

· 临床研究 ·

糖尿病视网膜病变合并糖尿病肾病的危险因素及其预测价值

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【摘要】 目的 探讨糖尿病视网膜病变(DR)合并糖尿病肾病(DN)的危险因素及预测价值。**方法** 回顾性分析2017年5月至2018年5月南京医科大学附属无锡市人民医院内分泌科收治的2型糖尿病(T2DM)患者1 969例,其中糖尿病视网膜病变(DR)合并糖尿病肾病(DN)患者609例,单纯DR患者746例,未并发DN和DR患者614例,比较3组患者的血糖、血压、肝功能和肾功能指标水平,分析DR合并DN的危险因素及预测价值。采用SPSS 18.0统计软件对数据进行分析。组间比较采用单因素方差分析或 χ^2 检验。多因素logistic回归分析DR合并DN的危险因素。受试者工作特征(ROC)曲线分析因素预测DR合并DN的价值。**结果** 除高密度脂蛋白胆固醇(HDL-C)水平和左侧颈动脉内膜中层厚度(IMT)外,3组患者其余指标差异均具有统计学意义($P<0.05$)。多因素logistic回归分析结果显示年龄($OR=0.966$, 95% CI 0.932~1.000; $P=0.049$)、白蛋白(ALB)($OR=0.872$, 95% CI 0.837~0.908; $P<0.001$)、服用他汀类药物($OR=0.400$, 95% CI 0.265~0.606; $P<0.001$)是DR合并DN的保护因素,高血压病程($OR=1.021$, 95% CI 1.005~1.037; $P=0.011$)、收缩压($OR=1.018$, 95% CI 1.007~1.029; $P=0.002$)、空腹血糖($OR=1.054$, 95% CI 1.002~1.108; $P=0.040$)、甘油三酯($OR=1.133$, 95% CI 1.021~1.256; $P=0.019$)、低密度脂蛋白胆固醇($OR=1.355$, 95% CI 1.017~1.805; $P=0.038$)、血尿酸($OR=1.124$, 95% CI 1.016~1.244; $P=0.023$)、胱抑素C($OR=2.466$, 95% CI 1.495~4.068; $P<0.001$)、眼底评分($OR=1.275$, 95% CI 1.088~1.494; $P=0.003$)、左室后壁厚度($OR=1.306$, 95% CI 1.051~1.622; $P=0.016$)和颈动脉粥样斑块形成($OR=1.578$, 95% CI 1.051~2.370; $P=0.028$)为危险因素。ROC曲线分析结果表明胱抑素C预测DR合并DN价值最高,AUC为0.677。**结论** T2DM患者DR合并DN的患病率较高,其发生与多种因素相关,其中,胱抑素C预测DR合并DN价值最高。

【关键词】 糖尿病,2型;糖尿病视网膜病变;糖尿病肾病

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Risk factors for diabetic retinopathy complicated with diabetic nephropathy and their predictive values

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【Abstract】 Objective To analyze the risk factors of diabetic retinopathy (DR) complicated with diabetic nephropathy (DN) and their predictive values. **Methods** A total of 1 969 cases with type 2 diabetes mellitus (T2DM) diagnosed in our department from May 2017 to May 2018 were recruited in this study. According to their clinical data, they were assigned into DR complicated with DN group (DR+DN, $n=609$), DR group ($n=746$) and without DR or DN group (non-DR+non-DN, $n=614$). Their blood glucose level, blood pressure and liver and renal functions were compared among the 3 groups. The risk factors for DR complicated with DN and their predictive values were analyzed. SPSS statistics 18.0 was used to perform the statistical analysis. Analysis of variance or Chi-square test was employed for different data types. Multivariate logistic regression analysis was used to analyze the risk factors for DR combined with DN. Receiver operating characteristic (ROC) curve analysis was applied to assess the predictive values for the obtained factors. **Results** Except the level of high-density lipoprotein cholesterol (HDL-C) and intima-media thickness (IMT) of left carotid artery, there were significant differences in other indices among the 3 groups ($P<0.05$). Logistic multivariate regression analysis showed that the protective factors for occurrence of DR complicated with DN was age ($OR=0.966$, 95% CI 0.932~1.000; $P=0.049$), albumin (ALB, $OR=0.872$, 95% CI 0.837~0.908; $P<0.001$) and statins ($OR=0.400$, 95% CI 0.265~0.606; $P<0.001$), while, the risk factors were course of hypertension ($OR=1.021$, 95% CI 1.005~1.037; $P=0.011$), systolic blood pressure

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($OR=1.018$, 95% CI 1.007–1.029; $P=0.002$), fasting blood glucose ($OR=1.054$, 95% CI 1.002–1.108; $P=0.040$), triglycerides ($OR=1.133$, 95% CI 1.021–1.256; $P=0.019$), low-density lipoprotein cholesterol ($OR=1.355$, 95% CI 1.017–1.805; $P=0.038$), blood urea nitrogen ($OR=1.124$, 95% CI 1.016–1.244; $P=0.023$), cystatin C ($OR=2.466$, 95% CI 1.495–4.068; $P<0.001$), score of fundus oculi ($OR=1.275$, 95% CI 1.088–1.494; $P=0.003$), thickness of left ventricular posterior wall ($OR=1.306$, 95% CI 1.051–1.622; $P=0.016$) and carotid atherosclerotic plaque ($OR=1.578$, 95% CI 1.051–2.370; $P=0.028$). ROC analysis revealed that cystatin C was the most significant predictor for occurrence of DR complicated with DN, with the area under ROC curve of 0.677. **Conclusion** In T2DM patients, the prevalence of DR complicated with DN is quite high, which is related to a variety of factors, and among them, cystatin C has the highest efficiency in the prediction.

【Key words】 diabetes mellitus, type 2; diabetic retinopathy; diabetic nephropathy

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糖尿病视网膜病变(diabetic retinopathy, DR)是2型糖尿病(type 2 diabetes mellitus, T2DM)患者最常见的微血管并发症,20%~40%的T2DM患者会出现DR^[1]。研究数据显示,2030年全球DR患者人数将达1.9亿,是20~60岁人群致盲的首要原因^[2]。糖尿病肾病(diabetic nephropathy, DN)也是糖尿病患者主要的慢性并发症,DN导致的慢性肾功能衰竭是糖尿病患者死亡的重要原因。我国T2DM患者DN的患病率已超30%,是导致终末期肾脏病的第二大病因^[3]。DR和DN均属于微血管并发症,二者之间存在一定的关联,DR患者合并DN并不少见,本研究针对DR患者合并DN的危险因素进行了分析,并对相关指标的预测价值进行了探讨。

1 对象与方法

1.1 研究对象

回顾性分析2017年5月至2018年5月南京医科大学附属无锡市人民医院内分泌科收治的T2DM患者1969例,其中DR合并DN患者609例,单纯DR患者746例,未并发DN和DR患者614例。纳入标准:T2DM诊断标准参考中华医学会糖尿病学分会2013年制订的《中国2型糖尿病防治指南》^[4]。DR诊断标准参考中华医学会眼科学会眼底病学组2014后制订的《我国糖尿病视网膜病变临床诊疗指南(2014年)》^[5],DN诊断标准参考中华医学会内分泌学分会2015年制订的《中国成人糖尿病肾脏病临床诊断的专家共识》^[6]。排除标准:合并有恶性肿瘤、急性冠脉综合征、自身免疫疾病、血液病、妊娠期或哺乳期患者;合并有除糖尿病外其他全身代谢疾病患者;临床资料不完整患者。

1.2 检测指标

详细询问病史,检测3组患者的收缩压(systolic blood pressure, SBP)、舒张压(diastolic blood pressure, DBP)、白蛋白(albumin, ALB)、空腹血糖(fasting blood glucose, FBG)、餐后血糖(postprandial blood

glucose, PBG)、空腹C肽(fasting C-peptide, FC)、餐后2h C肽(postprandial 2h C-peptide, PC)、甘油三酯(triglycerides, TG)、总胆固醇(total cholesterol, TC)、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)、总胆红素(total bilirubin, TBIL)、直接胆红素(direct bilirubin, DBIL)、血红蛋白(hemoglobin, Hb)、糖化血红蛋白(glycosylated hemoglobin A1c, HbA1c)、血尿酸(blood uric acid, BUA)、血尿酸氮(blood urea nitrogen, BUN)、血肌酐(serum creatinine, SCr)和胱抑素C(cystatin C, Cys C)水平。根据慢性肾脏病流行病学合作工作组(chronic kidney disease epidemiology collaboration, CKD-EPI)方程计算肾小球滤过率(glomerular filtration rate, GFR)。依据中华医学会眼科学会第3次全国眼科学术会议制订的《糖尿病视网膜病变分期标准》对眼底病变分期和评分,分值1~6分,评分越高,病变程度越重。

1.3 辅助检查

CV650型心脏彩色多普勒超声仪(飞利浦公司)检测患者的室间隔和左室后壁厚度,并判定是否存在室间隔增厚。应用C9型便携式颈动脉彩色多普勒超声分析仪(KONTED公司)检测患者左侧和右侧颈动脉内膜中层厚度(intima-media thickness, IMT),并判定是否有颈动脉粥样斑块形成。

1.4 统计学处理

采用SPSS 18.0统计软件对数据进行分析。计量资料用均数±标准差($\bar{x} \pm s$)表示,组间比较采用单因素方差分析。计数资料用例数(百分率)表示,组间比较用 χ^2 检验。多因素分析采用非条件多因素logistic回归分析。指标预测DR合并DN的价值采用受试者工作特征(receiver operating characteristic, ROC)曲线进行分析,曲线下面积(area under curve, AUC)作为预测价值指标。以 $P<0.05$ 为差异有统计学意义。

2 结 果

2.1 3 组患者检测指标比较

除 HDL-C 水平和左侧颈动脉 IMT 外,3 组患者其余检测指标差异均具有统计学意义($P<0.05$;表 1)。

2.2 多因素 logistic 回归分析 DR 合并 DN 的相关因素

以 DR 合并 DN 为因变量,3 组患者有统计学差异的检测指标为自变量,进行多因素 logistic 回归分析。结果显示年龄、ALB、服用他汀类药物是 DR 合并

表 1 3 组患者检测指标比较
Table 1 Comparison of detection indices among three groups

Item	DR+DN group (<i>n</i> = 609)	DR group (<i>n</i> = 746)	Non-DR+non-DN group (<i>n</i> = 614)	<i>F</i> / χ^2	<i>P</i> value
Age(years, $\bar{x}\pm s$)	60.12±11.38	61.47±9.82	61.54±10.31	3.688	0.025
Gender(male/female, <i>n</i>)	357/252	376/370	310/304	11.298	0.004
Smoking[<i>n</i> (%)]				19.984	<0.001
Yes	184(30.21)	159(21.31)	126(20.52)		
No	425(69.79)	587(78.69)	488(79.48)		
Height(cm, $\bar{x}\pm s$)	164.89±9.38	163.44±8.47	163.81±10.34	4.238	0.015
Body mass(kg, $\bar{x}\pm s$)	68.26±11.28	65.82±10.42	65.85±10.43	10.780	<0.001
BMI(kg/m ² , $\bar{x}\pm s$)	24.97±3.14	24.53±3.02	24.39±2.86	6.137	0.002
Duration of diabetic mellitus(years, $\bar{x}\pm s$)	13.84±7.52	13.78±7.41	10.12±6.84	54.254	<0.001
Duration of hypertension(years, $\bar{x}\pm s$)	8.45±9.55	6.78±9.28	7.07±9.11	5.944	0.003
HbA1c(% , $\bar{x}\pm s$)	9.10±2.05	8.75±1.91	8.09±1.96	41.706	<0.001
SBP(mmHg, $\bar{x}\pm s$)	139.01±17.37	133.08±14.40	130.26±14.19	52.204	<0.001
DBP(mmHg, $\bar{x}\pm s$)	82.21±9.66	79.65±8.11	79.23±8.27	21.516	<0.001
Hb(g/L, $\bar{x}\pm s$)	126.26±19.42	131.50±14.93	133.50±13.23	33.624	<0.001
ALB(g/L, $\bar{x}\pm s$)	34.64±5.31	37.24±3.70	38.18±3.54	116.681	<0.001
FBG(mmol/L, $\bar{x}\pm s$)	9.28±3.59	8.63±3.14	7.86±2.60	31.368	<0.001
PBG(mmol/L, $\bar{x}\pm s$)	19.17±4.87	18.75±4.50	16.69±4.96	48.579	<0.001
TBIL(mmol/L, $\bar{x}\pm s$)	12.19±5.19	13.29±4.86	13.81±5.22	16.325	<0.001
DBIL(mmol/L, $\bar{x}\pm s$)	4.79±2.97	5.14±2.61	5.71±2.77	17.254	<0.001
TG(mmol/L, $\bar{x}\pm s$)	2.26±2.84	1.74±1.47	1.79±1.46	13.082	<0.001
TC(mmol/L, $\bar{x}\pm s$)	4.72±1.29	4.33±1.03	4.46±0.98	22.333	<0.001
LDL-C(mmol/L, $\bar{x}\pm s$)	2.55±0.96	2.38±0.84	2.59±0.80	12.284	<0.001
HDL-C(mmol/L, $\bar{x}\pm s$)	0.99±0.32	0.99±0.28	0.99±0.26	0.116	0.890
Taking statins[<i>n</i> (%)]				98.861	<0.001
Yes	291(47.78)	459(61.53)	464(75.57)		
No	318(52.22)	287(38.47)	150(24.43)		
BUA(μ mol/L, $\bar{x}\pm s$)	318.64±91.56	285.43±73.63	287.08±71.06	35.693	<0.001
BUN(mmol/L, $\bar{x}\pm s$)	6.09±2.59	4.83±1.47	4.74±1.39	102.165	<0.001
SCr(μ mol/L, $\bar{x}\pm s$)	90.77±44.28	67.57±17.18	68.00±16.08	139.392	<0.001
Cys-C(mg/L, $\bar{x}\pm s$)	1.10±0.57	0.80±0.27	0.72±0.25	168.771	<0.001
GFR(ml/min, $\bar{x}\pm s$)	78.32±25.65	91.93±17.06	91.79±14.77	101.047	<0.001
FC(ng/ml, $\bar{x}\pm s$)	1.90±1.14	1.71±0.93	2.05±1.01	18.946	<0.001
PC(ng/ml, $\bar{x}\pm s$)	4.45±2.52	4.45±2.44	6.10±2.98	82.693	<0.001
Fundus oculi(scores, $\bar{x}\pm s$)	2.60±0.95	2.20±0.88	—	7.913	<0.001
Thickness of interventricular septum(mm, $\bar{x}\pm s$)	11.18±1.36	10.69±1.14	10.31±1.19	77.258	<0.001
Thickness of left ventricular wall(mm, $\bar{x}\pm s$)	10.49±1.08	10.05±0.99	9.71±0.97	91.801	<0.001
Interventricular septal thickening[<i>n</i> (%)]				117.727	<0.001
Yes	290(47.62)	217(29.09)	118(19.22)		
No	319(52.38)	529(70.91)	496(80.78)		
IMT of left carotid artery(mm, $\bar{x}\pm s$)	1.01±1.50	0.93±0.18	0.90±0.18	2.937	0.053
IMT of right carotid artery(mm, $\bar{x}\pm s$)	0.94±0.19	0.93±0.17	0.91±0.18	6.952	0.001
Atherosclerotic plaque of carotid[<i>n</i> (%)]				29.504	<0.001
Yes	375(61.58)	399(53.49)	283(46.09)		
No	234(38.42)	347(46.51)	331(53.91)		

DR: diabetic retinopathy; DN: diabetic nephropathy; BMI: body mass index; HbA1c: glycosylated hemoglobin A1c; SBP: systolic blood pressure; DBP: diastolic blood pressure; ALB: albumin; FBG: fasting blood glucose; PBG: postprandial blood glucose; FC: fasting C-peptide; PC: postprandial 2h C-peptide; TG: triglycerides; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TBIL: total bilirubin; DBIL: direct bilirubin; Hb: hemoglobin; HbA1c: glycosylated hemoglobin A1c; BUA: blood uric acid; BUN: blood urea nitrogen; SCr: serum creatinine; Cys C: cystatin C; GFR: glomerular filtration rate; IMT: intima-media thickness. 1 mmHg=0.133 kPa.

DN 的保护因素, 高血压病程、SBP、FBG、TG、LDL-C、BUN、Cys-C、眼底评分、左室后壁厚度和颈动脉粥样斑块形成为危险因素(表2)。

2.3 各因素预测 DR 合并 DN 的价值

ROC 曲线分析结果显示, 在应用各相关因素单独预测 DR 合并 DN 时, 其 AUC 均较小, Cys C 的预测价值最高, AUC 为 0.677(表3, 图1)。

3 讨 论

本研究 1 969 例 T2DM 患者中, DR 患者 1 355 例, 占 68.82%; DR 合并 DN 患者 609 例, 占全部 DR 患者的 44.94%, 占全部 T2DM 患者的 30.93%, 说明 DR 合并 DN 在 T2DM 患者多见。研究结果表明高

血压病程、营养、血糖、血脂、服用他汀类药物、肾功能、眼底病变、心血管病变等指标均与 DR 合并 DN 相关。文献报道糖尿病病程、高血压病史、HbA1c、SBP、FBG、BUA 与 DR 合并 DN 有关, 而血脂指标与其相关性较小, 体脂肪率和内脏脂肪面积等与其有一定相关性^[7], 肱三头肌皮褶厚度、Hb、前白蛋白、总蛋白、ALB 等营养指标也与 DN 发生密切相关^[8]。还有文献报道, 即使接受了相关干预治疗, 随着病程延长, T2DM 患者 DR 及 DN 的病情也仍在进展, SBP、TG、HbA1c 是 DR 的重要危险因素, 而年龄、HbA1c、SBP 是 DN 的重要危险因素^[9]。结合本研究结果, 笔者认为 HbA1c、FBG 等血糖指标, SBP 等血压指标, 及 ALB、TG 等与 DR 合并 DN 相关。

表 2 多因素 logistic 回归分析 DR 合并 DN 的危险因素

Table 2 Multivariate logistic regression analysis of risk factors of DR complicated with DN

Variable	<i>B</i>	<i>SE</i>	<i>Wald</i>	<i>OR</i> (95% <i>CI</i>)	<i>P</i> value
Age	-0.035	0.018	3.888	0.966(0.932-1.000)	0.049
ALB	-0.137	0.021	43.699	0.872(0.837-0.908)	<0.001
Taking statis	-0.915	0.211	18.788	0.400(0.265-0.606)	<0.001
Duration of hypertension	0.021	0.008	6.505	1.021(1.005-1.037)	0.011
SBP	0.018	0.006	10.033	1.018(1.007-1.029)	0.002
FBG	0.053	0.026	4.229	1.054(1.002-1.108)	0.040
TG	0.125	0.053	5.542	1.133(1.021-1.256)	0.019
LDL-C	0.304	0.146	4.298	1.355(1.017-1.805)	0.038
BUN	0.117	0.051	5.174	1.124(1.016-1.244)	0.023
Cys-C	0.903	0.255	12.488	2.466(1.495-4.068)	<0.001
Score of fundus oculi	0.243	0.081	8.988	1.275(1.088-1.494)	0.003
Thickness of left ventricular posterior wall	0.267	0.111	5.820	1.306(1.051-1.622)	0.016
Atherosclerotic plaque of carotid	0.456	0.208	4.829	1.578(1.051-2.370)	0.028

DR: diabetic retinopathy; DN: diabetic nephropathy; ALB: albumin; SBP: systolic blood pressure; FBG: fasting blood glucose; TG: triglycerides; LDL-C: low-density lipoprotein cholesterol; BUN: blood urea nitrogen; Cys C: cystatin C.

表 3 各相关因素预测 DR 合并 DN 的价值

Table 3 Value of various related factors in predicting DR patients complicated with DN

Variable	AUC	<i>SE</i>	95% <i>CI</i>	<i>P</i> value
Duration of hypertension	0.572	0.016	0.542-0.603	<0.001
SBP	0.600	0.015	0.570-0.630	<0.001
FBG	0.551	0.016	0.520-0.582	0.001
TG	0.571	0.016	0.541-0.602	<0.001
LDL-C	0.553	0.016	0.522-0.584	0.001
BUN	0.659	0.015	0.630-0.688	<0.001
Cys-C	0.677	0.015	0.648-0.706	<0.001
Score of fundus oculi	0.618	0.015	0.588-0.648	<0.001
Thickness of left ventricular wall	0.611	0.015	0.581-0.641	<0.001
Atherosclerotic plaque of carotid	0.540	0.016	0.510-0.571	0.010
Age	0.537	0.016	0.506-0.568	0.019
ALB	0.650	0.015	0.621-0.680	<0.001
Taking statins	0.431	0.016	0.401-0.462	<0.001

DR: diabetic retinopathy; DN: diabetic nephropathy; SBP: systolic blood pressure; FBG: fasting blood glucose; TG: triglycerides; LDL-C: low-density lipoprotein cholesterol; BUN: blood urea nitrogen; Cys C: cystatin C; ALB: albumin.

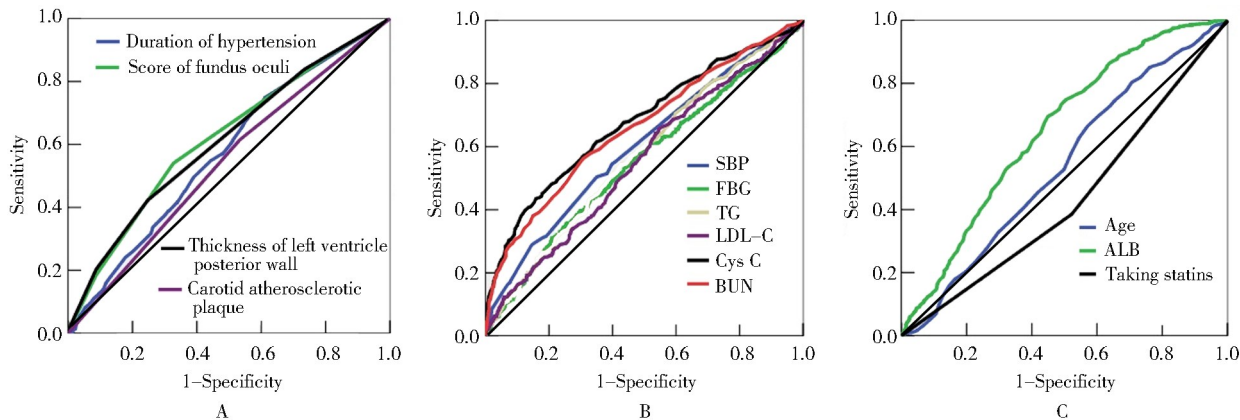


图1 各因素预测DR合并DN的ROC曲线

Figure 1 ROC curve of related factors for predicting DR complicated with DN

ROC: receiver operating characteristic; DR: diabetic retinopathy; DN: diabetic nephropathy; SBP: systolic blood pressure; FBG: fasting blood glucose; TG: triglycerides; LDL-C: low-density lipoprotein cholesterol; Cys C: cystatin C; BUN: blood urea nitrogen; ALB: albumin. A and B: risk factors; C: protective factors.

本研究结果还表明眼底病变程度也与DR合并DN相关,说明DR病情也可作为预测DN发病风险的参考依据。部分研究表明随着DR病情由非增殖性视网膜病变向增殖性视网膜病变发展,SCr和BUN水平也会随之升高,SCr、BUN水平与视网膜神经纤维层厚度呈负相关,DR病情进展可预测DN患者肾功能损伤的程度^[10,11]。

本研究表明服用他汀类药物为DR合并DN的保护因素,而且OR值达0.4,说明应用他汀类药物可使DR合并DN的风险降低,这反映了有效调节血脂水平对预防糖尿病微血管并发症的发生可能具有显著意义。因此对血脂异常的DR患者一般推荐应用他汀类或贝特类调脂药辅助治疗^[12]。本研究还提示左室后壁厚度、粥样斑块形成等心血管病变指标也与DR合并DN相关,可能的原因在于DR、DN等微血管并发症加重了心血管系统的器质性损害,患者通常血糖控制效果差,HbA1c等血糖指标水平较高,而较高的血糖水平是此类患者发生心血管事件的独立因素^[13]。

本研究表明各种因素中Cys C预测DR合并DN价值最高。DN患者的主要临床表现是蛋白尿增加和肾功能改变,因此临床诊断DN的主要依据是尿蛋白排泄率、尿微量白蛋白等尿蛋白指标,但部分DN患者在病程早期尿蛋白水平正常,依靠尿蛋白排泄率只能诊断Ⅱ~Ⅲ期DN^[14]。近年研究表明,早期DN患者的血清Cys C阳性率和诊断的灵敏度、特异度、准确度均高于BUN、SCr和尿β2微球蛋白等传统肾功能损害指标^[15],而且随着DR患者病情加重,血清Cys C水平也逐渐上升,其水平

与HbA1c、24h尿蛋白排泄率均呈正相关,提示Cys C可有助于预测DR患者合并发生DN的风险^[16]。本研究结果也表明Cys C预测DR合并DN价值最高,但其AUC未达0.7,仅为0.677。

综上所述,T2DM患者中DR合并DN患病率较高,其发生与多种因素相关,其中,Cys C预测DR合并DN的价值最高。

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