.583(95% CI: 0.51~0.66; 显示淡蓝色)增至0.697(95% CI: 0.641~0.752; 显示黑暗蓝色; 图2)。无症状CHD增量预测值表明, 在该样本中将PDR作为协变量纳入基本模型, 使C统计量从0.746(95% CI: 0.681~0.811)提高到0.762(95% CI: 0.699~0.825; $P=0.73$, 图3)。

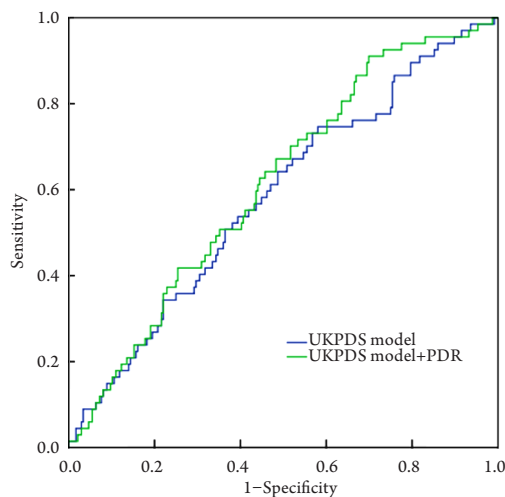


图2 基于两种危险因素建立的预估无症状CHD风险模型的AUC值

Figure 2 Demonstration of AUC values for two risk identification models

不合并PDR组的UKPDS模型AUC=0.583; 合并PDR组的UKPDS模型AUC=0.697。

UKPDS model AUC = 0.583; UKPDS model + PDR AUC = 0.697.

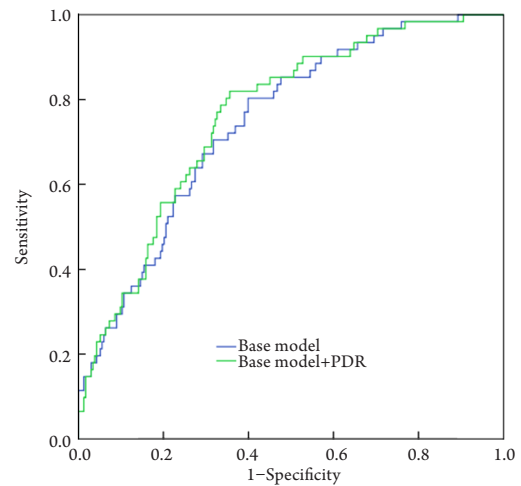


图3 基于两种危险因素建立的预估无症状CHD风险模型的AUC值(基础模型AUC =0.746, 合并PDR的基础模型AUC =0.762)

Figure 3 Demonstration of AUC values for two risk identification models (base model AUC=0.746, base model + PDR AUC =0.762)

纳入PDR使基础模型出现显著再分类, 识别无症状CHD的NRI值为5.9%(95% CI:1.4%~10.2%, $P=0.017$), IDI为0.004 ($P=0.02$)。

3 讨论

校正多个协变量影响后, 本研究结果表明: 与无糖尿病视网膜病变患者相比, 合并PDR的T2DM患者易患无症状CHD。

与不合并糖尿病的CHD患者相比, 既往无CHD史的T2DM患者发生心脏事件风险更高^[14]。一旦糖尿病并发症进展, 患者可能患有严重的自主神经失神经支配, 出现无症状CHD^[15]。因此, 有相当比例T2DM患者存在无症状CHD, 发生心血管事件^[16]风险增加。DR和CHD都是糖尿病患者重要临床并发症, 提示微血管病理改变在大血管病变中起重要作用^[17]。本研究结果表明: PDR可以识别糖尿病患者无症状CHD。一项组织病理学研究^[18-19]显示: 糖尿病患者心脏和脑组织与视网膜一样, 也存在明显小血管病变, 与本研究结果一致。

既往研究^[5]显示: DR病变的严重程度与T2DM全因病死率风险呈递进性相关。但Um等^[20]的最新研究表明: PDR在预测T2DM患者CHD方面较传统危险因素无额外影响。DR与CHD的关系仍有争

议, 这可能因为暴露程度的不同(如非增殖性DR与PDR)及结果定义(如无症状CHD与CHD)的差异, 这是本研究的新颖之处。

然而, 基于对亚洲人口认识有限^[8], 白种人与亚洲人群CHD风险关联性存在差异^[21]。因为这些CHD风险关联的差异, 有必要建立一个种族特异性的隐匿性CHD风险识别模型。根据本研究(UKPDS: AUC=0.583, 95% CI: 0.51~0.66。UKPDS + PDR: AUC=0.697, 95% CI: 0.641~0.752), 总人口的心血管风险评分显示低估糖尿病人群未来患CHD风险^[22]。在传统危险因素基础上加入PDR显著改善对T2DM患者无症状CHD识别。这也表明经眼科医生确诊的PDR具有改善CHD危险分层的潜力。

本研究仍存在几个局限性: 第一, 本研究仅为横断面研究; 第二, 在目前的分析中没有具体评估可能与PDR和CHD相关的遗传变异性; 第三, 本研究缺乏心脏自主神经病变(cardiac autonomic neuropathy, CAN)评估, 无症状CHD也可能与心脏自主神经病变有关, 心脏自主神经病变与血糖控制和糖尿病病程密切相关^[23]。尽管没有对CAN的描述, 但本研究分析发现血糖控制和糖尿病病程与CAN无相关性。

综上所述, PDR可以识别T2DM患者的无症状CHD风险, 并改进患者危险分层, 该结果需要在IPAD后续研究中得到证实, 这将为T2DM患者无症状CHD风险预测提供可靠信息。

参考文献

1. Yau JW, Rogers SL, Kawasaki R, et al. Global prevalence and major risk factors of diabetic retinopathy[J]. *Diabetes Care*, 2012, 35(3): 556-564.
2. Wackers FJ, Young LH, Inzucchi SE, et al. Detection of silent myocardial ischemia in asymptomatic diabetic subjects: the DIAD study[J]. *Diabetes Care*, 2004, 27(8): 1954-1961.
3. Scognamiglio R, Negut C, Ramondo A, et al. Detection of coronary artery disease in asymptomatic patients with type 2 diabetes mellitus[J]. *J Am Coll Cardiol*, 2006, 47(1): 65-71.
4. Kramer CK, Rodrigues TC, Canani LH, et al. Diabetic retinopathy predicts all-cause mortality and cardiovascular events in both type 1 and 2 diabetes: meta-analysis of observational studies[J]. *Diabetes Care*, 2011, 34(5): 1238-1244.
5. Zhu XR, Zhang YP, Bai L, et al. Prediction of risk of diabetic retinopathy for all-cause mortality, stroke and heart failure: evidence from epidemiological observational studies[J]. *Medicine*, 2017, 96(3): e5894.
6. Liew G, Mitchell P. Ranibizumab for neovascular age-related macular degeneration[J]. *N Engl J Med*, 2007, 356(7): 747-748.
7. Ciulla TA, Rosenfeld PJ. Antivascular endothelial growth factor therapy for neovascular age-related macular degeneration[J]. *Curr Opin Ophthalmol*, 2009, 20(3): 158-165.
8. Tong PC, Kong AP, So WY, et al. Interactive effect of retinopathy and macroalbuminuria on all-cause mortality, cardiovascular and renal end points in Chinese patients with type 2 diabetes mellitus[J]. *Diabet Med*, 2007, 24(7): 741-746.
9. 中华医学会眼科学会眼底病学组. 我国糖尿病视网膜病变临床诊疗指南(2014年)[J]. *中华眼科杂志*, 2014, 50(11): 851-865. Ophthalmology Group of Ophthalmology Society of Chinese Medical Association. Guidelines for clinical diagnosis and treatment of diabetic retinopathy in China (2014)[J]. *Chinese Journal of Ophthalmology*, 2014, 50(11): 851-865.
10. Stevens RJ, Kothari V, Adler AI, et al. The UKPDS risk engine: a model for the risk of coronary heart disease in Type II diabetes (UKPDS 56)[J]. *Clin Sci (Lond)*, 2001, 101(6): 671-679.
11. Newson RB. Comparing the predictive powers of survival models using Harrell's C or Somers' D[J]. *Stata J*, 2010, 10(3): 339-358.
12. Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, et al. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond[J]. *Stat Med*, 2008, 27(2): 157-172.
13. Pencina MJ, D'Agostino RB Sr, Steyerberg EW. Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers[J]. *Stat Med*, 2011, 30(1): 11-21.
14. Yusuf S, Sleight P, Pogue J, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients[J]. *N Engl J Med*, 2000, 342(3): 145-153.
15. Niakan E, Harati Y, Rolak LA, et al. Silent myocardial infarction and diabetic cardiovascular autonomic neuropathy[J]. *Arch Intern Med*, 1986, 146(11): 2229-2230.
16. Cosson E, Nguyen MT, Chanu B, et al. Cardiovascular risk prediction is improved by adding asymptomatic coronary status to routine risk assessment in type 2 diabetic patients[J]. *Diabetes Care*, 2011, 34(9): 2101-2107.
17. Ong YT, De Silva DA, Cheung CY, et al. Microvascular structure and network in the retina of patients with ischemic stroke[J]. *Stroke*, 2013, 44(8): 2121-2127.
18. Karnik AA, Fields AV, Shannon RP. Diabetic cardiomyopathy[J]. *Curr Hypertens Rep*, 2007, 9(6): 467-473.
19. Brooks BA, Franjic B, Ban CR, et al. Diastolic dysfunction and abnormalities of the microcirculation in type 2 diabetes[J]. *Diabetes Obes Metab*, 2008, 10(9): 739-746.

20. Um T, Lee DH, Kang JW, et al. The degree of diabetic retinopathy in patients with type 2 diabetes correlates with the presence and severity of coronary heart disease[J]. J Korean Med Sci, 2016, 31(8): 1292-1299.
21. Sone H, Tanaka S, Tanaka S, et al. Comparison of various lipid variables as predictors of coronary heart disease in Japanese men and women with type 2 diabetes: subanalysis of the Japan Diabetes Complications Study[J]. Diabetes Care, 2012, 35(5): 1150-1157.
22. Coleman RL, Stevens RJ, Retnakaran R, et al. Framingham, SCORE, and DECODE risk equations do not provide reliable cardiovascular risk estimates in type 2 diabetes[J]. Diabetes Care, 2007, 30(5): 1292-1293.
23. Vinik AI, Ziegler D. Diabetic cardiovascular autonomic neuropathy[J]. Circulation, 2007, 115(3): 387-397.

本文引用: 陆长峰, 周建博. 增殖性糖尿病视网膜病变对2型糖尿病患者无症状冠状动脉粥样硬化性心脏病的识别[J]. 临床与病理杂志, 2018, 38(8): 1709-1714. doi: 10.3978/j.issn.2095-6959.2018.08.019

Cite this article as: LU Changfeng, ZHOU Jianbo. Identification of proliferative diabetic retinopathy to asymptomatic coronary heart disease in type 2 diabetes mellitus individuals[J]. Journal of Clinical and Pathological Research, 2018, 38(8): 1709-1714. doi: 10.3978/j.issn.2095-6959.2018.08.019