Systematic Review of the Association Between Worsening Renal Function and Mortality in Patients With Acute Decompensated Heart Failure

Takayuki Yamada1,2,11, Hiroki Ueyama1,11, Nitin Chopra1, Takahiro Yamaji2, Kengo Azushima2,3, Ryu Kobayashi2, Sho Kinguchi2, Shingo Urate2, Toru Suzuki2, Eriko Abe2, Yusuke Saigusa4, Hiromichi Wakui2, Paulina Partridge5, Alfred Burger1, Claudio A. Bravo6, Maria A. Rodriguez7, Juan Ivey-Miranda8, Kouichi Tamura2, Jeffery Testani9 and Steven Coca10

1Department of Medicine, Mount Sinai Beth Israel, Icahn School of Medicine at Mount Sinai, New York, New York, USA; 2Department of Medical Science and Cardiorenal Medicine, Yokohama City University Graduate School of Medicine, Yokohama, Japan; 3Cardiovascular and Metabolic Disorders Program, Duke–National University of Singapore Medical School, Singapore; 4Department of Biostatistics, Yokohama City University School of Medicine, Yokohama, Japan; 5College of Arts and Sciences, University of Miami, Coral Gables, Florida, USA; 6Department of Medicine, Division of Cardiology, Columbia University Medical Center, New York, New York, USA; 7Department of Medicine, Division of Cardiology, Albert Einstein College of Medicine, Bronx, New York, USA; 8Cardiology Hospital, XXI Century National Medical Center, Mexican Social Security Institute, Mexico City, Mexico; 9Section of Cardiovascular Medicine, Yale University School of Medicine, New Haven, Connecticut, USA; and 10Division of Nephrology, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, New York, USA

Introduction: Outcomes in acute decompensated heart failure (ADHF) have remained poor. Worsening renal function (WRF) is common among patients with ADHF. However, the impact of WRF on the prognosis is controversial. We hypothesized that in patients with ADHF, the achievement of concomitant decongestion would diminish the signal for harm associated with WRF.

Methods: We performed a systematic search of PubMed, EMBASE, and the Cochrane Library up to December 2019 for studies that assessed signs of decongestion in patients with WRF during ADHF admission. The primary outcome was all-cause mortality and heart transplantation.

Results: Thirteen studies were selected with a pooled population of 8138 patients. During the follow-up period of 60–450 days, 19.2% of patients died. Unstratified, patients with WRF versus no WRF had a higher risk for mortality (odds ratio [OR], 1.71 [95% confidence interval {CI}, 1.45–2.01]; \( P < 0.0001 \)). However, patients who achieved decongestion had a similar prognosis (OR, 1.15 [95% CI, 0.89–1.49]; \( P = 0.30 \)). Moreover, patients with WRF who achieved decongestion had a better prognosis compared with those without WRF or decongestion (OR, 0.63 [95% CI, 0.46–0.86]; \( P = 0.004 \)). This tendency persisted for the sensitivity analyses.

Conclusions: Decongestion is a powerful effect modifier that attenuates harmful associations of WRF with mortality. Future studies should not assess WRF as an endpoint without concomitant assessment of achieved volume status.

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KEYWORDS: cardiorenal syndrome; heart failure; meta-analysis; mortality/survival

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prognosis. \(^5\) However, the impact of WRF during ADHF admission on prognosis is controversial. While it is well known that WRF is associated with poorer outcomes, it seems that several studies claim that WRF is unrelated to increased mortality in some patients. \(^6,7\) These findings suggest that this population is heterogeneous and that WRF may be caused by derangements in hemodynamics that are reversible in some patients with ADHF. \(^10\)

We hypothesized that in patients with ADHF, the achievement of concomitant decongestion including hemoconcentration, a decrease of B-type natriuretic peptide (BNP), and the absence of signs of congestion on physical examination would diminish the signal for harm associated with WRF.

**METHODS**

**Literature Search**

The search strategy was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses. \(^11\) We performed a systematic search of PubMed, EMBASE, and the Cochrane Library from inception to December 2019. The following keywords were applied: (“heart failure” [MeSH] OR HF OR “acute heart failure” OR AHF OR “acute decompensated heart failure” OR ADHF) AND (“acute kidney injury” [MeSH] OR AKI OR “worsening renal function” OR WRF OR creatinine) AND (edema [MeSH] OR “edema, cardiac” [MeSH] OR “pulmonary edema” OR congestion OR decongestion OR “natriuretic peptide, brain” OR BNP OR “N-terminal pro b-type natriuretic peptide” [NT-proBNP] OR “NT-proBNP” OR hemoconcentration OR hemoglobin OR hematocrit) AND (mortality [MeSH] OR “all-cause mortality” OR “hospital mortality” OR “heart transplantation” OR prognosis). We restricted the search to human studies. There were no language restrictions. Further manual searches of bibliographies for all relevant studies and review articles were conducted by 2 investigators (TYamad, HU).

**Study Selection and Data Extraction**

We included all studies that involved adult patients (\(>18\) years of age) who were admitted for ADHF where the outcomes were comparing patients with or without decongestion between patients with WRF and those without WRF. The primary outcome was a composite of all-cause mortality and heart transplantation. Studies were excluded if (i) they included nonhuman subjects and (ii) no crude mortality data or ORs for the study groups were available even after contact with the authors. All data from eligible studies were independently extracted by 2 investigators (TYamad, HU). Discrepancies were resolved by discussion among the 2 reviewers and by referencing the original report. The Newcastle-Ottawa Scale \(^12\) and the Newcastle-Ottawa Scale adapted for cross-sectional studies \(^13\) were used to assess the quality of nonrandomized studies. We considered studies to be of high quality if they had a score \(\geq 6\).

**Statistical Analysis**

All analyses were conducted using Review Manager version 5.3, \(^14\) and Comprehensive Meta-Analysis version 3 (Biostat, Englewood, NJ). ORs and 95% CIs were obtained directly from individual articles or by calculating from crude mortality using Mantel–Haenszel methods. A random effects model was used to determine the risk associated with the presence of WRF/decongestion and all-cause mortality or heart transplantation. All reported probability values were 2-sided, with significance set at \(P < 0.05\). Heterogeneity was assessed by the probability value of the \(\chi^2\) statistic and \(I^2\). \(^15,16\) We regarded an \(I^2\) of \(<40\%\) as “heterogeneity might not be important” and \(\geq 50\%\) as “may represent substantial heterogeneity” based on the suggestion of the Cochrane Handbook for Systemic Review of Interventions. \(^17\) Sensitivity analyses were performed for (i) the definition of WRF, (ii) short (\(\leq 180\) days) versus long (\(>180\) days) follow-up periods, (iii) the definition of decongestion, and (iv) prospective versus retrospective studies. Univariable meta-regression analysis was conducted to examine the effect of study-level variables: study size, age, sex, left ventricular ejection fraction, angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, beta-blockers (BBs), diuretics, creatinine, blood urea nitrogen, estimated glomerular filtration rate, hemoglobin level, proportion of WRF, achievement of decongestion, and presence of diabetes, hypertension, CKD, HF, coronary artery disease (CAD), and atrial fibrillation. The general linear method was used for meta-regression, weighting by study sample size.

Publication bias of studies with different sample sizes was assessed by the Begg and Mazumdar rank correlation test \(^18\) and the Egger regression test. \(^19\)

**RESULTS**

**Literature Search and Included Studies**

A diagram of the study selection is shown in Figure 1. Initially, a total of 4303 studies were obtained in the primary database search and 16 studies were identified through references. We removed 358 duplicate studies; 3961 studies were screened. By screening titles and abstracts, 3947 articles were excluded. By assessing full-text articles, 13 studies published up to December 2019 were selected for our meta-analysis according to the inclusion criteria. \(^20–32\) The pooled population consisted of 8138 patients. The prevalence of WRF was 27.8%. More than
half (55.4%) of those with WRF and 58.1% of those without WRF experienced decongestion.

Study Characteristics and Quality Assessment

The definitions of terms and characteristics of the included studies are listed in Tables 1 and 2, respectively.20–32 The median ages of patients in the included studies ranged from 56–78 years. The proportion of the history of HF varied from 46%–78% and left ventricular ejection fraction ranged from 20%–45%. Four prospective studies were identified in the meta-analysis, while the other 9 studies were retrospective or post hoc studies. Most studies regarded WRF as an increase in creatinine of >0.3 mg/dl from baseline, except studies by Stolfo et al.24 and Testani et al.,21 in which WRF was defined as a decrease in estimated glomerular filtration rate of ≥20%. The definition of decongestion varied by study. Six studies defined decongestion based on physical examination findings (such as jugular venous distention, hepatomegaly, edema, pulmonary rales, third heart sound, and a decrease in blood pressure); 5 studies regarded decongestion as a decrease in BNP or NT-proBNP; and 2 studies determined decongestion as hemoconcentration, such as an increase in hemoglobin or hematocrit. According to the Newcastle-Ottawa Scale, all studies were of high quality and had scores ≥6 (Supplementary Table S1).

WRF and All-Cause Mortality

After a follow-up period of 60–450 days, 19.2% of patients died; the crude mortality rates for patients with and without WRF were 26.6% and 16.6%, respectively. This resulted in a combined unadjusted OR for mortality of 1.71 (95% CI, 1.45–2.01, $P < 0.00001$; $I^2 = 29\%$) (Figure 2).20–32 The funnel plot is symmetric for the overall effect (Figure 3). The Begg and Mazumdar rank correlation test and the Egger regression test indicated no statistically significant publication bias (2-tailed $P$ values of 0.54 and 0.82, respectively).

Effect Modification of Decongestion on the Association Between WRF and All-Cause Mortality in Patients with ADHF

We divided patients with WRF into 2 groups: patients with or patients without decongestion, as defined as

Figure 1. Flow diagram for study selection.
above. The crude mortality rates for patients with WRF with and without decongestion were 15.2% and 38.8%, respectively. In patients without decongestion, WRF was associated with a higher risk of mortality (OR, 2.30 [95% CI, 1.79–2.94]; \( P < 0.00001; \, \, I^2 = 37\%\)) (Figure 4).\(^{20–32}\) On the other hand, the harmful effect of WRF was nullified by decongestion. In patients with WRF who achieved decongestion, mortality was not inferior to that in patients who did not have WRF (OR, 1.15 [95% CI, 0.89–1.49]; \( P = 0.30; \, \, I^2 = 28\%\)) (Figure 5).\(^{20–32}\) Moreover, patients with WRF who achieved decongestion were found to have lower mortality than those without WRF who did not reach decongestion (OR, 0.63 [95% CI, 0.46–0.86]; \( P = 0.04; \, \, I^2 = 46\%\)).

Second, we performed a sensitivity analysis stratified by follow-up period. The results are consistent in studies with a short period (≤180 days): overall OR, 1.80 [95% CI, 1.44–2.25]; \( P < 0.0001; \, \, I^2 = 39.3\%\); in decongested patients: OR, 1.15 [95% CI, 0.76–1.74]; \( P = 0.50; \, \, I^2 = 51.3\%\) and a long period (>180 days: overall OR, 1.33 [95% CI, 1.12–1.59]; \( P = 0.001; \, \, I^2 = 0\%\); in decongested patients: OR, 1.17 [95% CI, 0.88–1.56]; \( P = 0.28; \, \, I^2 = 0\%\)).

Third, we divided studies according to the definitions of decongestion. In 6 studies that defined decongestion based on physical examination findings, WRF was related to poor outcomes (OR, 1.55 [95% CI, 1.27–1.90]; \( P < 0.0001; \, \, I^2 = 22.8\%\) but not in the decongested group (OR, 1.10 [95% CI, 0.82–1.47]; \( P = 0.51; \, \, I^2 = 26.2\%\)). This tendency was similar in the 2 studies that defined decongestion as hemoconcentration (overall: OR, 2.17 [95% CI, 1.70–2.77]; \( P < 0.0001; \, \, I^2 = 0\%\); in decongested patients: OR, 1.66 [95% CI, 0.54–5.12]; \( P = 0.38; \, \, I^2 = 71.3\%\)). However, in 5 studies that regarded decongestion as a decrease in BNP or NT-proBNP, WRF did not show a statistically significant difference in either overall patients (OR, 1.29 [95% CI, 0.94–1.77]; \( P = 0.11; \, \, I^2 = 19.6\%\)) or decongested patients (OR, 1.23 [95% CI, 0.63–2.40]; \( P = 0.54; \, \, I^2 = 42.4\%\)).

Lastly, we separated prospective and retrospective studies. In 4 prospective studies, WRF was associated

### Table 1. Definitions of terms in included studies

| Author, yr | Study design | Definition of decongestion | Definition of WRF | Follow-up, d | Outcome |
|------------|--------------|----------------------------|------------------|--------------|---------|
| Breidhardt et al.\(^{19}\), 2015 | Prospective cohort | Increase >3 of the parameters (Hgb, Hct, Alb, and TP) after day 4 | Increase Cr ≥0.3 mg/dl | 90 | All-cause mortality |
| Brisco et al.\(^{46}\), 2016 | Post hoc analysis | NT-proBNP reduction >30% | Increase Cr ≥0.3 mg/dl | 60 | All-cause mortality |
| Fudim et al.\(^{58}\), 2018 | Post hoc analysis | No physical signs of congestion | Increase Cr ≥0.3 mg/dl | 180 | All-cause mortality |
| Martins et al.\(^{62}\), 2018 | Retrospective analysis | Increase in Hgb during hospitalization | Increase Cr ≥0.3 mg/dl | 180 | All-cause mortality |
| Meta et al.\(^{71}\), 2012 | Prospective cohort | No physical signs of congestion (third heart sound, pulmonary rales, jugular venous distention, hepatomegaly, or edema) | Increase Cr ≥0.3 mg/dl | 365 | Death, heart transplantation |
| Meta et al.\(^{72}\), 2018 | Post hoc analysis | No physical signs of congestion (orthopnea, edema, or jugular venous distention) | Increase Cr ≥0.3 mg/dl | 90 | All-cause mortality |
| Rao et al.\(^{73}\), 2019 | Post hoc analysis | NT-pro BNP reduction >30% | Increase Cr ≥0.3 mg/dl and >25% | 180 | All-cause mortality |
| Salih et al.\(^{74}\), 2015 | Retrospective cohort | NT-pro BNP reduction >30% | Increase Cr ≥0.3 mg/dl | 365 | All-cause mortality |
| Skolíski et al.\(^{75}\), 2019 | Prospective cohort | Not needed increase i.v. diuretics or ultrafiltration | Increase Cr ≥0.3 mg/dl or eGFR decrease >25% | 365 | All-cause mortality |
| Stolfo et al.\(^{76}\), 2017 | Prospective cohort | BNP reduction >40% | ≥20% decrease eGFR | 390 | All-cause mortality |
| Testani et al.\(^{77}\), 2011 | Retrospective analysis | SBP reduction over the median | ≥20% decrease eGFR | 180 | All-cause mortality |
| Watford et al.\(^{78}\), 2015 | Post hoc analysis | No physical signs of congestion (jugular venous distention, hepatomegaly, edema, pulmonary rales, and third heart sound) | Increase Cr ≥0.3 mg/dl | 450 | All-cause mortality |
| Wettersten et al.\(^{79}\), 2019 | Retrospective analysis | BNP reduction >30% | Increase Cr ≥0.3 mg/dl or eGFR decrease ≥50% | 365 | All-cause mortality |

Ab, albumin; BNP, brain natriuretic peptide; Cr, creatinine; eGFR, estimated glomerular filtration rate; Hct, hematocrit; Hgb, hemoglobin; NT-proBNP, N-terminal pro-brain natriuretic peptide; SBP, systolic blood pressure; TP, total protein; WRF, worsening renal function.

### Sensitivity Analyses

In the 11 studies that defined WRF as an increase in creatinine of >0.3 mg/dl from baseline, WRF was associated with higher mortality overall (OR, 1.64 [95% CI, 1.36–1.98]; \( P < 0.0001; \, \, I^2 = 49.2\%\)), but the effect was not seen in patients with decongestion (OR, 1.17 [95% CI, 0.89–1.53]; \( P = 0.27; \, \, I^2 = 38.1\%\)). However, in 2 studies that defined WRF as a decrease in estimated glomerular filtration rate of ≥20%, WRF did not show a statistically significant difference (OR, 1.28 [95% CI, 0.73–2.25]; \( P = 0.39; \, \, I^2 = 0\%\)).
Table 2. Baseline characteristics of included studies

| Author, yr | n | Age, yr | Male, % | HTN, % | DM, % | CAD, % | AB, % | LVEF, % | Hgb, g/dl | WRF, % | Decongestion, % | Odds ratio (95% CI) |
|------------|---|---------|---------|--------|-------|--------|-------|--------|-----------|--------|----------------|---------------------|
| Breidhardt et al., 2016 | 1019 | 77.9 | 54.9 | 30.6 | 76.2 | NA | 44 | 49.4 | 24.9 | N/A | 45 | 56.1 | 51.7 |
| et al., 2017 | 32 | 66.0 | 73.4 | 52.5 | 80.4 | NA | 34.5 | 63.8 | 83.4 | 100 | 1.8 | 6.1 | 18.1 |
| Fudim et al., 2018 | 2016 | 66.0 | 73.4 | 52.5 | 80.4 | NA | 34.5 | 63.8 | 83.4 | 100 | 1.8 | 6.1 | 18.1 |
| et al., 2018 | 1537 | 70 | 74.1 | 35.3 | 66.4 | 38.6 | 53.3 | 30.3 | 51.0 | 73.5 | 88.0 | 1.3 | 1.3 |
| et al., 2019 | 762 | 77.1 | 49.7 | 45 | 87.7 | NA | 34.5 | 63.8 | 83.4 | 100 | 1.8 | 6.1 | 18.1 |
| Metra et al., 2012 | 594 | 69.1 | 74 | 31.1 | 60.7 | NA | 22.5 | 35.3 | 38.6 | 53.3 | 30.3 | 51.0 | 73.5 | 88.0 | 1.3 | 1.3 |
| et al., 2018 | 188 | 74 | 60.7 | 31.1 | 60.7 | NA | 22.5 | 35.3 | 38.6 | 53.3 | 30.3 | 51.0 | 73.5 | 88.0 | 1.3 | 1.3 |
| et al., 2019 | 41.1 | 74 | 60.7 | 31.1 | 60.7 | NA | 22.5 | 35.3 | 38.6 | 53.3 | 30.3 | 51.0 | 73.5 | 88.0 | 1.3 | 1.3 |
| et al., 2015 | 618 | 79 | 41.9 | 36.2 | 60.7 | NA | 22.5 | 35.3 | 38.6 | 53.3 | 30.3 | 51.0 | 73.5 | 88.0 | 1.3 | 1.3 |
| et al., 2011 | 56.4 | 74.1 | 36.2 | 60.7 | NA | 22.5 | 35.3 | 38.6 | 53.3 | 30.3 | 51.0 | 73.5 | 88.0 | 1.3 | 1.3 |
| et al., 2010 | 42.1 | 74 | 60.7 | 31.1 | 60.7 | NA | 22.5 | 35.3 | 38.6 | 53.3 | 30.3 | 51.0 | 73.5 | 88.0 | 1.3 | 1.3 |
| et al., 2010 | 41.1 | 74 | 60.7 | 31.1 | 60.7 | NA | 22.5 | 35.3 | 38.6 | 53.3 | 30.3 | 51.0 | 73.5 | 88.0 | 1.3 | 1.3 |
| et al., 2010 | 41.1 | 74 | 60.7 | 31.1 | 60.7 | NA | 22.5 | 35.3 | 38.6 | 53.3 | 30.3 | 51.0 | 73.5 | 88.0 | 1.3 | 1.3 |
| et al., 2010 | 41.1 | 74 | 60.7 | 31.1 | 60.7 | NA | 22.5 | 35.3 | 38.6 | 53.3 | 30.3 | 51.0 | 73.5 | 88.0 | 1.3 | 1.3 |
| et al., 2010 | 41.1 | 74 | 60.7 | 31.1 | 60.7 | NA | 22.5 | 35.3 | 38.6 | 53.3 | 30.3 | 51.0 | 73.5 | 88.0 | 1.3 | 1.3 |

**Table 2.** Baseline characteristics of included studies.

**Author, yr:** Article author, year of publication.

**n:** Number of patients.

**Age, yr:** Mean age of patients.

**Male, %:** Percentage of male patients.

**HTN, %:** Percentage of patients with hypertension.

**DM, %:** Percentage of patients with diabetes.

**CAD, %:** Percentage of patients with coronary artery disease.

**AB, %:** Percentage of patients with atrial fibrillation.

**LVEF, %:** Left ventricular ejection fraction.

**Hgb, g/dl:** Hemoglobin level.

**WRF, %:** Percentage of patients with worsening renal function.

**Decongestion, %:** Percentage of patients who achieved decongestion.

**Odds ratio (95% CI):** Odds ratio and 95% confidence interval for the association between WRF and mortality.

**DISCUSSION**

In this systematic review and meta-analysis we examined the effect modification of decongestion on the association between WRF and mortality in patients with ADHF. Unstratified analysis showed that WRF was associated with higher mortality, a finding that is well known. This study divided WRF patients into 2 groups: patients with and without signs of decongestion at the time of hospital discharge. The results of the pooled analyses demonstrated that decongestion was associated with the mitigation of the harmful effects of WRF in patients with ADHF. This fact suggests that WRF in ADHF can be heterogeneous in terms of prognosis. Moreover, our study revealed that patients with WRF who achieved decongestion had a better prognosis compared with patients without WRF who did not accomplish decongestion.

Multiple mechanisms are involved in the pathophysiology of WRF; among them, venous congestion plays a central role. Studies have shown that elevated central venous pressure is associated with a higher risk of WRF. Venous congestion can lead to WRF via central venous pressure is associated with a higher risk of WRF. Venous congestion can lead to WRF via multiple mechanisms, including activation of the renin-angiotensin-aldosterone system, an increase in renal interstitial pressure, and sympathetic nervous system stimulation. Renal dysfunction resulting from neurohormonal or hemodynamic abnormalities (also known as vasomotor nephropathy) can be reversible.

This meta-analysis suggests that WRF caused by vasomotor nephropathy should be distinguished from WRF related to intrinsic kidney disease. It also indicates that aggressive diuresis can be warranted even though it may cause WRF because it is related to a better prognosis. Despite aggressive therapy, with poor prognosis, but not in decongested group (OR, 1.74 [95% CI, 1.33–2.27]; P < 0.0001; I² = 0%; and OR, 1.28 [95% CI, 0.63–2.58]; P = 0.49; I² = 43.1%, respectively). The results were similar in 9 retrospective studies as well but with high heterogeneity (overall: OR, 1.59 [95% CI, 1.27–1.99]; P < 0.0001; I² = 55.3%; decongested group: OR, 1.13 [95% CI, 0.85–1.49]; P = 0.40; I² = 33.6%).

**Meta-regression**

Meta-regression analysis for all 11 studies suggested that the proportion of CAD (P = 0.0004) and BB (P = 0.0023) contributed to overall heterogeneity (Table 3). In 11 studies that defined WRF as an increase in creatinine >0.3 mg/dl, meta-regression suggested that WRF accounted for heterogeneity but CAD and BB did not (P values for CAD, BB, and WRF were 0.20, 0.057, and 0.0013, respectively).
congestion at discharge is frequent and is associated with a higher risk of death or rehospitalization.\textsuperscript{35}

Meta-regression analysis suggested that the proportion of CAD, BB, and WRF could affect the result. It has been reported that the presence of CAD is independently associated with increased mortality in patients with ADHF,\textsuperscript{36} which is a possible explanation. A cohort study suggested that the use of BB was protective for in-hospital mortality in patients with ADHF who were complicated by WRF.\textsuperscript{37} Further studies can be warranted to assess the association between BB and mortality in patients with ADHF and WRF.

As far as we know, this is the first systematic review and meta-analysis that stratified patients with WRF into decongestion and nondecongestion groups.

The large number of patients analyzed is a strength of our study. We included 7730 patients, enough to show the statistically significant differences. The results are consistent with sensitivity analyses, which strengthens our findings.

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**Figure 2.** Forest plot of the association between worsening renal function (WRF) and mortality in patients with acute decompensated heart failure. Odds ratios are presented as means and 95% confidence intervals (CIs). M-H, Mantel–Haenszel.\textsuperscript{20–32}

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**Figure 3.** Funnel plot of worsening renal function and all-cause mortality. OR, odds ratio; SE, standard error.
Our study has several limitations. First, this analysis contained retrospective data that are subject to bias. Second, we used the reported crude data to calculate effect estimates for most of the studies, since multivariate-adjusted data were not available in most articles. Therefore, the results should be interpreted with caution because the data may be biased by confounding factors. Third, the definitions of decongestion varied among studies, based on physical examinations, hemoconcentration, or change in BNP. Moreover, the definition of WRF used in the main analysis and meta-regression varied as well. These factors may lead to heterogeneity. Finally, patients who achieve decongestion are likely less diuretic resistant and represent a less severe phenotype of cardiorenal syndrome.

In conclusion, decongestion is a powerful effect modifier that attenuates the harmful associations of WRF with mortality in ADHF. Future studies should not assess WRF in isolation as an endpoint without concomitant assessment of the volume status that accompanied the WRF.

**DISCLOSURE**

All the authors declared no competing interests.
Table 3. Meta-regression analyses of mortality on predictors

| Covariate                  | Coefficient | Standard error | 95% lower limit | 95% upper limit | Z value | Two-sided P value |
|----------------------------|-------------|----------------|-----------------|-----------------|---------|------------------|
| Study size                 | 0.0001      | 0.0002         | -0.0003         | 0.0006          | 0.59    | 0.56             |
| Age                        | 0.0046      | 0.013          | -0.021          | 0.031           | 0.35    | 0.73             |
| Male, %                    | -0.006      | 0.0086         | -0.022          | 0.012           | -0.58   | 0.56             |
| Diabetes, %                | -0.0048     | 0.012          | -0.028          | 0.018           | -0.42   | 0.68             |
| Hypertension, %            | 0.002       | 0.0073         | -0.012          | 0.016           | 0.27    | 0.78             |
| CKD, %                     | -0.011      | 0.014          | -0.039          | 0.018           | -0.74   | 0.46             |
| HF, %                      | -0.0007     | 0.0093         | -0.019          | 0.018           | -0.07   | 0.94             |
| CAD, %                     | -0.014      | 0.0039         | -0.021          | -0.006          | -3.6    | 0.0004           |
| Afb, %                     | 0.011       | 0.021          | -0.030          | 0.052           | 0.51    | 0.61             |
| LVEF, %                    | 0.011       | 0.0092         | -0.0070         | 0.029           | 1.20    | 0.23             |
| Age/ARB, %                 | 0.0020      | 0.0076         | -0.013          | 0.017           | 0.26    | 0.79             |
| BB, %                      | -0.016      | 0.0052         | -0.026          | -0.0056         | -3.05   | 0.0023           |
| Diuretics, %               | -0.008      | 0.0046         | -0.0098         | 0.0082          | -0.18   | 0.86             |
| Cr, mg/dl                  | -0.18       | 0.64           | -1.44           | 1.08            | -0.28   | 0.78             |
| BUN, mg/dl                 | -0.079      | 0.0057         | -0.0033         | 0.019           | 1.39    | 0.17             |
| eGFR, ml/min per 1.73 m²   | -0.024      | 0.018          | -0.058          | 0.011           | -1.33   | 0.18             |
| Hgb, g/dl                  | 0.048       | 0.24           | -0.42           | 0.51            | 0.2     | 0.84             |
| Proportion of WRF, %       | 0.011       | 0.0064         | -0.0020         | 0.023           | 1.65    | 0.099            |
| Achievement of decongestion, % | -0.030 | 0.0061 | -0.013 | 0.0069 | -0.59 | 0.55 |

ACEI, angiotensin-converting enzyme inhibitor; Afb, atrial fibrillation; ARB, angiotensin II receptor blocker; BB, beta blocker; BUN, blood urea nitrogen; CAD, coronary artery disease; CKD, chronic kidney disease; Cr, creatinine; eGFR, estimated glomerular filtration rate; HF, heart failure; Hgb, hemoglobin; LVEF, left ventricular ejection fraction; WRF, worsening renal function.

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AUTHOR CONTRIBUTIONS

TYamada designed the study, collected the data, contributed to the statistical analysis, and served as the primary author of the manuscript. HU collected the data, contributed to the statistical analysis, and served as an author of the manuscript (equivalent contributor). NC, KA, RK, SK, HW, and KT contributed to the statistical analysis and assisted with the writing of the manuscript. TYamaj, SU, TS, EA, PP, AB, and MAR contributed to the data collection and assisted with the writing of the manuscript. YS and JI-Ts, EA, PP, AB, and MAR contributed to the data collection and data analysis. CAB contributed to the data collection and assisted with the data analysis and writing of the manuscript. JT and SC contributed to study design and assisted with the writing of the manuscript.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Newcastle-Ottawa scale for assessment of quality of included studies (each asterisk represents if individual criterion within the subsection was fulfilled).

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