Clinical Investigation

Pupillary Light Reflex as a New Prognostic Marker in Patients With Heart Failure

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ABSTRACT

Background: Autonomic function can be evaluated based on the pupillary light reflex (PLR). However, the relationship between PLR and prognosis in patients with heart failure (HF) remains unclear. This study was performed to examine whether PLR could be used as a prognostic indicator in patients with HF.

Methods and Results: A retrospective review was performed in 535 consecutive Japanese patients hospitalized for acute HF (mean age 66.1 ± 13.7 y). PLR was recorded at least 7 days after hospitalization for HF with the use of a pupilometer. Fifty-three patients died over a median follow-up period of 1.3 years (interquartile range 0.6−2.3 y). After adjustment for several preexisting prognostic factors, including Seattle Heart Failure Score (SHFS), PLR as assessed by recovery time (time to 63% redilation) was independently associated with all-cause mortality (hazard ratio 0.50, 95% confidence interval 0.35−0.73; $P < .001$). The addition of recovery time to SHFS resulted in a significant increase in the area under the curve on receiver-operating characteristic curve analysis (0.69 vs 0.77; $P < .001$).

Conclusions: PLR assessed by recovery time was an independent predictor of mortality and added prognostic information to the SHFS in patients with HF. Our results suggest that PLR may be useful as a new prognostic marker in HF patients. (*J Cardiac Fail 2019;25:156−163*)

Key Words: Pupillary light reflex, autonomic, heart failure, mortality.

Heart failure (HF) is one of the leading causes of death globally.[1] Neuroendocrine dysregulation is among the most important pathophysiologic factors involved in the high mortality rate associated with HF.[2] Neuroendocrine dysregulation is observed mainly as an imbalance of autonomic control[3] and is characterized by markedly elevated sympathetic activation[4] and parasympathetic withdrawal.[5] Autonomic function is generally evaluated by heart rate variability obtained from Holter electrocardiography,[6] and its clinical implications have been demonstrated in patients with HF.[7,8] However, these methods are not applicable in non−sinus rhythm (SR) HF patients. Atrial fibrillation is one of the leading types of sustained arrhythmia in HF.[9] Studies in large representative HF cohorts indicated that atrial fibrillation and non-SR have prevalence rates of 20%−50%.[10−13] Moreover, measurement of heart rate variability requires continuous electrocardiographic monitoring for 24 hours, which is time consuming and not always possible.

The pupil radius is controlled by both the sympathetic and the parasympathetic autonomic nervous systems in response to environmental light, a mechanism called the pupil light reflex (PLR). Therefore, the pupillary radius response to an external light stimulus may provide an

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indirect means of assessing the integrity of neuronal pathways controlling pupil size.[14] A previous study suggested that changes in pupil size in response to light stimulus are based on the functional balance between sympathetic and parasympathetic activities.[15]

There are only limited data regarding the utility of PLR for predicting prognosis in HF patients. We hypothesized that PLR may have prognostic predictive capability, and this study was performed to investigate whether PLR can be used as a novel prognostic marker in patients with HF.

Methods

Study Population

A retrospective review was performed on 535 consecutive patients admitted to Kitasato University Hospital from July 2007 to May 2016 with acute HF who did not fulfill the following exclusion criteria: (1) missing PLR measurement, (2) age <18 years, (3) patients with dysautonomia, (4) a history of any ocular operations or disease affecting the pupillary reflex, and (5) failure to measure PLR. Acute HF was defined as the presence of volume overload and dyspnea at rest or with minimal activity. All patients underwent cardiac rehabilitation during hospitalization and we measured PLR to evaluate autonomic nervous function as an outcome of cardiac rehabilitation.

The study was performed in accordance with the tenets of the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Kitasato University Hospital.

Data Collection

Data on all variables were collected from electronic medical records. Biochemical and echocardiographic data were measured on admission. All other clinical data were measured just before discharge from the hospital. The B-type natriuretic peptide (BNP) concentration was measured with the use of a commercially available immunoradiometric assay (Shionogi, Osaka, Japan). The estimated glomerular filtration rate (eGFR) was defined according to the formula recommended by the Japanese Society of Nephrology as: $194 \times (\text{serum creatinine})^{1.094} \times (\text{age})^{0.287}$ in men, and $194 \times (\text{serum creatinine})^{1.094} \times (\text{age})^{0.287} \times 0.739$ in women.[16] The left ventricular ejection fraction (LVEF) was estimated by means of the Simpson method on 2-dimensional echocardiograms, and we defined reduced LVEF as <50%. The Seattle Heart Failure Score (SHFS) was derived in each patient from 14 variables (age, sex, New York Heart Association functional classification, LVEF, ischemic etiology, systolic blood pressure, diuretic agent dose, allopurinol use, statin use, lymphocyte percentage, serum sodium, cholesterol, hemoglobin, and uric acid).[17]

The end point of this study was all-cause mortality, as determined by a review of hospital electronic medical records.

PLR Measurement

PLR measurement was performed on both eyes at least 7 days after hospitalization for HF with the use of a portable infrared videopupillography system (Iriscorder Dual C10641; Hamamatsu Photonics, Hamamatsu, Japan), consisting of a goggle-shaped measurement portion with a charge-coupled device camera and a control portion with a video monitor and microcomputer with software controlling the light stimulus and data analysis. The camera was capable of taking a maximum of 60 frames per second. An infrared light source with a wavelength of 890 nm was used, and a light flash was produced by a light bulb embedded in the Iriscorder. The duration of the stimulus was 1 second. After setting the goggles on the patient's face and fully covering the patient's eyes, a 5-minute period was allowed for dark adaptation.[18] All patients were tested once between 09:00 and 12:00.[19,20]

The variables of PLR measured in this study were as follows[18,21,22]: constriction ratio (initial diameter before light stimulus − minimum diameter after light stimulus/initial diameter × 100) (%), maximum acceleration of constriction (mm/s^2), maximum velocity of constriction (mm/s), maximum velocity of dilation (mm/s), latency to constriction (ms), time to maximum constriction (ms), and recovery time[23] (time to 63% redilation) (ms). The measurement and recording necessary to obtain the above variables covered the changes in size of the pupil over a period of 5.0 seconds from application of the light flash. Each measurement of a total of 5.0 seconds in duration corresponds to a full reaction of the pupil, starting from initial reduction in diameter, maximum miosis, and return to normal.

Statistical Analyses

The results of normally distributed continuous variables are expressed as mean ± SD, and variables that were not normally distributed are presented as median (interquartile range). Categoric variables are expressed as n (%). The time for the end point was calculated as the number of days from the date of PLR measurement to the date of the event. At present, there are no established PRL variables for prediction of mortality, we first performed multivariable Cox regression analysis for all PLR variables by constructing 2 associative models using preexisting prognostic factors: model 1 used the SHFS as an adjusting variable; and model 2 included the SHFS, body mass index (BMI), log BNP, and eGFR. After Cox regression analyses, patients were divided into 3 groups based on tertile of the variable that was significantly associated with mortality in all models on Cox regression analyses, and baseline characteristics were compared between groups by means of 1-way analysis of variance, Kruskal−Wallis test, chi-square test, or Fisher exact test as appropriate. We performed Kaplan-Meier and log-rank tests to evaluate the prognostic predictive capability and assessed the dose−response correlation between PLR and mortality risk with the use of a Cox regression

model with spline functions with 4 knots at quartiles of the independent variable.

In addition, to assess for potential effect of modification on the association of PLR with mortality, we performed subgroup analysis of PLR in various subgroups relevant to HF prognosis, including sex, age (stratified at 65 and 75 years), LVEF (stratified at 50%), eGFR (stratified at 45 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$), diabetes, beta-blocker use, and heart rhythm (SR or non-SR) with adjustment for SHFS, BMI, log BNP, and eGFR.

Finally, to examine whether the parameters of PLR had complementary predictive capability to SHFS, receiver operating characteristic (ROC) curves were constructed for all-cause mortality during the study period with the use of the following models: SHFS only and SHFS plus PLR variable significantly associated with mortality in all models on Cox regression analyses. The areas under the curves (AUCs) were compared according to the method of DeLong et al.[24]

Analyses were performed with the use of SPSS version 22.0 (IBM Corp, Armonk, New York), Stata version 13.0 (Statacorp, College Station, Texas), and R version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria). In all analyses, a 2-tailed P value of $<.05$ was taken to indicate statistical significance.

Results

Study Population

The baseline characteristics for all subjects are presented in Table 1. The study population had a mean age of 66 ± 14 years, 64% were male, 45% were classified as non-SR, and 53% had reduced LVEF. Beta-blockers were prescribed at discharge for 77% of the patients, 85% received angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and 79% received diuretic agents. The medians of the constriction ratio, maximum acceleration of constriction, maximum velocity of constriction, maximum velocity of dilation, latency to constriction, time to maximum constriction, and recovery time were 26.5%, 37.1 mm/s^2, 3.1 mm/s, 1.8 mm/s, 316.7 ms, 908.4 ms, and 1275.0 ms, respectively.

Association of PLR With All-Cause Mortality

Over a median follow-up period of 1.3 years (interquartile range 0.6−2.3 years), a total of 53 deaths occurred in the patient population. The results of Cox regression analysis for all-cause mortality are presented in Table 2. Even after adjusting for prognostic models, only recovery time was a significant and independent predictor of mortality in our cohort.

The patient characteristics for groups stratified according to tertile of recovery time are presented in Table 3. Patients with long recovery time showed the highest BMI and low-density lipoprotein cholesterol. However, there were no differences in severity of HF (eg, LVEF, SHFS, and BNP), medications, or comorbidities between the groups. On Kaplan-Meier analyses followed by the log-rank test, all-cause mortality was significantly higher in the short recovery time group than the middle recovery time group ($P = .023$) and the long recovery time group ($P < .001$; Fig. 1). Furthermore, the middle recovery time group showed significantly higher all-cause mortality rate than the long recovery time group ($P = .015$). Fig. 2 shows the dose-response correlation of the

Table 1. Patient Characteristics (n = 535)

Characteristic	
Age, y	66.1 ± 13.7
Male	342 (63.9%)
Body weight, kg	58.4 ± 14.5
Height, cm	161.2 ± 9.4
BMI, kg/m^2	22.4 ± 4.3
Systolic blood pressure, mm Hg	125.3 ± 30.2
Diastolic blood pressure, mm Hg	72.6 ± 20.6
Heart rate, beats/min	82.5 ± 22.4
Ischemic etiology	184 (34.4%)
Non−sinus rhythm	238 (44.5%)
LVEF, %	46.4 ± 17.1
LVEF <50%	281 (52.5%)
NYHA functional class	
II	386 (72.1%)
III	147 (27.5%)
IV	2 (0.4%)
SHFS	1.12 (0.52−1.66)
Pupillary light reflex	
Constriction ratio, %	26.5 (20.3−32.3)
Maximum acceleration of constriction, mm/s^2	37.1 (27.9−41.8)
Maximum velocity of constriction, mm/s	3.1 (2.5−3.7)
Maximum velocity of dilatation, mm/s	1.8 (1.2−1.9)
Latency to constriction, ms	316.7 (300.0−350.0)
Time to the maximum constriction, ms	908.4 (658.4−1083.4)
Recovery time to 63% redilatation, ms	1275.0 (1033.3−1541.7)
Medications	
ACE inhibitor or ARB	457 (85.4%)
Beta-blocker	410 (76.6%)
Aldosterone blocker	272 (50.8%)
Diuretic agent	421 (78.7%)
Comorbidities	
Hypertension	328 (61.3%)
Diabetes	210 (39.3%)
Dyslipidemia	259 (48.4%)
Previous heart failure admission	207 (38.7%)
Previous myocardial infarction	86 (16.1%)
Current smoker	94 (17.6%)
Laboratory data	
Hemoglobin, g/dL	11.9 (10.5−13.8)
Albumin, g/dL	3.6 (3.3−4.0)
Total cholesterol, mg/dL	166 (140−191)
LDL cholesterol, mg/dL	92 (73−115)
Sodium, mEq/L	139 (137−141)
eGFR, $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$	50.3 (34.4−65.5)
hs-CRP, mg/dL	0.31 (0.10−0.93)
BNP, pg/mL	269.3 (121.1−557.9)

Values are presented as mean ± SD, n (%), or median (interquartile range). ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SHFS, Seattle Heart Failure Score.

Table 2. Univariate and Multivariate Cox Regression Models for All-Cause Mortality

Continuous Variable (Per SD Increase)	Univariate			Model 1: Adjusted by SHFS			Model 2: Model 1 + BMI + BNP + eGFR		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Constriction ratio	0.97	0.75−1.26	.821	1.05	0.80−1.36	.737	1.04	0.80−1.36	.777
Maximum acceleration of constriction	1.08	0.84−1.39	.559	1.18	0.92−1.53	.199	1.19	0.90−1.58	.233
Maximum velocity of constriction	0.88	0.68−1.14	.331	1.01	0.78−1.31	.944	0.99	0.76−1.30	.955
Maximum velocity of dilatation	1.21	1.00−1.45	.049	1.20	0.99−1.46	.065	1.20	0.98−1.45	.089
Latency to constriction	1.13	1.02−1.26	.020	1.13	0.99−1.28	.053	1.11	0.98−1.26	.092
Time to the maximum constriction	1.00	0.78−1.28	.992	1.05	0.81−1.35	.731	1.00	0.79−1.33	.853
Recovery time to 63% redilation	0.47	0.33−0.68	<.001	0.49	0.34−0.71	<.001	0.50	0.35−0.73	<.001

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

recovery time with mortality. Shorter recovery times were correlated with increased risk of mortality in both nonadjusted and fully adjusted models.

A longer recovery time was consistently correlated with favorable prognosis across various subgroups, even after adjusting for SHFS, BMI, BNP, and eGFR (Fig. 3). The favorable effect of longer recovery time was similar between SR and non-SR groups (SR: hazard ratio 0.56, 95% confidence interval [CI] 0.36−0.87; non-SR: hazard ratio 0.48, 95% CI 0.26−0.88; *P* for interaction = .64).

Complementary Prognostic Predictive Capability of PLR to SHFS

The AUCs on ROC curve analysis for the SHFS only and SHFS plus recovery time logistic regression models were

Table 3. Patient Characteristics According to Tertile of Recovery Time (time To 63% Redilation)

Characteristic	Short Recovery Time (n = 176)	Middle Recovery Time (n = 179)	Long Recovery Time (n = 180)	*P* Value
Age, y	66.9 ± 13.7	67.3 ± 13.5	64.1 ± 13.7	.054
Male	120 (68.2%)	110 (61.1%)	112 (62.2%)	.353
Body weight, kg	57.2 ± 12.8	57.7 ± 15.5	60.8 ± 14.9	.042
Height, cm	161.3 ± 9.0	160.5 ± 10.1	161.8 ± 9.1	.455
BMI, kg/m^2	21.9 ± 4.0	22.1 ± 4.4	23.1 ± 4.5	.023
Systolic blood pressure, mm Hg	125.1 ± 30.0	126.6 ± 29.3	124.3 ± 31.7	.779
Diastolic blood pressure, mm Hg	71.1 ± 20.3	85.9 ± 19.2	72.1 ± 22.5	.208
Heart rate, beats/min	84.2 ± 23.8	82.2 ± 20.1	81.2 ± 23.1	.449
Ischemic etiology	66 (37.5%)	64 (35.8%)	54 (30.0%)	.295
Nonsinus rhythm	78 (44.3%)	82 (45.8%)	78 (43.3%)	.893
LVEF, %	47.5 ± 16.7	44.9 ± 17.2	46.7 ± 17.3	.327
LVEF <50%	84 (47.7%)	94 (52.2%)	103 (57.5%)	.200
NYHA functional class				
II	119 (67.6%)	129 (72.1%)	138 (76.7%)	.061
III	57 (32.4%)	50 (27.9%)	40 (22.2%)	
IV	0	0	2 (0.1)	
SHFS	1.20 (0.65−1.80)	1.11 (0.58−1.71)	1.04 (0.54−1.60)	.215
Medications				
ACE inhibitor or ARB	152 (86.4%)	152 (84.9%)	153 (85.0%)	.910
Beta-blocker	134 (76.1%)	137 (76.5%)	139 (77.2%)	.970
Aldosterone blocker	91 (51.7%)	87 (48.6%)	94 (52.2%)	.760
Diuretic agent	144 (81.8%)	135 (75.4%)	142 (78.9%)	.337
Comorbidities				
Hypertension	105 (59.7%)	114 (63.7%)	109 (60.1%)	.715
Diabetes	72 (40.9%)	76 (42.5%)	62 (34.4%)	.257
Dyslipidemia	91 (51.7%)	89 (49.7%)	79 (43.9%)	.307
Previous heart failure admission	71 (40.3%)	69 (38.5%)	67 (37.2%)	.832
Previous myocardial infarction	28 (15.9%)	35 (20.0%)	23 (12.8%)	.206
Current smoker	30 (17.0%)	34 (19.0%)	30 (16.7%)	.808
Laboratory data				
Hemoglobin, g/dL	11.5 (9.9−13.7)	12.1 (10.5−13.7)	12.1 (10.8−14.0)	.048
Albumin, g/dL	3.6 (3.3−4.0)	3.7 (3.2−4.0)	3.7 (3.4−4.0)	.319
Total cholesterol, mg/dL	164 (140−192)	159 (135−186)	170 (142−197)	.234
LDL cholesterol, mg/dL	92 (70−113)	88 (70−110)	101 (80−122)	.043
Sodium, mEq/l	139 (136−141)	139 (137−141)	139 (137−141)	.659
eGFR, mL·min^{-1}·1.73 m^{-2}	53.4 (34.0−66.9)	48.9 (34.8−65.9)	49.1 (33.9−65.2)	.754
hs-CRP, mg/dL	0.30 (0.10−1.00)	0.38 (0.10−0.95)	0.28 (0.10−0.82)	.310
BNP, pg/mL	240.3 (114.2−532.3)	306.0 (121.4−639.5)	258.7 (124.2−558.4)	.718

Values are presented as mean ± SD, n (%), or median (interquartile range). Abbreviations as in Table 1.

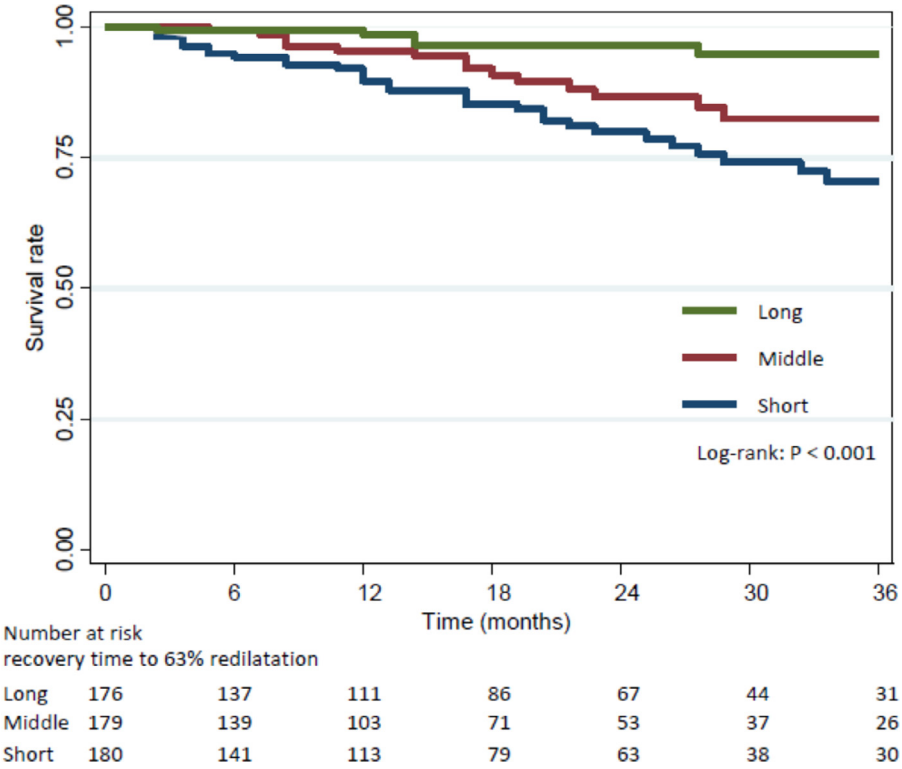

Fig. 1. Kaplan-Meier curve for all-cause mortality according to recovery time (time to 63% redilation). Survival of heart failure patients differed significantly according to the tertile of recovery time.

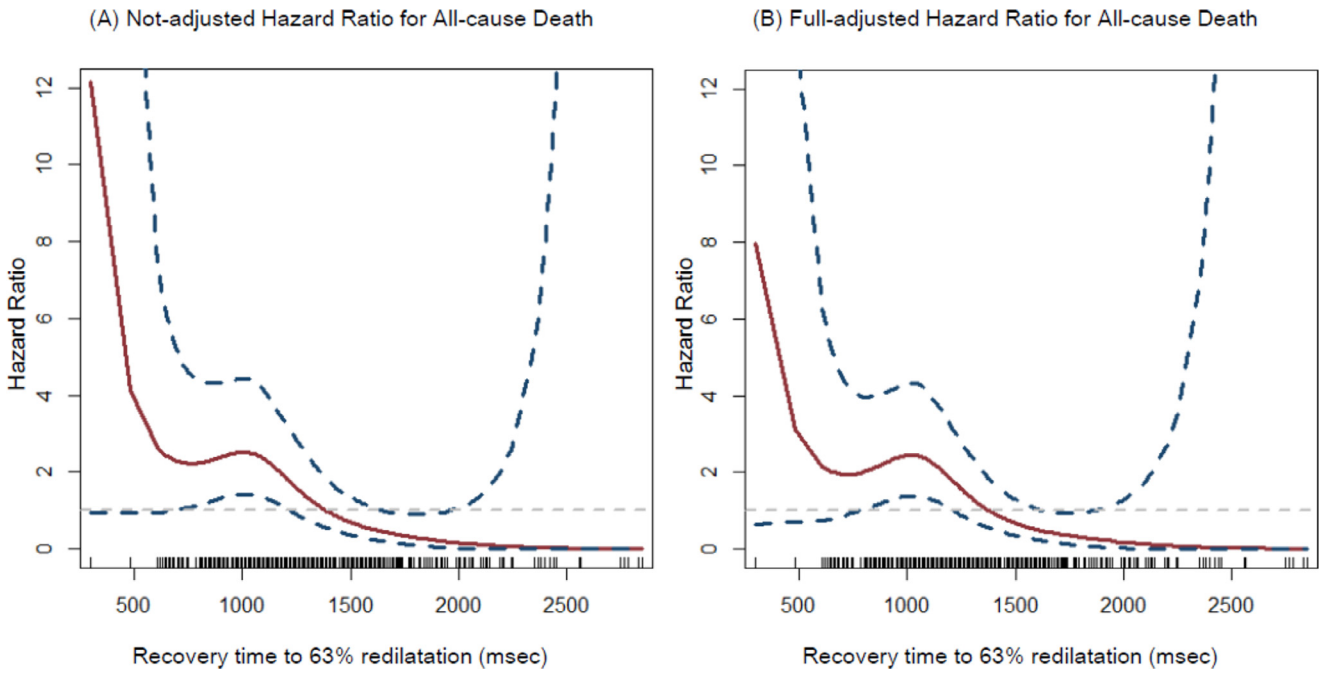

Fig. 2. Dose-response associations between recovery time (time to 63% redilation) and all-cause mortality. Dotted lines represent the 95% confidence intervals. Rug plots are shown along the *x*-axes of the graphs to depict the distributions of recovery time. Fully adjusted models were adjusted for Seattle Heart Failure Score, body mass index, log B-type natriuretic peptide, and estimated glomerular filtration rate.

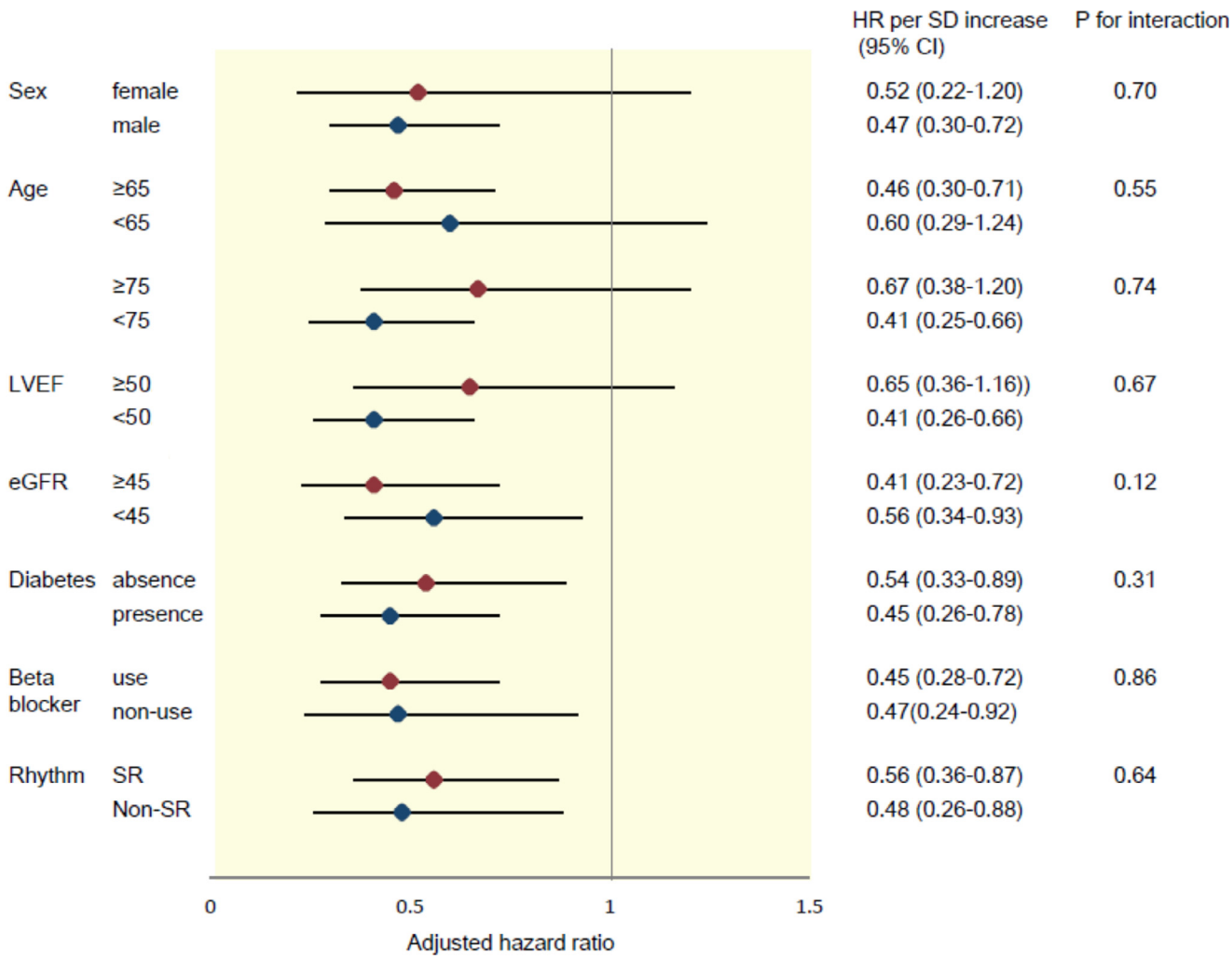

Fig. 3. Forest plot of hazard ratio (HR) for association of recovery time (time to 63% redilation) with mortality. Adjusted for the Seattle Heart Failure Score, body mass index, log B-type natriuretic peptide, and estimated glomerular filtration rate (eGFR). CI, confidence interval; LVEF, left ventricular ejection fraction; SR, sinus rhythm.

0.69 (95% CI 0.62−0.76) and 0.77 (95% CI 0.72−0.83), respectively (Fig. 4). The AUC for SHFS plus recovery time was significantly greater than that for SHFS only ($P < .001$).

Discussion

The results of the present study indicated that recovery time (time to 63% redilation) was independently associated with all-cause mortality and showed prognostic predictive capability complementary to SHFS in HF patients. When adjusted by heart rhythm, recovery time was consistently associated with all-cause mortality in both SR and non-SR HF patients. These results suggested that measuring PLR, which is a rapid, easy, and noninvasive method, can be used for risk stratification in HF patients. Previous studies confirmed the accuracy of PLR measurement,[25,26] and the examination conditions used in our study were identical for all patients, adding to the reliability of the results presented here.

Previous studies indicated that autonomic dysfunction assessed by heart rate variability was correlated with poor prognosis in patients with HF. In a study in patients with symptomatic HF, Adamson et al reported that the rates of all-cause mortality and readmission were higher in the group with low heart rate variability.[27] La Rovere et al reported that autonomic indexes obtained according to heart rate variability had independent predictive value for long-term outcome in HF patients from the GISSI-HF trial database.[8] However, non-SR patients were excluded from those studies because heart rate variability could not be used to assess their autonomic function.

The PLR can be measured with the use of a simple noninvasive method and provides insight into the balance of both branches of the autonomic nervous system,[28,29] and it has been shown to be correlated with heart rate variability.[30] PLR assessment has been used as a measure of autonomic function in multiple other conditions, including depression,[31] generalized anxiety disorder,[32] Alzheimer disease,[33] Parkinson disease,[33] hypertension,[34] obstructive sleep apnea,[35]

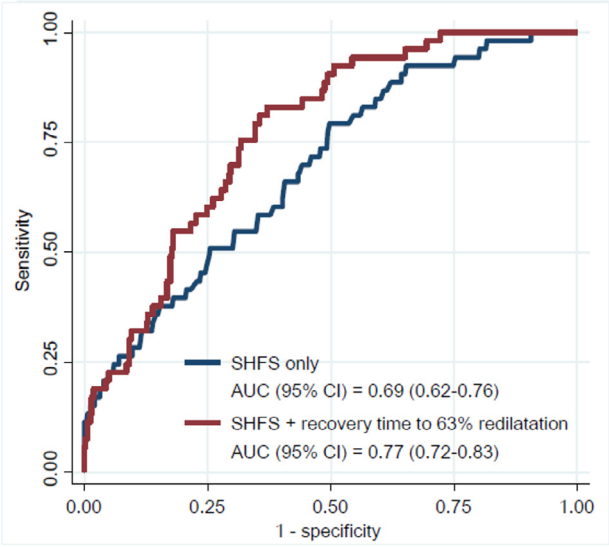

Fig. 4. Receiver operating characteristic curve of Seattle Heart Failure Score (SHFS) only and SHFS plus recovery time (time to 63% redilation) for all-cause mortality. The area under the curve (AUC) of SHFS plus recovery time (time to 63% redilatation) was significantly greater than that of SHFS only ($P < .001$). CI, confidence interval.

diabetes mellitus,[22,28] and HF.[21] Keivanidou et al reported that the PLR variables including dilatation indices differed significantly between control subjects and patients with HF.[21]

However, none of the earlier studies examined the correlation between the PLR and prognosis in patients with HF. To our knowledge, this is the first report indicating an independent association between PLR and all-cause mortality in HF patients.

Among the 7 variables examined in this study, only recovery time was independently associated with all-cause mortality and showed predictive capability complementary to the SHFS. We have no clear explanation for this finding. However, Hashimoto et al reported that topical administration of the cholinolytic agent tropicamide to healthy subjects resulted in the strongest reduction in recovery time, and that recovery time was increased in healthy subjects by topical administration of the adrenolytic agent guanethidine among the 7 variables used in this study.[36] These results suggested that recovery time may be the strongest variable reflecting activation of sympathetic activity and suppression of parasympathetic activity, which are important contributor to disease progression in HF. However, the mechanism underlying the correlation between the PLR and prognosis of HF has yet to be determined.

The PLR has good reproducibility[37] and can be measured rapidly, easily, and noninvasively in routine clinical practice by means of pupillometry. Furthermore, the results of the present study suggest that the PLR could be used in non-SR HF patients in whom autonomic function could not be assessed quantitatively. Therefore, PLR may be an alternate method to evaluate autonomic function in patients with HF to provide prognostic information in addition to conventional risk factors. Indeed, the independent prognostic predictability of PLR was retained even after adjustment for a wide range of potential confounders.

Study Limitations

This study had several limitations. First, this was a relatively small retrospective study with limited follow-up. We included patients who underwent PLR measurement at hospital discharge. Missing data can cause biased estimates. Second, the device used in the present study (Iriscorder Dual C10641) has not been validated in non-Asian populations. Third, many (39%) of the patients in this study had diabetes mellitus, which may have had impaired PLR owing to sympathetic neuropathy. Although the results of subgroup analysis showed no significant interaction, the presence or absence of diabetes may have affected our results because we did not take the severity and duration of diabetes into consideration. Fourth, the PLR may not be used in patients with severe retinopathy or other ophthalmologic diseases, because pupil mobility may be affected, which could lead to false conclusions. Finally, we could not compare the prognostic predictive capability between PLR and other autonomic indices, including heart rate variability, in this study.

Conclusion

PLR assessed by recovery time (time to 63% redilation) was shown to be an independent predictor of prognosis and added prognostic information to the SHFS in both SR and non-SR HF patients. Our observations suggested that assessment of PLR by recovery time could be useful as a new noninvasive prognostic predictor in HF patients.

Disclosure

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