Perelman School of Medicine
University of Pennsylvania

DBEI & CCEB RESEARCH DAY

A JOINT PROJECT OF

The Department of Biostatistics, Epidemiology and Informatics

AND

The Center for Clinical Epidemiology and Biostatistics

April 10, 2018 | INAUGURAL EVENT

#2018ResearchDay

Arthur H. Rubenstein Auditorium — Smilow Center for Translational Research
3400 Civic Center Blvd.

ABSTRACTS

Welcome

Thank you for joining us at the inaugural DBEI & CCEB Research Day! This event offers a snapshot of the latest research by the Department of Biostatistics, Epidemiology and Informatics and the Center for Clinical Epidemiology and Biostatistics and features this year's Brian L. Strom Visiting Professorship
Lecture.

The DBEI distinctively brings together expertise in biostatistics, epidemiology and informatics, to advance its mission:
To discover, teach and promote impactful ways to preserve health, manage chronic disease and treat acute illness, by capitalizing on synergies across our three scientific disciplines.

The CCEB is an interdisciplinary and interdepartmental program that links clinical epidemiology and biostatistics within the Perelman School of Medicine, the University of Pennsylvania Health System, and the Penn community to advance its mission:
To foster research and training in clinical epidemiology and biostatistics, and serve as a resource to the clinical-research community.

1 Abstract

Baseline Characteristics Associated with Use of Non-Invasive Ventilation in Amyotrophic Lateral Sclerosis

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Rationale: Respiratory failure due to neuromuscular weakness is the most common cause of death for patients with Amyotrophic Lateral Sclerosis (ALS). Non-invasive ventilation (NIV) can improve quality of life and potentially improve survival. In this study, we sought to determine the baseline risk factors for eventual initiation of NIV.

Methods: We performed a retrospective cohort study of 572 patients with ALS. All patients were seen in a Neurology outpatient clinic at the University of Pennsylvania between May 2010 and October 2016. We used univariate and multivariate Cox proportional hazard models, censoring at date of death or last visit date. The final multivariate model used backward elimination.

Results: The median age of diagnosis was 65.2 years and 58.4% were male. There were 812 person-years of follow-up time, and 45.5% (n=260) were initiated on NIV during the study period. The median time to NIV initiation was 184 days (interquartile range, 37 to 386 days). In a multivariate analysis, factors significantly associated with risk of NIV included older age at diagnosis, fewer years between symptoms and diagnosis, being underweight, African-American race, lower decile of percent predicted FVC, history of hypertension, lumbosacral symptom onset, and El Escorial criteria of Suspected ALS or Possible ALS.

Conclusion: We identified baseline risk factors that were significantly associated with initiation of NIV in ALS patients. These factors may reveal important mechanisms of respiratory failure in ALS, which could be targeted with novel therapies.

2 Abstract

Intensive Care Unit Capacity Strain and Outcomes of Critical Illness in a Resource-Limited setting: A Two-Center Study in South Africa

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Objective: To measure the association of ICU capacity strain with processes of care and outcomes of critical illness in a resource-limited setting. Methods: We performed a retrospective cohort study of 5,332 patients referred to the ICUs at two public hospitals in South Africa using the country's first published multicenter electronic critical care database. We assessed the association between multiple ICU capacity strain metrics (ICU occupancy, turnover, census acuity, and referral burden) at different exposure time points (ICU referral, admission, and/or, discharge) with clinical and process-of-care outcomes. The association of ICU capacity strain at the time of ICU admission with ICU length of stay (LOS), the primary outcome, was analyzed with a multivariable Cox proportional hazard model censoring on death.

Results: No measure of ICU capacity strain at the time of ICU admission was associated with ICU LOS, the primary outcome. ICU occupancy at the time of ICU admission was associated with increased odds of ICU mortality (OR = 1.07 per 10% increase in ICU occupancy, 95% CI 1.02-1.11, p = 0.004). Conclusion: In a resource-limited setting, ICU capacity strain at the time of ICU admission was not associated with ICU LOS. ICU occupancy at the time of ICU admission was associated with increased ICU mortality. Further work is needed to better characterize the role of ICU capacity strain metrics and their influence on process measures and patient outcomes in resource-limited settings.

3 Abstract

Investigating Cardiovascular Disease – Birth Month Associations in Canines: A Model Organism for Human Heart Disease

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The canine heart is a robust physiological model for the human heart. Recently, birth month associations have been reported and replicated in humans using clinical health records. While animals respond readily to their environment in the wild, a systematic investigation of birth season dependencies among pets and specifically canines remains lacking. We obtained data from the Orthopedic Foundation of Animals on 129,778 canines representing 253 distinct dog breeds. Among dogs that were not predisposed to cardiovascular disease, a clear birth season relationship is observed with peak risk occurring in June-August. Our findings indicate that acquired cardiovascular disease among dogs, especially those that are not predisposed to cardiovascular disease, appears birth season dependent. The overall odds ratio for the birth season effect was 1.02 among all dogs while adjusting for breed and predisposition effects. The effect of birth season on cardiovascular disease risk was higher among breeds not predisposed to disease. This indicates the possibility that certain breeds contract an environmentally driven cardiovascular disease. Studying birth season effects in model organisms can help to elucidate potential mechanisms behind the reported birth month associations observed in humans.

4 Abstract

A Machine Learning Algorithm to Classify FDA Category C Drugs

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Background: Many drugs commonly prescribed during pregnancy lack a fetal safety recommendation – called FDA 'category C' drugs. This study classifies these drugs into harmful and safe categories using knowledge gained from chemoinformatics (i.e., pharmacological similarity with drugs of known fetal effect) and empirical data (i.e., derived from Electronic Health Records).

Methods: Our fetal loss cohort contains 14,922 affected and 33,043 unaffected pregnancies and our congenital anomalies cohort contains 5,658 affected and 31,240 unaffected infants. We trained a random forest algorithm to classify drugs of unknown pregnancy class into harmful or safe categories, focusing on two distinct outcomes: fetal loss and congenital anomalies.

Results: Our models achieved an out-of-bag accuracy of 91% for fetal loss and 87% for congenital anomalies outperforming null models. Fifty-seven 'category C' medications were classified as harmful for fetal loss and eleven for congenital anomalies. This includes medications with documented harmful effects, including naproxen, ibuprofen and rubella live vaccine. We also identified several novel drugs, e.g., haloperidol, that increased the risk of fetal loss.

Conclusion: Our approach provides important information on the harmfulness of 'category C' drugs. Algorithms like this are needed, as no FDA recommendation exists for these drugs' fetal safety.

5 Abstract

Correlates of Sun Protection Behaviors in Racially and Ethnically Diverse U.S. Adults

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Although skin cancer incidence is highest among non-Hispanic whites, minority populations are often diagnosed with more advanced stage disease and are more likely to experience poor outcomes. People of color do not practice primary prevention of skin cancer according to recommendations, but public health education and interventions to promote sun protection behaviors have consistently targeted non-Hispanic white populations. The present study examines performance of sun protection behaviors in a multi-ethnic sample and whether demographic, lifestyle and psychosocial predictors of these behaviors differ by race and ethnicity. In this study, a probability-based sample of 1,554 adults completed an online survey in 2015. Main outcomes of interest included sunscreen use, wearing a sleeved shirt, and seeking shade. We stratified the sample into racial/ethnic groups (White, Black, Hispanic, Asian) and investigated demographic, lifestyle and psychosocial correlates of these behaviors in each group. Differences in adjusted estimates from each behavior-specific model were tested across strata. Racial/ethnic groups were significantly different in regards to sunscreen use and wearing a sleeved shirt, but similarly engaged in seeking shade. Results from multivariate ordered logistic regression models for each behavior revealed important demographic, lifestyle and psychosocial predictors and the importance of these correlates varied between racial/ethnic groups. This study provides insight into the practice and correlates of skin cancer prevention among a multi-ethnic sample. Our findings suggest that targeting public health education efforts and interventions to promote sun protection in minority populations may be a beneficial approach to addressing heightened skin cancer morbidity and mortality in these groups.

6 Abstract

Maternal Biomarkers of Cardiovascular Risk and Preterm Delivery

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Background: Epidemiological data suggest that women with a history of preterm delivery (PTD) have an increased risk to later maternal cardiovascular disease (CVD). We investigated if the biomarkers of endothelial dysfunction and circulating lipids which are known to be linked to the development of atherosclerosis were also detectable in pregnant women who delivered preterm.

Methods: In a case-control study nested within a large prospective epidemiological study of young, generally healthy pregnant women, cases who delivered preterm (<37 completed weeks gestation, n=240) and controls who delivered at term (n=439) were included. Circulating endothelial dysfunction biomarkers and lipid levels were measured. Potential confounding variables were controlled for all analyses.

Results: Elevated levels of soluble intercellular adhesion molecule-1 (AOR 1.73, 95% CI 1.09-2.74) and vascular cell adhesion molecule-1 (AOR 2.17, 95% CI 1.36-3.46) were positively associated with all PTD or spontaneous PTD. Elevated soluble E-selectin was increased only in PTD complicated by preeclampsia (AOR 2.32, 95% CI 1.22-4.40). Higher HDL-C (AOR 1.91, 95% CI 1.15-3.20) and apolipoprotein A1 concentrations (AOR 1.94, 95% CI 1.16-3.24) were significantly associated with increased odds of PTD. Maternal triglyceride, LDL, total cholesterol and apolipoprotein B were not associated with PTD.

Conclusion: Impaired endothelial function, biomarker of CVD is also present in women with preterm delivery. Elevated HDL-C and apoA1 being associated with risk for PTD are surprising and these data underscore the need for further research linking HDL-C function in women with PTD.

7 Abstract

Effect of Smartphone Breathalyzer Blood Alcohol Content Feedback on Willingness to Drive: A Laboratory Randomized Control Trial

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Background: We determined whether smartphone breathalyzer feedback increases drinkers' willingness to drive up to the legal limit of 0.08%.

Methods: We conducted a laboratory randomized control trial with 20 adults aged 21-39 with a previous history of binge drinking. Participants were given doses of vodka over 60 minutes with a target peak BAC of 0.10% and administered smartphone breathalyzer measurements every 20 minutes until the BAC declined to 0.03%. They were randomized to: 1) intervention – shown BAC measurement every 20 minutes; vs 2) control – blinded to BAC measurement. After each breathalyzer measurement participants were asked: 1) primary outcome – "How willing are you to drive a motor vehicle?" (1= not at all willing, 10=extremely willing); 2) "What is your perceived ability to drive a motor vehicle?" (1=not at all able, 10=very able); and 3) "Are you intoxicated?" (1=not at all, 10=very much). Outcome differences were analyzed using linear mixed models.

Results: The mean peak BAC was 0.09% (range: 0.07-0.12). At BACs of 0.04-0.07%, BAC feedback exposure was associated with an increase in willingness to drive (+3.49, CI: [1.89, 5.09]), an increased perceived ability to drive (+2.85, CI: [0.95, 4.75]), and a decreased perception of intoxication (-2.48, CI: [-3.78, -1.18]).

Conclusions: Smartphone breathalyzer testing may make drinkers more willing to drive up to the legal BAC limit of 0.08% in a range associated with increased crash risk (0.04-0.07%).

8 Abstract

EHR-Based Assessment of the Current Practice of Screening for Primary Aldosteronism

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Primary aldosteronism (PA) comprises ~5% of high blood pressure (hypertension) and is treatable with targeted medications or surgery. Clinical guidelines recommend screening for PA in specific subsets of hypertension patients, but it is unclear how well we actually identify these patients. Thus, we sought to describe the screening practices across our institution. We extracted clinical encounter, laboratory, diagnosis code, and note data from our clinical data repositories for patients with at least 5 encounters (or 3 distinct encounters' years) with blood pressure between 1/1/2007 and 12/31/2017. Patients with ≥2 encounters with hypertension diagnosis codes were considered to have hypertension and patients with ≥2 PA diagnosis codes, who met strict laboratory diagnostic criteria, or who underwent adrenal vein sampling were considered to have PA. We surveyed 2,208,984 office visits for 207,172 patients seen at 24 practice locations over 8.6 ± 4.2 (mean ± sd) years. The prevalence of hypertension was 24.6% ± 6.8% across sites. Among hypertension patients, only 0.5% ± 0.4% were documented to have PA. The distribution of PA frequencies across sites was strongly associated with the frequency of laboratory PA screening (3.3% ± 2.9%; r=0.9; $p=3x10^{-9}$) and referral to specialist providers (5.9% ± 7.0%; r=0.8; $p=1x10^{-5}$). The substantial gap between the frequency of PA we observed and the expectation from population studies, suggests that we are dramatically underdiagnosing PA. The strong correlation, among sites, between the PA frequency and both ordering PA screening tests and specialty referrals, implies that increased screening should lead to increased PA diagnoses.

9 Abstract

Networked Proceedings of PNAS: The Changing Landscape of Scientific Research

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Recent advances in the study of scientific research have revealed fascinating properties of the authors, papers, and incentive structures that exist in science. Yet how the current scientific landscape emerges from this complexity is not well understood. Here we use tools from network science to map the landscape of interconnected research topics in 65,290 articles published in the journal PNAS since 2000. We construct networks in which nodes represent topics of study and edges give the degree to which topics occur in the same papers. The network displays small-world architecture, with dense connectivity within scientific clusters and sparse connectivity between clusters. Notably, clusters tend not to align with assigned article classifications, but instead contain topics from various disciplines. To examine structural changes in the network over time, we created a temporal graph using a one-year sliding window. We found that small-worldness and edge strength consistently increased, suggesting growing connectivity within and between distinct topic clusters. Finally, we defined a novel measure of interdisciplinarity, which was positively associated with PNAS's impact factor. Broadly, this work suggests that research in PNAS crosses disciplines to a degree not previously known, and reveals potential benefits of such intellectual integration.

10 Abstract

Detection of Population-Based Gene Level Allele-Specific Expression by RNA-seq

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Allele-specific expression (ASE) can be quantified by the relative expression of two alleles in a diploid individual, and such expression imbalance may explain phenotypic variation and disease pathophysiology. Existing methods for gene-based ASE detection can only analyze one individual at a time, thus wasting shared information across individuals. To overcome this limitation, we develop GLMM-seq, a generalized linear mixed-effects model that can simultaneously model multi-SNP and multi-individual information. The model is able to detect gene-level ASE under one condition and differential ASE between two conditions (e.g., diseased vs. healthy controls). To model multiple individuals simultaneously, we further extend existing individual-based ASE detection methods using a weighted ordered p-value approach . Extensive simulations indicate that our methods perform consistently well under a variety of scenarios. We further apply our methods to real data in the Genetics of Evoked Response to Niacin and Endotoxemia Study, and our results will provide novel candidates for modulation of innate immune responses in humans.

11 Abstract

Translating Evidence into Practice: Effect of an Evidence-based Electronic Clinical Decision Support Tool on Provider Ordering for Venous Catheters

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Background: Peripherally inserted central catheters (PICCs) are a popular choice in the acute care setting for intravenous therapy. However, PICCs are associated with higher risk for venous thromboembolism and bloodstream infection, with multi-lumen PICCs having higher complication rates than single-lumen. Midline catheters can be an alternative; however, selection between catheters depends upon multiple factors. To reduce patient risk, a UPHS multidisciplinary panel developed evidence-based recommendations and implemented them in a point-of-care clinical decision support (CDS) tool (Figure 1). Embedded within provider workflow, the CDS led users through a series of questions. Relevant clinical data was also displayed to facilitate decision making. The recommended catheter was pre-selected by the CDS, but providers could also override.

Methods: Study timeframe was 11/1/2012 to 8/1/2015 and was divided into three periods. Two outcomes were evaluated: (1) proportion of PICC orders; (2) proportion of *double-lumen PICC orders. Adjusted random-effects regression models were used to account for provider correlated data.* Conclusions: CDS tools designed using factors that positively affect outcomes (e.g. stakeholder involvement, integration into workflow, recommendations for action, defaults) can be an effective means for changing practice.

Results: For outcome one, results suggested no statistically significant difference between study periods. Results for outcome two suggested a large statistically significant decrease between periods

Conclusion: Clinical pathways are one method to translate evidence into practice and reduce unnecessary variation in care. We demonstrate how a healthcare system can successfully utilize a framework and technology to support the development and dissemination of pathways.

12 Abstract

Variations in Transplantation Practice Among Centers with Regards to Donor Livers with Severe Transaminase Elevations

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The fastest growing demographic of deceased organ donors are those under 50 years of age who died of a drug overdose. Due to the mechanism of injury and the frequent delay between the drug overdose and time the patient is found, there is often prolonged period of hypoperfusion, likely predisposing livers from these donors to a higher risk of developing ischemic injury, or 'shock liver.' The transplantation practices of transplant centers in regard to donor organs with ischemic hepatitis are unknown. We performed a retrospective cohort study of UNOS (United Network for Organ Sharing) data on all deceased donors between May 1, 2007 and September 30, 2016. Ischemic hepatitis was defined as ≥1 record of AST ≥1,000 IU/L from laboratory data available in UNET. Regional differences in prevalence of ischemic hepatitis were determined using standard descriptive statistics. Of all deceased donor transplants that occurred between 2007 and 2016, 2,328 (3.9%) transplants were livers with ischemic hepatitis. In multivariable models, there is a greater than 60% lower odds of being transplanted among livers with ischemic hepatitis (OR: 0.36; 95% CI: 0.34-0.38, $p<0.001$). There was significant among-region variability in the percentage of transplanted livers that were from deceased donors with ischemic hepatitis ($p<0.001$), among-DSA variability, and among-center variations in utilization rates of livers with ischemic hepatitis. In conclusion, livers that develop ischemic hepatitis are significantly more likely to be discarded and are used variably at transplant centers throughout the country.

13 Abstract

Comparative Risk of Biologic Therapies and Risk of Glucocorticoids in Patients with Rheumatoid Arthritis Undergoing Elective Arthroplasty

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Objective: Patients with rheumatoid arthritis (RA) are at increased risk of infections after arthroplasty. Goals of this study were to compare post-operative infection risk in patients with RA exposed to different biologics and examine associations between glucocorticoid use and post-operative infections.

Methods: A retrospective cohort study using Medicare and Truven MarketScan® administrative data from 2006-September 2015 evaluated adults with RA undergoing elective inpatient primary or revision total knee or hip arthroplasty who had a recent infusion or prescription for abatacept, adalimumab, etanercept, infliximab, rituximab, or tocilizumab before surgery. Propensity adjusted analyses using inverse probability weights evaluated comparative risk of 30-day hospitalized infection, 30-day non-urinary hospitalized infection, 30-day readmission, and 1-year prosthetic joint infection (PJI) between biologics. Similar analyses evaluated risk associated with glucocorticoids.

Results: In 11,021 surgeries among 9,994 patients there were 860 (7.6%) hospitalized infections, 570 (5.2%) non-urinary hospitalized infections, 533/10,377 (5.1%) readmissions, and 246 (2.7/100 person-years) PJI. There were no significant differences in outcomes across biologics except for increased risk of PJI but not other outcomes in tocilizumab treated patients. In contrast, glucocorticoids were associated with a dose-dependent increase in the risk of all outcomes with >10mg prednisone vs. no glucocorticoids aOR (95% CI) of 2.14 (1.52-3.00), 2.05 (1.43-2.95), 1.66 (1.00-2.74), and aHR (95% CI) 1.73 (0.96-3.11) for the four outcomes respectively.

Conclusion: Risk of hospitalized infection, readmission, and PJI after arthroplasty was similar in patients with RA treated with different biologics. In contrast, glucocorticoid use, especially > 10mg/day, was associated with greater risk of these outcomes.

14 Abstract

Advances in Health Language Processing

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Natural language processing (NLP) methods are increasingly being utilized to mine knowledge from unstructured health-related texts. Recent advances in noisy text processing techniques are enabling researchers and medical domain experts to go beyond the information encapsulated in published texts (e.g., from clinical trials and systematic reviews) and structured questionnaires, and obtain perspectives directly from other unstructured sources such as electronic health records (EHRs) and social media posts.
Over the recent years, there has been a continuing transition from lexical and rule-based systems to learning-based approaches, because of the growth in annotated data sets and advances in data science.

We provide an overview of advances that UPenn's Health Language Processing lab has made in the last couple of years in this realm.

15 Abstract

Early Literacy Promotion Among Medicaid-Insured Children

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Background: Reach Out and Read (ROR), a national program promoting parent-child shared reading and distribution of age-appropriate books for children 6 months to 5 years of age at well child visits, has been shown to improve poor children's language development. Yet children participating in ROR still have language scores below national averages. It isn't clear whether promoting shared reading in the newborn period can improve poor children's home reading environment and language development.

Objective: To determine if initiating ROR in the newborn period is feasible and results in better home reading environment and language scores at 6 months.

Design/Methods:⊚We conducted a randomized controlled trial comparing early literacy promotion in the newborn period (ELP) to standard literacy promotion (SLP) using ROR framework. Parents in the ELP group received four developmentally appropriate books at well visits less than 6 months of age and weekly text messages promoting shared reading. Parents in the SLP arm received weekly text messages concerning child safety but no books or literacy promotion messages. We assessed feasibility as the proportion of well visits with books provided by clinicians prior to 6 months of age and outcomes as differences between groups on language acquisition (PLS-5 Score) and home reading environment (StimQ Reading Subscale Score) at 6 months of age.

Results:⊚120 parent-infant dyads were enrolled, and 99 (83%) completed the 6-month follow-up. The majority of parents in both groups were single, African-American, or with a high school education or less (Table 1). In the ELP group, the proportion that received a book at well visits was 98% at 1 week, 71% at 1 month, 67% at 2 months, and 73% at 4 months. At 6 months, there were no differences in PLS-5 scores between groups, but the ELP group demonstrated greater StimQ scores than the SLP group (Table 2).

Conclusions:⊚An evidence-based literacy promotion program adapted for use beginning in the newborn period was feasible to implement and improved the home reading environment of poor urban children. Future research is needed to determine whether early literacy promotion translates into greater language development later in childhood.

16 Abstract

Are Demographic Characteristics Associated with Advance Directive Completion? A Secondary Analysis of Two Randomized Trials

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Introduction Males, blacks, and those with less education less frequently complete advance directives (ADs). However, it remains unclear whether such groups differ in their willingness to complete ADs or have different opportunities to do so.

Methods and Findings: We performed secondary analyses of data from two RCTs. RCT 1 compared three ADs that differed in how information was presented to 484 people with serious illnesses. RCT 2 compared methods of encouraging AD completion among new healthcare system employees. All participants received standardized educational materials and an AD form.

The primary outcome was AD completion. Independent variables were measured demographics. Each trial was independently analyzed. We used multivariable logistic regression to examine associations between demographics and AD completion.

In RCT 1, 286 of 484 seriously ill outpatients (59.1%) completed an AD. In multivariable analyses, none of the measured patient characteristics were associated with AD completion (all $p > 0.10$). In RCT 2, 355 of the 1279 participating employees (27.8%) completed an AD. In fully adjusted models, black (OR= 1.51; 95% CI= 1.09-2.09) and mixed/other race participants (OR= 1.91; 95% CI = 1.33-2.76) were significantly more likely than white participants to complete an AD.

Discussion: When all individuals are given the same opportunities to complete ADs, demographic characteristics are not consistently associated with AD completion. By providing equal opportunities for AD completion among all patients, such efforts may reduce demographic differences in the intensity of end-of-life care patients receive.

17 Abstract*

Propensity Score Estimation with Missing Covariate Data

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Propensity scores are often used in observational studies to estimate treatment effects; however this approach can be complicated by missing covariate data. We impute the derived propensity score using a passive approach by multiply imputing the missing covariates and then estimating the propensity score. These propensity scores can be estimated by many different methods. Logistic regression has long been the preferred method for estimating propensity scores, but a misspecified model can result in meaningless propensity scores. Superlearner, an ensemble machine-learning algorithm that uses cross-validation to evaluate many different models, returns a propensity score based on a weighted average but can have inflated variance. The treatment effect estimate can then be obtained by combining the m imputed datasets by either averaging the propensity score for each individual across the datasets (across) or by estimating the treatment effect m times and then averaging those m treatment effect estimates (within). We explore combinations of these approaches to imputation and estimation using both propensity score matching and Cox models with inverse-probability treatment weights. We compare bias and efficiency across these various approaches using a National Cancer Database study on head and neck cancer.

* Indicates Flash Talk

18 Abstract

Implications for Signal Detection of Duplicated Case Reports of Stress Cardiomyopathy

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Introduction: Duplicated case reports represent an important issue in safety signal detection. We describe a case of 'extreme duplication' discovered in the course of a real-world signal evaluation of stress cardiomyopathy (Tako-Tsubo cardiomyopathy).

Method: The US FDA Adverse Events Reporting System database was searched and all cases with the drug of interest that reported adverse events encoding to MedDRA Preferred Terms (PT) Stress cardiomyopathy were obtained via a Freedom of Information request. Detailed information of each case including narratives was obtained. Information was reviewed to search for duplicated reports based on demographic characteristics, country of origin, reported PTs and case description. Manual review was complemented by statistical analysis to visualize the distribution of variables pertinent to duplicate detection. The impact of this report duplication on disproportionality analysis (DA) was assessed.

Results: There were 40 stress cardiomyopathy cases. After detailed manual review and statistical analysis of the aforementioned variables more than 60% of the cases were considered be duplicated. Disproportionality analysis was not significant after removing duplicated cases.

Conclusion: Duplicate reporting can impact signal detection, depending on various factors (e.g. overall distribution of duplicates in the database, ease of duplicate identification). Investigators should review all information to identify potential duplicates.

19 Abstract

PennSeq2: Efficient Quantification of Isoform-Specific Gene Expression from RNA-Seq Data using Weighted Likelihood Method

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The emergence of RNA-seq has provided a powerful tool to study gene regulation at isoform level. Correctly estimating isoform-specific gene expression is important for understanding complicated biological mechanisms and mapping disease related genes. We previously developed PennSeq, a statistical method for isoform-specific gene expression estimation. Here we developed PennSeq2, a successor of PennSeq, which employs a weighted likelihood framework to improve estimation efficiency. For each read, PennSeq2 assigns a weight based on the number of compatible isoforms to assure that more informative reads are given more weight in the likelihood function. PennSeq2 then employs an EM algorithm to estimate isoform-specific gene regression.

PennSeq2 has several advantages over PennSeq. First, the EM algorithm converges faster. Second, the efficiency of isoform expression estimation is significantly improved. Third, PennSeq2 yields equally accurate isoform expression estimation compared to PennSeq.

To show the superiority of PennSeq2, we conducted simulations and compared its performance with other algorithms e.g. PennSeq, CEM, Kallisto and Cuflinks. We simulated 10 million 76-bp paired-end reads and mapped them using Tophat. Isoform relative abundances from 1455 genes were estimated using PennSeq2 and all the algorithms above.

PennSeq2 got the highest squared Pearson correlations (R2=0.926) between the ground truths and estimated relative expression among all the algorithms, which demonstrate good estimation accuracy. Meanwhile, PennSeq2 reduces estimation uncertainty by 76% and running time by 90% compared to PennSeq. Currently, we are performing extensive simulations and real RNA-Seq data analysis to verify the benefits of PennSeq2.

20 Abstract*

Identifying Differential Alternative Splicing Events Using Single-Cell RNA Sequencing Data

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The emergence of single-cell RNA-seq (scRNA-seq) technology has made it possible to measure gene expression at cellular level. This breakthrough enables a wider range of research studies such as exploring splicing heterogeneity among individual cells. However, compared to bulk RNA-seq, there are two unique challenges for scRNA-seq analysis: high technical variability and low sequencing depth. To overcome these challenges, we proposed a statistical framework, SCATS (Single-Cell Analysis of Transcript Splicing), which achieves high sensitivity at low coverage by accounting for technical noise. SCATS has two major advantages. First, it employs an empirical Bayes approach to model technical noise by use of external RNA spike-ins. Second, it groups "exons" originated from the same isoforms, which reduces the multiple testing burden and allows more informative reads to be utilized for detecting splicing change. We evaluate the performance of SCATS by extensive simulations and the analysis of real scRNA-seq data. We believe that it will improve the power in identifying differential alternative splicing events in scRNA-seq studies.

21 Abstract*

PIE: A Prior Knowledge Guided Integrated Likelihood Estimation Method for Bias Reduction in Association Studies Using Electronic Health Records Data

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This study proposes a novel Prior knowledge guided Integrated likelihood Estimation (PIE) method to correct bias in estimation of associations due to misclassification of electronic health records (EHR)-derived binary phenotypes, and evaluates the performance of the proposed method by comparing it to two methods in common practice. We conducted simulation studies and data analysis of real EHR-derived data on diabetes from Kaiser Permanente Washington to compare the estimation bias of associations using the proposed method, the method ignoring phenotyping errors, the maximum likelihood method with misspecified sensitivity and specificity, and ML method with correctly specified sensitivity and specificity (gold standard). The proposed method effectively leverages available information on phenotyping accuracy to construct a prior distribution for sensitivity and specificity, and incorporates this prior information through the integrated likelihood for bias reduction. Our simulation studies and real data application demonstrated that the proposed method effectively reduces the estimation bias compared to the two current methods. It performed almost as well as the gold standard method when the prior had highest density around the true sensitivity and specificity. The analysis of EHR data from Kaiser Permanente Washington showed the estimated associations from PIE were very close to the estimates from the gold standard method and reduced bias by 60% - 100% compared to the two commonly used methods in current practice for EHR data. This study demonstrated that the proposed method can effectively reduce estimation bias caused by imperfect phenotyping in EHR-derived data by incorporating prior information through the integrated likelihood.

* Indicates Flash Talk

22 Abstract

A Causal Inference Approach to Cost-Effectiveness Visualization

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Policy decisions concerning the implementation of a treatment often reference the cost-effectiveness acceptability curve (CEAC). The CEAC aims to summarize uncertainty in estimates of cost-effectiveness but is prone to misinterpretation and is not sample size invariant. We present a new method of representing cost-effectiveness, the Determination Curve, based in causal inference techniques. The determination curve is shown to be both sample size invariant and readily interpretable. Further, the effects of confounding on this curve are considered alongside a proposed correction.

23 Abstract

Differences in CVD Prevalence and Beta-Blocker Prescription: International Comparative Study of CRIC and CKD-JAC

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Background: The history of cardiovascular diseases(CVDs) and prescribing patterns of antihypertensive agents, such as beta-blockers, are associated with incidence of CVD events. The aim of this study is to investigate differences in CVD history across two international chronic kidney disease(CKD) cohorts, harmonize data collected, and examine its adjusted association with beta-blocker usage.

Methods: We performed a cross-sectional study using baseline data from the Chronic Renal Insufficiency Cohort Study(CRIC, N=3939) and the CKD Japan Cohort Study(CKD-JAC, N=2977). To compare the prevalence of CVDs between CRIC and CKD-JAC, we firstly examined the concordance between self-reported and medical chart-based information regarding CVD history in a randomly-selected 156 CRIC participants. Second, we performed multiple imputation to estimate the medical chart-based CVD history in CRIC. Then, we examined potential effect modification of the association between CVD history and beta-blocker prescription by cohort in a logistic model.
Results: The Kappa statistics were 0.78, 0.83, 0.53, and 0.59 between the two data collection methods for coronary heart disease, congestive heart failure, stroke, and peripheral artery disease, respectively. The interaction between CVD history and beta-blocker use by cohort was statistically significant, both when we used self-reported history and medical chart-reviewed history in the CRIC Study(Odds ratios: 2.83 [2.15-3.73], 1.65[1.24-2.21], respectively).

Conclusion: The concordance between self-reported and medical chart-based CVD histories was moderate to excellent. The relative association between CVD history and beta-blockers modified by cohort was significant, even after removing the effect of differences in data collection methods.

24 Abstract

Integration of Transcriptomic Data Identifies Global and Cell-Specific Asthma-Related Gene Expression Signature

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Over 140,000 transcriptomic studies performed in healthy and diseased cell and tissue types, at baseline and after exposure to various agents, are available in public repositories. Integrating results of transcriptomic datasets has been an attractive approach to identify gene expression signatures that are more robust than those obtained for individual datasets, especially datasets with small sample size. We used Reproducible Analysis and Validation of Expression Data (RAVED), a pipeline that facilitates the creation of R Markdown reports detailing reproducible analysis of publicly available transcriptomic data, to analyze asthma and glucocorticoid response microarray and RNA-Seq datasets. Subsequently, we used three approaches to integrate summary statistics of these studies and identify cell/tissue-specific and global asthma and glucocorticoid-induced gene expression changes. Transcriptomic integration methods were incorporated into an online app called REALGAR, where end-users can specify datasets to integrate and obtain instant results that may facilitate design of experimental studies.

25 Abstract

The Relationship Between Readmission and Quality of Life in Clinical Trials of Telemonitoring and Structured Telephone Support in Heart Failure: A Systematic Review and Meta-Analysis

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4. Department of Medicine, the Hospital of the University of Pennsylvania

Importance: Although interventions focused on hospital readmissions for heart failure patients have had some limited success, reducing readmissions may not improve quality of life. Quality of life is arguably more important to patients, and efforts focused on readmission may not be optimal to improve quality of life. Objective:◎We performed a meta-analysis of randomized controlled trials of telemonitoring (TM) and structured telephone support (STS) in heart failure patients being discharged from the hospital to quantify the relationship between quality of life and readmission outcomes. Data Sources:◎A systematic search of the scientific literature was done according to PRISMA standards. Studies from January 1966 through August 31, 2016 were eligible. Study Selection:◎Studies were excluded if the interventions included home or extra clinic visits, etc. Primary analyses included studies that provided both quality of life and all-cause hospitalization results.

Results: Eleven studies including 4,527 participants were included. There was a lack of association between the QOL and all-cause readmission outcomes among clinical trials of either TM (regression coefficient -0.21, 95%CI -0.60 to 0.17, p-value = 0.28) or STS (regression coefficient -0.09, 95%CI -0.73 to 0.55, p-value = 0.78), where a negative coefficient represents worsening QOL as readmissions are reduced.

Conclusions: The effects of TM and STS interventions on readmission are not correlated with their effects on QOL. Focusing on readmission may not be an adequate patient-centered outcome, either as a metric of success or as the primary target for tailoring interventions.

26 Abstract

Detecting Mentions of Personal Medication Intake on Twitter

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1.University of Pennsylvania

2.Johns Hopkins University

Social media has been used for drug safety surveillance; however, studies typically do not distinguish posts that actually indicate the user's intake of the medication, perhaps because deriving this information poses challenges in natural language processing (NLP). Without this distinction, social media data will remain noisy and untapped for medication-related cohort studies. Towards improving and expanding the use of social media, we will present a publicly available, annotated corpus that can be used to train machine learning systems to automatically detect mentions of personal medication intake on Twitter. To build the corpus, we pre-processed a collection of tweets and queried them for 55 medications, including generated spelling variants. Two annotators annotated 10,260 tweets, with overlapping annotations for 10% of the tweets. Their inter-annotator agreement was $\kappa = 0.88$ (Cohen's Kappa). To account for the linguistic idiosyncrasies of how Twitter users might express their medication intake, each tweet is from a unique user. To demonstrate the utility of the annotated corpus as a training set for supervised classification, we performed experiments using several machine learning algorithms. We used a stratified 80-20 (training/test) split of the annotated data and only word n-grams (n = 1, 2, 3) as features, following standard pre-processing. The baseline results suggest that this annotated corpus can be used for training automated classification systems, and our error and feature analyses of the best performing classifier—Support Vector Machines (F = 0.67; Accuracy = 73.4%)—provide insights for improving the performance of the system in future work.

27 Abstract

Agnostic Phenotype Profiling of Denosumab Exposure: XGBoost-Guided Discovery in a Large United States Claims Cohort

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Denosumab is a therapeutic monoclonal antibody originally developed for alleviation of osteoporosis symptoms. Due to known anti-osteoclastic effect via RANKL inhibition, indication for denosumab has expanded to include treatment for various cancers. We posit that agnostic machine learning (**ML**)-based feature selection, guided by clinical classification software (**CCS**) hierarchies, can identify novel phenotype signals, in addition to identifying established denosumab therapeutic indications.

Adult patients with denosumab exposure between 2007 and 2016 were phenotyped within a large US-based insurance claims cohort. Denosumab exposed patients (n=70,610) were randomly assigned to 20% training(n=14,122) and 80% analysis(n=56,488) cohorts-first observed denosumab exposure served as the study index date. A 5% random population sample with equivalent index dates and inclusion criteria served as controls. CCS level 2 hierarchies annotated phenotype labels(n=146) for training, analysis, and control cohorts, including data from inpatient and outpatient diagnosis(ICD9&10) codes 12 months prior and post index date. XGBoost, a gradient boosting ML algorithm, was naively deployed to reduce our feature space. Following intra-population replication(A=0.846), phenotype features(n=31) were modeled as independent associations (odds ratio[95%CI]) with denosumab exposure, adjusting for age, gender, and US region of residence. Patients had a median enrollment of 53(12–199) months. Therapeutic indication of denosumab for treatment of osteoporosis(9.76[9.45-10.08]) was identified along with various primary(breast cancer-3.00[2.89-3.12]) and secondary malignancies(7.60[7.23-8.00]). Denosumab exposure was associated with increased prevalence of other bone disease(2.48[2.41-2.55), spondylosis (1.89[1.84-1.94]), eye disorders(1.71[1.67-1.76]), lower respiratory disease(1.64[1.59, 1.68]), and others. Feature importance (via XGBoost) and statistical effect (logistic regression) size measures characterized prevalent conditions differently weighted recommendations of feature importance.

28 Abstract*

Integrated Machine Learning Pipeline for Aberrant Biomarker Enrichment (i-mAB): Characterizing Clusters of Differentiation Within a Compendium of Systemic Lupus Erythematosus Patients

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Clusters of differentiation (CD) are cell surface biomarkers that denote key biological differences between cell types and disease state. CD-targeting therapeutic monoclonal antibodies (mABs) afford rich trans-disease repositioning opportunities. Within a compendium of systemic lupus erythematous (SLE) patients, we applied the Integrated machine learning pipeline for aberrant biomarker enrichment (i-mAB) to profile de novo gene expression features affecting CD20, CD22 and CD30 gene aberrance. First, a novel Relief-based algorithm identified interdependent features (p=681) predicting treatment-naïve SLE patients (balanced accuracy=0.822). We then compiled CD-associated expression profiles using regularized logistic regression and pathway enrichment analyses. On an independent general cell line model system data, we replicated associations (in silico) of BCL7A (padj=1.69e-9) and STRBP (padj=4.63e-8) with CD22; NCOA2 (padj=7.00e-4), ATN1 (padj=1.71e-2), and HOXC4 (padj=3.34e-2) with CD30; and PHOSPHO1, a phosphatase linked to bone mineralization, with both CD22 (padj=4.37e-2) and CD30 (padj=7.40e-3). Utilizing carefully aggregated secondary data and leveraging a priori hypotheses, i-mAB fostered robust biomarker profiling among interdependent biological features.

* Indicates Flash Talk

29 Abstract

Applying Predictive Analytics on Perioperative Data to Assess Physician Decision Making and Post-Operative Testing for Acute Myocardial Infarction

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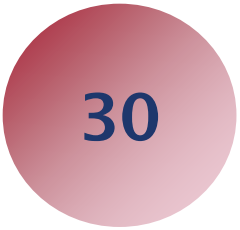
2. Lewis Katz School of Medicine, Temple University

We inform an active clinical debate around routine perioperative testing for acute myocardial infarction using predictive analytics to examine troponin ordering and risk of an elevated result or in-hospital death in non-cardiac surgery. Our model better predicts elevated results and in-hospital mortality when compared to traditional risk stratification tools and illustrates that clinicians incorporate this and more information in their troponin ordering decisions. These results suggest routine testing would increase low value perioperative testing.



Abstract

Statistical Modeling of Cellular Heterogeneity by Single-Cell RNA Sequencing

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Recent technological breakthroughs have made it possible to measure gene expression at the single-cell level, thus allowing biologists and clinicians to understand cellular heterogeneity and modify cell behavior through targeted molecular approaches. However, single-cell RNA sequencing protocols are complex. Even with the most sensitive platforms, the data are relatively sparse owing to a high frequency of drop-out events, and the related phenomenon of transcriptional bursting in which pulses of transcriptional activity are followed by inactive refractory periods. In this presentation, I will describe several statistical methods that aim to tackle these statistical challenges. Specifically, I will describe how to model allele-specific gene expression, detect differential splicing, and using single-cell RNA sequencing data to deconvolute cellular composition in bulk tissue gene expression data. I will illustrate our methods by showing results from ongoing collaborations. With the increasing commercial availability of single-cell RNA sequencing platforms, and growing interest in utilizing single-cell RNA sequencing in biomedical research, we believe that our methods will aid biomedical researchers to answer biologically and medically related questions and make exciting discoveries.

31 Abstract*

A Computational Method to Improve Missing Data Imputation in Electronic Health Record

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Clinical data of patients' measurements and treatment history stored in electronic health record (EHR) systems are starting to be mined for better treatment options and unknown disease associations. A primary challenge associated with utilizing the EHR data is the considerable missing data of the patients. Failure to address this issue can introduce significant bias into the EHR research. Currently, imputation methods solely rely on correlation structures among the structured phenotype variables in the EHR. However, existing Genome-Wide Association Studies (GWAS) have demonstrated that many human phenotypes have varying degrees of heritability and some of these phenotypes are routinely being measured in the EHR. Therefore, we developed a computational model that incorporates patients' genetic information to perform EHR data imputation. We used individual Single Nucleotide Polymorphism's association to phenotype variables in the EHR as input to construct a genetic score that quantifies the genetic contribution to the phenotype. The genetic score along with phenotype variables correlation are then used as predictors to Impute the missing values. To demonstrate the method performance, we applied our model to impute missing continuous cardiovascular related measurements as well as two binary diseases status in the electronic medical records and genomics (eMERGE) data. We show that incorporating genetic information can significantly increase the accuracy of imputation and as a result, increase power for other analyses. Compared to the state-of-the-art imputation methods, our method is the first EHR specific data imputation method that integrates patients' genetic information.

* Indicates Flash Talk

32 Abstract

Transcriptome-Guided Multimodel Imaging Genetic Analysis via a Novel Sparse CCA Algorithm

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A fundamental problem in brain imaging genetics is to investigate the association between genetic variations and quantitative traits (QTs) extracted from brain imaging data. Various prior knowledge such as group (e.g.,◎linkage disequilibrium block in genome) and network structure has been incorporated in existing association studies. Given the high dimensionality of imaging and genetic data, these priors can improve the stability in variable selection and interpretability of the results. However, majority of priors used only impose constraints on the genetic or imaging side, but not jointly connect imaging with genetics.

To bridge this gap, we propose to use the brain wide gene expression profile available in Allen human brain atlas as a two-dimensional prior to regularize the selection of both brain regions and genetic markers in◎the association analysis◎between the SNPs and imaging QTs◎from multiple modalities such as FDG and amyloid PET scans. With this prior, we expect to explore a set of genes jointly affecting a set of brain regions in both genetic and transcriptomic level. An alternating optimization algorithm is used to solve the formulated◎transcriptome-guided multimodel SCCA problem. Although the problem is not biconcave, a closed-form solution has been found for each of◎the two subproblems at the iteration. The empirical results on synthetic and real data show the proposed SCCA framework improves the robustness against noise and false positives/negatives, and facilitates the detection of relevant genes not only associated with the identified brain regions, but also differentially◎expressed there.◎

33 Abstract

Differences in Post-Transplant Hepatocellular Carcinoma Recurrence by Etiology of Liver Disease

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Liver transplantation is the preferred treatment for hepatocellular carcinoma (HCC), yet the five-year incidence of post-transplant recurrence is 8-20%. Although pre-transplant alpha fetoprotein (AFP) is a known risk factor for recurrence, etiology of liver disease has not been evaluated as a predictor, nor has an interaction term between AFP and etiology. To address this, we performed a retrospective cohort study using United Network for Organ Sharing data of transplant recipients with HCC between 2/2002 and 9/2016. Competing risks regression was performed to identify variables associated with HCC recurrence and test the interaction term of interest. Among 18,406 recipients, a total of 1,484 patients were diagnosed with HCC recurrence with median follow-up time 3.1 years. The overall risk of HCC recurrence was lowest in patients with alcoholic liver disease (subhazard ratio [SHR] 0.65, 95% CI 0.51 – 0.83). There was a significant interaction between AFP category and etiology of liver disease, with markedly increased risk of HCC recurrence in patients with high AFP and alcoholic liver disease relative to other etiologies. For example, the SHR was 7.04 (95% CI 3.66 – 13.54, p <0.001) in alcoholics with AFP >1000 versus AFP <100. In conclusion, risk of HCC recurrence differs by etiology of liver disease, and the significance of elevated pre-transplant AFP varies by etiology. Patients with alcoholic liver disease and elevated AFP are at uniquely high risk of HCC recurrence. Further studies are needed to explore the biological underpinnings of these findings.

34 Abstract

Predicting Natalizumab Effectiveness in Multiple Sclerosis Patients

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Multiple sclerosis (MS) is a demyelinating central nervous system disease characterized by the incidence of lesions and the loss of brain volume (atrophy). In this study, we focused on a relatively new biological therapy, natalizumab, which reduces the migration of inflammatory immune cells into the brain, and has been shown to decrease the number of new lesions patients develop. Our goal was to predict how long a patient will continue natalizumab treatment based on lesion count, as well as changes in lesion volume and ventricular volume, using retrospective analyses of magnetic resonance imaging (MRI). The dataset we worked with contained a sample of 35 MS patients who underwent MRI at three time points at the Hospital of the University of Pennsylvania. We performed a survival analysis to predict the number of days a patient stays on natalizumab treatment before stopping for ineffectiveness. The data indicate that patients who, before starting treatment, have more incident lesions or less atrophy tend to stay on natalizumab longer. Future investigation is needed to validate these exploratory findings.

35 Abstract*

Tacrolimus (TAC) Pharmacogenetics and Acute Kidney Injury after Lung Transplantation (LTx)

Todd A. Miano [1,2,3], Judd Flesch[4], Joshua Diamond[4], Jason Christie[2,3,4], Rui Feng[2,3], Caitlin Forker[4], Melanie Brown[4], Michelle Oyster[4], Edward Cantu[5], Mary Porteus[4], Laurel Kalman[4], Melanie Rushefski[4], Russel Localio[2,3], Michael Shashaty[2,4]

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Background: TAC, a cornerstone of immunosuppression after LTx, has an unpredictable dose response in the early post-operative period. Excessive TAC exposure is potentially nephrotoxic, but its impact on post-LTx acute kidney injury (AKI) is not well-quantified. Genetic variation of TAC metabolism could explain substantial variability of TAC dose response but is understudied in the early post-LTx period.

Methods: Retrospective cohort study of patients from one center of the multicenter Lung Transplant Outcomes Group study. We defined AKI using consensus criteria and TAC dose response by the concentration/dose (C/D) ratio. Cox regression was used to estimate the adjusted association between TAC concentration and AKI through post-LTx day 14. Linear mixed effects models were used to estimate adjusted associations between clinical and genetic variables and log-transformed TAC C/D ratio.

Results: AKI occurred in 290/484 (60%) patients and was independently associated with increasing TAC concentration: adjusted HR 1.5, (95%CI 1.2, 1.9) per 5-mg/dL increase. In 376 genotyped patients, a single loss-of-function (LoF) allele for CYP3A5 non-significantly reduced the C/D ratio: -21% (95%CI -72.6%, 14.9%), whereas two LoF alleles significantly reduced the C/D ratio: -140% (95%CI -243.5%, -70.7%). Clinical factors independently associated with TAC C/D ratio included exposure to voriconazole, amiodarone, and vasopressors; body weight; and hematocrit.

Conclusions: TAC concentration is an independent risk factor for AKI after LTx, while CYP3A5 function is associated with TAC dose response. Future studies should examine the effect of clinical and genetic dosing algorithms on outcomes in this cohort.

* Indicates Flash Talk

36 Abstract

Using a Clinical Pathway Development Framework and Internet-Based Dissemination Platform to Expedite the Implementation of Evidence into Practice

Nikhil Mull[1], Emilia Flores[1], Brian F. Leas[1], Matthew D. Mitchell[1], Julia A. Lavenberg[1], Neha Patel[1], Austin Williams[1], Craig A. Umscheid[1]

1. University of Pennsylvania Health System

Background: Unnecessary variation in care can adversely impact patient safety and care quality. Clinical pathways, defined as multi-disciplinary care plans, are a method for translating evidence into local settings and have been shown to reduce unnecessary variation and improve patient outcomes. In 2016, UPHS implemented a program to support the implementation of pathways throughout our health system. We use a technology platform (Dorsata Inc., Washington, DC) to provide access to content across our geographically distributed care settings and providers. Content is viewable through the internet and mobile app and can also be downloaded for offline use.

Methods: We use a multistep framework (grounded in the Knowledge-to-Action framework by Graham et al.) to facilitate pathway development and implementation, which includes facilitating clinical owner and stakeholder engagement, performing rapid evidence reviews, pathway prototyping, developing clinical decision support tools for EHR integration, and impact assessment.

Results: From January 2016-January 2018, 186 clinical pathways have been disseminated. Disease-based service lines account for 59% of all pathways. Engagement across other clinical domains is also robust: pulmonary/critical care (9%), nursing (6%), hematology (6%), and endocrinology (4%). Over 1,200 individuals have registered to use the mobile app, including physicians (41%), nurses (19%), advanced practitioners (18%), and pharmacists (4%). In the last 3-months, mean viewership has reached 2,150 per month.

Conclusion: Clinical pathways are one method to translate evidence into practice and reduce unnecessary variation in care. We demonstrate how a healthcare system can successfully utilize a framework and technology to support the development and dissemination of pathways.

37 Abstract*

SCORTEN Overestimates Mortality from Stevens-Johnson Syndrome /Toxic Epidermal Necrolysis in a Large, Multi-Institutional Cohort from the United States

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2. Department of Medicine, University of Pennsylvania
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SCORTEN is a SJS/TEN-specific severity of illness score developed to predict mortality. Because of differences in baseline risk factors and treatment protocols among various patient cohorts, the prognostic accuracy of SCORTEN varies. The objective of this study is to determine the predictive ability of SCORTEN in large, multi-institutional cohort of SJS/TEN patients from the US, explore additional mortality risk factors, and create an updated severity of illness score. Individuals >18 years of age with a diagnosis of SJS/TEN confirmed by a dermatologist were included. Among 370 patients, 54 (15.14%) did not survive to hospital discharge (SMR: 0.73). Five co-variates were independent predictors of in-hospital mortality: age, in years (OR: 1.05, 95%CI: 1.02–1.07), body surface area (BSA) involved, Day 0 (OR: 1.02, 95%CI: 1.01–1.04), serum bicarbonate <20mmol/L (OR: 2.90, 95%CI: 1.43–5.88), active/ongoing malignancy (OR: 4.40, 95%CI: 1.82–10.61), and dialysis (OR: 15.94, 95%CI: 3.38–66.30). A US-based severity of illness score was constructed that assigns 1 point for the presence of age >50 years, BSA, admission > 10%, and serum bicarbonate <20mmol/L, 2 points for active/ongoing malignancy and 3 points for dialysis. In conclusion, SCORTEN overestimated mortality in this large US cohort of SJS/TEN patients. Increasing the age to >50 years and adding dialysis to the model improved prognostication. Future use of an updated severity of illness score can provide improved prognostic information for patient care and clinical research.

* Indicates Flash Talk

38 Abstract

Galectin-3 and Risk for Progression of Chronic Kidney Disease (CKD): Findings from the Chronic Renal Insufficiency Cohort (CRIC) Study

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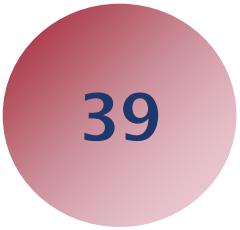
Galectin-3 is a marker of inflammation and fibrosis associated with increased cardiovascular risk. Here, we explored the association between plasma galectin-3 and the risk of CKD progression.

We measured galectin-3 at baseline in 3828 CRIC Study participants, a multi-center cohort of individuals with CKD. We evaluated the association between baseline Galectin-3 and time to CKD progression (halving of estimated glomerular filtration rate (eGFR) or initiation of renal replacement therapy) fitting Cox-PH models and the association with eGFR slopes fitting linear mixed effects models.

The overall multivariable association between galectin-3 and CKD progression was not significant (HR: 1.02, 95%CI 0.96 to 1.08), but an interaction by eGFR at baseline was observed (p-value: 0.052). Individuals with eGFR above 45ml/min/1.73m2 had higher risk for CKD progression (HR: 1.15; 95%CI 1.01 to 1.32) for each increase in 1 SD of galectin-3. The role of baseline eGFR and proteinuria as mediators in the pathway between galectin-3 and CKD progression was also evaluated. In this analysis, models without baseline eGFR revealed an increased risk for CKD progression across the spectrum of baseline eGFR (HR: 1.09, 95% 1.04 to 1.15). The association between higher levels of galectin-3 and steeper slopes of eGFR was significant after multivariable adjustment.

In conclusion, Galectin-3 was associated with a steeper decline of eGFR over time and increased risk for CKD progression among individuals with less severe CKD. Galectin-3 is a promising biomarker for assessment of the risk for CKD progression.



Abstract

Cox Regression with Doubly Truncated Data

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Truncation is a well-known phenomenon that may be present in observational studies of time-to-event data. While many methods exist to adjust for either left or right truncation, there are very few methods that adjust for simultaneous left and right truncation, also known as double truncation. We propose a Cox regression model to adjust for this double truncation using a weighted estimating equation approach, where the weights are estimated from the data both parametrically and nonparametrically, and are inversely proportional to the probability that a subject is observed. The resulting weighted estimators of the hazard ratio are consistent. The parametric weighted estimator is asymptotically normal and a consistent estimator of the asymptotic variance is provided. For the nonparametric weighted estimator, we apply the bootstrap technique to estimate the variance and confidence intervals. We demonstrate through extensive simulations that the proposed estimators greatly reduce the bias compared to the unweighted Cox regression estimator which ignores truncation. We illustrate our approach in an analysis of autopsy-confirmed Alzheimer's disease patients to assess the effect of education on survival.

40 Abstract*

Concordance of Hospitalized Endpoints Within the Linked Clinical Practice Research Datalink (CPRD) and Hospital Episode Statistics (HES) Databases Among Patients Treated with Oral Antidiabetic Therapies

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Pharmacoepidemiologic studies seeking to identify hospitalized outcomes in the United Kingdom's Clinical Practice Research Datalink (CPRD) may consider using linked Hospital Episode Statistics (HES) data. However, the proportion of hospitalizations captured in both databases is unknown.

We conducted a cross-sectional study from October 2009-September 2012 among English oral antidiabetic-treated (OAD) patients in CPRD with data available for HES linkage. Within CPRD, we used Read diagnosis codes linked to a hospital referral or consultation to identify initial hospitalizations for any diagnosis during each calendar year of the study period, and determined if a hospital admission was recorded in HES within +/-30 days. Next, we identified initial hospital admissions in HES and determined if a hospitalization was recorded in CPRD within +/-30 days. We repeated analyses using HES discharge (instead of admission) dates and determined the median difference (in days) between recorded CPRD and HES events.

Among 8,574 OAD-treated HES-linked patients in CPRD, 6,574 initial hospitalizations were identified in CPRD, and 5,188 (79% [95% CI, 78-80%]) were confirmed by a HES admission date within +/-30 days (median difference, +/-3 days [IQR, 1-7 days]). Comparatively, among 8,609 hospital admissions in HES, 4,803 (56% [95% CI, 55-57%]) hospitalizations were recorded in CPRD within +/-30 days (median difference, +/-4 days [IQR, 1-9 days]). Similar results were observed when using HES discharge dates. Our analyses found that, when utilized independently, CPRD captures about 56% of hospitalizations. Pharmacoepidemiologic studies employing CPRD to identify hospitalizations should consider linkage with HES to ensure adequate ascertainment of inpatient events.

* Indicates Flash Talk

41 Abstract

Intensity Normalization of MRI Images Across Subjects for the Analysis of Large Scale Studies Across Multiple Sites Applicable to Patients with GBMs and MS

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Intensity normalization is a crucial pre-processing step in the analysis of any study involving MRI images of multiple modalities to draw meaningful conclusions about treatment effects for diseases using radiomic features. Commonly used techniques such as histogram matching and z scoring in the context of tumors or white matter lesions used to diagnose neurodegenerative diseases like multiple sclerosis, may potentially disrupt the pathology of the original image in order to conform to a common atlas or template diluting the signal in the data. We extend a technique called RAVEL previously used in Alzheimer's disease to account for subject-wise random variation through control voxels◎to produce biologically interpretable and normalized intensities to facilitate between subject comparisons.

Abstract

Social Media Mining for Toxicovigilance: Automatic Monitoring of Prescription Medication Abuse from Twitter

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1. University of Pennsylvania

Our primary aims were to assess the possibility of utilizing social media as a resource for automatic monitoring of prescription medication abuse and to devise an automatic classification technique that can identify potentially abuse-indicating user posts.

We collected Twitter user posts (tweets) associated with three commonly abused medications (Adderall(®), oxycodone, and quetiapine). We manually annotated 6400 tweets mentioning these three medications and a control medication (metformin) that is not the subject of abuse due to its mechanism of action. We performed quantitative and qualitative analyses of the annotated data to determine whether posts on Twitter contain signals of prescription medication abuse. Finally, we designed an automatic supervised classification technique to distinguish posts containing signals of medication abuse from those that do not and assessed the utility of Twitter in investigating patterns of abuse over time.

Our analyses show that clear signals of medication abuse can be drawn from Twitter posts and the percentage of tweets containing abuse signals are significantly higher for the three case medications (Adderall(®): 23%, quetiapine: 5.0%, oxycodone: 12%) than the proportion for the control medication (metformin: 0.3%). Our automatic classification approach achieves 82% accuracy overall. To illustrate the utility of automatic classification, we show how the classification data can be used to analyze abuse patterns over time.

Our study indicates that social media can be a crucial resource for obtaining abuse-related information for medications, and that automatic approaches involving supervised classification and NLP hold promises for essential future monitoring and intervention tasks.

43 Abstract

Health Behaviors Among Elder Adults with Chronic Kidney Disease

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Background: Cardiovascular disease (CVD) is the leading cause of death among those with chronic kidney disease (CKD). To modify CVD risk, CKD patients are asked to engage in health behaviors.

Methods: Data from the Chronic Renal Insufficiency Cohort Study were analyzed using latent class analysis (LCA) to identify health behavior clusters, stratified by age. LCA was based on: BMI of >20 and ≤25kg/m2 vs. other, healthy diet vs. not, physical activity ≥150min/week vs. not, blood pressure ≤140/90mmHg vs. greater, never/past smoker vs. current, and <7.0% hemoglobin A1c vs. greater. Logistic regression assessed cluster associations with social and health factors. Cox proportional hazards models estimated hazard of CVD events, CKD progression, and death.

Results: Three clusters of health behaviors were identified among <65 and ≥65 years of age. Among <65 years, the cluster with the most healthy behaviors was associated with more self-efficacy and lower depressive symptoms. In this age group, in multivariable adjusted models, the clusters with less healthy behaviors had an increased risk of CVD events (32-81%), death (29-78%), and CKD progression (32-38%). Among ≥65 years, the cluster with the most healthy behaviors was associated with higher self-efficacy, social support, cognition, and less depressive symptoms. In this age group, the clusters with less healthy behaviors had a 49% increased risk of death.

Conclusion: Three clusters of health behaviors were identified that distinguish risk for clinical outcomes. Clusters with less health behaviors were associated with self-efficacy and depressive symptoms, which could serve as potential targets for intervention.

44 Abstract

X-meta: A Toolbox for Meta-Analysis

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X-meta is an open-sourced, well-documented and interactive toolbox for meta-analysis. There are three main components to this toolbox: An R package called XMETA, video tutorials and documentation for the package and an online analysis platform. XMETA package offers several functions for performing meta-analysis and visualizing outcomes, allowing users to conduct robust multivariate meta-analysis (mmeta), publication bias test (PB), outcome reporting bias test (ORB) and novel visualization tool (galaxy). Through the tutorials, reference documents and sample code, users can have a comprehensive exploration of the features found in XMETA and how they may apply to analytical work. The online meta-analysis system works with different available methods and a variety of formats of data, enabling users to quickly obtain the meta-analysis results without writing any code. Our team is building up the system by adding other practical features, such as proofing data, batch processing multiple files concurrently, and generating reports automatically.

45 Abstract

Presentation and Outcome of Biopsy-Proven Heptaocelluar Carcinoma by HIV Status

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Few studies have evaluated the impact of HCC pathology on survival by HIV and hepatitis C virus (HCV) infection status.

We performed a cohort study of HIV+ and uninfected patients with biopsy-proven HCC sampled between 2000 and 2016 within the Veterans Aging Cohort Study (VACS). Details of liver and tumor pathology were abstracted from clinical pathology reports; demographics comorbidities, American Joint Committee on Cancer stage were compared by HIV and RNA-confirmed HCV status. Kaplan Meier and Cox proportional hazards regression were used to compare median survival and determine factors associated with death, respectively.

Among 304 patients (median age, 58.4 years; 99% male; 59% black) with biopsy-proven HCC, 134 (44%) were HIV+ with no differences in demographics by HIV and HCV status. HIV+ patients more commonly were infected with HBV (14% vs. 3%; p<0.001), but not HCV infection (78% vs. 83%; p=0.18). There were no differences in tumor differentiation, prevalence of advanced hepatic fibrosis/cirrhosis, or HCC stage by HIV and HCV status. Median survival was shorter for HIV+ than uninfected patients (397 days vs. 565 days; log-rank: p=0.05). After adjustment for age, race, HBV, HCV, advanced hepatic fibrosis, and HCC stage, the risk of death was higher for HIV+/HCV- than HIV-/HCV- (HR, 2.21 [95% CI, 1.20-4.09]).

In these patients with biopsy-proven HCC, there were no differences in pathology by HIV and HCV status; however, HIV monoinfection had shorter survival after tissue biopsy, possibly reflecting differences in tumor biology, treatment approach or response.

46 Abstract

A Dual Modeling Approach to Automatic Segmentation of Cerebral T2 Hyperintensities and T1 Black Holes in Multiple Sclerosis

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Background and Purpose: Magnetic resonance imaging (MRI) is crucial for in vivo detection and characterization of white matter lesions (WML) in multiple sclerosis (MS). The most widely established MRI outcome measure is the volume of hyperintense lesions on T2-weighted images (T2L). Unfortunately, T2L are non-specific for the level of tissue destruction and show a weak relationship to clinical status. Interest in lesions appearing hypointense on T1-weighted images (T1L) ("black holes"), which provide more specificity for axonal loss and a closer link to neurologic disability, has thus grown. The technical difficulty of T1L segmentation has led investigators to rely on time-consuming manual assessments prone to inter- and intra-rater variability. This study aimed to develop an automatic T1L segmentation approach, adapted from a T2L segmentation algorithm.

Materials and Methods: T1, T2, and fluid-attenuated inversion recovery (FLAIR) sequences were acquired from 40 MS subjects at 3T. T2L and T1L were manually segmented. MIMoSA, an automated segmentation algorithm, was then employed.

Results: Using cross-validation, MIMoSA proved robust for segmenting both T2L and T1L. For T2L, a Sørensen-Dice coefficient (DSC) of 0.6 and partial AUC (pAUC) up to 1% false positive rate of 0.69 were achieved. For T1L, 0.48 DSC and 0.63 pAUC were achieved. The correlation between EDSS and manual versus automatic volumes were similar for T1L (0.32 manual vs. 0.34 MIMoSA) , T2L (0.34 vs. 0.34), and the T1L/T2L ratio (0.33 vs 0.28).

Conclusions: Though originally designed to segment T2L, MIMoSA performs well for segmenting T1 black holes in patients with MS.

47 Abstract*

Powerful Permutation Tests for Neuroimaging Using Voxel-wise Transformations

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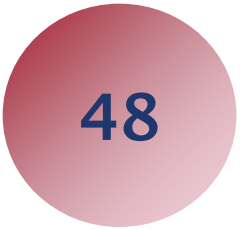
Typical statistical methods in neuroimaging result in hundreds of thousands of tests performed in an image, followed by the use of a multiple testing procedure (MTP) to control the family-wise error rate (FWER). Recent studies have demonstrated that widely used MTP procedures yield anticonservative FWERs. The permutation MTP is among few procedures shown to reliably control the number of false positives at the specified probability. Voxel-wise permutation tests work by randomly permuting the imaging data and using the distribution of the maximum value of the test statistic across all voxels in the image to compute adjusted p-values. While this procedure has intuitive appeal, anecdotally many investigators have noted it lacks power. We demonstrate that the procedure lacks power because neuroimaging data have voxels with heavy skew near the edge of the brain. These voxels cause the distribution of the maximum across the image to be heavily inflated. As a solution we apply the Yeo-Johnson transformation prior to permutation testing. The transformation yields a statistical image where all the voxels have approximately the same distribution and improves the power of the test.



Abstract

Approaches to Link Geospatially Varying Social, Economic and Environmental Factors with Electronic Health Record Data to Better Understand Asthma Exacerbations

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Electronic health record (EHR)-derived data has become an invaluable resource for biomedical research, but is seldom used for the study of the health impacts of social and environmental factors due in part to the unavailability of relevant variables. We describe how EHR-derived data can be enhanced via linking of external sources of social, economic and environmental data when patient-related geospatial information is available, and we illustrate an approach to better understand the geospatial patterns of asthma exacerbation rates in Philadelphia. Specifically, we relate the spatial distribution of asthma exacerbations observed in EHR-derived data to that of known and potential risk factors (i.e., economic deprivation, crime, vehicular traffic, tree cover). Areas of highest risk based on integrated social and environmental data were consistent with an area with increased asthma exacerbations, demonstrating that data external to the EHR can enhance our understanding of negative health-related outcomes.

49 Abstract

Adiposity and Fat Free Mass in CKD: Exploring Outcome Relationships

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Background: Adiposity is an independent risk factor of chronic kidney disease (CKD), but also found to be associated with slower renal function decline among CKD patients. This paradoxical observation is not fully understood. We sought to examine whether fat free mass modifies the association between adiposity and CKD progression.

Methods: We utilized data from the Chronic Renal Insufficiency Cohort (CRIC) Study, which is a prospective cohort with 3,939 CKD patients recruited across the United States. Fat mass and fat free mass were estimated by bioelectrical impedance analysis. Fat mass and fat free mass were indexed to height-squared and further standardized based on their respective means and standard deviations (SD). CKD progression was defined as halving of estimated glomerular filtration rate from baseline or initiating dialysis. We fit Cox proportional hazards model to examine the independent association between fat mass, fat free mass, and CKD progression.

Results: After adjusting for potential confounders, our results suggested a statistically significant interaction between fat mass and fat free mass. At a given fat free mass, one SD higher fat mass index was associated with a 17% lower hazard (HR 0.83, 95% CI 0.78-0.88) of CKD progression. However, this protective effect is attenuated by increasing fat free mass. At a given fat mass, each SD higher fat free mass was associated with a 21% higher hazard (HR 1.21, 95% CI 1.13-1.29) of CKD progression.

Conclusion: Adiposity is associated with slower CKD progression particularly in patients with lower fat free mass.

50 Abstract

Network-Based Genome Wide Study for Identifying Tissue-Specific Functional Interaction Modules: An Amygdala Imaging Genetic Study

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Network-based genome-wide association studies (GWAS) aim to identify functional modules from biological networks that are enriched by top GWAS findings. A majority of module identification studies employ tissue-free networks that lack phenotypic specificity. We employ a novel network-based GWAS (NetWAS) approach to identify modules from a tissue-specific functional network, and demonstrate it in an amygdala imaging genetic studies.

Participants include 989 ADNI subjects. GWAS of amygdala FDG-PET measures were performed to obtain 20,168 gene-level p-values. Amygdala-specific functional network was downloaded from GIANT (http://giant.princeton.edu/). Three NetWAS methods were implemented to reprioritize GWAS results: a previously proposed SVM-based approach that employ significant/nonsignificant status; two regression-based approaches, ridge regression (Ridge) and support vector regression (SVR), which utilize continuous p-values as responses. Genes were reprioritized according to predictions (in Ridge or SVR) or distance from hyperplane (in SVM). AUC of reprioritizations were assessed using documented AD genes as gold standard positives. Link clustering was employed on top reprioritizations to detect modules. Top GWAS findings were used to assess the enrichment of candidate modules, and identify significant ones. Functional annotation was performed on the identified modules. All NetWAS approaches yielded much denser interactions among top findings, and obtained higher AUCs than GWAS. Regression methods outperformed SVM, suggesting that continuous significance measures provide valuable information than binary status. Among top 50 Ridge findings, five modules were identified and enriched by top 50 GWAS findings. These modules were functionally annotated by neurodegenerative diseases, cognition, learning and memory.

51 Abstract*

Association of Change in Galectin-3 and Risk of Chronic Kidney Diease (CKD) Progression in the Chronic Renal Insufficiency Cohort (CRIC) Study: A Case-Cohort Study

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Kidney fibrosis is a final common pathway of CKD progression. However, it is unknown whether the change in plasma galectin-3 levels, a key marker of inflammation and fibrosis, is independently associated with kidney function decline among adults with CKD.

Methods: We conducted a case-cohort study including a random subcohort of 1300 individuals from CRIC study baseline, an ongoing, multi-center, prospective cohort of men and women with CKD. Participants were followed for the composite outcome of a 50% reduction in estimated glomerular filtration rate (eGFR) or onset of end-stage renal disease (ESRD). We calculated change in galectin-3 from baseline to year 2. Weighted logistic regression models estimated the relationship between two-year change in galectin-3 and CKD progression after Year 2.

Results: After excluding prevalent ESRD cases and those with missing data, 1180 individuals were included. Change in galectin-3 (mean: 4.0 ng/mL, SD: 8.1) was significantly associated with female gender, greater BMI, higher systolic blood pressure, lower baseline eGFR, and lower baseline galectin-3 levels. Analyses of kidney function decline showed that each 5-unit increase in galectin-3 was associated with a 14% greater odds (OR=1.14, 95% CI 1.01, 1.28) of CKD progression, independent of baseline biomarkers. Similarly, the highest, compared to the lowest, quartile of galectin-3 change was observed to have over a two-fold higher odds (OR=2.2, 95% CI 1.29, 3.75) of CKD progression.

Conclusion: Changes in plasma galectin-3 levels hold promise to become a novel marker of higher risk for CKD progression among diverse populations of adults with CKD.

* Indicates Flash Talk

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