

Yale School of Medicine Thesis Award Recipients — 2014

Novel Interdisciplinary Approaches to Understanding Kidney Transplantation Outcomes. Neel M. Butala, Chirag R. Parikh. Section of Nephrology, Department of Medicine, Yale School of Medicine, New Haven, CT. The John P. Peters Prize.

This thesis details two studies using novel approaches to understand kidney transplant outcomes: instrumental variables and social network analysis. Together, these studies demonstrate the value of interdisciplinary approaches to advance the field of kidney transplantation.

While some studies have found an association between delayed graft function (DGF) after kidney transplantation and worse long-term outcomes, a causal relationship remains controversial. In our first study, we investigate this relationship using an instrumental variables model (IVM), a quasi-randomization technique for drawing causal inferences. We identified 73,714 adult, deceased-donor, kidney-only transplant recipients from the Scientific Registry of Transplant Recipients (SRTR) between 1997 and 2010. We used cold ischemia time (CIT) as an instrument to test the hypothesis that DGF causes death-censored graft loss and mortality at 1 and 5 years post-transplant, controlling for an array of characteristics known to affect patient and graft survival. We compared our IVM results to a multivariable linear probability model (LPM). DGF occurred in 27 percent of our sample. Graft loss rates at 1 and 5 years were 6 percent and 22 percent, respectively, and 1-year and 5-year mortality rates were 5 percent and 20 percent, respectively. In the LPM, DGF was associated with increased risk of both graft loss and mortality at 1 and 5 years ($p < 0.001$). In the IVM, we found evidence suggesting a causal relationship between DGF and death-censored graft loss at both 1 year (13.6 percent increase; $p < 0.001$) and 5 years (16.2 percent increase; $p < 0.001$), and between DGF and mortality at both 1 year (7.1 percent increase; $p < 0.001$) and 5 years (11.0 percent increase; $p < 0.01$). We conclude that instrumental variables analysis supports a causal relationship between DGF and both graft loss and mortality.

Given growth in kidney transplant waiting lists and discard rates, donor kidney acceptance is an important problem. In our second study, we apply tools of social network analysis to examine whether Organ Procurement Organization (OPO) network centrality affects discard rates and recipient outcomes. We identified 96,364 kidneys recovered for transplant from deceased donors in SRTR between 2000 and 2010 and transplanted to adults without previous transplant or 0 HLA mismatches. We constructed the kidney transplant network for each year, with each OPO representing a node and each kidney sharing relationship between OPOs representing a directed tie between nodes. The primary exposures were OPO out-degree centrality and in-degree centrality. The primary outcomes were kidney discard, DGF, and 1-year graft loss. We constructed logistic regression models, restricting analysis to observations from the 50 percent of OPOs with highest discard rate and stratifying remaining OPOs into two groups by kidney volume. Models controlled for kidney donor risk index, mean waiting list time, and procurement year and region dummies. Among high-volume OPOs, an increase in one additional OPO to which a kidney was given by a procuring OPO in the procurement year was significantly associated with a 1.8 percent lower likelihood of discard for a given kidney (OR: 0.982, CI: 0.97, 0.995), but had no association with 1-year graft loss. We conclude that interventions to promote broader inter-OPO sharing should be developed to reduce discard rates.

Predictors of Emergency Department Use in Urban, Low-Resource Neighborhoods: Opportunities for Prevention. Iris A. Chandler; Lisa Rosenthal, PhD; Kathryn Gilstad-Hayden, MS; Jeannette R. Ickovics, PhD. Department of Chronic Disease Epidemiology, Yale University, School of Public Health. New Haven, CT. The Dr. Louis H. Nahum Prize.

To identify health behaviors that may be amenable to brief screening and intervention among children in the Emergency Department, we compared the prevalence of Emergency Department use among middle school children who report health behaviors known to contribute to childhood obesity versus their peers who did not.

Participants included 1,590 fifth, seventh, and eighth grade students who completed health surveys in 2011. Multivariate logistic regression was used to examine the association between health behaviors and Emergency Department use. Children who reported unhealthy dietary behaviors were more likely to use the Emergency Department. In particular, those who reported consumption of energy-dense foods like fried chicken, French fries, and ice cream (OR 1.20, 95% CI 1.06-1.37); fast food (OR 1.07, 95% CI 1.00-1.14); and sugar-sweetened beverages (OR 1.24, 95% CI 1.14-1.35) were more likely to use the Emergency Department. There was no association with fruit and vegetable consumption, physical activity, or screen time and Emergency Department use. Unhealthy dietary behaviors are associated with Emergency Department use in a low-resource urban population of middle school students. Further research should evaluate the effectiveness of brief diet screenings and interventions in the Emergency Department.

To identify depressive symptoms that may be amenable to brief screening and referral to treatment among adults in the Emergency Department, we compared the prevalence of Emergency Department use among adults who screened positive for depressive symptoms versus their peers who did not. Participants included 1,094 adults age 18 to 64 who completed health surveys in 2013. Multivariate logistic regression was used to examine the association between depressive symptoms and Emergency Department use. Adults who screened positive for depressive symptoms were more likely to use the Emergency Department (OR 1.70), even after controlling for various socio-demographic and health measures. In addition, the absolute number of Emergency Department visits was associated with the prevalence of positive screening for depressive symptoms. Among those who reported no ED visits, 8.5 percent screened positive for depressive symptoms, but this percentage rose to 29 percent for participants reporting more than five ED visits. The Cochran-Armitage Trend Test revealed a significant linear trend between number of ED visits and percentage of screening positive for depression (Z Statistic = -4.83, $p < 0.001$). Depressive symptoms are associated with Emergency Department use in a low-resource urban population of adults. Further research should evaluate the effectiveness of brief depression screenings and interventions in the Emergency Department.

Designing Multi-Layered Nanoparticles for Combination Gene and Drug Cancer Therapy. Asiri S. Ediriwickrema^a; Jiangbing Zhou^b; Mark Saltzman^c. ^aYale School of Medicine; ^bDepartment of Neurosurgery, Yale School of Medicine; ^cDepartment of Biomedical Engineering, Yale University, New Haven, CT. (Sponsored by Dr. Joseph Piepmeier and Dr. Abhijit Patel). The William U. Gardner Prize.

Cancer continues to be a highly prevalent and lethal disease, despite significant advances in understanding tumor biology and developing new chemotherapies. Major obstacles in cancer chemotherapy are drug resistance and systemic toxicities. Potential strategies for addressing these problems include delivering combination therapies to overcome drug resistance and utilizing synergistic agents to minimize dosing and subsequently drug toxicity. In turn, delivery can also be optimized to target the tumor site and consequently minimize systemic side effects. Polymer nanocarriers are gaining interest as vehicles for cancer therapeutics for their abilities to not only deliver multiple agents, but also target the tumor itself. Our goal is to design multi-layered polymer nanoparticles (MLNPs) for efficient de-

livery of small molecules and genetic material toward synergistically inhibiting tumor growth. The MLNPs were first optimized for transfection *in vitro* through delivery of plasmids encoding for luciferase (pLuc) and green fluorescent protein (pGFP). The particles were then evaluated for effective delivery of both a candidate small molecule, camptothecin (CPT), and a plasmid encoding for TNF related apoptosis inducing ligand (pTRAIL) (CT MLNPs). Co-delivery of CPT and pTRAIL *via* CT MLNPs were then evaluated for growth inhibition of brain, colorectal, and breast cancer cells *in vitro*. MLNPs were approximately 116 nm in diameter. They were able to delivery approximately 575 ng of plasmid per mg of particle and between 0.1 mg to 0.01 μ g of CPT per mg of particle. MLNPs were non-toxic, and human embryonic kidney cells (293T) transfected with pLuc-loaded MLNPs expressed comparable amounts of luciferase as cells transfected with the gold standard lipid formulation, Lipofectamine 2000. Thirty-seven percent of transfected 293T cells expressed GFP 72 h after transfection. Studies on tumor death kinetics related to CPT exposure and pTRAIL transfection suggested that simultaneous transfection and drug exposure provided the greatest inhibition of cell growth. MLNPs were able to provide the optimal timing for delivery of both agents. Synergy analysis of co-delivering CPT and pTRAIL *via* CT MLNPs, using the Chou-Talalay method, provided a combination index at 50 percent inhibition ranging between 0.31 and 0.53 for all cell lines. These CI values indicate a synergistic interaction between the two agents. For obtaining a 50 percent effect level, co-delivery with MLNPs resulted in providing 3.14-7.38 fold reduction in CPT and 4.66 to 6.09 fold reduction in pTRAIL. These initial results support our hypothesis that MLNPs can deliver both small molecule and genetic agents toward synergistically inhibiting tumor growth.

Regional Density of Cardiologists and Mortality for Acute Myocardial Infarction and Heart Failure. Vivek T. Kulkarni, Joseph S. Ross, Yongfei Wang, Brahmajee K. Nallamothu, John A. Spertus, Sharon-Lise T. Normand, Frederick A. Masoudi, Harlan M. Krumholz. Section of Cardiology, Department of Internal Medicine, Yale School of Medicine, New Haven, CT. The Dr. Marvin Moser Prize.

Cardiologists are distributed unevenly across regions of the United States. It is unknown whether patients in regions with fewer cardiologists have worse outcomes after hospitalization for acute myocardial infarction (AMI) or heart failure than patients in regions with more cardiologists. We hypothesized that patients hospitalized for AMI or heart failure in regions with lower density of cardiologists would have higher mortality than patients in regions with higher density.

Using Medicare administrative claims data from 2010, we examined the relationship between regional density of cardiologists and mortality after hospitalization for AMI and heart failure, using hospitalizations for pneumonia as a comparison. We defined density as the number of cardiologists divided by population aged ≥ 65 years within hospital referral regions, categorized into quintiles. We tested associations between density of cardiologists and 30-day and 1-year risk-standardized mortality for each condition. We used 2-level hierarchical logistic regression models that adjusted for characteristics of patients and hospital referral regions.

Our cohorts consisted of 171,126 admissions for AMI, 352,853 admissions for heart failure, and 343,053 admissions for pneumonia. Patients hospitalized for AMI (odds ratios [OR], 1.13; 95% confidence interval [CI], 1.06-1.21) and heart failure (OR, 1.19; 95% CI, 1.12-1.27) in the lowest quintile of density had modestly higher 30-day mortality risk compared with patients in the highest quintile, unlike patients hospitalized for pneumonia (OR, 1.02; 95% CI, 0.96-1.09). Patients hospitalized for AMI (OR, 1.06; 95% CI, 1.00-1.12), and heart failure (OR, 1.09; 95% CI, 1.04-1.13) in the lowest quintile had slightly higher 1-year mortality risk, unlike patients hospitalized for pneumonia (OR, 1.00; 95% CI, 0.95-1.05).

Patients hospitalized for AMI and heart failure in regions with lower density of cardiologists experienced modestly higher 30-day and 1-year mortality risk, unlike patients with pneumonia. These findings suggest that there is a relationship between regional density of

cardiologists and mortality for AMI and heart failure, which is concentrated in the early period after these acute events.

Family Life Events in the First Year of Acute Lymphoblastic Leukemia Therapy. Samantha Lau, Xiaomin Lu, Lyn Balsamo, Meenakshi Devidas, Naomi Winick, Stephen Hunger, William Carroll, Linda Stork, Kelly Maloney, Nina Kadan-Lottick. Section of Hematology and Oncology, Department of Pediatrics, Yale School of Medicine, New Haven, CT. The Peter F. Curran Prize.

Despite remarkable advances in cure rates, childhood acute lymphoblastic leukemia (ALL) may continue to result in considerable family strain. We sought to 1) measure incidence of divorce, reduced career opportunities, changes to work hours, home relocation, and changes to family planning at one year after ALL diagnosis and 2) identify family and patient factors associated with these events. We conducted a prospective cohort study of 159 children with average risk-ALL enrolled and treated on COG protocol AALL0331 at 31 selected sites. In the first year of ALL treatment, 46 percent of parents lost a job, 13 percent divorced/separated, 22 percent decided not to have more children, 51 percent declined occupational opportunities, 68 percent decreased work hours, and 27 percent of families relocated homes. In adjusted analyses, no unifying factors were associated with all family events. Relocation correlated with less maternal education (OR: 4.27 [95% CI: 1.43-12.82]). Declining parental opportunities associated with family income <\$50,000 (OR: 4.25 [95% CI: 1.50-12.02]) and child <5 years old (OR: 4.21 [95% CI: 1.73-10.25]).

Deciding not to have more children correlated with smaller family size, two to three vs. four to five (OR: 3.62 [95% CI: 1.10-11.96]). In summary, childhood ALL still confers a substantial family burden, especially in the earlier stages of treatment.

Toward a Medical Home for Adults with Sickle Cell Disease: A Longitudinal Analysis of High-Utilizing Patients. Daniel Freedman Weisberg. Yale School of Medicine, New Haven, CT. The Lidz Prize in Psychiatry.

Sickle cell disease (SCD) accounts for approximately 100,000 hospital admissions annually. Most admissions are for painful vaso-occlusive crises (VOCs). A small minority of patients with extremely high hospital use (EHHU) account for the majority of inpatient medical costs and exacerbate issues of distrust in the provider-patient relationship surrounding opioid analgesia, the mainstay of treatment for acute VOCs.

This study was designed to generate hypotheses surrounding the causes and consequences of EHHU in adults with SCD and describe the ability of a coordinated, multidisciplinary intervention based on the Patient-Centered Medical Home (PCMH) model to address these phenomena and mitigate EHHU.

We carried out a qualitative study of SCD patients with EHHU (defined as greater than 100 hospital days/year averaged over 3 years), pre- and post-intervention, as well as their family members, their medical providers, and a group of SCD patients with low hospital use (LHU). We conducted descriptive data analysis of hospital utilization and cost trends before and after the intervention. Forty in-depth, one-on-one interviews with 29 individuals took place from 2010 to 2014. We analyzed interview transcripts using narrative summaries and qualitative analysis software. Administrative data was abstracted to describe trends in overall and EHHU-specific trends of SCD health care resource utilization and inpatient and outpatient direct costs from 2008 to 2013.

Qualitative analysis yielded a common narrative of thwarted educational, social, and vocational development among SCD patients with EHHU due to repeated hospitalizations from a young age as well as accelerating opioid use. SCD patients with EHHU and matched LHU demonstrated similar experiences of provider distrust surrounding opioid use; however, patients with EHHU lacked the interpersonal and symptom-related strategies to ally with providers demonstrated by patients with LHU. Outside the hospital, SCD patients with EHHU were socially isolated and described symptoms of depression and suicidality. The im-

plementation of the medical home model of care coincided with decreases in overall acute care utilization trends among patients with SCD (13 percent ED visits, 55 percent inpatient days, 40 percent average length of stay (ALOS)), as well as reductions among the SCD patients with EHHU (32 percent ED visits, 78 percent inpatient days, 62 percent ALOS). During this same time period, there was a 16 percent and 30 percent increase in outpatient visits in SCD patients overall and patients with EHHU, respectively. Follow-up qualitative analysis of patients with EHHU demonstrated a difficulty adapting to new policies, as well as a tradeoff between the benefits of reintegrating into family/society and managing higher levels of pain at home.

In addition to reducing reliance on acute care and augmenting outpatient services, the medical home model may address the causes and consequences of EHHU in SCD in four key dimensions: first, psychiatric and social rehabilitation; second, improved therapeutic relationships through continuity of care; third, monitoring of opioid use with coordinated protocols; and fourth, overcoming cultural barriers through community outreach. The PCMH has been shown to reduce costs and improve clinical and patient satisfaction outcomes across a wide range of chronic diseases. This study demonstrates the same potential in a clinically and psychosocially complex, sub-specialty population.