Association of Time-to-Peak of Renal Blood Flow with Outcomes in Heart Failure: An Exploratory Comparative Analysis with Conventional Predictors

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Background: Time-to-peak of renal blood flow (TTPr), derived from Tc-99m diethylenetriaminepentaacetic acid (DTPA) renal scintigraphy, is a novel parameter for assessing renal perfusion.

Aims: To evaluate the prognostic significance of TTPr in patients with heart failure (HF).

Study Design: Retrospective, observational cohort study.

Methods: We analyzed 304 patients with HF who underwent Tc-99m DTPA renal scintigraphy to assess TTPr. TTPr values were compared between deceased and surviving patients. Cox regression analyses evaluated the prognostic value of TTPr. Model performance was assessed using the C-index, net reclassification improvement (NRI), and integrated discrimination improvement (IDI). Bootstrap internal validation (200 repetitions) generated optimism-corrected estimates, and the Holm–Bonferroni correction accounted for multiple testing in secondary analyses.

Results: During a median follow-up of 790 days, 79 patients (26.0%) died. For short-term outcomes (3-month mortality, n = 7), deceased patients showed a trend toward prolonged TTPr compared with survivors (59 s vs.

27 s, $p = 0.008$); multivariable analysis was not performed due to limited events. For long-term prognosis, TTPr was an independent predictor, demonstrating the highest corrected C-index among individual predictors ($p < 0.001$). After bootstrap correction, models incorporating TTPr [BM + TTPr and Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) + TTPr] showed modest but significant C-index improvements for all-cause and cardiovascular mortality (BM + TTPr: corrected ΔC-index = +0.018 and +0.020, both $p < 0.01$; MAGGIC + TTPr: corrected ΔC-index = +0.040 and +0.062, both $p < 0.001$), with reduced AIC. After Holm–Bonferroni correction, MAGGIC + TTPr significantly improved IDI at 1, 3, and 5 years for both endpoints (all adjusted $p = 0.012$), whereas NRI improvements were not statistically significant. Survival analysis using exploratory cut-offs (35 s for all-cause mortality, 33 s for cardiovascular mortality) revealed lower cumulative survival in the prolonged TTPr group ($p < 0.05$); these cut-offs require external validation.

Conclusion: Time-to-peak of renal blood predicted long-term outcomes in this HF cohort, showing potential incremental value. Prospective validation in broader populations is warranted before clinical implementation.

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INTRODUCTION

Cardiorenal syndrome (CRS) refers to the concurrent dysfunction of the heart and kidneys arising from complex pathophysiological disturbances. In patients with heart failure (HF), CRS is associated with poor prognosis.[1,2] Its pathogenesis is multifactorial, involving hemodynamic alterations, neurohormonal activation, inflammation, and oxidative stress. A key factor is reduced renal perfusion, primarily driven by hemodynamic changes.[3-5] Clinical detection of early renal perfusion deficits remains challenging. Standard assessments of renal function in HF, including serum creatinine and estimated glomerular filtration rate (GFR), are limited in capturing the dynamic changes in renal perfusion and hemodynamics that characterize early CRS. Due to the kidneys' robust autoregulatory mechanisms,[5,6] early perfusion changes may not immediately result in GFR decline or overt renal dysfunction. A decrease in GFR represents a late-stage event, occurring only after autoregulatory mechanisms fail. This diagnostic gap underscores the need for markers capable of detecting early alterations in renal perfusion, which could enable timely interventions and improve patient outcomes.

Tc-99m diethylenetriaminepentaacetic acid (DTPA) renal scintigraphy, a cornerstone of nuclear medicine, allows comprehensive evaluation of renal function, including perfusion, functional capacity, and structural integrity.[7,8] Preliminary data suggest that time-to-peak of renal blood flow (TTPr), derived from DTPA scintigraphy, may serve as a semiquantitative marker of renal perfusion in HF patients.[9] However, the prognostic significance of TTPr remains unclear. Therefore, this study aimed to evaluate the prognostic value of TTPr in patients with HF.

MATERIALS AND METHODS

This retrospective study included all consecutive patients with HF admitted between October 2017 and June 2022 who met the eligibility criteria and provided informed consent. No additional selection was performed. After stabilization with standard treatment, all patients underwent renal scintigraphy. Inclusion criteria were: age ≥ 18 years, documented HF signs and symptoms, and at least one of the following: left ventricular ejection fraction (LVEF) < 45%, or LVEF ≥ 45% combined with B-type natriuretic peptide (BNP) > 35 pg/mL, in conjunction with left ventricular hypertrophy, left atrial enlargement, or diastolic dysfunction. Exclusion criteria included hemodynamic instability, pulmonary embolism, advanced malignancies, multiorgan failure, and severe renal insufficiency, defined as a GFR < 30 mL/min/1.73 m². The study was conducted in accordance with the Declaration of Helsinki and approved by the Hebei Medical University First Hospital Clinical Research Ethics Committee (approval number: 2023-S00759, date: 29.06.2023). Informed consent was obtained from all individual participants included in the study.

Tc-99m DTPA renal scintigraphy

Tc-99m DTPA was prepared according to the manufacturer's instructions. The total administered dose was verified by measuring activity in the syringe before and after injection using a gamma camera (Infinia, General Electric Healthcare, USA) positioned 30 cm away for 10–30 seconds. Prior to the procedure, patients consumed 300 mL of water and were positioned supine. A bolus of 185 MBq Tc-99m DTPA (in 0.2–0.5 mL) was administered intravenously via the antecubital vein, immediately followed by a 10-mL saline flush. Imaging data were acquired using the Xeleris 3 Functional Imaging System on a 64 × 64 matrix. Acquisition began simultaneously with injection and continued for 60 seconds at 2 s/frame, followed by 20 minutes at 0.5 min/frame. The initial 60-second phase captured abdominal aortic and renal blood flow dynamics, while the subsequent 20-minute phase provided information on renal function.[10-12] Post-imaging, an experienced technologist delineated regions of interest (ROIs) for the abdominal aorta and both kidneys. ROIs were drawn three times in a blinded manner, and the average was used for analysis. GFR was calculated using Gate's method.[13] TTPr, defined as the interval from injection to peak activity in the renal ROIs, was used as a measure of renal perfusion.

Follow-up

Follow-up began on the date of the renal scintigraphy examination. The study population was monitored through outpatient visits, telephone contact, or review of medical records until May 31, 2023. The primary endpoint was all-cause mortality, and the secondary endpoint was cardiovascular mortality.

Statistical analysis

Statistical analyses were conducted using SPSS 22.0, R 4.3.1, and GraphPad Prism 9. Quantitative data are presented as mean ± standard deviation or median with interquartile ranges (IQRs), depending on the distribution. Two-group comparisons were performed using either the Student's t-test or the Mann–Whitney U test. Qualitative data are expressed as percentages and analyzed using the chi-square test or Fisher's exact test. Cox regression analysis was employed to evaluate long-term prognosis. The C-index was calculated to assess the discriminatory ability of individual predictors and multivariable models. To examine the incremental value of TTPr, net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were calculated. Exploratory subgroup analyses were performed to evaluate the consistency of TTPr's prognostic value across different patient populations. Survival analysis was conducted using Kaplan–Meier curves and log-rank tests. To obtain robust estimates of predictive performance, bootstrap internal validation with 200 repetitions was performed to calculate optimism-corrected C-indices, bias-corrected ΔC-index with 95% confidence intervals, and corrected NRI and IDI estimates. To account for multiplicity in exploratory analyses, the Holm–Bonferroni correction was applied to all secondary analyses, including comparisons of model performance metrics (C-index, NRI, IDI), subgroup analyses, and interaction tests. Adjusted p values are reported. A two-sided $p < 0.05$ was considered statistically significant before correction.

RESULTS

Demographics and clinical characteristics

The study included 304 patients with HF, with a median age of 59 years (IQR, 48–67), of whom 211 were male (69.4%). The median follow-up duration was 790 days (IQR, 459–1413). By the end of follow-up, 79 patients (26.0%) had died from all causes, and 71 (23.4%) from cardiovascular causes. Nine patients (3.0%) were lost to follow-up. Patients were categorized into survival and deceased groups, as detailed in Supplementary Table 1. The deceased group exhibited a longer TTPr than the survival group, with median values of 37 s (IQR, 30–55) vs. 25 s (IQR, 21–35), respectively.

Measurement reproducibility of TTPr

The intraobserver intraclass correlation coefficient (ICC) was 0.994 ($p < 0.001$), based on triplicate measurements by a single physician. The interobserver ICC was 0.993 ($p < 0.001$), derived from independent assessments by three physicians.

Short-term prognosis

Within the first 3 months, seven cases (2.3%) of all-cause mortality were recorded. patients who died within 3 months had a median TTPr of 59 s (IQR, 31–59) compared with 27 s (IQR, 21–59) in survivors ($p = 0.008$). Multivariable analysis was not performed due to the limited number of events.

Long-term prognosis

In univariate Cox regression analysis, predictors of cardiovascular mortality included systolic blood pressure (SBP), New York Heart Association (NYHA) class, TTPr, GFR, left atrium diameter, left ventricular end-diastolic diameter, LVEF, right atrial diameter, moderate-to-severe mitral and tricuspid regurgitation, creatinine, urea nitrogen, uric acid, total bilirubin, potassium, sodium, chloride, and BNP. All-cause mortality was predicted by the same factors, along with red cell distribution width. Multivariate analysis

identified SBP, TTPr, GFR, sodium, and BNP as independent predictors of both all-cause and cardiovascular mortality (Supplementary Table 2). To obtain robust estimates of predictive performance, optimism-corrected C-indices were calculated using bootstrap internal validation with 200 repetitions. When SBP, TTPr, GFR, sodium, and BNP were incorporated into the Cox regression model separately, TTPr demonstrated the highest corrected C-index and the lowest Akaike information criterion (AIC) for both endpoints ($p < 0.001$) (Supplementary Table 3).

Incremental predictive value of TTPr

To evaluate the incremental prognostic value of TTPr, prediction models were developed based on the five independent predictors identified in the multivariable analysis. Model stability was assessed using the events-per-variable (EPV) ratio. The primary Cox models included five predictors, with 79 events for all-cause mortality and 71 events for cardiovascular mortality, yielding EPVs of 15.8 and 14.2, respectively—both exceeding the recommended minimum of 10, indicating adequate stability. After bootstrap optimism correction with 200 repetitions, the augmented model BM + TTPr demonstrated a modest but significant improvement in the C-index (all-cause mortality: corrected ΔC-index = +0.018; cardiovascular mortality: +0.020; both $p < 0.01$) and a reduced AIC (Table 1). Similarly, Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) + TTPr showed sustained improvements over MAGGIC alone (all-cause mortality: corrected ΔC-index = +0.040; cardiovascular mortality: +0.062; both $p < 0.001$) (Table 1). NRI and IDI were also calculated (raw p values in Table 2). After Holm–Bonferroni correction for multiple testing across all NRI and IDI analyses, BM + TTPr vs. BM showed no significant improvements at any time point for either all-cause or cardiovascular mortality (all adjusted $p > 0.05$). In contrast, MAGGIC + TTPr versus MAGGIC significantly improved IDI for both all-cause and cardiovascular mortality at 1, 3, and 5 years (all adjusted $p = 0.012$), whereas improvements in NRI did not reach statistical significance after correction (all adjusted $p > 0.05$).

TABLE 1. Additional Prognostic Value of TTPr Over a Baseline Model for Predicting Clinical Outcomes of HF Patients.

Model	Corrected C-index (95% CI)	AIC	p
All-cause mortality			
Base model	0.75 (0.702, 0.811)	727.06	
Base model + TTPr	0.768 (0.721, 0.816)	720.66	0.004*
MAGGIC	0.693 (0.62, 0.756)	748.78	
MAGGIC + TTPr	0.733 (0.671, 0.785)	731.29	< 0.001**
Cardiovascular mortality			
Base model	0.766 (0.722, 0.839)	646.20	
Base model + TTPr	0.786 (0.752, 0.85)	636.27	< 0.001*
MAGGIC	0.68 (0.616, 0.741)	677.43	
MAGGIC + TTPr	0.742 (0.678, 0.816)	651.60	< 0.001**

Base model included SBP, GFR, BNP and sodium.
TTPr, time to peak of renal blood flow; MAGGIC, Meta-Analysis Global Group in Chronic Heart Failure; CI, confidence interval; AIC, Akaike information criterion; SBP, systolic blood pressure; GFR, glomerular filtration rate; BNP, B-type natriuretic peptide.
*p compared to base model.
**p compared to MAGGIC score.

TABLE 2. Reclassification Analyses for Prognostic Value of TTPr over a Baseline Model for Clinical Outcomes of HF Patients.

Model	1-year outcome NRI (95% CI)	1-year outcome IDI (95% CI)	3-year outcome NRI (95% CI)	3-year outcome IDI (95% CI)	5-year outcome NRI (95% CI)	5-year outcome IDI (95% CI)
All-cause mortality						
Base model						
Base model + TTPr	0.158 (-0.07, 0.468)	0.021 (0.001, 0.057)	0.105 (-0.095, 0.33)	0.007 (-0.012, 0.041)	0.201 (-0.031, 0.493)	0.052 (0.008, 0.115)
*p**	0.556	0.03	0.274	0.567	0.176	0.01
MAGGIC						
MAGGIC + TTPr	0.333 (0.069, 0.646)	0.051 (0.014, 0.128)	0.331 (0.028, 0.567)	0.047 (0.007, 0.116)	0.491 (0.08, 0.718)	0.085 (0.019, 0.158)
*p***	0.243	< 0.001	0.033	< 0.001	0.066	< 0.001
Cardiovascular mortality						
Base model						
Base model + TTPr	0.189 (-0.048, 0.481)	0.024 (0.001, 0.06)	0.146 (-0.116, 0.371)	0.013 (-0.014, 0.057)	0.286 (0, 0.599)	0.07 (0.014, 0.049)
*p**	0.476	0.05	0.231	0.438	0.113	0.02
MAGGIC						
MAGGIC + TTPr	0.433 (0.076, 0.663)	0.06 (0.016, 0.148)	0.476 (0.171, 0.746)	0.077 (0.019, 0.164)	0.655 (0.291, 0.936)	0.129 (0.043, 0.218)
*p***	0.196	< 0.001	0.004	< 0.001	0.026	< 0.001

Base model included SBP, GFR, BNP and sodium.
TTPr, time to peak of renal blood flow; MAGGIC, Meta-Analysis Global Group in Chronic Heart Failure; NRI, net reclassification improvement; IDI, integrated discrimination index; CI, confidence interval; SBP, systolic blood pressure; GFR, glomerular filtration rate; BNP, B-type natriuretic peptide.
p compared to base model.
**p* compared to MAGGIC score.
p values were adjusted for multiple testing using the Holm–Bonferroni method. After correction, statistical significance (adjusted $p < 0.05$) is indicated in the text; raw *p* values are presented in the table for transparency.

Survival analysis

Optimal TTPr cut-offs for predicting all-cause and cardiovascular mortality were identified as 35 s and 33 s, respectively, using the maximal selection test. Patients with prolonged TTPr demonstrated significantly lower cumulative survival rates ($p < 0.05$) (Figure 1a and b). However, because these cut-offs were derived and tested within the same dataset, the reported *p* values are subject to optimism bias and should be interpreted with caution. External validation is required to confirm these thresholds.

Subgroup analysis

Exploratory subgroup analyses were performed to assess the consistency of TTPr's prognostic value (Supplementary Figures 1 and 2). After Holm–Bonferroni correction for multiple testing across all subgroup analyses and interaction tests, none of the interaction terms remained significant (all adjusted $p > 0.05$). This indicates that the prognostic value of TTPr for both all-cause and cardiovascular mortality was consistent across all subgroups examined, including age, gender, body mass index (BMI), LVEF, NYHA class, and comorbidities.

DISCUSSION

This retrospective exploratory study highlighted the prognostic significance of TTPr in Tc-99m DTPA renal scintigraphy for HF patients and suggested its potential additive value beyond traditional markers such as BNP and GFR. TTPr may serve as a predictor of long-term prognosis, providing incremental information to established predictors and models.

Renal blood flow, dependent on the pressure gradient between mean perfusion pressure and venous pressure, is adversely affected in HF due to diminished forward flow and venous congestion.[5,14] TTPr, influenced by these hemodynamic alterations, reflects the velocity of renal perfusion, which is prolonged in HF.[15,16] This prolongation is not merely a marker of reduced flow but a direct hemodynamic signature of renal venous congestion. Elevated central venous pressure transmits to the renal veins, reducing the arteriovenous pressure gradient that drives perfusion. Sustained venous pressure can impair renal autoregulatory capacity. Normally, renal autoregulation—mediated by the myogenic response and tubuloglomerular feedback—maintains stable glomerular filtration across a range of perfusion pressures. Chronic venous congestion may induce renal interstitial edema, compromise the microvasculature
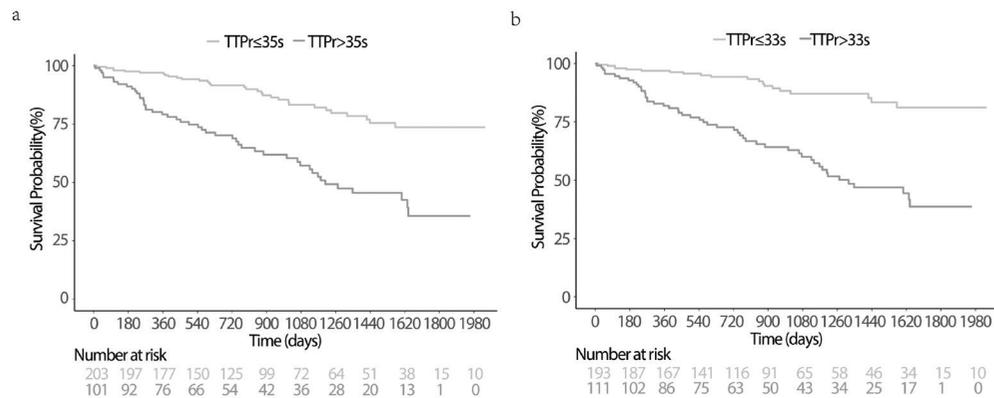
FIG. 1. Survival curves for all-cause mortality (a) and cardiovascular mortality (b) of HF patients.
TTPr, time-to-peak of renal blood flow; HF, heart failure.

and tubular structures, blunt autoregulatory responses, and create a vicious cycle of worsening perfusion and congestion. Prolonged impairment in renal perfusion can precipitate structural and functional renal changes, including interstitial edema, elevated intratubular pressure, and activation of inflammatory and fibrotic pathways, all of which contribute to renal function decline and are independently associated with adverse HF outcomes.[3,5,17] For short-term outcomes, the limited number of events precluded multivariable analysis to identify independent predictors. However, a trend toward prolonged TTPr was observed in patients with poor prognosis. For long-term outcomes, TTPr's predictive value remained statistically significant even after adjustments for sodium, BNP, SBP, and GFR. MAGGIC + TTPr models showed statistically significant improvements in predictive efficiency. Nonetheless, the absolute improvements in discrimination and reclassification were modest, and whether these translate into meaningful clinical benefits that alter patient management requires prospective evaluation using decision-analytic frameworks.

BNP, a well-established predictor of HF diagnosis and prognosis, is influenced by age, gender, BMI, and renal function.[18,19] Some studies have questioned its predictive efficiency, particularly in HFpEF.[20,21] In our long-term prognostic analysis, TTPr demonstrated predictive performance comparable to, and in certain contexts slightly superior to, BNP and showed no significant interaction with age, gender, or BMI. These observations provide preliminary evidence that TTPr may offer complementary prognostic information independent of common confounding factors. However, these findings are hypothesis-generating and warrant confirmation in larger prospective studies.

GFR, another critical prognostic factor in HF, showed somewhat lower predictive capability than TTPr in our cohort. GFR decline, indicative of severe renal impairment, typically emerges only after substantial disease progression and loss of renal autoregulatory compensation, limiting its ability to reflect early heart–kidney axis changes.[22] Many studies reported prognostic value only with marked GFR reduction; values above 50–60 mL/min/1.73 m² were not consistently associated with poor outcomes. Consequently, GFR is less predictive in patients with HF and preserved renal function.[23,24] In our study, we excluded patients with GFR < 30 mL/min/1.73 m²,

and the median GFR was 70 mL/min/1.73 m², explaining its relatively limited predictive power in this population. In contrast, TTPr may detect earlier hemodynamic alterations in HF, offering a potential indicator of renal perfusion changes that addresses limitations of conventional renal function assessments. However, by excluding patients with GFR < 30 mL/min/1.73 m², the generalizability of our findings to the broader HF population—particularly those with moderate to severe chronic kidney disease—is limited. Renal scintigraphy provided comprehensive insights, capturing both perfusion parameters, such as TTPr, and functional indicators, such as GFR, with GFR assessment accuracy surpassing most formula-based estimations.[25,26] While offering unique prognostic information, the clinical integration of renal scintigraphy is constrained by practical considerations, including radiation exposure, cost, and availability. Future studies should prospectively evaluate its net clinical benefit and cost-effectiveness in HF management.

Exploratory subgroup analyses revealed no significant heterogeneity in TTPr's prognostic value across patient subpopulations. Therefore, TTPr may serve as a broadly applicable prognostic marker in HF, and subgroup-specific claims are not supported by the current data. Prospective studies are required to further clarify its clinical utility and potential advantages.

This study has several limitations. First, its retrospective, single-center design and the selected cohort (stabilized ambulatory patients with preserved renal function) limit generalizability. The exclusion of patients with GFR < 30 mL/min/1.73 m² restricts applicability to the full HF spectrum, particularly those with advanced chronic kidney disease. The small sample size and low short-term event rate constrain the robustness and clinical interpretability of 3-month prognostic findings. Additionally, TTPr measurements, though reproducible in our hands, lack established reference ranges and widespread standardization. Prognostic cut-offs were derived and applied within the same cohort, introducing potential optimism bias; external validation is needed. Cardiovascular mortality analysis did not account for competing risks, potentially overestimating hazard ratios; future studies should consider Fine–Gray models. Finally, despite providing unique insights, renal scintigraphy faces practical limitations in clinical implementation, including cost, availability, and radiation exposure compared with standard blood tests. Future

studies should assess its cost-effectiveness in targeted HF populations. Despite these limitations, our findings suggest that TTPr, as a marker of renal perfusion kinetics, may provide incremental prognostic information in HF. Prospective, multicenter studies with prespecified endpoints and validation cohorts are warranted to confirm its clinical utility and define its optimal role in risk stratification.

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