

## ORIGINAL ARTICLE

## Abnormalities of Cardiac Situs and Heart Disease Diagnosed by Echocardiography in Patients with Biliary Atresia

Henrique de Assis Fonseca Tonelli,<sup>1</sup> Zilda Maria Alves Meira,<sup>2</sup> Sandra Regina Tolentino Castilho,<sup>1</sup> Adriana Furletti Machado Guimarães,<sup>2</sup> Tháís Costa Nascentes Queiroz,<sup>1</sup> Alexandre Rodrigues Ferreira<sup>1</sup>

Hospital das Clínicas da Universidade Federal de Minas Gerais,<sup>1</sup> Belo Horizonte, MG – Brazil  
Universidade Federal de Minas Gerais,<sup>2</sup> Belo Horizonte, MG – Brazil

### Abstract

**Background:** Left isomerism (LI) is a common finding in patients with biliary atresia (BA), and it can be identified by echocardiography. Several comorbidities may be present in patients with LI, including heart disease.

**Objective:** To investigate the prevalence of LI and heart disease in children (< 18 years of age) with BA followed-up at Hospital das Clínicas, UFMG.

**Methods:** This is a cross-sectional study involving patients diagnosed with BA between February 2016 and April 2020 who underwent transthoracic echocardiography and, in case of situs abnormalities, also electrocardiography.

**Results:** Our study recruited 58 patients (mean age: 3.08 years; female/male ratio: 1.5:1). The general prevalence of situs abnormalities was 8.6% (5/58) and the most common one was LI (4/5 or 80%). One patient had situs inversus. Among patients with situs abnormalities, the general prevalence of heart disease was 80% (4/5), apart from anomalies of the inferior vena cava), with pulmonary valve stenosis (PVS) as the only change seen (75% of mild forms and 25% of moderate forms). Among patients with situs abnormalities, the prevalence of rhythm changes was 80% (4/5), and low atrial rhythm was the most common finding (3/4 or 75%).

**Conclusion:** The prevalence of situs abnormalities in our sample was similar to that described in the literature. We observed an exclusive prevalence of PVS and a high prevalence of rhythm changes among patients with LI. Although the diagnosis of isomerism does not initially add much cardiovascular risk to the sample, possible late deterioration should be considered.

**Keywords:** Heterotaxy Syndrome; Heart diseases; Biliary atresia.

### Introduction

Biliary atresia (BA) occurs in 1:8000 to 1:23 000 live births, being responsible for over 50% of liver transplantations in children.<sup>1-3</sup> Among these patients, 7% to 12% have situs abnormalities known as left isomerism (LI) or polysplenia syndrome.<sup>4,5</sup> Similarly, 31% to 50% of all patients with LI have BA.<sup>1,6</sup>

The essential characteristic of LI is the unusual laterality and symmetry of the thoracic and abdominal viscera. In LI, left-sided structures are usually replicated (replacing the corresponding

morphologically correct structures).<sup>7-9</sup> Characteristic findings are: double left atrium, double left lung and left main bronchus; descending aorta positioned anterior to the spine (slightly to the right or to the left); stomach usually positioned to the right; transverse liver; polysplenia.<sup>2,3,4</sup>

Regarding situs abnormalities, special interest is given to the identification of the atrial situs, which is a significant factor in the association with several heart diseases. According to the principle of thoracoabdominal compliance, atrial situs may be inferred from an echocardiography assessing the

#### Mailing Address: Henrique de Assis Fonseca Tonelli

Hospital das Clínicas da Universidade Federal de Minas Gerais.  
Av Alfredo Balena 110, sala 301. Postal Code: 30130100, Belo Horizonte, MG – Brazil.  
E-mail: tonelux70@gmail.com

abdominal situs and estimated by the relative position of large vessels near the spine.<sup>7,8</sup>

Several comorbidities of varying severity may be present in patients with LI, such as craniofacial, musculoskeletal, tracheoesophageal, cardiac, and genitourinary malformations as well as malformations of the central nervous system and digestive system (intestinal malrotation, BA).<sup>7,8</sup>

In patients with LI, cardiac malformations are usually less significant than those found in cases of right atrial isomerism. Cyanogenic heart diseases are less common, and some cardiac defects may be only partially seen.<sup>7,8</sup> The absence of the right atrium and sinus node (a typical right atrial structure) is also part of the syndrome, resulting in risk of rhythm disorders.

The literature is scarce when it comes to the prevalence of heart disease among patients with BA and LI. Therefore, it is unknown if this population has particular heart conditions when compared to those with left atrial isomerism only.

The objective of this study was to investigate the prevalence of LI and structural heart disease among patients with BA followed-up by the Pediatric Hepatology team at Hospital das Clínicas (HC)/Universidade Federal de Minas Gerais (UFMG), considering that the diagnosis might have been underestimated.

## Methods

### Study design

This was a cross-sectional study involving patients diagnosed with BA at HC/UFMG from February 2016 to April 2020. Once the case was identified and after

the written consent form was signed, a transthoracic echocardiography was performed in all patients; in case of situs abnormalities, an electrocardiography was performed at the Department of Cardiology.

### Inclusion criteria

Patients with BA under 18 years of age and followed-up at the Pediatric Hepatology outpatient unit at HC-UFMG during the study period who agreed to take part in the research, regardless of the surgical approach (Kasai procedure or liver transplant), with an acceptable echocardiographic window to determine abdominal situs.

### Exclusion criteria

All patients with BA and followed-up at the same unit who did not agree to take part in the research or without an acceptable echocardiographic window.

### Data collection

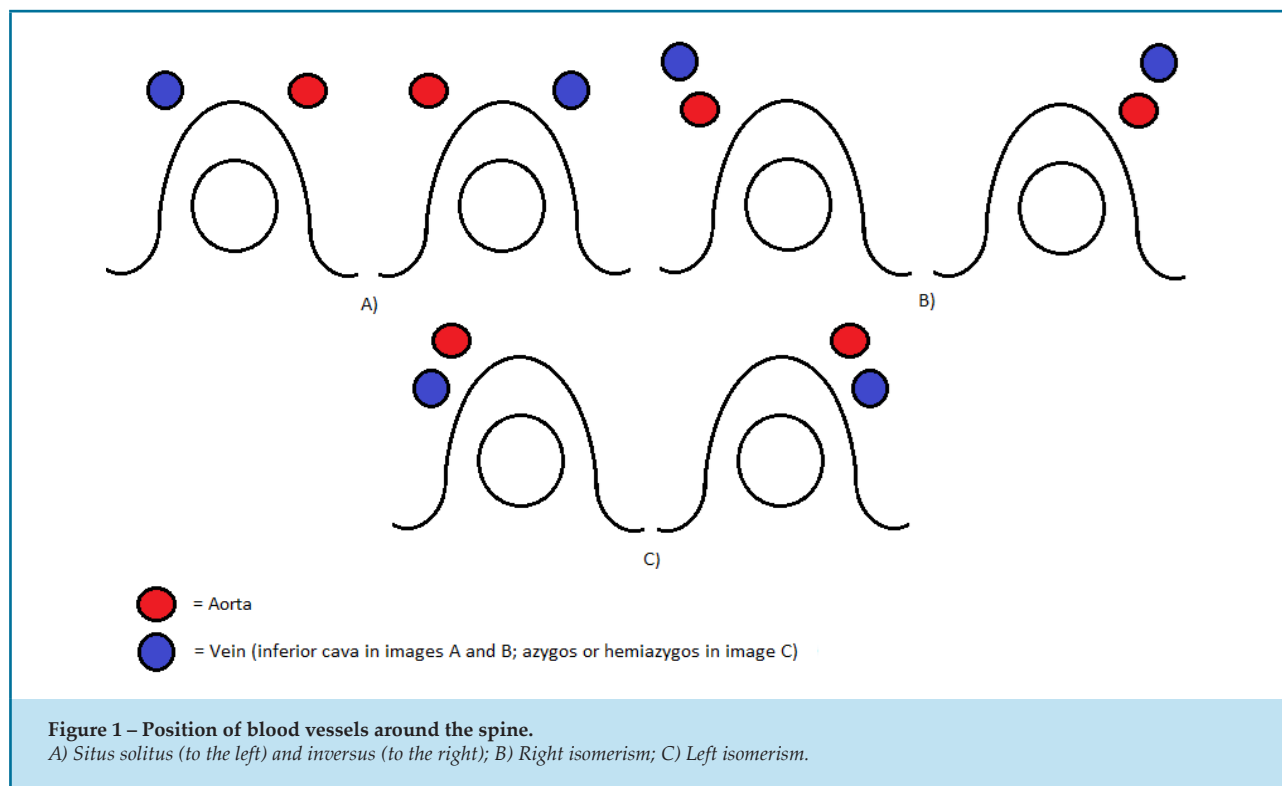
Echocardiographic assessment was performed according to the local routine and to national and international guidelines<sup>10,11</sup> using TOSHIBA APLIO 400 equipment (Tustin, CA, USA). Situs was assessed through longitudinal and transverse subcostal scanning using Doppler ultrasound. The connection between the inferior vena cava (IVC) and the right atrium was investigated at the longitudinal scan. The blood vessel distribution around the spine was identified at the transverse scan (Table 1 and Figure 1).

Electrocardiographic assessment was performed according to national and international guidelines,<sup>12,13</sup> using EDAN SE-3 MHE (Shenzhen, P.R. China) or PHILIPS

**Table 1 – Definition of abdominal situs via echocardiography**

Types of situs	Solitus	Inversus	Ambiguous
Position of the AO	Anterior and to the left	Anterior and to the right	AO <sup>‡</sup> and inferior vena cava side by side (to the right or to the left of the spine)
Position of the inferior vena cava* relative to the spine	Anterior and to the right	Anterior and to the left	Anterior vena cava = RI <sup>§</sup> Posterior vena cava = LI <sup>  </sup>
Connection between inferior vena cava –RA <sup>†</sup>	Present	Present	Present = RI; Absent = LI

\* Inferior vena cava: inferior vena cava or equivalent (azygos / hemiazygos); † RA: right atrium; ‡ AO: aorta; § RI: right isomerism; || LI: left isomerism.



PageWriter Trim III (Andover, MA, USA) equipment.

The following variables were reported and analyzed: identification data, patient situation regarding surgical interventions, which had been considered, situs classification, record of associated structural heart disease, and heart rhythm classification in patients with abnormal situs.

### Statistical analysis

Data were analyzed using SPSS for Windows, version 16.0 (SPSS Inc., Chicago, IL, USA).

Our descriptive analysis used frequencies or median and interquartile range values for categorical and continuous variables, respectively. A Kolmogorov-Smirnov normality test with a cut-off of 0.05 was used to test for normality of distribution.

### Ethical aspects

The present study is in accordance with Resolution 466/2012 of the National Health Council of the Brazilian Ministry of Health, meeting the required ethical standards, including free and informed consent of the participants. The study was approved by the institution's Research Ethics Committee, No. 77 0

203000-09.

### Results

Fifty-eight patients were recruited, 3 of whom had been referred from the hospital admissions unit (young infants recently diagnosed with BA). The remaining patients were referred from the Pediatric Hepatology outpatient unit at the same institution.

All 58 recruited patients met the selection criteria and research protocol requirements. Patient data are shown in Table 2.

Data distribution revealed a non-normal pattern (Kolmogorov-Smirnov normality test with  $p = 0.021$ ).

The patients' median age at the time of echocardiography was 3.08 years (interquartile range: 0.83–9.25 years). There was a predominance of female patients, with a 1.5:1 ratio compared to male patients. The median age of patients with situs abnormalities was 5 months (data not shown in the table).

Forty-two patients (72.4%) were in the postoperative period of a Kasai procedure, 10 (17.2%) were in the postoperative period of a liver transplant, and the remaining 6 (10.3%) were in the preoperative period of a Kasai procedure.

The overall prevalence of situs abnormalities in

**Table 2 – Patients recruited prospectively (n = 58)**

Characteristics	Scores
$M_d$ /(IR)* of age (years) at the time of echocardiography	3.08/(0.83 – 9.25)
Sex M/F <sup>†</sup> (%)	23 (39.7%)/35 (60.3%)
Pre-K/post-K/post-LT <sup>‡</sup> (%)	6 (10.3%)/42 (72.4%)/10 (17.2%)
Situs situation: A/N <sup>§</sup> (%)	5 (8.6%)/53 (91.4%)
Situs abnormality: LI/RI/SI <sup>  </sup> (%)	4 (80%)/0 (0%)/1 (20%)
Cardiac condition with abnormal situs: PVS <sup>¶</sup> /absent (%)	4 (80%)/1 (20%)
Severity of PVS in abnormal situs: light/moderate (%)	3 (75%)/1 (25%)
Rhythm in abnormal situs: LAR <sup>‡</sup> /N <sup>§</sup> (%)	4 (80%)/1 (20%)
Cardiac condition with normal situs: present/absent (%)	1 (1.9%)/52 (98.1%)
Interruption of the inferior vena cava in LI (%)	100%

\*  $M_d$ /(IR): median/interquartile range; <sup>¶</sup> PVS: pulmonary valve stenosis; <sup>†</sup> M/F: male/female; <sup>‡</sup> LAR: left atrial rhythm; <sup>‡</sup> Pre-K/post-K/post-LT: pre-Kasai/post-Kasai/post-liver transplant; <sup>§</sup> A/N: abnormal/normal; <sup>||</sup> LI/RI/SI: left isomerism/right isomerism/situs inversus.

the sample was 8.6% (5/58), and the most common abnormality was LI (4/5 or 80%). One patient had situs inversus.

Among patients with situs abnormalities, the overall prevalence of congenital heart disease, apart from anomalies of the IVC, was 80% (4/5). Pulmonary valve stenosis (PVS) was the only abnormality found in these patients, with 3/4 or 75% of mild forms (Doppler peak instantaneous gradient between 10mmHg and 35mmHg) and 1/4 or 25% of moderate forms (Doppler peak instantaneous gradient between 36mmHg and 64mmHg). The 4 patients with LI had interrupted IVC (agenesis of the suprahepatic segment) with no clinical implications.

All patients with a heart condition were on regular cardiology follow-ups.

Among patients with situs abnormalities, the overall prevalence of rhythm changes at electrocardiography was 80% (4/5). The most common change was low atrial rhythm (left atrium) (3/4 or 75%). The P-wave axis was shifted to the right (over 120°) in the patient with situs inversus.

Among patients with situs solitus, the overall prevalence of congenital heart disease was 1.9% (1/53): a case of persistent ductus arteriosus (small canal, with no clinical implications).

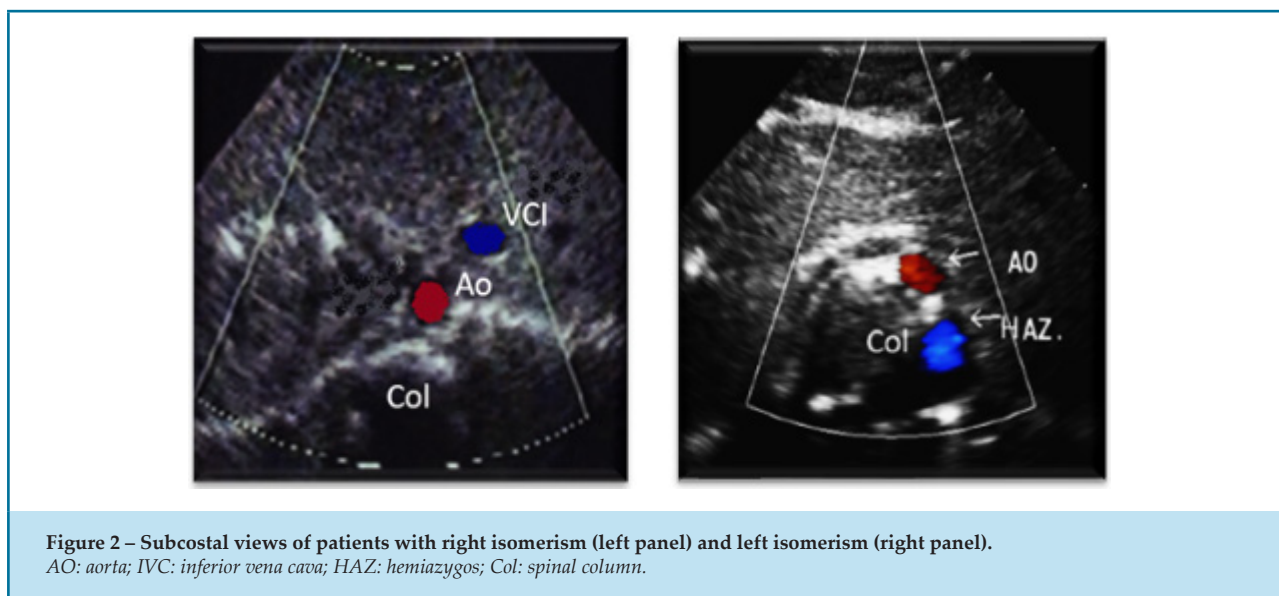
## Discussion

Our sample (58 patients) is small. On the one hand,

it reflects the small annual inflow of new cases (6 to 9 patients/year). On the other hand, it reflects the losses to follow-up due to death, transfer to other healthcare facilities, or to the Adult Hepatology unit of the same institution (for patients over 18 years old). Nevertheless, the number of cases is noteworthy as these are records from a single healthcare center.

Despite the availability of an echocardiogram database within the institution, the prospective record was chosen focusing on the diagnosis of situs, implying which implied in repeating the echocardiography in some patients. This strategy was aimed at optimizing the accuracy of the echocardiography in the definition of situs.

The definition of atrial situs depends on the correct identification of atrial appendages, which are structures more consistently related to atrial morphology (right or left). However, appendages are not easily accessed by transthoracic echocardiography, making the direct definition of atrial situs challenging. On the other hand, atrial situs is generally consistent with abdominal and thoracic situs. Even though thoracoabdominal situs discordance may be seen exceptionally, the identification of abdominal situs using conventional echocardiography allows the echocardiographer to infer atrial situs. Therefore, in the present study, situs evaluation was performed through the subcostal view of the echocardiogram, a widely available and non-



invasive technique that is reasonably accurate (Figure 2).

We were not able to determine the actual moment of echocardiographic diagnosis of situs, since not all patients had a previous echocardiography record in the institution's database. The median age of patients with situs abnormalities was significantly lower than that of the total sample (5 months compared to 3.08 years). These data suggest that all situs abnormalities were detected early on and were not seen in patients over one year of age at the time of echocardiography. An explanation for these findings is the poor prognosis of patients with polysplenia syndrome. Other authors have reported a lower survival rate with native liver among patients with BA and LI when compared to those with no LI.<sup>14,15</sup>

A clear predominance of BA was observed in female patients, reflecting similar findings in the literature.<sup>1-2</sup>

The general prevalence of situs abnormalities in the sample (8.6%) was similar to other records (between 7% and 12%),<sup>4,5</sup> with LI being the most common finding (80% of cases); this is in accordance with data in the literature<sup>4,5</sup>. One patient had situs inversus. Other cases of total or abdominal situs inversus in patients with BA have been described.<sup>16-18</sup>

The prevalence of congenital heart disease was 80% among patients with situs abnormalities and 100% among those with left atrial isomerism (no structural heart disease was detected in the patient with situs inversus). The only structural heart disease found in patients with situs abnormalities, except for the absence of the suprahepatic segment of the IVC (present in almost 100% of patients with LI), was PVS. The prevalence of structural heart

disease reported in the literature for patients with left atrial isomerism ranges from 91% to 97%.<sup>19-21</sup>

Among the cardiac abnormalities of LI found in the literature, the main ones are dextrocardia/mesocardia (24%–42% and 2% of all cases, respectively), anomalous pulmonary venous return (37%–56%), persistent left superior vena cava (33%–59%), unroofed coronary sinus (26%–42%), absence of the suprahepatic segment of the IVC (86%–100%), hepatic venous drainage into the left atrium (32%–41%), common atrium or interatrial communication (80%), total or partial atrioventricular septal defect (49%–80%), univentricular atrioventricular connection (20%–40%), ventricular septal defect (11%), transposition of the great arteries (5%–21%), double-outlet right ventricle (17%–37%), PVS or pulmonary atresia (28%–61%), and aortic stenosis/atresia or coarctation of the aorta (7%–45%).<sup>19,22-28</sup>

The literature on the prevalence of heart disease among patients with BA and LI is scarce. Using the MEDLINE, LILACS, and SciELO databases and associating the main descriptors in different manners, our search did not retrieve more than a few case series. Nevertheless, a Canadian study reported 25 cases of polysplenia among 328 patients (7.6%) using a national database of children with biliary atresia and including a 17-year period. Congenital cardiac defects were found in 26 patients. These included pulmonary stenosis (n = 12), ventricular septal defect (n = 10), atrial septal defect (n = 7), patent ductus arteriosus (n = 3), total anomalous pulmonary venous return (n = 3), double-outlet right ventricle (n = 3), bicuspid aortic valve (n = 3), dextrocardia (n = 2), atrioventricular canal defect (n = 2), tetralogy of

Falot ( $n = 2$ ), partial anomalous pulmonary venous return ( $n = 1$ ), hypoplastic aortic arch ( $n = 1$ ), aortic stenosis ( $n = 1$ ), and mitral stenosis ( $n = 1$ ).<sup>29</sup> Another report from the United Kingdom, a 28-year single-center retrospective study, described 43 cases of polysplenia among 548 patients (7.8%). Cardiac abnormalities were found in 25 patients, including tetralogy of Fallot ( $n = 1$ ), aortic arch abnormality and severe left pulmonary hypoplasia ( $n = 1$ ), aortic coarctation ( $n = 1$ ), hypoplastic left heart ( $n = 1$ ), ventricular septal defect ( $n = 5$ ), atrial septal defect ( $n = 7$ ), patent ductus arteriosus ( $n = 7$ ), and pulmonary artery stenosis ( $n = 1$ ). Nine infants required cardiac surgery.<sup>30</sup>

Considering the list of cardiac conditions described in patients affected by LI with or without heterotaxy, it would be reasonable to assume that other conditions might have been observed in this sample. The small absolute number of patients with situs abnormalities in this study prevents any conclusion regarding the real prevalence of cardiac disorders among these patients. Further studies, with larger sample sizes, are required to elucidate this matter in Brazil.

Other conditions of clinical interest associated with LI are sinus node dysfunction (escape rhythm with chronotropic incompetence), supraventricular arrhythmias — tachyarrhythmias and atrioventricular block (up to 71% of all cases, with 7%–22% of atrioventricular block), and the presence of dysfunctional spleens (increasing the risk of infections and sepsis).<sup>7,8,25,26</sup>

The overall prevalence of rhythm disorders among patients with situs abnormalities in this sample, at electrocardiographic assessment, was 80% (4/5). The most common one was low atrial rhythm (3/4 or 75%). The incidence of arrhythmias in patients with LI may reach 87% in 3 years of follow-up, with sinus node dysfunction (escape rhythm) being the most common one (around 60% of the cases), followed by total atrioventricular block (20% of all cases). The risk of sinus node dysfunction with an indication for pacemaker implantation reaches 19% in some case series, reinforcing the need for a long-term cardiology follow-up of such patients.<sup>21,31</sup> The abnormalities seen in patients in this study do not seem to lead to increased morbidity at the time of echocardiography. However, the escape rhythm in patients with LI may cause chronotropic incompetence during situations of high cardiac demand.

Despite the low complexity of heart diseases observed in this study and considering the cardiac conditions described in patients affected by BA and LI

in larger series, it is possible to infer that the associated cardiac abnormalities may be prognostically important and life-threatening even before biliary malformation can be treated.

The main limitation of this study, apart from the ones inherent to our methodology, are the possible losses of patients related to their death or transfer to other healthcare facilities. At all events, the sample included all patients who were being followed-up by the Pediatric Hepatology team at HC/UFGM during the study period.

The identification of LI is important for the medical specialties that manage most of the care of patients with BA. Even though the diagnosis of isomerism does not represent, at the moment of data collection, a high cardiovascular risk for the patients in our sample, it is important to acknowledge the possibility of late illness and the need for regular cardiology follow-ups.

## Conclusion

The prevalence of situs abnormalities in our sample was similar to that described in the literature. As expected, LI was the most common finding.

The prevalence of congenital heart disease in patients with situs abnormalities was high, as anticipated by the analysis of patients with LI only. We found an exclusive prevalence of PVS and a high prevalence of rhythm changes (escape rhythm) in patients with left atrial isomerism. However, due to the small number of affected patients, it is not possible to confirm whether PVS occurs in a preferential association with BA and LI.

Although the diagnosis of isomerism does not increase cardiovascular risk in patients in our sample at first, possible late deterioration should be considered, requiring continued monitoring.

## Acknowledgments

We would like to thank the pediatric cardiology residents at HC-UFGM, who took part in the triage and referral process of the research patients.

## Author contributions

Conception and design of the research: Tonelli HAF, Queiroz TCN. Acquisition of data: Tonelli HAF, Queiroz TCN, Meira ZMA, Guimarães AFM, Castilho SRT. Analysis and interpretation of the data: Tonelli HAF, Queiroz TCN. Statistical analysis: Tonelli HAF, Queiroz

TCN. Writing of the manuscript: Tonelli HAF, Queiroz TCN. Critical revision of the manuscript for intellectual content: Tonelli HAF, Queiroz TCN, Ferreira AR.

### Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

### Sources of Funding

There were no external funding sources for this study.

### Study Association

This study is not associated with any thesis or dissertation work.

### Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Universidade Federal de Minas Gerais under the protocol number 77.0.203000-09. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

## References

- Chandra RS. Biliary Atresia and Other Structural Anomalies in the Congenital Polysplenia Syndrome. *J Pediatr*. 1974;85(5):649-55. doi: 10.1016/s0022-3476(74)80508-1.
- Nio M. Japanese Biliary Atresia Registry. *Pediatr Surg Int*. 2017;33(12):1319-25. doi: 10.1007/s00383-017-4160-x.
- Belle SH, Beringer KC, Detre KM. Trends in Liver Transplantation in the United States. *Clin Transpl*. 1993:19-35.
- Varela-Fascinetto G, Castaldo P, Fox IJ, Sudan D, Heffron TG, Shaw BW, et al. Biliary Atresia-Polysplenia Syndrome: Surgical and Clinical Relevance in Liver Transplantation. *Ann Surg*. 1998;227(4):583-9. doi: 10.1097/0000658-199804000-00022.
- Karrer FM, Hall RJ, Lilly JR. Biliary Atresia and the Polysplenia Syndrome. *J Pediatr Surg*. 1991;26(5):524-7. doi: 10.1016/0022-3468(91)90697-r.
- Dimmick JE, Bove KE, McAdams AJ. Letter: Extrahepatic Biliary Atresia and the Polysplenia Syndrome. *J Pediatr*. 1975;86(4):644-5. doi: 10.1016/s0022-3476(75)80185-5.
- Perloff JK. The cardiac malpositions. In: Perloff JK, Marelli A, editors. *Clinical Recognition of Congenital Heart Disease*. 5th ed. Philadelphia: Saunders; 2003.
- Hagler DJ, O'leary PW. Cardiac Malpositions and Abnormalities of Atrial and Visceral Situs. In: Allen HD, Driscoll DJ, Shaddy RE, Feltes TF, editors. *Moss and Adams' Heart Disease in Infants, Children, and Adolescents: Including the Fetus and Young Adult V2*. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2008.
- Ho SY, Baker EJ, Rigby ML, Anderson RH, editor. *Atlas Colorido de Cardiopatias Congênitas: Correlações Clínico-Morfológicas*. Rio de Janeiro: Revinter; 1998.
- Lai WW, Mertens Mm Cohen MS, Geva T, editors. *Pediatric And Congenital Heart Disease: From fetus to Adults*. New Jersey: Wiley-Blackwell; 2009.
- Silva CE, Tasca R, Weitzel LH, Moisés VA, Ferreira LD, Tavares GM, et al. Normatização dos Equipamentos e Técnicas de Exame para Realização de Exames Ecocardiográficos. *Arq Bras Cardiol*. 2004;82(Suppl 2):1-10.
- Rijnbeek PR, Witsenburg M, Schrama E, Hess J, Kors JA. New Normal Limits for the Paediatric Electrocardiogram. *Eur Heart J*. 2001;22(8):702-11. doi: 10.1053/euhj.2000.2399.
- Guimarães JJ, Nicolau JC, Polanczyk CA, Pastore CA, Pinho JA, Bacellar MSC et al. Diretriz de Interpretação de Eletrocardiograma de repouso. *Arq Bras Cardiol*. 2003; 80 Suppl 2: 1-18.
- Chardot C, Carton M, Spire-Bendelac N, Le Pommelet C, Golmard JL, Auvert B. Prognosis of Biliary Atresia in the Era of Liver Transplantation: French National Study from 1986 to 1996. *Hepatology*. 1999;30(3):606-11. doi: 10.1002/hep.510300330.
- Lykavieris P, Chardot C, Sokhn M, Gauthier F, Valayer J, Bernard O. Outcome in Adulthood of Biliary Atresia: A Study of 63 Patients who Survived for over 20 Years with their Native Liver. *Hepatology*. 2005;41(2):366-71. doi: 10.1002/hep.20547.
- Rasool F, Mirza B. Polysplenia syndrome associated with situs inversus abdominus and type I jejunal atresia. *APSP J Case Rep*. 2011;2(2):18.
- Mathur P, Gupta R, Soni V, Ahmed R, Goyal RB. Biliary Atresia Associated with Polysplenia Syndrome, Dextrocardia, Situs Inversus Totalis and Malrotation of Intestines. *J Neonatal Surg*. 2014;3(1):9.
- Mirza B, Iqbal S, Sheikh A. Biliary Atresia Associated with Polysplenia Syndrome, Situs Inversus Abdominus, and Reverse Rotation of Intestine. *APSP J Case Rep*. 2012;3(2):14.
- Eronen MP, Aittomäki KA, Kajantie EO, Sairanen HI. Outcome of Left Atrial isomerism at a single institution. *Pediatr Cardiol*. 2012;33(4):596-600. doi: 10.1007/s00246-012-0184-0.
- Bhaskar J, Galati JC, Brooks P, Oppido G, Konstantinov IE, Brizard CP, et al. Survival Into Adulthood of Patients with Atrial Isomerism Undergoing Cardiac Surgery. *J Thorac Cardiovasc Surg*. 2015;149(6):1509-13. doi: 10.1016/j.jtcvs.2015.01.038.
- Anagnostopoulos PV, Pearl JM, Octave C, Cohen M, Gruessner A, Wintering E, et al. Improved Current era Outcomes in Patients with Heterotaxy Syndromes. *Eur J Cardiothorac Surg*. 2009;35(5):871-8. doi: 10.1016/j.ejcts.2008.12.018.
- Rose V, Izukawa T, Moës CA. Syndromes of Asplenia and Polysplenia. A review of Cardiac and Non-Cardiac Malformations in 60 Cases Withspecial Reference to Diagnosis and Prognosis. *Br Heart J*. 1975;37(8):840-52. doi: 10.1136/hrt.37.8.840.
- Sharma S, Devine W, Anderson RH, Zuberbuhler JR. Identification and Analysis of Left Atrial Isomerism. *Am J Cardiol*. 1987;60(14):1157-60. doi: 10.1016/0002-9149(87)90410-3.
- Gilljam T, McCrindle BW, Smallhorn JF, Williams WG, Freedom RM. Outcomes of Left Atrial Isomerism Over a 28-year Period at a Single Institution. *J Am Coll Cardiol*. 2000;36(3):908-16. doi: 10.1016/s0735-1097(00)00812-3.
- Lim JS, McCrindle BW, Smallhorn JF, Golding F, Caldaroni CA, Taketazu M, et al. Clinical Features, Management, and Outcome of Children with Fetal and Postnatal Diagnoses of Isomerism Syndromes. *Circulation*. 2005;112(16):2454-61. doi: 10.1161/CIRCULATIONAHA.105.552364.
- Bartram U, Wirbelauer J, Speer CP. Heterotaxy Syndrome – Asplenia and Polysplenia as Indicators of Visceral Malposition and Complex Congenital Heart Disease. *Biol Neonate*. 2005;88(4):278-90. doi: 10.1159/000087625.
- Yildirim SV, Tokel K, Varan B, Aslamaci S, Ekici E. Clinical Investigations over 13 Years to Establish the Nature of the Cardiac Defects in Patients Having Abnormalities of Lateralization. *Cardiol Young*. 2007;17(3):275-82. doi: 10.1017/s1047951107000479.

28. Lee SH, Kwon BS, Kim GB, Bae EJ, Noh CI, Lim HG, et al. Clinical Characteristics and Independent Factors Related to Long-Term Outcomes in Patients with Left Isomerism. *Korean Circ J*. 2017;47(4):501-508. doi: 10.4070/kcj.2016.0293.
29. Guttman OR, Roberts EA, Schreiber RA, Barker CC, Ng VL; Canadian Pediatric Hepatology Research Group. Biliary Atresia with Associated Structural Malformations in Canadian infants. *Liver Int*. 2011;31(10):1485-93. doi: 10.1111/j.1478-3231.2011.02578.x.
30. Davenport M, Tizzard SA, Underhill J, Mieli-Vergani G, Portmann B, Hadzić N. The Biliary Atresia Splenic Malformation Syndrome: A 28-Year Single-Center Retrospective Study. *J Pediatr*. 2006;149(3):393-400. doi: 10.1016/j.jpeds.2006.05.030.
31. Ozawa Y, Asakai H, Shiraga K, Shindo T, Hirata Y, Hirata Y, et al. Cardiac Rhythm Disturbances in Heterotaxy Syndrome. *Pediatr Cardiol*. 2019;40(5):909-913. doi: 10.1007/s00246-019-02087-2.

