Master student in Epidemiology – Major research project
Maria Kamarioti (4920449)
m.kamarioti@students.uu.nl

Worsening renal function and all-cause mortality in patients with heart failure: an update of the literature

Supervisor: dr. Robin I. Vernooij, Julius Centre, UMC Utrecht
Second reviewer: dr. Alicia Uijl

Julius Centre for Health Sciences and Primary Care Medicine, UMC Utrecht

Utrecht, 1st August 2022

Table of contents

Abstract **3**

Layman's Summary **4**

Introduction **5**

Heart Failure *5*

Renal Impairment in Heart Failure *5*

Objectives *6*

Methods **6**

Literature search *6*

Eligibility criteria *6*

Exclusion criteria *6*

Methodological appraisal and risk of bias *6*

Results **7**

Literature Search and Study Selection *7*

Study characteristics *7*

Study quality *7*

Definition of WRF *7*

Definition of HF *7*

WRF and All-Cause Mortality *8*

Worsening renal function and all-cause mortality in ADHF 8

Worsening renal function and all-cause mortality in AHF 8

Worsening renal function and all-cause mortality in CHF 9

Discussion **10**

WRF in acute heart failure *10*

WRF in chronic heart failure *11*

Strengths and Limitations *12*

Conclusion *12*

References **16**

Abstract

Background: Despite the numerous evidence-based treatments for heart failure (HF), its prognosis has only shown moderate improvements in the past decades. Worsening renal function (WRF) is common among patients with HF, however, its impact on prognosis remains controversial. Some studies have shown that WRF is associated with unfavorable outcomes in HF populations including increased short- and long-term mortality. Conversely, others did not reveal a specific prognostic value of WRF suggesting that it is probably not related to increased mortality in some HF patients.

Objective: The objective of this review is to give an update of the literature from 2012 onwards on the relationship between WRF and mortality in patients with all types of HF to further clarify the prognostic significance of WRF on HF, which has not been established yet.

Method: We performed a literature search of the PubMed database for studies that investigated the relationship between WRF and mortality in HF patients. The literature search was limited to studies conducted between 2012 to 2022. Our primary focus was on studies that examined the association between WRF and mortality in HF patients (≥ 18 years old) with a confirmed diagnosis of HF in either the 'acute or 'chronic' phase of the disease. Regarding WRF, we included only studies with a precise description of the WRF definition. The primary outcome measure was defined as all-cause mortality.

Results: Twelve studies were identified, six of which revealed WRF to be an independent predictor of all-cause mortality. However, there was inconsistency across the studies in terms of the definition of WRF, the timing of WRF occurrence, the type of HF patients, and the studied risk factors.

Conclusions: Taken together, there is still controversy regarding the prognostic impact of WRF on HF, and there is no gold standard to assess "true WRF." Therefore, future studies are required to investigate the relationship between WRF and HF by using a more consistent definition in terms of the timing of WRF occurrence, as well as by including more homogeneous populations with respect to the risk factors.

Layman's Summary

Background: While several strategies are available for the treatment of heart failure (HF), its prognosis has only shown moderate improvements in the past decades. Worsening of renal function (WRF) over time is common among patients with HF, however, its impact on prognosis remains controversial. Some studies have shown that WRF increases the risk of unfavorable outcomes in HF populations, including short- and long-term mortality. Conversely, others did not find such an association suggesting that it is probably not related to increased mortality in some HF patients.

Objective: The objective of this review is to give an update of the literature from 2012 onwards on the relationship between WRF and mortality in patients with HF to further clarify the prognostic significance of WRF on HF, which has not been established yet.

Method: We performed a literature search of the PubMed database for studies that investigated the relationship between WRF and mortality in HF patients. The literature search was limited to studies conducted between 2012 to 2022. Our primary focus was on studies that examined the association between WRF and mortality in HF patients (≥ 18 years old) with a confirmed diagnosis of HF. Regarding WRF, we included only studies with a precise description of the WRF definition. The primary outcome measure was defined as all-cause mortality.

Results: Twelve studies were identified, six of which found that WRF is significantly associated with all-cause mortality. However, there was inconsistency across the studies in terms of the definition of WRF, the timing of WRF occurrence, the type of HF patients, and the studied risk factors.

Conclusions: Taken together, there is still controversy regarding the prognostic impact of WRF on HF. Therefore, future studies are required to investigate the relationship between WRF and HF by using a more consistent definition in terms of the timing of WRF occurrence, as well as by including more homogeneous populations with respect to the risk factors.

Introduction

Heart Failure

Heart failure (HF) is a complex clinical syndrome in which the heart muscle does not pump blood as well as it should to meet the body's requirements. It is characterized by typical symptoms such as shortness of breath, fatigue, swelling in the legs, ankles, and feet, increased or irregular heart rate, and may be accompanied by signs of elevated jugular venous pressure, rales, and fluid retention (pulmonary and peripheral edema) (1-5). HF usually results from a structural or functional heart abnormality that leads to systolic and/or diastolic ventricular dysfunction. It has a large phenotypic heterogeneity including chronic HF (CHF) or acute HF (AHF) (4). The latter has been further divided into acute decompensated HF (ADHF) defined as the deterioration of pre-existing cardiomyopathy, such as coronary artery disease, and de novo AHF defined as the rapid development of typical symptoms and signs of HF which occurs in people with no history of heart disease (4, 5). Patients with HF are classified into three EF categories according to their symptoms and calculated left ventricular ejection fraction (LVEF), namely reduced (HFrEF: EF <40%; also, systolic HF), mildly reduced (HFmrEF: EF 40 – 49%), or preserved ejection fraction (HFpEF: EF >50%; also diastolic HF) (6, 7).

The global prevalence of HF exceeds 64 million, ranging from 1% to 3% in the general adult population in industrialized countries (3). Along with the worldwide aging of the population and developed treatment of cardiovascular events its prevalence is predicted to rise considerably within the next decades. In addition, HF is associated with increased costs of care making it a huge economic burden for healthcare systems worldwide. Patients with HF experience frequent hospitalizations, have a poor prognosis and suffer poor outcomes (3, 8, 9). HF is one of the leading and increasing causes of morbidity and mortality worldwide (3, 8). While there are several effective evidence-based treatments available for HFrEF, such as angiotensin-converting enzyme inhibitors (ACE-i), angiotensin receptor blockers (ARBs), beta-blockers, and developed device therapies, the prognosis of HF has only shown moderate improvement in the past decades. A recent meta-analysis of over 1.5 million HF patients of all types, estimated the 1-month, 1-, 2-, 5- and 10-year survival rates to be 96%, 87%, 73%, 57%, and 35%, respectively (10). On the other hand, HFpEF is a heterogeneous syndrome that currently represents one of the greatest challenges given that to date there have not been any proven therapies for this syndrome, thereby making HFpEF the most common form of HF worldwide (11-13). Thus, it is important to establish which clinical phenotypes are at higher risk of unfavorable outcomes.

Renal Impairment in Heart Failure

Most people with HF suffer from several cardiac and non-cardiac comorbidities which significantly contribute to disease progression, diminish the quality of life, and pose excess mortality risk (14, 15). Non-cardiovascular comorbidities such as renal impairment, diabetes mellitus, chronic obstructive pulmonary disease (COPD), obstructive sleep apnea, and anemia influence HF prognosis (15). Among them, renal dysfunction is the most prevalent one and has been strongly associated with clinical outcomes such as hospitalization and decreased survival in HF patients over the past decades (16-18). Chronic kidney disease (CKD) has long been identified as a prominent predictor of increased mortality and a higher risk of hospitalization in HF patients (16). It is identified by the presence of kidney injury or an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m2 or albuminuria ≥30 mg per 24 hours, persisting for at least 3 months (19-21). In addition, worsening renal function (WRF) is usually defined by an increase in serum creatinine (SCr) level of 0.3 mg/dL and/or a 25% reduction in eGFR compared to the value at admission, and represents the impairment of renal function over time (15, 22). Many studies have repeatedly shown that WRF in patients with acute and chronic HF is associated with unfavorable outcomes including increased short- and long-term mortality and has a prognostic impact comparable to CKD (15, 16, 23). In particular, in a meta-analysis performed by Damman et al. WRF was observed in 23% of all HF patients and was independently associated with all-cause mortality (HR: 1.95,

95%CI: 1.45–2.62, p<0.001) (16). Conversely, several studies did not reveal a specific prognostic value of WRF suggesting that it is probably not related to increased mortality in some patients (24, 25). Therefore, until now, the impact of WRF on prognosis has not been established yet, while there is consideration about whether the prognostic value of WRF depends on the type of HF.

Objectives

The objective of this review is to give an update of the literature from 2012 onwards on the relationship between WRF, and mortality in patients with HF to further clarify the prognostic significance of WRF on HF, which has not been established yet, as well as to investigate whether WRF has a different prognosis among patients with HFrEF and patients with HFpEF.

Methods

Literature search

A literature search was conducted between 2013 and June 2022, in the Pubmed database. We used keywords including renal function, renal insufficiency, renal dysfunction, renal failure, kidney failure, cardio-renal syndrome, creatinine, glomerular filtration rate, GFR, cystatin C, blood urea nitrogen, heart failure, and cardiac failure. We included only papers published in the English language. Furthermore, we used the ISSG search filter for systematic reviews in PubMed to identify key publications.

Eligibility criteria

Our primary focus was on studies that examined the association between WRF and mortality in HF patients. We included studies that involved exclusively adult individuals (≥8 years old) with a confirmed diagnosis of HF in either the ‘acute or ‘chronic’ phase of the disease. Regarding WRF, we included only studies with a precise description of the WRF definition– either an increase in SCr or cystatin C or a decrease in estimated GFR over time. The primary outcome measure was defined as all-cause mortality at any time during hospitalization, shortly after discharge, or long-term out hospital mortality. Mean or median follow-up times from individual studies were used.

Exclusion criteria

Studies were excluded if (i) they were conducted in non-human subjects, (ii) they did not provide crude mortality data or odds ratios for the study groups, (iii) they were published only in abstract form, (iv) they did not provide a clear definition for WRF, (v) no definition for HF was given, (vi) patients have been selected specifically based on another condition (e.g., patients receiving dialysis).

Methodological appraisal and risk of bias

The Newcastle-Ottawa Scale for cohort studies was used to appraise the methodological quality and measure the risk of bias in the eligible studies (26). The Newcastle-Ottawa Scale covers three domains (i) selection of the cohort, (ii) comparability of study groups, and (iii) the ascertainment of the outcomes. The total score ranges between 0 and 9, with more stars indicating higher quality and lower risk of bias. In the present review, we considered studies with a score of 7 or above to be of high quality.

Results

Literature Search and Study Selection

Initially, The PubMed search returned 4296 studies in total (Figure 1). We removed 36 duplicate studies; 4260 studies were screened. 248 were selected for full-text review and 3947 articles were excluded after the title and abstract screening. By assessing full-text articles, 12 studies published from 2012 onwards satisfied the review's inclusion/exclusion criteria.

Study characteristics

The design and sample characteristics for each study are summarised in Table 1. The included studies were published between 2013 and 2019. We identified three retrospective cohort studies, four prospective cohort studies, three registry studies and the remaining were post-hoc analyses from randomized control trials (RCTs). The sample sizes of the studies varied between n = 155 to n = 5625. Mean follow-up days ranged from 30 to 1132 days. The average age of the patients in the included studies varied between 56 and 80 years. Men and women were quite equally distributed across the studies. Left ventricular ejection fractions ranged from 32 to 60% and mean SCr from 1.06 to 1.74 mg/dl. The proportion of patients with diabetes mellitus ranged from 26 to 52%, with hypertension from 50 to 88%, and with ischemic heart disease (IHD) from 12 to 69%. Across the studies, the proportion of HF patients with preserved ejection fraction varied between 23 and 48%, while one study included exclusively patients with HFpEF. Regarding medication use, almost all the studies reported ACE-inhibitor or angiotensin receptor blocker use, as well as beta-blocker therapy. Only four studies assessed or reported dixogin use. Prevalence of WRF ranged between 12 and 51% and the 1-year mortality rate was between 9 and 43%.

Study quality

Overall, the included papers in this review were of high quality. According to the Newcastle-Ottawa Scale, 10 of the studies had scores above 7, thereby indicating high quality, while two of the included studies had a score of 6 and were considered of fair quality (Table 2).

Definition of WRF

Most of the studies defined WRF as an increase in SCr >0.3 mg/dL, sometimes together with a ≥25% increase in SCr, which is currently the most used definition, especially for patients with AHF. Few studies defined WRF as a ≥25% decrease in eGFR. We identified only one study that used a ≥0.3 mg/l increase in Cystatin C to define WRF (27). However, there was great variability across the studies in terms of the defined period during which WRF could occur. Usually, studies tested the occurrence of WRF at any time during hospitalization, or at any time during follow-up, while WRF 1 year after discharge was also studied.

Definition of HF

Six of the studies included acute heart failure (AHF) patients. Among them, one studied exclusively AHF patients with preserved ejection fraction. Five studies included acute decompensated heart failure (ADHF) patients while only one study included chronic HF patients.

WRF and All-Cause Mortality

Worsening renal function and all-cause mortality in ADHF

Among the studies that examined the relationship between WRF and all-cause mortality in ADHF patients, one was a prospective registry study (28), one was a post hoc analysis of an RCT study (27), and the remaining were cohort-based studies (29-31). Findings across these studies were inconsistent. In a prospective cohort study by Ueda et al., 233 patients with ADHF were split into 2 groups according to the presence or absence of WRF defined as >0.3 mg/dL absolute increase in SCr along with a ≥25% increase in SCr at 1 year following hospital discharge compared to the value at the time of discharge. Patients were followed for a mean period of 1077 days. According to Kaplan–Meier analysis, all-cause and cardiovascular mortality were significantly higher in those who developed WRF at one year (log-rank: p<0.0001). Moreover, in Cox proportional hazards analyses, 1-year WRF was a strong and independent predictor of all-cause and cardiovascular mortality both in the univariate and multivariate analysis (adjusted HR: 2.42; 95%CI: 1.41–4.11; p=0.002)

On the other hand, a subsequent prospective registry study of 762 ADHF patients, over a mean follow-up of 456 days showed that only persistent WRF was an independent predictor of mortality (adjusted HR: 1.71, 95%CI:1.31–2.35; p <0.0001). There was a significant association between WRF and increased mortality in the univariable Cox model, however, after adjustments for other risk factors, there was a borderline association between the two. In that study, WRF was defined as a ≥0.3 mg/dl inhospital increase in SCr compared to the baseline values (28). Okabe et al., in a prospective cohort of 301 patients with ADHF who were followed for a median period of 537 days presented similar findings (29). Both cardiovascular and all-cause mortality were significantly higher in those who developed WRF compared to those who did not (23.2% vs. 6.1%, p=0.001; 30.3% vs. 14.7%, p=0.001, respectively). In the univariate Cox proportional hazards analysis, the researchers found an association between WRF and both cardiovascular and all-cause death, however, after adjusting for confounders WRF was no longer associated with either cardiovascular death (adjusted HR: 2.49; 95%CI: 0.64–10.79; P = 0.19) or all-cause death (adjusted HR: 1.37; 95%CI: 0.45–4.05; p=0.57). Another report of 1232 patients hospitalized for ADHF, also showed that WRF defined by an increase of >0.3 mg/dl and >25% increase in sCr level at discharge and other definitions of WRF, including an increase of >25% in serum urea and/or a decrease of >25% in eGFR during hospitalization, were not associated with 180-day all-cause mortality. However, they reported that more severe WRF (increase of >0.5 mg/dl and >25% in sCr) was a predictor of mortality (adjusted HR: 1.87, 95%CI: 1.14–3.72, p=0.014) (30). In a substudy of the ASCEND-HF study, which was a multicenter, double-blind RCT trial of nesiritide compared with placebo, the researchers measured plasma Cystatin C levels from 811 patients with ADHF and followed them up for 180-day all-cause mortality. Similarly, WRF (defined as a ≥0.3 mg/l increase in Cystatin C 48 to 72 h after admission) was not predictive of adverse events. However, higher baseline Cystatin C levels were associated with a high risk of 180-day mortality (27).

Worsening renal function and all-cause mortality in AHF

We identified 3 retrospective cohort studies that investigated the relationship between WRF and AHF. Particularly, Caetano et al., assessed the inhospital, 30, and 90-day mortality risk among 155 patients admitted for AHF. The researchers defined cardiorenal syndrome (CRS) as a ≥0.3 mg/dl increase in SCr compared to admission values. Patients with CRS had higher in-hospital and 30-day mortality compared to those without (19.6% vs. 3.7%, p=0.001, OR: 6.4; 22.7% vs. 6.5%, p=0.004, OR: 4.2, respectively), and multivariate analysis revealed that CRS independently predicted of in-hospital mortality (32).

The other two retrospective studies examined the relationship between WRF and 1 year-mortality in AHF patients. Among 646 patients hospitalized for AHF, WRF was determined as an absolute increase in the Cr value of 26.4 mmol/L, or a relative increase of 1.5-2-fold compared with the baseline Cr value within 7 days after admission. In the

Kaplan-Meier analysis, WRF increased the risk of death, and the multivariate Cox proportional hazard analysis identified WRF as an independent strong predictor of 1-year mortality (adjusted HR:1.52, 95%CI: 1.09 - 2.13, p=0.014) (33). These results partially coincide with the recent retrospective study by Wettersten et al, among 814 AHF patients, which showed that only severe WRF and WRF with clinical deterioration were significantly associated with 1-year mortality (adjusted HR: 1.71, 95%CI: 1.09–2.69, p=0.020; adjusted HR: 1.98, 95%CI: 1.25–3.12, p=0.003, respectively). Severe WRF was a sustained increase of ≥0.5 mg/dL or ≥50% in SCr and WRF with clinical deterioration was non-severe WRF with renal replacement therapy, inotrope use, or mechanical ventilation. Non-severe WRF (nsWRF) had a trend towards increased risk but was not statistically significant (adjusted HR: 1.36, 95%CI: 0.96–1.93, p=0.079). Stratified analysis by B-type natriuretic peptide (BNP) status showed that WRF was only associated with 1-year mortality only in patients without decreased BNP (34).

In a post hoc analysis of the PROTECT RCT Study, researchers used repeated measurements of blood urea nitrogen (BUN) and creatinine to describe the course of renal function in 1962 AHF patients (35). For patients alive at 7 days, BUN, creatinine, and the rate of change in creatinine from baseline were the strongest independent predictors of death at 180 days. In sensitivity analyses, they found that definitions of WRF such as a ≥25% increase in SCr, a ≥0.3 mg/dL increase in SCr, or both, were strongly associated with all-cause mortality at 180 days.

Another study using the Korean Acute Heart Failure registry aimed to investigate the prognostic significance of WRF, in patients with HFpEF compared to patients with HFrEF (36). WRF was defined as a ≥0.3mg/dL absolute increase in Cr during admission. Among 5625 patients enrolled in the KorAHF registry, 55.2% had HFrEF, 23.0% had HFpEF and the rest had HFmrEF. Cox proportional hazard analyses, across the entire cohort, showed that WRF was an independent predictor of both 30-day mortality (HR: 1.66; 95%CI: 1.22–2.25; p=0.001) and 1-year mortality (HR: 1.39; 95%CI: 1.14–1.69; p=0.001). In the stratified analysis (HFrEF vs. HFpEF), WRF remained a significant predictor in both HF subgroups and had a larger effect size in HFpEF than in HFrEF both in terms of 3-month mortality (HR: 1.59, 95%CI: 1.10-2.29, p=0.013 for HFrEF and HR:1.86, 95%CI: 1.06-3.27, p=0.013 for HFpEF) and 1-year mortality (HR: 1.35, 95%CI: 1.06-1.71, p=0.014 for HFrEF and HR: 1.54, 95%CI: 1.08-2.18, p=0.016 for HFpEF). In addition, transient WRF (regarded as a recovered creatinine level at discharge) was a risk factor for 1-year mortality, while persistent WRF (defined as a non-recovered creatinine level) did not add any risk compared to transient WRF.

We identified one registry study that investigated the relationship between WRF and all-cause mortality only among HF patients with preserved ejection fraction (37). This recent study by Sato et al. was a post hoc analysis of the JASPER registry. The researchers defined WRF as a ΔCr ≥0.3 mg/dL in SCr levels at discharge minus the levels at admission. A decrease in eGFR of ≥20% during hospitalization was used as an alternative definition for WRF. The Kaplan-Meier analysis showed higher all-cause mortality in patients with WRF (log-rank P < .001). Moreover, Cox proportional hazard analysis revealed WRF to be a predictor of all-cause mortality (unadjusted HR: 2.73; 95%CI: 1.71–4.34; p<0.001). However, the researchers did not provide adjusted HRs.

Worsening renal function and all-cause mortality in CHF

We identified only one study that investigated the relationship between WRF and outcomes in CHF patients. This was a prospective cohort study among 892 CHF patients who were followed over 1132 days. WRF was defined either as a ≥25% decrease in eGFR or an increase in SCr ≥0.3 mg/dl. The researchers found an association between WRF and mortality in the unadjusted analysis, however, the association did not exist in the adjusted analysis (p=0.387 for ≥0.3 mg/dl increase in SCr and p=0.941 for ≥25% decrease in eGFR), suggesting that WRF in patients with HF may be a marker of progression of HF, but not an independent prognostic factor. In addition, the researchers showed that an improvement in eGFR was not associated with the outcome either (p = 0.453) (38).

Discussion

Worsening of renal function is common among patients with HF. In our review, we identified six studies that found WRF (defined as a ≥0.3 mg/dL increase in SCr) to be an independent predictor of all-cause mortality, while two studies showed that only severe WRF (defined by a ≥0.5 mg/dL increase in SCr) was strongly associated with mortality. We identified four studies that did not find an association between WRF and mortality and all were conducted in the setting of ADHF patients and one in CHF patients. However, the definition of WRF was not consistent across individual studies. Particularly, the marker of interest (SCr, eGFR, or Cystatin C), the level of change that was considered significant, but also the timing during which WRF occurred varied across the studies.

While WRF is a significant predictor of worse clinical outcomes, it remains unclear whether it is an independent prognostic risk factor for HF or whether it is a marker of progression of HF (39). Two previous meta-analyses, one in over 18.000 HF patients (40), and another in over 45.000 patients (16) reported that around 25% developed some level of WRF during follow-up. Furthermore, WRF was found to be a significant independent predictor of all-cause mortality in both meta-analyses (16, 40). However, the exact mechanism by which WRF drives unfavourable prognostic effects has yet to be determined (36). Testani et al. described some hypothetical mechanisms including inflammation, oxidative stress, or apoptosis induced by uremic toxins through which impairment in renal function may partially contribute to the adverse effect of WRF (39).

WRF in acute heart failure

Renal dysfunction in AHF patients involves complex and multifactorial mechanisms by hemodynamic and non-hemodynamic factors, which have not been completely elucidated (41). Numerous hemodynamic factors, including renal arterial hypoperfusion pressure, insufficient cardiac output, and increased central venous pressure contribute substantially to the decrease of renal blood flow and subsequently to the reduction of GFR (42, 43). Additionally, venous congestion, acute systolic blood pressure changes, and poor right ventricular function also play an important role in the development of WRF (43-45). Furthermore, an increase in intra-abdominal pressures is associated with elevated SCr levels, and strategies that reduce intra-abdominal pressures, including diuretics, paracentesis, or ultrafiltration, have been found to decrease SCr levels (46, 47). Impairment of renal function as a consequence of neurohormonal or hemodynamic disturbances can be reversible (41). In addition, non-hemodynamic factors such as activation of the renin-angiotensin-aldosterone (RAAS), of the sympathetic nervous system, inflammation, endothelial dysfunction, and oxidative stress, also trigger the development of WRF (48).

Results regarding the relationship between WRF and mortality in AHF patients were consistent across the included studies of this review. Five out of six studies, revealed WRF as an independent predictor of all-cause mortality (33, 35-37, 49), while the other study identified only severe WRF to be associated with mortality at 180 days (34). These findings are in line with results from the two previous meta-analyses, where WRF was also shown to be an independent predictor of all-cause mortality in AHF patients (16, 40). Considering the distinct pathophysiology between HFpEF and HFrEF, it is important to determine whether WRF has a different prognostic value between these two HF types. In our review, we retrieved two studies that examined the prognostic significance of WRF among AHF patients with HFpEF (36, 37). Both studies found that WRF was a significant predictor of long-term outhospital mortality in patients with HFpEF. Kang et al. further revealed that WRF had a bigger effect size in HFpEF than in HFrEF (36). Therefore, it is likely that WRF has a different prognosis in HFpEF patients, and it might even be associated with poorer outcomes compared to patients with HFrEF.

The effect of WRF on prognosis in acute decompensated HF patients remains questionable (50). While numerous reports have consistently shown that WRF is associated with poor outcomes (high rates of mortality and hospital readmission) (16, 23), others support that WRF is not related to increased mortality in all HF populations (24, 25). In

our review, results across the studies in ADHF patients were inconsistent. Out of five retrieved studies, only one found that one-year WRF (defined as a ≥0.3 mg/dL absolute increase in SCr along with a ≥25% increase in SCr at 1 year after discharge) independently predicted all-cause mortality (31). Moreover, the study by Salah et al., revealed that only severe WRF independently predicted all-cause mortality at 180 days (30). The other three studies did not find an association between WRF and mortality. These findings suggest that there is heterogeneity in this population, meaning that WRF might be triggered by hemodynamic disturbances which can be reversible in acute decompensated HF patients (27-29).

Recent studies support that WRF with decongestion is associated with a lower risk for adverse events and possibly with improved outcomes in AHF and accordingly that persistent congestion together with WRF is associated with poorer outcomes compared to WRF without congestion (51). Particularly, a recent meta-analysis that investigated whether decongestion modified the association between WRF and mortality among 7730 ADHF patients, showed that decongestion was associated with weakening of the adverse effects of WRF (50). In our review, we identified two studies that presented results in favor of this hypothesis. The study by Wattad et al. that investigated the interrelationship between WRF and persistent congestion in ADHF patients, showed that persistent congestion was more frequently observed in those who developed WRF than in those without WRF, while both persistent congestion and persistent WRF were significant predictors of mortality. Furthermore, multivariate analysis revealed a strong interaction between persistent congestion and WRF, signifying that the increased risk for mortality was observed primarily when both WRF and persistent congestion were present (28). The other study by Wittersen et al. examined the relationship between WRF and a decrease in B-type natriuretic peptide (BNP) with mortality in AHF. BNP is a well-established biomarker in both AHF and CHF, which has shown to decrease in AHF with decongestive therapy and with a decrease in cardiac pressures. This study found that decreased BNP was associated with better 1-year mortality despite the presence of WRF. In addition, WRF was a predictor of poor outcomes only in patients without decreased BNP (34). These findings suggest that the relationship between WRF and outcomes in AHF is driven by changes in volume status. WRF with decongestion might not be the result of actual renal impairment but a temporary hemodynamic or functional alternation without significant long-term implications. Therefore, WRF in ADHF patients can be heterogeneous with respect to prognosis.

In the past, studies have shown different relationships between persistent and transient WRF (52, 53). In our review, we identified a prospective registry study that found only persistent WRF as an independent predictor of mortality (28). In addition, another registry study showed that transient WRF (defined as a recovered creatinine value at discharge) was a comparable risk factor to persistent WRF for 1-year mortality (36). The differing definitions of WRF may partially account for this inconsistency across the studies. Given that the latter study defined transient WRF as a recovered creatinine level during hospitalization, it is possible that those who presented recovered renal function after discharge were classified in the persistent WRF subgroup, hence weakening the pure impact of persistent WRF.

WRF in chronic heart failure

In the setting of chronic HF, several different mechanisms can induce WRF. Changes in extracellular volume and blood pressure including congestion, hypotension, and dehydration are the main drivers of WRF in CHF patients (54). The meta-analysis by Damman et al. reported that WRF occurring without intervention is strongly associated with worse outcomes, while WRF in the setting of beneficial HF therapies, like RAAS antagonists or ACE-inhibitors seems to have a negligible effect on outcomes (16). In our review, we identified only one study in chronic HF patients (38). At the time of enrollment, 92% of patients in this cohort were on an ACE inhibitor or ARB therapy. This study did not detect an association between either worsening or improvement of renal function and all-cause mortality and the researchers suggested that in patients with properly treated chronic HF, WRF itself does not provide significant prognostic information and may not reflect poor outcomes, which is in line with the results from the previous meta-analysis.

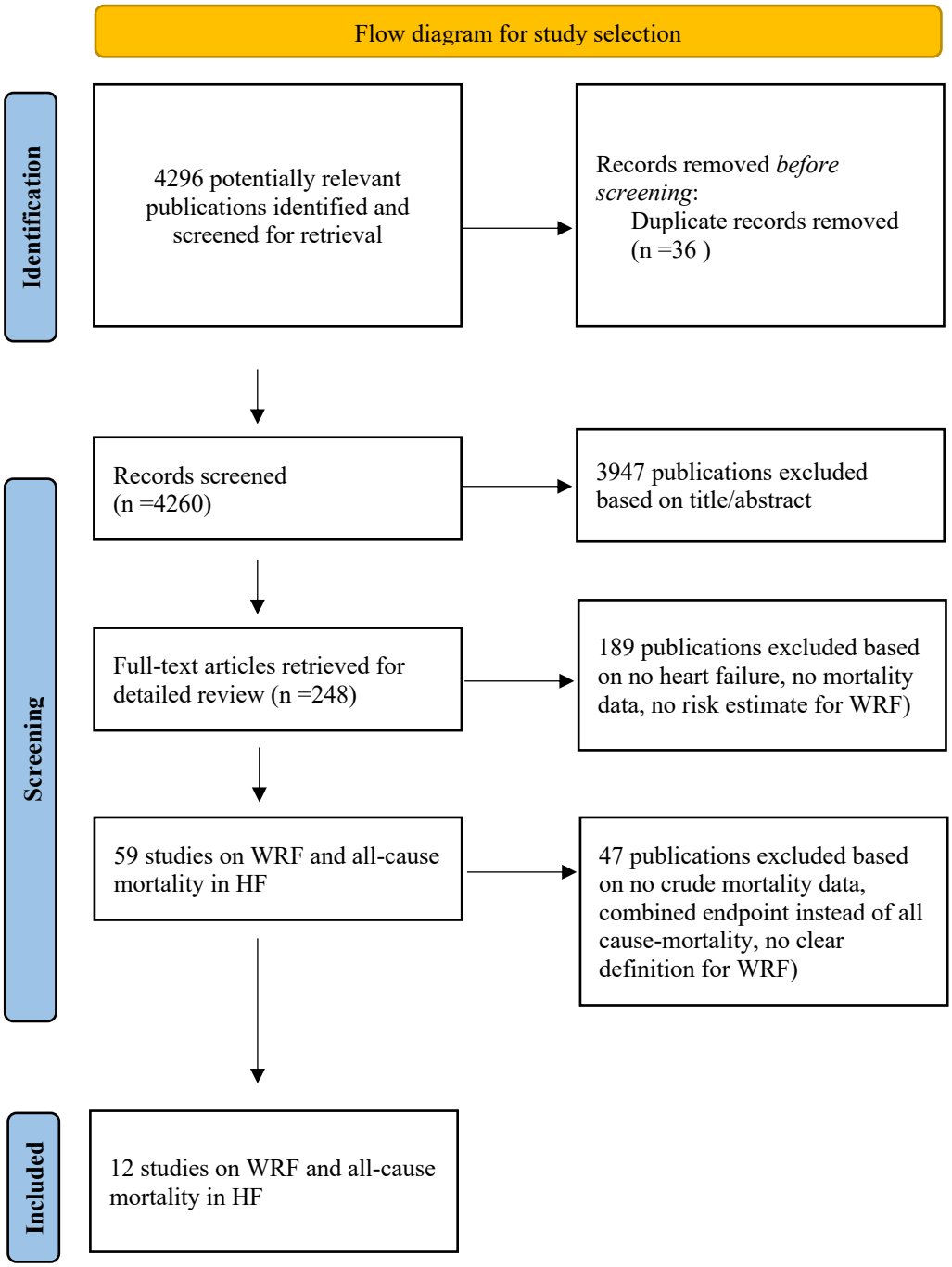
Strengths and Limitations

We included only studies that investigated all cause-mortality instead of the combined endpoint death and hospital readmission, which is a strength of our study. In addition, we included 12 studies, comprising a total population of 13.956 HF patients. However, our study has some limitations. Firstly, considering that this is not a systematic review, we might have not identified studies that met the inclusion criteria of our study. In addition, this review contained post hoc retrospective studies which are prone to bias and could result in residual confounding. The type of HF patients, the definition of WRF, the follow-up period, and the timing of WRF occurrence varied considerably among studies. These factors may lead to heterogeneity and may partially account for the inconsistent findings across the studies. Additional explanations for the heterogeneity across the studies include inconsistent inclusion/exclusion criteria, differing baseline renal function, and selection bias.

Conclusion

There remains controversy regarding the prognostic impact of WRF on HF, and there is no gold standard to assess "true WRF." The clinical setting, the cause of WRF, the timing of WRF, the days of follow-up, the treatment or initiation of therapy, and the related hemodynamic changes are crucial for evaluating the prognostic value of WRF. Therefore, future studies are required to investigate the relationship between WRF and HF by using a more consistent definition in terms of the timing of WRF occurrence, as well as by including more homogeneous populations with respect to the risk factors. Finally, given that recent reports have shown an interaction between WRF and congestion or decongestion, future studies should not assess WRF alone without concurrently assessing the volume status that accompanied the WRF.

Figure 1: Flow diagram for study selection



WRF, worsening renal function; HF, heart failure

Table 1: Characteristics of included studies

	Study design	n	Mean F U(days)	Age	Men (%)	LVEF (%)	HFPEF (%)	DM (%)	HT (%)	IHD (%)	sCr mg/dl	ACE-i /ARB (%)	BBL (%)	Diuretic (%)	Digoxin (%)	WRF (%)	All-cause mortality (%)	Definition WRF
AHF																		
Givertz, 2013	Substudy RCT	1962	180	70	67.1	32	—	45.8	79.5	69.4	1.5	ACE-i: 61.9, ARB: 16.0	76.7	—	—	—	16	≥25% increase in SCr, ≥0.3 mg/dL increase in SCr, or both at 7 days
Caetano, 2014	Retrospective cohort study	155	in-hospital, 30 and 90	74.1	50.3	—	48.4	30.3	67.1	29.7	1.43	82	40	—	26.7	29.7	9	≥0.3 mg/dL increase in SCr compared to admission values
Berra, 2015	Retrospective cohort study	646	365 days after admission	80*	55.1	—	43.2	30.7	—	43.3	—	60.7	40.6	58.7	—	23.7	29.7	≥0.3 mg/dL absolute increase in SCr, or a relative increase of 1.5-2-fold compared with the baseline Cr value within 7 days after admission
Kang, 2018	Registry	5625	30 and 365	68.5	53.2	37.7	23	39.9	62.1	37.6	1.49	—	—	Intravascular diuretics: 74.9	—	55.1	17.2	≥0.3 mg/dL increase in SCr during admission
Wettersten, 2019	Retrospective cohort study	814	in-hospital and 365	69	63	—	—	44	80.1	47	1.2	31.4	71.5	70.8	—	nsWRF: 32, sWRF: 10, WRF: 9	18	**Severe WRF (sWRF):** a sustained increase of ≥0.5 mg/dL or ≥50% in SCr, **Non-severe WRF (nsWRF):** a non-sustained increase of ≥0.3 mg/dL or ≥50% in SCr above the admission value during hospitalization
Sato, 2019	Registry	523	732* postdischarge	80.1	49.7	60	100	38.6	77.6	12.4	1.06	57.1	43.9	Spironolactone:16.3, LD: 51.8, Tolvaptan: 1	11	17.6	15.7	as Δcreatinine of ≥0.3 mg/dL at discharge minus that on admission or a decrease in eGFR of 20%
ADHF																		
Ueda, 2014	Cohort study	233	1077	72.2	56.7	45.1	38.2	45.1	76	32.2	—	91.9	57.9	LD: 85.8	—	20.6	28.3	≥0.3 mg/dL absolute increase in SCr in combination with a ≥25% increase in SCr from discharge to 1 year
Tang WHW, 2015	Substudy RCT	811	180	65.8	69.3	26	—	—	77.8	60.8	1.45	64.6	75.6	—	—	23	11.9	≥0.3 mg/l increase in CysC 48-72h after admission
Wattad, 2015	Prospective registry	762	456	77.1	49.9	45.9	—	51.6	87.7	—	1.39	71	66.1	Spironolactone: 21.9	10	27	42.9	≥0.3 mg/dl increase in SCr above baseline at any time during hospitalization
Salah, 2015	Individual patient data analysis	1232	180	74	60	—	26	32	50	49	1.52	66	57	95	—	WRF: 12%, sWRF: 6.9%	15	**WRF**: ≥0.3 mg/dL absolute increase in combination with a ≥25% increase in SCr, **sWRF**: ≥0.5 mg/dL absolute increase in combination with a ≥25% increase in SCr, eGFR (≥25% decrease), serum urea nitrogen (≥25% increase), and NT-proBNP ≥30% or >30% reduction) between admission and discharge
Okabe, 2016	Prospective cohort study	301	537*	73.1	61.1	42.3	32.9	34.9	70.7	29.9	1.17	39.5	27.9	LD: 38.2, Aldosterone antagonist: 15.6, Thiazide diuretics: 2.3	—	39.2	20.6	a ≥25% relative increase in SCr or ≥0.3 mg/dL absolute increase in SCr from the baseline.
CHF																		
Löffler, 2015	Prospective cohort study	892	1132	56	62	37	45	26	59	26	1.3	ACE-i: 68, ARB: 24	88	Potassium-sparing diuretics: 2, LD: 63	28	WRF (eGFR): 12%,	2.9	≥0.3 mg/dl increase in SCr or a ≥25% decrease in eGFR

For serum creatinine to convert from mg/dL to mmol/L multiply by 88.4.
ACE-i/ARB, angiotensin-converting enzyme inhibitor and/or angiotensin receptor blocker therapy; ADHF, acute decompensated heart failure; AHF, acute heart failure; BBL, beta-blocker therapy; CHF, chronic heart failure, DM, history of diabetes; HFPEF, heart failure with preserved ejection fraction; HT, history of hypertension; IHD, ischaemic heart disease; F/U, follow-up; LVEF, left-ventricular ejection fraction; sCr, serum creatinine; WRF, worsening renal function.

Table 2: New castle-Ottawa scale for assessment of the quality of included studies

	Selection				**Comparability**	**Outcome**			
Athor (year)	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertain-ment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis controlled for confounders	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	Total score
Givertz, 2013	–	*	*	*	**	*	*	*	8
Caetano, 2014	*	*	*	*	*	–	*	*	7
Berra, 2015	*	*	*	*	**	–	*	*	8
Kang, 2018	*	*	*	*	**	–	*	–	7
Wettersten, 2019	*	*	*	*	**	*	*	*	9
Sato, 2019	*	*	*	*	**	–	*	–	7
Ueda, 2014	*	*	*	*	**	–	*	*	8
Tang WHW, 2015	–	*	*	*	**	–	*	–	6
Wattad, 2015	*	*	*	*	**	*	*	–	8
Salah, 2015	*	*	*	*	**	*	*	*	9
Okabe, 2016	*	*	*	*	**	–	*	*	8
Löffler, 2015	*	*	*	*	*	–	*	–	6

References

1. Metra M, Teerlink JR. Heart failure. Lancet. 2017;390(10106):1981-95.
2. Schwinger RHG. Pathophysiology of heart failure. Cardiovasc Diagn Ther. 2021;11(1):263-76.
3. Savarese G, Becher PM, Lund LH, Seferovic P, Rosano GMC, Coats A. Global burden of heart failure: A comprehensive and updated review of epidemiology. Cardiovasc Res. 2022.
4. Arrigo M, Jessup M, Mullens W, Reza N, Shah AM, Sliwa K, et al. Acute heart failure. Nat Rev Dis Primers. 2020;6(1):16.
5. Kurmani S, Squire I. Acute Heart Failure: Definition, Classification and Epidemiology. Curr Heart Fail Rep. 2017;14(5):385-92.
6. Hajouli S, Ludhwani D. Heart Failure And Ejection Fraction. StatPearls. Treasure Island (FL): StatPearls Publishing

7. Bozkurt B, Coats AJ, Tsutsui H, Abdelhamid M, Adamopoulos S, Albert N, et al. Universal Definition and Classification of Heart Failure: A Report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure. J Card Fail. 2021.
8. Savarese G, Lund LH. Global Public Health Burden of Heart Failure. Card Fail Rev. 2017;3(1):7-11.
9. Groenewegen A, Rutten FH, Mosterd A, Hoes AW. Epidemiology of heart failure. Eur J Heart Fail. 2020;22(8):1342-56.
10. Jones NR, Roalfe AK, Adoki I, Hobbs FDR, Taylor CJ. Survival of patients with chronic heart failure in the community: a systematic review and meta-analysis. Eur J Heart Fail. 2019;21(11):1306-25.
11. Roh J, Hill JA, Singh A, Valero-Muñoz M, Sam F. Heart Failure With Preserved Ejection Fraction: Heterogeneous Syndrome, Diverse Preclinical Models. Circ Res. 2022;130(12):1906-25.
12. Upadhya B, Kitzman DW. Heart failure with preserved ejection fraction: New approaches to diagnosis and management. Clin Cardiol. 2020;43(2):145-55.
13. Adamczak DM, Oduah MT, Kiebalo T, Nartowicz S, Bęben M, Pochylski M, et al. Heart Failure with Preserved Ejection Fraction-a Concise Review. Curr Cardiol Rep. 2020;22(9):82.
14. Comín-Colet J, Martín Lorenzo T, González-Domínguez A, Oliva J, Jiménez Merino S. Impact of non-cardiovascular comorbidities on the quality of life of patients with chronic heart failure: a scoping review. Health Qual Life Outcomes. 2020;18(1):329.
15. van der Wal HH, van Deursen VM, van der Meer P, Voors AA. Comorbidities in Heart Failure. Handb Exp Pharmacol. 2017;243:35-66.
16. Damman K, Valente MA, Voors AA, O'Connor CM, van Veldhuisen DJ, Hillege HL. Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. Eur Heart J. 2014;35(7):455-69.
17. van Deursen VM, Urso R, Laroche C, Damman K, Dahlström U, Tavazzi L, et al. Co-morbidities in patients with heart failure: an analysis of the European Heart Failure Pilot Survey. Eur J Heart Fail. 2014;16(1):103-11.
18. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016;37(27):2129-200.
19. Vaidya SR, Aeddula NR. Chronic Renal Failure. StatPearls. Treasure Island (FL): StatPearls Publishing

20. Braun MM, Khayat M. Kidney Disease: Chronic Kidney Disease. FP Essent. 2021;509:20-5.

21. Chen TK, Knicely DH, Grams ME. Chronic Kidney Disease Diagnosis and Management: A Review. Jama. 2019;322(13):1294-304.
22. Shirakabe A, Hata N, Kobayashi N, Okazaki H, Matsushita M, Shibata Y, et al. Worsening renal function definition is insufficient for evaluating acute renal failure in acute heart failure. ESC Heart Fail. 2018;5(3):322-31.
23. Raichlin E, Haglund NA, Dumitru I, Lyden ER, Johnston MD, Mack JM, et al. Worsening renal function in patients with acute decompensated heart failure treated with ultrafiltration: predictors and outcomes. J Card Fail. 2014;20(5):376.e25-32.
24. Ather S, Bavishi C, McCauley MD, Dhaliwal A, Deswal A, Johnson S, et al. Worsening renal function is not associated with response to treatment in acute heart failure. Int J Cardiol. 2013;167(5):1912-7.
25. Lanfear DE, Peterson EL, Campbell J, Phatak H, Wu D, Wells K, et al. Relation of worsened renal function during hospitalization for heart failure to long-term outcomes and rehospitalization. Am J Cardiol. 2011;107(1):74-8.
26. Wells GA SB, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2012 [Available from: https://www.ohri.ca//programs/clinical_epidemiology/oxford.asp.
27. Tang WHW, Dupont M, Hernandez AF, Voors AA, Hsu AP, Felker GM, et al. Comparative assessment of short-term adverse events in acute heart failure with cystatin C and other estimates of renal function: results from the ASCEND-HF trial. JACC Heart Fail. 2015;3(1):40-9.
28. Wattad M, Darawsha W, Solomonica A, Hijazi M, Kaplan M, Makhoul BF, et al. Interaction between worsening renal function and persistent congestion in acute decompensated heart failure. Am J Cardiol. 2015;115(7):932-7.
29. Okabe T, Yakushiji T, Kido T, Oyama Y, Igawa W, Ono M, et al. Relationship between worsening renal function and long-term cardiovascular mortality in heart failure patients. Int J Cardiol. 2017;230:47-52.
30. Salah K, Kok WE, Eurlings LW, Bettencourt P, Pimenta JM, Metra M, et al. Competing Risk of Cardiac Status and Renal Function During Hospitalization for Acute Decompensated Heart Failure. JACC Heart Fail. 2015;3(10):751-61.
31. Ueda T, Kawakami R, Sugawara Y, Okada S, Nishida T, Onoue K, et al. Worsening of renal function during 1 year after hospital discharge is a strong and independent predictor of all-cause mortality in acute decompensated heart failure. J Am Heart Assoc. 2014;3(6):e001174.
32. Casado J, Montero M, Formiga F, Carrera M, Urrutia A, Arévalo JC, et al. Clinical characteristics and prognostic influence of renal dysfunction in heart failure patients with preserved ejection fraction. Eur J Intern Med. 2013;24(7):677-83.
33. Berra G, Garin N, Stirnemann J, Jannot AS, Martin PY, Perrier A, et al. Outcome in acute heart failure: prognostic value of acute kidney injury and worsening renal function. J Card Fail. 2015;21(5):382-90.
34. Wettersten N, Horiuchi Y, van Veldhuisen DJ, Mueller C, Filippatos G, Nowak R, et al. B-type natriuretic peptide trend predicts clinical significance of worsening renal function in acute heart failure. Eur J Heart Fail. 2019;21(12):1553-60.
35. Givertz MM, Postmus D, Hillege HL, Mansoor GA, Massie BM, Davison BA, et al. Renal function trajectories and clinical outcomes in acute heart failure. Circ Heart Fail. 2014;7(1):59-67.
36. Kang J, Park JJ, Cho YJ, Oh IY, Park HA, Lee SE, et al. Predictors and Prognostic Value of Worsening Renal Function During Admission in HFpEF Versus HFrEF: Data From the KorAHF (Korean Acute Heart Failure) Registry. J Am Heart Assoc. 2018;7(6).
37. Sato Y, Yoshihisa A, Oikawa M, Nagai T, Yoshikawa T, Saito Y, et al. Prognostic Impact of Worsening Renal Function in Hospitalized Heart Failure Patients With Preserved Ejection Fraction: A Report From the JASPER Registry. J Card Fail. 2019;25(8):631-42.
38. Löffler AI, Cappola TP, Fang J, Hetzel SJ, Kadlec A, Astor B, et al. Effect of renal function on prognosis in chronic heart failure. Am J Cardiol. 2015;115(1):62-8.
39. Testani JM, Brisco-Bacik MA. Worsening Renal Function and Mortality in Heart Failure: Causality or Confounding? Circ Heart Fail. 2017;10(2).

40. Damman K, Navis G, Voors AA, Asselbergs FW, Smilde TD, Cleland JG, et al. Worsening renal function and prognosis in heart failure: systematic review and meta-analysis. J Card Fail. 2007;13(8):599-608.
41. Mullens W, Damman K, Testani JM, Martens P, Mueller C, Lassus J, et al. Evaluation of kidney function throughout the heart failure trajectory - a position statement from the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2020;22(4):584-603.
42. Damman K, van Deursen VM, Navis G, Voors AA, van Veldhuisen DJ, Hillege HL. Increased central venous pressure is associated with impaired renal function and mortality in a broad spectrum of patients with cardiovascular disease. J Am Coll Cardiol. 2009;53(7):582-8.
43. Mullens W, Abrahams Z, Francis GS, Sokos G, Taylor DO, Starling RC, et al. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. J Am Coll Cardiol. 2009;53(7):589-96.
44. Dupont M, Mullens W, Finucan M, Taylor DO, Starling RC, Tang WH. Determinants of dynamic changes in serum creatinine in acute decompensated heart failure: the importance of blood pressure reduction during treatment. Eur J Heart Fail. 2013;15(4):433-40.
45. Verhaert D, Mullens W, Borowski A, Popović ZB, Curtin RJ, Thomas JD, et al. Right ventricular response to intensive medical therapy in advanced decompensated heart failure. Circ Heart Fail. 2010;3(3):340-6.
46. Mullens W, Abrahams Z, Skouri HN, Francis GS, Taylor DO, Starling RC, et al. Elevated intra-abdominal pressure in acute decompensated heart failure: a potential contributor to worsening renal function? J Am Coll Cardiol. 2008;51(3):300-6.
47. Mullens W, Abrahams Z, Francis GS, Taylor DO, Starling RC, Tang WH. Prompt reduction in intra-abdominal pressure following large-volume mechanical fluid removal improves renal insufficiency in refractory decompensated heart failure. J Card Fail. 2008;14(6):508-14.
48. Rangaswami J, Bhalla V, Blair JEA, Chang TI, Costa S, Lentine KL, et al. Cardiorenal Syndrome: Classification, Pathophysiology, Diagnosis, and Treatment Strategies: A Scientific Statement From the American Heart Association. Circulation. 2019;139(16):e840-e78.
49. Caetano F, Barra S, Faustino A, Botelho A, Mota P, Costa M, et al. Cardiorenal syndrome in acute heart failure: a vicious cycle? Rev Port Cardiol. 2014;33(3):139-46.
50. Yamada T, Ueyama H, Chopra N, Yamaji T, Azushima K, Kobayashi R, et al. Systematic Review of the Association Between Worsening Renal Function and Mortality in Patients With Acute Decompensated Heart Failure. Kidney Int Rep. 2020;5(9):1486-94.
51. Metra M, Cotter G, Senger S, Edwards C, Cleland JG, Ponikowski P, et al. Prognostic Significance of Creatinine Increases During an Acute Heart Failure Admission in Patients With and Without Residual Congestion: A Post Hoc Analysis of the PROTECT Data. Circ Heart Fail. 2018;11(5):e004644.
52. Aronson D, Burger AJ. The relationship between transient and persistent worsening renal function and mortality in patients with acute decompensated heart failure. J Card Fail. 2010;16(7):541-7.
53. Palmer JB, Friedman HS, Waltman Johnson K, Navaratnam P, Gottlieb SS. Association of persistent and transient worsening renal function with mortality risk, readmissions risk, length of stay, and costs in patients hospitalized with acute heart failure. Clinicoecon Outcomes Res. 2015;7:357-67.
54. Mewton N, Girerd N, Boffa JJ, Courivaud C, Isnard R, Juillard L, et al. Practical management of worsening renal function in outpatients with heart failure and reduced ejection fraction: Statement from a panel of multidisciplinary experts and the Heart Failure Working Group of the French Society of Cardiology. Arch Cardiovasc Dis. 2020;113(10):660-70.