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ORIGINAL ARTICLE

Prognostic value of plasma neutrophil gelatinase-associated lipocalin in patients with heart failure

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KEYWORDS
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Abstract
Background: Neutrophil gelatinase-associated lipocalin (NGAL) is an early marker of kidney injury. We sought to assess the prognostic value of this biomarker in patients with stable chronic heart failure (HF).
Methods: We studied 61 patients with chronic systolic HF who had been receiving optimal medical treatment for at least six months. Biomarkers were measured at baseline and included plasma NGAL, microalbuminuria, serum creatinine, and B-type natriuretic peptide (BNP). Estimated glomerular filtration rate (eGFR) was also calculated. Mean follow-up was 10.6± 6.6 months. The primary endpoint was time to first cardiovascular event, defined as a combination of cardiovascular death, HF hospitalization or emergency department visit due to HF. Variables independently related to events were determined using a Cox proportional hazards model.
Results: Fifteen (24.6%) patients reached the primary endpoint. Patients with events were more likely to have worse renal function at baseline and also higher NGAL levels (median 316 [interquartile range 122–705] vs. 107 [78–170]; p=0.006). NGAL correlated significantly with creatinine (r=0.50; p<0.0001), albuminuria (r=0.33; p=0.008), and eGFR (r=−0.47; p=0.0001) but not with BNP (r=0.003; p=0.97). The best NGAL cutoff as determined by ROC curve analysis was 179 ng/ml. Event-free survival was lower in patients with NGAL above this cutoff. Variables independently related to events were NGAL (HR 1.0035, 95% CI 1.0019–1.0052; p<0.0001) and male gender (HR 5.9, 95% CI 1.22–28.6; p=0.028).
Conclusion: NGAL correlated with other biomarkers of renal function but not with BNP and was independently associated with outcomes.

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PALAVRAS-CHAVE
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Valor prognóstico da lipocalina associada a gelatinase de neutrófilos em pacientes com insuficiência cardíaca

Resumo
Fundamentos: A lipocalina associada a gelatinase de neutrófilos (NGAL) é um marcador precoce de injúria renal. O objectivo desse estudo foi avaliar o valor prognóstico desse biomarcador em pacientes com insuficiência cardíaca (IC) crônica estável.
Métodos: Incluídos 61 pacientes com IC por disfunção sistólica sob tratamento otimizado por no mínimo seis meses. Os biomarcadores foram dosados basalmente e incluíam NGAL plasmático, microalbuminúria, creatinina sérica e o peptídeo natriurético do tipo B (BNP). A taxa de filtração glomerular estimada (eTFG) também foi calculada. O seguimento médio foi de 10,6±6,6 meses. O desfecho primário foi o tempo até o primeiro evento, definido como uma combinação de morte cardiovascular, hospitalização por IC ou visita à sala de emergência por IC. A análise multivariada foi feita pelo Modelo de Riscos Proporcionais de Cox.
Resultados: Quinze (24,6%) pacientes apresentaram um desfecho. Pacientes com desfecho apresentavam pior função renal e maiores níveis de NGAL (mediana 316 [variação interquartil de 122-705] *versus* 107 [78-170]; p=0,006). NGAL correlacionou-se significativamente com a creatinina (r=0,50, p<0,0001), albuminúria (r=0,33; p=0,008), e eTFG (r=—0,47; p=0,0001) mas não com BNP (r=0,003; p=0,97). O melhor corte de NGAL pela curva ROC foi 179 ng/mL. A sobrevida livre de eventos foi menor em pacientes com valores acima desse corte. As variáveis relacionadas de modo independente com eventos foram NGAL (razão de chances 1,0035, IC95% 1,0019-1,0052, p<0,0001) e sexo masculino (razão de chances 5,9, IC95% 1,22-28,6, p=0,028).
Conclusão: NGAL correlacionou-se positivamente com marcadores tradicionais de função renal, mas não com o BNP e foi preditor independente de eventos.

Introduction

Heart failure (HF) is a severe disorder associated with high morbidity and mortality.[1] Renal dysfunction as assessed by creatinine or estimated glomerular filtration rate (eGFR) has been associated with worse outcomes[2–4] in patients with HF. However, creatinine is a late marker of renal function and early markers of the disorder are required.

Neutrophil gelatinase-associated lipocalin (NGAL) is an early marker of kidney injury and has been found to be elevated in both plasma and urine in patients with HF.[5–7] NGAL is a 25 kDa protein covalently bound to matrix metalloproteinase-9 that was first isolated from neutrophils. It is produced by a wide variety of cells including respiratory and intestinal epithelial cells,[8–10] endothelial cells, renal tubular cells and cardiomyocytes.[7,11] Due to its association with kidney injury, inflammation and matrix remodeling, NGAL has been proposed as a marker of prognosis in patients with HF. However, data on patients under optimal treatment for chronic HF due to multiple etiologies are scarce. Additionally, the ability of NGAL to predict a decrease in eGFR over time has not been assessed. The aim of this study was to assess the prognostic role of plasma NGAL in patients with chronic HF and its relationship with traditional biomarkers of renal function and also with B-type natriuretic peptide (BNP), a marker of myocardial wall stress.

Methods

Patients

From April 2010 through July 2013, 61 patients with chronic HF, New York Heart Association (NYHA) functional class I–III, were prospectively included. Patients were recruited from the heart failure clinic of our medical school hospital. The diagnosis of HF was made on the basis of medical history, ongoing symptoms, and physical examination. All patients were on optimal medical treatment for HF for at least six months and had been clinically stable for at least three months before the study. All of them were on stable doses of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), beta-blockers, and spironolactone unless contraindicated. In all patients left ventricular ejection fraction (LVEF) was assessed by echocardiography using the Simpson method. All individuals had LVEF $\leq$50% at the time of inclusion. Patients under dialysis were excluded. The study was approved by the ethics committee of our hospital and written informed consent was obtained from all patients.

Study design

This was a prospective cohort study. Clinical characteristics and biomarkers were measured at baseline and were related