Long-Term Daily Activity is Associated with Exercise Capacity and Quality of Life in Pulmonary Arterial Hypertension

Andrew Hughes, Jeffrey Annis, Anna Hemnes, Alisha Lindsey, Kelly Burke, Evelyn Horn, Evan Brittain, and the PVDOMICS Study Group

Introduction: Reduced functional capacity is a hallmark of pulmonary arterial hypertension (PAH). Six minute walk distance (6MWD) is a common measure of functional capacity. Unlike the 6MWD, daily activity monitoring integrates behavioral aspects of physical capacity. We hypothesized that daily activity is associated with 6MWD and quality of life (QOL) in patients with PAH.

Methods: This study included patients with PAH from the NHLBI-funded Pulmonary Vascular Disease Phenomics (PVDOMICS) study. PVDOMICS collected 6MWD and QOL surveys (Minnesota Living with Heart Failure [MLHF] and Short Form-36 [SF-36]) data. Daily activity was measured using Fitbit devices which participants wore continuously for 12 weeks. Daily activity was expressed as average daily steps and graded intensity.

Results: We enrolled 45 patients with PAH (age, 48.1 $\pm$ 13.4 years) with median daily steps of 4146 (IQR: 2682-6977). Sedentary, fairly active, and very active minutes/day were 850 (IQR: 774-1093), 5.0 (IQR 2.0-7.6), and 2.1 (IQR 0.7-7.3). The median time between 6MWD and the start of daily activity monitoring was 32 days (IQR 11-53). Average daily steps correlated with 6MWD ($r = 0.70$, $p<0.001$), MLHF total score ($r = - 0.46$, $p=0.002$), MLHF physical and emotional domains, and the SF-36 physical component score. Among hemodynamic measures, average steps and fairly active minutes were most strongly associated with PA compliance ($r=0.46$ and $r=0.64$; both $p<0.05$). In contrast, 6MWD only correlated with the SF 36 physical component but no MLHF measures.

Conclusions: In a geographically diverse PAH cohort, long-term daily step counts are associated with exercise capacity and QOL. Daily activity measures capture behavioral information not captured by the 6MWD and correlated with prognostic hemodynamic measures. Daily activity monitoring and 6MWD represent complementary measures for the assessment of functional capacity in patients with PAH.

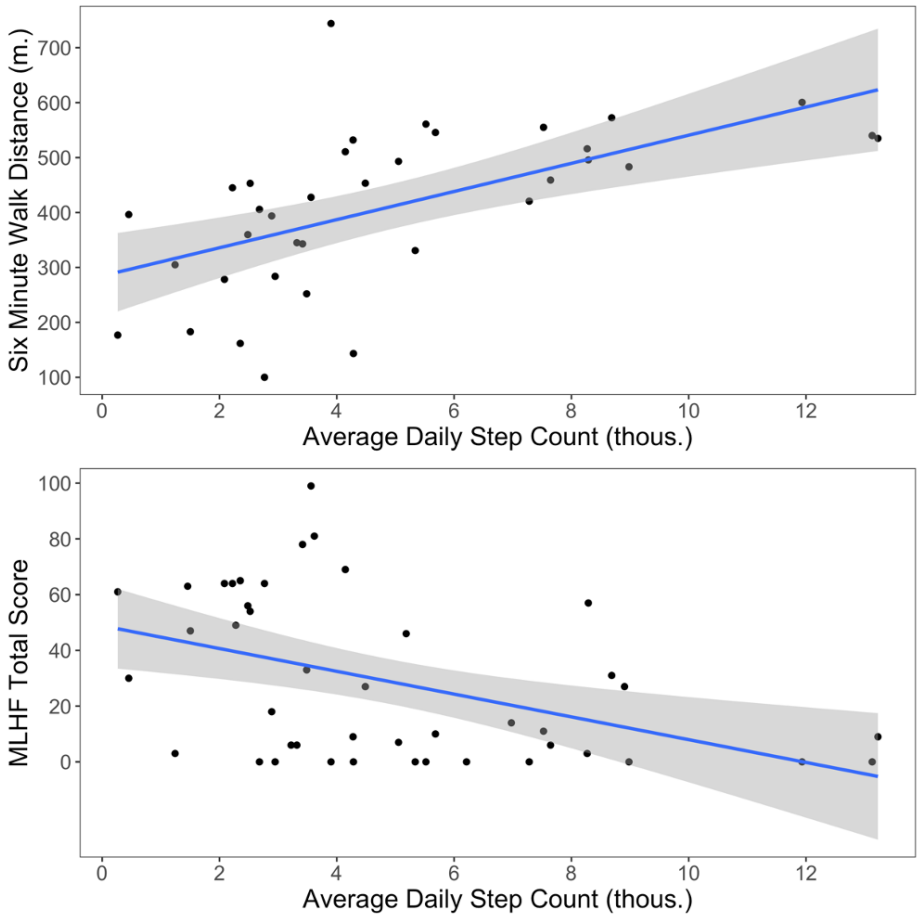

Figure 1: Correlation plot for average daily steps and 6MWD (top) and correlation plot for average daily steps and MLHF total score (bottom).

LONG-TERM DAILY ACTIVITY IS ASSOCIATED WITH EXERCISE CAPACITY AND QUALITY OF LIFE IN PULMONARY ARTERIAL HYPERTENSION

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INTRODUCTION

- Reduced functional capacity is a hallmark of pulmonary arterial hypertension (PAH).
- Six minute walk distance (6MWD) is the most commonly used method for assessing functional capacity and a ubiquitous endpoint in PAH clinical trials.
- Unlike the 6MWD, daily activity integrates physical, environmental, and behavioral inputs of functional capacity.
- Daily activity can be easily assessed with commercial wearable devices such as Fitbit or Apple Smartwatches.

HYPOTHESIS

- We hypothesized that daily activity was associated with 6MWD and Quality of Life (QOL) in patients with PAH.

METHODS

- The cohort was comprised of 45 patients with PAH from the NHLBI-funded Longitudinal Pulmonary Vascular Disease Phenomics (L-PVDOMICS) study.
- Daily activity was measured using Fitbit Charge 3 Activity Trackers, which patients wore continuously for 12 weeks.
- Activity measurements included: average daily steps and minutes of graded intensity (i.e. daily sedentary, fairly active, and very active minutes).
- QOL measures were assessed with the Minnesota Living with Heart Failure (MLHF) and Short-Form-36 (SF-36) surveys.
- Associations between activity, quality of life, and hemodynamic measures were analyzed with the Spearman's rank correlation test.

RESULTS

Table 1: Clinical Characteristics of Study Population

	Study Cohort (n=45)
Baseline Characteristics	
Age (years)	48.1 ± 13.4
BMI (kg/m^2)	30.8 (24.1 – 36.8)
PAH Etiology	
Idiopathic PAH	48.9% (22/45)
Connective Tissue Disease	20.0% (9/45)
Congenital Heart Disease	11.1% (5/45)
Familial PAH	11.1% (5/45)
Other	8.9% (4/45)
NYHA Functional Class (n=44)	
Class I	15.9% (7/44)
Class II	63.6% (28/44)
Class III	20.5% (9/44)
6 Minute Walk Distance (m)	436.3 (324.2 – 520.0)
Daily Activity Measurements	
Daily Step Count	4146 (2682 – 6977)
Daily Sedentary Minutes	849.9 (774.0 – 1092.6)
Daily Lightly Active Minutes	170.7 (140.3 – 213.4)
Daily Fairly Active Minutes	5.0 (2.0 – 7.6)
Daily Very Active Minutes	2.1 (0.7 – 7.3)
Quality of Life Measures	
MLHF Total Score	16.0 (2.3 – 56.3)
MLHF Physical	6.5 (0 – 26.3)
MLHF Emotional	3.0 (0 – 11.0)
SF-36 Physical	43.5 (31.0 – 51.2)
SF-36 Mental	52.8 (46.0-56.5)
Right Heart Catheterization Values	
Mean PA Pressure (mmHg)	38.5 (30.0 – 50.0)
PVR	4.6 (3.2 – 6.9)
PA Compliance	2.2 (1.4 – 3.3)

Table 2: Correlations between Activity, Quality of Life, and Hemodynamic Measures

	Spearman's rank correlation (r)	P value
Average Daily Step Correlations		
6 Minute Walk Distance	0.70	**< 0.001**
MLHF Total Score	- 0.46	**0.002**
MLHF Physical	- 0.43	**0.003**
MLHF Emotional	- 0.38	**0.01**
SF-36 Physical	0.50	**< 0.001**
SF-36 Mental	0.08	0.58
Mean PA Pressure	- 0.16	0.40
PVR	- 0.20	0.29
PA Compliance	0.46	**0.01**
Activity Intensity Correlations: Daily Very Active Minutes		
6 Minute Walk Distance	0.64	**< 0.001**
MLHF Total Score	-0.42	**0.005**
MLHF Physical	-0.40	**0.006**
MLHF Emotional	-0.35	**0.02**
SF-36 Physical	0.37	**0.01**
SF-36 Mental	0.06	0.67
6 Minute Walk Distance Correlations		
MLHF Total Score	- 0.31	0.07
MLHF Physical	- 0.31	0.06
MLHF Emotional	- 0.19	0.27
SF-36 Physical	0.52	**0.001**
SF-36 Mental	0.11	0.53

Abbreviations: Pulmonary Artery (PA), Pulmonary Vascular Resistance (PVR).

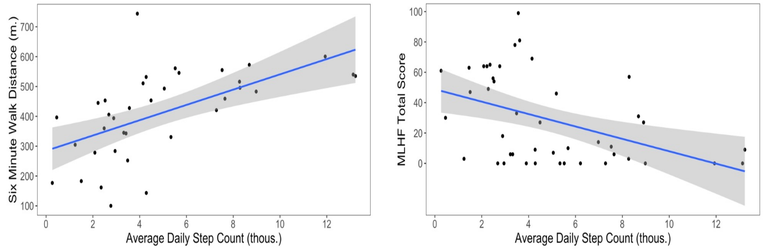
Minnesota Living with Heart Failure [MLHF]: higher scores indicate greater impairment.

Short Form-36 [SF-36]: Lower scores indicate greater impairment.

- The median time between 6MWD and the start of daily activity monitoring was 32 days (IQR 11-53).
- Average daily steps and very active minutes per day correlated with 6MWD, all MLHF measures, and the SF-36 physical component. In contrast, the 6MWD only correlated with the SF-36 physical component, but no MLHF measures.
- Daily sedentary and fairly active minutes were not associated with any QOL measures.

RESULTS (CONTINUED)

Figure 1: Correlation plot for average daily steps and 6MWD (left) and correlation plot for average daily steps and MLHF total score (right).



CONCLUSIONS

- In a geographically diverse PAH cohort, long-term daily step counts were associated with exercise capacity and QOL.
- Daily activity measurements reflect information not captured by 6MWD.

CLINICAL IMPLICATIONS

- Daily activity monitoring and 6MWD represent complementary measures for the assessment of functional capacity in patients with PAH.

FUTURE DIRECTIONS

- We will obtain longitudinal activity measurements over three years to investigate associations with all-cause mortality, PAH-related hospitalizations, and QOL.

DISCLOSURES

- Funding sources include: United Therapeutics (investigator initiated grant); NHBLI R61 HL 158941; FDA R01 FD 007627

Time-Driven Activity Based Costing Analysis of Fluorescein Angiography

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Meeting presentation: This data have been submitted for consideration at *** ARVO/ASRS

Source of Funding: Supported in part by a Research to Prevent Blindness unrestricted grant to the Vanderbilt Eye Institute. The sponsor or funding organization had no role in the design or conduct of this research.

Conflicts of Interest Statement: No conflicting relationship exists for any author

Running Head: TDABC of FA

Keywords: Retina, Imaging, Fluorescein Angiography, Cost

Purpose: To use electronic health record (EHR) time logs and Time-Driven Activity Based Costing (TDABC) to calculate the complete cost profile of office-based fluorescein angiography (FA).

Design: Economic analysis.

Subjects: Patients undergoing routine FA (CPT 92235) at Vanderbilt Eye Institute in Fiscal year 2022

Methods: Process flow mapping for routine FA was used to define the care episode. De-identified time logs were sourced from the EHR and manually validated to calculate durations for each stage. The cost of materials was calculated from internal financial figures. Cost per minute for space, equipment, and personnel were based on internal figures. Published fluorescein costs were used for base case analysis with scenario analysis based on a range of internal figures from pharmacy quotes. These inputs were used for a Time-Driven Activity Based Costing (TDABC) analysis.

Main Outcome Measures: TDABC cost of fluorescein angiography episode of care. Secondary scenario analyses focus on break even scenarios for key inputs including medication costs

Results: Cost analysis of office-based fluorescein angiography resulted in an average total cost of $116.35 (nominal) per interpreted image per patient, which was close to - $0.08 more than the maximum Medicare reimbursement for CPT 92235 in Mac Locality for Tennessee 10312 for FY 2022, $116.43 ($76.11 technical component and $40.33 physician component). The low contribution margin is driven primarily by the increased cost of fluorescein which comprises 42.2% of the episode. Recent price changes in fluorescein have outpaced inflation and do not necessarily correspond with reimbursement changes.

Conclusions: The current analysis here shows that the recently increased cost of fluorescein has driven up the cost of office-based fluorescein angiography relative to the current maximum allowable Medicare reimbursement leading to minimal contribution margin. Given conservative cost estimates here, it is unlikely for profitability to be achieved without changes in the cost of fluorescein or increased reimbursement. These results may be informative for policy discussion regarding appropriate reimbursement for codes using injectable fluorescein.

Title: Congruence Between ICD-10 Code and Written Documentation for Outpatient Encounters with Antibiotic Prescriptions

Authors: Charles Oertli, Milner Staub, and Sophie Katz

Objective: Antimicrobial stewardship programs (ASPs) often rely on *International Classification of Diseases, Tenth Revision* (ICD-10) codes to assess antibiotic appropriateness for provider feedback. Concordance between encounter ICD-10 codes and documented indication for antibiotics based on manual chart review varies greatly (74-95%) in the inpatient setting. Data on concordance between documented indication and ICD-10 code in the outpatient setting are scarce.

Study Design: Retrospective cohort study of 650 randomly selected outpatient encounters with antibiotic prescriptions from walk-in and retail clinics between July 15 to September 15, 2021, at Vanderbilt University Medical Center. We performed chart review to compare documented antibiotic indication to the top three encounter-associated ICD-10 codes. Twelve encounters were excluded due to insufficient available written documentation. The 95% confidence interval (CI) for proportion of encounters with concordant antibiotic indications was calculated using Stata version 15.1.

Results: Of the 638 antibiotic prescriptions with written documentation available for chart review, 204 (32%) were for amoxicillin, 102 (16%) amoxicillin/clavulanate, 61 (10%) cefdinir, and 56 (9%) azithromycin. We found that 84.6% (540/638; 95% CI 81.6% to 87.4%)) of encounters had concordant antibiotic indication based on documentation in the note and associated ICD-10 for the encounter. Of the encounters with concordant ICD-10 and documented indications, 64% (348/540), 24% (130/540), and 6% (35/540) were listed as the first, second, and third ICD-10 code respectively. An additional 5% (27/540) had a concordant ICD-10 code listed beyond the third position. A total of 125/638 (19.6%) encounters did not have the intended antibiotic indication as documented in the note in the top 3 associated encounter ICD-10 codes (whether a lower position or incongruent ICD-10 code with documentation). Of those encounters, 42/125 (34%) had a documented diagnosis of strep pharyngitis, 16/125 (13%) skin or soft tissue infection, 11/125 (9%) urinary tract infection, and 11/125 (9%) acute otitis media.

Conclusions: Our data suggest that outpatient antimicrobial prescriptions correlate relatively well with encounter ICD-10 codes. However, most ASP prescribing goals aim to reduce inappropriate prescribing to 10% or less of prescriptions based on indication. Therefore, providers may not trust individual prescribing feedback that is based on data that is only correct 85% of the time. For ASPs to accurately assess prescribing and provide trusted, meaningful recommendations and specific feedback to individual prescribers, more reliable and valid data are needed. We intend to evaluate whether requiring outpatient antibiotic indications on prescriptions increases data reliability and validity.

Using a QR Code to Connect Families to Food Resources – A Novel Tool for Addressing Food Insecurity in the Pediatric Emergency Department

Britta Roach, DO[1]; Ivory Shelton, MD[2]; Julia Bielanin[3]; Cristin Q. Fritz MD, MPH[2]; Holly Hanson MD, MS[1,2]

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Background

During the Covid-19 pandemic, food insecurity (FI) tripled in households with children. FI has been linked to poor health outcomes such as obesity, asthma, and depression, and increased rates of pediatric emergency department (PED) use. While connection to food resources can improve health outcomes, answering FI screening questions may invoke stigma among families who prefer anonymity. Additionally, the implementation of routine FI screening in the PED is challenging due to time constraints. Yet, the frequency that families will utilize anonymous, universal resources is unknown.

Objective

The aim of this study was to pilot and assess the use of universal resource provision in the PED through a poster with an anonymous and independently accessed Quick Response (QR) code.

Design/Method

Using https://www.qr-code-generator.com, a QR code was created to allow any user with a smartphone camera to access the website: ineedfoodnow.org. Created and trademarked by affiliates of Vanderbilt University, the website contains downloadable food resource packets in multiple languages, healthy food tips and videos, and additional website links to Aunt Bertha, Supplemental Nutritional Assistance Program (SNAP), and Women, Infants, and Children (WIC). The QR code was placed on food resource posters with information in English, Spanish, and Arabic. On December 28, 2021, fifty posters were displayed in triage, patient rooms, and shared bathrooms throughout the PED, which has an annual volume of approximately 50,000 visits. From January 1, 2022 to December 14, 2022, the number of unique scans per day and time of unique scans were tracked. Daily PED volumes were also recorded. We used descriptive statistics to characterize included variables.

Results

During the data collection period, there were 447 unique scans, with 0.84 scans per 100 patient encounters. The median number of scans per day was 1.0 (range 0-7 scans). Most scans occurred during midday (1601-2200, n=142) and evening (2201-0400, n=168).

Conclusions

This pilot demonstrates that the novel approach of universal resource provision through a poster containing an anonymous and independently accessed QR code is a viable method for providing food resources to families. Future focus groups with families with FI will provide insight

into acceptability of this approach as well as family's preferred method(s) of receiving food resource information in the PED.

Using a QR Code to Connect Families to Food Resources – A Novel Tool for Addressing Food Insecurity in the Pediatric Emergency Department

Britta Roach, DO[1]; Ivory Shelton, MD[2]; Julia Belanin[3]; Cristin Q. Fritz, MD, MPH[2]; Holly Hanson, MD, MS[1,2]
Departments of [1]Pediatric Emergency Medicine, [2]Pediatrics, and the [3] Vanderbilt University School of Medicine, Nashville, TN

Background

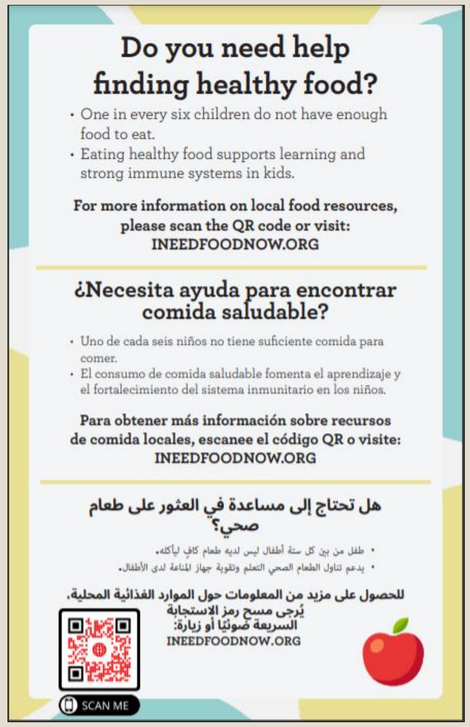
- During the Covid-19 pandemic, food insecurity (FI) tripled in households with children.
- FI has been linked to poor health outcomes and increased rates of pediatric emergency department (ED) use.
- Answering FI screening questions may invoke stigma among families who prefer anonymity.
- Additionally, the implementation of routine FI screening in the PED is challenging due to time constraints.
- Yet, the frequency that families will utilize anonymous, universal resources is unknown.

Study Aims

The aim of this study was to pilot and assess the use of universal resource provision in the PED through a poster with an anonymous and independently accessed Quick Response (QR) code.

Methods

From 01/01/22-12/14/22, 50 posters were displayed throughout the PED. Scans were tracked via an external website. Using descriptive statistics, QR scans were counted and analyzed by time of day and PED volume.



Results

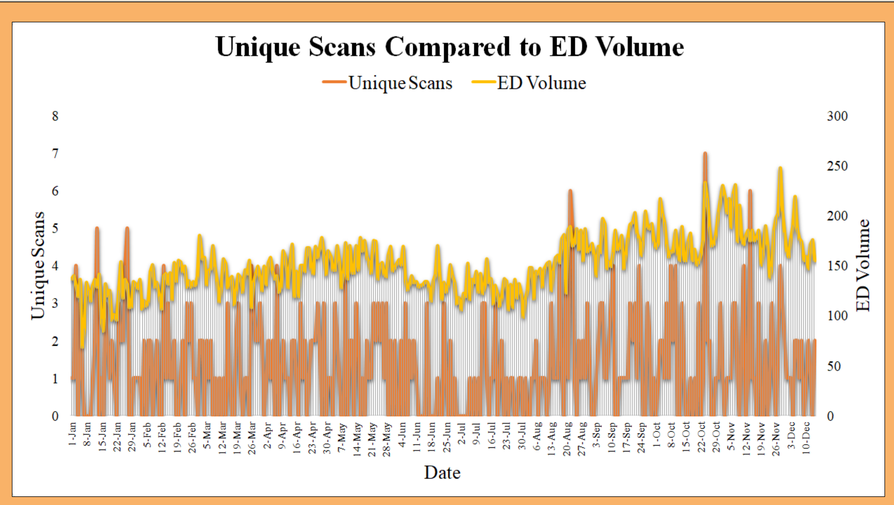


Figure 1: This run chart presents ED volume by date as compared to number of unique scans recorded. There were 447 unique scans, with 0.84 scans per 100 patient encounters.The median number of scans per day was 1.0 (range 0-7 scans).

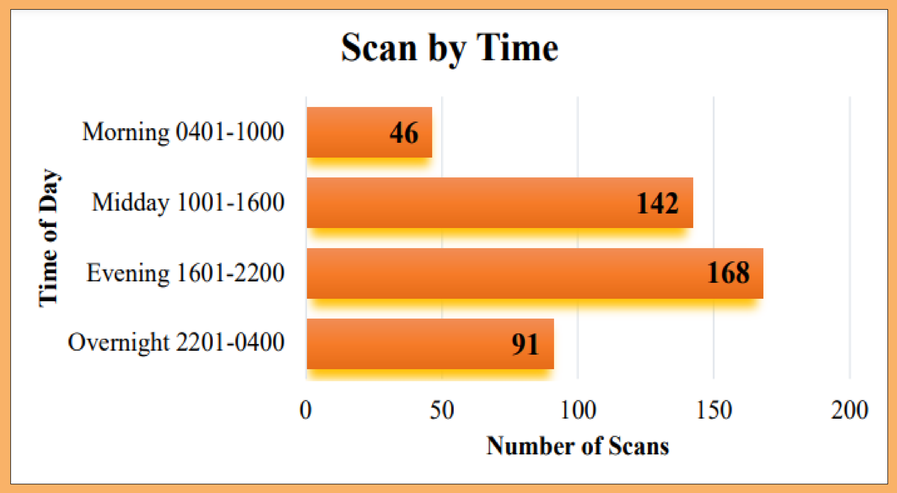


Figure 2: This histogram presents number of unique scans by time of day, grouped by 6 hour increments. Most scans occurred during midday (10:01-1600, n=142) and evening (16:01-22:00, n=168).

Conclusions

This novel approach of an anonymous and independently accessed QR code on a poster is a viable method for providing food resources to families.

Limitations

- Descriptive statistics represent summations but are not able to support inferences regarding the patient population in question.
- Due to anonymity, there is no direct feedback from families on acceptability of this approach or accessibility of resources.

Next Steps

Future focus groups with families with FI will provide insight into acceptability of this approach as well as family's preferred method(s) of receiving food resource information in the PED.

The authors of this poster have no disclosures. We would like to thank the Family Resource Center for helping to develop and print the posters.

Impact of 3D-Printed Model on Shared Decision Making, Education, and Anxiety in Patients undergoing Colorectal Surgery. The SEAD Cluster Randomized Trial.

Georgina Sellyn MA, Zoryas Moazzam, Hillary Samaras, Shannon McChesney MD, Michael Hopkins MD, Roberta Muldoon MD, Alexander Hawkins MD, Aimal Khan MD FACS

Introduction

Patients undergoing abdominal colorectal surgery often face anxiety due to poor understanding of their disease alongside the myriad of treatment options available. We hypothesized that patients taught preoperatively using 3D-printed models will demonstrate improved understanding of their surgery, experience lower anxiety levels, and perceive higher levels of involvement in their healthcare.

Methods

We conducted a randomized trial in sequential patients 18 years or older undergoing abdominal colorectal surgery. Six colorectal surgeons and 36 patients participated in this study from March to September 2022. Surgeons were cluster randomized to teach their patients about their medical condition and upcoming surgery using either the "3D-printed model" or "standard of care". The 3D-printed model had a modular design that allowed for removal and reattachment of bowel segments using magnets, as well as a stoma marking on the abdominal wall (figure1a). Patient anxiety and understanding of their disease with intended surgery were assessed before and after the clinic visit using the State-Trait Anxiety Inventory (STAI-6) and an Education Questionnaire respectively. The Education Questionnaire consisted of 8 items intended to assess patient understanding of their disease and surgery. Patient involvement in decision-making was measured using the Shared Decision-Making Questionnaire (SDM-9). McNemar Change Test was used to assess improvement in patient education in each arm, while ANCOVA tests were utilized to compare STAI-6 and SDM-9 scores after surgical consultation.

Results

The mean age of enrolled patients was 50.5 years (SD 15.7), with 63% being women. Patients taught using 3D-models felt more engaged in decision making compared to patients taught using standard of care (SDM-9 Score 3D-model score 91.4 vs standard of care score 83.9, $p<0.05$) (Figure1b). Additionally, patients taught using 3D-models were found to have a statistically significant improvement in their anxiety scores from baseline compared to patients taught with standard of care (STAI 3D-model score 48.6 to 47.1 vs. standard of care score 47.2 to 49.2, $p<0.05$) (Figure1c). Patients in both arms demonstrated improvement in their understanding of the disease and type of surgery without any significant difference between the two groups ($P\geq0.05$).

Conclusion

For patients undergoing major abdominal colorectal surgery, using 3D-models at the time of preoperative clinic visit results in lower patient anxiety levels and improved perception of involvement in their healthcare. Though a significant improvement was noted in patient understanding of their disease and intended surgery, it was equal to the improvement noted for patients taught using “standard of care”.

IMPACT OF 3D-PRINTED MODEL ON SHARED DECISION MAKING, EDUCATION, AND ANXIETY IN PATIENTS UNDERGOING COLORECTAL SURGERY: THE SEAD CLUSTER RANDOMIZED TRIAL

Georgina Sellyn MA, Zoryas Moazzam, Hillary Samaras, Shannon McChesney MD, Michael Hopkins MD, Roberta Muldoon MD, Alexander Hawkins MD, Aimal Khan MD FACS

VANDERBILT UNIVERSITY MEDICAL CENTER

INTRODUCTION

- Patients undergoing abdominal colorectal surgery often face anxiety which can be due to poor understanding of their disease and the myriad of available treatments
- We hypothesized that **patients taught preoperatively using 3D-printed models** will demonstrate **improved understanding of their surgery**, experience **lower anxiety levels**, and **perceive higher levels of involvement** in their healthcare

- **Randomized trial** in patients >18 years undergoing abdominal **colon or rectal surgery**
- **Six colorectal surgeons** and **36 patients** participated in this study from March to September 2022
- **Surgeons cluster randomized** to teach patients using either the "**3D-printed model**" or "**standard of care**"
- 3D-printed model allowed for **removal and reattachment of bowel segments using magnets** and had a **stoma marking** (Figure 1a)
- Patient anxiety and understanding was assessed before and after the clinic appointment, using the State-Trait Anxiety Inventory (**STAI-6**) and an **Education Questionnaire,** respectively
- Patient **involvement in decision-making** was measured using the **Shared Decision-Making Questionnaire (SDM-9)**

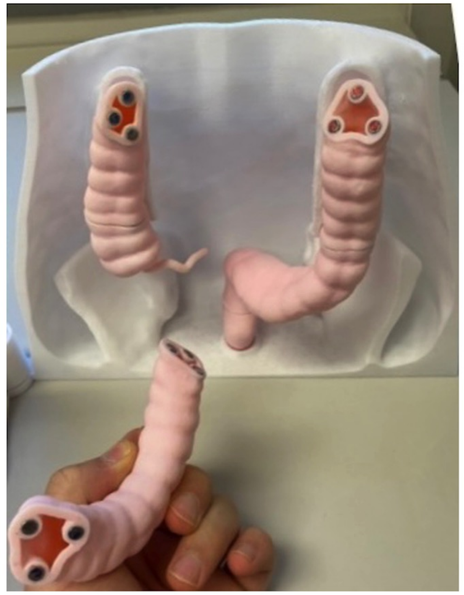


Figure 1a: The 3D-printed model.

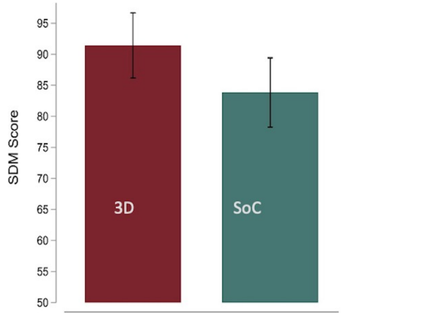


Figure 1b: Impact of 3D-printed model on Shared Decision Making.
3D= 3D-Model arm, SoC=Standard of Care arm

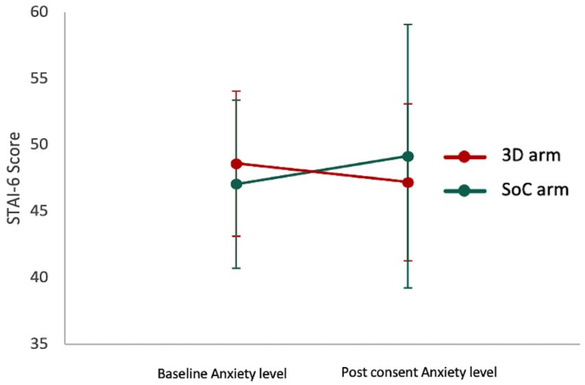


Figure 1c: Impact of 3D-printed model on patient anxiety level.
3D= 3D-Model arm, SoC=Standard of Care arm

- **Mean age** was **50.5 years** (SD 15.7), with **63% women**
- Patients taught using 3D-models felt **more engaged in decision making** compared to patients taught using standard of care (SDM-9 Score 3D-model score 91.4 vs standard of care score 83.9, $p<0.05$) (Figure1b)
- Patients taught using 3D-models were found to have a statistically significant **improvement in their anxiety scores** from baseline compared to patients taught using standard of care (STAI 3D-model score 48.6 to 47.1 vs. standard of care score 47.2 to 49.2, $p<0.05$) (Figure1c)
- Patients in **both arms** demonstrated **improvement in their understanding** of the disease and type of surgery without any significant difference between the two groups ($P>0.05$)

- For patients undergoing major abdominal colorectal surgery, using 3D-models at the time of preoperative clinic visit results in **lower patient anxiety levels and improved perception of involvement in their healthcare**
- Though significant improvement was noted in patient understanding of their disease and intended surgery, it was equal to the improvement noted for patients taught using "standard of care"

Primary Intestinal Angiosarcomas: Incidence, Survival Analysis, and Management: A Study from the SEER Database and Insights into Future Therapeutic Perspectives

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ABSTRACT:

Introduction: Tumors of the gastrointestinal tract originating from the endothelium are relatively rare. One of the most uncommon cancers in the digestive system, primary intestinal angiosarcoma (PIA) accounts for fewer than 1% of all gastrointestinal (GI) malignancies, including sarcomas. Approximately 0.001 % of all colorectal malignancies are angiosarcomas. Most of the information on this rare cancer comes from a small number of case reports; to our knowledge, only 17 cases of colonic angiosarcoma have been documented. The current study is the largest retrospective cohort explaining demographical, clinical, histological, and survival variables on this rare topic.

Methods: Demographic and clinical data were abstracted on 51 patients with PIA from the SEER research plus database (2000 – 2017). Data was described as numbers and percentages.

Results: A total of 51 cases of PIA were identified, comprising 32 male patients and 19 female patients. Most of the patients (n= 41) were diagnosed after the 6th decade of life and belonged to Caucasian ethnicity (n= 38). The most common primary tumor sites were the small intestine (n= 32), rectum (n= 7), large intestine, NOS (n= 4), sigmoid colon (n= 3), cecum (n= 2), appendix (n= 1), transverse colon (n= 1), and descending colon (n=1). Grading information was not available in most of the cases (n=25), but when the data was available, most of the PIA tumors were of grade 3 (poorly differentiated; n= 13), followed by grade 4 (undifferentiated/anaplastic; n= 12), and grade 1 (well-differentiated; n= 1). When histological information was available, all the tumors were hemangiosarcoma (n=51), while most of the PIA had distant spread (n= 16), followed by regional spread (n= 14), localized (n=11), and unknown stage (n=10). Most of the lymph nodes were not examined pathologically (n=25), while those which were examined had positive nodes (n= 7) and negative (n=18). Also, when the tumor size information was known (n= 38), most of the tumors were > 5cm in size (n= 27), followed ≤ 5 cm (n=11). Primary surgical resection was most common treatment modality (n= 42), followed by chemotherapy in (n=13) patients, and radiation (n= 4 (adjuvant= 4, neoadjuvant =0). Additionally, the lowest 5-year survival was noticed with neoplasm in the small intestine (18.2%), while the highest survival was observed when PIA was in the sigmoid colon and cecum (50%).

Conclusion: Primary intestinal angiosarcomas are extremely rare gastrointestinal tract malignancies that present more often in male Caucasian patients after the sixth decade of life. Primarily located in the small intestine, have a tumor size of >5 cm and presents with a distant

spread at diagnosis. Surgical resection of the tumor is the most common modality used for the treatment, followed by chemotherapy. PIA located in the small intestine has less favorable 5-year survival rates than the other tumors. Although the current study represents the most extensive retrospective data on this rare topic, it is hard to generalize the results due to the small sample size. We strongly recommend that all primary intestinal angiosarcomas patients be enrolled in clinical trials or international registries to better understand the role of more defined multimodality management.

Table 1: Demographical information of 51 Patients with Primary Intestinal Angiosarcomas from the Surveillance, Epidemiology, and End Results (SEER) database 2000-2017

Variable (n=51)		**Frequency (n)**
Age	<60	10
	>60	41
Gender	Female	19
	Male	32
Race	Caucasian	38
	African American	9
	Others	4

Table 2: Location of 51 Patients with Primary Intestinal Angiosarcomas from the Surveillance, Epidemiology, and End Results (SEER) database 2000-2017

Variable (n=51)	**Frequency (n)**
Location	
Small Intestine	32
Rectum	7
Large intestine, NOS	4
Sigmoid colon	3
Cecum	2
Appendix	1
Transverse colon	1
Descending Colon	1

Table 3: Tumor size and grading information of 51 Patients with Primary Intestinal Angiosarcomas from the Surveillance, Epidemiology, and End Results (SEER) database 2000-2017

Variable (n=51)	**Frequency (n)**
Tumor Size (cm)	
Unknown	13
Known	38
Size when known (n =38)	
≤ 5cm	11
>5 cm	27
Grade	
Unknown	25
Known	26
Grade where known (n =26)	

Grade 1: Well- differentiated	1
Grade 3: Poorly differentiated	13
Grade 4: Undifferentiated/anaplastic	12

Table 4: Staging and histological information of 51 Patients with Primary Intestinal Angiosarcomas from the Surveillance, Epidemiology, and End Results (SEER) database 2000-2017

Variable (n=51)	**Frequency (n)**
Stage	
Unknown	10
Known	41
Stage when known (n=41)	
Localized	11
Regional	14
Distant	16

Primary Intestinal Angiosarcomas: Incidence, Survival Analysis, and Management: A Study from the SEER Database and Insights into Future Therapeutic Perspectives

Table 5: Lymph node status and treatment options of 51 Patients with Primary Intestinal Angiosarcomas from the Surveillance, Epidemiology, and End Results (SEER) database 2000-2017

Variable (n=51)	**Frequency (n)**			
Lymph Nodes status				
No nodes were examined (¥)	25			
Nodes negative	18			
Nodes positive	7			
Treatment (overall cohort)	**Surgery**	**Radiation**		**Chemotherapy**
		Adjuvant	**Neoadjuvant**	
	42	4	0	13
Treatment (location)				
Small Intestine	29	3	0	10
Rectum	4	0	0	2
Large intestine, NOS	1	1	0	1
Sigmoid colon	3	0	0	0
Cecum	2	0	0	0
Appendix	1	0	0	0
Transverse colon	1	0	0	0
Descending Colon	1	0	0	0

¥= The assessment of lymph nodes is either clinical only/no lymph nodes are removed and examined/ a "dissection" of a lymph node drainage area is found to contain no lymph nodes at the time of pathologic examination.;

Table 6: Survival data of 51 Patients with Primary Intestinal Angiosarcomas from the Surveillance, Epidemiology, and End Results (SEER) database 2000-2017

Variable (n=51)	**1-year (%)**	**2-year (%)**	**3-year (%)**	**4-year (%)**	**5-year (%)**
Overall Survival without intervention (location)					
Small Intestine	36.4	22.7	18.2	18.2	**18.2**
Rectum	66.7	66.7	66.7	66.7	66.7
Large intestine, NOS	NA	NA	NA	NA	NA
Sigmoid colon	50	50	50	50	**50**
Cecum	50	50	50	50	**50**
Appendix	NA	NA	NA	NA	NA
Transverse colon	NA	NA	NA	NA	NA
Descending Colon	NA	NA	NA	NA	NA

NA: Not available

Table 7: Survival data of 51 Patients with Primary Intestinal Angiosarcomas from the Surveillance, Epidemiology, and End Results (SEER) database 2000-2017

Survival	**Small Intestine (%)**	**Rectum (%)**	**Large intestine, NOS**	**SC (%)**	**Cecum (%)**	**Appendix (%)**	**TC (%)**	**DC (%)**
1-year	40	100	NA	50	50	NA	NA	NA
2-year	25	100	NA	50	50	NA	NA	NA
3-year	20	100	NA	50	50	NA	NA	NA
4-year	20	100	NA	50	50	NA	NA	NA
5-year	20	100	NA	50	50	NA	NA	NA
Radiation								
1-year	NA	NA	NA	NA	NA	NA	NA	NA
2-year	NA	NA	NA	NA	NA	NA	NA	NA
3-year	NA	NA	NA	NA	NA	NA	NA	NA
4-year	NA	NA	NA	NA	NA	NA	NA	NA
5-year	NA	NA	NA	NA	NA	NA	NA	NA
Chemotherapy								
1-year	50	NA	NA	NA	NA	NA	NA	NA
2-year	37.5	NA	NA	NA	NA	NA	NA	NA
3-year	25	NA	NA	NA	NA	NA	NA	NA
4-year	25	NA	NA	NA	NA	NA	NA	NA

5-year	25	NA	NA	NA	NA	NA	NA	NA

SC: Sigmoid colon; TC: Transverse colon; NA: Not available.

“Evaluating New Assays for Bivalirudin Monitoring”

Raghavendran P, Tillman B, Wheeler A, Gailani D

Background: Direct Thrombin Inhibitors (DTIs) are becoming important anticoagulants in pediatric and adult patients. DTIs are monitored with the activated partial thromboplastin time (aPTT) and the activated clotting time (ACT), both complex assays, and performance may be altered by clinical conditions including inflammation, thrombosis, bleeding diathesis and others. More accurate assays for monitoring therapeutic anticoagulation are required for safe use. A clot-based diluted Thrombin Time (dTT) assay and chromogenic anti-IIa assays show preliminary promise in correlating with increasing doses of DTI, but more data is needed on how these assays relate to each other and to the aPTT in diverse patient populations.

Methods: Patients of any age who received bivalirudin between March 2020 and April 2022 were analyzed. Medical records were reviewed demographic data as well as adverse outcomes (bleeding, thrombosis, death) while on the medication. Plasma samples from patients drawn for aPTT standard of care clinic monitoring were analyzed using the chromogenic anti-IIa and dTT assays and were compared to aPTT measurements as well as bivalirudin dosing documented in the medical record.

Results: 32 patients were analyzed, from which 136 samples were tested with the chromogenic assay and 120 with the dTT. All samples also had aPTT tested simultaneously. Correlation between aPTT and the chromogenic and dTT assays was poor (Spearman coefficient 0.56 and 0.62, respectively). There was strong positive correlation between chromogenic and dTT assays when compared against each other (Spearman coefficient of 0.9239). When comparing the assays bivalirudin dose, there was much better correlation between chromogenic and clot-based assays to dose than aPTT to dose (Spearman coefficient of 0.22 for aPTT versus dose, 0.51 for chromogenic assay versus dose, 0.63 for dTT versus dose). When examining median chromogenic anti-IIa and dTT levels correlating to varying aPTT levels (60-70 seconds, 70-80 seconds, 80-90 seconds), there was incremental increase in median for each tier in both assays (median levels were 0.46, 0.53 and 0.59 µg/mL for chromogenic assay; median levels were 0.59, 0.75 and 1.26 µg/mL for dTT).

Conclusion: There is good correlation between the chromogenic and dTT assays as well as poor correlation between those assays and aPTT. There is also better correlation between bivalirudin dose and both the chromogenic and dTT assays compared to aPTT. This indicates newer tests have more stability with different clinical presentations and critical illness across the age spectrum for appropriate medication monitoring. Though more data is needed to assess how certain assay levels relate to clinical outcomes, data shows these newer tests can serve as more reliable monitoring for bivalirudin in adult and pediatric patients with varying clinical presentations.

EVALUATING NEW ASSAYS FOR BIVALIRUDIN MONITORING

PRASHANT RAGHAVENDRAN D.O., BENJAMIN TILLMAN M.D., ALLISON WHEELER M.D. M.S.C.I, DAVID GAILANI M.D.

VANDERBILT UNIVERSITY MEDICAL CENTER

INTRODUCTION

-Direct Thrombin Inhibitors (DTI) are anticoagulants that are used formultiple scenarios.

-DTIs are traditionally monitored with a activated partial thromboplastin time (aPTT) and activated clotting time (ACT)

-Varying degrees of illness cause interpatient variability in these assays

-Chromogenic anti-factor IIa and diluted thrombin time (dTT) measurements provide alternative means for assessing DTI effect

OBJECTIVE

To compare newer drug concentration assays to the currently used aPTT assay, and to determine if results from the newer assays more closely mirror bivalirudin doses in varying clinical situations.

METHODS

-Patients who received bivalirudin between March 2020 and April 2022 were retrospectively identified

-Data collection included patient demographics, indication for medicine use, hemoglobin, platelet count, renal and hepatic function

-Plasma from samples drawn for aPTT monitoring were assessed with chromogenic factor IIa (Biophen DTI) and clot-based dTT (Hemoclot Thrombin Inhibitor) assays designed to establish plasma bivalirudin concentration. Results were compared to aPTT values using linear regression.

-Medical records were reviewed for bleeding and thrombotic events

RESULTS

-**Study Cohort**: 32 patients, 3 less than 18 years old (1 less than 1 year old)

-26 patients on anticoagulation for venous (n=19) or arterial (n=2) thrombi

-9 patients on bivalirudin for Heparin-Induced Thrombocytopenia (HIT) and another 11 for suspected HIT

-4 patients on Extracorporeal Membranous Oxygenation (ECMO) support, 3 with Ventricular Assist Device (VAD) in place

-**Samples tested**: 136 anti-IIa chromogenic assay, 120 dTT assay

-The correlation between aPTT and the chromogenic and dTT assays was poor (Figures 1 and 2)

-Positive linear correlation between the chromogenic and clot-based assays (Figure 3)

-Positive correlation between chromogenic and dTT assay values with bivalirudin dose (Figures 5 and 6) compared to aPTT and dose (Figure 4)

-Examined median chromogenic anti-IIa and dTT levels correlating to varying aPTT levels (60-70 seconds, 70-80 seconds, 80-90 seconds): incremental increase in median for each tier in both assays

-median levels were 0.46, 0.53 and 0.59 µg/mL for chromogenic assay; median levels were 0.59, 0.75 and 1.26 µg/mL for dTT

-**Adverse events:** 15 subjects had adverse events: 9 (29%) bleeding, 4 (13%) deaths, and 1 (3%) venous and 1 (3%) arterial thrombus

-aPTT values preceding bleeding events ranged from 44-91 seconds (PTT monitoring range for therapeutic Bivalirudin is 60-90 seconds)

-24 (77%) patients required transfusions of PRBCs, platelets, FFP or cryoprecipitate. 9 of these patients (38%) received blood products for bleeding, with the remainder receiving them for clinician assigned lab thresholds

-PRBCs were the most transfused blood product in patients, and on average patients receiving transfusions while on bivalirudin required PRBC transfusions every 5 days; they required platelets, FFP and cryoprecipitate much less frequently

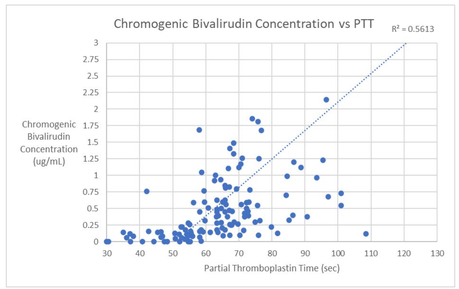

Figure 1. Partial Thromboplastin Time vs Chromogenic Bivalirudin Assay Levels.

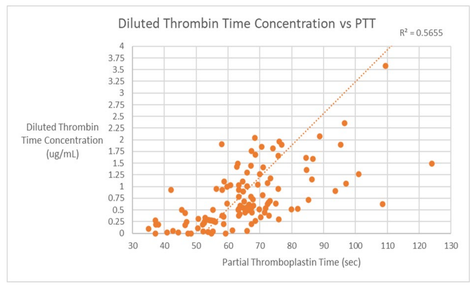

Figure 2. Partial Thromboplastin Time vs Diluted Thrombin Time Bivalirudin Concentration.

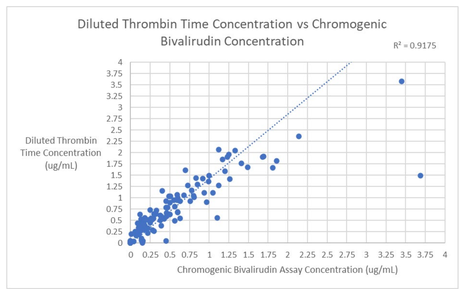

Figure 3. Chromogenic Bivalirudin Assay Levels vs Diluted Thrombin Time Bivalirudin Concentration Levels.

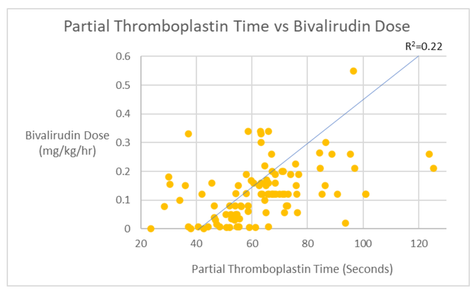

Figure 4. Partial Thromboplastin Time vs Bivalirudin dosing.

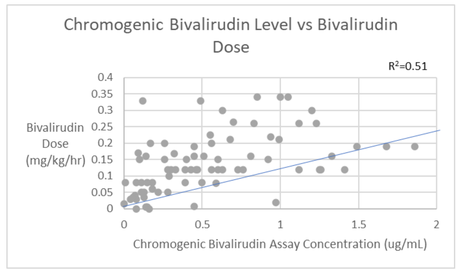

Figure 5. Chromogenic Bivalirudin Assay vs Bivalirudin dose.

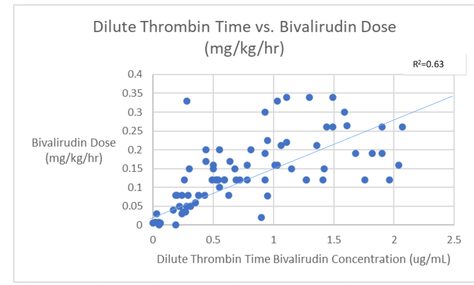

Figure 6. Dilute Thrombin Time Assay vs Bivalirudin Dose.

CONCLUSIONS

-Results from the chromogenic and clot-based bivalirudin assays correlated well with each other, but poorly with the aPTT

-Bivalirudin concentration assays correlated better with weight-based medication dosing than did the aPTT

-Suggestion of possible therapeutic range for dTT with future data

-29% patients had bleeding requiring blood product transfusion and 6% of patients had thrombosis events on bivalirudin in our cohort

-Larger sample sizes and further analysis is needed to correlate test results to clinical safety and efficacy

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Background: The COVID-19 pandemic has caused delays in scheduling non-emergent surgeries. Delay in presentation and/or surgical treatment for oncology patients with metastatic spinal disease could result in progression of the disease, which can complicate surgical care and worsen patient outcomes. The current study sought to determine if preoperative Spinal Instability Neoplastic scores (SINS) and Tokuhashi prognostication scores differed in patients receiving surgical care before and during the COVID-19 pandemic.

Methods: Retrospective review of electronic medical records between 3/1/19-3/1/21 at a tertiary medical center was performed to identify patients who underwent surgery for metastatic spine disease. Primary spinal tumors were excluded. Patients were separated into two groups base on their surgery date: before the COVID-19 pandemic (3/1/19-2/29/20) and during the COVID-19 pandemic (3/1/20-3/1/21). Primary outcomes included SINS and Tokuhashi scores. A variety of statistical tests were performed to compare the groups.

Results: 52 patients who underwent surgery before the COVID-19 pandemic were compared to 45 patients who underwent surgery during the COVID-19 pandemic. There was a significant difference between the before and during groups with respect to SINS (9.31±2.39 vs 10.84±2.75, p=0.004) and Tokuhashi scores (9.27±2.35 vs 7.89±2.76, p=0.009). Linear regression demonstrated time of surgery (before or during COVID-19 restrictions) was a significant predictor of SINS (β=1.37, 95% CI: 0.32-2.42, p=0.011) and Tokuhashi scores (β=-1.45, 95% CI: -2.48-(-0.41), p=0.006).

Conclusions: Patients with metastatic spinal disease who underwent surgery during the COVID-19 pandemic had worse SINS and Tokuhashi scores compared to patients who underwent surgery before the pandemic. This suggests the pandemic has impacted the severity of disease at presentation in patients with spinal metastases. We postulate restricted access to healthcare, difficulty in scheduling medical tests, or patients' reluctance to seek medical care during the COVID-19 pandemic has led to more progressive disease and a worse prognosis at the time of presentation.

Primary Cutaneous Leiomyosarcoma: Incidence, Survival Analysis, and Treatment Outcome, A Study from SEER Database

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Introduction: Leiomyosarcoma (LMS) of the skin is a rare malignant mesenchymal neoplasm that is commonly categorized as cutaneous or subcutaneous. LMS of the skin has a non-specific clinical presentation making it a difficult disease to diagnose and treat. This study aims to use the SEER database to identify demographic, clinical, and pathological factors affecting the prognosis, survival, and treatment of patients with leiomyosarcoma of the skin.

Methods: Demographic and clinical data of patients with skin LMS was extracted from 2000 - 2018. Statistical analysis was conducted with IBM SPSS© v24 software using multivariate analysis, univariate analysis, and Kaplan-Meier functions.

Results: 1014 total cases of LMS of the skin were identified. Most patients were between 60-79 years of age (43%), male (78.4%), and white (93.6%). Of the reported cases, most tumors were <2 cm (69.7%) and

the primary tumor origin was located laterally on the left (41.2%). The grading in known cases was as follows, 33.8% well-differentiated, 43.7% moderately differentiated, 10.4 poorly differentiated, and 11.9% undifferentiated. All cases with known lymph node status were negative for nodal metastasis. Moreover, of the cases with known metastasis status, only 0.2% of cases had metastasis to the lungs and another 0.2% had metastasis to both the lung and liver. Most tumors were treated with surgical resection (86.0%). The overall 5-year survival was 83.9% (95% Confidence Interval (C.I. 95%) = 80.8-86.6) and the 5-year cause-specific survival was 95.7% (C.I. 95%, 93.8-97.1). By treatment, the 5-year cause-specific survival was as follows: 42.9% (C.I. 95%, 9.8-73.4) chemotherapy, 96.3% (C.I. 95%, 94.4-97.6) surgery, and 92.4% (C.I. 95%, 73.0-98.1) radiation. Multivariable analysis depicted three factors associated with increased mortality: age >60 years, female gender, and undifferentiated tumor grading.

Conclusion: LMS of the skin constitutes 3% of all soft tissue sarcomas, commonly affecting white males aged 60-79 years. Most patients received the gold-standard treatment of surgical resection. Generally, LMS of the skin has an indolent course with a good prognosis, seen in its overall and cause-specific 5-year survival rates of 83.9% and 95.7%, respectively. Generic clinical presentation, nonspecific molecular markers, and lack of standardized effective therapeutic strategies suggest the need to establish improved personalized treatment and management guidelines for skin LMS, specifically for higher-risk and treatment-refractory disease into Future Therapeutic Perspectives

Table 1. Demographic profiles and tumor characteristics of1014 patients with leiomyosarcoma of the skin from the Surveillance, Epidemiology, and End Results (SEER) database, 2000 - 2018.

Variable (n=1014)		**Frequency (%)**
Age	10 - 19	6 (0.6%)
	20 - 29	21 (2.1%)

	30 - 39	60 (5.9%)
	40 - 49	104 (10.3%)
	50 - 59	183 (18.0%)
	60 - 69	218 (21.5%)
	70 - 79	218 (21.5%)
	≥ 80	204 (20.1%)
Gender	Male	795 (78.4%)
	Female	219 (21.6%)
Race	Unknown	37 (3.6%)
	White	949 (93.6%)
	Black	20 (2.0%)
	Asian or Pacific Islander	5 (0.5%)
	American Indian or Alaska Native	3 (0.3%)
Grade (n = 1014)		**Frequency (%)**
Unknown		680 (67.1%)
Known		334(32.9%)
Grade where known (n = 334)		
Well differentiated – Grade I		113 (33.8%)
Moderately differentiated – Grade II		146 (43.7%)
Poorly differentiated – Grade III		35 (10.4%)
Undifferentiated/Anaplastic – Grade IV		40 (11.9%)
Variable (n = 1014)		**Frequency (%)**
Size	Unknown	681 (67.2%)
	Known	333 (32.8%)
	Size where known (n = 333)	
	(0 cm) No tumor found	1 (0.3%)
	<2 cm	233 (70.0%)
	2 – 4 cm	78 (23.4%)

	>4 cm	21 (6.3%)

Table 2. Regional lymph node status and distant metastasis at the time of diagnosis of 1014 patients with leiomyosarcoma of the skin from the Surveillance, Epidemiology, and End Results (SEER) database, 2000 - 2018.

Nodal Status (n = 1014)	**Frequency (%)**
Unknown	996 (98.2%)
Known	18 (1.8%)
Nodal statuses where known (n = 18)	
Positive lymph nodes	0 (0%)
Negative lymph nodes	18 (100%)
SEER Metastasis (n = 1014)	**Frequency (%)**
Unknown	537 (53%)
Known	477 (47%)
Metastases where known (n = 477)	
No metastasis	475 (99.5%)
Lung metastasis only	1 (0.2%)
Liver + Lungs metastasis	1 (0.2%)

Treatment Characteristics:

Table 3: Treatment characteristics of 1014 patients with leiomyosarcoma of the skin from the Surveillance, Epidemiology, and End Results (SEER) database,2000-2018.

Treatment (n = 111928)	**Frequency (%)**
Chemotherapy only	1 (0.1%)
Chemotherapy + Surgery	8 (0.8%)

Combination therapy (Chemotherapy + Radiation + Surgery)	1 (0.1%)
Chemotherapy unknown | Radiation not done | Surgery done	863 (85.1%)
Chemotherapy unknown | Neither Radiation nor Surgery	79 (7.8%)
Chemotherapy unknown | Both Radiation and Surgery done	51 (5.0%)
Both Chemotherapy and Surgery unknown | Radiation not done	11 (1.1%)

Outcomes and Survival Analysis:

Table 4. Survival data of 1014 patients with Leiomyosarcoma of the skin from the Surveillance, Epidemiology, and End Results (SEER) database, 2000 - 2018.

Survival	**Overall Observed% (C.I. 95%)**	**Cause-specific survival% (C.I. 95%)**	**Chemotherapy% (C.I. 95%)**	**Surgery% (C.I. 95%)**	**Radiation% (C.I. 95%)**
1 year	96.8% (95.3-97.9)	99.0% (97.9-99.5)	85.7% (33.4-97.9)	98.9% (97.8-99.5)	100.0%)
2 years	93.0% (90.8-94.7)	98.2% (96.9-99.0)	71.4% (25.8-92.0)	98.4% (97.1-99.2)	96.3% (76.5-99.5)
3 years	89.3% (86.7-91.4)	97.1% (95.4-98.1)	42.9% (9.8-73.4)	97.7% (96.2-98.7)	92.4% (73.0-98.1)

4 years	86.6% (83.8-89.0)	96.7% (95.0-97.8)	42.9% (9.8-73.4)	97.4% (95.7-98.4)	92.4% (73.0-98.1)
5 years	83.9% (80.8-86.6)	95.7% (93.8-97.1)	42.9% (9.8-73.4)	96.3% (94.4-97.6)	92.4% (73.0-98.1)

Survival analysis by race:

Table 5. Survival by race data of 1014 patients with Leiomyosarcoma of the skin from the Surveillance, Epidemiology, and End Results (SEER) database, 2000 - 2018.

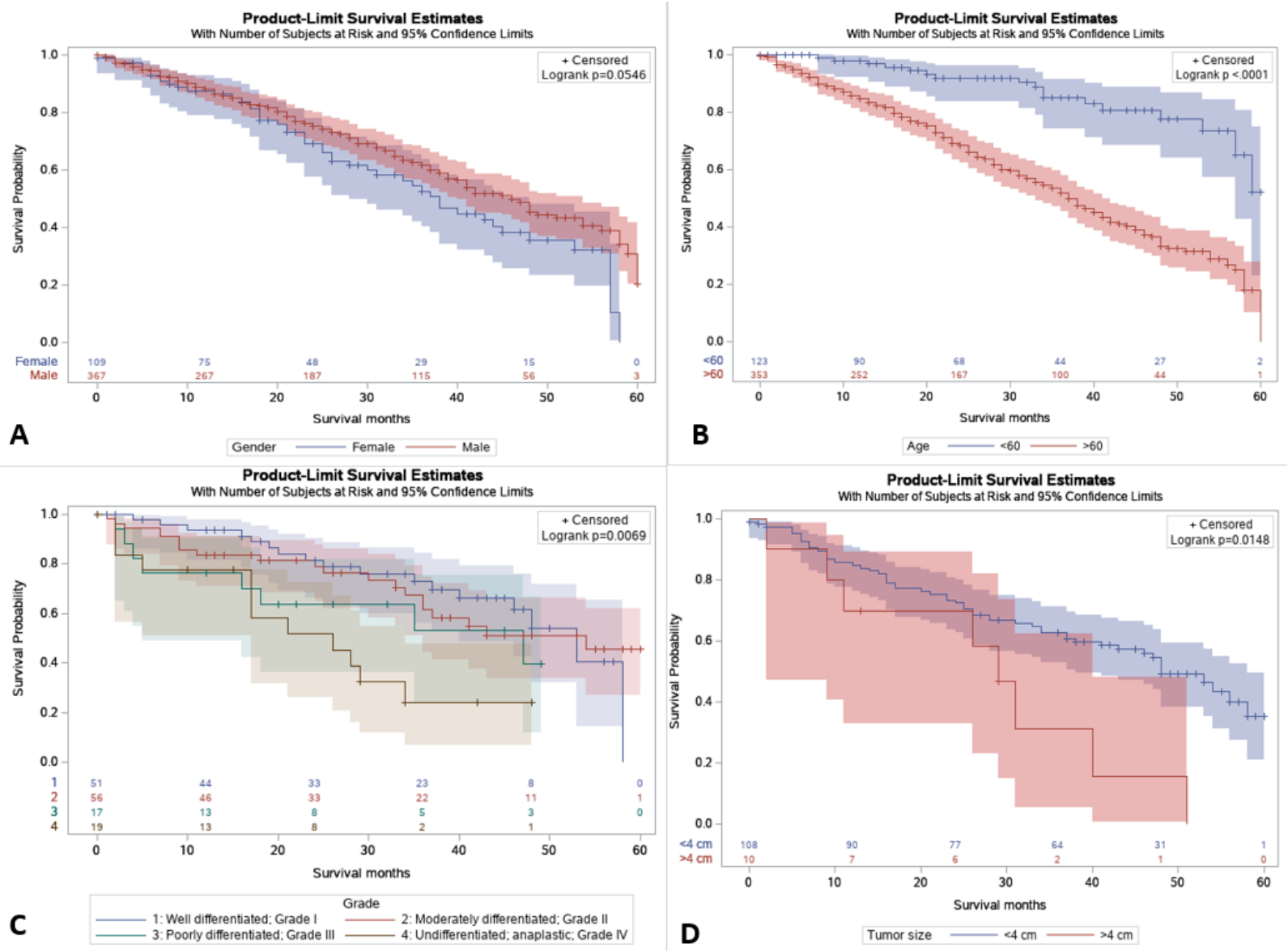
Survival	**White% (C.I, 95%)**	**Black% (C.I, 95%)**
1 year	99.1% (98.1-99.6)	100.0% (95%)
2 years	98.3% (97.0-99.1)	100.0% (95%)
3 years	97.1% (95.5-98.2)	100.0% (95%)
4 years	96.8% (95.0-97.9)	100.0% (95%)
5 years	95.8% (93.8-97.1)	100.0% (95%)

Cumulative survival by gender:

Table 6. Survival data of 1014 patients with leiomyosarcoma of the skin from the Surveillance, Epidemiology, and End Results (SEER) database, 2000 - 2018.

Survival	**Male%** **(C.I, 95%)**	**Female%** **(C.I, 95%)**
1 year	99.5% (98.3-99.8)	97.4% (93.3-99.0)
2 years	98.9% (97.5-99.5)	96.0% (91.2-98.2)
3 years	97.8% (96.1-98.8)	94.4% (89.1-97.2)
4 years	97.6% (95.8-98.6)	93.6% (87.9-96.6)
5 years	96.6% (94.4-97.9)	92.7% (86.7-96.0)

Primary Cutaneous Leiomyosarcoma: Incidence, Survival Analysis, and Treatment Outcome, A Study from SEER Database



Primary Cutaneous Leiomyosarcoma: Incidence, Survival Analysis, and Treatment Outcome, A Study from SEER Database

Figure 1: Survival of primary cutaneous leiomyosarcoma by gender (A), age (B), tumor grade (C), and by tumor size (D).

Primary Cutaneous Leiomyosarcoma: Incidence, Survival Analysis, and Treatment Outcome, A Study from SEER Database

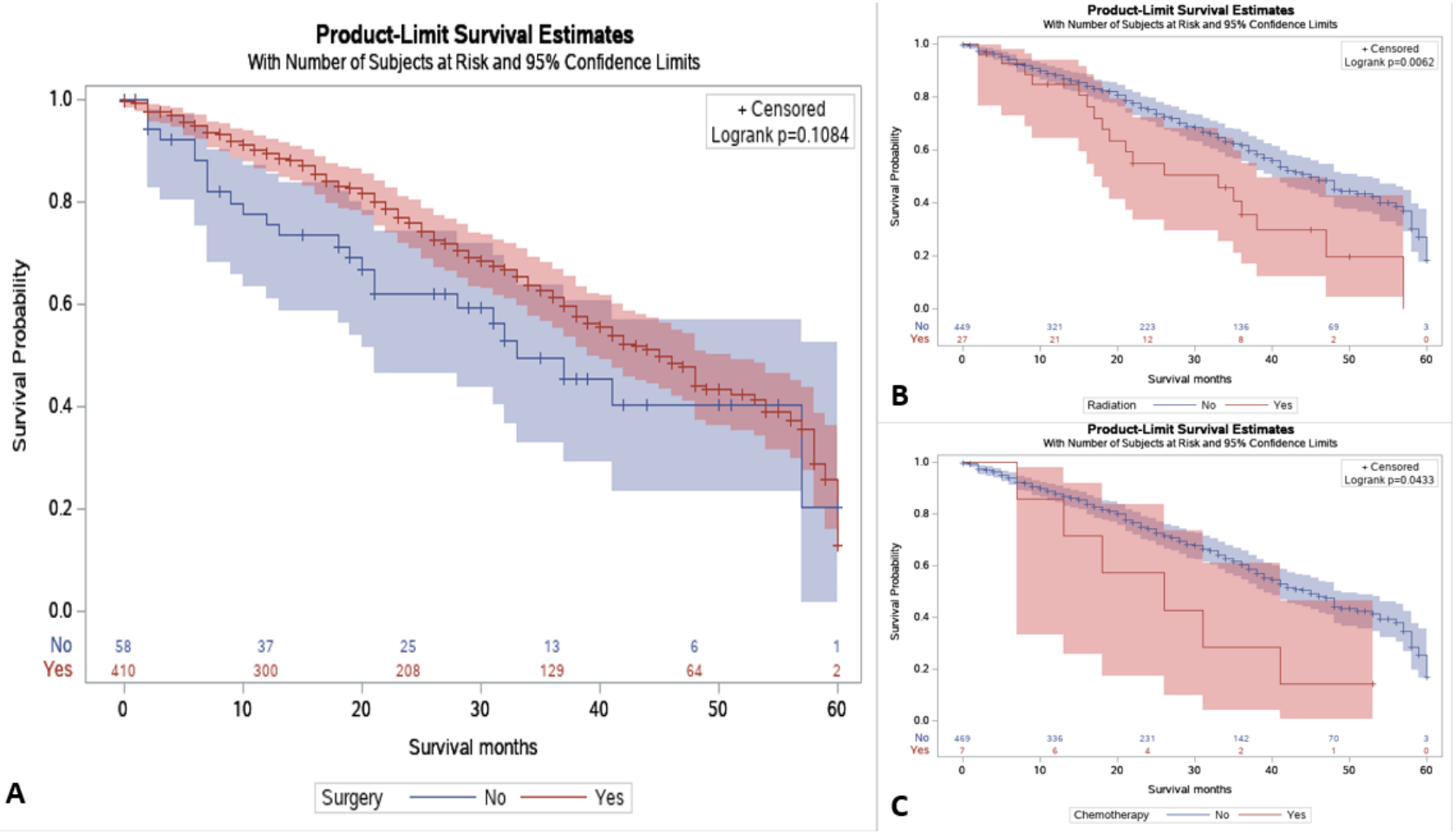


Figure2. Survival of primary cutaneous leiomyosarcoma by different treatment modalities (A) survival with surgery, (B) survival with radiation therapy, and (C) survival with chemotherapy.

Multivariable analysis:

Table 7. Multivariate analysis of independent factors influencing mortality of 1014 patients with leiomyosarcoma of the skin from the Surveillance, Epidemiology, and End Results (SEER) database, 2000 - 2018.

Variables		**Multivariate analysis; Hazard ratio (p-value)**
Age	>60	2.882 (0.009)
Gender	Female	2.743 (0.001)
Tumor grade	Undifferentiated/Anaplastic – Grade IV	4.015 (0.001)

Title: Superparamagnetic Iron Oxide (Magtrace ®) For Axillary Mapping In Patients with Ductal Carcinoma In Situ Undergoing Mastectomy: Single Institution Experience

Authors: Jamin K. Addae, M.D., MPH[1], Raeshell S. Sweeting, M.D., [1] Ingrid M. Meszoely, M.D., [1] Rachel L. McCaffrey, M.D., [1] Rondi M. Kauffmann, M.D., MPH, Mark C. Kelley, M.D., Ana M. Grau, M.D., Kelly Hewitt, M.D.

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Background
Axillary management of patients with a diagnosis of DCIS who wish to undergo mastectomy is in need of refinement. Current guidelines recommend upfront sentinel lymph node biopsy during the index operation due to the potential of upstaging to invasive cancer on final pathology. More recent evidence suggests that the use of superparamagnetic iron oxide dye (Magtrace®) can prevent unnecessary axillary surgery in this patient population, while offering the opportunity for delayed sentinel lymph node biopsy in the event of tumor upstage to invasive cancer. There is limited data regarding the use of Magtrace® outside of clinical trials. This study outlines a single institution's 12-month experience of using Magtrace® for axillary mapping in patients undergoing mastectomy for DCIS.

Methods
This is a retrospective single institution cross sectional study. All medical records of patients who underwent mastectomy for a diagnosis of DCIS from August 2021 to July 2022 were reviewed. All patients who had Magtrace® injected at the time of the index mastectomy were included in the study. Descriptive statistics of demographics, clinical information, pathology results and interval sentinel lymph node biopsy were performed.

Results
A total of 31 participants underwent 35 mastectomies for DCIS. The median age of the participants was 61 years (IQR=16; range 25 to 73years), and the majority of participants were female (96.8%). The most common indication for mastectomy was patient choice (42.9%) followed by diffuse extent of disease (28.6%). On final pathology, 68.6% (24/35) of mastectomy specimens had DCIS without any type of invasion, 20% (7/35) had invasive cancer and 11.4% (4/35) microinvasive disease. Of the 7 cases with upgrade to invasive disease, 2 (28.6%) of them underwent interval sentinel lymph node biopsy. Each case was reviewed to discuss the role of sentinel node biopsy in the patient's treatment. For the 2 patients who underwent interval SLNB, Magtrace® signal was easily detected on the skin surface in one patient and in the axilla in both patients. For the remaining 5 patients who did not undergo interval SLNB, 4 of them met the criteria for the American Board of Internal Medicine (ABIM) Choosing Wisely

recommendations. The last patient was reviewed at a multidisciplinary tumor board and was considered low risk based on her age and tumor biology (Table 2).

Conclusion

The use of supraparamagnetic iron oxide dye can prevent unnecessary axillary surgery in patients with DCIS undergoing mastectomy. Most patients operated on for DCIS did not have invasive disease. In most of those who did have invasive or microinvasive disease, the addition of sentinel node biopsy was not a factor in adjuvant decision making. The use of Magtrace® and delayed sentinel node biopsy affords the opportunity to avoid unnecessary axillary surgery and is a valuable step forward in axillary management. More data will be beneficial to evaluate the adoption, use and performance of this new technology outside of a clinical trial setting.

Table 1: Patient Characteristics

	Total Cohort (35)	Group with Invasive breast cancer (7)	Microinvasive (4)	Group with only DCIS (24)
Age (median)	**61.0**	**69.0**	**56.0**	**60.5**
BMI	**29.1**	**29.1**	**26.0**	**31.4**
Size of associated DCIS (mm)	**28.0**	**60.0**	**21.0**	**21.0**
Size of invasive cancer in mm, median (range)	**-**	**4 (2-7)**	**-**	**-**
Grade of DCIS, %				
1	**2.9**	**0**	**0**	**4.2**
2	**57.1**	**42.9**	**0**	**70.8**
3	**40.0**	**57.1**	**100.0**	**25.0**

Table 2. Characteristics of Patients with Incidental invasive breast cancer in mastectomy specimen

	Sentinel Node Biopsy	No Sentinel Node Biopsy
Number of Cases	2	5
Age/Age Range	42 & 59	69-73
Hormone Receptor Status	1Triple Negative and 1ER+/HER2-	All ER+/HER2-
Average Tumor Size in mm (range)	5 (3-7)	3.6 (2.5-4.5)
Decision process	Multidisciplinary Tumor Board	Choosing Wisely Recommendation*

ER+/PR+/HER2- was discussed at multidisciplinary tumor board and considered low risk for lymph node metastasis
ER: estrogen receptor
PR: progesterone receptor
HER2: human epidermal growth factor 2

SUPERPARAMAGNETIC IRON OXIDE (MAGTRACE ®) FOR AXILLARY MAPPING IN PATIENTS WITH DUCTAL CARCINOMA IN SITU UNDERGOING MASTECTOMY: SINGLE INSTITUTION EXPERIENCE

JAMIN K. ADDAE, M.D., MPH[1], RAESHELL S. SWEETING, M.D., [1] INGRID M. MESZOELY, M.D., [1] RACHEL L. MCCAFFREY, M.D., [1] RONDI M. KAUFFMANN, M.D., MPH, [1] MARK C. KELLEY, M.D., [1] ANA M. GRAU, M.D.,[1] KELLY HEWITT, M.D, [1]

VANDERBILT UNIVERSITY MEDICAL CENTER

BACKGROUND

Axillary management of patients with a diagnosis of DCIS who wish to undergo mastectomy is in need of refinement. Current guidelines recommend upfront sentinel lymph node biopsy during the index operation due to the potential of upstaging to invasive cancer on final pathology. More recent evidence suggests that the use of superparamagnetic iron oxide dye (Magtrace®) can prevent unnecessary axillary surgery in this patient population, while offering the opportunity for delayed sentinel lymph node biopsy in the event of tumor upstage to invasive cancer. There is limited data regarding the use of Magtrace® outside of clinical trials. This study outlines a single institution's 12-month experience of using Magtrace® for axillary mapping in patients undergoing mastectomy for DCIS

METHODS

This is a retrospective single institution cross sectional study. All medical records of patients who underwent mastectomy for a diagnosis of DCIS from August 2021 to July 2022 were reviewed. All patients who had Magtrace® injected at the time of the index mastectomy were included in the study. Descriptive statistics of demographics, clinical information, pathology results and interval sentinel lymph node biopsy were performed

Table 1. Inclusion and exclusion criteria for participants

Inclusion	Exclusion
Adults (≥18 years)	Preoperative diagnosis of invasive breast cancer
Diagnosis of DCIS	Mastectomy for invasive breast cancer
Mastectomy for DCIS	Gross palpable lymph node
Prophylactic contralateral mastectomy with incidental DCIS	

RESULTS

A total of 31 participants underwent 35 mastectomies for DCIS. The median age of the participants was 61 years (IQR=16; range 25 to 73years), and the majority of participants were female (96.8%). The most common indication for mastectomy was patient choice (42.9%) followed by diffuse extent of disease (28.6%). On final pathology, 68.6% (24/35) of mastectomy specimens had DCIS without any type of invasion, 20% (7/35) had invasive cancer and 11.4% (4/35) microinvasive disease. Of the 7 cases with upgrade to invasive disease, 2 (28.6%) of them underwent interval sentinel lymph node biopsy. Each case was reviewed to discuss the role of sentinel node biopsy in the patient's treatment. For the 2 patients who underwent interval SLNB, Magtrace® signal was easily detected on the skin surface in one patient and in the axilla in both patients. For the remaining 5 patients who did not undergo interval SLNB, 4 of them met the criteria for the American Board of Internal Medicine (ABIM) Choosing Wisely recommendations. The last patient was reviewed at a multidisciplinary tumor board and was considered low risk based on her age and tumor biology (Table 2). Unnecessary axillary surgery was avoided in 94% of cases.

[1]*Division of Surgical Oncology and Endocrine Surgery, Vanderbilt University Medical Center*

The authors have no disclosures. Rondi Dr. Kauffmann is supported by the National Institute of Health (Grant No. 3P50CA098131-20S1)

* Too few to report

RESULTS

Figure 1. Indications for mastectomy in patients with DCIS

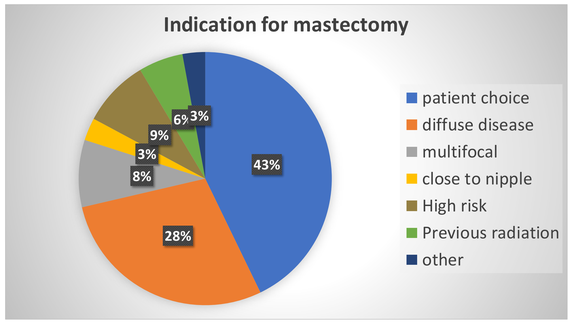
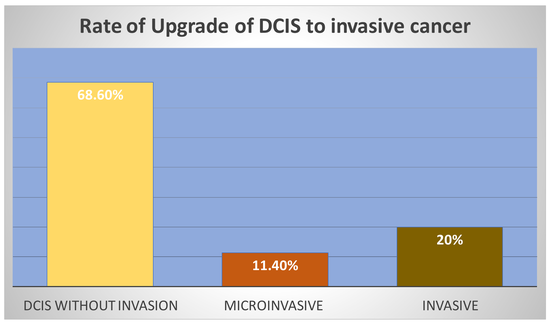


Figure 2. Rate of Upgrade of DCIS to invasive cancer



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	Total Cohort (35)	Group with Invasive breast cancer (7)	Microinvasive (4)	Group with only DCIS (24)
Age (median)	61.0	69.0	56.0	60.5
BMI	29.1	29.1	26.0	31.4
Size of associated DCIS (mm)	28.0	60.0	21.0	21.0
Size of invasive cancer in mm, median (range)	-	4 (2-7)	-	-
Grade of DCIS, %				
1	2.9	0	0	4.2
2	57.1	42.9	0	70.8
3	40.0	57.1	100.0	25.0

Table 2. Characteristics of Patients with Incidental invasive breast cancer in mastectomy specimen

Number of Cases	Sentinel Node Biopsy	No Sentinel Node Biopsy
Number of Cases	2	5
Age/Age Range	<60	69-73
Hormone Receptor Status	1Triple Negative and 1ER+/HER2-	All ER+/HER2-
Average Tumor Size in mm (range)	5 (3-7)	3.6 (2.5-4.5)
Decision process	Multidisciplinary Tumor Board	Choosing Wisely Recommendation*

CONCLUSIONS

The use of supraparamagnetic iron oxide dye can prevent unnecessary axillary surgery in patients with DCIS undergoing mastectomy. Most patients operated on for DCIS did not have invasive disease. In most of those who did have invasive or microinvasive disease, the addition of sentinel node biopsy was not a factor in adjuvant decision making. The use of Magtrace® and delayed sentinel node biopsy affords the opportunity to avoid unnecessary axillary surgery and is a valuable step forward in axillary management. More data will be beneficial to evaluate the adoption, use and performance of this new technology outside of a clinical trial setting.

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THE AMERICAN SOCIETY OF Breast Surgeons

Title: Association Between Preoperative Pain Phenotype and Postoperative Opioid Use after Scheduled Cesarean Delivery

Authors: Amelie Pham, MD, Sarah Osmundson, MD, MS, Alex Pedowitz, BS, Laura Sorabella, MD, Stephen Bruehl, PhD

Objective: Prior largely retrospective work suggests that pain-related and psychosocial factors influence opioid use following non-obstetric surgical procedures. We tested whether a *preoperative* patient phenotype reflecting elevated pain intensity and negative affect and decreased physical function is associated with increased postpartum opioid use after scheduled cesarean delivery.

Methods: This is a secondary analysis of a prospective cohort study examining associations between endogenous opioids and opioid use after cesarean. Patients without chronic pain and not regularly using opioids were enrolled preoperatively and completed validated pain and psychosocial measures. At 48 hours postpartum, participants completed a measure of positive subjective responses to early postoperative opioid use (e.g., feeling euphoric, happy, comfortable). At 2 weeks postpartum, they reported on opioid use. The primary outcome was total amount of opioids used in MMEs (inpatient and outpatient). Secondary outcomes were total duration of outpatient opioid use, number of tablets used, and using all prescribed opioids. We examined associations between preoperative phenotype measures and postoperative opioid outcomes using regression models controlling for age, BMI, and race.

Results: Characteristics of the 136 participants are displayed in Table 1. Results (Table 2) indicated that patients with a preoperative phenotype characterized by greater pain intensity, pain-related life interference; pain catastrophizing, anxiety, and depression used more opioids postpartum. Similar associations were observed for secondary outcomes. More positive subjective opioid analgesic responses at 48 hours were associated with greater opioid use.

Conclusion: A preoperative maternal phenotype reflecting elevated pain intensity, negative affect, and decreased physical function was associated with increased opioid use after scheduled cesarean delivery. Findings regarding positive subjective opioid responses support the role of reinforcement mechanisms as a contributor to outpatient opioid use.

Table 1: Demographic and Clinical Characteristics

Variable	Mean ± standard deviation or N (%) (n=136)
Age (years)	31.0 ± 5.3
Gestational age at delivery (weeks)	38.3 ± 1.5
Gravity	3.2 ± 2.0
Parity	1.4 ± 1.3
Maternal Body Mass Index at delivery (kg/m^2)	34.2 ± 8.2
Race or ethnicity*	
Non-Hispanic White	89 (65.4)
Non-Hispanic Black	22 (16.2)
Hispanic	15 (11.0)
Asian	3 (2.2)
Unknown or Other	7 (5.1)
Tobacco use*	8 (5.9)
College education or greater* (n=130)	76 (58.5)
Prior cesarean	97 (71.3)
Multiple Gestations	3 (2.2)
Public Insurance	37 (27.2)
Obesity (Body Mass Index ≥30 kg/m^2)	74 (61.7)
Chronic Hypertension	16 (11.8)
Pre-existing diabetes mellitus	8 (5.9)
Psychiatric disorders*	
Current	28 (20.5)
History	35 (25.7)
Currently taking medications	14 (10.3)
Spontaneous or induced labor	5 (4.2)
Hypertensive disorder of pregnancy	14 (10.3)
Length of stay	2.3 ± 0.6
Postdural headache	3 (2.2)
Blood patch required	2 (66.7)

*Self-reported

Table 2. Associations between preoperative pain and affect measures, postoperative opioid response, and on postpartum opioid use outcomes

Outcome[1]	Assessment Period	Phenotype or Opioid Response Measure[2]	R-square[3]	Beta[4] (SE)	P-value*
Total opioid use (in MMEs)	Preoperative	Pain Catastrophizing	.06	.25 (0.041)	.003
		PROMIS Physical Function	.04	-.21 (0.049)	.014
		PROMIS Anxiety	.05	.22 (0.043)	.010
		PROMIS Depression	.04	.21 (0.059)	.014
		PROMIS Pain interference	.08	.29 (0.045)	.001
		PROMIS Average pain intensity	.10	.34 (0.199)	.001
	48 hours post	Positive Opioid Response	.07	.28 (0.665)	.001
Total number of opioid tablets used	Preoperative	Pain Catastrophizing	.04	.19 (0.016)	.027
		PROMIS Physical Function	.01	-.12 (0.020)	.172
		PROMIS Anxiety	.03	.17 (0.017)	.044
		PROMIS Depression	.03	.18 (0.024)	.043
		PROMIS Pain interference	.04	.21 (0.018)	.018
		PROMIS Average pain intensity	.04	.20 (0.081)	.048
	48 hours post	Positive Opioid Response	.06	.25 (0.265)	.005
Total duration of opioids use	Preoperative	Pain Catastrophizing	.02	.13 (0.010)	.119
		PROMIS Physical Function	.05	-.22 (0.012)	.010
		PROMIS Anxiety	.01	.11 (0.011)	.181
		PROMIS Depression	.00	.02 (0.015)	.842
		PROMIS Pain interference	.04	.20 (0.011)	.017
		PROMIS Average pain intensity	.06	.25 (0.050)	.010
	48 hours post	Positive Opioid Response	.10	.33 (0.160)	<.001
Used all prescribed opioids	Preoperative	Pain Catastrophizing	-	.08 (0.033)	.017
		PROMIS Physical Function	-	-.12 (0.057)	.037
		PROMIS Anxiety	-	.08 (0.004)	.035
		PROMIS Depression	-	.08 (0.043)	.068
		PROMIS Pain interference	-	.04 (0.039)	.295
		PROMIS Average pain intensity	-	.34 (0.168)	.040
	48 hours post	Positive Opioid Response	-	-.66 (0.725)	.362

[1]A square root transformation was used to normalize the skewed distribution for all outcomes | [2]Phenotype or Opioid Response Measures: Pain Catastrophizing Scale reflecting on any pain experienced now or experienced in the past and indicating the degree to which each of the thoughts and feelings were experienced during pain episode | PROMIS-29 Profile v1.0 tool, with Tscores for Physical function, Anxiety, Depression, and Pain interference, and asking about "*How would you rate your pain on average in the last 7 days*?" | HOME questionnaire about a positive "Opioid Analgesic Response" after taking opioid medications postpartum | [3]R square defines how much of the variance in the outcome is explained by the exposure | [4]Linear regression and generalized linear model for binary outcome with beta coefficients and standard error s| *Statistically significant at p <.05

Association Between Preoperative Pain Phenotype and Postoperative Opioid Use after Scheduled Cesarean Delivery

Amelie Pham MD;[1] Sarah S Osmundson MD, MSCR;[1] Alex Pedowitz, BS;[1] Laura Sorabella, MD;[2] Stephen Bruehl, MD PhD[2]
[1]Department of Obstetrics and Gynecology and [2]Anesthesiology at Vanderbilt University

DEPARTMENT OF OBSTETRICS & GYNECOLOGY
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BACKGROUND & OBJECTIVE

- Pain-related and psychosocial factors influence opioid use following non-obstetric surgical procedures.
- **Objective**: To evaluate whether a preoperative maternal phenotype reflecting elevated pain intensity, negative affect, and decreased physical function is associated with increased postoperative opioid use after scheduled cesarean delivery.

METHODS

- Secondary analysis of a prospective observational study.
- **Eligibility**: Uncomplicated scheduled cesarean delivery, regional anesthesia, no opioid use disorder or chronic pain.
- **Preoperative period**: Completion of validated pain and psychosocial measures.
- **Postoperative period**: Completion of a measure of positive subjective responses to early postoperative opioid use at 48 hours and report on opioid use at 2 weeks.
- **Outcomes**: 1) Total amount of opioids used in MMEs (sum of inpatient and outpatient); 2) duration of outpatient opioid use, number of tablets used, and using all prescribed opioids.
- **Analysis**: Associations between preoperative phenotype measures and postoperative opioid outcomes using linear regression models, adjusting for age, BMI, and race.

RESULTS

- A total of 136 participants with 100% survey completion rate.
- Mean maternal age 31.0 ± 5.3 years, gestational age at delivery 38.3 ± 1.5 weeks, and maternal length of stay 2.3 ± 0.6 days.
- Majority of participants were obese (mean maternal BMI 34.2 ± 8.2 m/kg^2), Non-Hispanic White (65.4%), had private insurance (72.8%), and had a prior cesarean delivery (71.3%).
- Approximately ¼ of participants reported either a current or history of a psychiatric diagnosis (20.5%, 28/136, and 25.7%, 35/136; respectively) and 10.3% (14/136) reported currently taking medications for a psychiatric condition.

Associations between preoperative pain and affect measures, postoperative opioid response, and postpartum opioid use outcomes

Outcome[1]	Assessment Period	Phenotype or Opioid Response Measure[2]	R-square[3]	Beta[4] (SE)	P-value*
Total opioid use (in MMEs)	Preoperative	Pain Catastrophizing	.06	.25 (0.041)	**.003**
		PROMIS Physical Function	.04	-.21 (0.049)	**.014**
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Total number of opioid tablets used	Preoperative	Pain Catastrophizing	.04	.19 (0.016)	**.027**
		PROMIS Physical Function	.01	-.12 (0.020)	.172
		PROMIS Anxiety	.03	.17 (0.017)	**.044**
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		PROMIS Pain interference	.04	.21 (0.018)	**.018**
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Total duration of opioids use	Preoperative	Pain Catastrophizing	.02	.13 (0.010)	.119
		PROMIS Physical Function	.05	-.22 (0.012)	**.010**
		PROMIS Anxiety	.01	.11 (0.011)	.181
		PROMIS Depression	.00	.02 (0.015)	.842
		PROMIS Pain interference	.04	.20 (0.011)	**.017**
		PROMIS Average pain intensity	.06	.25 (0.050)	**.010**
	48 hours post	Positive Opioid Response	.10	.33 (0.160)	**<.001**
Used all prescribed opioids	Preoperative	Pain Catastrophizing	-	.08 (0.033)	**.017**
		PROMIS Physical Function	-	-.12 (0.057)	**.037**
		PROMIS Anxiety	-	.08 (0.004)	**.035**
		PROMIS Depression	-	.08 (0.043)	.068
		PROMIS Pain interference	-	.04 (0.039)	.295
		PROMIS Average pain intensity	-	.34 (0.168)	**.040**
	48 hours post	Positive Opioid Response	-	-.66 (0.725)	.362

[1]A square root transformation was used to normalize the skewed distribution for all outcomes | [2]Phenotype or Opioid Response Measures: Pain Catastrophizing Scale reflecting on any pain experienced now or experienced in the past and indicating the degree to which each of the thoughts and feelings were experienced during pain episode | PROMIS-29 Profile v1.0 tool, with Tscores for Physical function, Anxiety, Depression, and Pain interference, and asking about "How would you rate your pain on average in the last 7 days?" | HOME questionnaire about a positive "Opioid Analgesic Response" after taking opioid medications postpartum | [3]R square defines how much of the variance in the outcome is explained by the exposure | [4]Linear regression and generalized linear model for binary outcome with beta coefficients and standard errors | **Bold** is statistically significant at p <.05.

RESULTS CONT'D

- A preoperative maternal phenotype reflecting elevated pain intensity, negative affect, and decreased physical function was associated with increased total opioid use after scheduled cesarean delivery (Table).
- Similar associations were observed for secondary outcomes.
- More positive subjective opioid analgesic responses at 48 hours were associated with greater opioid use.

CONCLUSIONS

- Participants with a preoperative phenotype that is characterized by greater pain intensity, pain-related life interference, pain catastrophizing, anxiety, and depression used more opioids postpartum, both inpatient and outpatient.
- Findings regarding positive subjective opioid responses support the role of reinforcement mechanisms as a contributor to outpatient opioid use.

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2. *Bateman BT, Franklin JM, Bykov K, Avorn J, Shrank WH, Brennan TA, Landon JE, Rathmell JP, Huybrechts KF, Fischer MA, Choudhry NK. Persistent opioid use following cesarean delivery: patterns and predictors among opioid-naïve women. Am J Obstet Gynecol. 2016 Sep;215(3):353.e1-353.e18.*

We describe a preoperative maternal phenotype associated with increased postoperative opioid use after scheduled cesarean delivery.

TITLE: SPECIFIC CLINICAL FEATURES MAY DIFFERENTIATE EARLY CHILDHOOD ONSET FROM LATE CHILDHOOD ONSET PEDIATRIC EOSINOPHILIC ESOPHAGITIS

INTRODUCTION: Eosinophilic esophagitis (EoE) is a chronic, allergen-mediated clinicopathologic disease affecting all ages. While the differences between pediatric and adult onset EoE has been well documented, little is known about the differences within the pediatric onset EoE. Herein, we investigated if clinical features are distinct for early childhood onset EoE (eo-EoE; < 5 years) when compared to late childhood onset EoE (lo-EoE; 5-18 years).

METHODS: We reviewed medical records of 269 children (≤18 years) newly diagnosed with EoE at Monroe Carell Jr. Children's Hospital at Vanderbilt between May 2017 and October 2022. EoE was defined per the 2011 Consensus Guidelines. Their socio-demographic data, growth parameters, clinical presentation, allergic comorbidities, family history, esophagogastroduodenoscopy (EGD) findings rated per the endoscopic reference scoring system (EREFS), and esophageal histology (peak eosinophil count, and presence or absence of basal zone hyperplasia, eosinophilic microabscess, and lamina propria fibrosis) were extracted for analysis. The eo-EoE and lo-EoE groups were matched for gender, race, and ethnicity. Chi-squared and Fisher Exact tests were used for categorical data and paired t-tests for continuous variables.

RESULTS: In all, 50 children were in the eo-EoE group and 58 children were in the lo-EoE group. The mean (SD) age of the eo-EoE group was 1.86 (1.16) years and the lo-EoE group was 12.4 (3.33) years of age. Z-score for age (weight/length if age < 2 years or body mass index if age ≥ 2 years) was significantly lower for eo-EoE compared to lo-EoE [0.01 (1.48) vs. 0.80 (1.25); $P < 0.004$]. The eo-EoE group had significantly higher rates of eczema (54.0% vs. 17.2%; $P<0.001$), weight concerns (36.0% vs. 10.3%; $P = 0.002$), and feeding difficulties (30.0% vs. 0.0%; $P < 0.001$) compared to lo-EoE group. On the other hand, children in the lo-EoE group were more likely to present with abdominal pain (3.0% vs. 21.0%; $P < 0.001$) compared to children in the eo-EoE group. The total EREFS scores were lower in the eo-EoE group compared to the lo-EoE group [1.34 (0.96) vs 2.00 (1.28); $P=0.006$], and they were less likely to have edema (24.0% vs. 50.0%, $P = 0.009$). There were no differences between the groups with regards to family history of EoE or atopy and histologic findings.

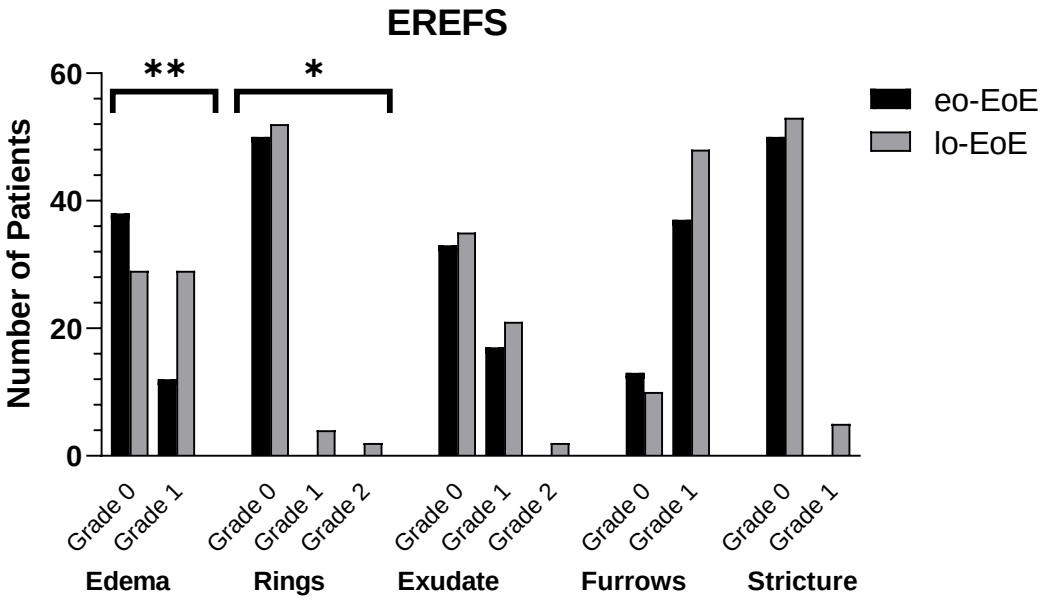
CONCLUSIONS: Clinical features such as feeding difficulties, atopic co-morbidities, growth faltering, and EoE-relevant endoscopic abnormalities can distinguish children with eo-EoE from lo-EoE even after accounting for gender, race, and ethnicity. These results deepen our understanding of the pediatric EoE. Further investigation is needed to understand why the presentation of eo-EoE differs from lo-EoE and why the endoscopic findings are relatively mild in eo-EoE, despite no difference in histologic findings.

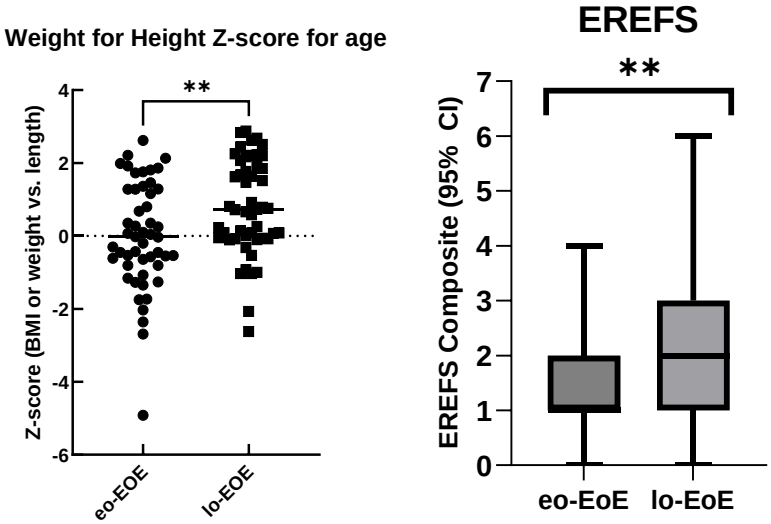
Table 1. Characteristics of the cohort at diagnosis

	eo-EoE (n=50)	lo-EoE (n =58)	P value
Age, Years [mean (SD)]	1.86 (1.16)	11.98 (3.36)	
Sex, n (%)			
Male	33 (66.0)	44 (75.9)	0.291
Female	17 (34.0)	14 (24.1)	
Ethnicity, n (%)			
Non-Hispanic	46 (92.0)	55 (94.8)	0.702
Hispanic	4 (8.0)	3 (5.2)	
Race, n (%)			
Caucasian	31 (62.0)	44 (75.9)	0.122
Black	15 (30.0)	8 (13.8)	
Other	4 (8.0)	6 (10.3)	
Z-score for age, weight for length < 2 yo or BMI >2 yo, mean (SD)	0.01 (1.48)	0.80 (1.25)	0.004
History of Eczema, n (%)	27 (54.0)	10 (17.2)	<0.001
History of Asthma/Reactive Airway Disease, n (%)	17 (34.0)	21 (36.2)	0.842
History of Food Allergies, n (%)	27 (54.0)	24 (41.3)	0.247
Family history of atopy, n (%)	20 (40.0)	20 (34.4)	0.690
Family history of EoE, n (%)	4 (8.0)	11 (19.0)	0.055
Presenting Symptoms, n (%)			
Choking/Dysphagia	36 (72.0)	49 (84.5)	0.157
Abdominal Pain	3 (6.0)	21 (36.2)	<0.001
Vomiting	29 (58.0)	24 (41.2)	0.122
Feeding Difficulties	30 (60.0)	0 (0.0)	<0.001
Weight Concerns	18 (36.0)	6 (10.3)	0.002

eo-EoE: Early childhood onset EoE; lo-EoE: Late childhood onset EoE; EoE: eosinophilic esophagitis; SD: standard deviation; IQR: inter-quartile range; EREFS: endoscopic reference score

Figure 1. Total number of patients within each EREFS subcategory by grading.





SPECIFIC CLINICAL FEATURES MAY DIFFERENTIATE EARLY CHILDHOOD ONSET FROM LATE CHILDHOOD ONSET PEDIATRIC EOSINOPHILIC ESOPHAGITIS

JORDAN BUSING, MD; MATTHEW BUENDIA, MD; GIRISH HIREMATH MD, MPH

VANDERBILT UNIVERSITY MEDICAL CENTER

Introduction

- Eosinophilic esophagitis (EoE) is a chronic, allergen-mediated clinicopathologic disease of the esophagus affecting all ages.
- Differences between pediatric and adult onset EoE have been well documented, however little is known about the clinicopathologic and endoscopic differences within pediatric onset EoE.
- We investigated if clinical features are distinct for early childhood onset EoE (eo-EoE; < 5 years) when compared to late childhood onset EoE (lo-EoE; 5-18 years).

Background

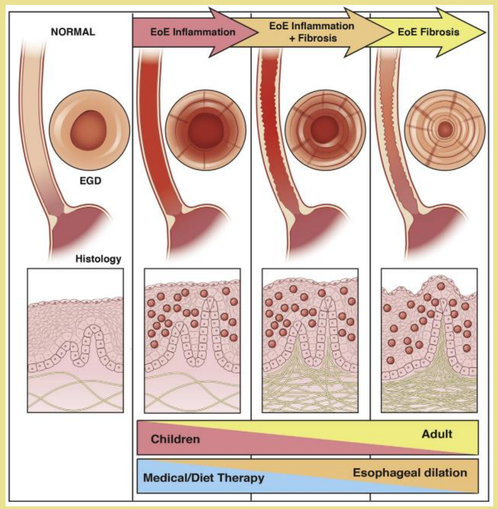
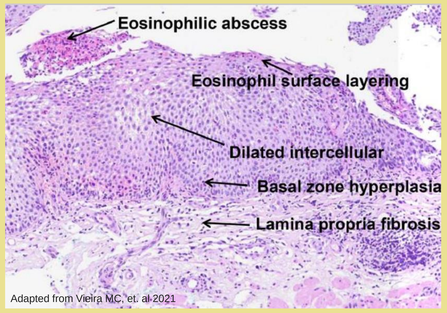


Figure 1. The natural progression of eosinophilic inflammation leading to fibrosis.(Dellon, Hirano 2018).

Special thanks:
Dr. Hiremath and Dr. Buendia for helping me construct and execute this project.

Methods

- We performed a retrospective chart review of 269 patients diagnosed with EoE (defined per the 2011 Consensus Guidelines) between May 2017 and October 2022.
- Socio-demographic data, growth parameters, clinical presentation, allergic comorbidities, family history collected. eo-EoE and lo-EoE groups were matched for gender, race, and ethnicity.
- Esophageal histology and endoscopic scoring were obtained for each patient.



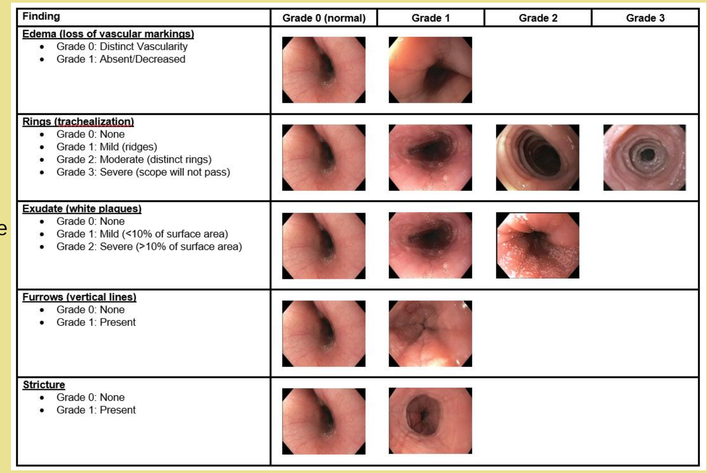


Figure 2 (left) Typical histologic findings in EoE demonstrated by eosinophilic infiltrate leading to inflammatory response and eventual lamina propria fibrosis. Figure 3 (above). Endoscopic Reference Scoring System (EREFS), a validated tool used to grade macroscopic findings of EoE during endoscopy.

Results

Table 1. Characteristics of the cohort at diagnosis

	eo-EoE (n=50)	lo-EoE (n =58)	P value
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eo-EoE: Early childhood onset EoE; lo-EoE: Late childhood onset EoE; EoE: eosinophilic esophagitis; SD: standard deviation; IQR: inter-quartile range; EREFS: endoscopic reference score

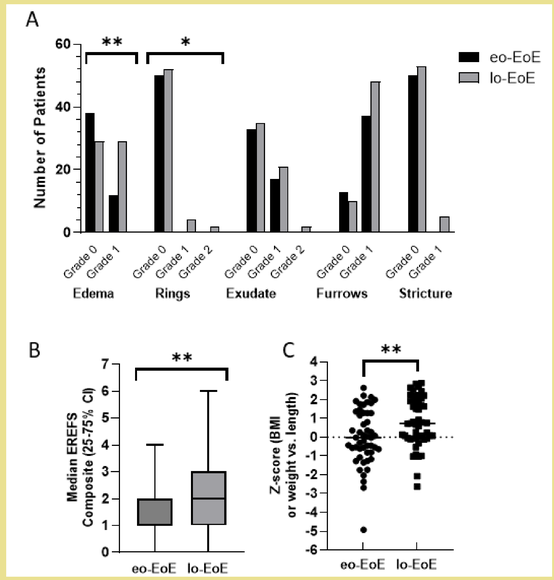
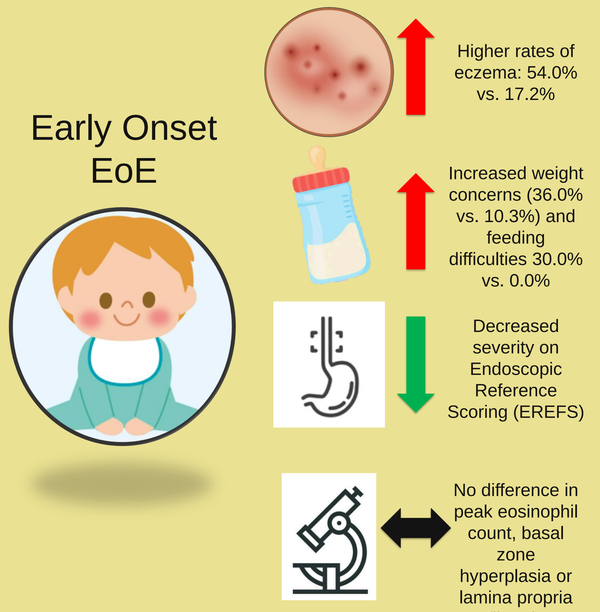


Figure 4. (A) Total number of patients within each EREFS subcategory by grading. (B) Total composite EREFS comparison between eo-EoE and lo-EoE demonstrating lower overall EREFS scores in eo-EoE. (C) Z-score for age (weight/length if < 2 years of body mass index if age ≥ 2 years) was significantly lower for eo-EoE compared to lo-EoE.

Results



Conclusions

- Clinical features such as feeding difficulties, atopic co-morbidities, growth faltering, and EoE-relevant endoscopic abnormalities can distinguish children with eo-EoE from lo-EoE even after accounting for gender, race, and ethnicity.
- These results deepen our understanding of the pediatric EoE. Further investigation is needed to understand why the presentation of eo-EoE differs from lo-EoE and why the endoscopic findings are relatively mild in eo-EoE, despite no difference in histologic findings.

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Loss of CFTR Reprograms Airway Epithelial IL-33 Release and Licenses IL-33 Dependent Inflammation

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RATIONALE: Increased type 2 inflammation has been described in people with cystic fibrosis (CF). Whether loss of cystic fibrosis transmembrane conductance regulator (CFTR) function contributes directly to a type 2 inflammatory response or secondarily due to chronic infection has been difficult to determine. The potent alarmin IL-33 has emerged as a critical regulator of type 2 inflammation. We tested the hypothesis that CFTR deficiency increases IL-33 expression/release and deletion of IL-33 reduces allergen-induced inflammation in the CF lung.

METHODS: Human airway epithelial cells (AECs) grown from NuLi ($CFTR^{wt/wt}$) and CuFi ($CFTR^{\Delta F508/\Delta F508}$) cell lines and both $Cftr^{+/+}$ and $Cftr^{-/-}$ (lacking airway infection) mice, were used in this study. Protein quantification of IL-33 and DUOX1 was performed by immunohistochemistry, Western blot analysis, and ELISA. Cytokines from IL-33 stimulated and polarized Th2 cells was quantified via ELISA. Pulmonary inflammation in $Cftr^{+/+}$ and $Cftr^{-/-}$ mice with and without IL-33 or ST2 germline deletion was determined by histological analysis, bronchoalveolar lavage (BAL) cellular and cytokine analysis.

RESULTS: CFTR deficiency increased IL-33 expression and release in both human AECs and mice following allergen challenge. DUOX-1 expression was increased in CFTR deficient human AECs and mouse lungs compared to CFTR sufficient AECs and mouse lungs. DUOX-1 inhibition in mice revealed that DUOX1 was necessary for the increased IL-33 release in $Cftr^{-/-}$ mice. Further, $Cftr^{-/-}$ Th2 cells express more of the IL-33 receptor, ST2 and IL-33 stimulation of $Cftr^{-/-}$ Th2 cells results in increased effector function compared to $Cftr^{+/+}$

Th2 cells**.** Deletion of IL-33 or ST2 decreased both type 2 inflammation and neutrophil recruitment in *Cftr*$^{-/-}$ mice with reductions in classical type 2 cytokines and the neutrophil chemokine, CXCL1.

CONCLUSIONS: This study is the first to demonstrate that CFTR regulates IL-33 release, through DUOX1 expression, and that the increase in IL-33 in CF airway epithelia represents an early immune system defect prior to infection. Modulation of the IL-33/ST2 axis represents a novel therapeutic target in allergen-induced type 2 high and neutrophilic inflammation in CF. Equally exciting is that this work highlights current animal models of CF as architypes to better understand the mechanistic interactions pertaining to IL-33 synthesis and release as well as the complex relationship between innate and adaptive immunity.

Loss of CFTR Reprograms Airway Epithelial IL-33 Release and Licenses IL-33 Dependent Inflammation

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CF Airway Disease

Airway disease in CF:
- inflammation and infection
- mucus accumulation
- airflow obstruction

Persistent high-intensity inflammation leads to permanent structural damage of the CF airways.

Impaired lung function eventually results in respiratory disease.

Type 2 inflammation is increased in CF

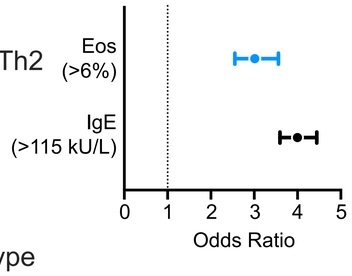
Type 2 inflammation exists in persons with CF:
ABPA, asthma, sinusitis, nasal polyposis.

BAL from CF airways is skewed towards Th17 and Th2 cytokines.

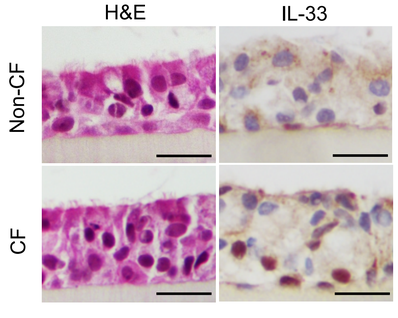
Type 2 biomarkers are elevated in CF

Mechanism for increased type 2 inflammation is unknown

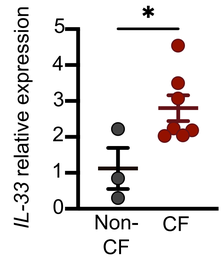
Odds of having elevated Type 2 inflammatory makers in CF compared to non-CF



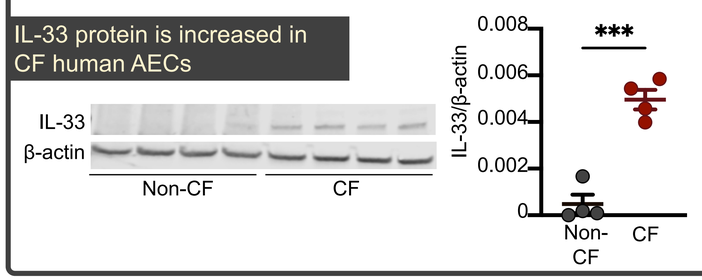
IL-33 is increased in CF airway epithelial cells (AECs)



IL-33 transcript is increased in CF human AECs

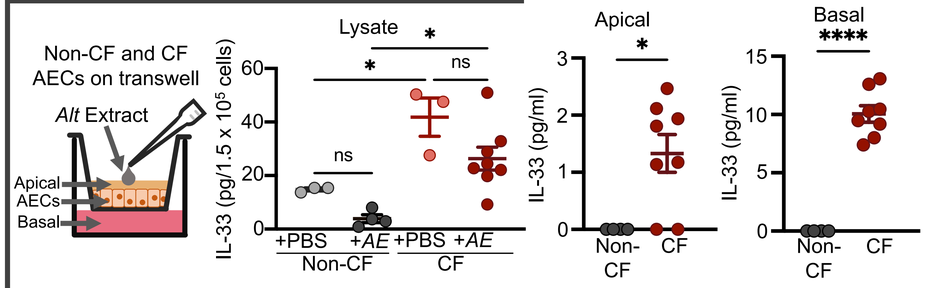


IL-33 protein is increased in CF human AECs

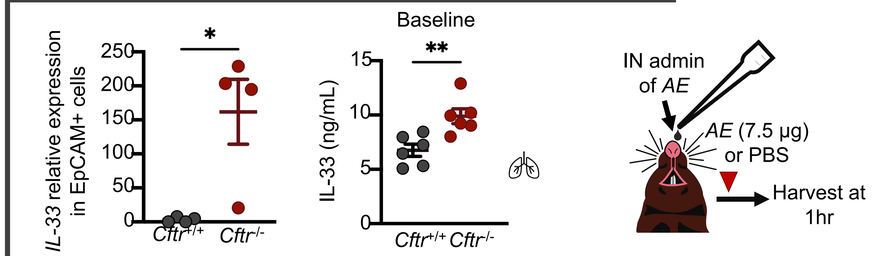


Alternaria extract (*AE*) challenge increases IL-33 release in CF

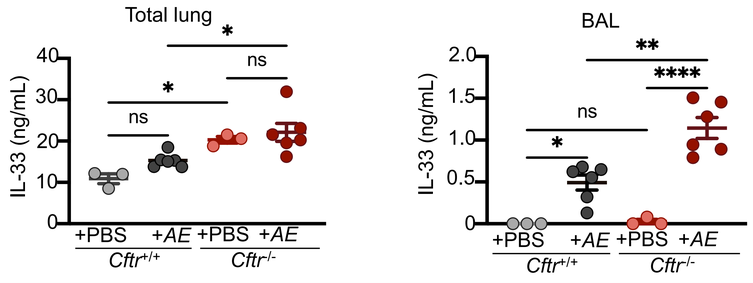
IL-33 release is increased in CF human AECs



Il-33 transcript and protein is increased in *Cftr*$^{-/-}$ murine lungs

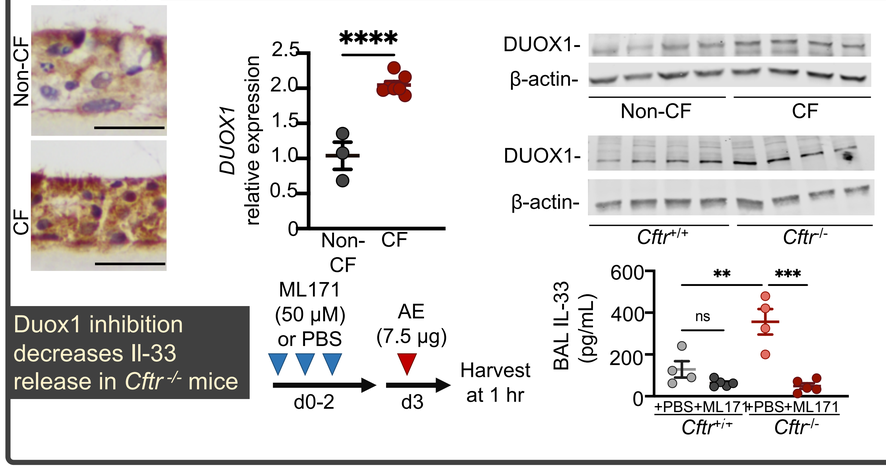


Il-33 release is increased in *Cftr*$^{-/-}$ murine lungs



DUOX1 inhibition with ML171 reduces IL-33 release in CF

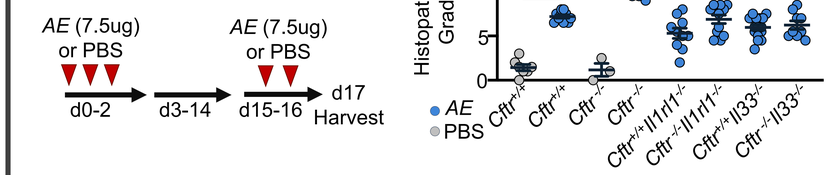
DUOX1 protein is increased in CF human AECs and *Cftr*$^{-/-}$ murine lungs

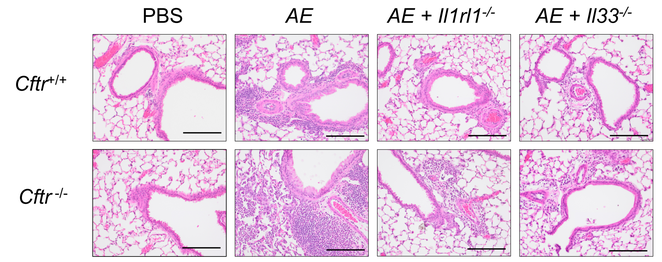


Duox1 inhibition decreases Il-33 release in *Cftr*$^{-/-}$ mice

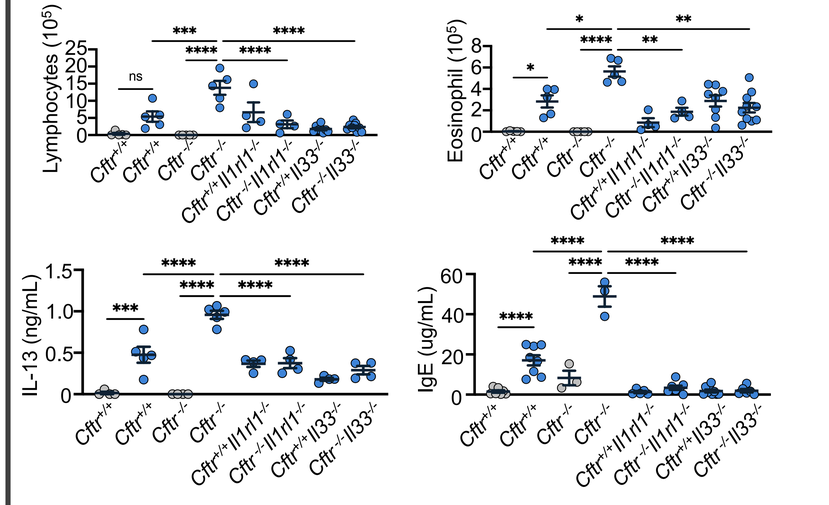
IL-33/St2 deletion reduces CF allergic inflammation

Il-33/St2 deletion reduces type 2 inflammation in *Cftr*$^{-/-}$ mice

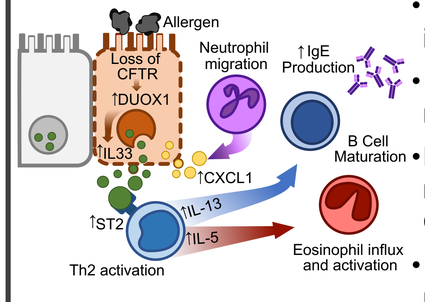




Il-33/St2 deletion in *Cftr*$^{-/-}$ mice reduces Type 2 immune cells and cytokines



Conclusions



- Type 2 inflammation is prevalent in CF lung disease.
- IL-33 release is increased in CF, mediated by DUOX1.
- Deletion of Il-33/St2 significantly reduces type 2 inflammation in CF.
- IL-33/ST2 targeting therapies may decrease CF inflammation.

P-values

* = P < 0.05, ** = P < 0.01, *** = P < 0.001, **** = P < 0.0001

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Cystic Fibrosis Foundation (COOK20L0)

Investigating the Rates of Pneumonia after Bronchoalveolar Lavage in Inhalation Injuries

Tyler J Murphy, MD; Derek A. Riffert, BS; Ronnie Mubang, MD; Mina F. Nordness, MD, MPH; Elizabeth D. Krebs, MD, MSc; Christopher Guidry, MD; Stephen Gondek, MD, MPH; Robel T. Beyene, MD

Smoke inhalation injuries (SIIs) result in up to 10,000 deaths annually in the US. Fiberoptic bronchoscopy at admission is the gold standard for diagnosis of SIIs among intubated patients. The role of simultaneous bronchoalveolar lavage (BAL) remains controversial. We explored the relationship between admission BAL and development of pneumonia in patients with presumed SII.

BAL at the time of admission is correlated with increased rates of pneumonia in patients with presumed SIIs.

We completed a retrospective analysis of intubated patients who underwent bronchoscopy on admission for presumed SII with or without BAL. Demographics and baseline characteristics (Table 1) were analyzed using chi-squared or Student's t-test analysis. Unadjusted and multivariable logistic regression assessing the effect of admission BAL on development of pneumonia were performed, adjusting for sex, length of stay, burn total body surface area (TBSA), and confirmed SII.

Of 98 patients evaluated, 40 patients (40.8%) had BALs collected at admission, 16 (16.3%) of which were positive. The BAL group had significantly more men and more confirmed SIIs (Table 1). 36 patients were treated for pneumonia, of which 30 (83%) met the National Healthcare Safety Network (NHSN) diagnostic criteria for pneumonia. BAL patients were more likely to be treated for pneumonia later in the admission in both unadjusted (OR 5.75, 95% CI 2.35, 14.1, p=<0.001) and multivariate (OR 5.29, 95% CI 1.59, 17.64, p=0.007) models. BAL patients were more likely to undergo a second bronchoscopy (52.5% vs 10.3%, p<0.001), receive antibiotics (66.7% vs 24.1%, p<0.01), and had a longer duration of antibiotics (6.16 vs 2.57, p=0.012).

These findings suggest that for intubated patients presumed to have SII, BAL on admission is correlated with subsequent pneumonia during the same admission. We recommend against the routine use of BAL at admission and further investigation should be considered to determine the effects of routine BAL in this population.

Table 1. Baseline Characteristics and Results

Characteristic	No BAL on Admission, N=58	BAL on Admission, N=48
Age	54 (±19)	52(±14)
Sex* *(Male)*	33 (57%)	31(78%)
TBSA (%)	19.9%	23%
Confirmed SII*	32 (55.7%)	35(87.5%)
Smoking/Lung Disease	15 (25.9%)	8 (20%)
Length of Stay*	16.8	28.2
Mean ICU Free Days, at 28 days	12	10.1
Mean Ventilator Free Days, at 28 days	16.6	12.5
Disposition Home/Psych/Jail Advanced Care Facility Died In Hospital	 28 (48.3%) 12 (20.7% 18 (31%)	 25 (62.5%) 10 (25%) 5 (12.5%)
Received Antibiotics*	13 (24.1%)	26 (66.7%)
Mean Days of Antibiotics*	2.57	6.16
Repeat Bronchoscopy*	6 (10.3%)	21 (52.5%)
Positive Admission BAL	N/A	16 (16.3%)

*Denotes significant difference across groups ($p \leq 0.05$)

Title: What is the ideal time to start radiation after metastatic spine surgery?

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Conflicts of Interest and Source of Funding:
Dr. Zuckerman reports being an unaffiliated neurotrauma consultant for the National Football League. Dr. Stephens is a consultant for Nuvasive and Carbofix and receives institutional research support from Nuvasive and Stryker Spine. Dr. Abtahi receives an institutional research support from Stryker Spine. No other perceived conflict of interest by any of the listed authors.

Abstract

Introduction. Radiotherapy (RT) has been shown to improve tumor control after metastatic spine surgery. The optimal timing between surgery and postoperative RT remains unclear. In patients undergoing metastatic spine surgery, we sought to: 1) report time to postoperative RT, 2)

describe the predictive factors of time to postoperative RT, and 3) determine if earlier postoperative RT is associated with improved local recurrence (LR) and overall survival (OS).

Methods. A single-center, retrospective cohort study was undertaken of all patients undergoing spine surgery for extradural metastatic disease between 02/2010-01/2021. Demographics and perioperative data were collected. The primary exposure variable was the time to postoperative RT, capped at 3-months to avoid RT not planned after surgery and dichotomized at <1 month vs. 1-3 months. The primary outcomes were LR, OS, and 1-year survival. Secondary outcomes were wound complication, Karnofsky Performance Scale (KPS), and *McCormick Scale (MMS)*. *Univariable/multivariable linear, logistic, and Cox regression were performed, controlling for age, BMI, tumor size, preoperative/postoperative chemotherapy, and preoperative RT.*

Results. Of 357 patients undergoing metastatic spine surgery, 76 (21.3%) received postoperative RT within 3-months. Mean age was 59.6±9.6 and 47 (61.8%) were males. Median (IQR) time to first postoperative RT was 33.8 (21.8, 42.8) days, and 34 (44.7%) patients received RT within the first month postoperatively. Stereotactic Body Radiotherapy (SBRT) was performed in 31 (40.8%) patients, with only 18 (23.7%) were targeted at the surgical site. However, patients with larger tumor size (β=-3.58, 95%CI=-6.59, -0.57, p=0.021) or new neurological deficits (β=-16.21, 95%CI=-32.21, -0.210, p=0.047) had a shorter time to RT on multivariable linear regression. On multivariable logistic regression, timing of RT did not affect the risk of LR (OR=5.24, 95%CI=0.091-55.7, p=0.096) or OS (OR=1.11, 95%CI=0.30-4.21, p=0.872). However, patients who received RT between 1-3 month postoperatively had lower odds of 1-year OS compared to patients receiving RT within 1 months (OR=0.18, 95%CI=0.04-0.74, p=0.022). No significant association was found between time to RT and LR/OS on multivariable Cox regression. Regarding the secondary outcomes, multivariable logistic/linear regression showed that patients who received RT within 1-month postoperatively had no significant differences in wound complications and KPS/MMS at last follow-up compared to 1-3 months.

Conclusions. In a cohort of patients undergoing metastatic spine surgery, 21.3% of patients received postoperative RT within 3-months. Patients who received RT within the first month postoperatively had a higher 1-year survival compared to patients receiving RT between 1-3 months postoperatively, with no significant impact on wound complications, performance score, and neurologic function.

What is The Ideal Time to Start Radiation After Metastatic Spine Surgery

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BACKGROUND

- Spinal metastatic tumors are extremely common among cancer patients
- Radiotherapy (RT) is known to improve tumor control after surgery
- Despite efficacy, the timing of postoperative RT is understudied

OBJECTIVES

- In patients undergoing metastatic spine surgery, we sought to:
  1. Report time to postoperative RT
  2. Describe predictive factors of time to postoperative RT
  3. Determine if earlier postoperative RT is associated with improved local recurrence and overall survival

METHODS

Study Design

- Retrospective, single institution cohort study (2010-2021)
- Inclusion criteria: Adult patients with metastatic extradural spinal tumors, who underwent spinal surgery for tumor resection and stabilization

RESULTS

- 357 patients underwent metastatic spine surgery
- 76 (21.3%) of patients received postoperative RT within 3 months
  - 34 (9.5%) received postoperative RT within 1 month
  - 42 (11.8%) received postoperative RT within 1-3 months

Preoperative Demographics	RT within 1 month	RT between 1-3 months	p-value
Age at Surgery	58.7 ± 8.4	60.4 ± 10.6	0.305
Gender			0.644
Male	22 (64.7%)	25 (59.5%)	
Insurance			**0.050**
Private	12 (35.3%)	19 (45.2%)	
Public	10 (29.4%)	18 (42.9%)	
Uninsured	12 (35.3%)	5 (11.9%)	
Primary Organ			0.065
Breast	2 (5.9%)	3 (7.1%)	
Lung	11 (32.4%)	5 (11.9%)	
Other	15 (44.1%)	30 (71.4%)	
Renal	6 (17.6%)	4 (9.5%)	
Comorbidities			0.319
2+	3 (8.8%)	9 (21.4%)	
Tumor Size (levels)	1.9 ± 1.6	1.4 ± 0.7	0.377
Oligometastasis	13 (38.2%)	8 (19.0%)	**0.013**
Decompressed	29 (85.3%)	42 (100.0%)	**0.015**
Type of RT			
Non-SBRT	31 (91.2%)	27 (64.3%)	
SBRT	3 (8.8%)	15 (35.7%)	**0.006**

Outcomes	RT within 1-month, N = 34	RT between 1-3 months, N=42	p-value
Time to last FU	296.8 ± 339.9	438.8 ± 476.1	0.073
Any Complication	11 (32.4%)	11 (26.2%)	0.556
New neurologic deficit	0 (0.0%)	5 (14.7%)	**0.015**
LOS (days)	8.2 ± 8.2	6.1 ± 4.5	0.588
Non-home discharge	15 (44.1%)	18 (42.9%)	0.912
LR	2 (5.9%)	11 (26.2%)	**0.019**
Time to LR	77.5 ± 4.9	172.3 ± 352.7	0.923
KPS last follow-up	57.5 ± 22.3	57.9 ± 22.9	0.878
MMS last follow-up	2.6 ± 1.4	2.5 ± 1.3	0.662
Death	26 (78.8%)	31 (75.6%)	0.747
Time to Death	737.9 ± 976.6	341.5 ± 430.0	0.640

RESULTS

Multivariate Analysis

Outcomes	Independent variable	OR/β (95% CI)	p-value
Wound Complication	Time to Postop RT (Continuous)	1.03 (0.95, 1.14)	0.417
KPS Last		0.03 (-0.37, 0.44)	0.865
MMS Last		-0.01 (-0.03, 0.01)	0.428
LR		1.02 (0.97, 1.08)	0.336
Overall Survival		1.00 (0.96, 1.05)	0.811
1-year survival		0.96 (0.91, 1.00)	0.071
Outcomes	Independent variable	OR/β (95% CI)	p-value
Wound Complication	RT within 1 month (vs. 1-3 months)	4.40 (0.40, 118.0)	0.266
KPS Last		0.31 (-12.88, 13.50)	0.126
MMS Last		-0.11 (-0.913, 0.69)	0.705
LR		5.24 (0.91, 55.70)	0.096
Overall Survival		1.11 (0.30, 4.21)	0.872
1-year survival		0.18 (0.04, 0.74)	**0.022**

KPS = Karnofsky Performance Scale. MMS = Modified McCormick Scale.

Controlling for age, tumor size, preop RT/chemo, postop chemo, RT type

Multivariate Analysis

Outcome variable	Independent variables	HR (95%CI)	p-value
LR	Time to postop RT	1.02 (0.97, 1.07)	0.430
Death		0.98 (0.98, 1.02)	0.950

Controlling for age, tumor size, preop RT/chemo, postop chem

CONCLUSIONS AND LESSONS LEARNED

- Patients who received RT within 1 month → higher 1-year survival
- No impact on wound complications, performance score, neurologic function, OS, or LR

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VANDERBILT UNIVERSITY MEDICAL CENTER

Vanderbilt Spine Outcomes Lab

Consultation Timing Matters: Safely Reducing Utilization of Computed Tomography Imaging for Pediatric Appendicitis via Earlier Surgical Consultation

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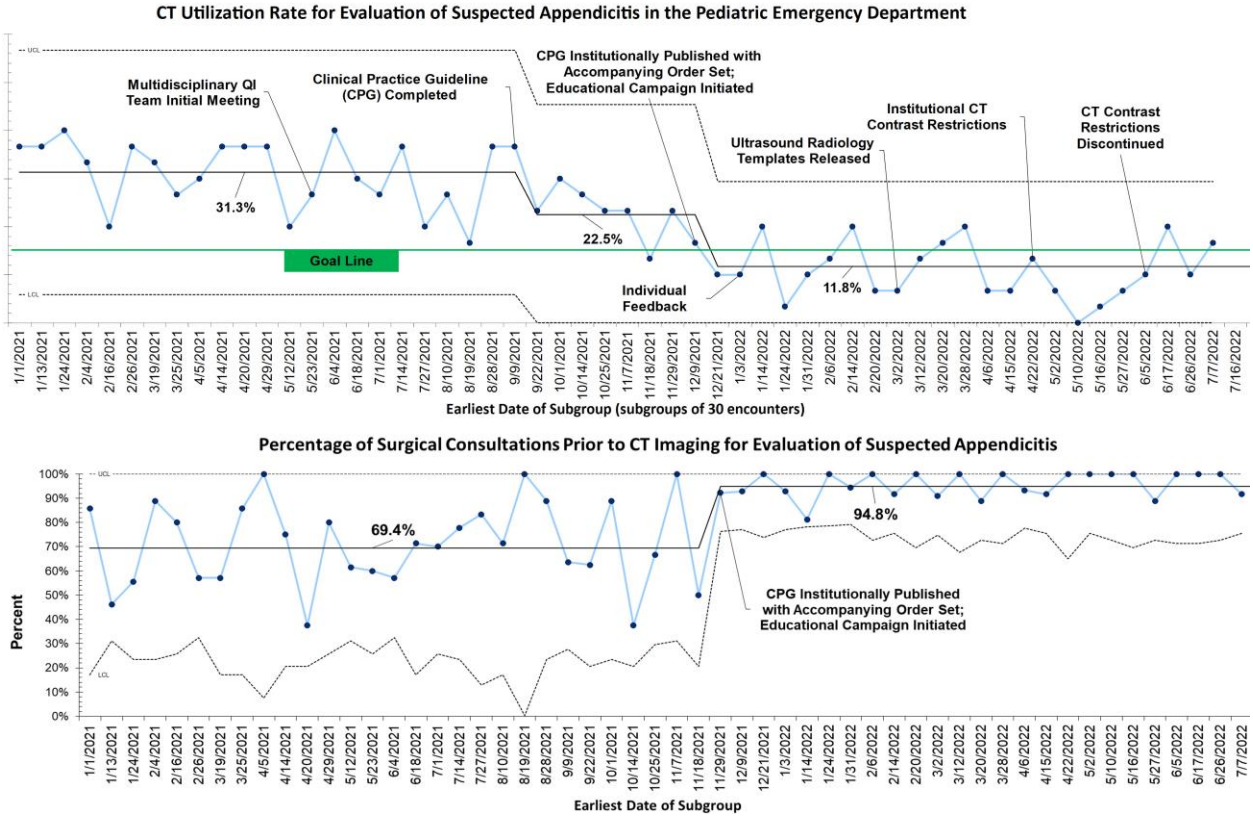
Purpose: Appendicitis is a common pediatric surgical emergency, yet there is significant variability in its diagnostic approach. Given the increased malignancy risk and costs associated with computed tomography (CT) in childhood, safe reduction of CT imaging in the workup of appendicitis is warranted. We aimed to reduce CT utilization in the diagnostic evaluation of pediatric appendicitis from 32% to 15% by implementing earlier surgical consultation.

Methods: Retrospective baseline data were obtained from 01/2021- 08/2021. Post-intervention data were collected prospectively. A multidisciplinary team developed a key driver diagram. A clinical practice guideline utilizing the Pediatric Appendicitis Score (PAS) and recommending surgical consultation prior to ordering CT imaging was published in 12/2021 with a corresponding order set. The primary outcome was CT utilization with balancing measures of negative-pathology appendectomies (NPA) and ED return within 72 hours. Data were analyzed using statistical process control charts and Nelson rules to detect special cause variation.

Results: The baseline period (n=624) demonstrated a CT utilization rate of 31.3%. Surgical consultation rate prior to CT imaging was 69.4%. In the post-intervention period (n=996), special cause variation was detected in CT utilization rate (centerline shift to 11.8%) and rate of surgical consultation prior to CT imaging (centerline shift to 94.6%). There was one ED return visit within 72 hours and no change in NPA rate.

Conclusions: Computed tomography imaging can be safely minimized in the workup of pediatric appendicitis. Earlier involvement of the surgical team and utilization of validated risk scores as key elements of an institutional clinical practice guideline facilitated the observed reduction in computed tomography utilization. Ongoing efforts include standardization of surgical consultation templates and continuous performance review.

Figure 1: CT Utilization Rate and Surgical Consultation Timing



Title: Ibrutinib Treatment Results in Increased Phosphorylation of the Erk1/2 Signaling Pathway in Atrial-Specific Human iPSC-Derived Cardiomyocytes (hiPSC-aCMs)

Authors: Matthew R. Fleming, Matthew J. O'Neill, Bjorn C. Knollmann, Javid J. Moslehi, and Dan M. Roden

Introduction: Cardiovascular sequelae of targeted cancer therapies may provide novel insights into cardiovascular biology and disease pathogenesis, including atrial fibrillation (AF). The Bruton tyrosine kinase (BTK) inhibitor ibrutinib has revolutionized treatment for B-cell malignancies but increases the incidence of AF compared with conventional chemotherapy. Recent data in mouse models have shown that ibrutinib-mediated AF likely results not from inhibition of BTK ("on target" effect), but from off-target inhibition of a different kinase, C-terminal Src kinase (CSK). The signaling pathway by which CSK inhibition results in AF remains unknown and thus may represent a novel molecular target for AF therapeutics.

Methods: We studied cellular monolayers of hiPSC-aCMs using extracellular field potential (EFP) recordings obtained by the Nanion CardioExcyte 96 system after 72-hour exposure to ibrutinib, the second-generation BTK inhibitor acalabrutinib (associated with less AF), or vehicle control. As an initial proteomic approach to identifying kinase signaling pathways altered upon inhibition of CSK and hence possibly predisposing to AF, we determined the relative phosphorylation state of 37 kinases in hiPSC-aCMs treated with ibrutinib or vehicle control using a human phospho-antibody array.

Results: EFP recordings from cellular monolayers of hiPSC-aCMs exposed to ibrutinib for 24 hours develop a striking increase in spontaneous beat-to-beat variability, an *in vitro* correlate of arrhythmogenic behavior. This effect was not seen with vehicle control or acalabrutinib. Treatment with ibrutinib for 72 hours resulted in increased phosphorylation of multiple kinases in the Erk1/2 pathway, including Erk1 T202/Y204 and Erk2 T185/Y187, in human phospho-kinase array studies. Conventional Western Blotting confirmed these results and showed that ibrutinib, but not acalabrutinib, resulted in increased Erk1/2 phosphorylation.

Conclusion: Off-target inhibition of CSK by ibrutinib may result in increased AF through increased phosphorylation in the Erk1/2 pathway and this is consistent with other recent reports implicating Erk1/2 signaling in AF. The downstream mechanisms by which this occurs remain unknown and thus represent a novel potential target for AF therapeutics.

Title

Simultaneous Profiling of Genotype and Transcriptome at Single Cell Resolution Identifies Cellular Programs Underlying Clonal Hematopoiesis Pathology

Authors

J. Brett Heimlich, Pawan Bhat, Alyssa C. Parker, Jessica Ulloa, Sydney Olson, P. Brent Ferrell MD. Alexander G. Bick MD, PhD

Introduction: Clonal hematopoiesis of indeterminate potential (CHIP) results from a clonal expansion of hematopoietic stem cells due to somatic mutations in genes such as DNMT3A or TET2. Patients with CHIP have poor cardiovascular outcomes. TET2 CHIP clones that make up >20% of blood increases risk. Whether CHIP mutated cells confer risk directly or through polarizing other cells is presently unknown as prior work has been unable to simultaneously resolve mutational status and transcriptome of an individual cell.

Methods: We performed single cell RNA-seq on blood from patients with DNMT3A CHIP (N=9), TET2 CHIP (N=8), and controls (N=6). We identified individual cell CHIP mutational status with a novel method that leverages mitochondrial mutations to identify cell lineage.

Results: Across 104,556 single cells, CHIP patients had a higher proportion of CD14 monocytes (32% vs. 18%). Within individuals, CHIP mutated cells exhibited a strong myeloid bias. At the extreme, 93% of TET2 mutated cells were monocytes in one patient. Comparing TET2 CHIP monocytes to controls identified a hyper-inflammatory phenotype with increased expression of inflammatory cytokines and their downstream targets, and elevated expression of adhesion molecules. Comparing TET2-mutated CD14 monocytes to unmutated monocytes within the same individual localized the inflammatory phenotype to the mutated cells. Conversely, this phenotype was not observed in DNMT3A CHIP monocytes either in aggregate or within the same individual.

Conclusions: Simultaneous, high-throughput, single-cell resolution of DNA mutation status and RNA transcriptomes identifies aberrant cellular programs in TET2-mutated CD14 monocytes. Our data support a simple mechanistic model for CHIP cardiovascular disease risk that is proportional to the number of mutated cells present. Differences observed between TET2 and DNMT3A provide a potential explanation for the differential pathogenicity of these two mutations.

Resolving CH peripheral blood transcriptional programs at single cell resolution

Alyssa C. Parker[1], J. Brett Heimlich[1], Pawan Bhat[1], Matthew T. Jenkins[1], Caitlyn Vlasschaert[2], Jessica Ulloa[1], Chad R. Potts[1], Sydney Olson[1], Alexander J. Silver[1], Ayesha Ahmad[1], Brian Sharber[1], Donovan Brown[1], Ningning Hu[1], Peter van Galen[3], Michael R. Savona[1], Alexander G. Bick[1], P. Brent Ferrell[1]

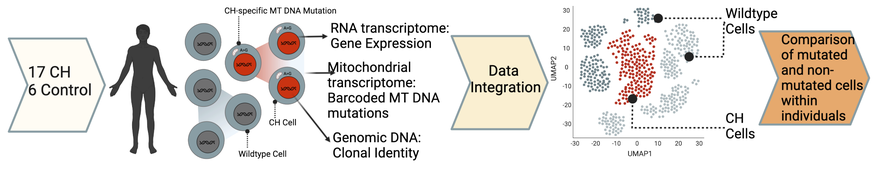
Affiliations: [1]Vanderbilt University School of Medicine, [2]Queen's University, [3] Brigham and Women's Hospital

INTRODUCTION

To date, efforts in genetics have focused on inter-individual variation but studying genetics through the lens of somatic mosaicism enables genetic investigation at the intra-individual level. Analysis of somatic mutations is challenging because current technology cannot simultaneously resolve mutation status and gene expression levels. Methods have been developed to predict mutation status based on gene expression, but success rates are typically limited to 1-9% of cells[1,2]. Recent developments have opened the possibility of robust lineage tracing using mitochondrial mutations[3]. We used mitochondrial lineage tracing to develop an improved method of profiling both somatic mutation status and gene expression for 100% of cells.

Figure 1: Somatic muations result in mosaicism throughout the body.

STUDY DESIGN



Deconvoluting Mutation Status

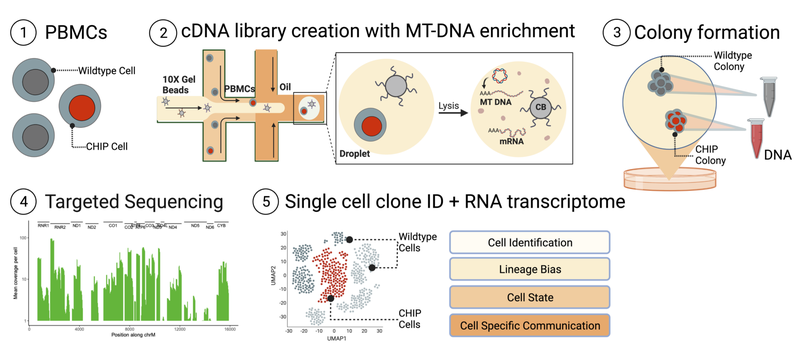


Figure 2: Workflow to resolve single-cell genotype and RNA transcriptome. Peripheral blood mononuclear cells (PBMCs) underwent scRNA-seq. cDNA was used to generate MT-DNA enriched reads retaining original cell barcodes (CBs). In parallel, PMBCs were plated in a methylcellulose assay prior to colony isolation and DNA extraction. Extracted DNA underwent targeted sequencing for CH and MT-DNA.

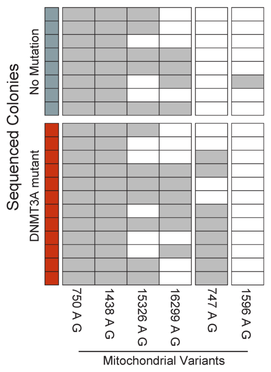


Figure 3: One mutation specific for CH-mutated colonies was identified (747 A>G). Matrix highlighting the presence of mitochondrial mutations identified in colonies. Rows represent colonies and color represents CH mutation status. Columns represent mitochondrial mutations. Shading notes presence of a mitochondrial mutation in a colony.

References: [1] Nam, *Nature* (2019). [2] Myers, *bioRxiv* (2022). [3] Miller, *Nat. Biotechnol.* (2022).

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RESULTS

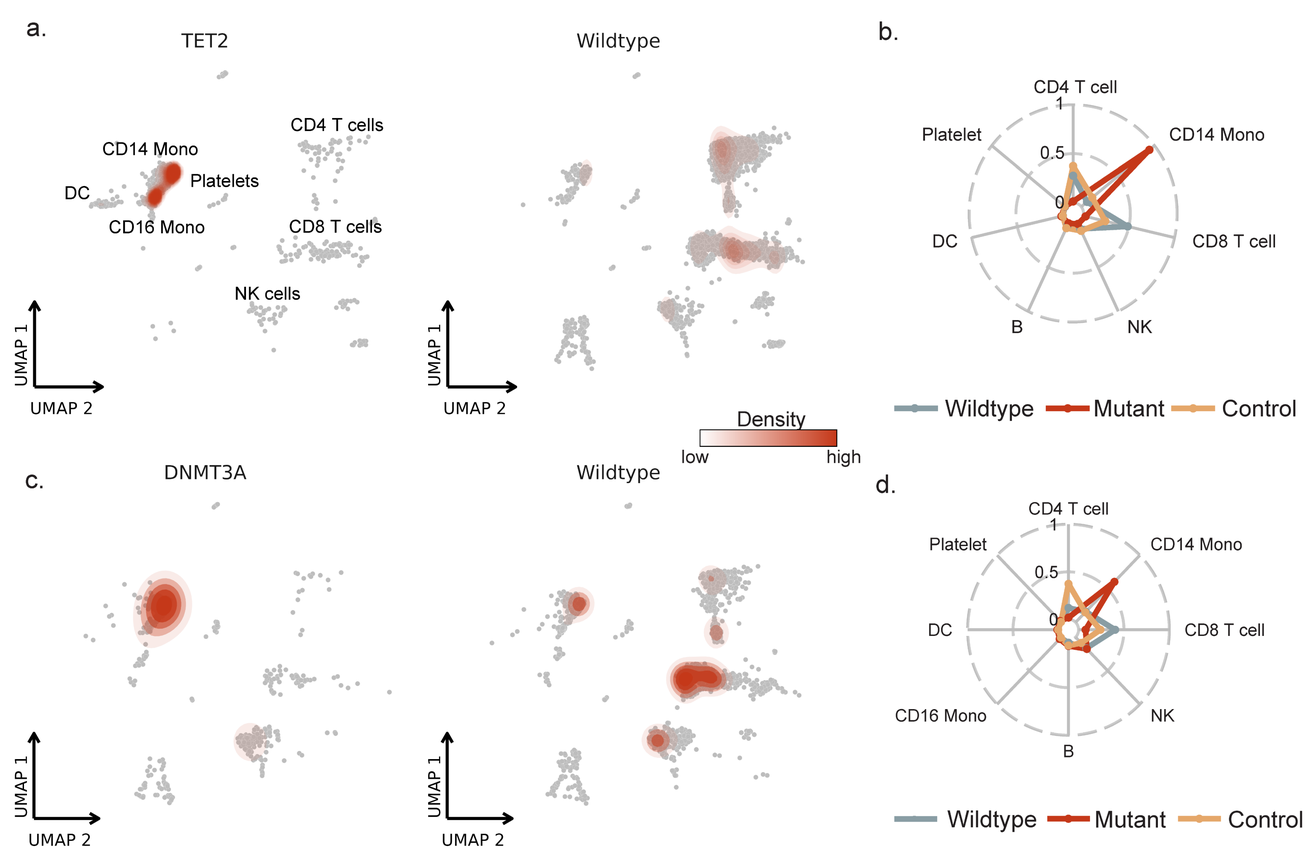

Figure 4: CD14+ monocytic skew present for patients with CH mutations.**a)** Density UMAP of mutated cells (left) and non-mutated (middle) exhibiting monocytic skew in both *TET2* and *DNMT3A* clones. **b)** Cell type proportions quantified in radar plots (right) (n = 4,425 and 872 in *TET2* and *DNMT3A,* respectively) plotted against non-mutated cells from within the same sample (n = 4,160 and 3,585). Aggregated controls (n = 36,373) plotted for reference.

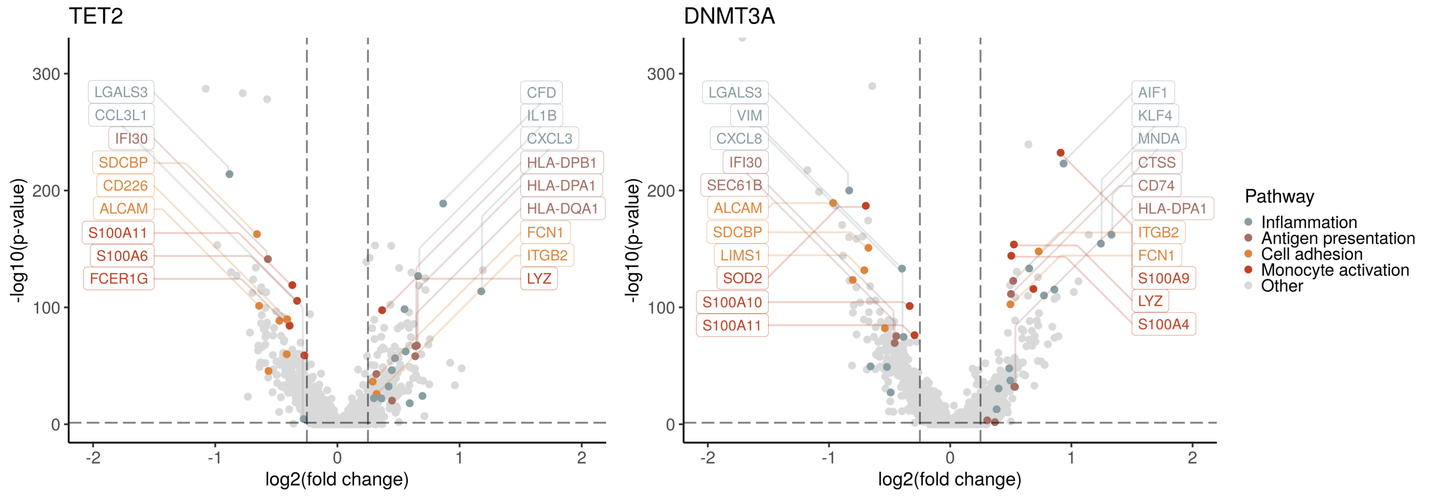

Figure 5: Basal gene expression analysis within the CD14+ monocyte cluster identified numerous differentially expressed gene across inflammation, antigen presentation, cell adhesion, and monocyte activation pathways in both (a) TET2 (n = 8) and (b) DNMT3A (n = 9) vs control samples (n=6). Significance of differentially expressed genes tested via Wilcoxon rank sum test (Seurat "FindMarkers" function, adjusted p < 0.05, abs(log2FC) > 0.25).

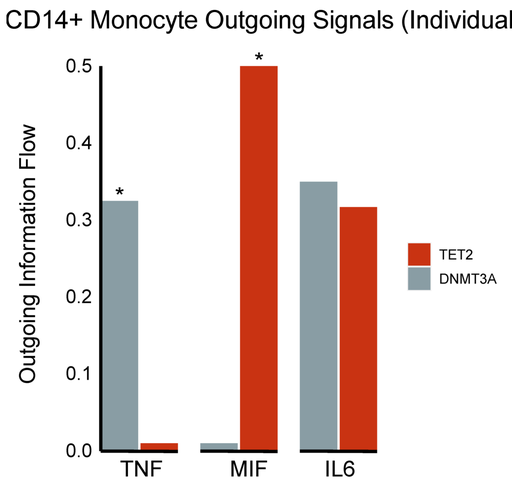

Figure 6: Quantitative outgoing signaling in mutated *TET2* and *DNMT3A* CD14+ monocytes compared to wildtype exposes divergent utilization of signaling pathways at baseline (* = p < 0.05 by permutation test).

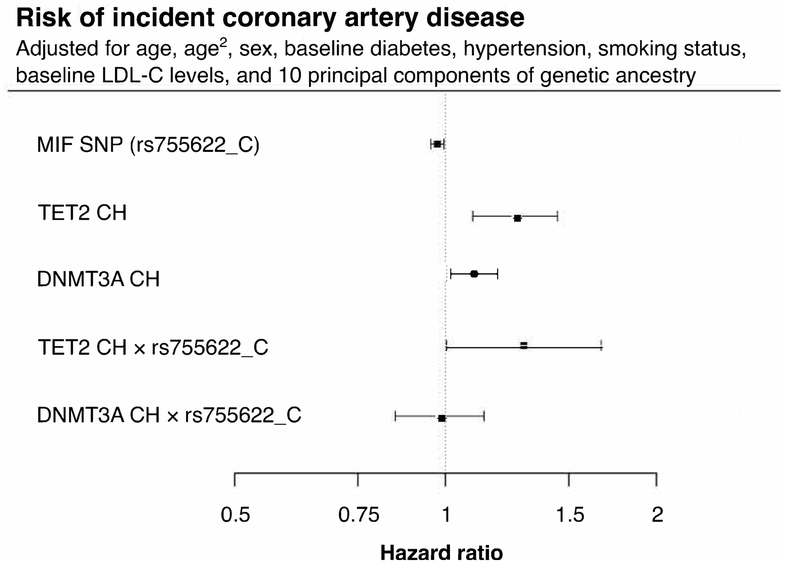

Figure 7: *TET2* CH with the *MIF* risk allele (rs755622) has a significantly elevated risk of incident CAD among 340,766 individuals in the UK Biobank. Error bars represent 95% confidence intervals. Imputed *MIF* expression is enhanced with the presence of rs755622 SNP.

CONCLUSION

Simultaneously resolving single-cell mutation status and gene expression revealed cell-intrinsic inflammatory pathophysiology in *TET2* CD14+ monocytes.

41st Annual Vanderbilt Research Forum - Abstract

Title: Chronic Toxicities from Adjuvant Anti-PD-1 Therapy for Advanced Melanoma: A Multicenter Study

Authors: Rachel S. Goodman, MBA[1]; J Randall Patrinely, MD, MBA[2]; Rachel Woodford, MBBS, MPhil[3]; Aleigha Lawless, BS[4]; Faisal Fa'ak, MD[5]; Asha Tipirneni, MD[6]; Hui-Ling Yeoh, MBBS, BMedSc[7]; Andrew Haydon, MBBS, FRACP, PhD[8]; Suthee Rapisuwon, MD[9]; Iman Osman, MD[10]; Janice Mehnert, MD[11]; Ryan Sullivan, MD[12]; Alexander M. Menzies, MBBS, PhD[13]; Matteo S. Carlino, MD, PhD[14]; Georgina Long, MD, PhD[15]; Douglas B. Johnson, MD, MSCI[16]

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Conflicts of Interest: DBJ has served on advisory boards or as a consultant for BMS, Catalyst Biopharma, Iovance, Jansen, Mallinckrodt, Merck, Mosaic ImmunoEngineering, Novartis, Oncosec, Pfizer, Targovax, and Teiko, has received research funding from BMS and Incyte, and has patents pending for use of MHC-II as a biomarker for immune checkpoint inhibitor response, and abatacept as treatment for immune-related adverse events.

Word Count: 296

Title: Chronic Toxicities from Adjuvant Anti-PD-1 Therapy for Advanced Melanoma: A Multicenter Study

Background: Anti-PD-1 therapy improves survival in advanced skin cancers and is increasingly used as adjuvant therapy for resected early-stage melanoma. Immune-related adverse events (irAEs) become chronic in 43% of high-risk melanoma patients treated with adjuvant anti-PD-1 therapy (1). The incidence, spectrum, and long-term outcomes of chronic irAEs in this population have not been well defined.

Objectives: To determine the incidence, characteristics, and long-term outcomes, including resolution versus persistence, of chronic immune-related adverse events from adjuvant anti-PD-1 therapy for resected high-risk melanoma.

Methods: Data was collected from six institutions from 2015 to 2022 on stage III to IV melanoma patients treated with adjuvant anti-PD-1 therapy. Patient demographics, treatment details, and acute, delayed, and chronic toxicity outcomes were tracked.

Results: Among 357 patients, 241 (67.5%) experienced acute irAEs, including 49 (20.3%) with grade 3-5 toxicities. Chronic irAEs, persisting 6 months after therapy cessation, developed in 163 (45.7%) patients, of which 86 (52.8%) were grade 2+ and four (2.5%) were grade 3-5. With long-term follow-up (median 1352 days), 37.4% (n=61) of patients experienced resolution of chronic toxicities at last follow-up. Of 417 toxicities, 187 (44.9%) became chronic. 32 (30.2%) cutaneous toxicities became chronic, compared with 155 (49.2%) non-cutaneous toxicities. Dermatitis/pruritis (82.6%, n=114) was the most common cutaneous irAE manifestation, followed by vitiligo (9.4%, n=13) and psoriasis (3.6%, n=5).

Conclusion: To date, this is the largest analysis of long-term toxicities in patients with adjuvant anti-PD-1 therapy for advanced melanoma. Chronic irAEs are common and often persist with long-term follow-up. Over half of chronic toxicities are significant (grade 2+) and can affect nearly every organ system. These findings underscore the importance of increased awareness of the likelihood of long-term and persistent toxicities when considering adjuvant therapies, and the need for long-term monitoring and management of patients who have undergone anti-PD-1 therapy.

References

1. Patrinely JR, Jr., Johnson R, Lawless AR, Bhave P, Sawyers A, Dimitrova M, et al. Chronic Immune-Related Adverse Events Following Adjuvant Anti-PD-1 Therapy for High-risk Resected Melanoma. JAMA Oncol. 2021;7(5):744-8.

Time to Clinic Presentation After Sports Related Concussion: Do Social Determinants Matter?

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Submitted for oral poster presentation at the American Association of Neurological Surgeons Conference, April 21st-23rd, Los Angeles, CA.

Introduction: Emerging evidence suggests that delayed time to concussion clinic is associated with prolonged recovery following sports related concussion (SRC); however, social determinants and clinical risk factors have not been investigated for their influence on time to evaluation. Thus, the aim of this study was to investigate the association between various social and clinical risk factors and time to presentation following SRC in young athletes.
Methods: A retrospective cohort study was conducted in a regional sports concussion center between 11/2017-04/2022. Participants were adolescents (12-18 years old) who sustained SRC. The primary measure was time to a concussion specialist. Patients were excluded if they were outside of the specified age range, presented to any healthcare provider after 14 days, presented to our clinic after 90 days, or had a prior history of brain surgery, meningitis, or seizures.
Results: A total of 945 participants met inclusion criteria. The mean age of athletes was 15.8 (SD=1.61), and the mean amount of time it took to present to clinic was 6.8 days (SD=9.03). Comparisons between time to presentation and our social determinant variables found no significant differences across race, school type, and insurance status, however, there was a statistically significant difference between ethnicity ($t=3.97$, $p=.007$) such that athletes who identified as Hispanic/Latino took longer to present to clinic than non-Hispanic/Latino athletes. There were also statistically significant differences found for loss of consciousness (LOC) ($p=.035$) and amnesia ($p=.006$) at time of injury, such that patients who experienced these symptoms took longer to present to clinic. Moreover, positive family history of psychiatric disorders ($p<.001$) or migraines ($p<.001$), as well as existing personal psychiatric history ($p<.001$) were associated with longer time to presentation. A multivariate linear regression of all risk factors was employed. Listed in order from greatest to least, significant predictors of time to clinic were family psychiatric history ($\beta=0.15$, $p<.001$), family migraine history ($\beta=0.14$, $p<.001$), insurance status ($\beta=0.10$, $p=.020$), ethnicity ($\beta=0.09$, $p=.027$), amnesia at time of concussion ($\beta=0.09$, $p=.036$), and sex ($\beta=0.080$, $p=.045$).
Conclusions: Our findings suggest that ethnicity, amnesia at time of concussion, family migraine history and family psychiatric history were all significant predictors of time to clinic presentation, where family histories of psychiatric disorders and migraines were the strongest predictors of timeliness. In order to better understand what groups are most at-

risk and in need of greater attention, further research is needed to confirm our findings and determine the mechanism by which these relationships exist.

Tables and Figures.

Table 1. Descriptive statistics of athletes across all study variables

Variables		**Mean ± Standard Deviation**
Age (years)		15.8 ± 1.61
Time to Any Healthcare Provider (days)		3.02 ± 3.39
Time to Concussion Clinic (days)		6.79 ± 9.03
Variables (included sample size)		**Frequency (%)**
Sex (n=945)	Male	627 (66.3%)
	Female	318 (33.7%)
Race (n=945)	White	656 (69.4%)
	Other	289 (30.6%)
Ethnicity (n=914)	Non-Hispanic/Latino	914 (96.7%)
	Hispanic/Latino	31 (3.3%)
School Type (n=653)	Public	458 (70.1%)
	Private	195 (29.9%)
Insurance Status (n=926)	Public	145 (15.7%)
	Private	781 (84.3%)
Prior Concussion History (n=937)	None	582 (62.1%)
	1 or more	355 (37.9%)
Loss of Consciousness (n=944)	No	819 (86.8%)
	Yes	125 (13.2%)
Amnesia (n=936)	No	757 (80.9%)
	Yes	179 (19.1%)
Learning Disability (n=940)	No	910 (96.8)
	Yes	30 (3.2%)
ADHD (n=940)	No	841 (89.5%)
	Yes	99 (10.5%)
Psych history (n=937)	No	848 (90.5%)
	Yes	89 (9.5%)
Migraine history (n=940)	No	844 (89.8%)
	Yes	96 (10.2%)
Family Psych History (n=917)	No	797 (86.9%)
	Yes	120 (13.1%)
Family Migraine History (n=927)	No	687 (74.1%)
	Yes	240 (25.9%)

Table 2. T-Tests of social and clinical variables on time to presentation

Variables		Time to Concussion Clinic	
		Mean ± Standard Deviation	**P-Value**
Race	White	6.62 ± 8.51	.366
	Other	7.19 ±10.12	
Ethnicity	Non-Hispanic/Latino	6.65 ± 8.73	**.007**
	Hispanic/Latino	11.10 ± 15.07	
School Type	Private	5.87 ± 8.82	.125
	Public	6.70 ± 9.25	
Insurance Status	Private	6.64 ± 9.05	.093
	Public	8.02 ± 9.20	
Sex	Male	6.43 ± 8.61	.086
	Female	7.50 ± 9.74	
Loss of Consciousness	No	6.55 ± 8.35	**.035**
	Yes	8.38 ± 12.60	
Amnesia	No	6.42 ± 8.55	**.006**
	Yes	8.47 ± 10.88	
Learning Disability	No	6.75 ± 8.97	.315
	Yes	8.43 ± 11.58	
ADHD	No	6.80 ± 9.08	.964
	Yes	6.84 ± 8.83	
Personal Psych History	No	6.29 ± 7.54	**<.001**
	Yes	11.60 ± 17.29	
Personal Migraine History	No	6.73 ± 9.27	.497
	Yes	7.40 ± 6.88	
Family Psych History	No	6.14 ± 7.57	**<.001**
	Yes	11.28 ± 15.38	
Family Migraine History	No	5.74 ± 7.31	**<.001**
	Yes	9.83 ± 12.42	

Table 3. Spearman correlations for age and prior concussion history

Variables	**Time to Specialist**	
	r_s	**p-value**
Age	-0.104	.001
Prior Number of Concussions	0.014	.663

Table 4. Multivariate regression analysis of social determinants and clinical predictors on time to clinic

Social Variables	Time to Clinic Presentation	
	OR/β (95% CI)	**p-value**
Race	0.01 (-2.35, 10.25)	.218
Ethnicity	0.089 (0.40, 6.69)	**.027**
School Type	0.01 (-1.24, 1.48)	.863
Insurance Status	0.10 (0.33, 3.77)	**.020**
Clinical Variables		
Loss of Consciousness	0.02 (-1.41, 2.43)	.604
Amnesia	0.09 (0.12, 3.38)	**.036**
Personal Migraine History	0.01 (-1.90, 2.16)	.900
ADHD	-0.02 (-2.42, 1.56)	.688
Personal Psychiatric History	0.04 (-1.18, 3.17)	.369
Learning Disability	0.073 (-0.24, 6.61)	.069
Prior Concussions	-0.07 (-1.20, 0.085)	.089
Family Migraine History	0.14 (0.95, 3.91)	**.001**
Family Psychiatric History	0.15 (1.525, 5.19)	**<.001**
Age	0.00 (-0.38, 0.39)	.989
Sex	0.08 (0.033, 2.68)	**.045**

Machine Learning Model Accurately Predicts Myxoid Soft Tissue Tumor Diagnosis

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INTRODUCTION: Benign and malignant myxoid soft tissue tumors have overlapping imaging, histological, and clinical features, which contributes to an indeterminate preoperative diagnosis in 30-40% of cases. As treatment strategies differ for these tumors, accurate preoperative diagnosis is critical. We trained a radiomics-based machine learning (ML) model to classify benign vs malignant myxoid tumors and compared its performance to that of musculoskeletal radiologists.

METHODS: 90 patients with a pre-treatment MRI and a histologically confirmed myxoid tumor were identified (45 myxomas and 45 myxofibrosarcomas). Radiomic features were extracted using PyRadiomics and a LASSO model was used for feature reduction. Using these features, five ML models were trained to classify tumors as either benign or malignant in an initial cohort of 40 patients, and then validated in a separate cohort of 50 patients. Two attending radiologists independently classified these 50 tumors as benign or malignant; in discordant cases, a third senior radiologist made the consensus diagnosis.

RESULTS: The best ML model was a logistic regression model with an AUC of 0.792. This ML model classified 78% (39/50) of tumors correctly compared to 74% (37/50) by radiology consensus. When radiologists 1 and 2 were discordant (14/50), the senior radiologist classified 50% of tumors (7/14) correctly compared to 86% (12/14) by the ML model. When radiologists 1 and 2 rated their confidence in the diagnosis as 'consistent with', they had a cumulative 95% accuracy (37/39) compared to 62% accuracy (38/61) when they rated their confidence as 'equivocal/probably'. In comparison, in these cases of lower confidence, the ML model had 74% accuracy (45/61).

DISCUSSION AND CONCLUSION: Overall, our ML model performed similarly to radiologists in predicting myxoid tumor diagnosis. However, radiologist confidence strongly correlated with diagnostic accuracy. These data suggest that radiomics may provide novel diagnostic utility when radiologist confidence is low or when radiologists disagree.

Machine Learning Model Accurately Predicts Myxoid Soft Tissue Tumor Diagnosis

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Introduction

- Differentiating benign and malignant musculoskeletal myxoid soft tissue tumors can be challenging due to their shared clinical, imaging, and histologic features.
- Our recent institutional experience of >200 patients revealed a nearly 30% indeterminate diagnosis rate after biopsy and prior to resection; histology commonly resulted as “low grade myxoid neoplasm”.
- As treatment strategy (resection type +/- adjuvant therapy) differs between myxomas and myxofibrosarcomas, accurate preoperative diagnosis is preferred.
- Radiomics, a method of machine learning that consists of large data extraction from medical images, has shown early potential in predicting diagnosis/prognosis of musculoskeletal tumors.

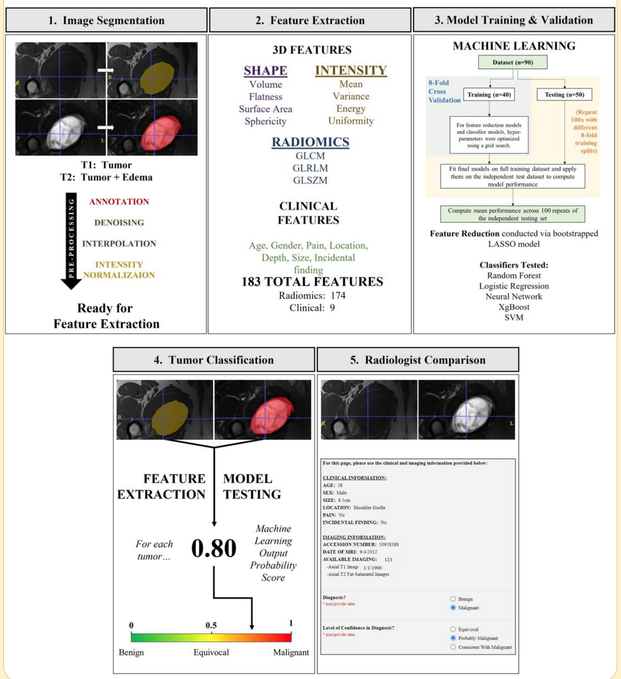
Questions

- Can a machine learning based predictive model reliably differentiate benign and malignant musculoskeletal soft tissue myxoid tumors?
- How does this model compare to musculoskeletal radiologists?

Study Design

- 40 patients with pre-treatment MRI and final resection histology confirmed myxoid tumors
- Baseline clinical features collected
- Manual image segmentation performed
- LASSO model used for MRI feature reduction
- Five ML classifiers were developed
- ML model was validated with new cohort
- ML model was compared to musculoskeletal radiologist consensus for new cohort

Figure 1. Study design.

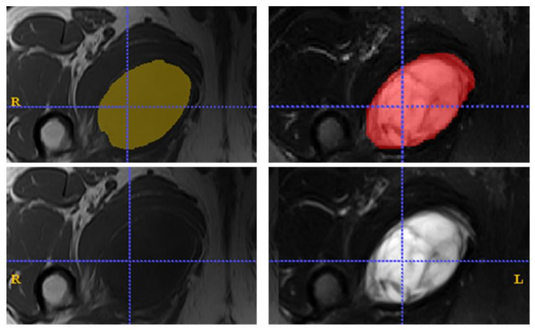


Tumor Segmentation

- 3D slicer software was used for manual tumor segmentation of axial MR images by a team of an orthopaedic oncologist, radiation oncologist, a radiation oncology resident and two medical students. All were reviewed by one attending musculoskeletal radiologist and edited as indicated.

- T1-weighted and T2-weighted MR axial images were segmented separately
  - T1 image = tumor alone segmented
  - T2 image = tumor + edema segmented

Figure 2. Example tumor segmentation.



T1-weighted image T2-weighted image

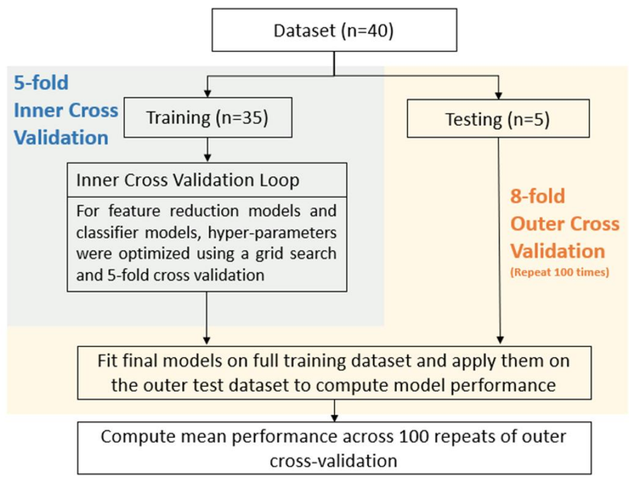
Feature Extraction

- pyRadiomics toobox was used to extract radiomics features from the processed images
- For each image, 87 3D radiomics features were extracted from the pre-defined ROI including:
  - 14 shape features
  - 18 first-order features
  - 23 Gray Level Co-occurrence Matrix (GLCM) features
  - 16 Gray Level Size Zone Matrix (GLSZM) features
  - 16 Gray Level Run Length Matrix (GLRLM) features
- LASSO model reduced features to avoid overfitting
- Features with low stability scores were removed

Model Construction & Validation

- Selected features trained machine learning models and nested-cross validation was utilized.

Figure 3. Model Construction & Validation Schematic.



Results

Table 1. AUC and Accuracy of ML models.

Classifier	Evaluation Metrics	T1 radiomics + T2 radiomics + Clinical features	Clinical Features
Random Forest	AUC	0.765 ± 0.038	0.589 ± 0.038
Ridge Regression		0.772 ± 0.053	0.627 ± 0.039
Neural Network		0.729 ± 0.058	0.540 ± 0.056
XGBoost		0.738 ± 0.039	0.569 ± 0.037
SVM		**0.780 ± 0.042***	0.359 ± 0.071
Random Forest	Accuracy	0.716 ± 0.045	0.599 ± 0.041
Ridge Regression		0.751 ± 0.049	0.640 ± 0.034
Neural Network		0.718 ± 0.057	0.514 ± 0.051
XGBoost		0.696 ± 0.046	0.597 ± 0.041
SVM		**0.757 ± 0.052***	0.548 ± 0.054

Figure 4. ROC for Model to Predict Malignancy.

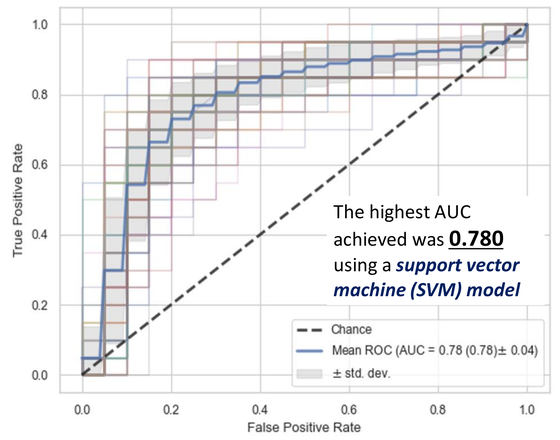
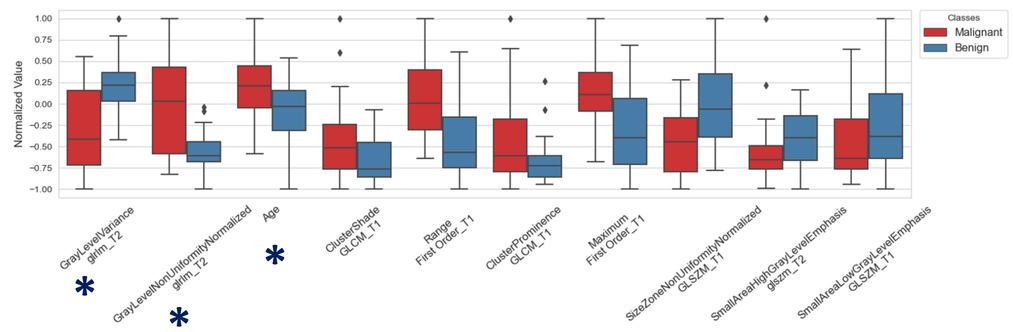


Figure 5. Box-and-whisker plots of the top-10 selected radiomics/clinical features.



For these features, the box plots between the two classes have relatively small overlapping regions, which indicate high discriminatory power between the two classes.

* = top 3 features

Figure 6. Performance of radiomics (ML) vs. two radiologists and radiologist consensus.

Performance	Radiomics (%)	Radiologist 1 (%)	Radiologist 2 (%)	Consensus (%)
Accuracy	78.0	72.0	76.0	74.0
Sensitivity	72.0	80.0	64.0	72.0
Specificity	84.0	64.0	88.0	76.0
PPV	81.8	69.0	84.2	75.0
NPV	75.0	76.2	71.0	73.1

Radiomics vs. Radiologists	Comparison[a]	P-Value
	Radiomics vs. Radiologist 1	0.146
	Radiomics vs. Radiologist 2	0.606
	Radiomics vs. Consensus	0.789

PPV = positive predictive value; NPV = negative predictive value; [a] = using McNemar test.

Key Takeaways

CURRENT PROBLEM:

- **Differentiating benign and malignant musculoskeletal myxoid soft tissue tumors can be challenging** due to their shared clinical, imaging, and histologic features.

WHAT THIS STUDY ADDS:

- Classification models using **T1 and T2 radiomics features + clinical features** perform **better** in differentiating benign and malignant myxoid soft tissue tumors than models **using clinical features alone.**
- The ML predictive model and radiologist consensus diagnosis were **relatively similar in this study**, though **the ML model was helpful in cases of radiologist discordance and/or when diagnosis is less certain to radiologists.**

FUTURE DIRECTION:

- Future studies include validation of these preliminary findings and **expansion to include other musculoskeletal tumors.**

Second Void Trials: Who Needs 'Em?

Postoperative urinary retention is a common complication of urogynecology surgery that is often monitored with postoperative trials of void (TOV). TOVs can vary tremendously between institutions with some using active versus passive TOVs. Our institution utilizes passive TOVs, but additionally allows patients two opportunities to pass prior to considering discharge with a foley catheter. However, utilization of a second TOV is uncommon and not well-described in current literature. The primary objective of this study is to investigate characteristics of patients requiring one versus two TOVs after urogynecology surgery. Secondary objectives include examining differences in opioid use, length of stay, and urinary tract infection rates between patients requiring one versus two TOVs.

As part of an IRB-exempt project implementing a new TOV protocol at Vanderbilt University Medical Center, patients undergoing urogynecology surgery between 12/1/2021 and 08/25/2022 were identified. Pertinent variables were collected both retrospectively and prospectively from the electronic medical record and collated in a HIPPA-compliant REDcap database. Microsoft Excel was used to calculate pertinent statistics.

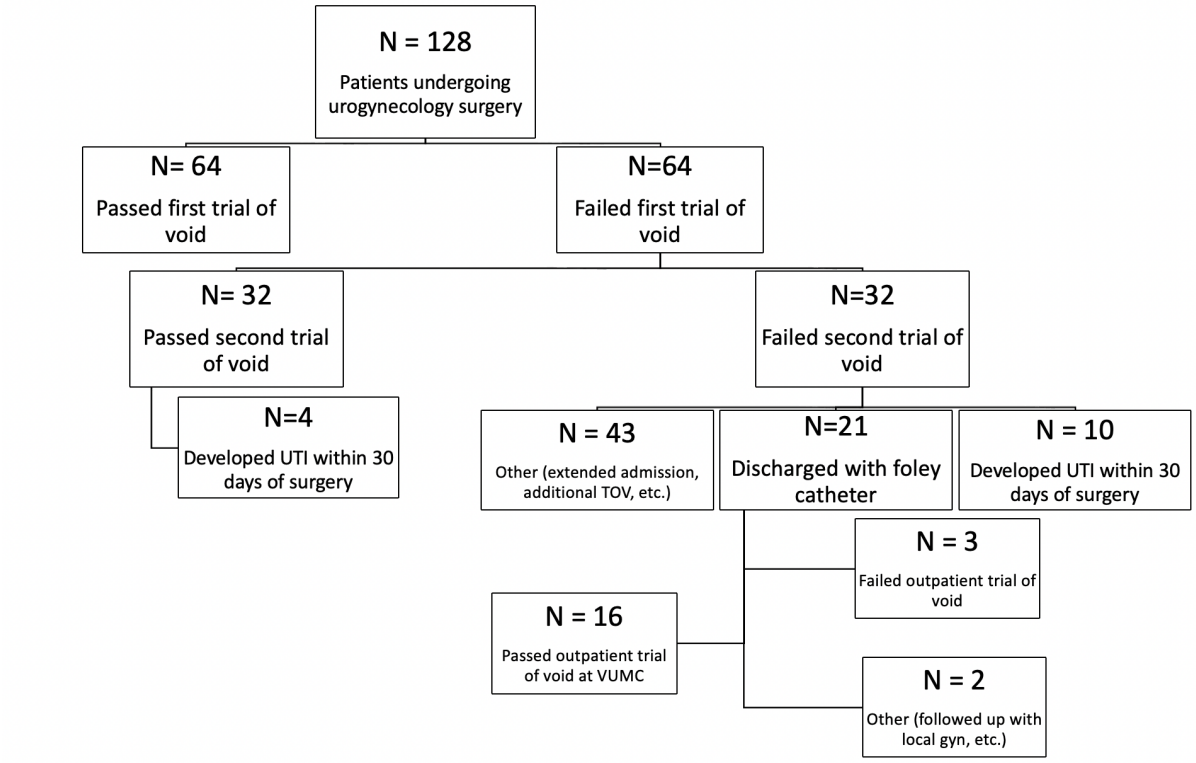
128 Patients were categorized into two groups; passing versus failing the first postoperative TOV. Figure 1 summarizes pertinent patient characteristics. Half of patients (n=64) failed their first TOV. Of the patients who failed their first TOV, 32 failed their second TOV. Patients who failed their first postoperative TOV were more likely to have had a colporrhaphy and/or paravaginal repair, and were more likely to have had robotic or laparoscopic surgery. Figure 1 summarizes patient outcomes from both groups. Notably, 15.63% of patients who failed their first TOV developed urinary tract infections compared to 6.3% of patients who passed. Patients who failed their first TOV were admitted to the hospital for approximately four additional hours compared to patients who passed.

A second attempt at a passive postoperative TOV brought overall TOV failure to 25% from 50% after a single trial. Future cost effective analysis is warranted to determine the efficacy of this approach to evaluating postoperative urinary function after urogynecology procedures.

Table 1:

	Variable	Failed First Trial of Void	Passed First Trial of Void	P-value
Demographics	Age (years) at surgery	59.85 years	57.42 years	0.27
	BMI	28.23	30.49	0.06
Surgical Approach	Vaginal Surgery	79.69%	82.8%	0.65
	Abdominal Surgery	3.13%	10.9%	0.08
	Laparoscopic Surgery	6.25%	1.6%	0.17
	Robotic Surgery	10.94%	4.7%	0.19
Surgical Procedure	Hysterectomy	43.75%	32.8%	0.20
	Anterior Repair	40.63%	18.8%	0.01
	Posterior Repair	35.94%	15.6%	0.01
	Paravaginal Repair	21.88%	7.8%	0.03
Opioid Use	Total MME	32.06 MME	33.15 MME	0.21
Duration	Minutes from Closure to Discharge	858.42 minutes	600.91 minutes	0.88

Figure 1:



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Duration	Minutes from Closure to Discharge	858.42 minutes	600.91 minutes	0.88

Shone's Complex: Not So 'Simple' After All

Lyana Labrada, Jeremy Mazurek, Christiane Haeffele, Dan Clark, Angela Weingarten, Tripti Gupta, Jonathan N. Menachem

Introduction:

Shone's Complex is described as a series of left sided obstructive lesions, including supramitral ring, subaortic obstruction, aortic coarctation, and parachute mitral valve. Although rare, an increasing number of these patients are being referred to quaternary heart transplant centers for advanced therapies. As these patients often present late in their disease course, they present challenges both in evaluating candidacy for transplant, and managing their post-operative courses. We present a series of four patients among two institutions with Shone's complex who were referred for advanced therapies evaluation, and underwent heart transplantation.

Summary

We present four cases from two institutions of patients with Shone's Complex who underwent either heart transplant alone (n=3), or combined heart-liver transplant (n=1). All four patients had evidence of group II pulmonary hypertension (PH), and 3 patients had pre-operative right heart catheterization demonstrating reversibility of PH with Nipride administration. Each patient was treated with pulmonary vasodilators pre-operatively, and one patient required long term continuation. Two out of the four patients had prolonged intubation requiring tracheostomy placement. Each patient had a prolonged hospitalization post-transplant (30, 31, 60, 115 days), and one patient died on the index hospitalization in the setting of multiple post-operative complications. These cases highlight several key factors in managing patients with Shone's Complex undergoing transplantation. Development of group II PH in the setting of long-standing left heart disease may require careful treatment with pulmonary vasodilators both pre-and post-operatively. Additionally, the presence of PH may complicate candidacy for single organ transplant, and must be carefully followed to assess the appropriate timing of transplant referral. Peri-operatively, patients are at increased risk for pulmonary complications given long standing disease, and often multiple prior sternotomies.

Conclusion:

Although Shone's Complex is often classified as 'simple congenital heart disease', patients who progress to the point of needing advanced therapies are often late in their heart failure course, with a lifetime of hemodynamic alterations which may subsequently affect their candidacy for transplant, need for dual organ transplant, and peri-operative management.

Implementation of a Point of Care Clinical Decision Support System Improves Recognition and Appropriate Linkage to Care of Patients with Non-Alcoholic Fatty Liver Disease within a Primary Care Clinic Setting

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BACKGROUND

- Recent guidelines have recommended screening for non-alcoholic fatty liver disease (NAFLD) within primary care settings by primary care providers (PCPs) using noninvasive testing tools
- Real-world performance of such screening can be limited by time constraints and workflow barriers

STUDY AIM

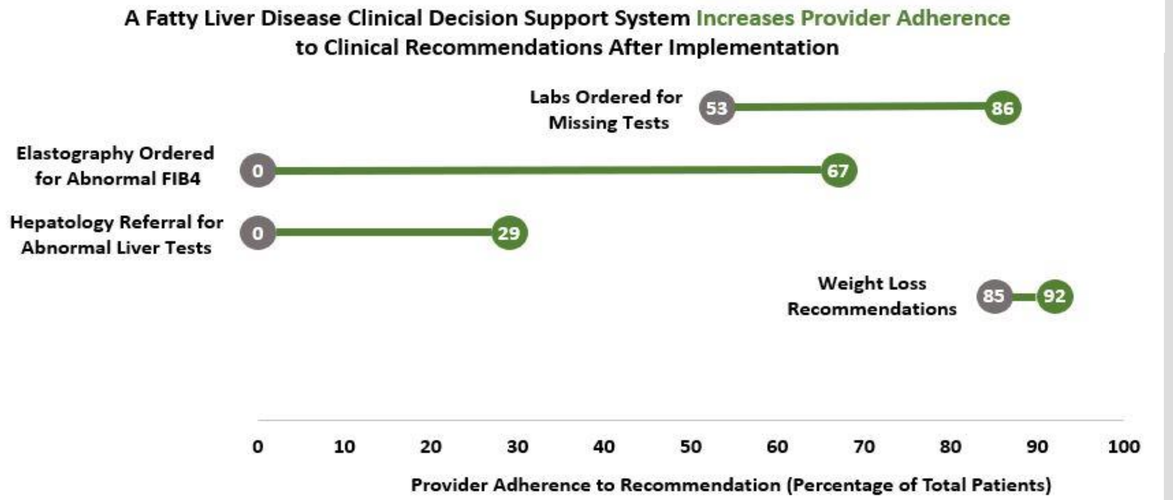
Assess the impact of implementation of a point of care clinical decision support system (CDSS) embedded within the electronic health record (EHR) on management of patients with NAFLD during primary care clinic visits

METHODS

- Prospective before-after study of patients seen by a pilot group of 42 PCPs at a single-institution primary care clinics
- Inclusion: in office or telehealth primary care visit, existing primary care provider within our institution, existing diagnostic codes for non-alcoholic fatty liver disease or non-alcoholic steatohepatitis
- Exclusion: liver transplant recipients, not established with hepatology
- Through an interruptive alert and dynamic order set, providers were presented with order recommendations for either laboratory tests, hepatology referral, or elastography (shear wave or magnetic resonance, depending on body mass index)

RESULTS

- 125 total patients included (66 pre-implementation, 59 post-implementation)
- Adherence to patient-specific guideline-based recommendations increased significantly for patients missing screening labs, those with elevated liver enzymes, and those with abnormal FIB4 scores (FIB4 > 1.3)
- Hepatology referrals increased significantly post-implementation



	Before Implementation N = 66 *n (%)*	After Implementation N = 59 *n (%)*	p-value
NAFLD Diagnosis Added to Visit Encounter	13 (20%)	29 (49%)	**< 0.001**
Total Alerts Fired	66 (53%)	59 (47%)	0.14
Provider Adherence to Guideline Recommendations	27 (41%)	39 (66%)	**0.005**
Missing Labs	19 (29%)	22 (37%)	
Recommended Action: Order Labs	10/19(53%)	19/22(86%)	**0.018**
Abnormal Liver Chemistry	17 (26%)	21 (36%)	
Recommended Action: Hepatology Referral	0/17 (0%)	6/21 (29%)	**0.024**
Normal Labs, Abnormal FIB4	10 (15%)	3 (5.1%)	
Recommended Action: Order Elastography	0/10 (0%)	2/3 (67%)	**0.038**
Normal Labs, Normal FIB4	20 (30%)	13 (22%)	
Recommended Action: Weight Loss Recommendations, No Further Testing	17/20(85%)	12/13(92%)	> 0.9

CONCLUSION

- Implementation of clinical decision support system within primary care practice can significantly increase adherence to guideline-based recommendations delivered at the point of care
- Native EHR technology can standardize equitable care delivery within primary care practices for patients with NAFLD

FUTURE DIRECTIONS

- Assess the impact of CDSS on NAFLD outcomes
- Identify persistent barriers to CDSS adoption from providers
- Expand the use of the CDSS tool within other clinical areas

ACKNOWLEDGEMENTS

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DISCLOSURES

None

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HIV is Associated With Worse Muscle Quality & Insulin Resistance in People with Type 2 Diabetes

Swartz, Alison Z., Koethe, John R., Silver, Heidi J.

Introduction: Insulin resistance (IR) in the muscle has been identified as the main defect of type 2 diabetes (T2DM). In people without HIV, decreased muscle quantity and decreased muscle quality (increased muscle fat) have been linked to worsened IR, by way of inflammatory changes in the muscle. People with HIV have increased baseline inflammatory markers, decreased muscle quantity, and decreased muscle quality compared to HIV negative people. However, the effects of muscle quality and quantity in people with HIV on IR are unknown.

Hypothesis: Markers of IR will be worse in HIV+ subjects at least in part by way of decreased muscle quantity and quality.

Methods: This subgroup analysis of the HATIM cohort study investigated 36 people with well-controlled HIV and 23 HIV- people with T2DM who had undergone body composition CT scans. Subjects were enrolled between 2017-2020 at VUMC. Mean CT-quantified skeletal muscle attenuation/radio density (SMD) in Hounsfield units (HU) at L3 was used to determine muscle quality. Skeletal muscle index (L3 muscle area (cm^2)/ height $(m)^2$) was used to evaluate muscle quantity. Markers of IR included the Homeostasis Model Assessment 1 of Insulin Resistance (HOMA1-IR) and fasting blood glucose (mg/dL). Statistical analyses were performed using R 4.2.2.

Results: HIV+ subjects with T2DM had significantly higher visceral fat (VAT)/subcutaneous adipose (SAT) ratio (mean 1.00 ± SD 0.68 vs 0.64 ± 0.39, p=0.02), higher fasting glucose (192 ± 81 mg/dL vs 137 ± 47 mg/dL, p=0.002) and significantly higher HOMA1-IR (19.8 ± 17.4 vs 10.8 ± 7.7, p=0.01) as compared to HIV- subjects. After adjusting for age, race, BMI, and sex, HIV was associated with decreased SMD (β_{HIV}=-8.0, p_{HIV} = <0.001, adj R^2=0.55) but not SMI (β_{HIV}=-1.31, p_{HIV} = .61, adj R^2=0.47). After adjusting for insulin use, sex, and race, SMA and SMI were positively associated with increased insulin resistance (β_{SMA}=0.51, p_{SMA}=0.01, β_{SMI}=0.36, p_{SMI}=0.04, adj R^2=0.51).

Conclusions: Patients with HIV demonstrated both decreased muscle quality and greater insulin resistance. However, decreased muscle quality was associated with decreased IR rather than greater IR as expected. Larger studies evaluating lifestyle factors and investigating non-diabetic, pre-diabetic, and diabetic patients could help understand why patients with HIV have poorer T2DM control, as well as identify potential effects of worsened muscle quality.

HIV is Associated With Worse Muscle Quality & Insulin Resistance in People with Type 2 Diabetes

Swartz, Alison Z., Koethe, R. John, Silver, Heidi J.

INTRODUCTION

- People with HIV (PWH) are at greater risk of type 2 diabetes (T2DM), and it is unclear why [1–5]
- Muscle is one of the most important organs for glucose regulation and is responsible for approximately 85% of insulin-mediated glucose uptake.[6,7]
  - In people without HIV, intramuscular fat is a stronger predictor of T2DM than visceral adipose tissue (VAT).[6–9]
  - In HIV- cohorts, decreased muscle mass has been linked to increased insulin resistance (IR)[7]
- Although PWH have greater skeletal muscle fat (decreased muscle quality)[21] and decreased muscle mass (decreased muscle quantity)[22] than HIV negative people, the relationship between muscle quality/quantity and insulin resistance in people with HIV and type 2 diabetes is unknown.
- This pilot study aims to investigate the relationship between muscle quality and IR and identify ideal sample sizes for future studies by comparing HIV+ patients with T2DM to HIV- patients with T2DM.

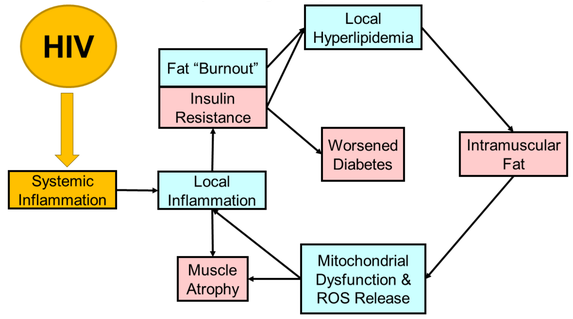
MATERIALS & METHODS

This is a subgroup analysis of the HIV, Adipose Tissue Immunology, and Metabolism Study (HATIM) study with methods previously described elsewhere.[20,21]

- **Population and Design**
  - 36 HIV+, 23 HIV- participants from VUMC enrolled from August 2017-March 2020, with race self-reported
  - **Inclusion Criteria:** Well-controlled HIV, completed body composition CT scan, and diabetes
  - **Exclusion Criteria:** Inflammatory/rheumatologic conditions, heavy alcohol or illicit drug use, current DPP-4 Inhibitor use
- **CT-Imaging**
  - Two non-contrast scans were performed, one at L3/L4 and one at the thorax
    - Muscle attenuation ranges from -29 to +150 Hounsfield units (HU), and fat attenuation ranges from -190 to -30 HU [13,14]
  - Osirix[15] software was used to determine SAT, VAT, pericardial fat, and liver attenuation
  - Automated software from the University of Alberta[16] was used to determine muscle area (SMA) and muscle radiodensity (SMD) at the L3/L4 level
- **Statistical Analysis**
  - Statistical analyses were performed in R-Studio using R 4.2.2.[19] Packages used include ggpubr, corrplot, dplyr, car, plyr, olsrr, MASS, generalhoslem, PRESS[20], and pwr.

HYPOTHESIS

- **Hypothesis:** Markers of diabetes control will be worse in T2DM HIV+ patients at least in part by way of worsened muscle quality.



RESULTS

Table 1: Demographics

Baseline Characteristic	HIV+ (n=36)	HIV- (n=23)	p-value
Age (Years)	51.22 ± 10.22	54.87 ± 11.23	0.21
Sex			<0.001#
Male	25 (69%)	5 (22%)	
Female	11 (31%)	18 (78%)	
Race (Self-Reported)			0.20#
White	16 (44%)	15 (65%)	
Black/Other	20 (56%)	8 (35%)	
BMI (kg/m^2)	36.39 ± 8.26	38.28 ± 5.74	0.30
Cytokines			
HS-CRP (mcg/ml)	9.13 ± 15.43	8.46 ± 7.9	0.83
IL1-β (pg/ml)	0.2 ± 0.09	0.42 ± 0.17	<0.001
IL-6 (pg/ml)	1.81 ± 1.01	2.63 ± 1.23	0.02
IL-8 (pg/ml)	7.89 ± 3.38	10.55 ± 3.43	0.01
Insulin Resistance			
HBA1c%	7.84 ± 2.13	7.08 ± 1.24	0.09
Fasting Glucose (mg/dL)	191.74 ± 80.68	137.17 ± 46.87	0.002
HOMA1-IR	19.81 ± 17.43	10.75 ± 7.7	0.01
On Non-Insulin Anti-Diabetic	27 (75%)	15 (65%)	0.61#
Taking Insulin	10 (28%)	2 (9%)	0.10^
Body Characteristics			
Skeletal Muscle Area (cm^2)	179.12 ± 36.1	159.12 ± 44	0.08
SMI (cm^2/m^2)	60.84 ± 11.06	57 ± 10.18	0.18
SMD (HU)	35.23 ± 7.06	36.4 ± 7.17	0.54
VAT/SAT Ratio	0.99 ± 0.67	0.65 ± 0.38	0.01
Waist Hip Ratio	1.00 ± 0.09	0.95 ± 0.09	0.02
Pericardial fat vol (cm^3)	136.94 ± 107.52	218.25 ± 124.03	0.01

Mean ± SD or Number (percentage), p-value; # Pearson's Chi-Squared, ^ Fisher's Exact, unmarked p-val are Welch Two-Sample T-test
HbA1c: Glycated Hemoglobin, HOMA-IR: Homeostatic model assessment for insulin resistance, VAT: Visceral adipose tissue, SAT: Subcutaneous adipose tissue, HU: Hounsfield Units, SMI: Skeletal Muscle Index, SMD: Skeletal Muscle Attenuation (HU)

Table 2 & 3: Linear Regressions

Outcome: SMD (HU) Adjusted R^2: 0.55 Predicted R^2: 0.47 Model p<0.001				Outcome: SMI (cm^2/m^2) Adjusted R^2: 0.47 Predicted R^2: 0.40 Model p<0.001			
Covariate	β-Coefficient	Std. Error	t-value	Covariate	β-Coefficient	Std. Error	t-value
HIV Positive	-7.98***	1.7	-4.69	HIV Positive	-1.31	2.55	-0.51
Male Sex	6.74***	1.61	4.18	Male Sex	9.87***	2.55	3.88
Age (years)	-0.29***	0.07	-4.09	BMI (kg/m^2)	0.74***	0.15	4.97
BMI (kg/m^2)	-0.25*	0.12	-2.06	Caucasian Race	-5.53*	2.33	-2.37
Caucasian Race	-3.05.	1.59	-1.92	Age (years)	-0.19.	0.11	-1.78
IL-6 (pg/mL)	-1.98*	0.84	-2.37				

Table 2: Linear Regression Model of fasting blood glucose and HOMA1-IR adjusted for insulin use, race, and sex.
*** p<0.001, **p<0.01, *p<0.05, . p<0.10. All multivariate linear regressions were performed in R Studio using R 4.2.2. Age, BMI (body mass index), visceral adipose tissue (VAT)/ subcutaneous adipose tissue (SAT) ratio, and cytokines were not significant effectors.

Outcome: Fasting Glucose Adjusted R^2: 0.57 Predicted R^2: 0.48 Model p<0.001				Outcome: HOMA1-IR Adjusted R^2: 0.51 Predicted R^2: 0.39 Model p<0.001			
Covariate	β-Coefficient	Std. Error	t-value	Covariate	β-Coefficient	Std. Error	t-value
SMI (cm^2/m^2)	1.25.	0.65	1.92	SMI (cm^2/m^2)	0.37*	0.14	2.56
SMD (HU)	3.23**	1.11	2.93	SMD (HU)	0.51*	0.24	2.10
HIV Positive	59.38**	18.06	3.28	HIV Positive	10.03*	4.03	2.49
Male Sex	-28.15	19.51	-1.44	Male Sex	-9.16*	4.30	-2.13
Caucasian Race	49.19**	16.29	3.02	Caucasian Race	12.80***	3.59	3.57
Insulin	104.58***	17.23	6.07	Insulin	21.04***	3.98	5.29

Table 3: Linear Regression Model of skeletal muscle attenuation and skeletal muscle index adjusted for age, race, BMI, and sex. Visceral adipose tissue (VAT)/ subcutaneous adipose tissue (SAT) ratio, insulin use, and cytokines (other than IL-6 with regards to SMD) were not significant factors.

CONCLUSIONS

- People with **HIV** and T2DM had **greater HOMA1-IR** and **greater fasting blood glucose**.
- Detecting a between-group difference of skeletal muscle quality or quantity will require a much larger sample size.
- **HIV** was associated with **decreased** skeletal muscle **quality** in linear regression models, but **not** skeletal muscle **quantity**.
- **Neither** lower skeletal muscle attenuation **nor** lower SMI were associated with worsened markers of diabetes. Additionally, VAT/SAT ratio and cytokines were not significant effectors.
- **In conclusion**: Although PWH had worsened markers of diabetes, body composition did not lead to worsened insulin resistance in this cohort.

DISCUSSION

- To our knowledge, this was the first study assessing the relationship between SMD and insulin resistance in HIV+ T2DM patients.
- Both the HIV+ and HIV- patients in this cohort had notably decreased SMD compared to previous studies of pre-diabetic people without HIV and HIV+ people without T2DM.[9,21]
- This study raises the concern that HIV+ patients have poorer control of diabetes even when controlled for race, sex, and insulin use, highlighting the importance of further research in this area.
- This study was limited by small sample size and did not have adequate power to identify differences in HbA1c, SMI, or skeletal muscle attenuation.
- This study did not account for lifestyle factors such as medication adherence, diet, and exercise, which are key regulators of glucose control.
- Clinically available markers of insulin resistance were used however more sensitive methods could improve future analysis.[18]
- Follow-up studies would ideally aim for approximately 600 individuals per group. Additionally, inclusion of non-diabetic and pre-diabetic individuals, with lifestyle measures and glucose tolerance testing, will allow for a better understanding of how changes in skeletal muscle fat affect IR.

ACKNOWLEDGEMENTS

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Sources:

Title: Incidence of High Risk and Malignant Findings in Patients Undergoing Gender Affirming Mastectomy, Review of 418 Patients

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Background
Insurance coverage expansion for gender affirming surgeries has increased the number of patients seeking gender affirming mastectomies (GAM). As the number of individuals seeking GAM increases, more will reach the recommended age of breast cancer screening prior to undergoing surgery and the incidence of high risk and malignant findings on final pathology may increase.

At this time, there are no standardized clinical guidelines regarding pre and post operative screening or clinical management for patients undergoing GAM who have findings on breast imaging or final pathology. Few studies have reported data on benign, atypical and malignant findings on pathology following GAM, and most of these studies do not describe the clinical characteristics of their sample population.

We report on the largest cohort of patients to date who underwent GAM as well as their clinical characteristics, pathological findings and clinical management. Our aim with this pilot study is to identify the incidence of high risk and malignant lesions to further inform a multi-institutional study, which will define risk factors to facilitate national guidelines for this unique patient population.

Methods
This is a retrospective single institution cross sectional study. All medical records of patients who underwent GAM from July 2019 to September 2022 were reviewed and clinicopathologic data collected. A total of 457 patients underwent GAM surgery during the study period, 39 of these patients did not have final pathology and were excluded from the study. Descriptive statistics of demographics, clinical information and pathology information were performed.

Results
A total of 418 patients were included in final analysis. The median age of the study participants was 25 (IQR 22.0, 31.0), the majority (79.9%) of the study participants identified as female to

male transgender (FTM), followed by non-binary (16.0%). Caucasians represented the majority of (81.8%) patients who underwent GAM followed by African Americans (9.7%). The remaining racial groups representing less than 9% of the entire study participants. Most of the study participants were either overweight or obese (65.4%). Eighty percent of patients were on testosterone prior to GAM surgery and the median duration of testosterone use prior to surgery was 21 months (IQR 12-36 months). There were a total of 3 (0.6%) high risk or malignant lesions found in specimens submitted for pathology review; 1 atypical lobular hyperplasia (ALH), 1 Paget's disease of the nipple and 1 case of ductal carcinoma in situ (Table 1). The patient with ALH underwent endocrine therapy. The patient with Paget's disease had his free nipple graft removed at a subsequent surgery as no disease was identified in the excised breast tissue. The patient with DCIS was advised to undergo additional surgery and endocrine therapy, however declined.

Conclusion

In the largest study to date of patients undergoing GAM, incidental high risk and malignant lesions remain rare in young FTM transgender and non-binary patients. Our aim is to develop a multi-institutional database to further refine risk factors in this population to develop conclusive national screening and management guidelines.

INCIDENCE OF HIGH RISK AND MALIGNANT FINDINGS IN PATIENTS UNDERGOING GENDER AFFIRMING MASTECTOMY, REVIEW OF 418 PATIENTS

JAMIN K. ADDAE, M.D., MPH[1], ZOE R. FINER, B.S.[2], HANNA L. SLUTSKY, M.D.[1], YA-CHING HUNG, M.D., MPH[3], SALAM A. KASSIS, M.D.[3], RACHEL L. MCCAFFREY, M.D.[1]

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BACKGROUND

Insurance coverage expansion for gender affirming surgeries has increased the number of patients seeking gender affirming mastectomies (GAM). As the number of individuals seeking GAM increases, more will reach the recommended age of breast cancer screening prior to undergoing surgery and the incidence of high risk and malignant findings on final pathology may increase.

Currently, there are no standardized clinical guidelines regarding pre and post operative screening or clinical management for patients undergoing GAM who have findings on breast imaging or final pathology. Few studies have reported data on benign, atypical and malignant findings on pathology following GAM, and most of these studies do not describe the clinical characteristics of their sample population.

We report on the largest cohort of patients in the United States to date who underwent GAM as well as their clinical characteristics, pathological findings and clinical management.

AIM: Identify the incidence of high risk and malignant lesions to further inform a multi-institutional study, which will define risk factors to facilitate national screening and management guidelines for this unique patient population.

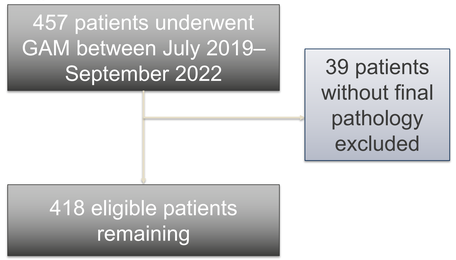
METHODS

This is a retrospective single institution cross sectional study. All medical records of patients who underwent GAM from July 2019 to September 2022 were reviewed and clinicopathologic data were collected. Descriptive analysis was performed.

Data collected include:

- Demographics
- Duration of exogenous testosterone use
- Exposure to non-testosterone hormone suppression
- Pre-operative imaging
- Pathology data

Figure 1. Study population



PATIENT DEMOGRAPHICS AND CLINICAL DATA

Table 1. Demographics and Clinical Data

Demographic	N (%) or Median (IQR)
Age (years)	25.0 (22.0 – 31.0)
Gender	
Female to Male (FTM)	334 (79.9)
Non-Binary	67 (16.0)
Other	17 (4.1)
Race/Ethnicity	
White	345 (82.5)
Black	41 (9.8)
Latino/Latina	12 (2.9)
Asian	8 (1.9)
Native American/Alaskan/Other	12 (2.9)
BMI at time of surgery (kg/m^2)	
15-20	26 (6.2)
21-30	208 (49.7)
31-40	137 (32.8)
>41	33 (7.9)
Not specified	14 (3.3)
Tobacco Use	
Nonsmoker	270 (64.6)
Former smoker	99 (23.7)
Current Smoker	48 (11.5)
Alcohol Use	
No alcohol use	201 (48.1)
Social alcohol use	56 (13.4)
1-7 drinks per week	122 (29.2)
>7 drinks per week	9 (2.2)
Not Specified	30 (7.2)
Testosterone use prior to surgery	
Yes	337 (80.6)
No	81 (19.4)
Duration of testosterone use (months)	21.0 (12.0, 36.0)

RESULTS

- Majority (79.9%) of patients identified as female to male transgender, followed by non-binary (16%).
- Caucasians represented the majority of (81.8%) patients who underwent GAM followed by African Americans (9.7%).
- Most of the study participants were either overweight or obese (65.4%).
- 80% of patients were on testosterone prior to GAM surgery and the median duration of use prior to surgery was 21 months.
- Total of 3 (0.6%) high risk or malignant lesions found in specimens submitted for pathology review; 1 atypical lobular hyperplasia (ALH), 1 Paget's disease of the nipple, and 1 ductal carcinoma in situ (DCIS).

Figure 2: Next steps for the 3 patients with high risk / malignant findings

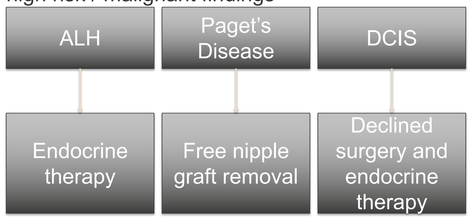


Table 2. Pathology Findings

Pathology	N (%)
Benign non-proliferative	
Fibrocystic changes	21 (5.0)
Fibroadenoma	8 (1.9)
Apocrine metaplasia	21 (5.0)
Proliferative disease without atypia	
Usual ductal hyperplasia	13 (3.1)
Sclerosing adenosis	2 (0.5)
Columnar cell change	5 (1.2)
Intraductal papilloma	3 (0.7)
Proliferative disease with atypia	
Atypical lobular hyperplasia	1 (0.2)
Malignant lesions	
DCIS	1 (0.2)
Paget's Disease	1 (0.2)

CONCLUSION

In the largest US study to date of patients undergoing GAM, incidental high risk and malignant lesions remain rare in young female-to-male transgender and non-binary patients. Our aim is to develop a multi-institutional database to further refine risk factors in this population to develop conclusive national screening and management guidelines.

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The Use of Endometrial Culture for Targeted Treatment of Endometritis in Patients Experiencing Infertility and Recurrent Pregnancy Loss

Objective: To evaluate whether endometrial culture in addition to endometrial biopsy reduces time to clear chronic endometritis (CE) and fewer endometrial biopsies in patients experiencing infertility and recurrent pregnancy loss (RPL).

Materials and Methods: This retrospective cohort study was performed at an academic tertiary care facility. We included patients (N=92) with endometritis (defined as either endometritis on pathologic evaluation or 5 plasma cells per high power field) who were evaluated in the reproductive infertility and endocrinology clinic for infertility or RPL from March 2018 to January 2022. In March 2021, the clinic implemented routine use of endometrial culture in addition to endometrial biopsy as part of the evaluation of infertility or RPL. We hypothesized that treatment of specific endometrial pathogens with reported sensitivities to antibiotics would result in a reduction in length of treatment to clear CE and fewer number of biopsies per patient. Patients evaluated prior to March 2021 with only endometrial biopsy (n=46) were compared to patients evaluated after March 2021 with endometrial culture in addition to endometrial biopsy (n=46). Patients who did not follow up to evaluate for clearance of endometritis were excluded from the study. Mean time to clearance and average number of biopsies were compared via students t-test.

Results: The mean time needed to clear chronic endometritis in the endometrial biopsy only cohort was 73.1 days, while the average time needed in the endometrial culture plus endometrial biopsy cohort was 51.4 days (p=0.018). The average number of biopsies per patient in the endometrial biopsy only cohort was 2.89, while the average number of biopsies in the endometrial culture plus endometrial biopsy cohort was 1.98 (p=0.00001).

Conclusions: Endometrial culture in addition to endometrial biopsy leads to a statistically significant decreased time to treat patients with CE and significantly fewer endometrial biopsies required per patient. Endometrial culture is a diagnostic tool that could reduce time needed to treat CE by targeting specific pathogens. Futures studies should investigate if this simple diagnostic tool reduces time to pregnancy in patients with CE.

Impact Statement: CE is present in up to 40% of patients with infertility and 28% of patients with RPL (5). With pathogen targeted evaluation of the endometrial microbiome comes the ability to tailor therapy and potentially improve reproductive outcomes (2).

Sources:

1. The diagnosis of chronic endometritis in infertile asymptomatic women: a comparative study of histology, microbial cultures, hysteroscopy, and molecular microbiology
2. Challenging dogma: the endometrium has a microbiome with functional consequences!
3. Incidence of microbial growth from the tip of the embryo transfer catheter after embryo transfer in relation to clinical pregnancy rate following in-vitro fertilization and embryo transfer.
4. Evidence that the endometrial microbiota has an effect on implantation success or failure.
5. Evidence that the endometrial microbiota has an effect on implantation success or failure

The Use of Endometrial Culture for Targeted Treatment of Endometritis in Patients Experiencing Infertility and Recurrent Pregnancy Loss

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BACKGROUND

- Chronic endometritis (CE) is defined as persistent inflammation of the endometrial lining of the uterus and has been linked to disruption of reproductive function
- CE is present in up to 40% of patients with infertility and 28% of patients with recurrent pregnancy loss (RPL)[1]
- CE is an asymptomatic condition conventionally diagnosed via three techniques: hysteroscopy, histology and culture[1]
- Multiple studies have shown that the uterine cavity is in fact not sterile, but hosts a small microbiome[2]
- The complex interplay of processes involved in a successful pregnancy is not well understood

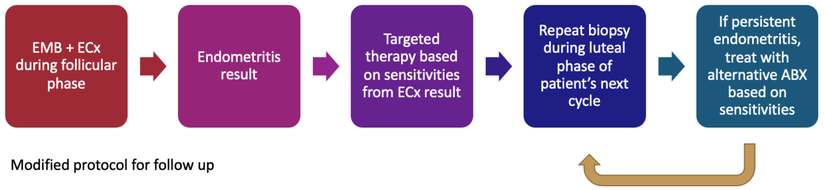
OBJECTIVE

- To evaluate whether endometrial culture (ECx) in addition to endometrial biopsy (EMB) reduces time to clear CE and results in fewer endometrial biopsies in patients with CE

METHODS

- Retrospective cohort study of patients (N=92) with endometritis evaluated in the reproductive infertility and endocrinology clinic for infertility or RPL from March 2018 to January 2022
- In March 2021, routine use of ECx in addition to EMB as part of the evaluation of infertility or RPL was implemented
- Patients evaluated prior to March 2021 with only endometrial biopsy (n=46) were compared to patients evaluated after March 2021 with endometrial culture in addition to endometrial biopsy (n=46)
- Patients who did not follow up to evaluate for clearance of endometritis were excluded from the study
- Mean time to clearance and average number of biopsies were compared via students t-test

Initial protocol for follow up



Modified protocol for follow up

Most Common Bacteria Identified	
Bacteria	% of result
Streptococcus agalactiae (group B)	15 (18)
Enterococcus faecalis	13 (16)
Gardnerella vaginalis	6 (7)
Escherichia coli	5 (6)
Staphylococcus aureus	3 (4)

Table 1

Intervention	Timeframe	Mean (days)	Standard Deviation (days)	Median (days)	P-value
EMB only	3/2018 – 3/2021	73.1	43	63.0	P = 0.018
EMB + culture	4/2021 – 1/2022	51.4	36	35.7	

Table 2: Mean time to clear CE

Intervention	Timeframe	Mean (# biopsies)	Standard Deviation (# biopsies)	Median (# biopsies)	P-value
EMB only	3/2018 – 3/2021	2.89	1.4	2	P = 0.00001
EMB + culture	4/2021 – 1/2022	1.98	0.9	2	

Table 3: Mean number of biopsies required to clear CE

RESULTS

- Pathogen results were evaluated, with Group B streptococcus being the most common in our sample. See table 1
- Mean time to clear CE in the endometrial biopsy only cohort was 73.1 days (p=0.018), while mean time to clear CE in the endometrial culture plus endometrial biopsy cohort was 51.4 days (p=0.018). See table 2
- Mean number of biopsies per patient in the endometrial biopsy only cohort was 2.89, while the average number of biopsies in the endometrial culture plus endometrial biopsy cohort was 1.98 (p=0.00001). See table 3

CONCLUSIONS AND IMPLICATIONS

- ECx in addition to endometrial biopsy leads to a statistically significant decreased time to treat patients with CE and significantly fewer endometrial biopsies required per patient
- ECx is a diagnostic tool that could reduce time needed to treat CE by targeting specific pathogens
- Futures studies should investigate if ECx reduces time to pregnancy in patients with CE
- With pathogen targeted evaluation of the endometrial microbiome comes the ability to tailor therapy and potentially improve reproductive outcomes (2)

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Abstract #14063

Title

Hypogonadotropic Hypogonadism is Associated with a Lower Incidence of Ovarian Cancer

Sarah Hmaidan, DO[1]; Michelle Roach, MD[1]; Donna Session, MD[2]
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Objective:

Persistently high levels of gonadotropins have been associated with an increased risk of epithelial ovarian cancer. This is supported by reduced risks with combined oral contraceptives and pregnancies. Based on this theory, we hypothesized that individuals with hypogonadotropic hypogonadism (HH) have a lower incidence of ovarian cancer.

Materials and Methods:

This was a retrospective case-cohort study performed in an academic tertiary care facility. The synthetic derivative, a de-identified patient database, was utilized to query female patients >49 to 89 years of age from 2002 to 2020. The HH group included the diagnoses of panhypopituitarism, Kallmann Syndrome, necrosis of the pituitary gland, and Sheehan Syndrome (n = 255). The control group included patients without the diagnosis of HH (n = 740,614). Both groups were queried for diagnosis of epithelial ovarian cancer.

Results:

No cancers were identified in the HH group, compared to 1474 in the control group. Fisher exact analysis demonstrated a p-value <.05 for each respective age group (Table 1).

Conclusions:

It's now widely accepted that most cases of epithelial ovarian cancer arise in the fallopian tubes. In addition, gonadotropin receptors are present in the fallopian tube and FSH increases the expression of a tumorigenesis associated gene in the fimbrial epithelium. This evidence suggests that lower levels of gonadotropins may reduce the risk of epithelial ovarian cancer. Therefore, strategies to reduce gonadotropins such as gnRH analogs may be protective, particularly for those at greatest risk for ovarian epithelial cancers, for example those with hereditary cancer genes.

Table 1

Age	Exposure	Number of Patients	Number of Ovarian Cancer Cases	Risk %
50-59	Yes	74	0	0
	No	226924	343	0.1512
60-69	Yes	92	0	0
	No	227663	475	0.2086
70-89	Yes	89	0	0
	No	286027	656	0.2293

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Table 1

Age	Exposure	Number of Patients	Number of Ovarian Cancer Cases	Risk %	ACS incidence (%) 2016-2018
Overall	Yes	983	0	0	
	No	1763012	1837	0.1042	
0-49	Yes	728	0	0	
	No	1022398	363	0. 0355	0.2
50-59	Yes	74	0	0	
	No	226924	343	0.1512	0.2
60-69	Yes	92	0	0	
	No	227663	475	0.2086	0.3
70-89	Yes	89	0	0	
	No	286027	656	0.2293	0.7

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N-ACETYLCYSTEINE MAY ATTENUATE HISTOPATHOLOGICAL FINDINGS OF EOSINOPHILIC ESOPHAGITIS BY REDUCING STAT6 ACTIVATION

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Background: Increased oxidative stress is thought to contribute to the pathophysiology of Eosinophilic Esophagitis (EoE). Thus, our aim was to determine whether N-acetylcysteine (NAC), an antioxidant known to reduce oxidative stress, could reduce esophageal inflammation in experimental EoE.

Methods: Immortalized human esophageal epithelial cells (EPC2-hTERT) were pre-treated with NAC for 1 hour and then with IL-13, a known activator of STAT6, (except for control) for 30 minutes. Cells were collected for immunoblot of phosphoSTAT6 (pSTAT6) and total STAT6. This experiment was repeated but IL-13 and NAC remained on the cells for 24 hours, and quantitative real-time PCR (qPCR) was done to assess relative gene expression of *CCL26,* a known target of STAT6 activation. In the absence of cells, recombinant IL13Rα1 was mixed with control and increasing doses of NAC and assayed on a Nanotemp Tycho to assess for qualitative structural changes. For *in vivo* experiments, eosinophilic esophagitis was induced in C57/BL6 mice with 1 µg recombinant IL-33 intraperitoneal (IP) injections daily for 7 days with or without NAC. Five groups of adult mice were tested: 1) Sucrose water with saline IP; 2) 3% NAC/Sucrose water with saline IP; 3) Sucrose water with IL-33 IP; 4) 3% NAC/Sucrose water with IL-33 IP; 5) 300 mg/kg NAC topical suspension with IL-33 IP. At the end of the 7 days, esophageal tissue was collected for histology.

Results: Pre-treatment of EPC2-hTERT cells with NAC prior to IL-13 led to a significant reduction in pSTAT6/STAT6 in a dose-dependent manner as compared with IL-13 alone (Fig. 1A-B). After 24 hours, *CCL26* expression was significantly reduced with NAC + IL-13 as compared with IL-13 alone (Fig. 1C). As previously reported, IL-33 induced esophageal basal cell hyperplasia (BCH) in mice compared to controls (Fig. 2A, 2C). Consumption of NAC in drinking water or the administration of a NAC topical suspension reduced IL-33 induced BCH (Fig. 2A). Furthermore, 3% NAC in drinking water significantly reduced MBP counts with a similar trend when administering NAC topical suspension (Fig. 2B, 2C). When recombinant IL13Rα1 was mixed with NAC, inflection temperatures measured on the Nanotemp Tycho were lowered in a dose-dependent fashion compared to IL13Rα1 alone.

Conclusion: NAC reduces STAT6 activation and *CCL26* expression induced by IL-13. NAC consumption via drinking water or by administration of an esophageal topical suspension attenuates IL-33 induced BCH and esophageal eosinophilia in mice. Targeting oxidative stress may serve as a novel pharmacologic pathway for the treatment of EoE.

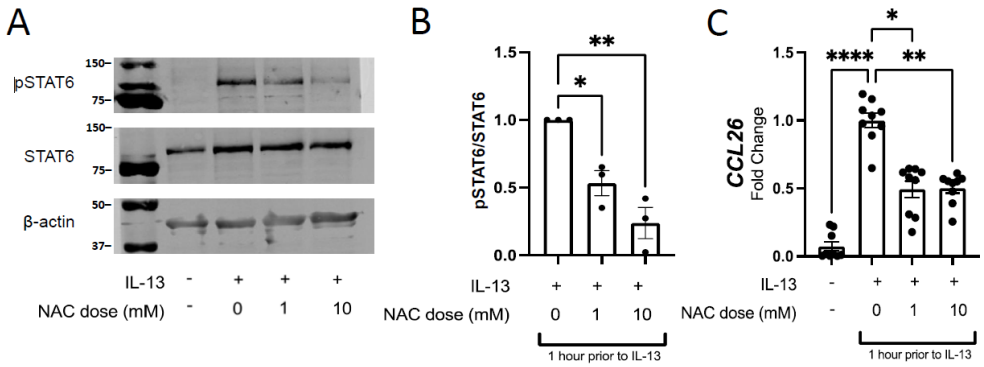


Figure 1: NAC reduces IL-13 activation of STAT6 and downregulates CCL26 expression. (A) Representative images from immunoblotting of EPC2-hTERT cells under NAC and IL-13 conditions probed with pSTAT6, STAT6 and β-actin. (B) Quantification of immunoblot expression as a ratio of pSTAT6/STAT6. When these cells were pretreated with NAC, a significant reduction in pSTAT6/STAT6 was noted in a dose-dependent manner as compared with IL-13 treatment alone (vs 1 mM, 47%,P<0.05; vs 10 mM, 76%, P<0.01, ANOVA test). (C) After 24 hours of treatment with NAC and IL-13, CCL26 gene expression induced by IL-13 was significantly reduced with 1- (54%, P<0.05, ANOVA) and 10-mM NAC (45%, P<0.01, ANOVA).

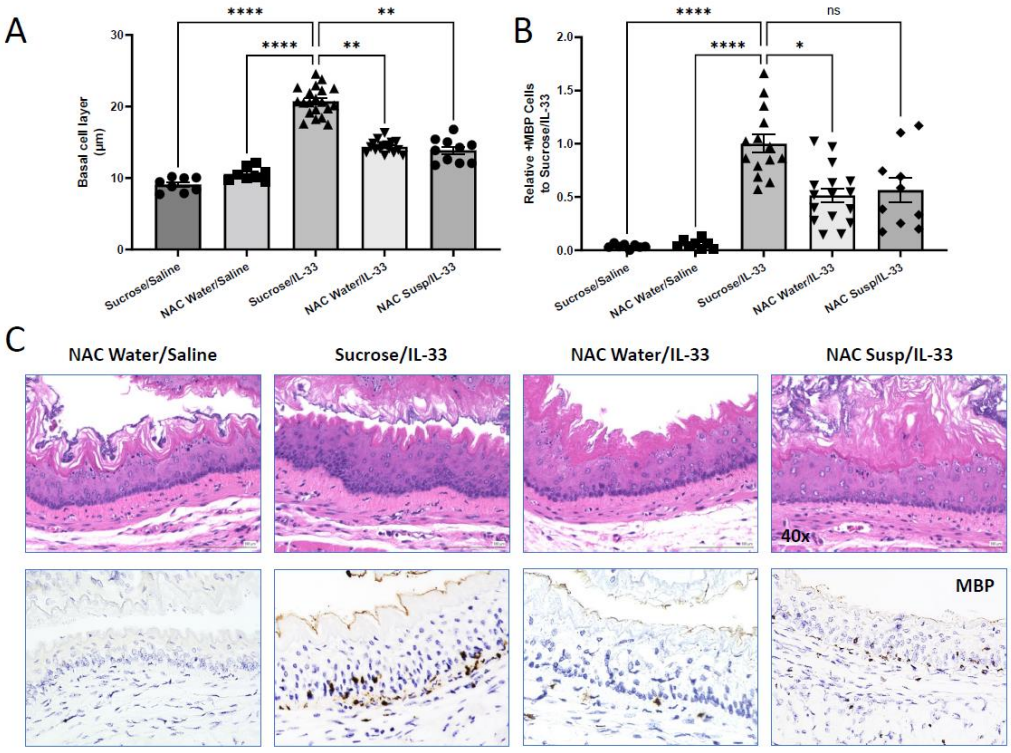


Figure 2: NAC attenuates basal cell hyperplasia and esophageal eosinophilia in an IL-33 experimental esophagitis in vivo murine model. (A) Treatment with IL-33 induced basal cell hyperplasia (20.72 μm) when compared to the negative controls (9.06 μm, 10.56 μm, P<0.0001, Kruskal-Wallis test). A significant reduction in basal cell thickness was noted with NAC drinking water and NAC suspension compared with no NAC treatment (vs NAC water, 14.37 μm, P=0.0010; vs NAC suspension, 12.07 μm, P=0.0016, Kruskal-Wallis test). (B) Relative ratio of major basic protein (MBP) cell counts normalized to experimental control group. IL-33 induced esophageal eosinophilia (1.00 vs 0.04 vs 0.06, P<0.0001, Kruskal-Wallis test). 3% NAC in drinking water significantly reduced MBP counts (1.00 vs 0.51, p<0.05, Kruskal-Wallis test) with a similar trend when administering NAC topical suspension (1.00 vs 0.56, p=0.19, Kruskal-Wallis test). (C) Representative images from H&E and MBP staining of mouse esophagus (Sucrose-Saline group not shown).

Evolving Management of Iatrogenic Upper Extremity Pseudoaneurysms: 30-year experience of a single quaternary care center (390 Words)

Patrick A. Stone, M.D.; Praveen Vimalathas; Layne Janda, M.D.; Jack Kinney; Jeff Stanley

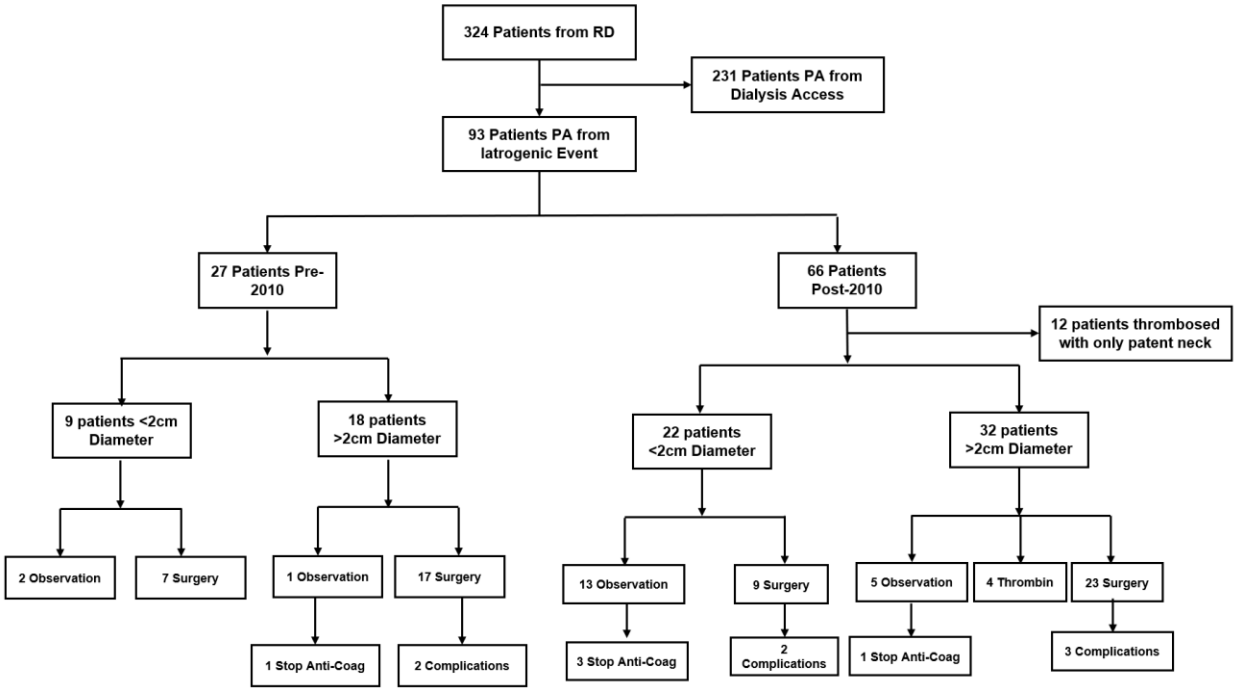
Objective (40 words)
While the natural history and treatment algorithm of femoral pseudoaneurysms has been established, the paucity of literature on the management of Upper Extremity Pseudoaneurysm (UEPSA) is lacking. We sought to evaluate a 30-year experience and management of this pathology.

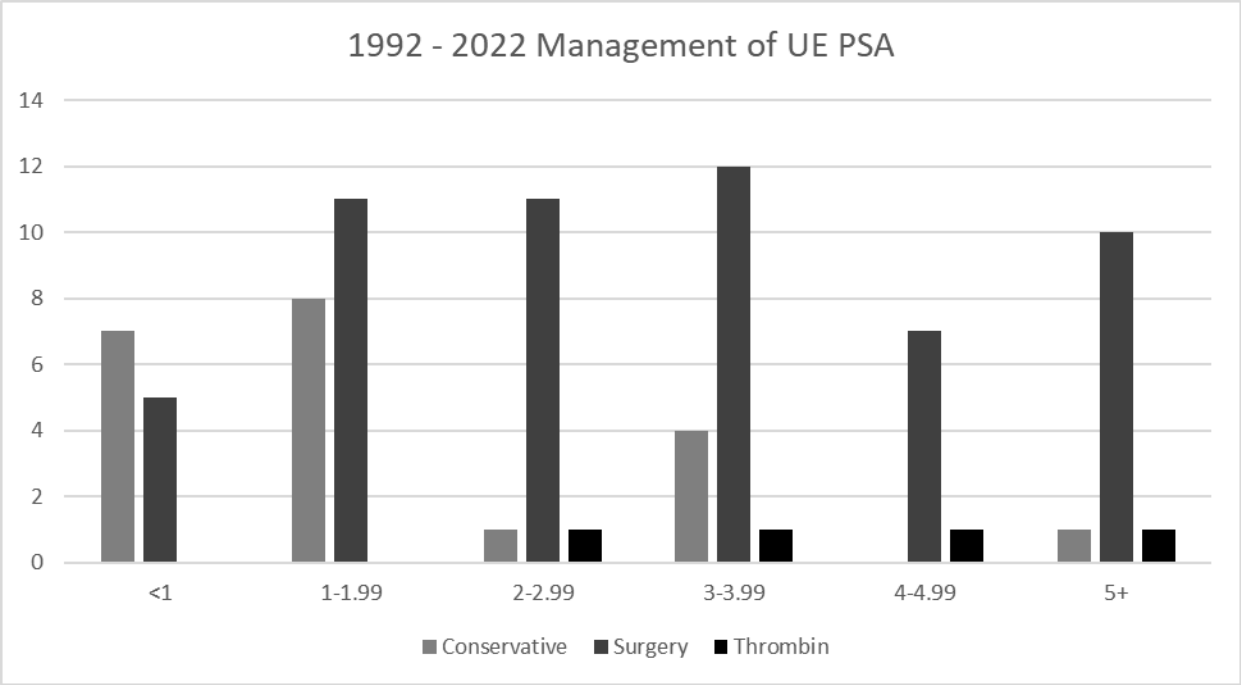
Methods (70 words)
We selected patients with an UEPSA utilizing ICD9/10 codes and identified 324, of which 81 met our strict criteria: 1) experienced an iatrogenic complication from catheter access site, arterial line insertions, and arterial punctures (PICC line insertions, ABG access sites, etc.), 2) had a thorough medication record from before UEPSA and, 3) established, prior patient care and adequate post-event care. UEPSAs due to dialysis site access or trauma were excluded.

Results (212 words)
A total of 81 patients were identified with UEPSA (37 brachial, 34 radial, 6 axillary, 4 ulnar; median age 60, 56% male, 79.0% Caucasian, 13.6% African American). The mean time between iatrogenic event and vascular surgery evaluation was 22 days. 69.1% underwent surgical repair, 25.9% received conservative management, and 4.9% underwent thrombin injection. 12.7% of surgical patients developed surgical complications. No complications were observed in conservatively managed nor thrombin injected patients. Of the UEPSAs managed conservatively, only 3 (12.5%) failed conservative management and after 21 days from initial ultrasound were recommended to pursue surgical correction; all 3 were greater than 2cm. All UEPSAs <2cm managed conservatively thrombosed less than 28 days, with a mean of 8.1 days by duplex ultrasound.

Separated into sizes, there were a total of 15 patients managed conservatively and 16 patients managed surgically with UEPSAs less than 2cm; in contrast for those with greater than 2cm UEPSAs, 6 patients were managed conservatively, 40 were managed surgically, and 4 with thrombin injection. By year, there was an obvious trend towards conservative management over the past decade. Prior to the end of 2010, there were 27 iatrogenic UEPSAs noted with only 11.1% managed conservatively, while after 2010 there were 54 iatrogenic pseudoaneurysms with 33.3% managed conservatively (Fig. 1, Fig. 2).

Conclusions (68 Words)
While prior to 2010, 88.9% of patients were recommended to proceed with surgical management regardless of size, our surgeons were able to manage 1/3 of UEPSAs conservatively resulting in a decreased necessity of surgery. Our robust patient sample demonstrates that patients with a <2cm diameter size of UEPSA are likely to benefit from conservative management. We recommend conservative management of pseudoaneurysms less than 2cm in the upper extremity.





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Title: Goldilocks and the Three Resuscitation Strategies: Intraoperative Fluid Management in the Surgical Treatment of Rectal Cancer

Background: Fluid management is a key part of surgical therapy. In colorectal surgery, the Enhanced Recovery After Surgery (ERAS) pathway has guidelines on intraoperative fluid management, including maintaining euvolemia and avoiding excessive fluid perioperatively. However, there is no specific optimal fluid management strategy in the treatment of primary rectal cancer. We aim to evaluate intraoperative fluid management strategies in patients undergoing surgery for rectal cancer. We hypothesize a restrictive or balanced strategy would correlate to decreased length of stay (LOS).

Methods: Adult patients with rectal cancer undergoing surgical resection from 2007-2017 were identified in the US Rectal Cancer Consortium. Patients were excluded if they required emergency or palliative surgery, had EBL >500mL, or had preoperative comorbidities affecting fluid administration (AKI, CKD, dialysis). Patients were grouped based on total volume of intraoperative crystalloid, albumin, and blood administration. Based on previously described cutoffs, we defined a restrictive fluid management strategy as < 5mL/kg/h, a balanced strategy as 5-8 mL/kg/h, and a liberal strategy as >8mL/kg/h. Primary outcome was postoperative LOS. Secondary outcomes were return of bowel function, total complications and complications categorized by organ system. A retrospective analysis was performed using negative binomial (count data), logistic regression (binary outcomes), and ordinal logistic regression (ordinal outcomes) models to evaluate the effect of restrictive, balanced, and liberal fluid management strategies.

Results: Of 399 patients that were included in the study, 322 (80.7%) patients fell into the liberal fluid management group, 50 (12.5%) in the balanced group, and 18 (4.5%) in the restrictive group. On both univariable and multivariable analyses, both balanced and restrictive strategies had shorter LOS compared to the liberal strategy (adjusted RR=0.9); however, these associations were not statistically significant. On multivariable analysis, age, ASA class, type of operation, and operative time were statistically associated with LOS (all p-values <0.001). Fluid management strategy was not associated with return of bowel function, the median number of postoperative complications, or postoperative creatinine. Age was significantly associated with return of bowel function (interquartile range OR=2.16, p= 0.001).

Conclusion: We did not observe an association between the amount of IV fluid administered during surgical treatment of rectal cancer and LOS or postoperative complications. Instead, patient characteristics —age, gender, ASA—and operation variables—operation type and time—are the primary drivers of post-operative outcomes. Future strategies to improve postoperative care should focus on these areas rather than fluid management.

Author
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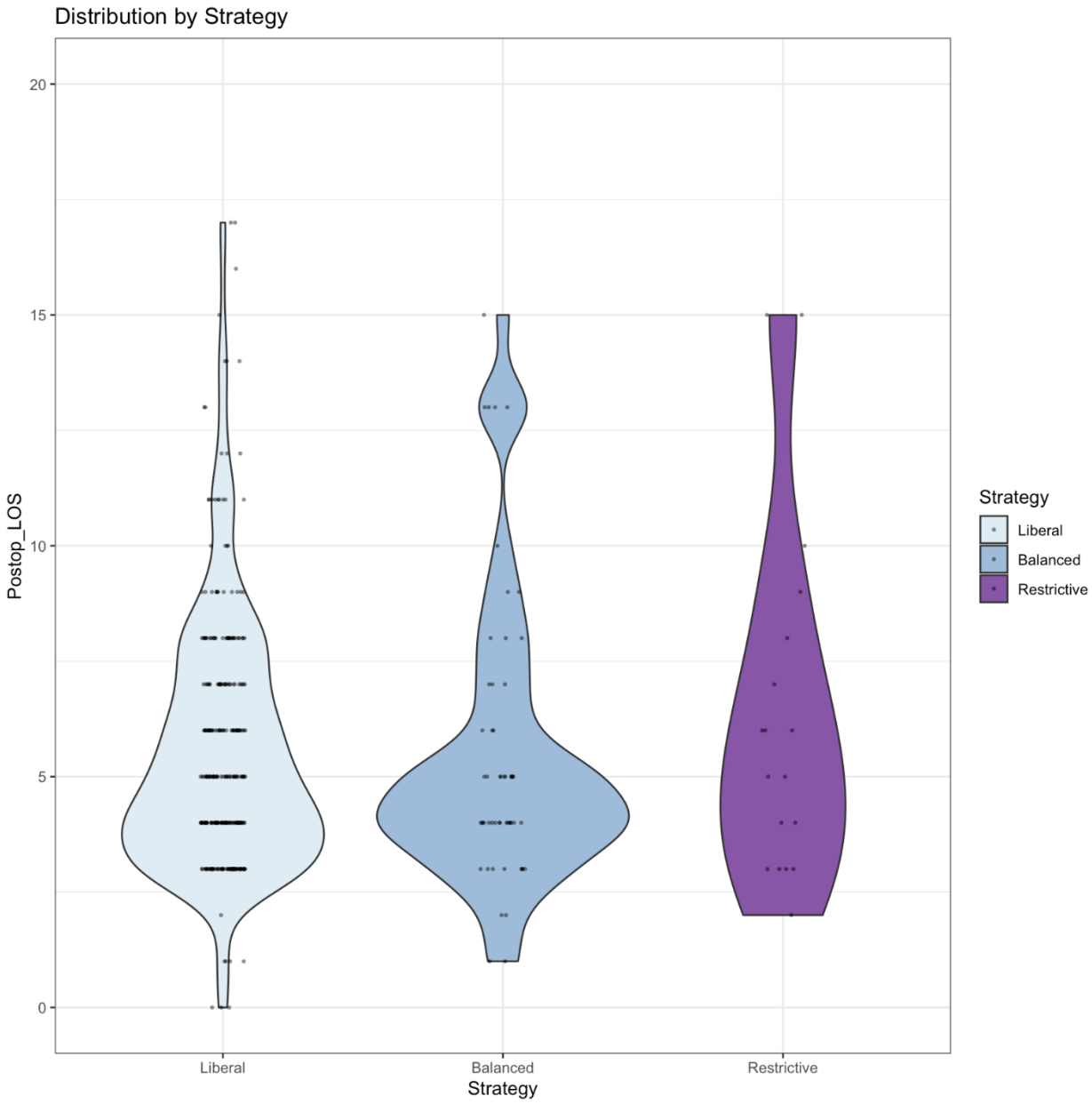

Figure 1: Univariable Model comparing postoperative length of stay with fluid management strategy.

Goldilocks and the Three Resuscitation Strategies: Rectal Cancer

Andrea Fa MD[1], Adriana C. Gamboa MD[2], Glen Balch, MD[2], Alexander T. Hawkins, MD, MPH[1]

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BACKGROUND

- Fluid management is a key part of surgical therapy
- Current ERAS guidelines emphasize euvolemia and avoiding excessive fluid in the peri-operative period but are overall nonspecific
- Previous studies have shown better outcomes when using a “balanced” management therapy rather than a “restrictive” or “liberal strategy.
- In the surgical treatment for rectal cancer, there is no established fluid management strategy

AIM STATEMENT

- **Aim**: Retrospectively analyze the impact of intraoperative fluid management strategies in patients undergoing surgery for rectal cancer.
- **Intervention:** Intraoperative Fluid Management Therapy (definitions based on the RELIEF trial guidelines)
- **Primary Outcome:** Length of Stay (LOS)
- **Secondary Outcomes:** Postoperative complications (SSI, AKI, return of bowel function, pulmonary complications)

METHODS

- Identified adult patients diagnosed with rectal cancer undergoing surgical resection 2007-2017 in the US Rectal Cancer Consortium
- Excluded palliative or emergency cases and patients with comorbid conditions affecting fluid administration
- Assessed possible covariates impacting primary and secondary outcomes, including ASA, age, operative details, and comorbid conditions.
- Utilized negative binomial, logistic regression, and ordinal logistic regression models to evaluate the effect of restrictive, balanced, and liberal fluid management strategies.

RESULTS

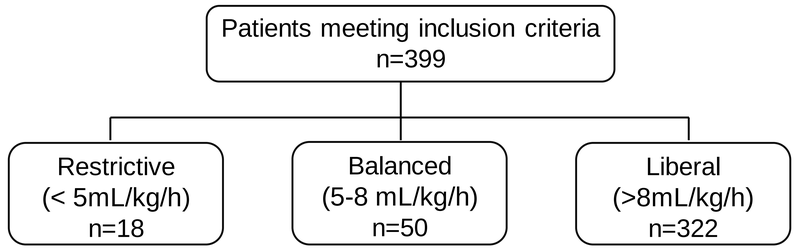

Figure 1: Patient distribution based on fluid management therapy

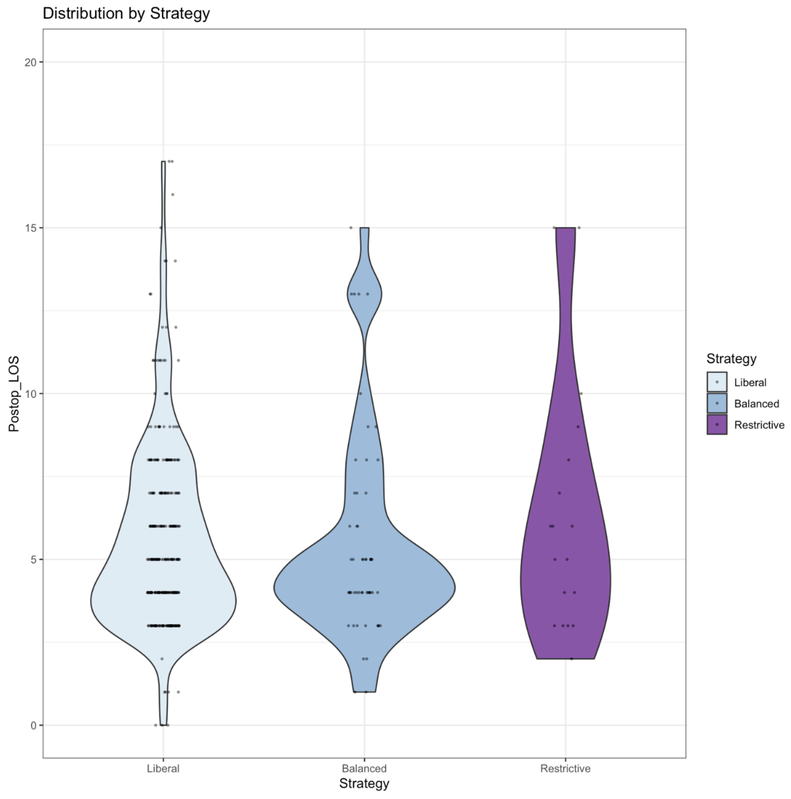

Figure 2: Univariable Model comparing the postoperative length of stay with fluid management strategy.

RESULTS

- On univariable and multivariable analysis, the balanced and restrictive strategies were associated with shorter LOS compared to the liberal strategy (adjusted RR=0.9). However, these associations were not statistically significant (p>0.3)
- On multivariable analysis, age, ASA class, type of operation, and operative time were statistically associated with LOS (all p-values <0.001)
- No fluid management strategy was associated with an increased rate of postoperative complications
- Age was significantly associated with return of bowel function (interquartile range OR=2.16, p= 0.001)
- No additional covariates were associated with increased rates of postoperative complications (all p-values >0.06)

CONCLUSIONS AND LESSONS LEARNED

- Intraoperative fluid management strategy was not associated with LOS or postoperative complication rate
- Patient characteristics (age, gender, ASA) and operation variables (operative approach, operative time) are primary drivers of postoperative outcomes
- Future work should focus on optimizing treatment based on these significant factors.

REFERENCES

Correlates of plasma NT-pro-BNP to cyclic GMP ratio in patients with heart failure with preserved ejection fraction: an analysis of the RELAX trial

Leonard Chiu[1], MD, MS; Sheila Collins[2], PhD; Anna Hemnes[3], MD; JoAnn Lindenfeld[2], MD; Deepak K. Gupta[2], MD, MSCI

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[2]Vanderbilt Translational and Clinical Cardiovascular Research Center, Vanderbilt University Medical Center, Nashville, Tennessee; Division of Cardiovascular Medicine, Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee
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Background: Cyclic guanosine monophosphate (cGMP) is a key second messenger which mediates the cardiovascular, renal, and metabolic protective effects of natriuretic peptides (NP) and nitric oxide pathways. Phosphodiesterases (PDE) 5, 6, and 9 specifically degrade cGMP, such that high NP to cGMP ratios may reflect PDE excess. Among patients with heart failure with reduced ejection fraction, higher NP to cGMP ratio associates with worse prognosis, but correlates of NP to cGMP ratio in patients with heart failure with preserved ejection (HFpEF) are less characterized. The RELAX trial tested the hypothesis that augmentation of cGMP through blockade of its breakdown by sildenafil, a PDE-5 inhibitor, improves peak oxygen consumption (VO2), left ventricular mass, and a clinical composite outcome based on time of death, time to hospitalization for cardiovascular or cardiorenal causes, and change in heart failure questionnaire from baseline over 24 weeks in patients with HFpEF.

Objectives: Using RELAX trial data, we aimed to examine 1) the cross-sectional correlates of NT-proBNP to cGMP ratio 2) whether sildenafil changed the NT-proBNP to cGMP ratio, and 3) whether the effect of sildenafil on outcomes varied according to baseline NT-proBNP to cGMP ratio.

Methods: We calculated the plasma NT-proBNP to cGMP ratio at randomization and week 24 end of the study, as well as the 24-week change. Correlates of NT-proBNP to cGMP ratio and its change were examined in multivariable-adjusted proportional odds models. Whether the effect of PDE-5 inhibition with sildenafil on the primary, secondary, and exploratory outcomes of the RELAX trial varied according to baseline NT-proBNP to cGMP ratio was examined by inclusion of a randomization by NT-proBNP to cGMP ratio interaction term into multivariable-adjusted proportional odds models.

Results: A total of 212 RELAX trial subjects had baseline measures of NT-proBNP and cGMP to calculate the ratio. In multivariable-adjusted models, baseline BMI, eGFR, and peak VO2 were each significantly and inversely associated with baseline NT-proBNP to cGMP ratio, while greater LV mass, troponin, and the presence of atrial fibrillation were associated with higher NT-proBNP to cGMP ratio (**Table 1**). These associations were also present at week 24. Left ventricular ejection fraction was not associated with NT-proBNP to cGMP ratio at baseline or 24 weeks. Randomization to sildenafil did not significantly alter the NT-proBNP to cGMP ratio from baseline to 24 weeks compared with placebo ($p = 0.17$). Baseline NT-proBNP to cGMP ratio did not modify the effect of sildenafil compared with placebo on 24-week change in peak VO2, LV mass, or the clinical composite outcome (p-interaction > 0.30 for all).

Conclusion: Among individuals with HFpEF included in the RELAX trial, higher NT-proBNP to cGMP ratio was associated with lower VO2, greater LV mass, and higher troponin. Inhibition of PDE-5 with sildenafil did not influence NT-proBNP to cGMP ratio, nor was its effect on outcomes modified by baseline NT-proBNP to cGMP ratio. Among patients with HFpEF, PDEs other than PDE-5 may contribute to the adverse cardiac phenotype associated with a high NT-proBNP to cGMP ratio.

Table 2: Correlates of Baseline Plasma NT-proBNP to cGMP Ratio		
Characteristic	**OR [95% CI]**	**P-value**
Age, years	1.00 [0.95, 1.05]	0.97
Female	1.66 [0.64, 4.32]	0.29
Race	0.62 [0.29, 1.31]	0.21
Body Mass Index, kg/m2	0.91 [0.85, 0.96]	0.001
Systolic Blood Pressure, mm Hg	1.00 [0.99, 1.02]	0.79
Estimated Glomerular Filtration Rate, ml/min/1.73m2	0.98 [0.96, 0.99]	0.005
Left Ventricular Mass, g	1.012 [1.004, 1.019]	0.005
Left Ventricular Ejection Fraction, %	0.99 [0.95, 1.03]	0.59
Troponin I, pg/mL	1.017 [1.002, 1.032]	0.023
C-reactive protein, mg/L	1.02 [0.96, 1.07]	0.52
Peak VO_2, ml/min/kg	0.80 [0.68, 0.93]	0.003
Atrial fibrillation	4.41 [1.02, 19.09]	0.047
Multivariable proportional odds model adjusted for all covariates listed.		

*

Correlates of Plasma NT-proBNP to Cyclic GMP Ratio in Patients with Heart Failure with Preserved Ejection Fraction: A Secondary Analysis of the RELAX Trial

VANDERBILT UNIVERSITY MEDICAL CENTER

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Vanderbilt Translational and Clinical Cardiovascular Research Center, Divisions of Cardiovascular and Pulmonary Medicine, Vanderbilt University Medical Center, Nashville, TN

BACKGROUND

- Cyclic guanosine monophosphate (cGMP) is a key second messenger which mediates the cardiovascular, renal, and metabolic protective effects of natriuretic peptides (NP) and nitric oxide pathways.
- Phosphodiesterases (PDE) 5, 6, and 9 specifically degrade cGMP, such that high NP to cGMP ratios may reflect PDE excess.
- Among patients with heart failure with reduced ejection fraction, higher NP to cGMP ratio associates with worse prognosis, but correlates of NP to cGMP ratio in patients with heart failure with preserved ejection (HFpEF) are less characterized.
- The RELAX trial tested the hypothesis that augmentation of cGMP through blockade of its breakdown by sildenafil, a PDE-5 inhibitor, improves peak oxygen consumption (VO2), left ventricular mass, and a clinical composite outcome based on time of death, time to hospitalization for cardiovascular or cardiorenal causes, and change in heart failure questionnaire from baseline over 24 weeks in patients with HFpEF.

OBJECTIVES

- Using RELAX trial data, we aimed to examine:

1) the cross-sectional correlates of NT-proBNP to cGMP ratio
2) whether sildenafil changed the NT-proBNP to cGMP ratio
3) whether the effect of sildenafil on outcomes varied according to baseline NT-proBNP to cGMP ratio.

METHODS

- Study design: Secondary analysis of the RELAX (PDE-5 Inhibition to Improve Clinical Status and Exercise Capacity in Heart Failure with Preserved Ejection Fraction) trial.
- Trial Identification: ClinicalTrials.gov: **NCT00763867**
- RELAX trial eligibility criteria:
  - 18 years of age or older,
  - NYHA class II to IV,
  - LVEF ≥ 50%,
  - peak VO2 ≤ 60% predicted with adequate resp exchange ratio ≥ 1.0),
  - evidence of heart failure in the 12 months prior (heart failure hospitalization, echocardiographic evidence of diastolic dysfunction with left atrial enlargement in the setting of long-term diuretic therapy for heart failure, or invasively documented elevation in LV filling pressure at rest);
  - N-Terminal Pro-B-Type Natriuretic Peptide (NT-proBNP) ≥ 400 pg/mL or BNP ≥ 200 pg/mL
- Randomization: sildenafil 20 mg tid then 60 mg tid for 12 weeks each vs. placebo (1:1)
- Endpoints
  - Primary: change in peak VO2 over 24 weeks
  - Secondary: clinical composite rank score
  - Exploratory: LV mass and circulating biomarkers
- Biomarkers: serum NT-proBNP (Roche Diagnostics) & plasma cGMP (RIA) measured at baseline and week 24 end of study
- Statistical analysis
  - NT-proBNP to cGMP ratio calculated at randomization and week 24
  - Categorized according to quartile of baseline NT-proBNP / cGMP
  - Multivariable ordinal logistic regression to examine correlates of NT-proBNP / cGMP
  - Unadjusted and multivariable adjusted ordinal logistic regression to examine impact of sildenafil on NT-proBNP, cGMP, and NT-proBNP to cGMP over 24 weeks
  - Randomization x NT-proBNP / cGMP interaction term to examine effect modification on trial outcomes

RESULTS

Table 1: Baseline Characteristics of RELAX Trial Patients by Quartiles of NT-proBNP/cGMP Ratio

	1st Quartile	2nd Quartile	3rd Quartile	4th Quartile
NT-proBNP/cGMP Ratio, med (IQR)	1.26 (0.81, 2.43)	6.45 (4.46, 7.65)	14.14 (11.22, 17.23)	33.01 (27.15, 44.72)
NT-proBNP, ng/L	94.32 (57.39, 176.8)	481.0 (356.4, 619.5)	1231.0 (836.6, 1528.0)	2462 (1643.0, 3101.0)
cGMP, pmol/mL	78.53 (57.44, 113.23)	86.04 (59.64, 105.26)	85.19 (67.06, 105.99)	67.07 (41.91, 83.71)
Age, years	62 (55, 67)	68 (63, 76)	73 (67, 80)	73 (65, 79)
Female, n (%)	30 (55.56)	22 (41.51)	29 (54.72)	22 (41.51)
Race, n (%)				
White	49 (90.74)	44 (83.02)	49 (92.45)	53 (100)
Black	2 (3.70)	7 (13.21)	2 (3.77)	0 (0)
Other	3 (5.56)	2 (3.77)	2 (3.77)	0 (0)
History of, n (%)				
Heart failure hospitalizations	18 (33.33)	22 (41.51)	16 (30.19)	21 (39.62)
Hypertension	46 (85.19)	42 (79.25)	45 (84.91)	47 (88.68)
Diabetes	23 (42.59)	26 (49.06)	18 (33.96)	24 (45.28)
Atrial fibrillation	13 (24.07)	26 (49.06)	34 (64.15)	36 (67.92)
MI or Revascularization	13 (24.07)	13 (24.53)	12 (22.64)	22 (41.51)
COPD	6 (11.11)	17 (32.08)	12 (22.64)	7 (13.21)
Vitals, median (IQR)				
Systolic blood pressure, mmHg	124 (112, 133)	124 (114, 140)	124 (111, 140)	122 (112, 137)
Body Mass Index, kg/m^2	35.41 (30.75, 41.29)	33.98 (28.32, 40.77)	33.23 (28.79, 36.45)	31.03 (28.31, 40.32)
Labs and biomarkers, median (IQR)				
eGFR, ml/min/1.73m^2	81.68 (68.21, 95.10)	62.06 (49.66, 78.04)	61.35 (43.47, 76.82)	52.31 (40.36, 67.32)
Troponin I, pg/mL	4.11 (2.91, 7.34)	9.33 (5.93, 19.32)	10.35 (6.13, 16.81)	16.92 (8.94, 41.68)
Aldosterone, pg/mL	155.06 (92.51, 242.36)	183.79 (123.33, 264.4)	236.52 (143.46, 317.8)	200.63 (137.43, 282.58)
Galectin 3, ng/mL	12.93 (9.82, 15.69)	13.82 (11.02, 16.79)	13.56 (11.53, 16.02)	15.91 (12.24, 21.45)
C-reactive Protein, mg/L	4.52 (2.05, 9.44)	2.92 (1.5, 6.96)	4.05 (1.91, 7.47)	3.61 (1.84, 10.1)
Cardiac function and structure, median (IQR)				
Left ventricular mass by MRI, gm	136.7 (102.8, 161.2)	140.9 (103.2, 187.9)	127.1 (101.7, 154.1)	142.2 (114.1, 211.4)
LVEF by MRI, %	66.9 (61.7, 69.8)	66.25 (57.45, 69.65)	63.6 (50.7, 69.4)	66.1 (49.7, 72.3)
E/A Ratio by ECHO	1.0 (0.89, 1.5)	1.44 (0.91, 2)	2.0 (1.12, 3.17)	3.0 (1.33, 3.4)
Left atrium volume by ECHO, cc	73.6 (62.4, 85.8)	100.7 (76.9, 123.5)	98.5 (75.9, 129.3)	108.3 (87.4, 137.8)
RVSP by ECHO, mmHg	34.2 (29.4, 41.4)	37.8 (32.0, 51.0)	43.44 (36.4, 48.6)	48.4 (36.4, 53.6)
Peak VO_2, ml/min/kg	14.4 (11.7, 16.7)	12.0 (10.9, 15.1)	11.2 (9.5, 13.8)	10.7 (9.4, 11.7)

Abbreviations: cGMP, cyclic guanosine monophosphate; COPD, chronic obstructive pulmonary disease; ECHO, echocardiogram; eGFR, estimated glomerular filtration rate; IQR, interquartile range; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; MI, myocardial infarction; NTpro-BNP, N-terminal pro b-type natriuretic peptide; RVSP, right ventricular systolic pressure

Table 2: Correlates of Baseline Plasma NT-proBNP to cGMP Ratio

Characteristic	OR [95% CI]	P-value
Age, years	1.00 [0.95, 1.05]	0.97
Female	1.66 [0.64, 4.32]	0.29
Race	0.62 [0.29, 1.31]	0.21
Body Mass Index, kg/m2	0.91 [0.85, 0.96]	0.001
Systolic Blood Pressure, mm Hg	1.00 [0.99, 1.02]	0.79
Estimated Glomerular Filtration Rate, ml/min/1.73m2	0.98 [0.96, 0.99]	0.005
Left Ventricular Mass, g	1.012 [1.004, 1.019]	0.005
Left Ventricular Ejection Fraction, %	0.99 [0.95, 1.03]	0.59
Troponin I, pg/mL	1.017 [1.002, 1.032]	0.023
C-reactive protein, mg/L	1.02 [0.96, 1.07]	0.52
Peak VO_2, ml/min/kg	0.80 [0.68, 0.93]	0.003
Atrial fibrillation	4.41 [1.02, 19.09]	0.047
Multivariable proportional odds model adjusted for all covariates listed.		

Table 3: Treatment Effect of PDE-5 Inhibition on Change in NT-proBNP/cGMP Ratio from Baseline to Week 24

	Sildenafil	No PDE-5 Treatment	Unadj. P-value	Adj. P-value
Change in NT-proBNP	14.5 (-90.0, 372.2)	-22.97 (-198.3, 138.8)	0.011	0.005
Change in cGMP	8.4 (-7.20, 21.0)	0.16 (-10.3, 15.3)	0.086	0.11
Change in NT-proBNP/cGMP Ratio	0.11 (-2.4, 3.0)	-0.57 (-4.3, 1.9)	0.17	0.57

*Values as median (IQR). Adjusted p-value from MV regression model adjusted age, female gender, and race

Table 4: Effect Modification of Baseline NT-proBNP to cGMP Ratio on Relationship between PDE-5 Inhibition and Endpoints

Outcomes	P-interaction
Peak VO_2	0.60
Left Ventricular Mass	0.31
Estimated Glomerular Filtration Rate	0.58
Troponin I	0.42
Composite score for worsening HF*	0.44

*Hierarchical rank clinical rank score based on time of death, time to hospitalization for cardiovascular or cardiorenal causes, and change in heart failure symptoms assessed by Minnesota Living with Heart Failure Questionnaire from baseline

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SUMMARY OF FINDINGS

- In MV-adjusted models, baseline BMI, eGFR, peak VO_2 inversely associated with baseline NT-proBNP to cGMP ratio, while greater LV mass, troponin and atrial fibrillation associated with higher NT-proBNP/cGMP ratio **(Table 2)**
- LVEF was not associated with NT-proBNP to cGMP ratio
- Randomization to sildenafil did not alter NT-proBNP/cGMP ratio from baseline to 24 weeks vs placebo (p=0.17) **(Table 3)**
- Baseline NT-proBNP to cGMP ratio did not modify the effect of sildenafil compared with placebo on 24-week change in peak VO_2, LV mass or a clinical composite outcome **(Table 4)**

CONCLUSIONS

- Among individuals with HFpEF included in the RELAX trial, higher NT-proBNP to cGMP ratio was associated with lower VO2, greater LV mass, and higher troponin.
- Inhibition of PDE-5 with sildenafil did not influence NT-proBNP to cGMP ratio, nor was its effect on outcomes modified by baseline NT-proBNP to cGMP ratio.
- Among patients with HFpEF, PDEs other than PDE-5 may contribute to the adverse cardiac phenotype associated with a high NT-proBNP to cGMP ratio.

Soluble guanylyl cyclase stimulation attenuates hyperoxia-induced vascular dysfunction in mice

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Introduction

We have previously shown that hyperoxia compared to normoxia impairs endothelium-dependent and -independent vasodilation but not the vasodilatory response to the heme-*independent* soluble guanylyl cyclase (sGC) activator cinaciguat.[1] These findings were most likely the result of hyperoxia-induced reduction in endothelial nitric oxide synthase (eNOS) function or impairment in nitric oxide (NO) binding or activation of sGC. To explore these mechanisms, we tested the hypothesis that activation of sGC with the heme oxidation state-*dependent* stimulator vericiguat would have reduced function in hyperoxia compared to normoxia, but vericiguat pre-treatment could improve endothelium-dependent and -independent vasorelaxation.

Methods

Vericiguat dose-response curves (10^{-10} to 10^{-4} M) were performed in aortic segments from mice treated with hyperoxia or normoxia during a renal ischemia reperfusion exposure that simulates surgical stress and organ injury. Mice were anesthetized, intubated, and ventilated with 21% (normoxia) or 100% (hyperoxia) oxygen during 30 minutes of renal ischemia and 30 minutes of reperfusion. Following sacrifice, the thoracic aorta was isolated, and 2mm segments were mounted on a wire myograph.

In separate mouse aortas, a single dose of 10^{-7} molar vericiguat or vehicle was administered prior to assessing endothelium-dependent vasorelaxation with acetylcholine (ACh) and endothelium-independent vasorelaxation with sodium nitroprusside (SNP). Vasodilator responses were quantified as the maximal theoretical response (E_{max}) and the effective concentration to elicit 50% relaxation (EC_{50}) using a sigmoid model and nonlinear mixed effects regression.

NO levels in mouse aorta were quantified using Electron Paramagnetic Resonance and iron diethyldithiocarbamate, a NO spin trap.

Results

Hyperoxia impaired vericiguat-induced vasodilation. The vericiguat EC_{50} was -5.53 log M (95% CI:-5.86 to -5.20, n=12) in hyperoxia and -6.08 log M (-6.41 to -5.76, n=12) in normoxia (p=0.02, **Figure A**). The E_{max} was 101.4% (98.9 to 107.0, n=12) in hyperoxia and 106.3% (102.9 to 113.1, n=12) in normoxia (p=0.07).

Vericiguat treatment did not impair vascular tension produced by norepinephrine. The median active tension in hyperoxia was 11.7 mN (IQR: 9.1-12.8, n=12) in vericiguat-treated vessels and 9.8 mN (8.7-11.6, n=20) in vehicle (p=0.12). In normoxia the median active tension was 7.2 mN (5.7-8.4, n=12) in vericiguat-treated vessels and 8.3 mN (6.8-9.3, n=20) in vehicle (p=0.24).

Vericiguat augmented endothelium-dependent relaxation, and restored the relaxation observed in severe hyperoxia to the level of relaxation observed in normoxia after vehicle. In hyperoxia, the E_{max} was 53.1% (46.3 to 60.0, n=20) in vehicle and 73.8% (65.8 to 81.8, n=12) after vericiguat (p<0.001). In normoxia, the ACh E_{max} was 76.4% (95% CI: 69.6 to 83.3, n=20) after vehicle and 91.5% (83.2 to 99.9, n=12) after vericiguat (p<0.01, **Figure B**). In hyperoxia,

the ACh EC_{50} was -7.63 log M (-7.75 to -7.52) in vehicle and -7.72 log M (-7.88 to -7.57) after vericiguat (p=0.37). In normoxia, the ACh EC_{50} was -7.60 log M (-7.75 to -7.44) in vehicle and -8.04 log M (-8.24 to -7.85) after vericiguat (p<0.001).

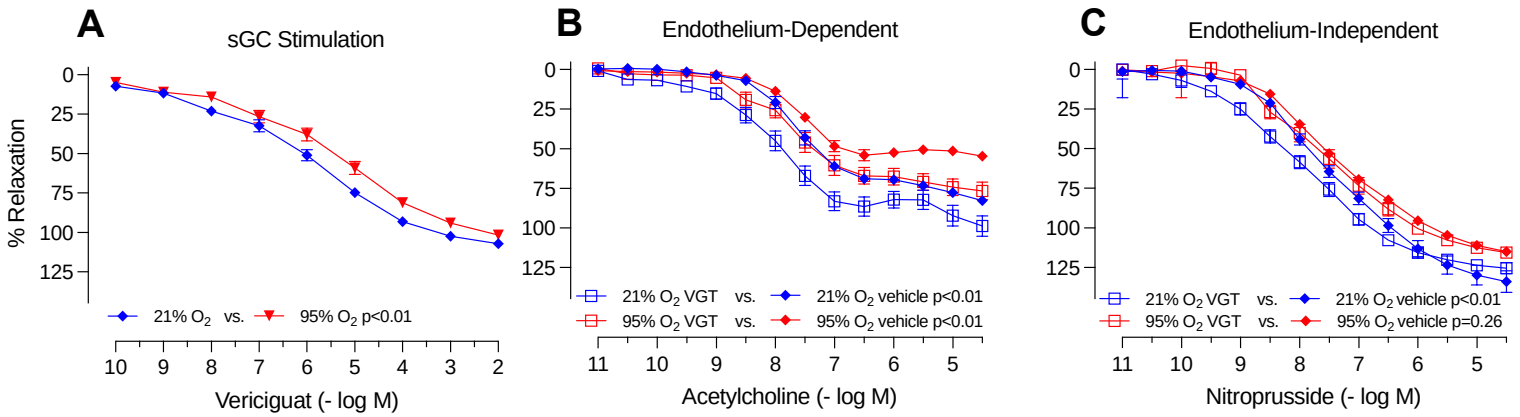
Vericiguat pre-treatment had modest effects on endothelium-independent relaxation (**Figure C**).

Hyperoxia did not significantly reduce aortic NO levels. Median NO intensity was 23.2 a.u. (IQR: 19.0-24.5, n=6) in hyperoxia and 25.2 a.u. (20.5-30.9, n=4) in normoxia (p=0.23).

Conclusions:

Hyperoxia impaired the vasodilation response to heme oxidation state-dependent sGC stimulation. Coupled with prior research demonstrating that hyperoxia does not affect heme-independent sGC activation, these data suggest that hyperoxia may oxidize the sGC heme moiety binding site of NO. Additionally, NO levels were not affected by hyperoxia treatment suggesting hyperoxia does not significantly alter eNOS function. Pre-treatment with an sGC stimulator to target this impairment improved endothelium-dependent but not -independent vasodilation without impairing the vasoconstrictive response to norepinephrine. These findings have important implications for surgical patients who often suffer from ischemia reperfusion injury and receive large doses of supplemental oxygen during surgery.

1. Shock, 58(4), 280-286, 2022.


A
sGC Stimulation
% Relaxation
0
25
50
75
100
125
21% O2 vs. 95% O2 p<0.01
10 9 8 7 6 5 4 3 2
Vericiguat (- log M)
B
Endothelium-Dependent
21% O2 VGT vs. 21% O2 vehicle p<0.01
95% O2 VGT vs. 95% O2 vehicle p<0.01
11 10 9 8 7 6 5
Acetylcholine (- log M)
C
Endothelium-Independent
21% O2 VGT vs. 21% O2 vehicle p<0.01
95% O2 VGT vs. 95% O2 vehicle p=0.26
11 10 9 8 7 6 5
Nitroprusside (- log M)