ISHLT2023 Roving Reporters – Reports from Advanced Heart Failure and Transplantation (AHFTX)

- **Wednesday, 19 April, 2023**
  - FEATURED ABSTRACT 01 at General Session I. Severe Pediatric Pulmonary Arterial Hypertension: Long-Term Outcomes of Reverse Potts Shunt and Transplantation
  - SESSION 09 (SYMPOSIUM). Diagnosis of Heart Transplant Rejection: Out With the Old, In With the New
  - SESSION 09 (SYMPOSIUM). Diagnosis of Heart Transplant Rejection: Out With the Old, In With the New
  - SESSION 16 (SYMPOSIUM). If at First You Don't Succeed, Try, Try Again! Heart Failure and Transplantation in Fontan Patients
  - SESSION 05 (ORAL). Shots! Shots! Shots! COVID-19 Vaccines in Heart Transplant Recipients
  - SESSION 14 (ORAL). Much Ado About Nothing: Using Artification Intelligence for the Best Heart Transplantation Outcomes
  - SESSION 21 (ORAL). Cardiac Allograft Vasculopathy: From Bench to Bedside
  - SESSION 26 (ORAL). Organ Allocation Strategy: Algorithms to Implement Equity
  - SESSION 27. New Tools for the Kids: Diagnosis of Heart Transplant Rejection and Registries for Heart Function in Pediatrics
  - MINI ORAL 01. Scanning the (Rocky Mountain) Horizon: Biomarker Discovery and Understanding Outcomes in Heart Transplantation
  - MINI ORAL 04. Outcomes, Predications, and Monitoring, Oh My! In the Wonderful World of Heart Transplant
- **Thursday, 20 April, 2023**
  - FEATURED ABSTRACT 03 at General Session II. Heart Transplantation Outcomes in Patients from Socioeconomically Distressed Communities
  - KEYNOTE PRESENTATIONS at General Session II: Health Equity and Advanced Heart and Lung Disease in the US and the UK
  - SESSION 30 (SYMPOSIUM). Exploring the Limits in Heart Transplantation in Children and Adults

- SESSION 44 (SYMPOSIUM). Mountain for Every Miracle! Field of Cardio-Oncology: The High-Yield Tips
- SESSION 34 (ORAL). Balancing the Scales: Healthcare Disparities in Heart Transplantation
- SESSION 42 (ORAL). Current Challenges in Pediatric Heart Transplant Selection and Outcomes

- **Friday, 21 April, 2023**
  - SESSION 58 (SYMPOSIUM). For All Ages: MCS Support in Congenital Heart Disease in Children and Adults
  - SESSION 65 (SYMPOSIUM). Cardiac Allograft Vasculopathy – What Does the Future Hold?
  - SESSION 79 (SYMPOSIUM). Unravelling Deaths in Heart Transplantation: Turning Tragedy into Triumph
  - SESSION 68 (ORAL). How It Started… How It's Going: Omics and AI in Heart Transplant Biopsies and Rejection Surveillance
  - SESSION 75 (ORAL). The Comedy of Errors: New Allocation Policy, DCD Donors… What About Primary Graft Dysfunction?
  - SESSION 77 (ORAL). New Frontiers in Biomarker Development: Antibodies, Omics, and Graft Injury
  - SESSION 82 (ORAL). More Than a Number: Navigating the Complexities of Psychosocial Support in Heart Transplantation
  - MINI ORAL 13. Analyzing the Present and Improving the Future in Heart Transplantation
  - MINI ORAL 16. The Winter's Tale: Hypothermic Machine Preservation of Donor Hearts

- **Saturday, 22 April, 2023**
  - FEATURED ABSTRACT 04 at General Session III. Comparing Long-Term Survival and Readmissions Between Heartmate 3 and Heart Transplant as Primary Treatment for Advanced Heart Failure
  - SESSION 89 (ORAL). Medications and Machines: Which Ones Improve Pediatric Heart Transplant Outcomes?
  - SESSION 90 (ORAL). All's Well That Ends Well: The Three P's to Transplant Success: Protection, Preservation, and (em)Powering the Donor Heart
  - SESSION 91 (ORAL). Multi-Organ Transplant Outcomes: When are Two Organs Better Than One in Heart Transplantation?
  - SESSION 93 (ORAL). A Midsummer Night's Dream: From Mitochondria to Xenotransplantation: Novel Research Coming to You!

Thank you to all of our ISHLT2023 Roving Reporters.

ADVANCED HEART FAILURE AND TRANSPLANTATION (AHFTX)

Jason Goldberg, MD, MS, Inova LJ Murphy Children's Hospital, Fairfax, VA USA
Luise Holzhauser, MD, University of Pennsylvania, Philadelphia, PA USA
Pei Jun Zhao, MD, MPH, London Health Sciences Centre / Western University, London, ON Canada

ADVANCED LUNG FAILURE AND TRANSPLANTATION (ALFTX)

Lourdes Chacon Alberty, MD, MCTM, Texas Heart Institute, Houston, TX USA
Rebecca Klingbeil, MSN, DNP, CRNA, Mayo Clinic, Jacksonville, FL USA

MECHANICAL CIRCULATORY SUPPORT (MCS)

Anju Bhardwaj, MD, University of Texas / McGovern Medical School, Houston, TX USA
Anjan Tibrewala, MD, Northwestern University, Chicago, IL USA

PULMONARY VASCULAR DISEASE (PVD)

Nancy Luo, MD, MHS, Sutter Health, Sacremento, CA USA

FEATURED ABSTRACT 01 at General Session I. Severe Pediatric Pulmonary Arterial Hypertension: Long-Term Outcomes of Reverse Potts Shunt and Transplantation

Presenter: ***Sebastian Hascoet, MD, PhD****, Marie Lannelongue Hospital Groupe Hospitalier Paris-Saint Joseph, Paris, France*

After an exciting conference welcome from program chairs **Andreas Zuckermann, MD** and **Howard Eisen, MD**, this featured abstract was introduced wherein **Sebastien Hascoet, MD, PhD** and colleagues from Marie Lannelongue Hospital in Paris, France presented a retrospective cohort study comparing 61 consecutive pediatric patients with severe pulmonary artery hypertension (PAH) undergoing Reverse Potts shunt (RPS) or listed for transplantation (lung or heart/lung).

They described the severity of the disease, noting those with NYHA Class IV symptoms having a life expectancy less than 2 years. The field has shown limited data regarding both interventions, limited mainly to small case series. The data presented stemmed from a 2007 high priority transplant listing status implemented for patients with severe PAH, which has led to improvement in access to transplant for these patients. There remains question, however, in choosing transplantation as opposed to RPS for such patients.

They reported 20 patients who underwent RPS and 41 patients listed for transplantation. Those listed for transplantation were older and had worse right ventricular function than those with RPS. In-hospital mortality was low, with one death in each group. After RPS, there was a significant decrease in prostacyclin use and NYHA class severity as well as a 75% transplant-free survival at 10 years.

Among those listed for transplant, 28 were transplanted, with a 5-year survival of 43% overall and 78% conditional upon hospital discharge. After implementation of the high-priority allocation status in 2007, waitlist mortality among those listed decreased from 52.6% to 13.6% (P=0.02) and post-transplant survial increased from 55.6% to 77.2. During this same period post-RPS survival increased from 57.1% to 74.7%.

Dr. Hascoet concluded with the proposal of criteria for which patients should undergo RPS vs. transplantation, noting transplantation (and not RPS) is likely the optimal therapy for those with suprasystemic pulmonary pressures, RV failure, ECMO support, or complex congenital heart disease.

The post-presentation discussion, led by **Lori West, MD, DPhil**, positions this study as an initial step towards multi-center trials evaluating these two therapies among children with severe PAH.

VIEW FULL ABSTRACT

– Commentary by Jason F. Goldberg, MD, MS

SESSION 09. Diagnosis of Heart Transplant Rejection: Out With the Old, In With the New

Co-chaired by **Jignesh Patel, MD, PhD**, of Cedars-Sinai Smidt Heart Institute in Los Angeles, and **Annalisa Angelini, MD**, of the University of Padua in Padova, Italy, this session provided a comprehensive update to the newest technologies used in diagnosing rejection.

First, **Carolyn Glass, MD, PhD**, from Duke University presented her center's work describing Machine Learning Histology. The goal of this technology is to use computing to view and diagnose rejection from endomyocardial biopsy (EMB) samples. The specific machine learning effort included a supervised convolutional neural network trained with biopsy reads from pathologists from over ten institutions. The goal of the work presented was to answer the question, "Can a machine learning algorithm determine rejection?" In training the network, machine learning had 97-99% accuracy in validation at the 'patch' level—partial slide reads, followed by 91% accuracy at the entire slide level in determining 2R cellular rejection vs non-rejection, which is similar to that of human expert interpretation. Next steps in this work include multi-institutional validation as well as further approvals along the FDA approval process.

Palak Shah, MD, MS, from the Inova Heart and Vascular Institute, presented work from the GRAfT consortium describing the role of microRNA in diagnosis of rejection. The *JHLT* article describing this work was presented in a concurrent session as "The Most Influential JHLT Heart Failure/Transplantation Paper in 2022." MicroRNAs are non-coding nucleotides that regulate gene expression; over 2,200 specific microRNAs have been identified in human circulation, and, importantly, they are very stable for evaluation during multiple freeze-thaw cycles. Prior work from the Paris and Padova transplant groups have described initial efforts studying microRNA's role in diagnosing acute cellular rejection (ACR) and antibody mediated rejection (AMR), with the current work from GRAfT describing the first validation among a large sample, including 116 patients from GRAfT and 37 from Stanford. In over 400 sequenced samples, Dr. Shah and colleagues identified ACR and AMR clinical scores scaled from 0-100, with a score > 65 able to differentiate rejection from non-rejection with excellent performance on receiver operating characteristic analysis. They are planning a larger cohort of > 800 samples to further describe the clinical utility of this evaluation in diagnosing rejection.

Daniel Kim, MD, from the University of Alberta described recent work studying MMDx-Heart a gene expression evaluation performed on EMB samples. He provided an excellent overview of the complex statistical analyses involved in MMDx's ability to assign phenotypes to biopsies, including archetypes of no rejection, ACR, AMR, and an 'injury' phenotype. He presented the principal component analysis (PCA) plots that are reported with each biopsy sample, which can be used to describe the degree to which each biopsy meets each of these phenotypes. These archetypes were derived from an initial set of 331 biopsies followed by a larger validation of nearly 900 biopsies. The technology is seeing rapid expansion in both pediatric and adult heart transplant biopsy evaluation, with multiple abstracts describing its use throughout the ISHLT meeting.

Luciano Potena, MD, PhD, from Bologna University Hospital provided an overview of gene expression profiling (GEP) currently used to evaluate the likelihood of rejection among adult heart transplant recipients. He described the efforts that led to development of the AlloMap® assay, the most widely used GEP technology, including the CARGO, CARGO2, and IMAGE trials, the latter being the only randomized controlled trial in the field, determining non-inferiority between a biopsy-minimizing AlloMap® strategy and traditional EMB practice. This methodology continues to gain use throughout heart transplant centers, with the ability to forego many biopsies among patients at low risk of rejection. The limitations of this technology include its inability to evaluate AMR, its high false-positive rate, as well as a lack of its application globally to low-resource centers. However, it may continue to be a valuable tool when coupled with the other technologies presented in this session.

Finally, **Kiran Khush, MD, MAS**, from Stanford University described the utilization of cell-free DNA (cfDNA) as well as donor derived exosomal analysis in the diagnosis of rejection. She described the development of cfDNA assays at Stanford, which were then validated in the multi-center D-OAR trial, leading to the development of the AlloSure® assay, followed by data from the SHORE trial, describing the technology's ability to predict rejection before a positive EMB. She then presented more contemporary genomic strategies including evaluation of DNA methylation patterns to determine the organ of origin of specific cfDNA, giving promise to detecting rejection in multi-organ transplant recipients. This was followed by an overview of exosomes: extracellular vesicles that contain DNA, RNA, and proteins that mediate cell-to-cell communication. Exosomes have been evaluated as biomarkers in cancer diagnosis, with emerging data showing their potential utility as transplant rejection biomarkers. More recent publications have also described the potential of exosomes to mediate allograft tolerance.

These presentations provided an excellent overview of these technologies, direct from the experts involved in their development, which was followed by a meaningful discussion including questions from multiple audience members regarding the implementation of these technologies to continue to improve the evaluation of allograft rejection.

VIEW SESSION DETAILS

– Commentary by Jason F. Goldberg, MD, MS

SESSION 09. Diagnosis of Heart Transplant Rejection: Out With the Old, In With the New

This symposium was in the Pecha Kucha Format, a Japanese term for the sound of conversation ("chit chat"). The 5 speakers each had 8 minutes to discuss the theme, using 20 slides total and only spending 20 seconds per slide. It truly was a fantastic chit chat on novelties in cardiac transplant rejection.

The symposium was co-moderated by **Jignesh Patel, MD, PhD**, from Cedars-Sinai Smidt Heart Institute in Los Angeles, and **Annalisa Angelini, MD**, of University of Padua in Padova, Italy.

The first chit-chatter was **Carolyn Glass, MD, PhD**, of Duke University Medical Center, with the talk "**Through the Looking Glass: Advances in Histology**." She walked us through recent advances in histology, which included digitalization of glass slides, development of AI machine leering (ML) algorithms for histological interpretation and building of institutional infrastructure for future clinical implementation and integration of algorithms. She presented one of the first ML algorithms to detect ACR using a supervised convolutional network approach. The developed ML algorithm was able to distinguish ACR with myocyte damage and ACR without myocyte damage with a validation accuracy of 97%. Importantly the ML algorithm had 91% accuracy to detect ACR ⩾2R from <2R ACR with multi-institutional validation currently in process.

Next, **Palak Shah, MD, MS**, from the Inova Heart and Vascular Institute, talked about "**Going Small: MicroRNA Analysis for the Diagnosis of Cardiac Allograft Rejection**." He presented exciting data from the GRAfT study on the use of circulating MicroRNA for detection of ACR and AMR. Differentially expressed MicroRNA for each rejection type were identified, with an overall stronger signature in AMR (AMR 27 MicroRNAs, ACR 12 MicroRNAs adjusted for age, gender, race, blood group and BMI). To allow clinical applicability, scores ranging 0-100 were developed for both ACR and AMR with a higher score suggesting a higher likelihood of rejection. A score threshold of 65 correlated with an AUC for detection of rejection of 0.86 for ACR and 0.84 for AMR. Thus, using the two scoring systems could allow for both screening for rejection as well as diagnostic differentiation of ACR and AMR (Shah et al. JHLT 2022). Dr. Shah concluded that pending further validation circulating MicroRNAs could permit a true liquid biopsy, could facilitate clinical decision making in cases of uncertainty such as unexplained graft dysfunction or elevated dd-cfDNA and possibly guide therapeutic management.

The next speaker was **Daniel Kim, MD** of the University of Alberta, with a great presentation on "**Delving Deeper into the Biopsy: Intragraft Gene Profiling**." Dr. Kim started with an introduction to the MolecularMicroscope®(MMDx-Heart), which takes the most relevant of over 20,000 gene transcripts and forms pathogenesis-based transcript groups: NKB (NK Cell Burden), IFNG (Interferon Gamma), IRRAT (Injury Transcript), QCMAT (Macrophage Transcripts), and QCAT (Cytotoxic T-Cell Transcripts). These are then reported via principal component analysis. This approach could also be used to answerer what traits (components) make a great basketball player. Turns out plots vary for the average NBA player when compared to the average ISHLT attendant,

at least per Dr. Kim. When adding a third component a 3-D model of archetypal analysis results, which attempts to identify distinct phenotypes rather than similarity clusters. And here again, phenotypes differ for LeBron James and Howard Eisen just as they do for quiescence, ACR, AMR and injury patterns, per Dr. Kim's explanation. He then went on to summarize that EMB provide a platform for molecular analysis leading to more in depth understanding of clinically relevant states. He concluded that intragraft gene profiling can add clarity in clinically and pathologically ambiguous situations, for example aid in characterizing the differences between rejection and injury. And that was it - MMDx made simple with the help of the NBA.

Following, **Luciano Potena, MD, PhD**, of Bologna University Hospital in Italy spoke about "**Gene Expression Profiling: What's in a Score?**" In 2006, Deng et al. introduced gene expression profiling with identification of 11 genes in peripheral blood mononuclear cells that were able to reliably differentiate quiescence from ACR (not AMR!) with a NPV 99.8% via a newly derived score (CARGO, Deng et al. AJT 2006). Genes are involved in cell migration, hematopoietic proliferation, T-cell priming, lymphocyte activation, steroid sensitivity, and platelet activation pathways. However, over the next (almost) 2 decades it became clear that the GEP-score has several limitations. For instance, it has only been studied in low-risk populations, does not detect AMR, rises with CMV infection, and there is no one absolute level of GEP identified that is definitively abnormal. To be a little provocative, Dr. Potena referenced the Egyptian Dream Book, which can predict the absence of rain in Cairo with a 96% NPV… well, in Cairo the average number of rainy days seems to be 15 days per year… roughly 4%. For comparison in GEP studies the average rate of rejection is 3%…. Dr. Potena then asked "Do we really need EMB in low-risk patients? What can we get from GEP? How accessible is GEP outside of high-income countries?" He concluded that we need to think outside of the box to design studies that can allow powerful technologies such as the GEP to be combined with in multiparametric assessments designed to improve personalization and precision of our current approaches in transplantation.

To finish, **Kiran Khush, MD, MAS**, of Stanford University concluded the session with the final chit-chat talk "**Capturing the Escaped: Cell Free DNA and Donor-Derived Exosomal Analysis**." Dr. Khush provided an overview of the development of the dd-cfDNA technology from a conceptual idea to assess graft injury just a few years ago all the way to the real world-validation D-OAR study, which established a NPV for acute rejection of 97% for dd-cfDNA levels <0.2% (Khush et al. AJT 2019). In addition, the GRAfT study provided external validity and reproduction with AUC 0.92 for acute rejection as well as correlation with graft dysfunction. Furthermore, Dr. Khush discussed how results of the GRAfT study raised the exciting possibility that dd-cfDNA might be able to differentiate ACR and AMR via degree of ddcf-DNA elevation and assessment of fragment length when using this research grade assay (Agbor-Enoh et al. Circulation 2021). Moreover dd-cfDNA levels start rising about 2 months before rejection becomes evident on biopsy. Dr. Khush explained that in these settings a negative biopsy should not be reassuring since early rejection might be developing. Similarly, development of pathological de-novo DSA also results in elevation of dd-cfDNA levels, which could be helpful when deciding on the need for treatment. Going forward tissue-specific methylation could help determinate the origin of dd-cfDNA and thus the technology could be used in multi-organ transplantation as well. Next, Dr. Khush changed gears a bit and talked about donor-derived exosomes, which are the new kids on the block and

might be able to detect acute rejection in early promising results and might be treatment targets inhibiting their role in initiating the alloimmune response. More to come!

In the end even LeBron James could not compete with Dr. Khush, who won the “best chit-chat talk” of the session!

VIEW SESSION DETAILS

– Commentary by Luise Holzhauser, MD

SESSION 16. If at First You Don't Succeed, Try, Try Again! Heart Failure and Transplantation in Fontan Patients

The experts in this session deftly addressed the challenges posed by patients with failing hearts after single ventricle palliation for congenital heart disease. The session was chaired by **Neha Bansal, MD**, of the Children's Hospital at Montefiore in New York; **David Peng, MD**, of the University of Michigan-Ann Arbor; and Rayan Yousefzai, of the Houston Methodist Hospital.

Estela Azeka, MD, from the University of Sao Paulo in Brazil, began by describing the long-term consequences of Fontan physiology, including both systolic and diastolic compromise, dysfunction of multiple organ systems, as well as growth derangement, decreasing exercise tolerance, and electrophysiologic complications. Dysfunction of the Fontan pathway itself leads to chronic fluid overload and effusions as well as low cardiac indices, elevated pulmonary pressures, and symptomatic cyanosis. Additionally, these patients are subject to lymphatic dysfunction, which leads to both protein-losing enteropathy and plastic bronchitis. The extracardiac sequelae of this physiology also include liver dysfunction, chronic kidney disease, and hemoptysis.

Next, **Amy Kiskaddon, PharmD**, a pharmacist from Johns Hopkins All Children's Hospital, evaluated the use of conventional heart failure therapies in Fontan physiology. She described the lack of significant data in the field as well as the difficulty in evaluating these therapies, including the lack of consensus regarding which outcomes to study. In a large sample evaluating overall medication use among Fontan patients, 50% received no medications, older age was the most common factor associated with medication use, and the following classes of medications were most commonly used: ACE inhibitors or angiotensin receptor blockers (ARBs), diuretics, mineralocorticoid receptor antagonists, beta-blockers, and vasodilators. She discussed the challenges of diuretic use, as sufficient volume is required for maintaining Fontan circulation. Reports of beta-blocker use are conflicting, though data exist regarding their improvement in functional status and ventricular performance. ACE inhibitors and ARBs showed no improvement in exercise capacity, though there was suggestion of decrease in end diastolic pressure and brain-type natriuretic peptide with these therapies. Emerging data have described promising physiologic benefits of ARNIs, SLGT2 inhibitors, and ivabradine among Fontan patients, though further study is needed.

Claire Irving, MBChB, MRCPCH, MD, from the Children's Hospital Westmead in Sydney, discussed elevated pulmonary pressure in Fontan patients. She described results from the Australia/New Zealand Fontan registry, showing that most Fontan patients survive to adulthood, with mortality, however, increasing by 10% each decade. She noted that increasing pulmonary vascular resistance and central venous pressure negatively affect forward flow of the Fontan circuit and lead to liver and kidney disease as well as decrease in exercise tolerance and functional status, and, ultimately, mortality. Much attention has been given to measuring pulmonary vascular resistance (PVR) within the Fontan circuit and determining what may be the optimal PVR. Dr. Irving noted that measuring the PVR is fraught with difficulty, as the use of anesthesia with positive end expiratory pressure as well as the presence of veno-venous collaterals makes measurement difficult. Contemporary guidelines have led to the definition of elevated Fontan

pressure of > 6 mmHg or indexed PVR (PVRi) of > 3 Woods units/m2. She provided an outline of medications used to augment PVR in Fontan patients, including prostaglandin E5 inhibitors, endothelin receptor antagonists, and prostacyclin analogues. Results from recent trials describing the use of these therapies, however, have been disappointing, including the following results: the 30-center FUEL trial showing that udenalfil therapy led to no improvement in maximum aerobic capacity (VO2 Max), the RUBATO trial of macitentan also showing no improvement in VO2 Max, and the TEMPO trial of bosentan showing a small but significant improvement in VO2 Max. She discussed timing for heart transplantation in Fontan patients, which is difficult to pinpoint, requires significant effort to measure end organ function, may be prolonged with VAD therapy, and is likely earlier than we think.

Viviane Nasr, MD, MPH, FASA, an anesthesiologist from Boston Children's Hospital, was up next to discuss peri- and post- operative challenges in heart transplantation of Fontan patients, which include a high likelihood of comorbid conditions, thromboembolic events, and electrophysiologic complications. As such, it is imperative to conduct a thorough preoperative evaluation of end organ function, coagulation parameters, and vascular access. Additionally, it is important to anticipate perioperative bleeding, necessitating large bore IV access and preparation of blood products. An airway and esophageal evaluation is important, evaluating factors such as ascites and gastroesophageal varices which relate to intubation, ventilation, and transesophageal echocardiogram probe manipulation. Post-operatively, in addition to anticipating bleeding, cardiopulmonary concerns include hypotension, vasoplegia, and pulmonary hypertension, necessitating appropriate vasoactive medications and, likely, inhaled nitric oxide.

Kathleen Simpson, MD, from the University of Colorado in Denver, finished the session by addressing heart transplantation as compared to heart and liver transplantation in Fontan patients as Fontan-associated liver disease (FALD) is common, occurring in nearly 40% of Fontan patients within ten years. In addition to FALD, these patients are also at risk for hepatocellular carcinoma (HCC). To date, there is no consensus on how to monitor liver function, fibrosis, or neoplastic development post-Fontan. Even in the setting of FALD, AST/ALT may be normal, and some have proposed using MELDXI scoring. Imaging for FALD has included elastography by MRI and ultrasound, though these are not standardized and deserve more rigorous study. It remains unclear whether heart transplantation alone may allow for FALD improvement or whether such patients should have a heart-liver transplantation. Survival rates after heart-liver transplantation may exceed that of heart transplantation alone, though numbers are limited, and a UNOS analysis has shown no survival differences between the two. A quite interesting topic is whether heart-liver transplantation leads to lower risk of rejection, which has been suggested in the literature but also requires more investigation. Dr. Simpson put a call out for a common language to describe FALD as well as research describing the long-term risks of post-transplant FALD and HCC.

VIEW SESSION DETAILS

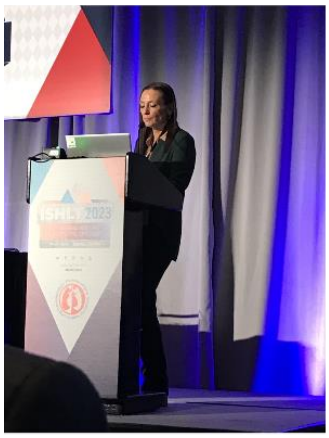
– Commentary by Jason F. Goldberg, MD, MS

SESSION 05. Shots! Shots! Shots! COVID-19 Vaccines in Heart Transplant Recipients

In this session, co-chaired by **Jonathan Hand, MD** of the Ochsner Medical Center in New Orleans and **Rebecca Kumar, MD** of Georgetown University Hospital Center in Washington, DC, there were 4 presentations on COVID-19 vaccines in heart transplant recipients.

To begin, **Daniel Rayner, BHSc** of McMaster University in Toronto presented a comprehensive living systematic review and network meta-analysis on the effect of COVID-19 vaccines in patients with solid organ transplantation. Among 5 randomized controlled trials, COVID-19 vaccines elicited antibody responses without significant adverse events. Among 21 observation studies, COVID-19 vaccination reduced the risk of infection and mortality with a dose-response relationship. However, the majority of patients from these studies were renal transplant patients. Audience questions included quantifying outcomes for waning vaccine immunity over time and the evolution of new COVID-19 variants. Stay tuned—this is a living review. Other audience suggestions included using quantiferon assay for testing COVID-19 immunity, which may become more widely available in the future.

Click here to view key slides from this presentation.



The following 3 related presentations were given by **Yael Peled, MD** of the Sheba Medical Center in Tel Aviv, Israel. Using case-control study design and live virus micro-neutralization assays, repeat COVID-19 vaccination reduced the risk of contracting COVID-19 and of hospitalizations. In addition, comparing patients with and without breakthrough infection, vaccine-induced neutralization antibody response predicted clinical COVID-19 immunity (cut-off thresholds were determined for each strain of COVID-19). Moreover, receiving the 5th dose bivalent mRNA booster vaccine led to higher neutralizing antibody titre. Audience discussion included the difference between humoral versus mucosal immunity (which was not measured in these studies). Another question was the relationship between immunogenicity and graft rejection. The speaker clarified that patients who had strong antibody responses after COVID-19 vaccination were not at higher risk of graft rejection.

Click here to view key slides from these presentations.

In summary, from this session, COVID-19 vaccination is effective at preventing COVID-19 infection and reducing the severity of infection. There is a dose-response relationship between the number of vaccine doses, antibody response, and clinical protection. But evolving COVID-19

strains and waning immunity present ongoing challenges.

VIEW SESSION DETAILS

– Commentary by Pei Jun Zhao, MD, MPH

SESSION 14: Much Ado About Nothing? Using Artification Intelligence for the Best Heart Transplantation Outcomes

In this session, moderated by **Kyung-Hee Kim, MD, PhD** of Incheon Sejong Hospital in Incheon, South Korea and **Nir Uriel, MD** of New York Presbyterian, we experienced four abstracts using an array of machine learning techniques to predict heart transplant outcomes.

First, **Nandini Nair, MD, PhD** of Texas Tech University Health Sciences Center aimed to predict the risk of post-transplant lymphoproliferative disease (PTLD) at years 1, 3 and 5, using data from the SRTR transplant registry years 1987 to 2021. The data in the abstract, entitled "***Machine Learning Ensemble Models for Predicting Post- Transplant Lymphoproliferative Disorder in Heart Transplant Recipients***," included 55,150 patients, of whom 1,742 experienced PTLD. Each case contained 84 variables, such as baseline patient characteristics, induction therapy, anti-rejection therapies, HLA type, etc. Missing values were imputed by the mean for continuous variables, or classified as unknown for categorical variables. About 65% of the data were used for training at each epoch, with 5-fold cross validation. Applying the Python Scikit-learn library, random forest with 3 boosting models (gradient boost, adaptive boost, and random under-sampling boost) were trained to maximize the area under the receiver operating characteristic curve (AUROC). In summary, the gradient boost model gave the best AUROC for predicting PTLD (0.735±0.048, 0.669±0.048, 0.649±0.027 at 1, 3, 5 years after transplantation). As for relative variable importance tested by variable permutation, Epstein-Barr virus (EBV), age, OKT3 immunosuppression, and anti-viral therapy. During the question period, the audience asked about the advantages of machine learning over traditional regression statistics. Dr. Nair shared that logistic and lasso regression resulted in lower AUROCs compared to random/boosted forest.

Next up, **Michael Killian, PhD, MSW** of Florida State University sought to predict rejection and mortality among pediatric heart transplant patients at 1, 3, and 5 years after transplant, using UNOS data from 1987 to 2019 (8201 patients), in an abstract entitled "***Predicting Health Outcomes Using Machine Learning in Pediatric Heart Transplantation Using UNOS Data***." A variety of machine learning and deep learning models were tested (XGBoost, lasso regression, support vector machine, random forest, stochastic gradient descent, multilayer perceptron, AdaBoost, and (deep) neural network). The exact structure and tuning parameters of these machine learning models were not specified. Overall, the authors found that random forest and AdaBoost (adaptive boosting) resulted in the greatest AUROC (around 0.7, as high as 0.76), while deep learning techniques (neural network, stochastic gradient descent) and support vector machine models performed poorly with AUROC hovering around 0.5. Variable importance was inferred by Shapley additive explanations. Top predictor variables shared by most models included graft function, days at status 1A, and prior cardiac surgery. In addition, the presenter commented on data quality challenges in UNOS, such as missing data and variable changes in some years. Missing data was filled in by multi-variable imputation, and highly collinear variables were removed. While the predictive ability of machine learning models was good, the audience wondered if the AUROC was high enough to use these models to make clinical decisions.

Jie Xu, PhD, of George Mason University in Fairfax, VA applied machine learning to heart transplant matching in an abstract entitled "***Explainable Machine Learning to Improve Donor-Recipient Matching at Time of Heart Transplant***." Using SRTR data (2006-2016 training set, 2017-2018 validation set) of donor and recipient clinical characteristics, supplemented by CMS master files, the group used ensemble learning with XGBoost, random forest, and elastic net models, to predict 1 year survival post-transplant. The final model had an AUROC of 0.624. Relatively important variables were prior blood transfusion, cardiac surgery, and recipient hemodynamics (cardiac output, vasoactive infusions). During the question period, Dr. Xu agreed with the audience on the need for a high-quality transplant dataset, including patient socioeconomic data.

Finally, **Rohan Goswami, MD** of the Mayo Clinic shared an abstract entitled "***Artificial Intelligence to Predict Death or Transplant in ATTR Amyloidosis Cardiomyopathy***," which used a neural network to predict death or transplant in ATTR amyloidosis cardiomyopathy for 256 patients between 1998-2020 (128 patients with ATTR, 36 death/transplant). The available variables were more extensive compared to the SRTR/UNOS dataset and included hemodynamic measurements (e.g., cardiac index), 6 minute walk distance, ejection fraction, NT-pro-BNP, etc. His team achieved an AUROC of 0.78, which was the highest in this session, despite having the least number of patients. The presenter explained that data quality and comprehensiveness were critical to the model's success. I asked Dr. Goswami for some details about the neural network's architecture (trained in SPSS). Interestingly, he said it only contained 2 hidden layers, with tanh activating functions.

In summary, for heart transplant outcomes, artificial intelligence models demonstrated higher predictive accuracy compared to traditional regression models. Still, AI models yielded promising but modest results, and is not yet ready for wide-spread clinical adoption. To advance the art of prediction, there was consensus among the speakers about the importance of high-quality data for model training.

VIEW SESSION DETAILS

– Commentary by Pei Jun Zhao, MD, MPH

SESSION 21. Cardiac Allograft Vasculopathy: From Bench to Bedside

This session focused on topics related to Cardiac Allograft Vasculopathy (CAV) development and new tools for CAV assessment. The session was co-chaired by **Sonia Mirabet Perez, MD, PhD**, from Hospital Sant Pau in Barcelona, and **Maria Dolores Cosio, MD, PhD**, from Hospital 12 Octubre in Madrid.

The first presentation with the title "***Cardiac Allograft Vasculopathy is Characterized by a Diverse and Unique Cellular Landscape***" was by **Benjamin Kopecky, MD, PhD**, from Washington University School of Medicine in Saint Louis. He presented results on a study focusing on cellular heterogeneity in explanted human hearts and a murine CAV model. Indeed, in both human and murine CAV, the authors found prominent and heterogenous populations of myeloid cells, T-cells, activated fibroblasts, and smooth muscle cells, as well as the presence of a tertiary lymphoid organ. Human hearts are either explanted at time of re-transplant or obtained at autopsy, and thus represent end-stage CAV. Consequently, the authors asked how to define the natural history and progression of CAV and how to understand when and how the identified cell populations transition into a pathological state. In a next step, they plan to investigate the functional relevance of these cell populations and putative cell-cell crosstalk in CAV development and progression using targeted genetic depletion models with the goal to identify potential targets to reduce the burden of CAV.

Next, **Marco Masetti, MD, PhD**, from Azienda Ospedaliero-Universitaria di Bologna in Bologna, Italy, presented on "***Restrictive Physiology: Playing with RHC Between CAV and AMR***." The authors showed that classifying CAV by using different hemodynamic profiles including restrictive physiology with less impaired values (RAP >8 mmHg, PCWP>15 mmHg and CI <2.5 l/min/sm) than given in the ISHLT definition could help stratify prognosis and suggested the systematic use of RHC to predict MACE and define graft function.

Sharon Chih, MBBS, from the University of Ottawa, followed, to discuss the abstract "***Cardiac Pet Flow Quantification Assessment of Early Cardiac Allograft Vasculopathy***." Seventy-four heart transplant patients underwent CAV testing via myocardial blood flow (MBF) quantification by PET as well as macrovascular CAV assessment via IVUS and microvascular CAV assessment by capillary density on myocardial biopsy at 3- and 12-months post HT. Interestingly, there was significant progression of epicardial but not microvascular CAV during the first year. There was improvement in graft MBF in the first year of transplant, but MBF at 3 months did not predict 1-year CAV progression. However, PET MBF and coronary vascular resistance at 1-year post transplant were associated with IVUS indices of CAV strengthening the data for use of PET for early non-invasive CAV surveillance.

Krishan Patel, MD, from Emory University in Atlanta presented "***Lipoprotein(a) Levels Predict Development of Cardiac Allograft Vasculopathy***." In this study, the authors identified Lp(a) levels as an independent predictor for development of angiographic CAV in a single center cohort of 149 patients. On average 10.6 years after transplant, 67.8 of patients had CAV1-3. Interestingly, each

10 mg/dL increase in Lp(a) increased the risk of developing CAV by 26%. When combined with traditional risk factors patients with Lp(a) and LDL>70 mg/dL had lower survival free from CAV. Pending further study, the authors suggested that Lp(a) could add in identifying patients in need for a more aggressive cholesterol reduction strategy.

Next, **David Couto-Mallon, MD**, from Hospital Universitario A Coruña in Spain presented the abstract entitled "***Influence of Donor Transmitted Coronary Artery Disease in Cardiac Allograft Vasculopathy: Results of the Donor Transmitted Coronary Artery Disease (DONOR-CAD) Study***." In this multicenter study, including 937 patients from 11 centers transplanted between 2008-2018, the authors showed that TCAD is present in 18% of patients and hemodynamically significant in 6.9%. Notably, CAD progression is increased 3.5 times in patients with TCAD. Donor age, TCAD, acute rejection and CMV mismatch were independent predictors of CAD progression.

Finally, **Quan Bui, MD**, from UC San Diego presented results on the study "***One Year Cardiac Allograft Vasculopathy (cav) Outcomes in Donor after Circulatory Death (dcd) Heart Transplant Recipients***." The goal of this study was to compare CAV outcomes in DCD and donor after brain death (DBD) in 165 HTx recipients. DCD recipients had lower UNOS status and less requirement of pre HTx IABP, but no difference in ECMO and inotrope use. DCD donors also had more hypertension. There was no difference in total ischemic time. Interestingly, the authors found no difference in the primary outcome of composite endpoint of death, PCI or CAV ⩾ ISHLT 2 and no difference in CAV parameters including intimal thickness and FFR at 1-year post transplant between DBD and DCD groups.

VIEW SESSION DETAILS

– Commentary by Luise Holzhauser, MD

SESSION 26. Organ Allocation Strategy: Algorithms to Implement Equity

Organ allocation algorithms have complex and deep-reaching affects on access to heart transplantation and outcomes. In this session, chaired by **Savitri Fedson, MD, MA**, of the Baylor College of Medicine in Houston and **Jacob Lavee, MD**, of the Sheba Medical Center in Tel Aviv, we will hear about disparities in heart transplantation and the quest for a more equitable allocation system that faces changing clinical practice and community needs.

First, **Daniel Johnson, BA** of the University of Chicago shared an abstract entitled "***Association of High-Priority Exceptions with Mortality Among Heart Transplant Candidates***," which analyzed the frequency of requesting exceptions to move transplant candidates up to higher priority status since the updated 2018 United States heart allocation policy. Of 125,666 candidates, 19.1% received exceptions at listing and 14.8% received exceptions after listing. In the status 1 group, 32.7% were exceptions. In the status 2 group, 40.3% were exceptions. Among candidates with exceptions, the most common was status 2 designation (41%). Moreover, controlling for status, the hazard ratio of mortality for candidates with exceptions compared to candidates without exceptions was 0.54. In conclusion, since 2018, there has been an increase in the frequency of requesting exceptions and candidates with exceptions had lower pre-transplant mortality compared to candidates whose status was based on standard criteria.

Next up, **Mohamed Hassanein, MD, PhD**, of Columbia University illustrated the geographic variation in heart transplantation for status 1 and 2 patients after the 2018 US heart allocation policy using UNOS data (2018 to 2022) in an abstract entitled "***Geographic Variation Exists in Heart Transplantation for Status One and Two Patients after the 2018 Heart Allocation Policy Change***." The median wait time for status 1 was 5 patient-days (range 3 to 6). For status 2, the wait time was 12 patient-days (range 7 to 16), with regional variation. After adjusting for covariates, the OPO region remained significantly associated with variation in transplantation and death or delisting. During the Q&A period, there was a sentiment among the audience that organ allocation policy needs to keep up with practice changes and community needs.

Christian Jacquelinet, MD, from Agence de la Biomédecine in Paris, discussed the French heart allocation system in the abstract "***Heart Transplant Allocation Policy Using an Algorithm: Putting the Pieces Together***." Candidates on the waitlist are assigned a cardiac risk index consisting of a mortality risk score, points for exceptions, donor-recipient age and size matching, graft loss risk, and gravity geographic model. Transplant priority is ranked by each candidate's index. When applied to transplant candidates from 2018 to 2020, the algorithm prioritized clinical markers while promoting equity. An audience member asked if such an algorithm, by design, has a latent risk of reinforcing current disparities. The speaker felt that, currently, the French heart allocation system is equitable.

Finally, **Roxana Moayedifar, MD**, of the Medical University of Vienna, studied the impact of the Paragonix SherpaPak organ transplant system on extended criteria organs in the GUARDIAN registry (176 SherpaPak, 132 ice storage). In the abstract "***Recipient Outcomes with Extended***

Criteria Donors: An Analysis of the Guardian Heart Registry," compared to the ice storage group, the SherpaPak cohort had greater travel distance (605 vs 356 nautical miles), less post-transplant mechanical circulatory support (20.5% vs 36.4%), and less primary graft dysfunction (6.3% vs 13.6%). The results are promising but further clinical evaluation is warranted.

VIEW SESSION DETAILS

– Commentary by Pei Jun Zhao, MD, MPH

SESSION 27. New Tools for the Kids: Diagnosis of Heart Transplant Rejection and Registries for Heart Function in Pediatrics

In this session, co-chaired by **Kevin Daly, MD**, of the Boston Children's Hospital, and **Melanie Everitt, MD**, of Children's Hospital Colorado, four abstracts will explore how blood biomarkers and molecular pathology can be used to help screen for rejection in children after heart transplantation.

First, **Carol Wittlieb-Weber, MD**, from Children's Hospital of Philadelphia discussed the creation of a prospective registry, via the ACTION network, of boys with dystropinopathy (Duchenne and Becker muscular dystrophy) and ventricular dysfunction (left ventricular ejection from ⩽ 45%), in an abstract entitled "***Taking ACTION. Creation of a Prospective Registry of Boys with Dystrophinopathy and Ventricular Dysfunction to Define Cardiac Medication Use and Optimize Guideline Directed Medical Therapy***." As Duchenne patients have had increased life expectancy from improvements in respiratory care, there has been greater study of their long-term cardiac outcomes. This is in contrast to Becker patients, who have been found to have earlier cardiomyopathy and cardiac mortality than Duchenne patients. The registry has enrolled 121 patients and collected data regarding goal directed medical therapy (GDMT) among these patients (defined as ACE inhibitor/Angiotensin Receptor Blocker/ARNI + beta-blocker + mineralocorticoid antagonist) which was found to be present in ~50%. It was also noted that ARNI and SLGT2 inhibitor use has increased over time. Dr. Wittlieb-Weber described ongoing work to address the lack of GDMT therapy among these patients, including a recent two-million-dollar grant from the Parent Project Muscular Dystrophy (PPMD) to further expand the registry and potentially improve outcomes for these patients.

Next, **Dafne Magnetta, MD**, from Lurie Children's Hospital in Chicago presented two abstracts, the first entitled "***High Sensitivity Troponin-I is Associated with Acute Rejection in Pediatric Heart Transplant Recipients***," which describes pro brain type natriuretic peptide (proBNP) and high sensitivity troponin (hsTn) use in the diagnosis of acute heart transplant rejection among a 51-patient single center sample. The data excluded samples within 60 days of transplant. It found that in the first five years post-transplant, hsTn had a steady decline, though serial proBNP levels varied. These investigators found a statistically significant association between elevated hsTn and acute rejection, with a doubling of hsTn associated with 33% increased odds of rejection. While proBNP levels were not associated with rejection, an elevated maximal proBNP was an independent predictor of graft loss.

Colin O'Halloran, MD, Dr. Magnetta's co-investigator at Lurie, shared an abstract entitled "***Utility of Molecular Microscope Diagnostic System (mmdx) in Addition to Histopathology for Rejection Surveillance in Pediatric Heart Transplantation***," which evaluated MMDx-Heart intragraft gene expression profiling along with endomyocardial biopsy (EMB) and showed only fair agreement (Cohen's kappa of 0.37 for acute cellular rejection and 0.27 for antibody-mediated rejection) between the two. Of the 115 EMBs evaluated, 21% had negative EMB for rejection but positive MMDx measure of rejection and 18% had negative EMB for rejection but positive MMDx measure

of graft injury. A meaningful part of this presentation was the commentary by Dr. Philip Halloran from the audience, one of the leading MMDx researchers, applauding Dr. O'Halloran both on his work as well as his similar last name.

Finally, Dr. Magnetta described the evaluation of acute rejection with MMDx-Heart, serum donor-derived cell free DNA (dd-cfDNA), and EMB in an abstract entitled "***Association Between Histopathology, Molecular Microscope Diagnostics, and Donor-Derived Cell- Free DNA for Rejection Surveillance in Pediatric Heart Transplantation***."

She described:

1. no significant association between dd-cfDNA elevation and acute rejection by EMB
2. multiple patients where MMDx-Heart was positive for rejection or injury but biopsy was negative, and
3. presence of injury or rejection on MMDx-heart associated with higher dd-cfDNA levels.

The receiver operating characteristic curves showed improved performance in evaluating rejection when adding both MMDx and EMB results together as compared to either alone. Her group evaluated a dd-cfDNA level of < 0.135%, which was associated with negative MMDx evaluation of rejection. This work is an important early step in increasing the use and study of these technologies among pediatric heart transplant recipients, as has been more widely evaluated in adult recipients.

VIEW SESSION DETAILS

– Commentary by Jason F. Goldberg, MD, MS

MINI ORAL 01. Scanning the (Rocky Mountain) Horizon: Biomarker Discovery and Understanding Outcomes in Heart Transplantation

This rapid-fire session featured abstracts focusing on omics approaches to marker discovery and exploring factors impacting heart transplant outcomes.

The session was co-chaired by **Katharina Wassilew, Dr med, DScmed, MHBA** from the Royal Brompton Hospital in London, and **Kentaro Noda, PhD** from the University of Pittsburgh.

The first abstract, "***Early Metabolomics Alterations in Recipient Plasma Predict the Outcome of Cardiac Transplantation***" was presented by **Richard Krebs**, a medical student from the University of Helsinki in Finland. The authors showed that targeted metabolic profiling in 83 transplant recipients within the first 24 hours after transplant may predict cardiac allograft outcomes, including hemodynamically significant rejection and mortality at 1-year.

Next, **Kishor Dhaygude, MSc, PhD**, also from the University of Helsinki, presented "***Donor Plasma Serine Levels and Its Connection to Heart Transplant Mitochondrial Dysfunction and Acute Rejection***." Serine has an important role in controlling mitochondrial metabolism, and interestingly, low donor plasma serine levels were associated with an increased risk of acute rejection—but not mortality.

We remained with the University of Helsinki when **Emil Holmstrom, MD** presented "***Inhaled Nitric Oxide is Associated with Decreased Incidence of Acute Rejections after Heart Transplantation in 5-Year Follow-Up***." iNO is routinely used to decrease pulmonary vascular resistance post heart transplantation. In this study of 84 heart transplant recipients, the authors show that iNO-recipients were sicker preoperatively—as to be expected—and had worse ischemia reperfusion injury, but less rejections and a trend to less CAV over 5-year follow up. This raises the need for further study to understand a possible long term protective effect.

Moving to sunny California, **Robert Chen, MD, MPH** from Stanford University in Palo Alto presented the next abstract "***Intracellular Cardiac Preservation Solution May Have Superior Clinical Outcomes to Extracellular Solution for Adult Heart Transplantation***," suggesting that intracellular cardiac preservation solution may be superior to extracellular cardiac preservation solution in terms of outcomes including length of stay, 1-year rejection, graft failure, and mortality especially in the setting of prolonged ischemic time > 3 hrs.

All the way from the Alps, **Alexia Clavier**, a PhD candidate from Inselspital in Bern, Switzerland presented "***Proteins Released During Ex-Vivo Perfusion are Promising Biomarkers for Cardiac Graft Quality: Studies in an Isolated Rat Heart Model of DCD***." The authors showed proteins released into the perfusate during early normothermic machine perfusion are promising for the use as biomarkers to evaluate graft quality or injury.

Next from the Mayo Clinic in Rochester, Minnesota, **Min Wang, MD** presented on "***Transcriptomic***

Profiling of Acute Cellular Rejection after Heart Transplantation," and the finding that whole blood RNA sequencing during acute cellular cardiac rejection identified significant perturbation of the cellular immune system with a gene signature that might potentially aid non-invasive rejection diagnostic. Further differentially expressed genes post rejection may indicate the response to rejection treatment and/or the possibility of chronic rejection.

Next, **Ienglam Lei, PhD** from the University of Michigan-Ann Arbor presented the abstract "***The Varied RNA Transcript Isoform Landscape During Human Donor Heart Preservation***" Authors showed that cold preserved human donor hearts undergo abundant transcript isoform level changes with reduced hypoxic response pyruvate kinase muscle isoenzyme expression. Expression of a shortened ARID5A isoform may contribute to immune activation in donor hearts and may affect occurrence of primary graft dysfunction.

Rodrigo Rubarth, MD from UC San Diego then discussed the abstract "***Early Graft Function by Hemodynamics is Similar Between Brain Death (DBD) and Circulatory Death Donors (DCD)***." Center data showed similar hemodynamic indices between DCD and DBD heart transplant recipients at 10 days post-transplant. Further, there were no significant differences in hemodynamics when comparing procurement methods (NRP vs OCS) and no differences in early graft function.

The next abstract, "***Cumulative Incidence and Risk Factors for Early Post-Transplant Lymphoproliferative Disorder in Adult Heart Transplant Recipients: Single-Centre Experience***" was presented by **Mark Peterzan, MBBS, MA, DPhil** from Harefield Hospital in London. Results showed that all patients with early PTLD (median 8 (8, 10) months post-transplant) were EBV D+R- mismatch and all had received rabbit antithymocyte globulin (RATG) induction. The authors asked if RATG induction should be avoided in mismatch recipients to reduce PTLD risk.

The session concluded with the abstract "***Clinical and Histopathological Cardiomyopathy Diagnosis Discrepancies in Heart Transplant***" presented by **Natasha Gorrie, MD** from St Vincent's Hospital in Sydney, Australia. Authors analyzed 376 HT patients from 2011-2020 at a single center and found that the frequency of clinical misdiagnosis as compared to the pathological diagnosis of the explanted heart decreased over time with the use of cardiac MRI (1 in 7 in 2020). Myocarditis and cardiac sarcoidosis were the most common missed diagnoses, underlining improvement potential using precision imaging techniques and genetic testing for other cardiomyopathies.

VIEW SESSION DETAILS

– Commentary by Luise Holzhauser, MD

MINI ORAL 04. Outcomes, Predications, and Monitoring, Oh My! In the Wonderful World of Heart Transplant

This is a rapid-fire session of nine presentations on cardiac transplant monitoring and risk prediction, co-chaired by **Omaima Ali, MD** from the Penn State Milton S. Hershey Medical Center and **Erik Henricksen, PharmD** of Stanford Healthcare.

Co-chair **Dr. Henricksen** began the session with an abstract titled "***Bye-Bye Biopsy? Comparing Short and Long-Term Outcomes after Adopting Early Non-Invasive Rejection Surveillance***," comparing donor-derived cell free DNA (ddcfDNA, CareDx AlloSure assay) surveillance versus endomyocardial biopsy (EMB) after heart transplantation. Both groups also received gene-expression profiling. There was no statistically significant difference in 3-year survival using EMB versus dd-cfDNA. Furthermore, the ddcfDNA group had a lower likelihood of experiencing acute cellular rejection >= 2R. The median number of endomyocardial biopsies in the first year after transplant was 3 in the dd-cfDNA group compared to 10 in the EMB group.

Next, **Kevin Clerkin, MD, MSc** of Columbia University Irving Medical Center in New York shared an abstract entitled "***Isolated Microvascular Cardiac Allograft Vasculopathy is Associated with an Increased Risk of Death or Retransplantation***," finding that isolated microvascular cardiac allograft vasculopathy, defined as myocardial blood flow reserve <= 2 by PET or angiography, increased the risk of death or retransplantation by a hazard ratio of 1.8 after adjusting for other clinical risk factors.

Samuel Kim, BA, of the University of California in Los Angeles, looked at postoperative renal failure after heart transplantation using UNOS data years 2018-2022 (10,545 patients of whom 14% experienced renal failure) in an abstract entitled "***Postoperative Renal Failure in Patients Undergoing Isolated Heart Transplantation: What are the Outcomes?***" Following heart transplantation, patients with renal failure, compared to patients without renal failure, experienced higher rates of primary graft dysfunction (5% vs 1%), 30-day mortality (12% vs 1%), 1-year survival (70% vs 95%), and 3-year survival (58% vs 80%).

Next, **William Marshall, MD**, of the Ohio State University, showed that donor-recipient age difference affected cardiac graft survival in patients with adult congenital heart disease in his presentation of the abstract "***The Impact of Donor-Recipient Age Difference on Graft Survival after Heart Transplant in Adults with Congenital Heart Disease***." Using UNOS data years 2000-2020 (1237 ACHD patients), donor-recipient age difference was divided into older donor (donor > 10 years older than recipient), equal age donor (within 10 years), and younger donor (donor > 10 years younger than recipient). Recipients who had an older donor, compared to recipients with equal age or younger donors, had lower 10 year survival (adjusted HR 1.39).

Joyce Zhou, MD, from Massachusetts General Hospital, presented "***Early Renal Outcomes Following Cardiac Transplantation Using Organs Procured after Circulatory Death***." The abstract compared DCD versus organs after brain death (DBD). Although DCD recipients compared to DBD recipients had

higher right ventricular pressures 1 week post-operatively (10 vs 8 mmHg), there was no significant difference in eGFR, acute kidney injury, and continuous veno-venous hemofiltration use.

Next, **Daniel Oren, MD, MSc** from Columbia University found that heart transplant recipients with microvascular cardiac allograft vasculopathy (defined as myocardial blood flow reserve < 2 on PET scan) had higher levels of dd-cfDNA (CareDx AlloSure) compared to patients without microvascular CAV (0.21% vs 0.11%). Most patients in the study, entitled "***Donor-Derived Cell-Free DNA in Heart Transplant Recipients with Microvascular Cardiac Allograft Vasculopathy***," were about 5 to 10 years after heart transplantation.

Jiho Han, MD of the University of Chicago tested the association of dd-cfDNA and antibody mediated rejection (AMR) in heart transplant recipients in the Surveillance HeartCare Outcomes Registry (942 patients), via the study "***Association of Early Testing of Donor Derived Cell-Free DNA with the Risk of Antibody Mediated Rejection in Heart Transplant Recipients***." Patients who developed AMR in months 4-12 had higher dd-cfDNA levels in the first 3 months post-transplant than those that did not develop AMR. But dd-cfDNA levels were not associated with acute cellular rejection, de novo DSA, CAV, or graft dysfunction within the first 4-12 months after heart transplantation.

Diego Rangel Sousa, MD, of Virgen del Rocío University Hospital in Spain, presented the study "***Elevated Lipoprotein A Levels and Development of Moderate or Severe Cardiac Allograft Vasculopathy***," which found that heart transplant recipients whose lipoprotein (a) Lp(a) was > 30 mg/dl were associated with increased risk of ISHLT grade 2-3 cardiac allograft vasculopathy. Median follow up was 84 months. 15 of 140 patients developed CAV 2-3.

Finally, **Gabriel Sayer, MD** of Columbia University compared the amount of concordance between CareDx AlloSure and Natera Prospera ddcfDNA assays in the study "***Comparison of Two Commercially Available Donor-Derived Cell-Free DNA Assays for Surveillance of Rejection in Heart Transplant Recipients***." 139 patients within 28 days of heart transplant had both ddcfDNA assays drawn within 48 hours of each other. AlloSure and Prospera showed strong correlation (r2 = 0.81). Using the pre-specified positive cutoff values of 0.12% for AlloSure and 0.15% for Prospera, 9% of paired samples had discordant results.

VIEW SESSION DETAILS

– Commentary by Pei Jun Zhao, MD, MPH

FEATURED ABSTRACT 03 at General Session II. Heart Transplantation Outcomes in Patients from Socioeconomically Distressed Communities

Presenter: ***Quidong Chen, MD****, Cedars-Sinai Medical Center, Los Angeles, CA USA*

On the second day of ISHLT2023, an enthusiastic audience sat in the Four Seasons Ballroom to hear the morning General Session. Around the sides of the room, people who did not have seats stood quietly, watching the stage intently. After inspiring keynote speeches by **Ala Stanford, MD, FACS, FAAP** (U.S. Dept of Health and Human Services) and **Caroline Patterson, BMBS, BMedSci, MD**(Royal Papworth Hospital) on promoting health equity for patients with advanced heart and lung diseases, Dr. Chen stepped onto the podium to present an abstract on heart transplantation outcomes in patients from socioeconomically distressed communities.

Using the distressed community index (DCI) at the zip-code level, the study illustrated the diverse socioeconomic backgrounds of heart transplant recipients in the Scientific Registry of Transplant Patients (SRTR) from the years 2005 to 2020. The DCI combines multiple social determinants of health—education level, poverty, unemployment, housing vacancies, median income, and business growth—into a number between 0 (no distress) and 100 (severe distress). For simplicity, the DCI was dichotomized to Distressed (DCI > 80) and others.

Patients from distressed communities were more likely to be non-White, be less educated, have public insurance, be diabetic, and require pre-transplant ventricular assist devices. They lived further away from their transplant center and received transplants at lower-volume centers. After transplant, they were more likely to experience acute rejection before hospital discharge, have more readmissions within 1 year, and have lower 5-year survival. Finally, as a continuous variable in a multivariable Cox model, the DCI was associated with risk of 5-year mortality.

A crescendo of applause erupted from the audience then faded into questions for the speaker. First, the distressed community index combines multiple socioeconomic components. So which components of the DCI are driving the disparity? Second, seeing geographic differences in heart transplant care and outcomes, what are solutions for improving health equity among heart transplant recipients? These questions echoed in the Four Seasons Ballroom and into the mind of the ISHLT community as we strive to improve transplant access and outcomes in our communities and around the world.

VIEW FULL ABSTRACT

– Commentary by Pei Jun Zhao, MD, MPH

KEYNOTE PRESENTATIONS at General Session II. Health Equity and Advanced Heart and Lung Disease in the US and the UK

Presenter: ***Ala Stanford, MD, FACS, FAAP****, U.S. Dept. of Health and Human Services, Philadelphia, PA USA*
Presenter: ***Caroline Patterson, BMBS, BMedSci, MD****, Royal Papworth Hospital, Cambridge, UK*

We had the great pleasure of listening to **Ala Stanford, MD, FACS, FAAP**, as she described the United States experience of health equity through her own fascinating journey from a pediatric surgeon to a Presidential Appointee for the U.S. Department of Health & Human Services. Dr. Stanford described the impact of the COVID-19 pandemic on predominantly African American neighborhoods in Philadelphia, where the access to centers for testing and vaccination was most limited. Dr. Stanford and the Black Doctors COVID-19 Consortium vaccinated nearly 4,000 Philadelphians at a walk-up clinic over the course of one weekend, 61% of whom were African American. Her team's efforts put Philadelphia at the highest share of vaccinated African Americans residents in cities with large Black populations. She continued to talk about health equity, explaining that this doesn't refer to a situation where everyone has a bike, but rather a size-appropriate bike that allows them to achieve an equitable speed.

Dr. Stanford discussed social determinants of health, and delineated how wealth is linked to home ownership, home ownership is linked to education, education is linked to health outcomes, and how health outcomes remain exacerbated by racial injustice. In 2021, the "Evaluation of Racial and Ethnic Disparities in Cardiac Transplantation" paper was published in *JAHA*, and discussed the impact on Black and Hispanic transplant patients, showing that Black and Hispanic patients were younger, more likely to be women, and have diabetes mellitus or renal disease. During the study period, the proportion of Black and Hispanic patients listed for transplant increased, but Black patients were less likely to undergo transplantation—even with the new allocation system—and had a higher risk of post-transplant death. The authors conclude that the new heart allocation system has increased rates of transplantation and decreased waitlist times for each race and ethnicity, but that Black patients are still less likely than white patients to undergo transplantation.

As a new strategy model in organ allocation, Dr. Stanford described the changes to the lung transplant distribution policy towards a Composite Allocation Score (CAS) in effect since 9 March of this year, including a CAS that combines a weighted priority for several attributes that reflect the candidate's need for a transplant and how well a candidate matches each individual organ offer.

While access to transplantation affects a small number of the population, minority health determines the health of the nation. By 2050, people of color are projected to make up over half of the United States by Census Bureau Data and it is of critical importance that we follow the 5 steps towards health equity: Acknowledge, **B**elieve, **I**dentify, **A**ct, **S**hare, standing for "**Acknowledge BIAS**."

After Dr. Stanford's presentation, **Caroline Patterson, BMBS, BMedSci, MD**, from Royal Papworth Hospital in Cambridge, presented impressive data on the United Kingdom's experience of health equity. The Universal Health Coverage (UHC) system in the UK is defined as follows: All individuals and communities receive the health services they need without discrimination and without financial hardship. The thinking is that countries that progress towards UHC will make progress towards other health related targets; therefore, most EU countries also follow this model. However, general socioeconomic, cultural, and environmental conditions, as well as social and community networks and individual lifestyle factors, have a great impact on parameters of health as depicted by the Dahlgren-Whitehead "Rainbow Model." Thus, healthy life expectancy greatly varies between communities in the UK.

Dr. Patterson pointed out that people in the most deprived areas spend a third of their lifetime in poor health. She presented a study showing that a higher level of deprivation is associated with shorter survival times after heart transplantation in England. The median overall survival and the conditional survival were 3.4 years shorter in the most vs least deprived areas ("Socioeconomic Deprivation and Survival after Heart Transplantation in England. *Circulation. Cardiovascular Outcomes 2016*"). Citing a second manuscript, she discussed how access to UHC alone does not mitigate the impact of socioeconomic status, and shared what the transplant community can learn from New Zealand's experience, where socioeconomic disparity is not linked to outcomes following heart transplantation ("Socioeconomic disparity is not linked to outcomes following heart transplantation in New Zealand. *Heart Lung Circ. 2020*").

To address health inequity in transplantation, the European Society for Organ Transplantation (ESOT) puts a focus on access to treatment, education, and awareness in organ transplantation by launching data-driven patient registries, working closely with patient associates, and developing health care professional communication guides. Dr. Patterson closed with a quote from the Kings Fund think tank: "*Despite universal healthcare, people in the UK (and elsewhere) experience systematic, unfair and avoidable differences in the health care they receive, and the opportunities they have to lead healthy lives, based on factors outside their direct control*."

We as the transplant community have a long way to go to address these disparities and overcoming them must be of utmost priority.

VIEW SESSION DETAILS

– Commentary by Luise Holzhauser, MD

SESSION 30. Exploring the Limits in Heart Transplantation in Children and Adults

This lively Pecha Kucha session exploring strategies for successfully transplanting "high risk," "un-transplantable," or "highly unlikely" children and adult candidates, and was co-chaired by **Manuela Camino Lopez, MD**, from Hospital Gregorio Marañon in Madrid, and **Kelly Schlendorf, MD**, from Vanderbilt University Medical Center in Nashville.

The session began with a discussion from **Neha Bansal, MD**, of the Children's Hospital at Montefiore in New York, regarding transplanting patients with a history of cancer. Such transplants continue to increase, along with increased rates of five-year survival from childhood cancer, which approaches 85%. Clinicians continue to struggle with the optimal cancer-free time interval after which it is "acceptable" for a childhood cancer survivor to undergo heart transplantation, which may depend on tumor type and has varied between 2 and 5 years, depending upon center-specific practice. Multiple anti-neoplastic agents can lead to cardiomyopathy, with anthracyclines and chest radiation being the most widely cited. In a Pediatric Heart Transplant Society (PHTS) evaluation of heart transplantation after anthracycline cardiomyopathy (ACM), survival did not differ from other causes of dilated cardiomyopathy but those with ACM had higher infection rates.

When evaluating specific tumor types, survivors of hematologic malignancies appear to have worse post-transplant survival than those of solid tumors. Additionally, all heart transplant recipients (regardless of pre-transplant cancer) are at risk for malignancy, with the most common neoplasms being EBV-related tumors (i.e., post-transplant lymphoproliferative related disorders) and skin malignancies.

Jong-Chan Youn, MD, PhD, from Seoul St. Mary's Hospital at the Catholic University of Korea, presented the challenges regarding weight loss for obese heart transplant candidates. Multiple studies have shown that these recipients encounter increased risk of post-transplant adverse events, such as myocardial infarction, chronic rejection, infection, and renal failure; however, rates of acute rejection, bleeding, and stroke do not appear to be increased in these recipients. Specifically related to pediatric recipients, a PHTS study showed that children who are obese at the time of transplant are at increased risk of graft loss. There has been much discussion about the appropriate body mass index (BMI) "cut-off" at which to preclude transplantation. Dr. Youn presented data suggesting that a cutoff of 35 may be appropriate, as these recipients have higher morbidity, mortality, and wait-time than those of BMI between 30 and 35. In evaluation of such patients for heart transplantation, a left ventricular assist device (LVAD) is often considered, including the consideration of bariatric surgery subsequent to LVAD placement. With the combination of these two therapies, well-supported patients have been shown to be successful in weight loss, transplantation, and/or myocardial recovery.

Next, **Kevin Daly, MD**, from Boston Children's Hospital presented an overview of transplanting in the setting of sensitization with high levels of antibodies to human leukocyte antigens (HLA-Abs).

Pre-transplant sensitization is increasing over time and is associated with decreased post-transplant survival, especially in the setting of post-transplant donor-specific antibody (DSA) development or positive crossmatch at the time of transplant. While many hospitals have developed desensitization strategies to decrease pre-transplant sensitization, it's not always possible to wait for the disappearance of HLA-Abs. This had led to the development of treatment protocols for transplanting against a positive crossmatch. Results of these strategies have shown favorable outcomes, including similar levels of post-transplant mortality between sensitized and non-sensitized patients; however, there are increased levels of rejection among sensitized patients. Dr. Daly presented therapies aimed at decreasing both pre- and post-transplant antibodies, including rituximab, intravenous immune globulin (IVIg), bortezomib, eculizumab, and, more recently, daratumumab. Overall, Dr. Daly led an important discussion regarding this difficult patient population, which is the subject of much research in both the pediatric and adult transplant communities.

Amanda Vest, MBBS, MPH, next discussed re-transplantation, especially after a pediatric patient has transitioned to adult care. She discussed indications for re-transplantation including, most commonly, coronary artery vasculopathy, followed by allograft dysfunction (either systolic or diastolic). Antibody-mediated rejection (AMR) is the least frequent indication for re-transplantation and is the most challenging, as it is difficult to find a matched donor in this setting. Dr. Vest discussed the important non-cardiac comorbidities that re-transplant candidates face, including chronic kidney disease, diabetes, osteoporosis, and psychosocial instability. The data show that re-transplantation outcomes are poorer than those of primary transplant, with one-year survival ranging from 54% for those transplanted for allograft dysfunction to 75% for those transplanted for coronary artery vasculopathy. It is important for adolescents approaching re-transplantation to have a favorable transition into adult congenital care. Dr. Vest discussed strategies for this, including a parallel visit with the pediatric and adult programs, avoiding making medication changes on the first adult visit, and setting appropriate expectations for the adult catheterization laboratory experience.

Finally, **Simon Urschel, MD**, from the University of Alberta, presented the historic experience of transplanting across the ABO barrier as well as a call for expansion of this practice. He described the pioneer efforts in this field led by Dr. Lori West in Edmonton in the late 1990s and early 2000s, which helped to rapidly expand ABO incompatible transplants to become the standard of care for children two years of age and younger. Long-term follow-up of these patients shows significant success, including less long-term sensitization of these patients compared to ABO compatible cohorts. In Canada and the United Kingdom, ABO incompatible transplants are performed up to approximately 9 years of age, which was led to decreased wait times, especially for candidates of blood group O. Dr. Urschel described work from Edmonton of more comprehensively typing blood group antibodies, which may continue to push the age limit of ABO incompatible transplants, allowing for shorter wait times and less waitlist mortality, especially for highly sensitized patients. His discussion is quite timely, as it comes off the heels of a recent unanimous UNOS vote among pediatric heart transplant physicians supporting the expansion of

ABO incompatible transplants for patients 18 years of age and younger.

VIEW SESSION DETAILS

– Commentary by Jason Goldberg, MD, MS

SESSION 44. Mountain for Every Miracle! Field of Cardio-Oncology: The High-Yield Tips

The symposium was co-chaired by **Maria Generosa Crespo-Leiro, MD**, from Hospital Universitario A Coruña, in Spain, and **Richard Cheng, MD, MSc**, from the University of Washington Medical Center in Seattle.

In the opening talk, "**Broken Hearts – LVAD or Heart Transplant in Patients With Recent Cancer: Who and When?**" **Bhavadharini Ramu, MD**, of the Medical University of South Carolina, showed LVAD complication rates in cancer and non-cancer patients. Comparable rates included VAD thrombosis, stroke, and infections; but there were lower rates of GI bleeding in cancer patients, possibly related to alterations of anti-platelet regimens. Interestingly, patients who underwent rescue LVAD and had subsequent recovery in the setting of acute Adriamycin-induced cardiomyopathy (ACM) had less severe myocardial fibrosis than those who did not.

Dr. Ramu then discussed how LVAD is a viable option for patients with malignancies as a bridge to transplant candidacy. Once transplanted patients with ACM tended to be younger, were more likely female, and had fewer co-morbidities but a higher PVR. These patients were less likely to be bridged to transplant with LVAD as compared to ICM and DCM. Dr. Ramu speculated that the less frequent LVAD use might have been related to more frequent RV involvement in ACM. Notably, there was no difference in 5-year survival between ACM, ICM, and DCM groups, and ACM was not associated with increased post-transplant malignancies (Ramu B, et al. *JACC Cardio-Onc 2021*).

In general, Dr. Ramu said that when to transplant after malignancy is a challenging question. She discussed organ failure factors, cancer factors, patient factors, and immunosuppression factors, which require a case-by-case discussion. To guide decision-making, the AST has published a consensus expert opinion statement. This paper provides guidance by providing 5-year cancer specific survival rates and suggested time interval to transplant (*Pretransplant solid organ malignancy and organ transplant candidacy AJT 2021*). Dr. Ramu concluded that cancer survivors account for a small percentage of LVAD and HT recipients, and VAD is a reasonable option with similar survival but increased RV failure and major bleeding. HT also is a valuable option with notably similar survival. In a final statement, she pointed out the need for further study of this specific patient population in a multidisciplinary approach.

Next, **Yael Peled, MD**, of Sheba Medical Center in Tel Aviv gave the talk "**Double Jeopardy: Managing Risk in Heart Transplant and MCS Patients With a History of Malignancy**." She started out with the quote "Things are not always as they seem." An important consideration for management of patients with a cancer history is that the risk of recurrence varies but overall, a history of pretransplant malignancy can increase post-transplant cancer risk. Thus, cancer prevention and early detection is of utmost importance for these high-risk patients. Novel technologies such as AI models to predict future lung cancer risk from a single CT-chest are promising. Liquid and synthetic biopsies assessing circulating tumor DNA can detect cancer non-

invasively and monitor response to treatment. Lastly, precision oncology profiles the DNA of cancer cells looking for specific mutations driving the tumor growth and delivers a personalized therapy.

De-novo malignancies post-transplant are an important contributor to morbidity and mortality and remain an unsolved challenge for the field with >10% of HT recipients affected between 5-10 years post-transplant, said Dr. Peled. Cancer risk factors specific to transplant include immunosuppression, oncoviruses, male gender, re-transplantation, and prior malignancy in addition to general population risk factors. Lastly, she provided a great transition to the upcoming debate with the conclusion that specific implications of immunotherapy for the HT transplant populations are yet to be characterized.

Daniel Zlotoff, MD, PhD, of Massachusetts General Hospital in Boston continued the session by presenting the Pro side of the debate on "**New Kids on the Block! Immunotherapy Can Be Employed in Heart Transplant Recipients With Cancer**." Dr. Zlotoff started with a discussion of immune checkpoint inhibitor (ICI) adverse events, including myocarditis, which occurs as a direct consequence of the ICI mechanism of action "taking the break off of T-cells." He provided a preview to his opponents' presentation and reviewed transplant specific limitations of ICI, which include reduced effectiveness of ICI given immunosuppression, and the fact that ICI might provoke rejection by disrupting the mechanism of peripheral immune tolerance.

Then, he provided answers to three key questions: 1) **How large are the oncologic benefits of immunotherapy?** His response was that transplant recipients have a 3x higher malignancy rate and higher associated mortality and thus these patients have more to gain from effective therapy. In general, 37% of SOT recipients had partial or complete response to ICI and 36-39% of all patients are eligible for ICI therapy. 2) **How high is the rejection risk with ICI?** Very high! Rejection occurred in 7 patients of 17 published case reports, which led to question 3) **Can rejection risk be minimized?** Dr. Zlotoff hypothesized that close rejection surveillance could mitigate the substantial risk. Further avoidance of dual checkpoint inhibitor blockade and cessation of ICI therapy once myocarditis or rejection occurs. Lastly, new treatment protocols for ICI myocarditis have improved outcomes and might be used for rejection treatment.

Dr. Zlotoff was optimistic to win the debate, but handed over to the **Con presentation** by co-chair **Maria Generosa Crespo-Leiro, MD**. She also asked three very pertinent questions. 1) **Have ICI proven to be safe in HT patients with cancer?** 2) **Have ICI been proven to be effective in HT patients with cancer?** and 3) **Should ICI be used in HT patients with cancer?**

To answer, Dr. Crespo-Leiro reiterated the substantially increased rejection risk by disruption of tolerance and discussed the risk of fatal ICI myocarditis. HT recipients with cancer have been excluded from clinical trials, but the ICI Thoracic Transplant Registry from the University of Utah provides concerning insight in 4 HT patients. Three out of 4 HT patients developed severe side effects including rejection, graft dysfunction, and death from cardiogenic shock or cancer. In addition to this grim picture, she brought yet another side effect to the table! Turns out ICI also cause accelerated plaque progression in atherosclerosis. In the end, she had the same answer to

all her questions: Probably not.

It remains, however, unknown if Dr. Zlotoff was convinced by her argument.

VIEW SESSION DETAILS

– Commentary by Luise Holzhauser, MD

SESSION 34. Balancing the Scales: Healthcare Disparities in Heart Transplantation

This session, co-chaired by **Larry Allen, MD, MHS**, of the University of Colorado and **Johanna Contreras, MD, MSC**, of Mount Sinai Hospital in New York, continues a theme of the earlier General Session, highlighting healthcare disparities in heart transplantation.

The first presentation, by **Sumanth Kidambi, MD**, of Stanford University Medical Center, analyzed racial disparities in pediatric heart transplantation in the United Network for Organ Sharing (UNOS) database from 1994 to 2019 (8,258 patients). Recipients identifying as Black or other non-white races experienced higher risk of 5-year graft failure by Kaplan-Meirs analysis. The audience asked about exploring underlying reasons for the observed racial disparity.

Next, **David Rekhtman, BS**, from the Perelman School of Medicine at the University of Pennsylvania in Philadelphia, studied racial differences in heart transplant waitlist outcome for patients on temporary mechanical circulatory support (ECMO, intra-aortic balloon pump, or temporary LVAD) using UNOS 2015-2021 data (9,736 patients, 5.8% on ECMO, 25% on IABP, and 11% on tLVAD). The era was divided into before and after the 2018 OPTN organ allocation policy change. Since 2018, for patients on temporary MCS, the incidence of dying on the waitlist was higher in the white population, while delisting due to sickness was higher in the non-white population. Audience members asked if patients who are delisted also had high mortality. The speaker answered that outcomes after delisting are not tracked by the UNOS database. Another audience member suggested cluster analysis to explore center effect in case of heterogeneous practice.

The third presentation, by **Catherine Kelty, PhD**, of Spectrum Health in Grand Rapids, assessed the impact of the 2018 OPTN organ allocation policy on the relationship between heart transplant allocation by zip code and median household income. In the UNOS database, patients from 2014 to Oct 2018 (old allocation system) were compared to patients from Oct 2018 to 2022 (new allocation system). Median household income was divided into tertiles of low, medium, and high. In both the old and new allocation systems, the incidence of transplant was higher in the high-income group. Under the new allocation system, the low-income group had a higher 1-year incidence of death or delisting (low 7.4%, middle 6%, high 5.4%). During the Q&A, audience members asked about confounding by the COVID-19 pandemic, variation in income within ZIP code regions, and hypothesized if patients from high income communities were listed higher or more likely to receive exceptions for higher status.

To close out the session, **Heidi Kim, PhD**, of the University of Texas Southwestern Medical Center in Dallas, used the Child Opportunity Index (COI) to compare outcomes after listing pediatric patients for heart transplant. The COI combines educational, health/environmental, and socioeconomic domains at the census tract level. 5,723 patients in UNOS years 2012-2020 were included. Patients from low COI neighborhoods had poorer survival from the time of listing (hazard ratio 1.21) and poorer survival after transplant (hazard ratio 1.22). Questions included changes in COI with time or if the patient moved to another neighborhood. Another audience

member felt that many socioeconomic factors are beyond healthcare's control, but present a need for advocacy.

VIEW SESSION DETAILS

– Commentary by Pei Jun Zhao, MD, MPH

SESSION 42. Current Challenges in Pediatric Heart Transplant Selection and Outcomes

This oral session was co-chaired by **Estela Azeka, MD**, of the University of São Paulo in Brazil, and **Simon Urschel, MD**, of the University of Alberta in Canada, and reviewed state-of-the-art science regarding selection of pediatric candidates for heart transplant and heart-kidney transplant.

To kick things off, **Jason Greenberg, MD**, of Cincinnati Children's Hospital, questioned the practice of obesity being a contraindication to pediatric heart transplantation in the abstract "***Obesity Should No Longer Be a Contraindication to Pediatric Heart Transplantation***." While adult ISHLT guidelines recommend body mass index (BMI) < 35, the "cut-off" for pediatric transplant is less clear. This research group queried the UNOS database from 2000 to 2022, evaluating nearly 8,000 pediatric heart transplants, 15% of which included recipients greater than the 95th percentile of BMI (the pediatric definition of obesity). They found obese patients were more likely to be male and non-white, have renal dysfunction, and inotrope and VAD use, as well as be less likely to have congenital heart disease. Obese patients had inferior post-transplant survival compared to non-obese patients in this unmatched sample. These researchers next performed propensity score matching between obese and non-obese patients for comorbidities and socioeconomic status. After matching, there was no mortality difference between obese and non-obese patients, prompting a provocative discussion of how to approach listing such patients evaluated for heart transplantation.

Bahaaldin Alsoufi, MD, from the University of Louisville, next evaluated heart transplant outcomes for patients previously palliated for hypoplastic left heart syndrome in "***Outcomes of Heart Transplantation in Children with Previously Palliated Hypoplastic Left Heart Syndrome***." This analysis required the difficult task of merging the PHIS and UNOS databases to provide both granular surgical data as well as comprehensive post-transplant outcomes. This research group found that patients transplanted in infancy were more likely to have significant clinical complications pre transplant, including ECMO, VAD, and inotrope use. They found that one-year survival ranged from 67-72%, with the majority of these deaths being perioperative. At 5 years post-transplant, > 70% of these patients remained alive, and at 10 years > 67% of these patients remained alive. On multivariable analysis, the only factor associated with decreased post-transplant survival was non-white race. Pre-operative ventilation, ECMO/MCS support, creatinine, or bilirubin were not significant predictors of survival. Overall survival was not significantly different for those patients transplanted earlier vs. later in childhood, but younger recipients have less rejection episodes over time.

Mohammed Absi from the University of Tennessee next presented outcomes from a single-center analysis of donor hearts transported with the SherpaPak™ cold storage preservation system compared to those transplanted with a traditional ice method. In the abstract, entitled "***Donor Heart Preservation Strategy Using a Cold Storage System for Pediatric Heart Transplantation***," SherpaPak™ data showed the ability to stabilize donor heart temperature between 4 and 8

degrees Celsius, which is favorable given previous reports of hearts preserved with traditional ice methods over-cooling below 2 degrees Celsius and encountering subsequent early graft injury. In 55 procurements, neither ischemic time nor primary graft dysfunction differed between the two groups. There was a significantly higher inotrope score and post-transplant pulmonary capillary wedge pressure for SherpaPak™ recipients, though one-year survival did not differ between groups. This year's ISHLT meeting included multiple reports of cold-storage systems, with evidence of decreased primary graft dysfunction and length of stay related to SherpaPakTM use in adult heart transplant recipients. There is certainly much more to learn about this technology in pediatric heart transplantation.

Next, **Swati Choudhry, MD**, from Texas Children's Hospital in Houston, presented results of heart-kidney transplantation vs. heart transplantation alone from the SRTR database in an abstract entitled "***Combined Heart Kidney Transplant: Risk Factors and Outcomes***." She showed the steady increase of heart-kidney transplants in the past decade and described the difficulty in determining whether heart transplant candidates with renal insufficiency should have heart-kidney or heart transplantation. In the retrospective review, heart-kidney recipients were older, more likely to be African American, and have pre-transplant hypertension or diabetes, but sensitization was similar between the two groups. Risk factors associated with reduced one-year survival after heart-kidney transplant included recipient age ⩾12 years, African American race, diabetes mellitus, and chronic dialysis at the time of transplantation. Using these factors, this research group assigned pre-transplant risk scores to each patient. They found that low risk patients with eGFR < 35 ml/min/1.73 m^2 undergoing heart-kidney transplant had significantly better one-year survival compared with those undergoing heart transplant alone with similar risk score and eGFR. There was no survival advantage for combined heart-kidney transplant over heart transplant alone in patients with high-risk scoring. These data may be helpful in evaluating whether patients with both cardiac and renal dysfunction should undergo heart alone or heart-kidney transplantation.

Next, **Lydia Wright, MD, MSc**, from Nationwide Children's Hospital in Columbus, shared an abstract entitled "***DQ Matching in Pediatric Heart Transplantation***." In this abstract, she evaluated the effects of matching patients at the DQ human leukocyte antigen locus, as mismatch at this locus has been associated with significant levels of post-transplant donor-specific antibodies as well as higher rates of graft dysfunction and mortality among adult heart transplant recipients. Since DQ mismatch is common among Black transplant recipients, this factor may be a significant mediator of the disparate post-transplant outcomes among these recipients. A retrospective UNOS evaluation was evaluated and found 38% of patients with DQ mismatch at 1 locus and 51% with DQ mismatch at both loci. Rejection-free survival was higher for children with 0 DQ mismatches compared to those with 1 mismatch or 2 mismatches. This survival advantage was most pronounced in female and Black recipients. In multivariable analysis controlling for clinical risk factors and non-DQ mismatch level, 0 DQ mismatches remained significantly associated with improved rejection-free graft survival compared to 2 mismatches. These results may lead to changes in clinical practice, especially where high-resolution donor HLA typing is able to more compatibly match donors and recipients.

Lastly, **Deipanjan Nanji, MD**, also from Nationwide Children's Hospital, performed a linkage of the

PHTS and PHIS databases to evaluate the effects of pre-transplant HLA desensitization therapies in "***Impact of Anti-HLA Antibody Desensitization Strategies in Pediatric Heart Transplant Recipients: A PHTS-PHIS Linkage Analysis***." Among 3,229 recipients, 10.8% of those with panel reactive antibody percentage (%PRA) > 10% underwent desensitization therapy. Those with higher PRA did have worse survival than those with lower PRA. However, desensitization therapies did not significantly alter %PRA or affect graft survival when comparing sensitized patients who did and did not receive these therapies. The median pharmacy charges for these therapies were nearly 10 thousand dollars, with a range of 4-28 thousand dollars. Dr. Nanji concluded that careful consideration and more research are needed regarding desensitization for sensitized pediatric heart transplant patients.

VIEW SESSION DETAILS

– Commentary by Jason Goldberg, MD, MS

SESSION 58. For All Ages: MCS Support in Congenital Heart Disease in Children and Adults

This session included international experts who have led the field in mechanical circulatory support (MCS) for congenital heart disease patients (CHD), and was co-chaired by **David Morales, MD**, of Cincinnati Children's Hospital and **Nathalie Roy, MD**, of Boston Children's Hospital. All presenters highlighted the complicated and individualized anatomical considerations, multiple comorbidities, anticoagulation issues, and previous surgical corrections that make this practice quite challenging.

Antonio Amodeo, MD, from Ospedale Pediatrico Bambino Gesù in Rome, discussed the use of extracorporeal membrane oxygenation (ECMO) for acute decompensated heart failure (ADHF) in CHD patients. He highlighted data showing that CHD-related complication is the most common cause of ADHF for children, and that it represents a significant burden of risk when compared to other ECMO recipients. As data continue to be accumulated on such patients, there is evidence that survival has improved over the past two years, approaching 40-50%. Data also show improvement in morbidity and quality of life after therapy. Considerations for ECMO use in CHD include the likely need for higher ECMO flow among palliated single ventricle patients. In the setting of Glenn and Fontan patients with elevated pulmonary vascular resistance, an additional inflow cannula placed via the internal jugular vein may be required.

Sebsastian Tume, MD, from Texas Children's Hospital in Houston, next discussed temporary MCS strategies for these patients. The main challenge of these patients is their small size as well as difficult anatomical considerations, which have required innovative strategies for devices such as Impella, Rotaflow, and Tandem heart. Evidence of end-organ dysfunction, however, should prompt consideration of these therapies. Many of these patients may already be on ECMO support, and these short-term MCS strategies may improve survival beyond what is possible with ECMO. These therapies may serve as a bridge to recovery, transplant, or to a more durable ventricular assist device (VAD). While data in these practices are lacking, Dr. Tume showed the Texas Children's experience with percutaneous VAD (Impella) as well as other small sample results, with survival to discharge approximately 50-70%.

Next, **Jennifer Conway, MD**, from the University of Alberta, discussed selection criteria for durable devices in CHD patients, describing CHD associated with 71% odds of dying or delisting within one year of transplant listing, which opens the possibility of benefit from VAD therapy. She reviewed a 2019 JHLT publication describing the Pedimacs data regarding these patients, showing a nearly even distribution of device selection between paracorporeal continuous, paracorporeal pulsatile, and intracorporeal devices. Congenital heart disease patients had significantly higher mortality post-VAD compared to non-CHD patients; however, survival was similar between these two groups six months after receiving intracorporeal devices. It is important to identify which patients may need these therapies before the development of ADHF, as single ventricle patients after stage 1 single ventricle palliation, for example, have improved outcomes with planned device placement as compared to "rescue" device placement. It is important for CHD practitioners to involve heart failure and MCS colleagues in caring for CHD

patients with suboptimal physiology, given the opportunity to examine these rapidly expanding MCS indications and placement strategies.

David Peng, MD, from the University of Michigan, next presented pre-implant considerations for Fontan patients. He described the approximately 70,000 patients alive with Fontan who have an unavoidable outcome of heart failure. While nearly 80% of single ventricle patients are alive one-year after Fontan completion, a significantly smaller number survive to adulthood and nearly one third who receive VAD require ECMO pre-VAD, presenting a likely underserved population of single ventricle patients who may benefit from VAD. Once the multi-system and correctable cardiac post-Fontan complications are addressed and heart failure remains, VAD may be indicated. It is important to obtain objective data in Fontan patients, such as exercise testing, cardiac MRI, and catheterization—specifically performing fluid bolus and pulmonary vascular resistance testing, coiling aortopulmonary collaterals, identifying and not intervening on important veno-venous collateral and fenestration "pop-offs," as well as considering CardioMEMs placement for hemodynamic monitoring. There is evidence that VAD can allow Fontan patients to have improved quality of life as well as the receipt of cardiac rehabilitation and pre-transplant desensitization when necessary. This therapy may also allow demonstration of a family's ability to carry out the complex care needed post-transplant. Overall, identifying single ventricle patients who may benefit from VAD is important before complications worsen and eliminate the possibility for VAD—breaking this cycle is crucial for single ventricle patients.

Finally, **Peta Alexander, MBBS**, from Boston Children's Hospital, described post-operative VAD management in patients with Fontan circulation. The post-operative aims are to improve cardiac output, reduce systemic venous hypertension, and preserve or improve end organ function; only the first may be possible in the early post-operative period, and others may get temporarily worse. It is important for the ICU team to discuss the case with the surgical and cardiology teams prior to the operation, identifying appropriate device selection, other lesions that may need to be addressed at time of procedure, postoperative imaging strategies, and the consideration of peritoneal dialysis placement. Bleeding is common postoperatively, and hemostasis is important to optimize fluid management and allow for extubation. Pulmonary vascular resistance may be worse in the early postoperative period, which should be treated with inhaled nitric oxide, PDE-5 inhibitors, and/or and prostacyclin analogs. Ventilator management includes obtaining the lowest possible mean airway pressure to maintain functional residual capacity as well as early extubation to facilitate negative pressure ventilation. In optimizing hemodynamics, systemic vascular resistance must be managed while maintaining a target systolic blood pressure and anticipating that cardiac output delivery post-VAD may be higher than what would be needed for biventricular patients. Contrary to what might be expected, there is often very little optimization needed of the device itself. It is important to continue monitoring of end organ function and ensure adequate rehabilitation, nutrition, and prevention of infection.

VIEW SESSION DETAILS

– Commentary by Jason Goldberg, MD, MS

SESSION 65. Cardiac Allograft Vasculopathy – What Does the Future Hold?

Co-chaired by **Stephan Ensminger, MD, DPhil**, of the University of Lübeck, and **Sharon Chih, MBBS**, of the University of Ottawa, this "Pecha Kucha" session (meaning "chit chat" in Japanese) moved quickly and featured novel methods of managing cardiac allograft vasculopathy (CAV). Five speakers took the stage sharing their unique perspectives on CAV. And the audience gets to vote for the winning speaker!

The first to present was **Guillaume Coutance, MD, PhD**, from Pitié-Salpetrière Hospital in Paris. After brief humor about his colleagues in the pathology department, he discussed the role of "deep phenotyping" of endomyocardial biopsy (EMB) samples to predict the risk of CAV. Using deep learning on pathology slides and clinical biomarkers, EMB samples taken at 1-year post-transplant could predict the risk of CAV at 5 years post-transplant with an AUC of 0.93.

The second presentation was from **Jun-Neng Roan, MD, PhD**, from National Cheng Kung University in Taiwan, on ex vivo gene therapy to prevent CAV. With advances in ex vivo perfusion technology, organs could be sustained outside of the body, providing a unique opportunity to modify them genetically in the laboratory. Gene delivery using adenovirus, adeno associated virus, and lentivirus vectors could transfect cells with high gene expression efficiency. As an example, green fluorescent protein was successfully transfected into a pig heart. Analogously, the genetic cascade of CAV could also be modified and prevented using ex vivo gene therapy in the future.

Next, **Kevin Clerkin, MD, MSc**, from Columbia University Irving Medical Center in New York, discussed biomarkers to detect or predict CAV. Traditionally, CAV is associated with elevated serum high sensitivity troponin and NT-proBNP with limited predictive value. CAV is also associated with novel biomarkers such as various miRNAs and dd-cfDNA levels. Emerging biomarkers include clonal hematopoiesis of indeterminate potential (ChIP) and IL-6R, which show ambivalent evidence. Moreover, serum and urine proteomics have demonstrated promising results on CAV prediction.

The fourth speaker was **Jon Kobashigawa, MD**, of Cedars-Sinai Heart Institute in Los Angeles, who received additional applause from the audience for being the recipient of the 2023 ISHLT Lifetime Achievement Award. He presented the pathophysiologic mechanisms of intimal thickening and vascular remodeling in CAV. Intravascular ultrasound (IVUS) has a long history of being used to screen for and to diagnose CAV. In the 10-year follow up of the multicenter everolimus vs azathioprine study, baseline maximal intimal thickness (MIT) of more than 0.66 mm, or MIT increase by more than 0.59 mm, at 1 year are associated with the composite outcome of cardiac death, re-transplantation, myocardial infarction, coronary revascularization, and CAV within 10 years of follow up.

The final speaker was **Kaushik Amancherla, MD**, from Vanderbilt University Medical Center in Nashville, who talked about a systems biology approach to CAV. He showcased diverse techniques

such as polygenic risk scores for outcome prediction, single cell transcriptomics showing cell lineages such as donor-derived endothelial cells, as well as advancement in bioinformatics. The advantage of the field of transplant is longitudinal tissue data from endomyocardial biopsies, while the challenges are small sample sizes.

This session sparked an interesting panel discussion. Multiple audience members lined up behind the microphones for questions. For example, should donors receive screening with IVUS. What about OCT? What is the optimal frequency of CAV surveillance? Dr. Kobashigawa thought that percent atherosclerosis volume would be a more comprehensive marker for future studies. Which genes to modify for ex vivo perfusion? Dr. Roan thought maybe molecules that are involved in ischemic injury. What is the best method to predict CAV? Dr. Coutance thought that tissue (endomyocardial biopsy) is the most accurate. How do you integrate these diverse approaches?

Amid a flurry of questions, the session was out of time. So, Dr. Chih, the session co-chair, asked the audience to vote for each presenter by applause. The loudest wins! To be scientific, I came equipped with an applause meter on my phone. But my seat was on the right side of the room, so applause from the right was louder than from the left. From Dr. Chih's vantage point on the stage, she announced that it sounded like a tie.

VIEW SESSION DETAILS

– Commentary by Pei Jun Zhao, MD, MPH

SESSION 79. Unravelling Deaths in Heart Transplantation: Turning Tragedy into Triumph

This symposium followed the "Pecha Kucha" chit-chat format with fast focused presentations, and addressed the current knowledge on modes of deaths in heart transplant recipients and how lessons learned from transplant deaths can help living transplant recipients. The session was co-chaired by **Douglas Greig, MD**, of P. Universidad Catolica de Chile in Santiago, and **Gregory Fishbein, MD**, of the David Geffen School. Of Medicine at UCLA.

Livia Goldraic, MD, MSc, of Hospital de Clínicas Porto Alegre, gave the first talk on "**Living on the Edge: Contemporary Epidemiology, Risk Factors and Modes of Death Following Heart Transplant**". She started with presenting a case of a 57 year old male, 12 years post-transplant, who developed CAV with restriction followed by ESRD needing dialysis complicated by vascular access related sepsis and he progressed to MOF. Dr. Livia asked, "What is the patient's cause of death?" Not only was the audience was uncertain but in general—even with use of updated classification systems—there is only moderate inter-reviewer agreement for the definition of cause of death post heart transplant, which is a distinct problem compared to other SOT (Wareham et al. *Medicine* 2018).

Dr. Goldraic walked the audience through a summary of (presumed?) causes of death as stratified by time of transplant with PGD leading early mortality and later development of CAV and malignancies. She discussed how difficult it is to define the cause of death in the setting of graft failure. Is it graft injury? AMR? ACR? And/or CAV? She stated that until we improve definitions, we will be left with this complex interplay of connected pathologies. She said that our current poor definitions of cause of death limit our ability to be certain of temporal trends post heart transplantation. She concluded with a reference to the recent New York Times article by the late **Amy Silverstein**, "**My Transplanted Heart and I Will Die Soon**", which has shaken the transplant community and calls for the urgent need to improve long-term post-transplant outcomes including malignancy, which is a cause of death for 1 in 4-5 transplant recipients.

Next, **Chieh-Yu Lin, MD, PhD**, of Washington University in St. Louis, spoke about "**The Supporting Role of Autopsy in Understanding Allograft-Related Deaths**." She discussed how important autopsy is for understanding the cause of death, but also to detect infectious diseases and malignancy, which help inform patient care. She shared the Wash U experience in 86 heart transplant autopsies, an ongoing collection of data. So far, autopsies have revealed unexpected anatomic findings in 5-10% of cases that had not been considered clinically. These included rejection, CMV myocarditis aortobronchial fistula, abdominal bleeding, and acute myocardial infarction. Further, Dr. Lin concluded that autopsy is not a dying art, and outlined novel molecular pathology tools that might improve insight into allograft immunity and longevity beyond the microscope.

Carmela Tan, MD, of the Cleveland Clinic gave the next presentation "**What's CAV Got To Do With It?**" She started with an overview of CAV pathogenesis and highlighted the crucial role of T-cells and interferon-γ in this process, stimulating smooth muscle proliferation and matrix deposition.

She discussed the distinct differences to atherosclerotic CAD, including the lack of compensation via artery enlargement as a consequence of intimal growth-related stenosis as seen in CAD. Importantly, while an atherosclerotic lesion might have not been flow limiting in the donor, a superimposed CAV lesion post-transplant can easily change that verdict and become relevant. Dr. Tan discussed how CAV assessment by angiography alone can underestimate CAV—especially in early stages—and mentioned that non-invasive imaging technologies are emerging but lack long term outcome data. She illustrated two cases of CAV with autopsy data showing the importance of microvascular involvement with heterogenous lesions as well as involvement of arteries supplying the conduction system associated with malignant arrhythmias. Dr. Tan summarized that detection of CAV remains suboptimal, the understanding of the pathogenesis of microvasculopathy is limited, and that the focus should be on modification of risk factors to prevent CAV progression.

Next **Ana Alba, MD, PhD**, of Toronto General Hospital, discussed the question "**Are Post-Transplant Sudden Deaths Predictable and Preventable?**" She pointed out that the risk for sudden death in heart transplant recipients is 3-10-fold higher than in the general population! SCD rates are even higher rates in patients treated for cellular rejection and those with severe CAV (Alba e al. *Clin Tx*2019). Specifically, the SCD risk for CAV3 is 5.4-8.3% as compared to patients with non-ischemic and ischemic CMP ranging 3-8% at 2 years, who would receive a primary prophylactic ICD. That raises the question: Is SCD post-transplant preventable? As far as assessable, 70% of heart transplant patients with SCD had brady-arrhythmias as initial rhythm and the remaining 30% tachy-arrhythmias. However, Dr. Alba pointed out that the rate of brady-arrhythmias leading to SCD is declining given transition to bi-caval anastomosis with preservation of the donor sinus node. Dr. Alba then asked, "What have we learned from ICD use post-HTx?" Data is largely limited to case series, which showed appropriate ICD therapies per year ranging 6-30% as compared to 10% in the general heart failure population. Per this data, transplant patients seem to receive ICDs later in the course. She mentioned that there is no data on the effect of medical therapy or revascularization to decrease SCD risk. In the end, Dr. Alba answered three questions rather than two: Is post-transplant SCD predictable? Yes, with some uncertainty. Is post-transplant SCD preventable? Yes, with *more*uncertainty. And lastly, can we do better? Always!

The final presentation of the session was given by **Dylan Miller, MD**, of Intermountain Central Lab in Utah. He talked about "**Failing Forward: Pathologic Examination of MCS Devices Removed for Complications and After Recovery**." An important fact first: turns out that the dentist in Dr. Miller's hometown was the first patient implanted with a total implanted heart by Dr. Jarvik. It is unknown what happened to the dental health of the town following the implant. After that important detail, Dr. Miller began with a description of the first pump thromboses seen at the epicenter of the bearings in the axial flow HMII in 2013/2014. He also spoke about how velour at the HMII drive line exit site as compared to silicone increased the risk for drive line infections leading to a practice change – a great example of failing forward, Dr. Miller said.

The centrifugal flow HVAD had a tendency for clot formation at the interface of rough and smooth surface parts of the two-textured design inflow cannula, which then could break off and be sucked into the pump in addition to intra-pump thrombus formation. The HM3 now has a fully

centered inflow tract – again an example of failing forward. However, the HM3 came with an open-ended band relief device to prevent kinking of the outflow graft—since it was open ended, pericardial fluid could enter and cause extrinsic compression of the outflow graft leading to outflow obstruction.

Dr. Miller mentioned that myocardial recovery results in increased flow through the aortic valve and less flow through the LVAD, which theoretically would lead to increased risk of pump thrombosis. However, the opposite has recently been published and was just presented at ISHLT2023 with the lowest pump thrombosis rates in patients with the highest ejection fraction (Olsen et al *JHLT* 2022, Kyriakopoulos et al. *JHLT* 2023). This was a surprise, Dr. Miller said and contradicts these longstanding assumptions.

After the great talks and a Q&A session the audience's gross motor skills were tested by performing waves to score the presentations and find the winner. In the end, the audience performance was so impressive that everyone was a winner.

VIEW SESSION DETAILS

– Commentary by Luise Holzhauser, MD

SESSION 68. How It Started… How It's Going: Omics and AI in Heart Transplant Biopsies and Rejection Surveillance

This session was co-chaired by **Chieh-Yu Lin, MD, PhD**, of Washington University in St. Louis, and **Carmela Tan, MD**, of the Cleveland Clinic.

The first abstract presentation was by **Arttu Lahtiharju, MD**, from the University of Helsinki, "***Detecting Rejection Infiltrates with Deep-Learning Algorithm from HE-Stained Clinical Endomyocardial Biopsies***." The authors showed that following training, a deep-learning algorithm using supervised learning was able to recognize tissue and distinguish rejection infiltrates from healthy tissue with great precision (>99%) but that it cannot yet distinguish myocyte damage in these preliminary results. In future steps, Dr. Lahtiharju discussed the plan to include ISHLT rejection grading and quantitative analysis in the algorithm. The team plans to add further staining modalities like masson trichrome stains to the model, as well as adding information using dd-cfDNA analysis or NGS.

Next, my fellow Roving Reporter **Jason Goldberg, MD, MS**, of the Inova Heart and Vascular Institute in Falls Church, presented a study named "***Dysregulated Circulating Proteins in Cellular and Antibody-Mediated Rejection, on Behalf of the Graft Investigators***." Authors hypothesized that differential expression of immune system and cardiovascular function proteins is associated with ACR and AMR. In this study, 104 patients from the GRAfT study were included, and 30 were found to have rejection. Dr. Goldberg showed that proteomics were able to distinguish between no rejection as well as ACR and AMR rejection types. Next, volcano plots nicely showed differentially up-and down-regulated proteins in ACR and AMR, with AMR having much more pronounced results than ACR (AMR with 23 differentially regulated proteins including NT-proBNP, ST2 and IGFBP2 vs 1 protein namely CXOL 10 in ACR). Following further results on KEGG pathway analysis comparing AMR and ACR, Dr. Goldberg concluded that proteomic evaluation identified specific protein profiles dysregulated in allograft rejection. Notably, AMR had a more pronounced cardiovascular pathology with upregulation of known heart failure bookmakers, whereas in ACR multiple pathways of immune system differentiation. He mentioned that future directions include use of proteomics to define immune function to provide targeted therapy, addition of other –omics like cfDNA and microRNA to rejection detection and severity grading, and lastly longitudinal proteomics evaluation to determine effects of early and late post-transplant events.

Nadia Fida, MD, of Houston Methodist Hospital, presented the abstract "***Diagnostic Performance of MMDx in Real World Heart Transplant Population: A Single Center Experience***." This study included 100 heart transplant recipients with 231 paired MMDx and histopathological results, as well as 113 biopsies with MMDx, histopathology, and dd-cfDNA results. The authors then investigated diagnostic accuracy (sensitivity, specificity, and NPV) as well as the agreement between the different testing modalities. Dr. Fida discussed that the agreement between MMDx and histopathology (HP) for any rejection was fair (Cohen's kappa, 0.32, $p<0.001$) and that MMDx had a higher specificity and NPV for any rejection, ACR and AMR when compared to HP. She then further deliberated that MMDx alone had a higher specificity than dd-cfDNA. Interestingly, the

addition of dd-cfDNA to MMDx did not increase sensitivity but specificity. Dr. Fida concluded that MMDx can be a valuable tool in the "real world" when monitoring heart transplant patients for rejection and discussed how combined results from MMDx, HP and dd-cfDNA might help clinical decision making with more data and learning to come.

The final presentation of the session was by **Alessia Giarraputo, MSc, PhD**, of the University of Padua, with the title "***Molecular Diagnostic Classification of Heart Allograft Rejection Based on the Targeted Banff Human Organ Transplant Gene Expression Panel***." The aim of this study was to identify gene expression signatures for heart transplant rejection and develop a diagnostic model based on targeted transcriptomes. A reference set with >600 endomyocardial biopsies was included and underwent transcriptome profiling in a dedicated workflow coupled with pathological evaluation. Molecular profiles for both ACR and AMR included clinically relevant transcripts reflecting the rejection-related pathophysiology. Dr. Giarraputo showed that the developed prediction model for AMR in the validation set had a diagnostic accuracy of 81.89% with a great test performance ROC AUC 0.86, which was superior to the model for ACR with a final accuracy of 77.85% and ROC AUC 0.79. Interestingly this technology can be used after histopathological assessment, in contrast to MMDx, which requires a certain pre-test probability to use the test before the HP diagnosis.

VIEW SESSION DETAILS

– Commentary by Luise Holzhauser, MD

SESSION 75. The Comedy of Errors: New Allocation Policy, DCD Donors… What About Primary Graft Dysfunction?

This session was co-chaired by **Maxime Tremblay-Gravel, MD, MSc**, of the Montreal Heart Institute, and **Ulrich Jorde, MD**, of Montefiore Medical Center in New York.

The first abstract was presented by **John Trahanas, MD**, from Vanderbilt University Medical Center in Nashville, entitled "***Normothermic Regional Perfusion Versus Direct Procurement and Preservation: Is There a Difference for DCD Heart Recipients?***" He described results from 104 transplanted DCD hearts from a single center. NRP donors were younger (25 vs. 31, P= 0.008) and donor distance was significantly shorter in the NRP group (320 vs. 544 miles, P=0.02). He discussed that recipient pre-operative risk factors, bypass time, and warm ischemic time were comparable between the groups. While there was a numerical difference in the rate of severe PGD with 12.9% in the OCS group vs 5.81% in the NRP group this was not statistically significant (p 0.3). There was no difference in inotrope scores at 24 and 72 hours, and no difference in 30-day and 1-year survival. Dr. Trahanas concluded that both NRP and OCS platforms can be safely used for DCD recoveries.

Next **Andreas Zuckermann, MD**, of the Medical University of Vienna, discussed the paper "***Validating the 2014 Consensus Primary Graft Definition: An Analysis on the 1,056 Patients from the Multi-Center Guardian Registry***." This abstract presented an analysis for the GUARDIAN registry, the largest multi-center registry focused on analysis of peri-operative outcomes following donor organ preservation, using the Paragonix SherpaPak® transport system as compared to traditional ice storage. So far, 1500 patients from 21 centers have been enrolled and patients transplanted between October 2015 and August 2022 were analyzed in this study. Patients were grouped into No PGD N=995, mild/moderate PGD N=126, and severe PGD N=100 based on the 2014 ISHLT PGD definition. Not surprisingly, patients with severe PGD had significantly lower 30-day, in-hospital and 1-year survival when compared to patients with mild/moderate or no PGD. Dr. Zuckermann pointed out that the separation of the survival curves continues to widen beyond the first 30 days post-transplant and continues through 6 months and 1 year, suggesting that PGD triggers a sequalae of complications. When analyzing PGD risk factors, the preservation method "SherpaPak vs ICE" had an OR of 0.6 (95%CI 0.39-0.96 p=0.03) for development of PGD, likely representing the most controllable risk factor. In addition, Dr. Zuckermann concluded that this analysis substantiates the 2014 ISHLT definition of severe PGD as a clear risk factor for reduced 1 year survival, and that there is an opportunity to re-define mild/moderate PGD definitions.

The following speaker was **Christine Premananthan**, a medical student from Cedars-Sinai Medical Center in Los Angeles. She presented the abstract "***Impact of the 2018 Adult Heart Allocation Policy Change on the Incidence of Primary Graft Dysfunction after Heart Transplantation***." The study cohort consisted of 615 patients, N=402 transplanted before the 2018 UNOS policy change and N=213 transplanted after. Use of pre-transplant MCS was significantly more common in the post-2018 era. Baseline donor characteristics were comparable except for higher inotrope use at procurement in the pre-2018 era. Notably, ischemic time was significantly longer with a higher incidence of > 4 hrs in the post-2018 era (24% vs 25%, p <0.01). Ms. Premananthan then

presented that rate of all-PGD was numerically higher in the post-2018 era, mostly driven by significantly more RV-PGD (3.7 vs 11.7%, p<0.01). However, after multivariable adjustment, the new policy era was not independently associated with the risk of developing PGD. She concluded that while RV-PGD was more common in the post-2018 era, this was not associated with inferior survival at one year post transplant. As for future direction, she suggested that adjunct strategies to reduce ischemic time might be warranted to decrease the incidence of RV-PGD.

The final presentation of the session was by **Kareem Sharaf, MSHS, MPH, PA-C**, of UC San Diego, who presented "***Cold Static Storage of Donation after Circulatory Death (DCD) Hearts Procured via Normothermic Region Perfusion (NRP): Effect of Ischemic Time on Outcomes***." For the purpose of this study, patients undergoing heart transplants were stratified by ischemic time (IT) to less than 4 hours (N=30) and greater/equal to 4 hours (N=26). Importantly, both donor and recipient characteristics were comparable between the groups. There was no significant difference between the IT groups both in aggregate PGD as well as when analyzed by grading into moderate and severe PGD. Further, there were no differences in first post-transplant cardiac index, ICU and hospital LOS, as well as 30-day survival. In conclusion Dr. Sharaf said that comparable short-term outcomes are seen in DCD allografts procured via NRP despite an increase in PGD usually seen with prolonged cold ischemic time.

VIEW SESSION DETAILS

– Commentary by Luise Holzhauser, MD

SESSION 77. New Frontiers in Biomarker Development: Antibodies, Omics, and Graft Injury

In this session, anti-HLA antibodies were explored in a variety of interesting scenarios. The session was co-chaired by fellow Roving Reporter **Lourdes Chacon** of the Texas Heart Institute in Houston, and **Indranee Rajapreyar, MD**, of Thomas Jefferson University Hospital in Philadelphia.

First, **Lee Baxter-Lowe, PhD**, from the University of California Los Angeles, Tvaluated the detection of donor specific antibodies (DSAs) to the HLA phenotypes stratified by race. The results identified a disproportionally higher number of those alleles present in Hispanic patients as most poorly represented in solid phase immunoassays utilized for antibody detection.

Jon Kobashigawa, MD, from the Cedars-Sinai Heart Institute, identified trends in AlloSure® and AlloMap® data after detection of *de novo* DSAs. They showed a rise in AlloMap® gene expression profiling scores and AlloSure® cell-free DNA levels before *de novo* DSA development followed by a subsequent decay in AlloSure® levels after *de novo* DSA was identified.

Akseli Salin, a PhD student from the University of Helsinki, identified serum proteomics signatures after ischemia-reperfusion injury post heart implantation, finding altered protein expression post-transplant, specifically for proteins responsible for complement activation, oxidative stress, and platelet degranulation. The aldolase protein was associated with severe primary graft dysfunction, and IGFBP2 was associated with allograft rejection.

Finally, **Lauren Truby, MD, MS**, from the University of Texas Southwestern Medical Center in Dallas, described metabolomic profiling during ex-situ perfusion, describing that the heart preferentially uses fatty acid metabolism; however, during stress, glycolysis is more preferred. These investigators identified the stress profile during ex-situ perfusion, showing the highest changes in metabolomic profile were those related fuel substrates, specifically among long-chain acyl carnitines (indicative of glycolysis), with greater levels of these substrates associated with increased ex-vivo perfusion time and with higher levels of lactate and troponin.

VIEW SESSION DETAILS

– Commentary by Jason Goldberg, MD, MS

SESSION 82. More Than a Number: Navigating the Complexities of Psychosocial Support in Heart Transplantation

Co-chaired by **Lisa Guertin, DNP**, of the University of Washington in Seattle, and **Lauren Schneider, PsyD**, of Stanford University, this session contained four presentations that analyzed psychosocial assessment tools and outcomes in heart transplantation.

First, **Lucas Keyt, MD**, of the University of California San Diego, examined the predictive value of the Stanford Integrated Psychosocial Assessment for Transplantation (SIPAT) score on outcomes after heart transplantation in 226 patients between 2020 to 2022. In a multivariable analysis, a SIPAT score >= 21 was not associated with graft dysfunction, rejection, 30-day readmission, or all-cause mortality. Audience members suggested testing individual domains of SIPAT, reassessing SIPAT as it may change with time, and whether a more predictive tool is needed.

Revanth Kosaraju, MD, of the University of California Los Angeles, came next, analyzing the long-term association between SIPAT score categories and 10-year outcomes in 51 patients transplanted between 2010 to 2011. SIPAT scores were categorized as excellent/good (low risk) or minimally acceptable to high risk (high risk). Compared to the low risk group, the high risk group had shorter mean survival (7.6 vs. 10.1 years) and lower rate of 10-year survival (47.1% vs. 79.4%). High risk group patients were more likely to reside in a county with greater income inequality (using Gini coefficient). Audience members again suggested serial SIPAT scores after transplant. They also asked about what health care providers can do to modify psychosocial risk factors within SIPAT and if it could improve long-term transplant outcomes.

Shifting gears, **Samantha Anthony, PhD, MSW**, shared her experience of piloting the iPeer2Peer mentorship program for adolescent thoracic transplant recipients at The Hospital for Sick Children and Stollery Children's Hospital in Toronto and Edmonton. 14 heart and 2 lung transplant recipients aged 12-17 years were matched with trained mentors aged 18-25 years who were also transplant recipients. Matched pairs communicated virtually over 15 weeks with at least weekly contact for peer support and disease self-management skills. Through questionnaires and interviews, mentees reported high satisfaction and would recommend the program to other patients. During question period, the CEO of Enduring Hearts, a funder of the project, was interested in having a similar program in the United States. As for specific questions, the speaker elaborated that mentor training took 2.5 days. Calls between mentors and mentees were recorded. One patient required referral to mental health. One mentee felt that their matched mentor was not an ideal personality fit. Audience members also mentioned similar programs such as CF Peer Connect for cystic fibrosis. Future directions are to pilot a program for parents of pediatric transplant recipients and for pediatric heart failure patients.

Finally, **Dipankar Gupta, MD**, from the University of Florida Gainesville College of Medicine, presented the Pediatric Psychosocial Assessment Tool (PPAT) for pre-transplant evaluation of 95 heart transplant recipients between 2016 to 2021. The PPAT contains 9 domains (home environment, family/social, finance/insurance, mental health/substance, child protection/law,

adherence, disease understanding, health literacy, and coping skills). Each domain is scored on a scale of 1-4 for a total score of 9-36. The PPAT score showed excellent internal consistency, but was not associated with the risk of hospitalization or rejection. An audience member noted that there was overlap between domains, such as health literacy and disease understanding.

VIEW SESSION DETAILS

– Commentary by Pei Jun Zhao, MD, MPH

MINI ORAL 13. Analyzing the Present and Improving the Future in Heart Transplantation

This mini oral session is a collection of 10 short presentations on the present and future of heart transplantation, co-chaired by **Martin Goddard, FRCS, FRCPath**, of Papworth Hospital in Cambridge, and **Scott Silvestry, MD**, of AdventHealth in Orlando.

Kevin Clerkin, MD, MSc, of Columbia University Irving Medical Center in New York, presented "***New System, Familiar Problem: Increased Wait Time for High Priority Heart Transplant Candidates***," which highlighted waitlist times after the 2018 OPTN heart allocation policy using the UNOS registry from 18 October 2018 to 8 July 2022. Status 1 median wait time has been consistent (about 4-5 days), while status 2 wait time is increasing (from 7 to 12 days). Wait time was longest for blood type O, and there were regional variations. During questions, an audience member felt that status 2 is turning into the old status 1A.

Kelsey Patel, DO, of Houston Methodist Hospital, presented "***The Impact of Donation after Circulatory Death Heart Transplants on Waitlist Time: A UNOS Analysis***." The impact of donation after circulatory death (DCD) on heart transplant wait times used UNOS data (pre-DCD 2018-2019, post-DCD 2019-2022, total 11,595 transplants). In DCD centers, wait time decreased from 36 to 27 days (pre-DCD vs post-DCD era), but in non-DCD centers, there was no significant change in wait time.

Lily Stern, MD, of Cedars-Sinai Heart Institute in Los Angeles, presented "***Proceeding with Heart Transplant in Flow Positive Cyto-Negative Prospective Donor-Specific Crossmatch in Highly Sensitized Patients: Saving Lives***," which explored outcomes for 60 highly-sensitized heart transplant patients (flow positive, cytotoxicity-negative crossmatch), compared to 540 non-sensitized patients. While there was more 1-year antibody-mediated rejection in the highly-sensitized group, 5-year outcomes of CAV, MACE (MI, CHF, PCI, pacemaker, stroke), and survival were similar. Audience members asked about transplant induction agents (e.g., ATG) and the desensitization protocol at the speaker's hospital.

McHale Anderson, MD, of the University of Utah, presented the relationship between pre-transplant waitlist death/delisting and meeting shock criteria by hemodynamic parameters (cardiac index, PCWP, systolic BP) using UNOS 2018 to 2022 data in the abstract "***Pre-Transplant Waitlist Mortality Not Associated with Severity of Shock Hemodynamics***." Interestingly, the severity of shock at presentation was not correlated with mortality. The speaker commented that hemodynamics is dynamic, so serial assessments may be more predictive of outcomes.

Dhaval Chauhan, MD, of Children's Mercy Hospital in Kansas City, presented "***Diminishing Effect of Blood Type on Waitlist and Heart Transplantation Outcomes in the Contemporary UNOS Allocation System***." The abstract explored the effect of blood type on waitlist time and mortality, using UNOS 2016 to 2021 data divided into pre- and post-2018 heart allocation policy. After the allocation policy change, time to transplant decreased across all blood groups, LVAD use was lower, and

waitlist mortality/removal and post-transplant mortality were similar between blood type O and non-O patients.

William Watson, DPhil, of Royal Papworth Hospital in Cambridge, presented "***Right Atrial Pressure and Rv-Pa Uncoupling May Improve Risk Stratification of Patients with Advanced Hf and Secondary Mitral Regurgitation***," which shows right heart catheterization parameters and outcome (death, heart transplantation, mechanical circulatory support) in 456 patients with secondary mitral regurgitation from 2010 to 2020. Prognosis was worse in severe MR. In mild-moderate MR, right atrial pressure > 10 mmHg or TAPSE/sPAP > 0.4 (marker of RV-PA uncoupling) conferred worse prognosis. Audience members remarked that MR is dynamic. For instance, after diuresis, severe secondary MR could become milder. They also suggested testing other markers of RV dysfunction, such as fractional area change.

Humera Ahmed, MD, of Seattle Children's Hospital, presented a decision tree for deciding if patients with Fontan failure and Fontan associated liver disease should undergo concurrent heart and liver transplant, applied to 7 patients between 2021 to 2022 in the abstract "***Initial Experience with a Decision Tree to Assess the Need for Concurrent Liver Transplant in Fontan Patients Undergoing Heart Transplant***." Patients were to receive concurrent liver transplant if signs of hepatic fibrosis on biopsy, portal hypertension on CT, and varices on upper GI endoscopy. In the end, all 7 patients were listed for heart transplant alone. Audience questions were, after heart transplant, if liver cirrhosis improved and if portal hypertension can still develop. Finally, an audience member commented that the decision tree can be simplified to its last step—endoscopy. If varices on endoscopy, then combined heart liver transplant.

Ryan Byrne, MD, of Baylor College of Medicine in Houston, applied the Kansas City Cardiomyopathy Questionnaire (KCCQ) to patients with adult congenital heart disease (ACHD) in 71 patients, median follow up 10 months in the abstract "***Predictive Validity of the Kansas City Cardiomyopathy Questionnaire in Adults with Congential Heart Disease***." Historically, the KCCQ was validated in the non-congenital heart failure population. Among ACHD patients, by Kaplan-Meier analysis, lower KCCQ score category (stratified into score of 0-50, 51-75, 76-100) was associated with worse NYHA class, increased death/hospitalization or death/procedures.

Hadi Javan, MD, of the University of Utah in Salt Lake City, tested the effect of acellular human amniotic fluid on myocardial infarction in Sprague Dawley rats in the abstract "***Acellular Human Amniotic Fluid Prevents the Development of Ischemic Heart Failure***." MI was induced by ligation of the left anterior descending artery. Rats that received IV amniotic fluid compared to normal saline at pre-ligation, post-ligation, and 2 weeks after ligation, had significantly lower infarct size (6% vs 40%) and higher ejection fraction (75% vs 35%) at 4 weeks. In vitro, H9C2 cells under hypoxia demonstrated higher cell viability when treated with amniotic fluid. A moderator exclaimed that it is the most bizarre and incredible presentation of the session. Another audience member wondered about the utility of amniotic fluid as a preservation fluid during organ transplant. Currently, the biologic mechanism of cardiac protection by amniotic fluid is unknown.

Finally, **Mark Hofmeyer, MD**, of Medstar/Washington Hospital Center in Washington, DC,

presented "***Genetic Signature of Dilated Cardiomyopathy Severity: The DCM Precision Medicine Study***." The abstract explored the genetic signature (by exosome sequencing) of dilated cardiomyopathy in the DCM Precision Medicine Study (1188 patients between 2016 to 2021). DCM patients were divided into 3 groups: VAD/transplant, ICD, or none. The VAD/transplant group had a higher frequency of pathogenic or likely pathogenic mutations compared to the ICD or none group.

VIEW SESSION DETAILS

– Commentary by Pei Jun Zhao, MD, MPH

MINI ORAL 16. The Winter's Tale: Hypothermic Machine Preservation of Donor Hearts

This mini-oral session included multiple abstracts describing the use of hypothermic (cold storage) devices for heart allograft preservation/transportation, and was chaired by **Darren Freed, MD, PhD, FRCSC**, of Stollery Children's Hospital in Edmonton, and **Roxana Moayedifar, MD**, of the Medical University of Vienna.

Multiple references were made to the multi-center results from the GUARDIAN registry, showing decreased length of stay and primary graft dysfunction among recipients where the SherpaPak® system was used for allograft preservation. First, **Masashi Kawabori, MD**, from Tufts Medical Center in Boston, showed how the SherpaPak® allowed for smaller heart transplant programs to increase transplant volumes by taking on longer distance cases, without decrease in survival.

Matthias Peltz, MD, from the University of Texas Southwestern in Dallas, presented an early description of the LifeCradle® hypothermic oxygenated perfusion device, which showed higher indices of aerobic metabolism and lower indices of anaerobic metabolism when comparing the device to conventional cold storage.

Niels Moeslund, MD, PhD, from the Aarhus University in Denmark, demonstrated a porcine model of XVIVO® hypothermic machine perfusion for DCD experimentation.

Spencer Finkbeiner from the University of Kansas Medical Center evaluated single center experience comparing SherpaPak® to standard ice storage, showing shorter length of stay in SherpaPak® recipients.

Joseph Mancuso, MD, also from the University of Kansas Medical Center, evaluated SherpaPak® among donors who died of drug overdose with long ischemic times, showing a trend towards reduction in MCS use and severe PGD.

Jacob Baer, DO, the third presenter from the University of Kansas Medical Center, evaluated SherpaPak® use in long donor down time and ischemic times, showing no difference in outcomes between ice and SherpaPak®.

Elizabeth Profita, MD, from Stanford University, described a single-center pediatric experience of SherpaPak®, showing its use in donors as small as 5.5 kg, with no difference in length of stay or primary graft dysfunction as compared to standard ice preservation.

David Kaye, MD, PhD, from Alfred Hospital in Melbourne, evaluated renal outcomes using XVIVO® for 6-8 hours, showing no post-operative mortality with the device as well as less renal replacement therapy and creatinine increase than conventional recipients.

Kristina Andrijauskaite, PhD, MS, MEd, from Vascular Perfusion Solutions, showed a novel,

portable, pulsatile hypothermic perfusion preservation device trialed among hearts rejected for transplantation, demonstrating higher contractility as compared to ice storage, as well as reduction in endothelial cell death and inflammatory markers.

Dan Meyer, MD, from Baylor Scott and White Health in Dallas, described SherpaPak® use in short (< 3 hours) ischemic times, showing no difference in primary graft dysfunction and survival when compared to conventional cold storage.

Overall, this was an exciting, fast-paced session, showing the promise and need for further investigation of these devices, especially in the setting of longer expected ischemic times and DCD.

VIEW SESSION DETAILS

– Commentary by Jason Goldberg, MD, MS

FEATURED ABSTRACT 04 at General Session III. Comparing Long-Term Survival and Readmissions Between Heartmate 3 and Heart Transplant as Primary Treatment for Advanced Heart Failure

Presenter: ***Michael Kirschner, BS****, Columbia University Medical Center, New York, NY USA*

In this abstract presented during the final plenary session of the meeting, Mr. Kirschner, a second-year medical student from New York University, presented data comparing long-term survival and readmission between 501 patients receiving Heartmate 3 or heart transplant as primary treatment. Heartmate 3 patients had higher age, BMI, and serum creatinine. In an unmatched analysis, those with Heartmate 3 had significantly lower 3-year survival. However, with propensity score matching, there was no survival benefit observed between the two devices. HM3 patients 18-58 years of age had superior survival compared to those aged 59 and older. Unplanned readmission was twice as high in the HM3 patients, with readmissions being related to infection, bleeding, and device malfunction.

These data suggest that HM3 provided comparable long-term survival to OHT as a primary treatment for heart failure, with the caveat that HM3 was associated with higher readmission rates. This is an important conclusion given the 2018 change to UNOS listing criteria that has significantly decreased transplantation rates for VAD patients.

VIEW FULL ABSTRACT

– Commentary by Jason F. Goldberg, MD, MS

SESSION 89. Medications and Machines: Which Ones Improve Pediatric Heart Transplant Outcomes?

This session included studies of out-of-pocket costs, SherpaPak® use, steroid-minimizing immunosuppression, and statin use for CAV among pediatric heart transplant recipients. The session was co-chaired by **Benjamin Mantell, MD, PhD**, of New York Presbyterian, and **Oliver Miera, MD**, of Deutsches Herzzentrum Berlin.

To start the session, **David Bearl, MD, MA**, of Vanderbilt Children's Hospital in Nashville, presented "***Out-of-Pocket Expenses Associated with Pediatric Heart Transplantation***," which featured data from a survey distributed to caregivers of pediatric heart transplant recipients inquiring about out-of-pocket expenses. The results included data from 146 respondents in 38 states. Median monthly expenses were $250 (IQR $75-$500). Twenty respondents had monthly expenses > $1,000. Respondents with commercial insurance (as compared to government insurance) had higher expenses, especially those with Affordable Care Act ("Marketplace") insurances. These expenses were not associated with complications or number of medications. Cardiac catheterizations and unplanned admissions were reported as the events that incurred the highest expenses.

Yuriy Stukov, MD, from the University of Florida, presented "***Pediatric Experience Using the Sherpapak Cardiac Transport System: A Subgroup Analysis of the Guardian Heart Registry***." Dr. Stukov described a subgroup analysis of the SherpaPak® GUARDIAN registry, reporting on 64 SherpaPak® patients and 62 standard ice storage patients, finding no significant differences in length of stay or primary graft dysfunction. This is contrary to adult GUARDIAN data, which shows improved length of stay and primary graft dysfunction with SherpaPak®.

Christina Hartje-Dunn, MD, from Boston Children's Hospital, presented "***Steroid Avoidance in Pediatric Heart Transplant***," which featured results of a steroid avoidance immunosuppression protocol. These patients were transplanted between 2006 and 2020, had low risk of AMR (i.e., no DSA and negative flow crossmatch at time of transplant). They received immunosuppression with ATG induction with methylprednisolone pre-treament for ATG doses, followed by tacrolimus and mycophenolate. Of the 150 patients reported with median follow-up of six years, 26% of patients had steroid-treated rejection episodes. Results included similar post-transplant outcomes to those reported from ISHLT registry data, including graft survival at 1 and 5 years of 94% and 87%.

Finally, **Madeline Townsend, MD**, from Cleveland Clinic Children's, reported on the effects of statin use in pediatric heart transplant recipients in "***Statin Use May Not Benefit Pediatric Heart Transplant Recipients: A PHTS Analysis***." The study noted benefits in the setting of adult transplant recipients with CAV and unclear benefit in children with CAV. She presented data from PHTS of 3485 recipients, with 17% having consecutive statin therapy, and 19% having intermittent statin therapy. By multivariate analysis, statin use was not associated with graft loss. Consecutive statin use was not associated with graft survival or freedom from CAV when compared to absent statin

use in unmatched or propensity-matched analyses.

VIEW SESSION DETAILS

– Commentary by Jason Goldberg, MD, MS

SESSION 90. All's Well That Ends Well: The Three P's to Transplant Success: Protection, Preservation, and (em)Powering the Donor Heart

This session on the final and snowy (!) day of ISHLT2023 was co-chaired by **Victor Pretorius, MD**, of UCSD in La Jolla, and **Filip Rega, MD**, of University Hospitals Leuven.

The first abstract was presented by **Lu Wang, MRCS, MA(Cantab), MB, BChir, BA(Hons)**, of Newcastle University, and was entitled "***Non-Ischaemic Heart Preservation to Improve Donor Heart Quality***." The main aim of the study was to compare LV function of human hearts preserved by non-ischemic heart perfusion (NIHP) vs. static cold storage (SCS) in hearts declined for transplant. The NIHP group consisted of 5 DBD and 3 DCD hearts. NIHP hearts were retrieved and perfused continuously with low flow oxygenated blood based perfusate at 8°C. Left ventricular biopsies were taken and hearts were then reperfused on a modified Langendorff system at 37°C for LV functional assessment. Dr Wang discussed that NIHP hearts had significantly better unloaded developed pressure, contractility, and relaxation and when compared to SCS hearts (all $p<0.001$) and notably less necroptosis. Further, NIHP hearts had better energy profiles after preservation and less ROS after reperfusion in addition to containing more phosphocreatine, which is crucial for energy transfer in cardiomyocytes. In the end, Dr. Wang concluded that NIHP can indeed safely preserve DCD and DBD hearts based on these exciting results.

Next, **Sanaz Hatami, MD, PhD**, of the University of Alberta, presented "***Superior Cardiac Protection in Combined Ex-Situ Perfusion of Heart and Liver: Lessons Learned***". The aim of the study was to assess the effects of combined normothermic ex-situ perfusion (ESHP) of pig hearts and livers. Hearts and livers were procured and perfused for 8 hours on a custom device in normothermia either as working heart (group H, n=6) or combined heart-liver perfusion (group HL, n=6). Dr. Hatami discussed that combined heart-liver perfusion was associated with better preservation of cardiac function, negligible edema formation, lower markers of oxidative stress, less myocardial damage, higher dynamic in energy production/utilization and preserved values of amino acids in perfusate and myocardium. She concluded that ESHP is associated with oxidative stress and alteration of myocardial energy metabolism and that antioxidative support protocols might be necessary for heart only ESHP.

Alison Brann, MD, of UC San Diego, discussed the abstract "***Impact of Functional Warm Ischemic Time on Short Term Outcomes in Donation after Circulatory Death Heart Transplantation***". Dr. Brann explained that in DCD the safe functional warm ischemic time (FWIT) traditionally has been considered <30 minutes. However, progression to circulatory arrest in DCD donors is unpredictable and often exceeds 30 minutes. In this study, both recipients of normothermic regional perfusion followed by cold storage (NRP-CSS) and normothermic machine perfusion using Organ Care systems (TransMedics) hearts were included and grouped by FWIT of < and > 30 min. A total of 86 patients were enrolled. Both donor and recipient characteristics were comparable. There was no difference between the groups in PGD, either 30-day survival or 1-year survival. Dr. Brann concluded that potential donors with FWIT >30 min can possibly be safely used for transplantation, especially if donor characteristics are otherwise favorable and further

ischemic insults are avoided.

The final presentation of the session was by **Chetan Pasrija, MD**, of Vanderbilt University Medical Center in Nashville: "***Prolonged Warm Ischemic Time is Safe for Cardiac Donation after Circulatory Death***". He explained that Vanderbilt anecdotally found excellent outcomes with DCD hearts with a prolonged functional donor warm ischemic time (f-DWIT) >30 min, prompting the program to remove WIT restrictions. In this study, recipients of both normothermic regional perfusion and direct procurement and preservation (OCS) were enrolled. A total of 97 patients were analyzed and grouped into FWIT > and < 30 min. Donor and recipient characteristics were comparable. Intraoperative RV function was less robust in the f-DWIT>30 min group (p 0.04) but there was no difference in PGD grades at 24 hours, 30-day and 1-year survival. The observed intraoperative RV dysfunction resolved early post-operatively and was not associated with higher inotrope scores. Like Dr. Brann, Dr. Pasrija concluded that within DCD donation a prolonged f-DWIT appears to be safe and associate with excellent outcomes. A great way to end the session.

VIEW SESSION DETAILS

– Commentary by Luise Holzhauser, MD

SESSION 91. Multi-Organ Transplant Outcomes: When are Two Organs Better Than One in Heart Transplantation?

In this late session, data were presented regarding patients undergoing multi-organ transplantation. The session was co-chaired by **Eileen Hsich, MD**, of the Cleveland Clinic Foundation, and **Cristiano Amarelli, MD**, of Monaldl Hospital in Napoli.

In "***Heart Retransplant Recipients with Borderline Renal Dysfunction Benefit from Combined Heart-Kidney Transplantation***," **Jad Malas, MD**, of Cedars-Sinai Medical Center in Los Angeles, discussed the use of heart-kidney transplantation among patients requiring heart re-transplantation who have renal dysfunction. Heart-kidney recipients with eGFR < 30 and 30-45 had higher unadjusted 5-year survival than those with GFR > 45. Heart-kidney transplant was independently associated with reduced risk of 5-year mortality in patients with eGFR < 30. These data present important rationale to consider heart-kidney transplantation in patients requiring heart re-transplantation with concomitant renal dysfunction.

Nicholas Hess, MD, from the University of Pittsburgh, described listing of patients for heart lung, heart kidney, and heart liver as compared to heart alone in "***Predictors of Transplantation and Waitlist Mortality Among Patients Listed for Combined Heart-Lung Transplantation: A UNOS Registry Analysis***." These multi-organ transplants have continued to increase over time, and those listed for multi-organ transplant have significantly higher wait times and waitlist mortality/deterioration, with heart-lung having the highest risk: nearly 3-fold risk of death/deterioration as compared to heart alone listings.

Negeen Shahandeh, MD, from UCLA, explored the hypothesis that multi-organ recipients have lower risk for CAV as compared to heart alone recipients. In "***Comparison of CAV Development in Simultaneous Multi-Organ and Isolated Heart Transplant Recipients in the United States***," multi-organ recipients had 35% lower risk of having CAV as compared to heart alone recipients. Hypotheses explaining this difference include chimerism of T-cells that are not reactive to the donor heart as well as neutralization of HLA antibodies in a liver allograft.

The final abstract was from **Salil Kumar, MD**, of Houston Methodist Hospital, describing a risk score for patients undergoing heart-kidney transplantation. In "***A Novel Simultaneous Heart-Kidney (sHK) Transplantation Risk Calculator Predicts Chronic Dialysis or Death at 1-Year: A UNOS Analysis***," the risk score included parameters of age, sex, BMI, previous malignancy, total bilirubin, creatinine, mean PA pressure, IV treatment for infection, and donor age. The risk score provided moderate discrimination of patients whose kidney graft failed or passed away at one year. These investigators thus proposed that candidates with high-risk scores be considered for delayed kidney transplant after heart transplantation.

VIEW SESSION DETAILS

– Commentary by Jason Goldberg, MD, MS

SESSION 93. A Midsummer Night's Dream: From Mitochondria to Xenotransplantation: Novel Research Coming to You!

Patricia Uber, PharmD, of Thomas Jefferson University Hospital in Philadelphia, and **Carlos Ortiz-Bautista, MD, PhD**, of Hospital Universitario Gregorio Marañón in Madrid co-chaired this session near the close of the conference.

The first abstract, "***Echocardiographic Evaluation of Two 10-Gene Modified Xenoheart Transplants into Brain Dead Decedents***" was presented by **Tajinderpal Saraon, MD**, of NYU Langone Health in New York.

In this study, two xenoheart transplants were performed using genetically modified pig hearts in brain dead decedents, who had been ruled out for organ donation and consented for whole body donation for research. The purpose of this study was to assess echocardiographic evaluation of the porcine heart function in the human physiological environment. Graft function was monitored POD0-POD3 with serial TEEs. Initially, Dr. Saraon showed anatomic images of human and pig hearts, and pointed out that the pig heart is rounder and shorter, overall more globular with a smaller RV. This would be relevant for biopsies and echo imaging. Notably, part of the 10-gene modification was growth hormone receptor knock out based on experience of transplant into baboons. Standard cold heart storage and immunosuppression was used. The first NYU xenotransplant had a donor pig weight of 70 kg and recipient 82 kg, the second transplant from 69 kg donor pig and a 57 kg recipient.

Xenotransplant #1 on POD 0 had great immediate graft function, LVEF 75%, but the heart was relatively small. That raised the question: how do you size-match xenotransplants? If applying human size matching criteria, the first heart would have been undersized, and notably has growth-hormone receptor gene knocked out, as Dr. Saraon mentioned. Subsequent TEEs revealed gradually declining LV function, eventually reaching 40-45% on POD 3. The RV followed a similar pattern with development of severe TR following endomyocardial biopsy on POD1 and Swan-Ganz catheter placement. Xenotransplant #2, which was appropriately sized per human criteria, also had hyperkinetic LV function initially and remained hyperkinetic through POD3. The RV function also remained robust with only mild TR.

In conclusion, Dr. Saraon described two successful porcine xenotransplants into two human descendants, one with declining and one with stable graft function possibly related to size matching. Further he said that next longer study duration of xenotransplantation is needed in addition to a XenoDonor heart graft growth curve study. He also thanked the donors and their families for their tremendous contribution to this important study.

Next, **Lukas Stastny, MD**, of the Medical University of Innsbruck, presented "***Monitoring of Mitochondrial Function in Donation after Circulatory Death: A Porcine Ex-Situ Heart Perfusion Model***". The aim of this study was to investigate bioenergetic function during 6 hours of ex-situ heart perfusion (ESHP) in a porcine DCD model. In this first analysis of mitochondrial respiratory

function during ESHP, Dr. Stastny showed that ESHP can preserve mitochondrial respiration in control hearts and that mitochondrial respiration is preserved over 3 hours in DCD hearts before declining after 6 hours. She stated that decreased complex I – linked respiration was the driving factor for lower respiration rates in DCD hearts and noted that mitochondrial outer membranes remained intact in both groups.

Nader Moazami, MD, of NYU Langone Health, continued the session with the abstract "***Two 10-Gene Modified Xenoheart Transplants into Brain Dead Decedents***". After hearing from Dr. Saraon about the echocardiographic assessment of graft function in these two xenoheart transplants into brain dead human decedents, who had been declined for organ transplantation and had donated their body to science, Dr. Moazami now presented the center's experience with daily transjugular biopsies. Standard procurement and cold storage were used, as well as standard approved immunosuppression including ATG-induction followed by complement inhibitor eculizumab, methylprednisolone, and mycophenolate mofetil.

As Dr. Saraon had discussed, the first transplanted heart was relatively small, needing vessel patch augmentation, which resulted in a long ischemic time of 4hrs 21 min. The second heart had an ischemic time <4 hrs and was appropriately sized per human sizing criteria based on the experience with the first transplant. The first recipient was on high dose dobutamine, but CI remained <2 mmhg and cvp>20 mmHg—all consistent with undersizing and ischemia-reperfusion injury given prolonged ischemic time. The recipient patient was on low dose dobutamine with significantly better hemodynamics.

Both hearts had subendocardial hemorrhage, more severe in the first recipient likely reflecting ischemia-reperfusion injury. Notably, daily endomyocardial biopsies showed no evidence of hyperacute rejection, ACR, or AMR in either heart. A major concern with xenotransplantation is transfection of zoonosis, which might have contributed to the outcome of the Maryland patient with transmission of CMV. In the NYU experience, however, no CMV or other endogenous porcine virus transmissions were detected.

Dr. Moazami concluded that while the pig heart is similar, it is not identical to the human heart, and pointed out the difficulty of size matching and the possibility of oversizing. There is much to learn and to discuss on the way to xenotransplantation. The question is how? Does a clinical trial make sense and how to get there?

The final presentation of the session was by **Nandan Mondal, MSc, MPhil, PhD**, of Baylor College of Medicine in Houston: "***Cardiac Mitochondrial Stress Burden and Impairment of Oxidative Phosphorylation are More Profound in Human Heart Donated after Circulatory Death Than Heart Donated after Brain Death***". Dr. Mondal started by discussing the important role of mitochondria in DCD warm ischemic time in regard to myocardial ischemia and oxidative phosphorylation. In this study, N=6 DBD and N=18 DCD hearts were compared. He showed that the severity in incremental cardiac stress burden and diminished oxidative phosphorylation in DCD hearts may lead to an imbalance in redox stress and cardiac injury with prolonged warm ischemic time. Based on this experiment, he suggested that 20 min of warm ischemic time seems safe, 40 min debatable and

60 min unsafe. He concluded his presentation with the question if modification of the DCD preservation method could extend the safe ischemic time?

VIEW SESSION DETAILS

– Commentary by Luise Holzhauser, MD