BOOK OF ABSTRACTS

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Title: Assessing cumulative immunosuppressive drug exposure: metrics, outcomes, and implications for transplant patients

Background: Immunosuppressive drugs are used in the long-term management of post-transplant patients to prevent rejection of transplanted organs. With no prior qualitative systematic review on the topic, we aimed to characterize the metrics used to measure cumulative immunosuppressant exposure and their associated outcomes in transplant patients.

Methods: We conducted a literature search using search terms related to maintenance immunosuppressants and cumulative exposure in Ovid MEDLINE, Ovid EMBASE, Cochrane CENTRAL, and Cochrane Database of Systematic Reviews. No date restrictions were applied. The search strategy was also applied to Google Scholar to investigate the grey literature. Studies were limited to the English language with adult human transplant patient populations. Study risk of bias was assessed using the Quality in Prognostic Studies tool where each domain was rated as low, medium, or high risk of bias.

Results: Twenty-eight articles were obtained after title, abstract, and full-text screening and included in our qualitative synthesis. Various solid-organ transplant populations were examined. Fifteen articles (54%) calculated the total dose of immunosuppression a patient received over their treatment period, while seven (25%) used long term area-under-the-curve of trough level concentrations to quantify cumulative immunosuppression exposure. Four (14%) articles investigated time-weighted metrics of calcineurin inhibitors, while the remaining three (11%) articles explored other cumulative metrics that could not be categorized in the other groups.

Conclusion: This review analyzed a comprehensive set of articles and metrics that predict long-term outcomes of immunosuppressive drugs in transplant patients. Based on their prognostic capabilities, we provided insight into promising metrics that have clinical value for predicting relevant outcomes. However, the wide variety of metrics identified also highlights the lack of standardization in the long-term management of transplant patients. Although certain metrics may demonstrate an association with outcomes, future studies should investigate their predictive power and potential use in clinical decision making.

Figure 1. Study flow diagram

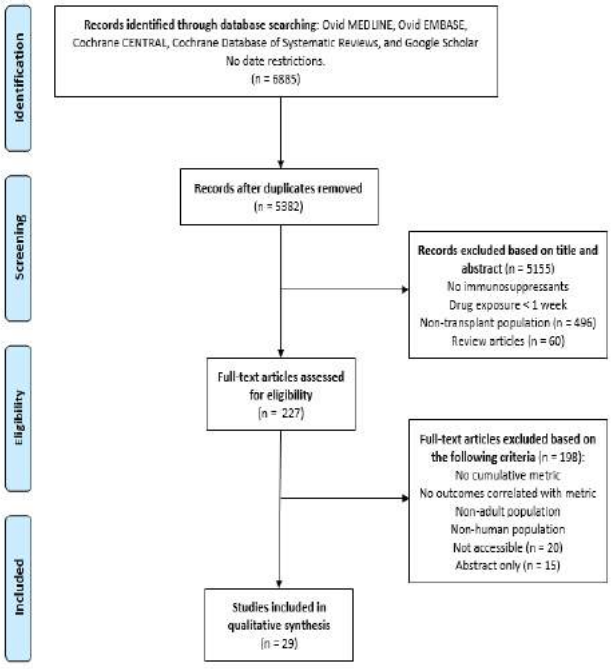
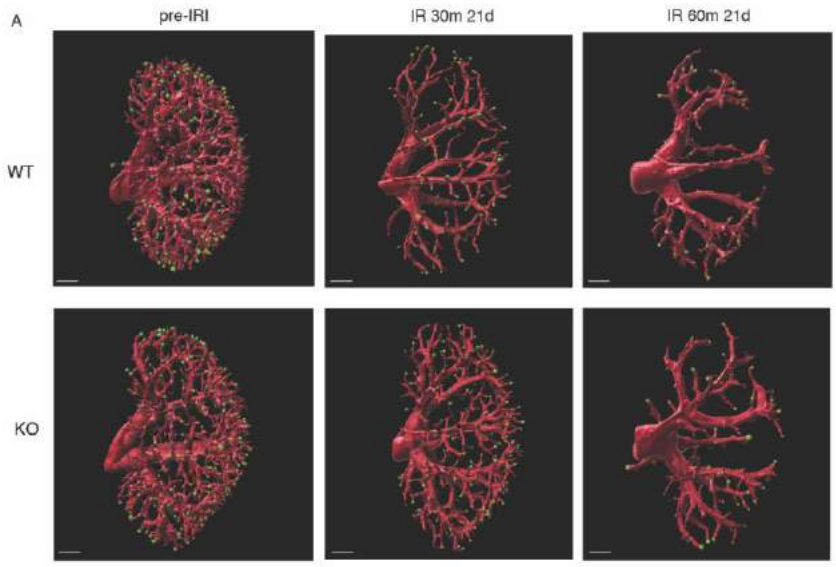


Table 1. Cumulative exposure metric relating to outcome

Metric	Outcome
Cumulative CNI Exposure	Once daily tacrolimus non-inferiority to prograf
	Vasodilation
	Renal hyalinosis, global glomerulosclerosis, fibrosis
Cumulative Steroid Exposure	Bone mineral density
	Squamous cell carcinoma
	Heart graft failure
	Renal graft rejection
	Non-inferiority between low and normal steroid doses
	1st tacrolimus blood level
Cumulative Exposure for Multiple drugs	tHcy concentration
	Fracture
	Heart graft failure and lipid levels and atherosclerosis
	Bone mineral density changes
OKT3 Cumulative exposure	Post-transplant lymphoproliferative disorder
Long-term AUC of CNIs	Short-term and long-term solid-organ transplant allograft function
	Mortality and graft loss
	Cumulative change in eGFR
	Insomnia
	Restless leg syndrome
	Serum concentrations of immunoglobulin heavy/light chain pairs and free light chains
Time-weighted Variability of Tacrolimus	Renal graft survival
Time-weighted Average of Tacrolimus	Cancer development within 3 years post-transplant
Average CNI AUC	Recurrence of hepatocellular carcinoma
MTOR/Steroids Time post-randomization	Renal function measured by eGFR, probability of freedom from major cardiac events
MPA AUC	Renal transplant acute rejection within 1 year post-transplant
Daily Defined Dose of mTOR inhibitors	Malignancy and mortality
Weighted Linear Combination of Azathioprine, Prednisone, and Cyclosporine	Basal cell carcinoma and squamous cell carcinoma

Caspase-3 regulates peritubular capillary dysfunction and transition from acute to chronic kidney disease after ischemia-reperfusion injury

Background: Ischemia-reperfusion injury (IRI) is a major risk factor for chronic renal failure. Caspase-3, an effector responsible for apoptosis execution, is activated within tubular epithelial structure and peritubular capillaries (PTC) in the early stage of IRI-induced acute kidney injury (AKI). We previously characterized the different cell deaths in tubular and microvascular compartments of IRI-induced acute kidney injury (AKI) and their relative importance on microvascular rarefaction and renal fibrogenesis in mild AKI. Here, we further characterize the role of caspase-3 in microvascular dysfunction and progressive renal failure in both mild and severe AKI. **Methods**: Unilateral renal artery clamping for 60 minutes with contralateral nephrectomy was performed in both wild-type (C57BL/6) or caspase-3-/- mice. **Results**: In the severe AKI model (60 minutes clamping), caspase-3-/- mice showed reduced PTC endothelial cell loss, decreased PTC collagen deposition, and α-SMA expression, and lower tubular injury scores on the long-term when compared to wild-type animals. Preservation of the peritubular microvasculature in caspase-3-/- mice led to reduced tubular ischemia, with lower hypoxia-inducible factor 1α (HIF1α) expression. Besides, intra-vital imaging and micro Computed Tomography (microCT) revealed preserved PTC permeability and better terminal capillary density in caspase-3-/- mice. Caspase-3-/- mice with severe IRI also showed better preservation of long-term renal function. **Conclusions:** Collectively, these results demonstrate the pivotal importance of caspase-3 in regulating long-term renal function after IRI and establish the predominant role of PTC dysfunction as a major contributor to progressive renal dysfunction.



Apoptotic exosome-like vesicles promote angiogenesis following severe vascular injury.

Background:

Ischemia-reperfusion injury (IRI) is an integral component of kidney transplantation and common cause of acute kidney injury (AKI). AKI leads to programmed cell death of endothelial cells (ECs) in peritubular capillaries favoring microvascular rarefaction. We previously showed that apoptotic endothelial cells secrete, in addition to classical apoptotic bodies, exosome-like vesicles (ApoExo) that regulate endothelial function. However, the precise role of ApoExo on the vascular response to injury remains unclear. Here, we investigate the impact of ApoExo on angiogenesis following vascular injury.

Method:

ApoExos were isolated by sequential ultracentrifugation from medium conditioned by apoptotic human ECs or murine ECs. Unilateral hind limb ischemia, a model of persistent vascular injury, was induced by femoral arteriectomy. Mice were injected intravenously with ApoExo every second day up to eight injections. Blood flow recovery monitored by laser Doppler, ischemic damage, ambulatory impairment and weight were measured at 0 to 21 days post-surgery. Mice were sacrificed at 21 days and capillary density was evaluated on the ischemic hindlimb. We also used in vitro assays with human ECs exposed to ApoExo to assess levels of apoptosis (measured by fluorescence microscopy), wound closure (scratch assay) and angiogenic activity (tube formation assay).

Results:

ApoExo-injected mice exhibited enhanced blood flow recovery and reduced ischemic damage from day 7 to 21 (Fig A). Capillary density was increased in the ApoExo-injected group, suggesting improved angiogenesis and better capillary repair (Fig B). *In vitro,* ApoExo inhibited apoptosis of ECs and promoted endothelial wound closure and tube formation (Fig C).

Conclusion:

Collectively, these results suggest that ApoExo can help restore the microvasculature following severe vascular injury by increasing the resistance of EC to apoptosis and by upregulating their migration and angiogenic activity. The release of ApoExo by damaged ECs likely represents a feedback loop aimed at favoring repair after vascular injury.

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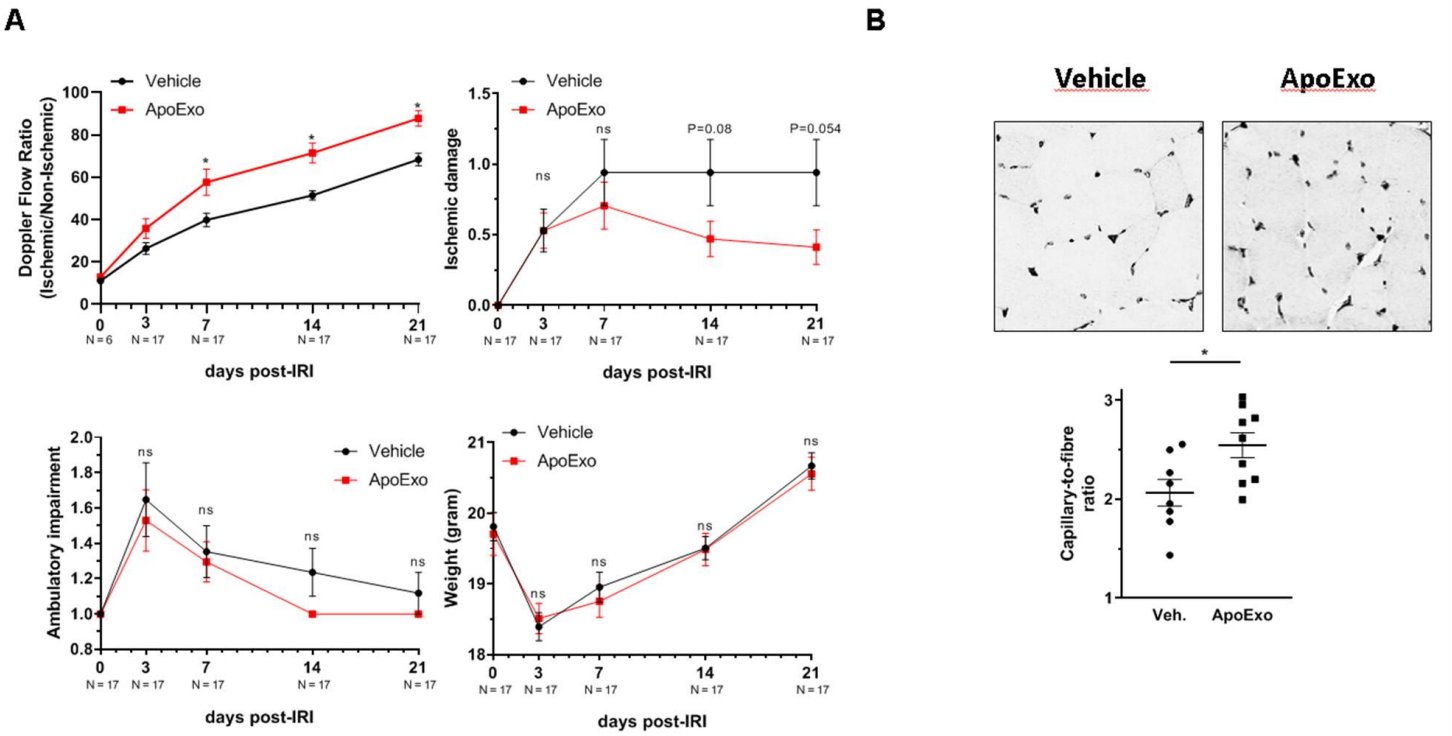
A
Vehicle
ApoExo
Doppler Flow Ratio (Ischemic/Non-Ischemic)
Ischemic damage
Ambulatory impairment
Weight (gram)
days post-IRI
ns
P=0.08
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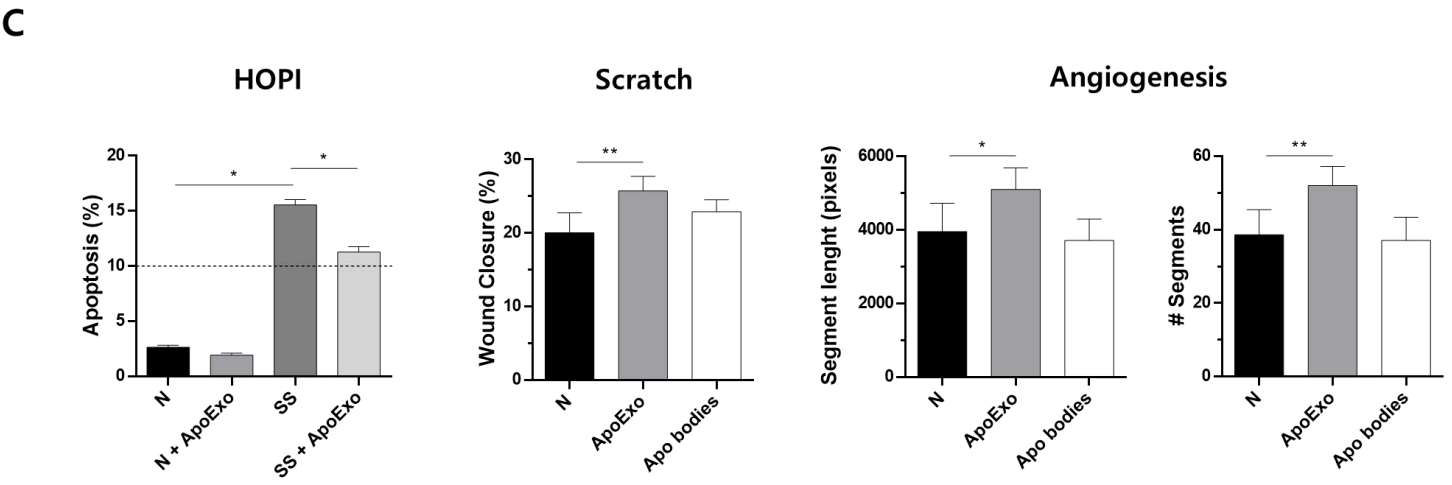
B
Vehicle
ApoExo
Capillary-to-fibre ratio
Veh.
ApoExo


C
HOPI
Scratch
Angiogenesis
Apoptosis (%)
N
N + ApoExo
SS
SS + ApoExo
Wound Closure (%)
ApoExo
Apo bodies
Segment lenght (pixels)
Segments

Contemporary Risk Factors for Ureteral Stricture Following Renal Transplant

Background: Ureteral strictures following renal transplant often require surgical repair, increase morbidity, and can impair graft function. Most studies assessing risk factors for ureteral stricture following renal transplant are over two decades old. Given that renal transplantation is a rapidly evolving field, the objective of this study was to re-examine risk factors for ureteral stricture in transplants performed over the past decade.

Methods: A retrospective analysis was performed on all renal transplant patients at Vancouver General Hospital between 2008-2020. Demographics, clinical parameters, and outcomes were compared between patients who did and did not develop ureteral strictures. Putative risk factors for ureteral stricture were then analyzed using a logistic regression.

Results: 1188 patients were included with a mean follow-up of 61.9±40.8 months. Ureteral stricture occurred in 26 (2.1%; mean time to stricture 103.5±150.7 days) patients, who had no demographic differences when compared to non-stricture patients. However, stricture patients had significantly higher rates of post-operative complications (delayed graft function, wound dehiscence, and infection), increased length of hospital stay, and decreased GFR at 1 year following transplant (all $p < 0.05$). On multivariate analysis, cold ischemia time >445 minutes and acute rejection showed a trend towards predicting strictures (both $p = 0.051$), while extended criteria donors were protective (OR 0.32, CI 0.12-0.89; $p = 0.028$). Approximately 1/3 of stricture patients were treated with balloon dilatation, 1/3 with surgery, and 1/3 were managed through stenting alone.

Conclusion: Ureteral stricture patients had higher rates of post-operative complications and reduced renal function at 1-year post-transplant when compared to non-stricture patients. Our findings support attempts to reduce cold ischemia time and to avoid acute rejection through best practice immunology and immunosuppression. Future research in a multicenter setting to increase the stricture patient sample size is warranted.

Utility and practice patterns of central venous line in renal transplant recipients in Canada

Background: The indications and practice patterns regarding Perioperative placement of central venous lines (CVL) is not standardized and is highly variable between Canadian centers. Serious complications can and do happen with CVL placement. Herein we describe the current indications and practice patterns amongst Canadian transplant programs.

Methods: This quality improvement analysis was conducted through a web-based survey distributed to physicians at 21 adult kidney transplant programs in Canada.

Results: 14 programs (12 surgeons and 12 nephrologists) responded to our questionnaire. Overall, routine use of CVL was reported by 58.3% while 41.7% provided specific criteria.

For recipients of living donor kidneys, 50% indicated routine use of pre-operative CVL. The remaining 50% mentioned high immunologic risk, anticipated delayed graft function and perceived need or plan for induction with anti-thymoglobulin (ATG) as reasons for using CVLs (Figure-1).

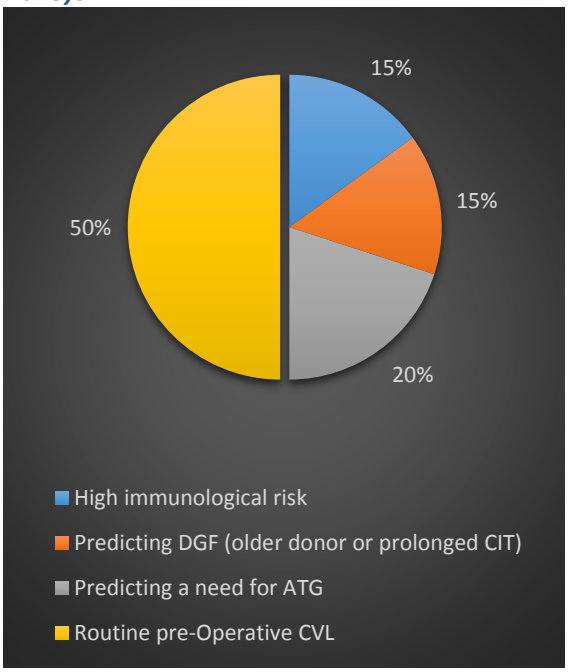
For deceased donor kidney recipients, 80% reported routine use of CVLs. Others added donor Acute Kidney injury (AKI) and donation after circulatory death (DCD) to the above indications (Figure-2). One program described use of peripherally inserted central catheters (PICC lines) as an alternative to CVLs.

Use of Chlorhexidine impregnated catheters was reported by 25%. 33% of respondents were not aware of catheter coating. The remaining 42% respondents reported not using Chlorhexidine impregnated catheters.

Anecdotal recall of complications attributed to CVL were reported by 50%. The most common complications were allergic reactions (91.7% respondents), significant hematoma (50%), pneumothorax (25%), catheter migration (16.7%), and carotid artery injury (8.3%).

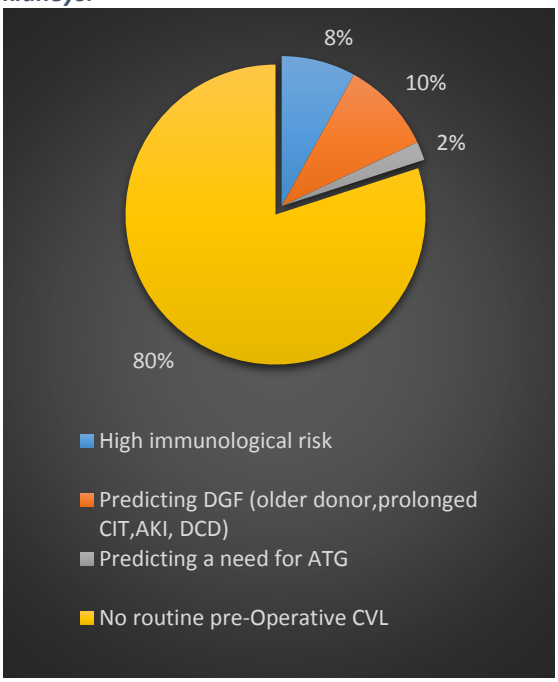
Conclusions: Use of CVLs in kidney transplant recipients at Canadian programs is vastly heterogeneous. Given the potential for serious CVL associated complications we recommend the risks and benefits of catheter placement be considered on a case by case basis and alternative options be explored when possible.

Figure 1- Use of CVL in recipients of living donor kidneys.



DGF: delayed graft function; CIT: cold ischemia time; ATG: anti-thymoglobulin; CVL: central venous line.

Figure 2- Use of CVL in recipients of deceased donor kidneys.



DGF: delayed graft function; CIT: cold ischemia time; AKI: acute kidney injury; DCD: donation after circulatory death; ATG: anti-thymoglobulin; CVL: central venous line.

Assessing Risk Factors of Non-Adherence and Post-Transplant Outcomes in Kidney Transplant Recipients

Background:
Kidney transplant recipients' (KTR) adherence to prescribed regimens is vital for optimal recovery and long-term graft function. The aim of this study was to identify factors of KTR non-adherence and its impact on post-transplant outcomes.

Methods:
A retrospective single-centre cohort study was conducted among KTR from January 1, 2003 to December 31, 2017. Non-adherence was defined as one or more of the following in the first year post transplant: (1) > 20% missed clinic visits, (2) > 20% missed laboratory visits, and/or (3) > 40% coefficient of variation of calcineurin inhibitor levels. Multivariable logistic and Cox proportional hazards models were fitted to identify adherence risk factors and outcomes, respectively.

Results:
From a total of 2,714 patients, 1,803 (66.4%) were included in the analysis. The mean recipient age was 51.7 (± 13.4) years, and 60.7% were male. Overall non-adherence was identified in 34.9% patients; 11.2% patients were non-adherent to clinic visits, 5.4% to lab tests, and 25.2% to medication. Recipient history of psychiatric disorders (OR 1.57 [95% CI: 1.22, 2.02]) or non-adherence (OR 1.82 [95% CI: 1.31, 2.54]) were independent risk factors for non-adherence. Private (vs. public) drug coverage reduced the risk for non-adherence (OR 0.62 [95% CI: 0.48, 0.80]). Any episode of non-adherence over the first-year after transplant was associated with total graft failure (HR 1.52 [95% CI: 1.20, 1.91]), death with graft function (HR 1.51 [95% CI: 1.11, 2.05]), and biopsy-proven acute rejection (HR 2.35 [95% CI: 1.38, 3.99]). A trend toward an increased risk of death-censored graph failure was observed (HR 1.39 [95% CI: 0.96, 2.01]).

Conclusion:
KTR adherence is influenced by psychosocial and socioeconomic determinants which impact post-transplant outcomes. Our results emphasize the need for multifaceted interventions to improve patient adherence. Further investigation is required to determine if our results are generalizable to younger patient populations.

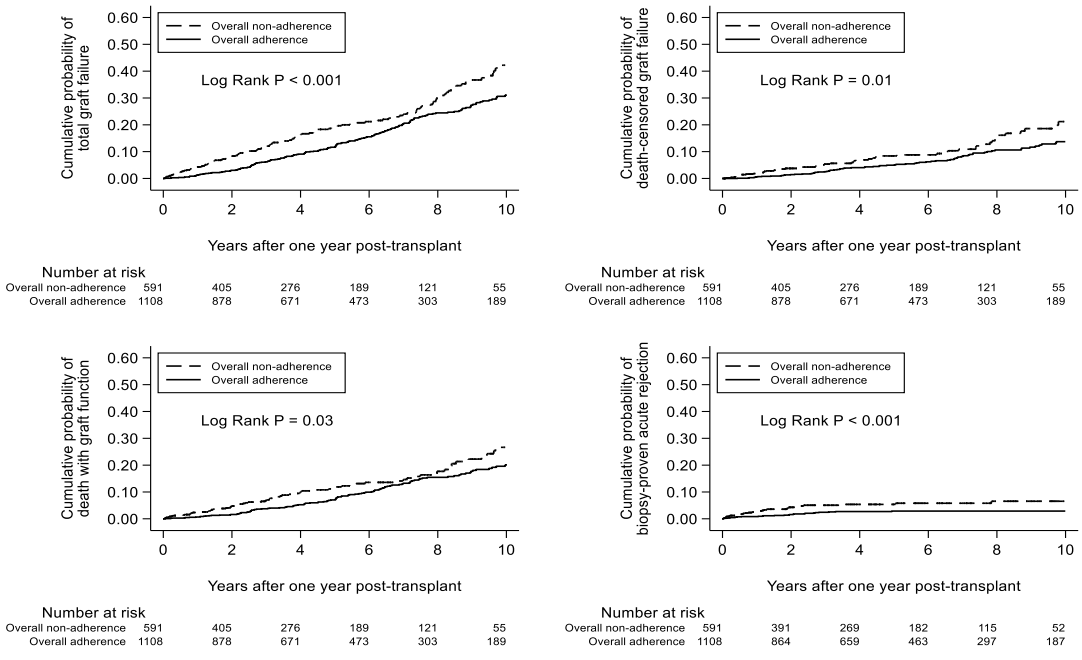


Figure 1. Kaplan-Meier estimates of total graft failure, death-censored graft failure, death with graft function, and biopsy-proven acute rejection starting one-year post transplant.

BANFF-IT, Computer-Assisted Reporting of Banff 2017 Classification of Kidney Allograft Biopsies

Background: A recent survey by the Banff Antibody-Mediated Injury Working group suggested that the Banff classification of antibody-mediated rejection (ABMR) is vulnerable to misinterpretation when applied in clinical practice. We describe the development of a computer program to aid in standardized diagnosis assignment of the 2017 Banff Classification.

Methods: In collaboration with the Rules and Dissemination Banff Working Group, we developed and applied a computer program assigning kidney allograft rejection diagnoses using the minimal dataset of parameters required by the diagnostic algorithms of the Banff 2017 Classification.

Results: The program was developed in R software and considered a minimal set of variables including Banff Lesion Scores, Additional Diagnostic Parameters (e.g., Acute Thrombotic Microangiopathy In The Absence Of Any Other Cause, Absence Of Recurrent Or De Novo Glomerulonephritis, Prior Evidence Of DSA) and Category 6 diagnoses. Through sequential application of rules based on this minimal set of variables, the program can assign all Banff Diagnostic categories such as acute and chronic active T-cell mediated rejection as well as active, chronic active, and chronic antibody mediated rejection (ABMR). Advantages of the program include the ability to assign diagnoses in a standardized fashion and within seconds even on very large datasets, capacity to flag suspected ABMR diagnoses when DSA is unavailable, and its adaptability to evolving diagnostic schemes. Limitations of the program include its reliance on the completeness and accuracy of a minimal set of variables and the need of a diagnostic oversight of a trained nephropathologist when applied for clinical purposes.

Conclusions: Automated computer algorithms assigning rejection diagnoses in a standardized fashion can serve as diagnostic aids in the service of pathologists and transplant clinicians. Their integration into electronic medical records and application as web-based tools in the context of clinical trials and observational studies can facilitate future knowledge synthesis.

Title: Infection with *Burkholderia cepacia* complex in cystic fibrosis patients following lung transplantation: A case series of recent experience

Background: Infection with *Burkholderia cepacia* complex (BCC) is associated with reduced survival in cystic fibrosis (CF) patients post lung transplantation.[1] Survival post lung transplantation has been increasingly linked to BCC genomovar type in retrospective studies.[2,3] Of the cepacia complex *Burkholderia cenocepacia* in particular confers the highest risk of death and has a high prevalence in Canada.[2,4] Survival rates 1, 3 and 5 years after lung transplantation are reported to be 76%, 60% and 49%, respectively.[5] Median survival for all CF patients is 8.02 years. In comparison to BCC negative patients, those infected with BCC have a lower survival (1.59 years versus 10.52 years).
Methods: This is a prospective case series of three adult CF patients at our tertiary care center with BCC post lung transplantation. Patient characteristics including age, BCC subtype, sex, survival, and current forced expiratory volume in 1 second are reported (Table 1).
Results: All patients are male, with an average age of 43.88 years and survival since transplant of 9.82 years. Two patients have mild reduction in FEV1 while one patient has moderate reduction.
Conclusions: Some regions in Canada have a particularly high prevalence of *B. cenocepacia*. [1,4] BCC is a major pathogen in CF with *B. cenocepacia* (genomovar III) accounting for 83% of all isolates in Canada.[6] CF patients infected with *B. cenocepacia* have a higher mortality rate than patients infected with other strains of BCC and those with non-genomovar III organisms may not have excess mortality risk post lung transplantation.[1,2] Experience suggests that patients should be informed of the higher risk of unfavorable outcomes post lung transplantation in those colonized with BCC. However, our case series shows that survival may be more favorable than reported in CF patients with BCC, including *B. cenocepacia* (genomovar IIIA) and *B. multivorans* (genomovar II).

Table 1. Characteristics of patients infected with *Burkholderia cepacia* complex (BCC)

Patient	BCC subspecies	Age (years)	Sex	Survival* (years)	Spirometry* (years)	Current FEV1 (L)	Current FEV1 (% predicted)
1	Genomovar II-multivorans	34.81	Male	8.75	7.80	4.04	86
2	Genomovar IIIA-Cenocpeacia	50.30	Male	8.99	8.03	2.63	73
3	Genomovar IIIA-Cenocpeacia	46.53	Male	11.71	10.82	3.76	99

*Time from lung transplantation
*Time from lung transplantation to most recent spirometry

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Assessing Health-Related Quality of Life (HRQoL) in Patients on Dialysis and Kidney Transplant Recipients using the PROMIS Global-10 survey

Background

The PROMIS (Patient-Reported Outcomes Measurement Information System) Global-10 survey has been used to assess HRQoL in population surveys and studies including patients with chronic medical conditions but not in patients with chronic kidney disease (CKD). Here we compare HRQoL between KT recipients (KTR) and patients on dialysis using the PROMIS Global-10 survey.

Methods

A cross-sectional convenience sample of adult KTRs and patients on dialysis completed the 10 item PROMIS Global-10 which yields a Global Physical Health (GPH) and a Global Mental Health (GMH) score. Sociodemographic and clinical characteristics were also collected. The two-sample t-test and multivariable linear regression were used to compare HRQoL between groups. Multiple imputation by chained equations was used to handle missingness.

Results

353 patients (mean(SD) age 56(15) years, 63% male, 53% White, and 68% transplanted) were enrolled.

Patients on dialysis vs KTRs were older (mean[SD] age 64[14] vs 52[14] years), less likely to be White (30% vs. 64%), and to have 4 or more comorbidities (73% vs. 37%.); $p<0.001$ for all.

Compared to patients on dialysis, KTRs had higher GPH (48[10] vs. 43[11], $p<0.001$) and near significantly higher GMH (49[10] vs 47[11], $p=0.055$). The proportion of patients with 5-point lower HRQoL (half SD, indicating potentially clinically significantly worse HRQoL) was lower among KTRs (47% vs 64%, $p=0.003$, and 32% vs 44%, $p=0.032$ for GPH and GMH, respectively).

After adjusting for age, sex, ethnicity, income, education, and comorbidity in linear regression, GPH ($b=2.8$, 95%CI: 0.1-5.4, $p=0.043$) but not GMH ($b=2.5$, 95%CI: -0.3-5.2, $p=0.075$) was significantly higher in KTRs.

Conclusion

The PROMIS Global-10 GPH but not GMH was higher among KTRs compared to patients on dialysis. Further studies are needed to assess the value of this brief, widely validated tool in assessing HRQoL among patients with CKD.

HLA Antibodies that we can see but we cannot detect

A 67-year-old AB+ve Caucasian male diagnosed with ESRD due to autosomal dominant polycystic kidney disease (ADPKD). He received a living unrelated kidney transplant in 2006. His renal allograft failed due to unknown reasons in 2019, so he is waiting for 2nd transplant. From March 2005 to April 2020, multiple sera for this patient were tested negative for class I and class II anti-HLA antibodies using one lambda single antigen beads (SAB). Nevertheless, FCXM(Flow cytometry crossmatch) with the living donor candidate (wife), were negative on T cells while positive on B cells, regardless of pronase treatment or not. The autologous crossmatch was negative. Current donor shares A3, B7, Cw7, DRB1*15:01, and DQB1*06:02 haplotypes with the 1st transplant. Different serum treatments, such as serial dilution, DTT, absorption, EDTA(routine or augmented concer tation), heat inactivation(56^{o}C), failed to detect any positive anti-HLA antibodies. The sera also tested negative for anti-HLA antibodies using one lambda PRA bead, Reflex bead, and Immuncor SAB. We did not find positive antibodies to Non-HLA antigens, such as MICA, angiotensin II type 1 receptor, and 37 autoantigens in One Lambda autoantibody panel (Groups 1, 2, and 3). Historically, the patient had not received therapeutical antibodies, such as rituximab. To determine the allo-reactivity in patient's sera, surrogate FCXMs with 24 donors were performed. All B-FCXM were positive with 8 donors who had DR15 (repeated MM from 1st transplant) (Table 1). None of the B-FCXM with 16 DR15-negative surrogate donors were positive. So likely, alloantibodies specific to the product of genes closely linked to DR15 might cause positive B-FCXM. Considering shared mismatched with failed 1st transplant, the risk for these alloantibodies can not be overlooked. In conclusion, positive FCXM in absent of detectable DSA with the solid-phase assay, requires interpretation with caution, rather than simply designated as false reactivity.

GB vs Allo Donors

Patient typing: A*01,A*02,B*08,B*49,C*07,C*07,DRB1*17 DQA1*05:01,DQA1*05,DQB1*02,DQB1*07,DPA1*01 ,DPA1*01,DPB1*04:01P

				B cells	
FCXM number	DRB1	DQB1	DQA	MESF B Cells	Δ MESF B cells
1.00	13, 15	6, -	1, -	3743	**2060**
2.00	13, 15	6, -	1, -	4341	**2197**
3.00	01:03, 15	5,6	1, -	5345	**3739**
4.00	7,15	2, 5	1, 2	4808	**3248**
5.00	15,-	6,-	5,-	8315	**6270**
6.00	15,17	2,6	1,5	6359	**4231**
7.00	1,15	5,6	1,-	3911	**2300**
8.00	12,15	5,7	1,5	8734	**7163**
9.00	11, 15	7, 6	1, 5	3406	**1794**
10.00	4, 11	7, 8	3, 5	2033	**97**
11.00	17,11	2, 7	5, -	1732	**-1470**
12.00	4, 7	8, 9	2, 3	1126	**-346**
13.00	1, -	5, -	1, -	1353	**-375**
14.00	17, 13	2, 6	1, 5	1452	**-817**
15.00	13, 16	5, 6	1,-	1835	**-2411**
16.00	17,7	2, -	2, 5	1434	**-546**
17.00	17, -	2, -	5, -	972	**-485**
18.00	4, 13	7, 8	3, 5	1280	**-448**
19.00	1,12	5,7	1,5	1865	**-783**
20.00	17,4	2,7	3,5	1048	**-383**
21.00	4,7	2,8	2,3	1525	**-1118**
22.00	11,12	7,-	5,-	1028	**-446**
23.00	1,9	9,5	1,3	1095	**-543**
24.00	1,11	7,5	1,5	1255	**-352**
First Donor's Typing	1, 15	5, 6	1,1		**Positive** / **Borderline**

BACKGROUND: Patients with end-stage kidney disease treated with renal replacement therapy (RRT, dialysis or kidney transplant) often experience anxiety symptoms. Currently, however, these symptoms frequently remain un-detected. Systematic screening for anxiety may help identify patients with moderate/severe symptoms, who may benefit from multidimensional assessment and support.

OBJECTIVE: To assess a 2-step approach, where an ultra-brief screening tool (Edmonton Symptom Assessment Survey-revised– Anxiety item (ESASr-A) or Generalized Anxiety Disorder-2 (GAD-2)) is followed by a more precise tool (Patient Reported Outcomes Measurement Information System Anxiety Computer Adaptive Test (PROMIS-A-CAT)), to screen for anxiety symptoms in patients on RRT.

METHODS: We performed secondary analysis of data collected between September 2017 and January 2020 in a multicenter, cross-sectional study. Patients on RRT completed ESASr, GAD-7, and PROMIS-A-CAT. Receiver operating characteristic curve analyses were used to assess each tool's discrimination against moderate/severe anxiety defined by a GAD-7 cut-off score ≥10. Screening performance was evaluated by sensitivity and specificity. Efficiency was characterized by the average number of questions completed by subjects in the different scenarios.

RESULTS: For the 2-step method, using a cut-off of ≥1 and ≥2 for ESASr-A and GAD-2, respectively, produced the best combination of sensitivity and specificity (ESASr-A sensitivity 0.70, specificity 0.94; GAD-2 sensitivity 0.81, specificity 0.94). Compared to administering only PROMIS-A-CAT to all patients, the 2-step screening reduced the average number of questions patients had to complete by 53% and 49%, for ESASr-A and GAD-2, respectively. This reduction was most pronounced among patients with low anxiety scores.

CONCLUSION: A 2-step screening method using either ESASr-A or GAD-2 followed by PROMIS-A-CAT has high specificity and moderate sensitivity, and can help improve the efficiency of identifying patients with anxiety symptoms. Screened in patients will need clinical assessment to establish diagnosis and decide on appropriate psychosocial support.

Identifying the needs of kidney transplant recipients that can be addressed by a web-based self-management program

ABSTRACT

Background: Kidney transplantation improves the quality of life (QOL) of patients with end-stage renal disease, however, post-transplant recovery of physical health and other aspects of QOL remain well below age- and sex-matched norms. While members of the health care team are focused on optimizing the biological responses to transplant, patients may have few or no tools at their disposal to engage in behaviors that optimize QOL.

Objective: We aimed to identify and describe the needs of kidney transplant (KTx) recipients that are appropriate to address through self-management.

Methods: We used four strategies to identify areas of concern post-kidney transplantation: 1) assessment of affected areas post-transplant in 51 KTx recipients using the patient-generated index to identify areas of QoL that are affected post-transplant; 2) review of the outcome domains suggested by the Standardized Outcomes in Nephrology-Transplantation (SONG-Tx) international initiative; 3) review of the domains included in QOL questionnaires for KTx recipients and patients with chronic kidney disease and 4) focus groups and key informant interviews with patients, clinicians, and researchers. We linked the identified themes to the International Classification of Functioning's code list and created a saturation table to visualize the most common areas of concern.

Results: The most prevalent identified topics (identified in $\geq$3 strategies) were physical activity; fatigue; pain; sleep; mental health; nutrition; sexual function; side effects of medication; religion and spirituality; personal relationships/social life; and heart and kidney health.

Conclusion: KTx recipients have many areas of concern post-transplant that can be addressed through self-management. The next steps will include the development of a comprehensive, evidence- and experience-based self-management web-based program tailored to this patient population to improve their QOL.

Title: Endothelial cells internalize apoptotic exosome-like vesicles via phosphatidylserine-dependent macropinocytosis

Background: Ischemia-reperfusion injury (IRI) induces endothelial apoptosis, which contributes to the maladaptive repair of vascular network through the release of exosome-like vesicles (ApoExo). We showed that ApoExo modulate gene expression, functions, and cell morphology of endothelial cells (EC) towards endothelial dysfunction. However, the mechanism by which EC internalize ApoExo remains unclear.

Methods: ApoExo were isolated by ultracentrifugation from serum-free media conditioned by fluorescently-labeled EC. Serum-starved primary human EC were then exposed to purified ApoExo *in vitro*. Confocal microscopy and flow cytometry were used to assess the uptake of ApoExo. Pharmacological inhibitors and gene silencing were used to probe uptake mechanisms. EC morphology was assessed by electronic microscopy (EM).

Results: Efficient uptake of ApoExo by EC was observed in a time- and concentration-dependent manner. The specificity of ApoExo uptake was supported by the significant decrease of fluorescent signal following the concomitant exposure with unlabeled ApoExo or with Triton X-100-treated ApoExo. ApoExo uptake was abolished at 4°C suggesting an energy-dependent mechanism. Blocking the actin polymerization using cytochalasin D decreased the uptake of ApoExo, while inhibition of classical endocytosis pathways did not, suggesting ApoExo are internalized by non-classical endocytosis. Disruption of membrane integrity by MβCD failed to block the internalization of ApoExo when used on cells. However, the use of MβCD on ApoExo significantly inhibited their uptake by EC. Annexin V, a phosphatidylserine (PS)-binding protein, decreased ApoExo uptake when used on vesicles, but not on cells. Morphology analysis revealed lamellipodia-like structures hallmark of macropinocytosis, which were also induced by ApoExo. EIPA, a macropinocytosis inhibitor, significantly abrogated ApoExo uptake.

Conclusion: Taken together, these results suggest that EC actively uptake ApoExo through PS-dependent macropinocytosis. This study highlights the potential molecular targets involved in ApoExo uptake. Inhibition of this internalization pathway could prevent EC dysfunction and alleviate maladaptive repair following IRI.

295 words

Availability of a Living Donor optimizes timing of Liver Transplant in Waitlisted NASH cirrhosis patients

Background & Aims: Nonalcoholic steatohepatitis (NASH) has become a leading indication for liver transplantation (LT). A crucial concern in NASH patients is their significant comorbid disease burden and lower MELD score than other etiologies. We hypothesized that patients with NASH cirrhosis would be advantaged by having access to living donor LT (LDLT), with specific patient subgroups being particularly advantaged due to LT being available before patients become too sick for transplant.

Methods: We retrospectively reviewed all adult NASH patients listed for LT in our program from November 2012 to May 2019. Patients with a potential living donor (pLD) available after listing were identified. We excluded patients with MELD exception points, fulminant liver failure, multi-organ transplant or retransplantation. All patients were followed from the time of listing to LT or dropout. Survival analyses with Cox PH models and time to LT with Fine and Gray's Competing risk models were performed.

Results: Out of 265 NASH cirrhosis listed patients, 167 were included. Mean age was 59.9±7.17 years; 53.9% were males. 80 patients had a pLD identified. 105 patients underwent LT (29 LDLT). Having a pLD was associated with a higher instantaneous rate of receiving a transplant (HR 1.6 [CI:1.06-2.35], p=0.02), especially in patients with age >60 years (p<0.01), height <165 cm (p=0.035), history of ischemic heart disease (p=0.036), diabetes (p=0.0025), and Na-MELD <20 (p=0.01). . Patients who were not transplanted, were older (p=0.012) and frailer (p=0.01). Moderate to severe frailty was associated with increased risk of death/dropout in non-transplanted patients (HR 2.95, [CI 1.49-5.81], p=0.001)

Conclusion: We demonstrated that waitlisted patients with NASH cirrhosis significantly benefit from access to a living donor, by optimizing the timing of transplant for subgroups (age >60 years, diabetes, height <165cm, and MELD Na <20) at the highest risk for dropout.

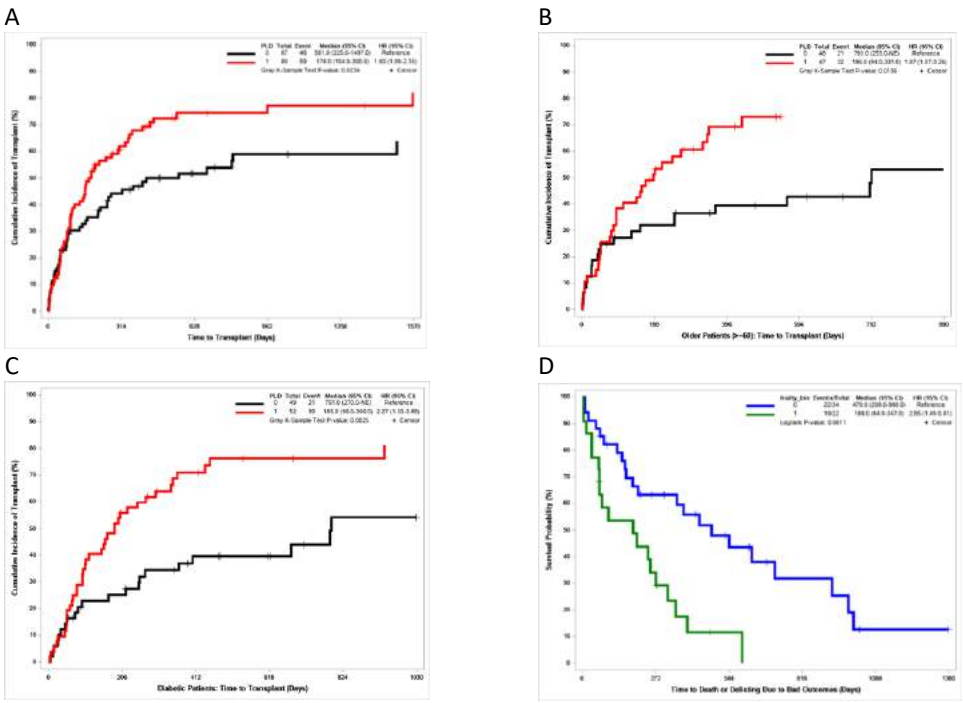


Figure 1. Impact of availability of a Living Donor on timing of Liver Transplant in Waitlisted NASH cirrhosis patients. ***1a. Competing risk analysis for time to transplant stratified by pLD:*** Having a pLD is associated with faster and higher access to transplant (p=0.02). ***1b. Association between age and time to transplant:*** In older patients, patients with pLD have faster time to transplant than those who do not have a pLD (p=0.01). ***1c. Association between diabetes and time to transplant:*** In diabetic patients, having a pLD is significantly associated with faster and more access to transplant (p=0.0025). ***1d. Time to death or delisting in patients with none to mild frailty vs moderate to severe frailty:*** Patients with moderate or severe frailty score are at significantly higher risk of death/delisting due to bad outcome if they do not receive transplant (p=0.0011).

Improving outcomes in kidney recipients: a randomized controlled trial of a pre-transplant education intervention

Background: Poor patient knowledge is a major problem following kidney transplant and patients desire more support. We developed a video-based education strategy to supplement education provided by the transplant team. Objective: To test the impact of this 6-part patient-oriented video series delivered electronically to patients undergoing assessment or waitlisted for kidney transplant.

Methods: A multi-center, randomized controlled trial was conducted in Saskatoon, Regina and Calgary. Adult participants were randomized (1:1) to the control (standard education), or the intervention group, consisting of electronic access to the videos (or DVDs if no internet) in addition to standard education. Differences between the groups in changes in transplant knowledge (primary outcome measured by the Kidney Transplant Understanding Tool), as well as education satisfaction, self-efficacy and quality of life (secondary outcomes) were evaluated by a pre-and post-intervention survey. Video viewing habits were analyzed and a sub-group analysis was performed, including only those that had objective evidence of watching ($\geq$80%) of each video.

Results: 132 participants completed the study(n=64 intervention, n=68 control), with enrolment from Regina(n=45), Saskatoon(n=42) and Calgary(n=45). Video viewing statistics in the intervention group indicated that 78%(50/64) watched the videos, with 70%(45/64) viewing them electronically, while 8%(5/64) received DVDs and self-reported participation. Demographics were similar between groups, with baseline knowledge scores of 55$\pm$6.5 and 56.3$\pm$6.7 in the intervention and control, respectively. The mean knowledge change in the intervention(2.7$\pm$3.9) was significantly higher than in the control group(0.9$\pm$3.6, $p<0.01$), with larger improvements(3.4$\pm$3.8) in patients who had watched at least 80% of the videos. Video group participants reported higher satisfaction with education ($p<0.05$) and expressed positive comments in open-ended feedback.

Conclusions: Electronic video education in the pre-transplant setting improved knowledge and satisfaction. High uptake and positive patient feedback suggests that this type of intervention is of utility and could enhance care for patients in remote locations.

Figure 1- Study Enrolment

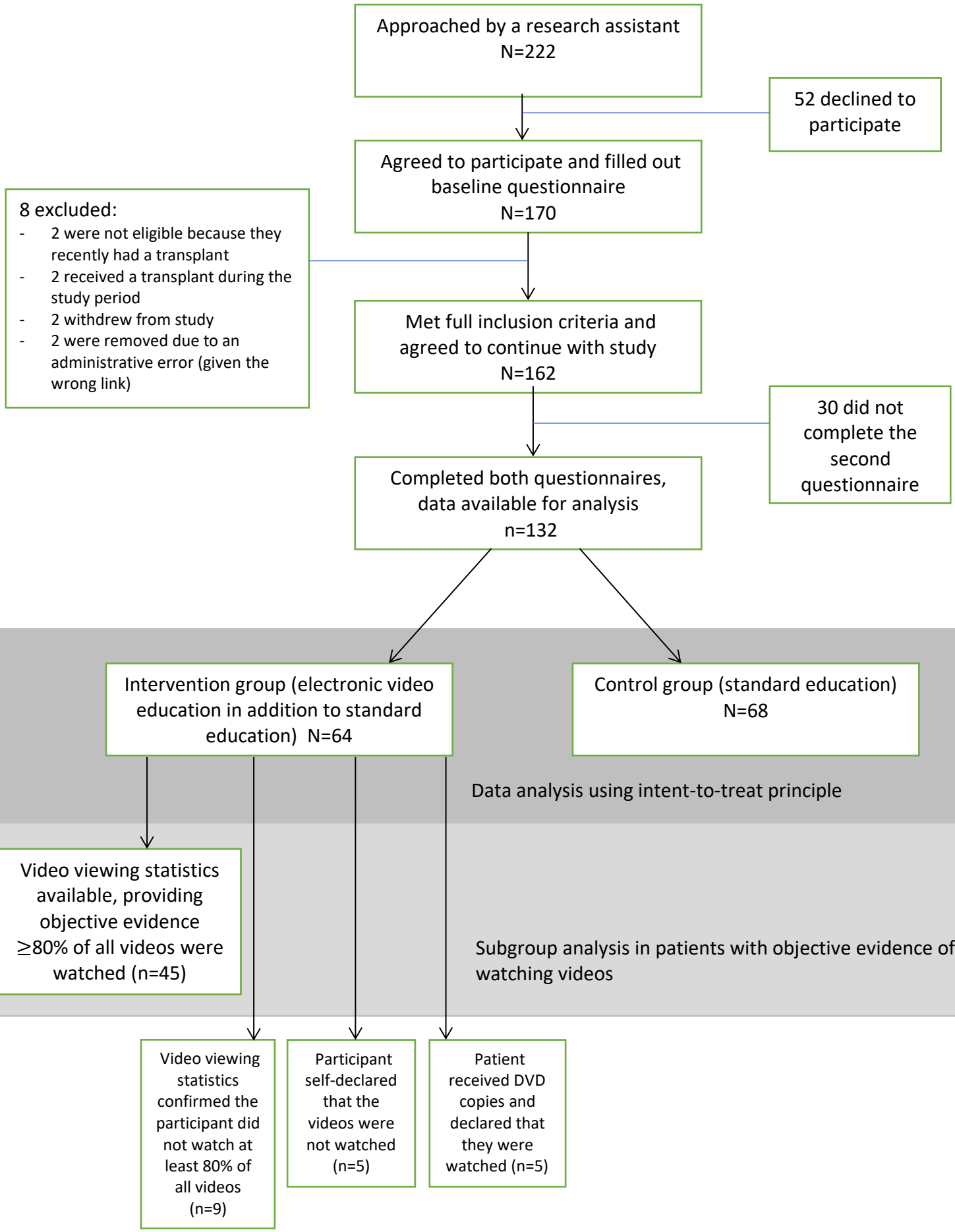


Table 1: Participant Demographics

Characteristics	Total		Control		Video	
	Count	%	Count	%	Count	%
	132	100	68	100	64	100
Age mean (SD)	51.2 (14.6)		52.1 (14.4)		50.3 (14.9)	
Gender						
Male	77	58.3	38	55.9	39	60.9
Female	54	40.9	29	42.6	25	39.1
Other	1	0.8	1	1.5	0	0
First Language						
English	114	86.4	61	89.7	53	82.8
Other	18	13.6	7	10.3	11	17.2
Ethnicity						
White	93	70.5	49	72.1	44	68.8
Hispanic/ Latino	2	1.5	1	1.5	1	1.6
Black/African American	2	1.5	2	2.9	0	0
First Nations/ Metis/ Inuit	19	14.4	10	14.7	9	14.1
Asian/ Pacific Islander	20	15.2	8	11.8	12	18.8
Other	1	0.8	0	0	1	1.6
Work Status						
Unemployed	13	9.8	6	8.8	7	10.9
Temporarily cannot work	2	1.5	1	1.5	1	1.6
Disability Income	36	27.3	18	26.5	18	28.1
Working	44	33.3	24	35.3	20	31.3
Retired	28	21.2	15	22.1	13	20.3
Other	6	4.5	3	4.4	3	4.7
Prefer not to say	3	2.3	1	1.5	2	4.1
Education						
Middle school	4	3.0	1	1.5	3	4.7
High school	37	28.0	18	26.5	19	29.7
University/Graduate studies	42	31.8	21	30.9	21	32.8
Trade/Technical training	45	34.1	27	39.7	18	28.1
Prefer not to say	4	3.0	1	1.5	3	4.7
Marital Status						
Unmarried	22	16.7	10	14.7	12	18.8
Married/ Common law	84	63.6	45	66.2	39	60.9
Divorced/Widowed/Separated	22	16.7	11	16.2	11	17.2
Prefer not to say	4	3.0	2	2.9	2	3.1
Support Person						
Yes	126	95.5	65	95.6	61	95.3
No	6	4.5	3	4.4	3	4.7
Living (Community)						
Rural	32	24.2	15	22.1	17	26.6
Urban	99	75	53	77.9	46	71.9
Rural reserve	1	0.8	0	0	1	1.6
Driving Distance to tx center						
Within 1 hour	91	68.9	50	73.5	41	64.1
Within 3 hours	29	22.0	12	17.6	17	26.6
Within 5 hours	4	3.0	2	2.9	2	3.1
More than 5 hours	2	1.5	1	1.5	1	1.6
Other	6	4.5	3	4.4	3	4.7
Previous transplant						
Yes	25	18.9	14	20.6	11	17.2
No	107	81.1	54	79.4	53	82.8

Background: We have recently shown the superiority of 10°C as an optimal temperature for the prolonged cold static preservation (CSP) of donor lungs. However, this approach is limited to 36h. Here, we hypothesized that the interjection of 2 short cycles of normothermic ex vivo lung perfusion (EVLP) during CSP would provide a cellular "recharge" period, allowing for multi-day lung preservation.
Methods: Donor lungs (n=4) from Yorkshire pigs (28-35kg) were flushed with a low-potassium dextran solution and subsequently preserved using 10°C CSP with an intermittent EVLP protocol (Fig 1A). After a total of 72h of preservation, a left lung transplant was performed followed by 4h of reperfusion. At 4h of reperfusion, isolated graft assessment was performed by clamping the contralateral pulmonary artery. To evaluate the contribution of the EVLP recharge periods, 3 control lungs were preserved solely with 10°C CSP for 72h and transplanted. Lung tissue biopsies were collected during the preservation period, and a longitudinal metabolomic analysis was performed to evaluate the metabolic contribution of EVLP after extended CSP.
Results: Histological lung structures remained intact during the intermittent EVLP periods and after transplantation (Fig 1B). After 3-days of preservation, post-transplant graft function was excellent. Lung function was stable and the recipient systemic oxygenation after excluding the contra-lateral lung was 422 ± 61 mmHg (Fig 1C). Lungs preserved purely in CSP for 72h developed massive pulmonary edema, resulting in recipient death. Metabolomic analysis revealed that EVLP plays an important role in the re-vitalization of key central carbon energy metabolites (Glucose, Succinate, N-Acetyl Aspartate: $p<0.0001$).
Conclusions: We demonstrate for the first time the feasibility of 3-day lung preservation leading to excellent early post-transplant outcomes. The thoughtful combination of CSP (10°C) and intermittent EVLP can open new opportunities to further prolong organ preservation and provide time for advanced lung treatments and repair.

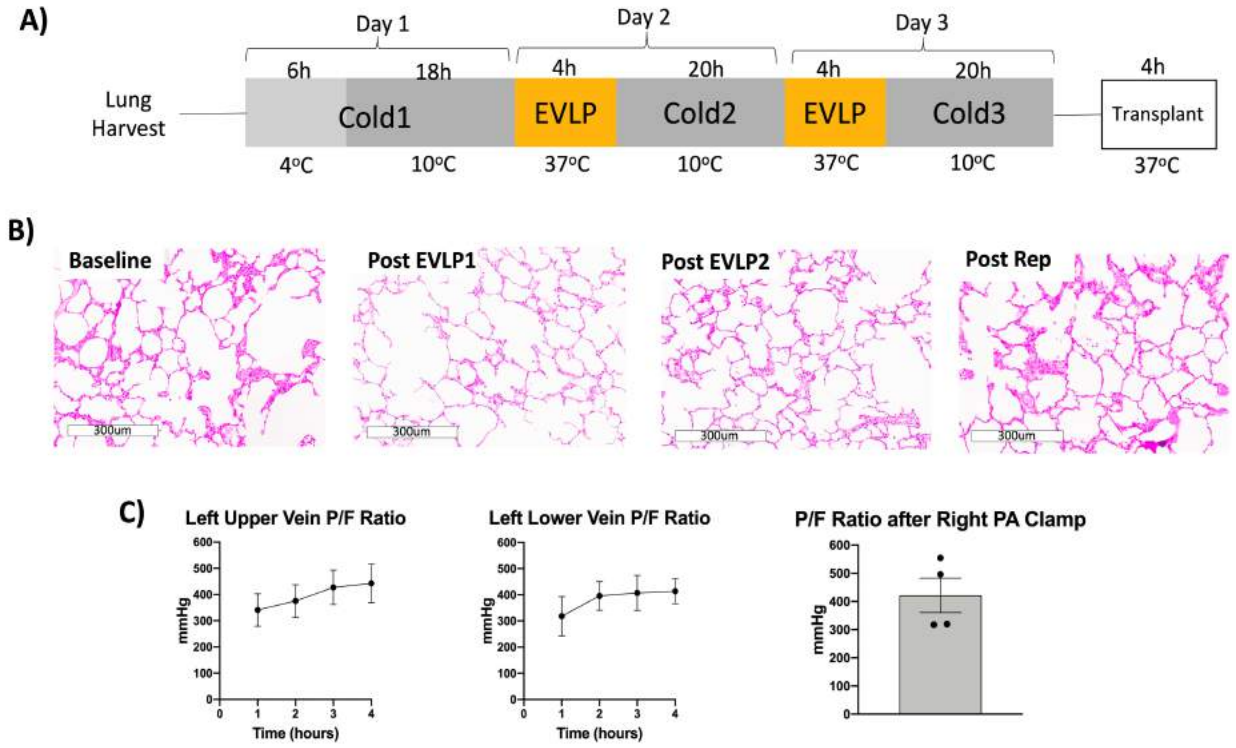


Fig 1. Extended 10°C cold storage with intermittent normothermic EVLP results in excellent post-transplant lung function. *P/F ratio: ratio of oxygen partial pressure to fraction of inspired oxygen, EVLP: Ex vivo lung perfusion, PA: Pulmonary artery. SEM: Standard error of mean. Rep: Reperfusion*
A) Intermittent EVLP protocol: Pig lungs were retrieved and stored for 6h at 4°C to simulate transportation to a transplant center, followed by continuous storage at 10°C storage. During the 10°C storage period, lungs underwent two short periods (4h/ea) of intermittent normothermic EVLP. After 3-days of preservation, a single-left lung transplant was performed and the recipient animal was monitored post-transplant for 4h. B) Representative histology before preservation, after EVLP1, after EVLP2, and post reperfusion during the intermittent EVLP protocol. (scale bar = 300 um) C) Physiologic results during 4h of lung graft assessment (data expressed as mean ± SEM).

It's not just about sex: pregnancy is a key driver in the development of HLA antibodies

Introduction: Sensitizing events in transplantation, such as previous transplantation, pregnancy and blood transfusion, can lead to development of HLA antibodies, which narrow donor selection and, if crossed, can negatively affect outcomes. Percent calculated panel-reactive antibody (cPRA) is used to define the level of antibody burden. Our aim was to compare cPRA in males *vs*. females on our kidney transplant waitlist and investigate the impact of pregnancy.
Methods: HLA antibody data were extracted from the HLA laboratory database. Data were analysed using GraphPad Prism. The Observed *vs*. Expected proportions and Mann-Whitney tests were used.
Results: In August 2020, 152 kidney patients were on the waitlist (68 females, 84 males). The ages of females *vs*. males were comparable (Table 1). Most females (81%) had pregnancy history. Similar proportions of females and males had previous transplants or transfusions. Excluding pregnancy, the proportion of patients without sensitizing events was higher in females than males. Overall, females had significantly higher cPRA than males (Figure 1). If pregnancy as a sensitizing event was excluded, no significant differences were observed in median cPRA between unsensitized males (n=24) vs. females (n=5). Comparing previously pregnant patients (n=55) and females without pregnancies (n=13), no significant differences in cPRA were observed, however the latter data were bimodally distributed, likely due to previous transplant and/or transfusion history. Indeed, in females awaiting their first transplant, previously pregnant females had increased cPRA *vs*. those with no pregnancy history (Figure 2).
Conclusion: Overall, female kidney patients had higher cPRA than males, which appears to be associated with a history of pregnancy. Our findings indicate that pregnancy creates challenges in finding a compatible kidney donor as compared to females who have not been pregnant *or* males. This finding impacts most female patients on the waitlist as the majority has a history of pregnancy.

Table 1: Demographics, %cPRA, and sensitizing events of active kidney transplant patients

	Female (n=68)		Male (n=84)	*P*-value
Age (years) (median, 95% CI)	56 (53-59)		57 (54-60)	ns
cPRA (%) (median, 95% CI)	78 (47-94)		22 (0-53)	0.003
	History of pregnancy (n=55)	No pregnancy (n=13)		
No (other) sensitizing events (%)	25/55 (45%)	5/13 (38%)	24/84 (29%)	0.02*
Previous transplant (+/- transfusion) (%)	18/55 (33%)	4/13 (31%)	36/84 (43%)	ns*
Transfusion only (%)	12/55 (22%)	4/13 (31%)	24/84 (29%)	ns*

*p value is a comparison of all females *vs.* males

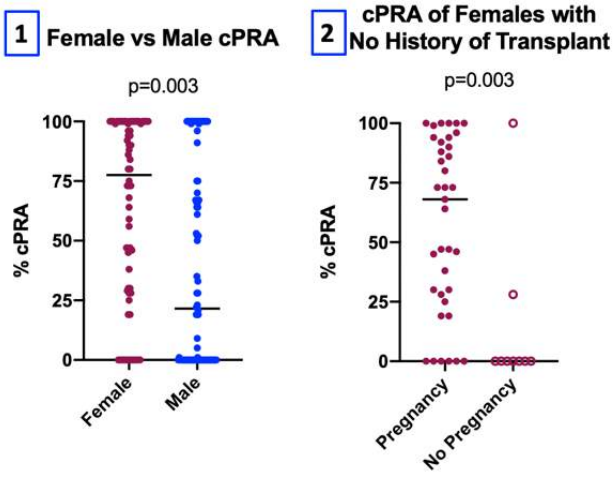


Figure 1. Females had a higher cPRA than males (median cPRA of 78% vs 22% for females vs males, respectively)

Figure 2. In females with no history of transplant, those with pregnancy had high cPRA than those who had not been pregnant (median cPRA of 68% vs 0%, respectively)

ANXIETY AND DEPRESSION IN IMMIGRANT LIVER TRANSPLANT RECIPIENTS

BACKGROUND

About 1 in 5 Canadians were born outside of Canada, therefore they are considered immigrants. Immigrant status may be associated with higher anxiety and depression compared to non-immigrants due to the psychological, financial, and social stressors associated with immigration. Chronic liver disease is frequent among immigrants, due to higher prevalence of hepatitis B and C infection. Liver transplant (LT) is the only definitive treatment for liver failure. Immigrant LT recipients (LTRs) may have greater anxiety and depression than non-immigrant LTRs. The objective was to assess if immigrant status is associated with self-reported anxiety and depression among LTRs.

METHODS

A cross-sectional cohort of adult LTRs completed the PROMIS CAT Anxiety and Depression item banks. Information about immigration status, sociodemographic, and clinical variables were also collected. Independent samples t-test was used to compare anxiety and depression scores between immigrants and non-immigrants. Multivariable linear regression was used to adjust for age, sex, income, ethnicity, and education. Information about age at immigration, years in Canada, and immigration method were also assessed.

RESULTS

145 participants were included: mean(SD) age 56(15) years, 70% male, 67% White, 28% immigrant. Mean(SD) anxiety score was 51(9), and mean(SD) depression score was 50(9). Immigrants, compared to non-immigrants, had lower depression and similar anxiety scores. Upon adjustment for potential confounders, anxiety and depression scores were similar between groups (b[95% CI] 1.0[-2.6–4.6], p=0.583, and -2.5[–6.0–1.0, p=0.160). Mean(SD) time since immigration was 38(17) years, mean(SD) age at immigration was 21(15) years. Most immigrants (90%) were landed immigrants. When adjusted for age and sex, older age at immigration was associated with a lower depression score (-0.3[-0.5—0.1], p=0.005).

CONCLUSION

Anxiety and depression among LTRs were similar between immigrants and non-immigrants. Immigrants who immigrated at an older age had lower depression scores.

A Systematic Review of Frailty Assessment Tools in Solid Organ Transplantation

Background: The evaluation of frailty has the potential to inform the selection process of transplant candidates because of its association with adverse outcomes in all solid organ transplant groups. We aimed to identify the most commonly used frailty assessment tools in each organ group and describe frailty's effect on pre- and post-transplant outcomes.

Methods: The search strategy was executed on July 22, 2019 and rerun on July 3, 2020 in the following databases: MEDLINE, EMBASE, Emcare, Cochrane CENTRAL, and Cochrane Database of Systematic Reviews. Studies were included if solid organ transplant candidates or recipients were assessed with a validated and multidimensional frailty assessment tool. All stages of the review were performed independently by two authors (JW and KM), and disagreements were resolved through discussion with a third author (OF). The protocol was registered in the PROSPERO registry (CRD42020138588).

Results: We identified 80 primary articles and 11 different frailty assessment tools. The most cited frailty tools are the Fried Frailty Phenotype (FFP) [51%], the Short Physical Performance Battery (SPPB) [26%], and the Liver Frailty Index (LFI) [16%]. The most commonly used frailty assessment tools in each organ group were the FFP (kidney), LFI (liver), SPPB (lung), and a modified FFP (heart). During the pre-transplant period, the prevalence of frailty for kidney, liver, lung, and heart patients ranged from 12.3% to 54.1%, 13.9% to 43.2%, 9.9% to 65.0%, and 20.4% to 42.3%, respectively. Most articles assessed frailty at the time of transplant evaluation (42 articles) compared to waiting list (29), transplant admission (16), and post-transplant (15).

Conclusion: There is significant heterogeneity in frailty assessment tools among and within each organ group. Future studies are required to determine whether improving frailty (as measured by the existing tools) through dietary or physical intervention can lead to better outcomes on the waitlist and after transplant.

HLA-DPB1*03:01/20:01 allele combination typing using Luminex-RSSO challenges and resolution.

The human leukocyte antigen (HLA) complex on chromosome 6 is the most polymorphic region of the human genome, and although doubly polymorphic heterodimeric molecules are comparatively rare in human biology, this is a significant feature of the HLA class II gene antigens. The HLA-DQ and HLA-DP loci are characterized by having more diversity in genes for the alpha chains than HLA-DR. This results in less imbalance between levels of alpha and beta diversity; the ratio of beta/alpha known alleles is approximately 4:1 for these genes.

Aim: Design of hybridization probes and quality control for DNA HLA typing of certain alleles may be challenging due to a lack of DNA sequence with some known alleles to serve as quality control. Unexpected hybridization patterns in RSSO typing may suggest either the presence of novel alleles or non-specific probe hybridization. Recently, we experienced an unexpected typing pattern with a DPB1 typing.

Method: Subjects were potential solid organ donors and a recipient. Low resolution typing of HLA class I and class II were performed by RSSO (LABType kits from One Lambda) and real time PCR methodologies. High resolution typing of HLA-DPB1 was performed by using SSP.

RSSO testing revealed that the deceased and potential living donors plus recipient HLA typed as DPB1*20:01, DPB1*03:01 (Group 1, frequent on both alleles). These subjects were HLA typed again using SSP and real time PCR. In two of these cases the subjects HLA typed as DPB1*06:01 instead of DPB1*20:01. RSSO was repeated and again produced the same DPB1*20:01, DPB1*03:01 result with good bead reactivity including controls. The only way to achieve DPB1*06:01 instead of DPB1*20:01 involved adjusting 3 beads which included changing a very negative bead (#18) into a positive. One of the subjects typed as DPB1*20:01, DPB1*03:01 using RSSO and was confirmed by SSP and real time PCR.

The DPB1* typing was assigned using alleles in Group1, with no questionable beads. Investigation into the probes of DPB1*20:01 indicated that the probes are coated on beads 6, 7, 11, 20, 22, 23, 29, 36, 43, 60, 92 and 96 are within exon 2. All probes of DPB1*03:01 are coated on beads 6, 7, 11, 20, 22, 23, 24, 36, 60, and 96. Probes of DPB1*06:01 are coated on beads 7,11, 20 23, 29, 36, 43, 60. 92, 96 plus beads 18, 85 and 89 which in our case needed to be adjusted to assign DPB1*06:01 allele typing. It is possible that the beads involved in these RSSO reactions are not behaving as expected or that the presence of a second allele in this case DPB1*03:01, interferes with the ability of FUSION to analyze patterns differentiating between DPB1*06:01 and DPB1*20:01. See figure below.

Conclusions: Our findings suggest that the probes on beads 18, 85, 89 non-specifically hybridized to the allele of DPB1*20:01 or DPB1*03:01 instead of DPB1*06:01. These probes may require further improvement. It is important to be aware of these RSSO typing

issues so that the DPB1* typing assignment can be confirmed by another molecular method. This finding may be discussed with the manufacturer and the DNA may serve for the QC.

ROBUST, RELIABLE, NON-SEQUENCING INTERMEDIATE/HIGH RESOLUTION HLA TYPING FOR EPITOPE MATCHING BY LINKAGE BIOSYSYTEMS LINKSEQ GENOTYPING

Background

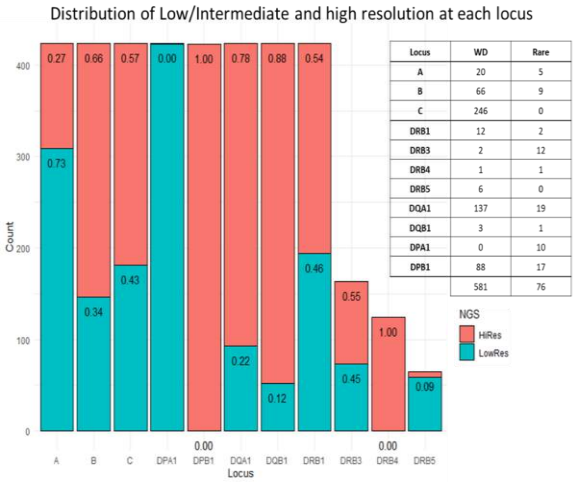
Since conventional NGS-based HLA genotyping cannot yet provide high resolution typing with the speed required for deceased donor workup for epitope matching, we have employed a simple, non-sequencing based technique to examined the feasibility of this method in determining allele and epitope level typing for matching purposes.

Methods

211 sequential deceased donors were HLA typed using the LinkSeq SABR 384 qPCR-SSP assay at 11-loci. All samples were prepared according to the manufacturer's protocol and run on a Roche 480 Light Cycler. All deceased donors were retrospectively sequenced by NGS using the Omixon Holotype v2 assay, following manufacturer's protocol, sequenced on an Illumina MiSeq and analysed using Twin v3.4 software.

Results

The LinkSeq assay is particularly capable of resolving alleles in the class II region, to high resolution (2 field). However, many other alleles are not fully resolved, resulting in low/intermediate resolution typing only. Of the 4642 alleles typed, 98.8% alleles were defined as common; 1.1% were well-documented, and 0.1% were rare. Most of the well-documented alleles were in class I (C) and class II (DQA), while the majority of rare alleles were found in the class II region (DRB3, DQAQ and DPA/B). Taking into account only class II, high resolution typing could be accurately assigned 80% of the time without further investigation.



Locus	WD	Rare
A	20	5
B	66	9
C	246	0
DRB1	12	2
DRB3	2	12
DRB4	1	1
DRB5	6	0
DQA1	137	19
DQB1	3	1
DPA1	0	10
DPB1	88	17
	581	76

Fig1. Distribution of low and high resolution HLA typing of each class 1 and class 2 gene locus using the Linkage BioScience LinkSeq SABR kit, and the number of well documented or rare alleles observed, based on the CWD 2.0.

Conclusion

Whilst rapid non-sequencing assays are not yet capable of resolving all alleles to high resolution, the LinkSeq kit coverage is sufficient to resolve 80% of the alleles observed in an ethnically diverse population for the class II loci. Because of the importance of class II loci in the development of antibody mediated rejection and the emerging focus of epitope matching for the major class II genes, this rapid and easily standardised assay can provide appropriate data for our deceased donor population to facilitate epitope matching for the majority of kidney patients.

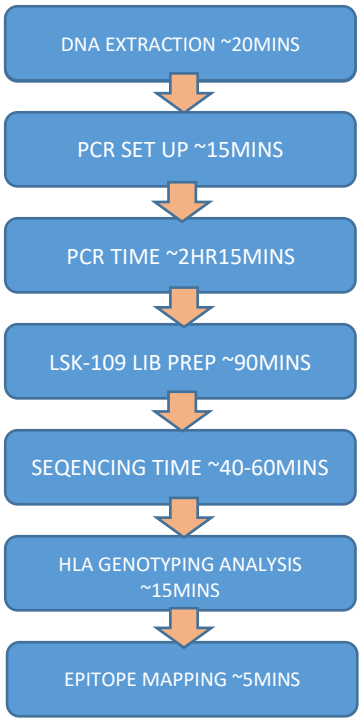
Next-generation Nanopore Sequencing Provides Robust and Reliable Allele and Epitope Level HLA Typing for Deceased Donors in Less than 6 hours.

Background

Nanopore sequencing offers enormous potential which may prove valuable in transplantation where turnaround time is critical, particularly for deceased donation. Our goal is to develop a robust and reliable protocol for deceased donor typing that could provide high-resolution HLA sequence and epitope data in a turnaround time of approximately 6hrs from sample acquisition.

Methods

50 donors (n=25) and kidney recipients (n=25) previously typed using both LinkSeq RT-PCR (Linkage BioScience) and Holotype v3 NGS (Omixon) were included. Samples were amplified using Omixon Omnitype 11 locus single tube assay. Amplicons were prepared using the 1D ligation kit (SQK-LSK109) and run on a standard R9.4 flow cell. 20 subjects were also sequenced using R10.3 flow cells. Each flow cell was run for ~1-6 hours. FAST5 files were live basecalled using MinKNOW GUI high accuracy mode. HLA allele assignment was performed blind by our collaborators at Omixon and in-house using GenDX NGSEngine 2.18 with IMGT 3.40.0. Two field typings were then input to HLA Matchmaker v3 for each donor/recipient pair.



Results

HLA allele assignment was performed blind and allele concordance was assessed only to 2 field typing.

Omixon Pipeline: 3rd or 4th field typing achieved for 100% of alleles. Concordance of 97% accuracy for class 1 and 95% for class 2.

GenDX NGSengine: 4 field typing achieved for 100% of alleles. Concordance of 98% accuracy for class 1 and 97% for class 2.

Conclusion

Nanopore sequencing using the current R9.4 or the advanced R10.3 flow cell permits robust and reliable definition of HLA alleles and epitopes for deceased donors within a mean time of 6hrs. This deceased donor workup offers major clinical benefits, in particular for highly sensitized recipients.

PRECISION MEDICINE IN KIDNEY TRANSPLANTATION: COMPARING ACTUAL AND PREDICTED EPITOPE MISMATCHES IN DECEASED DONOR KIDNEY TRANSPLANTATION

Background

Eplet-matching for human leukocyte antigens (HLA) offers an important strategy to improve kidney transplant outcomes. We documented the population distribution of antibody-verified eplets in a Canadian population by next-generation sequencing (NGS) and using simulation models demonstrated the potential for matching at cardinal eplets at the provincial level. Here, we describe the observed eplet-mismatch profiles in BC and compare results to a simulated baseline model of organ allocation.

Methods

NGS of 11 HLA genes was performed on 3,286 transplant donors/patients in BC and eplets were allocated using HLAMatchmaker. Eplet mismatches were compared between donor-recipient pairs transplanted between 2008-2018 and simulated pairs derived from organ donors and patients awaiting kidney transplant, based on blood-group identity and time on waitlist, adjusted for national and provincial waitlist sizes and donor rates.

Results

There were 1,180 deceased donor-recipient pairs transplanted and 1,524 simulated pairs (repeated 10x). The 1,180 pairs showed a mean total (i.e. antibody-verified and non-verified) mismatch of 44.92 across all 11 genes, 16.33 for class I, 28.59 for class II, 12.44 for DRB1/3/4/5, 11.66 for DQA+DQB1, and 4.50 for DPA1+DPB1. The mean antibody-verified eplet mismatch of the transplanted and simulated pairs were 21.66 and 27.41 across all genes, 9.97 and 10.45 for class I genes, 11.69 and 16.96 for class II genes, 5.10 and 6.53 for DRB1/3/4/5, 3.16 and 5.86 for DQB1, and 8.27 and 12.39 for DRB1/3/4/5+DQB1, respectively. Observed mismatches were lower than predicted by simulation, primarily at class II genes ($p < 0.05$) (Figure1).

Conclusion

This study defined eplet mismatches in a Canadian cohort and demonstrated that the observed averaged mismatch is lower than predicted, perhaps reflecting the biological effect of sensitization in promoting closer identity. These data support the feasibility of performing precise matching at cardinal class II gene loci for deceased donor transplantation within Canada.

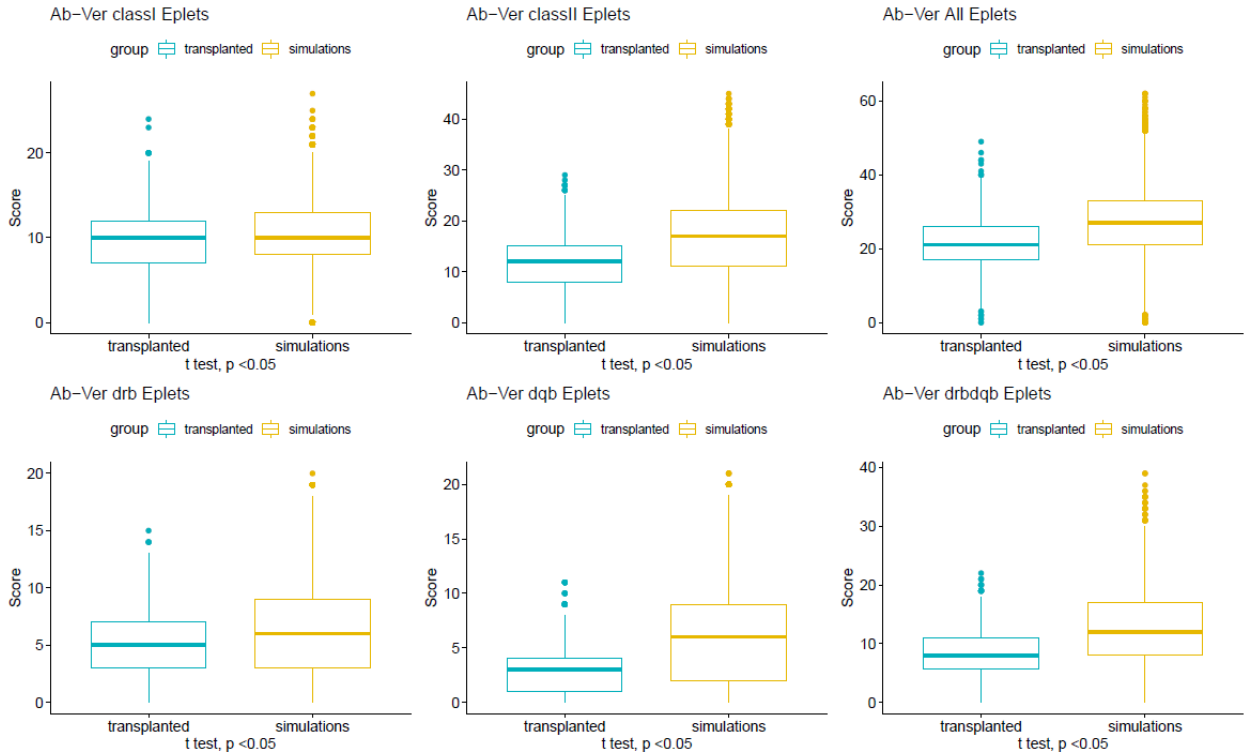


Figure 1. Box plots of the antibody-verified (ab-ver) eplet mismatches at various HLA gene combinations as observed in a BC transplant population (transplant) from 2008 – 2018 and a simulated organ allocation model (simulations) based on blood group identity and national waitlist size and donor rates. P values were determined using the two-sample t-test.

Lifelong, Universal *Pneumocystis jirovecii* Pneumonia Prophylaxis: Patient uptake and adherence after kidney transplant

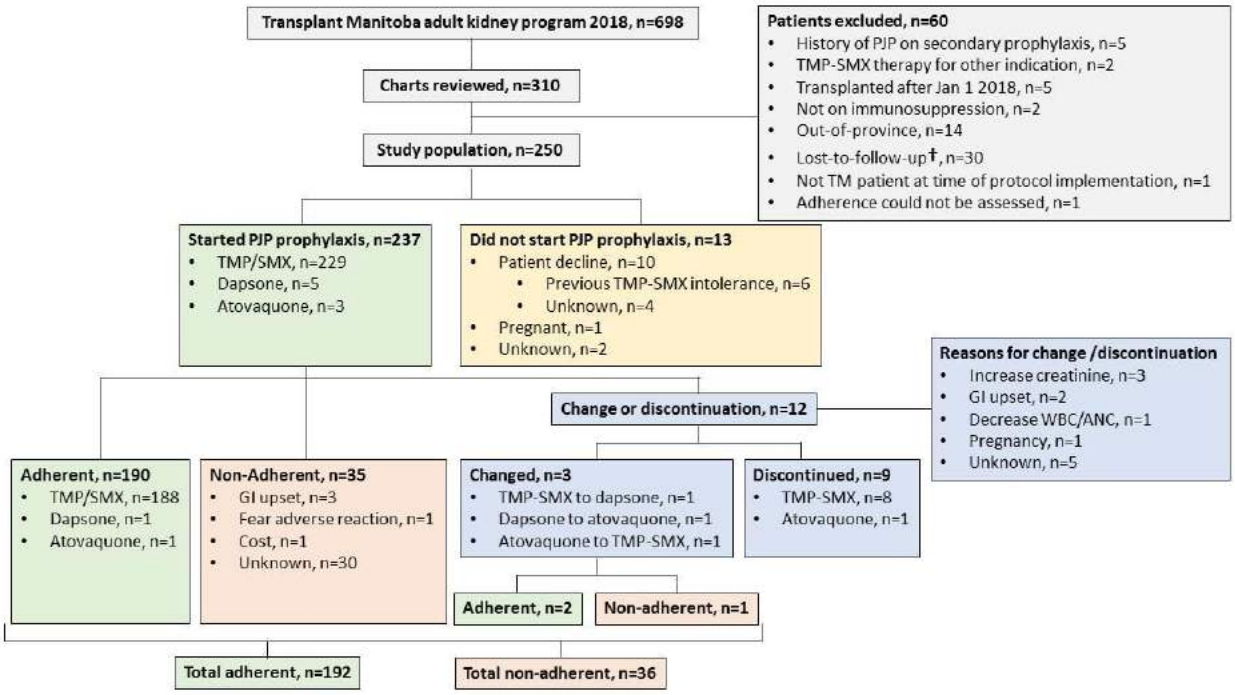
Background: *Pneumocystis jirovecii* pneumonia (PJP) is a significant cause of morbidity and mortality in transplant patients yet little is known about their adherence to prophylaxis. The goal of this study was to evaluate patient uptake and long-term adherence after implementing universal, lifelong PJP prophylaxis.

Methods: This retrospective cohort study evaluated an adult kidney transplant program 18-months after initiating trimethoprim-sulfamethoxazole (TMP-SMX) 80/400mg thrice-weekly following a cluster of PJP cases. The protocol incorporated multi-modal patient education and drug tolerability strategies to improve adherence, including a modified re-challenge strategy for TMP-SMX intolerance. Adherence was independently confirmed by the transplant pharmacist and nurse for each patient, with an a priori target ≥75% population on prophylaxis.

Results: Initial uptake was high with 237/250 (94.8%) patients starting prophylaxis. Long-term maintenance was high with 192/237 (81.0 %) patients remaining on prophylaxis at 18-months. Of the remaining 45 patients who initiated prophylaxis, 36/237 (15.2%) were non-adherent and 9/237 (3.8%) discontinued prophylaxis by 18-months. Reasons for non-adherence included gastrointestinal upset, fear of drug reactions and cost; but the majority of reasons were not delineated by the patients (31/36, 86.1%). There was a statistically significant increase in serum creatinine 3.3µmol/L (0.3-6.3µmol/L 95%CI) and potassium 0.08mmol/L (0.03-0.15mmol/L 95%CI) in those prescribed TMP-SMX with only 3/237 (1.3%) patients discontinuing TMP-SMX for an increase in creatinine.

Conclusion: High rates of patient uptake (94.8%) and long-term adherence (81.0%) were observed after implementing universal lifelong PJP prophylaxis. This may be due in part to the in-depth patient education and drug tolerability strategies employed.

Figure: Patient population and outcomes



†Patients who were "lost to follow-up" were those who had died, failed transplant, or had not return to clinic for assessment since prophylaxis protocol implementation.

Abbreviations: ANC, absolute neutrophil count; GI, gastrointestinal; PJP, *pneumocystis jirovecii* pneumonia; SCr, serum creatinine; TMP-SMX, trimethoprim-sulfamethoxazole; WBC, white blood cell count.

Barriers to Accessing Living Donor Kidney Transplantation Among Tamil Canadians - A Literature Review

Abstract (Word Count=297)

Background
Living donor kidney transplant (LDKT) is the medically preferred treatment for many patients with kidney failure. However, South Asian Canadians are less likely to receive LDKT, but little data exists about Canadian-Tamils. Importantly, a majority of Canadian-Tamils are recent immigrants, and therefore knowledge and attitudes about LDKT may reflect beliefs from their native country. In this review, we summarize barriers to LDKT that have been identified in Sri Lanka and Tamil Nadu which may be relevant to a Canadian context.

Method
OVID, PubMed, ProQuest, and Google Scholar were searched between January and August 2020 for relevant studies in English-language journals and grey literature. Studies on LDKT, kidney transplant, kidney disease, and/or organ transplant included reference to Sri Lanka, Tamil Nadu, Indian-, Sri Lankan-, and Canadian-Tamils. Other search terms included religion, history, social, family, and migration.

Results
We included 18 articles assessing knowledge, attitude, and practice of kidney donation and transplant among Sri Lankan- and Indian-Tamils. Findings suggest that the highly gendered work roles in Tamil communities (males are sole breadwinners in many families) may favor deceased kidney donation over LDKT. Therefore, donor or recipient surgery involving men can lead to a significant loss of family income. Furthermore, findings show generational differences in attitudes about kidney donations: younger Tamils show more willingness to consider donation compared to older generations. Apparently, religion plays little or no role in transplant or donation decisions. Knowledge about different aspects of kidney donation and transplant, however, was low.

Conclusions
We found that factors including knowledge about kidney donation and transplant, gender, age, and income may act as a barrier to accessing LDKT in Canadian-Tamil communities. Further qualitative research examining systemic factors affecting access to LDKT in Canadian-Tamil communities is needed to develop and implement culturally sensitive educational programs to reduce these barriers.

The use of Checklist in Organ Donation Processes: A Systematic Review Protocol

Background: Non-conformities in organ donation processes often lead to family refusal to organ donation[1, 2]. Organ donation processes are complex and fast-paced, requiring attention to detail to prevent adverse events and errors (i.e., disease transmissions, transplant recipient deaths, etc.). To improve those processes and prevent adverse events and errors, appropriate tools should be used. The use of checklists in healthcare settings allow better control over health activities with more reliable and predictable outcomes[3, 4]. Even though there are organ donation processes checklists available, there is still a lack of standards in their use.

Objective: We are proposing a systematic approach to collate, compare, contrast and synthesize the evidence related to effectiveness of the use of checklists in organ donation programs to ensure safety in organ donation.

Methods

We will perform a systematic review using the Joanna Briggs Institute methodology for systematic reviews. First, the title and protocol from this systematic review will be registered/published at JBI repository. Followed by a three-step search strategy employed to PUBMED, CINAHL, EMBASE and LILACS. Two independent researchers will screen references first by title and abstract screening, and then by full text screening. Conflicts will be resolved with a third researcher. The reference list from the included articles will be screened for additional sources. All included references will be assessed for quality and results will be presented in tables and descriptively

Results: We anticipate the systematic review protocol publication by March 2021, with search on databases starting in April 2021. Data extraction and synthesis by July 2021, and final manuscript published by November/2021.

Conclusion

Results from this article will be used to inform decision-making related to check-list use to tackle non-conformities in organ donation processes. The expected outcomes of this review will provide quality data to the development of evidence-based checklists for organ donation programs.

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Frailty and its implications for early post-transplant outcomes among kidney transplant recipients

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Background: Frailty is associated with poor early outcomes in kidney transplant recipients (KTRs). Frailty metrics are often not clinically available, thus making assessment of frailty difficult. The objectives of this study are: 1) to assess frailty with an index constructed using clinically available data and 2) to investigate the implications of frailty on early outcomes, including early hospital readmissions (EHRs) and delayed-graft function (DGF) among KTRs.

Methods: This was a single-centre retrospective cohort study with KTR transplanted between July 1st 2008-December 31st 2017. EHR was defined as the first hospitalization event within 30 days after transplant discharge while DGF was defined as the requirement of dialysis within 7 days of transplant, as well as, the duration of dialysis required to resolve it. The frailty index consisted of thirteen elements assessing the cumulative level of physical and psychosocial deficits of the patient. The elements were adopted from our centre-specific nursing admission assessment that's routinely administered prior transplant. Risk factors and clinical outcomes were assessed using Cox proportional hazard models.

Results: Our final cohort size was 1,530 KTR. The median frailty index was 1.5 (IQR: 0.5, 2.0). An increase in frailty index score, or increase in the patient's extent of frailty, was significantly associated with EHR (HR: 1.17, 95% C.I.: 1.05, 1.29), after adjusting for all risk factors. Similarly, an increase in frailty index score was also significantly associated with DGF (OR= 1.24, 95% C.I.: 1.07, 1.43), after adjusting for all risk factors. Furthermore, a change in frailty index was significantly associated with the duration of DGF (OR= 1.89, 95% C.I.: 1.03, 3.46).

Conclusions: A frailty metric was created using assessments that are easily accessible. Frailty was found to be significantly associated with EHR and DGF among KTRs. The standardization of frailty assessments may be warranted to help improve provision of care for KTRs.

THE PSYCHOSOCIAL HEALTH OF KIDNEY RECIPIENTS IN CANADA'S KIDNEY PAIRED DONATION PROGRAM: AN INTEPRETATIVE PHENOMENOLOGICAL ANALYSIS

Sophia Bourkas and Marie Achille - Université de Montréal

Keywords: kidney diseases, kidney transplantation, qualitative research, interpretative phenomenological analysis, clinical psychology, behavioral medicine

Background. Kidney paired donation (KPD) matches incompatible donor-recipient pairs so that both transplants can be completed. National-level KPD programs have been implemented in the U.K., Canada, Australia, the U.S., the Netherlands, and countries in Europe. Despite their widespread implementation, empirical studies on the psychosocial implications of KPD are lacking. However, the involvement of at least two donors in KPD may exacerbate recipients' burden related to debt of gratitude, guilt, and worries about the donor's health and graft failure, documented by previous research. The primary objective of this study was therefore to gain an in-depth understanding of recipients' experience in KPD, with a focus on psychosocial adjustment. *Methods.* This study employed a qualitative research approach. Individual interviews were conducted with eight participants recruited through the Kidney Foundation of Canada's website, and the nephrology clinic of a university-affiliated hospital in Montreal, Quebec. Data analysis followed principles of Interpretative Phenomenological Analysis. *Results.* Four inter-related themes emerged from participants' discourse: *1) A more emotionally charged relationship with the known donor, 2) Approach-avoidance strategies when navigating the relationship with the anonymous donor, 3) Adapting to periods of destabilization within PKD*, and *4) Multi-layered gratitude*. Results call attention to recipients' emotionally charged journey, the need to define the anonymous donor(s), and ways of coping with KPD-specific challenges. Guilt and gratitude were also prominent. *Conclusion.* These results are considered in relation to existing literature on the topic. Issues relevant to the transplant community's continuing clinical and research efforts to understand the experience of KPE programs are discussed.

Differences in Transplant Decision Making Between Asian and White ESKD Patients

Background
Compared to Whites, Asian Canadians with end stage kidney disease (ESKD) are less likely to receive living donor kidney transplant (LDKT). We explored the importance of pros and cons in the kidney transplant (KT) decision making for Asian Canadians with ESKD.

Methods
Cross-sectional convenience sample of adults with ESKD in Toronto completed the Transplant Decisional Balance Survey. Ethnicity (White, Asian[South and East], other) was self-identified. Patients rated importance of positive and negative outcomes to their decision about KT on a scale from 1-5 (“not important” - “extremely important”). LDKT and deceased donor KT (DDKT) pro/con scores were calculated by summing individual item scores. Items were then dichotomized (not/slightly/moderately vs very/extremely important) and their association with ethnicity was analyzed in multivariable logistic regression models.

Results
Among the 539 participants (mean[SD] age 57[13] years, 62% male), 23% were Asian, and 45% were White. The LDKT pro, LDKT con, and DDKT pro scores were similar between the groups. However, Asian patients rated DDKT con significantly higher (median [IQR]: 9[5,13] vs 12[8,16]; p=0.002).

LDKT and DDKT pro items were not significantly associated with ethnicity. In univariable analysis, compared to White patients, Asians were more likely to indicate that pain from surgery (OR, 2.27 [95% CI: 1.32, 3.90]), taking many medications post-transplant (OR, 2.08 [95% CI: 1.32, 3.27]), and "if transplant failed it would be a lot of work/pain for nothing" (OR, 3.07 [95% CI: 1.66, 5.70) were very/extremely important to their transplant decision. These associations remained significant after adjusting for sociodemographic variables, comorbidity, and transplant knowledge, (OR, 1.97 [95% CI: 1.10, 3.54]), (OR, 1.90 [95% CI: 1.14, 3.17]), (OR, 3.38 [95% CI: 1.65, 6.90], respectively).

Conclusion:
Anticipated pain, concerns about post-transplant medications and potential unsuccessful transplant weighs into KT decisions among Asian Canadians with ESKD more than for Whites.

Transplant Decision Making Concerns for African, Caribbean and Black Canadian patients with end stage kidney disease

Background
Compared to Whites, African, Caribbean and Black (ACB) Canadians with end stage kidney disease (ESKD) are less likely to receive a living donor kidney transplant (LDKT). We explored the importance of pros and cons for kidney transplant (KT) decisions for ACB patients with ESKD.

Methods
Cross-sectional convenience sample of adults with ESKD in Toronto completed the Transplant Decisional Balance Survey. Ethnicity was self-identified. Patients rated importance of positive and negative outcomes to KT decision from 1-5 (“not important” - “extremely important”). Individual items were scored to yield LDKT and deceased donor KT (DDKT) pro/con scores. Items were dichotomized (not/slightly/moderately vs very/extremely important) and their association with ethnicity was analyzed in multivariable logistic regression.

Results
Among the 539 patients (mean[SD] age 57[13] years, 62% male), 27% were ACB, and 45% were White. ACB patients were more likely to live in areas with material deprivation (20% vs 72%, $p<0.001$).
The LDKT scores and DDKT pro score were similar between the groups. However, ACB patients rated DDKT con (9[5,13] vs 12[5.5,16]; $p=0.002$) higher than Whites.

In univariable analysis, ACB patients were more likely to indicate that "taking many medications post-transplant" (OR, 2.79 [95% CI: 1.76, 4.44]), "pain from surgery" (OR, 1.88 [95% CI: 1.15, 3.05]), "health problems due to transplant" (OR, 1.72 [95% CI: 1.12, 2.63), and "trouble paying for medications" (OR, 2.98 [95% CI: 1.81, 4.90), were important to transplant decision. These associations remained significant for "taking many medications" (OR, 2.15 [95% CI: 1.30, 3.56) and "trouble paying for medications" (OR, 1.71 [95% CI: 1.03, 2.83) after adjusting for sociodemographic variables, comorbidity, and transplant knowledge.

Conclusion:
Concerns about post-transplant medications and anticipated financial strain weighs into KT decisions among ACB Canadians with ESKD more than for Whites.

Application of Machine Learning to Analyze Immune Cellular Compartments in a Pre-Transplant Cohort

Background: Chronic kidney disease affects 1 in 10 Canadians with estimated costs of over $2 billion/year. Advanced stages of the disease lead to uremia, accompanied by profound disturbance of the immune response comprising both impaired immune defense and enhanced inflammation. This dysregulation of the immune system is reflected in changes in function as well as composition of the immune system. We captured these changes by quantifying lymphocyte- (CD4 T-, CD8 T, B- and NK-cells) and monocyte subpopulations as well as the expression of several activation markers during uremia.

Methods: We have developed a flow cytometric immunophenotyping assay to detect high resolution cellular subpopulations based on cellular surface markers. Samples of 35 uremic patients and 12 healthy controls were immunophenotyped and analyzed using a custom R/Bioconductor pipeline. Due to the complexity of these multidimensional data we used machine learning algorithms like uMAP to reduce complexity and FlowSOM to cluster the immune cells into different subpopulations. Key immune populations that contribute to the state of chronic activation of the immune system in uremic patients were compared to healthy controls as well as correlated with other factors known to impact immune cells, such as time on / type of dialysis and primary diagnosis.

Results: In a preliminary analysis of the CD8 T-cell panel we discovered an increased frequency of TEMRA CD27+ cells, a terminally differentiated effector memory T cell subset, in uremic patients (Fig. 1). This analysis also revealed other key players in the cellular compartments that show an immunophenotype of uremia and provides insight into how modifications in these cellular subsets drive disease progression.

Conclusion: With more understanding of the dysregulation observed in these disease states, we hope to recognize the onset of the disease earlier and develop more specific and targeted therapies.

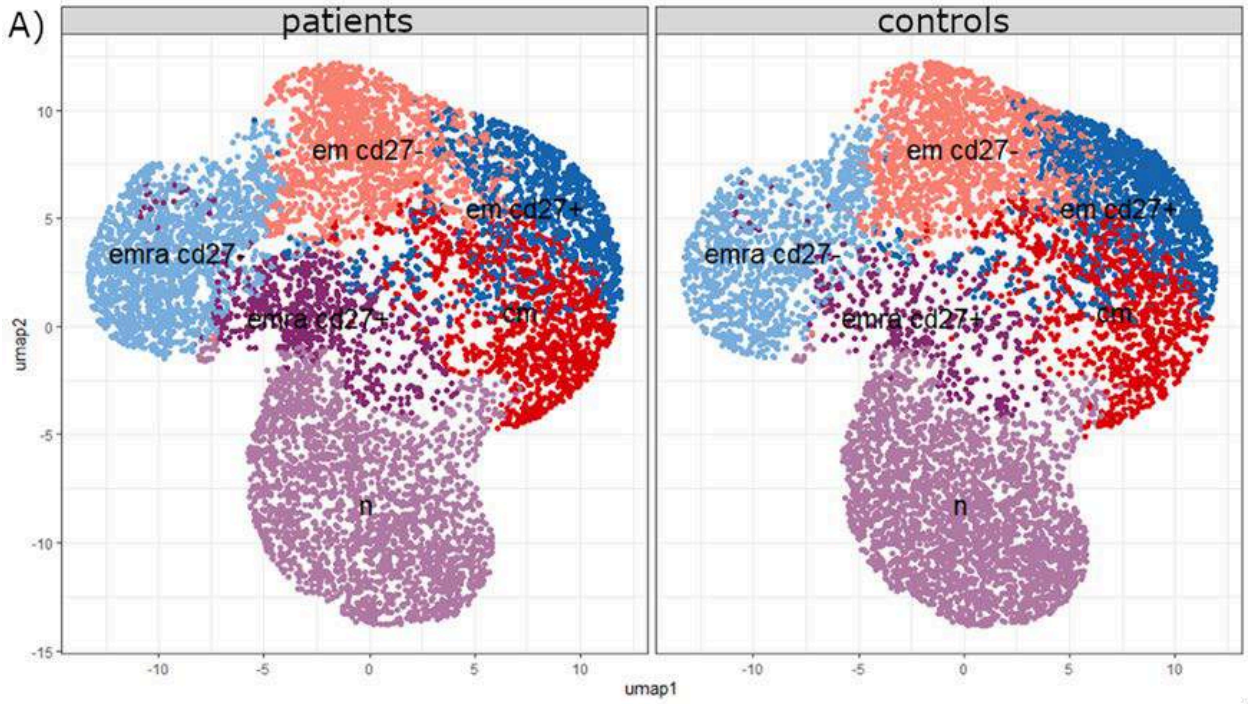


Fig 1) A) uMAP diagram comparing CD8 T cell subpopulations clustered using FlowSOM in uremic patients and healthy controls. (cm.. central memory, em.. effector memory, n.. naive)

Age and Sex Determine Conversion from Immediate Release to Extended Release Tacrolimus in a Multi-Centre Cohort of Canadian Pediatric Renal Transplant Recipients

Background: Extended release tacrolimus (ER-Tac), taken only once per day, is associated with improved adherence. This is the first study to report on the patient and clinical factors that influence physicians to convert patients from immediate release to extended release tacrolimus.

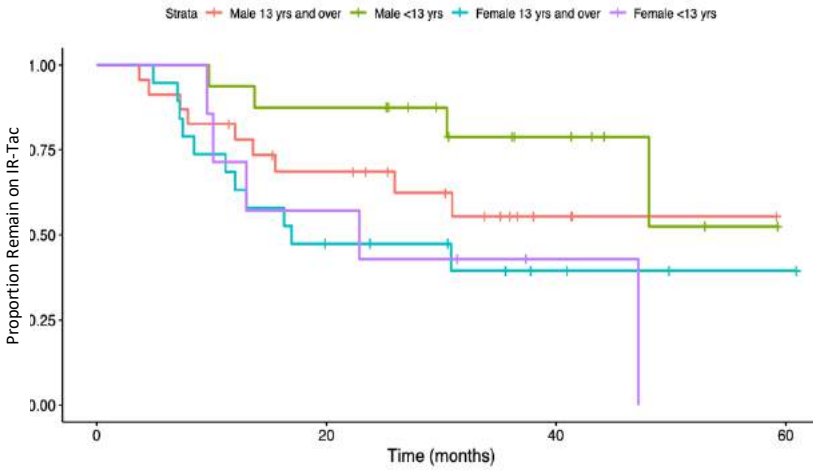
Methods: This prospective multicentre observational study followed Canadian pediatric kidney transplant recipients for up to five years post-transplant. Cox Proportional Hazards Regression was used to examine the influence of factors on conversion to ER-Tac.

Results: Sixty-six participants were included. Our study population reflected a typical pediatric transplant population with a preponderance toward males (61.9%) and living donor kidney donation (53.6%). Total follow-up time was equivalent between the converted and unconverted groups. The likelihood of conversion more than doubled for every additional year of age at the time of transplant, (HR 2.54, CI 1.83, 3.54, p < 0.001). The impact of age reduced by three percent for every month after transplant (HR 0.97, CI 0.95, 0.98, p <0.001). Girls were more likely to be converted (HR 3.78, CI 1.35, 10.6, p 0.01). None of the following were significant predictors of conversion in the final regression model: Adherence measures (medication adherence measure (MAM-MM) and tacrolimus variability), individual reported barriers to adherence, renal function, rejection, and transplant centre. ***Conclusions*****:** ER-Tac was preferentially prescribed to older age and female patients, features that correlate with worse graft outcomes and poorer adherence. We found no link between individualised markers of adherence/graft risk, such as prior history of rejection, kidney function decline, or non-adherence, with subsequent conversion. Clinicians appeared to base ER-Tac conversion decisions on demographic features that speak to pre-conceived notions of risk, without a case-by-case evaluation of susceptibility to poor outcomes. This use of heuristics is significant: ER-Tac is not targeted to patients who may reap the most benefit, those with demonstrable non- adherence, with potential implications for their long-term adherence trajectory and graft outcomes.

Cox Proportional Hazards Regression Assessing the Influence of Co-Variates on Conversion to ER-Tacrolimus, Exploratory and Multivariable Analyses

	Exploratory Model		Final Model	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age at transplant	2.06 (1.62, 2.63)	<0.001***	2.54 (1.83, 3.54)	<0.001***
Age at transplant (years):Time from transplant (months) interaction	0.97 (0.96, 0.98)	<0.001***	0.97 (0.95, 0.98)	<0.001***
Age Adjusted Model				
Female sex (reference male)	4.40 (1.69, 11.48)	0.0025**	3.78 (1.35, 10.6)	0.011**
Non-white race (reference white)	1.16 (0.49, 2.75)	0.74	-	-
ESRD (reference glomerular disease)				
Non-glomerular	1.72 (0.70, 4.25)	0.23	-	-
Unknown	3.86 (0.65, 22.8)	0.14	-	-
Transplant date (reference 2012-2014)	0.45 (0.16, 1.30)	0.14	-	-
DD Kidney (reference LD)	0.54 (0.20, 1.44)	0.22	-	-
HLA A, B mismatch	1.03 (0.73, 1.46)	0.86	-	-
HLA DR, DQ mismatch	1.07 (0.59, 1.96)	0.82	-	-
Baseline PMBS	1.04 (0.98, 1.11)	0.18	-	-
Baseline AMBS	0.03 (0.94, 1.12)	0.55	-	-
Induction therapy				
Basiliximab	0.51 (0.10, 2.68)	0.43	-	-
Anti-thymoglobulin	1.64 (0.56, 4.82)	0.37	-	-
Tacrolimus Preparation (reference capsule)	2.18 (0.28, 17.11)	0.46	-	-
Recent rejection (reference no rejection)	0.64 (0.28, 1.46)	0.29	-	-
Tacrolimus trough CV%	1.05 (0.99, 1.10)	0.10	1.04 (0.99, 1.10)	0.13
MAM-MM % ‡	0.95 (0.75, 1.20)	0.65	-	-
eGFR	1.03 (0.99, 1.07)	0.073	1.01 (0.97, 1.06)	0.47

Exploratory Model: adjusted for age and age:time interaction only. Final Model: Adjusted for candidate predictors (p<0.1) identified in exploratory model. *p<0.05 ** p<0.01 ***p<0.001. ‡*MAM-MM %:* self-reported adherence- percentage of tacrolimus doses reported taken on time (neither missed nor late). *Abbreviations:* LCO – latest conversion opportunity, HR – hazard ratio, CI – confidence interval, ESRD – end-stage renal disease, DD - deceased donor, LD – living donor, Percentage, PMBS - parent medication barrier scale, AMBS - adolescent medication barrier scale, eGFR: estimated glomerular filtration rate, CV%: percentage coefficient of variance - represents tacrolimus trough level variability, HLA – human leucocyte antigen, MAM-MM - medication adherence measure medication module.



Transplantation Activity and Risk Factors during the ramp-down phase of the COVID-19 Pandemic: Results of Phase I of the LIST-COVID-19 study

Introduction: The COVID-19 pandemic has indirectly affected transplantation due to the ramp-down of activity and low availability of donors. Data is needed on transplantation activity and how these varied by factors such as a country's income level, COVID-19 incidence, and solid organ.

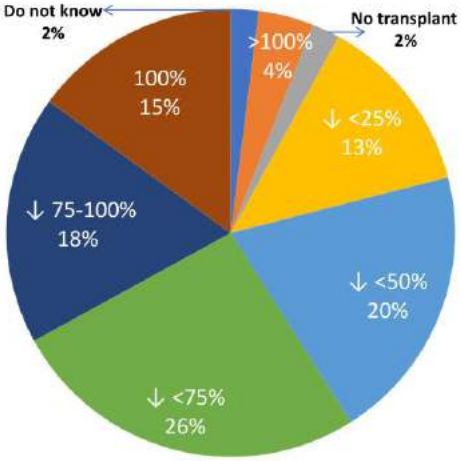
Methods: We conducted a survey of physicians from 80 different countries who take care of patients with a solid organ transplant. Survey was designed using an iterative process and was administered electronically. Only one physician per transplant program at each center was recruited and a quota sampling method was used to ensure a heterogeneous sample. We conducted a descriptive and a comparative analysis of survey responses.

Results: Of the 1,268 eligible physicians contacted, 513 returned completed responses for a response rate of 40.4%. Overall, 77% of the respondents reported performing at least one transplant during the ramp down phase and 79% anticipate a decline in their transplant volumes of varying magnitudes (Figure 1). Both these responses were modified by the income-level of the country and the type of organ (Table 1). Interestingly, the cumulative incidence of COVID-19 was not associated with the odds of doing a transplant. However, a very high cumulative incidence was associated with maintaining transplant volumes ≥75%. About 70% agreed or strongly agreed that centre-level factors such as increased utilization of hospital resources or ICU being overwhelmed were major risks to their program.

Table 1: Univariable logistic regression (Odds ratio and confidence interval with significant values in bold)

	Performing a transplant	Maintaining a transplant volume ≥75%
Income (Ref: low/lower-middle)		
Upper-middle income	0.72 (0.40 – 1.33)	1.49 (0.76 – 2.91)
High income	**2.98** (1.68 – 5.28)	**3.24** (1.82 – 5.74)
Organ (Ref: heart/lung/liver)		
Kidney or pancreas transplant	**0.29** (0.17 – 0.47)	**0.36** (0.24 – 0.52)
COVID-19 (Ref: ≤ 2000 people per million population)		
2001-4000	1.07 (0.62 – 1.84)	1.48 (0.90 – 2.44)
4001-8000	1.54 (0.84 – 2.82)	1.15 (0.68 – 1.95)
>8000	1.67 (0.88 – 3.19)	**2.06** (1.20 – 3.51)

Figure 1: Anticipated change in transplant volume in 2020



Conclusion: Transplant physicians from 80 different countries foresee a major decline in transplant volumes and this impact varies by income level and type of organ, but less so by COVID-19 incidence. Our future work entails how health system level factors, such as health financing and workforce/capacity, explain these differences. With this, we hope to generate knowledge that can inform practice and policy to mitigate the effects of the pandemic on transplantation globally.

Photoacoustic imaging: A new tool for assessing pre-transplant kidney quality

Background: Current methods for assessing deceased donor kidneys are suboptimal. We have developed a new, non-invasive algorithm based on photoacoustic imaging (PAI), a laser-based ultrasound modality. PAI can accurately assess donor kidney fibrotic burden, an important predictor of post-transplant outcome.

Methods: The feasibility of this new approach was tested in a unilateral ureteral obstruction (UUO) mouse model. n = 10 mice underwent UUO surgery and were followed for 7 or 14 days (n = 5/timepoint); n = 5 animals received sham surgery. A total of 30 kidneys were imaged using a unique PAI algorithm that separated the contributions of collagen from that of oxy/deoxyhemoglobin in the kidney (Fig. 1a). The same algorithm was then tested in n = 5 *ex vivo* human kidneys with various levels of fibrosis, in a setting that mimicked human kidney transplantation (Fig. 1b). Histological measures of fibrosis were used to evaluate the accuracy of the PAI-based collagen estimation algorithm.

Results: Fig. 2a shows increasing levels of fibrosis observed as the ureter is obstructed for longer periods of time. A strong correlation was observed between the PAI estimates of collagen and gold standard histology measures over a wide range of fibrosis severity (Fig. 2b, $r^2 = 0.99$). As PAI can non-invasively scan the entire 3D kidney volume, we next tested whether it could be used to image intra-renal variations in fibrosis distribution. As shown in Fig. 3a, PAI performed every 0.5 mm on both surfaces of the kidney revealed large variations in collagen scores even within a given kidney, that correlated tightly with histology measures (PSR and Trichrome, Fig. 3b).

Conclusion: Our novel PAI approach accurately quantifies fibrosis levels in *ex vivo* kidneys. This technique could potentially be used to measure donor kidney fibrotic burden, and thus guiding kidney allocation.

Fig. 1

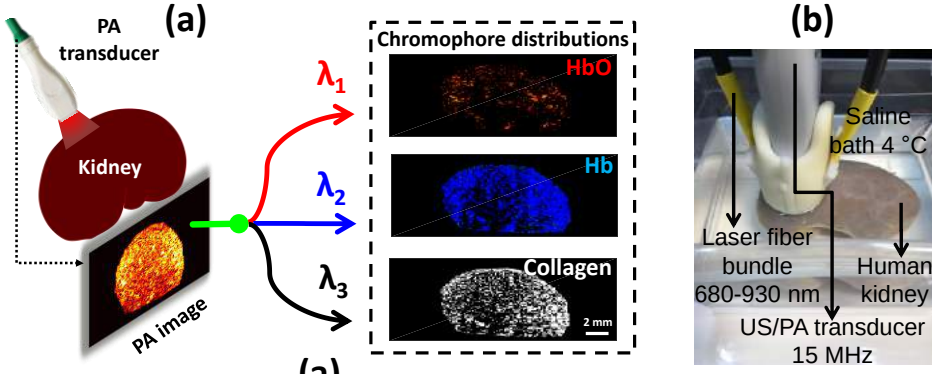


Fig. 2

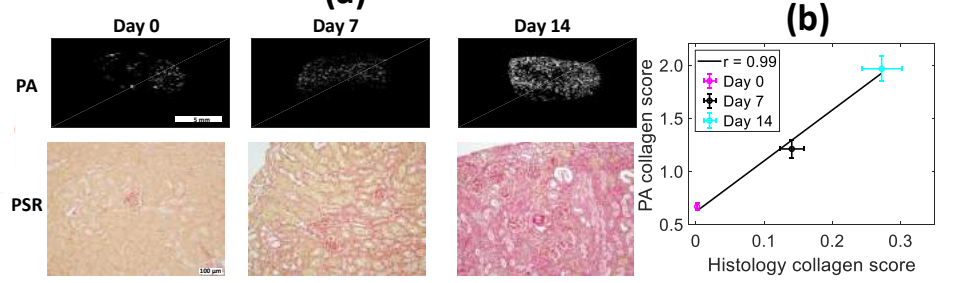
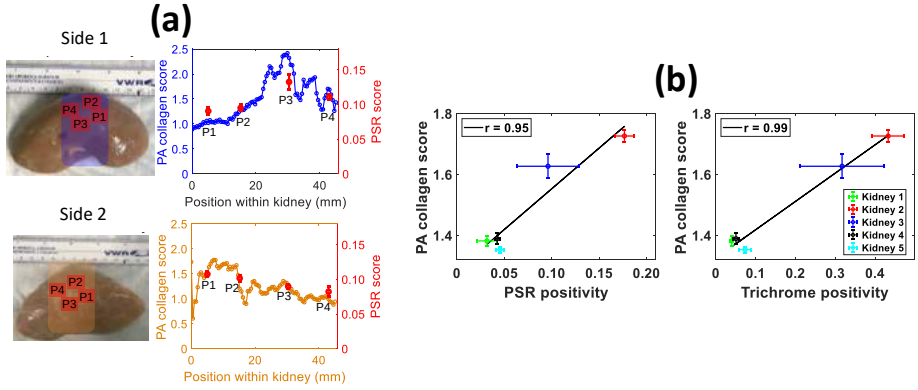


Fig. 3



Barriers to Accessing Living Donor Kidney Transplantation in Bangladeshi Communities in Canada – A Literature Review

Background:
From a medical perspective, living donor kidney transplant (LDKT) is the preferred treatment for many patients with kidney failure. Published data has demonstrated that South Asian Canadians are less likely to undergo LDKT compared to White patients, with little to no data on Bangladeshi-Canadians in particular. In this review, we summarize potential barriers to LDKT for Bangladeshi-Canadian communities.

Methods:
PubMed, OVID, Web of Science and Google Scholar were searched between January and August, 2020 for relevant studies in English-language journals and grey literature. Articles addressing Bangladeshi and Bangladeshi-Canadian communities, LDKT, kidney transplant, kidney disease, access, barriers, education, knowledge, culture, and religion were included in the review.

Results :
15 articles were included in the review. Gaps in transplant-related knowledge, a lack of awareness about the benefits of LDKT, concerns regarding the donor's safety, and negative attitudes toward solid organ transplantation may present potential barriers for Bangladeshi-Canadians to pursue LDKT. The majority of Bangladeshi-Canadians identify as Muslims, and faith-related concerns regarding Islamic perspectives on organ transplantation often contribute to reduced LDKT willingness. A large proportion of Bangladeshi-Canadians are recent immigrants with attitudes and perspectives carried over from Bangladesh. Immigration and settlement patterns in Canada may reinforce social norms that may also impact community attitudes toward transplant. Systemic factors such as language barriers and socioeconomic status may also result in reduced access to transplant. However, many of these barriers are speculative and have not been supported by robust data.

Conclusion:
Religiosity, systemic factors such as language barriers and socioeconomic status, and lack of transplant-related knowledge may act as barriers to accessing LDKT in Bangladeshi-Canadian communities. Further quantitative and qualitative research is needed to understand factors affecting access to LDKT in Bangladeshi-Canadian communities. Community-based, culturally tailored education may increase knowledge about organ transplantation and LDKT and support informed treatment decisions.

A collaborative approach to supporting direct contact between a donor family and heart transplant recipient

Background:

Anonymity of organ donor and transplant recipient identities is the norm in practice in deceased organ donation in Canada. Internationally, direct contact is possible in the United States and Israel; however, there is limited literature describing the process of facilitating direct contact or the experience of donor families and transplant recipients who establish direct contact.

Anonymous correspondence programs are widely facilitated in Canada and internationally to support the communication and relational needs of donor families and transplant recipients. However, advocacy around the need for direct contact and the ethical responsibility of organ procurement organizations to support the autonomy of donor families and transplant recipients with respect to privacy is growing.

BC Transplant developed a policy and process for supporting consenting adult donor families and transplant recipients to establish direct contact, which became available in November 2019.

Method:

A case study method is utilized to describe the legislative and policy structure and collaborative process of facilitating direct contact between a donor family and transplant recipient in British Columbia. Qualitative interviews illustrate the perspectives of the donor family and transplant recipient before, during, and after direct contact is established.

Results:

A donor family and heart transplant recipient are guided through a consent process and collaborate with the program facilitator to communicate needs and boundaries, develop a plan, and establish direct contact with each other. Increases in feelings of support, safety, and confidence in a positive outcome are reported by the donor family and transplant recipient through collaboration with the program facilitator.

Conclusion:

Respect for the autonomy of donor families and transplant recipients is crucial to providing support that is responsive to the needs of this community. Further qualitative research with a larger sample of donor families and transplant recipients in direct contact can increase understanding of their experience and needs and establish best practices in facilitating direct contact.

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Background
Life-saving organ transplantation is limited by a severe organ demand-supply imbalance. Improving societal perceptions of organ donation and transplantation (ODT) amongst youth may be a helpful strategy. Educational programs designed to inform youth about ODT are currently limited. Here, we aimed i) to describe the implementation of a High School Outreach Initiative (HSOI) established to help address the knowledge gaps about ODT amongst youth in the Greater Toronto Area (GTA); and ii) to evaluate the effectiveness of the HSOI in changing attitudes about ODT amongst youth receiving these presentations.

Methods
The HSOI was formed in March 2012, creating a model (Figure 1) to deliver informative presentations across the GTA. In order to assess impact of the program on student knowledge of organ donation and registration, matched pre- and post-presentation surveys (n=1224) were administered during a two-year period (2017-2019). Additional factors such as awareness of donor registration, importance of donation, intent to register, and willingness to talk to their families were collected and analyzed.

Results
Since the implementation of the HSOI, a total of 590 presentations have been delivered to over 38,700 students at 102 high schools across the GTA. During the quantitative examination period, only 16.5% of students stated they were knowledgeable about ODT prior to receiving the presentation, however, this number increased to 84.2% afterwards ($p < 0.0001$). In addition, of the students who were not willing to register to be an organ donor prior to the presentation (n=358), 48% of them were then willing to register after receiving the presentation ($p < 0.0001$).

Conclusions
The HSOI demonstrates itself as a feasible approach to inform youth about ODT and positively influences their attitudes about ODT. Future directions include expanding this youth educational initiative into different provinces across Canada.

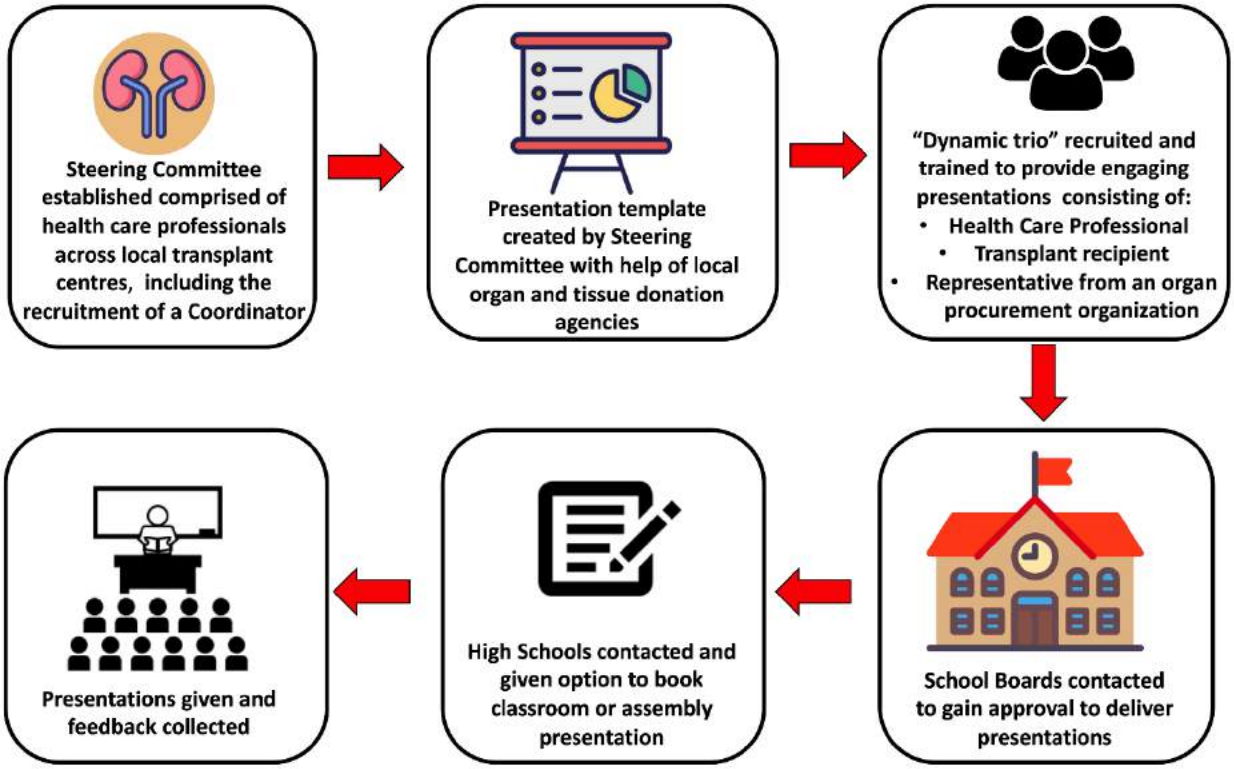


Figure 1. Implementation model of High School Outreach Initiative (HSOI)

RESOLVING ANTI-HLA SPECIFIC COMPLEXITIES USING PHENOTYPE BEADS: A DUAL ASSAY CONSIDERATION

Aim

To evaluate the use of Immucor LIFECODES Identification (IMID) kits to assess non-HLA specific reactivity patterns as observed on the One Lambda LABScreen single antigen bead (OLSAB) assay.

Methods

16 serums with Class I patterns and 20 serums with Class II patterns were run on OLSAB assay followed by IMID kits. The OLSAB assay was set up following the Rapid Optimized SAB (ROB) protocol, which is a modified version of the manufacturer's protocol. An additional two final wash steps was added to decreased background fluorescence. The IMID kits were set up following a modified manufacturer's protocol, using a centrifugation and flick method as opposed to vacuum manifold method.

Results

The two assays utilize different manufacturing processes of coating purified recombinant protein onto beads (OLSAB) versus using protein derived from EBV transformed cell lines with native phenotypic expression (IMID). We hypothesised that the difference in recombinant versus native protein may result in differences in observed non-HLA specific reactivities. Our lab routinely tests patient serum using OLSAB kits to determine HLA Class I and Class II antibody specificities. Many of these reactivity patterns seen on the OLSAB assay appear to be non-HLA specific and cannot be correlated with other laboratory tests. In addition, epitope and cross-reactive analysis reveals no discernable explanation for the observed non-specific patterns.

Disproving the presence of many non-specific HLA specificities may lead to significant changes to reported PRA percentages**.** DQA1*05:01/DQB1*02:01 reactivity is observed in the OLSAB assay but often yields a negative crossmatch. The IMID assay was able to confirm or eliminate alternative calls due to having additional DQA1*05 antigens in the beadset.

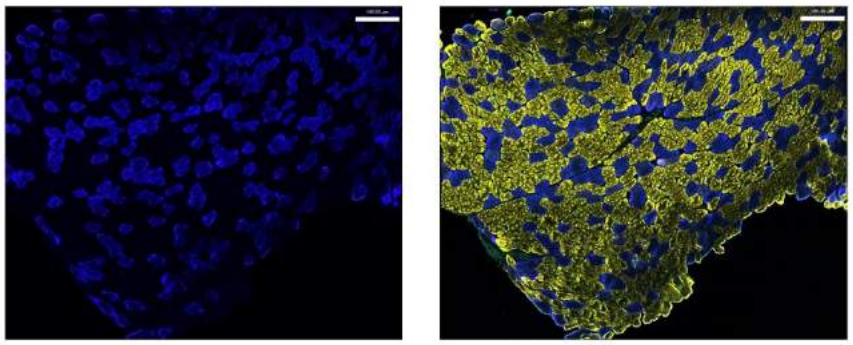
Conclusions

We believe using the IMID kits would be a beneficial tool to help deconvolute complex, non-specific reactivities seen on OLSAB in order to better reveal biological reactivity.

Histological characterization of skeletal muscle in children with end-stage liver disease and myopenia at time of liver transplantation.

Mager DR[1,2], Dunichand-Hoedl A[1], Mazurak V[1], Dajani K[3], Ayala-Romero A, Shapiro, J[3], Bigam D[3], Kneteman, NM, Noga M[4], Montano-Loza[5], Yap J[2], Gilmour SM[2].
[1]Department of Agricultural, Food and Nutritional Science, [2]Department of Pediatrics, [3]Department of Surgery, [4]Department of Medicine, [4]Department of Radiology and Diagnostic Imaging, [5]Department of Medicine University of Alberta

Background: Myopenia occurs in 30-40% of children awaiting LTx. No information regarding skeletal muscle histology associated with myopenia in children is available. The study objective was to evaluate the histological features of skeletal muscle in children at time of liver transplantation (LTx).
Methods: Children were recruited from the Stollery Children's Hospital Pediatric LTx Clinics. SMM (cm^2) was quantified at three muscle sites (psoas, paraspinal, rectus abdominus) using slices obtained at the L3-vertebrae from abdominal imaging (MR/CT). Skeletal muscle mass index (SMMI; cm^2)/height $(m)^2$) values were compared to age-sex matched healthy controls. Myopenia was defined as SMMI z-scores <-2. Rectus abdominus (<1 cm^3) biopsies were collected at the LTx incision site. Muscle fiber tissues were demarcated using laminin and dystrophin immunofluorescence stains for quantification of muscle fiber area, total muscle fiber count and muscle fiber types. Fiber types were classified based on isoforms of myosin heavy chain (MyHC). Comparison between ± myopenia was done using Mann-Whitney tests.
Results: Children (0.9-9.3 years; 5M/2F) with cholestatic liver diseases were studied. Myopenia was present in 28.5% of children. Percentage of MyHC type 1 (oxidative fibers), MyHC type IIA fibers and MyHC IID were 56.8 ± 11.1%, 47.3 ± 16.6% and 8.2 ± 3.2%, respectively. Although children with myopenia tended to have a lower number of total muscle fibers (258 ± 169 vs 457 ± 80; p=0.09) and a lower number of Type IIA muscle fibers (82+17 [+ myopenia] vs 175 ± 57 [- myopenia]; p=0.07), no significant differences in the proportions of type 1A, type IIA and Type IID fibers were observed in children ± myopenia.



Conclusions: Histological features in children ± myopenia included higher proportions of MyHC Type 1 muscle fibers (oxidative) and lower total muscle fiber number and MyHC Type IIA fibers in children with myopenia at LTx.

Impact of Kidney-only versus multi-organ diseased donors on early renal allograft function

Background: Traditionally during deceased abdominal organ recovery the kidneys are the last organs to be removed. Herein we address whether the real or perceived longer extraction time post vascular clamp has any impact on early allograft function.

Methods: From 2013 -2017, consecutive kidney transplant recipients from deceased organ donors were reviewed. Delayed graft function (DGF) was the primary outcome. Secondary outcomes of interest were rejection and graft loss rate. Deceased kidney donors who had at least one other abdominal organ recovered (liver and/or pancreas) were labeled as multi-organ donors (MOD) and compared to kidney-only donors (KOD) with respect to recipient outcomes. T-test, Chi-square, univariable and multivariable analysis were performed as appropriate.

Results: Data on 238 kidney transplant recipients and 211 respective donors were captured. Of these, 32.7% were from KOD while 67.3% were from MOD. Overall DGF rate was 39.34%. The DGF rate in MOD group was significantly lower than in KODs (28.16% vs. 62.31%; P<0.0001).

In both groups of donation after circulatory death (DCD) and neurologic determination of death (NDD), MODs had lower DGF rates as opposed to KODs (OR=0.30, 95% CI=0.09-0.97 in DCDs and OR=0.52, 95% CI=0.18-1.48 in NDDs).

DCD-MODs had a DGF rate of 40% which was not statistically different than DGF rate in NDD-KOD and NDD-MOD (p=0.3). Multivariable logistic regression modeling showed the only factor with a significant negative impact on DGF rate was DCD-KOD (OR=5.2, CI=2.40-11.26; p<0.0001). Recovery of multiple abdominal organs had no negative impact on rejection rate (p=0.25), graft loss rate (p=0.28), or time to rejection as opposed to KODs (P=0.16).

Conclusion: MOD versus KOD does not appear to affect renal allograft function.

We hypothesize that better quality organs from MOD could explain DCD-MODs having similar DGF rates as NDD donors.

Table 1- Demographic data.

	Variables	KOD	MOD	P-value
Donor Population	Mean Age (years) (SD)	51.78 (14.95)	47.76 (19.40)	0.1314
	DCD; NO. (%)	52 (75.36)	15 (10.56)	<0.0001
	ECD; NO. (%)	28 (40.58)	66 (46.48)	0.462
	Male; NO. (%)	52 (75.36)	78 (54.93)	0.0043
	Obesity; NO. (%)	30 (43.48)	24 (16.90)	<0.0001
Recipient Population	Mean Age (years) (SD)	57.94 (13.81)	55.68 (14.05)	0.2719
	Male; NO. (%)	45 (65.22)	87 (61.27)	0.6500
	Presence of Obesity; NO. (%)	23 (39.66)	35 (31.25)	0.3078
	First Tx; NO. (%)	62 (89.86)	127 (89.44)	>0.9999
	Caucasian; NO. (%)	45 (65.22)	94 (66.20)	0.8785
	DM; NO. (%)	22 (31.88)	44 (31.21)	>0.9999
	Listing (days); Mean (SD)	1101 (12.5)	1187 (13.4)	0.6575
	PRA; Mean (SD)	19.99 (31.75)	24.72 (36.06)	0.3539
Ischemia	CIT; Mean (SD)	671.7 (238.7)	674.6 (300)	0.9460
	WIT; Mean (SD)	53.13 (29.48)	44.35 (18.6)	0.0117

DGF: delayed graft funtion; DCD: donation after circulatory death; ECD: expanded criteria donor; Tx: Transplant; DM: diabetus melitus; CIT: cold ischemia time; WIT: warm ischemia time.

Table 2- Multivariable analysis for DGF.

Variable	Odds Ratio (95% CI)	P-value
Donor Male vs Female	1.46 (0.74-2.87)	0.27
Donor Obesity	1.36 (0.64-2.89)	0.41
CIT	1.00 (0.99-1.00)	0.10
WIT	1.01 (0.99-1.03)	0.12
KOD-DCD*	5.20 (2.40-11.26)	**<0.0001**
MOD-DCD*	1.68 (0.54-5.19)	0.37
KOD-NDD*	1.75 (0.52-5.88)	0.36

*versus MOD-NDD

Monitoring chronic lung allograft dysfunction by quantifying renin angiotensin system-regulated proteins in bronchoalveolar lavage

Background

Chronic lung allograft dysfunction (CLAD) limits long-term survival after lung transplantation. Renin-angiotensin system (RAs) is implicated in fibrogenesis in both kidney and lung disease. We previously identified 6 RAs-regulated proteins (RHOB, BST1, LYPA1, GLNA, TSP1, LAMB1) in kidney tissue and urine of patients with kidney allograft fibrosis. We hypothesize that RAs is active in CLAD and that the same RAs-regulated proteins could serve as biomarkers of CLAD in Bronchoalveolar Lavage (BAL).

Methods

We performed immunofluorescence staining of angiotensin receptors (AGTR1 and AGTR2) and immunohistochemical staining of TSP1 in 10 explanted CLAD lungs, compared to 5 control lungs. We developed parallel reaction monitoring assays for 2 peptides of each RAs-regulated protein. We quantified them in a set of BAL samples from 40 lung transplant recipients. We have developed machine learning algorithms for prediction of CLAD on the basis of RAs-regulated proteins.

Results

We observed significantly more AGTR1+ cells in CLAD versus control lungs (p=0.04) and a trend toward higher expression of TSP1 in CLAD samples compared to controls. Parallel reaction monitoring assays showed that RHOB, BST1 and LYPA1 peptides were numerically higher in the BAL of CLAD patients in comparison to those with acute >10% decline in lung allograft function and controls (figure 1A). Two machine learning algorithms identified CLAD from levels of all peptides with accuracy of 0.86 (figure 1B).

RHOB, BST1 and GLNA peptides were increased in BAL of patients who developed CLAD at follow up (figure 2A). Importantly, all peptides combined had a predictive value for CLAD of 0.97, when using SVM machine learning algorithm (figure 2B).

Conclusion

Our pilot data support the hypothesis that RAs is involved in CLAD and that RAs-regulated proteins may help identify patients with active CLAD. We are validating these findings using a larger cohort and established endpoints.

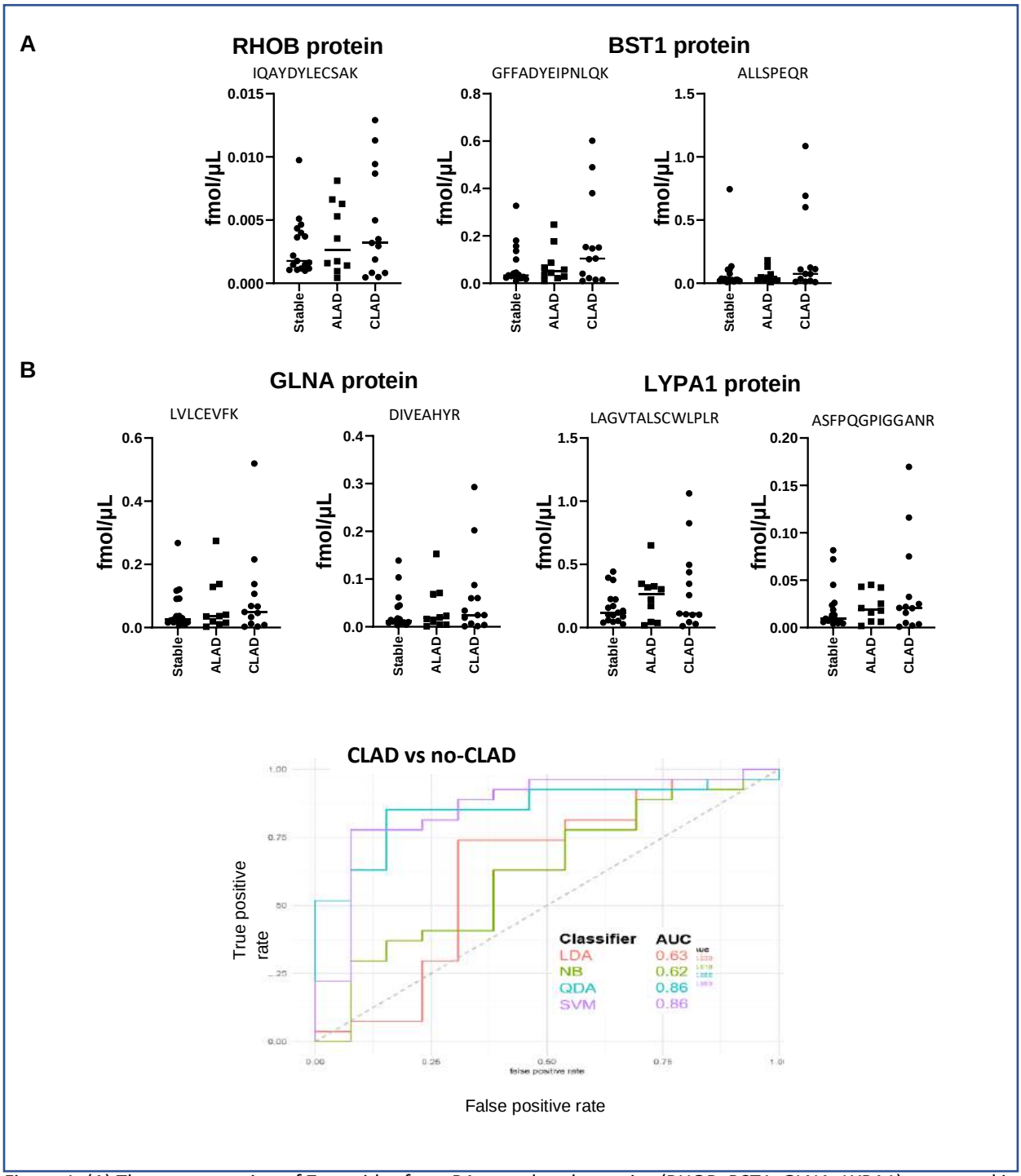


Figure 1. (A) The concentration of 7 peptides from RAs-regulated proteins (RHOB, BST1, GLNA, LYPA1) measured in BAL in 3 different groups of patients according to their clinical status at the time of bronchoscopy, defined by their pulmonary function tests (stable patients, patients with acute lung allograft dysfunction (ALAD), and patients with chronic lung allograft dysfunction (CLAD)). (B) the performance of combined peptide concentrations in discriminating CLAD from no-CLAD (that combines stable and ALAD) using different machine learning algorithms.

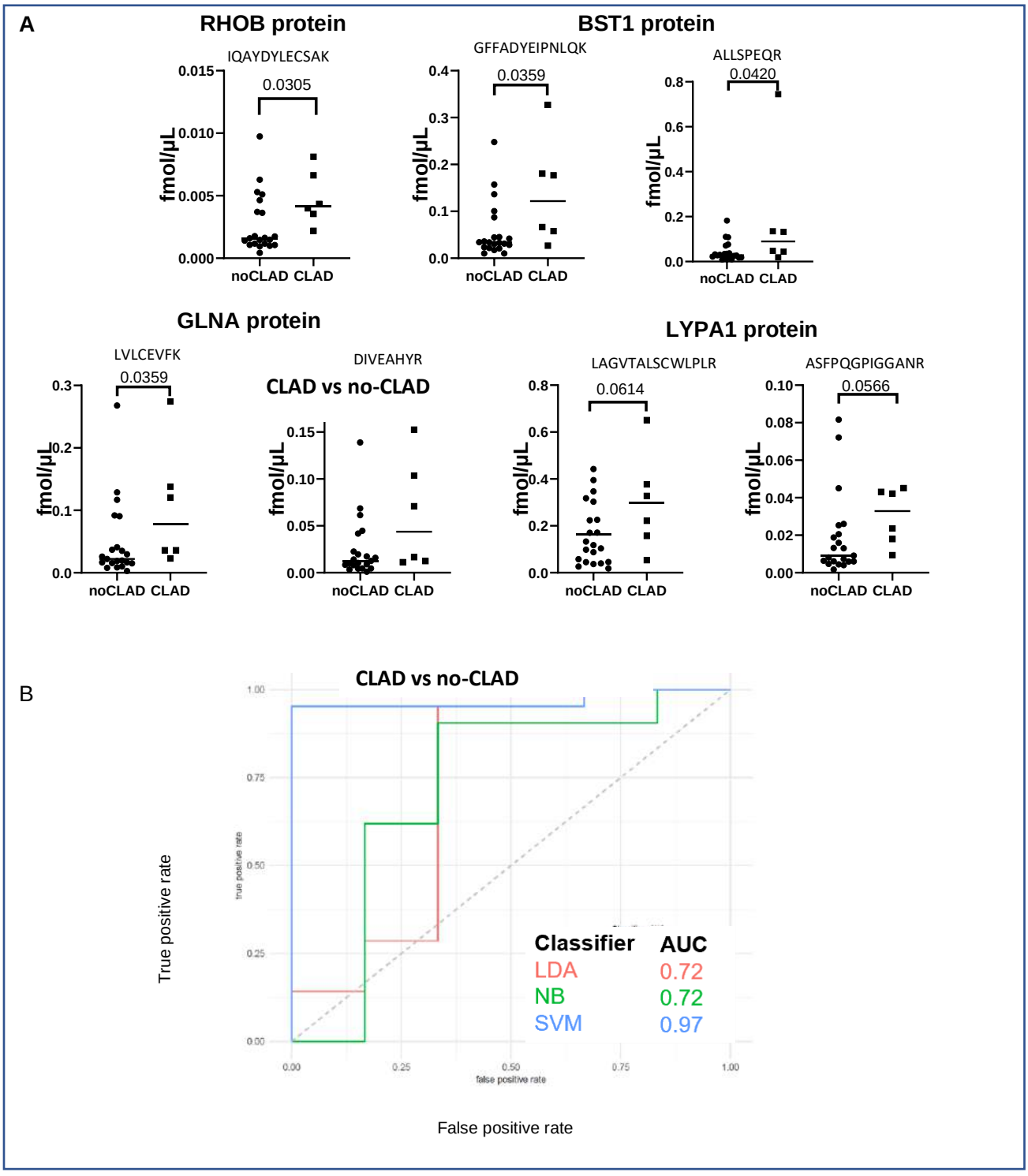


Figure 2. (A) The concentration of 7 peptides from RAs-regulated proteins (RHOB, BST1, GLNA, LYPA1) in BAL of patients who developed CLAD at follow up. (B) The performance of different machine learning algorithms combining 7 peptides for prediction of subsequent CLAD status at follow-up.

Autoantibodies against TRIM21 and CENPB are Increased in Antibody-Mediated Rejection after Kidney Transplantation

BACKGROUND

Antibody-mediated rejection (AMR) causes >50% of late graft failures in kidney transplantation. Although donor-specific antibodies against HLA cause AMR, antibodies against non-HLA antigens are also associated with rejection. Identifying critical non-HLA auto/allo-antibodies will improve our understanding of antibody-mediated injury.

METHODS

Sera from 91 kidney transplant patients from University Health Network in Toronto, with AMR (n=43), 'Mixed' rejection (n=20), acute cellular rejection (ACR, n=16), and acute tubular necrosis (ATN, n=12) were analyzed using an antigen microarray platform. We quantified IgG and IgM antibodies against 135 non-HLA antigens. Anti-HLA and non-HLA antibodies were measured pre-transplant, at the time of indication biopsy, and post-biopsy. Findings were validated in 60 kidney transplant patients from CHUM, Montreal. Mann-Whitney test was used to assess differences between groups. $P<0.05$ was considered significant.

RESULTS

Seventeen non-HLA antibodies were significantly increased ($P<0.05$) in AMR/Mixed cases compared to ACR or ATN pre-transplant, nine at-biopsy and six post-biopsy. AMR/Mixed group showed significantly higher pre-transplant levels of anti-TRIM21 and anti-CENPB IgG, compared to ACR. Together with anti-CENPB IgM, these antibodies were also significantly increased in the AMR/Mixed group at biopsy. Levels of anti-TRIM21 and anti-CENPB IgG pre-transplant and at biopsy correlated with the presence of microvascular lesions, but not with tubulitis or interstitial/total inflammation ($P<0.05$). At diagnosis, anti-TRIM21 and anti-CENPB IgGs correlated with the presence of anti-HLA class I/II ($P<0.05$). Finally, we demonstrated significantly higher levels of anti-TRIM21 IgG in AMR/Mixed compared to ACR, and a trend towards higher levels of IgG and IgM anti-CENPB, in the Montreal cohort.

CONCLUSIONS

This is the first study that implicates autoantibodies against TRIM21 and CENPB proteins in humoral rejection. These antibodies were increased pre-transplant and at biopsy in patients with AMR, and correlated with microvascular lesions and anti-HLA antibodies. Further independent validation of these antibodies and their targets is warranted in AMR.

Describing Intersections of International Organ Donation and Death Investigation Systems

Background

Death investigators (DIs) such as coroners, medical examiners, and forensic pathologists play important and evolving roles in deceased organ donation, as they have jurisdiction over decedent organs during sudden or unexpected deaths. DIs communicate with organ donation organizations (ODOs) to gather case-specific information and release or restrict organs when determining the cause and manner of death. This mixed-methods study aims to identify the breadth of roles and decision-making processes that allow or prevent deceased donation in DI cases.

Methods

The exploratory mixed-method approach includes two phases: an investigative interview study and a scoping review of the literature. Interviews were initially unscripted but evolved with successive participants to include predetermined questions. These informed the inclusion criteria and screening checklist for a scoping review. The primary investigator searched five databases, with no date or language restrictions, in November 2019: PubMed, OVID, Web of Science, TRIP, and CINAHL.

Results

Investigators interviewed 6 DIs and 4 ODO professionals from 4 countries to identify common and contrasting practices and inform a scoping review. Thirty eligible papers described 8 common themes with country-specific nuances. These include: shared (ODO-DI) protocols for early communication around each case; shared (ODO-DI) standards and education for donation and death investigation practices; DI support staff or teams established to facilitate organ donation; donation-specific legislation enacted to enhance DI and/or ODO operations; DI authority to order additional testing and imaging before organ recovery; authority of specific DIs to veto donation decisions; DI attendance at organ recovery; and surgeon responsibility to record evidence during organ recovery.

Conclusion

These findings have many cultural and resource-allocation implications and expose gaps in the international literature describing ODO-DI practice intersections. A better understanding of the rationale and execution for varied ODO and DI systems may serve to advance both organ donation and death investigation efficacy.

Hemagglutination Titres in Pediatric Heart Transplant Assessment: The Good, the Bad, and the Alternative

Aim: ABO-incompatible (ABOi) pediatric heart transplantation safely increases the donor pool as infants do not produce ABO antibodies until age 6-12 months. Cardiac endothelium is decorated with only subtype II ABH glycans, but ABO-A red blood cells used for hemagglutination have glycan subtypes II/III/IV; standard hemagglutination is driven mainly by IgM. Thus, the assay measuring ABO-antibodies in ABOi heart transplant is inadequate for antibody subtype-specificity and isotype analysis, and therefore immune risk assessment. We developed ABO-glycan single antigen beads to measure IgG and IgM ABO-antibodies in infants awaiting transplant.

Methods: All twelve ABO-A/B subtypes A-I to A-VI and B-I to B-VI were coupled to Luminex beads. Patients ≤24 months listed for transplant were identified (n=31). Some had sequential samples; 86 samples were available (n=40 ABO-O, n=46 ABO-A). All samples were tested for IgG and IgM antibodies; 55 were also tested by hemagglutination. Some patients received blood products pre-collection, a limiting factor for this study.

Results: Median age at sample was 8.2 and 9.9 months (ABO-O and -A, respectively) with no significant difference between groups. Antibodies to subtype-II A and B were analysed. In ABO-O patients, anti-B-II IgG ($p<0.001$) and IgM ($p=0.035$) were higher than ABO-A patients (*Figure 1A/1B*). In ABO-O patients, anti-A-II was higher than anti-B-II ($p<0.0001$) for IgG but not for IgM (*Figure 1B/1C*). High MFI IgG ABO-antibodies were detected in very young patients, possibly passively acquired in utero. Hemagglutination titres did not predict IgG or IgM MFI (*Figure 2*).

Conclusions: Luminex-based ABO antibody characterization offers a promising hemagglutination alternative. Extensive transfusion in some patients makes assessment of ABO antibodies challenging but this issue exists for all antibody detection methods. Using this method, early life production of non-self ABO antibodies appears to differ between blood groups. This method of ABO-antibody detection may allow more accurate ABOi-transplant immune risk assessment.

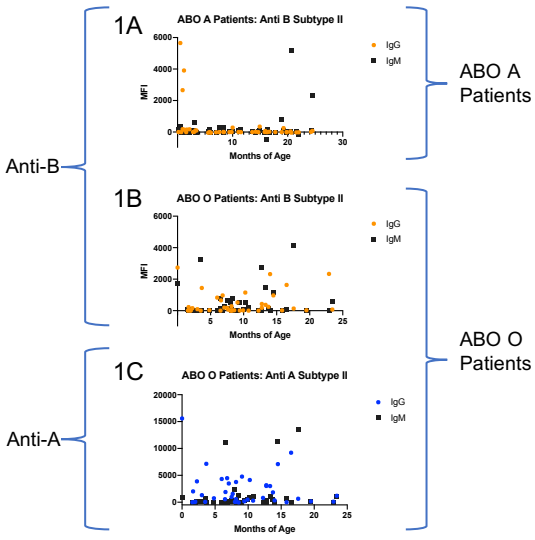


Figure 1: There are lower levels of anti-B-II in the ABO A patients (*1A*) as compared to ABO O (*1B*) for both IgG and IgM. The ABO O patients have higher levels of IgG anti-A-II as compared to anti-B-II but they have comparable levels of IgM for these 2 specificities (*1B and 1C*). The data shown here are specific to reactivity to subtype II A and B glycan structures; *these are the only ABO antigens on cardiac vascular endothelium*.

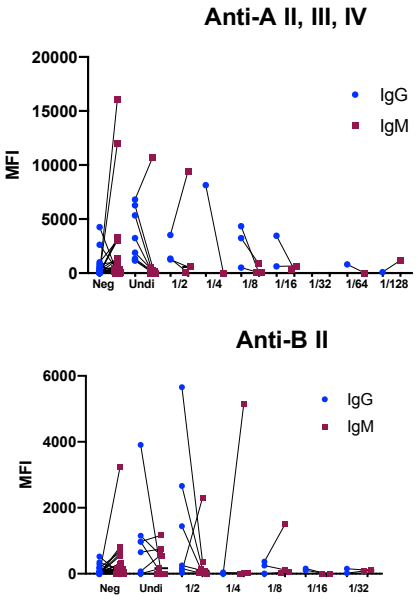


Figure 2: This figure compares red-cell specific antibodies detected by the hemagglutination method to those detected by the Luminex assay. There is a wide range of both IgM and IgG anti-A and anti-B MFI antibodies for each hemagglutination titre. Some high titres had very low MFI IgG and IgM antibody levels.

Background: Kidney transplant recipients are given induction therapy to rapidly reduce the immune response and prevent rejection. Guidelines recommend that an interleukin-2 receptor antibody (basiliximab) be the first-line agent and that a lymphocyte-depleting agent (anti-thymocyte globulin [ATG]) be reserved for those at high immunologic risk.

Objective: To determine the incidence, risk factors, and outcomes for patients who receive both basiliximab and ATG for induction compared to either agent alone.

Methods: We performed a retrospective cohort study in incident adult kidney transplant recipients from 2013-2018 using the transplant electronic medical record at the University of Alberta Hospital in Edmonton, Canada. Differences between induction groups were compared using chi-square test for categorical variables and Kruskal-Wallis tests for continuous variables. We performed multivariable logistic regression modeling with type of induction therapy as the dependent variable and the case-level factors as the predictors (adjusted odds ratio).

Results: In all, 430 kidney transplant recipients were followed for a mean of 3.9 years (standard deviation 1.5). Of these, 71% (n=305) received basiliximab alone, 22% (n=93) received ATG alone, and 7% (n=32) received both basiliximab and ATG. After adjusting for age and sex, compared to the basiliximab alone group, patients were more likely to receive dual induction therapy if they were sensitized (calculated panel reactive antibody $\geq$80%), had diabetes mellitus or peripheral vascular disease, or experienced delayed graft function. Compared to the ATG alone group, the dual induction therapy group had worse graft function at 1 year (mean eGFR 42 vs. 59 mL/min/1.73 m^2, p=0.0008) and an increased risk of all-cause graft failure (31% vs. 13%, p=0.02) and death-censored graft failure (16% vs. 4%, p=0.03).

Conclusions: In our study, 1 out of 10 recipients who were treated with basiliximab also received ATG for induction therapy. These patients experienced worse outcomes than those treated with ATG alone.

Background: After kidney transplantation, optimization of graft function and avoidance of nephrotoxic medications is essential. Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used for pain management but are potentially nephrotoxic. The 2009 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for the Care of Kidney Transplant Recipients recommends that NSAIDs be avoided in kidney transplant recipients. Currently, it is unclear whether physicians are adhering to this guideline recommendation.

Methods: We conducted a retrospective cohort study using linked healthcare databases in Alberta, Canada to follow adult kidney transplant recipients from 2008 to 2017. We determined the frequency and pattern of NSAID prescriptions (prescriber and drug), and the proportion of prescriptions that had post-fill testing of serum creatinine and hyperkalemia. We also studied the incidence of acute kidney injury (AKI, defined by a serum creatinine increase of $\geq$50% or $\geq$26.5 μmol/L [0.3 mg/dL] from baseline) and hyperkalemia (defined as potassium ≥5.5 mmol/L) within 30 days of the prescription.

Results: Of the 1,730 kidney transplant recipients, 189 (11%) had at least one NSAID prescription during follow-up (280 unique prescriptions in total). The majority of NSAID prescriptions were from family physicians (67%), with the most common NSAIDs being naproxen and indomethacin. Approximately 25% and 50% of prescriptions were followed by laboratory testing with a serum creatinine and potassium level within 14 and 30 days, respectively. Of those with lab measurements within 30 days, 11% of recipients had AKI and 5% had hyperkalemia.

Conclusion: Approximately 1 in 10 kidney transplant recipients are prescribed an NSAID, but only half of these prescriptions have testing of graft function and hyperkalemia within 30 days.

Of those with post-fill testing, 1 in 10 prescriptions were associated with AKI. Further education for safer prescribing is warranted.