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Original Article / *Özgün Makale*

Predictors of pulmonary hypertension after atrial septal defect closure: Impact of atrial fibrillation

Atriyal septal defekt kapama sonrası pulmoner hipertansiyonun öngördürücüleri: Atriyal fibrilasyonun etkisi

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ABSTRACT

Background: In this study, we aimed to evaluate the course of pulmonary artery systolic pressure, to identify factors associated with pulmonary arterial hypertension, and to determine the impact of atrial septal defect closure on clinical outcomes in long-term follow-up.

Methods: Between March 2008 and August 2020, a total of 547 adult patients (193 males, 354 females; median age: 37 years; range, 27.5 to 47 years) with secundum atrial septal defect were retrospectively analyzed. Of these patients, 304 underwent percutaneous defect closure and 243 underwent isolated surgical repairs. Pulmonary arterial hypertension was defined as a non-invasively estimated pulmonary artery systolic pressure of ≥40 mmHg at the final follow-up after atrial septal defect closure. Factors associated with pulmonary arterial hypertension were analyzed.

Results: Sixty-nine (12.6%) patients presented with pulmonary arterial hypertension at the final follow-up. A total of 35 (6.4%) patients had persistent atrial fibrillation before atrial septal defect closure, and 22 of these 35 patients had pulmonary arterial hypertension during long-term follow-up. Older age at the time of atrial septal defect closure (HR: 4.76; 95% CI: 2.68-8.44; p<0.001), the presence of persistent atrial fibrillation (HR: 2.18; 95% CI: 1.21-3.91; p=0.009), and greater right ventricular basal diameter (HR: 4.78; 95% CI: 2.57-8.84; p<0.001) were found to be associated with late pulmonary arterial hypertension.

Conclusion: The presence of persistent atrial fibrillation may be used to predict patients at higher risk for pulmonary arterial hypertension after atrial septal defect closure.

Keywords: Atrial septal defect, persistent atrial fibrillation, pulmonary hypertension, surgical closure, transcatheter closure.

ÖZ

Amaç: Bu çalışmada, pulmoner arter sistolik basıncının seyri değerlendirildi, pulmoner arteriyel hipertansiyon ile ilişkili faktörler belirlendi ve atriyal septal defekt kapatılmasının uzun dönem takipte klinik sonuçlar üzerine etkisi araştırıldı.

Çalışma planı: Mart 2008 ile Ağustos 2020 tarihleri arasında sekundum atriyal septal defektli toplam 547 erişkin hasta (193 erkek, 354 kadın; medyan yaş: 37 yıl; dağılım, 27.5-47 yıl) retrospektif olarak incelendi. Bu hastaların 304'üne perkütan defekt kapatma ve 243'üne izole cerrahi onarım yapıldı. Pulmoner arteriyel hipertansiyon, atriyal septal defekt kapatma sonrasında son takipte non-invaziv olarak ölçülen ≥40 mmHg pulmoner arter sistolik basıncı olarak tanımlandı. Pulmoner arteriyel hipertansiyon ile ilişkili faktörler incelendi.

Bulgular: Altmış dokuz (%12.6) hastada son takipte pulmoner arteriyel hipertansiyon tespit edildi. Atriyal septal defekt kapatılmadan persistan atriyal fibrilasyonu olan 35 (%6.4) hasta vardı ve bu 35 hastanın 22'sinde uzun süreli takipte pulmoner arteriyel hipertansiyon saptandı. Atriyal septal defektin kapatıldığı zaman ileri yaş (HR: 4.76; %95 GA: 2.68-8.44; p<0.001), persistan atriyal fibrilasyon varlığı (HR: 2.18; %95 GA: 1.21-3.91; p=0.009) ve artmış sağ ventrikül bazal çapı (HR: 4.78; %95 GA: 2.57-8.84; p<0.001) geç dönem pulmoner arteriyel hipertansiyon ile ilişkili bulundu.

Sonuç: Persistan atriyal fibrilasyon varlığı, atriyal septal defekt kapama sonrasında pulmoner arteriyel hipertansiyon açısından yüksek riskli hastaların öngörülmesinde kullanılabilir.

Anahtar sözcükler: Atriyal septal defekt, persistan atriyal fibrilasyon, pulmoner hipertansiyon, cerrahi kapatma, transkateter kapatma.

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Atrial septal defects (ASDs) are one of the most common congenital heart diseases in adults, with secundum ASD being the most common subtype, with a 2:1 female predominance.[1] Patients with secundum ASD are at risk of developing pulmonary arterial hypertension (PAH) due to chronic volume overload caused by a left-to-right shunt.[2] Pulmonary arterial hypertension has been demonstrated to increase cardiovascular morbidity and mortality and occurs in 6 to 35% of patients with secundum ASD.[3,4] The ASD closure can reduce right atrial and ventricular dilatation, improve right ventricular function, lower pulmonary artery pressure, and increase cardiopulmonary functional capacity.[5] However, remodeling of the pulmonary vasculature is not completely reversible, particularly in patients with ASD repair at an older age.[6] Chronic volume overload can cause histological changes in the intima and media of the medium-sized and small pulmonary arteries, such as medial hypertrophy, laminar intimal fibrosis, plexiform lesions, and necrotizing arteritis, which can lead to marked luminal narrowing and ultimately the development of PAH.[7,8] However, the increased pulmonary flow does not uniformly cause the PAH in all ASD patients, and it is unknown why some patients are more likely to develop PAH. This suggests that PAH develops as a result of multiple factors rather than a simple volume overload.[9] Although previous studies have shown that greater defect size, older age at the time of ASD closure, female sex, increased mean pulmonary artery pressure, and a higher degree of tricuspid regurgitation before ASD closure are associated with PAH, there is still insufficient data on associated risk factors for the evolution of PAH, late after ASD closure.[10-13] Furthermore, little is known about its relationship to clinical outcomes.

In the present study, we aimed to estimate the prevalence of PAH in adults undergoing surgical or transcatheter ASD closure, to identify parameters associated with PAH, and to determine its impact on clinical outcomes at long-term follow-up.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at Koşuyolu Training and Research Hospital, Department of Cardiology between March 2008 and August 2020. Indication for ASD closure was the presence of a hemodynamically significant left to right shunt (signs of right ventricle volume

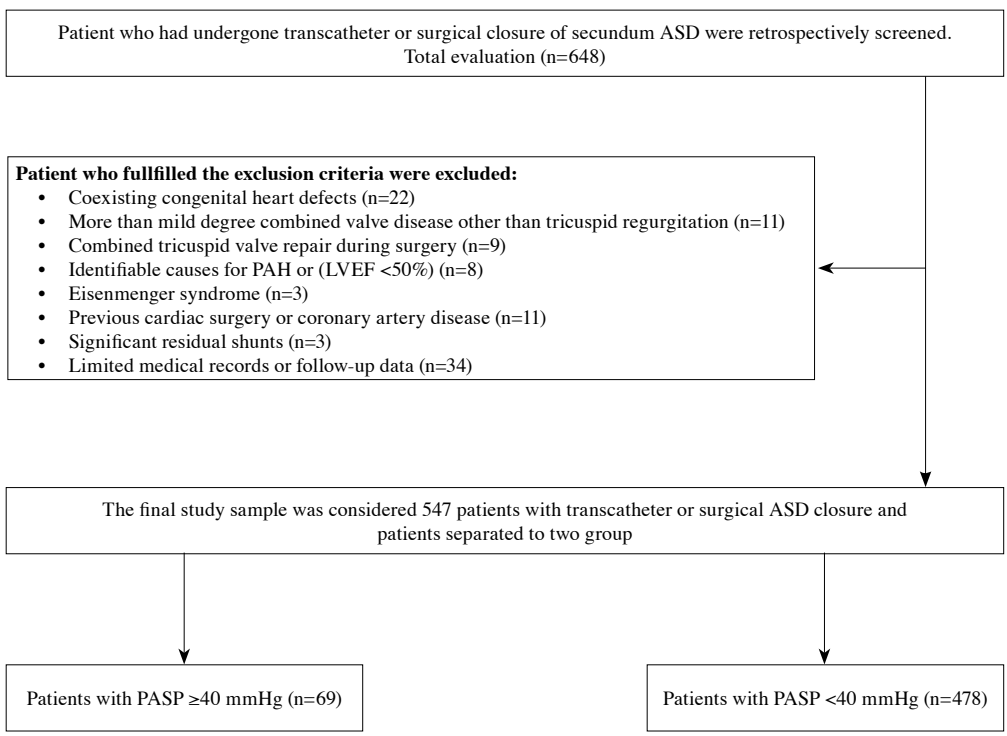


Figure 1. Study flow chart.

ASD: Atrial septal defect; PAH: Pulmonary arterial hypertension; LVEF: Left ventricle ejection fraction; PASP: Pulmonary artery systolic pressure.

overload) regardless of age and symptoms.[9] The primary treatment strategy was transcatheter ASD closure when the defect morphology was appropriate; however, patients with unsuitable defect morphology underwent surgical treatment. A total of 547 adult patients (193 males, 354 females; median age: 37 years; range, 27.5 to 47 years) with secundum ASD were included in this study. The study flow chart is shown in Figure 1.

All patients included in the study underwent transthoracic and transesophageal echocardiography for pre-procedural assessment. After the procedure, patients were followed regularly (first month, at six months, and annually thereafter) by non-invasive examinations including clinical examination, echocardiography, electrocardiography, Holter monitoring, or exercise testing. New York Heart Association (NYHA) functional classes were also assessed at each visit. Diagnostic catheterization was performed only in selected patients with clinical or echocardiographic suspicion of PAH prior to ASD closure.[9]

Baseline clinical and demographic characteristics of the patients, symptoms and functional class, rhythm status, presence of risk factors contributing to PAH, cardiovascular medication, pre- and post-procedural echocardiographic studies were derived retrospectively with a detailed review of medical records.

The patients were classified according to rhythm status before ASD closure: Those with no history of atrial fibrillation (AF), patients with a history of paroxysmal AF, and patients with persistent AF.[14] A rhythm control strategy was adopted for both paroxysmal and persistent AF patients, but only patients with paroxysmal AF were in sinus rhythm at the time of ASD closure.

The study population was divided into two groups according to the pulmonary artery systolic pressure (PASP) value at the latest follow-up: PASP ≥40 mmHg or PASP <40 mmHg. At the most recent follow-up after ASD closure, PAH was defined as a non-invasively estimated PASP of 40 mmHg or more.[11,15] The clinical endpoint was defined as cardiovascular mortality and hospitalization for cardiac decompensation. Patients were followed regularly from the date of the ASD closure until the date of the first event occurrence or the end of follow-up, whichever occurred first.

Transthoracic and two or three-dimensional transesophageal echocardiography were performed in all patients before the procedure. After the procedure, echocardiography was performed at each follow-up visit. The dimensions and functions of the left and right heart chambers including tricuspid regurgitation and estimated PASP value were measured according to the recommendations of the American Echocardiographic Association.[16] The average of three measurements was used for the analysis.

Statistical analysis

Statistical analysis was performed using the R version 4.01 software (R Foundation for Statistical Computing, Vienna Austria) with "rms" "survival," "ggplot2" packages. Continuous data were presented in median and interquartile range (IQR, 25^{th}-75^{th} percentile), while categorical data were presented in number and frequency. We used the Mann-Whitney U test for independent continuous data comparisons and the Pearson chi-square or Fisher exact test for categorical data comparisons. A two-tailed p value of <0.05 was considered statistically significant.

To detect parameters associated with late PAH, a multivariable Cox proportional hazard regression model was used. The effect of each parameter was reported using a hazard-ratio (HR) and a 95% confidence interval (CI). The relevant parameters of the multivariable regression model were selected according to the literature, consensus opinion by an expert group of physicians, and our focused variable, the persistent AF. In addition, a visual depiction of event-free survival between patients with and without PAH at the latest follow-up was made with the Kaplan-Meier curve, and the log-rank test was used for group comparison.

RESULTS

Three hundred three patients underwent transcatheter ASD closure, and 244 patients underwent surgical ASD repair. In the surgical procedure, the ASD was closed with a pericardial patch in 113 (46.3%) patients and by primary suture in the remaining patients. There was no residual shunt in patients who underwent surgical ASD repair. Hemodynamically insignificant residual shunts were detected in 13 patients who underwent transcatheter ASD closure and no re-intervention was performed in these patients.

The patients were divided into two groups according to the PASP value at the latest follow-up: PASP ≥40 or PASP <40 mmHg. The median follow-up period after ASD repair was 68 (IQR: 44 to 88) months.

The baseline characteristics of both groups are summarized in Table 1. Patients with PASP ≥40 mmHg

Table 1. Baseline clinical characteristics

	All (n=547)				PASP ≥40 mmHg (n=69)				PASP <40 mmHg (n=478)				
Variables	n	%	Median	Min-Max	n	%	Median	Min-Max	n	%	Median	Min-Max	*p*
Age at ASD closure (year)	37		37	27.5-47	56		56	52-63			35	27-44	<0.001*
Sex													
Female	354	64.7			45	65.2			309	64.6			0.92
BMI (kg/m^2)			26.3	24.7-28.1			26.4	25.2-27			26.3	24.7-28.3	0.86
Hypertension	100	18.3			19	27.5			81	16.9			0.03*
Diabetes mellitus	29	5.3			4	5.8			25	5.2			0.84
Max diameter (mm)			19	16-24			24	21-26			18	15-24	<0.001*
Persistent AF	35	6.4			22	31.9			13	2.7			<0.001*
Transcatheter repair	303	55.4			33	47.8			270	56.5			0.176
Pre-procedural NYHA I	295	53.9			11	15.9			284	59.4			<0.001*
Pre-procedural NYHA II	216	39.5			39	56.5			177	37			<0.001*
Pre-procedural NYHA III	36	6.6			19	27.5			17	3.6			<0.001*
Post-procedural NYHA I	451	82.4			41	59.4			410	85.8			<0.001*
Post-procedural NYHA II	85	15.5			21	30.4			64	13.4			<0.001*
Post-procedural NYHA III	11	2			7	10.1			4	0.8			<0.001*

PASP: Pulmonary artery systolic pressure; ASD: Atrial septal defect; BMI: Body mass index; AF: Atrial fibrillation. NYHA: New York Heart Association functional class; * p<0.05.

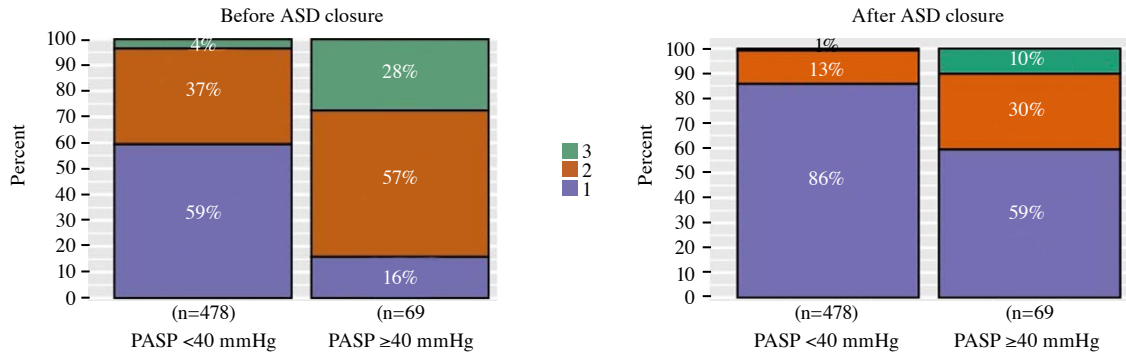


Figure 2. New York Heart Association functional class before and after atrial septal defect repair in patients whose PASP ≥40 mmHg and those with PASP <40 mmHg at the latest follow-up.

ASD: Atrial septal defect; PASP: Pulmonary artery systolic pressure.

were older than those with PASP <40 mmHg (56 *vs*. 35 years, p<0.001), were more likely to have hypertension (27.5% *vs*. 16.9%, p=0.03) and had a larger defect size (24 *vs*. 18 mm, p<0.001). Moreover, in patients with PASP ≥40 mmHg, persistent AF was more likely to be present (31.9% *vs*. 2.7%, p<0.001). There was no significant difference between surgical or transcatheter ASD closure in either group (p=0.176) (Table 1).

Of the patients with PASP ≥40 mmHg, 19 (27.5%) were in NYHA Class III at baseline, while 3.6% of those with PASP <40 mmHg were in NYHA Class III (p<0.001). After ASD repair, NYHA functional class improved in 30 (51.7%) of the 58 patients from NYHA Class II or III to I. Functional deterioration occurred only in two patients with PASP ≥40 mmHg. Among patients with PASP <40 mmHg, the proportion of patients with NYHA Class ≥II symptoms was reduced by 64.9% (Figure 2).

In 164 of 547 patients, the PASP was ≥40 mmHg before ASD closure. Normalization of PASP (<40 mmHg) occurred in 115 (70.2%) patients, and 49 (29.8%) patients had persistently elevated PASP (≥40 mmHg) after ASD closure. Among the 383 patients with PASP <40 mmHg before ASD closure, 20 (5.2%) developed new PAH during long-term follow-up after ASD closure (Figure 3). There were 69 patients with PASP ≥40 mmHg at the final follow-up after ASD repair.

Echocardiographic parameters before and at the latest follow-up after ASD closure are presented in Table 2. Patients with PASP ≥40 mmHg had larger right atrial major and right ventricular basal diameter, higher PASP and tricuspid regurgitation before ASD closure than those with PASP <40 mmHg. Compared to baseline echocardiographic values, significant reductions in these parameters were observed for both groups. However, patients with PASP ≥40 mmHg still had larger right atrial major, right ventricular basal diameter, higher PASP value, and more tricuspid regurgitation after the ASD closure than those with PASP <40 mmHg (Table 2).

Before ASD closure, 35 (6.4%) patients had persistent AF and 42 (7.6%) patients had a history of paroxysmal AF. All 35 patients with pre-existing persistent AF remained in AF during follow-up after ASD closure. In addition, two patients with paroxysmal AF prior to ASD closure developed persistent AF at follow-up. Meanwhile, 17 of 42 patients with preprocedural paroxysmal AF

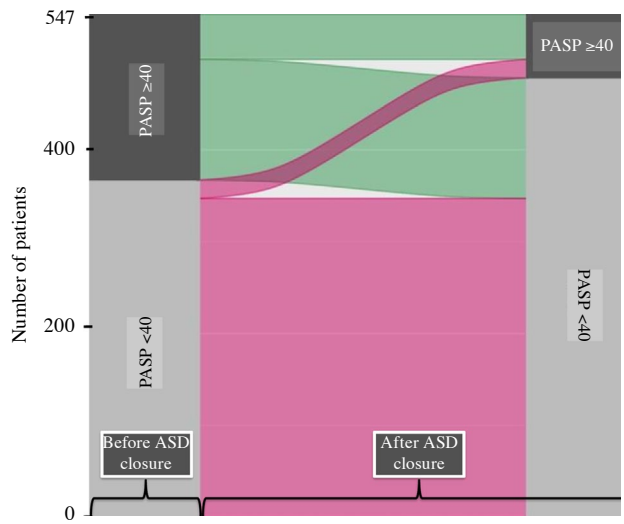


Figure 3. The change in pulmonary artery systolic pressure before and after ASD closure.

Pulmonary hypertension was much more common in patients with PASP ≥40 mmHg (27.5% *vs*. 5.4%) compared with patients with PASP <40 mmHg before ASD closure.

Table 2. Echocardiographic characteristics before and at the latest follow-up after atrial septal defect closure

	All (n=547)				PASP ≥40 mmHg (n=69)				PASP <40 mmHg (n=478)				
Variables	n	%	Median	Min-Max	n	%	Median	Min-Max	n	%	Median	Min-Max	*p*
Pre RV basal diameter (mm)			38	34-37			47	45-51			37	33-45	<0.001*
Post RV basal diameter (mm)			34	29-42			44	42-48			33	28-38	<0.001*
Pre RA major diameter (mm)			47	41-53			49	45-53			46	41-53	0.005*
Post RA major diameter (mm)			43	40-46			45	42-50			42	39-46	<0.001*
Pre TAPSE (mm)			22	20-24			20	18-23			22	20-24	<0.001*
Post TAPSE (mm)			20	18-22			18	15-21			21	18-22	<0.001*
Pre St (cm/sn)			14	14-15			14	13-16			14.2	14-15	0.11
Post St (cm/sn)			13	12-14.5			13	11-14			13	12-14.8	0.03*
Pre PASP (mmHg)			35	29-44			48	38-57			34	28-42	<0.001*
Post PASP (mmHg)			29	24-35			45	42-48			28	24-32	<0.001*
Pre TR													
Mild	396	72.4			33	47.8					363	75.9	<0.001*
Moderate	108	19.7			15	21.7					93	19.5	<0.001*
Severe	43	7.9			21	30.4					22	4.6	<0.001*
Post TR													
Mild	513	93.8			56	81.2			457	95.6			<0.001*
Moderate	27	4.9			9	13			18	3.8			<0.001*
Severe	7	1.3			4	5.8			3	0.6			<0.001*
Pre-procedural LA diameter (mm)			35	32-37			35	34-38			35	32-37	0.20
Post-procedural LA diameter (mm)			35	32-37			35	33-39			35	32-37	0.19
Pre-procedural LVEDD (mm)			45	43-47			46	43-47			45	43-46	0.21
Post-procedural LVEDD (mm)			45	44-47			46	43-48			45	44-47	0.66
Pre-procedural LVESD (mm)			27	25-30			27	25-30			27.5	25-30	0.64
Post-procedural LVESD (mm)			28	25-30			27	24-30			28	25-30	0.68
Pre-procedural LVEF (%)			64	60-65			65	59-65			64	60-65	0.39
Post-procedural LVEF (%)			65	60-65			63	60-65			65	60-65	0.39

PASP: Pulmonary artery systolic pressure; RV: Right ventricle; RA: Right atrium; TAPSE: Tricuspid annular plane systolic excursion; St: Tricuspid annulus systolic velocity; TR: Tricuspid regurgitation; LA: Left atrium; LVEDD: Left ventricle end-diastolic diameter; LVESD: Left ventricle end-systolic diameter; LVEF: Left ventricle ejection fraction; * p<0.05.

Table 3. Predictors of pulmonary hypertension after atrial septal defect closure

		Univariable HR			Multivariable HR		
Variables	Range	Median	95% CI	*p*	Median	95% CI	*p*
Age (increase from)	27 to 46	7.46	4.93-11.27	<0.001	4.76	2.68-8.44	<0.001*
Sex Female		1.06	0.64-1.74	0.81	0.68	0.40-1.15	0.14
Max diameter (increase from)	16 to 24	2.01	1.54-2.63	<0.001	0.83	0.43-1.61	0.58
Pre TR (increase from mild to severe)		5.90	3.31-10.5	<0.001	0.71	0.33-1.49	0.36
Pre RV basal diameter (increase from)	34 to 46	6.54	4.10-10.44	<0.001	4.78	2.57-8.84	<0.001*
Treatment type (transcatheter)		0.91	0.56-1.50	0.72	0.78	0.41-1.49	0.45
Pre PASP (increase from)	29 to 44	3.27	2.50-4.29	<0.001	1.33	0.75-2.35	0.33
Persistent AF		5.59	3.35-9.33	<0.001	2.18	1.21-3.91	0.009*

HR: Hazard ratio; CI: Confidence interval; TR: Tricuspid regurgitation; RV: Right ventricle; PASP: Pulmonary artery systolic pressure; AF: Atrial fibrillation. Pre: Pre-procedural; * p<0.05.

remained in sinus rhythm during follow-up, while the other 23 patients had recurrence of paroxysmal AF. Additionally, 32 (5.8%) patients developed new paroxysmal AF episode after ASD closure and sinus rhythm was maintained with electrical (n=8) or medical cardioversion with amiodarone (n=24).

The first treatment strategy was rhythm control for all patients. However, in 23 of 35 patients with long-standing persistent AF at follow-up, the treatment strategy was changed from rhythm control to rate control since sinus rhythm could not be achieved despite repeated electrical and medical cardioversion attempts.

We used Cox regression analysis to identify parameters associated with the presence of PASP ≥40 mmHg at last follow-up after ASD closure, regardless of pre-existing or newly developed PAH.

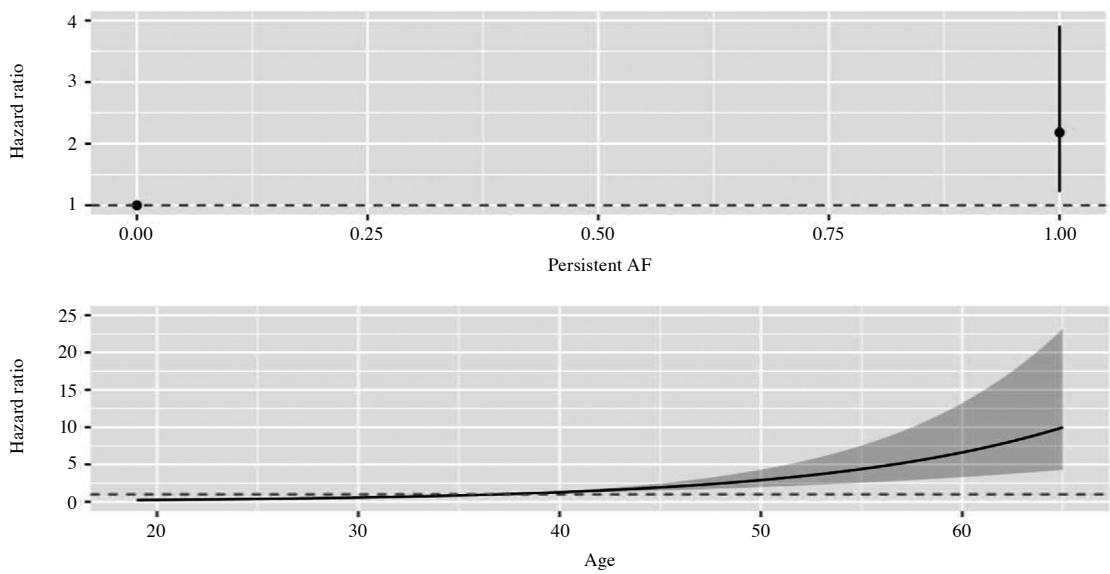
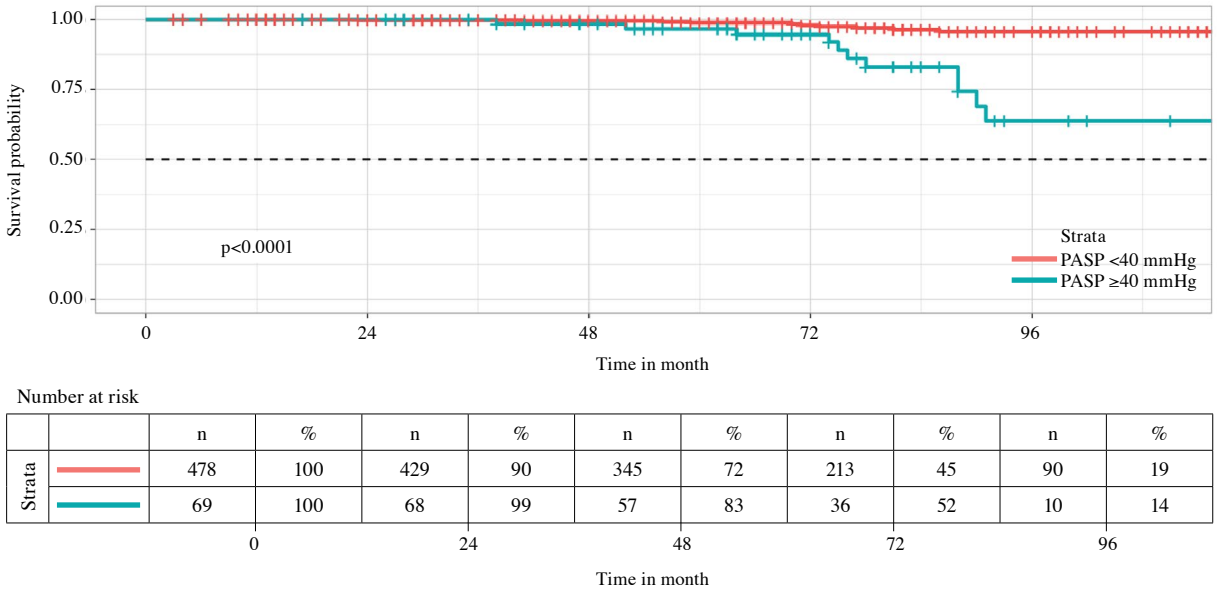


Figure 4. Hazard ratio-plot for persistent atrial fibrillation and age.
The presence of persistent AF and advanced age (>40 years) increase the risk of developing pulmonary hypertension in long-term follow-up.
AF: Atrial fibrillation; ASD: Atrial septal defect.



Number at risk

		n	%	n	%	n	%	n	%	n	%
Strata		478	100	429	90	345	72	213	45	90	19
		69	100	68	99	57	83	36	52	10	14

0 24 48 72 96

Time in month

Figure 5. Kaplan-Meier curves of event free survival by presence and absence of PAH at last follow-up after ASD closure. The event-free survival rate at long-term follow-up after ASD closure was worse in patients who developed PAH (PASP ≥40 mmHg) (p<0.001).

PASP: Pulmonary artery systolic pressure; PAH: Pulmonary arterial hypertension; ASD: Atrial septal defect.

Older age (increase from 27 to 46) at the time of ASD closure (HR: 4.76; 95% CI: 2.68-8.44; p<0.001), the presence of persistent AF (HR: 2.18; 95% CI: 1.21-3.91; p=0.009), and greater right ventricular basal diameter (increase from 34 to 46) (HR: 4.78; 95% CI: 2.57-8.84; p<0.001) were found to be associated with PAH (Table 3, Figure 4).

Twelve (17.3%) patients with PAH and 13 (2.7%) of the 478 with non-PAH were hospitalized for heart failure during the follow-up period after ASD repair. Of these 12 patients with PAH, four died during follow-up. The first death was a 56-year-old man who died from right heart failure at 10 months postoperatively. The second death occurred in a woman as a result of pneumonia. The third death was a 72-year-old woman who died, possibly from an ischemic cerebrovascular accident associated with AF, at 22 months postoperatively. The fourth death occurred in a 67-year-old patient outside the hospital and the exact cause was unknown. The event-free survival rate was worse in patients with PASP ≥40 mmHg than in those with PASP <40 mmHg (p<0.001) (Figure 5).

DISCUSSION

The main findings of this study are that older age at the time of ASD repair, the presence of persistent AF, and increased right ventricular basal diameter before ASD closure were significantly associated with PAH at long-term follow-up after ASD closure.

The long-standing left-to-right interatrial shunt causes structural and electrophysiological changes such as anisotropic conduction delay or functional block in the right atrium.[17] These electrophysiological changes have been shown to play a key role in the development of AF.[18] Therefore, AF is the byproduct of chronic right heart volume overload in patients with secundum ASD, suggesting irreversible atrial damage.[4] Considering this, Humenberger et al.[13] revealed that the prevalence of paroxysmal atrial arrhythmia could decrease after ASD closure, but the frequency of persistent AF did not. Seeing that longer exposure to chronic volume overload is associated with AF formation, we hypothesized that the presence of persistent AF, which is a possible reflection of irreversible atrial damage due to long-term hemodynamic overload, may be associated with PAH.

In this study, the presence of persistent AF was found to be an independent predictor of PAH after ASD closure. In line with our result, the presence of PAH after ASD closure was related to a higher prevalence of atrial arrhythmias.[19] Moreover, Thilén et al.[20] showed that the presence of AF (particularly

chronic AF) reduced the potential for positive cardiac remodeling after ASD closure.

Chronic right ventricular volume overload causes geometric and histological changes in the right ventricle, including dilation and even myocardial fibrosis.[6] Likewise, our study showed that patients with PAH had significantly larger right ventricular basal diameter both before and after ASD closure. Furthermore, a larger right ventricular basal diameter (increase from 34 to 46) was associated with the presence of PAH after ASD closure.

As PASP increases continuously with age, a significant proportion of patients with ASD may develop PAH during long-term follow-up.[3] In this study, 73.9% of patients with PASP ≥40 mmHg at long-term follow-up after ASD closure were older than 50 years of age, and multivariate analysis revealed that advanced age (increase from 27 to 46), at the time of ASD closure was significantly associated with PAH. Similarly, older age was associated with the development of PAH in previous studies.[3,10,11]

Nonetheless, the present study has several limitations. First, this is a retrospective study from a single-center experience. Second, patients with severe or irreversible PAH (Eisenmenger syndrome), combined tricuspid valve repair at the time of surgery, and heart failure were excluded. Therefore, it is not possible to draw a conclusion for these patients. Finally, although the median follow-up was 68 months, longer clinical and functional follow-up data may provide more information about PAH and associated risk factors.

In conclusion, our study results provide important mechanistic insight that patients with persistent atrial fibrillation are at an increased risk for the development or persistence of pulmonary arterial hypertension after atrial septal defect closure. Therefore, the presence of persistent atrial fibrillation may be used to predict the risk of pulmonary hypertension after atrial septal defect closure.

Ethics Committee Approval: The study protocol was approved by the Koşuyolu Training and Research Hospital Local Ethics Committee Ethics Committee (date/no: 2021/16/555). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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