PROGNOSTIC ROLE OF ADVANCED ECHOCARDIOGRAPHY IN CARDIOVASCULAR RISK ASSESSMENT: INSIGHTS FROM A COMMUNITY-BASED SCREENING PROGRAM

Ph.D. thesis

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1. Introduction

1.1. Preventive cardiology: The importance of cardiovascular risk assessment

Preventive cardiology is a fundamental domain of cardiovascular medicine focused on identifying and reducing cardiovascular risk factors to prevent the onset of heart disease, decrease first cardiovascular events, and slow disease progression in those with existing conditions. With cardiovascular diseases (CVD) remaining the leading global cause of death, 17.9 million deaths in 2019 (32% of all deaths), their importance has grown considerably. Preventive efforts focus on controlling modifiable risk factors through lifestyle interventions and proven pharmacotherapies, which markedly lower major cardiovascular event rates. Integrating structured preventive programs into routine care is vital for reducing the public health burden of CVD. To achieve meaningful outcomes, accurate cardiovascular risk assessment tools are necessary to enable personalized preventive strategies. The success of preventive cardiology depends on both effective therapies and robust, evidence-based risk evaluation.

1.1.1 Estimation of cardiovascular risk: use of traditional risk prediction models

Accurate cardiovascular risk assessment is essential in preventive cardiology, allowing early detection and intervention for those at risk of CVD. Commonly used tools include Systemic Coronary Risk Evaluation 2 (SCORE2), SCORE 2 Older Persons (SCORE2-OP), the American College of Cardiology/American Heart Association (ACC/AHA) pooled cohort equations, and the Framingham Risk Score. While these models are widely used, their precision is limited in complex groups such as older adults and individuals with obesity, where physiological changes and comorbidities alter risk beyond what standard scores capture. These limitations highlight the need for complementary methods that assess subclinical cardiac structure and function. Such approaches can improve risk prediction in populations where conventional scoring is insufficient.

1.1.1.1 Challenges of risk stratification of the elderly

Cardiovascular risk assessment in older adults presents unique challenges due to age-related physiological changes, the burden of multimorbidity, and the inherent limitations of conventional risk models. Commonly implemented predictive tools demonstrated limited accuracy in elderly populations. Recently, to further improve the accuracy of risk predictions, SCORE2-OP, a competing-risk-adjusted model for individuals aged over 70 years without pre-existing CVD, was developed and validated to estimate 5- and 10-year risk of incident CVD. Still, these models may either underestimate or overestimate risk due to age-associated alterations in cardiovascular physiology, including increased vascular stiffness, left ventricular hypertrophy, and diastolic dysfunction, which are not fully captured by traditional scoring systems.

Another significant limitation is the frequent presence of subclinical CVD (silent atherosclerosis, myocardial fibrosis, diastolic dysfunction, or early-stage heart failure with preserved ejection fraction) in older adults, which often remains undetected using conventional risk markers alone. Therefore, refining cardiovascular risk assessment in the elderly may require a shift from traditional scoring systems toward a more integrative approach that accounts for age-related physiological changes, subclinical cardiac alterations, and competing health risks.

1.1.1.2 Challenges in cardiovascular risk estimation: the impact of obesity

The prevalence of overweight and obesity is rising globally, affecting populations across both developed and developing regions. Overweight and obesity are characterized by abnormal or excessive fat accumulation that poses significant health risks. Recent studies have shown that even individuals previously classified as "metabolically healthy obese" are at a higher risk of adverse cardiovascular outcomes compared to their metabolically healthy normal-weight counterparts. Overall, the interplay of increased cardiac workload and metabolic dysregulation renders individuals with obesity susceptible to progressive cardiovascular pathology, even in the absence of conventional risk factors.

In this context, non-invasive and widely available imaging modalities, particularly echocardiography, have gained prominence for their ability to detect early functional cardiac changes, offering a practical and feasible approach to refine cardiovascular risk assessment.

Elderly and obese individuals frequently exhibit early functional changes that remain undetected by standard clinical assessments. Echocardiography, with its ability to non-invasively assess both structural and functional cardiac parameters, offers a valuable opportunity to enhance risk assessment where traditional models reach their limitations.

1.2 Advanced Echocardiographic Techniques in Cardiovascular Risk Assessment

Traditional cardiovascular risk models often fail to accurately stratify risk in individuals without overt disease, particularly in the elderly and those with obesity, where complex physiological and metabolic changes can mask early pathology. Echocardiography has emerged as a cost-effective and accessible modality for enhancing prognostic accuracy by detecting subclinical myocardial dysfunction.

Diastolic function is often impaired before systolic dysfunction in the elderly, so diastolic function assessment, along with left atrial (LA) function, is critical for refined risk assessment. Speckle-tracking echocardiography (STE)- derived peak atrial longitudinal strain (PALS) offers early detection of diastolic dysfunction and has shown prognostic significance across various clinical conditions (Figure 1).

While left ventricular ejection fraction (LVEF) is routinely used to assess systolic function, it is load-dependent and insensitive to early LV dysfunction. STE-derived left ventricular global longitudinal strain (LVGLS) can detect early LV dysfunction and has been linked to predicting adverse outcomes even with preserved LVEF. Myocardial work (MW) analysis offers a load-adjusted assessment of LV contractility that extends beyond LVGLS and LVEF (Figure 2).

Advanced echocardiographic techniques could provide a feasible and cost-effective approach for detecting early cardiac dysfunction and predicting prognosis in the elderly and individuals with obesity.

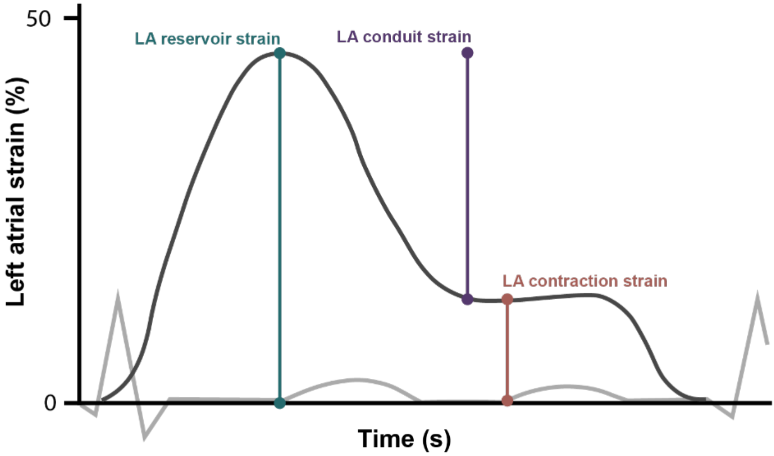

Figure 1. *Schematic illustration of strain-time curve depicting phasic left atrial strain indices. LA – left atrial.*

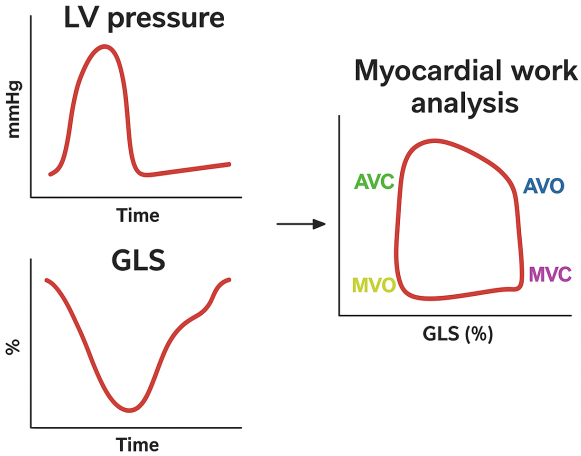

Figure 2. *Schematic workflow of myocardial work analysis. AVC, aortic valve closure; AVO, aortic valve opening; GLS – global longitudinal strain; LV, left ventricle; MVC, mitral valve closure; MVO, mitral valve opening.*

2 Objectives

2.1 Investigation of the long-term prognostic importance of peak atrial longitudinal strain in a community-based screening sample comprising elderly individuals

Left ventricular diastolic dysfunction frequently precedes systolic dysfunction and is associated with comparable adverse long-term outcomes. Thus, assessing LV diastolic function, along with LA function, may provide more sensitive biomarkers to detect early dysfunction and predict long-term prognosis. Despite the well-known importance of LA mechanics in diastolic function evaluation, data are scarce regarding the long-term prognostic power of LA longitudinal strain and its potential added value on top of LV function indices. Accordingly, our aim was to determine the long-term prognostic importance of STE-derived peak atrial longitudinal strain (PALS) in a community-based screening sample comprising elderly individuals.

2.2 Evaluating the impact of overweight and obesity on myocardial work measures and assessing their prognostic power in a low-risk, community-based cohort

Although both LVEF and LVGLS are sensitive indicators of LV systolic function, both are notably affected by various factors, including loading conditions and heart rate. In contrast, MW provides insights into LV contractility that extend beyond more traditional measures, as it accounts for afterload, allowing a more accurate assessment of systolic performance. Accordingly, our objective was to evaluate the impact of overweight and obesity on myocardial work measures and to assess their prognostic power in a low-risk, community-based cohort.

3 Methods

The Budakalász Study was a cross-sectional, voluntary screening program in Central Hungary that assessed health and cardiovascular risk. Study procedures included: questionnaires, anthropometry, blood pressure measurement, electrocardiography (ECG), echocardiography, carotid duplex scan, ankle-brachial index, and laboratory tests. Females >40 and males >35 years were invited for cardiac computed tomography (CT) examination. The Framingham CVD risk score was calculated.

All participants gave informed consent. Both studies adhered to the Declaration of Helsinki and were approved by the Medical Research Council (ETT-TUKEB No. 13687–0/2011-EKU).

In the first study, carotid duplex scan was performed (Vivid i ultrasound system, 12L-RS linear probe, GE Healthcare, Horten, Norway), which was post-processed offline (GE EchoPAC) to measure carotid IMT according to the recommendations of the 2012 Mannheim Consensus. Cardiac CT (256-slice Philips Brilliance iCT) was also performed, and coronary calcium was quantified (Heartbeat-CS, Philips). Agatston score was calculated and reported as 0 or non-0.

Echocardiographic assessment

Using a commercially available ultrasound system (Vivid i, 3Sc-RS transducer), three experienced echocardiographers obtained all echocardiograms, which were analyzed offline by two investigators blinded to outcomes and clinical data, using commercially available software packages (AutoStrain LV and AutoStrain LA, TomTec Imaging Systems, Unterschleißheim, Germany, and Ultrasound Workspace, Philips Medical Systems, Netherlands) in both studies.

STE focused on apical four-chamber views, measuring LVGLS, PALS, and peak atrial contraction strain (PACS).

For the second study, LVGLS curves and volumetric indices were analyzed, and segmental GLS curves were exported as text files for custom software that reconstructed LV pressure curves using brachial cuff systolic pressure, reference LV pressure waveforms, and tissue doppler imaging (TDI)-derived valvular timing. Strain and pressure curves were concatenated to generate pressure–strain loops. Global myocardial work index (GWI), global constructive work (GCW), global wasted work (GWW), and global work efficiency (GWE) were calculated.

3.1 Study outcomes

For both studies, follow-up data (status [dead or alive], date of death) were obtained from Hungary's National Health Insurance Database. The primary endpoint for both studies was all-cause mortality.

3.2 Statistical analysis

Statistical analysis was performed using dedicated software (SPSS v22, IBM, Armonk, NY, USA). Continuous variables are expressed as mean ± standard deviation (SD), whereas categorical variables are reported as frequencies and percentages. After the verification of normal distribution of variables using the Shapiro–Wilk test, the clinical and echocardiographic characteristics were compared with unpaired Student's *t* test or Mann–Whitney *U* test for continuous variables, and chi-squared or Fisher's exact test for categorical variables, as appropriate. Cox proportional hazards models were used to compute HRs with 95% CIs. Covariates included in multivariable models were selected based on clinical relevance and intergroup differences. Collinearity of variables was tested at each multivariable model by the variance inflation factor (excessive if the variance inflation factor > 3). In the first study, receiver operating characteristic (ROC) curves were generated to assess the discriminatory power of PALS for the endpoint. Youden's index was used to identify the optimal cut-off point; the resulting value or the conventionally used 39% value was then used to dichotomize the study population. Outcomes of the dichotomized groups were visualized on Kaplan–Meier curves and compared by the log-rank test. In the second study, the previously established lower limit of normal value (GWI value of 1292 mmHg%) was used to dichotomize the study population. Outcomes of the dichotomized groups were visualized on Kaplan–Meier curves and compared by the log-rank test. The prognostic performance of the established GWI cutoff was further evaluated using multivariable Cox proportional hazard models, including covariates of clinical relevance and intergroup differences, as described above. In both studies, a two-sided *P*-value of 0.05 was considered statistically significant.

4 Results

4.1 Investigation of the long-term prognostic importance of peak atrial longitudinal strain in a community-based screening sample comprising elderly individuals

4.1.1 Conventional 2D and speckle-tracking echocardiographic parameters

Subjects with adverse outcomes had significantly higher LV end-diastolic diameter, LV mass index (LVMi), and indexed end-diastolic (EDVi) and systolic volumes (ESVi). Diastolic function markers showed higher mitral A-wave velocity, lower E/A ratio, prolonged deceleration time, reduced mitral annular e′ velocities, and elevated E/e′ ratios in those with adverse events. Left atrial volume index (LAVi) was also significantly higher. STE analysis revealed significantly lower LVGLS and PALS among those with adverse outcomes, while PACS showed no difference.

4.1.2 Prognostic value and discriminatory power of PALS

Multivariable Cox regression was performed using significant variables from univariable analysis (Table 1). In Model 1 (Framingham risk score, PALS, LVGLS), both PALS and Framingham score were independently associated with adverse outcomes. In Model 2 (Framingham score, PALS, carotid IMT), all three were independent predictors, while in Model 3 (Framingham score, PALS, Agatston score), only PALS and Framingham score were significant predictors of all-cause mortality (Table 1). Using the standard cut-off value of 39% for PALS, individuals with lower PALS had a 2.5-fold higher risk for all-cause mortality (HR 2.499, 95% CI 1.334–4.682) (Figure 3, Figure 4).

ROC analysis was performed to assess the discriminatory power of PALS for the endpoint. Using Youden's index, we calculated the optimal cut-off value of 32.6% with a sensitivity of 56.4% and specificity of 75.3% (Figure 5). When using this cut-off, in subjects with lower PALS values, the risk of all-cause mortality was more than three times higher than in subjects with PALS values above 32.6% (HR: 3.424 [95% CI: 1.694–6.919], $p < 0.001$) (Figure 6).

Table 1. Independent predictors of all-cause mortality

	Multivariable Cox regression					
	Model 1		**Model 2**		**Model 3**	
	HR [95% CI]	**P**	**HR [95% CI]**	**P**	**HR [95% CI]**	**P**
Framingham risk score	1.056 [1.032 - 1.081]	**<0.001**	1.042 [1.015-1.071]	**0.003**	1.046 [1.020-1.073]	**<0.001**
PALS	0.967 [0.939 -0.995]	**0.023**	0.954 [0.924-0.985]	**0.004**	0.967 [0.941-0.993]	**0.012**
LV GLS	1.032 [0.938-1.134]	0.521	-		-	
IMT	-		14.62 [1.036-206.24]	**0.047**	-	
Agatston score (non 0)	-		-		2.536 [0.742-8.669]	0.138

CI, confidence interval; HR, hazard ratio; IMT, carotid intima-media thickness; LV GLS, left ventricular global longitudinal strain; PALS, peak atrial longitudinal strain

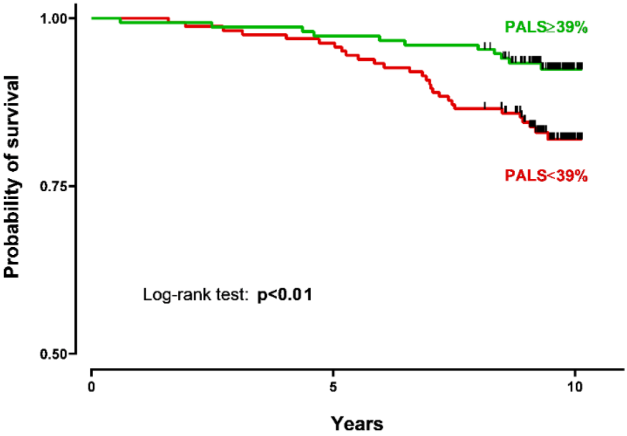

Figure 3. *Kaplan-Meier survival curves using a cut-off value of 39%*

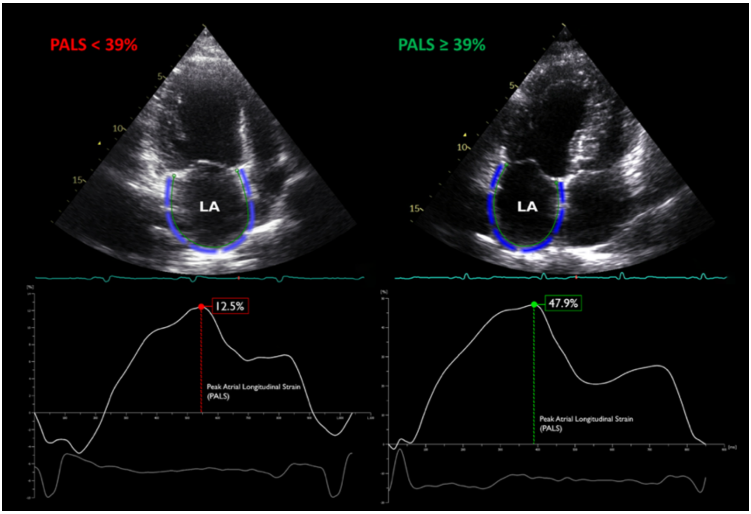

Figure 4. *Representative cases of subjects below (indicated with red) and above 39% (indicated with green) of peak atrial longitudinal strain (PALS). Subject with 12.6% PALS met the primary endpoint during the follow-up period.*

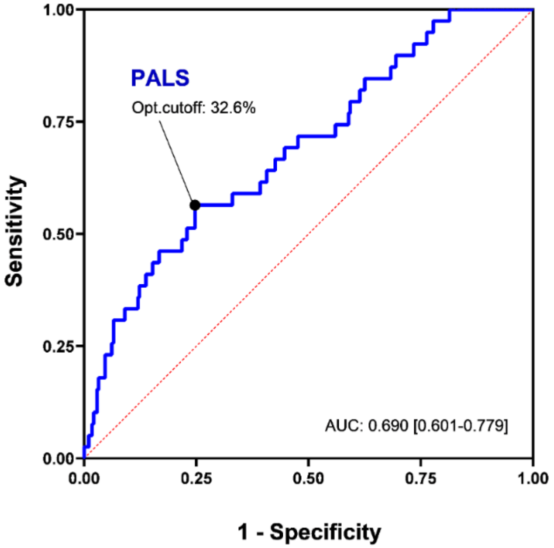

Figure 5. *Receiver operating characteristic curve illustrating the discriminatory power of PALS with regard to the endpoint.*

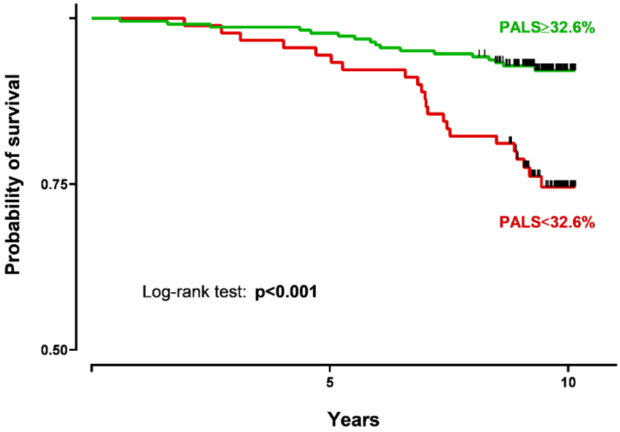

Figure 6. *Kaplan-Meier survival curves based on the optimal cut-off value (32.6%) of PALS assessed with receiver operating characteristic analysis.*

4.2 Evaluating the impact of overweight and obesity on myocardial work measures and assessing their prognostic power in a low-risk, community-based cohort

4.2.1 Conventional 2D and speckle-tracking echocardiography-derived parameters according to the primary outcome

Participants with adverse outcomes had larger LV internal diameters and higher LVMi, EDVi, and ESVi, while LVEF was similar across groups. STE and MW analysis-derived metrics revealed significantly lower LVGLS and GWI in the deceased group, along with higher GWW and lower GWE, while GCW did not differ between groups.

4.2.2 Conventional 2D and speckle-tracking echocardiography-derived parameters according to BMI groups

Individuals in the obese group exhibited higher values of LV end-diastolic dimensions and LVMi, whereas patients in the overweight group had higher LV EDVi. Interestingly, LVEF was significantly lower in the normal weight group compared to the groups with overweight and obesity. Regarding diastolic function, the E/A ratio was lower along the increasing weight groups, whereas the E/e' average ratio showed higher values with each weight group. Regarding STE-derived indices, LVGLS declined across the three weight groups, with normal-weight individuals having the highest absolute LVGLS values and subjects with obesity having the lowest. Concerning MW indices, GWI and GCW values were significantly lower in the obese group, while there was no difference between the normal-weight and overweight groups.

4.2.3 Long-term prognostic value of LV systolic function in different weight groups

We have performed univariable Cox regression analysis in the total cohort and within the 3 different weight groups (Table 2). Focusing on the prognostic value of LV systolic function, in the total cohort, LVEF was not associated with the adverse outcome, whereas LVGLS, GWI, GWE, and GWW were significant predictors of all-cause mortality (Table 2). Conversely, when assessing the normal weight group, only LV GLS was a predictor of the adverse outcome, whereas LVEF or MW metrics were not (Table 2). In the overweight group, LVGLS, along with GWE and GWW, were significant predictors, whereas LVEF, GWI, and GCW were not (Table 2). Finally, in the obese group, only GWI emerged as a significant predictor of all-cause mortality (Table 2). To adjust for potential clinical cofounders, multivariable Cox regression models were built. When adjusting for female sex, BMI, and systolic blood pressure, GWI still remained an independent significant predictor of all-cause mortality in the total cohort, and in patients with overweight and obesity, but interestingly not in patients with normal weight (Table 2).

Furthermore, participants were dichotomized based on a previously established GWI cut-off value of 1292 mmHg%. Applying this threshold, GWI effectively differentiated between high-risk and low-risk groups in terms of all-cause mortality in the total cohort, and in the overweight and obese groups, but not in the normal weight group (Figure 7). As the Kaplan–Meier survival curves indicate, those overweight subjects with GWI values below 1292 mmHg% experienced more than 3-fold increase in the risk of all-cause mortality (Figure 7C). Similarly, in the obese group (Figure 7D) and in the total cohort (Figure 7A), participants with GWI values below the cut-off had more than 2-times increased risk for adverse events. Moreover, multivariable Cox proportional-hazards models were built, adjusting for the previously used confounders (female sex, SBP, and BMI). Even after adjusting for relevant clinical variables, the guideline-based GWI cutoff was independently associated with the outcome, as patients with GWI values below 1292 mmHg% experienced a higher risk of all-cause mortality in the total cohort and in all weight groups, respectively.

Table 2. Association of echocardiography-derived LV systolic function metrics with all-cause mortality in different weight groups using univariable and multivariable Cox regression

Univariable Cox regressions in different subgroups								
	Total Cohort (n=1330)		**Normal weight (n=405)**		**Overweight (n=526)**		**Obesity (n=399)**	
	HR [95% CI]	**p-value**	**HR [95% CI]**	**p-value**	**HR [95% CI]**	**p-value**	**HR [95% CI]**	**p-value**
LVEF	0.971 [0.941-1.002]	0.066	0.966 [0.892-1.045]	0.385	0.961 [0.918-1.007]	0.093	0.972 [0.924-1.021]	0.259
LVGLS	1.100 [1.049-1.154]	**<0.001**	1.156 [1.031-1.295]	**0.013**	1.089 [1.014-1.170]	**0.020**	1.051 [0.967-1.141]	0.239
GWE	0.947 [0.914-0.981]	**0.002**	1.012 [0.915-1.119]	0.823	0.917 [0.874-0.963]	**<0.001**	0.964 [0.906-1.025]	0.238
GWI	0.958 [0.924-0.992]	**0.017**	1.001 [0.919-1.090]	0.984	0.976 [0.917-1.019]	0.212	0.929 [0.875-0.986]	**0.015**
GCW	0.979 [0.944-1.015]	0.243	1.002 [0.916-1.096]	0.970	1.003 [0.952-1.058]	0.902	0.943 [0.887-1.003]	0.064

GWW	1.194 [1.041-1.369]	**0.011**	0.938 [0.618-1.424]	0.764	1.341 [1.121-1.604]	**0.001**	1.109 [0.836-1.425]	0.419
Multivariable Cox regressions in different subgroups								
Female sex	0.517 [0.367-0.728]	**<0.001**	0.224 [0.091-0.553]	**0.001**	0.679 [0.411-1.120]	0.129	0.600 [0.335-1.075]	0.086
SBP	1.029 [1.019-1.038]	**<0.001**	1.049 [1.030-1.067]	**<0.001**	1.028 [1.014-1.041]	**<0.001**	1.012 [0.993-1.032]	0.209
BMI	1.016 [0.981-1.053]	0.365	0.832 [0.678-1.022]	0.080	0.938 [0.783-1.122]	0.482	1.027 [0.946-1.116]	0.526
GWI	**0.923 [0.889-0.959]**	**<0.001**	0.934 [0.856-1.019]	0.122	**0.922 [0.872-0.975]**	**0.005**	**0.920 [0.863-0.981]**	**0.011**

BMI, body mass index; CI, confidence interval; EF, ejection fraction; GCW, global constructive work; GWE, global work efficiency; GWI, global work index; GWW, global wasted work; HR, hazard ratio; LV, left ventricle; LVGLS, left ventricular global longitudinal strain; SBP, systolic blood pressure

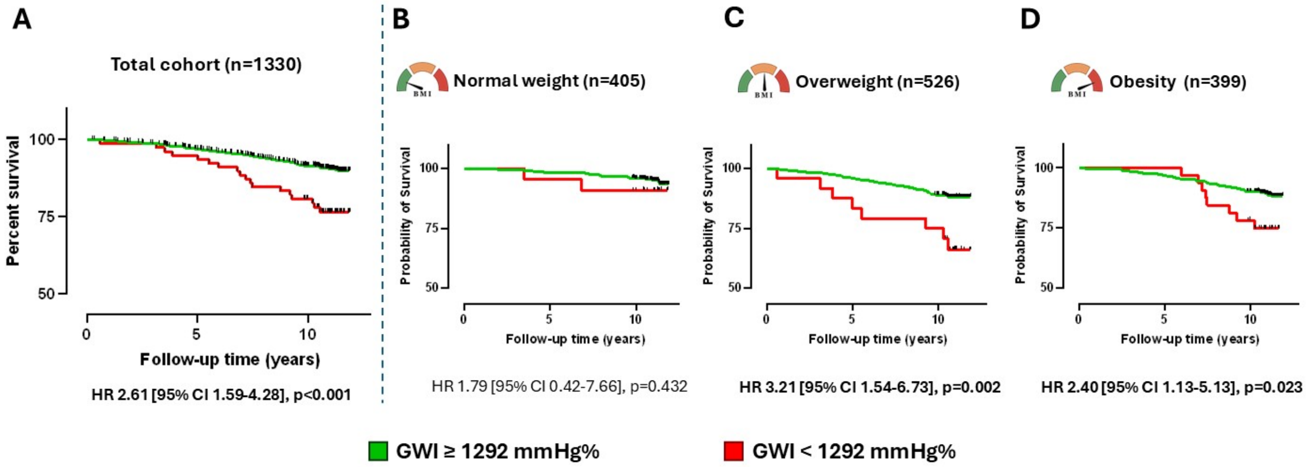

Figure 7. *Kaplan–Meier survival curves using the previously published cut-off value of 1292 mmHg% in total cohort (A), normal weight (B), overweight (C) and obese (D) group. CI, confidence interval; GWI, global myocardial work index; HR, hazard ratio*

5 Conclusion

In our first study, we determined the long-term prognostic importance of STE-derived peak atrial longitudinal strain (PALS) in a community-based screening sample of elderly individuals. PALS offered incremental value in cardiovascular risk stratification in a community-based cohort, beyond the assessment of LV systolic functional parameters such as LVEF and LVGLS. By multivariable regression models, PALS was found to be a significant and independent predictor of long-term all-cause mortality. These results emphasize the importance of a thorough evaluation of LA mechanics in an elderly population.

Regarding the second study, we assessed the impact of overweight and obesity on myocardial work measures and investigated their prognostic power in a low-risk, community-based cohort. Myocardial work analysis-derived metrics were found to be robust and independent predictors of all-cause mortality in low-risk individuals with different stages of obesity. These findings underscore the limitations of conventional echocardiographic measures, which may underestimate cardiovascular risk in overweight and obese populations, highlighting the potential of MW analysis to refine risk stratification and improve prognostic accuracy in this growing patient cohort.

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