SRC Analytical Methods Subcommittee Meeting Minutes

Analytical Methods Subcommittee Teleconference

April 29, 2022, 11:30 AM – 2:00 PM CDT

Voting Members:	**HRSA:**	**SRTR Staff:**
David Vock, PhD (co-Chair)	Adriana Martinez	Ryutaro Hirose, MD
Shu-Xia Li, PhD	Shannon Dunne, JD	Jon Miller, PhD
Brent Logan, PhD		Josh Pyke, PhD
Not in attendance:		David Zaun, MS
Andrew Schaefer, PhD		Grace Lyden, PhD
Katherine Panageas, PhD		Larry Hunsicker, MD
		Nicholas Wood, PhD
Ex-Officio Members:		**Not in attendance:**
Jon Snyder, PhD		Ajay Israni, MD, MS
(SRTR co-Chair)		

Welcome and opening remarks

Dr. David Vock called the Analytical Methods Subcommittee (AMS) meeting to order. He reviewed the agenda and went over conflict of interest management.

Modeling offer acceptance and discard in simulation models

Dr. Nicholas Wood first presented on offer acceptance modeling, which included a liver simulated allocation model (LSAM) and acuity circles policy case study. In 2018, the Scientific Registry of Transplant Recipients (SRTR) simulated several circular liver allocation policies using LSAM while the Organ Procurement and Transplantation Network (OPTN) was transitioning away from the use of donor service areas (DSAs) and regional allocation based on the 11 OPTN regions. The OPTN implemented the acuity circles allocation policy in February 2020. This system uses concentric circles drawn at 150, 250, and 500 nautical miles (NM) around the donor hospital and allocates to the highest acuity patients within each circle.

Dr. Wood compared observed data following implementation of acuity circles to what was predicted within the simulations. The 3-year simulation used data from July 2013 to June 2016, and ran 10 iterations. Three primary metrics of interest were median travel distance between the donor and the candidate's center, the median model for end-stage liver disease (MELD) at transplant (MMaT), and variance in median MELD at transplant (vMMAT). vMMaT across DSAs is a way of summarizing geographic disparities within the system.

Median travel distance under the previous allocation policy (Share 35) was simulated to be 89 NM versus 184 NM for acuity circles. Dr. Wood presented the 1-year rolling average of the observed median travel distance from 2010 to present, demonstrating that the median travel distance was stable at approximately 85 NM in the years preceding acuity circles and increased to approximately 145 NM rapidly after the implementation of acuity circles, which was lower than the 184 NM predicted by LSAM.

LSAM predicted the MMaT under Share 35 to be 29 and under acuity circles to be 31, implying that acuity circles would be better able to get livers to candidates with higher MELD scores. Dr. Wood presented the observed 1-year rolling average of MMaT, which was stable at 29 in the years preceding acuity circles and did not change after acuity circles.

LSAM predicted vMMaT of 11 under Share 35 and predicted a substantial reduction to 4.4 under acuity circles. Dr. Wood then presented the 1-year rolling average of vMMaT, which dropped when acuity circles went into effect but rebounded to levels commensurate with what was observed under Share 35. Dr. Wood concluded there has not been any persistent change to vMMaT.

Dr. Wood said these results appear to have been a result of the offer acceptance model used by the LSAM and the method LSAM uses to determine if a liver will be discarded rather than transplanted. The simulation used two logistic regression models to predict offer acceptance based on candidate status (status 1A vs not-1A). Both models used offer/sequence number as a predictor. Dr. Wood stated that the earlier a candidate is in match run, the greater the chance of accepting the offer. The offer acceptance model was used for both Share 35 and acuity circles, meaning there was an assumption that offer acceptance behavior does not change from one allocation system to the other, and that the probability of acceptance based on offer number is independent of the allocation system being modeled.

Dr. Wood posited that this assumption was proven false, since median offer number at acceptance was five under Share 35 and nearly doubled to eight or nine following the implementation of acuity circles. Dr. Wood said this proved that the relationship between offer number and the probability that a candidate would accept the liver changed under acuity circles.

Dr. Wood then presented the relationship between offer number and the median MELD score for candidates at that offer number. The predicted MELD score at the median offer number at acceptance under Share 35 was 29, which was the same as the observed MMaT under Share 35. LSAM assumes this static relationship between offer number and probability of acceptance, which means that the distribution of offer number acceptance in the simulation for acuity circles looks roughly the same. Because of the way the acceptance model works, the median number of offer acceptance in the simulation is roughly the same for both allocation systems. The median MELD score at offer eight or nine under acuity circles is 29, which is as observed. Dr. Wood said this suggested the acceptance model that LSAM used was overoptimistic about who is accepting the liver, predicting acceptance earlier in the match run than was actually observed under acuity circles. This resulted in LSAM predicting a higher MELD score at transplant and a subsequent reduction in vMMaT that has not been realized following implementation of acuity circles.

Dr. Larry Hunsicker hypothesized less willingness to accept an offer from donors who are farther away than would have been predicted. Dr. Wood speculated that this was because more offers were being received, leading to more declines in hopes of getting a better quality organ. If the LSAM stratified by donor region, all would have the same median offer number acceptance of five. In reality, it varies by location of recovery. Dr. Wood noted that the simulation assumes "average" acceptance behavior for all programs in the country and that this, coupled with the apparent behavior change observed following implementation of acuity circles, likely resulted in predictions that were not realized.

Dr. Wood showed two graphs with the predictive MMaT versus the actual MMaT by DSA, comparing Share 35 and acuity circles. Share 35 had a larger variance. He proposed this was related to differences in center-specific behavior. Under acuity circles, the simulation predicted little vMMaT across the DSAs, explaining a low vMMaT according to LSAM. In reality, there was still a wide vMMaT across DSAs. Dr. Wood said this was happening because, while geography does impact access, the other factor affecting geographic disparity was the vast variation in offer acceptance practices across transplant centers, which explains why LSAM was inaccurate in its MMaT predictions.

The LSAM also underpredicted the vMMat during the study period under Share 35 from 2013-2016. The predicted variance was 11 versus an actual variance of 16-18. The study assumed a liver was discarded after 250 offers. If the simulation was rerun with 60 offers before discard instead of 250, the simulation yielded a predicted vMMaT under Share 35 of 14.5, closer to reality. Dr. Wood said this suggested it is difficult to predict who will receive a transplant late in the match run.

Dr. Jon Snyder asked if the data could inform where the right discard point would be, rather than just picking 250. Dr. Wood said the problem with that is whatever percentile was chosen for offer number acceptance of Share 35 versus acuity circles, acuity circles are higher. Dr. Josh Pyke added that the 250 offer cut-off was selected as a tuning parameter for the LSAM baseline scenario. The same methodology would not have to be used in future simulation work. He also suggested that if the models were selected using the least absolute shrinkage and selection operator (LASSO) method, the shrinkage approach might have overprioritized predictors good at early match run discrimination but bad at late match run discrimination. Dr. Wood thought it had less to do with LASSO and was more about what features were chosen to inform the LASSO model. Dr. Vock said the rate of organ offers was important as a predictor to add to the model. Framing it as a survival problem may be helpful, such as using the offer number as the time component in the survival model. Dr. Wood suggested using candidate characteristics instead of offer numbers. Dr. Grace Lyden said time since last offer might be easier to implement into the simulation.

Dr. Wood proposed improvements to the models. Future simulations should not include offer/sequence number as a predictor of offer acceptance due to concern of overfitting to specific behavioral things related to the current allocation system. In addition, he suggested clustering transplant centers based on historical transplant offer acceptance patterns. The clustering could use the k-means algorithm (or similar clustering algorithm), enabling it to capture differences in center behavior, and organically solve the problem of vast differences between adult and pediatric candidates.

Dr. Wood moved on to discard modeling within the simulation. He reviewed recommendations from the AMS meeting in June 2021, which discussed the issue of modeling discards in simulations, and previous simulations that unrealistically assume organs are discarded after a set number of offers. One fundamental difficulty with modeling discard is not knowing the point in the match run when an organ procurement organization (OPO) stopped offering the organ. The previous discussion concluded that without better data collection, discards should not be modeled, meaning only transplanted organs should be included in the simulation. In simulation, offered organs should only be discarded if the match run was exhausted.

Dr. Wood said data on the new kidney allocation system may provide a way to model discards without having a data quality issue. He first discussed match-run complexity, noting the paper by Adler et al,[1] which demonstrated an increase in network complexity after the implementation of the circular kidney allocation system ("KAS250"). Adler and colleagues raised concerns, and called for monitoring of the new system, as it might have detrimental effects on utilization and cold ischemic time given more connections between OPOs and transplant centers (ie, increased complexity). Based on that work, Dr. Wood and colleagues came up with a metric to quantify the complexity of match runs: the "center number at offer 50" (C50). C50 is the number of unique transplant centers on the match run by offer number 50, with the idea being that the higher the number is, the more complex the match run is. It was hypothesized that more transplant centers receiving offers early in the match run leads to more opportunity for delays and discards.

To test this, they looked at kidney-alone match-run data, and median/mean C50, nationally and by donor region. Dr. Wood showed a graph with a 1-year rolling average, looking at the mean C50 for all match runs for deceased donor kidneys and kidney-alone match runs in the previous year. The figure demonstrated that the kidney policy that went into effect in 2021 increased the average C50 to over 12 for average complexity of the match run.

Dr. Wood also showed a map by donor region comparing approximately 6 months of pre–circles era data (10/5/2020 through 03/14/2021) to 6 months of circles era data (03/15/2021 through 10/05/2021). The darker the color, the higher the increase in C50. The West Coast experienced no change, the Midwest had a modest increase, and the East Coast had a large increase where the match runs have 15 more centers on average within the first 50 offers than under DSA-based allocation.

Dr. Wood then reviewed discard rate since the circles allocation policy went into effect. A 1-year rolling average of discard rate showed the discard rate increased since circular allocation policy went into effect, such that the first year of circular allocation had a record high discard rate of 24.7%, or one in four recovered kidneys was discarded. The discard rate was 21.4% in the COVID-19 era (before KAS250) compared with 20.2% prior to the pandemic. COVID-19 did not appear to be a large driving factor in the increase in discards.

Dr. Wood asked, "Is the increase in match-run complexity the cause of the increase in discards?" To answer this, Dr. Wood used regression models for predicting the probability of discard using pre–circles era data. The first was a one-predictor model where the kidney donor risk index (KDRI) was used to predicted discard. The second was a two-predictor model considering both KDRI and C50, along with the interaction between KDRI (</> 1.0) and C50.

The two models were used to predict discards on data after KAS250 was implemented, and compared the observed and expected number of discards for each model. Any differences could be contributed to match-run complexity.

KDRI was observed to be slightly higher on average after the implementation of circular allocation. C50 increased from 7.1 to 12.6, and the overall discard rate increased from 19.7% to 24.5%. There was no difference in discard rate between the pre-KAS250 era and KAS250 era for the highest quality kidneys or KDRI less than 1, but there was an increase in discard of kidneys with a KDRI greater than or equal to 1 from 25.8% to 30.8%.

The results from the model showed the predicted discard rate was 21.8% (using the KDRI-only model). For the model for KDRI+C50, C50 significantly affects the probability of discard, depending on the KDRI. C50 KDRI less than 1 has a significant negative coefficient, meaning that the higher C50 is, the less likely the kidney is to be discarded for the highest quality kidneys. C50 for KDRI greater than or equal to 1 is significant and positive, meaning the higher the C50, the more likely that the kidney will be discarded for the lower quality kidneys. If the model was applied to the era after KAS250 allocation implementation, the predicted number of discards is 5334, or 354 additional discards, giving a predicted discard rate of 23.4%. The actual discard rate was 24.5%, meaning the discard rate is still underpredicted. Dr. Wood said COVID-19 might play a role in this because the model was fit using mostly pre–COVID-19 data.

Dr. Ryutaro Hirose suggested characterizing the nature of the centers high in the match run, such as being more or less likely to accept kidneys. This would lead to major implications in policy development, like offering certain kinds of kidneys to a different subset of centers. He also cautioned against making complexity reduction a main goal. Dr. Wood agreed, saying the goal should be increasing utilization. Dr. Hirose added that distance may be weighed against the quality of the kidney.

Dr. Wood proposed a two-step placement model. Instead of linking discard and offer acceptance together, they could be separated—first modeling discard and, if not discarded, then modeling acceptance. Nondiscarded organs would then be offered down the match run until acceptance. This process sidesteps the question of when in the match run an organ is discarded, instead predicting if it will be transplanted. If the discard model only accounts for donor factors, it cannot distinguish between two allocation systems because both are fed the same donor cohort. However, if in addition to donor factors, the discard model also includes factors about the match run, then the difference can be inferred between allocation systems. Match-run complexity and its relationship to probability of discard provides a way to model discards by sidestepping data limitations.

Dr. Pyke asked how well this relationship was understood, and if it would persist. He also expressed concern over embedding complexity as a singular or primary driver of discards in the simulations as a part of the report given to the committees, because committee members may minimize complexity above all other considerations. He also asked if anything should to done on a technical level to prevent this from going wrong. Dr. Wood thought the relationship was causative but not necessarily so. He added there were other ways of changing allocation policy practice that could address this problem. Dr. Hirose said there were many ways to get rid of the effect if causative, as much of it involves workflows with offers going down serially, not parallel.

Dr. Lyden asked what needed to be included in the model for discard, to ensure the best quality when comparing different allocation systems. Dr. Wood said it was important to be wary of how discard was defined. Specifically, if discard is defined by including all livers where allocation was attempted, then that would show where increased complexity corresponds to increased discard under the new allocation system. Because of this, Dr. Hirose proposed using utilization as a metric instead.

Dr. Wood agreed with Dr. Pyke's concern regarding committee and utilization. He suggesting setting an acceptable discard rate, or having maximum utilization and minimum discards so organs can be offered as broadly as possible. Dr. Hirose cautioned on how increasing utility to the maximum may negatively affect equity metrics.

The committee supports the direction SRTR is taking with the modifications to the simulation process and continues to support the idea that transplanted organs are included in the future simulations and offered until acceptance while discard modeling undergoes continued development.

Closing business

With no other business being heard, the meeting concluded. The next meeting is to be scheduled for summer 2022.

Reference

1. Adler JT, Husain SA, King KL, Mohan S. Greater complexity and monitoring of the new Kidney Allocation System: implications and unintended consequences of concentric circle kidney allocation on network complexity. *Am J Transplant.* 2021 Jun;21(6):2007-2013. doi: 10.1111/ajt.16441. Epub 2021 Jan 2.