True worsening renal function identifies patients with acute heart failure with an ominous outcome

Mateusz Sokolski1,2,3, Robert Zymliński1,2, Justyna M. Sokolska1,2,3, Jan Biegus1,2, Waldemar Banasiak1, Piotr Ponikowski1,2

1 Department of Heart Diseases, Wroclaw Medical University, Wroclaw, Poland
2 Center for Heart Disease, Clinical Military Hospital, Wroclaw, Poland
3 Department of Cardiology, University Hospital Zurich, Zurich, Switzerland

Introduction  Organ dysfunction, including renal disturbances, occurs frequently in patients with acute heart failure (AHF),1,4 but the importance of worsening renal function (WRF) has not been well recognized. There is evidence that an increase in creatinine levels is associated with poor outcome only if the clinical status of a patient does not improve.2 It has been shown that WRF is related to tubular injury, expressed by increased levels of urinary neutrophil gelatinase-associated lipocalin and urinary kidney injury molecule 1.4 On the other hand, an increase in creatinine levels with simultaneous effective decongestion and hemoconcentration is related to better outcome.5

In light of this evidence, WRF can be divided into true WRF and pseudo-WRF by the extension of the most commonly used definition of creatinine/estimated glomerular filtration rate (eGFR) changes (approximating to stage 1 acute kidney injury, proposed by the Acute Kidney Injury Network, or severity class “Risk” according to the RIFLE criteria [risk, injury, failure, loss of kidney function, end-stage kidney disease]) with clinical response to treatment.6 Worsening heart failure (WHF) is a meaningful event during hospitalization for AHF that expresses treatment response. It can be defined as worsening of symptoms and signs of heart failure (HF) or the lack of improvement that requires intensification or additional therapy. The condition has been associated with worse outcomes in a few clinical studies.7 We decided to combine these 2 important events (WRF and WHF) and identify patients with true WRF according to the new definition. We also analyzed the predictors and evaluated the predictive role of true WRF.

Patients and methods  The study population included consecutive patients who were hospitalized at the Centre of Heart Diseases, 4th Military Hospital, Wroclaw, Poland, with a primary diagnosis of AHF, between July 2008 and August 2010 (Supplementary material, Figure S1). The inclusion criteria were as follows: age ≥18 years; the diagnosis of AHF based on the European Society of Cardiology criteria as the primary cause of hospitalization8,9; and patient’s written consent to participate in the study. The exclusion criteria included: clinical diagnosis of concurrent acute coronary syndrome; cardiogenic shock; end-stage renal disease requiring renal replacement therapy (or planned renal replacement therapy); and exposure to nephrotoxic agents during the first 3 days of hospitalization.

After confirming the diagnosis of AHF, patients were admitted and demographic data, clinical history, comorbidities, and previous therapies were recorded. During hospitalization, every patient underwent standard clinical evaluation and received guideline-recommended treatment.8 The choice of a diuretic regimen was left to a physician’s discretion. The study protocol was approved by the local ethics committee, and the study was conducted in accordance with the Declaration of Helsinki.

Worsening renal function was defined as an increase of 0.3 mg/dl or higher in serum creatinine levels or a decrease by more than 25% in eGFR (expressed in ml/min/1.73 m², from the Modification of Diet in Renal Disease equation), as compared with the baseline values during the first 3 days of hospitalization. Patients who developed WRF were classified either as having true WRF or pseudo-WRF. The former group encompassed patients with simultaneous presence of WHF, defined as deterioration or no improvement of HF signs and symptoms
that required intensifying or adding intravenous HF therapy (loop diuretics, vasoactive agents), or ultrafiltration or renal replacement therapy during the first 3 days of hospitalization (including patients who died). The remaining patients who demonstrated only isolated changes in creatinine (increase of 0.3 mg/dl or higher) or eGFR (decrease by more than 25%) levels were classified as having pseudo-WRF.

Data on survival were obtained directly from patients or their relatives (telephone contact), from the HF clinic and hospital database. No patient was lost to follow-up. The primary endpoint was all-cause death at 365 days. The duration of follow-up of survivors and patients in whom an event occurred after 12 months was censored at 365 days.

**Statistical analysis** Normally distributed continuous variables were presented as means with SD. Variables with a skewed distribution were expressed as medians with interquartile range (IQR). The categorical variables were expressed as numbers with percentages. The differences between the groups were tested using the analysis of variance (ANOVA Kruskal–Wallis test) or χ² test, where appropriate. The associations between true WRF and clinical and laboratory variables were tested using univariate and multivariate logistic regression models. The variables that predicted true WRF in the univariate analysis were included into the multivariate model. Kaplan–Meier curves were constructed to estimate the effect of true WRF on 12-month all-cause mortality. The Cox proportional hazards model was used to calculate the hazard ratio (HR) with corresponding 95% confidence interval (95% CI) for all-cause mortality. A P value of less than 0.05 was considered statistically significant. Statistical analysis was performed using the STATISTICA 13 data analysis software system (StatSoft, Inc., Tulsa, Oklahoma, United States).

**Results** **Study population** A total of 266 patients (mean [SD] age, 67 [12] years; 188 men [71%]) were enrolled in the study. The study group included 194 patients (73%) with previous HF, and 135 patients (51%) with HF of ischemic etiology. The main causes of AHF were inadequate diuretic therapy in 130 patients (49%) and high blood pressure in 59 patients (22%).

**Prevalence and characteristics of patients with true worsening renal function** True WRF occurred in 11 (4%) and pseudo-WRF in 27 patients (10%), whereas the remaining 228 patients (86%) did not develop WRF. Differences in clinical and laboratory parameters between all 3 groups are presented in **TABLE 1**. No predictors of true WRF were identified in the multivariate logistic regression model.

**Mortality** During 1-year follow-up, 73 patients (27%) met the endpoint, including 9 deaths (82%) in patients with true WRF, 3 (11%) in those with pseudo-WRF, and 61 (27%) in those without WRF (P <0.001). Patients with true WRF had higher mortality when compared with all subgroups separately. The Kaplan–Meier estimates of 1-year mortality between subgroups are shown in Supplementary material, **Figure S2**.

The role of WHF as a factor responsible for poor outcome was verified. A group of 64 patients (24%) with isolated WHF was distinguished. Long-term mortality was 30 (47%) in this group. In the univariate Cox model, the occurrence of true WRF and isolated WHF was associated with an increased risk of death (HR, 5.46; 95% CI, 2.70–11.04 and HR, 2.63; 95% CI, 1.65–4.20, respectively; all P <0.001). In the bivariate Cox model, a stronger association was observed between true WRF and an increased risk of death compared with isolated WHF (HR, 8.15; 95% CI, 3.89–17.10 and HR 3.24; 95% CI, 2.00–5.30, respectively; all P <0.001). Adjustments for other prognosticators (previous HF, diabetes mellitus, baseline systolic blood pressure, catecholamine use on admission, baseline N-terminal pro-B type natriuretic peptide, and urea) were performed. Only true WRF was the predictor of mortality (HR, 4.25; 95% CI 1.93–9.36; P <0.001) (Supplementary material, **Figure S3**).

**Discussion** Our study investigated the definition of true WRF in the light of clinical characteristics and impact on prognosis in AHF patients. The main finding of our study is that around 14% of patients develop WRF during early hospitalization, and only 4% have true WRF defined as a rise in creatinine levels and/or a drop in eGFR in combination with an unfavorable clinical course. Patients with true WRF had an extremely high 12-month mortality rate.

The key pathophysiological mechanisms affecting the heart and peripheral organs, including the kidney, are congestion and hypoperfusion. Congestion with high intra-abdominal pressure seems crucial in cardiorenal interaction. Patients who developed true WRF had more frequent symptoms of right ventricular failure such as peripheral edema and ascites, and had lower albumin levels and a trend for higher concentrations of bilirubin and liver enzymes, suggesting fluid overload and/or simultaneous liver synthetic dysfunction. This pathomechanism is closely linked with the therapeutic effect.

The response to therapy used in AHF is complex and varies widely between individuals. The occurrence of WRF, especially with simultaneous persistent congestion, as mentioned previously, may be associated with unfavorable outcome. An important finding of our study is that patients with pseudo-WRF had the best outcome. These patients achieved better therapeutic effects with a significantly higher reduction of weight. This disproportion reveals a considerable need to distinguish WRF related to effective decongestion and hemocoagulation and true WRF, which greatly affects prognosis.
TABLE 1  The characteristics of patients with true worsening renal function, with pseudo-worsening renal function, and without worsening renal function in the first 48 hours

| Parameter                    | True WRF (n = 11) | Pseudo-WRF (n = 27) | Without WRF (n = 228) | P value |
|------------------------------|-------------------|---------------------|-----------------------|---------|
| Demographic and clinical variables |                   |                     |                       |         |
| Age, y, mean (SD)            | 70 (11)           | 69 (13)             | 67 (11)               | 0.22    |
| Women, n (%)                 | 2 (18)            | 9 (33)              | 67 (29)               | 0.65    |
| Weight, kg, mean (SD)        | 83 (10)           | 83 (20)             | 82 (18)               | 0.78    |
| Systolic BP, mm Hg, mean (SD)| 118 (28)          | 137 (32)            | 127 (30)              | 0.09    |
| Diastolic BP, mm Hg, mean (SD)| 68 (17)         | 75 (14)             | 74 (15)               | 0.35    |
| Heart rate, bpm, median (IQR)| 80 (70–90)        | 79 (70–95)          | 86 (70–100)           | 0.3     |
| Pulmonary congestion, n (%)  | 8 (73)            | 25 (93)             | 186 (82)              | 0.25    |
| Peripheral edema, n (%)      | 10 (91)           | 12 (44)             | 142 (62)              | 0.02    |
| Elevated JVP, n (%)          | 6 (55)            | 8 (30)              | 73 (32)               | 0.62    |
| Ascites, n (%)               | 5 (45)            | 1 (4)               | 40 (18)               | 0.04    |
| Previous HF, n (%)           | 11 (100)          | 18 (67)             | 165 (72)              | 0.10    |
| Ischemic HF etiology, n (%)  | 8 (73)            | 14 (52)             | 113 (50)              | 0.32    |
| LVEF, %, mean (SD)           | 36 (16)           | 43 (11)             | 34 (14)               | 0.04    |
| Weight change, % (IQR)       | 0.0 (–1.3 to 3.2) | –1.9 (–2.9 to –1.3) | –2.0 (–3.5 to –0.6)   | 0.04    |
| Comorbidities                |                   |                     |                       |         |
| Hypertension, n (%)          | 5 (45)            | 16 (59)             | 128 (57)              | 0.73    |
| AF, n (%)                    | 4 (36)            | 11 (41)             | 114 (51)              | 0.43    |
| CAD, n (%)                   | 9 (82)            | 14 (52)             | 114 (50)              | 0.12    |
| Prior MI, n (%)              | 7 (64)            | 8 (30)              | 80 (35)               | 0.12    |
| Diabetes, n (%)              | 5 (45)            | 10 (37)             | 83 (37)               | 0.85    |
| CKD, n (%)                   | 5 (45)            | 11 (41)             | 87 (39)               | 0.89    |
| Baseline laboratory parameters |                 |                     |                       |         |
| NT-proBNP, pg/ml, median (IQR)| 8500 (5272–16005) | 3912 (2949–6059)    | 5621 (3264–11755)     | 0.11    |
| Sodium, mEq/l, mean (SD)     | 139 (2)           | 139 (4)             | 140 (5)               | 0.59    |
| Potassium, mEq/l, mean (SD)  | 4.4 (0.8)         | 4.2 (0.6)           | 4.2 (0.6)             | 0.52    |
| Troponin I, ng/ml, median (IQR)| 0.09 (0.03–0.10) | 0.06 (0.04–0.17)    | 0.06 (0.03–0.10)      | 0.56    |
| AST, IU/l, median (IQR)      | 51 (23–113)       | 29 (20–50)          | 28 (21–41)            | 0.11    |
| ALT, IU/l, median (IQR)      | 57 (24–93)        | 28 (16–56)          | 25 (17–45)            | 0.16    |
| GGTP, IU/l, median (IQR)     | 110 (58–166)      | 72 (45–92)          | 79 (42–120)           | 0.51    |
| Bilirubin, mg/dl, median (IQR)| 1.6 (0.7–2.3)    | 0.9 (0.7–1.4)       | 1.4 (0.8–2.4)         | 0.047   |
| Albumin, mg/dl, mean (SD)    | 3.6 (0.4)         | 4.0 (0.4)           | 3.8 (0.7)             | 0.03    |
| WBC, G/l, median (IQR)       | 9 (8–12)          | 8 (6–12)            | 8 (7–11)              | 0.68    |
| Hemoglobin, g/l, mean (SD)   | 12 (11)           | 13 (2)              | 13 (2)                | 0.02    |
| CRP, mg/l, median (IQR)      | 29 (19–42)        | 5 (3–26)            | 13 (6–33)             | 0.02    |
| Creatinine, mg/dl, median (IQR)| 1.3 (1.0–2.8)   | 1.2 (1.1–1.6)       | 1.20 (1.0–1.5)        | 0.58    |
| eGFR, ml/min/1.73 m², median (IQR)| 53 (22–75)    | 49 (37–67)          | 55 (43–69)            | 0.54    |
| Urea, mg/dl, median (IQR)    | 32 (28–63)        | 22 (18–31)          | 25 (19–34)            | 0.06    |
| Treatment before hospitalization |             |                     |                       |         |
| Loop diuretic, n (%)         | 3 (27)            | 2 (7)               | 16 (7)                | 0.055   |
| ACEI/ARB, n (%)              | 7 (64)            | 15 (56)             | 153 (67)              | 0.48    |
| β-Blocker, n (%)             | 7 (64)            | 19 (70)             | 158 (69)              | 0.91    |
| MRA, n (%)                   | 4 (36)            | 8 (30)              | 96 (42)               | 0.44    |
| Treatment at admission       |                   |                     |                       |         |
| IV LD, n (%)                 | 10 (91)           | 22 (81)             | 205 (90)              | 0.41    |
| IV nitroglycerin n (%)       | 6 (55)            | 12 (44)             | 95 (42)               | 0.69    |
| Catecholamines, n (%)        | 2 (18)            | 0 (0)               | 25 (11)               | 0.14    |

a True WRF vs pseudo-WRF (P < 0.05); b True WRF vs without WRF (P < 0.05); c Pseudo-WRF vs without WRF (P < 0.05)

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; AF, atrial fibrillation/flutter; ALT, alanine transaminase; ARB, angiotensin receptor blocker; AST, aspartate transaminase; BP, blood pressure; CAD, coronary artery disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; GGTP, γ-glutamyltranspeptidase; HF, heart failure; IV, intravenous, IQR, interquartile range; JVP, jugular venous pressure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal fragment of the prohormone brain natriuretic peptide; WBC, white blood cell; WRF, worsening renal function

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Study limitations We studied a relatively small number of patients with true WRF, and larger prospective studies are necessary to assess the pathophysiology and role of true WRF in AHF, also taking into account the clinical profile, comorbidities, and etiology of HE. Another limitation is the fact that our study protocol did not cover further changes in kidney function, total doses of diuretics, and treatment at discharge, which are important factors in the assessment of the decongestion process.

SUPPLEMENTARY MATERIAL
Supplementary material is available at www.mp.pl/paim.

ARTICLE INFORMATION

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CONFLICT OF INTEREST MS, RZ, JMS, JB, PP report receiving personal fees from Wroclaw Medical University outside the submitted work. WB have nothing to disclose.

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