

# 尿 NGAL 与 IgA 肾病早期诊断及预后的关系

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**摘要:** **目的** 探讨尿中性粒细胞明胶酶相关脂质运载蛋白(NGAL)在IgA肾病早期诊断中的价值及其与IgA肾病患者肾脏累积存活率的关系。**方法** 病例组为山西医科大学第二医院2017年3月至2018年7月经肾穿刺活检确诊的原发性IgA肾病患者39例,对照组为同期健康体检者55例。收集所有对象一般及临床资料并对其进行尿NGAL检测。将IgA肾病患者按照肾小管间质损伤面积占比分为轻度、中度和重度组;按照尿NGAL中位数分为尿NGAL高、低水平组。比较各组尿NGAL水平;分析尿NGAL、尿肾损伤分子-1(KIM-1)对IgA肾病的早期诊断效能;分析尿NGAL与各临床指标的相关性;比较不同尿NGAL水平组及不同程度肾小管间质损伤组间的肾脏累积存活率。**结果** 病例组与对照组之间及不同程度肾小管间质损伤组之间,尿NGAL水平差异有统计学意义( $P<0.05$ )。ROC曲线显示,尿NGAL对IgA肾病早期诊断的曲线下面积(AUC=0.809)大于尿KIM-1的曲线下面积(AUC=0.746)。Spearman相关性分析显示,IgA肾病患者尿NGAL与尿中KIM-1、N-乙酰- $\beta$ -D-氨基葡萄糖苷酶(NAG)、视黄醇结合蛋白(RBP)、 $\alpha$ 1-微球蛋白( $\alpha$ 1-MG)、血清肌酐(SCr)及24h尿蛋白定量呈正相关( $P<0.05$ ),与肾小球滤过率(eGFR)呈负相关( $P<0.05$ )。Kaplan-Meier生存分析显示,尿NGAL高水平组IgA肾病患者的肾脏累积存活率低于尿NGAL低水平组,重度肾小管间质损伤组IgA肾病患者的肾脏累积存活率低于轻、中度肾小管间质损伤组( $P<0.05$ )。**结论** 尿NGAL检测在IgA肾病的早期诊断及预后评估方面具有一定的临床应用价值。

**关键词:** IgA肾病; 中性粒细胞明胶酶相关脂质运载蛋白; 肾损伤因子1; 早期诊断; 肾脏累积存活率

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## Association of urinary NGAL and early diagnosis and prognosis of IgA nephropathy

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**Abstract:** **Objective** To investigate the value of urinary neutrophil gelatinase-associated lipocalin (NGAL) in the early diagnosis of IgA nephropathy and its relationship with the cumulative survival rate of kidney in patients with IgA nephropathy. **Methods** The case group consisted of 39 patients with primary IgA nephropathy diagnosed by renal biopsy in the Second Hospital of Shanxi Medical University from March 2017 to July 2018, and the control group consisted of 55 healthy people in the same period. Patients with IgA nephropathy were divided into mild, moderate and severe groups according to the proportion of renal tubulointerstitial injury area, and into high and low urinary NGAL groups according to the median urine NGAL. The levels of urinary NGAL in each group were compared. To analyze the early diagnostic efficacy of urine NGAL and urine kidney injury molecule-1 (KIM-1) for IgA nephropathy. The correlation between urinary NGAL and various clinical indicators was analyzed. The cumulative survival rate of the kidney was compared among groups with different urinary NGAL levels and groups with different degrees of tubulointerstitial injury. **Results** There were statistically significant differences in urinary NGAL levels between the case group and the control group, as well as between groups with different degrees of tubulointerstitial injury ( $P<0.05$ ). ROC curve showed that the area

under the curve (AUC=0.809) of urine NGAL for the early diagnosis of IgA nephropathy was larger than that of urine KIM-1 (AUC=0.746). In Spearman's correlation analysis, urine NGAL of IgA nephropathy patients showed a positive correlation with urine KIM-1, N-acetyl- $\beta$ -D-glucosaminidase (NAG), retinol binding protein (RBP),  $\alpha$ 1-microglobulin ( $\alpha$ 1-MG), serum creatinine (SCr) and 24-h urine protein quantitation ( $P<0.05$ ), and a negative correlation with estimated glomerular filtration rate (eGFR) ( $P<0.05$ ). Kaplan-Meier survival analysis showed that the cumulative renal survival rate of patients with IgA nephropathy in the urine high level group of NGAL was lower than that in the urine low level group of NGAL ( $P<0.05$ ), and the cumulative renal survival rate of patients with IgA nephropathy in the severe tubulointerstitial injury group was lower than that in the mild and moderate tubulointerstitial injury groups ( $P<0.05$ ).

**Conclusion** The detection of urinary NGAL has certain clinical application value in the early diagnosis and prognostic evaluation of IgA nephropathy.

**Keywords:** IgA nephropathy; Neutrophil gelatinase-associated lipocalin; Kidney injury molecule-1; Early diagnosis; Cumulative survival rate of kidney

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IgA 肾病是截止目前我国接受肾穿刺活检的患者中最常见的一种原发性肾小球疾病,其占比可高达 58.2%<sup>[1-3]</sup>。IgA 肾病发病机制复杂,临床表现多样,病理表现以系膜区免疫球蛋白沉积为特征,临床表现以血尿最为突出,该病从最初被认为是一种良性疾病发展至现在被认为是一种慢性进展性疾病,IgA 肾病患者在肾活检确诊后 20 年内有 30%~40% 的患者进展至终末期肾病(ESRD)<sup>[4-5]</sup>。目前 IgA 肾病是导致我国慢性肾脏病(CKD)的主要原因之一,因此,找到可以早期识别疾病及预测疾病进展的标志物,帮助临床医生早期准确的判断病理损伤程度及预后,对进展风险大的患者尽早干预,有助于延缓疾病进展和减少 ESRD 的发生。临床上,在 IgA 肾病患者的肾活检组织中发现除了有最基本的肾小球病理改变外常常还可见肾小管间质损伤的病理改变,且伴有肾小管间质损伤患者的远期预后相对较差,尿中性粒细胞明胶酶相关脂质运载蛋白(urinary neutrophil gelatinase-associated lipocalin,NGAL)作为肾小管间质损伤的标志物之一,其在急性肾损伤中的作用已被广泛研究,但关于其在 IgA 肾病中作用的研究相对较少<sup>[6]</sup>。因此,本研究拟通过对患者的临床病理资料及随访资料进行分析,探讨尿 NGAL 检测在 IgA 肾病早期诊断及预后评估方面的作用。

## 1 资料与方法

**1.1 一般资料** 本研究为单中心、回顾性研究。本课题组共收集 2017 年 3 月至 2018 年 7 月于山西医科大学第二医院行肾穿刺活检诊断为 IgA 肾病的患者 53 例。纳入标准:(1) 在山西医科大学第二医院行肾穿刺活检经组织病理学确诊为原发性 IgA 肾病;(2) 确诊时估算肾小球滤过率(eGFR) $>15$  ml/

(min $\cdot$ 1.73 m<sup>2</sup>);(3) 临床基线资料完整。排除标准包括:(1) 临床基线资料不完善;(2) 继发性和遗传性肾脏疾病,如乙型病毒性肝炎、过敏性紫癜、银屑病、甲状腺疾病、系统性红斑狼疮、肝炎后肝硬化、干燥综合征等;(3) 确诊时血清肌酐(SCr) $>445$   $\mu$ mol/L;(4) 随访时间 $<1$  年。最终 39 例 IgA 肾病患者(男性 21 例,女性 18 例)符合入组标准作为病例组,选取同期健康体检者 55 例(男 28 例,女 27 例)作为对照组。此外,按肾小管间质损伤程度将病例组患者分为轻度组 13 例,中度组 13 例,重度组 13 例;按尿 NGAL 中位数将病例组患者分为尿 NGAL 高水平组 19 例,尿 NGAL 低水平组 20 例。研究获得本院伦理委员会的批准[批件号:(2019)YX(069)号]。

### 1.2 方法

**1.2.1 临床资料收集** 记录所有纳入对象的基本资料,包括年龄、性别、BMI;病例组记录肾穿前相关实验室指标,包括 24 h 尿蛋白定量、尿 N-乙酰- $\beta$ -D-氨基葡萄糖苷酶(NAG),尿视黄醇结合蛋白(RBP),尿  $\alpha$ 1-微球蛋白( $\alpha$ 1-MG)及血清肌酐(SCr)。

**1.2.2 尿 NGAL、尿肾损伤分子-1(KIM-1)检测** 所有对象于检验当日留取合格尿标本(清洁中段晨尿 10 ml),尿标本离心留取上清液后,严格按照试剂盒(试剂盒购自上海西唐生物科技有限公司)说明书,采用 ELISA 法检测尿 NGAL 及 KIM-1 水平。

**1.2.3 肾脏病理** 所有肾组织标本均通过经皮穿刺活检获得。标本固定、脱水、透明、浸蜡等处理,再将标本包埋在石蜡中,然后切成 4  $\mu$ m 切片,切片用 HE、PAS、过碘酸六胺银(PASM)、马松三色(Masson)染色并行光镜、电镜及免疫荧光检查。最终组织病理学结果由本院病理科诊断判定。参照 Banff 病理分级标准将 IgA 肾病患者按照肾小管间质损伤面积占

比分为3组:0%~5%(轻度组),6%~25%(中度组),>25%(重度组)。

1.2.4 随访及终点事件 IgA 肾病患者肾脏穿刺出院后进行门诊、电话等方式随访,随访时间为肾脏穿刺日至截止日期或发生终点事件的时间。本研究随访截止日期为2021年12月31日,随访内容主要为SCr水平,随访过程中若出现复合终点事件则随访终止。本研究的复合终点为ESRD发生及SCr较基线翻倍。肾脏累积存活率=T时刻仍未发生复合终点事件的患者数/观察总患者数(即患者自观察之日起经历了T个单位时间后仍未发生复合终点事件的概率)。

1.3 统计学方法 所有分析使用SPSS 25.0软件进行。正态分布的计量资料以 $\bar{x}\pm s$ 表示,两组间比较采用两独立样本t检验;非正态分布的计量资料以中位数(下四分位数,上四分位数) $[M(Q_L, Q_U)]$ 表示,两组间和三组间比较分别采用Mann-Whitney U检验和Kruskal-Wallis检验;计数资料以例数表示,组间比较采用 $\chi^2$ 检验;相关性分析采用Spearman检验;评价诊断效能用ROC曲线分析;对不同尿NGAL水平组间和不同肾小管损伤程度组间肾脏累积存活率采用Kaplan-Meier生存分析,比较采用log-rank检验。 $P<0.05$ 为差异有统计学意义。

## 2 结果

2.1 病例组与对照组基线资料及尿NGAL水平比较 病例组与对照组基线资料比较差异无统计学意义( $P>0.05$ )。病例组患者的尿NGAL水平较对照组显著升高( $P<0.01$ )。见表1。

2.2 尿NGAL、KIM-1对IgA肾病早期诊断的ROC曲线 绘制尿NGAL与尿KIM-1对IgA肾病早期诊断的ROC曲线,发现尿NGAL曲线下面积(AUC)大于尿KIM-1,其中尿NGAL早期诊断的AUC为0.809,约登指数为0.497,截断值为11.359,灵敏度为89.7%,特异度为60.00%;尿KIM-1早期诊断的AUC为0.746,约登指数为0.450,截断值为0.072,灵敏度为79.50%,特异度为65.50%。见图1。

2.3 IgA肾病患者中不同程度肾小管间质损伤组间尿NGAL水平比较 NGAL水平依肾小管间质损伤轻度→中度→重度递升,差异有统计学意义( $P<0.05$ )。见表2。

2.4 尿NGAL与临床各指标间的相关性分析 Spearman秩相关性分析发现,在IgA肾病患者中,尿NGAL与尿中KIM-1、RBP、 $\alpha$ 1-MG、NAG和血清Scr、

24h尿蛋白定量均呈正相关关系( $r=0.328、0.499、0.375、0.533、0.558、0.377, P<0.05$ ),而与eGFR呈负相关关系( $r=-0.574, P<0.05$ )。

2.5 IgA肾病患者中不同尿NGAL水平组的肾脏累积存活率分析 对39例IgA肾病患者通过电话、门诊长期随访,其中9例患者出现终点事件(尿NGAL高水平组8例,尿NGAL低水平组1例)。Kaplan-Meier分析显示,尿NGAL低水平组的肾脏累积存活率显著高于尿NGAL高水平组( $\chi^2=5.660, P<0.05$ )。见图2。

2.6 IgA肾病患者中不同程度肾小管间质损伤组的肾脏累积存活率分析 Kaplan-Meier分析显示,不同程度肾小管间质损伤组间肾脏累积存活率比较差异有统计学意义( $\chi^2=9.448, P<0.05$ ),其中重度肾小管间质损伤组的肾脏累积存活率显著偏低。见图3。

表1 病例组与对照组基线资料及尿NGAL水平比较  
Tab.1 Comparison of baseline data and urine NGAL levels between case group and control group

组别	例数	男/女 (例)	年龄 (岁, $\bar{x}\pm s$ )	BMI ( $\bar{x}\pm s$ )	尿NGAL [ng/ml, $M(Q_L, Q_U)$ ]
病例组	39	21/18	36.36 $\pm$ 14.60	24.00 $\pm$ 3.65	35.18(12.98, 68.18)
对照组	55	28/27	38.33 $\pm$ 13.29	24.09 $\pm$ 3.68	9.20(6.13, 19.46)
$\chi^2/t/Z$ 值		0.08	0.68	0.12	5.09
P值		0.78	0.50	0.91	<0.01

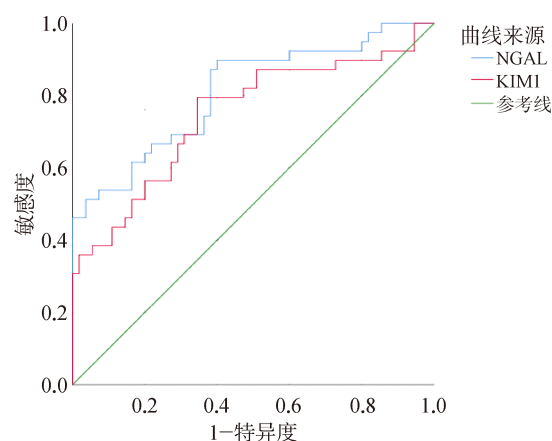


图1 尿NGAL与尿KIM-1对IgA肾病早期诊断的ROC曲线  
Fig.1 ROC curve of urinary NGAL and urinary KIM-1 in early diagnosis of IgA nephropathy

表2 不同程度肾小管间质损伤组间尿NGAL水平比较  
Tab.2 Comparison of urinary NGAL levels among groups with different degrees of tubulointerstitial injury

组别	例数	尿NGAL[ng/ml, $M(Q_L, Q_U)$ ]
轻度组	13	12.66(6.57, 13.37)
中度组	13	35.18(24.45, 42.38) <sup>a</sup>
重度组	13	82.33(67.98, 99.22) <sup>ab</sup>
H值		33.41
P值		<0.01

注:与轻度组比较,<sup>a</sup> $P<0.05$ ;与中度组比较,<sup>b</sup> $P<0.05$ 。

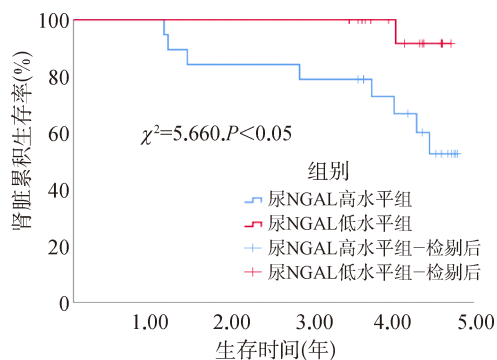


图2 不同尿 NGAL 水平组 IgA 肾患者的肾脏累积存活率比较

Fig. 2 Comparison of cumulative renal survival rate of IgA nephropathy patients with different urinary NGAL levels

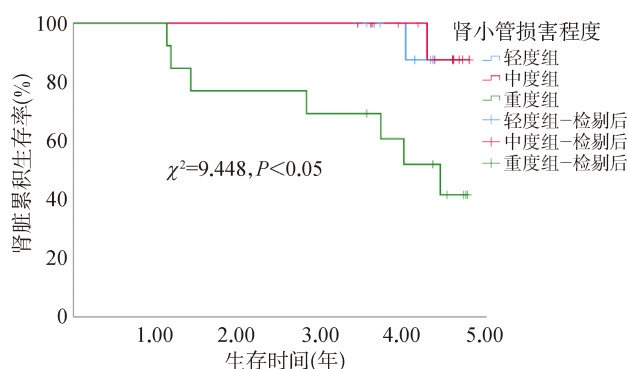


图3 不同程度肾小管间质损伤组 IgA 肾患者的肾脏累积存活率比较

Fig. 3 Comparison of cumulative renal survival rate of IgA nephropathy patients with different degrees of tubulointerstitial injury

### 3 讨论

IgA 肾病是一种在系膜区可见广泛 IgA 沉积的肾小球疾病,其常伴有肾小管间质的损伤,其发病机制复杂,临床表现高度可变,疾病的发生与发展受到多种因素影响<sup>[7-10]</sup>。既往研究表明,肾小管间质损伤与 IgA 肾病的病情进展相关,而 NGAL 作为肾小管间质损伤最具有代表性的标志物之一,近来也被认为与 IgA 肾病的发生与发展相关<sup>[11-13]</sup>。

NGAL 是一种在活化中性粒细胞中被发现的载脂蛋白,生理状态下其在肾组织中呈现低表达状态,可被肾小球自由滤过并经肾小管大量重吸收,因此,一般情况下尿液中仅存在极低水平的 NGAL<sup>[14]</sup>。然而当肾组织出现缺血、毒性或炎性损伤时,尿液中会出现大量的 NGAL,这可能与肾小管上皮细胞的合成分泌增加及近端小管的重吸收受损有关<sup>[14-15]</sup>。既往研究表明,NGAL 对急性肾损伤的早期诊断及损伤后肾脏的转归具有预测作用<sup>[16-17]</sup>。NGAL 在预测 CKD 进展中的作用也得到证实<sup>[18-19]</sup>。然而,NGAL 在预测 IgA 肾病进展中的作用尚存在争议<sup>[13,20]</sup>。

已有研究证明尿 KIM-1 对 IgA 肾病的早期诊断及预后评估具有重要价值<sup>[21]</sup>。本研究 IgA 肾病患者尿液中 NGAL 水平较健康对照组显著升高,ROC 曲线分析发现,与尿 KIM-1 相比,尿 NGAL 对 IgA 肾病有更高的早期诊断效能。尿 KIM-1、NAG、RBP 及  $\alpha$ 1-MG 均是肾小管间质损伤的重要标志物<sup>[22]</sup>。本研究 Spearman 相关性分析发现,尿 NGAL 与这四种生物标志物存在显著相关性,且尿 NGAL 水平随着肾小管间质损伤程度的加重显著升高,再次验证了尿 NGAL 与肾小管间质损伤之间的相关关系。相关性分析还发现尿 NGAL 与 24 h 尿蛋白定量、血清肌酐呈正相关,与 eGFR 呈负相关,而尿蛋白及基础肾功能均被认为与 IgA 肾病的预后相关。Kaplan-Meier 生存曲线分析发现,重度肾小管间质损伤组患者的肾脏累积存活率显著低于轻中度损伤患者,尿 NGAL 高水平患者的肾脏累积存活率较尿 NGAL 低水平患者显著降低,因此,肾小管间质损伤对 IgA 肾病的预后具有预测价值,高水平尿 NGAL 与 IgA 肾病的不良预后相关。

本研究尚存在一定的局限性。首先,本研究案例来源单一,样本数量有限,仅对患者进行了一次尿 NGAL 的检测,缺少随访过程中的再次检测。其次,随访时间相对较短,且随访过程中未能进一步排除药物等因素干扰。因此,还需要更多高质量随访研究来确定尿 NGAL 与 IgA 肾病预后之间的确切关系。

综上所述,尿 NGAL 检测在 IgA 肾病的早期诊断及预后评估方面均具有一定的临床应用价值。

利益冲突 无

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