Available online at www.medicinescience.org

ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2026;15(1):276-9

Cardiac abnormalities and clinical follow-up in children with noonan syndrome: A single-center retrospective study

Emine Yurdakul Erturk[1], Taner Kasar[2]

[1]*Ordu University, Faculty of Medicine, Department of Pediatrics, Ordu, Türkiye*
[2]*Ordu University, Faculty of Medicine, Department of Pediatric Cardiology, Ordu, Türkiye*

Received 12 October 2025; Accepted 08 December 2025
Available online 23 February 2026 with doi: 10.5455/medscience.2025.10.276

Abstract

Noonan Syndrome (NS) is a RASopathy with a high burden of congenital heart disease. This study aims to summarize the demographic characteristics, cardiovascular findings, genetic results, applied interventions, and follow-up outcomes of pediatric NS cases followed at our center. Pediatric NS cases followed between December 2017 and August 2025 were examined in a single-center, retrospective, and descriptive design. Demographic data, echocardiography (ECHO) and 12-lead electrocardiography (ECG) findings, genetic analysis results, cardiac interventions, and follow-up outcomes were compiled from electronic records. Continuous variables were summarized descriptively. Nine children were included in the study (median age 8 years; range 2 months–14 years; 66.7% female). The most common accompanying pathology was pulmonary stenosis (PS, 6/9; 66.7%). Among the pulmonary stenosis cases, it was mild in one, moderate (valvular) in one, severe in three (two valvular, one associated with valve dysplasia/severe pulmonary artery hypoplasia), and borderline moderate-severe in one. Hypertrophic cardiomyopathy (HCM) was detected in 3/9 (33.3%) cases (1 obstructive, 2 non-obstructive). Other associated pathologies included atrial septal defect (ASD, 3/9), ventricular septal defect (VSD, 1/9), bicuspid aortic valve (BAV, 1/9), and mitral valv prolapsusu (MVP, 1/9). In genetic analysis, PTPN11 was dominant (5/9, 55.6%); RAF1 mutation was detected in two cases, SOS1 and KRAS mutations were each found in one case. Four patients (44.4%) underwent surgery: three underwent balloon pulmonary valvuloplasty and one with obstructive HCM underwent septal myectomy+mitral repair. In this pediatric NS series, PS was the dominant lesion, and HCM was a significant source of morbidity. Ballon valvuloplasty outcomes appear to be sensitive to valve morphology, and an early surgical approach may be appropriate for persistent/recurrent gradients. The findings emphasize the importance of structured follow-up supported by genotype information and point to the need for larger multicenter studies.

Keywords: Noonan syndrome, rasopathy, pulmonary stenosis, hypertrophic cardiomyopathy, pediatric cardiology

Introduction

Noonan Syndrome (NS) is a clinical condition, mostly inherited in an autosomal dominant manner, characterized by distinctive facial dysmorphism (hypertelorism, ptosis, low-set ears), short stature, varying degrees of developmental delay, lymphatic system anomalies, and cardiac defects [1,2]. The incidence of NS has been reported as 1/1000–1/2500 live births, making it one of the most common syndromic causes of congenital heart disease (CHD) after Trisomy 21 [3,4]. At the molecular level, it has been shown that the NS phenotype largely depends on gain-of-function variants in the RAS/MAPK signaling pathway, and therefore conditions associated with NS are grouped under the heading "RASopathies" [5].

Cardiac involvement is one of the primary determinants of presentation and follow-up in NS, with the frequency of heart disease reported to exceed 80% in different series; the most common lesions reported are valvular pulmonary stenosis (PS), atrial septal defect (ASD), and hypertrophic cardiomyopathy (HCM) [1,6]. Long-term outcomes of percutaneous ballon pulmonary valvuloplasty (BPV) for PS can be variable in NS, with suboptimal responses reported in some studies [6,7]. The clinical presentation and natural history of HCM associated with NS can be associated with a worse prognosis compared to non-syndromic HCM; this necessitates careful individualization of

CITATION
Yurdakul Erturk E, Kasar T. Cardiac abnormalities and clinical follow-up in children with noonan syndrome: A single-center retrospective study. Med Science. 2026;15(1):276-9.

Corresponding Author: Emine Yurdakul Erturk, Ordu University, Faculty of Medicine, Department of Pediatrics, Ordu, Türkiye
Email: eyurdakul52@hotmail.com

DOI: 10.5455/medscience.2025.10.276

risk stratification and management strategies [8,9].

In recent years, multicenter network studies and large single-center cohorts have detailed the diversity of the cardiac phenotype in RASopathies, the potential higher-than-expected frequency of atypical defects, and the clinical implications of genotype-cardiac phenotype correlations [10,11]. The combined assessment of cardiovascular abnormalities and gene mutations in children with NS is important for more accurate prediction of prognosis and the development of targeted treatment approaches [10,12].

This study addresses the demographic data, cardiovascular findings, applied interventions, genetic analyses, and follow-up outcomes of nine pediatric NS cases followed at our center. Our literature review revealed that, aside from case reports and limited reviews, there is no cohort or registry-based study in our country examining the cardiovascular findings of NS.

Material and Methods

This single-center, retrospective, descriptive study included pediatric patients diagnosed with NS and followed at the Ordu University Training and Research Hospital, Pediatric Cardiology Outpatient Clinic. Hospital electronic health records and archive files were retrospectively reviewed for the period covering December 2017 to August 2025. A total of 9 pediatric patients with regular follow-up during this period and with data suitable for the study were included. Patients suspected based on clinical and family history and those diagnosed through genetic examination (in our hospital and external centers) were included. For each case, demographic data (age, sex) were recorded; echocardiography (ECHO) findings and 12-lead surface electrocardiography (ECG) results were systematically reviewed for cardiac assessment. Reported molecular test results were added to the file for patients who underwent genetic analysis. Additionally, applied medical treatments and performed interventional/surgical procedures were recorded; follow-up duration, mortality, and clinical outcomes were analyzed within the scope of follow-up data.

The study was approved by the Ordu University Non-Interventional Scientific Research Ethics Committee (decision no: 2025-283). Informed consent was not required due to the retrospective design. All processes were conducted in accordance with the principles of the Helsinki Declaration; patient privacy was protected by de-identification of the data.

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as mean ± standard deviation (SD) if the normality assumption was met, or as median (minimum–maximum) if not; categorical variables are presented as number (n) and percentage (%). Due to the limited sample size, findings were reported primarily using descriptive statistics.

Result

The median age of the total 9 patients included in the study was 8 years (2 months–14 years), with 6 females (66.7%) and 3 males (33.3%). The mean follow-up duration was calculated as 61.1 months (2–88 months). In patients with available genetic testing, PTPN11 mutation was the most frequently detected variant, identified in 5/9 (55.6%) cases. Other genetic changes were identified as RAF1 (n=2), SOS1 (n=1), and KRAS (n=1). Demographic and clinical characteristics are summarized in Table 1.

Table 1. Demographic and clinical characteristics (Total number of patients, n=9)

Parameter	Value
Age, median (min–max)	8 years (2 months–14 years)
Sex	Female= 6 (66.7%)
	Male= 3 (33.3%)
Follow-up duration, mean (min–max), months	61.1 (2–88)
Cardiovascular findings, n (%)	PS= 6 (66.7)
	HCM= 3 (33.3)
	ASD= 3 (33.3)
	MR= 2 (22.2)
	VSD= 1 (11.1)
	MVP= 1 (11.1)
	BAV= 1 (11.1)
	AR= 1 (11.1)
	Pulmonary artery hypoplasia= 1 (11.1)
Genetic, n (%)	PTPN11 = 5 (55.6)
	KRAS = 1 (11.1)
	RAF1 = 2 (22.2)
	SOS1 = 1 (11.1)
Interventional procedure, n (%)	Transcatheter intervention= 3 (33.3)
	Surgical intervention= 2 (22.2)
Exitus, n (%)	1 (11.1)

PS: pulmonary stenosis, HCM: hypertrophic cardiomyopathy, ASD: atrial septal defect, MR: mitral regurgitation, VSD: ventricular septal defect, MVP: mitral valve prolapse, BAV: bicuspid aortic valve, AR: Aortic regurgitation. Percentages are calculated based on total N; multiple cardiovascular findings may coexist in the same patient

Echocardiographic findings revealed PS as the most frequent cardiac anomaly, present in 6/9 (66.7%) cases. Among these, PS was mild in one case, moderate (valvular) in one case, severe in three cases (two valvular, one associated with pulmonary valve dysplasia/severe pulmonary artery hypoplasia), and

DOI: 10.5455/medscience.2025.10.276

moderate-severe in one case. HCM was diagnosed in three patients (33.3%); one was obstructive and two non-obstructive. Other associated lesions included ASD; 3/9, 33.3%, ventricular septal defect (VSD); 1/9, 11.1%, bicuspid aortic valve (BAV); 1/9, 11.1%, and mitral valve prolapse (MVP); 1/9, 11.1%. The clinical characteristics of the patients are detailed in Table 2.

At least one characteristic ECG abnormality was detected in 8/9 (88.9%) of the cases. The most frequent patterns were right ventricular hypertrophy (RVH); 5/9 and left ventricular hypertrophy (LVH); 3/9. More rarely, strain pattern (1/9) and Wolff-Parkinson-White syndrome (WPW) syndrome (1/9) were recorded. Interventional or surgical treatment was applied in 4/9 (44.4%) cases. One of them underwent septal myectomy and mitral valve repair due to obstructive HCM. Three patients were treated with BPV for significant valvular PS; one of these three subsequently required surgical pulmonary valvotomy during follow-up. The two cases with non-obstructive HCM were followed under β-blocker therapy. Two cases with mild and moderate PS were followed with clinical monitoring only. One patient followed in the neonatal period, with severe pulmonary artery hypoplasia and critical PS, died at 2 months of age.

Table 2. Clinical characteristics of patients with noonan syndrome

Year (yrs)	Sex	Genetic	ECHO findings	ECG findings	Treatment	Follow-up
10	F	RAF1	PS (moderate-severe)	RVH	BPV	48
14	F	RAF1	HCM (obstructive) MR (moderate) AR (mild)	LVH-Strain	Septal myectomy+ mitral valve repair	84
4	M	KRAS	PS (mild)	Normal	Clinical fallow-up	40
11	F	PTPN11	HCM (non-obstructive) ASD, MVP	LVH, WPW	ß-bloker	88
6	M	PTPN11	PS (valvüler, moderate), ASD, VSD, BAV	RVH	Clinical fallow-up	72
11	F	SOS1	PS, PVD (severe)	RVH	BPV	66
3	F	PTPN11	HCM (non-obstructive), ASD	LVH	ß-blocker	82
8	M	PTPN11	PS (valvular, severe)	RVH	BPV, Pulmonary valvulotomy	68
2 months	F	PTPN11	PS, Pulmonary artery hypoplasia (severe)	RVH	Clinical fallow-up Medical therapy	Exitus at 2nd month

F: Female, M: Male, ECHO: Echocardiography, ECG: Electrocardiography PS: Pulmonary stenosis, RVH: Right ventricular hypertrophy, BPV: Ballon pulmonary valvuloplasty, HCM: Hypertrophic cardiomyopathy, MR: Mitral regurgitation, AR: Aortic regurgitation, LVH: Left ventricular hypertrophy, ASD: Atrial septal defect, MVP: Mitral valve prolapse, WPW: Wolff-Parkinson-White syndrome, VSD: Ventricular septal defect, BAV: Bicuspid aortic valve, PVD: Pulmonary valve dysplasia

Discussion

Our national literature search indicates that there is no cohort/registry-based study systematically evaluating the cardiovascular findings of NS in Turkey; publications remain largely limited to case reports and limited reviews. In this context, to our knowledge, the series we present is the first cohort in our country to jointly and systematically address the cardiovascular phenotype, applied interventions, genetic data, and follow-up outcomes in pediatric NS.

The detection of PS as the dominant lesion in our cohort (66.7%) and the significant frequency of HCM (33.3%) are generally consistent with the reported diversity and burden of the cardiac phenotype in NS [12]. The frequent association of PS with valve dysplasia in NS and the management challenges of this phenotype have been emphasized in detail in multicenter and single-center series [12]. In our data, ECG abnormalities were common (especially RVH/LVH and WPW in one case), consistent with findings suggesting that unusual ECG patterns can be frequently seen in NS [12]. Genetically, our distribution dominated by PTPN11 (5/9, 55.6%) and the detection of RAF1 and SOS1 at lower rates aligns with the genotype spectrum and cardiac phenotype correlations reported in large series of RASopathies [11].

Regarding real-world practice in the management of pulmonary stenosis, the need for surgical valvotomy during follow-up in one of the three cases in our cohort who underwent BPV is consistent with the literature indicating that dysplastic valve morphology in NS can create relative resistance to balloon valvuloplasty [10]. Indeed, studies examining recent and medium-to-long-term outcomes have shown that residual gradient and the need for re-intervention may increase after pulmonary BPV in pediatric NS cases [13]. Therefore, in the approach to PS in NS, it is clinically rational to carefully evaluate echocardiographic morphology (dysplasia, commissural fusion, annular size) and to consider surgical valvotomy with a low threshold if the initial intervention fails [14].

The variable presentation according to age and the need for different treatment pathways in our HCM cases (obstructive and non-obstructive) are consistent with reviews indicating that HCM in NS can be more heterogeneous and sometimes have a more unfavorable course compared to non-syndromic HCM [9]. Given the natural history of RASopathy-specific HCM, the

DOI: 10.5455/medscience.2025.10.276

frequency of concomitant CHD, and the tendency for diagnosis at an early age, it is recommended that risk stratification be performed dynamically along with genotype information [10]. The association of HCM with RAF1 and, more rarely, BRAF mutations has been repeatedly reported in large cohorts; it should be remembered that in obstructive phenotypes, septal myectomy can provide symptom control in selected cases, but the risk of re-obstruction is not completely eliminated [11].

The relatively frequent association of PS/ASD in cases with PTPN11 mutation in our cohort is also supported by recent single-center/large series data [11]. Similarly, the tendency for PS and accompanying valvular/conduction findings in SOS1 mutation exhibits a pattern consistent with previous genotype-phenotype analyses [11]. These findings demonstrate that integrating routine cardiological follow-up with genetic results in NS has clinical value for prognosis prediction and intervention timing [14].

The most common congenital heart disease in Noonan syndrome, as in our cohort, is pulmonary stenosis. The standard treatment for PS is balloon valvuloplasty, but reintervention is required in up to 65% of cases due to high pulmonary gradients. The case in our cohort, which presented in the neonatal period with severe pulmonary artery hypoplasia and critical PS and resulted in death in the second month, reminds us that severe right ventricular outflow tract obstruction and associated pulmonary vascular anomalies in NS can increase the risk of early mortality [14]. It has been reported that individuals with Noonan syndrome and pulmonary stenosis carrying the PTPN11 mutation are at higher risk for intervention [15]. The only case lost in our cohort also had PS, severe pulmonary artery hypoplasia, and the PTPN11 mutation. However, our patient died at 2 months of age before surgical intervention could be performed. In such cases, multidisciplinary management from birth, close collaboration with cardiac surgery and advanced intensive care facilities for early intervention strategies and, if necessary, palliative/staged approaches, is critically important [14].

The limitations of our study include its single-center and retrospective design, small sample size, and referral bias; therefore, the generalizability of the findings may be limited.

Conclusion

In our small, single-center pediatric NS series, pulmonary stenosis was the most frequent lesion, and hypertrophic cardiomyopathy was a significant source of morbidity. The dominance of PTPN11 in the genotype distribution and its association with PS/ASD, as well as the tendencies for HCM/valvular phenotypes with RAF1/SOS1, are noteworthy findings. It was observed that BPV outcomes may be influenced by valve morphology, and surgery should be considered early in case of failure or recurrence.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical Approval
The study received ethical approval from the Ordu University Non-Interventional Scientific Research Ethics Committee (approval date 26.09.2025) (decision no: 2025-283).

References

1. Romano AA, Allanson JE, Dahlgren J, et al. Noonan syndrome: clinical features, diagnosis, and management guidelines. Pediatrics. 2010;126:746-59.
2. Roberts AE, Allanson JE, Tartaglia M, Gelb BD. Noonan syndrome. Lancet. 2013;381: 333-42.
3. Allanson JE, Hall JG, Hughes HE, et al. Noonan syndrome: the changing phenotype. Am J Med Genet. 1985;21:507-14.
4. Marino B, Digilio MC, Toscano A, et al. Congenital heart diseases in children with Noonan syndrome: an expanded cardiac spectrum with high prevalence of atrioventricular canal. J Pediatr. 1999;135:703-6.
5. Aoki Y, Niihori T, Narumi Y, et al. The RAS/MAPK syndromes: novel roles of the RAS pathway in human genetic disorders. Hum Mutat. 2008;29:992-1006.
6. Prendiville TW, Gauvreau K, Tworog-Dube E, et al. Cardiovascular disease in Noonan syndrome. Arch Dis Child. 2014;99:629-34.
7. McCrindle BW; VACA Registry Investigators. Independent predictors of long-term results after balloon pulmonary valvuloplasty. Circulation. 1994;89:1751-9.
8. Hickey EJ, Mehta R, Elmi M, et al. Survival implications: hypertrophic cardiomyopathy in Noonan syndrome. Congenit Heart Dis. 2011;6:41-7.
9. Lioncino M, Monda E, Verrillo F, et al. Hypertrophic cardiomyopathy in RASopathies. Heart Fail Clin. 2022;18:19-29.
10. Calcagni G, Adorisio R, Martinelli S, et al. Clinical presentation and natural history of hypertrophic cardiomyopathy in RASopathies. Heart Fail Clin. 2018;14:225-35.
11. Leoni C, Blandino R, Delogu AB, et al. Genotype-cardiac phenotype correlations in a large single-center cohort of patients affected by RASopathies. Am J Med Genet A. 2022;188:431-45.
12. Sun L, Xie YM, Wang SS, Zhang ZW. Cardiovascular abnormalities and gene mutations in children with Noonan syndrome. Front Genet. 2022;13:915129.
13. Holzmann J, Tibby SM, Rosenthal E, et al. Results of balloon pulmonary valvoplasty in children with Noonan's syndrome. Cardiol Young. 2018;28:647-52.
14. Linglart L, Gelb BD. Congenital heart defects in Noonan syndrome: diagnosis, management, and treatment. Am J Med Genet C Semin Med Genet. 2020;184:73-80.
15. Calcagni G, Limongelli G, D'Ambrosio A, et al. Cardiac defects, morbidity and mortality in patients affected by RASopathies. CARNET study results. Int J Cardiol. 2017;245:92-8.