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ORIGINAL ARTICLE

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Incidence and natural history of neonatal isolated ventricular septal defects: Do we know everything? A 6-year single-center Italian experience follow-up

Alberto Cresti MD[1] | Raffaele Giordano MD[2] | Martin Koestenberger MD[3] | Isabella Spadoni MD[4] | Marco Scalese PhD[5] | Ugo Limbruno MD[1] | Susanna Falorini MD[6] | Stefania Stefanelli MD[1] | Andrea Picchi MD[1] | Francesco De Sensi MD[1] | Angela Malandrino MD[7] | Massimiliano Cantinotti MD[4,5]

[1]Department of Cardiology, Misericordia Hospital, Grosseto, Italy

[2]Department of Advanced Biomedical Sciences, University of Naples Federico II, Naples, Italy

[3]Division of Pediatric Cardiology, Medical University of Graz, Graz, Austria

[4]Fondazione G. Monasterio CNR-Regione Toscana, Massa and Pisa, Italy

[5]Institute of Clinical Physiology, Pisa, Italy

[6]Department of Pediatrics, Misericordia Hospital, Grosseto, Italy

[7]Department of Cardiology, Santa Maria alle Scotte Hospital, University of Siena, Siena, Italy

Correspondence
Raffaele Giordano, Department of Advanced Biomedical Sciences, University of Naples Federico II, Naples, Italy.
Email: r.giordano81@libero.it

Abstract

Background: Despite ventricular septal defects (VSDs) are the most common congenital heart diseases (CHDs) in the neonatal period, their incidence and natural history are still debated and their follow-up and management strategies remain controversial. Our aim was to evaluate the incidence and natural history of isolated VSDs.

Methods: From January 1996 to December 2015 all neonates with a CHD suspicion were referred to the Cardiological Department of Grosseto Misericordia Hospital. Only newborns with confirmed isolated VSD were enrolled in this study and followed for 6 years.

Results: Our 343 newborns with an isolated VSD (incidence of 10.45/1000/births) account for 64% of all detected CHDs. VSDs location were as follows: muscular (73.8%), perimembranous (11.3%), inlet (1%), and outlet (0.8%). Of the located VSDs, 90% were small, 7.5% moderate, and 2.5% large, respectively. Spontaneous closure was observed in 96 (29.2%) of the VSD patients at 6-month, 198 (60.2%) at 1-year, 261 (79.3%) at 2-year, and in 302 (91.8%) at 6-year follow-up. Risk factors for defect persistence were a perimembranous location ($P = .001$; HR: 0.508, CI: 0.342-0.755), detection of multiple defects ($P = .043$; HR: 0.728, CI: 0.536-0.990), and male gender ($P < .048$; HR: 0.783, CI: 0.615-0.998), respectively.

Conclusions: We here provide an incidence and natural history of neonatal isolated VSDs in a neonatal Caucasian population. These data may be useful for the development of expert consensus/standard recommendation guidelines for the follow-up and VSD management, data that are currently lacking.

KEYWORDS

children, echocardiography, neonates, ventricular septal defects

1 | INTRODUCTION

Ventricular septal defects (VSDs) are the most common type of congenital heart diseases (CHDs) in newborns. However, the exact incidence and the natural history of these defects remain controversial, with important implications on their management and follow-up. A meta-nalysis of 53 studies in 2002 reported a mean VSD incidence of 3.45/1000 live births[1]; however, small VSDs were excluded in these studies, most of which were carried out in the 1980s, therefore their data may be unrepresentative in the current era. Nowadays, the widespread use of neonatal and fetal echocardiography[2,3] allows the diagnosis of small defects that once could have been missed.[4]

Thus, VSD estimates in newborns need to be updated. In recent studies describing the prevalence of neonatal CHDs, the reported birth incidence of VSDs greatly varied among different authors and according to the different screening methodologies (ie, echocardiographic screening only for CHD suspicion or for all healthy newborns), from 5/1000 up to 53.2/1000.[5–8]

Various aspects of the natural history of isolated VSDs still remain unclear. Particularly, the rate of spontaneous closure is being debated. Studies evaluating the natural history of VSDs are limited and incomplete to date[4,9–11] due to the fact that lots of authors evaluated only perimembranous or muscular defects,[12] and, furthermore, because a long-term follow-up is often missing, as several series evaluated only the first year of life.[4] Among criteria of spontaneous closure, older studies included the disappearance of the typical murmur, without echocardiographic confirmation, which is a questionable methodology, since tiny shunts may be silent at auscultation.[13] Moreover, most reports derive from tertiary centres[4,12,13] where a selection bias may have occurred, while single-center databases may have been underpowered.[11] The lack of clear data on the natural history of VSDs is not only self-limiting but has also a clinical impact. In fact, the follow-up and management strategy of an isolated VSD is often controversial.[14] Questions occur such as: how often does a follow-up investigation have to be performed or when can patients be discharged? Recent surveys have revealed a great discordance among pediatric cardiologists (even operating within the same country) on the follow-up frequency of small to moderate VSDs, and no guidelines/experts consensus opinions are currently available.[14,15] Thus, VSDs are often simple defects with a clinical dilemma.

Aim of the study was to analyses the actual incidence and natural evolution of detected isolated VSDs in a long follow-up period.

2 | METHODS

2.1 | Patient population

From January 1996 to December 2015 all newborns with a suspicion to have a CHD were referred to the echocardiography laboratory of the Cardiological Department of Grosseto Misericordia Hospital. Newborns diagnosed to have a VSD were entered into our database. The total average annual province population consisted in 218 563 inhabitants (99.8% Caucasian, average age 45.7 years). The province average annual birth rate in the 1996–2015 period was 1559 newborns per year.

Inclusion criteria were all neonates with isolated VSDs evaluated within the first month of life.

Exclusion criteria were children >1 month of age. VSDs associated with other CHDs such as atrioventricular septal defect, tetralogy of Fallot, transposition of the great arteries, tricuspid atresia, pulmonary stenosis, and coarctation of the aorta.

2.2 | Study protocol

At the first visit, a physical exam, a 12-lead electrocardiogram and a transthoracic echocardiography were performed. A chest x-ray and a pulse oximetry were prescribed in cases of large defects or of symptoms such as tachypnea, respiratory distress, poor feeding. Follow-up was scheduled at fixed time intervals: 1 month, 6 months, 1 year, 2 years, and then annually if the defect was still present. Follow-up was considered completed after 6 years or, in case of complete defect closure, spontaneous or surgical. Closer evaluations were prescribed in case of moderate to large shunts. In case of large defects or symptoms patients were evaluated by a heart team including a cardiologist and a cardiac surgeon of the tertiary referral center (Fondazione CNR-Regione Toscana Gabriele Monasterio, Massa, Italy). Large shunts with right-to left shunts, volume ratio (Q_p/Q_s) > 2, signs or symptoms of pulmonary congestion, or growth retardation, were the main indications for surgery. The study was in line with the ethical standards of the Declaration of Helsinki. Consensus to participate was achieved by parents/tutor/legal guardians.

2.3 | Echocardiography

All echocardiographic exams were performed at Cardiological Department of Grosseto Misericordia Hospital by two experienced pediatric cardiologists (A.C. and S.S.) who were certified by the Italian Society of Echocardiography (SIEC) with a Level III competence. An Acuson Sequoia 512 ultrasound system model (Siemens Healthcare Ultrasound System, Erlangen, Germany) was used from 1998 to 2001 and a Vivid-7 ultrasound system model (GE-Healthcare, Milan, Italy) from 2002 to 2015. Both Systems were equipped with dedicated neonatal high frequency probes (bandwidth 10–4 MHz).

2.4 | Nomenclature

Although many VSD nomenclatures have been proposed,[16] we chose the classification derived from Soto et al.[17] Single or multiple VSDs may be present and different types of defects may coexist. Spontaneous closure was defined as the absence of color flow mapping shunt. The defect size was measured by the bidimensional imaging, unless borders are not clearly detectable; in that case, alternatively, the thickness of the color jet through the septum may be used, although the latter method may lead to an overestimation of the size. Although there is no standardization to define VSD size by echocardiography (ie, how to define small, moderate, or large defects),[18] we followed the classification proposed by Liu et al.[19] Thus, VSDs were defined "small," when less than 3 mm, "medium," in case they were 3–5 mm, or "large" if more than 5 mm, respectively. We preferred this simple classification to the ratio of the defect diameter to the aortic root (a defect is small when the ratio is less than one third and large when equal to the aortic root).[19] However, assuming a median aortic root diameter in the newborn of 9–10 mm,[20] the results of the two methods are similar.[12]

2.5 | Statistical analysis

Categorical variables were expressed as number of cases and percentages. Continuous variables were expressed as mean ± SD. Events rates (spontaneous closure or surgical closure) were estimated with Kaplan-Meier curves and compared by the log-rank test. The association of selected variables with outcome were assessed with Cox's

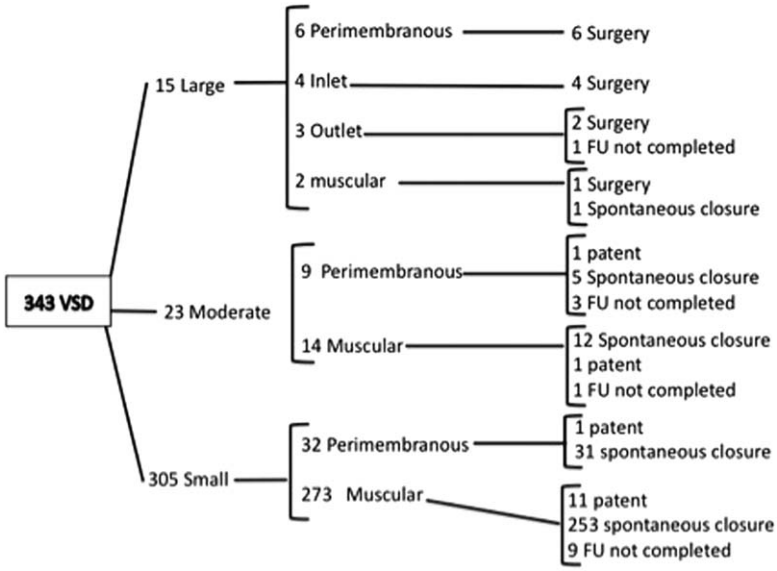

FIGURE 1 Flowchart showing the natural history of the 343 VSDs studied

proportional hazard model using stepwise multivariable procedures, a significance of 0.05 was required for a variable to be included into the multivariable model. Hazard ratios (HR), with the corresponding 95% confidence interval (CI), were estimated. The following co-variates were analyzed: age, sex, type, number of defects, severity, associated pathologies. Statistical significance was set at $P < .05$. Statistical Package for the Social Sciences (SPSS release 17.0, Chicago, IL) was used for the analysis.

3 | RESULTS

A total number of 31.185 live-births was registered in our province from January 1996 to December 2015, 16 822 males and 14 363 females (male/female ratio: 1.17), respectively. The average annual population was 218 563 inhabitants and the average birth rate was 1.559 newborns per year.

A total number of 10 167 echocardiographic exams for suspicion of CHD were performed in the live-birth population with an average of 509 exams per year, accounting for 32.6% of all newborns. Among the screened population, 532 CHDs were diagnosed, with an incidence rate of 17/1000 newborns per year. A total number of 343 isolated VSDs were found, with an incidence rate of 10.45/1000/births (male/female ratio: 0.73) and accounting for 64% of all CHDs. A single defect was the most common (84%), while multiple VSDs were found only in 55 cases (16%). Two VSDs were present in 51 newborns and three VSDs in only 4 neonates (respectively, 15% and 1.5% of the total), while no cases of "Swiss cheese" septum were found in our investigated population.

Muscular VSD was found in 289 cases (73.8%), whereas 47 perimembranous (11.3%), 4 inlet (1.1%), and 3 outlet VSDs (0.87%) were found. Depending on the defect size, VSDs were termed "small" in 305 patients (88.9% of all VSDs), "moderate" in 23 (6.7%), and 15 were termed "large" (VSDs) (4.4%). Defect locations and sizes are summarized in Figure 1.

3.1 | Natural and surgical history in isolated VSDs

A complete follow-up (6-year follow-up time or complete closure/surgery) was achieved in all cases except for 14 of them (that are still on follow-up intermediate steps). Spontaneous closure was observed in 302 newborns (91.8%), a VSD persistence, at 6-year follow-up, was found in 14 cases (4.2%), while 13 patients (4%) required surgical intervention. In surgically treated patients, the median age at operation was 7 months (2–26 months). A perimembranous location and defect size (vs muscular type) were associated with increased risk of surgery ($P = .09$) (Figure 1).

3.2 | Rate and timing of spontaneous closure

Spontaneous closure of VSD was observed in 96 patients (29.2%) at 6-month, in 198 (60.2%) at 1-year, in 261 (79.3%) at 2-year, and in 302 (91.8%) at 6-year follow-up. Excluding 13 surgically treated patients (3.9% of all VSDs), natural closure rate was found to be 91.8%. Spontaneous closure was more frequent and earlier in muscular vs perimembranous VSDs (33% vs 9% at 6-month follow-up; $P = .001$), 66.6% vs 27.3% at 1-year ($P < .001$), 85% vs 52% at 2-year ($P < .001$), and 95% vs 81.8% at 6-year ($P = .001$) follow-up. Rate and timing of spontaneous closure for different types of VSDs are summarized in Tables 1 and 2. The significant difference in the VSD closure among muscular vs perimembranous VSDs is highlighted in the Kaplan-Meier closure curves ($P = .001$), as shown in Figure 2 on panel C-D. Muscular midventricular defects tend to close earlier (80.6% at 1-year follow-up) compared to apical ($P = .43$) and marginal ($P = .24$) VSDs. However, no significant differences were seen.

3.3 | Factors influencing spontaneous closure

The multivariate analysis showed that risk factors of a defect persistence were perimembranous site ($P = .001$; HR:0.508, CI 0.342–0.755),

TABLE 1 Rate and timing of spontaneous VSD closure according to different types of defects

Spontaneous closure		6 Months	1 Year	2 Years	6 Years	Surgery
Muscular central	164 (50%)	62 (38%)	133 (81%)	152 (92.7%)	160 (97%)	1 (0.6%)
Muscular apical	81 (24.6%)	23 (28.4%)	41 (50.6%)	62 (76.5%)	75 (92.5%)	0
Muscular marginal	24 (7.3%)	6 (25%)	10 (41.7%)	18 (75%)	22 (91.6%)	0
Muscular multiple	10 (3%)	1 (10%)	2 (20%)	6 (60%)	9 (90%)	0
Total muscular	279 (84.8%)	92 (33%)	186 (66.6%)	238 (85%)	266 (95%)	-
Perimembranous	44 (13.4%)	4 (9%)	12 (27.3%)	23 (52%)	36 (81.8%)	6 (13.6%)
Inlet	4 (1.2%)	0	0	0	0	4 (100%)
Outlet	2 (0.6%)	0	0	0	0	2 (100%)
Total	329	96 (29.2%)	198 (60.2%)	261 (79.3%)	302 (91.8%)	13 (3.9%)

multiple defects ($P = .043$; HR: 0.728, CI: 0.536–0.990), and male gender ($P < .048$; HR: 0.783, CI: 0.615–0.998). Results of the multivariate analysis are reported in detail in Table 3 (surgical patients have been excluded). Interestingly, size was not found to be a risk factor for VSD persistence. However, large VSDs underwent surgery in 13 out of 14 cases, thus they were excluded. Cox's analysis revealed no significant differences in the closure rate between moderate and small defects ($P = .456$), however, there was a great patient size discrepancy between these two groups (ie, 305 small vs 23 moderate sized VSDs), that may affect results. During the follow-up, no cases of death or IE occurred. In the few cases of moderate and large defects (19 and 2 cases, respectively) that still remained open at follow-up investigation, aortic valve prolapse, aortic regurgitation, left ventricle-to-right atrium shunt, subaortic ridge, and infundibular stenosis never developed.

4 | DISCUSSION

Isolated VSDs are very common lesions, generally easy to diagnose and manage, but they pose controversial clinical questions. Are they totally benign lesions? Will they close completely and what will the closure time be? How often will we have to follow up such defects? How should we communicate their presence to parents? VSD incidence widely varied among studies,[7,21–23] with differences mainly related to study protocols (ie, inclusion criteria, sample size, and population evaluated) and to the era in which they were performed (with older studies poorly applicable to the current era).

TABLE 2 Timing of spontaneous closure: mean and median age (months) ± standard deviation according to different VSD types

	Mean age of closure (months ± SD)	Median age of closure (months ± SD)
Perimembranous	45 ± 7.8	24 ± 5.4
Muscular VSD	20 ± 1.76	12 ± 0.43
Muscular central	15.3 ± 1.7	12 ± 0.37
Muscular apical	26.6 ± 3.9	12 ± 1.9
Muscular marginal	26 ± 4,4	24 ± 3.1
All	24 ± 1.9	12 ± 0.445

Isolated VSDs were the most common CHDs, accounting for 64% of all CHDs, with an incidence rate of 10.45/1000 per year. This incidence is in line with recent publications, ranging from 1.35 to 17.3 per 1000 live births.[7,21] Lower incidences are reported only in a retrospective study reviewing medical records,[22] that did not evaluate small VSDs. Higher incidences (from 21.3/1000 to 56.6/1000 in preterm neonates[7,8] were reported when echocardiographic examination was routinely performed in all newborns, regardless of a CHD suspicion. However, such an "unselective" echocardiographic screening of all newborns will lead to the discovery of silent and very small VSDs without clinical relevance, a practice not supported by clinical utility and cost/benefit ratio data. In our study, an echocardiographic examination was performed in 32.6% of all newborns within the first month of life for suspicion of CHDs, mostly for murmurs.

Not only the incidence but also the natural history of isolated VSDs is still a matter of debate, with limited evidence. Most studies focus on single defects: perimembranous type, muscular, or apical VSDs.[7] Other studies, instead, have a limited follow-up period.[4,9,23] There are only few studies evaluating the natural history of all types of neonatal VSDs[12] and with a long follow-up period (ie, >2 years).[23,24]

We report data on one of the longest follow-up period (6 years) in wide series of neonates with isolated VSDs over a period of 20 years. Our study mainly deal with small muscular defects (detected in 305 newborns) reporting rate and timing of spontaneous closure that tend to confirm previous observations.[12,13,23–27] Spontaneous VSD closure is a well-known phenomenon occurring during the first year of life in a high percentage of cases.[12] A great number of tiny defects can close quickly, even in the first month of life.[27] In our series, the timing of natural closure was 29.2% (of all VSDs) at 6-month follow-up, 60.2% at 1-year, 79.3% at 2-year, and 91.8% of all defects at 6-year follow-up. The closure time we have described in the first year of life is similar to the ones reported by Lin et al.[23] and Turner et al.[13] in smaller cohorts.

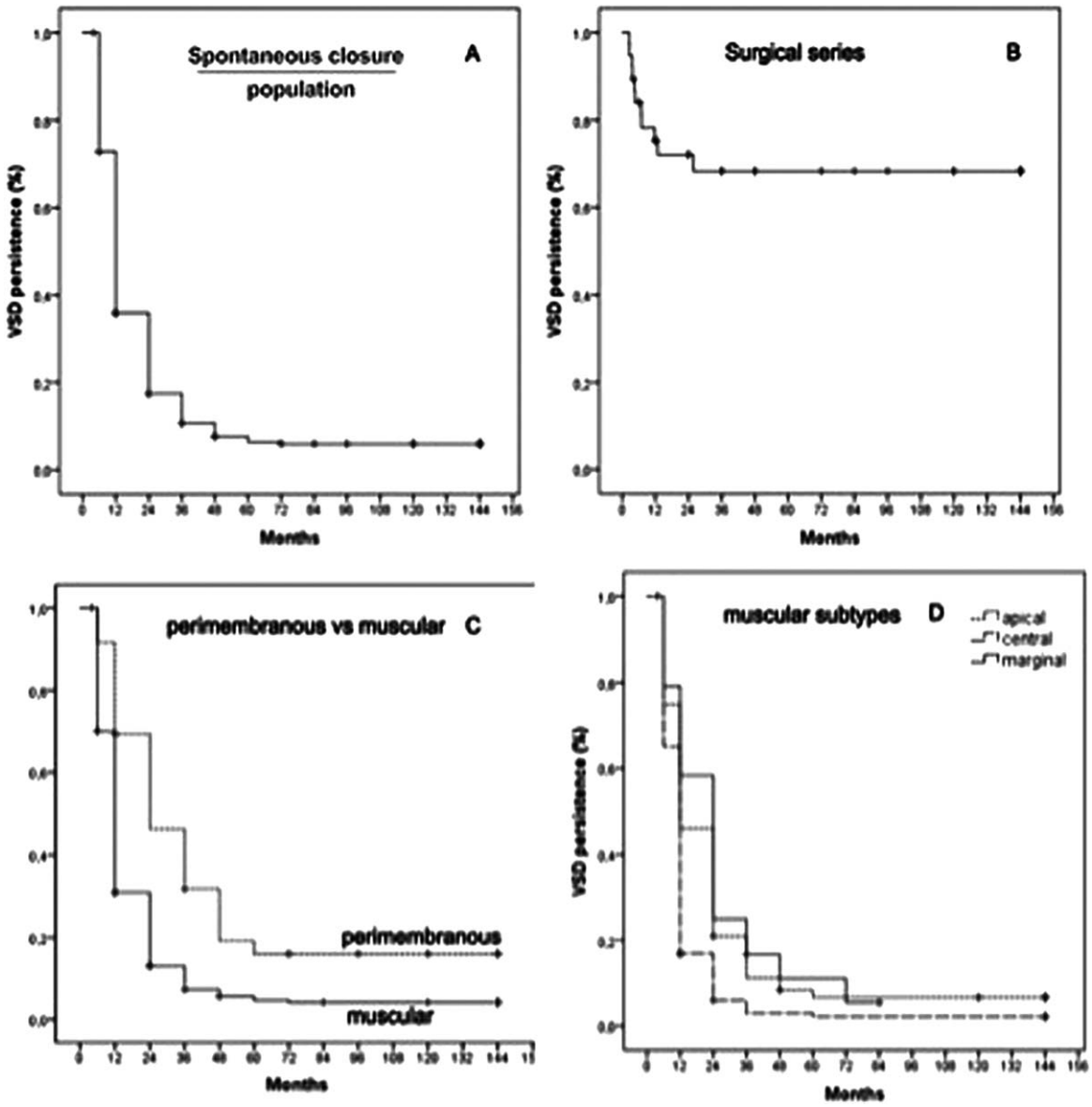

FIGURE 2 Shows the Kaplan-Meier actuarial closure curves. (A) Actuarial closure curve in the spontaneous closed VSD population. (B) Actuarial closure curve in the surgically closed VSD population. (C) Actuarial closure curves in perimembranous and muscular VSD, a significant difference was present (see text). (D) Actuarial closure curves in muscular VSD subtypes, differences present in the first 2 years are not statically significant at 6 (see text)

Erdem et al.[24] recently reported a large cohort of 799 new-borns with VSDs of different sizes, followed for 32.8 ± 30 months, finding a spontaneous closure rate of 78% in muscular and 59% in perimembranous VSDs after 2 years. Also, the incidences of defects requiring surgery we reported (ie, 3.9%) tend to confirm previous observations.[28]

Regarding risk factors for a VSD persistence, we could confirm previous observations[11,13,24] indicating that the number of defects and their locations are important predictors of spontaneous closure. However, we found that male gender was associated with a lower rate of spontaneous closure. This is new evidence, difficult to explain, needing confirmation in larger studies.

Whether the site of muscular defects affects the probability of a spontaneous closure is a controversial issue. In older studies, apical defects seemed to be the most prone to closure[25]; more recent reports showed that mid-ventricular defects had a higher probability of closing.[26,27,29,30] In our experience, among muscular VSD at 2-year follow-up the probability of spontaneous closure was higher for central type compared to apical and marginal type ($P = .003$ and $P = .006$, respectively; Table 2), whereas at 6-year follow-up no more statistical differences were present ($P = .6$). A reduction of the probability of spontaneous closure after the second year of life has been recently reported by Xu et al.,[31] although the possibility of closure until adolescence[15,26] and even in adult life are described.[11]

From a clinical point of view, interpretation of data may be challenging. It is known that in case of large to moderate perimembranous and subarterial VSDs follow-up is warranted for possible complications

TABLE 3 Cox multivariate analysis of factors potentially affecting the risk of spontaneous closure in isolated VSD. Male gender, perimembranous site and multiple defects were associated with increased risk of defect persistence

			95% CI	
	P	HR	Inferior	Superior
Male vs female	.048	0.783	0.615	0.998
Ref muscular				
Perimembranous	.001	0.508	0.342	0.755
Number	.043	0.728	0.536	0.990
Size	.456	0.840	0.530	
Associated pathologies	.123	0.700	0.445	1.102
Moderate vs small size	.456	0.840	0.530	1.33

such as aortic valve prolapse, aortic regurgitation left ventricle-to-right atrium shunt, subaortic ridge, and infundibular stenosis.[24] We did not experience similar complications but our series involved mainly small VSDs, with the follow-up of only two large and 19 moderate sized VSDs. In contrast in minor muscular VSDs whether to follow-up or not (and how often to follow-up) remain a clinical dilemma. In such cases the remote possibility of long-term complications has to be balanced over the risk to generate parental anxiety and the need of useless (and expensive) examination repetition.[18] The possibility of Infective Endocarditis (IE) is a major concern, anyhow its risk is low (ie, 1.5–2.4 per 1000 patient-years, lifetime risk of 12%).[32] Indications for IE prophylaxis are also controversial. Current Guidelines for IE management[33] do not recommend IE antibiotic prophylaxis for unoperated VSDs, despite they had been previously classified at moderate IE risk.[34–36] In our series, we found no IE cases. In our institutional adult IE database, however, VSDs accounted for 9.7% of 205 consecutive cases (unpublished data). Another unresolved issue is the follow-up protocol; in fact, high volume providers believe that, in case of small defects, the cost/benefit ratio for a follow-up may not be worth the effort.[15] Otherwise, other authors have suggested that, irrespective of dimensions, VSDs persisting in adulthood should be followed since they may lead to severe complications (ie, IE, aortic regurgitation, occurrence of arrhythmias).[37] This question remains open and further long-term follow-up studies are warranted.

5 | STRENGTHS AND LIMITATIONS

This study has several strengths: (1) a homogeneous cohort of newborns was enrolled, (2) a rigid Institutional protocol was attended for the follow-up and management of these children, (3) a long-term follow-up is available.

The study has also some limitations. We performed an echocardiography in all neonates with a suspicion of cardiac disease. Scanning all neonates may allow the diagnosis of silent, tiny defects, thus leading to a further increase in the incidence of neonatal VSDs. However, the clinical consequence of silent, tiny defects is probably small and some authors have even raised the question whether these small defects fulfil or not the criteria of CHD as defined by Mitchell et al.[28,38] of "a structural abnormality of the heart or intrathoracic vessels of functionally or potentially functionally significance." The retrospective design is another limitation, despite our rigid surveillance intervals and the fact that no patients were lost at the follow-up. Data from different ethnic backgrounds were lacking; however, the homogeneity of our population may eliminate any bias of different racial compositions and allow comparisons with populations of different races and ethnicity.

6 | CONCLUSIONS

We describe the incidence of VSDs and natural history in a long-term follow-up in a defined Italian region. Our study confirms that VSDs are the most common CHD in newborns. Muscular defects are the most frequent ones with most of them being small. The probability of a VSD spontaneous closure is high, even after the first year of life. Muscular VSDs have a higher spontaneous closure rate and tend to close earlier compared to perimembranous VSDs. Among muscular VSDs, midventricular ones have a higher closure rate within the first follow-up year, but at 6-year follow-up, no more significant differences can be found.

Our data may provide helpful information for the development of currently lacking guidelines/expert consensus recommendations for the management and follow-up of VSDs in children. Wider studies and expert consensus statements are warranted.

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COMPLIANCE WITH ETHICAL STANDARDS

The study complies with the Declaration of Helsinki, the locally appointed ethics committee has approved the research protocol and informed consent has been obtained from the subjects.

The authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation. All authors had full access to the data in the study and take responsibility for the integrity and the accuracy of the data analysis.

CONFLICT OF INTEREST

The authors have no financial interest in this manuscript.

AUTHOR CONTRIBUTIONS

Concept/design and drafting article: Cresti

Performed data analysis/interpretation: Giordano, Koestenberger, Spadoni

Performed statistic analysis: Scalese

Performed data collection: Limbruno, Falorini, Stefanelli, Picchi

Critical revision: De Sensi, Malandrino

Approved the article and performed a critical revision: Cantinotti

ORCID

Raffaele Giordano MD http://orcid.org/0000-0002-8046-810X

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