ORIGINAL RESEARCH ARTICLE

Prognostic value of pupil area for all-cause mortality in patients with heart failure

Kohei Nozaki[1]*, Nobuaki Hamazaki[1], Shohei Yamamoto[2,3], Kentaro Kamiya[3,4], Shinya Tanaka[5], Takafumi Ichikawa[1], Takeshi Nakamura[3], Masashi Yamashita[3], Emi Maekawa[6], Atsuhiko Matsunaga[3,4], Minako Yamaoka-Tojo[3,4] and Junya Ako[6]

[1]Department of Rehabilitation, Kitasato University Hospital, 1-15-1 Kitasato, Minami-ku, Sagamihara, Kanagawa 252-0375, Japan; [2]Department of Epidemiology and Prevention, Center for Clinical Sciences, National Center for Global Health and Medicine, Tokyo, Japan; [3]Department of Rehabilitation Sciences, Kitasato University Graduate School of Medical Sciences, Sagamihara, Japan; [4]Department of Rehabilitation, School of Allied Health Sciences, Kitasato University, Sagamihara, Japan; [5]Department of Rehabilitation, Nagoya University Hospital, Nagoya, Japan; [6]Department of Cardiovascular Medicine, Kitasato University School of Medicine, Sagamihara, Japan

Abstract

Aims The area of the pupil can be used as an indicator of autonomic function. However, the relation between pupil area and prognosis in heart failure (HF) patients remains unclear. This study was performed to examine whether pupil area can be used as a prognostic indicator in patients with HF.

Methods and results This retrospective review was performed in 870 consecutive patients (mean age: 67.0 ± 14.1 years, 37.0% women) hospitalized for acute HF. Pupil area was measured with a pupilometer at least 7 days after hospitalization for HF. The primary endpoint was all-cause mortality, and the secondary endpoint was readmission due to HF. A total of 131 patients died, and 328 patients were readmitted because of HF over a median follow-up of 1.9 (interquartile range: 1.0–3.7 years) years. After adjustment for several pre-existing prognostic factors, including Seattle Heart Failure Score (SHFS), pupil area was shown to be independently associated with all-cause mortality (hazard ratio: 0.72; 95% confidence interval: 0.59–0.88; $P = 0.001$) and readmission due to HF (hazard ratio: 0.82; 95% confidence interval: 0.73–0.93; $P = 0.003$). Addition of pupil area to SHFS significantly increased the area under the receiver-operating characteristic curve for all-cause mortality (0.69 vs. 0.72, respectively; $P = 0.034$).

Conclusions Pupil area is an independent predictor of all-cause mortality and readmission due to HF and adds prognostic information to SHFS in patients with HF. The results presented here suggest that pupil area may be useful as a prognostic marker in patients with HF.

Background

Heart failure (HF) is one of the leading causes of death around the world.[1] The high mortality rate associated with HF is influenced by a number of pathophysiological factors, among which neuroendocrine dysregulation is one of the most important.[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] Generally, autonomic function is evaluated on the basis of heart rate variability as determined by Holter electrocardiography,[6] and its clinical implications have been demonstrated in patients with HF.[7,8] However, these methods are not applicable in patients with non-sinus rhythm (SR) HF.[9] Atrial fibrillation is one of the leading types of sustained arrhythmia in HF. Previous studies in large representative HF cohorts indicated prevalence rates of 20–50% for both atrial fibrillation and non-SR.[9–12] Measurement of heart rate variability requires continuous electrocardiogram monitoring for 24 h, which is time consuming and is not always possible in all patients.

The radius of the pupil is controlled by both the sympathetic and the parasympathetic autonomic nervous systems in response to environmental light, via a mechanism referred to as the pupillary light reflex (PLR). We reported previously that PLR was useful to predict the prognosis in patients with HF.[13] However, measurement of PLR can be difficult, especially in older patients because it requires them to keep their eyes open for 5 s. On the other hand, pupil area is useful as an index of autonomic function and can be measured more easily than PLR because the result can be obtained instantaneously and does not require the patient to keep their eyes open for several seconds.

We postulated that pupil area may have prognostic predictive capability, and this study was performed to investigate whether pupil area can be used as a novel prognostic marker in patients with HF.

Methods

Study population

A retrospective review was performed in an initial population of 2074 consecutive patients admitted to Kitasato University Hospital between January 2012 and December 2017 with acute HF who did not fulfil the following exclusion criteria: (i) missing pupil area measurement; (ii) age < 18 years; and (iii) a history of any ocular operations or diseases that would affect pupil function. Acute HF was defined according to the Framingham criteria.[14] All patients underwent cardiac rehabilitation during the period of hospitalization, and PLR was measured to evaluate autonomic function as an outcome of cardiac rehabilitation. This 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 the patients' 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 using 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: $194 \times$ (serum creatinine)$^{1.094} \times$ (age)$^{0.287}$ in men and $194 \times$ (serum creatinine)$^{1.094} \times$ (age)$^{0.287} \times 0.739$ in women.[15] The left ventricular ejection fraction (LVEF) was estimated using Simpson's method on two-dimensional echocardiograms. The Seattle Heart Failure Score (SHFS) was derived in each patient from 14 variables (age, sex, New York Heart Association functional classification, LVEF, ischaemic aetiology, systolic blood pressure, diuretic agent dose, allopurinol use, statin use, lymphocyte percentage, serum sodium, cholesterol, haemoglobin, and uric acid).[16]

Pupil area measurement

Pupil area measurement was performed on both eyes at least 7 days after hospitalization for HF using 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. A 5-min period was allowed for dark adaptation after the goggles were set on the patient's face and the patient's eyes were fully covered.[17] All patients were tested once between 09:00 and 12:00.[18]

Endpoint

The primary endpoint of this study was all-cause mortality, and the secondary endpoint was the rate of readmission due to HF. In addition, we also investigated whether the cause of death was cardiovascular or non-cardiovascular. The time for the endpoint was calculated as the number of days from the date of pupil area measurement to the date of the event.

Statistical analyses

The results of normally distributed continuous variables are expressed as means (±standard deviation), and variables without a normal distribution are presented as the median (interquartile range). Categorical variables are expressed as numbers and percentages. For missing data on confounders, we performed multiple imputation using the chained equations method, assuming that analysed data were missing at random. The results from 20 imputed data sets were combined for analysis using Rubin's formula.[19] Patients were divided into the small pupil area group and large pupil area group according to the median pupil area. Baseline characteristics were compared using the unpaired Student's *t* test or the Mann–Whitney *U* test for continuous variables and the χ^2 test or Fisher's exact test for categorical variables as appropriate.

The influence of pupil area on survival was examined using the Kaplan–Meier method with the log-rank test. In addition, multivariable Cox regression analysis was performed for pupil area by constructing two associative models using

pre-existing 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. The dose–response correlation between pupil area and mortality risk was also assessed using a Cox regression model with spline functions with three knots at quartiles of the independent variable. Moreover, sensitivity analysis was performed to address reverse causality after excluding patients who died within the first 6 months of follow-up. Furthermore, to investigate the potential effect modification on the association of pupil area with mortality, we performed subgroup analyses of pupil area in various subgroups relevant to HF prognosis, including sex, age (stratified at 65 and 75 years), LVEF (stratified at 40% and 50%), eGFR (stratified at 45 mL/min/1.73 m^2), history of diabetes and

prior HF admission, beta-blocker use, and heart rhythm (SR or non-SR) with adjustment for SHFS, BMI, log BNP, and eGFR. Finally, to examine whether the pupil area had complementary predictive capability to SHFS, receiver-operating characteristic curves were constructed for all-cause mortality during the study period using the SHFS only and SHFS plus pupil area models. The areas under the curves (AUCs) were compared according to the method of DeLong et al.[20]

Analyses were performed using SPSS version 25.0 (IBM Corporation, Armonk, NY, USA), Stata version 15.0 (StataCorp LP, College Station, TX, USA), and R version 2.5-1 (R Foundation for Statistical Computing, Vienna, Austria). In all analyses, a two-tailed $P < 0.05$ was taken to indicate statistical significance.

Table 1 Patient characteristics stratified according to pupil area

	Overall (n = 870)	Small pupil area (n = 434)	Large pupil area (n = 436)	P value
Age (years)	67.0 ± 14.1	69.8 ± 10.8	64.5 ± 14.9	<0.001
Female (%)	322 (37.0)	155 (35.7)	167 (38.3)	0.587
Height (cm)	160.7 ± 10.1	159.7 ± 10.0	161.8 ± 10.2	0.403
Body weight (kg)	57.8 ± 14.2	56.3 ± 12.2	59.4 ± 15.9	<0.001
BMI (kg/m²)	22.3 ± 5.5	22.1 ± 4.8	22.6 ± 6.1	0.011
SBP (mmHg)	118 ± 29	119 ± 29	116 ± 28	0.738
DBP (mmHg)	69 ± 19	68 ± 19	70 ± 19	0.291
HR (bpm)	82 ± 20	81 ± 20	83 ± 21	0.244
Non-SR (%)	286 (32.9)	157 (36.2)	129 (29.6)	0.036
LVEF (%)	47.4 ± 16.9	47.8 ± 16.9	47.1 ± 16.9	0.870
LVEF < 40%	316 (36.3)	154 (35.3)	163 (37.5)	0.578
LVEF ≥ 50%	429 (49.3)	215 (49.3)	214 (49.2)	0.867
NYHA functional class				
I/II	693 (79.7)	328 (75.2)	365 (83.7)	0.028
III/IV	177 (20.3)	106 (24.4)	71 (16.3)	< 0.001
SHFS	0.95 (0.41–1.57)	1.09 (0.56–1.67)	0.76 (0.22–1.44)	<0.001
Pupil area (mm²)	16.6 (12.0–21.8)	11.9 (8.9–14.2)	21.8 (19.2–26.0)	<0.001
Medications (%)				
ACE inhibitor or ARB	700 (80.4)	354 (81.6)	346 (79.4)	0.588
Beta-blocker	637 (73.2)	315 (72.6)	322 (73.9)	0.934
Aldosterone blockers	411 (47.2)	189 (43.5)	222 (50.9)	0.097
Diuretic agents	680 (78.2)	344 (79.3)	336 (77.1)	0.644
Statin	398 (45.7)	223 (51.4)	175 (40.1)	0.061
Comorbidities (%)				
Hypertension	518 (59.5)	277 (63.8)	241(55.3)	0.102
Diabetes mellitus	301 (34.6)	177 (40.8)	124 (28.4)	0.078
Dyslipidaemia	377 (43.3)	199 (45.9)	178 (40.8)	0.127
Atrial fibrillation	236 (27.1)	130 (30.0)	106 (24.3)	0.067
Ischaemic aetiology	278 (32.0)	138 (31.8)	140 (32.0)	<0.001
Prior HF admission	366 (42.1)	197 (45.4)	169 (38.8)	0.045
Current smoker (%)	154 (17.7)	58 (13.4)	96 (22.0)	0.001
Laboratory data				
Haemoglobin (g/dL)	11.9 (10.4–13.7)	11.5 (10.2–13.4)	12.2 (10.6–14.1)	<0.001
Albumin (g/dL)	3.6 (3.2–3.9)	3.6 (3.2–3.9)	3.6 (3.2–4.0)	0.445
LDL cholesterol (mg/dL)	92.0 (72.0–114.0)	87.0 (68.5–108.0)	98.0 (77.0–119.5)	<0.001
Sodium (mEq/L)	139.0 (136.8–140.0)	139.0 (136.0–140.0)	139.0 (137.0–140.0)	0.691
eGFR (mL/min/1.73 m²)	51.0 (35.0–65.0)	46.0 (31.6–59.6)	56.5 (40.0–68.4)	<0.001
hs-CRP (mg/dL)	0.32 (0.1–1.0)	0.34 (0.11–1.04)	0.30 (0.10–0.93)	0.426
BNP (pg/mL)	294.9 (134.0–639.5)	311.8 (155.8–657.8)	268.7 (114.8–599.6)	0.027
All-cause mortality (%)	131 (15.0)	87 (20.0)	44 (10.1)	<0.001
Cardiovascular death (%)	90 (10.3)	61 (14.1)	29 (6.7)	<0.001
Readmission due to HF (%)	328 (37.7)	205 (47.2)	123 (28.2)	<0.001

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, heart rate; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SBP, systolic blood pressure; SHFS, Seattle Heart Failure Score; SR, sinus rhythm.

Results

Study population

After excluding patients for whom pupil area measurements were not available (*n* = 694), those <18 years old (*n* = 8), and those with a history of any ocular operations or diseases (*n* = 498), 870 patients were included in this study.

Table 1 shows the baseline characteristics of all patients and groups stratified according to pupil area. The mean age of the total patient population was 67.0 ± 14.1 years, 37.0% of patients were female, 32.8% were classified as non-SR, and 36.3% had reduced LVEF. Beta-blockers were prescribed at discharge for 74.1% of the patients, 80.4% received angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and 78.1% received diuretic agents. The median of pupil area was 16.6 mm^2. Relative to the large pupil area group, patients in the small pupil area group were older and had lower body weight, BMI, haemoglobin, low-density lipoprotein cholesterol, and eGFR and had greater severity of HF (e.g. SHFS and New York Heart Association functional classification) and prevalence of prior HF admission.

Association between pupil area and prognosis

A total of 131 deaths due to all causes and 328 readmissions due to HF occurred in the patient population over a median follow-up period of 1.9 years (interquartile range: 1.0–

3.7 years). Cardiovascular deaths occurred in 90 patients. Patients with small pupil area had significantly higher rates of cardiovascular death (61 in the pupil area group vs. 29 in the large pupil area group; *P* < 0.001). Kaplan–Meier survival curve followed by log-rank test is shown in *Figure 1*. The survival rate was significantly lower, and rate of readmission due to HF was higher in the small pupil area group than the large pupil area group (both *P* < 0.001). *Table 2* shows the results of Cox regression analysis for all-cause mortality and readmission due to HF. Even after adjusting for prognostic models, pupil area was a significant and independent predictor of all-cause mortality [hazard ratio (HR): 0.72; 95% confidence interval (CI): 0.59–0.88; *P* = 0.001] and readmission due to HF (HR: 0.82; 95% CI: 0.73–0.93; *P* = 0.003) in our cohort.

As shown in *Figure 2*, smaller pupil area was significantly correlated with increased risk of all-cause mortality in patients with HF.

Sensitivity analysis excluding patients who died within 6 months of follow-up did not noticeably affect the estimated association between pupil area and all-cause mortality (adjusted HR: 0.71; 95% CI: 0.57–0.90; *P* = 0.005).

Larger pupil area was consistently associated with favourable prognosis across various subgroups, even after adjusting for SHFS, BMI, BNP, and eGFR (*Figure 3*). The favourable effect of larger pupil area was comparable between SR and non-SR groups (SR, HR: 0.65; 95% CI: 0.48–0.88; non-SR, HR: 0.76; 95% CI: 0.57–1.00; *P* for interaction = 0.109).

Figure 1 Kaplan–Meire curve for all-cause mortality and readmission due to HF according to pupil area. Survival rate was significantly poorer and rate of readmission due to HF was significantly higher in the small pupil area group than the large pupil area group. HF, heart failure.
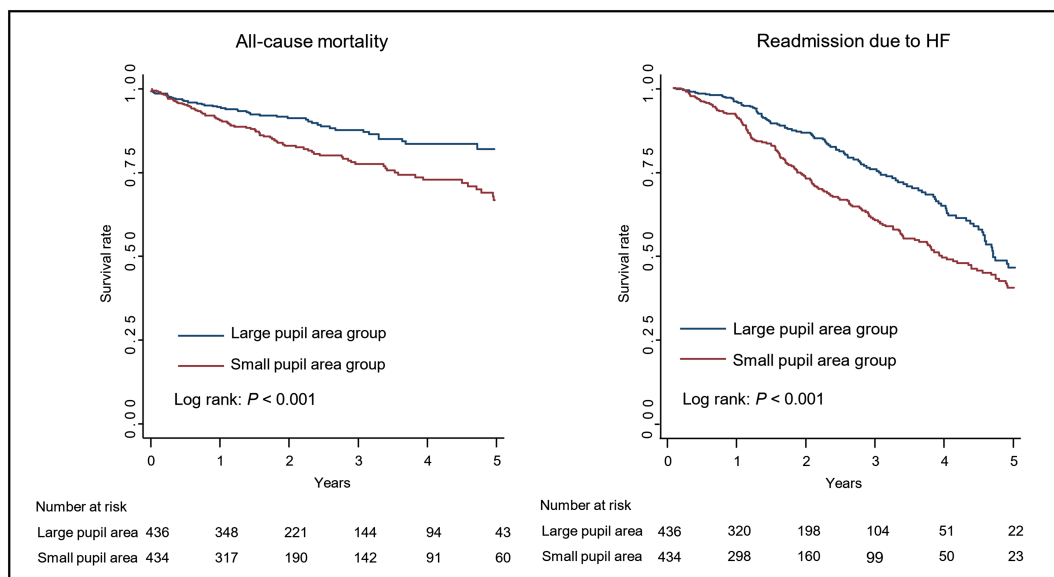
Table 2 Univariate and multivariate Cox regression models for all-cause mortality and readmission due to HF

	Univariate			Model 1			Model 2		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
All-cause mortality	0.62	0.51–0.75	<0.001	0.69	0.57–0.84	<0.001	0.72	0.59–0.88	0.001
Readmission due to HF	0.72	0.65–0.82	<0.001	0.78	0.70–0.88	<0.001	0.82	0.73–0.93	0.003

Model 1 was adjusted by Seattle Heart Failure Score, whereas Model 2 was adjusted by Seattle Heart Failure Score, body mass index, B-type natriuretic peptide, and estimated glomerular filtration rate.
CI, confidence interval; HF, heart failure; HR, hazard ratio.

Figure 2 Restricted cubic spline of associations of pupil area 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 pupil area. Hazard ratios were estimated from Cox proportional hazards models. CI, confidence interval.
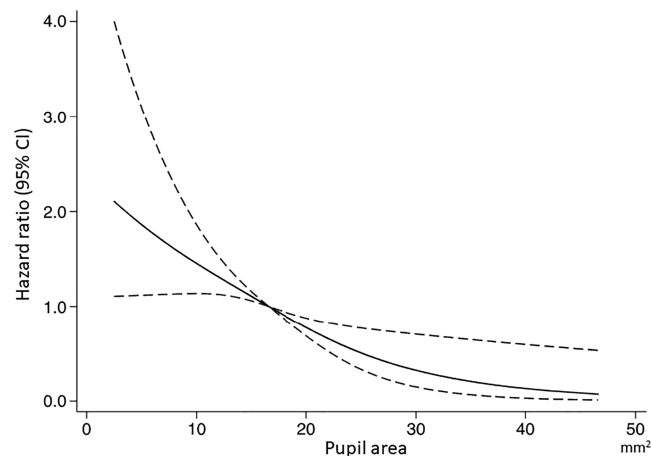
Complementary prognostic predictive capability of pupil area to Seattle Heart Failure Score

The AUCs on receiver-operating characteristic curve analysis for the SHFS only and SHFS plus pupil area logistic regression models were 0.69 (95% CI: 0.65–0.74) and 0.72 (95% CI: 0.66–0.78), respectively (*Figure 4*). The AUC for SHFS plus pupil area was significantly greater than that for SHFS only (*P* = 0.034).

Discussion

The results of the present study indicated that pupil area was independently associated with all-cause mortality and showed complementary prognostic predictive capability to SHFS in HF patients. When adjusted by heart rhythm, pupil area was consistently associated with all-cause mortality in both SR and non-SR HF patients. These results suggested that pupil area, which can be determined rapidly, easily, and non-invasively, can be used for risk stratification in HF patients. In addition, previous studies confirmed the accuracy of pupil area measurement, and the examination conditions used in our study were identical for all patients, thus 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 previous study in patients with symptomatic HF, Adamson *et al*. reported that the rates of all-cause mortality and readmission were higher in the low heart rate variability group.[21] La Rovere *et al*. reported that autonomic indexes obtained by heart rate variability showed independent predictive value for long-term outcome in HF patients from the GISSI-HF trial database.[7] However, these studies excluded non-SR patients because their autonomic function could not be assessed on the basis of heart rate variability.

Pupil area measurement is a simple, non-invasive method that provides insight into the balance of both branches of the autonomic nervous system.[22] Pupil area assessment has been used as a measure of autonomic function in a number of other conditions, including rheumatoid arthritis,[23] Alzheimer's disease,[24] Parkinson's disease,[24] obstructive sleeping apnoea,[25] and diabetes mellitus.[22,26] However, none of these previous studies examined the correlation between

Figure 3 Forest plots of subgroup analyses of the associations between pupil area and all-cause mortality. All subgroups were adjusted for the Seattle Heart Failure Score, body mass index, log B-type natriuretic peptide, and eGFR. CI, confidence interval; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; SR, sinus rhythm.
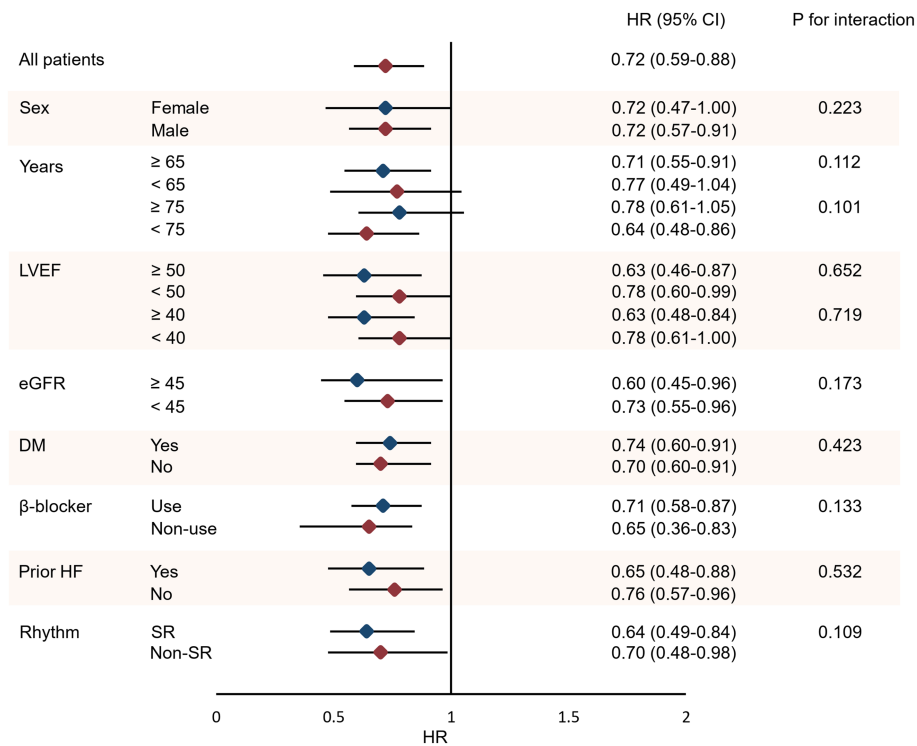
		HR (95% CI)	P for interaction
All patients		0.72 (0.59–0.88)	
Sex	Female	0.72 (0.47–1.00)	0.223
	Male	0.72 (0.57–0.91)	
Years	≥ 65	0.71 (0.55–0.91)	0.112
	< 65	0.77 (0.49–1.04)	
	≥ 75	0.78 (0.61–1.05)	0.101
	< 75	0.64 (0.48–0.86)	
LVEF	≥ 50	0.63 (0.46–0.87)	0.652
	< 50	0.78 (0.60–0.99)	
	≥ 40	0.63 (0.48–0.84)	0.719
	< 40	0.78 (0.61–1.00)	
eGFR	≥ 45	0.60 (0.45–0.96)	0.173
	< 45	0.73 (0.55–0.96)	
DM	Yes	0.74 (0.60–0.91)	0.423
	No	0.70 (0.60–0.91)	
β-blocker	Use	0.71 (0.58–0.87)	0.133
	Non-use	0.65 (0.36–0.83)	
Prior HF	Yes	0.65 (0.48–0.88)	0.532
	No	0.76 (0.57–0.96)	
Rhythm	SR	0.64 (0.49–0.84)	0.109
	Non-SR	0.70 (0.48–0.98)	

Figure 4 Receiver-operating characteristic curves of SHFS only and SHFS plus pupil area for all-cause mortality. The AUC of SHFS plus pupil area was significantly greater than that of SHFS only. AUC, area under the curve; SHFS, Seattle Heart Failure Score.

SHFS
AUC = 0.69

SHFS + pupil area
AUC = 0.72
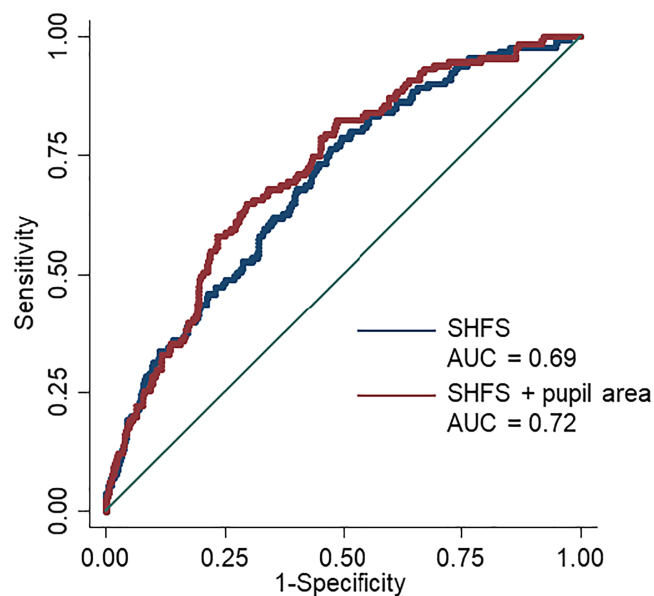
pupil area and prognosis in patients with HF. To our knowledge, this is the first study to indicate an independent association between PLR and all-cause mortality in HF patients.

We used the SHFS as an adjusting variable, because this is one of the best risk scores for HF with the use of easily obtained clinical characteristics, which provides an accurate estimate of survival (AUC for 1-year survival: 0.725). In the present study, although the AUC for prediction of all-cause mortality was greater when pupil area was added to SHFS, the AUCs were low compared with the original report. Shiraishi *et al*. investigated the validity of the SHFS in Japanese HF patients and concluded that the SHFS showed adequate performance in Japanese HF patients with reduced ejection fraction but not in HF patients with preserved ejection fraction (AUCs for 1-year survival: 0.75 and 0.69, respectively).[27] We believe that the AUCs for all-cause mortality were small because the number of HF patients with reduced ejection fraction was lower in our study.

Typical autonomic nervous dysregulation in HF involves sympathetic activation or parasympathetic suppression, in which the pupil is dilated, thus increasing its area. However, the results of the present study suggested that small pupil area was associated with poor prognosis in patients with HF. Although the mechanism underlying this association has yet to be determined, we postulated that it may be similar to the mechanism of chronotropic incompetence. Chronotropic incompetence is defined as the inability to adequately increase heart rate during exercise to match cardiac output to metabolic demands and is associated with poor exercise tolerance and high mortality rate.[28,29] Autonomic dysfunction has been reported to be responsible for chronotropic incompetence.[30] We measured pupil area after dark adaptation in this study, and the pupils commonly dilate in the dark because of appropriate autonomic nervous activity. However, in patients with HF, it is possible that dysregulation of the pupil occurred because of autonomic dysfunction, which would prevent the pupil from dilating appropriately in the dark. HF was more severe in the small pupil area group than the large pupil area group in the present study, and the degree of autonomic dysfunction may have been more severe in the former.

Measurement of pupil area has good reproducibility and can be obtained rapidly, easily, and non-invasively in routine clinical practice by pupillometry. The results of the present study suggested that pupil area could be used in non-SR HF patients in whom autonomic function could not be assessed quantitatively using existing methods. Therefore, measurement of pupil area may be a useful alternative method to evaluate autonomic function in patients with HF, which is capable of providing additional prognostic information to conventional risk factors. Indeed, the independent prognostic predictive capability of pupil area was retained even after adjustment for a wide range of potential confounding factors in the present study.

Limitations

This study had several limitations. First, this was a relatively small retrospective study with limited follow-up. The study population consisted of patients undergoing pupil area measurement at hospital discharge. Missing data can cause biased estimates. Second, pupil area may not be used in patients with severe retinopathy or other ophthalmological diseases because these conditions may affect pupil mobility, which could lead to false conclusions. Finally, we could not compare the prognostic predictive capability between pupil area and other autonomic indices, including heart rate variability, in this study.

Conclusions

Pupil area was shown to be an independent predictor of prognosis and added prognostic information to SHFS in both SR and non-SR HF patients. Our observations suggested that assessment of pupil area could be a useful new non-invasive prognostic predictor in HF patients.

Conflict of interest

None declared.

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Author contributions

The contributions of all authors are as follows: K.N., N.H., and K.K. interpreted the data and wrote the paper; S.T. and E.M. designed the study; T.I., T.N., and S.Y. collected and analysed data; S.Y. provided statistical support and conceptual advice; and M.T., A.M., and J.A. drafted and critically revised the manuscript for important intellectual content.

All of the authors have read and approved the final version of the manuscript.

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