Pediatric Cardiology (2021) 42:1483–1487
https://doi.org/10.1007/s00246-021-02682-2

REVIEW PAPER

From Other Journals: A Review of Recent Articles by Our Editorial Team

Tarek Alsaied[1,2] · **Awais Ashfaq**[3]

Accepted: 15 July 2021 / Published online: 20 July 2021

Abstract
In this review, we provide a brief description of recently published articles addressing topics relevant to pediatric cardiologists. Our hope is to provide a summary of the latest articles published recently in other journals in our field. The articles address (1) outcomes for COVID-19 infection in adults with congenital heart disease which showed no increased mortality compared to the general population, (2) hepatorenal dysfunction before transplantation in patients with Fontan is associated with increased mortality, (3) abnormal Von Willebrand factor metabolism and angiopoietin signaling may contribute to pulmonary AVM formation in children with a Glenn circulation, (4) low cardiac output after the Norwood procedure which improves with higher hemoglobin and with milrionone, (5) a comparison of staged versus complete repair in neonatal tetralogy of Fallot reveiling the pros and cons of each strategy, (6) the long–term outcomes of early repair of complete atrioventricular canal show no difference in outcomes in patients who were repaired below 3 months of life.

Keywords Heart transplantation · Fontan · COVID-19 · Collaterals · Tetralogy of Fallot · Norwood · Atrioventricular septal defect · Atrioventricular canal

COVID-19 in Adults with Congenital Heart Disease [1]

Adults with congenital heart disease (CHD) have been considered as potentially high risk for the novel coronavirus disease-19 (COVID-19) mortality or other complications. This is based on the increased risk for COVID-19 complications in adults with preexisting conditions including cardiovascular disease though few data exist in CHD. This study sought to define the impact of COVID-19 in adults with CHD and to identify risk factors associated with adverse outcomes. The study was a collaboration between multiple centers. The study included adults ≥ 18 years with CHD who had confirmed or clinically suspected COVID-19. The data collected included clinical information, anatomic diagnosis, comorbidities, echocardiographic findings, symptoms, course of illness, and outcomes. The predictors of death or severe infection were determined. 58 adult CHD centers worldwide participated and a total of 1044 infected patients (age: 35.1 ± 13.0 years; range 18 to 86 years; 51% women) were included. Most patients (87%) had laboratory-confirmed coronavirus infection. The cohort included 118 (11%) patients with single ventricle and/or Fontan physiology, 87 (8%) patients with cyanosis, and 73 (7%) patients with pulmonary hypertension. There were 24 COVID-related deaths (case/fatality: 2.3%). Factors associated with death included male sex, diabetes, cyanosis, pulmonary hypertension, renal insufficiency, and previous hospital admission for heart failure. Worse physiological stage, based on the adult CHD new classification, was associated with mortality ($p = 0.001$), whereas anatomic complexity or defect group was not. The study concluded that COVID-19 mortality in adults with CHD is consistent with the general population. The most vulnerable patients for mortality are patients with worse physiological stage, such as cyanosis and pulmonary hypertension, whereas anatomic complexity does not appear to predict infection severity. This study is consistent with previous observations from single–center studies and the clinical experience. Patients with worse physiology including cyanosis or pulmonary hypertension deserve the most attention.

✉ Tarek Alsaied
tarek.alsaied84@gmail.com

1 Pittsburgh Children's Hospital Medical Center, Heart Institute, 3333 Burnet Avenue, Pittsburgh, PA 45215, USA

2 Department of Pediatrics, University of Pittsburgh, Pittsburgh, PA, USA

3 Heart Institute, Johns Hopkins All Children's All Children's Hospital, St. Petersburg, FL, USA

Hepatorenal Dysfunction Assessment with the Model for End-Stage Liver Disease Excluding INR Score Predicts Worse Survival After Heart Transplant in Pediatric Fontan patients [2]

Multiple organ dysfunction may develop after the Fontan operation due to the unique physiology, most notably affecting the liver and kidney. This study evaluated the utility of Model for End-Stage Liver Disease Excluding INR (MELD-XI) score, a score evaluating the function of both liver and kidney to identify Fontan patients at increased risk for morbidity and mortality post–heart transplant. The study used the Pediatric Heart Transplant Society database to identify Fontan patients listed for heart transplant between January 2005 and December 2018. MELD-XI scores were calculated at listing and at heart transplant. The formula for calculation is MELD-XI = 5.112 × loge (total bilirubin) + 11.76 × $\log_e$ (creatinine) + 9.44. A multivariable analysis was conducted to identify risk factors for post–heart transplant mortality. Demographic, clinical characteristics, and survival differences were evaluated and compared between the high ≥ 11.5 and low < 11.5 MELD-XI score cohorts. The study included 565 Fontan patients who underwent transplantation, 524 (93%) had calculable MELD-XI scores at the time of heart transplant: 421 calculable at listing and 392 calculable at listing and at heart transplant. On multivariable analysis, only MELD-XI score (squared) (hazard ratio, 1.007), history of protein-losing enteropathy (hazard ratio, 2.1), and ventricular assist device use at transplant (hazard ratio, 3.4) were risk factors for early phase post–heart transplant mortality. Patients with high MELD-XI scores at heart transplant had inferior survival post–heart transplant ($p = 0.02$). Additionally, those patients were significantly more likely to have elevated brain natriuretic peptide, elevated pulmonary capillary wedge pressure and to need mechanical ventilation or ECMO. Patients in the high MELD-XI score cohort at wait listing and heart transplant tend to have the worst post–heart transplant survival although not statistically significant ($p = 0.42$). The study concluded that MELD-XI, an easily calculated score, serves as a valuable aid in identifying pediatric Fontan patients at increased risk for post–heart transplant mortality. This study confirms again the importance of end organ function at the time of heart transplantation in post-transplant outcomes. This is similar to other diseases where hepatic and renal dysfunction is associated with worse outcomes [2].

Abnormalities in the Von Willebrand–Angiopoietin Axis Contribute to Dysregulated Angiogenesis and Angiodysplasia in Children with a Glenn Circulation [3]

Children with a bidirectional superior cavopulmonary connection (Glenn circulation) develop dysregulated angiogenesis and pulmonary angiodysplasia in the form of arteriovenous malformations (AVMs). The pathophysiology of AVMs in patients with Glenn remains unclear. There is no targeted therapy. The von Willebrand factor (vWF)– angiopoietin axis plays an important role in normal Angiogenesis and AVM formation in multiple diseases.

This interesting study evaluated the levels of vWF, angiopoietin 1 (which is important to stabilize vessel formation) and angiopoietin 2 (which destabilizes vessel formation) in 22 Glenn patients compared to 20 age-matched normal controls. The blood samples from the Glenn patients were collected at the pre-Fontan catheterization from the inferior vena cava (IVC) and the branch pulmonary arteries (PA). Glenn patients had lower vWF levels, lower angiopoietin 1 and higher angiopoietin 2 compared to controls. Within Glenn patients, angiopoietin 1 (which stabilizes vessel formation) were lower in the PA compared to IVC. Patients with Glenn and pulmonary AVMs had lower angiopoietin 1 in the pulmonary circulation compared to Glenn patients without AVMs. In parallel, differences in multiple angiogenic and inflammatory signaling peptides were observed between Glenn patients and controls, which indicated derangements in multiple angiogenic pathways in Glenn patients. These findings support the hypothesis that abnormal vWF metabolism and angiopoietin signaling dysregulate angiogenesis and contribute to pulmonary AVM formation in children with a Glenn circulation. vWF is secreted from the endothelial cells and the absence of pulsatile flow in Glenn may result in decreased levels of vWF secretion from the pulmonary endothelium. The vWF–angiopoietin axis may be a target to correct angiogenic imbalance and reduce pulmonary angiodysplasia in Glenn patients.

Interventions Associated with Treatment of Low Cardiac Output After Stage 1 Norwood Palliation [4]

Morbidity and mortality after Stage 1 Norwood palliation (S1P) of hypoplastic left heart syndrome remain above 10% despite improved outcomes. Hemodynamic changes post S1P are often grouped together under "low cardiac

output (CO)" associated with worse outcomes. The authors have previously described an organized approach to different hemodynamic states based on Ohm's law and Fick principle dividing them into low CO, high systemic vascular resistance (SVR), low SVR, and high CO [5]. In this study, the authors aimed to identify the levels of support needed with each hemodynamic state and assess transitions from a low CO state. Postoperative hemodynamic data for 48 h were maintained in their institutional database along with arterial blood gases, mixed venous saturations and cerebral and somatic near infrared spectroscopy (NIRS). Vasoactive support consisted of milrinone, epinephrine and norepinephrine and titrated to a target MAP > 45 mm Hg, arterial saturations > 75%, SvO2 > 50%, cerebral NIRS > 50% and somatic NIRS > 60%. Circulatory states were divided based on MAP and somatic NIRS into 4 categories as mentioned above. A fifth state was added to include ECMO support.

Data from 10,272 h in 214 patients were analyzed with 194 (91%) surviving to discharge. ECMO was used in 24 patients (11%) with resultant reduced survival. A low CO state was observed in 142 (67%) patients for 1007 h (10.8%) again with reduced survival. Older age, longer bypass and circulatory arrest time were associated with a higher risk subgroup among low CO patients. Compared to high CO state, low SVR and high SVR states were not higher risk and the high CO state conferred protection. The low CO state was characterized by lower milrinone but higher catecholamine dose reflecting the need for higher inotropy and mechanical ventilation. Of the 1071 transitions into low CO, 166 (11.1%) occurred from high SVR, 147 (6.8%) form low SVR, and 10 (1.4%) from high CO. Successful transition out of low CO was associated with increased milrinone dose and hemoglobin concentration. Of the 1084 transitions from low CO, 7 (0.7%) were to ECMO, 181 (16.7%) to high SVR, 125 (11.5%) to low SVR, and 75 (6.9%) to high CO. Successful transition to increasing milrinone and hemoglobin concentration decreased the odds of remaining in low CO from 1.56 to 0.64 ($p < 0.001$). The authors concluded that maintaining or increasing inodilator and hemoglobin levels was associated with improved hemodynamic conditions and was predictive of successful future transitions from the low CO state.

Comparison of Management Strategies for Neonates with Symptomatic Tetralogy of Fallot [6]

Infants born with tetralogy of Fallot (TOF) typically undergo definitive repair sometime during the first year of life. A subset of neonates will manifest symptoms and require early intervention that may consist of primary repair or staged procedures via surgical or transcatheter approach to augment pulmonary blood flow. This study was undertaken to conduct a multi-center comparison of staged versus primary repair treatment strategies. A multi-center retrospective study was performed including all neonates with TOF who underwent intervention from 2005 until 2017 at 9 centers involved with the Congenital Cardiac Research Collaborative. The primary outcome was death or heart transplantation while secondary outcomes were hospital stay, cardiopulmonary bypass time, anesthesia, ventilation and inotrope use as well as complications and rates of reintervention. Outcomes were analyzed by component parts: Initial Palliation (IP), subsequent Complete Repair (CR), Primary Repair (PR) as well as by cumulative approach with a Staged Repair (SR: IP + CR).

The cohort consisted of 572 patients, of which 342 patients underwent SR (IP: surgical, $n = 256$; transcatheter, $n = 86$) and 230 patients who underwent PR. Surgical IP included systemic to pulmonary shunt ($n = 241$) and right ventricular outflow tract (RVOT) procedures ($n = 15$), whereas transcatheter IP included balloon pulmonary valvuloplasty ($n = 47$), patent ductus arteriosus stent ($n = 28$), and RVOT stent ($n = 11$). Pre-procedural ventilation, prematurity, DiGeorge syndrome, and pulmonary atresia were more common in the SR group ($p \leq 0.01$). The observed risk of death was not different between the groups (10.2% vs 7.4%; $p = 0.25$) at median 4.3 years. After adjustment, the hazard of death remained similar between groups (HR: 0.82; 95% CI 0.49 to 1.38; $p = 0.459$), but it favored SR during early follow-up (< 4 months; $p = 0.041$). Secondary outcomes favored the SR group in component analysis, whereas they largely favored PR in cumulative analysis. Re-intervention risk was higher in the SR group ($p = 0.002$ driven by increased early (< 3 months) but not late re-intervention. There was no difference in the risk of in-hospital mortality between groups (OR: 0.57; 95% CI 0.26 to 1.24; $p = 0.16$), no differences in the rate of procedural complications (OR: 0.84; 95% CI 0.6 to 1.19; $p = 0.33$) or hospital complications (OR: 1.13; 95% CI 0.79 to 1.61; $p = 0.51$). In this multicenter comparison of SR or PR for management of neonates with sTOF, the authors concluded that early mortality and neonatal morbidity were lower in the SR group, but cumulative morbidity and reinterventions favored the PR group, findings suggesting potential benefits to each strategy.

Long-Term Outcome After Early Repair of Complete Atrioventricular Septal Defect in Young Infants [7]

The current standard approach for elective repair of complete atrioventricular septal defect (cAVSD) has been 3–6 months of age in many centers. Early mortality with this approach has been less than 3% with a survival of approximately 90%

Table 1 Summary of the 6 studies in this review

Author	Study summary
Broberg et al.	COVID-19 in adults with congenital heart disease Multi-institutional study including adults with congenital heart disease (CHD) 1044 patients, median age 35 years up to 86 years 118 (11%) patients with Fontan physiology, 87 (8%) with cyanosis, and 73 (7%) with pulmonary hypertension Mortality was seen in 24 (2.3%). Risk factors of moratlity included: male sex, diabetes, cyanosis, pulmonary hypertension, renal insufficiency, and previous hospital admission for heart failure. Worse physiological factors including Eisenminger, cyanosis and pulmonary hypertension associated with moratliy while anatomic factors did not. CHD is not necessarily associated with worse outcomes with COVID-19 infection. Worse physiologic factors are associated with increased mortality
Amdani et al.	Hepatorenal dysfunction predicts worse survival after heart transplant in pediatric Fontan patients 565 Fontan patients underwent transplantation between 2005 and 2018 Used the Pediatric Heart Transplant Society database Model for End-Stage Liver Disease Excluding INR (MELD-XI) score was calculated On multivariable analysis, MELD-XI was independent predictor for early mortality MELD-XI, an easily calculated score, serves as a valuable aid in identifying pediatric Fontan patients at increased risk for post-heart transplant mortality
Bartoli et al.	Abnormalities in the Von Willebrand (vWF)–Angiopoietin Axis Contribute to Dysregulated Angiogenesis and Angiodysplasia in Children With a Glenn Circulation 22 patients with Glenn compared to 20 normal controls. Blood level of vWF and angiopoitin from IVC and PA during pre-Fontan cath were compared to normal controls Glenn patients had lower vWF and angiopoietin 1 which stabilized blood vessels and higher angiopoeitin 2 which destabilized blood vessels Glenn patients with AVMs had lower angiopoietin 1 compared to patients without AVMs Abnormal vWF metabolism and angiopoietin signaling dysregulate angiogenesis and contribute to pulmonary AVM formation in children with a Glenn circulation
Hoffman et al.	Interventions associated with treatment of low cardiac output after Stage 1 Norwood palliation 10,272 h of data were analyzed in 214 patients Low CO was observed in 142 patients Low CO and ECMO had increased mortality risk Increased milrinone and hemoglobin levels were associated with successful transition out of low CO Maintaining or increasing inodilator and hemoglobin levels was associated with improved hemodynamic conditions and was predictive of successful future transitions from the low–CO state
Goldstein et al.	Comparison of management strategies for neonates with symptomatic tetralogy of Fallot Staged repair compared to primary repairs among neonates with symptomatic TOF Primary outcome was death 342 patients unerwent SR (IP: surgical, $n=256$; transcatheter, $n=86$) followed by complete repair (CR), 230 underwent primary repair (PR) Risk of death was not different between groups at 4.3 years ($p=0.25$) Reintervention higher in SR group ($p=0.002$) Secondary outcomes favored SR in component analysis, but favored PR in cumulative analysis In this multicenter comparison, early mortality and neonatal morbidity were lower in the SR group, but cumulative morbidity and reinterventions favored the PR group, findings suggesting potential benefits to each strategy
Ramgren et al.	Long-term outcome after early repair of complete atrioventricular septal defect in young infants 304 patients over a 25-year period Divided into < 3 months and > 3 months patient groups Mean follow-up was 13.2 years 30-day mortality was 1% with no difference between groups Freedom from LAVV reoperation was 92.6% at 20 years No difference in LAVV reoperation in young infants compared with older infants The authors concluded that their data demonstrated that excellent long-term survival could be achieved with early repair for complete atrioventricular septal defect, and the need for reoperations due to left atrioventricular valve regurgitation was low

IVC Inferior vena cava, *PA* Pulmonary arteries, *CO* Cardiac output, *COVID-19* Corona virus disease 2019, *ECMO* extracorporeal membrane oxygenation, *MELD-XI* Model for End-Stage Liver Disease Excluding INR, *TOF* Tetralogy of Fallot, *SR* staged repair, *IP* Initial Palliation, *CR* Complete Repair, *LAVV* left atrioventricular valve

at 10-year follow-up [8]. However, some patients develop congestive heart failure within the first months of life and earlier surgical intervention must be entertained. The objective of this study was to evaluate authors experience over a 25-year period on early repairs to assess survival and identify risk factors for left atrioventricular valve (LAVV)-related re-operations.

All surgeries were primarily done at 2 centers of similar size in Sweden divided by geographic referral patterns. A total of 8 surgeons performed the repairs with 2 patch repair being the primary choice. A total of 304 consecutive patients underwent surgical correction for cAVSD between April 1993 and October 2018. The primary outcome measures were survival and the need for LAVV-related re-operation after surgical repair for cAVSD in patients younger than 3 months compared with those aged more than 3 months. The results for young infants (aged < 3 months; n = 55; mean age 1.6 ± 0.6 months) were compared with older infants (aged > 3 months; n = 249; mean age, 5.1 ± 5.2 months). Mean follow-up was 13.2 ± 7.8 years (median, 14.0 years; interquartile range, 7.0–20.0). The Kaplan–Meier method was used to assess overall survival and freedom from left atrioventricular valve-related reoperation.

Overall, 30-day mortality was 1.0% (3/304) with no difference between young and older infants ($p = 1.0$). Overall survival in the total population at 20- year follow-up was 95.1% ± 1.3%. Independent risk factors for poor survival were the presence of an additional ventricular septal defect ($p = 0.042$), previous coarctation of the aorta ($p < 0.001$), persistent left superior vena cava ($p = 0.026$), and genetic syndromes other than Trisomy 21 ($p = 0.017$). Freedom from left atrioventricular valve-related reoperation was 92.6% ± 1.7% at 20 years. A total of 19 patients (6.3%) required 26 LAVV-related reoperations after the initial cAVSD repair, 4 patients needing second LAVV reoperation and 3 patients a third reoperation. Four of the 19 patients requiring LAVV-related reoperation had their reoperation in the early postoperative period. Independent predictors for LAVV-related reoperation were persistent LSVC (HR, 5.9; 95% CI, 1.3–27; $p = 0.020$), preoperative severe AV valve regurgitation (HR, 4.6; 95% CI, 1.5–15; $p = 0.007$), and the presence of an unbalanced AV valve/ventricle (HR, 8.0; 95% CI, 2.6–29; $p < 0.001$). There was no significant difference in left atrioventricular valve-related reoperation in young infants compared with older infants (P = 0.084). The study demonstrated excellent long-term results with early repair for cAVSD, and the need for reoperations due to left atrioventricular valve regurgitation was low. The authors concluded that primary correction in patients aged less than 3 months, when clinically necessary, is well tolerated and palliative procedures can be avoided in the majority of patients (Table 1).

Authors' Contributions The author summarized the recent published literature in this review. In this review we provide a brief description of recently published articles addressing topics relevant to pediatric cardiologists. Our hope is to provide a summary of the latest articles published in other journals in our field.

Funding Not applicable.

Declarations

Conflict of interest All authors declare that they have no conflict of interest.

References

1. Broberg CS, Kovacs AH, Sadeghi S, Rosenbaum MS, Lewis MJ, Carazo MR et al (2021) COVID-19 in adults with congenital heart disease. J Am Coll Cardiol 77(13):1644–1655
2. Amdani S, Simpson KE, Thrush P, Shih R, Simmonds J, Knecht K et al (2021) Hepatorenal dysfunction assessment with the Model for End-Stage Liver Disease Excluding INR score predicts worse survival after heart transplant in pediatric Fontan patients. J Thorac Cardiovasc Surg. https://doi.org/10.1016/j.jtcvs.2021.02.014
3. Bartoli CR, Hennessy-Strahs S, Dowling RD, Gaynor JW, Glatz AC (2021) Abnormalities in the von willebrand-angiopoietin axis contribute to dysregulated angiogenesis and angiodysplasia in children with a glenn circulation. JACC Basic Transl Sci 6(3):222–235
4. Hoffman GM, Niebler RA, Scott JP, Bertrandt RA, Wakeham MK, Thompson NE et al (2021) Interventions associated with treatment of low cardiac output after stage 1 norwood palliation. Ann Thorac Surg 111(5):1620–1627
5. Hoffman GM, Ghanayem NS, Scott JP, Tweddell JS, Mitchell ME, Mussatto KA (2017) Postoperative cerebral and somatic near-infrared spectroscopy saturations and outcome in hypoplastic left heart syndrome. Ann Thorac Surg 103:1527–1535
6. Goldstein BH, Petit CJ, Qureshi AM, McCracken CE, Kelleman MS, Nicholson GT et al (2021) Comparison of management strategies for neonates with symptomatic tetralogy of Fallot. J Am Coll Cardiol 77(8):1093–1106
7. Ramgren JJ, Nozohoor S, Zindovic I, Gustafsson R, Hakacova N, Sjögren J (2021) Long-term outcome after early repair of complete atrioventricular septal defect in young infants. J Thorac Cardiovasc Surg 161(6):2145–2153
8. St Louis JD, Jodhka U, Jacobs JP, Mayer JE, He X, Hill KD et al (2014) Contemporary outcomes of complete atrioventricular septal defect repair: analysis of the society of thoracic surgeons congenital heart surgery database. J Thorac Cardiovasc Surg 148:2526–2531