**Thesis**

# PLSVC And Its Impact on Mortality

## - A Meta-Analysis -


submitted by

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**-**

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## Affidavit

I declare on my honour that I have written this thesis independently and without any help from others, except guidance from my supervisors, and that I have not used any sources other than those indicated, and that I have marked the passages taken verbatim or in substance from the sources used as such.

Graz, den 26.01.2024 Andrei-Antonio Michael Caracioni eh

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***"Citius, Altius, Fortius"*** **- Pierre de Coubertin (1894)**

# 1 Abstract in German / Zusammenfassung in Deutsch

## *1.1 Hintergrund*

Die Persistierende Linke Obere Hohlvene (PLSVC) wurde erstmals in der rezenten medizinischen Geschichte von Dr. J. J. Charles am Queens College in Cork (Irland) im Jahr 1889 beschrieben. Die anatomische Anomalie einer PLSVC ist häufig asymptomatisch, wenn sie nicht mit angeborenen Herzkrankheiten (CHD) in Verbindung steht. Sie tritt mit einer Inzidenz von 0,3-0,5% bis maximal 2% in der allgemeinen Bevölkerung auf. Im Falle einer Assoziation mit CHD kann die Gesamtprävalenz auf bis zu 3-12,7% steigen. Embryologisch entwickelt sich eine persistierende PLSVC, wenn die Involution der linken gemeinsamen Kardinalvene und des herznahen Teils der linken oberen Kardinalvene fehlt. Studien waren kontrovers hinsichtlich des Einflusses von PLSVC als Risikofaktor für die Mortalität auf das postoperative Kurz- und Langzeitergebnis.

Wir haben retrospektiv den Einfluss der persistierenden linken oberen Hohlvene (PLSVC) auf das Ergebnis der Herzchirurgie in einer Metaanalyse überprüft und analysiert.

## *1.2 Methoden*

Wir haben die entsprechenden PICOTS-Kriterien festgelegt und mithilfe von Booleschen Suchbegriffen (*("Persistent Left Superior Vena Cava" OR PLSVC) AND (Mortality OR Outcome) AND ("Cardiac Surgery")*) auf PubMed und Google Scholar nach entsprechenden Publikationen gesucht. Nur Originalartikel in englischer Sprache wurden einbezogen, wobei Abstracts, Buchkapitel, Fallberichte und Übersichtsartikel ausgeschlossen wurden. Es wurden 29 Ergebnisse auf PubMed und 1660 auf Google Scholar erzielt. Titel und Abstracts wurden gesichtet, und 36 Artikel haben den Screening-Schritt bestanden, wobei nur 12 Publikationen nach in-depth Evaluation mittels Newcastle-Ottawa-Skala untersucht worden sind. Wir behielten 3 qualitativ hochwertige Studien bei. Die Studie von Keizman et al. wurde zu unseren Zwecken in der PLSVC-Metaanalyse in zwei Teilstudien aufgeteilt, da er Ergebnisse für frühzeitige Todesfälle und 5-Jahres-Überleben gemessen hat.
Microsoft Excel für Mac (2023, Version 16.80) wurde für die Berechnung von Pivot-Tabellen, den festen gepoolten Effektmaß, die Homogenitätstests mit der

zwischenstudienbezogenen Varianz (Tau-Quadrat) sowie das zufallsbasierte gepoolte Effektmaß verwendet.

## *1.3 Ergebnisse*

Die *fixed-effect pooled effect measure* von 5.246 repräsentiert die konsistente durchschnittliche Auswirkung von PLSVC auf die Mortalität über die Studien hinweg. Dies legt nahe, dass Personen mit PLSVC über eine mehr als 5-fach höhere Wahrscheinlichkeit verfügen, post-operativ zu versterben, im Vergleich zu jenen ohne PLSVC. Das Konfidenzintervall (CI) von 4,544 bis 5,947 bietet ein schmales, hohes Maß an Vertrauen.

Unser Q-Wert von 11,9 aus dem Homogenitätstest, der signifikant über 3 Freiheitsgraden liegt, deutet auf eine mögliche verringerte Konsistenz zwischen den eingeschlossenen Effektgrößenmessungen hin, höchstwahrscheinlich mit einer potenziellen Hypothese der Heterogenität. Allerdings zeigt unser p-Wert von 0,992 an, dass die beobachtete Variabilität in den Effektgrößen statistisch nicht signifikant ist. Die Unterschiede in den Effektgrößen zwischen den Studien sind statistisch eher auf Zufall als auf systematische Unterschiede zurückzuführen.

Die *random-effects pooled effect measure* von 5.463 beim festen Effekt repräsentiert die durchschnittliche Auswirkung von PLSVC auf die Mortalität über die Studien hinweg. Dies legt nahe, dass Personen mit PLSVC über eine fast 5,5-fach höhere Wahrscheinlichkeit verfügen, post-operativ zu versterben, im Vergleich zu jenen ohne PLSVC.

## *1.4 Conclusion*

Die Entdeckung einer isolierten PLSVC, ohne zusätzliche damit verbundene kardiale Anomalien, wird in der Regel als gutartiger Zustand betrachtet. PLSVC kann aufgrund veränderter anatomischer Zugangswege jedoch problematisch sein. Dennoch ist ein Zugang möglich und kann einen alternativen Weg für eine erfolgreiche Geräteimplantation darstellen. Berg et al. stellten in einer retrospektiven Überprüfung fest, dass die Auswirkungen von PLSVC auf das Ergebnis von den begleitenden Bedingungen abhängen. Daher wird die Mortalität durch begleitende angeborene Herzkrankheiten in Gegenwart von

PLSVC beeinflusst. Dies hängt von der Studienpopulation, den begleitenden Strukturen, den Studienbeschränkungen und der Erfahrung des Zentrums ab.

Unsere kombinierte Studienpopulation ergab eine Gesamteffektmaßzahl von 5,463 nach Anpassung an die Unterschiede zwischen den Studien, was die konsistente durchschnittliche Auswirkung von PLSVC auf die Mortalität über die Studien hinweg repräsentiert. Dies deutet darauf hin, dass Personen mit PLSVC eine um fast das 5,5-fache höhere Wahrscheinlichkeit haben, post-operativ zu versterben, im Vergleich zu jenen ohne PLSVC.

# 2 Abstract in English


## *2.1 Background*

Persistent Left Superior Vena Cava (PLSVC) was first reported in current medical history by Dr. J. J. Charles at Queens College in Cork (Ireland) back in 1889. The anatomic anomaly of a PLSVC is frequently asymptomatic when not associated with congenital heart disease (CHD). It occurs with an incidence of 0.3-0.5% up to maximally 2% within the general population. In case of association with CHD, the overall prevalence may increase to up to 3-12.7%. Embryologically, in the absence of the involution of the left common cardinal vein and the heart-proximal part of the left superior cardinal vein, a persistent PLSVC evolves. There is no consensus on the impact of PLSVC as a risk factor for mortality on post-operative short-, and long-term outcome following cardiac surgical interventions.
We performed a systematic literature review and meta-analysis of the impact of persistent left superior vena cava (PLSVC) on the primary endpoint of mortality following cardiac surgery.

## *2.2 Methods*

We established the corresponding PICOTS-criteria and thoroughly searched using Boolean search terms (*("Persistent Left Superior Vena Cava" OR PLSVC) AND (Mortality OR Outcome) AND ("Cardiac Surgery")*) on PubMed and Google Scholar. Included were only original articles in English with exclusion of abstracts, book chapters, case reports, and reviews. Twenty-nine results on PubMed and 1660 on Google Scholar were obtained. Titles and abstracts were screened, and 36 articles passed the first screening step, while only 12 were included for further in-depth screening. In the final review using the Newcastle-Ottawa-Scale, we evaluate the twelve studies. We retained three high-quality studies. The study by Keizman et al. was subdivided into two sub-studies for our purposes in the PLSVC meta-analysis, as it provided results for early deaths and 5-year survival measurements.
Microsoft Excel for Mac (2023 version 16.80) was used for pivot table calculations, fixed-effect pooled effect measure, homogeneity testing with between-study variance (Tau-squared), as well as random-effects pooled effect measure.

## *2.3 Results*

The consistent average impact of PLSVC on mortality across studies was 5.246 (CI 95% 4.544, 5.947) determined through the fixed-effect pooled effect measure.

Homogeneity testing resulted in a Q-value of 11.9 (significantly over 3 degrees of freedom), indicative of heterogeneity. However, a p-value of 0.992 indicates that the observed variability in effect sizes is not statistically significant, thus, the differences in effect sizes among the studies are statistically due to random chance rather than systematic differences.

The random-effects meta-analysis after adjusting for between-study-variance with tau-squared, supported by a variance of 0.745679809, displays a 5.463 (CI 95% 3.77, 7.155) consistent average impact of PLSVC on mortality across studies.

These results indicate that the presence of a PLSVC increases the likelihood of death by 5.5-fold, compared to the absence of a PLSVC.

## *2.4 Conclusions*

An isolated PLSVC, without any additional associated cardiac anomalies, is generally considered a benign condition, however, alters morbidity and mortality when associated with CHDs.

Our pooled study population elicited an overall effect measure of 5.463 after between-study-variation adjustment, representing the consistent average impact of PLSVC on mortality across studies. These results indicate that the presence of a PLSVC increases the likelihood of death by 5.5-fold, compared to the absence of a PLSVC.

# 3 PUBLICATIONS CREATED DURING THESIS

No publication was written or submitted during the preparation of the thesis. However, a publication is planned.

# INDEX

# 4 Abbreviations

**APVR** Anomalous Pulmonary Venous Return

**AS** valvular Aortic Stenosis

**ASD** Atrial Septal Defect

**AVSD** AtrioVentricular Septal Defects

**CCV** Common Cardinal Vein

**CHD** Congenital Heart Disease

**CI** Confidence Interval

**CoA** Coarctation of the Aorta

**CS** Coronary sinus

**CT** ComputerTomography

**CTM** ConoTruncal Malformations

**CV** Cardinal Vein

**DILV** Double Inlet Left Ventricle

**DOLV** Double Outlet Left Ventricle

**DORV** Double Outlet Right Ventricle

**ECG** ElectroCardioGram

**HLH** Hypoplastic Left Heart

**HRH** Hypoplastic Right Heart

**ITVP** Inferior Transverse Venous Plexus

**IV** Innominate vein

**IVC** Inferior Vena Cava

**LBCV** Left BrachioCephalic Vein

**LICV** Left Inferior Cardinal Vein

**LIJV** Left Internal Jugular Vein

**LOL** Left-Sided Obstructive Lesions

**LSCV** Left Subclavian Vein

**LSCV** Left Superior Cardinal Vein

**LSICV** Left Superior Intercostal Vein

**LSVC** Left Superior Vena Cava

**MRI** Magnetic Resonance Imaging

**OR** Odds Ratio

**PA** Pulmonary Atresia

**PAPVC** Partial Anomalous Pulmonary Venous Connection

**PDA** Persistent Arterial Duct,

**PFO** Persistent Foramen Ovale

**PLSVC** Persistent Left Superior Vena Cava

**PST** Pulmonary STenosis

**RA** Right Atrium

**RICV** Right Inferior Cardinal Vein

**RIJV** Right internal jugular vein

**RSCV** Right subclavian vein

**RSCV** Right Superior Cardinal Vein

**RSVC** Right Superior Vena Cava

**RVOTO** Right Ventricular Outflow Tract Obstruction

**SA** Single Atrium

**SE** Standard Error

**STVP** Superior Transverse Venous Plexus

**SV** Single-Ventricle (context dependent)

**SV** Sinus Venosus (context dependent)

**SVC** Superior Vena Cava

**TAPVC** Total Anomalous Pulmonary Venous Connection

**TGA** Transposition of the Great Arteries

**TOF** Tetralogy of Fallot

**UV** Umbilical Vein

**Var** Variance

**VSD** Ventricular Septal Defect

**VV** Vitelline Vein

# 5 List of Figures & Tables

# 6 Introduction

## 6.1 Preamble & Incidence

Persistent Left Superior Vena Cava (PLSVC) was reported in an first in-depth review cross-species research by Dr. Marshall in 1850 and by Dr. J. J. Charles at Queens College in Cork (Ireland) in 1889 (1), and . (2,3) However, the first report is assigned to Dr. W. Cheselden who reported it in *volume 28 of Philosophical Transactions* back in 1713, as an anatomical observation. (4) ) Today, we understand that it represents the most prevalent variation within the spectrum of thoracic venous system anomalies, with no difference observed between male and female population. (5–8)

The anatomic anomaly of a PLSVC is mostly asymptomatic when not associated with congenital heart disease (CHD). It occurs with an incidence of 0.3-0.5% up to maximally 2% within the general population. It is often only identified in adulthood during planned or emergent medical procedures. In case of association with CHD, the prevalence can increase to up to 3-12.7%. (8–10) A retrospective review of patients undergoing cardiac surgery for partial anomalous pulmonary venous connection (PAPVC) highlighted a correlation between PLSVC and PAPVC with an incidence of up to 17.6%. (11)

## 6.2 General Implications

PLSVC occurs at an incidence of 0.3-0.5% up to maximally 2% within the general population, compared to 3 -12.7% in pooled patient populations with CHD. (8–10) The incidence of PLSVC in CHD depends on the type of CHD. (12) PLSVC has been suggested as an indicator necessitating comprehensive evaluation to exclude the presence of concomitant (non-)cardiac embryopathies, when being diagnosed during prenatal echocardiographic screening. (13–15)

### 6.2.1 PLSVC Anatomy

The persistence of the left superior vena cava (PLSVC) arises due to incomplete embryological involution of at least 20%, depending on anatomical variations, of the venous return from left supracardiac structures. In the most common cases of PLSVC, this aberrant vein drains the ipsilateral upper extremity and the hemilateral left head and neck region. It originates through confluence of common the left jugular vein and the ipsilateral subclavian vein. The common jugular vein takes off from the common junction of the internal and external jugular veins at the angulus venosus. Eventually additional veins contribute to the inflow: the intercostal veins, hemiazygos veins, and the azygos venous system. Finally, it drains in over 80-90% of the cases into the right atrium via end-to-side anastomosis to the coronary sinus, and the remaining through other venous pathways as indicated in Figure 1. (16–20)

### 6.2.2 Anatomical Variations

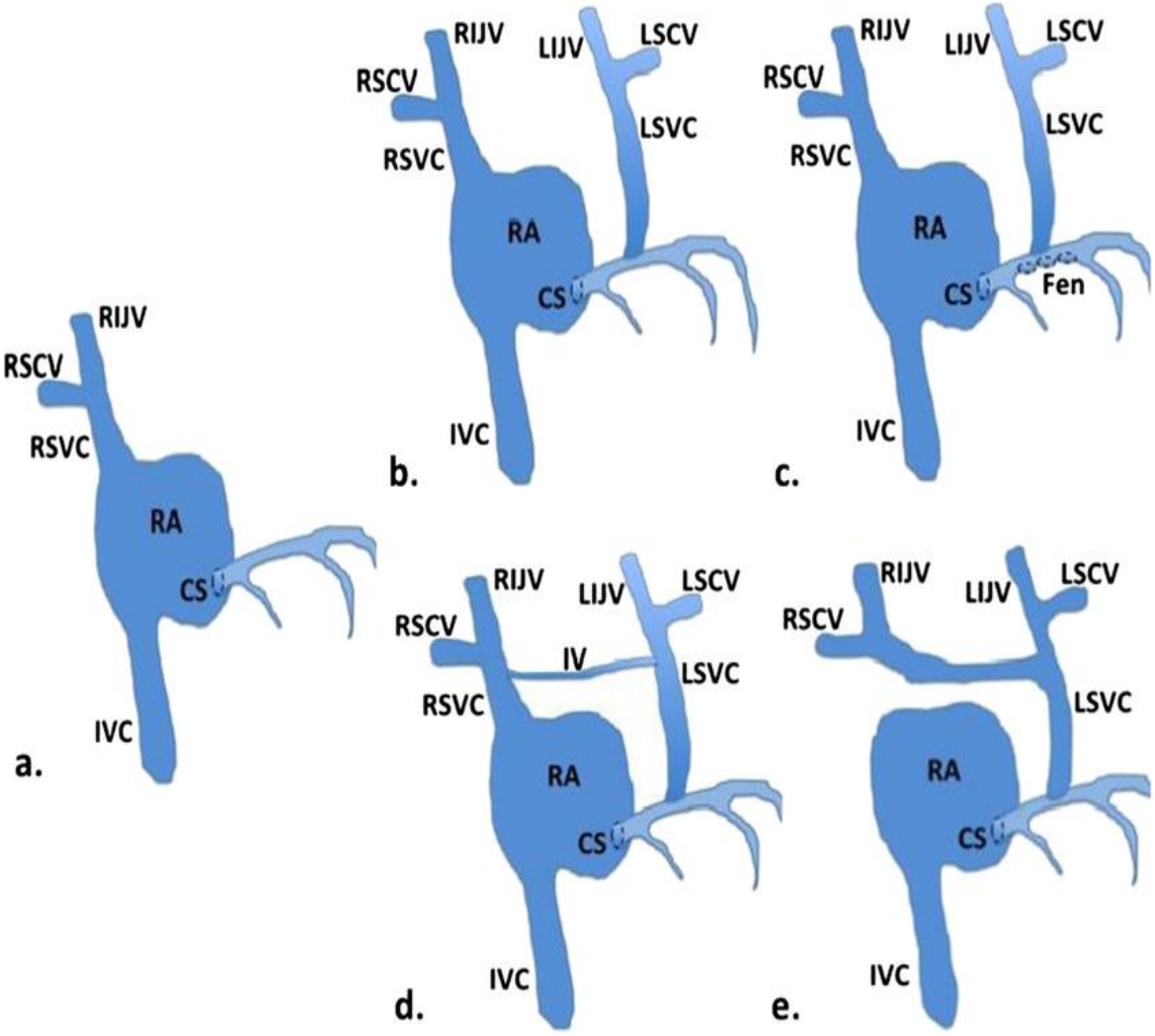


Figure 1 Examples of Certain PLSVC Anatomic Variations (21)

Rizkallah J, Burgess J, Kuriachan V. Absent right and persistent left superior vena cava: troubleshooting during a challenging pacemaker implant: a case report. BMC Res Notes. 2014 Dec;7(1):462.DOI:10.1186/1756-0500-7-462 (21)

*a. Typical venous drainage into the right atrium. b. Persistent left superior vena cava and its tributaries draining into the coronary sinus. c. Persistent left superior vena cava draining into the left atrium by means of an unroofed coronary sinus. d. Persistent left superior vena cava draining into the coronary sinus and also connected to the right superior vena cava by an innominate vein. e. Persistent left superior vena cava with an absent right superior vena cava as identified in this case report. CS = Coronary sinus; Fen = Fenestrations; IV = Innominate vein; IVC = Inferior vena cava; LIJV = Left internal jugular vein; LSCV = Left subclavian vein; LSVC = Left superior vena cava; RA = Right atrium; RIJV = Right internal jugular vein; RSCV = Right subclavian vein; RSVC = Right superior vena cava. (21)*

### 6.2.3 Drainage into Cardiac Structures

The persistent left superior vena cava can drain into various vascular, cardiac structures, depending on its embryological development. In the majority of cases, the PLSVC drains into the right atrium through the coronary sinus, but if this pathway is obstructed due to lack of development of the coronary sinus, the PLSVC can directly connect to the right atrium. (17,22)

The embryological origin of the coronary sinus corresponds to the sinus venosus, which forms around the third intrauterine week and drains into the posterior wall of the right atrium. In addition, evolutionarily, the sinus venosus gives rise to the primordial atrium. In the subsequent week, the sinus venosus further develops into the right and left horns. The left horn eventually transforms into the coronary sinus (CS). (23–25) The morphology of the coronary sinus, may have an impact on the local hemodynamic conditions, defined by the shape itself. The shape can vary significantly, ranging from filiform, varicoid, bifid, to conical. (26–29) The coronary sinus (CS) varies in length, typically ranging from 3 to 5.5 cm. During ventricular systole, it receives blood from the ventricular veins and during atrial systole, it discharges this blood into the right atrium. (23,30)

In the remaining 10-20% of cases, the PLSVC drains into the left atrium. (17) This typically suggests the presence of a partially or completely unroofed coronary sinus, leading to indirect drainage. (31) ) Some reports, however, indicate additional anatomically indirect drainage variations. The PLSVC can also directly insert into the left atrial appendage through a hemiazygos continuation or even directly into the LA. (32,33)

It is noteworthy to mention that the combination of an atrial septal defect (ASD) and PLSVC drainage into the left atrium via an unroofed coronary sinus is known as Raghib syndrome. (22) The coronary sinus in those cases can be either partially or completely unroofed. However, an unroofed CS does not embryologically imply the presence of a PLSVC, neither does vice versa. (34)

A table to summarize the different observed PLSVC drainage pathway, while using contrast agent. (35)

| | Normal Finding | Isolated PLSVC (=PLSVC without RSVC) | PLSVC with RSVC | PLSVC with unroofed CS |
|---|---|---|---|---|
| Injection of Contrast Agent into Left Arm | RA | CS → RA | CS → RA | LA |
| Injection of Contrast Agent into Left Arm | RA | CS → RA | RA | LA |

Table 1Echocardiographic PLSVC Detection Algorithm

Uçar O, Paşaoğlu L, Ciçekçioğlu H, Vural M, Kocaoğlu I, Aydoğdu S. Persistent left superior vena cava with absent right superior vena cava: a case report and review of the literature. Cardiovasc J Afr. 2010;21(3):164–6. (35)

PLSVC = persistent left superior vena cava; RSVC = right superior vena cava; CS = coronary sinus; RA = right atrium; LA = left atrium

*Echocardiographic PLSVC Detection Algorithm including Drainage Pathway using Contrast Agent (35) Detectable through venous agitated saline injection, when injected through the left cubital vein, there is initially filling of the left atrium observed in the echocardiogram, followed by appearance in the right atrium. (36,37) The same principle is used for in the detection of a PFO. (38)*

### 6.2.4 Associated Anomalies

#### 6.2.4.1 Most Common Associated Anomalies According to Perles et al. (13)

The most prevalent cardiac anomalies associated with PLSVC, based on odds ratio, can be categorized into three groups: atrioventricular septal defects (AVSD), conotruncal malformations (CTM), and left-sided obstructive lesions (LOL). (13,16)

| AVSDs | LOLs | CTMs |
|---|---|---|
| primum atrial septal defect | aortic stenosis | tetralogy of Fallot |
| canal lesions | bicuspid aortic valve | double outlet right ventricle |
| cleft mitral valve | coarctation of the aorta | transposition of the great arteries |
| | discrete subaortic membrane | pulmonary atresia |
| | mitral stenosis | truncus arteriosus |
| | supramitral ring | interrupted aortic arch |
| | cor triatriatum | aortopulmonary window |

Table 2 The most Prevalent Cardiac Anomalies associated with PLSVC (Based on OR) (13,16)

#### 6.2.4.2 Highest Incidence of Cardiac Anomalies According to PLSVC Index According to Nagasawa et al. (12)

In a systematic evaluation involving more than 1900 patients with CHD compared to over 2800 healthy newborns serving as controls, a direct correlation between PLSVC and CHD was observed. Particularly, patients with CoA exhibited a 23.7% frequency of presenting with a PLSVC as well. In congenital cardiac malformations such as DORV, there was a statistically significant occurrence of 24.6%, attributed to the absence of involution of the left common cardinal veins and the heart-proximal part of the left superior cardinal vein. The incidence of PLSVC in VSD cases was found to be up to 6.1%. (12,13)

| Highest PLSVC incidence CHDs | | |
|---|---|---|
| DORV | CoA | VSD |
| 24.6% | 23.7% | 5.1 – 6-1% |

Table 3 Highest CHD Incidence According to PLSVC Index(12,13)

PLSVC incidence in patients with Trisomy 21 and atrial septal defect (ASD) was significantly higher compared to healthy neonates. (12)

#### 6.2.4.3 Most Common Cardiac Anomalies Associated with PLSVC According to Lendzian et al. (39)

Anomalies of the caval veins are statistically significantly more prevalent in association with complex CHDs compared to simple CHDs, whereof SVC anomalies are more commonly present than IVC anomalies. A limitation of this study is due to the exclusion of neonates with transposition of the great arteries or coarctation of the aorta. (39)

Lendzian et al. classified congenital heart disease into:

a.) simple CHD including atrial septal defect (ASD), persistent foramen ovale (PFO), ventricular septal defect (VSD), pulmonary stenosis (PST), Coarctation of the Aorta (CoA), persistent arterial duct (PDA), and valvular aortic stenosis (AS).

b.) complex forms, such as transposition of the great arteries (TGA), atrioventricular septal defect (AVSD), single-ventricle (SV) lesions, pulmonary atresia (PA), anomalous pulmonary venous return (APVR), Tetralogy of Fallot (TOF), double outlet right ventricle (DORV), single atrium (SA), hypoplastic left heart (HLH), hypoplastic right heart (HRH), and double inlet or outlet left ventricle (DILV/DOLV). (16,39)

| Malformations of the Venous System associated with * | | | |
|---|---|---|---|
| Simple CHD | | Complex CHD | |
| VSD | 8.7% | SV | 16.3% |
| ASD | 6.5% | AVSD / TOF | 8.7% |
| CoA / PDA | 3.3% | ASD + VSD | 5.4% |
| PST / Subvalvular AS | 1.1% | DORV / PA | 4.3% |
| | | TAPVR / TGA | 2.2% |

Table 4 Malformations of the Venous System associated with Simple and Complex CHD(16,39)

PDA = persistent ductus arteriosus; CoA = Coarctation of the Aorta; PST = pulmonary stenosis; PA = pulmonary atresia; AS = aortic stenosis; SV = single ventricle; AVSD = atrio-ventricular septal defects; TOF = tetralogy of Fallot; DORV = double outlet right ventricle; TAPVR = total anomalous pulmonary venous return; TGA = transposition of the great arteries; "/" = or; "+" = in combination they represent a complex CHD with a "%" representation of

* A limitation of this study is due to the exclusion of neonates with transposition of the great arteries or coarctation of the aorta.

#### 6.2.4.4 Most Common (A-)Cyanotic Heart Diseases Associated with PLSVC According to Ari et al. (40)

In a retrospective analysis of 2663 patients with congenital heart disease (CHD), 88 were additionally diagnosed with a PLSVC. The most common to the least common concomitant CHD with PLSVC were VSD (23.9%), DORV (14.8%), TOF 11.4%, CoA (9.1%), pulmonary atresia and TGA (6.8% each), AVSD and ASD (5.7% each), pulmonary valve stenosis (4.5%), tricuspid atresia (3.4%), PDA (2.3%), as well as HLHS (1.1%). (16,40)

Based on statistical significance, the following CHDs in patients with PLSVC were identified:

| Most Common CHDs *[1] | | PLSVC associated statistically significant most. commonly with *[1] (*[2]) | | | |
|---|---|---|---|---|---|
| VSD | 23.9 % | a-cyanotic CHDs | | Cyanotic CHDs | |
| DORV | 14.8 % | VSD | 23.9 % (44.7 %) | DORV | 14.8 % (31.7 %) |
| TOF | 11.4 % | CoA | 9.1 % (17.0 %) | TOF | 11.4 % (24.4 %) |
| CoA | 9.1 % | ASD | 5.7 % (10.6 %) | TGA | 6.8 % (14.6 %) |
| Pulmonary Atresia | 6.8 % | AVSD | 5.7 % (10.6 %) | Pulmonary Atresia | 6.8 % (14.6 %) |
| TGA | 6.8 % | | | | |
| ASD | 5.7 % | | | | |
| AVSD | 5.7 % | | | | |
| Pulmonary Valve Stenosis | 4.5% | | | | |

| | |
|---|---|
| Tricuspid atresia | 3.4 % |
| PDA | 2.3 % |
| HLHS | 1.1 % |
| PAPVC | 1.1 % |

Table 5(A-)Cyanotic CHDs Statistically Significant Most Commonly in PLSVC Subgroup and Total Population (40)

*[1] : "%" referring to the total amount of CHDs in the PLSVC study population ( $n_{total}$ in PLSVC subpopulation = 88).*

*[2] : "%" referring to the total amount of CHDs in the respective cyanotic vs acyanotic PLSVC study sub-population ( $n_{total}$ in PLSVC subpopulation cyanotic = 41; $n_{total}$ in PLSVC subpopulation a-cyanotic = 47 ).*

In the overall CHD population, irrespective of PLSVC presence, in decreasing order: VSD (31.7 %), ASD (13.4 %), PDA (10.0 %), CoA (9.2 %), pulmonary valve stenosis (6.4 %), TOF (6.3 %), DORV (5.5 %), TGA (5.3 %), have been reported. (40)

#### 6.2.4.5 Most Common Concomitant Anomalies in Patients with PLSVC with and without Heterotaxy According to Berg et al. (41)

Prenatal diagnosis of PLSVC and heterotaxy were established using fetal echocardiography. Out of the 82 patients with PLSVC, slightly less than half also exhibited heterotaxy ($n_{Heterotaxy}$ = 37; 45%). Among these 37 cases, 13 patients survived. Reasons for mortality included active interventions such as termination of pregnancy, or passive outcomes such as intrauterine fetal death, neonatal death, and childhood death. (41)

| PLSVC | | | |
|---|---|---|---|
| + Heterotaxy associated with | | - Heterotaxy associated with | |
| Complete AVSD | 75 % * | VSD | 41 % * |
| RVOTO | 58 % * | CoA | 34 % * |

Table 6 PLSVC associated CHDs in the Context of Heterotaxy and without Heterotaxy(16,41)

*RVOTO = right ventricular outflow tract obstruction*

*: "%" : % may be over 100% as it each referred in this table to the total amount of PLSVC, so cAVSD and ROTO can be present in the same case

It is important to note that heterotaxy is associated with significant mortality. Therefore, it should be emphasized that the implications of PLSVC on the outcome is solely dependent on the associated conditions. Thus, mortality is impacted by associated CHDs, compared to cases where no additional CHDs are present. (41)

In this study, during pre-natal echocardiography, a dilated coronary sinus was not detected in heterotaxy cases. (41) A possible hemodynamic explanation for the presence of non-pathological coronary sinus findings could be the concurrent presence of an unroofed coronary sinus, which appears to be a near-universal occurrence in cases exhibiting right or left isomerism. (41–43)

### 6.2.5 Electrophysiological Implications

PLSVC is often an incidental radiological finding in adults. Commonly identified during central venous access procedures or detected during catheter-based interventions for cardiac arrhythmia ablation, as well as device implantation. (44,45) PLSVC can pose a problem due to altered anatomical access routes. However, access is possible and may present an alternative pathway for successful device implantation. (46)

It has been demonstrated that PLSVC can lead to tachycardic rhythm disturbances (i.e., supra-ventricular tachycardia, atrial fibrillation), and in some cases bradyarrhythmia like atrio-ventricular blocks. (47–50) The cause can be attributed to the malalignment of embryonic conduction tissue during the initial stages of cardiac development. (45,47)

### 6.2.6 Procedural Implications

The importance of persistent left superior vena cava (PLSVC) is of high significance. It is imperative to identify it at an early stage if complex procedures are planned. It is crucial to take it into account, especially when cannulation of the venae cavae is considered. In cardiopulmonary bypass procedures, the presence of a PLSVC necessitates the cannulation of not only the inferior vena cava and the mostly orthotopic superior vena cava, but also the inclusion of the superior vena cava sinistra into the bypass circuit. (51,52)

There are two examples illustrating the need to know of a PLSVC: First, when a Glenn procedure is performed in the context of univentricular physiology, bilateral bidirectional cavopulmonary anastomoses play an important operative step regarding PLSVC incorporation. (53) Secondly, the PLSVC also constitutes a relative contraindication for retrograde cardioplegia infusion due to its drainage into the coronary sinus. In this scenario, the cardioplegic solution would not be adequately flushed retrogradely into the coronary vessels. (13,16,22) Moreover, if a PLSVC drains to the left atrium, it represents a 50 – 70 % risk of paradoxal thromboembolism via right-to-left shunting. This needs further clinically relevant imaging, evaluation, and intervention. (54,55)

### *6.3 Detection of a PLSVC*

Detection of a PLSVC is often considered an incidental finding when no other CHD is present. PLSVC can be considered a benign finding. (13,16,17,41) Definitive diagnosis is made by various imaging tools. (6,16,56,57) As an intra-operative finding, or even only as late as on autopsy, a PLSVC is possibly detected. (58,59)

The main PLSVC diagnostic method, also considering incidental findings, is trans-thoracic and possibly trans-esophageal echocardiography using a bubble-study protocol, which indicates filling of the coronary sinus, before entering the atrial structure. (36,60) Regarding PLSVC drainage structures, the bubbles will be most likely seen secondly in the right atrium, and in rare cases in the presence of an unroofed CS, or direct drainage into the left atrium. So a PLSVC can be determined by injection via the left extremity, and in cases of an isolated PLSVC, injection in the right extremity can be used. (16,17,31–33,40–43). The main indicator for triggering further PLSVC investigative imaging is a dilated CS. However, in heterotaxy syndrome, a dilated CS is always present. Without the bubble study, only indicative imaging signs suspects the presence of a PLSVC presence, , which are influenced by the hemodynamic aspect of the CS filling status. (16,41–43)

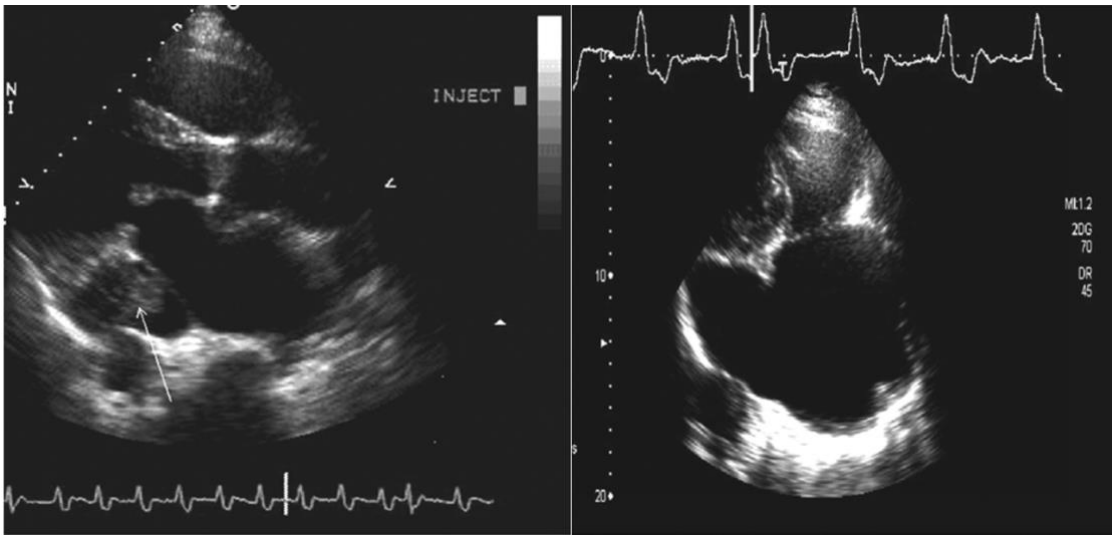


Figure 2 Cardiac Sonography with Bubble Study (36)

Bhatti S, Hakeem A, Ahmad U, Malik M, Kosolcharoen P, Su Min Chang. Persistent left superior vena cava (PLSVC) with anomalous left hepatic vein drainage into the right atrium: role of imaging and clinical relevance. Vasc Med. 2007 Nov;12(4):319–24.

*On the left image we can perceive bubbles filling initially the coronary sinus (indicated by arrow). Afterwards, only right atrial bubbles are detected. Furthermore, on the right image a significant enlargement of the right atrium can be seen.*

For further information regarding the PLSVC pathway and presence of isolated PLSVC (without right superior vena cava) see chapter *"3.2.3. Drainage Into Cardiac Structures"*.

Further investigations, such as multidetector computer tomography can be used to detect PLSVC using an iodinated contrast agent. In children and neonates, it may be limited due to need of sedation. For detailed image interpretation, ECG-gated cardiac CT may help. Contrast is needed, but the injection site and traveling route are irrelevant as the PLSVC is detected during delayed venous phase images. (16,56,57)

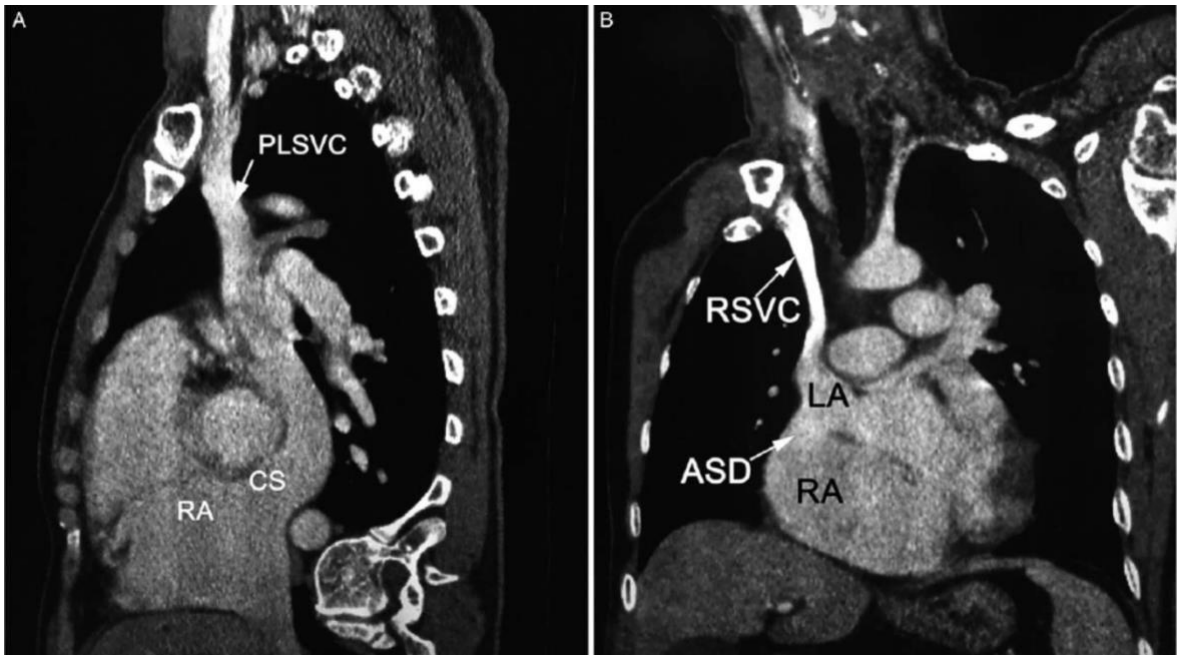


Figure 3 Cardiac Multidetector CT Indicating PLSVC Presence with Special Case of RSVC Drainage into LA(61)

Li L, Ji KQ, You CY. Persistent left superior vena cava associating with anomalous right superior vena cava drainage, atrial septal defect and atrial fibrillation: a case report. Chin Med J (Engl). 2019 Jan 20;132(2):220–2. (61)

*The two images depict an PLSVC draining into the CS, which shows its confluence to the right atrium (RA). Moreover, a cardiac shunt can be identified as an atrial septal defect (ASD) between the RA and left atrium (LA). In this particular case the RSVC drains directly into the LA, instead of the RA. (61)*

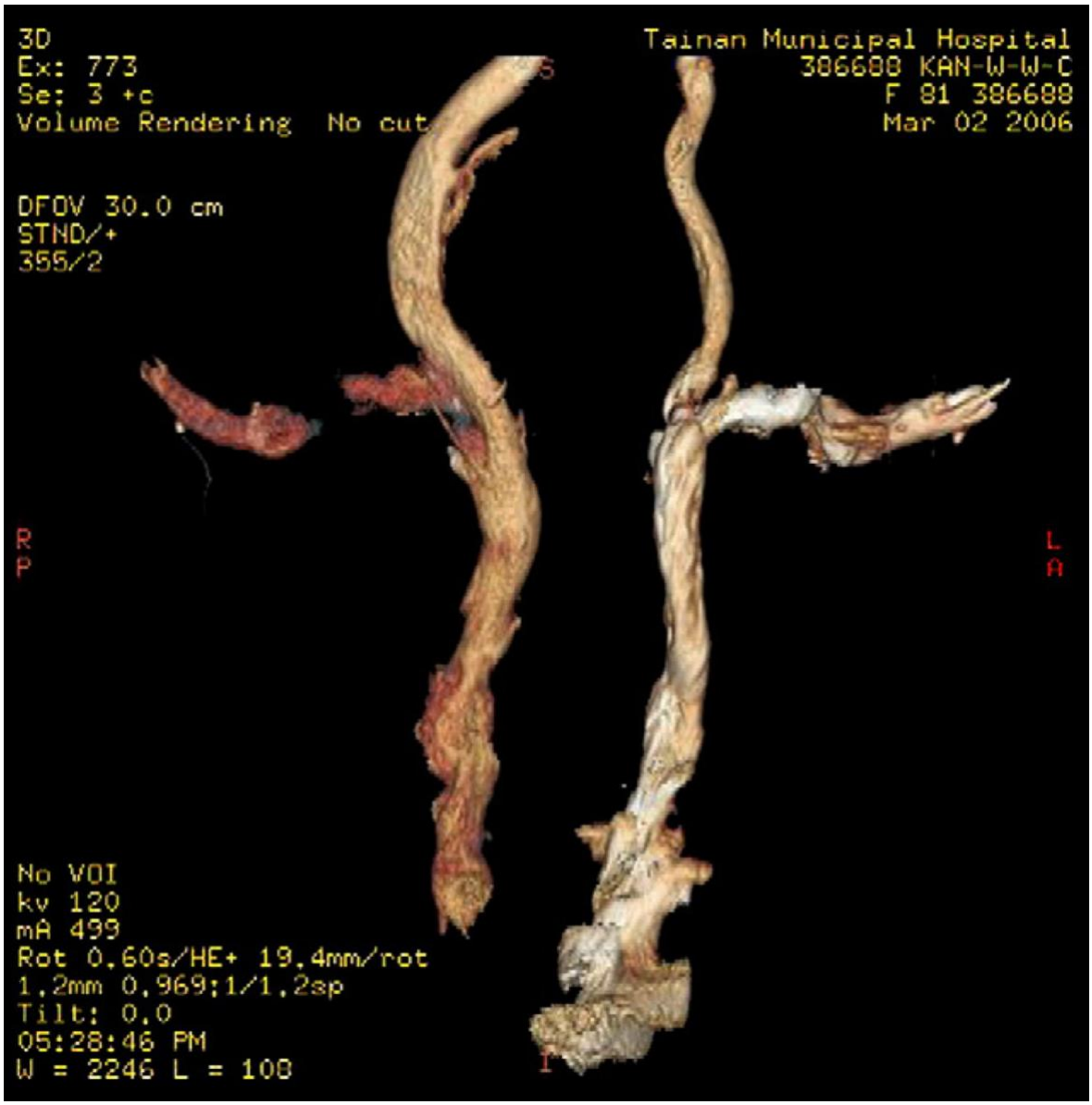


Figure 4 Multi-Slice CT Image with 3D Reconstruction of Bilateral SVC after CT-Heart-Removal(62)

Fang CC, Jao YTFN, Han SC, Wang SP. Persistent left superior vena cava: Multi-slice CT images and report of a case. Int J Cardiol. 2007 Sep;121(1):112–4. (62)

Another non-invasive and radiation-free method using non-iodinated contrast agent to evaluate the presence of a PLSVC, is magnetic resonance imaging (MRI). The assessment of the flow direction is possible and enhances deductive medical decision-making. One limitation is artifacts due to cardiac rhythm changes. (6,16,56)

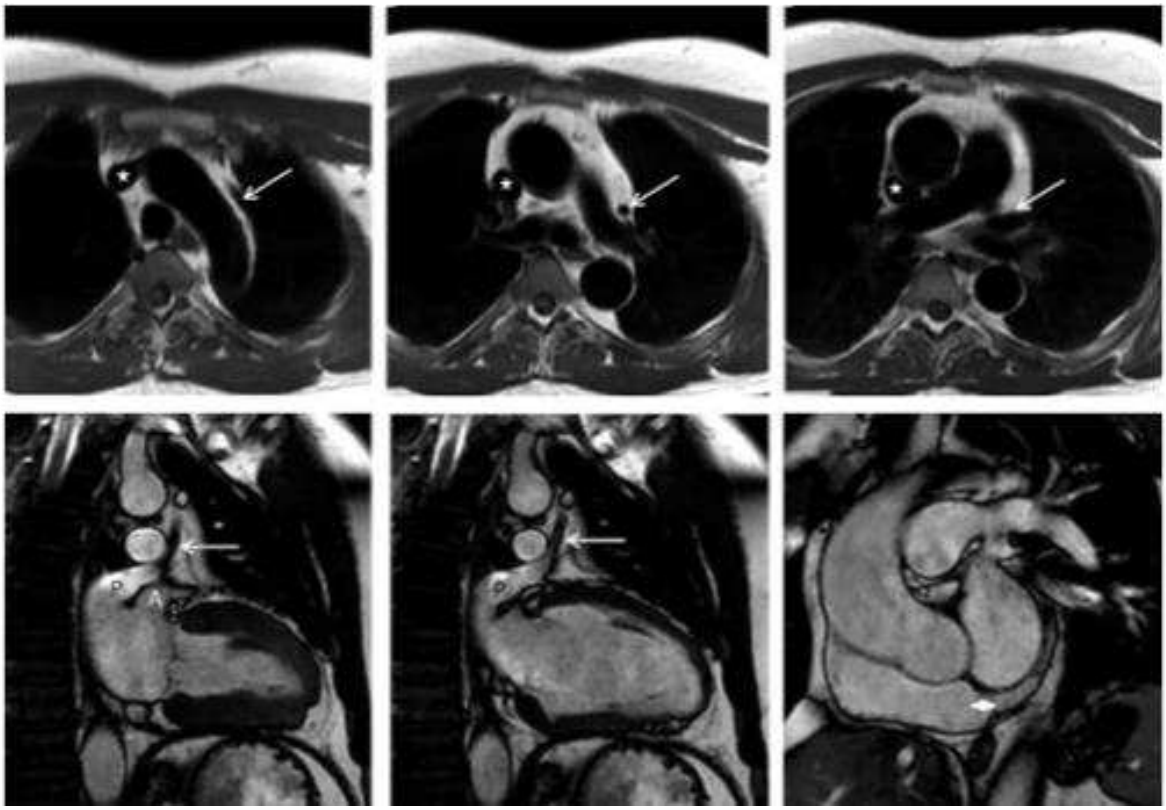

Figure 5 PLSVC seen by Cardiac MRI in Axial T1(63)

*Blokland D, Lentjes GW, Velthuis BK, Chamuleau SAJ, Rienks R. Persistent left superior vena cava draining into the left superior pulmonary vein in a scuba diver: A case report and literature study. Scand J Med Sci Sports. 2019 Aug;29(8):1265–9. (63)*

*Upper panel: Axial T1 black blood images display the persistent left superior vena cava (PLSVC) indicated by the arrow and the right superior vena cava denoted by the star. Lower panel: Two-chamber cine images of the left ventricle during systolic (left) and diastolic (middle) phases reveal the PLSVC (arrow) draining into the left superior pulmonary vein (P) situated behind the left atrial appendage (A). In the right image, a short-axis cine image at the atrial level illustrates the connection (diamond) between the non-dilated coronary sinus and the right atrium. (63)*

However, invasive, but being considerate the gold standard for PLSVC detection is angiography, providing the most detailed anatomic and hemodynamic assessment. Significant considerations are radiation exposure, and usage of iodinated contrast agents possibly causing renal insufficiency, thyrotoxicosis, as well as allergic reactions. (6,16,35,56,64,65)

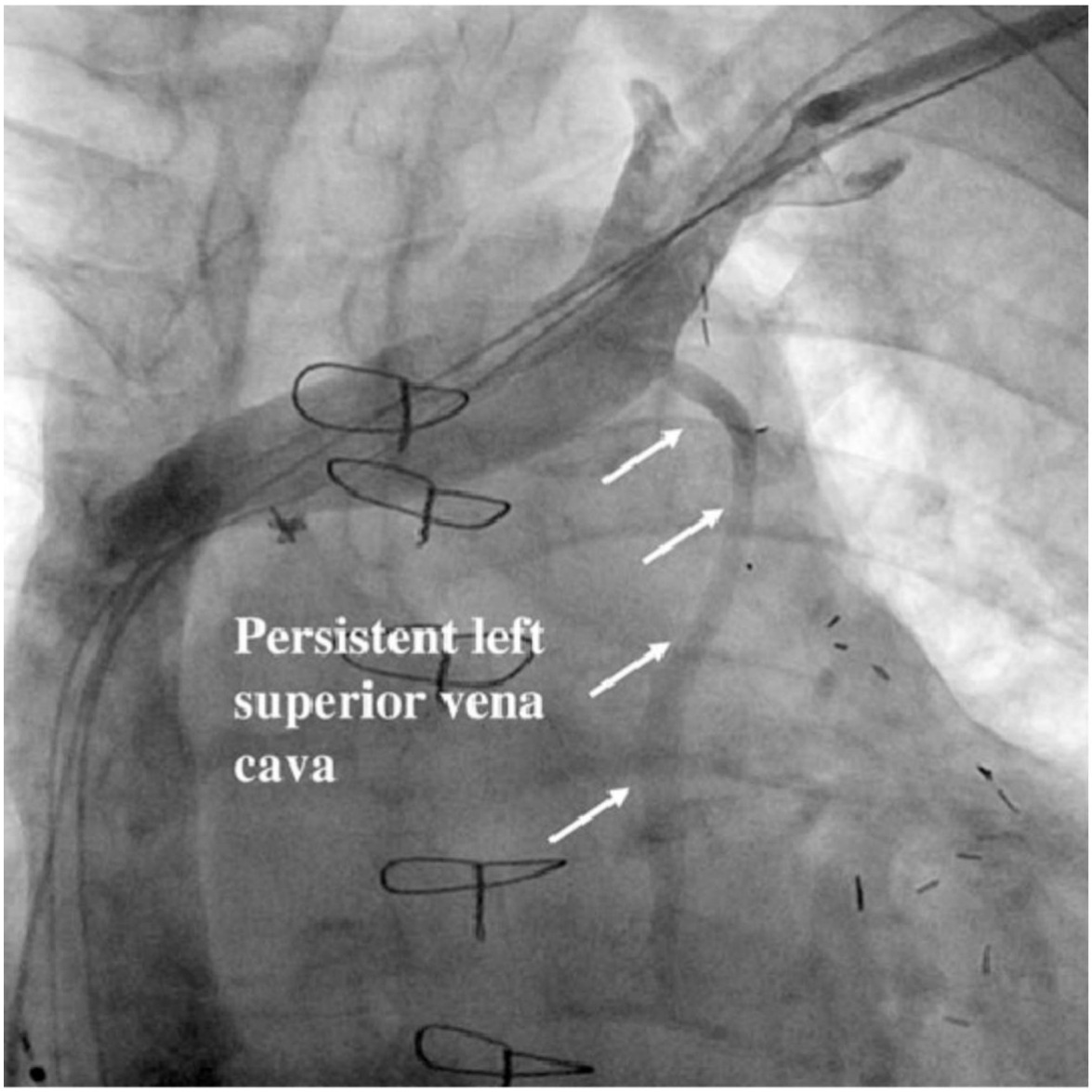


Figure 6 Angiogram of the Innominate Vein Showing Presence of PLSVC (66)

Stevenhagen J, Meijer A, Bracke FA, Van Gelder BM. Coronary sinus atresia and persistent left superior vena cava with the presence of thrombus complicating implantation of a left ventricular pacing lead. Europace. 2008 Mar 1;10(3):384–7. (66)

## *6.4 Embryology*

### 6.4.1 General Embryology

PLSVC is classified under the umbrella of systemic vascular anomalies, as a specific form of anomalous pulmonary venous connections. It is part of the subcategory of systemic vascular anomalies, distinct from bronchopulmonary and mixed anomalies. (67)

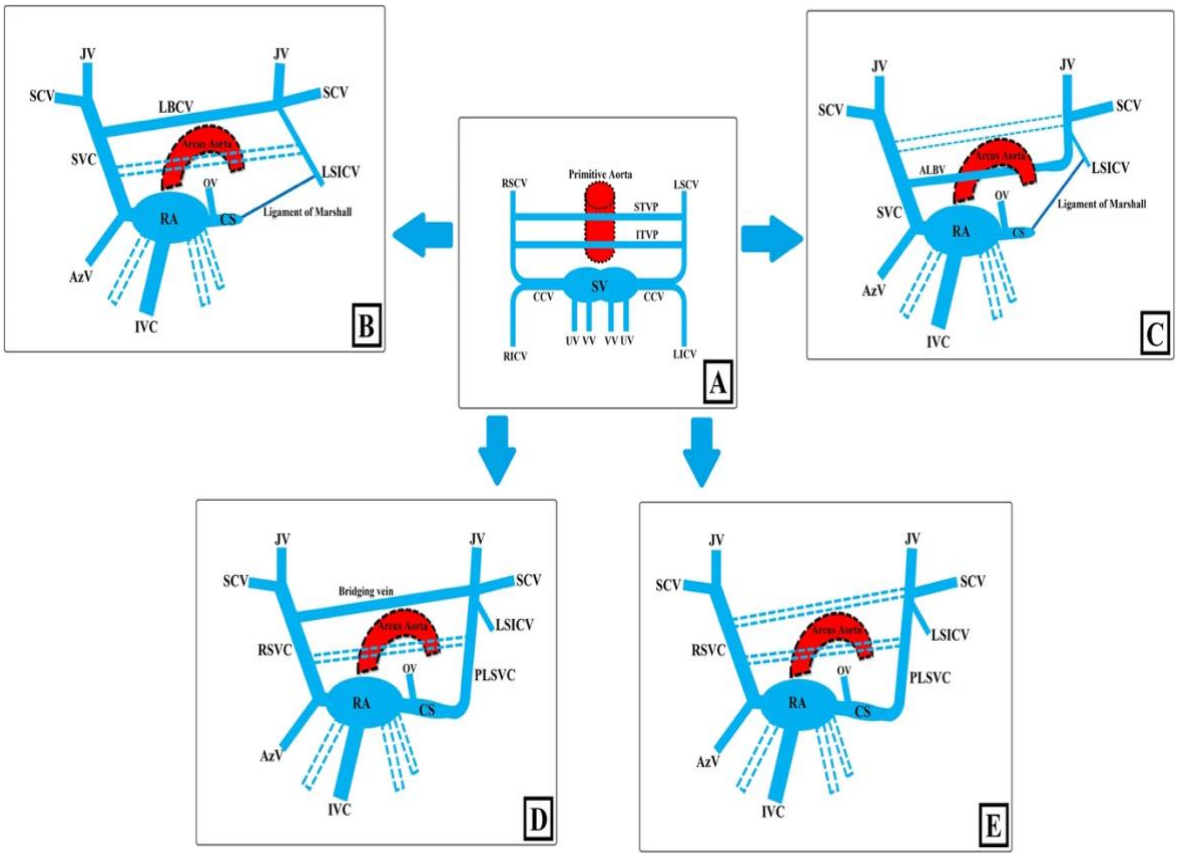


Figure 7 Developmental Stages of Primitive Venous System and Embryology of PLSVC(16)

*Azizova, A., Onder, O., Arslan, S. et al. Persistent left superior vena cava: clinical importance and differential diagnoses. Insights Imaging 11, 110 (2020). https://doi.org/10.1186/s13244-020-00906-2*

As depicted in Figure 1, embryology in the 5th gestational week (Panel A) involves bilaterally formed venous returns such as vitelline (VV), umbilical (UV), and cardinal veins (CV). The double-horned sinus venosus (SV) receives influx from the common cardinal veins, which on each side receive the fused superior and inferior cardinal veins (RSCV / LSCV + RICV / LICV → right / left common cardinal vein (CCV)). Additionally, the respective paired vitelline and umbilical veins flow into the SV. In the supra-cardiac venous

circulation, communications develop between the superior cardinal veins: superior and inferior transverse venous plexus (STVP, ITVP). (16,17,19,22)

Three weeks later (8th gestational week) (Panel B), the internal jugular veins, as well as subclavian and brachiocephalic veins, originate from the respective ipsilateral superior cardinal veins. Embryologically, the SCV arises from the heart-proximal portion of the RSVC, merging with the right common CV. The inferior vena cava evolutionarily originates from the right vitelline vein. Both venae cavae empty into the right atrium, which originates from the right horn of the sinus venosus. The heart-distal portion of the LSCV evolves into the left superior intercostal vein (LSICV), which, along with the left common CV, forms the ligament of Marshall over its involuted portion. The left horn of the sinus venosus gives rise to the oblique vein (OV) of the left atrium, as well as the coronary sinus (CS). The latter is connected to the LSICV through the ligament of Marshall. The RICV becomes the azygos vein. (12,17,19,22,68,69)

The embryological origin of the coronary sinus corresponds to the sinus venosus, which forms around the third intrauterine week and drains into the posterior wall of the right atrium. Additionally, evolutionarily, the sinus venosus gives rise to the primordial atrium. In the subsequent week, the sinus venosus further develops into the right and left horns. The left horn eventually transforms into the coronary sinus (CS). (23–25)

The transverse venous plexus gives rise to the left brachiocephalic vein (LBCV) from the STVP, while the ITVP regresses due to mechanical forces exerted by the growing aorta and pulmonary artery. LICV, left VV, and both UVs involute. In Figure C, an anatomical variant is evident, where regression of the STVP occurs due to a high-positioned aortic arch. Consequently, the ITVP transforms into an aberrant left brachiocephalic vein. (16)

In the absence of the involution of the left common CV and the heart-proximal part of the LSCV, a persistent PLSVC evolves (Figures D & E). A venous communication between the two superior venae cavae can exist through the left brachiocephalic vein (LBCV), also known as a bridging vein (Figure D). However, this can also involute, leading to a lack of inter-superior venae cavae communications via LBCV (Figure E). (12,16,17,19,22,68,69)

### 6.4.2 PLSVC Embryological Development Impacts Cardiac Anatomic Structures

In the same way as PLSVC development is influenced by surrounding structures and exerted pressures (12,16,17,19,22,68,69), a developing / developed PLSVC can impact cardiac formation and anatomy. (16,17,20,22)

Due to the direct pressure exerted by the emerging PLSVC, compression of the dilated coronary sinus (CS) in the region of the left atrium can result in a reduction of the mitral valve area. An observed phenomenon is the presence of a common left pulmonary vein trunk, potentially explained by the limited space due to the dilated CS. Indirectly, through volume variability, increased blood flow through the CS and subsequently reduced flow through the right superior vena cava (RSVC) can lead to diminished RSVC dimensions. Elevated flow volume through the CS due to the influx of the PLSVC may lead to the atrophy of cardiac venous valves such as Thebesian and/or Vieussens valves. (16,17,20,22)

### 6.4.3 PLSVC Embryological Development

At present, two antithetical hypotheses stand as primary explanations for the development of a persistent left superior vena cava (PLSVC).

#### 6.4.3.1 Low Left Atrial Pressure Theory Hypothesis

Reduced left atrial pressures may arise from congenital anomalies such as atrial septal defect, which is subsequently associated with diminished development of the left atrium (LA) and, consequently, leads to a smaller volume of the LA over time. As a result, there might not be sufficient mechanical pressure exerted on the common and left cardinal veins, ultimately affecting the future coronary sinus. Thus, the left common cardinal vein and the heart-proximal segment of the left superior vena cava evolve into a persistent left superior vena cava. (13,16)

#### 6.4.3.2 Obstructive Theory Hypothesis

It is based on the principle that congenital anomalies of the heart, induced by a dilated coronary sinus due to persistent left superior vena cava (PLSVC), lead to left-heart obstruction through space restriction. However, Bartsota et al. refuted this theory in a retrospective case series review involving patients with a normal situs and a single PLSVC draining into the coronary sinus, particularly concerning coarctation of the aorta. (13,16,70)

# 7 MATERIAL & METHODS

## 7.1 Study Design

We performed a systematic literature review and meta-analysis of the impact of a persistent left superior vena cava (PLSVC) on the primary outcome of mortality following cardiac surgery.

The following medical databases were searched with the respective Boolean search terms from 26$^{th}$ of May 2023 up to and including September 9, 2023: PubMed & Google Scholar - ("Persistent Left Superior Vena Cava" OR PLSVC) AND (Mortality OR Outcome) AND ("Cardiac Surgery"). Twenty-nine results on PubMed and 1660 on Google Scholar were obtained.

Inclusion and Exlusion Criteria have been based on the PICOTS criteria.

The following PICOTS criteria were established from articles identified through database and register review:

**PICOTS-Criteria**

Population: The population includes all children and adults who were diagnosed with Persistent Left Superior Vena Cava (PLSVC) either pre-, intra-, or post-intervention and who underwent cardiac surgery after birth for any congenital heart disease.

Intervention: The intervention is any cardiac surgery performed after birth on individuals with diagnosed PLSVC and congenital heart diseases.

Comparison: The comparison group includes individuals undergoing surgery for congenital heart diseases but without a diagnosis of PLSVC.
Outcome: The primary outcome is mortality, which will be assessed using data analysis based on selected articles. If possible, patients' / patient population's outcome influenced by non-cardiac related events was excluded.
Time: All studies are included, regardless of timeframe of the study.
Study Design: A meta-analysis is intended, provided that enough data for extraction and analysis is available.
Setting: In-patients with follow-up as out-patients or through phone/written communication were assessed.

Newcastle-Ottawa Scale for Quality Assessment
For quality assessment, we used the Newcastle-Ottawa Scale without extension of criteria, such as statistical analysis outcome and interventional focus. This scale evaluates the quality of each study individually by dissecting the selection of study groups, comparability of groups, and outcome assessments.

## 7.2 Data Synthesis and Statistical Analysis

All information was extrapolated and compiled from the selected studies. In our examination of likelihood of death in patients with PLSVC compared to the control group (no PLSVC identified), we used the OR.

We included and analyzed only high-quality studies that met our PICOTS criteria. Since Keizman et al. explored two consecutive time frames (early death and 5-year survival), we represent each timeframe separately in our meta-analysis.
For each study, we computed the odds ratio (OR), standard error (SE), variance (Var), and confidence interval of the odds ratio (CI) with corresponding upper and lower limits.

We used Microsoft® Excel for Mac© 2023 version 16.80 for pivot table calculations, fixed-effect pooled effect measure, homogeneity testing with between-study variance (Tau-squared), as well as random-effects pooled effect measure.

Variations in study outcome, i.e., heterogeneity due to methodological and clinial differences, between the studies was tested with the Cochran's Q. However, one caveat needs to be noted that this test has low power when applied to analyses of small numbers of studies as it is the case in our meta-analysis.

Next steps included to calculate the pivot table calculations, fixed-effect pooled effect measure, random-effects pooled effect measure based on weighted effect-measurements, homogeneity testing with between-study variance (Tau-squared), as well as pivot table creation. (71–74)

All extrapolated and compiled data was listed in corresponding pivot tables for each study and odds for each event group, OR, ln (OR), upper and lower limit of CI at 95%, SE using ln (OR), and of course the Var were calculated.

For calculations we used the following equations:

- Odds = $\frac{group's\ event}{group'snon-event}$
- OR = $\frac{exposed\ risk\ group}{non-exposed\ risk\ group}$
- Upper CI = $exp((ln\ (OR)\ +\ 1{,}96 * SE)$
- Lower CI = $exp((ln(OR)\ -\ 1{,}96 * SE)$
- SE (ln (OR)) = SQRT(1/a+1/b+1/c+1/d); with a-d being the correspondent squares in the respective contingency table
- Variance = (1/a + 1/b + 1/c + 1/d) with a-d being the correspondent squares in the respective contingency table

**Keizmann et al. Early Mortality**

| | PLSVC Group | Control Group |
|---|---|---|
| Event (Death) | 4 | 3 |
| Non-Event (Survivor) | 14 | 77 |
| | | |
| Odds | 0,285714286 | 0,038961039 |
| **OR** | **7,333333333** | |
| Ln (OR) | 1,992430165 | |
| **Upper CI 95%** | **36,38155474** | |
| **Lower CI 95%** | **1,478160517** | |
| Standard Error SE (ln (OR)) | 0,817159053 | |
| **Variance** | **0,667748918** | |

Table 7 Keizmann et al. Early Mortality

*Calculations and Results for OR, ln (OR), Upper CI 95%, Lower CI 95%, SE (ln (OR)), Var*

**Keizmann et al. 5-Year Mortality**

| | PLSVC Group | Control Group |
|---|---|---|
| Event (Death) | 4 | 5 |
| Non-Event (Survivor) | 14 | 75 |
| | | |
| Odds | 0,285714286 | 0,066666667 |
| **OR** | **4,285714286** | |
| Ln (OR) | 1,455287233 | |
| **Upper CI 95%** | **17,96785982** | |
| **Lower CI 95%** | **1,022233428** | |
| Standard Error SE (ln (OR)) | 0,731274165 | |
| **Variance** | **0,534761905** | |

Table 8 Keizmann et al. 5-Year Mortality

*Calculations and Results for OR, ln (OR), Upper CI 95%, Lower CI 95%, SE (ln (OR)), Var*

**Giuliani-Poncini et al. Overall Mortality**

| | PLSVC Group | Control Group |
|---|---|---|
| Event (Death) | 5 | 8 |
| Non-Event (Survivor) | 47 | 324 |
| | | |
| Odds | 0,106382979 | 0,024691358 |
| OR | 4,308510638 | |
| Ln (OR) | 1,460592285 | |
| Upper CI 95% | 13,7232061 | |
| Lower CI 95% | 1,352691477 | |
| Standard Error SE (ln (OR)) | 0,591069383 | |
| Variance | 0,349363015 | |

Table 9 Giuliani-Poncini et al. Overall Mortality

*Calculations and Results for OR, ln (OR), Upper CI 95%, Lower CI 95%, SE (ln (OR)), Var*

**Ramgren et al. Overall Mortality**

Ramgren et al. furnished information regarding the CI limits and HR, so to the formulas were re-equilibrated and the SE (ln (HR)) and variance Extrapolated.

| | |
|---|---|
| Hazard Ratio (HR) | 6,10 |
| Ln (HR) | 1,808288771 |
| Upper CI 95% | 29 |
| Lower CI 95% | 1,2 |
| Standard Error SE (ln (HR)) | 0,795411765 |
| Variance | 0,632679875 |

Table 10 Ramgren et al. Overall Mortality

*Calculations and Results for OR, ln (OR), Upper CI 95%, Lower CI 95%, SE (ln (OR)), Var*

Given the calculations above, fixed-effect pooled effect-measure analysis was performed.

- fixed-effect pooled effect measure = SUM (Effect Size / Variance) / SUM (1 / Variance)

- variance of pooled effect measure = 1 / SUM (1 / Variance)

- CI Lower Limit 95% = Fixed Effect Pooled Effect Measure - 1,96 * SQRT (Variance of Pooled Effect Measure)

- CI Higher Limit 95% = Fixed Effect Pooled Effect Measure + 1,96 * SQRT (Variance of Pooled Effect Measure)

- k = with k being the number of included studies in the meta-analysis

| Study ID | Year | Effect Size Measure | Effect Measure | Variance | 1/Variance | Effect Measure / Var |
|---|---|---|---|---|---|---|
| | | | | | | |
| Keizman et al. (Early Mortality) | 2019 | OR | 7,333333333 | 0,667748918 | 1,497568882 | 10,9821718 |
| Keizman et al. (5y Mortality) | 2019 | OR | 4,285714286 | 0,534761905 | 1,869991095 | 8,014247551 |
| Giuliani-Poncini et al. | 2013 | OR | 4,308510638 | 0,349363015 | 2,862352211 | 12,33247495 |
| Ramgren et al. | 2020 | HR | 6,10 | 0,632679875 | 1,58057817 | 9,64152684 |
| | | | | | | |
| Sums | | | | | 7,810490359 | 40,97042114 |

Table 11 Display of All 4 Data Sets for Fixed-Effect Meta-Analysis

We determined the Q of the homogeneity testing and corresponding p-value, using the formula: = SUM ((Effect Measure) ^2 / Variance) - ((SUM Effect Measure / Variance) / (SUM 1/ Variance)))

For the random-effects meta-analysis we calculated the between-study variance, known as tau-squared using following formula: = MAX [0; (Q-(k-1))/(((SUM(1/Variance)) - (((SUM(1/Variance) ^2))/(SUM(1/Variance))))]

Tau-Squared (Between Study Variance) = 1,562641492

We calculated the following data using tau-squared for between-study-variance inclusion.

| Study ID | Year | Effect Size Measure | Effect Measure^2 / VAR | (1/Variance) ^2 | 1 / (Variance + Tau^2) | Effect Measure / (Variance + Tau^2) |
|---|---|---|---|---|---|---|
| | | | | | | |
| Keizman et al. (Early Mortality) | 2019 | OR | 80,53592653 | 2,242712555 | 0,321585044 | 2,35829032 |
| Keizman et al. (5y Mortality) | 2019 | OR | 34,34677522 | 3,496866696 | 0,335952606 | 1,439796883 |
| Giuliani-Poncini et al. | 2013 | OR | 53,13459953 | 8,193060182 | 0,358267375 | 1,543598798 |
| Ramgren et al. | 2020 | HR | 58,81331372 | 2,498227353 | 0,325253144 | 1,984044181 |
| | | | | | | |
| Sums | | | 226,830615 | 16,43086679 | 1,341058169 | 7,325730182 |

Table 12 Display of all 4 Data Sets for Random-Effects Meta-Analysis using Tau-Squared Correction

## 7.3 Outcome

The consistent average impact of PLSVC on mortality across studies was 5.246 (CI 95% 4.544, 5.947) determined through the fixed-effect pooled effect measure.
Homogeneity testing resulted in a Q-value of 11.9 (significantly over 3 degrees of freedom), indicative of heterogeneity, supported by a variance of 0.745679809 (CI 95% 3.77, 7.155) after adjusting for between-study-variance with tau-squared. However, a p-value of 0.992 indicates that the observed variability in effect sizes is not statistically significant, thus, the differences in effect sizes among the studies are statistically due to random chance rather than systematic differences.
The fixed-effect pooled effect measure of 5.463 represents the consistent average impact of PLSVC on mortality across studies. These results indicate that the presence of a PLSVC increases the likelihood of death by 5.5-fold, compared to the absence of a PLSVC.

# 8 RESULTS

## *8.1 Overall Results*

Eleven duplicates were removed after comparing the databases. Articles that did not include interventions in the field of cardiac surgery or combined procedures as in collaboration with cardiology or another device implantation were also removed. Thirty-six remaining articles were retained. For each one, one full-text article was retrieved.
We excluded all fifteen case reports. In addition, seventeen studies were excluded due to lack of non-existent, insufficient information, or lack of possible sufficient PLSVC-information-extrapolation regarding impact of PLSVC on outcome, Moreover, all articles were screened for interventions on CHDs.
At total of 12 articles met the eligibility criteria.

The Newcastle-Ottawa Scale was used for quality assessment of these twelve articles.

## Newcastle-Ottawa Scale for PLSVC impact on CHDs

| Study | Keizman et al. 1/30/2024 10:32:00 AM | Kogon et al. (75) | Said et al. (76) | Ling et al. (77) | Mercan et al. (78) | Ramgren et al. (79) | Brancaccio et al. (80) | Chen et al. (81) | Onan et al. (82) | Van Son et al. (83) | Rodefeld et al. (84) | Giuliani-Ponciani et al. (8) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Selection of Study Groups** | | | | | | | | | | | | |
| Representativeness of Exposed Cohort (1) | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 1 |
| Selection of Non-Exposed Cohort (1) | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Ascertainment of Exposure (1) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Outcome Not Present at Start (1) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| **Comparability of Groups** | | | | | | | | | | | | |
| Control for Important Factors (1) | 1 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 1 | 1 | 1 |
| Additional Factors (1) | 1 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| **Outcome Assessment** | | | | | | | | | | | | |
| Assessment of Outcome (1) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Follow-Up Length (1) | 1 | 1 | 1 | 1 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 |
| Adequacy of Follow-up (1) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 1 |
| Total NOS Score (Max 9) | 9 | 9 | 5 | 5 | 5 | 8 | 6 | 6 | 5 | 4 | 4 | 8 |
| Assessed Quality | High | High | Moderate | Moderate | Moderate | High | Moderate | Moderate | Moderate | Low-Moderate | Low-Moderate | High |
| Statistical Analysis | Yes | Yes | No | No | Yes | Yes | No | Yes | No | Yes | Yes | Yes |
| Statistical Analysis regarding PLSVC | Yes | Yes | No | No | No | Yes | No | No | No | No | No | Yes |
| Intervention focused on | Univentr. heart | Univentr. heart | PAPVC | PAPVC | Various congenital heart defects | cAVD | DORA | URCSS | Various congenital heart defects | Various congenital heart defects | Cor Triatriatum | Various congenital heart defects |
| PLSVC as risk factor increasing mortality (yes = increases mortality; No = indifferent / does not increase mortality; probably = report | Short term yes; long term no; overall survival no | No | Probably not | Probably not | no intra-operative mortality; no information on long-term outcome | Yes | Probably not | Probably not | Probably not | --- | --- | Yes |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| includes no conclusion regarding PLSVC impact on mortality but enough data in furnished to possibly extrapolate this information ) | | | | | | | | | | | | |

Table 13Newcastle-Ottawa Scale for PLSVC Impact on CHDs

PIRSMA Flow-Chart for Study Identification:

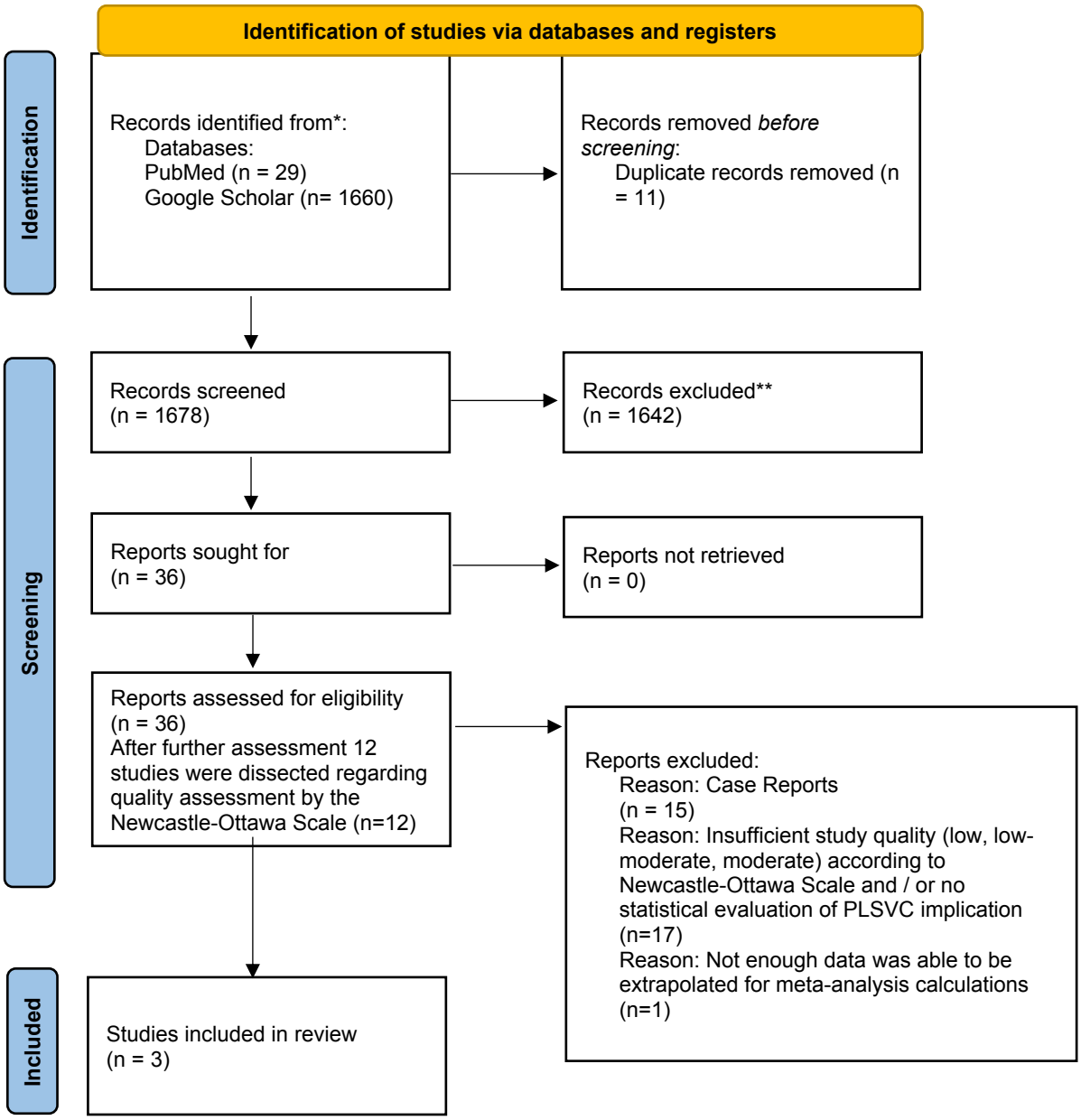


Table 14 PRISMA-Flow-Diagram - PLSVC in Cardiac Surgery based on PRISMA 2020 Flow Diagram for New Systematic Reviews © (85)

In conclusion, we retained 3 studies of high quality (assessed using Newcastle-Ottawa Scale) to include in our PLSVC impact on CHD retrospective evaluation.

Addressing study selection bias poses a challenge in our meta-analysis in utilizing funnel plots for display. The absence of sufficient information from excluded studies hinders the extrapolation necessary to create a pivot table and calculate OR. Moreover, several studies, characterized as retrospective reviews or case series, lack details on outcome assessment, specifically regarding mortality. This lack of comprehensive data makes it unfeasible to generate a funnel plot using the effect measures from each study.
The fixed-effect metanalysis gave rise to these results:

| Fixed-Effect Metanalysis on PLSVC Impact on Mortality | |
|---|---|
| | |
| fixed-effect pooled effect measure | 5,246 |
| variance of pooled effect measure | 0,128032934 |
| CI Lower Limit 95% | 4,544 |
| CI Higher Limit 95% | 5,947 |

Table 15 Display of all 4 Data Sets for Fixed-Effect Meta-Analysis

We proceeded with the homogeneity testing using k-1 degrees of freedom: 3.

Following formulas have been used: = SUM ((Effect Measure) ^2 / Variance) - ((SUM Effect Measure / Variance) / (SUM 1/ Variance)))

| Homogeneity Test (Q) | 11,9 |
|---|---|
| p-value | 0,992 (>0.05) |

Table 16 Display of Homogeneity Testing (Q) & Respective P-Value

The random-effects metanalysis gave rise to the following results using the between-study variance Tau-Squared:

| Random-Effects Metanalysis on PLSVC Impact on Mortality | |
|---|---|
| | |
| Random-effects pooled effect measure | 5,463 |
| variance of pooled effect measure | 0,745679809 |
| CI Lower Limit 95% | 3,77 |
| CI Higher Limit 95% | 7,155 |

Table 17 Display of all 4 Data Sets for Random-Effects Meta-Analysis using Tau-Squared Correction

## *8.2 Display of Forrest Plots and Meta-Analysis Data Sets*

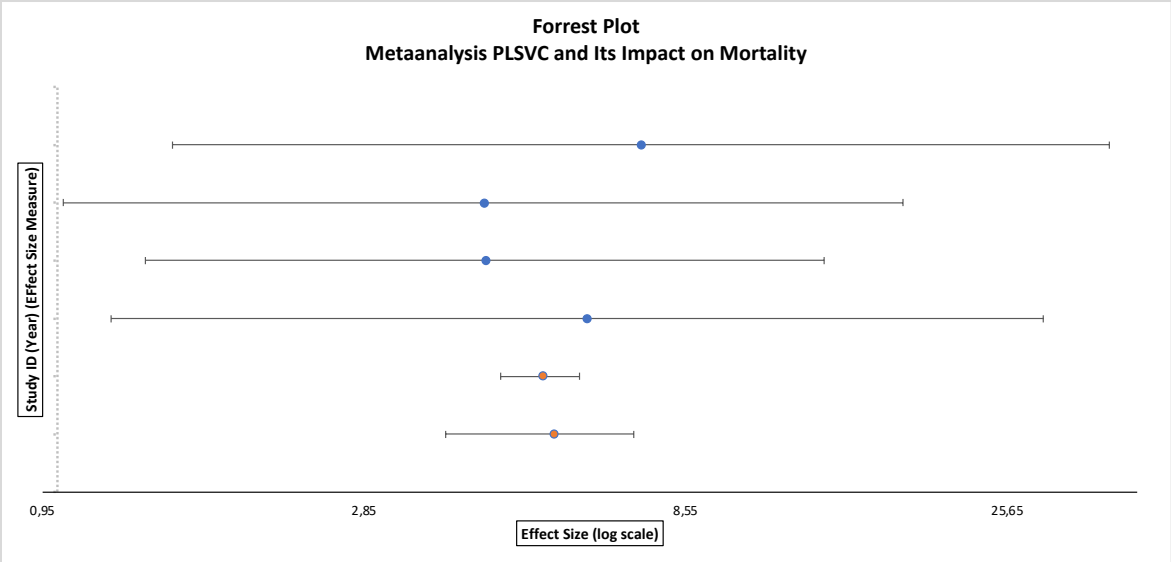


Table 18 Simple Forrest Plot - Meta-Analysis for PLSVC Impact on Mortality

The effect size following pooling of effects from all included studies is depicted as pooled score in the forest plot.

| Study | Year | Effect Size | Outcome | Effect Size Measure | Effect Size Measure [95% CI] |
|---|---|---|---|---|---|
| | | | | | |
| Keizman et al. | 2019 | OR | Early Mortality | 7,33 | 7.33 [1.48; 36.00] |
| Keizman et al. | 2019 | OR | 5-Year Mortality | 4,29 | 4.29 [1.02; 17.97] |
| Giuliani-Poncini et al. | 2013 | OR | Overall Mortality | 4,31 | 4.31 [1.35; 13.72] |
| Ramgren et al. | 2020 | HR | Overall Mortality | 6,10 | 6.10 [1.20; 29.00] |
| | | | | | |
| **FE Model (pooled effect measure)** | | | | **5,25** | **5.25 [4.54; 5.95]** |
| **RE Model (pooled effect measure)** | | | | **5,46** | **5.46 [3.77; 7.16]** |

Table 19 Display of Data Set for Meta-Analysis with Included Studies and Pooled Effect Measurements for Fixed-Effect and Random-Effects Meta-Analysis

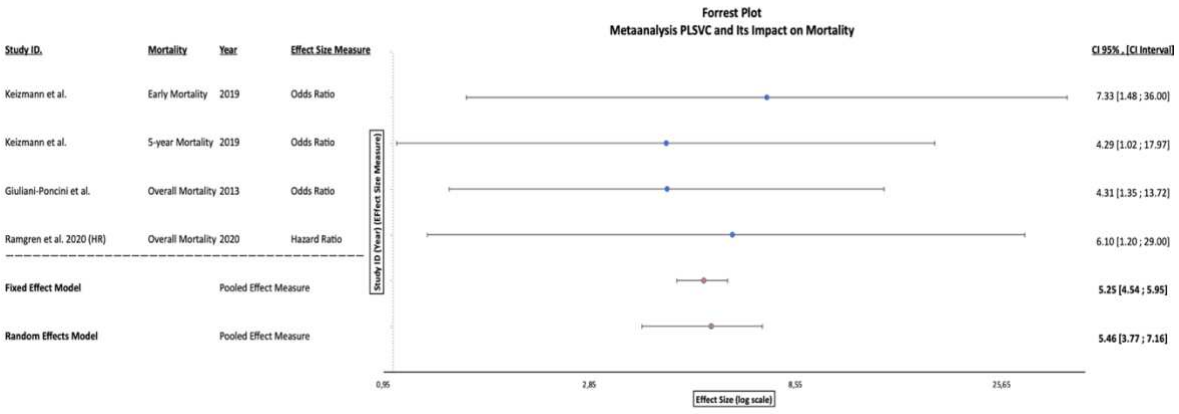


Table 20 Elaborate Forrest Plot - Meta-Analysis for PLSVC Impact on Mortality

## *8.3 Statistical Results and Interpretation*

### 8.3.1 Homogeneity Testing (Q) and P-Value

We tested for homogeneity among the included studies and their statistical analysis.
Our $H_0$ hypothesis: There is no statistically significant heterogeneity among the effect size, with the observed variability being due to chance alone.
Our $H_1$ hypothesis: There is statistically significant heterogeneity among the effect size, with the observed variability not being due to chance alone. We have set our alpha (α) at 5% (0.05), which represents the probability of committing a type I error by rejecting the $H_0$ hypothesis at a 5% risk of concluding presence of statistically significant impact of PLSVC on mortality when there isn't.
A p-value below 0.05 indicates statistically significant findings for rejecting the null hypothesis, while accepting the alternative $H_1$ hypothesis. A p-value above 0.05 indicates nonsignificant findings. This implies that suggesting insufficient evidence to reject the null hypothesis. This implies that the $H_0$ hypothesis cannot be rejected. In conclusion with p being above 0.05, the observed effect may be due to random chance.
Q is compared to the degrees of freedom in this study (k-1 = 3, which k being $n_{\text{number of total included studies}}$). A low Q-value suggests minimal variability among the effect sizes of the included studies. This indicates a most likely homogeneous set of studies. On the opposite, an elevated Q-value means less consistency, and higher variability with most likely potential heterogeneity. The Q-value is compared to the degrees of freedom (k-1=3, with k being $n_{\text{umber of included studies}}$). Q is above 3, which implicates an observed variability among the included effect sizes measurements.

Our Q-value of 11.9 being significantly over 3 degrees of freedom, implying a decreased level of consistency among the included effect size measurements with the potential of heterogeneity. However, our p-value of 0.992 indicates that the observed variability in effect sizes is not statistically significant. The differences in effect sizes among the studies are statistically due to random chance rather than systematic differences.

Based on the degree of heterogeneity, a fixed effect or a random effect model is selected for analysis, respectively.

### 8.3.2 Fixed-Effect Meta-Analysis

The fixed-effect analysis explores the relationship between PLSVC and its impact on overall mortality. The main measures for interpretation are pooled effect measure, the variance of the pooled effect measure, and the 95% CI.
The fixed-effect pooled effect measure of 5.246 represents the consistent average impact of PLSVC on mortality across studies. This suggests that individuals with PLSVC have an over 5-fold higher likelihood of experiencing the endpoint, i.e., mortality, compared to those without PLSVC.
The low variance of 0.128032934 strengthens the fact that only minimal variability is present between each study's effect size. The CI ranging from 4.544 to 5.947, offers a narrow, high level of confidence.

In summary, the fixed-effect meta-analysis supports a clinically relevant, statistically significant impact of PLSVC on mortality. The low variance and narrow CI highlight the results consistency.

### 8.3.3 Random-Effects Metanalysis

The random-effects analysis explores the relationship between PLSVC and its impact on the overall mortality after adjusted for between-study-variance. The main used measures for interpretation are pooled effect measure, the variance of the pooled effect measure, and the 95% CI.
The random-effects pooled effect measure of 5.463 represents the consistent average impact of PLSVC on mortality across studies.
These results indicate that the presence of a PLSVC increases the likelihood of death by 5.5-fold, compared to the absence of a PLSVC.
The significantly higher variance of 0.745679809 indicates heterogeneity after being adjusted for between-study-variance with tau-squared. The CI ranging from 3.77 to 7.155 offers a larger CI with wider level of confidence.

In summary, the random-effects meta-analysis supports a clinically relevant, statistically significant impact of PLSVC on mortality.

### 8.3.4 Comparison Between Fixed-Effect and Random-Effect Meta-Analysis

Random effects models assume that the effect size is variable due to heterogeneity between studies, in contrast to fixed effects models which assume a common pooled effect size among all studies. Therefore, heterogeneity testing is needed.

The observed heterogeneity in the fixed-effect meta-analysis (Q 11.9 being above 3 degrees of freedom) is statistically due to random chance; $H_0$ hypothesis of no statistically significant heterogeneity among the effect size, with the observed variability being due to chance alone, cannot be rejected in this case (p-value of 0.992 above 0.05).

The random-effects pooled measurements, with tau-squared (1.563) adjusted for between-study-variance present with a slightly higher pooled effect size measure. The $CI_{\text{pooled random-effects size measure}}$ is larger than the $CI_{\text{pooled fixed-effect size measure}}$ which encompasses a broader range of possible effect size measurements, due to tau-squared adjusted possible higher potential for between-study-variation. The random-effects model shows a statistically significant association using a more cautious estimation for PLSVC as a risk factor for elevated overall mortality in cardiac surgical interventions.
Random-effects models allows for effect size to vary from study to study and thus, better adjust for high heterogeneity between studies.

# 9 DISCUSSION

## *9.1 Discussion*

To dissect and conclude the overall outcome characteristics, and limitations of the pooled results, we imperatively need to describe each study on its own.

Giuliani-Poncini et al. studied 371 patients with a median age of 2.75 years (interquartile range 0.65–6.63). 47 children (12.7%) presented with PLSVC. The occurrence of the event (death) and non-event (survivor) between the PLSVC and non-PLSVC group was investigated. In eight PLSVC patients, an association with partial or complete unroofed CS was found. In two cases, coronary sinus ostial atresia co-existed. (8) PLSVC can potentially remain undetected in routine preoperative echocardiographic screening which complicates the operative procedure. There are no clear signs of a PLSVC on routine screening. However, it may be suspected with , unexpectedly low SpO2% saturations or echocardiographic finding of dilated CS, without apparent cardiac explanation. (8,86,87)
Moreover, PLSVC may lead to unexpected complications post-operatively. (8)

Ramgren et al. investigated a cohort of 304 patients undergoing surgical correction for cAVSD between April 1993 and October 2018. The cohort was divided into young infants (n=55) (<3 months with mean age 1.6 ± 0.6 months) and older infants (n=249) (>3 months with mean age, 5.1 ± 5.2 months). The mean follow-up was 13.2 ± 7.8 years. (79)
The 30-day mortality was 1.0% (3/304), without statistically significant difference between young and older infants. The overall survival at 20-year follow-up was 95.1%. Notably, the median age at the time of repair remained relatively stable over the three decades. The multivariable analysis showed that PLSVC (present in 9 patients), VSD, CoA were identified as risk factors for mortality among all included CHD. (79)
In conclusion the presence of certain associated cardiac anomalies significantly influences overall survival. (79)

Keizman et al., was divided for our purposes in this PLSVC-meta-analysis into two substudies, as the authors of this study measured early death outcome and 5-year survival.

In this study, the cohort of 98 patients was categorized into two groups based on the presence (88 patients) or absence of bilateral SVC (18 patients). (53)

Before the total cavopulmonary anastomosis intervention, both groups exhibited similar demographic and physiological characteristics. The ages were 4.3 ± 1.72 years in the unilateral SVC group, compared to 4.8 ± 3.21 years in the bilateral SVC group, respectively. Mean end-diastolic ventricular pressures and pulmonary vascular resistances were comparable between the groups. (53)

However, postoperatively, patients with PLSVC experienced more often a stormy postoperative course, Fontan failure, and early mortality, but overall survival after 5-year follow-up was impacted by a double-sided SCV. Multivariate analysis identified heterotaxy as an independent risk factor for mortality. (53)

The authors concluded that due to the small sample size, the study lacked the power to reach a statistically significant 5-year outcome difference regarding mortality. However, PLSVC was statistically significantly associated with an atrio-ventricular canal defect, dextrocardia, or heterotaxy syndrome, respectively. Other CHDs such as TGA, TAPVR, situs inversus, and aortic arch obstruction were also present but were not associated with the presence of PLSVC. (53)

As indicated in the PRISMA-flowchart, we excluded Kogon et al.'s study due to not enough data presented to be extrapolated for meta-analysis calculations. However, it is crucial to include this study in the discussion section for global comprehension of outcome in univentricular heart related interventions. Kogon et al. conducted a retrospective review of 270 patients who underwent a bidirectional Glenn operation between 2001 and 2007. 226 patients underwent unilateral, while 44 patients underwent bilateral Glenn anastomoses. The median age at the time of surgery for the entire cohort was 5.5 months (range of 2.5 months - 12 years). Almost 50% had a morphological single left ventricle, 44% presented with a morphological single right ventricle, and almost 10% had either two ventricles that could not be partitioned or indeterminate single ventricular morphology. Additionally, 12 patients (4%) had an associated interrupted inferior vena cava with azygous or hemizygous continuation to a superior vena cava. Important to note, almost 300 operations were performed before the bidirectional Glenn operation (222 of the 270 patients) took place. (75)

In comparing the two groups (unilateral SVC vs. bilateral SVC), children in the bilateral bidirectional Glenn group were significantly older, with a higher incidence of an interrupted inferior vena cava, and were exposed to longer cardiopulmonary bypass time . (75)

However, there was no difference in any of the outcome variables. Outcomes were unaffected by the presence of a left superior vena cava or cannulation strategy. (75)

In conclusion, it is worth noting that this study stands in contrast to the findings of Keizman et al. regarding univentricular hearts. (53,75)
Kogon et al.'s study displayed a higher age regarding the bilateral SVC group at the time of intervention. They declared this finding as expected due to the induced delay for operative procedure to facilitate bilateral superior vena cava cannulation and cavopulmonary anastomoses. (75)This may possibly have a positive impact on the outcome, as Reddy et al. demonstrated the age-impact on the outcome. The cut-off age for early-, and late events, as well as mortality, lies at 2 months. (75,88) So postponing the intervention for supposed higher risk groups (PLSVC patients), may alter the outcome.

## *9.2 Overall Conclusion*

The main conclusion of this study is that patients with PLSVC and associated CHD undergoing open heart surgery have a 5.5-fold increased risk of mortality according to a meta-analysis of three studies. Based on these findings, it is imperative to put more emphasis on the pre-operative diagnosis of a PLSVC despite the fact that PLSVC without associated cardiac anomalies is generally considered a benign lesion (11,16,41). Pre-operative screening primarily through echocardiography, also allows for better pre-, intra- and post-operative planning (8) . Pre-operatively and post-postoperatively, a PLSVC may pose a risk due to altered anatomical access routes and would require alternative pathways for successful catheter or line placements (46) As indicated by the presented studies, especially in complex congenital cardiac lesions such as a single ventricle physiology, intra-operative strategies need to incorporate the altered anatomy for successful completion of a e.g., Glenn procedure.
Berg et al., stated in a retrospective review, that PLSVC's implication on the outcome depends on the associated defects. Thus, mortality is impacted by associated CHDs in the presence of PLSVC. (41), however, impacted by the study population, associated infrastructure, and center experience.

## *9.3 Limitations*

As stated by Keizman et al. (53), assembling a dataset for PLSVCs poses a challenge due to the rarity of the PLSVC diagnosis, limiting the sample size compared to the non-PLSVC comparator group. Furthermore, only retrospective chart reviews and no prospective randomized controlled trials are available for analysis.

For this meta-analysis, one study was divided into two parts based on the primary outcome, each presenting a different outcome within the respective time frames.

Furthermore, it is important to mention problems arising from the difference in sample size of the studies included in a meta-analysis. Results can be influenced by studies with small sample size leading to lack of power to detect an effect, or by allowing for studies with larger sample sizes to have more weight resulting in bias.

It is evident that larger, prospective studies conducted over an extended period of time, with rigorous stratification and imperative subgroup analysis concerning PLSVC and its associated CHD or non-CHD cardiac malformations, are necessary. Both subgroups and the entire population must be assessed for pathophysiological cofactors, surgical intervention parameters, and post-operative complications comprehensively.

However, at the current time and to the best of our knowledge, it stands as the only existing meta-analysis on the impact of PLSVC on mortality in CHD patients. It transcends being merely a clear and distinct orientation, serving as a crucial reference point for future planned interventions and underscoring the importance of pre-operative screening, in regard to the consistent impact of PLSVC on mortality.

# 10 DECLARATION OF INTERESTS

I declare no conflict of interest, no known competing financial interests or personal relationships that could have appeared to influence the work reported in this thesis.

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