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· 临床研究 ·

血清胱抑素 C 作为新型肾功指标在狼疮肾炎中的临床意义 *

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摘要 目的: 探讨血清胱抑素 C 在狼疮肾炎的诊断及治疗监测中的临床意义。**方法:** 检测 106 名狼疮肾炎患者的血清胱抑素 C (sCysC)、血清肌酐(sCr)、尿素氮(BUN)、肾小球滤过率(GFR), 24 小时尿蛋白(uTP)、血清白蛋白(sAlb)、C- 反应蛋白(CRP)水平, 分析 sCysC 与上述指标的相关性及其在治疗过程中的动态变化, 并与传统肾功能指标(sCr、BUN)进行比较。**结果:** ① 治疗前, 血清 sCysC 水平与 uTP、sAlb、SLEDAI、CRP 均显著相关, 且优于 sCr 及 BUN。② 治疗中, 血清 sCysC 水平与 uTP、sAlb 的相关性均优于 sCr 及 BUN。③ 血清 sCysC 水平随激素及免疫抑制剂治疗显著改善, 这一趋势见于 BUN 并未见于 sCr; 激素及 CTX 治疗结束后, 血清 sCysC 水平显著改善, 这一趋势见于 sCr 并未见于 BUN。④ 治疗前, sCr 与 sCysC 联合计算所得 eGFR 与各项指标相关性最高。**结论:** sCysC 在狼疮肾炎早期肾损害诊断、治疗过程以及监测疗效的敏感性均优于传统 sCr 和 BUN。sCysC 单独及 sCysC 联合 sCr 计算的 GFR 均优于单独 sCr 计算获得的 GFR。sCysC 在 LN 中不仅可作为肾功能的新评价标志物, 可能也作为炎症反应的标志物。

关键词: 系统性红斑狼疮; 狼疮肾炎; 胱抑素 C; 诊断治疗标志物

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Clinical Significance of sCysC as A New Renal Function Evaluation Index in Lupus Nephritis*

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ABSTRACT Objective: To explore the clinical significance of sCysC in the diagnosis, treatment and monitoring of lupus nephritis.

Methods: 106 patients with lupus nephritis confirmed by renal biopsy were selected from the department of Nephrology of affiliated Hospital of China Medical University from May 2007 to December 2014. The renal function indexes (sCysC, sCr, BUN, GFR), nephritis activity indexes (uTP, sAlb), systemic disease activity indexes (SLEDAI), immune inflammatory response indexes (C3, C4, IgG, ANA, dsDNA, ESR and CRP) of patients with lupus nephritis were detected, the correlation between sCysC and lupus activity, nephritis activity, dynamic changes in the treatment process were analyzed and compared with the traditional renal function index. **Results:** ① sCysC was significantly correlated with uTP, sAlb, SLEDAI and CRP, and the correlation was better than sCr and BUN. ② In the process of treatment, the correlation between sCysC and UTP, sAlb is better than that of sCr and BUN. ③ The level of sCysC improved significantly with the treatment of hormone and immunosuppressant, which was found in BUN but not in sCr, while the level of sCysC improved significantly at the end of treatment of hormone and CTX, which was also found in the sCr but not in the BUN. ④ eGFR based on combination of sCysC and sCr before treatment showed strongest correlation with other indicators, and the eGFR based on sCysC during treatment showed stronger correlation with other indicators. ⑤ Before treatment, 60.6% of the patients with normal sCr had a rise in serum sCysC, while 69.6% of the patients with normal sCr had a rise in sCysC, suggesting that sCysC could respond to the decline of renal function earlier than sCr. **Conclusions:** sCysC has better sensitivity in early renal damage, process of treatment and monitoring of therapeutic effect than sCr and BUN. eGFR based on sCysC or combination of sCysC and sCr calculation presented a better correlation with renal and systemic disease activity.

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ties. sCysC can be used not only as a new marker of renal function, but also as a marker of inflammatory response in LN.

Key words: Systemic lupus erythematosus; Lupus nephritis; Cystatin C; Diagnostic-therapeutic biomarker

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前言

系统性红斑狼疮(SLE)是一种可引起多脏器损害的自身免疫性疾病^[1,2],尤以肾脏损伤最为常见^[3],狼疮肾炎(LN)所致的肾功能衰竭是 SLE 患者最常见的死亡原因之一^[4,6]。选择理想的指标对 LN 早期肾损伤的早期诊断与及时治疗是改善 SLE 患者预后,降低病死率的关键环节^[7]。血清胱抑素 C(sCysC)是近十几年发现的反映肾功能下降的新型诊断标志物^[8-11]。在慢性肾脏病中,尤其是原发性肾脏病中,其敏感性被认为高于传统肾功能评价指标肌酐(sCr)及血尿素氮(BUN)^[12]。然而,胱抑素 C 在继发性狼疮肾炎患者中的临床应用罕见报道。

Silva 等的报道指出胱抑素 C 的水平不受激素治疗的影响^[13]。Chew 等发现 sCysC 与高敏 C 反应蛋白(CRP)独立相关,认为胱抑素 C 可能受炎症反应的影响^[14]。Gheita 等通过研究证实了 sCysC 与肾损害指数、肾活检分级显著相关,与血清白蛋白呈负相关,并认为 sCysC 有助于预测肾活检级别^[15]。本研究回顾性分析了狼疮肾炎患者的临床资料,旨在探讨 sCysC 在 LN 的诊断及治疗监测中的临床意义。

1 资料与方法

1.1 一般资料

选取 2007 年 5 月至 2014 年 12 月中国医科大学附属第一医院肾内科收治的 106 名经肾活检证实为狼疮肾炎患者,肾活检病理分型依据 2003 年 ISN/ACR 分类标准。其中,男 17 例,女 89 例,年龄 10~70 岁,平均 34.6 ± 1.3 岁。病程 2~64 个月不等。随访记录完整患者为 65 人,治疗方式包括激素联合环磷酰胺治疗,激素联合其他免疫抑制剂(FK506,骁悉,雷公藤,来氟米特等)治疗。

1.2 数据收集与分析

收集治疗前患者的肾功能指标:sCysC、sCr、BUN、肾小球滤过率(eGFR),肾炎活动指标:24 小时尿蛋白(uTP)、血清白蛋白(sAlb),系统疾病活动指标 SLEDAI,免疫炎症反应指标:补体 C3(C3)、补体 C4(C4)、免疫球蛋白 G(IgG)、抗核抗体(ANA)、双链 DNA(dsDNA)、红细胞沉降率(ESR)和 CRP 等数据。并收集治疗过程中 1、3、6、12、24 个月 sCysC、sCr、BUN、uTP、sAlb 和 SLEDAI 的变化。进行如下数据分析:1)治疗前及治疗中肾功能指标(sCysC、sCr、BUN、eGFR)与系统疾病活动及肾脏病活动指标的相关性;2)sCysC 随着激素及各种免疫抑制剂治疗的动态变化(免疫抑制剂包括 CTX 及上述其他各种免疫抑制剂);3)sCysC 在激素及 CTX 治疗前及治疗终止时表达。

1.3 统计学方法

采用 GraphPad Prism 8 软件用于数据统计学分析。指标相关性分析采用 Pearson 检验,治疗前后各检测指标两组间差异采用配对 t 检验。治疗前后各检测指标多组间差异采用 One-way ANOVA。以 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 治疗前 sCysC 与 sCr 及 BUN 的相关性比较

在治疗前,sCysC 不仅与肾炎活动性(uTP、sAlb)明显相关,而且与 SLE 活动指数(SLEDAI)、系统炎症反应(CRP)明显相关($P < 0.05$),且 sCysC 与 uTP、sAlb、SLEDAI、CRP 的相关性均优于 sCr 及 BUN。但 sCysC 与 C3、C4、IgG、ANA、DsDNA 及 ESR 无明显相关性(数据未显示)。该结果提示 sCysC 可能作为 LN 早期肾脏损害及 SLE 活动评估的更为敏感及准确的指标,见图 1。

2.2 治疗中 sCysC 与 sCr 及 BUN 的相关性分析

在 LN 激素及免疫抑制剂治疗过程中,sCysC 与 uTP、sAlb、SLEDAI 均显著相关($P < 0.05$),且 sCysC 与 uTP、sAlb 的相关性均优于 sCr 及 BUN,但是与 SLEDAI 相关性未见优势,果提示在 LN 治疗监测过程中,sCysC 较 sCr 和 BUN 更能反映肾脏病的活动情况,但是受 SLE 系统活动指标影响较小,见图 2。

2.3 激素及免疫抑制剂治疗所致的 sCysC 的动态变化

反映 LN 活动的指标(uTP、sAlb、SLEDAI)随着激素及免疫抑制剂治疗各阶段显著改善($P < 0.05$),sCysC 水平随激素及免疫抑制剂治疗各阶段显著改善($P = 0.0043$),这一趋势也略见于 BUN($P = 0.0207$)但并未见于 sCr($P = 0.099$),提示 sCysC 在对 LN 治疗效果监测上要优于 sCr,见图 3。

2.4 激素及 CTX 治疗前后血清 sCysC 水平的比较

激素及 CTX 治疗后反映 LN 活动的指标(uTP、sAlb、SLEDAI)及血清 sCysC 水平均显著改善($P < 0.05$),这一趋势也见于 sCr($P = 0.0017$)并未见于 BUN($P = 0.0717$)(图 4)。此结果提示 sCysC 在对 LN 激素联合环磷酰胺治疗优于 BUN,结果表明 sCysC 在监测 LN 治疗效果上有着更好的稳定性,见图 3、图 4。

2.5 sCysC、sCr 及二者联合所得 eGFR 相关性分析

eGFR(EPI-Cr)与 uTP、sAlb、SLEDAI、CRP 均无相关性($P > 0.05$);eGFR(EPI-sCysC)与 sAlb、SLEDAI、CRP 均有相关性,但与 uTP 无相关性;eGFR(EPI-Cr+sCysC)与 uTP、sAlb、SLEDAI、CRP 均相关($P < 0.05$),且相关性优于 EGFR(EPI-sCysC)(图 5)。该结果表明在治疗前,使用 sCr 及 sCysC 联合计算的 eGFR 来评估 LN 患者的肾功能,能更好的判断肾脏病活动情况,见图 5。

3 讨论

SLE 患者约有 50%~70%累及肾脏,占女性继发性肾小球疾病的首位^[16,17]。早期发现 SLE 的肾脏损伤及时使用激素与免疫抑制剂治疗,逆转肾脏的病理进程进而延缓 ESRD 的发展达到提高患者生存率^[18,19]。大量研究显示 sCysC 作为肾清除率的指标优于 sCr 及 BUN^[20,21]。目前,临床常用的反映肾小球功能的指标是 BUN 和 sCr。BUN 首先被作为肾功能的评价指标,但它不符合内源性 eGFR 标志物的要求,当 eGFR 减少到正常值的 40%以前,BUN 水平升高缓慢,并且与外源性(来源于蛋白质摄

入)及内源性(来源于感染、肾上腺皮质激素的应用、胃肠出血等)的尿素负荷大小有关,更重要的是肾小管对 BUN 有明显的被动重吸收作用。肌酐基本符合内源性 GFR 标志物的要求,目前国内外用 sCr 作为临床常规评估肾小球滤过功能受损的指

标。但只有当 GFR 由正常下降至 1/2 时,sCr 才有明显变化,而且受性别、饮食、肌肉量等因素的影响。因此,BUN 和 sCr 只能反映中、重度的肾功能损害^[22,23]。

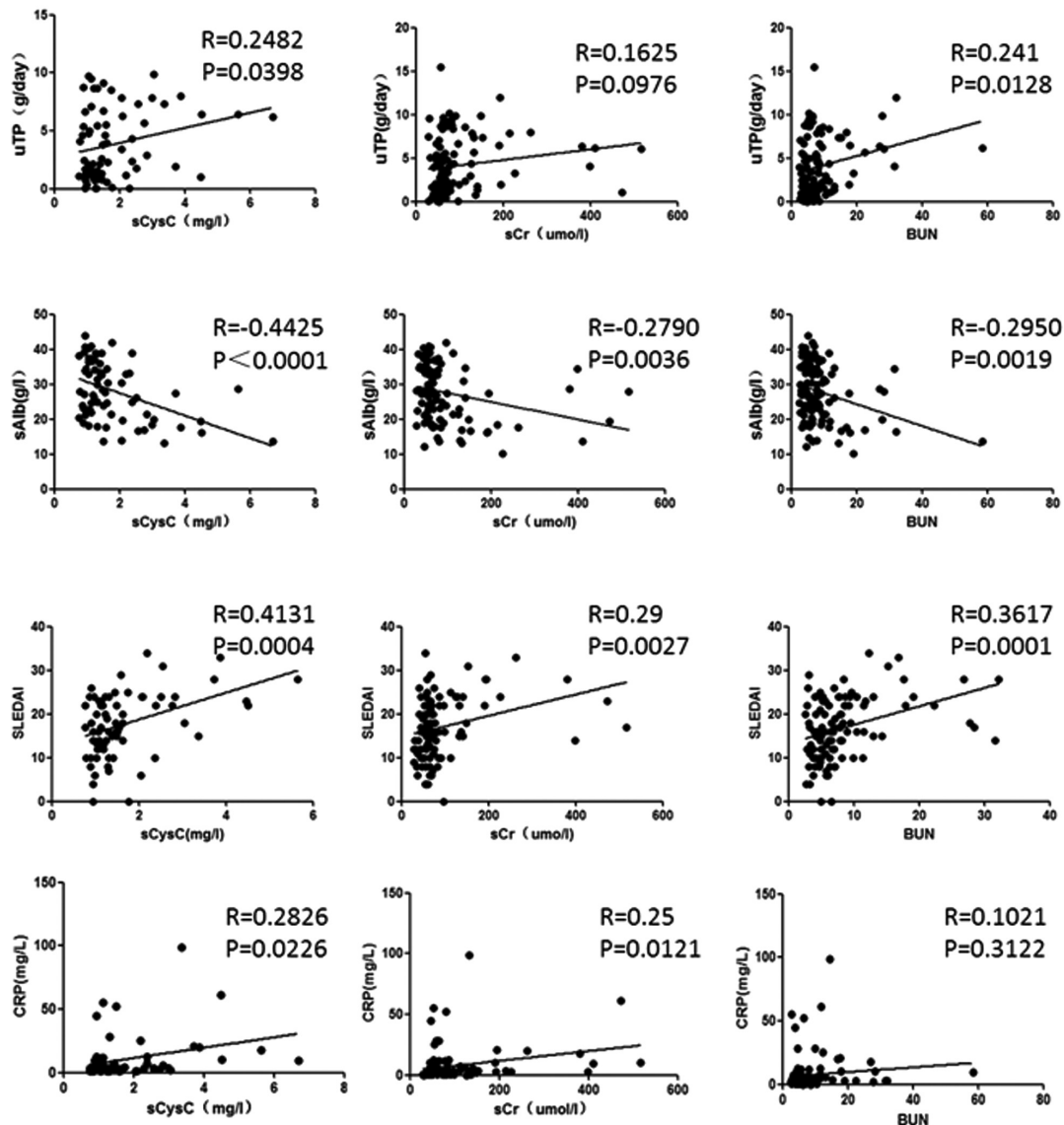


图 1 治疗前 sCysC 与 sCr 及 BUN 的相关性分析

Fig.1 Comparison of sCysC with sCr and BUN in the correlation efficiency with disease activity of lupus nephritis(pre-treat)

Correlations between indexes of renal function(sCysC, sCr, BUN) and disease activity(uTP, sAlb, SLEDAI, CRP) before treatment are showed above. Data are presented as scatterplot. sCysC is positively correlated with uTP, SLEDAI and CRP, but negatively correlated with sAlb.sCysC also presented higher R value in the correlations with uTP, sAlb, SLEDAI and CRP than sCr and BUN.

sCysC 是一种半胱氨酸蛋白酶抑制剂,也被称为 γ -微量蛋白或 γ -后球蛋白,广泛存在于各种组织的有核细胞和体液中,是一种相对分子质量低、碱性非糖基化蛋白质,相对分子质量为 13.3KDa,由 122 个氨基酸残基组成,可由机体所有有核细胞产生,产生率恒定。其等电点高(PI=9.3),在血液环境中带正电荷,故不受肾小球滤过膜的孔径屏障和电荷屏障的影响,可自由通过肾小球滤过膜而被清除,是一种反映 GFR 变化的内源性标志物。sCysC 在近曲小管重吸收,但重吸收后被完全代谢分解,不返回血液。因此,其在血液中的水平由肾小球滤过决定,而不依赖任何外来因素,如性别、年龄、饮食的影响,是一

种反映 GFR 变化的理想同源性标志物^[24-28]。在双侧输尿管梗阻的小鼠模型中,sCysC 随着肾积水的加重而增加,更能反映肾功能的变化^[29]。sCysC 能在盲肠结扎穿刺诱导的败血症小鼠中早期检测急性肾损伤和更好地反映 eGFR^[30]。在糖尿病患者中,sCysC 是其进展为糖尿病肾病的早期预测指标, cysC 阈值为 0.91 mg/L 可作为中国人早期 DN 的诊断标准^[31,32]。但是 sCysC 对 LN 肾损害中的早期诊断和治疗监测效果罕见报道。本研究旨在探索 sCysC 在 LN 中的临床应用价值。

sCysC 与其他指标相关性分析结果显示在治疗前,sCysC 与 uTP、sAlb、SLEDAI、CRP 相关性均优于 sCr 及 BUN,但与

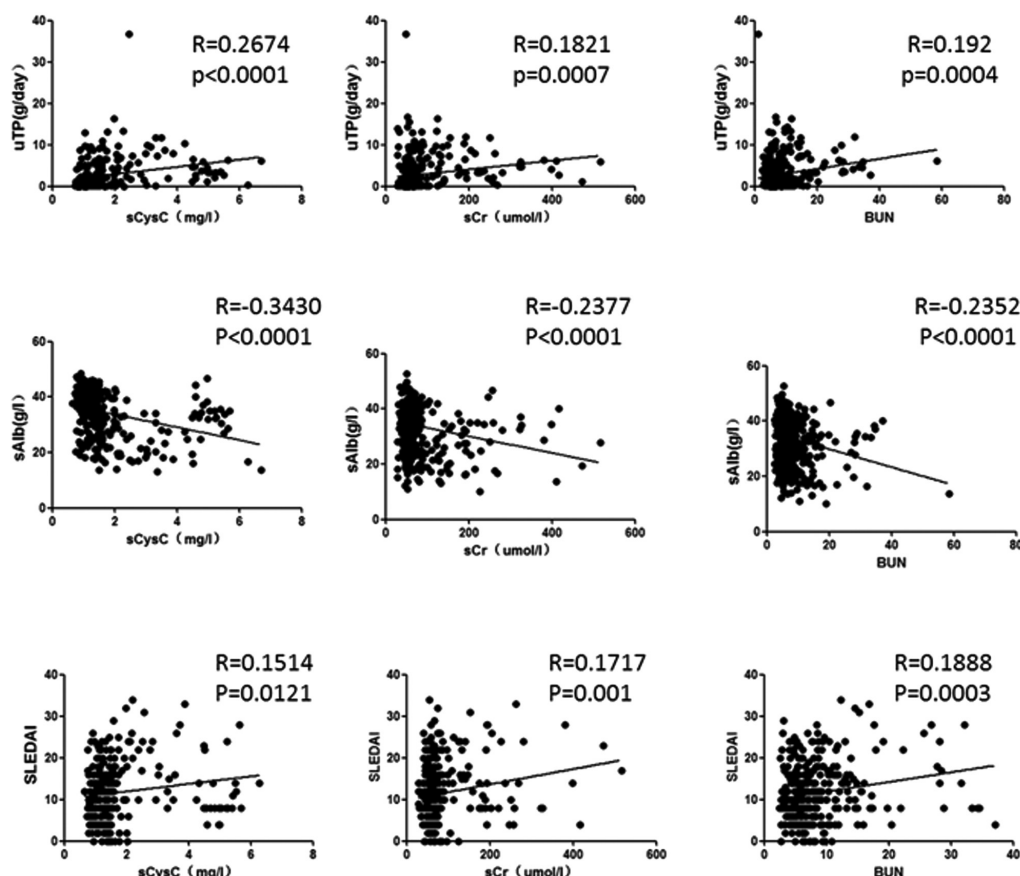


图2 治疗中 CysC 与 sCr 及 BUN 的相关性分析

Fig.2 Comparison of sCysC with sCr and BUN in the correlation efficiency with disease activity of lupus nephritis(During treatment)

Correlations between indexes of renal function(sCysC, sCr, BUN) and disease activity(uTP, sAlb, SLEDAI, CRP) during treatment are showed above. sCysC are positively correlated with uTP and SLEDAI, and negatively correlated with sAlb. sCysC also presented higher R value in the correlations with uTP and sAlb than sCr and BUN, but didn't show superiority in SLEDAI.

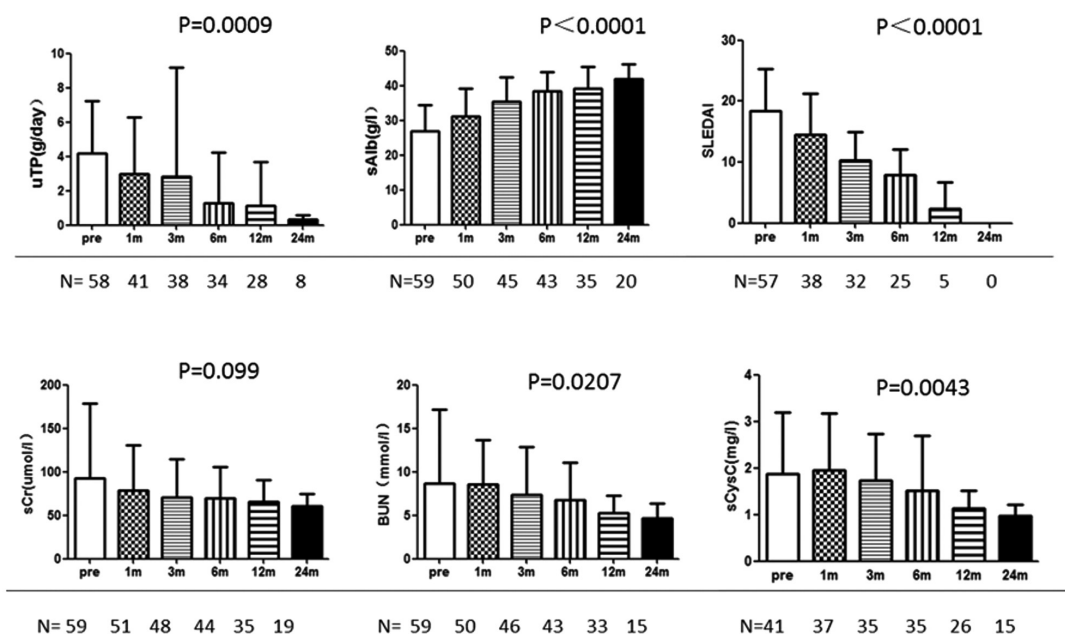


图3 sCysC 随着激素及免疫抑制剂治疗的动态变化

Fig.3 Dynamic changes of renal function along with steroid and immunosuppressants

The changes of disease activity and renal function at different phases were showed above. Data were collected before treatment and after 1,3,6,12 and 24 months. All the indicators of disease activity were significantly improved after after hormones and immunosuppressive therapy ($P < 0.05$). sCysC level was significantly decreased at each stage after hormones and immunosuppressive therapy ($P = 0.0043$), this trend is seen in BUN ($P = 0.0207$) but not found in Scr ($P = 0.099$).

LN 的免疫指标 C3、C4、IgG、ANA、DsDNA 无明显相关性。当加入治疗随访数据后, sCysC 与 uTP、sAlb 的相关性均优于 sCr 及 BUN, 但与 SLEDAI 相关性未见优势。由于 uTP、sAlb 可反映 LN 疾病活动情况, SLEDAI 可反映 SLE 系统疾病活动, 说

明 sCysC 在 LN 中与肾脏病活动指数及系统疾病活动指数显著相关, 且相关性优于血 BUN 和 Scr。同时, sCysC 与 CRP 相关而与免疫指标无相关性, 说明 sCysC 可能与 LN 的系统炎症反应有关, 但与 LN 的免疫反应无关。

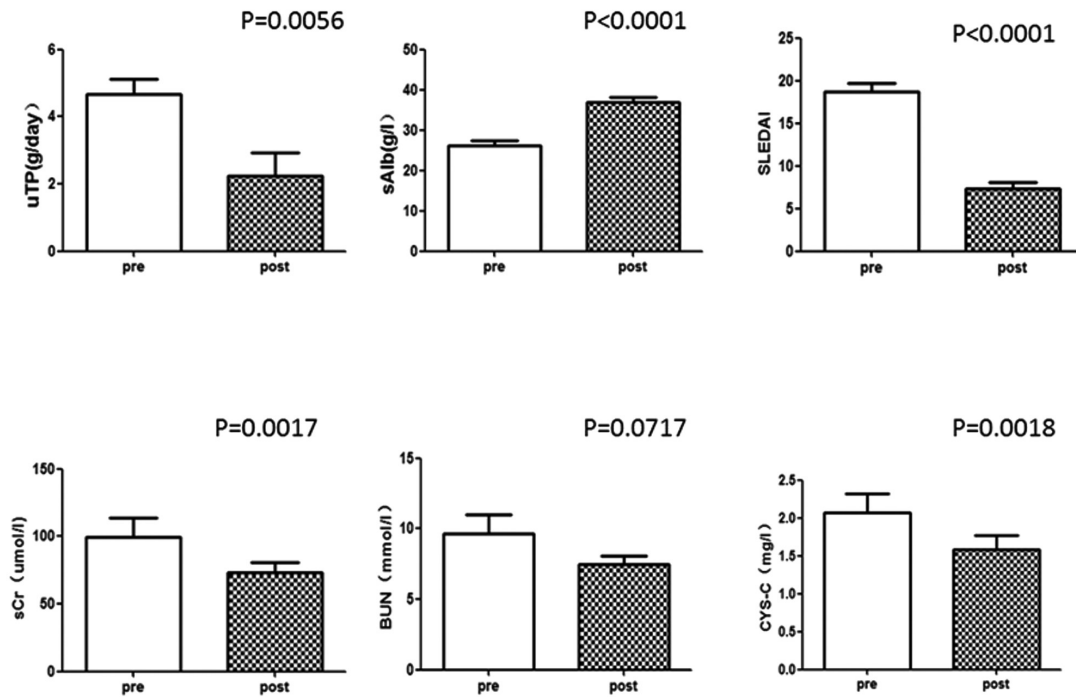


图4 激素及 CTX 治疗前后血清 sCysC 水平的比较

Fig.4 Changes of sCysC and traditional biomarkers before and after CTX treatment

Indicators before and after the treatment of hormones and the end of CTX are shown in the bar charts above. uTP, sAlb, SLEDAI, sCysC and sCr all significantly improved after hormones and the end of CTX treatment ($P < 0.05$). sCysC levels were significantly decreased after hormones and the end of CTX treatment ($P = 0.0018$), this trend is also seen in Scr ($P = 0.0017$) but not seen in BUN ($P = 0.0717$).

本研究还观察了 sCysC 在 LN 治疗效果监测中的意义, 结果显示血清 sCysC 水平无论在激素联合不同种类免疫抑制剂还是激素联合 CTX 治疗前后都显著改善, 而 BUN 在免疫抑制剂组治疗后显著改善, 在 CTX 组无明显改善; sCr 在 CTX 组治疗后显著改善, 而在免疫抑制剂组无明显改善。这表明 sCysC 在监测 LN 治疗效果上有着更好的稳定性。在由 sCysC、sCr 及二者结合计算所得 eGFR 与 LN 及系统性疾病相关性分析中, 我们发现在治疗前, 使用 sCr 及 sCysC 联合计算的 eGFR 来评估 LN 患者的肾功能, 能更好的判断肾脏病活动情况, 从而更好的指导治疗。在 LN 治疗效果监测过程中, 单用 sCysC 计算的 eGFR 评估肾功能更能反映肾脏病及系统性疾病活动情况。在 71 名 sCysC 和 sCr 同时检测的患者中, 当 sCysC 开始升高时(上限 0.95 mg/L), sCr 正常(上限 104 μmol/L)的患者有 43 人, 占 60.6%(图 7a)。在治疗过程中, 所有 sCysC 和 sCr 同时检测的 299 对数据中, 当 sCysC 升高时, sCr 正常的有 208 例, 占 69.6%(图 7b)。这表明 sCysC 反映肾功能早期损伤的敏感度较 sCr 高, 即在没采用 sCysC 测定肾功能之前, 会有 60%左右已经有肾功能损害的患者会被漏诊。错过患者治疗的最佳时机是造成 LN 病情恶化的主要原因, 早期根据 sCysC 升高给予治疗方案可能改善 LN 患者的预后。

综上所述, sCysC 在狼疮肾炎早期肾损害诊断, 治疗过程中监测疗效的敏感性均优于传统 sCr 和 BUN, 应用 sCysC 水平

对狼疮肾炎开始早期干预治疗、监测疗效决定减药停药时机的指导意义值得临床医生高度重视。同时, 结合 sCysC 计算 eGFR 可能更准确地反映肾小球滤过率, sCysC 在 LN 中不仅可作为肾功能的新型评价标志物, 可能也作为炎症反应的标志物。

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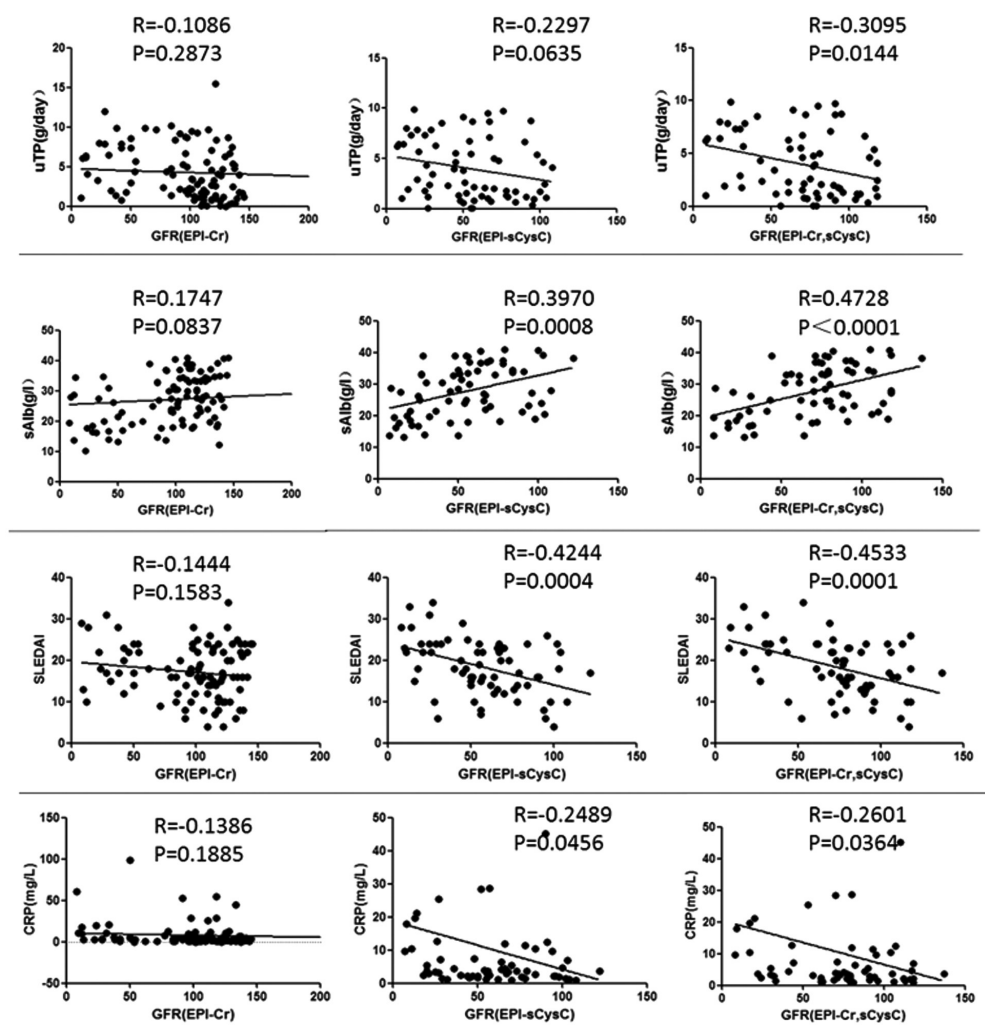


图5 由 sCysC、sCr 及二者结合计算所得 GFR 相关性分析

Fig.5 Comparison of eGFR (calculated by three equations: sCysC alone, sCr alone, combined sCysC and sCr) in correlation efficiency with disease activity of lupus nephritis (pre-treat)

GFR(EPI-Cr) presented no correlations with uTP, sAlb, SLEDAI and CRP ($P > 0.05$); GFR(EPI-sCysC) showed correlations with sAlb, SLEDAI and CRP, but showed no correlation with uTP; GFR(EPI-Cr, sCysC) presented higher R value in the correlations with uTP, sAlb, SLEDAI and CRP.

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