

doi: 10.13241/j.cnki.pmb.2014.28.028

胱抑素在肾综合征出血热患者中的动态变化及意义

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摘要 目的:观察肾综合征出血热(HFRS)患者血清胱抑素的动态变化,并探讨其临床意义。方法:选取2010年10月至2013年06月哈尔滨医科大学附属第二医院感染科住院肾综合征出血热患者106例为研究对象,按病期(发热期、极期、多尿期、恢复期)采集血液标本,采用免疫比浊法检测血清胱抑素(CysC)水平,用全自动生化仪分析血尿素氮(BUN)、血肌酐(SCr)水平,比较不同分期及分型HFRS患者的CysC的水平,并分析CysC与BUN和SCr的相关性。结果:HFRS患者血清CysC各期均明显高于健康对照组($P<0.05$),病程极期时达高峰,多尿期时开始下降,恢复期时明显降低、但仍高于对照组;重症组患者在发病早期和极期时均显著高于轻症组($P<0.05$)。CysC与BUN和SCr的Pearson相关系数分别为 $r=0.7688$ 和 $r=0.8071$ ($P<0.05$),CysC与BUN和SCr之间有很好的正相关性。结论:血清CysC可较为敏感地反映HFRS患者肾脏损伤,其检测对于病情的发展和预后判断均有重要的临床意义。

关键词: 血清胱抑素C;肾综合征出血热;肾脏损伤

中图分类号: R512.8 **文献标识码:** A **文章编号:** 1673-6273(2014)28-5511-03

Clinical Significance and Dynamic Changes of CysC in Patients Suffering from Hemorrhagic Fever with Renal Syndrome (HFRS)

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ABSTRACT Objective: To study the dynamic changes of CysC and investigate the clinical significance in patients with HFRS. **Methods:** A total of 106 patients with HFRS admitted to department of infectious diseases were enrolled in this study from October 2010 to June 2013. Blood samples were collected at different phases of HFRS, and the levels of serum CysC, BUN and SCr were tested with different methods. The levels of CysC were compared in patients among different stages and phases of HFRS, and the correlation was analyzed. **Results:** The levels of serum CysC in patients with HFRS increased significantly in febrile phase, reached its peak in hypotensive and oliguric phase and then decreased gradually in diuretic phase but still higher than that of normal in convalescent phase ($P<0.05$). The levels of CysC, BUN and SCr in severe group were higher than in light group in different stages ($P<0.05$). The Pearson correlation coefficient of CysC, BUN and SCr was 0.7688 and 0.8071, respectively ($P<0.05$). There existed that serum CysC had a good positive correlation with BUN and SCr. **Conclusions:** Serum levels of CysC might be a sensitive indicator for kidney injury and be of prognostic importance in patients with HFRS.

Key words: Serum cystatin C; Hemorrhagic fever with renal syndrome; Kidney injury

Chinese Library Classification(CLC): R512.8 **Document code:** A

Article ID: 1673-6273(2014)28-5511-03

前言

肾综合征出血热(HFRS)是由汉坦病毒引起的一种自然疫源性疾病^[1],是我国重点防治传染病之一^[2],而肾脏损害是HFRS早期也是最主要的临床特征^[3]。胱抑素(cystatin, CysC)作为近年新的内源性肾功能指标,是一个较为理想的反映内源性肾小球滤过率(glomerular filtration rate, GFR)指标^[4],其检测对诊断HFRS患者肾脏损害具有一定的临床实用价值^[5]。本文通过分析临床各期及各型HFRS患者血清CysC、尿素氮

(BUN)及肌酐(SCr)的动态变化,旨在探讨血清CysC测定在HFRS患者肾功能评价中的应用。

1 材料与方法

1.1 临床资料

研究对象为我院2010年10月-2013年6月收治的HFRS患者共106例(男86例,女20例,年龄18-68岁,平均年龄43岁)。诊断与分型根据卫生部颁布的《流行性出血热诊断标准及处理原则》^[6],其中轻型30例、中型54例、重型18例、危重型14例。入选标准:皆有典型临床表现,且血清HFRS特异性IgM抗体阳性,所有病例均排除既往有肾脏疾病史。分型标准:轻型、中型、重型、危重型。分期标准:发热期、低血压休克期、少尿期、多尿期和恢复期。为方便比较,将轻型与中型合并

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(收稿日期:2014-02-17 接受日期:2014-03-15)

为轻症组,重型与危重型合并为重症组。因低血压休克期持续短暂且常与少尿期重叠,故将此二期(称为极期)合并统计。正常对照组为 90 例(男 62 例,女 28 例,年龄 19-71 岁,平均年龄 48 岁),为我院健康体检者,肝肾功能指标正常且无肾脏疾病史。

1.2 方法

按病期(发热期、极期、多尿期和恢复期)采集血样,对照组人群血样一次性采集,样本存放 -80℃ 低温冰箱待检;应用比浊法检测 CysC;BUN(速率法)和 SCr(酶法)测定采用 PPD 生化分析仪(美国 Roche 公司)。

1.3 统计学分析

全部数据采用 SPSS13.0 统计软件包处理,数据采用($\bar{x} \pm s$)

表示,采用组间 t 检验进行统计学分析,CysC 与 BUN、SCr 的相关性用 Pearson 系数表示。显著性检验水准 $\alpha=0.05, P<0.05$ 时差异具有统计学意义。

2 结果

2.1 CysC 与 BUN、SCr 在 HFRS 患者各期的变化

由表 1 可见,与对照组比较,各期 CysC 与 BUN、SCr 均明显增高($P<0.05$),发热期开始升高,极期时达到最高值(峰值),多尿期时开始下降,恢复期明显降低。而 CysC 发热期(2.27 ± 0.73)mg/L 与多尿期 (2.11 ± 0.75)mg/L 比较无显著差异($P>0.05$),在恢复期时仍明显高于健康对照组($P<0.05$)。

表 1 HFRS 患者各期 CysC、BUN 与 SCr 水平比较

Table 1 Comparison of CysC, BUN and SCr in different phases of HFRS

Group	n	CysC(mg/L)	BUN (mmol/L)	SCr (umol/L)
Control group	90	0.65± 0.11	4.80± 1.08	67.88± 11.73
HFRS group	106			
Febrile phase		2.27± 0.73*	17.34± 8.28*	278.52± 142.70*
Hypotensive and oliguric phase		3.88± 1.29*	28.14± 12.95*	581.12± 272.00*
Diuretic phase		2.11± 0.75* Δ	14.08± 6.13*	196.92± 93.95*
Convalescent phase		1.41± 0.47*	7.27± 2.26*	95.02± 24.84*

注:与对照组比较,* $P<0.05$;与发热期比较, $\Delta P>0.05$ 。

Note: compared with control group, * $P<0.05$; compared with febrile phase, $\Delta P>0.05$.

2.2 不同临床类型 HFRS 患者 CysC 与 BUN、SCr 水平比较

由表 2 可见,与对照组比较,轻症组与重症组 CysC 与 BUN、SCr 均明显高于对照组($P<0.05$);重症患者组在病程各

期 CysC 与 BUN、SCr 水平均明显高于轻症患者组,差异均有显著性($P<0.05$)。而发热期轻症组、重症组患者 CysC 水平分别与多尿期比较,差异无显著性($P>0.05$)。

表 2 不同临床类型 HFRS 患者 CysC、BUN 与 SCr 的水平比较

Table 2 Comparison of CysC, BUN and SCr in different stages of HFRS

Group	n	CysC(mg/L)	BUN (mmol/L)	SCr (umol/L)
Control group	90	0.65± 0.11	4.80± 1.08	67.88± 11.73
HFRS Light group	74			
Febrile phase		2.05± 0.55*	14.72± 5.25*	221.11± 79.60*
Hypotensive and oliguric phase		3.40± 1.13*	22.89± 8.42*	448.2± 198.54*
Diuretic phase		1.91± 0.62* Δ	12.72± 5.70*	177.04± 81.11*
Convalescent phase		1.31± 0.43*	6.95± 2.21*	89.22± 18.72*
HFRS Severe group	32			
Febrile phase		2.78± 0.84**	23.42± 10.65**	411.28± 167.31**
Hypotensive and oliguric phase		4.73± 1.16**	40.29± 13.52**	888.49± 134.43**
Diuretic phase		2.58± 0.82** Δ	17.20± 6.01**	242.78± 106.21**
Convalescent phase		1.64± 0.48**	8.01± 2.22**	108.47± 37.59**

注:与对照组比较,* $P<0.05$;与轻症组比较,** $P<0.05$;与发热期比较, $\Delta P>0.05$ 。

Note: Compared with control group, * $P<0.05$; compared with light group, ** $P<0.05$; compared with febrile phase, $\Delta P>0.05$.

2.3 HFRS 患者血清 CysC 与 BUN、SCr 水平相关性分析

将血清 CysC 与 BUN、SCr 测得的相应值进行相关处理,以 CysC 为横坐标作散点图,并求相关系数(r)。图 1A 示 CysC

与 BUN 的相关关系,图 1B 示 CysC 与 SCr 的相关关系,其相关系数分别 ($r=0.7688$ 和 $r=0.8071, P<0.05$)。结果表明 CysC 与 BUN、SCr 呈高度正相关。

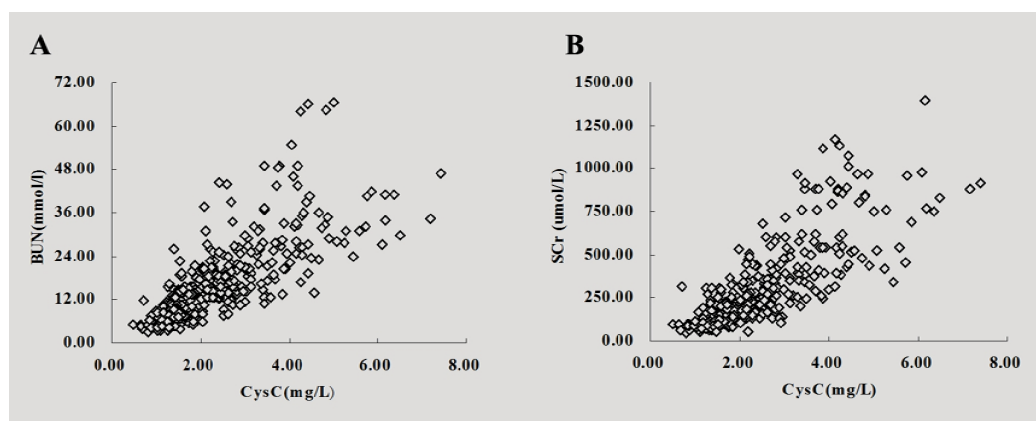


图1 HFRS患者 CysC 与 BUN、SCr 的相关关系

Fig.1 The correlation between CysC and BUN、SCr in patients of HFRS

3 讨论

汉坦病毒引起的肾综合征出血热(HFRS),其病理损伤表现为多脏器组织小血管的广泛损害及功能失调,其中肾脏尤为明显、表现为急性肾功能衰竭^[7],也是导致患者死亡的主要原因之一^[8]。肾小球滤过率(GFR)被认为是评价肾小球滤过功能最客观的指标,尽管尿素氮、肌酐等标志物在临床上评价肾功能时应用比较广泛,但因其影响因素较多,在评估 GFR 时存在着一定的不准确性。因此,寻找更为敏感且判断肾功损伤的生物标志物,也是临床研究的一个热点。

胱抑素(CysC)是一种半胱氨酸蛋白酶抑制剂,其相对分子量为 13Kd,基因编码位于 20 号染色体上^[9],几乎所有的有核细胞均能表达^[10],主要作用是保护细胞免受内源性或外源性蛋白酶水解。血清 CysC 水平主要由 GFR 决定,其机体的产生速率十分稳定,其血清浓度不受患者性别、身高、年龄及肌肉等因素影响,故 CysC 可以作为一个较理想的反映 GFR 变化的内源性标志物^[12-13]。1985 年 CysC 首次被报道用于肾功能测定^[14],国内外相继研究结果均支持 CysC 可作为较 SCr 和 BUN 更好地反映 GFR 的内源性指标^[15-17]。此外,近年来 CysC 作为评价肾功能损伤的指标,在多种肾脏损伤中日益得到关注与应用^[18-20]。

本文研究表明 CysC 在发病早期就开始升高,在极期(低血压休克期或少尿期)时达到峰值,而多尿期时开始下降,恢复期明显降低,其消长趋势与 HFRS 疾病的发展过程基本一致,并且与 BUN 和 SCr 水平的变化相平行,与国内一些学者报道的相一致^[21]。这一结果说明检测血清 CysC 变化可较敏感地反映 HFRS 患者肾脏损伤。而在不同临床类型的 HFRS 患者各期 CysC 变化中,表现为重症患者在病程各期 CysC 水平均明显高于轻症患者组,这提示 CysC 水平与病情轻重具有一定的相关性。因此,检测血清 CysC 水平对初步判断患者病情具有一定的前瞻性。值得关注的是,CysC 在恢复期虽明显下降,但仍高于健康人群水平,相对滞后于 BUN 和 SCr 的恢复时间。

此外,本研究发现 CysC 与 BUN 和 SCr 有良好的统计相关性,提示 CysC 也能作为判断 HFRS 患者肾功能异常的良好指标。尽管 BUN 和 SCr 水平是反映 HFRS 患者病情的客观指标之一,但鉴于 HFRS 患者 CysC 也存在明显变化,因此联合血清 CysC 与 BUN 和 SCr,对判断和估计 HFRS 患者病情及预后

有着一定的临床价值,而且 CysC 可作为一个更好的反映 HFRS 患者肾功能变化的内源性指标。

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