

KIM1、TIMP2 及炎症指标与 2 型糖尿病肾病进展风险的相关性研究

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【摘要】 目的 检测不同程度肾脏疾病的糖尿病患者中血清肾损伤分子-1 (KIM-1)、金属基质蛋白酶抑制剂-2 (TIMP2)、白介素 6 (IL-6) 和 C 反应蛋白 (CRP) 的水平, 并评估其与糖尿病肾脏进展风险的关系。方法 选取 2022 年 3 月至 2023 年 3 月东莞厚街医院收治的 65 例 2 型糖尿病患者纳入研究, 根据患者肾脏病变的严重程度, 按照改善全球预后指南将糖尿病肾病 (DKD) 分为低风险组 (n=19)、中风险组 (n=22) 和高风险组 (n=24), 同期选择 20 例体检健康者作为对照组。比较各组受试者血清 KIM-1、TIMP-2、IL-6、CRP、糖化血红蛋白 (HbA1c)、尿蛋白/肌酐比值 (UACR)、低密度脂蛋白胆固醇 (LDL-C)、空腹血糖 (FPG)、血清总胆固醇 (TC)、肾小球滤过率 (eGFR)、高密度脂蛋白胆固醇 (HDL-C)、25 羟维生素 D₃ [(25(OH)D₃)] 和甘油三酯 (TG) 的水平, 采用 Pearson 法分析血清 TIMP-2、KIM-1 与 DKD 糖脂代谢、肾功能指标的相关性, 利用受试者工作 (ROC) 曲线分析血清 KIM-1、TIMP-2、IL-6、CRP、KIM-1 与 TIMP-2 联合检测对 DKD 疾病进展的预测价值。结果 四组受检者血清 LDL-C、HDL-C 和 CRP 水平比较差异均无统计学意义 (P>0.05); 对照组血清 FPG、HbA1c、TIMP2、KIM-1 水平分别为 (5.13±0.56) mmol/L、(5.56±0.30)%、(4.91±0.76) ng/mL、(0.46±0.33) ng/mL, 明显低于低风险组的 (12.17±9.82) mmol/L、(9.45±2.46)%、(11.51±25.01) ng/mL、(1.00±0.68) ng/mL 及中风险组的 (11.35±10.63) mmol/L、(9.73±2.82)%、(30.23±17.42) ng/mL、(1.26±1.31) ng/mL 和高风险组的 (8.04±7.69) mmol/L、(9.27±2.21)%、(30.51±46.01) ng/mL、(1.63±1.09) ng/mL, 而低风险组的血清中 TIMP2、KIM-1 水平明显低于中风险组、高风险组, 差异均有统计学意义 (P<0.05); 高风险组患者的血清 CREA、IL-6 水平分别为 (122.00±79.23) μmmol/L、(3.51±5.92) pg/mL, 明显高于低风险组的 (77.00±42.70) μmmol/L、(0.50±2.79) pg/mL 和中风险组的 (74.00±32.25) μmmol/L、(1.34±3.61) pg/mL, 差异均有统计学意义 (P<0.05); 经 Spearman 相关分析结果显示 2 型糖尿病肾病患者 TIMP-2、KIM-1 与 HbA1c、IL-6、UACR 均呈正相关 (P<0.05), 而 TIMP-2、KIM-1 与 eGFR 呈负相关 (P<0.05); 经 ROC 分析结果显示, KIM-1、TIMP-2、IL-6、CRP 以及 KIM-1 联合 TIMP-2 预测 2 型糖尿病肾病进展风险的曲线下面积 (AUC) 分别为 0.869、0.867、0.751、0.633 和 0.935, KIM-1 联合 TIMP-2 预测较各单一指标预测的准确度更高。结论 血清 KIM-1、TIMP-2、IL-6、CRP 水平升高与 2 型糖尿病肾病疾病进展密切相关, 其中 KIM-1 联合 TIMP-2 预测 2 型糖尿病肾病进展风险的价值较高。

【关键词】 糖尿病肾病; 肾损伤分子-1; 金属基质蛋白酶抑制剂-2; 炎症因子; 相关性

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Correlation of KIM1, TIMP2, and inflammatory markers with the risk of progression of type 2 diabetic nephropathy. SUN Xiao-fang¹, YIN Li-ming², BAO Li-wen¹, LIAO Zhi-wei¹, FU Wen-jin², WANG Shao-bo¹. Department of Endocrinology¹, Department of Clinical Laboratory², Houjie Clinical Medical College, Guangdong Medical University, Dongguan 523960, Guangdong, CHINA

【Abstract】 Objective To measure the levels of blood clear kidney injury molecule-1 (KIM-1), metalloproteinase inhibitor-2 (TIMP2), interleukin 6 (IL-6), and C-reactive protein (CRP) in diabetic patients with different de-

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gresses of kidney disease, and to evaluate their relationship with the risk of progression of diabetic kidney disease (DKD).

Methods A total of 65 patients with type 2 diabetes who were admitted to Dongguan Houjie Hospital from March 2022 to March 2023 were selected for inclusion in the study. Based on the severity of renal lesions, the patients were divided into low-risk group ($n=19$), medium-risk group ($n=22$), and high-risk group ($n=24$) according to the Kidney Disease: Improving Global Outcomes (KDIGO), and 20 healthy patients during the same period were selected as the control group. The blood levels of KIM-1, TIMP-2, IL-6, CRP, glycosylated hemoglobin (HbA1c), urine albumin-to-creatinine ratio (UACR), low-density lipoprotein cholesterol (LDL-C), fasting blood glucose (FPG), serum total cholesterol (TC), estimated glomerular filtration rate (eGFR), high-density lipoprotein cholesterol (HDL-C), 25-hydroxyvitamin D₃ [25(OH)D₃] and triglycerides (TG) were compared among the four groups. Pearson method was used to analyze the correlation of serum TIMP-2, KIM-1 with DKD glucose and lipid metabolism and renal function indexes. Receiver operating curve (ROC) was used to analyze the predictive value of serum KIM-1, TIMP-2, IL-6, CRP, and KIM-1 combined with TIMP-2 for DKD progression. **Results** There were no significant differences in the levels of serum LDL-C, HDL-C, and CRP among the four groups ($P>0.05$). The serum levels of FPG, HbA1c, TIMP-2, and KIM-1 in the control group were (5.13 ± 0.56) mmol/L, (5.56 ± 0.30)%, (4.91 ± 0.76) ng/mL, and (0.46 ± 0.33) ng/mL, respectively, significantly lower than (12.17 ± 9.82) mmol/L, (9.45 ± 2.46)%, (11.51 ± 25.01) ng/mL, (1.00 ± 0.68) ng/mL in low-risk group and (11.35 ± 10.63) mmol/L, (9.73 ± 2.82)%, (30.23 ± 17.42) ng/mL, (1.26 ± 1.31) ng/mL in medium-risk group, and (8.04 ± 7.69) mmol/L, (9.27 ± 2.21)%, (30.51 ± 46.01) ng/mL, (1.63 ± 1.09) ng/mL in high-risk group, respectively; the serum levels of TIMP-2 and KIM-1 in the low-risk group were significantly lower than those in the medium-risk group and the high-risk group; the differences were statistically significant ($P<0.05$). The serum CREA and IL-6 levels in the high-risk group were (122.00 ± 79.23) μ mol/L and (3.51 ± 5.92) pg/mL, respectively, significantly higher than (77.00 ± 42.70) μ mol/L and (0.50 ± 2.79) pg/mL in the low-risk group and (74.00 ± 32.25) μ mol/L, (1.34 ± 3.61) pg/mL in the medium-risk group ($P<0.05$). Spearman correlation analysis showed that TIMP-2 and KIM-1 were positively correlated with HbA1c, IL-6, and UACR in patients with type 2 diabetic nephropathy ($P<0.05$), while TIMP-2 and KIM-1 were negatively correlated with eGFR ($P<0.05$). The area under the curve (AUC) were 0.869, 0.867, 0.751, 0.633, and 0.935, respectively, and the prediction accuracy of KIM-1 combined with TIMP-2 was higher than that of each indicator alone. **Conclusion** Elevated serum levels of KIM-1, TIMP-2, IL-6, and CRP were closely related to the progression of type 2 diabetic nephropathy, and KIM-1 combined with TIMP-2 had a high value in predicting the risk of progression of type 2 diabetic nephropathy.

【Key words】 Diabetic nephropathy; Kidney injury molecule-1; Metalloproteinase inhibitor-2; Inflammatory factors; Correlation

糖尿病肾病(diabetic kidney disease, DKD)是由慢性高血糖所致的肾损害,病变可累及全肾,是糖尿病患者进入终末期肾脏病的主要原因。DKD以持续的白蛋白尿和(或)肾小球滤过率的进行性降低为临床特点,随着疾病的发展可发生水肿、血压升高等,如果不能得到有效的治疗,会发展成终末期肾病,危及患者的生命。因此早期诊断和干预对延缓DKD病情发展、改善预后具有重要临床意义。近年来研究报道,肾损伤分子1(kidney injury molecule 1, KIM-1)和金属基质蛋白酶抑制剂-2(tissue inhibitor of metalloproteinase 2, TIMP-2)、炎症因子在DKD发病机制中有一定的参与作用^[1-7]。有研究发现,维生素D可抑制炎症因子分泌,在慢性炎症反应中具有重要作用,可反映肾脏的损伤程度^[8]。但目前对早期糖尿病肾病进展风险缺乏有效的预测指标,很多糖尿病肾病进展到临床糖尿病甚至终末期肾脏病才被发现。本研究通过检测患有不同程度糖尿病肾病的患者中KIM-1、TIMP-2、白介素6(interleukin-6, IL-6)和C反应蛋白(C-reaction protein, CRP)的水平,评估其与2型DKD疾病进展的关系,以

探讨适合预测早期糖尿病肾病进展风险的标记物。

1 资料与方法

1.1 一般资料 经我院医学伦理委员会批准,收集2022年3月至2023年3月期间东莞厚街医院收治的65例2型糖尿病合并糖尿病肾病患者作为研究对象。纳入标准:(1)符合糖尿病肾病诊断标准^[9];(2)糖尿病肾病风险组符合2022年“改善全球肾脏病预后组织”指南确立的风险评估^[10-11];(3)病历资料完整。排除标准:(1)认知功能障碍及相关精神疾病;(2)糖尿病的急性并发症;(3)有心肝脑功能障碍及恶性肿瘤病史;(4)其他继发性肾脏疾病,如狼疮肾炎、乙型肝炎病毒相关性肾小球肾炎;(5)既往行肾移植、肾脏代替治疗;(6)妊娠或哺乳期妇女;(7)近期服用肾毒性药物。根据改善全球预后指南将研究对象分为低风险组($n=19$)、中风险组($n=22$)和高风险组($n=24$)。另选取同一时间段本院健康体检者20例作为对照组。

1.2 方法

1.2.1 资料收集 以病史采集方式收集患者的一般资料,包括年龄、性别、病程、体质量指数(BMI)等。

1.2.2 检测方法 受试者空腹 8 h 后采集静脉全血样本, 放置 30 min 后颠倒混匀, 在 3 000 r/min 速度下离心 15 min, 吸取样本上清液存放在 -80℃ 的超低温冰箱中以备检测, 采取酶法检测血清总胆固醇(TC)水平, GPO-POD 法检测甘油三酯(TG)水平, 采用直接法检测高密度脂蛋白胆固醇(HDL-C)、低密度脂蛋白胆固醇(LDL-C)水平, 用双胍法测定血肌酐(CREA), 用己糖氧化酶法检测空腹血糖(FPG), 用酶联免疫吸附法测定血清 KIM-1、TIMP-2、25(OH)D₃、IL-6 和 CRP 水平。检测仪器为贝克曼库尔特 AU5800 全自动化生化仪, 使用奥迪康全自动糖化血红蛋白分析仪 AC6600 检测糖化血红蛋白(HbA1c), 取受检者晨时中段尿采用免疫比浊法即时测量尿蛋白/肌酐比值(UACR)。根据收集患者的性别、年龄和血肌酐结果通过 MDRD 公式得出肾小球滤过率(eGFR), 试剂盒购自上海碧云天生物, 检测步骤参考说明书。

1.3 统计学方法 应用 SPSS25.0 统计软件进行统计学分析, 计数资料比较采用 χ^2 检验; 符合正态分布

的计量资料以均数±标准差($\bar{x}\pm s$)表示, 多组间比较采用单因素方差分析; 不服从正态分布的计量资料以 M (QR) 表示, 多组间比较采用 Kruskal-Wallis 检验。采用 Spearman 相关分析血清 KIM-1 和 TIMP-2 与各临床资料变量间的关系。采用受试者工作特征(ROC)曲线及曲线下面积(AUC)评估分析 KIM-1、TIMP-2、IL-6、CRP、KIM-1 联合 TIMP-2 水平对预测糖尿病肾病进展风险的价值。以 $P<0.05$ 为差异具有统计学意义。

2 结果

2.1 四组受检者的临床资料比较 四组受检者血清 LDL-C、HDL-C 和 CRP 比较差异均无统计学意义($P>0.05$); 对照组中 FPG、HbA1c、TIMP-2、KIM-1 水平明显低于低风险组、中风险组、高风险组, 而低风险组中 TIMP-2、KIM-1 水平明显低于中风险组、高风险组, 高风险组中 CREA、IL-6 水平明显高于低风险组、中风险组, 差异均具有统计学意义($P<0.05$), 见表 1。

表 1 四组受试者的临床和实验室指标比较($\bar{x}\pm s$, 例(%), M (QR))

Table 1 Comparison of clinical and laboratory parameters among the four groups of subjects [$\bar{x}\pm s$, n (%), M (QR)]

临床资料/实验室指标	高风险组(n=24)	中风险组(n=22)	低风险组(n=19)	正常对照组(n=20)	F/ χ^2 /H 值	P 值
病程(年)	10.00 (7.00)	2.00 (7.15) ^a	1.00 (2.00) ^a	-	16.916	0.001
性别					0.231	0.901
男性	14.00 (58.34)	13.00 (59.10)	12.00 (63.16)	13.00 (65.00)		
女性	10.00 (41.66)	9.00 (40.90)	7.00 (36.84)	7.00 (35.00)		
年龄(岁)	55.08±8.19	51.44±10.82	50.15±7.22	50.30±6.27	0.549	0.570
BMI (kg/m ²)	25.09±4.09	25.33±3.73	24.09±4.24	24.27±2.41	1.023	0.315
FPG (mmol/L)	8.04 (7.69)	11.35 (10.63)	12.17 (9.82)	5.13 (0.56) ^{abc}	32.639	0.001
HbA1c (%)	9.27±2.21	9.73±2.82	9.45±2.46	5.56±0.30 ^{abc}	16.468	0.001
TG (mmol/L)	1.60 (0.90)	1.88 (2.86)	1.64 (1.53)	1.26 (0.99)	4.036	0.258
TC (mmol/L)	4.90 (2.37)	5.76 (1.58)	4.75 (2.00)	4.98 (1.24)	3.492	0.322
HDL-C (mmol/L)	1.20 (0.28)	1.07 (0.54)	1.05 (0.40)	1.27 (0.25)	5.578	0.134
LDL-C (mmol/L)	3.42±1.12	3.22±0.94	3.04±1.05	3.28±0.91	0.425	0.735
CREA (μ mol/L)	122.00 (79.23)	74.00 (32.25) ^a	77.00 (42.70) ^a	85.50 (27.00) ^a	20.197	0.001
eGFR [mL/(min·1.73 m ²)]	44.15 (43.47)	96.85 (36.95) ^a	88.00 (42.70) ^a	90.15 (29.05) ^a	27.761	0.001
UACR (mg/g)	431.73 (1 141.20)	74.76 (77.53) ^a	16.74 (15.50) ^{ab}	-	45.552	0.001
IL-6 (pg/mL)	3.51 (5.92)	1.34 (3.61) ^a	0.50 (2.79) ^a	0 ^{ab}	22.889	0.001
CRP (mg/L)	1.76 (1.63)	1.26 (5.84)	1.64 (3.51)	0.83 (1.70)	7.553	0.056
25(OH) D ₃ (ng/mL)	18.05 (5.33)	23.35 (14.55) ^a	25.10 (10.60)	21.70 (5.53)	9.574	0.023
TIMP-2 (ng/mL)	30.51 (46.01)	30.23 (17.42)	11.51 (25.01) ^{ab}	4.91 (0.76) ^{abc}	41.034	0.001
KIM-1 (ng/mL)	1.63 (1.09)	1.26 (1.31) ^a	1.00 (0.68) ^{ab}	0.46 (0.33) ^{abc}	46.788	0.001

注: 与高风险组比较, ^a $P<0.05$; 与中风险组比较, ^b $P<0.05$; 与低风险组比较, ^c $P<0.05$ 。

Note: Compared with that in high-risk group, ^a $P<0.05$; compared with that in medium-risk group, ^b $P<0.05$; compared with that in the low-risk group, ^c $P<0.05$.

2.2 血清 TIMP2 和 KIM1 与 DKD 各临床资料的相关性 Spearman 相关分析结果显示, 2 型糖尿病肾病患者的 TIMP-2、KIM-1 与 HbA1c、IL-6、UACR 均呈正相关($P<0.05$), TIMP-2、KIM-1 与 eGFR 均呈负相关($P<0.05$), 见表 2。

2.3 KIM-1、TIMP-2、IL-6、CRP 和联合检测

(KIM-1+TIMP-2) 分别预测 2 型糖尿病肾病进展风险的价值 经 ROC 分析结果显示 KIM-1、TIMP-2、IL-6、CRP 以及 KIM-1 联合 TIMP-2 预测 2 型糖尿病肾病进展风险的 AUC 分别为 0.869、0.867、0.751、0.633 和 0.935, KIM-1 联合 TIMP-2 预测较各单一指标预测的准确度更高, 见图 1~图 5、表 3。

表 2 血清 TIMP2 和 KIM1 与 DKD 各临床资料的相关性

Table 2 Correlation of serum TIMP2 and KIM1 with clinical data of diabetic kidney disease

项目	TIMP2		KIM1	
	r 值	P 值	r 值	P 值
病程(年)	0.194	0.122	0.114	0.377
年龄(岁)	0.215	0.048	0.174	0.118
BMI (kg/m ²)	0.141	0.208	0.194	0.086
FBG (mmol/L)	0.373	0.001	0.458	0.001
HbA1c (%)	0.475	0.000	0.565	0.001
FC (ng/mL)	0.142	0.311	-0.08	0.583
TG (mmol/L)	0.206	0.079	0.192	0.109
TC (mmol/L)	0.141	0.230	0.075	0.536
HDL-C (mmol/L)	-0.106	0.368	-0.193	0.108
LDL-C (mmol/L)	0.146	0.216	0.031	0.796
血 CREA	0.126	0.255	0.144	0.203
血 Ua	0.087	0.435	0.044	0.698
血 BUN	0.198	0.073	0.210	0.061
eGFR	-0.239	0.029	-0.257	0.022
UACR	0.383	0.002	0.550	0.001
IL-6	0.386	0.000	0.473	0.001
CRP	0.206	0.058	0.188	0.090
25(OH)D ₃	-0.139	0.206	-0.050	0.655

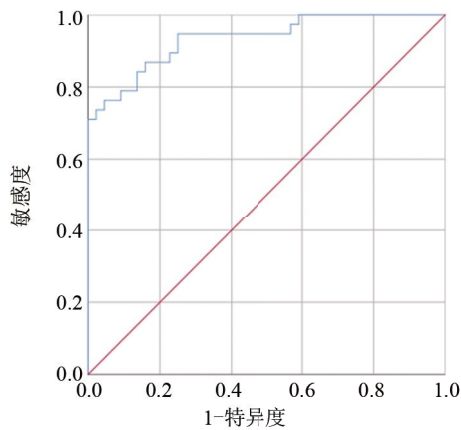


图 1 KIM-1 联合 TIMP-2 预测 2 型糖尿病肾病进展风险的 ROC

Figure 1 ROC of KIM-1 combined with TIMP-2 in predicting the risk of progression of type 2 diabetic nephropathy

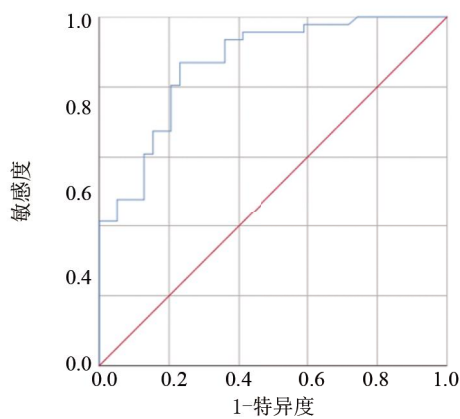


图 2 TIMP-2 预测 2 型糖尿病肾病进展风险的 ROC

Figure 2 ROC of TIMP-2 in predicting the risk of progression of type 2 diabetic nephropathy

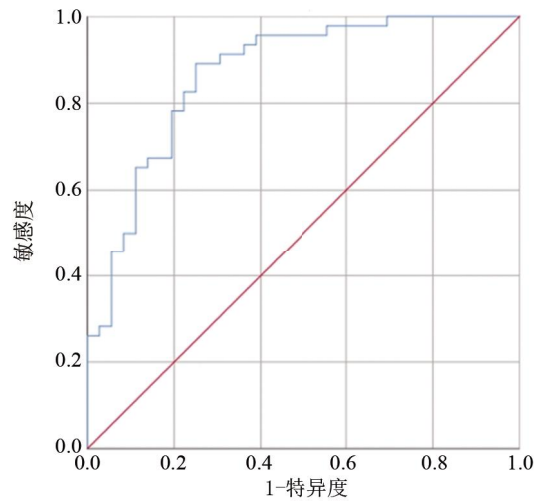


图 3 KIM-1 预测 2 型糖尿病肾病进展风险的 ROC

Figure 3 ROC of KIM-1 in predicting the risk of progression of type 2 diabetic nephropathy

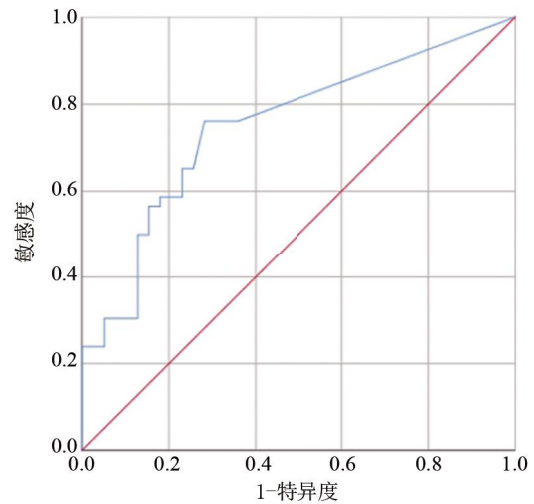


图 4 IL-6 预测 2 型糖尿病肾病进展风险的 ROC

Figure 4 ROC of IL-6 in predicting the risk of progression of type 2 diabetic nephropathy

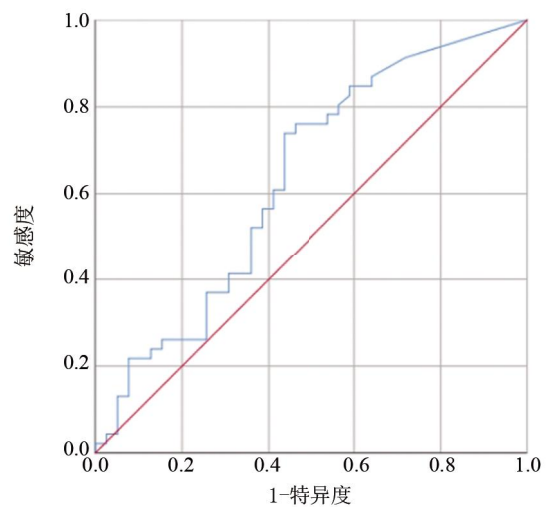


图 5 CRP 预测 2 型糖尿病肾病进展风险的 ROC

Figure 5 ROC of CRP in predicting the risk of progression of type 2 diabetic nephropathy

表 3 KIM-1、TIMP-2、IL-6 和 CRP 及联合检测(KIM-1+TIMP-2) 评估 2 型糖尿病肾病进展风险的价值

Table 3 Value of KIM-1, TIMP-2, IL-6, CRP, and combined detection (KIM-1 + TIMP-2) in assessing the risk of progression of type 2 diabetes nephropathy

指标	AUC	95%CI	灵敏度(%)	特异度(%)	约登指数
TIMP-2	0.867	0.792~0.942	100	97.4	0.610
KIM-1	0.869	0.790~0.948	100	94.4	0.974
IL-6	0.751	0.646~0.855	76.1	35.9	0.120
CRP	0.633	0.512~0.754	91.3	71.8	0.630
联合检测	0.935	0.883~0.987	100	97.7	0.977

3 讨论

随着生活和饮食习惯的改变,糖尿病已经成为继心脑血管疾病、恶性肿瘤之后影响人类健康的第三大因素。长期处于高血糖环境中会导致微血管基底膜增厚和微环境障碍,可累及全身各组织器官,其中肾脏常累及靶器官。糖尿病肾病的发病机制复杂,早期病理表现为肾小球基底膜增厚、系膜扩张、肾小球硬化^[9]。DKD 早期无明显临床表现,临床常以持续性白蛋白尿和(或)肾小球滤过率进行性下降为主要特征,但通过尿蛋白和肾小球滤过率无法早期识别和预测糖尿病肾病的进展风险,确诊时患者已错过最佳治疗时机,影响生活质量。因此,早期预测 DKD 的进展风险对疾病的诊断及治疗至关重要。

KIM-1 是一种新型的 I 型跨膜糖蛋白,属于免疫球蛋白基因超家族,表达于肾近端小管上皮细胞^[2,12]。正常情况下,肾脏组织几乎不表达 KIM-1 蛋白,但是在缺氧、炎症等刺激下 KIM-1 的表达水平显著升高^[13-14]。有研究发现,在大量蛋白尿患者中 KIM-1 处于高水平状态^[15],而 KIM-1 的慢性表达使肾小管间质纤维化及炎症因子累积,这可反映肾脏早期进展风险,可作为肾功能不全的潜在预测标志物^[16]。Gutiérrez 等^[17]发现 KIM-1 是肾脏替代疗法最强的个体预测因子,也强调了肾小管损伤在糖尿病和晚期 CKD 患者肾脏疾病进展中的重要性,同时尿液 KIM-1 已经用于在临床前药物开发中检测肾损伤。TIMP-2 是基质金属蛋白酶(matrix metalloproteinases, MMPs)的内源性抑制剂,是分子量为 22 kDa 的蛋白质^[18-19]。MMP 家族在糖尿病导致的慢性肾脏疾病中也有作用^[20],TIMP-2 可激活 MMP 促进细胞凋亡而损伤肾脏^[21],在肾脏的各种损伤中 TIMP2 显著增加,同时在肾小球疾病和肾纤维化中也有相关作用,亦可作为早期肾损伤预测标志物^[22-23]。

本研究发现,KIM-1、TIMP-2 水平在不同风险组中有明显的差异,对照组健康者中 TIMP-2、KIM-1 水平明显低于低风险组、中风险组、高风险组;而低风险组中 TIMP-2、KIM-1 水平明显低于中风险组、高风险组;差异均有统计学意义($P < 0.05$)。根据 ROC 曲线分析显示:KIM-1 预测 2 型糖尿病肾病进展风险的 AUC

为 0.869、灵敏度为 100%、特异度为 94.4%,TIMP-2 预测 2 型糖尿病肾病进展风险的 AUC 为 0.867、灵敏度为 100%、特异度为 97.4%;说明 KIM-1、TIMP-2 对糖尿病肾病患者肾病疾病进展的评估具有较高价值。目前已有相关研究结果说明 KIM-1、TIMP-2 作为早期标志物及早期肾损伤预测标志物的可能性,本研究结果发现单个指标的敏感度有限,联合检测能提高预测的敏感性和特异性。研究显示:KIM-1 联合 TIMP-2 预测 2 型糖尿病肾病进展风险的 AUC 优于 TIMP-2、KIM-1 单独检测价值,说明联合检测 TIMP-2、KIM-1 水平变化能够更有效地预测糖尿病肾病的进展风险,从而为临床治疗提供及时、有效的预测价值。

糖尿病肾病发生核心在于糖脂代谢紊乱和肾血流动力学改变。其中炎症因子和细胞协同其他机制促使炎症反应的发生,是 DKD 持续发展的关键性因素。高 HbA1c 水平会降低红细胞对氧的亲合力,从而加重组织缺氧及血管内皮损伤,高糖环境会使肾脏中的糖基化终末产物过度堆积,进一步加重肾损伤^[24]。本研究发现炎症指标 CRP、IL-6 水平在不同糖尿病肾病风险组有明显的差异。对照组健康者中 FPG、HbA1c 水平明显低于低风险组、中风险组、高风险组;高风险组中 IL-6 水平明显高于低风险组、中风险组,差异均有统计学意义($P < 0.05$),经 Spearman 相关分析显示 2 型糖尿病肾病患者 TIMP-2、KIM-1 分别与 HbA1c、IL-6 均呈正相关,说明炎症标志物及高血糖与 2 型糖尿病肾损伤的进展密切相关。糖尿病患者常伴有维生素 D 缺乏,25(OH)D₃ 缺乏可激活肾血管紧张系统,加重肾小球硬化和纤维化,因此 25(OH)D₃ 的变化也可反映糖尿病肾病患者肾功能损伤程度^[8]。

综上所述,高血糖及炎症因子与糖尿病肾病的疾病进展密切相关,KIM-1 联合 TIMP-2 预测 2 型糖尿病肾病进展风险评估优于 TIMP-2、KIM-1。因此 KIM-1 联合 TIMP-2 可作为一种新的替代性预测指标,从而更早识别和预测糖尿病肾病进展的风险,但本研究仍有局限性,应拓宽样本来源,以进一步丰富研究结果。

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