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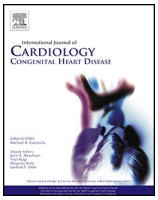

Pulmonary arterial hypertension with left to right shunts: When to treat and/or close?

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ABSTRACT

Pulmonary arterial hypertension (PAH) is defined as increase in mean pulmonary arterial pressure and pulmonary vascular resistance (PVR). It can be associated with congenital heart disease (CHD) with the following subtypes: 1) uncorrected left-to-right (L-R) intracardiac shunt leading to overload of the pulmonary circulation and a progressive increase of PVR; 2) Eisenmenger syndrome, appearing when a large post-tricuspid shunt is left uncorrected and pulmonary vascular disease (PVD) is severe, so the shunt becomes bidirectional or right-to-left, causing cyanosis; 3) PAH after shunt closure, when PVR arises after a defect correction; and 4) PAH associated with small or coincidental defects. While the treatment of patients with Eisenmenger syndrome is well established, the treatment of patients with PAH in whom there is a L-R shunt (with no cyanosis) remains unclear and requires expertise. In such patients, correction of the defect may be contemplated if there is mild PVD and a significant L-R shunt. Others may benefit from a "treat and repair" strategy, which involves the use of PAH therapy to achieve a drop in PVR, with the aim of achieving operability criteria. Cardiac catheterization is at the center of the evaluation and follow-up of these patients, collecting "baseline" data and providing the opportunity to challenge the pulmonary circulation, manipulate the loading status, or temporarily occlude the defect. This article provides a detailed overview of the pathophysiology and treatment options for patients with PAH associated with a L-R congenital shunt, including current approaches to operability and the use of PAH therapies.

1. PAH in patients with an unrepaired left-right shunt: they grey zone between two extremes

Current guidelines [1] identify four different clinical conditions among patients with pulmonary arterial hypertension (PAH) associated with congenital heart disease (CHD) (PAH-CHD) (Table 1). PAH-CHD due to left-to-right (L-R) shunt and the longstanding exposure of the pulmonary vascular bed to increased flow and pressure can result in vascular remodelling and progressive increase in pulmonary vascular resistance (PVR); Eisenmenger's syndrome, where the intracardiac shunt was initially L-R and progressively becomes right-to-left (R-L) or bidirectional; PAH after CHD is repaired, it may appear immediately after the defect correction or years later; PAH with small or coincidental cardiac defect haemodynamically not significant.

It is important to correctly classify patients into one of these four pathophysiologic groups, as this affects their management and has implications in terms of short and long-term outcome.

From a pathophysiological point of view, the onset and rate of progression of pulmonary vascular disease (PVD) depends on the type and size of the congenital heart defect. Large post-tricuspid defects, such as ventricular septal defects (VSDs), atrio-ventricular septal defects (AVSD) and aorto-pulmonary windows typically result in early onset and rapid progression to significant PVD during early childhood, if left unrepaired. The overall likelihood of developing PAH is about 50 %, 90 % and 100 % for patients with an unrepaired VSD, complete AVSD or large aorto-pulmonary window respectively, reflecting the range of anatomical features and severity of the shunt [2–4].

The rate of progression of PVD also differs between patients with similar anatomy for reasons yet unknown. The fact that patients with Down syndrome are more prone to develop PVD early in infancy

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Table 1
Clinical classification of pulmonary arterial hypertension associated with congenital heart disease. PVR: pulmonary vascular resistance; PAH: pulmonary arterial hypertension.

PAH associated with prevalent systemic-to-pulmonary shunts	• Correctable • Non-correctable **Include moderate-to-large defects. PVR is mildly to moderately increased and systemic-to-pulmonary shunting is still prevalent, whereas cyanosis at rest is not a feature.**
Eisenmenger syndrome	Includes all large intra- and extracardiac defects that begin as systemic-to-pulmonary shunts and progress to severely elevated PVR and to reverse (pulmonary-to-systemic) or bidirectional shunting. Cyanosis, secondary erythrocytosis, and multiple organ involvement are usually present. Closing the defects is contraindicated.
PAH after defect correction	Congenital heart disease is repaired, but PAH either persists immediately after correction or recurs/develops months or years after correction in the absence of significant, post-operative, haemodynamic lesions.
PAH with small/coincidental defects	Markedly elevated PVR in the presence of cardiac defects considered haemodynamically non-significant (usually ventricular septal defects <1 cm and atrial septal defects <2 cm of effective diameter assessed by echocardiography), which themselves do not account for the development of elevated PVR. The clinical picture is very similar to idiopathic PAH. Closing the defects is contraindicated.

suggests a role for genetics in this process [5,6]. The propensity towards PVD also differs within patients with pre-tricuspid shunts, ranging between 5 and 10 % in patients with large shunts relating to atrial septal defects (ASDs) or partial anomalous pulmonary venous drainage (PAPVD). The mechanisms responsible for the development of PVD in this minority of patients with pre-tricuspid defects remains unclear, and the disease is rarely as severe as in individuals with large post-tricuspid shunts, who typically evolve into Eisenmenger syndrome within the first two decades of life [7]. Indeed, a significant proportion of adults with PAH and a L-R shunt have a pre-tricuspid defect, while adults with post-tricuspid defects who have not yet evolved into Eisenmenger syndrome either have a small/borderline defect, or (very rarely and for reasons unknown) have a large defect with a "compliant" pulmonary vascular bed.

Heath and Edwards [8], Wood [9] and Wagevoort [10] have all described a "point of no return" in terms of PVD, where histological changes become irreversible and repair of the defect should not be undertaken. Yet a reliable clinical method for identifying this point still eludes us. Irreversible PVD may develop prior to reversal of the shunt, while patients with Eisenmenger syndrome are almost certain to have surpassed this point of no return in terms of operability. This has major implications in terms of clinical management, as closing a shunt when advanced, irreversible PVD has developed can have significant short and long-term consequences and is not recommended [1].

In this review, we discuss the expert management of patients with PAH-CHD and a L-R shunt, based on the available literature and expert opinion.

2. Reasons for and against closing a cardiac defect, and the influence of pulmonary arterial hypertension

A congenital L-R shunt, when significant, can cause volume loading of the right or left ventricle, with short and long-term implications in terms of arrhythmia, heart failure, exercise intolerance etc. Moreover, the shear stress to the pulmonary vascular bed can, over time, trigger PVD [11]. Repairing such defects is generally recommended, though with some important caveats and exceptions: the presence of established PVD is one of these exceptions.

Preventing the development of PVD, especially in its more severe form, i.e. Eisenmenger syndrome, is one of the targets of early repair of CHD and a significant challenge for paediatric cardiologists. Eisenmenger syndrome is at the extreme spectrum of the PAH-CHD and is a multiorgan condition characterized by a severely raised PVR with reversal of the shunt that becomes bidirectional. Chronic hypoxaemia manifests as cyanosis, which can be mild or severe and is more evident on physical activity. Chronic cyanosis is associated with haematological changes, such as secondary erythrocytosis, thrombocytopenia, predisposition to bleeding and thrombosis (e.g. haemoptysis, cerebrovascular accidents), an increased risk of complications from endocarditis, e.g. brain abscesses, arrhythmia, multiorgan failure and sudden death. Timely shunt closure of large defects is, thus, essential for reducing the risk of such devasting events, though this is not always possible.

An increasing number of CHD patients are diagnosed with PAH after defect repair. These are either patients who may have developed PAH prior to (an often late) closure of the defect, while others are diagnosed with PAH after a short or, at times, longer "honeymoon" period of months or years [12]. These patients are deemed to carry a poorer prognosis compared to stable adult patients with Eisenmenger syndrome [13], perhaps as a direct consequence of the shunt closure. In fact, experts believe that the right ventricle of many Eisenmenger patients is optimally adapted to the increased afterload and is "unloaded" by R-L shunting though the unrepaired defect, supporting cardiac output at the expense of cyanosis. On the contrary, patients with PAH after shunt closure have "lost their relief valve" and often experience progressive dilation and dysfunction of the right ventricle, with more significant right ventricle-to-pulmonary vascular bed uncoupling.

A cardiologist needs to make an informed decision, based on limited evidence and their expertise, on whether it is in the patient's best interest to close a cardiac defect when there is evidence of PVD, or manage the CHD conservatively. Invasive haemodynamics play an important role in this process. Current guidelines do not recommend open or thoracoscopic lung biopsy for the diagnosis of PAH due to related procedural risks (pneumothorax, pleural effusion, bleeding, infection) and poor diagnostic utility [1].

3. Haemodynamic assessment for deciding on operability

Current guidelines on adults with congenital heart disease [14] and pulmonary hypertension [1] suggest that surgical or interventional shunt closure must be decided upon and performed in expert centres, based on a full clinical assessment that includes invasive haemodynamics, rather on procedural feasibility alone. Shunt closure is contraindicated in patients with Eisenmenger syndrome and should be avoided in most patients with small or coincidental defects that behave similar to idiopathic PAH and often benefit from an open communication as a relief valve for the right ventricle [15]. Therefore, defect closure may only be considered for patients with a clinically significant (volume loading) left-right shunt, providing there is no significant/irreversible PVD. Several studies have shown that patients with a pre-closure PVR >5 Wood Units (WU) and/or pulmonary to systemic flow ratio (QP/QS) < 1.5 are unlikely to benefit from defect repair, but can deteriorate with persistent and, at times, progressive PAH after shunt closure [16,17].

Complete (unfenestrated) shunt closure is currently considered safe in patients with L-R shunting and a PVR <3 WU [1,14]. A weaker indication for defect closure is given for patients with a significant L-R shunt and a PVR<5WU. Guidelines recommend against closure of a shunt if PVR ≥5 WU [1,14]. Patients in this latter group who have an atrial septal defect may be amenable to a treat-and-(fenestrated) repair,

providing PAH therapies achieve a drop in PVR to <5WU. However, recent data from the North American ASD-PAH (NAAP) Multicenter Registry suggest that, in selected patients with uncorrectable ASD-PAH, defect repair may be effective if PVR after PAH therapy becomes <6.5 WU [18].

Nevertheless, although PAH therapy plays a key role in patients with advanced PVD and small shunts, in CHD with L-R shunts it may initially cause right ventricular volume overload with the risk of long-term right ventricular dysfunction and poor prognosis, unless the threshold for operability is reached [19].

Patients with a PVR≥5WU and a post-tricuspid shunt should be referred to specialist centres for additional consideration, though the guidelines do not clarify the process that these expert centres should follow, allowing a measure of flexibility that should be approached with great caution [1,14]. A multiparametric strategy is recommended when deciding whether to close a congenital shunt in the presence of PAH, which is not based solely on invasive haemodynamic data. For example, formal assessment of exercise capacity and blood testing (see secondary erythrocytosis) are important in detecting desaturation that may only occur on exercise due to dynamic nature of the shunt; exercise-induced desaturation should, indeed, point against shunt closure. Age should also be considered: while patient of all ages can benefit from ASD closure, patients repaired before the age of <25 years have better long-term outcomes, especially in terms of arrhythmic burden [20,21], while ASD closure after the age of 40 years does not reduce the arrhythmic burden, but is helpful in abolishing right ventricular volume loading, which is detrimental in the long-term [22]. In older patients and patients with left heart disease, raised left-sided filling pressures are likely to influence the direction and severity of the shunt across an atrial septal defect, and may confound invasive haemodynamic assessment [23]. Therefore, in patients with an ASD and evidence of systemic ventricular dysfunction or other left-sided lesion, careful evaluation with pre-intervention testing (such as temporary balloon occlusion and/or fluid challenge) should be considered, though little information is available to guide interpretation (see below).

While no established echocardiographic or other imaging criteria exist that should influence the decision to repair a congenital defect in the presence of PAH, it is important to remember the role of the right ventricle in this setting. Partial or complete closure of a L-R shunt at atrial/pre-tricuspid level is aimed at reducing the volume load to the right ventricle, potentially improving its size and coupling to the pulmonary circulation. Patients considered for closure typically present with dilated, hyperdynamic (volume loaded) right ventricles. More severely impaired, incoordinate right ventricles should raise the suspicion of significant PVD and should be investigated thoroughly, as they are less likely to benefit (or may even be harmed) by closure of the defect.

4. Patients with "borderline" haemodynamics: to close or not to close? Dynamic tests in the catheter lab

Beyond the baseline right heart catheterization, additional information can be obtained by challenging the pulmonary circulation, manipulating the loading status, or temporarily closing the defect.

Vasoreactivity testing by oxygen administration or inhaled nitric oxide (NO) has long been part of the operability assessment of patients with CHD. A significant reduction in PVR during acute vasoreactivity testing was considered a point in favour of shunt closure, though data to support this are limited. Hence, current guidelines [1,14] do not recommend acute vasoreactivity testing when deciding whether to close any type of CHD. Moreover, 100 % oxygen alone has fallen out of favour, replaced by NO and other pulmonary vasodilators.

Balloon occlusion testing (of the defect) can be used to calculate PVR and left-sided filling pressures in the absence of the shunt. This is used in patient with ASDs and consists of temporarily closure of the defect with a compliant balloon, such as a sizing balloon used to select the size of the device. During defect occlusion, a catheter is kept in the pulmonary circulation to monitor changes in mean pulmonary arterial pressure (mPAP) and pulmonary arterial wedge pressure (PAWP), as well as take blood samples, while a pigtail catheter can be kept in the left ventricle to monitor changes in left ventricle filling pressure. A significant increase of mPAP or PAWP (left ventricle filling pressure) indicate an increased probability of residual (post-repair) PAH or raised left-sided filling pressures after shunt closure, respectively. Nevertheless, no robust data on parameter thresholds are available so far.

Fluid challenge is a recognized technique for manipulating filling pressures and the pulmonary circulation, most commonly used to ascertain left ventricle diastolic dysfunction [24]. A recent study [25] analysed the haemodynamic changes induced by fluid challenge and balloon occlusion testing in 50 patients with an ASD with a significant L-R shunt (QP/QS > 1.5), a normal or mildly raised PVR (PVR <5 WU), and normal left-sided filling pressures (PAWP ≤15 mmHg). Compared to patients with a normal PVR (<2 WU), individuals with a PVR ≥2 WU experienced a smaller increase in pulmonary blood flow (0.3 [0.1, 0.5] vs 2.0 [1.5, 2.8] L/min, $p < 0.0001$) and a decrease of QP/QS (−0.22 [−0.3, −0.15] vs 0.14 [−0.09, 0.27], $p < 0.0001$) following fluid challenge. These changes have been attributed to a "stiffer", less compliant pulmonary circulation in patients with a PVR ≥2 WUand would support the most recent definition of PAH that uses 2WU as a cutoff. A minority of patients (8 %) reached a PAWP ≥18 mm following fluid challenge plus balloon occlusion testing. These patients and require careful monitoring around the time of intervention, using diuretics to reduce left sided filling pressures and a fenestrated device to allow off-loading of left atrial pressures, whilst reducing right ventricular volume.

Additional tests are, thus, available to us in the catheter lab for challenging or manipulating the pulmonary circulation, and for better understanding the cardio-pulmonary pathophysiology. Yet, evidence is limited on these tests, none of which are currently recommended for routine use as part of the decision-making process regarding operability in CHD.

5. The role of PAH-specific therapy in reducing PVR and optimising haemodynamics: Can we extend the therapeutic window?

There is currently evidence on the use of advanced therapies for PAH in symptomatic patients with Eisenmenger syndrome [26] and patients with PAH after CHD repair [27,28], with the potential to improve symptoms and clinical outcomes. Bosentan, a dual endothelin receptor antagonist (ERA), was the first drug studied in small randomized clinical trial (RCT) in Eisenmenger syndrome [29], showing improvement in haemodynamics (indexed PVR reduction 5.9 ± 2.8, $p < 0.05$) and exercise capacity (increased 6MWD 53 m, $p < 0.01$) without compromising SpO_2 compared to placebo. There is now evidence to support a sustained, long-term beneficial effect of bosentan in Eisenmenger patients [30]. A RCT using macitentan [31], a newer-generation ERA, in Eisenmenger patients failed to reach its primary endpoint (6MWD change at 16 weeks follow-up), but showed a decreased in N-terminal pro-brain natriuretic peptide (ratio of geometric means, 0.80; 95 % CL, 0.68, 0.94) and a significant reduction in indexed PVR in the subset of patients who underwent hemodynamic assessment (ratio of geometric means, 0.87; 95 % CL, 0.73, 1.03). Less robust studies with ambrisentan [32] and the phosphodiesterase type 5 inhibitors (PDE-5i), sildenafil and tadalafil, have also shown favourable functional and haemodynamic effects in Eisenmenger patients. Current practice in expert centres follows a sequential symptom-orientated treatment strategy in Eisenmenger syndrome, starting with a single oral drug (ERA or PDE-5i) and escalating therapy to double oral therapy [33], followed by introduction of prostanoids, when required [34]. Subcutaneous prostacyclin analogue infusion (treprostinil) is preferred to intravenous therapy, due to a theoretical risk of paradoxical embolism and increased risk of endocarditis in Eisenmenger patients.

Evidence for PAH therapy has also recently emerged for patients with PAH after CHD correction, with 2 large randomised trials using macitentan [35] and selexipag [36], that included a minority of such patients. Experts believe that patients with PAH after shunt closure, and those with small/coincidental defects, should be treated similarly to idiopathic PAH patients [1,14,37].

Unfortunately, to date, there no evidence on the use of PAH therapies in patients with PAH-CHD and a L-R shunt. While PAH therapy may have a role, especially for patients with more advanced PVD and smaller shunts, a drug-induced drop in PVR is likely to substantially increase the shunt fraction and cause volume loading, with adverse long-term effects, unless the threshold for operability is achieved. Balancing the beneficial effects of a more compliant pulmonary vascular bed and the reduction in right ventricular afterload, against the detrimental effect of chronic volume loading can be difficult and requires careful multiparametric assessment and expertise.

In the last decade, several case reports and series have explored the practice of "treat and repair" for patients with PAH-CHD and L-R shunt who do not fulfil operability criteria at baseline assessment. "Treat-and-repair" uses PAH therapy to optimise pulmonary haemodynamics, i.e. lower PVR to operability levels, mainly in patients with pre-tricuspid shunts, though some cases of post tricuspid shunts have been reported.

There are several limitations in the available evidence on this issue. Beyond the limited sample size and retrospective nature of the reports [38–50], there is significant heterogeneity across studies with respect to the underlying CHD, baseline haemodynamics and criteria adopted to decide on treatment (e.g. haemodynamic thresholds and the use of acute vasodilator testing with different compounds). Kijima et al. [51] reported a case series of 22 patients with ASD and PAH. Eight patients received PAH-specific medications and 14 patients did not. The treated group had higher baseline PVR compared with the untreated group (9.6 $\pm$ 3.8 vs. 4.2 $\pm$ 1.0 WU, $p < 0.01$), there was thus a "referral bias". After treatment with PAH-specific medications, PVR decreased to 4.0 $\pm$ 0.8 WU ($p < 0.01$) in the treated group. All 22 patients underwent successful percutaneous ASD closure. During a treatment period of 52 $\pm$ 48 months, the World Health Organization Functional Classification (WHO-FC) significantly improved (3.0 $\pm$ 0.5 to 2.0 $\pm$ 0.0, $P < 0.01$) in the treated group as well as in the non-treated group (2.1 $\pm$ 0.6 to 1.5 $\pm$ 0.5, $P < 0.01$).

Taniguchi et al. [52] reported two cases of patients with secundum ASD and severe PAH successfully treated with surgical or transcatheter closure after combination medical therapy with and ERA (bosentan) and a PDE5-i (sildenafil or tadalafil). Bradley et al. [53] treated 12 patients with ASD and PAH (PVR 8.8 $\pm$ 1.2 WU; QP:QS 1.1 $\pm$ 0.1) with PAH therapy. Five out of 12 were considered "responders" based on a PVR reduction >30 % and underwent successful ASD closure at 1.3 $\pm$ 0.3 years after initiation of medical therapy.

Regarding patients with PAH and post-tricuspid shunt, Hu et al. [54] used a treat-and-repair strategy with bosentan and surgical repair in 41 patients with non-restrictive VSD. The VSD was partially closed using a valved patch that allowed R-L (for right ventricular offloading if right-sided pressures reached systemic levels), but not L-R shunting. Two cases died during hospitalization. None of the remaining 39 patients died during a 3-year follow-up, but the vast majority remained on PAH therapy [38].

We can conclude that there is currently insufficient evidence for a long-term benefit of a treat-and-repair approach in adult patients with PAH-CHD and prevalent L-R shunts; larger prospective studies providing robust long-term data are needed [55].

6. Conclusions

The management of patients with PAH-CHD and L-R shunt is complex and must be tailored to each patient (Fig. 1). A "treat-and-repair'' strategy may increase the rate of operability of PAH-CHD patients with L-R shunts and borderline haemodynamics; one should, however, keep in mind that the literature on the treat-and-repair strategy remains rather inconclusive with regards to long-term outcomes, and this

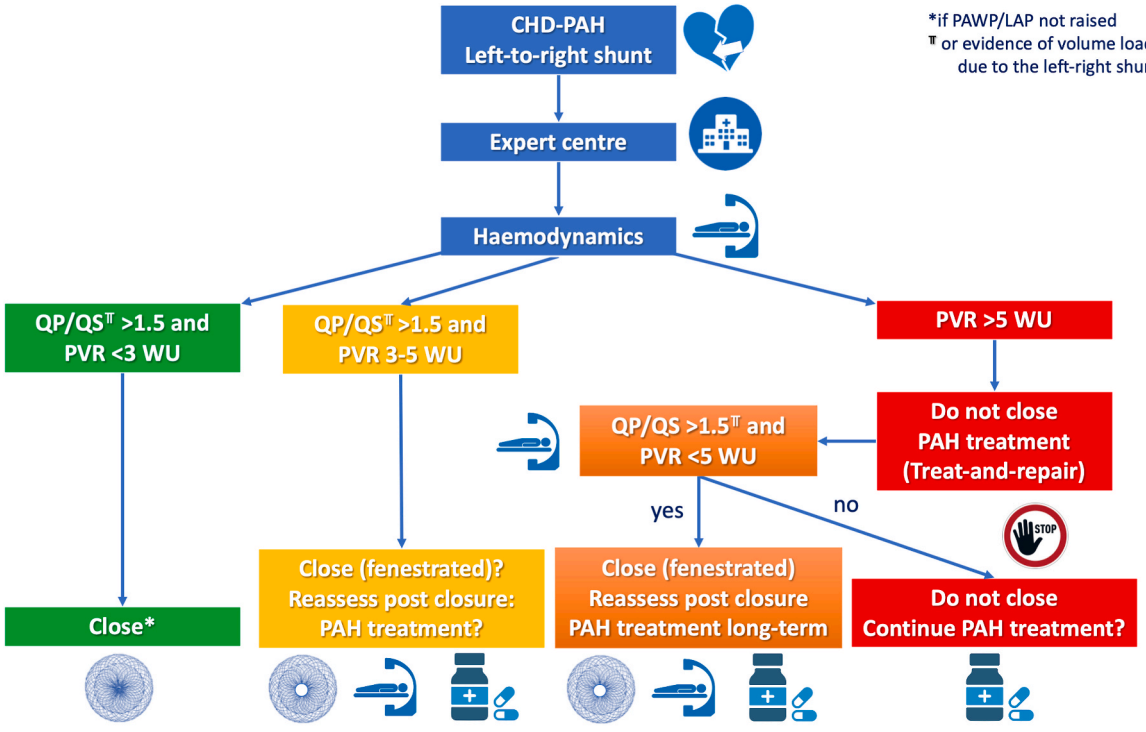

Fig. 1. Proposed algorithm for patients with PAH-CHD due to ASD and left-to-right shunt.
CHD: congenital heart disease; LAP: left atrial pressure; PAH: pulmonary arterial hypertension; PAWP: pulmonary artery wedge pressure; PVR: pulmonary vascular resistance; QP: pulmonary flow; QS: systemic flow; WU: Wood Units. Green colour: agreement to close; red colour agreement not to close; yellow and orange colour: area of uncertainness. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

approach is not without risks. There is no evidence on the long-term treatment of inoperable patients with PAH and a L-R shunt with PAH therapies. All patients with PAH and a L-R shunt must be evaluated, treated and followed in tertiary expert centres, and eligibility for shunt closure should never be based on procedural feasibility alone.

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CRediT authorship contribution statement

Michele D'Alto: Writing – original draft, Validation, Methodology, Conceptualization. **Emanuele Romeo:** Writing – review & editing, Visualization, Investigation. **Paola Argiento:** Supervision, Methodology, Conceptualization. **Andrea Vergara:** Investigation, Data curation. **Eleonora Caiazza:** Investigation. **Antonio Orlando:** Methodology. **Rosa Franzese:** Conceptualization. **Giancarlo Scognamiglio:** Investigation, Data curation. **Berardo Sarubbi:** Data curation, Conceptualization. **Konstantinos Dimopoulos:** Investigation, Writing - original draft.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper, other than two of them (MA and KD) serving in the IJCCHD Editorila Board.

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