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Ventricular morphology of single-ventricle hearts has a significant impact on outcomes after Fontan palliation: a meta-analysis

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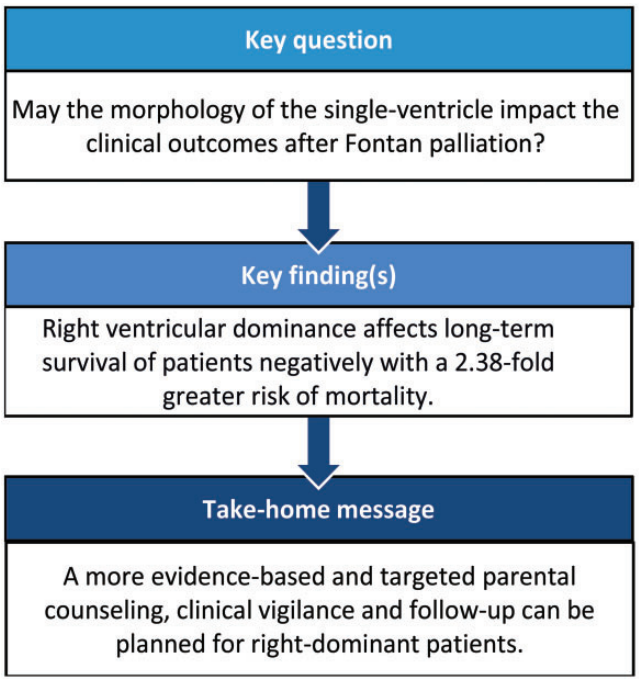
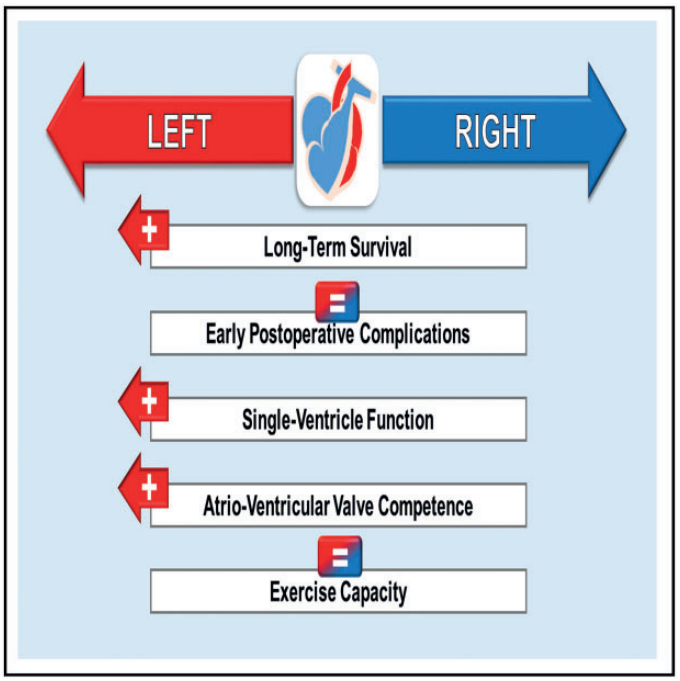




Abstract

OBJECTIVES: A conclusive interpretation of the role of ventricular dominance in outcomes after Fontan palliation has not been formulated yet. We conducted a systematic review and meta-analysis of scientific literature to give an insight into the impact of ventricular morphology in single-ventricle palliation, focusing on its influence on survival, morbidities, ventricular performance and functional capacity.

METHODS: A systematic review of PubMed, Web of Science and Scopus databases was performed. A random-effect meta-analysis was conducted, and survival data were reconstructed using the published Kaplan–Meier survival curves.

RESULTS: Twenty-seven studies were selected, for a total of 4529 left-dominant versus 4844 right-dominant patients. Estimated survival at 1, 5, 10, 20 and 30 years of follow-up was 0.99 [95% confidence interval (CI) = 0.98–0.99], 0.95 [95% CI = 0.94–0.96], 0.92 [95% CI = 0.91–0.93], 0.86 [95% CI = 0.84–0.88] and 0.68 [95% CI = 0.65–0.83] for left-dominant patients and 0.94 [95% CI = 0.93–0.95], 0.89 [95% CI = 0.88–0.9], 0.85 [95% CI = 0.83–0.87], 0.69 [95% CI = 0.63–0.75] and 0.59 [95% CI = 0.5–0.69] for right-dominant patients, respectively. Survival was statistically lower for right-dominant patients ($P < 0.001$), with an hazard ratio for the mortality of 2.38 (2.03–2.80); also, they displayed significantly longer hospital stay, worse ventricular function, larger ventricular volumes and a higher incidence of moderate or severe atrioventricular valve regurgitation when compared to left-dominant patients.

CONCLUSIONS: According to our meta-analysis, the morphology of the dominant ventricle has a significant impact on outcomes after Fontan palliation. Right-dominant patients experience an inferior long-term survival when the anatomical right ventricle is included in the systemic circulation.

Keywords: Fontan • Ventricular morphology • Meta-analysis

ABBREVIATIONS

AV	Atrioventricular
CIs	Confidence intervals
EDVi	End-diastolic volume indexed
EF	Ejection fraction
ESVi	End-systolic volume indexed
HR	Hazard ratio
LV	Left ventricular
ORs	Odds ratios
RV	Right ventricular
SV	Single ventricle
VO_2	Oxygen uptake

INTRODUCTION

Five decades after the first surgical treatment for a single-ventricle (SV) cardiac anomaly by Fontan and Baudet [1], the most recent series are reporting excellent long-term survival after Fontan operation [2]. However, the Fontan circulation remains a palliative-time-limited solution, in which progressive ventricular dysfunction, multiple organ impairment and chronic Fontan circulation failure affect the long-term prognosis. Several risk factors for premature failure have been identified [i.e. myocardial contractile dysfunction, atrioventricular (AV) valve regurgitation, elevated transpulmonary gradient] [3, 4] and technical modifications of the original procedure, as well as careful patient selection and medical management, have been introduced to mitigate their impact on clinical outcomes [5, 6].

Although the anatomical diagnosis is a not-modifiable variable that may impact the patient's prognosis, several authors have investigated whether the anatomical morphology of the dominant ventricular chamber may influence the long-term outcomes of patients following a successful Fontan completion. However, current literature is still inconclusive about this issue [7–16].

With the rationale of providing a current overview of the impact of ventricular dominance on SV palliation, we conducted a systematic review and meta-analysis of scientific literature, which aims to assess if the ventricular morphology in SV patients may influence: early- and long-term survival after Fontan operation; postoperative course and the onset of early complications; long-term ventricular performance; and functional capacity.

MATERIALS AND METHODS

Ethical statement

Ethics approval and patients' consent were obtained by each research group. Our institutional Ethics Review Board waived the need for ethics approval for the pooled analysis.

Data collection

A systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement protocol [17]. This study was prospectively registered on the PROSPERO database (CRD42021291583). The PubMed, Web of Science and Scopus databases were systematically searched in March 2022, using the search string: ((ventricular morphology) OR (ventricular dominance)) AND ((Fontan) OR (single ventricle)). During studies selection by 2 authors (Matteo Ponzoni and Massimo A. Padalino), any initial disagreement regarding eligibility was resolved by discussion among all the authors and then agreement by consensus.

Inclusion criteria

After duplicates removal, manuscripts underwent the first screening on the title and abstract and subsequent full-text revision, using the following inclusion criteria: (i) study population composed of patients who completed the Fontan palliation; (ii) availability of preoperative diagnosis and dominant SV morphology; (iii) clinical outcomes stratified according to ventricular morphology; (iv) studies reporting survival, measures of ventricular or functional status or significant morbidities; and (v) papers written in English after 1970.

Exclusion criteria

Excluded studies were the ones: (i) enrolling patients with only 1 anatomic diagnosis or 1 ventricular morphology; (ii) reporting univentricular patients that did not complete Fontan palliation; (iii) not providing stratified clinical outcomes on ventricular dominance; (iv) describing ventricular dimensions which were not indexed to patients' body surface area; (v) providing survival of patients without graphical representation of Kaplan–Meier curves

and patients at risk; (vi) case reports and series with <5 patients; and (vii) reviews and meta-analyses.

Data extraction

Two authors (Matteo Ponzoni and Luca Vedovelli) extracted data to a pre-set Excel abstraction form. Extracted data were: publication year, the number of patients, age at study and age at Fontan operation, follow-up period, gender, ventricular morphology distribution, cohort period, survival, patients at risk, hospital stay, major postoperative morbidities rate, SV function and volumes by echocardiography, catheterization or magnetic resonance imaging, AV valve dysfunction (defined by moderate or severe regurgitation), peak oxygen uptake (VO_2) and percentage of predicted peak VO_2. Considered parameters of SV function and dimensions were: percentage of patients with more than moderate dysfunction at qualitative assessment, ejection fraction (EF), end-diastolic volume indexed (EDVi), end-systolic volume indexed (ESVi) and stroke volume indexed. Patients with biventricular or undefined ventricular morphology were excluded from subsequent analyses.

Quality assessment

The risk of bias at the study level was assessed by 2 reviewers (Matteo Ponzoni and Luca Vedovelli) by using the Appraisal tool for Cross-Sectional Studies (AXIS) [18]. The AXIS 20-item tool assesses the quality of cross-sectional studies based on the following criteria: clarity of aims/objectives and target population; appropriate study design and sampling framework; justification for the sample size; measures taken to address non-responders and the potential for response bias; risk factors/outcome variables measured in the study; clarity of methods and statistical approach; appropriate result presentation, including internal consistency; justified discussion points and conclusion; discussion of limitations; and identification of ethical approval and any conflicts of interest. The scoring system conforms to a 'yes', 'no' or 'do not know/comment' design. We classified the studies into 4 quality categories based on the number of 'yes' answers for each of the 20 questions included in the AXIS tool [19]: 'high' (>15 positive answers), 'medium' (between 10 and 15), 'low' (between 5 and 9) and 'very low' (<5).

Statistical analysis

Data description. The study characteristics are presented descriptively as mean and standard deviation or median (interquartile range) in the case of quantitative variables and counts and percentages in the case of categorical variables.

Meta-analysis. A random-effect meta-analysis has been carried out on the study outcomes. The heterogeneity is estimated from the studies' intervention effects and standard errors included in the meta-analysis via Der Simonian and Laird Estimator [20]. The LV was used as a reference to measure the odds ratios (ORs) of analysed variables. The I^2 measure has been considered to quantify the heterogeneity. The measure expresses the percentage of between-study variability related to heterogeneity rather than chance [21]. The study-specific estimates with the 95% confidence intervals (CIs) have been reported representing the pooled meta-analytical estimate in a forest plot.

Effect modifiers. Several univariable meta-regression models have been computed to assess whether the study characteristics may act as effect modifiers on the final meta-analysis estimate when >3 studies were included in the meta-analysis. Considered variables for meta-regression were: publication year, age at study, age at Fontan, sex and follow-up years.

Subgroup analysis. The subgroup meta-analyses have been reported in Supplementary Material, File SII by estimating the pooled effects stratifying according to (i) age at Fontain by considering cut-off the median across studies of 4 years; (ii) prevalence of male by considering cut-off the median across studies of 0.6; and (iii) follow-up duration by considering cut-off the median across studies of 6 years. The pooled and individual mean row estimate for the studies and the pooled results are reported in a forest plot together with the chi-square test for the subgroup differences.

Publication bias. The publication bias has been visually assessed by considering a Funnel plot representation. A funnel plot is a scatter plot of the study-specific effect sizes (log OR or mean difference) against the standard error on the ordinate axis. When there is no publication bias, the data points in such a plot should form a roughly symmetrical, upside-down funnel. The symmetry has been also assessed by considering the linear regression test of the Egger test for asymmetry in the funnel plot.

Influential analysis. The influential analysis (Supplementary Material, File SII) to investigate the presence of possible influence leverage of some studies on the pooled estimate has been performed via the Leave-One-Out procedure. Each study in the meta-analysis has been removed and the pooled effect calculated with the i^2 to investigate an outlier or an influential study among the considered evidence.

Survival analysis. The survival data were reconstructed using the algorithm as indicated by Guyot *et al.* [22], considering survival after Fontan completion. The global log-rank test was reported on the plot. The pooled hazard ratios (HRs) were calculated via the Cox regression model on the reconstructed individual patient data with their related CI. A frailty term has been included in the model to account for correlation within the data reconstructed in the same study. Survival curves were obtained with the Kaplan–Meier method. Outcomes were presented as pooled proportions for data synthesis. Computations were performed in R 4.0.1 [23] system with metafor [24] package.

RESULTS

After the removal of duplicates, a total of 4391 reports were identified; full-text eligibility was assessed for 106 of them, but only 27 articles could be included (Fig. 1 and Table 1) [7–16, 25–41]. Figure 2 summarizes the quality assessment of selected reports using AXIS. Quality resulted in being high in 9 (33%) of papers and medium in 18 (67%). Quality assessment of each study is provided in Supplementary Material, Fig. S1.

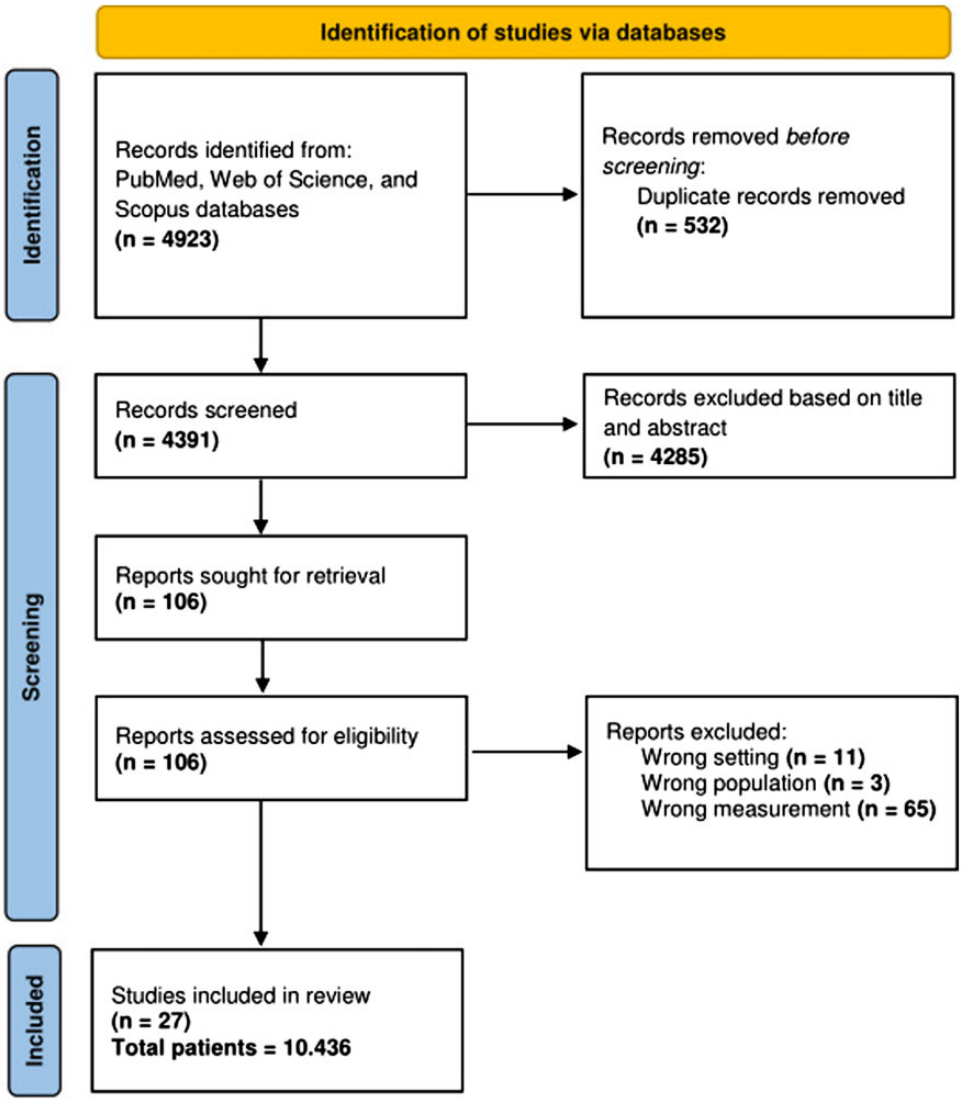


Figure 1: PRISMA 2020 flow diagram for new systematic reviews.

Patient characteristics

A total of 10 436 patients were identified across the series. Left ventricular (LV) dominance was present in 4529 patients (prevalence range 27–67%), right ventricular (RV) dominance in 4844 (prevalence range 33–73%) and undefined dominance or a biventricular circulation in 1063 (prevalence range 5–21%). The mean/median age at study ranged from 2.7 to 16.7 years, while age at Fontan completion ranged from 2 to 6.1 years, with a mean/median follow-up ranging from 1.4 to 11.4 years (Table 1).

Survival

Ten manuscripts (for a total of 2737 LV-dominant and 2601 RV-dominant patients) met the eligibility criteria for survival analysis. Survival estimates between LV- and RV-dominant groups were comparable in 4 series, while survival was statistically better for LV-dominant patients in the remaining 6 (Fig. 3).

The meta-analysis conducted on the identified studies evidenced an estimated survival at 1, 5, 10, 20 and 30 years of follow-up of 0.99 [95% CI = 0.98–0.99], 0.95 [95% CI = 0.94–0.96], 0.92 [95% CI = 0.91–0.93], 0.86 [95% CI = 0.84–0.88] and 0.68 [95% CI = 0.65–0.83] for LV-dominant patients and of 0.94 [95% CI = 0.93–0.95], 0.89 [95% CI = 0.88–0.9], 0.85 [95% CI = 0.83–0.87], 0.69 [95% CI = 0.63–0.75] and 0.59 [95% CI = 0.5–0.69] for RV-dominant patients, respectively. The estimated survival resulted to be statistically lower for RV-dominant patients ($P < 0.001$, Fig. 3), with an HR for the mortality of 2.38 (2.03–2.80).

Postoperative course

The postoperative course was analysed in 6 reports (Table 2). The median hospital stay ranged from 6 to 16 days for LV-dominant patients versus 8–17 days for RV-dominant ones. From pooled analysis, patients with a dominant LV had a significantly shorter hospital stay with a mean difference of -2.35 (-3.56, -1.13) days (I^2 = 40%, $P = 0.199$; Supplementary Material, Fig. S2). A similar rate of early main postoperative complications occurred in both groups of patients. In particular, LV dominance did not result to be a protective factor for the occurrence of arrhythmias (OR: 0.57 [0.19, 1.68]; I^2 = 71%, $P = 0.03$), nor for prolonged pleural effusions (OR: 1.04 [0.56, 1.95]; I^2 = 71%, $P = 0.04$) at pooled

Table 1: Included studies ($n = 27$) and demographic characteristics of patients

First author	Year	*n*	Age at study (years), median (IQR)/mean SD: SD	Age at Fontan (years), median (IQR)/mean SD: SD	Male, *n* (%)	Cohort period	Follow-up (years), median (IQR)/mean SD: SD	Dominant LV, *n* (%)	Dominant RV, *n* (%)	Mixed SV/ biventricular, *n* (%)
Moon J	2020	1162	–	2.2 (1.8–3.1)	705 (61)	1985–2018	8.3 (2.0–15.4)	484 (42)	678 (58)	–
Powell AW	2020	103	16.7 SD: 5.5	3.8 SD: 1.7	53 (52)	2013–2018	–	65 (63)	38 (37)	–
West C	2019	137	–	2.8 (2.3–3.9)	85 (62)	2004–2016	5.8 (2.4–9)	55 (40)	82 (60)	–
Iyengar AJ	2019	1186	–	–	–	–	–	719 (61)	467 (39)	–
Vitanova K	2019	405	–	2.0 (1.6–2.7) [LV], 2.2 (1.7–2.8) [RV]	–	1997–2017	5.0 (0.7–9.4) [RV], 7.2 (2.3–13.1) [LV]	170 (42)	235 (58)	–
Ghelani SJ	2018	193	16 (11–23)	3 (2.2–4.9)	122 (63)	2003–2017	6.2 (3.6–9.5)	101 (52)	92 (48)	–
Fauziah M	2018	162	–	5.5 (3–22)	97 (60)	2008–2018	2.2 (0.9–4.5)	74 (46)	88 (54)	–
Oster ME	2018	3807	–	–	–	1982–2003	–	1421 (37)	1615 (42)	771 (20)
Erikssen G	2018	395	–	3.4	218 (55)	1972–2016	11.4 SD: 7.3	166 (42)	195 (49)	34 (9)
Pessotti CFX	2018	59	–	4.5 SD: 2.4	40 (70)	2000–2014	4.1 SD: 3.1	30 (51)	29 (49)	–
Steflik D	2017	17	12 (6–20) [LV], 7 (4–11) [RV]	–	12 (63)	–	–	5 (29)	12 (71)	–
Nordmeyer S	2017	173	–	3.7 (1.3–42)[LV], 3.6 (1.5–38)[RV]	91 (53)	1995–2013	–	109 (63)	64 (37)	–
Alsoufi B	2016	530	0	–	318 (60)	2002–2012	5.4 SD: 3.9	199 (38)	302 (57)	29 (5)
Kamata M	2016	72	–	3.3 SD: 1.7	43 (60)	2009–2014	–	20 (28)	37 (51)	15 (21)
Bossers SS	2015	99	12.5 SD: 3	3.3 SD: 1.2	59 (60)	–	–	63 (64)	36 (36)	–
Garnreiter JM	2014	118	–	–	–	2005–2008	–	32 (27)	86 (73)	–
d'Udekem Y	2012	499	–	5 (1.3–16)	309 (62)	1990–2008	6.6 SD: 5.3	210 (42)	250 (50)	39 (8)
Petko C	2012	51	7.8 SD: 4.8 [LV], 7.7 SD: 2.7 [RV]	–	32 (63)	–	–	22 (43)	29 (57)	–
Celik M	2012	40	4.8 SD: 2.8 [LV], 6.8 SD: 3.3 [RV]	–	21 (53)	1997–2007	5.8 SD: 3.2 [LV], 5.9 SD: 3.1 [RV]	25 (63)	15 (37)	–
Ohuchi H	2011	95	11 SD: 4 [LV], 12 SD: 4 [RV]	5 SD: 3 [LV], 7 SD: 4 [RV]	–	1979–1999	6 SD: 4 [LV], 75SD: 3 [RV]	47 (50)	33 (35)	15 (15)
Ando M	2011	359	2.7 SD: 3.9 [LV], 2.8 SD: 6.7 [RV]	–	197 (55)	1978–2008	10.5 SD: 8.3 [LV], 5.5 SD: 6.5 [RV]	140 (39)	156 (43.5)	63 (17.5)
Anderson PA	2008	546	11.9 SD: 3.4	3.4 SD: 2.1	328 (60)	–	–	265 (49)	184 (34)	97 (18)
Giardini A	2008	53	14 SD: 6	5.9 SD: 2.8	30 (57)	1991–2008	–	29 (55)	24 (45)	–
McGuirk SP	2003	103	–	4.4 (1.9–12.9)	77 (75)	1996–2001	1.4 (0.1–5.2)	44 (42)	59 (58)	–
Akagi T	1993	24	5.5 SD: 2.8 [LV], 6.5 SD: 3.5 [RV]	6.1 SD: 3.7	15 (58)	1985–1990	–	16 (67)	8 (33)	–
Sano T	1988	28	6.4 SD: 6.1 [LV], 5.7 SD: 4.1 [RV]	–	–	–	–	12 (43)	16 (57)	–
Shimazaki Y	1986	20	4 SD: 4	–	–	–	–	6 (30)	14 (70)	–

IQR: interquartile range; LV: left ventricle; RV: right ventricle; SD: standard deviation; SV: single ventricle.

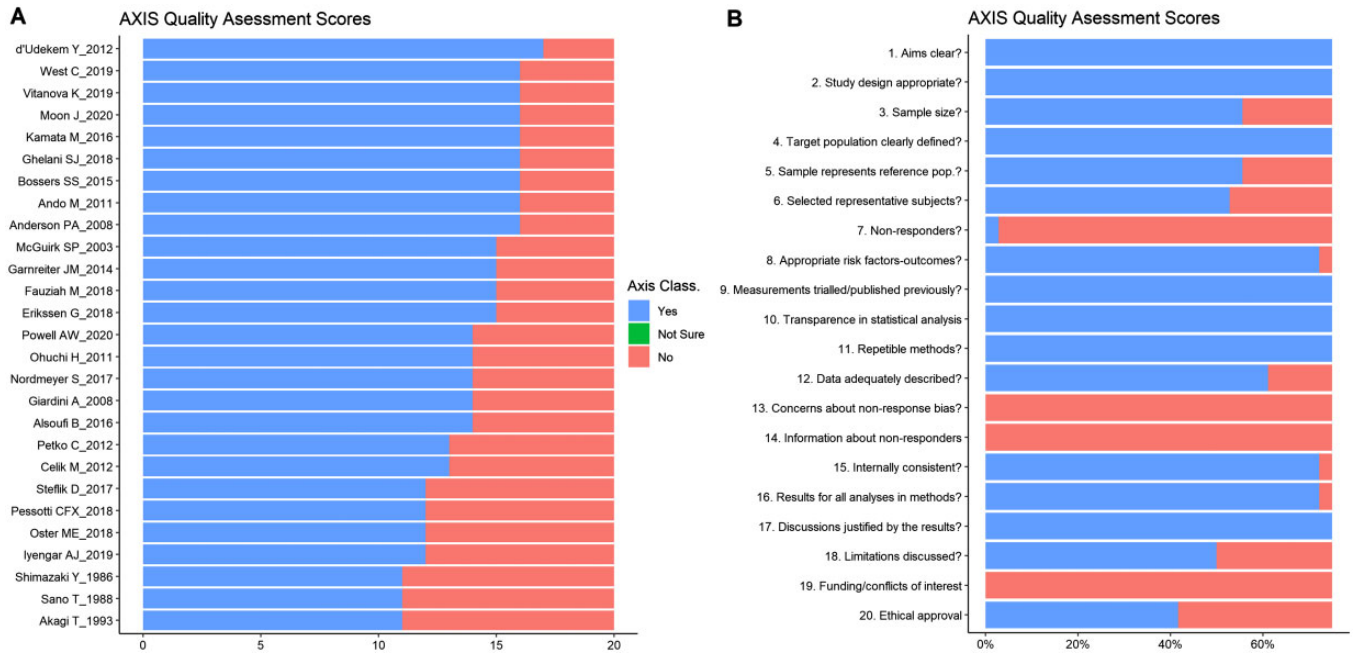
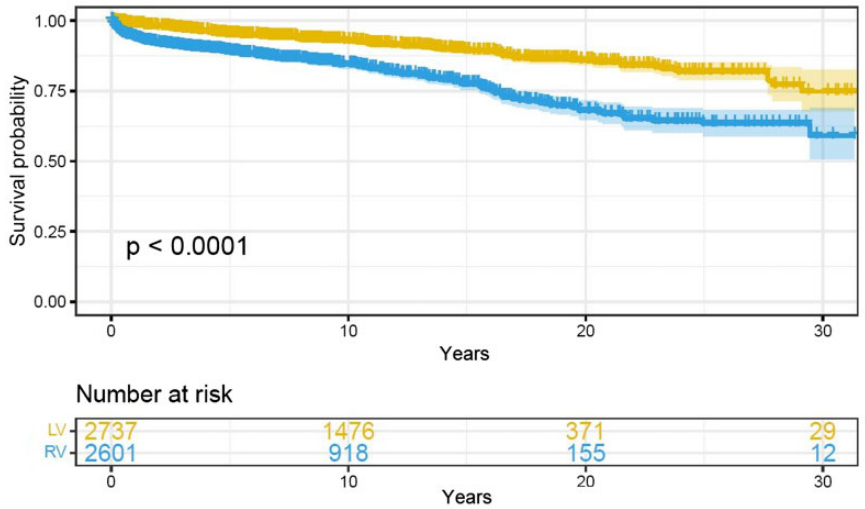


Figure 2: Summary of quality assessment of reports using AXIS. (**A**) Selected studies sorted by overall quality and (**B**) rate of fulfilment of each quality item of AXIS across selected papers. Blue colour indicates AXIS criteria fully satisfied; red colour indicates AXIS criteria not satisfied. AXIS: Appraisal tool for Cross-Sectional Studies.



First Author	Year	Hazard Ratio (95% CI) (LV as reference)
Moon J	2020	**1.71** (1.21-2.43)
West C	2019	**2.78** (1.04-7.45)
Iyengar AJ	2019	**2.02** (1.16-3.53)
Vitanova K	2019	1.59 (0.54-4.67)
Ghelani SJ	2018	2.25 (0.97-5.21)
Oster ME	2018	**2.41** (1.8-3.21)
Erikssen G	2018	**2.91** (1.94-4.38)
Alsoufi B	2016	1.5 (0.66-3.39)
d'Udekem Y	2012	**3.37** (2.14-5.29)
McGuirk SP	2003	2.08 (0.22-20.07)
Pooled HR		**2.38 (2.03-2.80)**

Figure 3: Kaplan–Meier curves of estimated survival according to ventricular dominance and estimated HR for mortality across selected studies ($n = 10$). HR: hazard ratio; LV: left ventricle; RV: right ventricle.

Table 2: Postoperative course and major morbidities across reports ($n = 6$)

First author	Year	Hospital stay (days), median (IQR)			Arrhythmia (%)			Pleural effusion (%)		
		Dominant LV	Dominant RV	*P*-Value	Dominant LV	Dominant RV	*P*-Value	Dominant LV	Dominant RV	*P*-Value
West C	2019	6 (5–9)	8 (6–16)	**<0.001**	–	–	–	–	–	–
Fauziah M	2018	16 (11–22)	17 (13–23)	0.092	37	63	0.150	49	51	0.338
Nordmeyer S	2017	13 (4–100)	15 (5–53)	0.6	5	27	**<0.001**	35	40	0.60
Kamata M	2016	–	–	–	0	3	0.619	–	–	–
Celik M	2012	–	–	–	52	53	ns	–	–	–
McGuirk SP	2003	–	–	–	–	–	–	36	44	0.54
	Range	(6–16)	(8–17)		(0–52)	(3–63)		(35–49)	(40–51)	

IQR: interquartile range; LV: left ventricle; ns: not significant; RV: right ventricle. Bold values represent statistical significance.

analysis (Supplementary Material, Fig. S2). A unit increase in the prevalence of male enrolled in the studies was found to have a protective modifier effect on meta-analysis pooled OR of pleural effusions (0.01, 95% CI = 0.001, 0.45; $P = 0.019$).

Single ventricle's function and dimensions

A total of 15 reports analysed SV function between RV and LV groups at medium- or long-term follow-up (Table 3). In particular, from qualitative assessment, moderate or more SV dysfunction was present in 0–48% of LV-dominant patients and 3–64% of RV-dominant patients, with a similar pooled prevalence between groups (OR: 1.39 [0.29, 1.75]; $I^2 = 83\%$, $P < 0.01$) (Fig. 4).

Prevalence of AV valve moderate or severe regurgitation across reports ranged from 0 to 43% and from 14 to 67%, in LV and RV groups, respectively. Pooled analysis proved LV morphology to have a significantly reduced risk of developing AV valve incompetence (OR: 0.41 [0.21, 0.80]; $I^2 = 90\%$, $P < 0.001$; Fig. 4). Age at Fontan acted as effect modifier (OR: 1.25, 95% CI = 1.04, 10.91; $P = 0.042$).

From pooled analysis, LV-dominant patients displayed a 5% [2–7%] higher EF respect to RV patients (mean difference; $I^2 = 90\%$, $P < 0.001$; Fig. 4). Effect modifiers on mean difference values were age at Fontan (0.026, 95% CI = 0.012, 0.04; $P < 0.01$) and male sex (-0.95, 95% CI = -1.89, -0.002; $P = 0.049$). EDVi resulted comparable between study groups (mean difference of -5.10 [-14.59, 4.40] ml/m^2; $I^2 = 91\%$, $P < 0.001$). On the other hand, ESVi was statistically lower in LV-dominant patients, who presented an 8.72 [11.14, 6.30] ml/m^2 smaller SV from pooled analysis ($I^2 = 30\%$, $P = 0.038$).

Exercise capacity

Six authors investigated exercise capacity in Fontan patients (Table 4). From the meta-analysis of selected studies, peak VO_2 resulted comparable between LV- and RV-dominant groups (mean difference of 0.52 [-1.49, 2.52] ml/kg/min; $I^2 = 92\%$, $P < 0.001$), even if LV-dominant patients presented a predicted peak VO2, which was slightly greater (mean difference of 3% [1, 6%]; $I^2 = 66\%$, $P < 0.001$; Supplementary Material, Fig. S3). Age at study (-0.86, 95% CI = -1.14, -0.57, $P < 0.01$) had a effect modifier on the study-specific mean difference values of peak VO_2.

Publication bias

The funnel plots in Fig. 4 revealed the presence of several study estimates outside the confidence bounds of the funnel representation for the greater part of the considered end points, except for ESVi. However, the Egger test did not show a statistically significant asymmetry for the considered end points.

Influential analysis

The Leave-One-Out meta-analysis highlighted that the pooled estimates are similar by removing the single studies with a heterogeneity level similarly high for each study removal attempt (Supplementary Material, Tables S3, S5, S7 and S9). An influential leverage issue has been instead evidenced by removing the Moon 2020 study for the Rate of ventricular Dysfunction (Supplementary Material, Table S1). The removal of the above-mentioned study highly inflated the OR estimate reducing the overall heterogeneity level.

Subgroup analysis

Lower pooled estimates for the EF mean differences have been evidenced for the values of age at Fontan lower than 4 years (Supplementary Material, Table S6). A similar subgroup difference pattern was found for EDVi (Supplementary Material, Table S8). The prevalence of males is a relevant source of heterogeneity for the rate of qualitative ventricular dysfunction (Supplementary Material, Table S2), the rate of AV valve dysfunction (Supplementary Material, Table S4) and the EDVi (Supplementary Material, Table S8). Few studies are available to perform a subgroup comparison for the follow-up duration by considering a cut-off the median of 6 years (Supplementary Material, Tables S2, S4, S6, S8 and S10).

DISCUSSION

Due to different myocardial fibres' architecture and contraction patterns [14], the RV is considered to be less adaptable than the LV to work as a single propulsive force in an SV circulation, predisposing to premature ventricular dysfunction and possibly to all the well-known morbidities associated with the failing Fontan [6, 42, 43]. However, a conclusive answer to whether a single RV is worse than a single LV is yet to be given. Thus, we conducted this meta-analysis of ventricular morphology's impact on clinical and functional outcomes after the Fontan procedure as an evidence-based attempt to reply to this question. To the best of our knowledge, ours is the first meta-analysis to specifically address this issue.

We collected 4529 patients with LV dominance and 4844 with RV dominance, followed up to 11 years after Fontan completion. As we were focusing primarily on patients' survival, our analysis confirmed on a broad sample of subjects that survival of patients with LV dominance is better than in patients with a dominant RV. In addition to the well-known mortality and morbidity burdens generated by the usually more complex pre-Fontan staging in RV-dominant patients (particularly the Norwood palliation for hypoplastic left heart syndrome) [44], our study proves that, even after a successful Fontan operation, RV morphology represents a 2.38-fold greater risk factor for mortality.

Noticeably, if we consider follow-up times of survival curves across reports, we observe that the SV morphology does not seem to affect patients' prognosis early after the Fontan operation. All series supporting RV equivalence to LV in terms of survival tend to exhibit a shorter follow-up. Conversely, most reports show better long-term follow-up outcomes for patients with LV morphology (Table 1 and Fig. 3). Our estimated Kaplan–Meier curves reflect this tendency, displaying a constant inferior survival for RV-dominant patients that differs more profoundly as follow-up time increases, with an apparent diverging point after 10 years from Fontan completion (Fig. 3). We may speculate that, if the anatomical RV manages to remodel its geometry and mechanics on the systemic circulation, it can effectively work as a systemic pumping chamber for years, before starting a gradual decline in its performance.

As observed in patients with hypoplastic left heart syndrome [45], the anatomical RV, when included in the systemic

Table 3: Measures of single-ventricle function and dimensions and atrioventricular valve competence across studies ($n = 15$)

First author	Year	SV dysfunction (%)			AV valve dysfunction (%)			EF (%), median (range)/mean SD: SD			EDVi (ml/m^2), median (range)/mean SD: SD			ESVi (ml/m^2), median (range)/mean SD: SD		
		Dominant LV	Dominant RV	*P*-Value	Dominant LV	Dominant RV	*P*-value	Dominant LV	Dominant RV	*P*-Value	Dominant LV	Dominant RV	*P*-Value	Dominant LV	Dominant RV	*P*-Value
Moon J	2020	5.8	18	**<0.001**	13	36	**<0.001**	–	–	–	–	–	–	–	–	–
Powell AW	2020	22	18	0.9	43	62	**0.04**	–	–	–	–	–	–	–	–	–
Vitanova K	2019	6.5	6.8	0.893	–	–	–	57.8 SD: 6.1	57.2 SD: 5.3	0.285	–	–	–	–	–	–
Ghelani SJ	2018	–	–	–	5.9	24.4	**<0.001**	55% (47–60)	53% (47–58)	0.347	84 (73–109)	110 (83–133)	**<0.001**	39 (29–53)	49 (36–73)	**<0.001**
Pessotti CFX	2018	7	23.3	**0.04**	–	–	–	–	–	–	–	–	–	–	–	–
Steflik D	2017	–	–	–	–	–	–	54% (47–66)	45% (34–54)	0.160	–	–	–	–	–	–
Bossers SS	2015	48	64	0.086	38	67	**0.012**	55 SD: 8	49 SD: 9	**0.001**	88 SD: 20	91 SD: 20	0.467	40 SD: 13	47 SD: 16	**0.030**
Garnreiter JM	2014	–	–	–	25	44	0.058	–	–	–	–	–	–	–	–	–
Petko C	2012	0	3	ns	0	14	**<0.001**	–	–	–	–	–	–	–	–	–
Ohuchi H	2011	–	–	–	–	–	–	57 SD: 10	45 SD: 9	**<0.001**	73 SD: 35	64 SD: 15	ns	–	–	–
Ando M	2011	–	–	–	20.9	66.9	**<0.001**	–	–	–	–	–	–	–	–	–
Anderson PA	2008	–	–	–	15	18	**<0.001**	60 SD: 9	56 SD: 12	**<0.001**	79 SD: 22	93 SD: 29	**0.003**	34 SD: 14	43 SD: 21	**0.011**
Akagi T	1993	–	–	–	–	–	–	55 SD: 8	48 SD: 13	ns	62 SD: 15	63 SD: 22	ns	28 SD: 8	34 SD: 17	Ns
Sano T	1988	–	–	–	–	–	–	54 SD: 6	52 SD: 6	ns	188 SD: 53	179 SD: 61	ns	88 SD: 31	84 SD: 27	ns
Shimazaki Y	1986	–	–	–	–	–	–	56 SD: 3	54 SD: 8	ns	–	–	–	–	–	–
	Range	(0–48)	(3–64)		(0–43)	(14–67)		(54–60)	(45–57.2)		(62–188)	(63–179)		(28–88)	(34–84)	

AV: atrioventricular; EDVi: end-diastolic volume indexed; EF: ejection fraction; LV: left ventricle; ns: not significant; RV: right ventricle; SD: standard deviation. Bold values represent statistical significance.

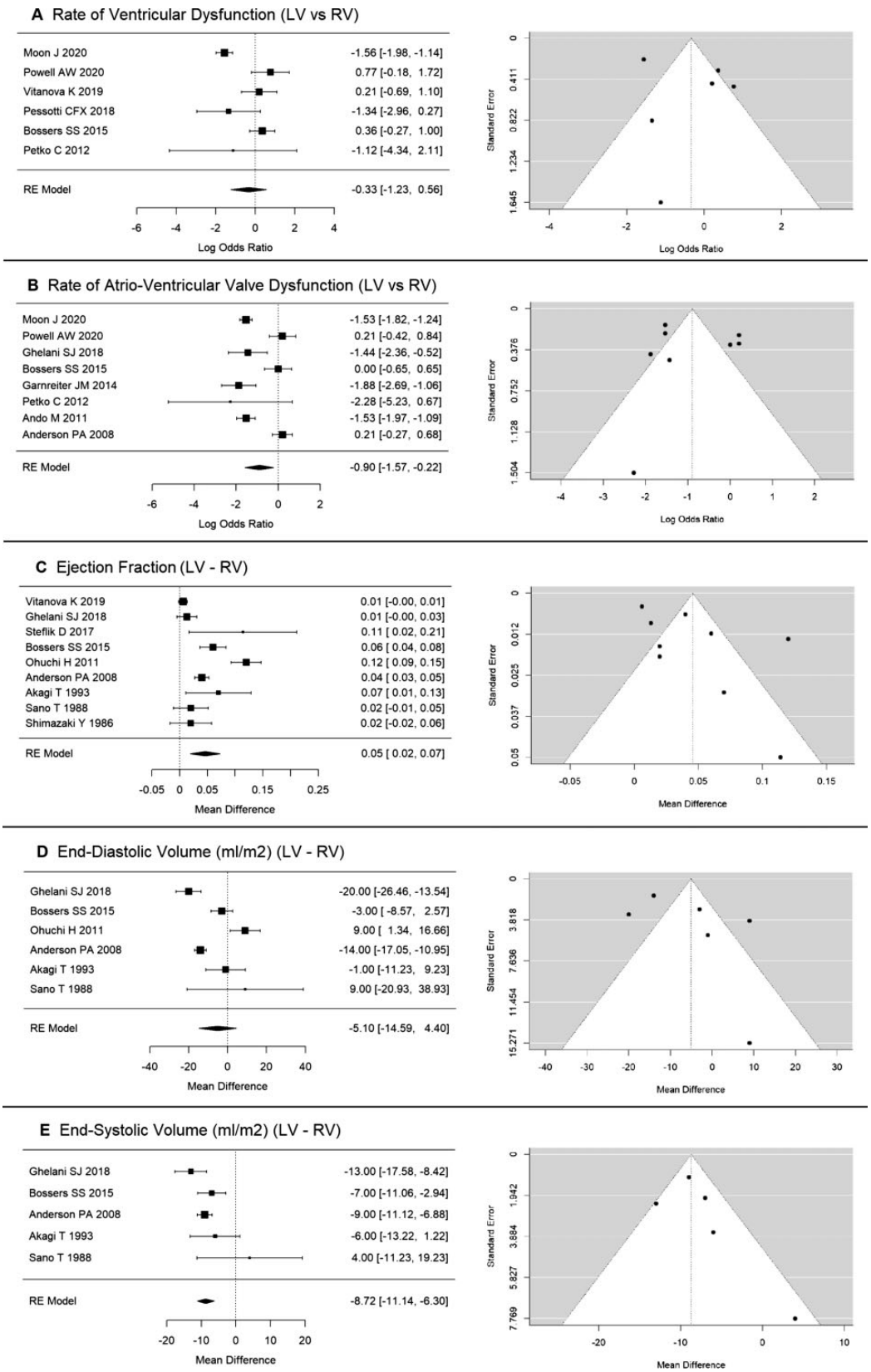


Figure 4: Results of pooled analysis of indices of ventricular function and dimensions between LV and RV-dominant patients across selected reports ($n = 15$). (**A**) Odds ratio for qualitative ventricular dysfunction, which was balanced between groups (-0.33 [-1.23, 0.56]). (**B**) OR for AV valve significant incompetence; LV dominance was protective for this occurrence (-0.90 [-1.57, -0.22]). (**C**) Mean difference of EF, which was 5% [2%, 7%] higher for LV-dominant patients. (**D**) Mean difference of end-systolic volume indexed, which was similar between the 2 groups (-5.10 [-14.59, 4.40] ml/m^2). (**E**) Mean difference of end-systolic volume indexed, which was 8.72 ml/m^2 larger for RV-dominant patients. LV: left ventricle; RV: right ventricle.

Table 4: Functional capacity measured as peak VO_2 and percentage of predicted peak VO_2 across studies ($n = 7$)

First author	Year	Peak VO_2 (ml/kg/min), mean SD: SD			% of predicted VO_2 peak (%), mean SD: SD		
		Dominant LV	Dominant RV	*P*-Value	Dominant LV	Dominant RV	*P*-Value
Vitanova K	2019	30.9 SD: 8.2	30.4 SD: 9.2	ns	73.9 SD: 16.5	70.8 SD: 20.7	Ns
Bossers SS	2015	–	–	–	74 SD: 15	75 SD: 13	0.707
Petko C	2012	37 SD: 10	34 SD: 7	ns	–	–	–
Ohuchi H	2011	27 SD: 4	25 SD: 4	**<0.05**	–	–	–
Anderson PA	2008	27 SD: 7	26 SD: 7	0.226	66 SD: 17	63 SD: 16	**0.031**
Giardini A	2008	–	–	–	64 SD: 11	56 SD: 10	**<0.05**
	Range	(26.7–37)	(25–34)		(64–74)	(56–75)	

ns: not significant. Bold values represent statistical significance.

circulation, can mimic the LV preferential longitudinal contraction. However, the vulnerable period of adaptation for the myocardial fibres to manage the circulatory volume unloading that occurs after the Fontan operation comes at the cost of longer intensive care unit stay and clinical course, as reported in previous series [8, 29, 43, 46]. On the other hand, it may as well be influenced by the more complex surgical staging (i.e. Norwood operation) that has led to the Fontan completion. In fact, RV morphology has been proven to represent an independent risk factor for prolonged respiratory and inotropic support after Fontan operation, increasing the need for intensive medical management in such patients [46]. In the present study, we can confirm on a larger scale that patients with dominant RV morphology require a significantly higher hospitalization time after Fontan operation. The pooled hospital stay is 2 days longer than patients with a dominant LV, even though the rates of postoperative arrhythmias and pleural effusions were comparable between groups.

Of note, once adapted to the systemic circulation, the anatomic RV seems to be able to perform efficiently enough for several years. This adaptive remodelling, together with the better peri- and postoperative management and care, may have contributed to the improved early- and medium-term prognosis for RV-dominant patients [13–16]. However, it is well known that during its clinical history, the RV appears to deteriorate and decline its function gradually. As anticipated by Suntratonpipat *et al.* [47] and Kaneko *et al.* [48], progressive systolic and diastolic dysfunctions occur for the systemic RV. These authors investigated the myocardial deformation indices by speckle tracking analysis in SV patients from the early postoperative period [47] until Fontan completion [48]. They both observed an impairment of myocardial contractility, which was evident from worse global strain and strain ratio parameters for patients with RV dominance, caused by a possible inadequate compensatory hypertrophy [40]. Coronary perfusion abnormalities have been hypothesized in patients with hypoplastic left heart syndrome treated with a modified Blalock–Taussig shunt at the time of the Norwood operation [44, 49]. A diastolic coronary steal caused by the shunt may result in chronic myocardial hypoperfusion, further compromising ventricular performance in the early stages of palliation. Circumferential strain indices, which have been proved to be associated with ventricular-arterial coupling [28], can persist impaired after >10 years from Fontan operation, affecting the prognosis of patients negatively [14]. Our meta-analysis supports the previous findings, showing lower pooled EF and larger ventricular volumes in RV-dominant patients.

Furthermore, we attested that a merely qualitative echocardiographic evaluation of ventricular function is inadequate to assess the underlying contractile impairment in SV patients with RV dominance. In fact, despite the equally balanced pooled prevalence of qualitative ventricular dysfunction in both RV- and LV-dominant patients, it is of note that the risk of moderate or severe AV valve regurgitation (a marker of ongoing volume overload and deteriorating ventricular performance [50]) is more significant in RV-dominant patients. As reported by Ando *et al.* [36], when the tricuspid valve is included in the systemic circulation, it may require surgical repair in up to 67% of patients at 30-year follow-up. Since systemic AV valve regurgitation is a well-known risk factor for mortality [7, 12, 32], early intervention on an incompetent AV valve should always be considered to reduce excessive preload on the SV to preserve it from further functional deterioration [11].

Last, it is worth noting that overall Fontan patients seem to experience a satisfactory functional status, as shown by a similar pooled peak VO_2 between LV- and RV-dominant groups. The predicted peak VO_2 has been noticed to be slightly greater for LV-dominant patients but with minimal clinical implications. However, this finding may be misleading since an exercise test requires discrete patient collaboration, and it is usually evaluated in long-term survivors [25, 31, 35, 37, 38], who are certainly a cohort of healthier patients, underestimating the real impact of ventricular morphology on the exercise capacity of Fontan patients.

Limitations

Performing meta-analyses of non-randomized clinical trials may raise several concerns. However, randomized clinical trials and prospective studies in univentricular palliation are rare, and none of them is designed to assess clinical outcomes according to SV morphology. We recognize that large registries of univentricular patients have not satisfied our selection criteria, reducing the size of our cohort. We analysed survival following Fontan completion, but we acknowledge that SV morphology acts also on pre-Fontan staging outcomes. The different surgical steps required to achieve the Fontan circulation are known to possess different risks and clinical results, affecting patients' prognosis from birth. Moreover, SV morphology is just one of the numerous and still not completely known determinants of the long-term prognosis of Fontan patients. Many postoperative complications and indexes of ventricular performance have been investigated in Fontan patients. However, the paucity of manuscripts reporting data stratified according to ventricular dominance and satisfying inclusion criteria did not allow us to perform an accurate meta-analysis on these

parameters. Heterogeneity between selected papers resulted significantly high, although several variables have been identified as effect modifiers in meta-analysis. Finally, age at the study was different across reports, contributing to the above-mentioned high heterogeneity of data. Observational data have been considered in our analyses, for this reason, the control of the confounding effect could be only partially performed in comparison with meta-analyses including randomized clinical trials. Finally, the individual patient data reconstruction of the Kaplan–Meier with the estimation of an overall HR leads to characterizing the long-term survival end point for a huge composed cohort of patients. However, this combined estimate does not account for the patient's specific characteristics and confounding factors affecting the outcome.

CONCLUSIONS

The morphology of the dominant ventricle has an influence on clinical outcomes late after Fontan palliation. RV dominance significantly affects patients' long-term survival, representing a 2.38-fold greater risk factor for mortality. The compensatory mechanisms of adaptation and remodelling, which the RV undergoes to sustain the systemic circulation, require a longer hospitalization in the early postoperative course. During follow-up, progressive systolic and diastolic dysfunctions occur, as demonstrated by reduced EF, larger ventricular volumes and more frequent AV valve significant regurgitation in RV-dominant patients.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

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Data availability

The data underlying this article are available in the article and in its online supplementary material.

Author contributions

Matteo Ponzoni: Conceptualization; Data curation; Investigation; Writing—original draft. **Danila Azzolina:** Data curation; Formal analysis; Writing—review & editing. **Luca Vedovelli:** Data curation; Formal analysis; Writing—review & editing. **Dario Gregori:** Data curation; Formal analysis; Visualization. **Giovanni Di Salvo:** Visualization. **Yves D'Udekem:** Supervision; Writing—review & editing. **Vladimiro Vida:** Visualization. **Massimo A. Padalino:** Conceptualization; Supervision; Writing—original draft; Writing—review & editing.

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