The product of eGFR and hemoglobin may help predict mortality in systolic heart failure patients without severe anemia and renal failure

eGFR ve hemoglobin çarpımı, ciddi anemi ve böbrek yetersizliği olmaksızın sistolik kalp yetersizliği olan hastalarda mortaliteyi öngörmede yardımcı olabilir

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ABSTRACT

Objectives: Cardiorenal anemia syndrome is defined in patients with heart failure (HF). Although individual influences of renal impairment and anemia were shown previously, complex interaction between the kidney, bone marrow, and the heart renders decision making relatively inefficient in patients with milder forms of these diseases. We aimed to investigate whether product of estimated glomerular filtration rate (eGFR) and hemoglobin (Hb) predicts outcomes in patients with HF.

Study design: The study included 148 consecutive patients (89 males, 59 females; mean age 68±10 years) who were hospitalized with acutely decompensated systolic HF and discharged alive. Discharge Hb levels were measured. Renal function was estimated via the MDRD (Modification of Diet in Renal Disease) formula. The eGFR x Hb product was derived, and cut-off was defined using the ROC (receiver operating characteristic) analysis. The influence of eGFR x Hb product on mortality was analyzed after a follow-up period of up to 34 months (mean 8.2±5.5 months).

Results: The mean Hb was 12.7±2 g/dl, the mean creatinine was 105±46 μmol/l, and the mean eGFR was 61±23 ml/min/1.73 m^2. Eighty-two patients (55.4%) had an eGFR of <60 ml/kg/m^2. During the follow-up, 27 patients died. Optimal cut-off level of eGFR x Hb product to predict mortality was found to be ≤788 with a sensitivity of 82.6% and specificity of 51.3%. In multivariate Cox proportional analysis, only eGFR x Hb product ≤788 (HR 4.488, 95% CI 1.500-13.433, p=0.007) and presence of atrial fibrillation (HR 2.644, 95% CI 1.113-6.280, p=0.028) were independent predictors of mortality in patients with HF.

Conclusion: We concluded that the product of eGFR and Hb might be useful in prediction of mortality among patients with systolic HF.

ÖZET

Amaç: Kardiyorenal anemi sendromu kalp yetersizliği (KY) hastalarında tanımlanmıştır. Renal bozukluğun ve aneminin ayrı ayrı etkileri daha önce ortaya konmuş olsa da, böbrek, kemik iliği ve kalp arasındaki karmaşık etkileşim, hastalığı daha hafif olan kişilerde karar verme işlemini nispeten verimsiz kılar. Bu çalışmada, tahmini glomerül filtrasyon hızı (eGFR) ve hemoglobin (Hb) çarpımının KY hastalarında sonlanımı öngörmedeki rolünü araştırmayı amaçladık.

Çalışma planı: Çalışmaya, akut dekompanse sistolik KY tanısıyla hastaneye yatırılıp taburcu edilen ardışık 148 hasta (89 erkek, 59 kadın; ort. yaş 68±10) alındı. Taburcu edilirken Hb düzeyleri ölçüldü, böbrek fonksiyonu MDRD (Modification of Diet in Renal Disease) formülü ile belirlendi. eGFR x Hb çarpımı hesaplanarak, ROC (alıcı işletim karakteristiği) analiziyle kesim değeri çıkarıldı. Hastaların 34 aya varan takipleri (ort. 8.2±5.5 ay) sonrasında eGFR x Hb çarpımı değerinin ölüm üzerindeki etkisi araştırıldı.

Bulgular: Hasta grubunda ortalama Hb 12.7±2 gr/dl, ortalama kreatinin 105±46 μmol/l ve ortalama eGFR 61±23 ml/dk/1.73 m^2 bulundu. Seksen iki hastada (%55.4) eGFR <60 ml/kg/m^2 idi. İzlem sırasında 27 hasta öldü. eGFR x Hb çarpımının mortaliteyi öngörmede kesim değeri ≤788 bulunurken, duyarlığı %82.6, özgüllüğü %51.3 idi. Çokdeğişkenli Cox orantılı analizinde, sadece eGFR x Hb çarpımının ≤788 olması (HR 4.488, %95 GA 1.500-13.433, p=0.007) ve atriyal fibrilasyon varlığı (HR 2.644, %95 GA 1.113-6.280, p=0.028) sistolik KY hastalarında ölümün bağımsız öngördürücüleri olarak bulundu.

Sonuç: eGFR x Hb çarpımının sistolik KY olan hastalarda ölümün öngörülmesinde yararlı olabileceği sonucuna varıldı.

Received: January 8, 2011 *Accepted:* December 13, 2011

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Impaired renal function has consistently been shown to influence prognosis of patients with cardiovascular disease including heart failure.[1,2] Due to organ cross-talk, the heart and kidney interact so profoundly that the term "cardiorenal syndrome" has been introduced to the literature in order to define different spectra of this interaction.[3] On the other hand, anemia, particularly when it coexists with abnormal renal function, is also predictive of poor outcomes in patients with HF.[2] This negative interaction, hence, yielded the term "cardiorenal anemia syndrome".[4,5] This coexistence is not by chance, and is thought to be related with progression of HF, and hence, poor prognosis.[5] However, it does not affect prognosis unless functional regression is substantial.[2] Therefore, concurrent deterioration (decrease in glomerular filtration rate and decrease in hemoglobin) might represent a more sensitive indicator of outcomes than does each individual parameter, small changes of which might be indicating acute or temporary insults in some occasions. In this study, we aimed to investigate whether product of estimated glomerular filtration rate and hemoglobin predicts outcomes in patients with HF.

PATIENTS AND METHODS

All consecutive patients who were hospitalized in our institution and discharged alive with a discharge diagnosis of systolic HF between January 2007 and January 2010 were identified using a computer-generated list obtained from our hospital automation database and were evaluated retrospectively. After review of all data from electronic records, 323 patients were evaluated. Patients were included if they had symptomatic HF in the past six months with a left ventricular ejection fraction of <45%, measured by echocardiography during index hospitalization. Criteria for exclusion included the presence of the following: ejection fraction ≥%45, recent acute coronary syndromes, primary valvular or congenital heart disease, recent ischemia requiring revascularization (all patients had undergone coronary angiography), previous diagnosis of malignancy, other well established reasons for anemia, severe anemia (≤7 g/dl), chronic renal disease (estimated glomerular filtration rate <30 ml/kg/m^2) or renal replacement therapy. After exclusion of 175 patients, statistical data were obtained from the remaining 148 patients (89 males, 59 females; mean age 68±10 years) with systolic HF, who were hospitalized with acutely decompensated HF and discharged alive. The current study, as part of a larger investigation, was approved by the local institutional ethics committee.

Abbreviations:

eGFR *Estimated glomerular filtration rate*
Hb *Hemoglobin*
HF *Heart failure*

Since hemodilution and/or hemoconcentration due to the use of hemodynamically active drugs might affect Hb levels during hospital stay, and discharge creatinine has been shown to be a strong predictor of outcomes in patients with HF,[6,7] serum creatinine (μmol/l) and Hb (g/dl) levels at discharge or the last measurement before discharge were considered. Renal function was estimated via the MDRD (Modification of Diet in Renal Disease) formula.[8] Impaired renal function was defined by an eGFR value of <60 ml/min/1.73 m^2. Of note, none of the patients had eGFR <30 ml/kg/m^2. According to the WHO criteria, anemia was defined as an Hb concentration of <13.0 g/dl for males and <12.0 g/dl for females, and patients were classified into two for survival analysis. Then, the eGFR x Hb product was derived, and cut-off was defined using the ROC (receiver operating characteristic) curves.

Transthoracic echocardiograms were obtained during index hospitalization in all the patients. Echocardiographic examinations were performed by experienced echocardiographers via a Vivid 7 system (GE Medical System) with 2.5-5 MHz probes. Digital records of echocardiographic examinations were evaluated offline. Ejection fraction was calculated by the modified Simpson's method, and chamber sizes were defined according to recent guidelines.[9] Mitral and tricuspid regurgitations were quantified according to the recent guidelines.[9] Systolic pulmonary artery pressure was calculated as described previously.[9] Hypertension was defined as blood pressure ≥140/90 mmHg on more than two occasions during office measurements or being on antihypertensive treatment. Diabetes mellitus was defined as fasting blood sugar ≥126 mg/dl or being on antidiabetic treatment. Those who reported smoking during index admission were considered to be current smokers. Basic rhythm in the last recording before discharge was noted. Body mass index (kg/m^2) was measured at discharge. Discharge prescriptions of beta-blockers and angiotensin converting enzyme inhibitors/angiotensin receptor blockers were also considered.

The primary outcome was all-cause mortality. Clinical status including the presence of at least one heart failure-related hospitalization was evaluated by inviting patients for a control visit or interviewing patients, their relatives, and/or treating physician. The

follow-up period was up to 34 months (mean 8.2±5.5 months) after discharge.

Statistical analysis

Parametric data were expressed as mean ± standard deviation, and categorical data as percentages. Data were processed using the SPSS 16.0 statistical software. Independent parameters were compared via the independent samples t-test, and via the Mann-Whitney U-test if there was an abnormal distribution. Categorical data were evaluated by the chi-square test as appropriate. Correlations were analyzed via the Spearman's correlation test.

For the prediction of mortality, ROC curve analysis was performed to identify the optimal cut-off of the eGFR x Hb product. Area under the curve (AUC)

Table 1. Baseline characteristics of the patients who survived and who died during follow-up

	Survived (n=121)			Died (n=27)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (years)			67±10			69±11	0.430
Gender							0.439
Male	71	58.7		18	66.7		
Female	50	41.3		9	33.3		
Body mass index (kg/m^2)			24.6±3.7			23.3±3.1	0.219
Hypertension	44	36.4		12	44.4		0.437
Diabetes mellitus	19	15.7		9	33.3		**0.045**
Coronary artery disease	101	83.5		24	88.9		0.769
Atrial fibrillation	21	17.4		11	40.7		**0.012**
NYHA class III/IV	69	57.0		14	51.9		0.625
Rehospitalization	77	63.6		26	96.3		**<0.001**
Medications at discharge							
Beta-blocker	102	84.3		24	88.9		0.766
ACE inhibitor/ARB	107	88.4		25	92.6		0.737
Echocardiographic findings							
Left ventricular ejection fraction (%)			32±6			30±8	0.347
Left ventricular diastolic diameter (cm)			5.5±0.7			5.6±0.7	0.365
Left atrium size (cm)			4.6±0.7			4.6±0.6	0.919
Moderate-to-severe mitral regurgitation	42	34.7		11	40.7		0.557
Presence of pericardial effusion	17	14.1		2	7.4		0.528
Presence of right ventricular dilatation	62	51.2		18	66.7		0.142
Moderate-to-severe tricuspid regurgitation	37	30.6		7	25.9		0.629
Systolic pulmonary artery pressure (mmHg)			32±12			38±15	**0.028**
Mild-to-moderate aortic regurgitation	5	4.1		1	3.7		1.000
Laboratory findings							
eGFR x Hemoglobin product			822±360			611±199	**<0.001**
eGFR x Hemoglobin ≤788	59	48.8		23	85.2		**<0.001**
Creatinine (µmol/IL)			97±39			141±58	**0.001**
Presence of high creatinine	47	38.8		18	66.7		**0.008**
eGFR (MDRD, ml/kg/m^2)			64±24			47±15	**0.001**
Hemoglobin (g/dl)			12.7±2.0			12.8±2.0	0.811
Presence of anemia	51	42.2		14	51.9		0.360

NYHA: New York Heart Association; ACE: Angiotensin converting enzyme; ARB: Angiotensin receptor blocker; eGFR: Estimated glomerular filtration rate; MDRD: Modification of Diet in Renal Disease.

was calculated as measure of the accuracy of the test and compared with the use of the Z-test.

Outcome curves were generated using the Kaplan–Meier analysis for patients having above and below the eGFR x Hb cut-off point and the groups were compared by the log-rank test.

We used the univariate Cox proportional hazards analysis to quantify the association of variables with mortality. Variables that were found to be statistically significant in univariate analysis and correlated with eGFR x Hb were used in a multivariate Cox proportional hazards model with a forward stepwise method to determine the independent prognostic factors of mortality in patients with HF.

Patients were censored if alive at the end of the follow-up. A p value <0.05 was accepted as significant.

RESULTS

Considering all the patients, the mean Hb was 12.7±2 g/dl, the mean creatinine was 105±46 μmol/l, and the mean eGFR (MDRD) was 61±23 ml/min/1.73 m^2. Eighty-two patients (55.4%) had an eGFR of <60 ml/kg/m^2.

The patients were classified into two groups as those who survived and those who died (Table 1). During the follow-up, 27 patients died. Of note, none was due to accidents. Patients who died had higher frequencies of diabetes mellitus and atrial fibrillation, higher systolic pulmonary artery pressure, lower eGFR x Hb product, higher creatinine level and were more frequently rehospitalized for worsening of HF during the follow-up (Table 1).

Optimal cut-off level of eGFR x Hb product to predict mortality was found to be ≤788 with a sensitivity of 82.6% and specificity of 51.3% (Area under curve 0.670, %95 CI 0.585-0.747, Fig. 1).

In correlation analysis (Table 2), eGFR x Hb was significantly correlated with age (p=0.001), creatinine (p<0.001), eGFR (p<0.001), Hb level (p=0.001), presence of anemia (p<0.001), systolic pulmonary artery pressure (p=0.008), presence of right ventricular dilatation (p=0.020), and left atrium size (p=0.045). There was no significant correlation between eGFR x Hb product and other parameters (p>0.05).

All parameters were included into univariate Cox proportional hazard analysis for mortality. Parameters that were found to be predictors of mortality in univariate analysis were then enrolled into multivariate Cox proportional analysis for mortality (Table 3). Only eGFR x Hb product of ≤788 (HR 4.488, 95% CI 1.500-13.433, p=0.007) and presence of atrial fibrillation (HR 2.644, 95% CI 1.113-6.280, p=0.028) were independent predictors of mortality in patients with HF.

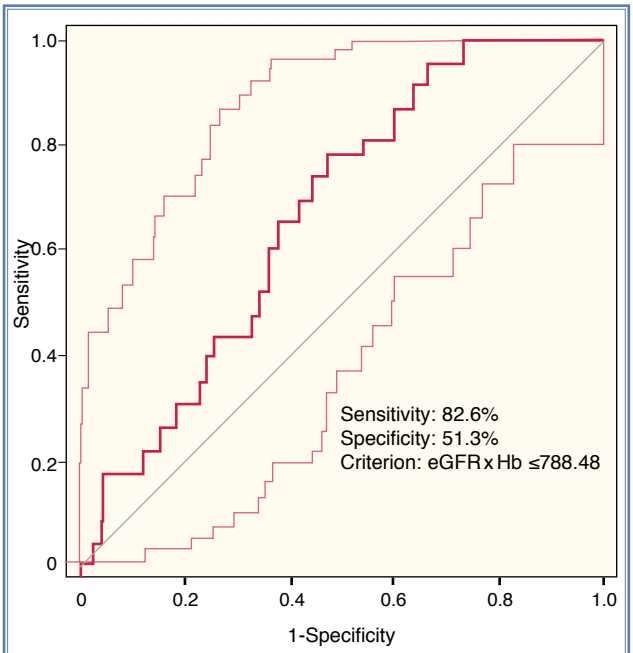

Figure 1. ROC curve of eGFR x hemoglobin product for prediction of mortality.

Survival curves produced for eGFR x Hb product showed that having eGFR x Hb ≤788 was significantly associated with poor survival during follow-up (p=0.004, Fig. 2).

DISCUSSION

Data from previous studies have shown that impaired renal function and anemia act synergistically, increasing mortality risk.[10-12] Kidney dysfunction and con-

Table 2. The results of univariate correlation analysis

	r	*p*
Age	-0.272	**0.001**
Creatinine	-0.849	**<0.001**
eGFR (MDRD, ml/kg/m^2)	0.923	**<0.001**
Hemoglobin	0.539	**0.001**
Presence of anemia	-0.442	**<0.001**
Systolic pulmonary artery pressure	-0.224	**0.008**
Right ventricular dilatation	-0.197	**0.020**
Left atrium size	-0.170	**0.045**

GFR: Glomerular filtration rate; MDRD: Modification of Diet in Renal Disease.

Table 3. Univariate and multivariate Cox proportional hazard analyses for mortality

	Univariate			Multivariate		
	HR	95% CI	*p*	HR	95% CI	*p*
Creatinine	1.007	1.001-1.014	**0.021**			
eGFR (MDRD)	0.971	0.946-0.996	**0.022**			
Atrial fibrillation	3.274	1.331-8.055	**0.010**	2.644	1.113-6.280	**0.028**
eGFR x Hemoglobin ≤788	2.762	1.112-6.860	**0.029**	4.488	1.500-13.433	**0.007**
Systolic pulmonary artery pressure	1.035	1.003-1.068	**0.031**			
Rehospitalization	7.810	1.054-57.862	**0.044**			
Age	1.020	0.982-1.058	0.310			
Presence of anemia	1.364	0.640-2.908	0.422			
Presence of right ventricular dilatation	1.463	0.655-3.269	0.353			
Left atrium size (cm)	0.846	0.516-1.385	0.506			
Hemoglobin	1.012	0.901-1.347	0.346			
Body mass index	0.890	0.752-1.053	0.175			
Gender	0.904	0.395-2.069	0.812			
Hypertension	0.609	0.277-1.343	0.219			
Diabetes mellitus	1.508	0.666-3.414	0.324			
Coronary artery disease	0.504	0.150-1.699	0.269			
Left ventricular ejection fraction	0.974	0.917-1.036	0.405			
Left ventricular diastolic diameter	1.139	0.656-1.975	0.644			
Presence of pericardial effusion	2.246	0.524-9.632	0.276			
Moderate-to-severe mitral regurgitation	0.690	0.311-1.528	0.360			
Moderate-to-severe tricuspid regurgitation	1.358	0.570-3.232	0.489			
Mild-to-moderate aortic regurgitation	1.298	0.174-9.662	0.799			
NYHA class III/IV	1.302	0.601-2.822	0.503			
Beta-blocker at discharge	0.517	0.153-1.744	0.288			
ACE inhibitor / ARB at discharge	0.471	0.108-2.048	0.315			

HR: Hazard ratio; CI: Confidence interval; NYHA: New York Heart Association; ACE: Angiotensin converting enzyme; ARB: Angiotensin receptor blocker; eGFR: Estimated glomerular filtration rate; MDRD: Modification of Diet in Renal Disease.

current anemia should be considered critical steps of progression of HF towards death rather than as discrete accompanying comorbidities. We need to understand better the pathophysiology of anemia in HF in relation with deterioration of renal function in order to identify effective management strategies. In previous studies, renal impairment defined by means of eGFR and anemia and classified by arbitrary thresholds were utilized for prediction of outcomes. In these studies, patients were usually classified under certain categories based on these thresholds.[2,10-12] From previous studies and epidemiological data, it is known that there is a significant relationship between anemia and renal impairment, which is not linear.[13,14] There are several pathophysiological mechanisms which influence organ cross-talk in the setting of HF. Furthermore, some patients with HF and normal range of creatinine might be under higher risk categories.[15] Besides, it is known that most patients with HF have either normal or near normal creatinine, though most of the deaths occur in this group of patients.[16,17] Hence, categorization of patients based either alone on Hb or on creatinine might not reflect overall population, though patients with the highest and lowest risk are nicely represented. Furthermore, in milder cases, it might not be possible to estimate relative contribution of each parameter to mortality. On the other hand, anemia as a prognostic indicator might be influenced by several cytokines related to congestion of gut, which could potentially worsen renal function, and also by drugs even in the absence of chronic renal in-

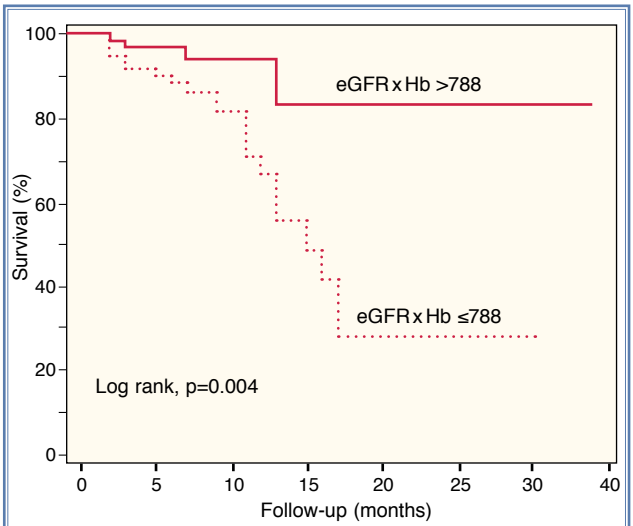

Figure 2. Kaplan-Meier curve for eGFR x hemoglobin product for mortality.

sufficiency.[16,18,19] In our study, eGFR x Hb product was found to be an independent predictor of mortality in patients with systolic HF, along with the presence of atrial fibrillation. Moreover, in the survival analysis, neither creatinine nor Hb, as opposed to previous studies, was predictive of mortality in this cohort. Hence, utilization of eGFR x Hb product might make sense in the overall population of HF.

In a study with similar objectives,[2] which was a retrospective analysis of a larger trial, eGFR x hematocrit product was used for predicting mortality in patients with HF. The authors found out that lower GFR and hematocrit were associated with a higher prevalence of traditional risk factors such as hypertension, lower ejection fraction, use of antiarrhythmics and diuretics, and diabetes. They also added that lower GFR and lower hematocrit alone were associated with a higher risk for mortality. In addition, the product of these two parameters predicted a higher risk than did the two parameters individually. It was hypothesized that four mechanisms were related with this outcome. First, hematocrit level may be a critical marker for cardiac functions. It is known that severe HF may cause anemia. Second, reduced hematocrit may be related with increased inhibitor cytokines. Third, the authors suggested that reduced hematocrit may worsen ischemia in a failing heart. Fourth explanation was that reduced hematocrit could be a reason for cardiac remodeling because of increases in venous return and cardiac work. The authors emphasized that the last mechanism was prominent in patients with end-stage kidney disease and it might be impossible to distinguish among four suggested mechanisms. In conclusion, these results raise two questions: is it feasible to correct anemia with erythropoietin and will anemia correction affect mortality and/or morbidity? The first question remains unsolved due to conflicting results. Prospective studies on the etiology of anemia and methods of correcting it are needed to answer the second question.

Limitations

Our study was limited by its relatively small sample size, though event rate was acceptable. Furthermore, a single-tertiary center experience might not reflect overall behavior of patients with HF. One of the main limitations is its retrospective and nonrandomized enrolling style. Calculations depending on 24-hour urine output are more reliable for determining renal functions than eGFR. The fact that we did not know whether there was a renal parenchymal disease limits our retrospective results.

Another limitation of this study is the lack of data about patients' discontinuation of one or more drugs, namely, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, or beta-blockers. Although discharge prescriptions were documented, future therapy of patients was unclear. Another problem related with discharge was that patients' dry weight at hospital discharge was not available in the records.

On the other hand, exclusion of patients with severe anemia and severe renal disease (i.e., patients with eGFR <30 ml/kg/m^2) might have caused dilution of expected influence of creatinine and Hb alone, and hence, this could possibly be the reason for lack of significant divergence of survival curves individually. However, it is important to keep in mind that, even though they represent relatively milder cases, these patients reflect general population of HF, and that patients at the extremes of organ dysfunction (severe anemia, chronic renal disease requiring renal replacement therapy) are rare, and they are already known to have poor prognosis.

In conclusion, eGFR x Hb product seems to be useful in predicting mortality among patients with systolic HF, who do not manifest significant impairment in renal function and severe anemia.

Conflict-of-interest issues regarding the authorship or article: None declared

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Key words: Anemia; glomerular filtration rate; heart failure, systolic/mortality; kidney diseases/complications; risk factors.

Anahtar sözcükler: Anemi; glomerül filtrasyon hızı; kalp yetersizliği, sistolik/mortalite; böbrek hastalığı/komplikasyon; risk faktörü.