




BMJ Open Prognostic significance of dipstick proteinuria in heart failure with preserved ejection fraction: insight from the PURSUIT-HFpEF registry

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ABSTRACT

Objective The semiquantitative urine dipstick test is a simple and convenient method that is available in the smallest community-based healthcare clinics. We sought to clarify the prognostic significance of dipstick proteinuria in patients with heart failure (HF) with preserved ejection fraction (HFpEF).

Design A Prospective multicenter Observational study of patients with Heart Failure with preserved Ejection Fraction (PURSUIT-HFpEF) registry.

Participants and setting We assessed 851 discharged-alive patients in the PURSUIT-HFpEF registry who were initially hospitalised due to an acute decompensated HFpEF (EF \geq 50%) and elevated N-terminal-pro-brain natriuretic peptide (\geq 400 ng/L) at Osaka University Hospital and other 30 affiliated hospitals in the Kansai region of Japan. Patients received a urine dipstick test, and were divided into two groups according to the absence or presence of proteinuria. A trace or more of dipstick proteinuria was defined as the presence of proteinuria.

Main outcome measures A composite of cardiac death or HF rehospitalisation.

Results Median age was 83 years and 473 patients (55.6%) were female. Five hundred and two patients (59%) were proteinuria (–) and 349 patients (41%) were proteinuria (+). The composite endpoint and HF rehospitalisation occurred more often in proteinuria (+) individuals than proteinuria (–) individuals (log-rank $p=0.006$ and $p=0.007$, respectively); but cardiac death did not (log-rank $p=0.139$). Multivariable Cox regression analysis showed that the presence of proteinuria was associated with the composite endpoint (HR: 1.47, 95% CI 1.07 to 2.01, $p=0.016$), and HF rehospitalisation (HR: 1.48, 95% CI 1.07 to 2.05, $p=0.020$), but not with cardiac death (HR: 1.52, 95% CI 0.83 to 2.76, $p=0.172$).

Conclusions Dipstick proteinuria may be a prognostic marker in patients with HFpEF. Evaluation of proteinuria by a urine dipstick test may be a simple but useful method for risk stratification in HFpEF.

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Strengths and limitations of this study

- The large prospective multicenter observational study with essential information to clarify the association between dipstick proteinuria and prognosis in real-world patients with heart failure with preserved ejection fraction (HFpEF).
- Enough sample size and event number enable the detailed adjustment for essential confounding factors in multivariable Cox regression analysis.
- Detailed subgroup analyses are useful to estimate the impact of proteinuria in patients with specific characteristics.
- The East Asian elderly HFpEF population in this study may limit the generalisability of the results to other populations.
- Further study is needed to compare the prognostic utility of dipstick proteinuria with that of urinary albumin-to-creatinine ratio.

BACKGROUND

Heart failure (HF) with preserved ejection fraction (HFpEF) is a major public health issue worldwide, especially in ageing societies such as Japan. It is associated with poor clinical outcomes.^{1,2} Although a growing body of research has been conducted to understand the complex pathophysiologic abnormalities of HFpEF, no optimal and effective treatment has yet been established.^{3,4}

Chronic kidney disease (CKD) is one of the most common comorbidities and frequently associated with patients with HFpEF.^{5–7} It is closely related to HFpEF development, and worsens its prognosis through different pathways including volume expansion, systemic inflammation, arterial stiffening and hypertension, neurohormonal changes and

worsening cardiac mechanics.^{6 8 9} Proteinuria is not only a well-known marker of CKD but also reflects endothelial microvascular dysfunction and systemic inflammation,¹⁰ and is associated with cardiac remodelling and cardiovascular events.^{5 11–13} Proteinuria may appear earlier than the deterioration of renal function detected by the elevation of serum creatinine.^{14 15} Several methods are used to detect proteinuria in random urine samples, including the urine dipstick test and the urinary albumin-to-creatinine ratio (UACR). Although UACR has advantages over the urine dipstick test in sensitivity, quantification and accuracy, and is reported to be a prognostic indicator in patients with HFpEF,^{11 13} measurement of UACR requires expensive equipment and may not be practical in daily practice. It was not performed routinely on patients in this registry. Previous studies assessing renal function by both estimated glomerular filtration rate (eGFR) and proteinuria demonstrated that proteinuria in addition to eGFR was useful for risk stratification and prognosis in HF.^{7 16} Although the predictive value of proteinuria has been previously reported,^{7 12 13} the prognostic impact of isolated proteinuria detected by the urine dipstick test on clinical outcomes in patients with HFpEF remains to be elucidated.

Here, we investigated the prognostic significance of dipstick proteinuria on adverse outcomes in patients with HFpEF using the database of the *Prospective mUlticenteR obServational stUdy of patIenTs with Heart Failure with preserved Ejection Fraction* (PURSUIT-HFpEF) registry.

METHODS

The PURSUIT-HFpEF registry is being conducted by Osaka University Hospital in collaboration with 30 local hospitals in the Kansai region of Japan.¹⁷ This study collects and records extensive clinical, echocardiographic, therapeutic and prognostic data of patients hospitalised for acute decompensated HFpEF, for use in clarifying clinical questions and explaining the pathophysiology of this entity. This registry enrolled patients with HFpEF admitted due to decompensated HF diagnosed using the Framingham heart failure diagnostic criteria.¹⁸ HFpEF was diagnosed when a case satisfied the following criteria: (1) left ventricular ejection fraction $\geq 50\%$ as measured using the modified Simpson method or Teichholz method by transthoracic echocardiography (TTE) and (2) N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) ≥ 400 ng/L or BNP ≥ 100 ng/L on admission. We excluded patients aged < 20 years, those with severe valvular diseases (aortic stenosis, aortic regurgitation, mitral stenosis or mitral regurgitation) due to structural changes in valves detected by TTE on admission, those with acute coronary syndrome on admission, those with a life expectancy of < 6 months due to non-cardiac diseases, those with a history of heart transplantation and those considered ineligible for the study by the attending physicians.

Data collection

Investigational cardiologists and research nurses at the participating institutions are encouraged to enrol consecutive patients in the study and record necessary data on admission, at discharge and at follow-up visits into the electric medical record systems. Data on demography, medical history and comorbidities were collected on admission. Body mass index (BMI; calculated as weight in kilograms divided by height in m^2), systolic blood pressure, heart rate, atrial fibrillation (AF), New York Heart Association (NYHA) classification, laboratory and echocardiographic data and medications were obtained at discharge. The cut-off values for diastolic function parameters (mean e' septal and lateral wall, mean E/e' , left atrial volume index, tricuspid regurgitation velocity and left ventricular mass index) were based on the clinical guideline released from the European Society of Cardiology in 2016.³ The recorded data are then transferred to the data centre of Osaka University Hospital via a secure internet connection for processing and analysis.

Study subjects

Of the data of 1024 cases enrolled in the registry between May 2016 and July 2020, we excluded 16 cases of in-hospital death, 9 cases of cardiac amyloidosis and sarcoidosis, 6 cases of pulmonary arterial hypertension and 142 cases without urinary protein measurements (10 cases of hemodialysis). We excluded cases with cardiac amyloidosis or sarcoidosis or pulmonary arterial hypertension from this analysis, as well as cases with severe valvular diseases from the registry because of their markedly different characteristics, specific haemodynamic and pathophysiological features from common HFpEF. Most randomised clinical trials^{19–21} and observational studies²² of HFpEF have excluded these cases. Consequently, we analysed 851 discharged-alive cases and classified them into two groups according to the absence (502 cases, 59%) or presence (349 cases, 41%) of proteinuria (figure 1).

Patient and public involvement

There was no patient and public involvement in the design, conduct, choice of outcome measures and plans for dissemination of the study results.

Definition of proteinuria and CKD

A urine dipstick test was performed at discharge. Proteinuria \geq 'trace' by dipstick was defined as positive, which usually means microalbuminuria (UACR ≥ 30 mg/g) as described in previous studies.^{7 23 24} CKD was defined as either one of the following conditions lasting for > 3 months: (1) findings suggesting kidney damage, that is, abnormal findings in blood or urine tests, imaging studies or pathological evaluations and (2) eGFR < 60 mL/min/1.73 m^2 .²⁵ For sensitivity analyses, we tried to classify patients using different cut-off points of proteinuria. First, we included patients with proteinuria (–) and 'trace' proteinuria into one group (called 'proteinuria \leq trace'), and compared them with those with proteinuria $\geq 1+$. In

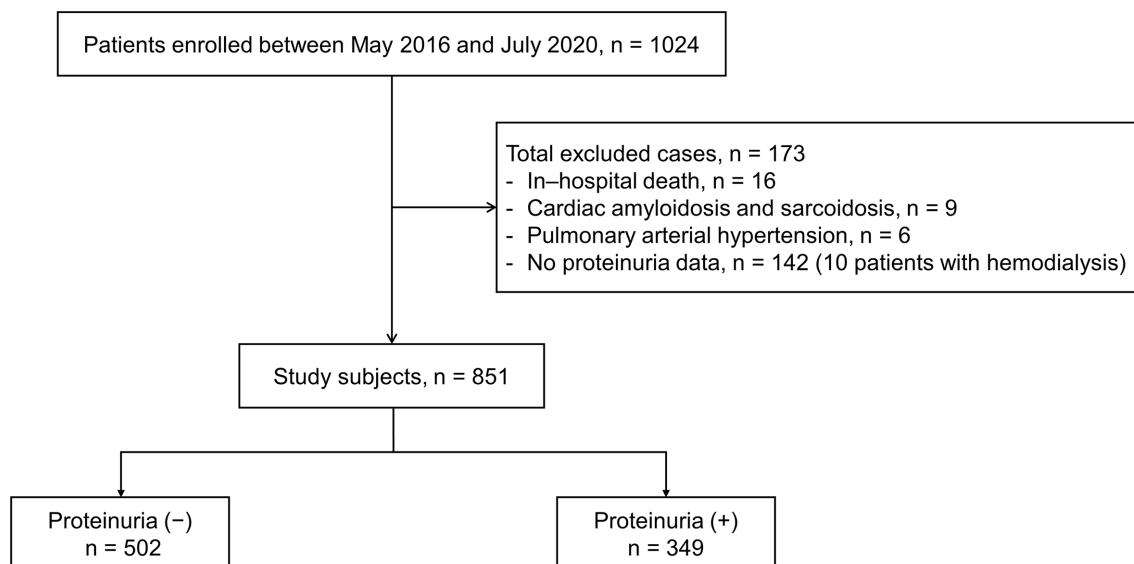


Figure 1 Patient selection and classification.

addition, we classified patients into three groups (proteinuria (-), trace or proteinuria 1+ and proteinuria $\geq 2+$) to explore a linear association between the severity of proteinuria and risk of the composite endpoint.

Study endpoint

The primary endpoint of this study was a composite of cardiac death or HF rehospitalisation, whereas the secondary endpoint was individual cardiac death or HF rehospitalisation occurring after discharge. Enrolled patients were followed up at outpatient clinics and clinical outcomes data including mortality, detailed causes of death and HF rehospitalisation were collected by direct contact or phone call with patients or relatives or through the National Vital Statistics to ensure a high follow-up rate.

Statistical analysis

Considering the explorative and observational nature of the current study, no formal sample size was calculated. We have enrolled all consecutive patients who fulfilled the criteria mentioned in the part of 'Study subjects'. Continuous variables were presented as median (IQR: 25%–75%), and were compared using a non-parametric Mann-Whitney U test. Categorical variables were expressed as number (%), and were compared using the χ^2 test. Survival curves of the study cohort stratified by the absence or presence of proteinuria were estimated using the Kaplan-Meier analysis and statistical differences were detected using the log-rank test. Incidence rates of clinical outcomes according to proteinuria status were calculated with the number of events divided by person-years. Univariable and multivariable Cox regression analyses were performed to clarify the independent prognostic impact of proteinuria on the disease outcomes. Major confounding factors considered based on their clinical importance and findings in previous studies,^{7 26} namely, age; female sex; BMI; hypertension; diabetes mellitus

(DM); previous myocardial infarction (MI); stroke; cancer; heart rate; AF; NYHA classification \geq III; haemoglobin; eGFR; serum albumin; log-transformed NT-pro-BNP; and use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) and/or diuretics were added into the multivariable Cox regression model for the composite endpoint. Adjusted covariates were assessed with multicollinearity test and proportional hazard assumption test using Schoenfeld residuals. All covariates showed absence of multicollinearity. All covariates, except serum albumin (Schoenfeld residuals $p < 0.05$), satisfied the proportionality test. We dealt with the violation of proportionality using a time-dependent covariate method.^{27 28} An interaction term between time and serum albumin was included in the time-dependent multivariable Cox regression models, in addition to serum albumin itself and other fixed covariates. We removed four covariates, namely, stroke, cancer, heart rate and NYHA \geq III from the multivariable Cox regression models for the secondary endpoint to avoid overfitting. In addition, to examine whether the prognostic impact of proteinuria varied in different subgroups of patients, multivariable Cox regression analyses controlling for age and female sex were conducted for subgroups of age ≥ 83 years (median) versus age < 83 years, male versus female, DM (-) versus DM (+), previous HF admission (-) versus previous HF admission (+), AF (-) versus AF (+), eGFR < 60 mL/min/1.73 m² versus eGFR ≥ 60 mL/min/1.73 m², NT-pro-BNP < 1050 ng/L (median) versus NT-pro-BNP ≥ 1050 ng/L, ACEI/ARBs (-) versus ACEI/ARBs (+), β -blocker (BB) (-) versus BB (+) and mineralocorticoid receptor antagonists (MRAs) (-) versus MRAs (+). We selected clinically important subgroups for the management of HFpEF. We evaluated multiplicative interactions between proteinuria and other covariates by introducing the product of proteinuria and a covariate of interest as the interaction terms in the multivariable

Table 1 Baseline patient characteristics

	Proteinuria (-)	Proteinuria (+)	Total	Missing	P value
	n=502	n=349	n=851		
Age, years	83 (78, 87)	82 (76, 87)	83 (77, 87)	0	0.073
Female, n (%)	300 (59.8)	173 (49.6)	473 (55.6)	0	0.003
Body mass index, kg/m ²	21.3 (18.8, 23.9)	22.2 (19.3, 25.3)	21.5 (19.0, 24.3)	8	0.002
Systolic blood pressure, mm Hg	115 (104, 126)	124 (110, 137)	118 (106, 130)	0	<0.001
Heart rate, beats/min	70 (61, 79)	71 (62, 80)	70 (61, 80)	0	0.506
Medical history, n (%)					
Previous HF admission	115 (23.4)	92 (27.1)	207 (24.9)	19	0.227
Hypertension	415 (82.8)	302 (87.0)	717 (84.6)	3	0.096
Diabetes mellitus	131 (26.5)	154 (44.1)	285 (33.8)	7	<0.001
Dyslipidaemia	194 (39.1)	159 (45.7)	353 (41.8)	7	0.057
Previous myocardial infarction	27 (5.5)	31 (9.0)	58 (6.9)	16	0.047
COPD	33 (6.9)	30 (9.0)	63 (7.8)	43	0.273
Chronic kidney disease	162 (32.5)	171 (49.4)	333 (39.5)	7	<0.001
Stroke	79 (15.9)	53 (15.4)	132 (15.7)	10	0.848
Cancer	58 (11.8)	41 (11.9)	99 (11.8)	15	0.975
AF at discharge, n (%)	203 (40.5)	123 (35.2)	326 (38.4)	1	0.120
NYHA \geq III, n (%)	38 (7.7)	23 (6.6)	61 (7.3)	12	0.547
Laboratory data at discharge					
Haemoglobin, g/L	115 (102, 128)	110 (98, 124)	113 (101, 126)	1	0.020
eGFR, mL/min/1.73 m ²	45.0 (34.4, 58.5)	37.4 (23.6, 51.7)	41.8 (30.3, 55.4)	12	<0.001
Albumin, g/L	35 (32, 38)	33 (31, 37)	34 (31, 37)	13	<0.001
Na, mEq/L	139 (137, 141)	140 (137, 142)	139 (137, 141)	2	0.023
K, mEq/L	4.3 (3.9, 4.6)	4.3 (3.9, 4.6)	4.3 (3.9, 4.6)	1	0.309
NT-pro-BNP, ng/L	891 (388, 1903)	1290 (564, 2777)	1050 (469, 2359)	74	<0.001
CRP, mg/L	2.2 (1.0, 6.5)	3.6 (1.4, 11.2)	2.7 (1.1, 8.2)	7	<0.001
Fasting glucose, mmol/L	5.27 (4.77, 6.22)	5.66 (5.05, 7.05)	5.44 (4.88, 6.55)	43	<0.001
LVEF (modified Simpson) at discharge, %	61.0 (56.0, 65.8)	61.0 (55.0, 65.6)	61.0 (55.7, 65.6)	105	0.470
Mean e' septal and lateral wall <9 cm/s*, n (%)	382 (85.3)	273 (89.8)	655 (87.1)	99	0.069
Mean E/e' \geq 13,* n (%)	181 (40.7)	164 (54.1)	345 (46.1)	103	<0.001
LAVI>34 mL/m ² ,* n (%)	345 (80.4)	237 (79.3)	582 (79.9)	123	0.702
TR velocity >2.8 m/s,* n (%)	118 (24.3)	108 (32.0)	226 (27.5)	28	0.014
LVMi \geq 115 g/m ² for males* or \geq 95 g/m ² for females,* n (%)	218 (45.5)	172 (52.0)	390 (48.1)	41	0.071
Positive at least one index of functional or structural alterations,† n (%)	462 (93.7)	326 (96.4)	788 (94.8)	20	0.080
Medications at discharge, n (%)					
ACEIs/ARBs	282 (56.2)	186 (53.3)	468 (55)	0	0.406
β -blockers	275 (54.8)	188 (53.9)	463 (54.4)	0	0.793
Diuretics	408 (81.3)	291 (83.4)	699 (82.1)	0	0.430
MRAs	200 (39.8)	131 (37.5)	331 (38.9)	0	0.498

Values are presented as number (%) and median (IQR).

*Cut-off values were based on 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure.³

†Functional or structural alterations: mean e' septal and lateral wall <9 cm/s or mean E/e' \geq 13 or LAVI>34 mL/m² or TR velocity >2.8 m/s or LVMi \geq 115 g/m² for males or \geq 95 g/m² for females.

ACEIs, angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; ARBs, angiotensin receptor blockers; COPD, chronic obstructive pulmonary disease; CRP, C reactive protein; eGFR, estimated glomerular filtration rate; HF, heart failure; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; LVMi, left ventricular mass index; MRAs, mineralocorticoid receptor antagonists; NYHA, New York Heart Association; TR, tricuspid regurgitation.

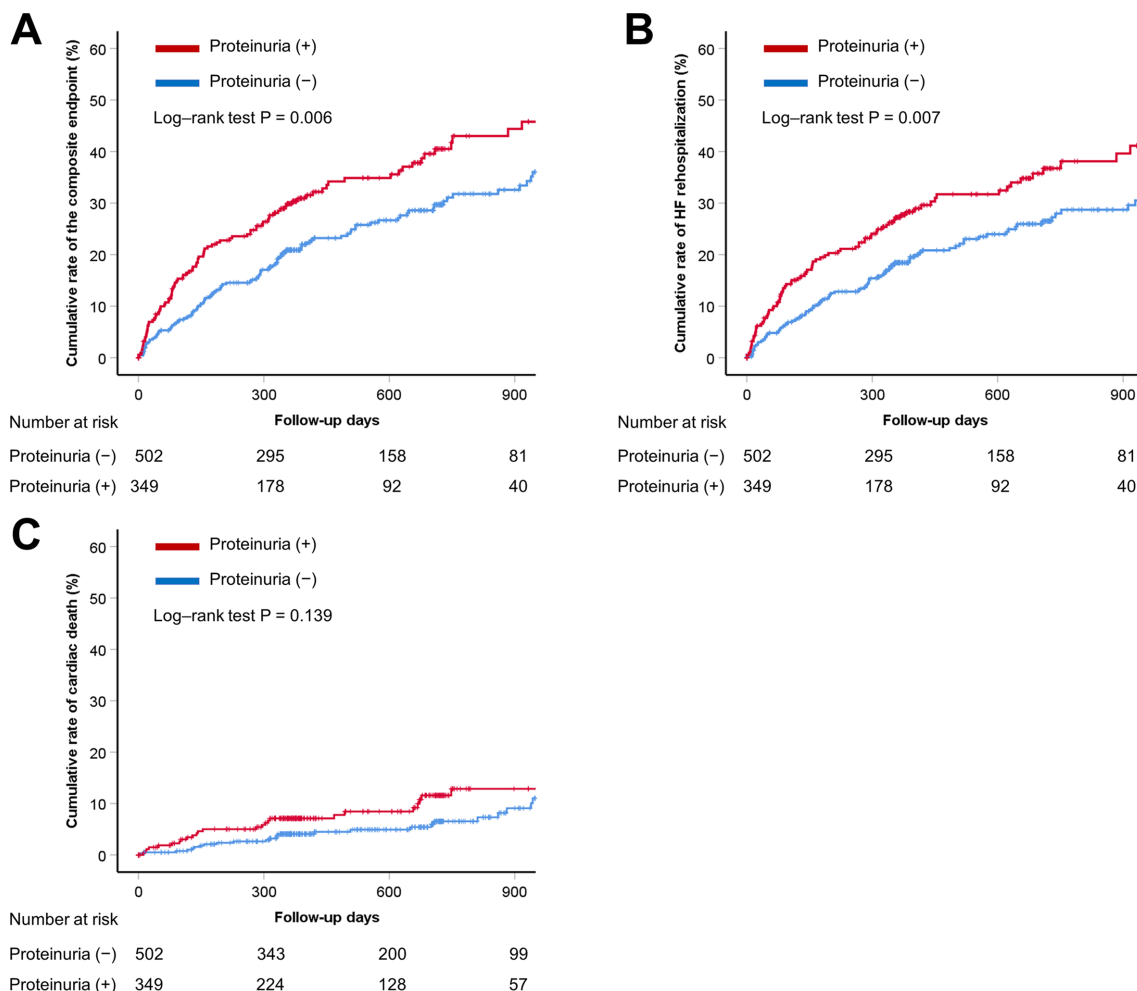


Figure 2 Kaplan-Meier curves according to the absence or presence of proteinuria. (A) Composite endpoint of cardiac death or HF rehospitalisation, (B) HF rehospitalisation and (C) cardiac death. HF, heart failure.

Cox regression models for the composite endpoint in addition to proteinuria and that covariate of interest themselves. A two-sided p value of <0.05 and p value for

interaction tests of <0.10 were considered statistically significant. We described the number of missing data in [table 1](#). Listwise deletion was conducted for missing data

Table 2 Incidence rates and hazard ratios of clinical outcomes according to the absence or presence of proteinuria

	Proteinuria	Person-year	Cases	IR per 100	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Primary endpoint						
Composite of cardiac death or HF rehospitalisation	(-)	577.25	114	19.7		
	(+)	334.20	99	29.6	1.46 (1.11 to 1.91)	1.47 (1.07 to 2.01)
Secondary endpoint						
Cardiac death	(-)	675.47	28	4.1		
	(+)	413.56	26	6.3	1.49 (0.88 to 2.55)	1.52 (0.83 to 2.76)
HF rehospitalisation	(-)	577.25	97	16.8		
	(+)	334.20	87	26.0	1.49 (1.11 to 1.99)	1.48 (1.07 to 2.05)

Adjusted variables for primary endpoint: age, female sex, body mass index, hypertension, diabetes mellitus, previous myocardial infarction, stroke, cancer, heart rate, atrial fibrillation, NYHA \geq III, haemoglobin, eGFR, serum albumin (treated as a time-dependent covariate), log-transformed NT-pro-BNP, use of ACEI/ARBs and diuretics.

Adjusted variables for secondary endpoint: age, female sex, body mass index, hypertension, diabetes mellitus, previous myocardial infarction, atrial fibrillation, haemoglobin, eGFR, serum albumin (treated as a time-dependent covariate), log-transformed NT-pro-BNP, use of ACEI/ARBs and diuretics.

ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; eGFR, estimated glomerular filtration rate; HF, heart failure; IR, incidence rate; NT-pro-BNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association.

in the multivariable Cox regression models. Any suspicious data were double-checked for accuracy by investigators to mitigate potential bias. All analyses were carried out using IBM SPSS Statistics for Windows V.26.0.

RESULTS

Baseline characteristics of the study population

Detailed case characteristics are presented in [table 1](#). Median age was 83 years, and 55.6% of the study subjects were female. Briefly, compared with cases without proteinuria, cases with proteinuria were more likely to be male; to have higher BMI, blood pressure, prevalence of diabetes, previous MI, CKD, higher NT-pro-BNP and C reactive protein (CRP); and to have lower haemoglobin, eGFR and serum albumin. There were no significant differences in the discharge medications between the two groups. Cases with proteinuria had a significantly higher prevalence of high mean E/e' and high tricuspid regurgitation velocity than those without. Of 851 total study subjects, 788 (94.8%) had at least one positive criterion for functional or structural alterations as previously recommended.³

Clinical outcomes

During a median follow-up of 344 (18–676) days, 213 cases (25%) reached the composite endpoint. The composite endpoint and HF rehospitalisation occurred more frequently in cases with proteinuria compared with those without (log-rank $p=0.006$, $p=0.007$, respectively) ([figure 2A,B](#)). In contrast, the cardiac death rate was not significantly different between the two groups (log-rank $p=0.139$) ([figure 2C](#)). The detailed incidence rates of these clinical events are shown in [table 2](#).

Univariable Cox regression analysis revealed that the presence of proteinuria was associated with the composite endpoint and HF rehospitalisation, but not with cardiac death. Multivariable Cox regression analysis indicated that the presence of proteinuria was independently associated with the composite endpoint and HF rehospitalisation, but not with cardiac death ([table 2](#)).

Subgroup analyses demonstrated that the impact of proteinuria on the composite endpoint differed between cases administered and not administered MRAs (p value for interaction= 0.080 ; [figure 3](#)). In contrast, there were no significant interactions between proteinuria and

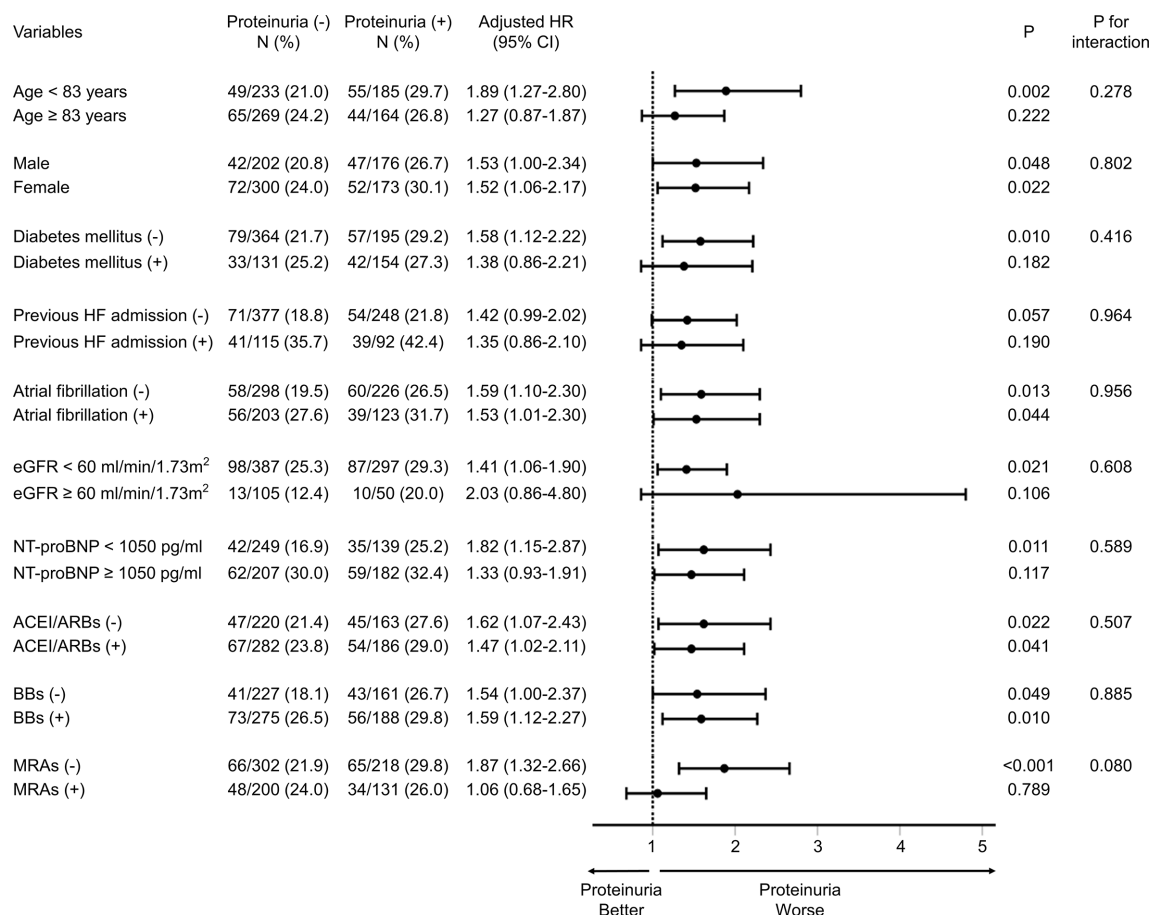


Figure 3 Subgroup analysis to examine the impact of proteinuria on the composite endpoint in different subgroups of patients. HRs were calculated by multivariable Cox regression analysis adjusting for age and female sex. ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; BBs, β -blockers; eGFR, estimated glomerular filtration rate; MRAs, mineralocorticoid receptor antagonists; NT-pro-BNP, N-terminal pro B-type natriuretic peptide. Black spots and bar lines indicate adjusted HRs and their 95% CIs, respectively.

other different subgroups of patients, implying a similar prognostic value of proteinuria in these patients for the composite endpoint.

For sensitivity analyses, we constructed the survival curves for the composite endpoint using different cut-off points of proteinuria. Patients with proteinuria $\geq 1+$ were more likely to reach the composite endpoint than those with proteinuria \leq trace, which was similar to the result in [figure 2](#) (online supplemental figure A). When stratifying patients into three groups according to the severity of proteinuria, the composite endpoint showed a linear increase with the severity of proteinuria (log-rank $p=0.011$) (online supplemental figure B).

DISCUSSION

We found that the presence of proteinuria detected by urine dipstick test was an independent negative prognostic factor in patients with HFpEF. The prognostic significance of proteinuria was independent of apparent renal function, the severity of HF and other major confounding factors. Sensitive analysis showed that the risk of adverse outcomes increased in a linear manner with the severity of proteinuria. This study is the first to clarify the prognostic impact of sole dipstick proteinuria on clinical outcomes in HFpEF.

Prognostic impact of proteinuria in HFpEF

An elevated UACR is reportedly associated with an increased risk of cardiovascular events, including all-cause death and HF rehospitalisation in patients with diseases such as diabetes,²⁹ hypertension³⁰ and stable coronary artery disease,³¹ as well as in the general population.³² Elevated UACR is a marker of poor prognosis in both HF with reduced ejection fraction (HFrEF) and HFpEF.^{11 26} Miura *et al*⁷ reported that proteinuria detected with a dipstick test in combination with eGFR was associated with all-cause death in patients with HFpEF. Our current findings are similar to these previous studies, despite the fact that we focused on the cardiac events in our cohort and the identification of proteinuria with a simple dipstick test as a warning sign that should then set off a cascade of testing. However, it should be noted that proteinuria did not have a significant prognostic value for cardiac death in this study, while Miura *et al*⁷ found the opposite, although the measurement of eGFR was similarly calculated. This discrepancy may be caused by a smaller sample size with a smaller number of cardiac deaths, and a shorter follow-up period in this study. The older age of our cohort, which may mask the prognostic impact of proteinuria on mortality, may also relate to this discrepancy. Smith *et al*¹⁶ found that CKD evaluated using both eGFR and urine dipstick protein was associated with adverse clinical outcomes in a community-based cohort of patients with HF with much younger age in a Western country. Racial disparity, different patient background and phenotypes especially between Asian and Western patients with HFpEF such as prevalence of obesity and AF,

and disease severity may limit the generalisability of the results found by Smith *et al* to any elderly HFpEF cohorts like ours, especially in an ageing society. To the best of our knowledge, this is the first study that clarifies the prognostic significance of sole dipstick proteinuria in elderly HFpEF cohort in an East Asian country. Proteinuria detected with a dipstick test was associated with poor prognosis irrespective of renal function, implying the usefulness of this simple urinary analysis in identifying high-risk patients at point of care. Our study confirms and extends the prognostic value of a random dipstick proteinuria test, a cost-effective and simple method at point-of-care settings, especially as a predictor of HF rehospitalisation in patients with HFpEF, while adding knowledge to the existing literature on this topic of interest. This quick urinary dipstick test suffices to be used as a screening test to identify a worse prognosis in HFpEF, allowing selection of these patients to undergo a more extensive workup while sparing patients with normal findings.

Prevalence of proteinuria in HFpEF

Proteinuria was detected in 41% of this study cohort, which was higher than in previous studies (approximately 30%).^{7 16} This discrepancy may be due to the fact that this cohort included much older patients with severely reduced eGFR at baseline in addition to a higher prevalence of cardiovascular comorbidities. Moreover, previous studies included cases of both HFrEF and HFpEF, while CKD was reported to be less prevalent in HFrEF.¹⁶ In contrast, substudies of randomised controlled trials (RCTs) and an observational study of HFpEF found that the proportion of albuminuria assessed by UACR was 25%–35% and 11%–14% for microalbuminuria and macroalbuminuria, respectively,^{11 26 33} which shared similar findings with our results, despite the different nature of the study cohorts. Therefore, these results suggest that proteinuria is common both in the real-world HFpEF population and in the highly selected populations of RCTs.

Mechanisms underlying the association between proteinuria and prognosis

Although the mechanisms underlying the association between proteinuria and worse clinical outcomes in HFpEF are not fully understood, possible mechanisms include activation of the renin-angiotensin system (RAS), sympathetic overactivity, oxidative injury and endothelial dysfunction.³⁴ These disorders cause progression of cardiac alterations including increased cardiomyocyte stiffness and interstitial fibrosis,^{35 36} which may lead to progression of left ventricular diastolic dysfunction causing pulmonary hypertension, in turn leading to right ventricular dysfunction and ultimately elevation of central venous pressure. Elevated central venous pressure is known to cause renal injury, resulting in proteinuria and deterioration of GFR,³⁷ forming the vicious cycle of the cardiorenal syndrome. Activation of RAS, sympathetic overactivity or oxidative injury are all associated with vascular injury with increased vascular resistance

and stiffness, as well as promoting sodium and water retention.^{34–37} Taken together, these mechanisms may be associated with the more frequent rehospitalisations for HF due to increased afterload. In accordance with this hypothesis, patients with proteinuria had a higher systolic blood pressure in this study (table 1).

Clinical implications

Our findings indicate the prognostic value of proteinuria detected by urine dipstick test in HFpEF. The finding of positive dipstick proteinuria, which is a convenient, low cost and cost-effective method in the screening context,³⁸ should alert physicians of the possibility of early kidney damage regardless of eGFR in this population. Appropriate interventions will be needed in this high-risk population. Selvaraj *et al*³³ reported that spironolactone significantly alleviated proteinuria compared with placebo and that a reduction in albuminuria was independently associated with favourable outcomes. The results of subgroup analysis in this study showed that patients taking MRAs appeared to have a lower risk of the study outcomes than those not taking them, suggesting the potential benefits of this drug in patients with HFpEF presenting with proteinuria. Interestingly, proteinuria had different prognostic meanings between patients with and without MRA use, which was not the case in those with and without ACEI/ARBs. These findings suggest that MRAs, through their more diverse and possibly stronger positive effects than those of ACEI/ARBs on the endothelial dysfunction and oxidative stress that are problematic in patients with HFpEF presenting with proteinuria,^{20–33} may be the reason. RAS blockade is widely known for its therapeutic efficacy in reducing systemic and intraglomerular hydrostatic pressure, which improves proteinuria.³⁹ This effect may potentially prevent or delay the progression of kidney dysfunction. Although RAS blockade is reported to simultaneously offer beneficial clinical outcomes in different patient populations, including patients with hypertension, diabetes, CKD and HFpEF,^{40–43} it remains unknown whether similar favourable effects may be observed in patients with HFpEF having proteinuria. Further investigations are warranted to clarify whether interventions including the use of MRAs or RAS inhibitors to reduce or reverse the severity of proteinuria may improve outcomes in this cohort.

Limitations

Several limitations of this study need to be considered. First, a proteinuria dipstick test may be affected by variations in urine concentration. More concentrated samples may indicate higher levels of proteinuria than may actually be present, while less concentrated samples may give a false-negative or only a trace reading. Second, it should be noticed that the urine dipstick test has low sensitivity and high false-positive rates for the detection of a trace concentration of albuminuria.²⁴ On the contrary, the sensitivity analysis in online supplemental figure A may suggest that the frequency of false-positive for the

detection of trace proteinuria was not so high, and that patients with ‘trace’ proteinuria really had proteinuria. In contrast, it is relatively accurate for the detection of an ACR >300 mg/g (dipstick $\geq 1+$).²⁴ Third, given the use of a single dipstick urinalysis, the possibility of missing transient proteinuria cannot be ruled out. Fourth, although the type of urine dipstick test kit may be of interest, we did not have this data. Dipstick kit was left to the discretion of attending physicians and the availability of the kit at each institution. Fifth, we were unable to compare the prognostic utility between dipstick proteinuria and UACR, a well-established prognosticator, due to the unavailability of urine albumin data. Sixth, we cannot determine the precise causal relationship between proteinuria and the severity of HFpEF and clinical outcomes due to the nature of this observational study design. Last but not least, patients included in this study were predominantly East Asian patients with HFpEF having highly prevalent cardiovascular comorbidities. Therefore, the results of this study should be extrapolated with caution in the context of Western patients with HFpEF. Nonetheless, these findings might be useful in Asian patients with HFpEF living in Western countries. In these medically fragile patients, a dipstick test performed between scheduled urinalyses and other major follow-up examinations may flag patients in need of immediate attention.

CONCLUSION

This study suggests that dipstick proteinuria may be a prognostic marker in the population predominantly including elderly patients with HFpEF having highly prevalent cardiovascular comorbidities. Evaluation of proteinuria by urine dipstick test may be a simple, practical but useful method for risk stratification in HFpEF even in community-based healthcare settings.

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