ESC HEART FAILURE
ESC Heart Failure 2020; **7:** 2581–2588
Published online 30 June 2020 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.12835

ORIGINAL RESEARCH ARTICLE

New renal haemodynamic indices can predict worsening of renal function in acute decompensated heart failure

Amir Mostafa[1]*, Karim Said[1], Walid Ammar[1], Ahmed Elsayed Eltawil[2] and Magdy Abdelhamid[1]

[1]*Cardiology Department, Kasr Alainy School of Medicine, Cairo University, New Cairo, 5th settlement, Cairo, 11865, Egypt;* [2]*Clinical Pathology Department, Kasr Alainy School of Medicine, Cairo University, Cairo, Egypt*

Abstract

Aims Worsening of renal function (WRF) is a common complication in patients with acute decompensated heart failure (ADHF). We aimed to evaluate the role of intrarenal Doppler ultrasound (IRD) in the early prediction of WRF in this patient group.

Methods and results Among 90 patients (age: 57.5 ± 11.1 years; 62% male) hospitalized with ADHF, resistivity index (RI), acceleration time (AT), and pulsatility index (PI) were measured on admission and at 24 and 72 h. WRF was defined as increased serum creatinine ≥0.3 mg/dL from baseline. Adverse clinical outcomes were defined as the composite of death, use of vasopressors, and need for ultrafiltration for refractory oedema. WRF developed in 40% of patients. Mean values of renal AT, RI, and PI on admission were 59.7 ± 15, 0.717 ± 0.08, and 1.5 ± 0.48 ms, respectively. At 24 h, there was significant decrease in AT (to 56.7 ± 10 ms, $P = 0.02$) and renal RI (to 0.732 ± 0.07; $P < 0.001$); these changes were maintained up to 72 h. Renal PI showed no significant changes. Independent predictors of WRF were renal AT at 24 h and admission values of renal RI, left ventricular ejection fraction, and plasma cystatin C. Renal AT at 24 h ≥ 57.8 ms had 89% sensitivity and 70% specificity for the prediction of WRF. Independent predictors for adverse clinical outcomes were left ventricular end systolic dimension and WRF.

Conclusions Among ADHF patients receiving diuretic therapy, measurement of renal AT and RI by IRD can help identify patients at increased risk for WRF.

Keywords Acute decompensated heart failure; Intrarenal Doppler ultrasound; Worsening of renal function

Received: 7 November 2019; Revised: 15 May 2020; Accepted: 27 May 2020
**Correspondence to:*
Amir Mostafa Abdel Megeed, Cardiology Department, Kasr Alainy School of Medicine, Cairo University, New Cairo, 5th settlement, Cairo 11865, Egypt. Tel: +20010035670 41. Email: amirmostafa_2007@hotmail.co.uk.

Introduction

Worsening of renal functions (WRFs) is a common complication in patients with acute decompensated heart failure (ADHF) with an incidence between 20% and 50%[1–3] and with increased risk of morbidity and mortality.[4] Early identification of WRF is an important key point for proper management and prevention of subsequent complications. Unfortunately, the early identification of WRF is highly challenging as the use of serum creatinine and estimated glomerular filtration rate (eGFR) has multiple limitations.[5] Accordingly, efforts are directed to discover better predictors for the development of WRF.

Alternation of the intrarenal haemodynamics, mediated by low renal perfusion pressure and neuro-hormonal activation, may contribute to the development of WRF in response to diuretic use among patients with ADHF.[6–8] Therefore, identification of changes in renal haemodynamics in these patients may aid in the early detection of WRF and hence in the prevention of its consequences. Intrarenal Doppler ultrasound (IRD) is a non-invasive bedside tool with good accuracy in defining changes in renal hemodynamics.[9] Furthermore, IRD-derived indices were previously shown to be associated with increased cardiovascular events.[10,11] However, no adequate data exist to describe the relation between changes in IRD indices and WRF when diuretic therapy is initiated or intensified in ADHF

patients. Accordingly, this study was conducted to describe changes in selected IRD-derived indices used to evaluate hemodynamic alterations in hospitalized ADHF patients receiving diuretic therapy and to study the potential relation between these changes and the development of WRF.

Methods

This was a prospective study that recruited patients with ADHF admitted to the Heart Failure Unit of the Cardiology Department in Kasr Alainy Hospital, Cairo University between June 2016 and January 2017. The investigation conforms with the principles outlined in Declaration of Helsinki[12] and was approved by the ethical committee. All patients provided informed consents.

Patients with ADHF were defined based on the presence of rapid onset of, or change in symptoms (breathless, ankle swelling, and fatigue) and/or signs (elevated jugular venous pressure, pulmonary crackles, and peripheral oedema) of heart failure requiring intravenous diuretic therapy.[13] Only patients with New York Heart Association function Class III or IV were included with no specific inclusion criterion based on left ventricular (LV) ejection fraction.

Patients were excluded from the study if they were <18 years or having one of the following: cardiogenic shock, acute myocardial infarction, atrial fibrillation, eGFR < 30 mL/min, stenotic valvular heart disease beyond moderate severity, sepsis, pregnancy, renovascular disease, obstructive uropathy, or technical difficulties in imaging renal vessels by IRD.

All eligible patients had IRD and echocardiographic examinations within 6 h of admission and after 24 and 72 h thereafter. During hospitalization, all patients were followed up with special emphasis on the response to diuretic therapy and changes in renal functions.

Assessment of response to diuretics

Per protocol, all patients received IV furosemide; the route of administration (IV boluses or infusion), the titration of the dose, and the addition of other diuretic agents in case of inadequate response were left to the discretion of the treating physicians. For every patient, the total daily furosemide dose and the 72 h cumulative furosemide dose were calculated.

Response to diuretics was assessed daily in the first 3 days of admission in terms of change in the clinical status, change in body weight, and total net fluid loss defined as the total amount of urine output minus the total amount of fluid intake at 72 h.

A sample of blood was taken on admission for the measurement of serum urea, serum creatinine, and plasma cystatin C. In addition, serum creatinine, eGFR (calculated by Cockcroft–Gault formula),[14] and serum urea levels were measured daily for the first 72 h while plasma cystatin C levels were measured at 24 and 72 h. WRF was defined as an increase in the serum creatinine level $\geq$0.3 mg/dL within 72 h of admission.[15]

Echocardiographic examination

Within 6 h of admission, all patients had transthoracic echocardiography to measure LV dimensions; LV ejection fraction by Simpson's method; indexed left atrial volume; diastolic function, E/e ratio over the lateral mitral annulus; severity of mitral and tricuspid regurgitation; pulmonary artery systolic pressure; and tricuspid annular peak systolic excursion.[16] Calculation of E/e ratio and pulmonary artery systolic pressure was repeated at 24 and 72 h.

Intrarenal duplex examination

Intrarenal Doppler ultrasound studies were performed using Philips iE3 machine (Philips Medical Systems, Andover, Massachusetts) equipped with sector array transducer of 3.5 and 5 MHz for both kidneys. Measurements of the renal resistivity index (renal RI), pulsatility index (renal PI) and acceleration time (renal AT) were performed at the level of the segmental, interlober, and arcuate arteries in the upper, middle, and lower thirds of each kidney, and then, the average of these measurements were taken. To standardize the measurements, all studies were performed in the supine position, from the lateral lumbar window with attempt to make the angle between the ultrasound beams and the flow direction of the examined vessels of the kidney less than 30°, and patients were asked to avoid Valsalva.[17]

Renal RI was computed as PSV-EDV/PSV where PSV indicates peak systolic velocity and EDV indicates end-diastolic velocity. Renal AT was measured as the time from the beginning of systole to the maximum systolic velocity. Renal PI was calculated as PSV-EDV/mean velocity where mean velocity is the sum of the PSV and EDV divided by 2.[17]

'Adverse clinical outcome' was defined as the composite of death, need for ultrafiltration for refractory oedema, and use of vasopressors for hypotension during the whole period of hospitalization.

Statistical analysis

All statistical analyses were performed using SPSS for Windows (17.0, SPSS Inc.). All continuous variables—except for duration of hospitalization—showed normal distribution when assessed by Kolmogorov–Smirnov test. Continuous variables were presented as mean

± standard deviation while categorical data were summarized as number (percentage). Analysis of variance test was used to assess differences in laboratory and IRD variables obtained on admission and at 24 and 72 h. Bivariate correlations were analysed by Pearson's test.

Clinically relevant variables were used to identify univariate predictors of WRF using Student sample *t*-test for continuous variables and χ^2-square test for categorical variables; then, stepwise multiple linear regression analysis was performed to assess the independent predictors. Variables used in univariate comparison were age, gender, body mass index, diabetes, systolic blood pressure, prior heart failure hospitalization, coronary artery disease, use of angiotensin blockers, laboratory variables (admission levels of creatinine, urea, cystatin C, sodium, and potassium), echocardiographic variables [LV volumes and ejection fraction, E/e ratio, and tricuspid annular peak systolic excursion (TAPSE)], pulmonary artery systolic pressure, and IRD variables (renal RI, renal PI, and renal AT on admission and at 24 h). Same variables—in addition to WRF—were used to identify independent predictors of adverse clinical outcome.

Receiver operating characteristics curves were used to choose cut-offs with best sensitivity and specificity. A P value $\leq$ 0.05 was considered to indicate statistical significance.

Intraobserver variability was expressed as the mean percent error, derived as the absolute difference between the two sets of observations, divided by the mean of the observations then intraclass correlation coefficient was obtained. Mean difference and mean percent error were 0.01 (1.1%) for renal RI, 0.09 (1.4%) for renal PI, 2 ms (1.3%) for renal AT, and 0.05 mg/dL (1.3%) for serum creatinine respectively. Corresponding intraclass correlation coefficient values were 0.94, 0.93, 0.95, and 0.94 ($P < 0.001$).

Results

Among 102 eligible patients, 12 patients were excluded during the course of the study because of technical difficulties in assessing the intrarenal vessels (six patients), death before completing the follow up studies (three patients) and consent withdrawal (three patients). Accordingly, 90 patients constituted the study population.

Baseline characteristics

Baseline clinical characteristics of the study population are listed in *Table 1*. Main causes of heart failure were ischemic cardiomyopathy in 62 patients (69%), idiopathic dilated cardiomyopathy in 18 patients (20%), and valvular heart disease in 10 patients (11%).

Response to diuretic therapy

Furosemide was given as intermittent IV boluses in 72 patients (80%) and as intravenous infusion in 18 patients (20%). Mean total daily dose of furosemide was 97 ± 59 mg, and the 72 h cumulative furosemide dose was 604 ± 344 mg. The total net fluid loss was 2357 ± 765 mL, and the mean decrease in body weight in 72 h was 2.5 kg (range 0–7 kg). The majority of patients (73%) were in New York Heart Association function Class II at 72 h after admission.

Table 1 Baseline characteristics of the study participants

Variable	
Clinical and laboratory data	
Age (year)	57.5 ± 11.1
Male	56 (62.2)
Body mass index (kg/m^2)	29.3 ± 4.9
Body mass index ≥ 30	43 (47.8)
Current smokers	32 (35.6)
Diabetes mellitus	46 (51.1)
Hypertension	48 (53.3)
Heart failure hospitalization in past 6 months	60 (66.7)
Heart rate (bpm)	95.2 ± 20
Respiratory rate (cycle per minute)	28.7 ± 6.2
Elevated jugular venous pressure	71 (78.9%)
Pulmonary rales	89 (98.9%)
Peripheral oedema	75(83.3%)
Systolic blood pressure (mmHg)	136.5 ± 21.27
Heart rate (beat per minute)	95.2 ± 20
NYHA class	
III	25 (27.8)
IV	65 (72.2)
Comorbidities	
Coronary artery disease	62 (68.9)
Peripheral arterial disease	5 (5.6)
Cerebrovascular disease	7 (7.8)
Medications on admission	
Diuretics	65 (72.2)
Renin angiotensin blockers	55 (61.1)
Spironolactone	38 (42.2)
B-blocker	39 (43.3)
Oral hypoglycaemic	26 (28.9)
Insulin	20 (22.2)
Haemoglobin (g/dL)	12.07 ± 2.2
Serum potassium (mEq/L)	4.2 ± 0.7
Serum sodium (mEq/L)	137 ± 4.5
Echocardiographic data	
LV ejection fraction (%)	35.6 ± 9.3
LV ejection fraction < 40%	49 (54)
LV end-systolic dimension (cm)	4.97 ± 0.94
LV end-diastolic dimension (cm)	6.2 ± 0.9
Indexed left atrial volume (mL/m^2)	49 ± 8
Pulmonary artery systolic pressure (mmHg)	37.8 ± 22.2
TAPSE (cm)	1.77 ± 0.37
Moderate to severe mitral incompetence	49 (54.4)
Moderate to severe tricuspid incompetence	27 (30)
Mitral E/e ratio	10.01 ± 4.6
Diastolic dysfunction grade III/IV	22 (24)

LV, left ventricle; NYHA, New York heart association; TAPSE, tricuspid annular peak systolic excursion.
Data are presented as number (%) or mean ± standard deviation.

Renal functions and haemodynamics

Within 72 h of admission, there was significant increase in serum creatinine and plasma cystatin C associated with significant decline in eGFR (*Table 2*). WRF developed in 36 patients (40%) among whom 14 patients (39%) developed WRF in the first 24 h. Notably, only five patients (5.5%) had eGFR < 60 mL/min on admission.

At 24 h, there was significant increase in renal RI and decrease in renal AT; these changes were maintained up to 72 h. Renal PI showed no significant changes during the study period (*Table 2*).

Predictors of worsening of renal function

Multivariate stepwise regression analysis using significant variables obtained by comparing patients with vs. without WRF (*Table 3*) revealed four independent predictors that can explain 40% of the variability of WRF (*Table 4*). Renal AT at 24 h $\geq$ 57.8 ms had 89% sensitivity and 70% specificity for the prediction of WRF (area under the curve 0.8; $P = 0.0001$) with a positive predictive value of 65% and a negative predictive value of 90% (*Figure 2*). When patients were dichotomized on the basis of renal AT at 24 h, those with

Table 2 Changes in renal functions and intrarenal duplex

	Admission	Fu-24 h	Fu-72 h	P^a
Renal function				
Serum creatinine (mg/dL)	1.14 ± 0.26	1.26 ± 0.39	1.31 ± 0.35	0.0001
Serum urea (mmol/L)	60.9 ± 38	64.07 ± 39.8	67.96 ± 42.7	0.033
eGFR (mL/min)	87.3 ± 26.6	82.98 ± 34.6	77.5 ± 27.2	0.02
Plasma cystatin C (mg/L)	1822.7 ± 553	2027.9 ± 710	2,102 ± 729	0.05
Intrarenal duplex				
Renal RI	0.717 ± 0.08	0.732 ± 0.07	0.734 ± 0.077	0.0001
Renal PI	1.5 ± 0.48	1.48 ± 0.44	1.52 ± 0.47	0.74
Renal AT (ms)	59.7 ± 15	56.7 ± 10	56.6 ± 10	0.02

ANOVA, analysis of variance; AT, acceleration time; eGFR, estimated glomerular filtration rate; PI, pulsatility index; RI, resistivity index.
Data are presented as mean ± standard deviation.
[a]*P* by repeated measures analysis of variance.

Table 3 Univariate predictors of WRF

Variable	No WRF ($n = 54$)	WRF ($n = 36$)	*P*
LV ejection fraction (%)	38.3 ± 7.7	31.6 ± 10.1	0.001
LV end-systolic diameter (cm)	4.78 ± 0.82	5.25 ± 1	0.01
TAPSE (cm)	1.85 ± 0.34	1.64 ± 0.39	0.01
Moderate to severe mitral regurgitation	26 (48.1)	23 (66.7)	0.05
Moderate to severe tricuspid regurgitation	11(20.4)	16(44.4)	0.015
Serum creatinine (mg/dL)	1.01 ± 0.28	1.31 ± 022	0.05
Serum urea (mmol/L)	51.85 ± 31.2	74.53 ± 43.4	0.005
Plasma cystatin C (mg/L)	1663.7 ± 451	2004.9 ± 630	0.05
Renal RI on admission	0.7 ± 0.07	0.74 ± 0.06	0.026
Renal RI at 24 h	0.718 ± 0.07	0.754 ± 0.06	0.015
Renal PI on admission	1.4 ± 0.4	1.59 ± 0.4	0.05
Renal PI at 24 h	1.4 ± 0.43	1.59 ± 0.46	0.047
Renal AT at 24 h (ms)	52 ± 10	63 ± 9	0.001

AT, acceleration time; LV, left ventricle; PI, pulsatility index; RI, resistivity index; TPASE, tricuspid annular peak systolic excursion; WRF, worsening of renal function.
Data are presented as number (%) or mean ± standard deviation.

Table 4 Multivariate regression analysis for predictors of WRF

Variable	Standardized coefficient B	Unstandardized coefficients	T	*P*	95% confidence interval
AT at 24 h (ms)	0.374	16.4 ± 3.9	4.2	0.0001	8.55 to 24.23
Renal RI on admission	0.26	1.8 ± 0.58	3.05	0.003	0.6 to 2.93
LV ejection fraction (%)	−0.25	−0.01 ± 0.005	−2.8	0.006	−0.23 to −0.004
Plasma cystatin C on admission (mg/L)	0.23	0	2.6	0.01	0.555 to 0.789

AT, acceleration time; LV, left ventricle; RI, resistivity index; WRF, worsening of renal function.
$R = 0.622$ and $R^2 = 0.36$.

renal AT ≥ 57.8 ms showed lower LV ejection fraction (33.6 ± 10% vs. 38 ± 7.8%; *P* = 0.02); larger LV end systolic dimension (5.08 ± 1 cm vs. 4.8 ± 0.8 cm; *P* = 0.02); lower TAPSE (1.66 ± 0.4 cm vs. 1.89 ± 0.3 cm; *P* = 0.004) than did patients with shorter renal AT. Moreover, renal AT at 24 h showed significant correlations with LV ejection fraction (*r* = −0.286, *P* = 0.006) and TAPSE (*r* = −0.28, *P* = 0.006). Renal RI on admission ≥ 0.752 had 70% sensitivity and 68% specificity for the prediction of WRF (area under the curve 0.63; *P* = 0.003). (*Figure 1*).

Predictors of adverse clinical outcomes

The median hospital stay was 6.2 days (range between 4 and 16) with adverse clinical outcomes occurring in 20 patients (22%) [need for vasopressors in 11 patients (12%), ultrafiltration for refractory oedema in 6 patients (7%), and death in 4 patients (4%)]. Among 10 variables that were included in multivariate linear regression analysis, two variables appeared to independently predict adverse clinical outcomes: increased LV end systolic dimension and WRF (*Tables 5* and *6*).

For the prediction of adverse clinical outcomes, LV end systolic dimension ≥5.0 cm showed 85% sensitivity and 70% specificity (area under the curve 0.801; *P* = 0.0001) and WRF was associated with 75% sensitivity and 70% specificity (area under the curve 0.725 and *P* = 0.003). (*Figure 2*).

Discussion

The main finding of this study is that renal AT and RI measured by IRD have important role in predicting WRF in patients with ADHF receiving diuretic therapy.

In patients with ADHF, WRF can be attributed to alterations in renal haemodynamics related to vascular and parenchymal abnormalities. Vascular abnormalities include renal arterial vasoconstriction mediated by several neural, hormonal, and inflammatory pathways including activation of renin-angiotensin-aldosterone system.[18] In addition, renal venous congestion is associated with increased renal interstitial pressure leading to direct compression of renal vessels with reduction of vascular compliance.[19] Furthermore, use of diuretics can lead to reduction in intravascular volume and renal perfusion with more activation of the sympathetic and renin-angiotensin-aldosterone system. Diuretics also have deferential effect on the blood flow in the renal cortex and medulla as they decrease medullary blood flow compared with the cortex which increases the risk of medullar ischemia.[20,21]

Renal acceleration time and worsening of renal function

Renal AT is unexplored but potentially helpful index in the evaluation of renal haemodynamics. To the best of our knowledge, this is the first study to address and detect a significant role for renal AT in the early prediction of WRF in patients with ADHF and to establish a cut-off point (≥57.8 ms, 24 h after admission) for this prediction. Renal AT is determined by several interacting intrarenal and cardiovascular variables. Intrarenal variables include maximal velocity of blood flow, arterial compliance, and vascular resistance[22,23] while cardiovascular variables include systolic and diastolic pressure and time, pulse pressure, cardiac output, and heart rate.[22,23] Accordingly, AT in ADHF is a moving target that reflects the dynamic interactions of the aforementioned variables. This was obvious in our study where renal AT showed significant shortening in the first 24 h when compared with admission values; on the other hand, renal AT was longer in patients with WRF compared with patients without. The shortening of renal AT is likely mediated by increased vascular resistance related to the activation of renin-angiotensin

Figure 1 Receiver operating characteristics curve analysis. (A) Renal acceleration time at 24 h and (B) renal resistivity index at 24 h for prediction of worsening of renal function. AUC, area under the curve.

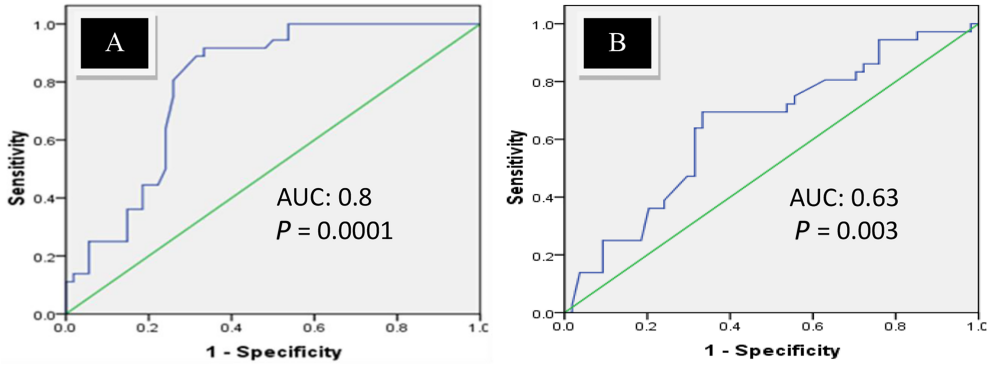


Table 5 Univariate analysis of adverse clinical outcome

Variable	Composite outcome		*P*
	Yes (*N* = 20) 22%	No (*N* = 70) 78%	
Clinical variables			
Age (year)	58.1 ± 10	55.1 ± 13	0.28
BMI (kg/m^2)	29. ± 4.7	30.3 ± 5.4	0.3
Gender			0.01
Male	17(85%)	39(55.4%)	
Prior HF Hosp.	17(85%)	43(61.4%)	0.05
Heart Rate (bpm)	95.1 ± 20	95.2 ± 18	0.9
Comorbidities			
Diabetes mellitus	8(40%)	38(54.3%)	0.26
Hypertension	10(50%)	38(54%)	0.73
Admission medications			
ACEI/ARBs	13(65%)	42(60%)	0.68
Aldosterone antagonists	8(40%)	30(42.9%)	0.82
B-blockers	10(50%)	29(41.4%)	0.49
Admission Echocardiographic data			
LV end-systolic diameter (cm)	4.7 ± 0.8	5.7 ± 0.9	0.0001
PASP (mmHg)	37.3 ± 22	39.3 ± 23	0.7
Moderate/Severe MR	14(70%)	36(51.4%)	0.14
Moderate/Severe TR	9(45%)	18(25.7%)	0.09
Admission renal functions			
Serum creatinine (mg/dL)	1.12 ± 0.25	1.21 ± 0.26	0.2
Urea (mmol/L)	56.3 ± 32	77.1 ± 50	0.03
eGFR (mL/min)	86.1 ± 23	91.7 ± 35	0.4
Plasma cystatin C (mg/L)	1723 ± 463	2064 ± 657	0.01
WRF	15(75%)	21(30%)	0.001
Intrarenal duplex data on admission			
Mean RI	0.713 ± 0.07	0.733 ± 0.07	0.2
Mean PI	1.44 ± 0.4	1.65 ± 0.4	0.05
Mean AT (ms)	59 ± 15	59 ± 14	0.9
Intrarenal duplex data at 24 h follow up			
Mean RI	0.726 ± 0.07	0.753 ± 0.06	0.12
Mean PI	1.43 ± 0.4	1.67 ± 0.5	0.02
Mean AT (ms)	55 ± 9	61 ± 14	0.02
Intrarenal duplex data at 72 h follow up			
Mean RI	0.726 ± 0.08	0.76 ± 0.7	0.07
Mean PI	1.46 ± 0.43	1.74 ± 0.52	0.01
Mean AT (ms)	55 ± 10	60 ± 12	0.09

ACEI, angiotensin converting enzyme inhibiters; ARBs, angiotensin receptors blockers; AT, acceleration time; BMI, body mass index; E/e', lateral mitral annular E wave/e' wave; eGFR, estimated glomerular filtration rate; HF, heart failure; LV, left ventricle; MR, mitral regurgitation; PASP, pulmonary artery systolic pressure; PI, pulsatility index; RI, resistivity index; TAPSE, tricuspid annular peak systolic excursion; TR, tricuspid regurgitation; WRF, worsening of renal function.
[a]Data are presented as number (%) or mean ± standard deviation.

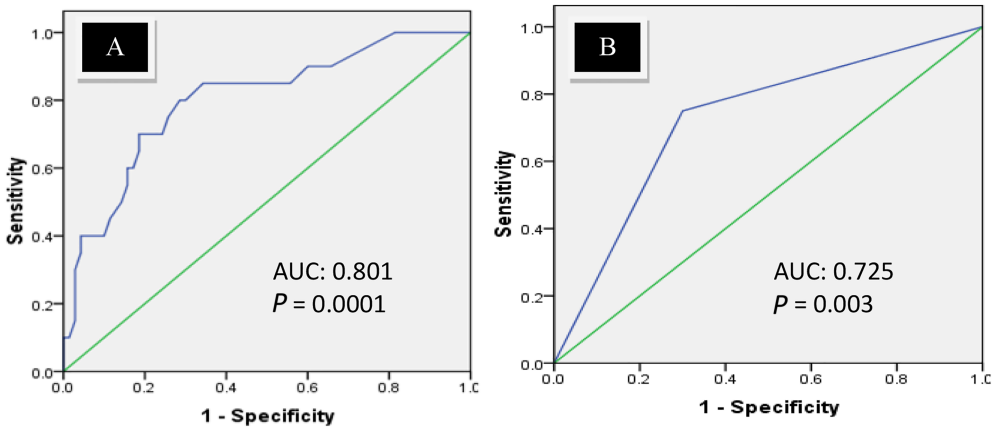
Table 6 Multivariate regression analysis for predictors of adverse clinical outcome

Variable	Standardized coefficient B	Unstandardized coefficients	T	*P*	95% confidence interval
LV end systolic volume (cm)	0.386	0.17 ± 0.04	4.13	0.0001	0.089–0.254
WRF	0.286	0.243 ± 0.08	3.1	0.003	0.085–0.4

LV, left ventricle; WRF, worsening of renal function.
$R = 0.54$ and $R^2 = 0.27$.

related to the use of diuretic therapy. Low flow velocity mediated by poor cardiac function and excess diuresis may explain the prolonged renal AT in patients at increased risk for WRF. This is supported in our study by the finding that renal AT has significant negative correlations with LV ejection fraction and TAPSE and also by the finding that patients with prolonged renal AT (≥57.8 ms at 24 h) had lower LV and right ventricular systolic functions. Taken together, longer renal AT may identify a group of ADHF patients at increased risk of heart failure-related adverse events. Actually, in this study, longer AT 24 h after admission was a univariate predictor for in-hospital adverse clinical outcome, but this association disappeared when adjusted by multivariate analysis in favour of variables known to significantly reflect LV systolic dysfunction (LV end-systolic diameter) and renal dysfunction (WRF).

Figure 2 Receiver operating characteristics curve analysis. (A) Left ventricular systolic dimension and (B) worsening of renal function for prediction of the adverse clinical outcomes. AUC, area under the curve.



Renal resistivity index and worsening of renal function

In our study, renal RI showed modest sensitivity and specificity for the prediction of WRF.

The relation between renal RI and WRF likely reflects several mechanistic pathways, including intrarenal arterial vasoconstriction, reduced vascular compliance, endothelial dysfunction, and renal venous congestion.[24–26]

The role of renal RI in prediction of WRF in patients with heart failure was addressed in few studies. In one study,[27] renal RI independently predicts WRF in patients with chronic heart failure while in other study,[28] in patients with ADHF, admission renal RI was significantly associated with WRF at Day 3 as well as renal RI at Day 3 for WRF at discharge.

In this study, admission level of plasma cystatin C—and not serum creatinine—was an independent predictor for the development of WRF. Plasma cystatin C is a sensitive marker to early and also to mild changes in renal function and—contrary to serum creatinine—is not affected by age, gender, and muscle mass.[29,30]

The incidence of WRF in this study is relatively high (40%); however, it is concordant with rates reported by other studies.[1–3] This high rate can be attributed to the lower serum creatinine threshold used to define WRF in our study compared with other definitions and also to the higher prevalence of factors known to increase the risk WRF including hypertension and diabetes. In other studies, the incidence was lower,[31] and this can be explained by difference in patients comorbidities.

Similar to other studies, lower LV ejection fraction was independent predictor of WRF,[7,19] which likely reflects reduced renal blood flow.

This study is predominantly limited by the small number of patients recruited so results should be validated in large multicentre study. Also, the study recruited selected population with many exclusion criteria to avoid confounding variables; thus, the results cannot be applied to general ADHF population. Renal AT depends on heart rate,[22,23] and because renal AT was not adjusted to the heart rate in our study, our results should be applied with caution in patients with heart rate outside the range (70–115 beats per minute) of heart rate in our population.

Conclusions

Findings in our study suggest that intrarenal haemodynamics, particularly renal AT and RI, are independent parameters that can help identify ADHF patients at increased risk for WRF. IRD is a rapid non-invasive simple bedside tool that can be used routinely to obtain these parameters. This is particularly important when we consider the lack of well-validated model or score to predict WRF in patients with ADHF. It is recommended to make use of all the available variables including the IRD parameters to enhance our ability for early and accurate prediction of WRF.

Conflict of interest

None declared.

References

1. Forman DE, Butler J, Wang Y, Abraham WT, O'Conner CM, Gottlib SS, Loh E, Massie BM, Rich MW, Stevenson MW, Young JB, Krumholz HM. Incidence, predictors at admission, and impact of worsening renal function among patients hospitalized with heart failure. *J Am Coll Cardiol* 2004; **7**: 43–61.
2. Damman K, Jaaesma T, Voors AA, Navis G, Hillege HL, Van Veldhuisen DJ. Both in-and out-hospital worsening of renal function predict outcome in patients with heart failure: results from the Coordinating Study Evaluating Outcome of Advising and Counseling in Heart Failure (COACH). *Eur J Heart Fail* 2009; **11**: 847–854.
3. Maeder MT, Rickli H, Pfisterer ME, Muzzarelli S, Ammann P, Fehr T, Hack D, Weilenmann D, Dieterie T, Kiencke S, Estlinbaum W, Brunner-La Rocca HP. Incidence, clinical predictors, and prognostic impact of worsening renal function in elderly patients with chronic heart failure on intensive medical therapy. *Am Heart J* 2012; **163**: 407–414.
4. Schrier RW. Role of diminished renal function in cardiovascular mortality: marker or pathogenetic factor? *J Am CollCardiol* 2006; **47**: 1–8.
5. Manjunath G, Tighiouart H, Coresh J, Macleod B, Salem DN, Griffith JL, Levey AS, Sarnak MJ. Level of kidney function as a risk factor for atherosclerotic cardiovascular outcomes in the community. *Am Coll Cardiol J* 2003; **55**: 41–47.
6. Schrier RW. Cardiorenal versus renocardiac syndrome: is there a difference? *Nat Clin Pract Nephrol* 2007; **3**: 637.
7. Heywood JT. The cardiorenal syndrome: lessons from the ADHERE database and treatment options. *Heart Fail Rev* 2004; **9**: 195–201.
8. Bongartz LG, Cramer MJ, Doevendans PA, Joles JA, Braan B. The severe cardiorenal syndrome: 'Guyton revisited'. *Eur Heart J* 2005; **7**: 11–17.
9. Tublin ME, Tessler FN, Murphy ME. Correlation between renal vascular resistance, pulse pressure, and the resistive index in isolated perfused rabbit kidneys. *Radiology* 1999; **213**: 258–264.
10. Ciccone M, Lacoviello M, Gesualdo L, Puzzovivo A, Antoncecchi V, Doronzo A, Monitillo F, Citarelli G, Paradies V, Favale S. The renal arterial resistance index: a marker of renal function with an independent and incremental role in predicting heart failure progression. *Eur Heart Fail J* 2014; **16**: 210–216.
11. Ennezat PV, Marechaux S, Six-Carpentier M, Pincon C, Sediri I, Delsart P, Gras M, Mounier-Vehier C, Gautier C, Montagine D, Jude B, Asseman P, Le Jemtel TH. Renal resistance index and its prognostic significance in patients with heart failure with preserved ejection fraction. *Nephrol Dial Transplant* 2011; **26**: 3908–3913.
12. Rickham PP. Human experimentation. Code of ethics of the world medical association. Declaration of Helsinki. *Br Med J* 1964; *18*; **2**: 177.
13. Ponikowski P, Adriaan A, Stefan D, Hector B, John GF, Andrew JS, Volkman F, Jose Raman G, Veli-Pekka H, Ewa A, Mariell J, Cecilia L, Petros N, John T, Burkert P, Jillian P, Giuseppe M, Luis M, Frank R, Frans H, Van der Peter M. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J 2016* 2016; **18**: 891–975.
14. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; **16**: 31–41.
15. Metra M, Nodari S, Parrinello G, Bordonali T, Bugatti S, Danesi R, Fontanella B, Lombardi C, Milani P, Verzura G, Cotter G, Dittrich H, Massie BM, Dei CL. Worsening renal function in patients hospitalized for AHF: clinical implications and prognostic significance. *Eur Heart Fail J* 2008; **10**: 188–195.
16. Nagueh SF, Applenton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, Waggoner AD, Flachskampf FA, Pellikka PA, Evangelista A. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *J Am Soc Echocardiogr* 2009; **22**: 107–133.
17. Pearce JD, Craven TE, Edwards MS, Corriere MA, Crutchley TA, Fleming SH, Hansen KJ. Associations between renal duplex parameters and adverse cardiovascular events in the elderly: a prospective cohort study. *Am J Kidney Dis* 2010; **55**: 281–290.
18. Arendshorst WJ, Brannstrom K, Ruan X. Actions of angiotensin II on the renal microvasculature. *J Am Soc Nephrol* 1999; **11**: S149–S161.
19. Mullens W, Abrahams Z, Francis GS, Sokos G, Taylor DO, Starling RC, Young JB, Tang WHW. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. *Am Coll Cardiol J* 2009; **53**: 589–596.
20. Silke B. Hemodynamic impact of diuretic therapy in chronic heart failure. *Cardiology* 1994; **84**: 115–123.
21. Dobrowolski L, Badzynska B, Sadowski J, Grzelec- Mojzesowicz M. Renal vascular effects of furosemide in the rat: influence of salt loading and the role of angiotensin II. *Exp Physiol* 2001; **86**: 611–616.
22. Naeije R, Torbicki A. More on the noninvasive diagnosis of pulmonary hypertension: Doppler echocardiography revisited. *Eur Respir J* 1995; **8**: 1445–1449.
23. Sung CK, Lee HK, Kim SH. Evaluation of factors influencing arterial Doppler waveforms in an in vitro flow Phantom. *Ultrasonography* 2017; **36**: 39–52.
24. Ohta Y, Fujii K, Ibayashi S, Matsumura K, Tsuchihashi T, Kitazono T, Ooboshi H, Kamouchi M, Hirakata H, Ogata T, Kuroda J, Lida M. Renal and carotid vascular resistance assessed with Doppler sonography. *J Clin Ultrasound* 2008; **36**: 85–90.
25. Lubas A, Kade G, Niemczyk S. Renal resistive index as a marker of vascular damage in cardiovascular diseases. *Int Urol Nephrol* 2014; **46**: 395–402.
26. Raff U, Schwarz TK, Schmidt BM, Schneider MP, Schmieder RE. Renal resistive index—a valid tool to assess renal endothelial function in humans? *Nephrol Dial Transplant* 2010; **25**: 1869–1874.
27. Lacoviello M, Monitillo F, Leone M, Citarelli G, Doronzo A, Antonececchi V, Puzzovivo A, Rizzo C, Lattarulo MS, Massari F, Caldarola P, Ciccone M. The renal arterial resistance index predict worsening of renal function in chronic heart failure patients. *Cardiorenal Med* 2017; **7**: 42–49.
28. Bihry N, Corman I, Baudet M, Cohen-Solal A. Renal arterial resistance index versus biomarkers for predicting acute kidney injury in acute heart failure. *Arch Cardiovasc Dis* 2015; **7**: 23–24.
29. Johan PE, Lassus, Markku S, Keijo J, Kari P, Krista S, Reijo S, Harjola VP. Markers of renal function and acute kidney injury in acute heart failure: definitions and impact on outcomes of the cardiorenal syndrome. *Eur Heart J* 2010; **31**: 2791–2798.
30. Raquel L, Javed B, Steve E, Anekwe O, Adefisayo O, Mike F, Adrian H, Kerry L, Brenda L, Elizabeth O. Cystatin C as a Biomarker of Worsening Renal Function in Acute Hear t Failure: Insights from the DOSE Study. *J Card Fail* 2011; **17**: S58.
31. Chioncel O, Mebazaa A, Maggioni AP, Veli-Pekka H. Acute heart failure congestion and perfusion status-impact of the clinical classification on in-hospital and long term outcomes; insights from the ESC-EORP-HFA Heart Failure Long Term Registry. *Eur J Heart Fail* 2019; **21**: 1338–1352.