Initial Diastolic Dysfunction is a Powerful Predictor of 5-year Mortality in Peripheral Arterial Disease Patients undergoing Percutaneous Transluminal Angioplasty

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Abstract

Background

Peripheral arterial disease (PAD) and heart failure share common risks and are associated with increased morbidity and mortality. However, it is unknown whether cardiac function can be an independent predictor of long-term mortality in patients with PAD.

Methods

In total, 902 patients who underwent percutaneous transluminal angioplasty for PAD were enrolled. The patients were categorized into three groups according to the left ventricular ejection fraction (LVEF): reduced EF (< 40%, n = 62); mid-range EF (40–49%, n = 76); and preserved EF (≥ 50%, n = 764). Echocardiographic (EF, ratio of mitral inflow velocity to annular velocity E/e′ ≥ 15, and others) and clinical parameters were tested using stepwise logistic regression analysis to determine independent predictors of 5-year mortality.

Results

A higher proportion of patients with reduced EF had ischemic heart disease than those with preserved EF (77.4% vs. 56.8%, $p < 0.001$). Up to 5 years, patients with reduced EF and mid-range EF showed a higher incidence of total death than those with normal EF. However, there was no difference in the incidence of myocardial infarction, stroke, and revascularization among the three groups. After multivariable adjustment, the ratio of E/e′ ≥ 15 was the only strong predictor of total mortality (hazard ratio, 6.14; 95% confidence interval, 3.7–10.1;$p < 0.01$).

Conclusion

Patients with PAD and reduced EF undergoing PTA had a higher incidence of total death during the 5-year follow-up. Initial tissue Doppler E/e′ ≥ 15, a non-invasive estimate of left atrial filling pressure, was the only independent predictor of long-term mortality.

Introduction

Lower extremity peripheral arterial disease (PAD) is a manifestation of systemic atherosclerosis and is associated with increased cardiovascular morbidity and mortality [1)2)]. Patients with PAD have a 3-fold increased risk of death from all causes and a 6-fold increased risk of death from cardiovascular disease within a 10-year period when compared with patients without PAD [3)]. An estimated > 200 million people

have PAD worldwide, with a spectrum of symptoms ranging from none to severe [4)5)]. Despite the high morbidity and mortality, patients with PAD are often underdiagnosed and undertreated.

Although the reason for the poor prognosis in patients with PAD is unknown, high prevalence of coexistent cardiovascular disease (coronary artery disease, chronic heart failure [HF], or stroke) has frequently been mentioned as the likely cause of PAD occurrence [6)7)]. Patients with PAD have a high comorbidity burden, which has significant implications for clinical management.

However, the cardiac function of patients with PAD has not been studied systematically. Limited data are available on the association between cardiac function and PAD, especially in patients who underwent percutaneous transluminal angioplasty (PTA). In addition, diastolic dysfunction has not been yet reported in patients with PAD who underwent PTA, whereas left ventricular (LV) systolic dysfunction has been described[8)]. We aimed to evaluate the association between PAD and heart failure in patients with symptomatic PAD who underwent PTA. We also analyzed the effect of these abnormal cardiac findings on long-term cardiovascular outcomes in these patients.

Method

We obtained data from the PTA registry of Korea University Guro Hospital (KUGH), Seoul, South Korea. This registry has been described in detail in previous studies. This single-center, prospective, all-comers registry was started in 2004 and designed to reflect real-world clinical practice. The study protocol was approved by the Medical Device Institutional Review Board of KUGH (protocol #MD12018). The study population included a total of 902 consecutive patients with symptomatic PAD who underwent PTA of the iliac, femoral, popliteal, tibial, and peroneal arteries from September 2004 to August 2017. The data were collected by trained study coordinators using standardized case report forms [9)].

.Coronary and Peripheral Angiography and Revascularization

Standard techniques were used for PTA. Coronary and peripheral angioplasties were performed with a crossover approach or an anterograde ipsilateral femoral approach using 5 ~ 6 French sheaths. If there are significant coronary fixed stenosis (> 70% diameter stenosis), direct percutaneous coronary intervention (PCI) or staged PCI within the same hospitalization period was recommended and performed. Post-intervention dual antiplatelet therapy with aspirin 100 mg and clopidogrel 75 mg once daily or additional cilostazol 100 mg twice daily was given for at least 6 months, while aspirin 100 mg and/or clopidogrel 75 mg was given daily thereafter. Medications beneficial for cardiovascular health, including renin-angiotensin-aldosterone blockers, beta-blockers, and statins, were also prescribed according to practice guidelines.

Echocardiography

All patients underwent echocardiography examinations. Patients with transthoracic echocardiography (TTE) findings not suitable for the quantitative assessment of LV ejection fraction (LVEF) or diastology

were excluded. The ratio of the transmitral Doppler E wave velocity and the early diastolic velocity (e′) at the septal annulus (E/e′ ratio) was evaluated to estimate LV filling pressure. One best LVEF value for each patient was determined using a hierarchical approach: volumetric LVEF calculated using the 2D Simpson's biplane method was preferred, followed by other calculated LVEF methods, followed by visual estimation if these other methods were unavailable. We divided the patients into three groups according to LVEF values: preserved LV function, LVEF ≥ 50%; mid-range LV function, 40% ≤ LVEF < 50%; and reduced LV function, LVEF < 40%. LV mass was calculated using ASE formula [10]. LV regional wall motion was analyzed visually using the standard 16-segment model. Pulmonary artery systolic pressure (PASP) was estimated from the peak tricuspid regurgitation (TR) velocity obtained using continuous-wave Doppler echocardiography and estimated right atrial pressure as previously described [11].

Baseline Clinical Characteristics

Baseline patient characteristics were determined based on chart review and included age, sex, hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, coronary artery disease (CAD), renal insufficiency, current smoking, and family history of CAD.

Study Endpoints and Major Clinical Outcomes

The primary study endpoint was all-cause death, and the key secondary study endpoint was patient-oriented composite outcome (composite of all-cause death, any myocardial infarction [MI], stroke, or any repeat revascularization) at the 5-year or last follow-up. The cause of all deaths was considered cardiac unless an undisputed non-cardiac cause was present. MI was defined as symptom recurrence or the presence of electrocardiographic changes in association with an increase in cardiac biomarker levels above the upper limit of normal; cases of periprocedural MI were not included as clinical outcomes. Stroke was defined as the presence of neurological deficits confirmed by a neurologist on the basis of imaging study findings. Clinically driven revascularization that occurred after discharge from the index hospitalization was coded as a repeat revascularization event.

Statistical Analysis

Continuous variables are presented as mean and standard deviation when normally distributed or as median when not normally distributed. Demographic and echocardiographic factors were analyzed among groups using analysis of variance for continuous variables and chi-square for categorical variables. Kaplan-Meier and Cox regression analyses were used to determine associations between echocardiographic variables in patients with PAD and outcomes during the 5-year follow-up. Age, sex, hypertension, diabetes mellitus, dyslipidemia, CAD, and clinically important echocardiographic findings found to be univariate predictors of mortality were entered into multivariate models as predictors of mortality and for secondary study endpoints. A restricted cubic spline function allowed us to estimate a smooth nonlinear relationship between echocardiographic parameters and outcome in a regression model [12]. All statistical tests were 2-tailed, with probability values < 0.05 considered significant. All data analyses were performed using SPSS for Windows version 20 (SPSS, Inc., Chicago, IL, USA).

Results

Baseline Characteristics and Echocardiographic Findings according to LV Function

The mean patient age was 68 ± 10 years; 77% of the patients were male. The patients' baseline characteristics and cardiovascular risk factors according to LVEF are listed in Table 1. Compared with patients with preserved EF, a higher proportion of patients with reduced EF had renal insufficiency, atrial fibrillation, and CAD. The other baseline characteristics were similar between groups. Over 80% of the enrolled patients underwent coronary angiography, and the reduced EF group had more left main lesions or multi-vessel disease. However, the limb characteristics were similar among the groups (supplementary Table 1). The echocardiographic findings are listed in Table 2. The reduced EF group had more cases of RWMA, mitral regurgitation, elevated E/e', and elevated PASP. Valve calcification descriptions by echocardiography specialist cardiologists were similar among groups (Table 2).

Table 1
Baseline clinical characteristics according to EF

Variables, n (%)	Reduced EF (n = 62 pts)	Mid-range EF (n = 76 pts)	Preserved EF (n = 764 pts)	p value
Baseline characteristic				
Sex, male	48 (77.4)	62 (81.5)	590 (77.2)	0.685
Age, year	66.3 ± 10.2	68.3 ± 9.6	68.0 ± 10.7	0.255
Body mass index	22.2 ± 3.3	23.4 ± 3.5	23.1 ± 3.3	0.511
Blood pressure, mmHg				
Systolic	138.2 ± 25.1	143.2 ± 30.1	143.5 ± 24.7	0.308
Diastolic	72.6 ± 12.0	73.9 ± 15.4	72.4 ± 26.3	0.107
Heart rate, beats per minute	84.4 ± 19.0	80.8 ± 21.9	78.7 ± 13.9	0.052
Initial diagnosis				
Wound	43 (69.3)	39 (51.3)	481 (62.9)	0.069
Gangrene	18 (29.0)	15 (19.7)	213 (27.8)	0.299
Claudication	6 (9.6)	17 (22.3)	160 (20.9)	0.094
Resting pain	7 (11.2)	11 (14.4)	88 (11.5)	0.742
Berger's disease	2 (3.2)	0 (0.0)	20 (2.6)	0.341
Patient risks				
Hypertension	46 (74.1)	56 (73.6)	541 (70.8)	0.758
Diabetes mellitus	46 (74.1)	47 (61.8)	570 (74.6)	0.055
Medications	43 (69.3)	39 (51.3)	488 (63.8)	0.056
Insulin	20 (32.2)	21 (27.6)	249 (32.5)	0.677
Dietary	0 (0.0)	4 (5.2)	22 (2.8)	0.199
Duration, years	19.8 ± 10.4	13.6 ± 11.3	16.3 ± 11.8	0.935
Dyslipidemia	9 (14.5)	7 (9.2)	106 (13.8)	0.511
Stroke	17 (27.4)	15 (19.7)	127 (16.6)	0.088

AF, atrial fibrillation; CABG, coronary artery bypass grafting; EF, ejection fraction; PCI, percutaneous coronary intervention; PTA, percutaneous transluminal angioplasty

Data are shown as mean ± SD or number (percentage).

Variables, n (%)	Reduced EF (n = 62 pts)	Mid-range EF (n = 76 pts)	Preserved EF (n = 764 pts)	p value
Hemorrhage	2 (3.2)	2 (2.6)	15 (1.9)	0.545
Ischemia	15 (24.1)	13 (17.1)	112 (14.6)	0.127
Chronic renal insufficiency	**31 (50.0)**	**29 (38.1)**	**209 (27.3)**	**< 0.001**
Dialysis	**20 (32.2)**	**20 (26.3)**	**125 (16.3)**	**0.001**
Atrial fibrillation	**16 (25.8)**	**15 (19.7)**	**56 (7.3)**	**< 0.001**
Persistent or permanent AF	**9 (14.5)**	**9 (11.8)**	**28 (3.6)**	**< 0.001**
History of smoking	28 (45.1)	47 (61.8)	392 (51.3)	0.120
Current smoker	13 (20.9)	31 (40.7)	248 (32.4)	0.046
Alcohol consumption	14 (22.5)	20 (26.3)	236 (30.8)	0.300
Currently	6 (9.6)	17 (22.3)	183 (23.9)	0.036
Coronary artery disease	**48 (77.4)**	**57 (75.0)**	**434 (56.8)**	**< 0.001**
Prior CABG	7 (11.2)	4 (5.2)	28 (3.6)	0.021
Prior PCI	20 (32.2)	23 (30.2)	171 (22.3)	0.080
PCI during PTA	**23 (37.0)**	**27 (35.5)**	**186 (24.3)**	**0.014**

AF, atrial fibrillation; CABG, coronary artery bypass grafting; EF, ejection fraction; PCI, percutaneous coronary intervention; PTA, percutaneous transluminal angioplasty

Data are shown as mean ± SD or number (percentage).

Table 2
Baseline echocardiographic parameters

Echocardiographic variables, n (%)	Reduced EF (n = 62 pts)	Mid-range EF (n = 76 pts)	Preserved EF (n = 764 pts)	p value
LV ejection fraction, %	**33.2 ± 7.7**	**48.3 ± 4.0**	**63.8 ± 3.3**	**< 0.001**
Regional wall motion abnormalities	**55 (88.7)**	**59 (77.6)**	**67 (8.7)**	**< 0.001**
LAD	48 (77.4)	29 (38.1)	21 (2.7)	< 0.001
LCX	34 (54.8)	30 (39.4)	20 (2.6)	< 0.001
RCA	42 (67.7)	36 (47.3)	40 (5.2)	< 0.001
Mitral annular calcification*	12 (19.3)	13 (17.1)	107 (14)	0.423
Aortic valve calcification*	9 (14.5)	9 (11.8)	82 (10.7)	0.644
Mitral regurgitation†	**28 (45.1)**	**21 (27.6)**	**128 (16.7)**	**< 0.001**
Aortic valve regurgitation†	15 (24.1)	15 (19.7)	130 (17.0)	0.324
Tricuspid valve regurgitation‡	14 (22.5)	7 (9.2)	65 (8.5)	0.001
Left ventricular hypertrophy§	24 (38.7)	31 (40.7)	187 (24.5)	0.001
LV diastolic dysfunction grade#	0.96 ± 0.78	0.85 ± 0.60	0.88 ± 0.4	0.902
E/e' ratio	**20.6 ± 10.0**	**15.4 ± 7.0**	**13.0 ± 5.3**	**< 0.001**
PASP, mmHg	**37.8 ± 12.3**	**33.1 ± 9.0**	**31.5 ± 8.2**	**< 0.001**

*Evaluation by the echocardiography specialist

†More than mild

‡Reduced EF patient group had more than moderate tricuspid regurgitation.

§Left ventricular hypertrophy (LVH) was defined as increased LV mass index (LVMI) (≥ 96 g/m^2 in females, ≥ 116 g/m^2 in males).

Diastolic dysfunction is considered in our laboratory when Doppler inflow is consistent with a normal pattern (1 point), abnormal relaxation (1 point), pseudonormalization (2 points), or restrictive patterns (3 points).

LAD, left anterior descending artery; LCx, left circumflex artery; LV, left ventricle; PASP, pulmonary artery systolic pressure; RCA, right coronary artery

In-Hospital Complications according to LV Function

Reduced EF was associated with a higher incidence of red blood cell transfusion (p = 0.025), post-procedural aneurysm (p = 0.009), and significantly longer stay in the intensive care unit (ICU, p < 0.001) than the other LVEF types (supplementary Table 2).

All-Cause Mortality and Major Cardiovascular Events according to EF

The overall 30-day postoperative mortality rate was 2.0%. The mortality and cardiovascular morbidity rates did not differ significantly according to EF at 30 days (supplementary Table 2). During a median follow-up of 5 years, 140 total cardiovascular events occurred: 81 deaths, 8 MIs, 48 percutaneous coronary intervention (PCI) and 28 cerebral infarctions. The causes of death were stroke, MI, HF aggravation, or sudden cardiac death. Despite our best efforts, we could not identify the causes of 29 cases of sudden death. Total deaths were higher in the reduced EF group (n = 12 [19.7%]) than in the preserved EF group (n = 59 [8.9%]). Kaplan-Meier curves showed significant differences in survival among each of the two groups according to EF (reduced EF vs. preserved EF, $p < 0.01$; mid-range EF vs. preserved EF, $p < 0.01$; Fig. 1A). However, there was no significant difference in survival between the reduced and mid-range EF groups. Similar trends were found in total cardiovascular events: these events were 1.4 time more common in patients with reduced EF than in those with preserved EF (reduced EF vs. preserved EF, $p = 0.04$; Fig. 1B).

Predictors of All-Cause Mortality and Major Cardiovascular Events

The independent predictors of long-term mortality and combined events were identified using multiple stepwise Cox regression analysis (Fig. 2). After adjustment for age, chronic kidney disease, and HbA1c values, EF remained the only significant predictor of all-cause mortality (hazard ratio [HR], 0.96; 95% CI, 0.96–0.99; $p = 0.04$]. Interestingly, after additional adjustment for other variables, E/e′ and longer ICU stay were independent predictors of all-cause mortality (E/e′: HR, 1.11; 95% CI, 1.07–1.16; $p < 0.001$; and longer ICU stay: HR, 1.06; 95% CI, 1.03–1.09; $p < 0.01$; Fig. 1A). Heart rate was the other independent predictor of mortality (HR, 1.02; 95% CI, 1.00–1.04; $p = 0.01$). However, heart rate was not an independent predictor of major cardiovascular events (Fig. 2B). Each of these models was then re-run with the sequential replacement of E/e′ with left atrial (LA) size, transmitral E wave velocity, transmitral E/A ratio, PASP, and tissue Doppler e′ velocity. None of these measures significantly predicted all-cause mortality or major cardiovascular events with adjustment for covariates. E/e′ remained the only significant echocardiographic predictor of risk.

All-Cause Mortality and Major Cardiovascular Events according to E/e′

To estimate a smooth nonlinear relationship between E/e′ and outcome in a regression model, we used a restricted cubic spline function. Figure 3 shows the predicted 5-year probability of death as a function of E/e′ using splines and by varying the degrees of freedom. Mortality rate was increased abruptly after the range of E/e′ was over 15. E/e′ values were subsequently divided into two groups for Kaplan-Meier survival analysis (E/e′ < 15 vs. E/e′ ≥ 15). Using the log-rank test, we found that patients with E/e′ ≥ 15 had more than 6 times higher risk of mortality (Fig. 4A) as those with E/e′ < 15 (HR, 6.14; 95% CI, 3.7–

10.1; p < 0.01). Similarly, all-cause cardiovascular events were 2.8 times more common (95% CI, 2.0–4.0; p < 0.01) in patients with E/e' ≥ 15 than in patients with E/e' < 15 (Fig. 4B).

Survival Analysis in Patients with Preserved EF

Most of the patients (n = 764 [85%]) had preserved EF. Additional analysis was performed considering only patients with preserved EF to confirm that E/e' was the most important echocardiogram variable in this group. Similarly, E/e' was found to be an independent predictor of all-cause mortality and major cardiovascular events in the subgroup of patients with preserved EF (HR, 1.12; 95% CI, 1.07–1.17 for all-cause mortality; HR, 1.07; 95% CI, 1.03–1.12 for major cardiovascular events; p < 0.01). Kaplan-Meier curves showed significant intergroup differences according to E/e' cut-off values (p < 0.001; Figs. 5A, 5B). The 5-year survival rate was 97.1% among patients with E/e' < 15, compared to the 81% observed among those with E/e' ≥ 15 and preserved EF. Patients with higher E/e' (≥ 15) had a 6.8 times higher risk of death (HR, 6.8; 95% CI, 3.8–12.3; p < 0.01) and a 3.1 times higher risk of a major cardiovascular event (HR, 3.1; 95% CI, 2.1–4.5; p < 0.01). Patients with E/e' ≥ 15 were more likely to have multi-vessel disease (43% for E/e' ≥ 15 vs. 28% for E/e' < 15; p < 0.01), chronic total occlusion (11% for E/e' ≥ 15 vs. 5.5% for E/e' <15; p = 0.02), elevated creatinine (2.8 ± 3.1 mg/dL for E/e' ≥ 15 vs. 1.6 ± 2.0 mg/dL for E/e' < 15; p < 0.01), and longer ICU stay (1.2 ± 5.2 days for E/e' ≥ 15 vs. 0.5 ± 2.5 days for E/e' < 15; p = 0.04). Other variables were similar between the two groups.

Discussion

There were three main findings of the present study in patients with PAD who underwent PTA. First, patients with PAD undergoing PTA with reduced LVEF had higher incidence of total death during the 5-year follow-up. Second, an initial tissue Doppler E/e' ≥ 15, a non-invasive estimate of high LA filling pressure, was the only independent predictor of long-term mortality. Third, patients with preserved EF who have high LV filling pressure and PAD might be at increased risk of myocardial ischemia, which was related to a higher 5-year mortality rate. To the best of our knowledge, this is the first study to demonstrate echocardiographic prognostic predictors in patients with PAD undergoing PTA during long-term follow-up.

LV Systolic Dysfunction and PAD

The presence of PAD is associated with a 2-fold increase in the prevalence of HF. Given that HF and PAD share many risk factors including increased age, diabetes, smoking, atherosclerosis, and poor renal function, it is not surprising that the prevalence of LV systolic dysfunction in patients with PAD is 5.3–13.9% [5)13)]. The association between PAD and cardiovascular disease and the increasing prevalence of HF in industrialized countries suggest that PAD is an important medical concern in patients with HF. In this study, over 70% of patients had hypertension and diabetes mellitus and approximately 50% of patients were smokers. Among patients with PAD who underwent PTA, 6.8% had reduced LV systolic function (≤ 40%), whereas 15% had LV systolic dysfunction including mid-range EF (EF ≤ 50%); this prevalence of LV systolic dysfunction was similar to those reported in other studies. Patients with LV

dysfunction had increased chronic renal insufficiency and atrial fibrillation. However, in 2002, Kelly et al. reported a 28% prevalence of moderate or greater LV systolic dysfunction in 255 patients with PAD [14]. Although the characteristics of their patients were similar to those of our patients in terms of age, sex, and prevalence of ischemic heart disease, the patients in their study were considerably more often current smokers (78%) and had different ethnicities. Our study findings demonstrate that the prevalence and burden of CAD were high among patients with LV systolic dysfunction who had PAD (77.4% of those with reduced EF vs. 56.8% of those with preserved EF; $p < 0.001$) and LV dysfunction was associated with an increased risk of mortality and major cardiovascular events in patients with PAD who underwent PTA. Based on current guidelines, patients who are smokers and have known CAD and/or diabetes mellitus should undergo an ABI assessment to screen the presence of PAD. Obtaining ABI measurements in these patients at risk and with concomitant systolic HF will enhance PAD detection in this specific population. Similarly, patients with symptomatic PAD confirmed by a low ABI must be referred for echocardiography to screen LV dysfunction and detect RWMA. Ward et al. reported that, among patients with symptomatic PAD referred for echocardiography, there was a high prevalence of clinically important echocardiographic findings, including LV dysfunction [15]. In addition, evaluation of the coronary arteries along with subsequent optimal treatment of patients of PAD who underwent PTA may improve survival[16]. However current indications for screening TTE in patients with PAD are limited. Prospective echocardiographic screening studies and detection of LV dysfunction are warranted in patients with symptomatic PAD.

LV Diastolic Dysfunction and PAD

Another interesting finding in our study is the association of diastolic dysfunction and long-term cardiovascular outcomes in patients with PAD. We have confirmed that E/e' is the most important variable affecting survival rates in all patients with PAD. As reduced LV function has some correlation with E/e', the analysis was conducted again only in patients with preserved EF. In this study, E/e' was found to be an independent predictor of all-cause mortality and major cardiovascular events in patients with preserved EF (HR, 1.12; 95% CI, 1.07–1.17 for all-cause mortality; HR, 1.07; 95% CI, 1.03–1.12 for major cardiovascular events; $p < 0.01$). Some meta- analyses reported that PAD and HF are associated with increased mortality, hospitalization, and adverse health outcomes [13)17)]. However, the studies included in these analyses delineated HF with regard to clinically apparent systolic dysfunction. Asymptomatic patients with diastolic HF or structural heart changes were not included in those reviews. Yamasaki et al. suggested the association of diastolic dysfunction in patients with PAD [18]. However, the number of patients in that study was small (n = 120), and the relationship between PAD and LV diastolic function remains unclear. Yanaka et al. evaluated LV diastolic function using echocardiography in 1,121 patients and applied the American Society of Echocardiography/European Association of Cardiovascular Imaging guidelines for the diagnosis of LV diastolic dysfunction [19]. They showed a higher prevalence of LV diastolic dysfunction in patients with PAD (n = 200) regardless of the severity of PAD (non-PAD, n = 921). Additionally, multivariate logistic regression analysis showed that PAD was an independent predictor of LV diastolic dysfunction (adjusted OR, 1.77; $p = 0.01$). They showed that the prevalence of LV diastolic dysfunction was higher in patients with PAD than in those without PAD. These findings suggest

that patients with PAD should be evaluated for LV systolic and diastolic function in echocardiography. However, the authors did not imply the role of diastolic dysfunction in survival among patients with PAD, and the number of patients with PAD was relatively small (n = 200) to evaluate clinical outcome differences. In our study, we enrolled 764 patients with significant and symptomatic PAD who had preserved EF and who underwent PTA, and the mean E/e′ was 13.0 ± 5.3. This value is relatively higher than that of normal healthy people [20]. Among patients with preserved EF, the 5-year mortality rate was 2.9% in those with E/e′ < 15 (n = 15 of 525), whereas it was high, that is, 19%, in those with E/e′ ≥ 15 (n = 44 of 239). This result has a very important clinical interpretation. In patients with PAD and HF, claudicating calf pain and wounds from critical limb ischemia limits their ability to exercise and potentially precludes them from achieving exercise training. Moreover, as reported by Fowkes et al., patients with PAD are often asymptomatic, but even when symptoms are present, it may be extremely difficult for some patients with HF to discern claudication symptoms from fatigue owing to a chronic low output state or poor effort tolerance [21]. Therefore, PAD can often be missed in the risk stratification of patients with HF and functional limitations. Because of functional limitations, many patients with HF may not ambulate to the extent to which symptoms of PAD occur, thereby precluding its identification. The inspection and recognition of diastolic function in patients with PAD is essential because most physicians recognize reduced EF to a certain extent, and preserved EF can be confirmed on normal ultrasonography.

Why Would E/e′ Predict Cardiovascular Outcomes?

An elevated E/e′ is a marker for high LV filling pressure [22]. Using a cut-off of > 15 for an elevated medial E/e′ ratio with exercise, the sensitivity and specificity for predicting elevated LV filling pressure (measured invasively) were in excess of 80–85%, similar to the diagnostic accuracy of myocardial ischemia with stress echocardiography and quite acceptable for clinical practice [23]. An elevated E/e′ is a strong predictor of death following MI [24] and superior to other clinical or echocardiographic features. More recently, it was also demonstrated to predict cardiac events in subjects following coronary angiography and survival in those with established cardiac arrhythmias, but the predictor has not been examined prospectively in terms of primary prevention until now. One possible explanation is that the cumulative burden of atherosclerosis per patient is proportionate to the degree of diastolic dysfunction. Therefore, this measure may act as a surrogate for the overall effect of PAD on the myocardium, which, in turn, may predict adverse cardiovascular outcomes. In our study, patients with preserved EF and elevated E/e′ were more likely to have multi-vessel disease (43% for E/e′ ≥ 15 vs. 28% E/e′ < 15; $p < 0.01$) and chronic total occlusion (11% for E/e′ ≥ 15 vs. 5.5% E/e′ < 15; $p = 0.02$). Hidden ischemic insult might be a cause for high LV filling pressure and eventual mortality.

Limitations

This study has several limitations. First, it was conducted in a single tertiary referral hospital. Although we prospectively enrolled all consecutive patients, referral bias could not be excluded; thus, the results might be difficult to generalize. However, considering the wide range of clinical and echocardiographic

parameters in our study population, the validity of our study might not be altered. Second, this was a retrospective investigation, and our patient population was a subgroup selected from overall patients who had undergone routine echocardiography with angiography; thus, some selection bias is unavoidable.

Conclusions

Patients with symptomatic significant PAD and reduced LVEF had a higher incidence of total mortality during the 5-year follow-up. In addition, diastolic dysfunction was the only independent predictor of long-term mortality in patients with PAD. These findings suggest that the systolic and diastolic function of patients with PAD should be evaluated. In patients with diastolic dysfunction, presence of coexisting CAD should be cautiously evaluated and monitored during follow-up.

Abbreviations

EF: ejection fraction

HF: heart failure

LV: left ventricle

MI: myocardial infarction

PAD: peripheral arterial disease

PCI: percutaneous coronary intervention

PTA: percutaneous transluminal angioplasty

RWMA: regional wall motion abnormality

TTE: transthoracic echocardiography

Declarations

- Ethical Approval and Consent to participate: It is approved by the hospital’s IRB. Informed consent to participate in the study were obtained from participants.

- Consent for publication: All authors read and approved the final manuscript

- Availability of data and materials: All data can be checked by sending an email to Correspondence.

- Competing interests: none

- Funding: none

- Authors' contributions: KHK and SWR contributed to the idea and design of this study, prepared and verified the clinical coding, analyzed the data, wrote the first draft, and contributed to the subsequent drafts. BGC, JKB, WHK prepared and verified the clinical coding and analyzed the data. BGC, JKB, CUC, and HSS contributed to the data collection and revised the manuscript. KHK and SWR are the principal investigators and contributed to the idea and design of this study, interpreted and analyzed the data, and contributed to the subsequent drafts. All authors have read and approved the final version for publication.

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Figures

Figure. 1

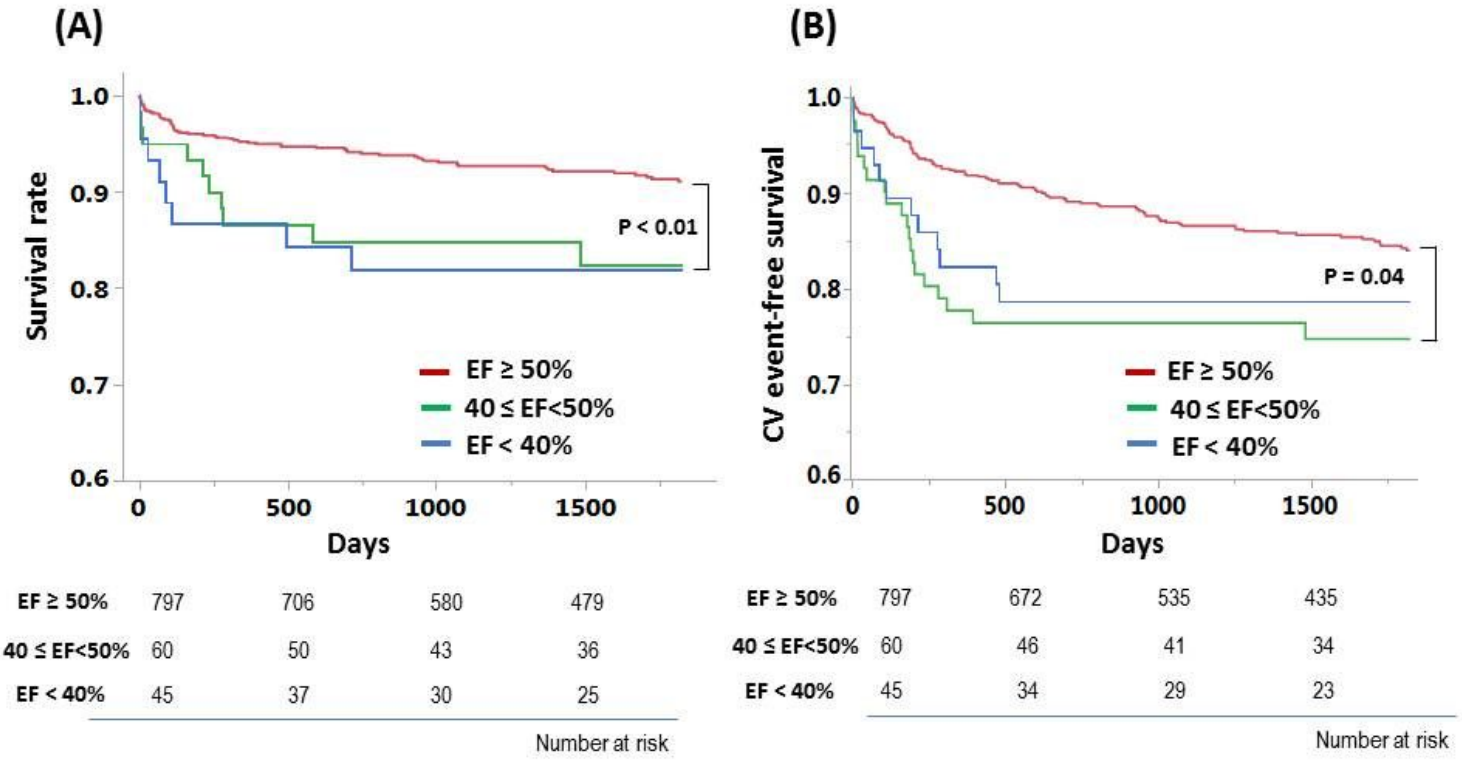

Figure 1

Kaplan-Meier curves showing freedom from death (A) and cardiovascular events (B) according to ejection fraction. CV, cardiovascular; EF, ejection fraction

Figure. 2

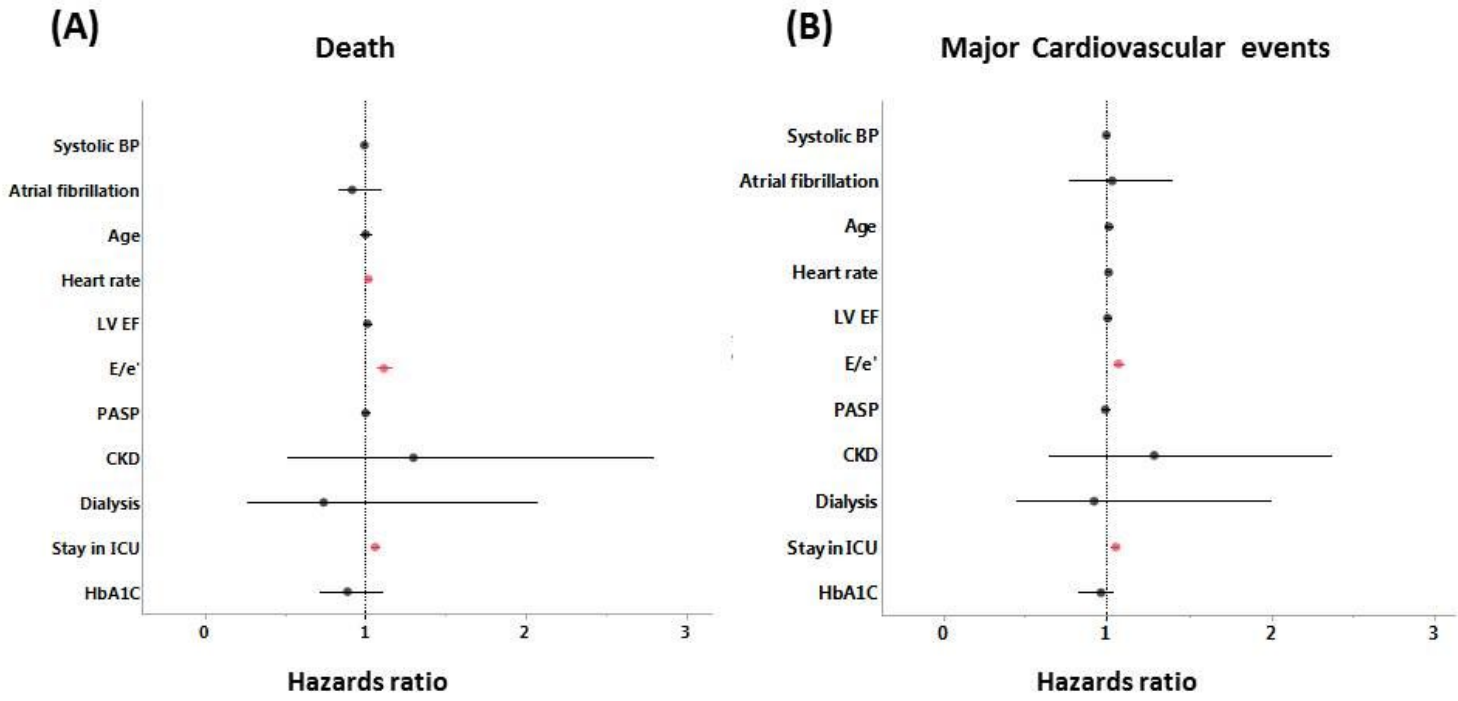

Figure 2

Forest plot displaying hazard ratios predicting all-cause death (A) and major cardiovascular events (B) Red dots show significant prognostic factors for death and major cardiovascular events (p <0.01). BP, blood pressure; CKD, chronic kidney disease; EF, ejection fraction; ICU, intensive care unit; LV, left ventricle; PASP, pulmonary artery systolic pressure

Figure. 3

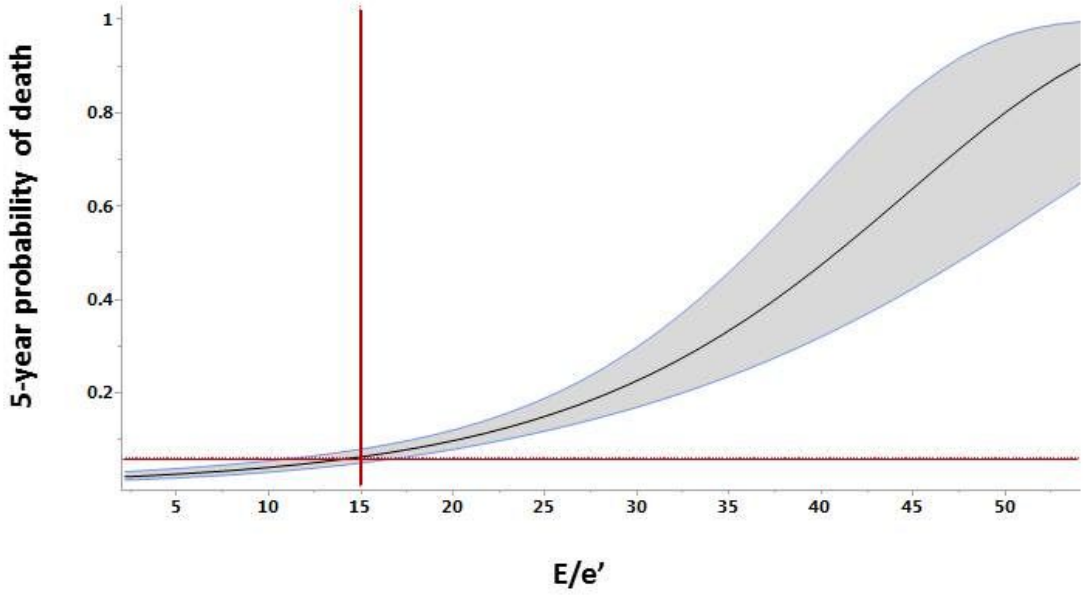

Figure 3

A smooth nonlinear relationship between E/e and outcome in a regression model.

Figure. 4

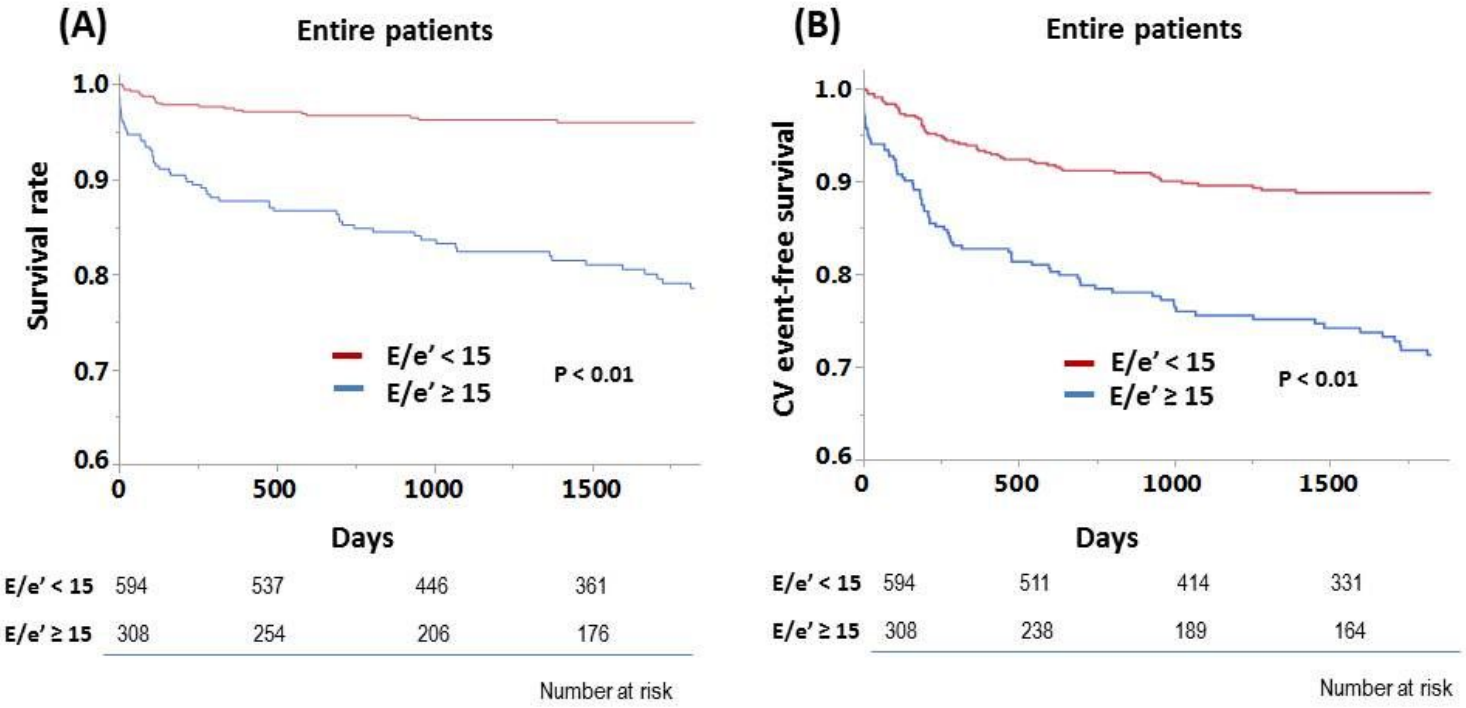

Figure 4

Kaplan-Meier curves showing freedom from death (A) and cardiovascular events (B) according to E/e among all patients PAD. CV, cardiovascular; PAD, peripheral arterial disease

Figure. 5

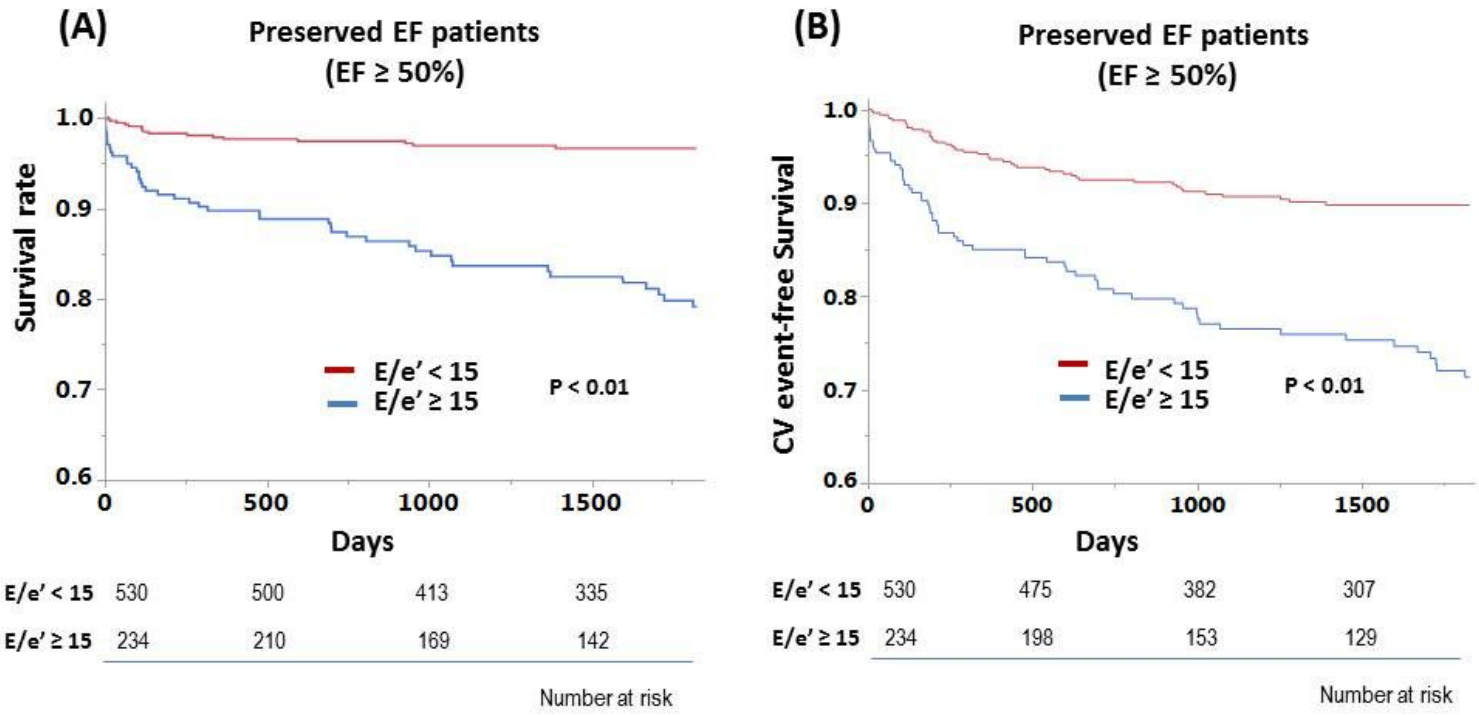

Figure 5

Kaplan-Meier curves showing freedom from death (A) and cardiovascular events (B) according to E/e among patients with preserved ejection fraction. EF, ejection fraction

Supplementary Files

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- SupplementaryTables.docx