SPOTLIGHT ON RESEARCH IN MEDICINE

Recognized abstracts from Dalhousie Medicine 2018 RIM Research Day

Evaluating the use of the Dalhousie Computerized Assessment Battery for detecting Post-Operative Cognitive Dysfunction in the perioperative setting

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Post-Operative Cognitive Dysfunction (POCD) is difficult to predict and diagnose, and can have potentially severe consequences in the long-term, particularly to the elderly. The purpose of our study was to examine the feasibility of using a new computerized test battery, the Dalhousie Computerized Assessment Battery (DalCAB) perioperatively to detect cognitive changes after surgery.

Methods: Fifty patients, ≥55 years, ASA scores of \leq 3 undergoing major (>30 minutes) noncardiac surgery. The study used a repeated measures design. Patients completed the DalCAB and tests of general cognition, mood and pain (MoCA; HADS; VAS for pain severity) at baseline and at 3 months postoperatively. Univariate and Z-score analysis was used to evaluate differences.

Results: The pilot study had a screening rate (85.4%), participation rate (56.2%), testing time (87 minutes), attrition rate (12%) and complete datasets (93%). No cognitive deficits were present at baseline in the surgical group. One patient (2.3%) was classified as having POCD using the MoCA compared to 6 patients (13.6%) using the DalCAB. Visual working memory was most impaired. No statistical differences were present in anxiety, depression and pain scores in the POCD group.

Conclusions: This study found an incidence of POCD of 13.6% based on the DalCAB that aligns with previous quantitative battery reports suggesting increased sensitivity compared to the MoCA (2.3%). The incidence of POCD appears to be independent of pre- and post-operative anxiety, depression and pain levels. The future of the DalCAB's clinical utility is promising given the demonstrated feasibility of this computerized test.

Award winner: Platform Presentation Winner, RIM Research Day 2018

Exploring the role of pediatric medical camps in supporting adolescents with chronic illness in their readiness for adulthood

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Department: Pediatrics

Objectives: To explore adolescent perspectives around the impact of attendance at a pediatric medical camp on their readiness for adulthood. Background: For adolescents living with a chronic illness, transitioning to adulthood involves psychosocial competencies that may be difficult to foster in a clinical environment. Socializing with peers with similar illnesses in a recreational environment may enhance development of these competencies and impact the adolescent's perception of their readiness for adulthood. Methods: Adolescents age 14-17 from 4 pediatric medical camps were

Methods: Adolescents age 14-17 from 4 pediatric medical camps were recruited for focus groups at their respective camps that utilized a semi-structured guide to gather information on their camp experience and perceptions on their readiness for adulthood. Sessions were recorded and transcribed verbatim. Analysis involved an open coding and inductive approach, with similar concepts iteratively collapsed into higher level themes

Results: A total of 29 adolescents [19F; mean age 16.2(14-17)] participated. All participants felt there were aspects of the camp that enhanced their readiness for adulthood. The camp environment normalized their illness

and allowed participants to bond with their peers and form a support system. Competencies learnt included confidence, independence, and skills to communicate about their illness. Though the education participants received prior to camp varied, many felt camp helped them become more comfortable transitioning to adulthood in terms of both medical and non-medical issues.

Conclusions: There are competencies adolescents can gain from participating in pediatric medical camps alongside peers with similar illnesses, which may address some of the psychosocial aspects of transitioning to adulthood.

Honourable mention for platform presentation

A novel t(6;22)(p21;q11.2) translocation in relapsed acute promyleocytic leukemia: a proposed marker of resistant disease

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Acute Promyelocytic Leukemia (APL) is a rare subtype of AML characterized by t(15;17). Treatment with all trans retinoic acid (ATRA) and arsenic trioxide (ATO) has been shown to be highly effective at inducing complete remission in the majority of patients. However, resistance and relapse still occurs in a subset of patients, and novel therapies that aim to cure resistant APL are limited. Here, we report a case of a 4-year-old boy that presented with relapsed APL while undergoing maintenance therapy and was found to have a chromosomal abnormality. Better risk-stratification for APL patients and markers of aggressive disease are needed moving forward.

Objectives: Characterize a unique translocation and establish a model of APL therapy response using zebrafish xenotransplantation.

We examined the patient sample using G-band karyotyping of bone marrow metaphases, FISH testing with whole chromosome paint and locus specific probes. To develop a model of APL for future drug screening, human cell line NB4 were xenografted into zebrafish embryos and treated with ATO and ATRA, and treatment response was assessed using flow cytometry.

FISH analysis confirmed a distinct t(6;22)(p21;q11.2) in our patient sample. To our knowledge, this is the first time a t(6;22) mutation in childhood APL has been reported. A zebrafish xenotransplantation model of APL was established and can be used to identify promising therapeutics.

The novel t(6;22) may represent a marker of resistant APL, and the zebrafish model of APL can be used to further characterize the role this translocation may play in resistance.

Honourable mention for platform presentation

The reduction of heterotopic ossification incidence following hip arthroscopy in patients treated with celecoxib

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Department: Division of Orthopedics

Heterotopic ossification (HO) is a known complication following hip arthroscopy. Traditionally, surgical excision has been postponed until the formation is "matured". This can be an excessive delay for patients suffering from functional mobility issues. Therefore, a prophylactic treatment that reduces the formation of HO would be ideal.

Objectives: Our primary objective is to determine the rate of HO formation following hip arthroscopy in patients treated prophylactically with and without Celebrex. Our secondary objective is to assess the clinical outcome (iHOT score) and determine the relationship between patient's demographic

factors and outcome.

Methods: A retrospective chart review from prospectively collected data was performed. 516 patients who received hip arthroscopic surgery between 2012 and 2016 were identified. Among the patient population 280 patients received Celebrex and 236 patients did not. Post-operative radiographs were analyzed and quantified using the Brooker scoring system for assessing HO formation. iHOT scores at pre- and post-operative dates were compared and stratified by treatment and demographics.

Results: The treated group showed significantly less HO development post-operatively when compared to the non-treated group (p <0.001). The change in iHOT score from pre-operative to most recent was significant when stratified by treatment (p <.028). Additionally, the formation of HO when the study population was stratified by sex was significant (p <.0001). Conclusions: The findings of this study suggest that Celebrex significantly reduces the prevalence of HO formation following hip arthroscopic surgery. Furthermore, it appears to have a clinical correlation by significantly improving the patient outcome (iHOT score).

Honourable mention for platform presentation

Evaluation of a Freely Available Automatic Algorithm for the Calculation of Area-Based and Volumetric-Based Mammographic Breast Density

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Department: Department of Radiology

The BI-RADS lexicon for categorization of mammographic breast density has shown that women with dense breasts have an increased risk of developing breast cancer (BC). Recently, there has been an effort to develop automatic algorithms that reliably measure mammographic density.

Objectives: Compare estimates of cancer risk for women using area-based (AB) breast density measures versus volume-based (VB) breast density measures, and to evaluate validity of AB percent density (PD) measures from an automatic algorithm.

Methods: Case-controlled study, involving 1287 women aged 40-75, from the Nova Scotia Breast Cancer Screening Program. AB and VB PD were calculated using an automated algorithm, while AB PD was also estimated by three radiologists. Interclass correlation coefficients (ICCs) were used to assess algorithm internal reliability (IR) and validity. Inter-rater reliability (IRR) for BI-RADS categorization was evaluated using Cohen's Kappa. The relationship between PD and BC risk was assessed using multiple logistic regression, and reported as an adjusted odds ratio (AOR).

Results: Algorithm AB PD AOR for developing BC was 5.24 (BI-RADS 4 versus 1). Algorithm ICCs for IR and validity were 0.61 and 0.39, respectively. IRR Kappa was 0.02. The VB AOR for development of BC was 1.5 (BI-RADS 3 versus 1).

Conclusions: Women with extremely dense breasts based on algorithm AB PD, had an AOR of developing BC consistent with literature values. IR of algorithm AB PD was good, but validity and IRR between algorithm and radiologists BI-RADS categorization, were poor. Algorithm VB PD failed to identify any women with extremely dense breasts.

Honourable mention for platform presentation

Comparison of treatment outcomes between morphine and concomitant morphine and clonidine regimens for neonatal abstinence syndrome

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Rationale: In 2010, the tertiary-care center involved in this study adjusted the treatment guidelines for neonatal abstinence syndrome (NAS) to include concomitant clonidine and morphine administration as first-line therapy. This study is the first evaluation of this practice change.

Objectives: To examine whether the addition of clonidine to the morphine regimen for treatment of NAS is associated with a shorter length of treatment compared to morphine alone. To determine the incidence of NAS in the study population from 2007-2015.

Methods: Using a retrospective cohort design, infants treated for NAS resulting from opioid exposure delivered between 2006-2015 (n=174), were identified using the Nova Scotia Atlee Perinatal Database (NSAPD). Maternal and infant characteristics were collected from the NSAPD. The database was augmented with chart review for treatment information.

Results: The incidence of NAS in the study population increased five-fold from 1.48/1000 live births in 2007 to 7.50/1000 live births in 2015. Of the 174 infants, 22 were treated with morphine and 100 were treated with morphine + clonidine. Longer length of treatment (p=0.004) and higher peak morphine dose (p=0.045) were observed in the combination group. Conclusion: The increase in incidence of NAS is consistent with recent published reports. The increase in length of treatment and peak morphine dose seen in the morphine + clonidine group contrasts previous work on this treatment combination. Further study on the impact of clinical characteristics such as methadone and anti-depressant exposure on the association is warranted.

Honourable mention for platform presentation

Loss of cholinergic neurons in nucleus subputaminalis in neurodegenerative disorders presenting as Primary Progressive Aphasia

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Rationale: Primary Progressive Aphasia (PPA) is a syndrome characterized by isolated impairment in language function at disease onset. The cholinergic system has been implicated in language function, and cholinergic deficits have been seen in PPA. One major source of cholinergic neurons is the nucleus basalis of Meynert (nbM). A posterior subdivision of the nbM, the nucleus subputaminalis (NSP), is postulated to be specifically implicated with language.

Objectives: We aimed to confirm the involvement of the NSP in PPA, and to explore whether individuals who present with progressive aphasia and develop different clinical and neuropathological profiles, show a similar involvement of the NSP. This was done by comparing the abundance of choline acetyltransferase (ChAT), a marker of cholinergic neurons, in the nbM and NSP in normal and PPA cases.

Methods: Cytoarchitecture of the basal forebrain was studied using Nissl staining of cells in normal (n=5) and PPA (n=5) brains. ChAT immunohistochemical staining was used to label cholinergic neurons, which were quantified using Neurolucida software.

Results: PPA cases showed significant loss of cholinergic neurons in the NSP, compared to normal. Though there was a trend towards loss of cholinergic neurons overall in the nbM, this was not significant compared to normal. Conclusion: Regardless of the underlying pathology, all cases with clinical language deficits characteristic of PPA showed marked loss of cholinergic neurons in the NSP. This provides evidence for the involvement of the NSP in language dysfunction and can have significant clinical implications in the medical management of patients with PPA.

Honourable mention for platform presentation

Factors affecting pain management and imaging practices of patients presenting to the Emergency Department with non-specific low back pain

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Department: Community Health and Epidemiology

Rationale: Low back pain (LBP) is a common and disabling problem and patients often present to the emergency department (ED) for management. There appears to be a wide variation in management of patients with LBP among emergency physicians and compared with practice guidelines. The relationship between patient characteristics, physician characteristics, and LBP management decisions in the ED has not been well studied.

Objectives: Describe the agreement between patient and provider ratings of LBP severity, and to explore the relationship between patient and physician pain ratings on LBP management practices in the ED, including analgesic use and diagnostic testing.

Methods: We conducted a prospective, single-centre observational study between June and November 2016. The study sample included 125 adult patients who presented to the QEII ED with non-specific LBP, and 43 physicians. Data was collected from patient and treating physician questionnaires, from the Emergency Department Information System database and from patient charts. Logistic regression models will be used to describe the association between patient and physician pain ratings and management practices.

Preliminary Results: Patient participants had a median age of 41 years and 69% were male. Mean self-reported low back pain severity (NRS, range 0-10) was 7.7 (SD 1.9). Mean physician assessment of patient pain was 5.7 (SD 2.1). Logistic regression models will be used to describe the association of analgesic use and imaging with patient and physician characteristics.

Conclusion and Relevance: Findings may guide development of an educational intervention to improve management of patients with low back pain in the ED.

Award winner: Poster Presentation

Constraint Programming and Column Generation for Automated Treatment Planning in Brachytherapy

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Rationale: Brachytherapy is a minimally invasive form of radiation therapy for prostate cancer that involves the permanent implantation of radioactive sources inside of the prostate gland. Treatment planning in brachytherapy consists of a decision making process for the placement of radioactive sources in order to deliver an effective dose of radiation to cancerous tissue while sparing the surrounding healthy tissues, such as the urethra and rectum. Although this decision making process may be automated, current automated planning methods, such as mixed-integer linear programming (MILP), prove to be undesirably slow when using high-resolution anatomical data sets to produce treatment plans.

Objectives: Develop a novel optimization modelling approach that integrates column generation and constraint programming to improve the solution time performance of a large-scale mathematical optimization model capable of producing clinically acceptable automated treatment plans for prostate brachytherapy. Column generation is an efficient algorithm used for locating pertinent solutions in highly combinatorial problems, while constraint programming is a suitable paradigm for seeking feasible clinical solutions.

Methods: We partitioned an established MILP model into a novel master problem and subproblem duo for the column generation process. While the master problem was similar in design to the original MILP model, the new subproblem sought out appropriate patterns of radioactive source loading in needles.

Results: We demonstrated the ability to produce automated treatment

plans, using high-resolution data sets, with solution times suitable for preoperative planning using column generation.

Conclusions: Column generation is an appropriate optimization modelling approach for producing automated treatment plans, using high-resolution anatomical data sets, with solution times suitable for pre-operative planning in interstitial low-dose rate prostate brachytherapy. The study will further incorporate constraint programming into the current model and investigate its treatment planning solution time performance for intra-operative planning.

Award winner: Poster Presentation

Patient-Controlled Analgesia versus Continuous Opioid Infusion for the Treatment of Mucositis Pain Following Hematopoietic Stem Cell Transplantation: A Retrospective Review

Matthew Foss, Mary Lynch

Department: Department of Anesthesia, Pain Management & Perioperative Medicine

Rationale: Myeloablative chemotherapy prior to hematopoietic stem cell transplantation (HSCT) often results in the development of painful oral mucositis. Treatment involves high levels of opioid consumption resulting in significant side effects. Prior studies have shown that, compared to continuous opioid infusion (COI), PCA results in less opioid consumption and shorter duration of therapy but no absolute reductions in pain scores.

Objectives: The goal of this study was to determine the success of PCA implementation in this patient population along these same measures.

Methods: This was a retrospective chart review of HSCT patients one year before and after the transition from COI to PCA at the QEII Health Sciences Centre in Halifax, Nova Scotia. Opioid doses were standardized between patients by converting to oral morphine equivalents (OME). Pain scores were calculated using a weighted average over therapy duration. Groups were compared using independent-samples t-tests.

Results: Twenty-three patients received COI with three requiring naloxone. Twenty-two patients received PCA. The PCA group had significantly less opioid use (M=506.0, SD=239.9) than the COI group (M=1181.5, SD=659.9), t(36)=3.64, p<0.001, d=1.13. Additionally, the PCA group required fewer days of intravenous opioid therapy (M=5.28, SD=3.29) than the COI group (M=7.67, SD=2.97), t(40), p=0.018, d=0.76. There was no difference in average pain scores between groups.

Conclusions: This study demonstrates a successful transition from COI to PCA with reduced opioid consumption, decreased therapy duration, and fewer cases requiring naloxone. Consistent with the literature, there was no reduction seen in pain scores. Further work is needed to effectively reduce the pain experienced by patients undergoing HSCT.

Award winner: Poster Presentation

Impact of preoperative anemia on transfusion rates in primary and revision hip arthroplasty: a retrospective analysis

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Department: Department of Anesthesia, Pain Management & Perioperative Medicine

Rationale: Lower extremity joint arthroplasty can be lead to significant blood loss, and the need for blood transfusion. The use of blood products is associated with a variety of adverse outcomes including infection, circulatory overload, and transfusion reaction.

Objectives: The objective of this quality improvement study is to identify the prevalence of preoperative anemia at our institution, and elucidate its impact on perioperative transfusion in elective patients undergoing primary or revision hip arthroplasty.

Methods: Data for this study was collected from four databases at our institution. Elective patients undergoing primary or revision hip arthroplasty were selected. Transfusion was defined as the receipt of a red blood cell transfusion on the surgical day through to postoperative day five. The primary outcome was the effect of preoperative anemia on transfusion rates.

Results: The overall transfusion rate was 7.6%. Transfusion rates for primary

and revision arthroplasty were 5.8% and 18.7% respectively. Patients with a preoperative hemoglobin between 100 and 120 g/L were 4.5 times more likely to be transfused than those with a hemoglobin between 121 and 140 g/L, and 15.4 times more likely than those greater than 140 g/L. Preoperative anemia was common, with 11.5% of all patients having a preoperative hemoglobin of 120 g/L or less.

Conclusion: Preoperative anemia was common and was significantly associated with higher transfusion rates. These findings reinforce the need to optimize hip arthroplasty patients prior to surgery, where possible. As a quality control study, these findings may help direct policy regarding the deferral of elective hip arthroplasty patients who are anemic preoperatively.

Award winner: Poster Presentation

Evaluation of a Low-Threshold/High-Tolerance Methadone Maintenance Treatment Clinic in Saint John, New Brunswick, Canada: Seven Year Retention Rates

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Rationale: Patients at Low-Threshold/High-Tolerance (LTHT) methadone maintenance treatment (MMT) clinics are not denied access to methadone due to lack of ancillary services, nor discharged involuntarily for continued illicit drug use. Studies suggest this has a positive impact on retention. Retention is a crucial outcome, as the potential benefits of treatment cannot be appreciated if programs cannot retain patients.

Objective: To report the retention rate in years one through seven of a LTHT MMT clinic in Saint John, NB $\,$

Methods: Data was collected on each patient who began MMT at the clinic between August 4, 2009 and August 4, 2010. Retention rates were determined by comparing the total number of patients enrolled in the clinic by August 4th, 2010 to the number of these patients still in the program after each of years one through seven. If a patient was no longer receiving methadone from the clinic, the reason for separation was determined.

Results: The one-year retention rate was 91%; two-year, 84%; three-year, 74%; four-year, 67%; five-year, 54%, six-year, 45%; and the seven-year retention rate was 39%. Of the 113 patients separated from the clinic after seven-years, 33 successfully weaned off methadone, 39 transferred to a different clinic to receive MMT, 9 were incarcerated, 2 died, and 25 voluntarily withdrew. Reason for separation unknown for 5.

Conclusion: Canada's Best Practice Guidelines for MMT advocate for the use of low-threshold programs, and non-punitive approaches to illicit drug use to both increase access to, and retention in MMT. We have identified the retention rates in years one through seven at an LTHT MMT clinic in Saint John, NB.

Award winner: Poster Presentation

Rapid clinical assessment of the sublingual microcirculation - visual scoring using microVAS in comparison to standard semi-automated analysis

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Rationale: Alterations in human microcirculation occur in many disease states leading to morbidity and mortality, however assessing the microcirculation is not standard clinical practice. Standard microcirculation analysis using semi-automated analysis is expensive, time consuming, and expertise dependent making it unfeasible. We proposed a novel visual scoring system (microVAS) for the analysis of microcirculation videos that can be performed at the patient bedside in real time.

Objective: Validate our microVAS score by training health professionals unfamiliar with the microcirculation field to use our microVAS score and compare their scores to the standard method of semi-automated analysis using AVA3 software.

Methods: Using a prospective double-blind study design, we recruited and

trained 20 participants to use our microVAS score. Participants scored 40 videos (from 22 healthy and 18 septic patients) for MFI and PPV. The same 40 videos were analyzed by an expert using the gold standard semi-automated method of analysis. The results of the participants and the expert were analyzed by Pearson's linear regression. Krippendorff's alpha was used to assess inter-rater reliability of the participants.

Results: Overall correlation of MFI was r=0.3283 (95% CI 0.27 - 0.39), p<0.05; overall correlation of PPV was r=-0.1123 (95% CI -0.18 to -0.04), p<0.05. The Krippendorff's alpha for MFI was 0.56 (healthy videos: $\alpha=0.34$, sepsis videos: $\alpha=0.31$). For PPV Krippendorff's alpha was 0.43 (healthy videos: $\alpha=0.56$, sepsis videos: $\alpha=0.17$).

Conclusions: Overall for both MFI and PPV, there was a small correlation between our microVAS score and AVA 3 scores. Regarding inter-rater reliability both MFI and PPV showed fair agreement between raters. Going forward multiple improvements to the microVAS scoring system as well as the training program are suggested to improve reliability and consistency.

Award winner: Poster Presentation

Development a novel FI-Heart using cardiovascular risk factors to predict increased risk of mortality

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Rationale: The concept of frailty was developed to explain the heterogeneity in clinical outcomes for older adults. As cardiovascular disease (CVD) is the leading cause of death and hospitalizations in older adults, there is a growing interest in the link between frailty and CVD. A frailty index (FI-Heart) based on cardiovascular risk factors may offer valuable prognostic insights in decision-making and care.

Objective: Our objectives are to develop a FI-Heart; compare the FI-Heart to a standardized FI; and to investigate whether FI-Heart can predict mortality.

Methods: A FI-Heart was developed by secondary analysis of 2003-2004 and 2011-2012 cohorts from NHANES database. A 26-item FI-Heart was constructed in accordance to guidelines in creating frailty indices. The FI-Heart was compared to a standardized FI previously developed using the NHANES database.

Results: The FI-Heart showed non-linear increase with age (2003-2004: R2=0.8718, p<0.0001; 2011-2012: R2=0.9244, p<0.0001). There were no significant differences in age-matched FI scores between the FI-Heart and Standardized FI (2003-2004: T=175, p=0.206; 2011-2012: T=209, p=0.091). There was no significant difference in FI-Heart scores between the 2003-2004 and 2011-2012 cohorts (T=155, p=0.198). Higher FI-Heart scores were associated with higher risk of mortality.

Conclusion: The FI-Heart showed non-linear increase with age, typical characteristic of frailty indices. The was no significant difference in FI-Heart and standard FI scores in age-matched individuals. Additionally, the FI-Heart demonstrated an association with increased mortality risk. The FI-Heart can be a feasible tool for use in risk assessment of cardiovascular disease and may have significant value in decision-making and prognosis.

Award winner: Poster Presentation

Adolescent Traumatic Brain Injuries: Time of Occurrence and Links with Current Academic Performance and Physical Injuries

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Department: Community Health and Epidemiology

Rationale: Traumatic brain injuries (TBIs) during adolescence are associated with adverse outcomes, but if the age at which TBIs occur influences the degree of detriment is unknown.

Objectives: We evaluated the relationship between the age of adolescents at the time of their first and most recent TBI, and current academic performance and other physical injuries.

Methods: Data for this cross-sectional population-based study were derived from the 2015 Ontario Student Drug Use and Health Survey (OSDUHS) administered to adolescents in grades 7 to 12.

Results: One in 5 students reported a history of TBI. TBIs were more prevalent in males, compared to females, and males were 2-times as likely to had their first and most recent TBI in grades 5 to 8. Sports-related TBIs accounted for 41.1% of all TBIs. A history of TBI was associated with lower academic performance and more physical injuries. The first and most recent TBIs occurring in all grades assessed were associated with poorer academic performance, especially in older grades. Students with a history of TBI(s) that frequently sought treatment for other physical injuries, were more likely to have acquired TBIs in older grades.

Conclusions: The prevalence of TBIs among the adolescents reported here is higher than reported from emergency room data, but consistent with regional survey data. Results suggest that the adverse TBI outcomes observed are affected by the age at which TBIs occur. Greater effort to track the prevalence and correlates of TBIs in large-scale epidemiological data is needed.

Award winner: Poster Presentation

