

4067

Cancer-related fatigue during combined treatment of androgen deprivation therapy and radiotherapy is associated with mitochondrial dysfunction

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OBJECTIVES/GOALS: Combined androgen deprivation therapy (ADT) and radiation therapy (RT) is the standard of care treatment for non-metastatic prostate cancer (NMPC). Despite the efficacy, treatment-related symptoms including fatigue greatly reduce the quality of life of cancer patients. The goal of the study is to examine the influence of combined ADT/RT on fatigue and understand its underlying mechanisms. **METHODS/STUDY POPULATION:** Sixty-four participants with NMPC were enrolled. Fatigue was assessed using the Functional Assessment of Cancer Therapy–Fatigue. Mitochondrial function parameters were measured as oxygen consumption from peripheral blood mononuclear cells (PBMCs) extracted from participants' whole blood. An ADT/RT-induced fatigue mouse model was developed with fatigue measured as a reduction in voluntary wheel-running activity (VWRA) in 54 mice. Mitochondrial function was assessed in the ADT/RT mouse brains using Western blot analysis of Glucose transporter 4 (GLUT4) and transcription factor A, mitochondrial (TFAM). **RESULTS/ANTICIPATED RESULTS:** Fatigue in the ADT group was exacerbated during RT compared to the non-ADT group. This effect was specific to fatigue, as depressive symptoms were unaffected. PBMCs of fatigued subjects exhibited decreased ATP coupling efficiency compared to non-fatigued subjects, indicative of mitochondrial dysfunction. The ADT/RT mice demonstrated a synergistic effect of ADT and RT in decreasing VWRA. Brain tissues of ADT/RT mice exhibited decreased levels of GLUT4 and TFAM suggesting that impaired neuronal metabolic homeostasis may contribute to fatigue pathogenesis. **DISCUSSION/SIGNIFICANCE OF IMPACT:** These findings suggest that fatigue induced by ADT/RT may be attributable to mitochondrial dysfunction both peripherally and in the central nervous system (CNS). The synergistic effect of ADT/RT is behaviorally reproducible in a mouse model, and its mechanism may be related to bioenergetics in the CNS.

4123

Characterization of Physical Restraint and Sedative Use for Treatment of Agitation in the Emergency Department

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OBJECTIVES/GOALS: Agitation has high prevalence in the emergency department (ED), but limited evidence exists regarding clinical decisions to use sedatives and physical restraint. We examined clinical factors and agitation attributes impacting thresholds for sedative and restraint use in the emergency setting. **METHODS/STUDY POPULATION:** We conducted a prospective cohort study of adult patients (>18 yo) with acute or escalating agitation during their ED visit at an urban tertiary care referral center. Consecutive patients requiring security presence or scoring >1 on an agitation scale were

enrolled during randomized 8-h blocks. We recorded patient characteristics, staff/team factors, and environmental/systems data as well as scores on 3 validated agitation scales: Agitated Behavior Scale, Overt Aggression Scale, and Severity Scale. We performed descriptive analyses, bivariable analyses, and logistic regression modeling of factors with relation to sedative/restraint use. We observed 95 agitation events on unique patients over 2 months. **RESULTS/ANTICIPATED RESULTS:** Median age was 42, and 62.1% were male. Most frequent chief complaints were alcohol/drug use (37.9%) and psychiatric (23.2%). Majority of events (73.7%) were associated with sedative/restraint use. Factors related to treatment course or staff interactions were the primary reasons for agitation in 56.8% of events. A logistic regression model found no association between demographics and odds of sedative/restraint use. Overt Aggression Scale scores were associated with significantly higher odds of sedative use (AOR 1.62 [1.13–2.32]), while Severity Scale scores had significantly higher odds of restraint use (AOR 1.39 [1.12–1.73]) but significantly lower odds of sedative use (AOR 0.79 [0.64–0.98]). **DISCUSSION/SIGNIFICANCE OF IMPACT:** External factors may be important targets for behavioral techniques in ED agitation management. Further study of the Severity Scale may allow for earlier detection of agitation and identify causal links between agitation severity and use of sedatives and restraints.

4573

Characterization of vascular disease in an Acta2 mutant mouse model

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OBJECTIVES/GOALS: ACTA2 R179 carriers present with early-onset stroke; occlusive lesions of the distal internal carotid artery and branches are filled with cells staining positive for smooth muscle cell (SMC) markers. We will identify pathways leading to increased SMC proliferation and migration and thus occlusion. **METHODS/STUDY POPULATION:** We generated an *Acta2*^{SMC-R179C/+} mouse model, which expresses the *Acta2* R179C mutation in SMCs via the SM22a-Cre-Lox system. rt-PCR performed in aortic tissue confirms the presence of the mutation in the mutant mice and absence in mice with only the floxed allele (WT). We will determine phenotypic differences between mutant and WT brains using micro CT, vascular casting, histology, and immunostaining. We will characterize mutant SMC phenotype in culture by assessing expression of contractile genes and stem cell markers, proliferation, and migration. Single cell RNA (scRNA) sequencing of the brain will assess differential gene expression and cell populations between mutant and WT mice. **RESULTS/ANTICIPATED RESULTS:** Mutant mice have decreased blood pressure compared to WT mice from 8–24 weeks old, consistent with the phenotype seen in ACTA2 R179 patients. We expect to see occluded and straighter cerebrovascular arteries and white matter changes in the *Acta2*^{SMC-R179C/+} mice. iPSC-derived SMCs from patients show de-differentiation, continued expression of stem cell markers, and increased proliferation and migration. We expect to see a similar phenotype in *Acta2*^{SMC-R179C/+} mouse SMCs in culture. Via scRNA sequencing, we expect to see altered transcriptional profiles in mutant mice brains including upregulated proliferative pathways in SMCs, glial cell activation, and gene expression changes in neurons. **DISCUSSION/SIGNIFICANCE OF IMPACT:** These

studies will contribute important information on the pathogenesis of the cerebrovascular disease in *ACTA2* R179 patients. These results may aid in identifying treatments to prevent or decrease risk of developing strokes in those with known predisposition to cerebrovascular occlusive disease.

4441

Comparing 3 methods of assessment of psoas area as a proxy for sarcopenia in predicting short-term outcomes in trauma patients 55 years and older

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OBJECTIVES/GOALS: **Specific Aim 1** To examine sex distribution of psoas cross sectional area (CSA) on CT imaging in a cohort of trauma patients age 55 and older. We will use three methods of assessing psoas CSA: psoas CSA averaged between left and right, average psoas CSA adjusted for height, and average psoas CSA adjusted for body surface area (psoas index). **Specific Aim 2** Use multivariable logistic regression prediction modeling to compare the 3 methods of CT psoas muscle measurement widely used in the literature in their ability to predict a composite of in-hospital morbidity and mortality in trauma patients ages 55 and older. **METHODS/STUDY POPULATION:** The Maine Medical Center Trauma Registry is maintained by the Trauma Surgery Service at Maine Medical Center in Portland, Maine, the only Level-1 trauma center in the state. After receiving approval from the Institutional Review Board of Maine Medical Center for this retrospective cohort study, we queried the Maine Medical Center Trauma Registry for all adults 55 years and older who underwent evaluation by the Trauma Service between January 1, 2015 and January 1, 2019. In the case of multiple admissions within the study time period, only a patient's index admission was used. MaineHealth IMPACS imaging software was used to measure bilateral psoas CSA on each patient CT. The Maine Medical Center electronic medical record was queried for additional clinical information including the ICD codes associated with each patient encounter. Data analysis was performed using R statistical software (R project, Vienna, Austria). Data is reported as median + IQR for CSA measurements. The agreement between the three methods of quantifying psoas CSA was evaluated using Pearson correlation (R package "stats"). Inter-rater reliability of psoas muscle measurements was evaluated using intra-class correlation (R package "irr"). Prediction models for the composite outcome of in-hospital morbidity and mortality were constructed using multivariable logistic regression. Bootstrapping was used for internal validation and shrinkage to avoid overfitting. Models including psoas CSA were compared to a baseline model without psoas CSA to evaluate incremental added predictive ability. **RESULTS/ANTICIPATED RESULTS:** This cohort provides a basis for examining the population distribution of psoas CSA in adults 55 years and older. IN addition to a high level of agreement between the three methods of measuring psoas CSA (Spearman coefficient > 0.9), there was also high level of inter rater reliability in psoas muscle assessment (intraclass correlation 0.9). We anticipate that psoas CSA adjusted for body surface area will add the most incremental predictive ability to a model predicting in-hospital morbidity and mortality.

DISCUSSION/SIGNIFICANCE OF IMPACT: Given the heterogeneity of health status amongst elderly trauma patients, a major challenge lies in the rapid objective identification of those elderly trauma patients who are frail. Due to the limitations in current frailty measures, there has been a surge of interest in surrogate markers of frailty, such as muscle mass, as predictive factors of poor outcomes after trauma. Several studies have found that sarcopenia is associated with post injury morbidity and mortality. Estimates of the prevalence of sarcopenia among trauma patients vary across studies due to differences in definition and sample characteristics. In order to appropriately categorize patients as sarcopenic, the population distribution of psoas CSA on CT must be established. The psoas measurement that best correlates with outcomes has yet to be determined, and it is unclear which measurement should be implemented in usual practice. Our main objective is to improve the outcomes of sarcopenic patients hospitalized with trauma by implementing in the future patient-centered interventions which will account for sarcopenia.

4465

Comparing Children's Physical Activity Accumulation Between a Nature-Based and Traditional Pre-K School Setting

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OBJECTIVES/GOALS: The primary aim of this observational study was to explore minute by minute differences in children's in-school PA accumulation while attending a nature-based compared to a traditional Pre-K program. **METHODS/STUDY POPULATION:** Participants from a single Pre-K program wore an accelerometer at the waist during school for two consecutive weekdays in the winter, chosen for consistent weather conditions. In this program, one day was spent at a nature-based site, and one day at a traditional classroom location. Accelerometer data was analyzed using Butte (2014) vector magnitude activity thresholds summed by minute across each day. Paired-sample t-tests were applied on a minute-by-minute basis at a significance of $p < 0.001$ to determine the point(s) at which PA accumulation diverged between settings. Direct observation (DO) conducted by a trained researcher also documented activities children engaged in each school day. **RESULTS/ANTICIPATED RESULTS:** In-school PA differed significantly between settings beginning at minute 37 of classroom time. Based on results obtained through DO, this coincided with the end of unstructured free play time and the start of structured activities across both days. In a traditional classroom setting, structured activities included classroom-based learning, while the nature-based setting incorporated a 10-minute outdoor walk prior to the start of classroom learning. This walking period altered the trajectory of total in-school PA accumulation between program locations, with participants maintaining a significantly greater PA accumulation while in a nature-based setting through the end of the school period. **DISCUSSION/SIGNIFICANCE OF IMPACT:** Compared to a traditional setting, nature-based programs allow for more active structured periods in school. A 10-minute teacher-led walk can significantly improve the trajectory of children's PA accumulation throughout the remainder of a school day.