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**The Shrunken pore syndrome is associated with declined right  
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HARVEST study**

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## Abstract

The close relationship between heart and kidney diseases was studied with respect to the “Shrunken pore syndrome” that is characterized by a difference in renal filtration between cystatin C and creatinine. Patients were retrieved from the HeARt and brain failure inVESTigation trail (HARVEST) which is an ongoing study undertaken in individuals hospitalized for the diagnosis of heart failure. Ninety-five of 116 patients who underwent transthoracic echocardiograms (TTE) were eligible for this study. We used four different formulas for estimated glomerular filtration rate (eGFR); CKD-EPI<sub>creatinine</sub>, CKD-EPI<sub>cystatin C</sub>, LMrev and CAPA. Presence of the syndrome was defined as  $eGFR_{cystatin\ C} \leq 60\%$  of  $eGFR_{creatinine}$  and absence of the syndrome as  $eGFR_{cystatin\ C} >90\%$  and  $<110\%$  of  $eGFR_{creatinine}$ . In a linear regression model, adjusted for age and sex, and the “Shrunken pore syndrome” defined by the equation pair CAPA and LMrev and the equation pair CKD-EPI<sub>cystatin C</sub> and CKD-EPI<sub>creatinine</sub>, echocardiographic parameters were studied. The “Shrunken pore syndrome” showed statistically significant associations with measurements of right ventricular (RV) systolic function; (TAPSE and RV S') (according to the equation pair CKD-EPI<sub>cystatin C</sub> and CKD-EPI<sub>creatinine</sub>)

In conclusion, heart failure patients with the “Shrunken pore syndrome” are at increased risk of having RV systolic dysfunction whilst heart failure patients without “Shrunken pore syndrome” seem protected. These findings may indicate common pathophysiological events in the kidneys and the heart explaining the observed increased risk of mortality in subjects with the “Shrunken pore syndrome”.

Key words: cardiorenal syndrome, creatinine, cystatin C, echocardiography, estimated glomerular filtration rate

## **Introduction**

Cystatin C has consequently been shown to be a more powerful risk marker of cardiovascular disease, hospitalization and death compared to creatinine [1,2], although the reasons behind these findings are yet poorly understood. One hypothesis for the supremacy of cystatin C as a risk marker is that an increase in cystatin C, with a molecular mass of 13343 Da, signals a shrinking of the pores in the glomerular membrane earlier than an increase in creatinine with a molecular mass of 113 Da. Both creatinine and cystatin C are freely filtered over the healthy glomerular membrane. However, with increasing molecular masses the sieving coefficient for molecules is decreased. It has been observed in some cases that the filtration of cystatin C is less than for creatinine and it is hypothesized that this may be due to shrinking of the pores [3]. The “Shrunken pore syndrome” was recently suggested for the pathophysiologic state in patients characterized by an estimation of their glomerular filtration rate (GFR) based upon cystatin C, which is lower or equal to 60% of their estimated GFR (eGFR) based upon creatinine, i.e. when  $eGFR_{\text{cystatin C}} \leq 60\%$  of  $eGFR_{\text{creatinine}}$  [4]. Most recent data have identified the prevalence of the “Shrunken pore syndrome” to be associated with a significant rise in mortality in patients undergoing elective coronary artery bypass grafting (CABG) [5,6] and heart catheterization [7]. The mechanism behind the increased mortality in this high-risk group is yet to be defined and although prevalent left ventricular (LV) systolic dysfunction was entered as a covariate in the multivariate Cox regression analysis in

this study, no adjustment was done for right ventricular (RV) dysfunction, which indeed could have affected the observed long term association seen between the “Shrunken pore syndrome” and mortality. While chronic kidney disease (CKD) is an established predictor of poor survival in patients with heart failure (HF) [8,9], the pathophysiology of CKD in heart failure is complex. Traditional theories point at LV systolic dysfunction causing a decrease in arterial perfusion pressure and renal blood flow as the main source of renal dysfunction in patients with impaired cardiac output [10]. However, RV dysfunction has recently been associated with CKD (as measured by eGFR by the simplified Modification of Diet in Renal Disease (MDRD) formula) as well as with a significant poorer survival in outpatients with chronic systolic HF. These data suggest RV dysfunction to be one of the possible mechanistic links between HF and CKD [11].

Therefore, in this study we aimed to examine if subjects with or without the “Shrunken pore syndrome” differed in risk of having cardiac dysfunction (e.g. RV dysfunction) as measured by echocardiographic imaging in a high risk HF population recruited from the ongoing HeARt and brain failure inVESTigation trail (HARVEST).

## **Materials**

The HeARt and brain failure inVESTigation trail (HARVEST) is an ongoing study undertaken in individuals hospitalized for the diagnosis of HF in the city of Malmö, Sweden. The inclusion criteria for the HARVEST study are admission to medical or cardiology clinical for treatment under the diagnosis CHF (regardless if the CHF is chronic or newly discovered). The only exclusion criterion is the inability to deliver oral and written consent to the study. For patients with severe cognitive impairment,

defined as mini mental test examination (MMSE) score <13 points, the relatives are instead be informed and asked for permission for the patient's behalf. This has been entered in the method section. Between March of 2014 and November of 2015, 143 consecutive patients hospitalized for HF were included. Of those, 116 underwent transthoracic echocardiograms (TTE), blood sample donations and a clinical examination. Technically adequate TTE's were present in 109 subjects. Excluding subjects with missing covariate data resulted in 95 eligible subjects. The study was approved by the Ethical Review Board at Lund University, Sweden. A written informed consent was obtained from all participants.

## **Methods**

The re-examination included anthropometric measurements and blood samples drawn after overnight fast. Systolic (SBP) and diastolic (DBP) blood pressure was obtained after 10 minutes of rest in the supine position. Body mass index (BMI) was calculated as kg/m<sup>2</sup>. Body surface area (BSA) was calculated according to DuBois formula [12]. Prevalent diabetes was defined as either self-reported physician diagnosis of type 2 diabetes or use of antidiabetic medication, or fasting plasma glucose  $\geq 7$  mmol/L.

### **Laboratory assays and GFR estimations**

Measurements of creatinine and cystatin C were carried out at the Department of Clinical Chemistry, Skåne University Hospital in Malmö, participating in a national standardization and quality control system. The analyses were performed during November 2015. Plasma creatinine was measured using an enzymatic colorimetric assay with an IDMS-traceable calibrator on the Hitachi Modular P analysis system

(Roche, Basel, Switzerland) [13]. The total analytical imprecision was 3.0% (with a concentration of 60  $\mu\text{mol/L}$  in control sample) and 1.4% (with a concentration of 578  $\mu\text{mol/L}$  in control sample; normal reference range: 60–100  $\mu\text{mol/L}$  for men and 50–90  $\mu\text{mol/L}$  for women). The plasma level of cystatin C was determined by an automated particle-based immunoassay, adjusted to the international reference preparation ERM-DA 471/IFCC [14], using the Hitachi Modular P analysis system and reagents from DAKO (Dako A/S, Glostrup, Denmark). The total analytical imprecision was 2.1% (with concentration of 1.0 mg/L in control sample) and 1.7% (with concentration of 4.0 mg/L in control sample).

The CAPA [14] and the CKD-EPI<sub>cystatin C</sub> [15] estimating equations, based on cystatin C, were used to estimate GFR. So were the LMrev [13] and CKD-EPI<sub>creatinine</sub> [15] estimating equations based on creatinine. The best estimate of GFR is the mean of eGFR<sub>cystatin C</sub> and of eGFR<sub>creatinine</sub> (eGFR<sub>mean</sub>) and this is true also when eGFR<sub>cystatin C</sub> and eGFR<sub>creatinine</sub> differ significantly [13,15-18]. We used the eGFR<sub>mean</sub> to describe the renal function in the whole cohort.

### **Echocardiography**

Conventional TTEs were obtained using an Philips IE33 (Philis, Andover, Massachusetts, A, USA) with a 1-5 MHz transducer (S5-1), or with a GE Vingmed Vivid 7 Ultrasound (GE, Vingmed Ultrasound, Horten, Norway) with a 1-4 MHz transducer (M3S). Experienced sonographers performed all studies. Cine loops were obtained from standard views (parasternal long axis, apical 4- and 2-chamber). Measurements were done offline using Xcelera 4.1.1 (Philips Medical Systems, Netherlands) according to the recommendations of the American Society of Echocardiography [19].

Internal left and right ventricular dimensions were measured from parasternal long axis view at end-diastole. Measurements of wall thickness were obtained in two-dimensional end-diastolic parasternal long axis view. Left ventricle mass (LVM) was calculated according to Devereux formula:  $LVM (g) = 0,8 \{ 1,04[(LVd+PWd+IVSd)^3 - LVd^3] \} + 0,6$ . Left ventricular volumes were calculated using biplane Simpson method of disks, by manual tracing (papillary muscles included in the cavity) in two-dimensional end-diastolic and end-systolic frames defined as the largest and smallest left ventricular cavities, respectively, in apical 4- and 2-chamber projections. Ejection fraction (EF) was calculated automatically from end-diastolic volumes (EDV) and end-systolic volume (ESV) using following formula:  $EF=(EDV-ESV)/EDV$ .

Right ventricular systolic function was measured using Tricuspid annular plane systolic excursion (TAPSE) and pulsed tissue Doppler (DTI)-derived tricuspid annular systolic velocity (S'). For TAPSE measurements, M-mode images in apical 4-chamber view, with the cursor optimally aligned along the direction of the tricuspid annulus, were obtained. For S'-wave velocity measurements, pulsed DTI images were obtained in apical 4-chamber view on the free-wall side of the right ventricle, with basal segment and the annulus aligned with the Doppler cursor.

For assessment of left atrium (LA) volumes, the biplane area-length method was used:  $LA \text{ volume} = (0.85 \times \text{area apical 4-chamber} \times \text{area apical 2-chamber})/(\text{shortest atrial length})$ . The values were indexed to BSA. The LA endocardial borders were manually traced in both apical 4-chamber and 2-chamber views.

Right atrium (RA) volumes were obtained using a single plane disk summation technique in a dedicated apical 4-chamber view.

## Statistics

The variables are presented as absolute numbers with percentages and mean with standard deviation. The cross-sectional association of echocardiographic parameters, divergent cardiac chamber volumes, RV and LV systolic function and LVM in relation to baseline “Shrunken pore syndrome” status (identified both by the equation pair CAPA and LMrev and by the equation pair CKD-EPI<sub>cystatin C</sub> and CKD-EPI<sub>creatinine</sub>) [13-15] was studied using linear regression analysis adjusted for age and sex with the concordant echocardiographic measurement as the dependent variable in model adjusting for age and sex (model 1). The prevalence of “Shrunken poor syndrome was defined as a variable comparing subjects with SPS compared to all other study subjects as defined by either by the equation pair CAPA and LMrev and by the equation pair CKD-EPI<sub>cystatin C</sub> and CKD-EPI<sub>creatinine</sub> and concordantly the absence of the poor syndrome was defined as a variable comparing subjects without SPS compared to all other study subjects as defined by either by the equation pair CAPA and LMrev and by the equation pair CKD-EPI<sub>cystatin C</sub> and CKD-EPI<sub>creatinine</sub>. Echocardiographic variables that were significantly associated with any of the shrunken pore model definitions in this initial age and sex adjusted linear regression analysis were further tested in a multivariate linear regression model 2 (adjusted for age, sex, BMI, SBP and prevalent diabetes) again with the echocardiographic variables as the dependent variable..

As all echocardiographic parameters were normally distributed the echocardiographic variables with significant association ( $p < 0.05$ ) with baseline shrunken pore status in the fully adjusted linear regressions according to model 2 were also tested with these variables dichotomized according to existing guidelines (i.e. tricuspid annular plane systolic excursion (TAPSE)  $< 16$  mm and tricuspid anular systolic velocity (RV S $\dot{}$ )  $<$

10 cm/s)<sup>18</sup>. All analyses were performed using IBM SPSS Statistics version 23 (SPSS, Chicago, IL). All tests were 2-sided, whereby  $P < 0.05$  was considered statistically significant.

## **Results**

### **Study population characteristics**

The study population is described in table I (study participants characteristics) and supplementary table I (echocardiographic variables).

The “Shrunken pore syndrome” was identified both by the equation pair CAPA and LMrev and by the equation pair  $\text{CKD-EPI}_{\text{cystatin C}}$  and  $\text{CKD-EPI}_{\text{creatinine}}$  in this study.

The definition of having or not having prevalent “Shrunken pore syndrome” was for both the CAPA/LMrev ratio and  $\text{CKD-EPI}_{\text{cystatin C}} / \text{CKD-EPI}_{\text{creatinine}}$  ratios  $\leq 0.6$  (prevalent) and ratios  $>0.9$  and  $<1.1$  (not prevalent), respectively. Thus we identified 10 subjects with and 29 subjects without the “Shrunken pore syndrome” according to equation pair CAPA and LMrev and 21 subjects with and 19 subjects without according to equation pair  $\text{CKD-EPI}_{\text{cystatin C}}$  and  $\text{CKD-EPI}_{\text{creatinine}}$ . This resulted in a prevalence of the “Shrunken pore syndrome” of 10.5% (10/95) and 22.1% (21/95), respectively. Patients without the “Shrunken pore syndrome” showed an  $\text{eGFR}_{\text{mean}}$  of 47.5 mL/min/1.73m<sup>2</sup> compared to 47.3 mL/min/1.73m<sup>2</sup> for those with the “Shrunken pore syndrome” (ns).

### **Shrunken pore syndrome and association with RV systolic function parameters as continuous variables**

In the age and sex adjusted linear regression analysis exploring the association between the “Shrunken pore syndrome” as defined by the equation pair CAPA and LMrev and the equation pair CKD-EPI<sub>cystatin C</sub> and CKD-EPI<sub>creatinine</sub> and echocardiographic parameters, the “Shrunken pore syndrome” showed statistically significant associations with measurements of RV systolic function; (TAPSE and RV S´) (according to the equation pair CKD-EPI<sub>cystatin C</sub> and CKD-EPI<sub>creatinine</sub>) and RA volume (according to the equation pair CAPA and LMrev ) (Table II).

In the fully adjusted linear regression analysis adjusted for model 2, measurements of RV systolic function; (TAPSE and RV S´) remained significantly associated with the “Shrunken pore syndrome” defined by the equation pair CKD-EPI<sub>cystatin C</sub> and CKD-EPI<sub>creatinine</sub> (Table III). Thus, subjects with prevalent “Shrunken pore syndrome” were significantly associated with attenuated RV systolic function defined by RV S´ (Beta coefficient (B), standard error (SE); -1.35 (0.64) p=0.038 and borderline significantly with attenuated RV systolic function according TAPSE (B: -2.13 (1.23), p=0.086. In accordance, subjects without prevalent “Shrunken pore syndrome” were significantly associated with improved RV systolic function defined by RV S´ (B: 1.75 (0.67) p=0.010 and also significantly associated with improved RV systolic function defined by TAPSE (B: 2.83 (1.28), p=0.029 (Table III).

### **Shrunken pore syndrome and validation of cut-off points for RV systolic dysfunction**

RV systolic dysfunction was defined according to the American Society of Echocardiography guidelines (e.g. TAPSE < 16 mm and RV S´ < 10 cm/s) [20].

Subjects with “Shrunken pore syndrome” as defined by the equation pair CKD-EPI<sub>cystatin C</sub> and CKD-EPI<sub>creatinine</sub> had a significantly 3.5 fold increased risk of having RV systolic dysfunction as defined by TAPSE < 16 mm (Odds ratio (95% CI); 3.51 (1.12-11.00), p=0.031 and a borderline significant 2.2 fold risk of having RV systolic dysfunction as defined by RV S' < 10 cm/s (OR 2.25 (0.76-6.72), p=0.145) in the multivariate logistic regression analysis adjusted according to model 2 (Table IV). In accordance, subjects without the “Shrunken pore syndrome” had a significantly decreased risk of RV systolic function as defined by TAPSE < 16 mm (OR 0.23 (0.06-0.89), p=0.033) as well as RV S' < 10 cm/s (OR 0.24 (0.08-0.74), p=0.014) in the multivariate logistic regression analysis adjusted according to model 2 (Table IV).

## Discussion

The key finding of this study is that HF patients with “Shrunken pore syndrome” as defined by equation pair CKD-EPI<sub>cystatin C</sub> and CKD-EPI<sub>creatinine</sub> are at increased risk of having RV systolic dysfunction whilst HF patients without “Shrunken pore syndrome” are protected from RV dysfunction.

The concept of the “Shrunken pore syndrome” was suggested from a recent study of 1349 consecutive patients, for which eGFR was requested at the Department of Clinical Chemistry [4]. To estimate GFR, both the LMrev-equation based upon creatinine, and the CAPA-equation based upon cystatin C, were used and the “Shrunken pore syndrome” was defined by eGFR<sub>cystatin C</sub> being less or equal to 60% of eGFR<sub>creatinine</sub> in a patient [4]. In a most recent follow up study by Dardashti and coworkers, prevalence of the “Shrunken pore syndrome” was identified as an

independent risk factor of increased mortality after CABG surgery after 3.5 years of follow up, displaying hazard ratios (HR) for mortality of 2.74; 95% CI (1.73–4.34),  $p < 0.001$  for the “Shrunken pore syndrome” defined by the equation pair CKD-EPI<sub>cystatin C</sub> and CKD-EPI<sub>creatinine</sub> with a cut-off of 60% and HR of 3.45; 95% CI (1.81–6.56),  $p < 0.0001$  for the “Shrunken pore syndrome” defined by the equation pair CAPA and LM<sub>rev</sub> with a cut-off of 60% (which are the same cut-offs used in this study). However, Dardashti et al. found no associations in their study between LV systolic function (as measured as ejection fraction (EF%)) and prevalence of the “Shrunken pore syndrome” in either of the two definitions of the syndrome [5]. In concordance with these findings, in our study, prevalence of the “Shrunken pore syndrome” was not associated with LV systolic dysfunction (EF%) (Table II). Unfortunately, no comparable measurements for RV systolic function were accounted for in the study by Dardashti and coworkers [5].

Although we found convincing associations between subjects with and without the “Shrunken pore syndrome” and risk of RV systolic dysfunction as defined by the equation pair CKD-EPI<sub>cystatin C</sub> and CKD-EPI<sub>creatinine</sub> with a cut-off of 60%, this could not be reproduced to “Shrunken pore syndrome” as defined by the equation pair CAPA and LM<sub>rev</sub> with a cut-off of 60%, although the directionality of the results were all in line with results from the “Shrunken pore syndrome” as defined by the equation pair CKD-EPI<sub>cystatin C</sub> and CKD-EPI<sub>creatinine</sub>. We stipulated that the reason behind this could be a lack of power since the CAPA and LM<sub>rev</sub> cut-off of 60% only defined 10 patients with the “Shrunken pore syndrome” compared to 21 with CKD-EPI<sub>cystatin C</sub> and CKD-EPI<sub>creatinine</sub> cut-off of 60%. Hence, the CKD-EPI<sub>creatinine</sub> estimation equation produced significantly higher GFR estimates than LM<sub>rev</sub> in the patient cohort studied here. The average GFR value for the cohort was 59

mL/min/1.73 m<sup>2</sup> as estimated by CKD-EPI<sub>creatinine</sub>, whereas the averages estimated by CKD-EPI<sub>cystatin C</sub>, LM<sub>rev</sub> and CAPA were 42, 53 and 43 mL/min/1.73 m<sup>2</sup>, respectively (Table I). This means that relatively minor changes in estimates based upon CKD-EPI<sub>cystatin C</sub> are required to reach the criterion of eGFR<sub>cystatin C</sub> < 60% of eGFR<sub>creatinine</sub>, when the equation pair CKD-EPI<sub>cystatin C</sub> and CKD-EPI<sub>creatinine</sub> is used. Therefore, to compare the potential of the two equation pairs to identify patients with RV systolic dysfunction we increased the cut-off level defining “Shrunken pore syndrome” by the equation pair CAPA and LM<sub>rev</sub> to eGFR<sub>cystatin C</sub> < 70% of eGFR<sub>creatinine</sub> and related it to RV systolic function. Though the prevalence thus increased (n=20), this redefinition of the “Shrunken pore syndrome” was still not significantly associated with RV dysfunction, however the directionality was still coherent with that of the “Shrunken pore syndrome” defined by the equation pair CKD-EPI<sub>cystatin C</sub> and CKD-EPI<sub>creatinine</sub> with a cut-off of 60% equation (supplementary Table II). The reason behind this discrepancy of the two eGFR pairs is most likely due to the fact that CKD-EPI<sub>creatinine</sub> results in a higher level than LM<sub>rev</sub> and thus more persons are defined as having the “Shrunken pore syndrome” with the pair CKD-EPI<sub>cystatin C</sub> and CKD-EPI<sub>creatinine</sub>. However, this has to be further investigated in larger HF populations.

Attenuated LV systolic function and renal blood flow are strong factors of kidney dysfunction (e.g. GFR) in patients with chronic HF, so-called forward failure. However, while decreased LV systolic function may contribute to decreased renal blood flow and decreased GFR in advanced HF, elevated renal venous pressure from backward failure due to RV dysfunction may also play an important and possibly earlier role in the pathophysiology of impaired renal function in chronic HF. This

might explain our findings showing a significant association between the “Shrunken pore syndrome” and RV dysfunction, whilst no associations were seen for LV systolic dysfunction [21,22].

The association between the “Shrunken pore syndrome” and RV dysfunction may be part of the link between the heart and the kidneys, the so-called “Cardiorenal syndrome” [23]. We hypothesize that the difference in filtration fraction between cystatin C and creatinine in the glomerular membrane in those with the “Shrunken pore syndrome” may describe similar endothelial and structural changes in the coronary vessels and/or microcirculation of the myocardium as in the kidney. In the beginning of the pathophysiological process, affecting heart and kidneys, a narrowing of the pores in the endothelium may be a common pathway in both organs and part of the explanation for the cardiorenal syndrome. We can demonstrate that the renal function, based on  $eGFR_{\text{mean}}$  from both creatinine and cystatin C, was similar between those without and with “Shrunken pore syndrome” indicating that the two groups did not differ in this respect.

Our study has both strengths and limitations. By consecutively including patients admitted to the hospital with the diagnosis of HF and no other exclusion criteria (except for not being able to give consent to the study) we have most likely mimicked a representative HF population. Also by adjusting for other known risk factors such as age, sex, diabetes status, BMI and systolic blood pressure, we believe that we illustrated that the “Shrunken pore syndrome” may have a role in RV dysfunction. The HARVEST trial is conducted at a single regional center, which usually limits the applicability to other populations. However, a multi-center study would probably

result in a greater inter-intra observer bias in echocardiographic measurements. As this is a cross-sectional study, it shares the inherent limitations about causality and control as all cross-sectional studies. Furthermore, our sample size was relatively small and despite significant associations, the results warrant replication in a larger cohort.

Finally, the study was undertaken in individuals of mainly Swedish descent, and the conclusions may not be generalizable to all ancestries.

## **Conclusion**

Heart failure patients with “Shrunken pore syndrome” are at increased risk of having RV systolic dysfunction whilst HF patients without “Shrunken pore syndrome” seem protected. These findings might serve as a mechanistic explanation for the previously observed increased risk of mortality in subjects with the “Shrunken pore syndrome”.

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**Table I. Baseline Characteristics of the HARVEST population**

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<b>Study sample</b>	
<b>N</b>	95
<b>Sex (% women)</b>	29.5
<b>Age (years)</b>	73.5 ( $\pm$ 11.2)
<b>Systolic BP (mmHg)</b>	132.6 ( $\pm$ 24.9)
<b>Diastolic BP (mmHg)</b>	77.6 ( $\pm$ 11.7)
<b>Body mass index (kg/m<sup>2</sup>)</b>	27.5 ( $\pm$ 5.5)
<b>Prevalent diabetes (%)</b>	37.9
<b>Cystatin C (mg/L)</b>	1.7 ( $\pm$ 0.5)
<b>Creatinine (mmol/L)</b>	112.3 ( $\pm$ 42.7)
<b>eGFR (mL/min/1.73 m<sup>2</sup>) according to:</b>	
<b>CAPA</b>	43.3 ( $\pm$ 17.2)
<b>LMrev</b>	52.7 ( $\pm$ 20.7)
<b>CKD-EPI<sub>cystatin C</sub></b>	42.3 ( $\pm$ 18.6)
<b>CKD-EPI<sub>creatinine</sub></b>	58.9 ( $\pm$ 23.3)

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Data are expressed as mean ( $\pm$ SD). BP=blood pressure; GFR=glomerular filtration rate.

**Table II. Echocardiographic predictors in subjects with and without the Shrunken Poor Syndrome (SPS) among 95 patients with systolic heart failure adjusted for age and sex.**

Variable	Subjects with SPS based on the CKD-EPI formula (n=21 of the total 95 subjects)		Subjects without SPS based on the CKD-EPI formula (n=19 of the total 95 subjects)		Subjects with SPS based on the CAPA and LMrev formula (n=10 of the total 95 subjects)		Subjects without SPS based on the CAPA and LMrev formula (n=29 of the total 95 subjects)	
	Beta-coefficient (SE)	p-value	Beta-coefficient (SE)	p-value	Beta-coefficient (SE)	p-value	Beta-coefficient (SE)	p-value
EF (%)	3.65 (3.96)	0.358	5.09 (4.18)	0.226	3.78 (5.41)	0.448	-5.20 (3.59)	0.151
LA (ml/m <sup>2</sup> )	3.44 (5.64)	0.544	-5.64 (5.97)	0.346	8.41 (7.67)	0.276	4.69 (5.14)	0.363
RA (ml/m <sup>2</sup> )	0.715 (6.01)	0.906	-7.19 (6.33)	0.259	-0.80 (8.21)	0.923	<b>11.09 (5.36)</b>	<b>0.041</b>
RVID (mm)	1.93 (1.48)	0.196	-0.31 (1.59)	0.848	2.23 (2.03)	0.274	-1.66 (1.36)	0.223
IVSd (mm)	0.21 (0.89)	0.813	0.23 (0.94)	0.812	-0.38 (1.22)	0.755	0.36 (0.81)	0.654
LVID (mm)	-0.10 (2.57)	0.969	-1.09 (2.72)	0.689	-1.32 (3.51)	0.708	0.56 (2.34)	0.812
PWd (mm)	0.06 (1.58)	0.969	0.13 (1.68)	0.941	1.23 (2.15)	0.570	1.81 (1.43)	0.209
LVID (mm)	-1.61 (3.05)	0.600	-3.78 (3.22)	0.242	-2.43 (4.16)	0.561	1.62 (2.78)	0.561
LVM (g)	9.79 (20.6)	0.636	3.15 (21.9)	0.886	7.07 (29.2)	0.785	3.71 (18.8)	0.844
TAPSE (mm)	-2.00 (1.24)	0.111	<b>3.09 (1.30)</b>	<b>0.019</b>	-2.52 (1.70)	0.143	1.07 (1.15)	0.354
RV S' (cm/s)	<b>-1.23 (0.64)</b>	<b>0.058</b>	<b>1.84 (0.67)</b>	<b>0.008</b>	-1.23 (0.88)	0.166	0.03 (0.60)	0.963

Linear regressions are adjusted for age and sex. Data are expressed as mean  $\pm$  SD. EF; ejection fraction, RA; right atrium, RVID; right ventricular inner diameter diastole, LVID; left ventricular inner diameter diastole, IVSd; interventricular systolic diameter diastole, LVI; left ventricular inner diameter systole, PWd; posterior wall diameter diastole, LVM; left ventricular mass, TAPSE; tricuspid annular plane systolic excursion, RV S'; tricuspid annular systolic velocity. Figures in bold indicate

statistical significant difference. n=95 subjects.

**Table III. Multivariate analysis of echocardiographic predictors in subjects with and without the Shrunken Poor Syndrome (SPS) among 95 patients with systolic heart failure**

Variable	Subjects with SPS based on the CKD-EPI formula (n=21 of the total 95 subjects)		Subjects without SPS based on the CKD-EPI formula (n=19 of the total 95 subjects)		Subjects with SPS based on the CAPA and LMrev formula (n=10 of the total 95 subjects)		Subjects without SPS based on the CAPA and LMrev formula (n=29 of the total 95 subjects)	
	Beta-coefficient (SE)	p-value	Beta-coefficient (SE)	p-value	Beta-coefficient (SE)	p-value	Beta-coefficient (SE)	p-value
RA (ml/m <sup>2</sup> )	-1.33 (6.00)	0.824	-8.19 (6.27)	0.195	-3.83 (8.24)	0.642	9.07 (5.51)	0.103
TAPSE (mm)	-2.13 (1.23)	0.086	<b>2.83 (1.28)</b>	<b>0.029</b>	-2.49 (1.69)	0.145	1.45 (1.15)	0.211
RV S' (cm/s)	<b>-1.35 (0.64)</b>	<b>0.038</b>	<b>1.75 (0.67)</b>	<b>0.010</b>	-1.19 (0.89)	0.184	0.05 (0.61)	0.931

Linear regressions are adjusted for age, sex, body mass index (BMI), prevalent diabetes and systolic blood pressure (SBP). RA; right atrium, TAPSE; tricuspid annular plane systolic excursion, RV S'; tricuspid annular systolic velocity. Figures in bold indicate statistical significant difference. n=95 subjects.

**Table IV: Prevalence of Shrunken Poor Syndrome based on the CKD-EPI formula and relations to cut off limits for impaired RV systolic dysfunction**

Dichotomous variables	TAPSE (below 16 mm)			RV S' (below 10 cm/s)		
<i>Regressions below are adjusted for age and sex</i>						
	OR	95% CI	p-value	OR	95% CI	p-value
Prevalent SPS according to CKD-EPI formula (n=21)	<b>3.12</b>	<b>1.11-8.76</b>	<b>0.031</b>	2.11	0.73-6.07	0.166
No SPS according to CKD-EPI formula (n=19)	<b>0.28</b>	<b>0.09-0.90</b>	<b>0.032</b>	<b>0.24</b>	<b>0.08-0.73</b>	<b>0.012</b>
<i>Regressions below are adjusted for age, sex, BMI, prevalent diabetes and systolic blood pressure</i>						
	OR	95% CI	p-value	OR	95% CI	p-value
Prevalent SPS according to CKD-EPI formula (n=21)	<b>3.51</b>	<b>1.12-11.00</b>	<b>0.031</b>	2.25	0.76-6.72	0.145
No SPS according to CKD-EPI formula (n=19)	<b>0.23</b>	<b>0.06-0.89</b>	<b>0.033</b>	<b>0.24</b>	<b>0.08-0.74</b>	<b>0.014</b>

Logistic regression analysis adjusted for model 1 and model 2 respectively. SPS; shrunken poor syndrome. TAPSE; tricuspid annular plane systolic excursion, RV S'; tricuspid annular systolic velocity. n=95 subjects.

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