Circulation Journal
Circ J 2022; 86: 709–714
doi:10.1253/circj.CJ-21-0759

ORIGINAL ARTICLE
Acute Heart Failure

Prevalence and Prognostic Relevance of Isolated Tubular Dysfunction in Patients With Acute Heart Failure

Taishi Dotare, MD; Sayaki Ishiwata, MD, PhD; Yuya Matsue, MD, PhD; Yutaka Nakamura, MD; Tsutomu Sunayama, MD; Daichi Maeda, MD, PhD; Shoichiro Yatsu, MD, PhD; Shoko Suda, MD, PhD; Takao Kato, MD, PhD; Masaru Hiki, MD, PhD; Takatoshi Kasai, MD, PhD; Tohru Minamino, MD, PhD

Background: Renal dysfunction includes glomerular dysfunction (GD) and tubular dysfunction (TD); however, there is limited information regarding the prevalence, coexistence, and prognostic relevance of TD and GD among patients with acute heart failure (AHF).

Methods and Results: This study reviewed 489 patients with AHF who had undergone testing at the time of their admission to identify GD (estimated glomerular filtration rate <60 mL/min/1.73 m^2) and TD (urinary β-2-microglobulin ≥300 μg/gCr). Patients were grouped according to the presence/absence of GD and TD as having neither condition (n=116), isolated TD (n=101), isolated GD (n=83), or coexisting GD plus TD (n=189). During a median follow up of 466 days (interquartile range: 170–871 days), 107 deaths were observed. Kaplan-Meier curve analysis revealed that, relative to the absence of a GD and TD group, higher mortality rates were observed in the groups with isolated TD, isolated GD, and coexisting GD plus TD (log-rank P<0.001). Similarly, the adjusted Cox regression analyses revealed that significantly higher risks of mortality were associated with isolated TD, isolated GD, and coexisting GD plus TD. Moreover, isolated GD and isolated TD were both independently associated with increased risks of all-cause mortality.

Conclusions: As a significant proportion of patients with AHF had isolated TD and an increased risk of mortality, patients with AHF should be screened for TD even if they do not have GD.

Key Words: Acute heart failure; Glomerular dysfunction; Mortality; Tubular dysfunction

Acute heart failure (AHF) is a major health problem that continues to have a high mortality rate despite improving treatment options.[1] Renal dysfunction is a major comorbidity that is prevalent among patients with AHF and is strongly associated with poor clinical outcomes.[2,3] Thus, understanding the complicated and bidirectional association between these conditions is crucial to improving treatment outcomes in this high-risk population.[4]

Renal dysfunction includes glomerular dysfunction (GD) and tubular dysfunction (TD), although less attention is paid to TD in clinical practice. However, recent biomarker studies have clearly shown that TD is prevalent among patients with chronic heart failure and is associated with adverse events, independent of the presence of GD.[5–7] Nevertheless, there is limited information regarding the prevalence and prognostic relevance of GD and/or TD among patients with AHF, especially regarding isolated TD (i.e., TD without GD). Therefore, this study evaluated the prevalence, coexistence, and prognostic relevance of TD and GD among Japanese patients with AHF.

Methods

This retrospective study collected data from the Juntendo University Database for Acute Heart Failure, which includes all patients with AHF who were hospitalized in the intensive care unit or coronary care unit of Juntendo University Hospital between January 2015 and December 2019. Consecutive patients with AHF had been registered if they were ≥18 years old and had a confirmed diagnosis of AHF made by experienced cardiologists according to

Received August 26, 2021; revised manuscript received November 9, 2021; accepted November 28, 2021; J-STAGE Advance Publication released online December 25, 2021 Time for primary review: 24 days

Department of Cardiovascular Biology and Medicine (T.D., S.I., Y.M., Y.N., T.S., D.M., S.Y., S.S., T. Kato, M.H., T. Kasai, T.M.), Cardiovascular Respiratory Sleep Medicine (S.I., Y.M.), Juntendo University Graduate School of Medicine, Tokyo; Department of Cardiology, Osaka Medical and Pharmaceutical University, Osaka (D.M.); Sleep and Sleep-Disordered Breathing Center, Juntendo University Hospital, Tokyo (T. Kasai); and Japan Agency for Medical Research and Development-Core Research for Evolutionary Medical Science and Technology (AMED-CREST), Japan Agency for Medical Research and Development, Tokyo (T.M.), Japan

Mailing address: Yuya Matsue, MD, PhD, Department of Cardiovascular Biology and Medicine, Juntendo University Graduate School of Medicine, 3-1-3 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan. E-mail: yuya8950@gmail.com

ISSN-1346-9843

Table 1. Baseline Characteristics of the Groups According to the Presence of Glomerular and/or Tubular Dysfunction

Variables	Neither (n=116)	Isolated TD (n=101)	Isolated GD (n=83)	Coexisting (n=189)	P value
Age (years)	67±13	73±15	79±10	79±10	<0.001
Male sex (%)	79 (68.1)	53 (52.5)	47 (56.6)	117 (61.9)	0.102
SBP (mmHg)	129±27	140±27	124±25	138±27	<0.001
DBP (mmHg)	81±21	86±21	70±18	77±21	<0.001
Heart rate (beats/min)	96±29	97±26	90±29	88±25	0.014
LVEF (%)	41 [28–57]	49 [35–64]	52 [36–64]	55 [37–65]	<0.001
NYHA class III/IV at admission (%)	70 (60.3)	65 (65.0)	52 (64.2)	108 (57.8)	0.623
Cardiac implantable electronic device (%)					0.387
Pacemaker	13 (11.2)	12 (11.9)	10 (12.0)	20 (10.6)	
ICD	2 (1.7)	0 (0)	0 (0)	2 (1.1)	
CRT-D/CRT-P	6 (5.2)	1 (1.0)	2 (2.4)	2 (1.1)	
Medical history (%)					
Heart failure	45 (38.8)	33 (32.7)	44 (53.0)	88 (46.6)	0.022
Hypertension	48 (42.1)	61 (61.0)	49 (60.5)	108 (58.4)	0.012
Diabetes	32 (27.6)	28 (27.7)	28 (33.7)	70 (37.0)	0.244
COPD	9 (8.0)	3 (3.0)	9 (11.5)	16 (8.9)	0.178
CAD	15 (13.3)	22 (22.0)	27 (34.6)	66 (36.3)	<0.001
Prescription at admission (%)					
Loop diuretics	38 (33.9)	30 (30.9)	44 (57.1)	89 (52.0)	<0.001
ACE-I/ARB	35 (31.0)	43 (43.0)	40 (50.0)	84 (46.4)	0.028
β-blocker	38 (32.8)	34 (33.7)	33 (39.8)	91 (48.1)	0.024
MRA	23 (19.8)	17 (16.8)	25 (30.1)	32 (16.9)	0.069
SGLT2i	5 (4.3)	2 (2.0)	2 (2.4)	2 (1.1)	0.323
Prescription at discharge (%)					
Loop diuretics	100 (87.7)	84 (84.0)	66 (89.2)	136 (79.5)	0.157
ACE-I/ARB	82 (71.9)	77 (77.0)	46 (62.2)	107 (62.6)	0.046
β-blocker	94 (82.5)	84 (84.0)	47 (63.5)	118 (69.0)	0.001
MRA	23 (19.8)	17 (16.8)	25 (30.1)	32 (16.9)	0.069
SGLT2i	6 (5.2)	2 (2.0)	3 (3.7)	4 (2.2)	0.426
Laboratory data at admission					
Hemoglobin (mg/dL)	13.5±2.3	12.3±2.6	11.6±2.6	10.9±2.0	<0.001
Creatinine (mg/dL)	0.8 [0.7–1.0]	0.8 [0.7–1.0]	1.3 [1.1–1.6]	1.5 [1.1–2.2]	<0.001
Blood urea nitrogen (mg/dL)	18 [15–21]	18 [14–24]	31 [22–46]	30 [24–45]	<0.001
Sodium (mEq/L)	140±4	140±4	139±5	140±4	0.276
NT-proBNP (pg/dL)	2,789 [1,436–5,833]	3,851 [2,209–5,583]	5,297 [3,006–12,519]	7,987 [3,793–19,648]	<0.001
β-2-microglobulin (μg/gCr)	119 [61–169]	1,199 [507–2,489]	58 [16–126]	5,340 [1,598–18,002]	<0.001
Cystatin C (mg/dL)	1.01 [0.93–1.13]	1.05 [0.92–1.19]	1.72 [1.38–2.03]	1.93 [1.58–2.49]	<0.001
GWTG-HF risk score	40 [35–45]	39 [35–44]	46 [41–51]	43 [38–49]	<0.001

ACE-I/ARB, angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy-defibrillator; CRT-P, cardiac resynchronization therapy-pacemaker; DBP, diastolic blood pressure; GD, glomerular dysfunction; GWTG-HF, Get With The Guidelines®-Heart Failure; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; SGLT2i, sodium-glucose cotransporter 2 inhibitor; TD, tubular dysfunction.

the Framingham criteria.[8] Patients were not registered, regardless of whether they had AHF, acute coronary syndrome, primary pulmonary hypertension, or pericardial disease. The present study excluded cases in which the B-type natriuretic peptide (BNP) concentration at admission was <100 pg/mL or the N-terminal pro-BNP (NT-proBNP) concentration was <300 pg/mL, as the primary diagnosis in these cases might not be heart failure.[9,10] The present study also excluded patients who were receiving maintenance hemodialysis. The retrospective study protocol was approved by the institutional review board of Juntendo University Hospital, which waived the requirement for

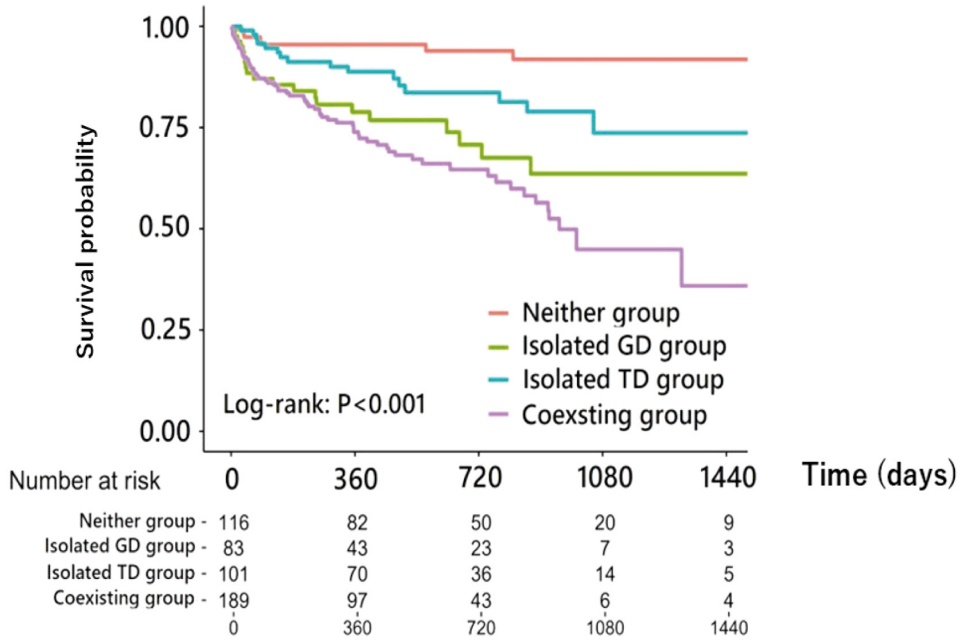

Figure. Kaplan-Meier curves for overall survival according to the presence of tubular and/or glomerular dysfunction (TD/GD). There were significant differences between the 4 groups (log-rank P<0.001), and the group with isolated TD had poorer outcomes than the group with neither condition.

informed consent based on the retrospective observational study design. This study was conducted in accordance with the principles of the Declaration of Helsinki.

All patients were followed from the date of the index admission until June 2020. The primary outcome of interest was all-cause mortality, which was evaluated based on information from clinical visits or recorded deaths. For those who died, the cause of death was categorized into cardiovascular and non-cardiovascular death according to the classification used in the RELAX-AHF (Efficacy and Safety of Relaxin for the Treatment of Acute Heart Failure) study.[11] In addition, we collected baseline data regarding the patients' clinical characteristics, medical history, drug prescription(s) at admission and discharge, and events. All patients who are admitted to our intensive care or coronary care units because of AHF are expected to undergo a routine risk assessment within 24 h using cardiovascular and renal biomarkers, which include urinary β-2 microglobulin (B2MG), urinary creatinine, and serum cystatin C concentrations. All tests were performed immediately after blood and spot urine sample collection. We used a urinary B2MG concentration, which was adjusted for the urinary creatinine concentration of >300 mg/gCr to diagnose TD, as this value predicts the prognosis among patients with chronic heart failure.[12,13] The Chronic Kidney Disease Epidemiology Collaboration formula with serum creatinine and cystatin C was used to identify GD (estimated glomerular filtration rate [eGFR]: <60 mL/min/1.73 m^2), as it provides better accuracy and precision than the Modification of Diet in Renal Disease formula, among patients with heart failure.[14] The results for TD and/or GD were used to classify the patients as having neither condition, isolated TD (TD but not GD), isolated GD (GD but not TD), or coexisting GD plus TD.

Normally distributed continuous variables were expressed as mean±standard deviation and non-normally distributed variables were expressed as median (interquartile range). Categorical variables were expressed as number (percentage). Continuous variables were compared between groups using one-way analysis of variance or the Kruskal-Wallis test, as appropriate. Categorical variables were compared between groups using the chi-squared test or Fisher's exact test, as appropriate. The fractional polynomials method was used to identify optimal transformations.[15]

Survival outcomes were evaluated using the Kaplan-Meier method and log-rank test. All-cause mortality was evaluated according to the Get With the Guidelines®-Heart Failure (GWTG-HF) risk score and log-transformed BNP (log BNP) concentration at admission. The GWTG-HF risk score consists of age, systolic blood pressure, heart rate, blood urea nitrogen, sodium, chronic obstructive pulmonary disease, and race,[16] and adjustment for the GWTG-HF risk score has been well validated among Japanese patients with heart failure.[17,18] Adding the log BNP concentration to the GWTG-HF risk score has also been shown to improve the performance of prognostic models.[19] Multiple imputation to account for missing covariate data was performed using 20 datasets that were created via a chained equations procedure.[20] Parameter estimates were obtained for each dataset and subsequently combined to produce an integrated result using the method described by Barnard and Rubin.[21] Differences were considered statistically significant at 2-tailed P values of <0.05. All analyses were performed using R software (version 3.6.3; R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org).

Table 2. Unadjusted and Adjusted Cox Regression Analyses of All-Cause Death

Groups	Unadjusted			Adjusted for GWTG-HF risk score + log NT-proBNP		
	HR	95% CI	P value	HR	95% CI	P value
Neither		Reference			Reference	
Isolated TD	2.43	1.04–5.70	0.040	2.43	1.04–5.70	0.041
Isolated GD	4.83	2.12–10.9	<0.001	3.31	1.42–7.74	0.006
Coexisting	6.80	3.24–14.3	<0.001	5.07	2.35–10.95	<0.001

CI, confidence interval; HR, hazard ratio. Other abbreviations as in Table 1.

Results

A total of 744 patients were potentially eligible during the study period, although 255 patients were excluded (4 patients were receiving dialysis and 251 patients had missing data regarding cystatin C, B2MG, or urinary creatinine concentrations). Thus, the study included 489 patients (60.5% male) with a mean age of 75±13 years. The adjusted B2MG concentration range was 0.5–154,606.7 mg/gCr and the eGFR range was 5.0–141.5 mL/min/1.73 m^2. Based on the results for GD and/or TD, the patients were categorized as having neither condition (n=116), isolated TD (n=101), isolated GD (n=83), or coexisting GD plus TD (n=189). The clinical characteristics of the 4 groups are shown in **Table 1**. The presence of TD was associated with older age, higher systolic blood pressure, hypertension, coronary artery disease, prescription of angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers at admission, lower hemoglobin concentration, and higher concentrations of C-reactive protein and NT-proBNP. The presence of GD was associated with older age, heart failure, hypertension, chronic obstructive pulmonary disease, coronary artery disease, prescriptions of angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers and mineralocorticoid receptor antagonists at admission, lower hemoglobin concentration, and higher concentrations of creatinine, blood urea nitrogen, C-reactive protein, and NT-proBNP.

During a median follow up of 466 days (interquartile range: 170–871 days), 107 deaths were observed (68 were cardiovascular deaths, and 39 were non-cardiovascular deaths). In more detail, in-hospital death occurred in 30 patients and major adverse renal events, including the need for continuous hemodiafiltration or hemodialysis, occurred in 22 patients. In addition, we observed heart failure re-hospitalization in 76 patients during the follow-up period. The Kaplan-Meier curve analysis revealed that isolated GD and isolated TD were both associated with poorer survival rates, and the group with coexisting GD plus TD had the poorest prognosis (**Figure**). Similar associations were observed in the multivariable Cox regression analyses that were adjusted for GWTG-HF risk score and log NT-proBNP concentration (**Table 2**). Relative to the group with neither condition, poor survival was independently associated with isolated GD (hazard ratio: 2.45, 95% confidence interval: 1.48–4.06; P<0.001) and isolated TD (hazard ratio: 1.76, 95% confidence interval: 1.12–2.76; P=0.014).

Discussion

This retrospective single-center study evaluated 489 patients who were hospitalized because of AHF and provided novel insights regarding the relationships of GD and TD with clinical outcomes among patients with AHF. In this cohort, isolated TD (20.6% of patients with AHF) identified at admission was independently associated with mortality, regardless of the presence of GD, and may provide additional prognostic information in this setting. This result highlights the importance of considering both GD and TD when patients with AHF are admitted to hospital.

Previous studies have revealed conflicting results regarding the prognostic relevance of TD among patients with AHF. For example, a study of 260 patients with AHF revealed that the urinary neutrophil gelatinase-associated lipocalin (NGAL) concentration at admission was independently associated with a poor prognosis after adjustment for other prognostic factors, including the eGFR.[22] However, a prospective study evaluated the plasma NGAL concentration at admission for 927 patients with AHF and revealed that plasma NGAL was not superior to serum creatinine for predicting in-hospital adverse events.[23] Another study of 1,588 patients with AHF revealed that plasma kidney injury molecule-1 adjusted for serum creatinine was associated with rehospitalization for heart failure but not mortality.[24] Given the results of those and other studies,[25–27] it is unclear whether other tubular markers have clinical and prognostic relevance, although creatinine is an inexpensive and readily measurable tubular function biomarker that is already used in our clinical practice. Nevertheless, our results suggest that identifying TD using a urine sample, which is readily available to be conducted in clinical practice, can help improve the prognostic value of routine glomerular function evaluations.

The present study revealed that isolated TD was relatively common and had prognostic relevance among patients with AHF. A previous study of 315 patients with chronic heart failure revealed isolated TD in 39 patients (12.4%),[13] although it was not clear whether isolated TD was associated with mortality. To the best of our knowledge, ours is the first study to demonstrate that approximately 20% of patients with AHF had isolated TD, and this subgroup had a high mortality rate even after adjusting for other prognostic factors. The relatively high prevalence of isolated TD in our population may be related to the differences between acute and chronic heart failure. Renal tubular epithelial cells have a regenerative ability after they are exposed to ischemia,[28] which suggests that some tubular epithelial cells are injured during the acute phase of heart failure and may regenerate during the chronic phase. Therefore, our results suggest that it is important to consider tubular function among patients with AHF or chronic heart failure, even if they have preserved glomerular function.

The present study was not designed to clarify the pathophysiological differences between patients with GD and/or

TD. However, previous studies have suggested that TD might precede GD in patients with heart failure, and we observed that patients with isolated TD were generally younger and less likely to have a history of heart failure. In patients with AHF, the proximal tubular cells may be the first to be damaged by the acute reduction in kidney perfusion, as this segment is the most exposed to ischemia.[28] Patients with early GD and diabetes mellitus are conventionally thought to have dysfunction of the glomerular arterioles,[29] although it is possible that TD may precede GD in patients with diabetes mellitus.[30] In addition, a previous study has indicated that urinary B2MG is a useful marker for early diabetic nephropathy that was diagnosed via kidney biopsy among patients with diabetes.[31] Thus, although the disease mechanisms may be substantially different between TD in patients with diabetes and heart failure, we believe that tubular function should be evaluated to potentially identify kidney injury or high-risk patients with AHF, even if they have preserved glomerular function. Further research is needed to test this hypothesis among patients with acute and chronic heart failure.

Although there is no approved therapy specific for patients with AHF complicated with tubular injury, there are several interventions that may be effective. As venous congestion has been shown to be associated with tubular injury,[32] optimizing volume status and systemic perfusion might be particularly important. A previous study has shown that TD precedes GD, and angiotensin-converting enzyme inhibitors improved tubular function in such patients.[33] Sodium-glucose cotransporter-2 inhibitors are a promising intervention for patients with AHF and TD, given that this has been shown to be associated with better prognosis in patients with diabetes and worsening heart failure, and improvement of TD.[34,35] However, these hypotheses need to be evaluated in future randomized clinical studies.

This study has several limitations. First, we only measured the urinary B2MG concentration at admission for AHF and thus cannot comment on whether the urinary B2MG values fluctuated during the patient's clinical course. Moreover, because most of our study patients had their B2MG levels measured after the initial treatment, this possibly significantly affected the B2MG values. We could not evaluate the effect of treatment provided to patients before biomarker measurement of B2MG values. Second, the study only evaluated a relatively small sample of patients at a single center. Third, although we used a validated risk score to adjust for potential confounding factors, it is possible that unknown and/or unmeasured factors might have influenced our results. Finally, we excluded 250 of 774 patients because of missing B2MG data at the time of admission, which could be a source of selection bias.

Conclusions

Among hospitalized patients with AHF, isolated GD and isolated TD were both independently associated with all-cause mortality. Furthermore, isolated TD was observed in a substantial proportion of patients with AHF and was associated with greater mortality in this group. Therefore, we believe it is important to screen patients with AHF for TD even if they do not have GD.

Source of Funding

This research was partially supported by AMED under Grant Number JP21ek0109543.

Disclosures

Y.M. and T. Kasai are affiliated with a department endowed by Philips Respironics, ResMed, Teijin Home Healthcare, and Fukuda Denshi, and Yuya Matsue received an honorarium from Otsuka Pharmaceutical Co and Novartis Japan. Other authors have no conflicts of interest to declare.

T.M. is a member of *Circulation Journal*'s Editorial Team.

IRB Information

This study was approved by the institutional review board of Juntendo University Hospital (Reference no. 20-020).

Data Availability

The deidentified participant data will not be shared.

References

1. Writing Group Members: Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Executive Summary: Heart Disease and Stroke Statistics--2016 Update: A report from the American Heart Association. *Circulation* 2016; **133:** 447–454.
2. Hata N, Yokoyama S, Shinada T, Kobayashi N, Shirakabe A, Tomita K, et al. Acute kidney injury and outcomes in acute decompensated heart failure: Evaluation of the RIFLE criteria in an acutely ill heart failure population. *Eur J Heart Fail* 2010; **12:** 32–37.
3. 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:** 455–469.
4. Rastogi A, Fonarow GC. The cardiorenal connection in heart failure. *Curr Cardiol Rep* 2008; **10:** 190–197.
5. Damman K, Masson S, Hillege HL, Maggioni AP, Voors AA, Opasich C, et al. Clinical outcome of renal tubular damage in chronic heart failure. *Eur Heart J* 2011; **32:** 2705–2712.
6. Nymo SH, Ueland T, Askevold ET, Flo TH, Kjekshus J, Hulthe J, et al. The association between neutrophil gelatinase-associated lipocalin and clinical outcome in chronic heart failure: Results from CORONA*. *J Intern Med* 2012; **271:** 436–443.
7. Jungbauer CG, Birner C, Jung B, Buchner S, Lubnow M, von Bary C, et al. Kidney injury molecule-1 and N-acetyl-beta-D-glucosaminidase in chronic heart failure: Possible biomarkers of cardiorenal syndrome. *Eur J Heart Fail* 2011; **13:** 1104–1110.
8. Ho KK, Anderson KM, Kannel WB, Grossman W, Levy D. Survival after the onset of congestive heart failure in Framingham Heart Study subjects. *Circulation* 1993; **88:** 107–115.
9. Maisel A. B-type natriuretic peptide levels: Diagnostic and prognostic in congestive heart failure: What's next? *Circulation* 2002; **105:** 2328–2331.
10. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, 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 J Heart Fail* 2016; **18:** 891–975.
11. Felker GM, Teerlink JR, Butler J, Hernandez AF, Miller AB, Cotter G, et al. Effect of serelaxin on mode of death in acute heart failure: Results from the RELAX-AHF study. *J Am Coll Cardiol* 2014; **64:** 1591–1598.
12. Otaki Y, Watanabe T, Takahashi H, Narumi T, Kadowaki S, Honda Y, et al. Association of renal tubular damage with cardiorenal anemia syndrome in patients with heart failure. *Int J Cardiol* 2014; **173:** 222–228.
13. Otaki Y, Watanabe T, Shishido T, Takahashi H, Funayama A, Narumi T, et al. The impact of renal tubular damage, as assessed by urinary beta2-microglobulin-creatinine ratio, on cardiac prognosis in patients with chronic heart failure. *Circ Heart Fail* 2013; **6:** 662–668.
14. Valente MA, Hillege HL, Navis G, Voors AA, Dunselman PH, van Veldhuisen DJ, et al. The Chronic Kidney Disease Epidemiology Collaboration equation outperforms the Modification of Diet in Renal Disease equation for estimating glomerular filtration rate in chronic systolic heart failure. *Eur J Heart Fail* 2014; **16:** 86–94.
15. Hosmer DW Jr, Lemeshow S, Sturdivant RX. Model-Building Strategies and Methods for Logistic Regression. *In*: Walter A.

Shewhart, editor. Applied Logistic Regression, 1st edn. New York: Wiley, 2000; 100–103.
16. Peterson PN, Rumsfeld JS, Liang L, Albert NM, Hernandez AF, Peterson ED, et al. A validated risk score for in-hospital mortality in patients with heart failure from the American Heart Association get with the guidelines program. *Circ Cardiovasc Qual Outcomes* 2010; **3:** 25–32.
17. Lyle M, Wan SH, Murphree D, Bennett C, Wiley BM, Barsness G, et al. Predictive value of the Get With The Guidelines-Heart Failure risk score in unselected cardiac intensive care unit patients. *J Am Heart Assoc* 2020; **9:** e012439.
18. Suzuki S, Yoshihisa A, Sato Y, Kanno Y, Watanabe S, Abe S, et al. Clinical significance of Get With The Guidelines-Heart Failure risk score in patients with chronic heart failure after hospitalization. *J Am Heart Assoc* 2018; **7:** e008316.
19. Shiraishi Y, Kohsaka S, Abe T, Mizuno A, Goda A, Izumi Y, et al. Validation of the Get With The Guideline-Heart Failure risk score in Japanese patients and the potential improvement of its discrimination ability by the inclusion of B-type natriuretic peptide level. *Am Heart J* 2016; **171:** 33–39.
20. van Buuren S, Boshuizen HC, Knook DL. Multiple imputation of missing blood pressure covariates in survival analysis. *Stat Med* 1999; **18:** 681–694.
21. Barnard J, Rubin DB. Small-sample degrees of freedom with multiple imputation. *Biometrika* 1999; **86:** 948–955.
22. Nakada Y, Kawakami R, Matsui M, Ueda T, Nakano T, Takitsume A, et al. Prognostic value of urinary neutrophil gelatinase-associated lipocalin on the first day of admission for adverse events in patients with acute decompensated heart failure. *J Am Heart Assoc* 2017; **6:** e004582.
23. Maisel AS, Wettersten N, van Veldhuisen DJ, Mueller C, Filippatos G, Nowak R, et al. Neutrophil gelatinase-associated lipocalin for acute kidney injury during acute heart failure hospitalizations: The AKINESIS Study. *J Am Coll Cardiol* 2016; **68:** 1420–1431.
24. Emmens JE, Ter Maaten JM, Matsue Y, Metra M, O'Connor CM, Ponikowski P, et al. Plasma kidney injury molecule-1 in heart failure: Renal mechanisms and clinical outcome. *Eur J Heart Fail* 2016; **18:** 641–649.
25. Kawai K, Kawashima S, Miyazaki T, Tajiri E, Mori M, Kitazaki K, et al. Serum beta2-microglobulin concentration as a novel marker to distinguish levels of risk in acute heart failure patients. *J Cardiol* 2010; **55:** 99–107.
26. Palazzuoli A, Ruocco G, Pellegrini M, De Gori C, Del Castillo G, Franci B, et al. Comparison of neutrophil gelatinase-associated lipocalin versus B-type natriuretic peptide and cystatin C to predict early acute kidney injury and outcome in patients with acute heart failure. *Am J Cardiol* 2015; **116:** 104–111.
27. Funabashi S, Omote K, Nagai T, Honda Y, Nakano H, Honda S, et al. Elevated admission urinary N-acetyl-beta-D-glucosamidase level is associated with worse long-term clinical outcomes in patients with acute heart failure. *Eur Heart J Acute Cardiovasc Care* 2020; **9:** 429–436.
28. Sharfuddin AA, Molitoris BA. Pathophysiology of ischemic acute kidney injury. *Nat Rev Nephrol* 2011; **7:** 189–200.
29. Dai H, Liu Q, Liu B. Research progress on mechanism of podocyte depletion in diabetic nephropathy. *J Diabetes Res* 2017; **2017:** 2615286.
30. Hasegawa K, Wakino S, Simic P, Sakamaki Y, Minakuchi H, Fujimura K, et al. Renal tubular Sirt1 attenuates diabetic albuminuria by epigenetically suppressing Claudin-1 overexpression in podocytes. *Nat Med* 2013; **19:** 1496–1504.
31. Papale M, Di Paolo S, Magistroni R, Lamacchia O, Di Palma AM, De Mattia A, et al. Urine proteome analysis may allow noninvasive differential diagnosis of diabetic nephropathy. *Diabetes Care* 2010; **33:** 2409–2415.
32. Husain-Syed F, Grone HJ, Assmus B, Bauer P, Gall H, Seeger W, et al. Congestive nephropathy: A neglected entity? Proposal for diagnostic criteria and future perspectives. *ESC Heart Fail* 2021; **8:** 183–203.
33. Gilbert RE, Cooper ME. The tubulointerstitium in progressive diabetic kidney disease: More than an aftermath of glomerular injury? *Kidney Int* 1999; **56:** 1627–1637.
34. Griffin M, Rao VS, Ivey-Miranda J, Fleming J, Mahoney D, Maulion C, et al. Empagliflozin in heart failure: Diuretic and cardiorenal effects. *Circulation* 2020; **142:** 1028–1039.
35. Bhatt DL, Szarek M, Steg PG, Cannon CP, Leiter LA, McGuire DK, et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. *N Engl J Med* 2021; **384:** 117–128.