Impaired renal function and mortalities in acute heart failure with different phenotypes

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Abstract

Aims Impaired renal function (IRF) prevails in patients with acute heart failure. The study aimed to investigate the prevalence of on-admission IRF and its association with short-term and long-term mortalities in patients hospitalized for HF with reduced (HFrEF), mildly reduced (HFmrEF), and preserved (HFpEF) left ventricular ejection fraction (LVEF).

Methods Patients hospitalized for acute heart failure were enrolled and stratified by LVEF into three phenotypes as HFpEF (≥50%), HFmrEF (40–49%), and HFrEF (<40%). IRF was defined as an estimated glomerular filtration rate of ≤60 mL/min/1.73m² on admission. National Death Registry was linked for the identification of mortality.

Results Of 2613 patients enrolled, 673 (25.7%) had HFrEF, 367 (14.0%) had HFmrEF, and 1573 (60.1%) had HFpEF, whereas IRF was prevalent among 63.7, 68.6, and 67.5% of them, respectively. IRF significantly correlated with higher long-term mortality in each phenotype of HF. However, IRF was associated with 90-day and 1-year mortality in subjects with HFrEF and HFmrEF, but not HFpEF. After accounting for age, gender, hypertension, diabetes, coronary artery disease, atrial fibrillation, stroke, serum sodium, de novo heart failure, date of enrolment, and systolic blood pressure <90 mmHg or use of inotropic agents, IRF remained related to 5-year mortality in patients with HFrEF (hazard ratio and 95% confidence interval: 1.346, 1.034–1.751), HFmrEF (2.210, 1.435–3.404), and HFpEF (1.493, 1.237–1.801).

Conclusions On-admission IRF was independently predictive of long-term mortality in patients hospitalized for HF, irrespective of HF phenotypes. Furthermore, IRF was also associated with short-term mortality in HFrEF and HFmrEF, but not in HFpEF.

Keywords Acute heart failure; Impaired renal function; Left ventricular ejection fraction; All-cause mortality

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Introduction

Impaired renal function (IRF) prevails in patients with heart failure (HF), which has jeopardized the clinical outcomes regardless of left ventricular ejection fraction (LVEF).1,2 In a cohort of 40 230 subjects with chronic heart failure (CHF), Löfman et al. have demonstrated that patients with HF who had preserved LVEF (HfPEF) were more likely to have IRF, defined as estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73m², when those with mildly reduced (HFmrEF) or reduced LVEF (HFrEF).2 Although IRF was more common in HfPEF, it had less prognostic impacts than in other phenotypes of HF.4 The results of MAGGIC study of CHF subjects also suggested a modest association between renal dysfunction and mortality in patients with HfPEF, in contrast to HFrEF.3,4

Compared with CHF, acute heart failure (AHF) was related to higher clinical risks of mortality and HF re-hospitalization.5 Due to the cardiorenal interplay and the use of diuretics, IRF was even more prevalent in AHF. The ADHERE Registry...
reported that around 60% of the patients hospitalized for AHF had IRF and more than 70% of the AHF patients would experience an increase in creatinine during hospitalization. However, the prognostic significance of IRF in AHF with different phenotypes has not been clearly documented. In this study, we therefore investigated the prevalence of on-admission IRF and its association with short-term and long-term mortalities in patients hospitalized for HF with reduced (HFrEF), mildly reduced (HFmrEF), and preserved (HFpEF) LVEF.

Methods

Study population

The study population was drawn from an intramural registry, which enrolled patients hospitalized for HF from October 2003 to December 2012 at Taipei Veterans General Hospital. Patients with acute coronary syndrome, severe infection, severe hepatic disease, haematopoietic diseases, and active malignancy were excluded from this analysis. The investigation conformed to the principles outlined in the Declaration of Helsinki. The institutional review board of Taipei Veterans General Hospital waived the informed consent and approved this study.

Laboratory data and echocardiography

Every participant has undergone a standard echocardiographic study conforming to the guidance of American Society of Echocardiography. Left ventricular internal dimension at diastole and systole (LVIDd and LVIDs) and LVEF were recorded accordingly. Pulmonary artery systolic pressure (PASP) was estimated, and the peak velocity of early (E) and late (A) mitral inflow were obtained. The measures of tissue velocity (e′) at septal mitral annulus by using tissue Doppler were acquired. The phenotypes of HF were classified as HFrEF (LVEF < 40%), HFmrEF (LVEF of 40–49%), and HFpEF (LVEF ≥ 50%).

Demographic characteristics, haemogram, and biochemistry were recorded in a web-based electronic medical recording system. Estimated glomerular filtration rate (eGFR) was determined by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. IRF was referred to an eGFR of <60 mL/min/1.73m² on admission. Because the commercialized measure for N-terminal pro-brain natriuretic peptide (NT-proBNP; Roche Diagnostics, Basel, Switzerland) was only available after 2009, there were missing values of NT-proBNP in this cohort.

Follow-up

The dates and causes of mortality for the study cohort were obtained by linking our database with the National Death Registry through a personal identification number given to every Taiwan citizen.

Statistical analysis

Continuous variables were presented as means and standard deviations. Categorical variables were expressed as the absolute numbers and relative frequencies. Student’s t-test and chi-square tests were calculated for the baseline characteristics comparisons where appropriate. Logistic regression analysis was performed for the associations between different subgroups of baseline characteristics and IRF. Kaplan–Meier survival curve analysis demonstrated the outcomes of IRF in each phenotype of HF. Cox proportional hazards models were used to determine IRF in the prediction of short-term and long-term mortalities. All the statistical analyses were performed using SPSS v.20.0 software (SPSS, Inc., Chicago, IL, USA), and the performed tests were two-sided. A P value of <0.05 was considered statistically significant.

Results

A total of 2613 patients (age 76.3 ± 12.8 years, 67% men) were analysed, whereas 673 (25.7%) had HFrEF, 367 (14.0%) had HFmrEF, and 1573 (60.1%) had HFpEF. The prevalence of on-admission IRF in HFrEF, HFmrEF, and HFpEF were 63.7, 68.6, and 67.5%, respectively (P value = 0.174). Table 1 demonstrates the comparisons between patients with and without on-admission IRF in HFrEF, HFmrEF, and HFpEF. In short, patients with on-admission IRF were older, were less likely to be de novo HF, but more prevalent of male gender and hypertension, and had lower haemoglobin and higher NT-proBNP in each HF phenotype. The on-admission systolic blood pressure (SBP), LVIDs, and LVIDd were higher, prevalence of AF was lower, and the use of beta blockers was higher in patients with IRF than the counterpart in HFpEF subgroup but not in HFmrEF and HFrEF. In addition, the prevalence of diabetes was higher in HFmrEF or HFpEF subjects with IRF than those without IRF.

Associations between impaired renal function and mortality

During a mean follow-up duration of 27.8 ± 20.6 months, there were 1091 (43.0%) deaths. The Kaplan–Meier survival curve analyses showed that patients with on-admission IRF had a significantly lower long-term survival probability than
their counterparts in each HF phenotype (Figure 2). With further categorization of renal function by eGFR of >90, 60–90, 30–60, and <30 ml/min/1.73 m², the 5-year mortality rate generally increased along with the deterioration of renal function (Figure 2). Among subjects with HFrEF but not HfmrEF or HfPEF, further decline in eGFR of <30 ml/min/1.73 m² was associated with worse clinical outcomes than those with eGFR of 30–60 ml/min/1.73 m² (Figure 2).

On-admission IRF was associated with higher mortality in subjects with HFrEF and HfmrEF, regardless of the follow-up duration (Figure 3). But in subjects with HfPEF, IRF carried higher mortality risks only at 3-year and 5-year but not at 90-day or 1-year follow-up.

In the Cox proportional hazards model, IRF was crudely associated with 5-year mortality in each HF phenotype (Table 2, Model 1). After accounting for age and gender, IRF remained significantly related to the clinical outcomes, regardless of HF phenotypes (Table 2, Model 2). On-admission IRF persistently correlated with 5-year mortality, independent of age, gender, hypertension, diabetes, coronary artery disease, atrial fibrillation, stroke, serum sodium, and de novo heart failure, date of enrolment, and SBP < 90 mmHg or use of inotropic agents, in patients with HFrEF, HfmrEF, and HfPEF [hazard ratios and 95% confidence intervals (CI): 1.346 (1.034–1.751), 2.210 (1.435–3.404), and 1.493 (1.237–1.801), respectively (Table 2, Model 3). With further adjustment for NT-proBNP in multivariate Cox regression analysis, IRF was not related to the long-term outcomes in each HF phenotypes (Table S1, Model 2).

### Associations between baseline characteristics and impaired renal function

Age, gender, hypertension, diabetes, ischaemic heart disease, atrial fibrillation, and SBP were associated with the presence of on-admission IRF in the total study population (Figure 4). SBP was associated with IRF only in HfPEF (odd ratios and 95% CI per 10 mmHg: 1.095, 1.053–1.138), but not in HFrEF or HfmrEF (interaction P value = 0.018). Otherwise, age, hypertension, diabetes, and ischaemic heart disease (HR: 1.73 m² was associated with worse clinical outcomes than their counterparts in each HF phenotype (Figure 2). With further categorization of renal function by eGFR of >90, 60–90, 30–60, and <30 ml/min/1.73 m², the 5-year mortality rate generally increased along with the deterioration of renal function (Figure 2). Among subjects with HFrEF but not HfmrEF or HfPEF, further decline in eGFR of 30–60 ml/min/1.73 m² was associated with worse clinical outcomes than those with eGFR of 30–60 ml/min/1.73 m² (Figure 2).

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gender, presence of hypertension, diabetes, ischaemic heart disease, and atrial fibrillation were equally related to IRF in all phenotypes of HF.

Discussion

This study has demonstrated that on-admission IRF prevailed in patients with AHF, regardless of LVEF that only 36.3, 31.4, and 32.5% of HFrEF, HFmrEF, and HFpEF had preserved renal function. Age, gender, hypertension, diabetes, ischaemic heart disease, atrial fibrillation, and SBP were all associated with the presence of IRF. In addition, SBP was predictive of IRF predominantly in HFpEF but not in HFrEF or HFmrEF.

The on-admission IRF was an independent risk factor of 5-year mortality in all phenotypes of HF, after accounting for age, gender, hypertension, diabetes, coronary artery disease, atrial fibrillation, stroke, serum sodium, and de novo heart failure, date of enrolment, and SBP < 90 mmHg or use of inotropic agents. However, IRF may be related to short-term clinical outcomes only in subjects with HFrEF or HFmrEF.

The prevalence of impaired renal function in AHF

IRF has been prevalent in patient with CHF that 55% of the study population in MAGGIC cohort has an eGFR of <60 mL/min/1.73m² and the presence of IRF was slightly predominantly in subjects with HfPEF rather than HFrEF. However, Ather et al. have demonstrated a conflict result in an ambulatory cohort of veterans with CHF that 51.9% of HFrEF had IRF, overtaking the 48.8% of HfPEF. Although the ADHERE database has demonstrated an even higher prevalence that 64% of AHF patients had IRF, Park et al. suggested IRF equally distributed among patients with HfPEF (49%) and HFrEF (52%) in the Korean Heart Failure (KorHF) Registry. In this study, we also reported a high prevalence of 66.7% IRF among patients hospitalized for HF, regardless of the phenotypes. The prevalence of IRF were 63.7, 68.6, and 67.5% in HFrEF, HFmrEF, and HfPEF, respectively.

The associated characteristics with impaired renal dysfunction in AHF

Among the study population of 2613 AHF subjects, older age, male gender, hypertension, diabetes, ischaemic heart disease, atrial fibrillation, and SBP were associated with IRF. In the phenotype-stratified analysis, SBP correlated with IRF only in subjects with HfPEF but not HFrEF and HFmrEF. The study results may echo what Viau et al. have presented that the increased afterload from increased SBP would jeopardize the renal blood flow and then deteriorate the kidney function in subjects with AHF, especially in HfPEF.
Löfman et al. reported that IRF was more likely to correlate with mortality in HFmrEF and HFrEF rather than in HFpEF. In AHF population, KorHF Registry also suggested the short-term prognostic impacts of severe renal dysfunction with an eGFR of <30 mL/min/1.73m² was attenuated in patients with HFpEF, compared with HFrEF. In the present

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**Figure 2** The Kaplan–Meier survival curve analyses, stratified by estimated glomerular filtration rate (eGFR) of ≥90, 60–90, 30–60, and < 30 mL/min/m² in subjects with heart failure and reduced (HFrEF, A), mildly reduced (HFmrEF, B), or preserved (HFpEF, C) ejection fraction subjects.
study, we have further shown that the mortality risks of IRF, referred to an eGFR of $< 60$ mL/min/1.73m$^2$, were attenuated in HFpEF within a year. However, the independent long-term survival impacts of IRF were observed similarly in all three phenotypes of the AHF patients. The results may support that IRF may impose a short-term risk of mortality in hospitalized HF patients with LVEF $< 50%$.

**Study limitations**

There are some limitations within this study. Given the nature of a registry, the existed selection bias remains a concern even we have adjusted all available confounders to demonstrate the independent relation of IFR with mortality. Although NT-proBNP may mitigate the prognostic impacts of
IRF, NT-proBNP was only available in 39% of the study population. The sample size was not sufficiently powered to demonstrate whether IRF was related to the outcomes, independent of NT-proBNP in each phenotype of AHF. Though the renal function prior to the index hospitalization was not available in this registry, the pre-discharge IRF has also been related to the clinical outcomes (Figure S1). Given the haemodynamic perturbations in AHF may deteriorate the renal function, on-admission eGFR may reflect not only the background kidney function. After accounting for age, gender, and pre-discharge IRF, on-admission IRF remained correlated with all-cause mortality (Table S1, Model 1). In addition, nephrilysin inhibitor or sodium-glucose co-transporter 2 inhibitors were not available during the enrolment. Moreover, the study population consisted mostly Asian older patients, which could jeopardize the generalizability of the study results to other populations. Further studies are needed to validate the independently prognostic impacts of IRF in various HF phenotypes.

Conclusions

IRF is an independent prognostic factor related to long-term survival of patients hospitalized for HF, regardless of the LVEF. Age, male gender, hypertension, diabetes, ischaemic heart disease, atrial fibrillation, and SBP were all related to the presence of IRF. However, SBP was predominantly associated with IRF in patients with HFrEF. In contrast to patients with IRF, subjects with HFrEF would have better short-term clinical outcomes than those with HFrEF and HFrEF. But in
the long run, IRF was independently correlated with mortality, regardless of the phenotypes. The results may suggest IRF not only a co-morbidity in HFpEF, but also a risk factor in HFrEF and HFmrEF among AHF patients.

Conflict of interest
None declared.

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Supporting information
Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. The probability of mortality within 90 days, 1 year, 3 years and 5 years among patients with and without pre-discharged impaired renal function (IRF) in each phenotype of heart failure. (* Indicated P value of <0.05, compared with patients with IRF in each phenotype.) HFrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IRF, impaired renal function.

Table S1. Sensitivity analysis.

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