ORIGINAL ARTICLE

Estimation of glomerular filtration rate in type 2 cardiorenal syndrome diagnosis

Elena Bivol[1], Livi Grib[1], Alexandra Grejdieru[1]

Abstract: Cardiovascular disease prevalence is steadily increasing leading to high mortality and morbidity. The diagnosis of cardiorenal syndrome is a real challenge. **Objectives –** Estimation of glomerular filtration rate in cardiorenal syndrome diagnosis in patients with heart failure with reduced and mid-range ejection fraction. **Methods –** The prospective study included 170 patients with reduced and mid-range ejection fraction heart failure (HF) hospitalized during January 2016 – December 2017 period in the Cardiology Unit of Municipal Clinical Hospital „Holy Trinity" in Chisinau. **Results –** A total of 170 patients were evaluated: 83 subjects with chronic HF and cardiorenal syndrome (CRS) and 87 subjects with chronic HF without renal involvement. The estimated glomerular filtration rate (eGFR) estimated by means of EPI equation based on cystatin C and creatinine level had a mean of 43.40 ± 1.29 ml/min/1.73 m^2 in cardiorenal syndrome group and a mean of 78.29 ± 1.34 - ≤60 mL/min/1.73 m^2 in the group without kidney involvement. **Conclusions –** Study results confirm the superiority of GFR estimation by means of EPI equations based on cystatin C and creatinine level for cardiorenal syndrome screening and early diagnosis.
Keywords: cardiorenal syndrome, heart failure, glomerular filtration rate, cystatin C, creatinine.

Rezumat: Prevalenţa afectării cardiorenale este în continuă creştere şi este însoţită de mortalitate şi morbiditate înaltă, iar diagnosticul sindromului cardiorenal este o adevarată provocare. **Obiective –** Estimarea ratei filtrării glomerulare în diagnosticul sindromului cardiorenal la pacienţi cu insuficienţă cardiacă şi fracţie de ejecţie redusă şi intermediară. **Metode –** Studiul prospectiv a inclus 170 de pacienţi cu insuficienţă cardiacă cronică (ICC) cu fracţie de ejecţie (FE) redusă şi inter-mediară, spitalizaţi în perioada ianuarie 2016 - decembrie 2017 în Clinica de Cardiologie, SCM „Sfânta Treime" Chişinău. **Rezultate –** Au fost evaluaţi 170 de pacienţi: 83 de subiecţi cu insuficienţă cardiacă cu sindrom cardiorenal şi 87 de subiecţi cu insuficienţă cardiacă fără afectare renală. Rata estimativă a filtrării glomerulare (RFGe) apreciată prin ecuaţia EPI în baza cistatinei C şi a creatininei a avut valoarea medie de 43,40±1,29ml/min/m^2 în lotul cu sindrom cardiorenal şi 78,29±1,34 - ≤60 mL/min/1,73m^2 în lotul fără afectare renală. **Concluzii –** Rezultatele studiului confirmă superioritatea estimarii RFG prin ecuaţiile Epi în baza cistatinei C sau ecuaţia EPI în baza cistatinei C şi a creatininei cu scop de screening sau diagnostic precoce al sindromului cardiorenal.
Cuvinte cheie: sindromul cardiorenal, insuficienţă crdiacă, rata de filtrare glomerulară, cistatina C, creatinină.

INTRODUCTION

International definitions and agreements regarding staging of acute, chronic kidney disease and renal injury are under constant review. In 2002, NKF-KDOQI[1] proposed a staging model for CKD (*chronic renal disease*) based on five estimated glomerular filtration rate (eGFR) intervals. Subsequently, the model was approved by KDIGO (*Kidney Disease Improving Global Outcomes*) with some changes. CKD was defined as an eGFR <60 ml/min/1.73 m^2, this threshold representing half of the normal GFR for young adults. Additionally, the threshold represents the point value at which there is an increase in prevalence and severity of several cardiovascular risk factors and in CKD specific laboratory changes[2]. The applicability of KDIGO criteria in CKD and renal involvement definition in patients with HF has already been proven for an eGFR threshold < 60 ml/min/1.73 m^2. This critical point was used in a series of HF studies[3] and registries[4] in order to assess significant renal involvement and prognostic value in relation to morbidity, mortality, and re-hospitalization rate. Glomerular filtration rate (GFR) is interna-

---

[1] „Nicolae Testemiţanu" State University of Medicine and Pharmacy, Chisinau, Republic of Moldavia

⬧ **Contact address:**
Elena Bivol, „Nicolae Testemiţanu" State University of Medicine and Pharmacy, Chisinau, Republic of Moldavia.
E-mail: bivol.e@gmail.com

tionally recognized as the best overall kidney index[5]. Although existing equations are adjusted for several parameters that influence creatinine level, such as age, gender and race, GFR estimates should be interpreted with caution[6]. A further concern is validation of equations in test populations. These issues should be taken into account when assessing renal involvement in HF, considering that most participants are over 65 years old[7] with GFR decreasing gradually with age. The MDRD formula is validated in this population, although CKD-EPI is more accurate in some cases[8].

Purpose of the study: Estimation of glomerular filtration rate in cardiorenal syndrome diagnosis in patients with heart failure with reduced and mid-range ejection fraction.

Material and methods: The prospective study included 170 patients with heart failure (HF) with reduced and mid-range ejection fraction, 83 subjects with type 2 cardiorenal syndrome (CRS) and 87 subjects with no renal involvement, hospitalized during January 2016 – December 2017 period in the Cardiology Unit of Municipal Clinical Hospital „Holy Trinity" in Chisinau, Republic of Moldova.

The type 2 CRS was diagnosed according to the working group of the 11th Conference of the Consensus ADQI (2013)[9,10].

Inclusion criteria:
- CHF diagnosis (as defined in the 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure)[11].
- LVEF ≤49%.
- No previous renal impairment (CKD) or documented onset of heart failure prior to renal impairment onset.
- Age over 18 years.

Exclusion criteria:
- Presence of primary kidney disease (congenital kidney disease or kidney disorders prior to cardiac disease).
- Inflammatory, traumatic kidney disease (that cannot be explained by CHF).
- Steroid treatment.
- Patients with acute cardiac/cerebrovascular events.

Arterial hypertension was defined according to 2018 ESC/ESH Guidelines for the management of arterial hypertension criteria (sistolic BP ≥140 mmHg and/or diastolic BP≥90 mmHg)[12].

Standard echographic views (Hitachi HI VISION Avius device) using the Simpson biplane method adjusted for frame rate optimization were obtained to measure chamber dimensions and evaluate global and regional left ventricular function.

NT-proBNP (*N-terminal pro-B-type natriuretide*) – was assessed using electrochemiluminescence immunoassay (ECLIA). Cutt-off value for non- acute patients was considered 125 pg/ml.
- Creatinine – was determined through kinetic method (Siemens Dimension EXL 200). Cutt-off value: in male <1.2 mg/dL, in female <1.0 mg/dL.
- Cistatine-C – determinated through the nephelometric method. Cutt-off value: under 50 y.o.: 0.55-1.15 mg/l; older than 50 y.o.: 0.63-1.44 mg/l.

BUN - determinated through the spectrophotometric method.

Evaluation of renal function aimed at assessing estimated glomerular filtration rate (eGFR) according to previously described formulas and degree of renal involvement according to K/DOQI classification: renal involvement with normal GFR (G1) ≥90 ml/min/1.73 m^2; renal involvement with slightly reduced GFR (G2): 60-89 ml/min/1.73 m^2; renal involvement with moderate GFR decrease (G3a): 45-59 ml/min/1.73 m^2 and GFR (G3b): 45-59 ml/min/1.73 m^2; severe GFR decrease (G4): 15-29 ml/min/1.73 m^2; end-stage renal disease (ESRD) with GFR (G5) <15 ml/min/1.73 m^2.

We assessed GFR using CKD-EPI equation based on cystatin C and creatinine levels (GFR reference values ≤60 ml/min/1.73 m^2) in order to evaluate CRS prevalence, divide study groups, and perform comparative analysis.

CKD-EPI equation based on cystatin C and creatinine levels (ml/min/1.73 m^2) = GFR_{cyscr} = 135 × min $(S_{Cr}/\kappa, 1)$ α × max $(S_{Cr}/\kappa, 1)$ − 0.601 × min $(S_{cys}/0.8, 1)$ − 0.375 × max $(S_{cys}/0.8, 1)$ − 0.711 × 0.995 Age × 0.969 [in women] × 1.08 [in African American race], where Scr is serum creatinine, κ is 0.7 for women and 0.9 for men, α is −0.248 for women and −0.207 for men, min indicates the minimal value for S_{Cr}/κ or 1, max indicates the maximal value for S_{Cr}/κ or 1, and Scys is serum cystatin C.

Additionally, GFR was determined by other formulas:
- CKD-EPI equation based on creatinine level GFR_{epi} (ml/min/1.73 m^2) = 141 x min $(S_{Cr}/k, 1)$ α x max $(S_{Cr}/k, 1)$ − 1.209 x 0.993 age x 1.018 [for

women] x 1.159 [for African American race], where S_{Cr} is serum creatinine level (mg/dL), k is 0.7 for women and 0.9 for men, α is –0.329 for women and –0.411 for men, min is the minimal value of S_{Cr}/k or 1 and max is the maximal value of S_{Cr}/k or 1.

- CKD-EPI equation based on cystatin C level (ml/min/1.73 m^2) = GFR_{cys} = 133 x min (S_{cys}/0.8, 1) – 0.499 x max (S_{cys}/0.8, 1) – 1.328 x 0.996 age x 0.932 [for women], where Scys is serum cystatin C.
- Short MDRD equation (Modification of Diet în Renal Disease) based on 4 variables: GFRm (ml/min/1.73 m^2) = 186 x (serum creatinine μmol/l x 0,0113) – 1,154 x age (years) – 0.203 x 1. 212 (for African American race) x 0,742 (for women);
- Classical Cockroft Gault equation: GFRCG creatinine clearance (ml/min/1.73 m^2) = [140 – age] x weight (kg) x 1.23 (for men) or x 1.04 (for women)/serum creatinine μmol/l.
- Simple equation based on cystatin C: 100/cystatin C (mg/l); GFR100/cys (ml/min).

It is more prudent to take into account the result of the patient's actual GFR, not the GFR result that the patient could have if his BSA were 1.73 m^2. Indexation of GFR for BSA can induce relevant differences in patients with abnormal body size.

GFR estimation equations are adjusted to standard body surface area (1.73 m^2). We checked the diagnostic value of unadjusted and adjusted to body surface area equations. Unadjusted eGFR was assessed by MDRD, CKD-EPI based on creatinine, CKD-EPI based on cystatin C and CKD-EPI based on cystatin C and creatinine: eGFR (ml/min) x BSA (m^2)/1.73, where

body surface area BSA (m^2) = (W 0.425 x H 0.725) x 0.007184.

ETHICAL ASPECTS
The participants were informed about the subject, purpose and rules of the study. Each participant signed and agreed on admission to participate in the research process, their data being processed anonymously.

STATISTICAL ANALYSIS
All data was statistically analyzed using the SPSS v20 for Windows, Microsoft Excel for Windows 10 software, univariate statistical analysis (frequency, mean, range, and median) and comparison test being performed variables Chi_2, Student's t test comparing two means (quantitative). Data was expressed as mean ± SD, while for p-value we were using the two-tailed test.

RESULTS
We determined a mean GFR_{cyscr} value of 43.40 ± 1.29 ml/min/1.73 m^2 (95% CI 40.82-45.98, p <0.05) for the study group with variations ranging from 14 to 59 ml/min/1.73 m^2. The control group had a mean eGFR of 78.29 ± 1.34 (95% CI 75.63-80.94, p <0.05), ranging from 60 to 113 ml/min/1.73 m^2 (Figure. 1).

According to K/DOQI stages of renal involvement we identified G1 stage in 25.29% cases and G2 stage in 74.71% cases, comprising the control group; G3a stage in 54.9% cases; G3b in 29.3% cases; G4 in 14.6% cases and G5 in 1.2% (1 patient), comprising the study group.

Table 1 represents mean eGFR values calculated by different equations. Comparative analysis determined a high variability among obtained values: ranging from 37.77 ml/min/m^2 by CKD-EPI equation based on cysta-
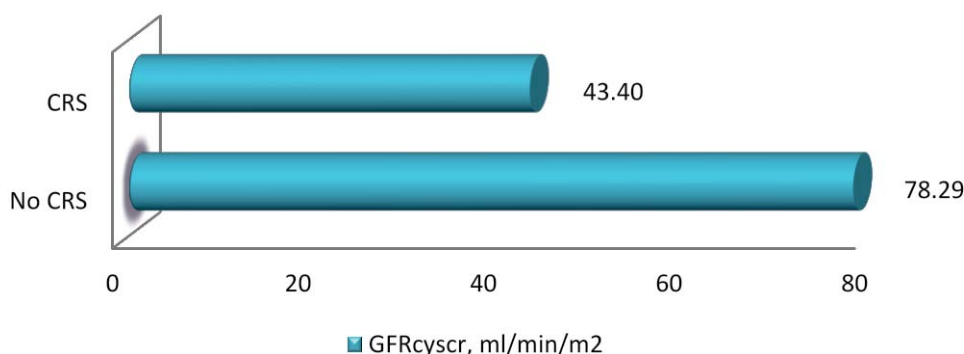

Figure 1. GFR_{cyscr} value in patients with/without CRS.

Romanian Journal of Cardiology
Vol. 29, No. 3, 2019

Elena Bivol et al.
Estimation of glomerular filtration rate in type 2 cardiorenal syndrome diagnosis

Table 1. Mean eGFR values according to different equations in subjects with and with no renal involvement

Estimated GFR	CRS (83 subjects) Mean ± SEM	No CRS (87 subjects) Mean ± SEM	p
GFR$_{cyscr}$	43.39±1.29	78.29±1.34	<0.0001
GFR$_{cyscr}$G	50.92±1.63	91.91±1.89	<0.0001
GFR$_{cys}$	37.77±1.41	67.64±1.79	<0.0001
GFR$_{cys}$G	44.34±1.72	79.22±2.17	<0.0001
GFR$_{epi}$	55.39±2.34	91.93±1.62	<0.0001
GFR$_{epi}$G	64.74±2.78	108.1±2.51	<0.0001
GFR$_m$	54.27±2.28	94.85±2.49	<0.0001
GFR$_m$G	62.62±2.74	111.19±3.44	<0.0001
GFR100/cistatine	60.51±1.79	92.14±2.15	<0.0001
GFR$_{CG}$	70.37±3.25	125.6±5.06	<0.0001

Table 2. Comparative assessment of GFR estimation equations

Statistical parameter	GFR$_m$	GFR$_{epi}$	GFR$_{cys}$	GFR100-$_{cys}$	GFR$_{CG}$
AUC	0.91	0.92	0.94	0.9	0.87
Optimal criterion	≤70	≤73	≤50	≤71.94	≤91.1
Sensitivity, %	80.7	84.34	84.15	78.05	83.1
Specificity, %	86.0	87.36	84.34	89.39	78.2
Predictive positive value (VPP), %	68.9%	71.9%	73.8%	73.9%	59.3%
Predictive negative value (VPN), %	92.1%	93.6%	93.7%	91.5%	92.4%
p	<0.001	<0.001	<0.001	<0.001	<0.001

tin C to 70.37 ml/min/m^2 by Cockroft Gault classical equation for the study group; and from 67.64 ml/min/m^2 by CKD-EPI equation based on cystatin C to 125.6 ml/min/m^2 by Cockroft Gault equation for the control group. The extreme values in both groups were obtained using these two formulas, whereas the results obtained using the unadjusted cystatin C CKD-EPI equation had the closest values compared to CKD-EPI equation results based on cystatin C and creatinine (formula used for sample division): 44.33 mL/min/1.73 m^2 vs. 43.39 ml/min/1.73 m^2 in the study group and 79.22 vs. 78.29 ml/min/1.73 m^2 in the control group. In our study, equations based only on serum creatinine overestimated GFR values compared to serum cystatin C equations (Table 1).

We examined ROC curves for GFR estimation equations in order to assess diagnostic value of each test relative to GFR$_{cyscr}$. Ideally, the efficacy of a GFR estimation test should be compared to GFR measured by plasma and urinary clearance of exogenous markers. Inulin is an ideal exogenous marker, but alternative markers such as iothalamate, EDTA, DTPA and iohexol can be used as well. Unfortunately, measurement of exogenous markers clearance is complex, expensive and difficult to apply in routine clinical practice.

The ROC (*Receiver Operating Characteristics*) curve is a bidimensional curve where Y axis indicates sensitivity while X axis indicates specificity. The curve helps us measure a model's efficiency. The higher the area under the curve (maximum is 1), the better the model. Analyzing data in Table 1, the AUC (area under the ROC curve) has maximal values for GFR$_{cys}$ (0.94) and GFR$_{epi}$ (0.92) equations compared to GFR$_{cyscr}$, while having a minimal value (0.87) for Cockroft Gault

equation. Maximum sensitivity was assessed for GFR$_{epi}$ (84.34%) and GFR$_{cys}$ (84.15%), but for the optimal different criterion GFR ≤ 73ml/min/m^2 vs. GFR ≤ 50 ml/min/m^2. GFR100-cys showed maximum specificity (89.39%), however the smallest sensitivity (78.05%) relative to GFRcyscr. The maximum positive predictive value was established for GFR100-cys (73.9%) and GFR$_{cys}$ (73.8%), while the lowest positive predictive value (59.3%) was found for eGFR based on classical Cockroft Gault equation. Absence of renal involvement was most accurately appreciated by cystatin C based eGFR (negative predictive value -93.7%, p
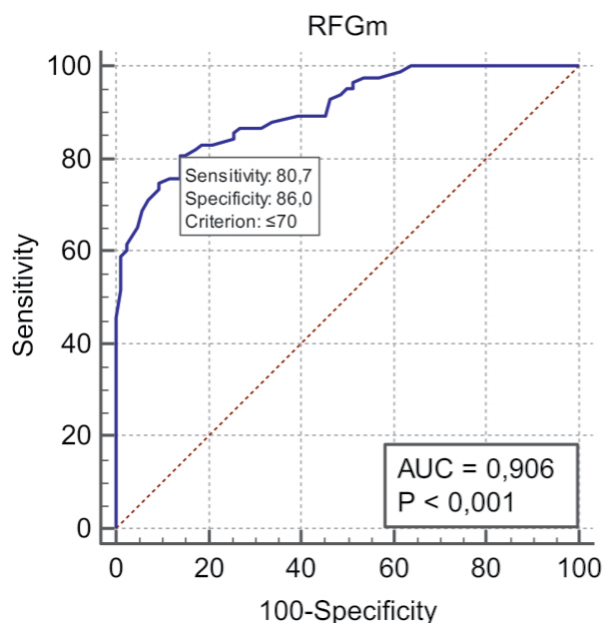

Figure 2. ROC curve for MDRD equation.

<0.001) and GFR$_{epi}$ (negative predictive value -93.6%, p <0.001).

When comparing adjusted and unadjusted for body surface area GFR estimation methods (Figures 2-8), we notice an increased efficiency for adjusted equations: 0.906 vs. 0.901 for GFR$_m$ and GFR$_{mG}$ respectively; 0.915 vs. 0.905 for GFRepi and GFR$_{epiG}$; 0.936 vs.

0.928 for GFRcys and GFR$_{cysG}$. The difference may also be due to equation selection to which the adjusted GFR$_{cyscr}$ was calculated.

Table 1 data and Figures 2-8 demonstrate that all examined models are effective for renal involvement diagnosis in HF patients. All estimation methods proved to be excellent diagnostic models except for the classical Cockroft Gault equation estimation method (AUC 0.87, p <0.001) that was appreciated as a good estimation model from sustained data having a value analysis p = 0.0001. The maximal diagnostic value was established for unadjusted CKD-EPI equations based on cystatin and creatinine levels, and adjusted CKD-EPI based on cystatin and creatinine.

We analyzed age influence on GFR, dividing patients into groups using the 65-year delimitation threshold (Figure 9).

We obtained the following results: for the group with no renal involvement GFR$_{cyscr}$ was 81.02 ± 1.82 ml/min/m^2 in the below 65-year age group and 74.42 ± 1.77 ml/min/m^2 in the ≥65-year group (p <0.05). The study group had GFRcyscr values of 44.48 ± 2.18 ml/min/m^2 in the below 65-year age group and 42.88 ± 1.62 ml/min/m^2 in the ≥65-year group (p>0.05). For both groups, GFRcyscr was elevated in advanced age subjects.

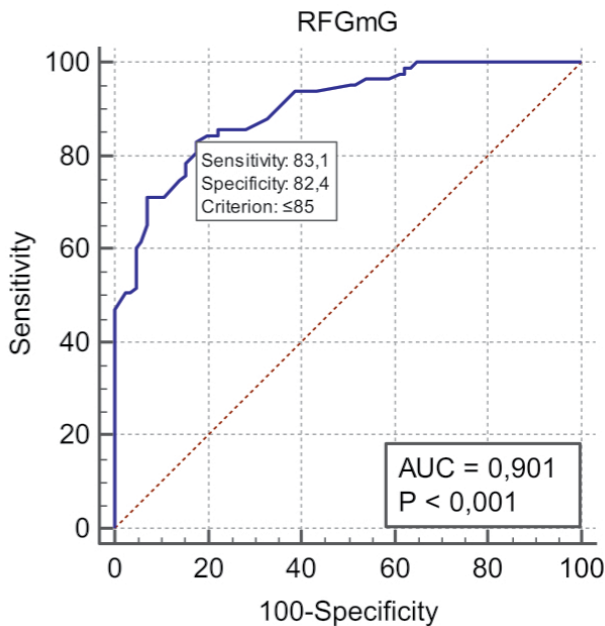Subsequently, we assessed hypertension influence on eGFR level. (Fig. 10)

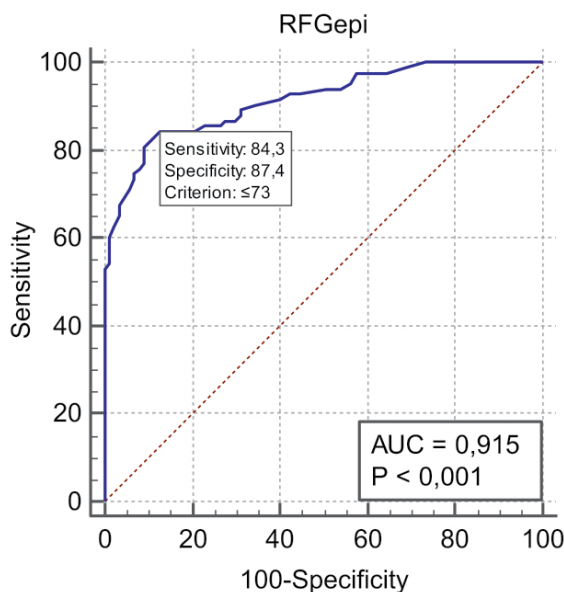

Figure 3. ROC curve for unadjusted MDRD equation.

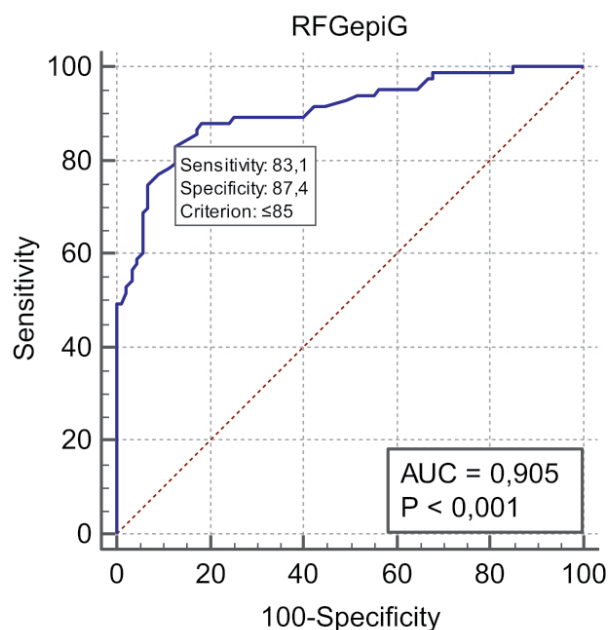**Figure 4.** ROC curve for creatinine based CKD-EPI equation.

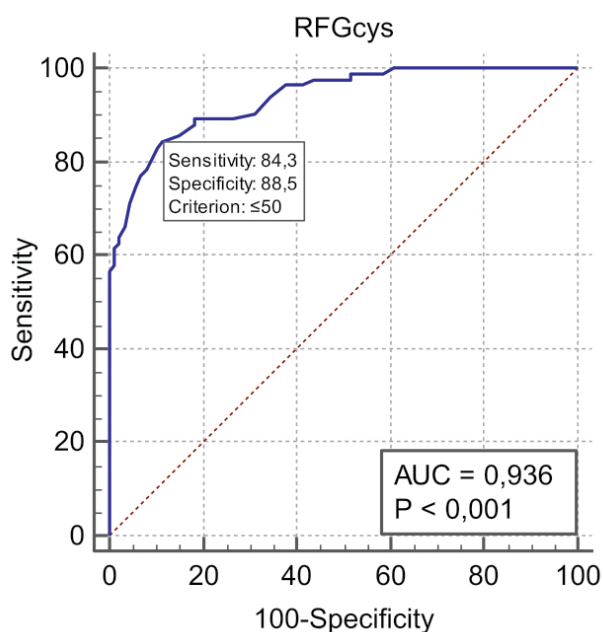**Figure 5.** ROC curve for unadjusted creatinine based CKD-EPI equation.

Romanian Journal of Cardiology
Vol. 29, No. 3, 2019

Elena Bivol et al.
Estimation of glomerular filtration rate in type 2 cardiorenal syndrome diagnosis

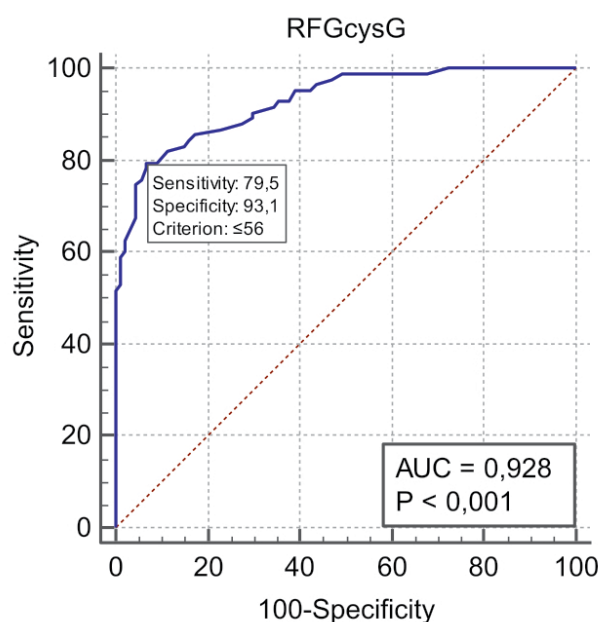**Figure 6.** ROC curve for cystatin based CKD-EPI equation.

Figure 7. ROC curve for unadjusted cystatin based CKD-EPI equation.
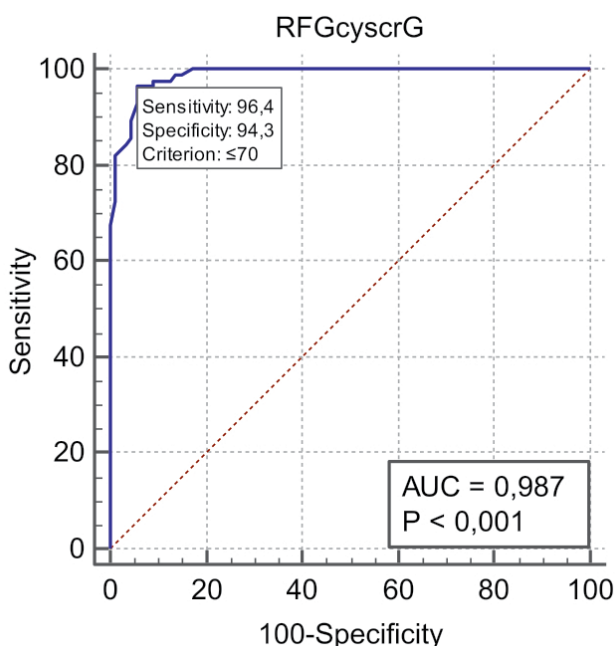

Figure 8. ROC curve for unadjusted cystatin and creatinine based CKD-EPI equation.

The recorded level of GFR_{cyscr} in patients with CRS had lower values in case of hypertension association with values of 42.76 ± 1.48 ml/min/m² vs. 46.27 ± 2.48 ml/min/m² in the absence of hypertension (p <0.05). No statistically significant differences were found in the control group: 78.35 ± 1.63 ml/min/m² for hyper-tensive subjects vs. 78.10 ± 2.19 ml/min/m² in the absence of hypertension (p > 0.05). The phenomenon, however, is not due solely to hypertension presence but also to coexisting factors – left ventricular ejection fraction (LVEF) in control group was lower in patients without hypertension 37% vs. 41.16% (p <0.01) and NT proBNP levels were significantly higher in non-hypertensive subjects 4712.05 pg/dl vs. 1974.17 pg/dl (p <0.001), suggesting a more serious evolution of HF in this group.

Next, we evaluated serum cystatin level. Mean cystatin C value was 1.79 ± 0.06 mg/dl (95% CI 1.67-1.91) for patients with CRS and 1.12 ± 0.02 mg/dl (95% CI 1.09-1.19) in those without CRS (p <0.001). Test sensitivity was 78.05% while specificity was 89.39% for the optimal creatinine >1.38 mg/dl criterion, with the positive predictive value -90.2% and negative predicti-ve value -76.4%.

Further, we evaluated serum creatinine levels in our groups. Mean creatinine value was 1.38 ± 0.07 mg/dl (95% CI 1.24-1.52) for patients with CRS and 0.79 ± 0.02 mg/dl (95% CI 0.75-0.84) in those without CRS (p <0.001). Test sensitivity was 78.05% while specificity was 86.36% for the optimal creatinine >0.92 mg/dl le-vel, positive predictive value being 87.8% and negative predictive value 75.8%.

Serum BUN level was 10.88 ± 0.54 mmol/l in pa-tients with impaired renal function and 8.28 ± 0.28 mmol/l in those with a GFR >60 ml/min/m² (p <0.001).
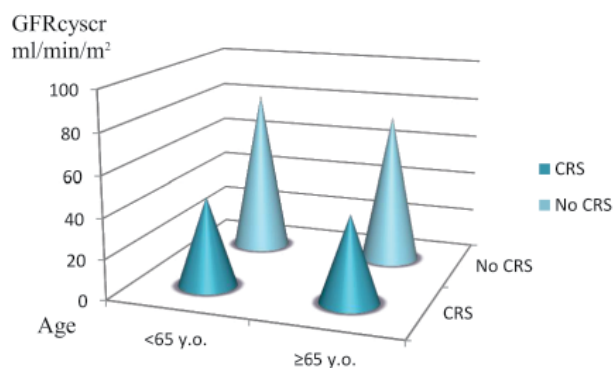
Figure 9. Patients' distribution according to age groups.

equation will be 32.94%, by cystatin based CKD-EPI equation will be 66.47%, by unadjusted cystatin based CKD-EPI equation will be 48.24%, by creatinine based CKD-EPI equation will be 28.82%, by unadjusted creatinine based CKD-EPI equation will be 21.18%, by MDRD equation will be 30.59%, by unadjusted MDRD equation will be 22.94%, by cystatin-100 based equation will be 36.47% and by Cockroft Gault classical equation will be 20.59% (p <0.001).

This phenomenon was also described by Swedish researcher Åkerblom in 2015 who performed a unicentric observational study involving outpatient car-
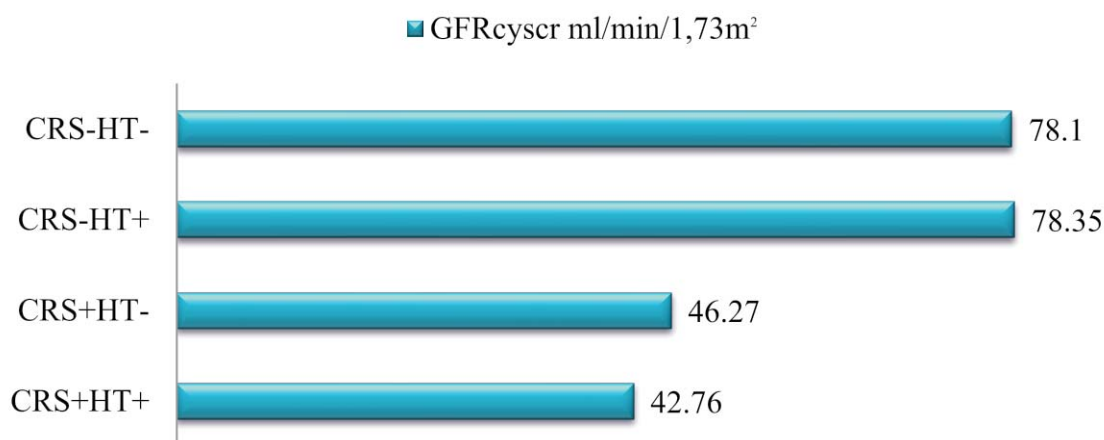

Figure 10. GFR_{cyscr} level according to hypertension and CRS presence.

DISCUSSIONS

Improving cardiorenal risk assessment and stratification is crucial. In real life, measuring GFR with an exogenous marker is rarely possible. Thus, we continue relying on GFR assessment by endogenous markers such as creatinine and cystatin C. We usually classify patients according to eGFR making no difference among molecules used for measurement. Basically, we assume that we will have the same result for any of the markers.

In order to highlight the difference between GFR estimation methods in clinical practice (other than AUC), we will exemplify. If we assume that we have a cohort of 170 subjects comprised of all participants from our study, not dividing them into two different study groups, CRS rate assessed by cystatin and creatinine based CKD-EPI equation will be 48.82%, by unadjusted cystatin and creatinine based CKD-EPI

diac patients (n = 2716), cardiology unit patients (n = 980), coronary heart disease unit patients (n = 1464). He attempted to reclassify patients with non-acute cardiac disease distributed inaccurately according to $eGFR_{epi}$ compared to $eGFR_{cys}$. Differences are more evident in more critical situations when we need firmer decisions, however Åkerblom demonstrated that only 53 out of 143 patients with GFR_{cys} could be diagnosed with GFR_{epi}, whereas in 8 cases significant kidney involvement was excluded[13]. Overestimations of creatinine-based GFR were recorded in all groups, with a mean of 10 ml/min/m^2 at a GFR level <90 ml/min/m^2. Several studies have assessed the delayed creatinine elevation in acute cardiac pathology, so Swedish researchers split outpatient and cardiology unit patients in groups without acute pathology. In patients with GFR_{cys} <30 ml/min/m^2, GFR_{epi} had a 13 ml/min/m^2 (22 vs. 35 ml/min/m^2) higher level; for GFR_{cys} = 30 – 59 ml/min/m^2, GFR_{epi} had a 16 ml/min/m^2 (44 vs.

Romanian Journal of Cardiology
Vol. 29, No. 3, 2019

Elena Bivol et al.
Estimation of glomerular filtration rate in type 2 cardiorenal syndrome diagnosis

60 ml/min/m^2) higher level; for GFR$_{cys}$ = 60 – 89 ml/min/m^2, GFRepi had a 10 ml/min/m^2 (74 vs. 84 ml/min/m^2) higher level and for GFR ≥90 ml/min/m^2, there was a 1 ml/min/m^2 difference (101 vs. 102 ml/min/m^2). Another study performed by Kervella D et al. compared GFR levels assessed by different methods in a cohort of subjects with type 2 CRS. Their results confirm GFR overestimation using GFR$_{epi}$ equation (41 ± 20mL/min/1.73 m^2) compared to GFR$_{cys}$ (30 ± 15 mL/min/1.73 m^2), GFRcyscr (34 ± 15 mL/min/1.73 m^2) or GFRm (26 ± 11 mL/min/1.73 m^2)[14].

In conclusion, GFR estimation in HF patients will be more accurate when using adjusted/unadjusted CKD-EPI equations based on cystatin and creatinine levels, adjusted cystatin based CKD-EPI and adjusted creatinine based CKD-EPI.

Analyzing the ROC curve in order to assess cystatin C in CRS diagnostic value, we obtained an AUC of 0.9 (95% CI 0.84-0.94, p <0.001), cystatin C level being an excellent model for CRS diagnosis, but less accurate compared to eGFR. Cystatin C levels can be affected by thyroid dysfunction or steroid use, and can have reduced specificity in concomitant infections15, situations that cannot be totally excluded in hospitalized patients.

Existing studies assess cystatin C as a marker for early differential diagnosis of acute renal injury, and as a prognostic parameter in these patients[16]. As a routine kidney biomarker, compared to serum creatinine, cystatin C is disadvantaged by higher costs, limited accessibility and number of specialists familiar with its reference values and limited use in GFR estimation formulas[17]. Serum creatinine has remained a „gold standard" in clinical practice, being affordable and cost-effective, with medical staff being familiar with its interpretation, and having evidence to support its use in clinical setting. Studies evaluating worsening renal function impact in HF are not an exception to this approach[18,19].

When examining the ROC curve for assessing creatinine diagnostic value in CRS, we obtained an AUC value of 0.877 (95% CI 0.81-0.93, p <0.001). In this way, although creatinine level is a good model for CRS diagnosis, it is less efficient compared to cystatin C and GFR estimated by most equations, except for the Cockroft Gault equation with similar diagnostic value (AUC-0.87).

Serum BUN level was higher in patients with impaired renal function. Similar data were obtained by Palazzuoli[21] who performed an analysis of a cohort of 246 subjects or by Salim[20] who investigated a cohort of 563 subjects with or without HF either associated or not with renal changes.

Traditional renal biomarkers do not provide information regarding the level or cause of kidney dysfunction. Creatinine may be influenced by food intake, muscle mass, gender, medication and other disorders, having, in addition, a slow response compared to other renal biomarkers. Serum BUN level can be influenced by hepatic dysfunction, gastrointestinal hemorrhages, dehydration, steroid use, or protein intake[3].

CONCLUSIONS

1. GFR assessment plays a key role in cardiorenal syndrome diagnosis. Compared to GFR$_{cyscr}$, maximum diagnostic value was found for GFRcys (AUC ROC 0.94) and GFR$_{epi}$ (AUC ROC 0.92) equations, maximal sensitivity was determined for GFRepi (84.34%) and GFR$_{cys}$ (84.15%), while GFR$_{100-cys}$ had maximum specificity (89.39%).
2. GFR estimation using the EPI equation based on cystatin C level or based on cystatin C and creatinine level could be used for the purpose of CRS screening or early diagnosis.
3. Glomerular filtration rate estimation using the classical Cockroft Gault equation showed minimal diagnostic value (AUC ROC 0.87) and the lowest positive predictive value (59.3%).

Conflict of interest: none declared.

References
1. Levey, A.S., Coresh, J., Balk, E., Kausz, A.T., Levin, A., Steffes, M.W. et al „National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification." National Kidney. 2003;139(7):605.
2. Sarnak M.J., Levey A.S., Schoolwerth A.C., Coresh J., Culleton B., Hamm L.L. et al „Kidney Disease as a Risk Factor for Development of Cardiovascular Disease: A Statement From the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention" Circulation. 2003; 108:2154–2169.
3. Silva, P., Nikitin, N.P., Witte, K.K.A., Rigby, A.S., Loh, H. „Effects of applying a standardised management algorithm for moderate to severe renal dysfunction in patients with chronic stable heart failure." European Journal of Heart Failure. 2007; 9:415–423. ISSN: 1879-0844.0.
4. Heywood, J.T., Fonarow, G.C., Yancy, C.W., Albert, N.M., Curtis, A.B., Stough, W.G. et al. „Influence of renal function on the use of guideline-recommended therapies for patients with heart failure." Am J Cardiol., 2010. 105(8):1140-6., ISSN: 0002-9149.
5. Eknoyan G., Levin N.W. Impact of the New K/DOQI Guidelines. Vols. Blood Purif 2002;20:103–108. https://doi.org/10.1159/000046992,
6. Michels WM1, Grootendorst DC, Verduijn M, Elliott EG, Dekker FW, Krediet RT. Performance of the Cockcroft-Gault, MDRD, and new CKD-EPI formulas in relation to GFR, age, and body size. Vols. Clin J Am Soc Nephrol. 2010 Jun;5(6):1003-9. doi: 10.2215/CJN.06870909.

7. Rácz O., Lepej J., Fodor B., Lepejová K., Jarčuška P., Kováčová A. and The Hepameta Study Group. Pitfalls in the Measurements and Assesment of Glomerular Filtration Rate and How to Escape them. Vols. EJIFCC. 2012 Jul; 23(2): 33–40.

8. McAlister FA1, Ezekowitz J, Tarantini L, Squire I, Komajda M, Bayes-Genis A, Gotsman I, Whalley G, Earle N, Poppe KK, Doughty RN and Investigators., Meta-analysis Global Group in Chronic Heart Failure (MAGGIC). Renal dysfunction in patients with heart failure with preserved versus reduced ejection fraction: impact of the new Chronic Kidney Disease-Epidemiology Collaboration Group formula. Vols. Circ Heart Fail. 2012 May 1;5(3):309-14. doi: 10.1161/Circheartfailure.111.966242.

9. Cruz, D.N., Schmidt-Ott, K.M., Vescovo, G., House, A.A., Kellum, J.A., Ronco, C., Mccullough, P.A. „Pathophysiology of Cardiorenal Syndrome Type 2 în Stable Chronic Heart Failure: Workgroup Statements from the Eleventh Consensus Conference of the Acute Dialysis Quality Initiative (ADQI)." Contrib Nephrol., 2013; 182:117-36. ISSN:1662-2782.

10. Rangaswami, J., Bhalla, V., Blair, J.E.A. et. al. „Cardiorenal Syndrome: Classification, Pathophysiology, Diagnosis, and Treatment Strategies: A Scientific Statement From the American Heart Association". Circulation. 2019 March; 139(16):e840-e878. https://doi.org/10.1161/CIR.0000000000000664

11. Ponikowski, P., Voors, A.A., Anker, S.D., Bueno, H., Cleland, J.G.F., Coats, A.J.S. et al. „ Ghidul ESC de diagnostic şi tratament al insuficienţei cardiace acute şi cronice 2016." Romanian Journal of Cardiology. 2017, 27(4): 545-642.

12. Williams, B., Mancia, G., Spiering, W., Agabiti Rosei, E.A., Michel Azizi, M. „Ghidul ESC/ESH 2018 pentru managementul hipertensiunii arteriale." Romanian Journal of Cardiology. 2018; 28(4): 69-177. ISSN: 1220-658X.

13. Åkerblom A., Helmersson-Karlqvist J., Flodin M., Larsson A. Comparison between Cystatin C- and Creatinine-Estimated Glomerular Filtration Rate in Cardiology Patients. Vols. Cardiorenal Med 2015;5:289–296; DOI: 10.1159/000437273.

14. Kervella D., Lemoine S., Sens F., Dubourg L., Sebbag L.,Cystatin C Versus Creatinine for GFR Estimation in CKD Due to Heart Failure. doi: 10.1053/j.ajkd.2016.09.016. Epub 2016 Nov 18, Vols. Am J Kidney Dis. 2017;69(2):320-323;

15. DammanK., Testani J. "The kidney in heart failure: an update", European Heart Journal (2015) 36, 1437–1444. doi:10.1093/eurheartj/ehv010.

16. Löfman I., Szummer K., Hagerman I., Dahlström U., Lund L.H., Tomas Jernberg T.,. Prevalence and prognostic impact of kidney disease on heart failure patients . Vols. Open Heart 2016; 3:e000324. doi: 10.1136/openhrt-2015-000324.

17. Ruggenenti P., Perna A., Mosconi L., Pisoni R., and Remuzzi G., "Urinary protein excretion rate is the best independent predictor of ESRF in non-diabetic proteinuric chronic nephropathies," Kidney International, vol. 53, no. 5, pp. 1209–1216, 1998.

18. Fu S., Zhao S.,Ye P, Luo L. Biomarkers in Cardiorenal Syndromes. BioMed Research International, Vols. Volume 2018, Article ID 9617363, 8 pages. https://doi.org/10.1155/2018/9617363.

19. Lulloa L Di., . BellasibA., Barberaa V., Russoc D., Russoc L., Ioriod B., Cozzolinoe M.,. Pathophysiology of the cardio-renal syndromes types 1–5: An uptodate. s.l.: Indian Heart Journal 69 (2017) 255–265, Vol. doi: http://dx.doi.org/10.1016/j.ihj.2017.01.005.

20. Shiba N., Matsuki M., Takahashi J., Tada T. Prognostic Importance of Chronic Kidney Disease in Japanese Patients With Chronic Heart Failure.,. Vols. Circ J 2008; 72: 173 –178.

21. Kimmenade RR, Brunner-La Rocca CT, Worsening Renal Function in Heart Failure. , Journal Of The American Colleg E Of Cardiology, Vols. VOL. 69, NO. 1, 2017. ISSN0735-1097http://dx.doi.org/10.1016/j.jacc.2016.11.016.