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SHORT COMMUNICATION

Plasma P-selectin is a predictor of mortality in heart failure with preserved ejection fraction

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Abstract

Aims The aim of the study was to assess the association of P-selectin with outcomes in heart failure with preserved ejection fraction (HFpEF).

Methods and results This is a prospective, observational study of 130 HFpEF patients who underwent clinical profiling, blood sampling, 6 min walk testing, Minnesota Living with Heart Failure Questionnaire evaluation, echocardiography, cardiovascular magnetic resonance imaging, calculation of the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) risk scores, and blinded plasma P-selectin measurement. Patients were followed up for the endpoint of all-cause mortality. The HFpEF subgroup with higher P-selectin levels [overall median 26 372, inter-quartile range (19 360–34 889) pg/mL] was associated with lower age, higher heart rate, less prevalent atrial fibrillation, more frequent current smoking status, and lower right ventricular end-diastolic volumes. During follow-up (median 1428 days), there were 38 deaths. Following maximal sensitivity and specificity receiver operating characteristic curve analysis, P-selectin levels above 35 506 pg/mL were associated with greater risk of all-cause mortality [hazard ratio (HR) 2.700; 95% confidence interval (CI) 1.416–5.146; log-rank $P = 0.002$]. Following multivariable Cox proportional hazards regression analysis and when added to MAGGIC scores, only P-selectin (adjusted HR 1.707; 95% CI 1.099–2.650; $P < 0.017$) and myocardial infarction detected by cardiovascular magnetic resonance imaging (HR 2.377; 95% CI 1.114–5.075; $P < 0.025$) remained significant predictors. In a final model comprising all three parameters, only P-selectin (HR 1.447; 95% CI 1.130–1.853; $P < 0.003$) and MAGGIC scores (HR 1.555; 95% CI 1.136–2.129; $P < 0.006$) remained independent predictors of death. Adding P-selectin (0.618, $P = 0.035$) improved the area under the receiver operating characteristic curve for mortality prediction for MAGGIC scores (0.647, $P = 0.009$) to 0.710, $P < 0.0001$.

Conclusions Plasma P-selectin is an independent predictor of mortality and provides incremental prognostic information beyond MAGGIC scores in HFpEF.

Keywords P-selectin; Mortality; Heart failure with preserved ejection fraction; Meta-Analysis Global Group in Chronic Heart Failure risk score

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Background

Selectins of cell adhesion molecules are integral mediators of platelet activation and endothelial function[1] and have been implicated in the pathophysiology of heart failure (HF) with preserved ejection fraction (HFpEF).[2] P-selectin is the largest of the selectins, and its increased expression has previously shown adverse association with outcomes across a range of cardiovascular disease[1] including coronary artery disease, hypertension, atrial fibrillation (AF), and HF with reduced ejection fraction.[3] However, there are limited data for its prognostic utility in HFpEF,[4] a condition currently with no effective therapies.[2]

Table 1 Baseline demographics stratified according to median P-selectin and Cox proportional hazards regression analysis

	HFpEF ≤ median P-selectin (≤26 372 pg/mL) *n* = 65	HFpEF > median P-selectin (>26 372 pg/mL) *n* = 65	*P* value	Univariable predictors of outcome		Multivariable predictors of outcome (when added to MAGGIC score)	
				Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Demographics							
Age (years)[a]	74 ± 9	71 ± 10	0.040	—	—	—	—
Male (%)[a]	32 (49)	33 (51)	0.861	—	—	—	—
Heart rate (b.p.m.)	68 ± 12	73 ± 15	0.042	—	NS		
Systolic BP (mmHg)[a]	150 ± 24	142 ± 26	0.065	—	—	—	—
Diastolic BP (mmHg)	75 ± 13	74 ± 12	0.901	0.668 (0.474–0.942)	0.022	0.763 (0.521–1.119)	0.166
Body mass index (kg/m^2)[a]	34 ± 8	33 ± 6	0.471	—	—	—	—
Prior HF hospitalization (%)	41 (63)	44 (68)	0.580	1.958 (0.925–4.142)	0.079	1.844 (0.870–3.907)	0.110
Atrial fibrillation (%)	26 (40)	15 (23)	0.038	—	NS		
Diabetes (%)[a]	31 (48)	34 (52)	0.599	—	—	—	—
Hypertension (%)	59 (91)	59 (91)	1.000	—	NS		
COPD[a]	7 (11)	9 (14)	0.593	—	—	—	—
Smoking history (%)	30 (46)	38 (58)	0.160	—	NS		
Current smoker (%)[a]	2 (3)	8 (12)	0.048	—	—	—	—
Beta-blocker (%)[a]	44 (68)	45 (69)	0.850	—	—	—	—
ACEi or ARB (%)[a]	55 (85)	57 (88)	0.612	—	—	—	—
Aldosterone antagonist (%)	21 (32)	20 (31)	0.850	—	NS		
Loop diuretic (%)	56 (86)	49 (75)	0.119	4.837 (1.164–20.100)	0.030	3.914 (0.925–16.562)	0.064
NYHA—III/IV (%)[a]	23 (35)	17 (26)	0.182	—	—	—	—
6 min walk test distance (m)	180 (100–250)	190 (133–260)	0.215	—	NS		
MLHF score	49 (25–62)	47 (25–67)	0.902	—	NS		
MAGGIC score	20 ± 6	19 ± 6	0.121	1.516 (1.097–2.095)	0.012	—	—
Blood							
Urea (mmol/L)	8 ± 4	9 ± 4	0.245	—	NS		
Creatinine (mmol/L)[a]	88 (73–113)	89 (75–117)	0.852	—	—	—	—
eGFR	65 (53–83)	68 (53–83)	0.978	—	NS		
Haemoglobin (g/L)	126 ± 18	132 ± 26	0.176	0.703 (0.500–0.988)	0.043	0.786 (0.554–1.116)	0.178
BNP (pg/mL)	152 (84–261)	113 (51–260)	0.142	1.427 (0.985–2.066)	0.060	1.302 (0.881–1.923)	0.186
P-selectin (pg/mL)	19 382 (15 743–24 578)	34 730 (29 435–40 771)	<0.00001	1.610 (1.029–2.521)	0.037	1.707 (1.099–2.650)	0.017
Echocardiography							
E/e′	13 ± 5	13 ± 5	0.545	1.340 (0.974–1.844)	0.072	1.178 (0.820–1.692)	0.376
CMR							
LVEF (%)[a]	57 ± 5	55 ± 5	0.084	—	—	—	—
LVEDVI (mL/m^2)	81 ± 18	78 ± 20	0.359	—	NS		
LVESVI (mL/m^2)	35 ± 10	35 ± 11	0.979	—	NS		
LVMI (g/m^2)	53 ± 16	52 ± 14	0.674	1.358 (1.003–1.837)	0.048	1.350 (0.980–1.861)	0.066
LV remodelling—mass/LV volume	0.66 ± 0.14	0.68 ± 0.18	0.440	—	NS		
RVEF (%)	54 (49–61)	55 (48–60)	0.758				
RVEDVI (mL/m^2)	85 ± 20	76 ± 18	0.016	1.348 (0.993–1.829)	0.055	1.254 (0.918–1.712)	0.155
RVESVI (mL/m^2)	40 ± 15	35 ± 13	0.051	1.390 (1.032–1.873)	0.030	1.325 (0.970–1.811)	0.077
LAVImax (mL/m^2)	58 ± 28	49 ± 23	0.057	1.369 (1.011–1.854)	0.043	1.303 (0.960–1.768)	0.089

(*Continues*)

Table 1 (continued)

	HFpEF ≤ median P-selectin (≤26 372 pg/mL) $n = 65$	HFpEF > median P-selectin (>26 372 pg/mL) $n = 65$	*P* value	Univariable predictors of outcome		Multivariable predictors of outcome (when added to MAGGIC score)	
				Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
LAEF (%)	30 ± 17	34 ± 16	0.159	—	NS		
LGE positive—MI (%)	8 (12)	12 (18)	0.331	2.147 (1.012–4.551)	0.046	2.377 (1.114–5.075)	0.025
ECV (%)	29 ± 5	27 ± 4	0.097	—	NS		
iECV	14 ± 4	14 ± 4	0.732	—	NS		

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BNP, B-type natriuretic peptide; b.p.m., beats per minute; BP, blood pressure; CI, confidence interval; CMR, cardiovascular magnetic resonance imaging; COPD, chronic obstructive pulmonary disease; ECV, extracellular volume; eGFR, estimated glomerular filtration rate; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; iECV, indexed extracellular volume; LAEF, left atrial ejection fraction; LAVImax, maximal left atrial volume indexed; LGE, late gadolinium enhancement; LV, left ventricular; LVEDVI, left ventricular end-diastolic volume indexed to body surface area; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end-systolic volume indexed to body surface area; LVMI, left ventricular mass index; MAGGIC, Meta-Analysis Global Group in Chronic Heart Failure; MI, myocardial infarction; MLHF, Minnesota Living with Heart Failure Questionnaire; NS, not significant; NYHA, New York Heart Association; RVEDVI, right ventricular end-diastolic volume indexed to body surface area; RVEF, right ventricular ejection fraction; RVESVI, right ventricular end-systolic volume indexed to body surface area.
Six minute walk test distance, MLHF score, eGFR, and BNP were $\log_{10}$ transformed prior to outcome analysis. Values are mean ± SD, *n* (%), or median (inter-quartile range). The *P* values are for the *t*-test or χ^2 test.
[a]Parameters comprising the MAGGIC score.

Aims

The aim of the present study was to assess the association of P-selectin with mortality in a well-characterized group of HFpEF.

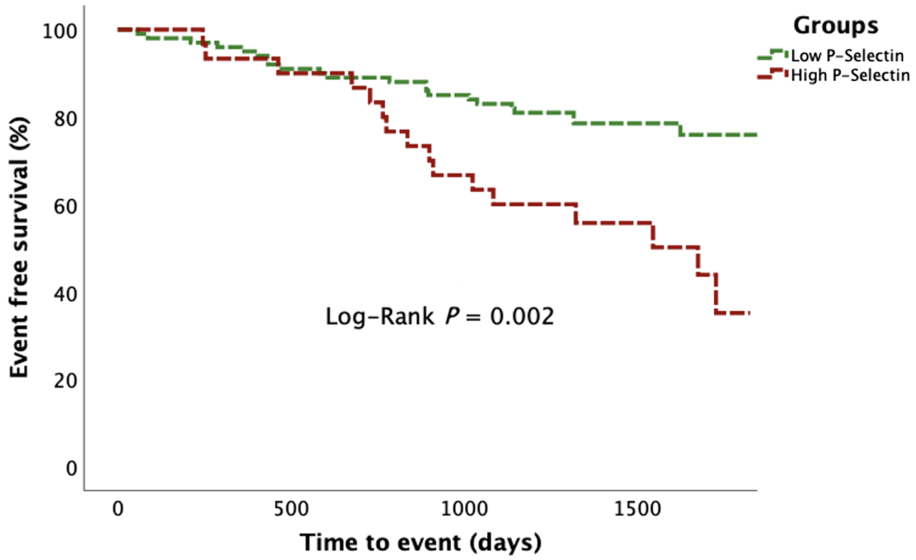
Methods

Patients were recruited from the Developing Imaging And plasMa biOmarkers iN Describing HFpEF (DIAMOND-HFpEF) study: a single-centre, prospective, observational cohort study as previously detailed.[5] All patients underwent clinical profiling, 6 min walk testing, Minnesota Living with Heart Failure Questionnaire evaluation, blood sampling [renal function, B-type natriuretic peptide (BNP), and haemoglobin], transthoracic echocardiography, and cardiovascular magnetic resonance imaging (CMR) during the same visit. Blinded single-batch testing of P-selectin levels was undertaken in 130 HFpEF patients from residual supernatant plasma stored at −80°C in cryotubes using a Luminex® bead-based multiplex assay (Bristol Myers Squibb, Princeton, New Jersey, USA), enabling high-throughput biomarker profiling as previously described.[6] Patients were followed up for the endpoint of all-cause mortality. BNP, 6 min walk test distance, and Minnesota Living with Heart Failure Questionnaire scores were $\log_{10}$ transformed prior to survival analysis. *Z*-standardization of continuous variables was undertaken to enable comparison of hazard ratios (HRs) based upon 1-SD increase in the predictor variable. In particular, we assessed the prognostic performance of P-selectin against a base model of the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) risk score: a validated, strong predictor of mortality in HFpEF.[7] The MAGGIC score comprises the following domains: age, ejection fraction, systolic blood pressure, body mass index, creatinine, New York Heart Association class, smoking status, diabetes, chronic obstructive pulmonary disease, time since HF first diagnosed, beta-blocker, and angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker usage. All components comprising MAGGIC scores were available for analysis except the time of HF diagnosis, for which no points were allocated.

Results

As reported previously,[5] CMR data to measure diffuse fibrosis, that is, extracellular volume and indexed extracellular volume, were not acquired in a subset of patients ($n = 46$). Baseline characteristics stratified according to overall median P-selectin levels [26 372, inter-quartile range (19 360–34 889) pg/mL] are shown in *Table 1*. The HFpEF subgroup with higher P-selectin levels was associated with lower

Figure 1 Kaplan–Meier survival analysis. Kaplan–Meier survival curves stratified according to high and low P-selectin levels (optimal threshold value—35 506 pg/mL) derived from maximal sensitivity and specificity receiver operating characteristic curve analysis.



age, higher heart rate, less prevalent AF, more frequent current smoking status, and lower right ventricular end-diastolic volumes. During median follow-up of 1428 days (1153–1663), there were 38 deaths. Using maximal sensitivity and specificity receiver operating characteristic (ROC) curve analysis, a P-selectin threshold value of >35 506 pg/mL best discriminated HFpEF patients into a subgroup with events. In Kaplan–Meier analysis (*Figure 1*), the group with P-selectin values above this threshold was associated with greater risk of all-cause mortality [HR 2.700; 95% confidence interval (CI) 1.416–5.146; log-rank $P = 0.002$]. Excluding components of the MAGGIC score, there were 12 parameters demonstrating univariate association with the endpoint of $P < 0.1$ including diastolic blood pressure, previous HF hospitalization, loop diuretic use, haemoglobin, BNP, echocardiographic E/E', indexed left ventricular mass indexed, indexed right ventricular end-diastolic and end-systolic volumes, indexed maximal left atrial volume, myocardial infarction detected by CMR, and plasma P-selectin. Following multivariable Cox proportional hazards regression analysis and when added to MAGGIC scores, only P-selectin (adjusted HR 1.707; 95% CI 1.099–2.650; $P < 0.017$) and myocardial infarction (HR 2.377; 95% CI 1.114–5.075; $P < 0.025$) remained significant predictors. In a final model comprising all three of the aforementioned parameters and following stepwise forward and backward selection methods, only P-selectin (HR 1.447; 95% CI 1.130–1.853; $P < 0.003$) and MAGGIC scores (HR 1.555; 95% CI 1.136–2.129; $P < 0.006$) remained independent predictors of death. The areas under the ROC curve for predicting all-cause mortality (see Supporting Information, *Figure S1*) were MAGGIC scores (0.647, $P = 0.009$) and P-selectin (0.618, $P = 0.035$). The addition of P-selectin to MAGGIC scores improved the area under the ROC curve to 0.710, $P < 0.0001$.

Conclusions

Our study is the first to demonstrate that P-selectin is strongly associated with mortality in an extensively characterized population with HFpEF encompassing clinical, biochemical, and gold-standard CMR imaging parameters. Furthermore, P-selectin levels appear to confer incremental prognostic information beyond MAGGIC scores and may help risk stratify HFpEF subjects into high-risk and lower-risk categories. While P-selectin levels are elevated in HF with reduced ejection fraction, there are conflicting data regarding association with adverse outcomes in this setting.[3,8] Our data in HFpEF corroborate and extend the signal for increased risk associated with P-selectin as recently demonstrated in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial study, which showed univariate association with outcomes but not when adjusted for MAGGIC scores.[4] In our study, even following similar adjustment as well as accounting for historically strong prognostic markers such as BNP and CMR-derived imaging parameters, P-selectin remained independently associated with mortality. We hypothesize that P-selectin is intimately involved in the milieu of inflammation, endothelial dysfunction, and microvascular dysfunction as proposed in the now widely accepted paradigm for HFpEF. Beyond its prognostic role, future studies are needed to explore whether P-selectin may serve as a potential biomarker of treatment response as well as a potential therapeutic target itself.[2] Our study limitations include the single-centre study design with a relatively small sample size, necessitating further evaluation in additional populations. The data for time of HF diagnosis were not available for many patients in our

study. However, this component was uniformly excluded from all patients for MAGGIC score derivation to minimize systematic bias. In addition, data regarding concomitant antiplatelet or antithrombotic therapies, which could potentially influence plasma levels of P-selectin, were not available. P-selectin has been proposed as a marker of vascular events such as thrombosis in HF previously,[1,8] and while we have presented data pertaining to all-cause mortality, stratification into cardiovascular vs. non-cardiovascular deaths is lacking. Contrary to our findings, a previous study[9] has reported an association of higher P-selectin levels in AF subjects. The smaller left atrial size (albeit of borderline significance, $P = 0.057$) and hence less prevalent AF in our higher P-selectin HFpEF subgroup likely partly explains this difference. Furthermore, the aforementioned study (AF $n = 90$; controls $n = 79$) excluded elderly subjects (>75 years) as well as those with hypertension, coronary artery disease, diabetes, and HF, which are additional, potential confounders.

In conclusion, plasma P-selectin is an independent predictor of mortality and provides incremental prognostic information beyond MAGGIC scores in HFpEF.

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Conflict of interest

None declared.

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Author contributions

P.K. recruited the patients, supervised the study visits, and CMR scans (with A.S. and J.N.K.), analysed the data, performed the statistical analysis, and drafted the initial manuscript along with J.R.A. G.S.G. undertook follow-up outcome data collection. P.K., I.B.S., L.L.N., and G.P.M. conceived the study. All authors critically revised the manuscript for important intellectual content, approved the final version for submission, and agreed to be accountable for all aspects of the work in ensuring that questions relating to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics statement

The study complied with the Declaration of Helsinki, and the National Research Ethics Service approved the study. Written informed consent was obtained from all subjects prior to participation.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Receiver operator characteristics analysis of MAGGIC scores, P-Selectin and the combined model to predict outcomes.

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