Distinction in Medical Research Instructions (revised 7/18/25):

An emphasis on medical research. Distinction in Medical Research (DMR) proposals need to fit the broad definition of "medical research", i.e., investigations, experiments, and studies to discover, develop, or verify knowledge relating to the causes, diagnosis, treatment, prevention, or control of human diseases. Medical research can be pre-clinical (basic science), translational, epidemiological, or clinical.

Hypothesis-driven research. Proposals must employ inferential approaches and hypothesis testing. Narrative literature reviews, dataset establishment, case reports, and QI projects are **not** suitable for the DMR Program.

Mentorship and relationships with ongoing research projects. Projects can be derived from the overall research program of a mentor (PI), but must be individualized for each applicant with unique objectives & aims that can be achieved within the timeframe of the DMR Program.

Individual vs. collaborative research. Although students are encouraged to work together, each DMR application must have its own lead "Principal Investigator". The rationale is that the DMR program is trying to provide students with the experience of leading a research project. Therefore, each DMR applicant must have their own unique research question(s), even if the overall project may be a collaboration across multiple students.

Concrete and actionable plan. Your proposal should be very clear and well-defined in its goals, structure, methodology, and requirements. Be specific when defining your terms. Consider your potential reviewers and their understanding of your topic. Ask yourself the question, "If I had the funding, participants, and equipment today, could **someone else** begin my study tomorrow?"

Applications should follow an NIH style grant (sections in quotes are from NIH grant writing guides). For the DMR application, a section for Specific Aims (1 page) and Research Strategy (4 pages) are required.
*For more detail, see **2.1 The Art of Scientific Grant Writing PPT slides** online material.*

Specific Aims (**1 page**, 11-point font, 0.5 inch margins)

The Specific Aims page should include the following components/guidelines:

- Significance of the problem (1-3 sentences).
- Scientific premise (3-6 sentences; short list of evidence supporting the hypothesis, highlighting preliminary data, if applicable).
- Highlight the knowledge gap within the context of Significance (1 sentence).
- Build to an overarching hypothesis (1 sentence, **bolded**).
- Provide a succinct, clear description (1 bolded hypothesis sentence, accompanied by 2-5 sentences on methods/expected results) for each SA.
- Impact statement (2-3 sentences); how will completion of proposed experiments change the field?

Research Strategy (**4 pages total**, 11-point font, 0.5 inch margins)

Significance Section (~1 page)

- **"Overview of the Problem" Section. "**Explain the importance of the problem or critical barrier to progress that the proposed project addresses." Expands upon the disease-relevance mentioned in the first few lines of the SA page.
- **Scientific Premise Section(s). "**Describe the scientific premise for the proposed project, including consideration of the strengths and weaknesses of published research or preliminary data crucial to the support of your application." Make use of "Mini-Review style" **bolded subheadings**, taking the reader through a structured review of the evidence underlying the "legs" of the scientific premise. Use of one or more schematics is advised.
- **"Scientific Impact" Section. "**Explain how the proposed project will improve scientific knowledge, technical capability, and/or clinical practice in one or more broad fields." Expands on the "Impact Statement" at the end of the SA page.

Innovation Section (~0.5 pages)

- **"**Explain how the application challenges and seeks to shift current research or clinical practice paradigms."
- "Describe any novel theoretical concepts, approaches or methodologies, instrumentation or intervention(s) to be developed or used, and any advantage over existing methodologies, instrumentation, or intervention(s)."
- "Explain any refinements, improvements, or new applications of theoretical concepts, approaches or methodologies, instrumentation, or interventions."

This section is usually broken into two main sections: *Conceptual Innovation* and *Technical Innovation*. For each section, innovation points can be listed to make it easier for reviewers to quickly comprehend and transfer to their own reviews.

Approach Section (~2.5 pages)

Approach sections vary widely but the following sections should be considered:

- **"Overall study design" Section:** Briefly recapitulate the SAs, emphasizing how they logically flow and interrelate, but in a non-dependent manner (1 paragraph).
- Section(s) on resources that require rationale/justification, such as human clinical databases, transgenic mouse lines, cell culture lines, and/or other resources that require explanation to understand the approach (1-2 paragraphs).
- **"Preliminary Studies" Section:** Pilot experiments and preliminary data that support the hypothesis, accompanied with any data figures with figure legends. Figure legends are recommended to be no less than 10-point font (0.5-2 pages).

- **"Rigor, reproducibility, power, and sex as a biological variable (SABV)" Section:** Rationale for sample numbers chosen (i.e. power analysis), ensuring rigor in experimental design (i.e. avoiding bias, blinding), and sexes used (or justification for using only one sex). Any discussion of sex should be accompanied by relevant references that support the use of sex in the experimental design (1 paragraph).
- **"Strengths of the multidisciplinary team" Section:** Gives context to the complementary expertise and roles of collaborators mentioned, including those writing Letters of Support (1 paragraph, if applicable). It is a concise summary provided to reviewers before they view the biosketches.

Budget/Budget Justification and Facilities/Resources (**1 page total**)

Budget and Budget Justification

- For each Specific Aim, identify all costs that are necessary and reasonable.
- Include any necessary statistical software (i.e. Prism, SPSS, etc.).
- Include Biorender, an elegant graphics tool that is not provided to medical students.
- Include bibliographic (i.e. Readcube) or other software that incurs cost.
- Estimating "person-months" needed to complete each experiment will give you a sense for scale and scope.
- Some typical budget categories to consider:
    - Staff (i.e. paying yourself, consultants, and/or junior trainees)
    - Travel
    - Supplies
    - Publication costs

Facilities and Resources

- **Will the scientific environment in which the work will be done contribute to the probability of success?** Identify/list any organizational affiliations that demonstrate to the reviewers that the working environment at TTUHSC is conducive to project success.
- **Will the scientific environment in which the work will be done contribute to the probability of success?** List any institutional support, relevant equipment, and other physical resources available to the applicant and/or mentor that are relevant to the project proposed.
- **Will the project benefit from unique features of the scientific environment, subject populations, or collaborative arrangements?** Point out any unique features or special resources (i.e. West Texas demographics, unique cross-campus collaborations, local conferences, interdisciplinary strengths, etc.).

References (**no page limit**)

Common bibliographic software:

- **Endnote** is available from the TTUHSC library (https://ttuhsc.libguides.com/endnote)
- **ReadCube** (https://www.readcube.com)
- **Mendeley** (https://www.mendeley.com)
- **Zotoro** (https://www.zotero.org)
- **Overleaf** (https://www.overleaf.com)
- **LaTex** (https://www.latex-project.org)

TEXAS TECH UNIVERSITY HEALTH SCIENCES CENTER™

American Heart Association
2024 Topic-Focused Funding Proposal

Project Title:	**Intravascular Ultrasound (IVUS) Guided Percutaneous Coronary Intervention for Patients with Myocardial Infarction: A Randomized Control Trial**
Pilot Study Project Investigator(s):	Principal Investigator: [redacted] Department of Internal Medicine, Texas Tech University Health Sciences Center (TTUHSC), Lubbock, TX, 79430 Co-Investigator: [redacted] Department of Internal Medicine, TTUHSC, Lubbock, TX, 79430 Co-Investigator: [redacted] Texas Tech University Health Sciences Center School of Medicine, Lubbock, TX, 79430
Sponsoring Institution:	Texas Tech University Health Sciences Center School of Medicine, Division of Cardiology, Department of Internal Medicine
Address/Phone Number/Email:	[redacted]
Amount Requested:	$ 504,000

Abstract: Myocardial infarction is defined as the ischemic necrosis of the heart's muscular tissue and is caused by insufficient oxygen delivery for the tissue's demand. This is most commonly due to coronary artery disease and remains a leading cause of mortality in the United States. Emergency revascularization for patients with catheterization is the standard treatment. This procedure is used to assess the patency of coronary arteries and restore flow to these vessels, if occluded. Angiography has been conventionally used to visualize blockages and the restoration of flow during catheterization but is a lower resolution medium than the emerging intravascular ultrasound (IVUS) technology. In this prospective study, we will employ IVUS to potentially identify and reduce atherosclerotic plaque load compared to traditional angiography assisted catheterization. 200 qualified patients with myocardial infarction will be assigned to receive either IVUS guided or angiography guided coronary catheterization. We will measure percentage stenosis of coronary vessels prior to and after intervention, as well as number of recurrent acute coronary syndrome (ACS) events across a 2-year postprocedural period. All data will be subject to analysis with statistical significance at $p < .05$.

PI's Name: [redacted] **AHA2024**
Title: Intravascular Ultrasound (IVUS) Guided Percutaneous Coronary Intervention for Patients with Myocardial Infarction: A Randomized Controlled Trial

Significance:

Studies have shown that intravascular ultrasound (IVUS) guidance, a technique that uses an ultrasound probe mounted on catheter tip, better assists interventionalists in appraising vascular lesions and selecting the right stent and catheter sizes when compared to traditional angiography guided percutaneous coronary intervention (PCI)[1]. This is an intuitive improvement as the technology images vasculature from within and provides a three-dimensional view of healthy tissue and plaque load. However, comparative findings have yet to be clearly elucidated in patient care environments. There remains little data comparing angiography and IVUS in acute myocardial infarction patients with respect to all-cause mortality and major adverse cardiac events[2]. More studies are required to establish if either technology is superior in reducing recurrence of acute coronary events. Conducting a randomized control trial wherein both aforementioned imaging measures are compared will allow for the potential reformation of how operators visualize and eliminate coronary atherosclerotic disease as X-ray angiography is the current and most common medium. With the potential widespread adoption of IVUS, physicians may also be able to greatly reduce the occupational hazard of scattered radiation exposure within interventional suites[3-4]. Furthermore, for patients that may not tolerate contrast, such as those with chronic kidney disease (CKD), minimal or contrast-free PCI using IVUS guidance serve as promising alternatives [5].

Innovation:

Intravascular ultrasound (IVUS) represents a groundbreaking innovation in vascular interventions, providing real-time, 3-dimentional images of the interior of blood vessels using high frequency soundwaves. If approved, this study would be the first long-term randomized control trial comparing IVUS and X-ray angiography guidance for coronary interventions in acute myocardial infarction patients. Comparing real-world outcomes would allow interventionalists to determine the best visual modality for their patients and procedures. Furthermore, testing the hypothesis that IVUS significantly reduces all-cause mortality and recurrent acute coronary events may allow a variety of interventional procedures to implement ultrasound guidance in lieu of angiography. This pending change in imaging preference or reduction in reliance on scattered radiation-based guidance would lend to lower risk of cancer in patients and interventionalists alike[6]. Ultimately, this study aims to make interventional suites safer for all those within and tests real-world acute myocardial infarction patient outcomes with hopes to reduce major adverse cardiac events.

Research Strategy:

1. *Background*

As the most common subset of heart disease, the number one contributor to the death toll annually in the United States, coronary artery disease requires immediate intervention when the plaque load is great enough to interrupt blood supply to the myocardium or cause significant symptoms of coronary blockage[7]. Acute myocardial infarction (AMI) is a manifestation of coronary artery disease which causes a blockage of the coronary arteries sufficient to occlude blood flow. Infarction occurs when the muscle of the heart necroses due to the lack of nutrients secondary to blood flow disruption. The sequelae of AMI may be debilitating and include heart failure, arrythmias, and cardiogenic shock. Patients suspected to be suffering from AMI must immediately undergo a non-surgical procedure of percutaneous coronary intervention (PCI) via radial/femoral artery access to restore the lumen of coronary arteries and thus perfusion to the ischemic/infarcted tissues[8]. This revascularization effort is guided in real-time by X-ray fluoroscopy as contrast depicts the coronary anatomy and assists operators in selecting the correct balloon, stent, or both for luminal restoration.

The adoption of alternative imaging for PCI guidance has been slow, likely due in part to the barriers of prohibitive expenses, additional training, and prolonged time within procedures[9]. Intracoronary imaging, despite its slowed adoption, provides great benefit to operators as it generates a greater resolution and dimensional image of vasculature and plaque burden[10]. Giving interventionalists a clearer target for revascularization may also lend to lower rates of lumen restenosis and reduce the overall costs of additional procedures on healthcare systems. A systematic review analyzed the cost-effectiveness of IVUS as an adjunct to angiography in 2006 and revealed that IVUS guidance would be less costly by a millions of dollars annually when accounting for the avoidance of additional revascularization procedures[10]. A systematic review released in 2023 compared IVUS and angiography guidance for chronic total occlusion (CTO) PCI across five-studies with a total of 2320 patients. The authors noted there was no significant difference in major adverse cardiac events (MACE), yet stent thrombosis was significantly reduced in the IVUS group[11]. 19 studies analyzed in a systematic review comparing IVUS and X-ray angiography guided PCI indicated that IVUS-PCI reduced the risk of cardiovascular death and postprocedural MI[12]. This review included the EXELLENT, ULTIMATE, and OPTICUS trials, which all had follow-ups occurring until 1-year post-procedure. Other limitations of the previous studies comparing IVUS and angiography include inconsistent IVUS criteria for stent placement/post-dilatation and use of various generations of drug-eluting stents. Our study aims to build upon these previous trials and reduce heterogeneity within the IVUS criteria, lesion location/size compared, and stents used.

2. *Research Questions*

- Does IVUS guided PCI produce a greater reduction in coronary vessel stenosis and recurrence of acute coronary events over a 2-year post-procedure period when compared to contrast-enhanced X-ray coronary angiography (CA)?
- Can the use of IVUS as a surrogate to angiography reduce major adverse cardiac events and overall mortality in patients suffering from acute myocardial infarction?

3. Objectives (inclusive of specific aims)

- Test the hypothesis that IVUS guided PCI reduces rate of coronary re-stenosis and recurrent myocardial infarctions when compared to X-ray angiography guided PCI
- Identify all adult patients at the University Medical Center suffering from AMI within upcoming 2-3 calendar years who have no history of PCI or CABG (to obtain adequate patient volume)
    - Allow randomization of patients undergoing PCI to receive X-ray angiography or IVUS guidance within their procedure
- Follow-up at 1-year and 2-year postprocedural intervals status-post IVUS/X-ray angiography guided PCI for initial AMI for evaluation of restenosis
    - Also assess for recurrence of acute coronary syndrome after the procedure at the annual follow-up visits
- Complete descriptive statistical analysis of data collected
- Compare rates of ACS and coronary restenosis amongst the three study groups collected within the first and second year follow-up appointments

4. Hypothesis

- Our hypothesis is that patients who have undergone IVUS guided PCI will have a reduction in coronary artery stenosis compared to those with X-ray-guided PCI at 2-years post-procedure
- We also hypothesize that patients who have undergone IVUS-guided PCI will have lower rates of major adverse cardiac events and overall mortality in patients suffering from acute myocardial infarction

5. Preliminary Data

- The currently available literature on our research question consists of 9 randomized control trials and 10 observational studies conducted within the past 22 years. A meta-analysis including these randomized control trials and observational studies revealed 33% relative risk reduction in cardiovascular death and 0.71 relative risk of recurrent MI in patients receiving IVUS guided PCI vs. CA guided PCI[12]
- As mentioned previously, these trials were limited in their follow-up length, often terminating at 6-months or 12-months post-procedure. Many of these studies utilized various stents and multiple generations of drug-eluting/bare metal stents. Considering the drastic improvement in resolution and miniaturization of IVUS catheters, we believe our randomized control trial will better represent the current and evolved utility of IVUS

6. Methods

- Study Sites: University Medical Center Hospital, 602 Indiana Avenue, Lubbock, TX, 79415
- Design:
    - This is a prospective study that involves adult patients suffering from an initial acute myocardial infarction. Patient data, including demographic information, percent stenosis prior to PCI, and history of adverse cardiac events will be collected in the interventional phase of the study. This portion of the trial is expected to span two to three years based on the average cardiogenic shock patient volume of 80-100 eligible patients per year at UMC. In this phase, the

group of 200 selected patients will be blindly divided into two subsets based on intervention type – one receiving IVUS guided PCI and one receiving X-ray angiography guided PCI. Following their procedure, patients will be scheduled for supplementary follow-up appointments at 1-year and 2-year timepoints for optical coherence tomography (OCT) if available, and IVUS if unavailable, to reassess percent stenosis (specifics discussed further in the measurement section below). Additionally at these yearly intervals, data including numbers of major adverse cardiac events and mortality will be recorded for both groups. Following the conclusion of this study, recorded data will be analyzed using two tailed t-tests. Significance will be determined at $p<0.05$.

- Recruitment:
    - Inclusion Criteria:
        - Age >40 years old
        - Suffering from initial AMI
        - No history of major adverse cardiac events
    - Exclusion Criteria:
        - Age >70 years old
        - History of major adverse cardiac events
        - Any patient with a history of previous cardiac surgery
        - Any patient with CKD or any other condition
        - Any patient with current or prior history of cocaine, anabolic steroids, or other illicit drug use due to cardiotoxic effects
- Measurement:
    - Demographical data will be collected including age, sex, race, ethnicity, height, weight, BMI, and co-morbidities
    - Clinical data measured on day of hospital admission as well as yearly follow-up visits will include blood pressure, pulse, oxygen saturation, respiration rate, and troponin levels
    - Imaging data will include percent stenosis at the start of the study ideally based on intravascular optical coherence tomography (OCT)
        - It is imperative to have consistent and high-resolution imaging modalities to compare percent stenosis in coronary vessels before and after PCI. Therefore we will aim to have OCT assess stenosis in both IVUS (treatment) and X-ray angiography (control) patient groups
        - If OCT is unavailable at our center, we may use IVUS in both control and treatment groups prior to PCI and during yearly post-procedure visits. This will ensure a high-resolution measurement of percent stenosis at time of PCI as well as percent stenosis reduction at post-procedure visits when comparing treatment and control groups
        - This flexibility in design (OCT vs IVUS) allows our study to avoid contingency on funding of OCT as it is a costly imaging modality
    - Primary outcome: percent stenosis for surviving patients at yearly follow-up visits at the site of previous target lesion
    - Secondary outcomes:
        - Seattle Angina Questionnaire (SAQ) to assess angina and physical limitations due to coronary symptoms

        - Quality of life assessment using QOLS (quality of life scale) assessment
        - Major adverse cardiac events (MACE) such as stroke, myocardial infarctions, and revascularization procedures
        - Rehospitalization rates related to cardiovascular events
        - Participant physical functional status using SPPB (short physical performance battery) assessment
        - All cause 1-year and 2-year mortality
        - Cost of respective procedure (+ revascularization/cardiac rehospitalization costs if applicable)
- Randomization:
    - Patients will be randomly assigned to either the control group (X-ray guided PCI) or the treatment group (IVUS guided PCI) following study enrollment
    - Following collection, data will be analyzed by research personnel blinded to data received from both groups.
- Intervention:
    - Optical coherence tomography will be done on all patients at the beginning of the study to assess percent stenosis at initial AMI
        - If optical coherence tomography is unavailable, IVUS will be used to collect this measurement instead as discussed prior
    - Following OCT (or IVUS) based vessel patency measurement, patients will undergo either IVUS guided PCI or X-ray guided PCI based on study-assigned group
    - At 1 and 2-year follow-up visits, patients will again undergo OCT, if available, and IVUS if OCT is unavailable to reassess for percent stenosis

7. Expected Results

- We expect that patients who have received IVUS guided PCI will have lower immediate and long-term percent coronary artery stenosis when compared to patients who received X-ray guided PCI.
- We also expect that patients assigned to the IVUS guided PCI group will have a lower relative risk of major adverse cardiac events and mortality in the following 2-year time-period.

References

1. Ahmad M, Mehta P, Reddivari AKR, et al. Percutaneous Coronary Intervention. [Updated 2023 Jun 5]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK556123/
2. Alasnag M, Ahmed W, Al-Bawardy R, Shammeri OA, Biswas S, Johnson TW. Optimising PCI by Intracoronary Image-guidance. Front Cardiovasc Med. 2022 May 13;9:878801. doi: 10.3389/fcvm.2022.878801. PMID: 35647055; PMCID: PMC9136172.
3. Burlacu A, Tinica G, Brinza C, Crisan-Dabija R, Popa IV, Covic A. Safety and Efficacy of Minimum- or Zero-Contrast IVUS-Guided Percutaneous Coronary Interventions in Chronic Kidney Disease Patients: A Systematic Review. J Clin Med. 2021 May 6;10(9):1996. doi: 10.3390/jcm10091996. PMID: 34066543; PMCID: PMC8125490.
4. Darmoch, Fahed, et al. "Intravascular ultrasound imaging–guided versus coronary angiography–guided percutaneous coronary intervention: a systematic review and meta-analysis." Journal of the American Heart Association 9.5 (2020): e013678.
5. Groenland FTW, Neleman T, Kakar H, Scoccia A, Ziedses des Plantes AC, Clephas PRD, Chatterjee S, Zhu M, den Dekker WK, Diletti R, Zijlstra F, Mahmoud KD, Van Mieghem NM, Daemen J. Intravascular ultrasound-guided versus coronary angiography-guided percutaneous coronary intervention in patients with acute myocardial infarction: A systematic review and meta-analysis. Int J Cardiol. 2022 Apr 15;353:35-42. doi: 10.1016/j.ijcard.2022.01.021. Epub 2022 Jan 15. PMID: 35041893.
6. Ho TL, Shieh SH, Lin CL, Shen WC, Kao CH. Risk of cancer among cardiologists who frequently perform percutaneous coronary interventions: a population-based study. Eur J Clin Invest. 2016 Jun;46(6):527-34. doi: 10.1111/eci.12628. Epub 2016 Apr 15. PMID: 27018993.
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12. Writing Committee Members, et al. "2022 ACC/AHA key data elements and definitions for chest pain and acute myocardial infarction: a report of the American heart association/American college of cardiology joint committee on clinical data standards." Journal of the American College of Cardiology80.17 (2022): 1660-1700.

Key Personnel

[redacted], BS: Medical Student and Student Researcher

- I have spent the past 5+ years researching neural gene modification and cardiogenic shock. My thorough interest in the dynamic nature of the cardiovascular system and the intricacies of neural transmission has kept me curious throughout my medical training. My current research mostly consists of clinical work and incorporates the breakthroughs from bench scientists from across the world. I am very grateful for the tutelage and guidance I have received from my mentors at University of Texas at Dallas and Texas Tech University Health Sciences Center. With their support, I have worked to sharpen my skills in data processing and analysis as well as manuscript/abstract publication. My interests remain focused on cardiology and neural transmission, particularly hemodynamics within cardiothoracic procedure anesthesia. I have presented our institution's findings at various national conferences for interventional cardiology including CRT, AMP, and CVI. I continue to ask novel questions to understand how to improve the field of interventional cardiology and more importantly improve the outcomes of patients suffering from debilitating cardiovascular conditions. Organizing this study would allow our institution to improve the utilization of novel imaging technology to improve patient outcomes worldwide.
- Professional Positions
    - American Society of Anesthesiologists (ASA) Student Member
    - American Medical Association Student Member
    - Texas Medical Association Student Member
    - MD Candidate (2025) at Texas Tech University Health Sciences Center School of Medicine
    - TTUHSC School of Medicine Class of 2025 Treasurer/Secretary
    - MSG Treasurer (2022-2023)
    - Permian Basin Research Day 2024 Student Representative
- Peer Reviewed Articles
    - [redacted]
- Facilities
    - University Medical Center

    - Texas Tech Physicians Clinic - Cardiology
- Environment
    - This study will be entirely conducted in the clinical setting within the UMC hospital for PCI procedures and adjacent Texas Tech Physicians clinic utilized for follow-up visits
    - The resources requested, including OCT and IVUS probes will be purchased prior to the start of our randomized control trial

Budget Worksheet

Organization Name: Texas Tech University Health Sciences Center
Project Name: **Intravascular Ultrasound (IVUS) Guided Percutaneous Coronary Intervention for Patients with Myocardial Infarction: A Randomized Control Trial**
Funding Request Amount: $ 504,000

Budget Line Item	**Request**	**Total Program Budget**
1. Imaging:		
a. OCT Catheter: $600 x 200 patients x 3 visits	$360,000	$360,000
b. IVUS Probe: $100,000	$100,000	$100,000
c. X-ray Angiography Probes and contrast dye: $438 x 100 patients	$43,800	$43,800
Total (4)	**$503,800**	**$503,800**
Other Program Income	**$0.00**	**$0.00**

A limitation of the above budget worksheet is the ambiguity of cost in regards to medical imaging equipment. We will aim to partner with manufacturers such as Philips to reduce the above costs and improve price transparency in the budget. We will certainly be able to conduct our study in the case OCT catheters are beyond our budget as we may instead rely on more affordable IVUS technology.

Protocol

TITLE: Predictive Modeling of 1-Year Outcome Following Pediatric Decompressive Craniectomy Using Machine Learning and Artificial Intelligence

PRINCIPAL INVESTIGATOR:
[redacted] Department of Pediatrics, TTUHSC [redacted]

INVESTIGATORS:
[redacted] School of Medicine, Texas Tech University Health Sciences Center

[redacted] Demartment of Neurosurgery, Oklahoma University

[redacted] School of Medicine, Texas Tech University Health Sciences Center

[redacted] Department of Mathematics, The University of Texas Permian Basin

Abstract

There remains a need for accurate prediction of outcome following pediatric traumatic brain injuries, especially following decompressive craniectomies. Though some predictive models exist, they are not robust and machine learning has yet to be applied. The aim of this study was to develop a classification random forest algorithm and an artificial neural network to accurately predict 1-year outcome following decompressive craniectomies in the pediatric population. This will be a prospective study in which clinical, laboratory and imaging studies will be collected over a 3-year period with 6 month and 1 year follow up periods. Along with traditional statistical models, predictive algorithms will be created utilizing random forest classification and artificial neural networks. The success of the algorithms will be evaluated via standard metrics such as accuracy, recall the f-1 score, and area under the receiver operator curve.

SIGNIFICANCE

While many studies have examined prognostic factors on outcomes within the adult population, fewer studies examine the features and prognostic factors within the pediatric traumatic brain injury (TBI) population.[1,2] For much of the past century, outcomes and prognostic factors were evaluated by use of standard statistical analysis. Though this has proven useful, the advent of machine learning and artificial intelligence has opened a plethora of doors of new methods for prognostication. Furthermore, machine learning techniques have been proven to be superior tools for predicting outcomes in patients that have sustained a TBI.[1,3-8] Multiple studies have found success at predicting TBI outcomes within both pediatric and adult patients.[4,5,9-11] Though little has been done for the prognostication of decompressive craniectomies (DC) following TBI in both pediatric and adult populations. Hanko et. al. utilized classification and survival random forest to predict outcomes at 6 months for adult patients undergoing a DC. They had reasonable success with an area under the receiver operating curves ranging from 0.787-0.873.[9] This indicates the possibility of utilizing machine learning to predict outcomes following decompressive craniectomies. More studies are needed to further create machine learning and artificial neural networks in pediatric patients. Furthermore, this would be one of few prospective studies for pediatric decompressive craniectomies and the only study utilizing machine learning and artificial technology for outcome prediction. In the future, models such as these may serve to aid physician decision on when to operate and to provide realistic outcome prediction for the health care team and families.

INNOVATION

To our knowledge, this would be the first study in which machine learning techniques and artificial neural networks are utilized for the creation of an algorithm for the prediction of outcome following pediatric decompressive craniectomy. Furthermore, this would be one of few prospective studies for pediatric decompressive craniectomies and the only study utilizing machine learning and artificial technology for outcome prediction. The creation of an algorithm able to accurately predict outcome following pediatric DC could aid in counseling of patient's families with more accurate prediction capabilities and aid in hospital utilization of limited recourses. Though our algorithm if successful would still be far from clinically applicable, it will be an important step in the progression of machine learning and artificial technology utilization in neurological surgery.

STRAGETY

I. Background

Traumatic brain injury remains among the leading causes of disability and death within the pediatric population. An important treatment modality for severe TBI, especially in the setting of hemorrhagic intracranial lesions and intractable intracranial hypertension is decompressive craniectomy. This procedure is characterized by the removal of a part of

skull, typically coupled with a duraplasty, in order to evacuate hemorrhagic lesions and allow of cerebral expansion thus lowing intracranial pressure (ICP).
DC remains a controversial treatment modality especially considering the DECRA and RESCUEICP studys.[1,12] The DECRA study, published in 2011, was a randomized trial of DC for retractable ICP. Despite DECRA showing no benefit of DC, this study is highly criticized as patients included were age 15-60 with no stratification of results based on age. Furthermore, the methodology of randomization was flawed, and there was a failure to limit surgical intervention in patients whose ICP was above 20 but were not severe enough to necessarily warrant decompressive craniectomy.[1,13] In the RESCUEICP trial (2016), decompressive craniectomy was associated with decreased mortality; however, it was associated with increased patients in a vegetative state and severely disabled. Moreover, DC led to the same percentage of patients with a good outcome than those in the medical group.[14] This indicates that though mortality is improved, patient quality of life is not. To this point, only one randomized control trial in decompressive craniectomies exists. The study by Taylor et. al. was a randomized trial including 14 patients. Other larger retrospective studies exist in the pediatric population with most showing favorable outcomes in patients undergoing DC.[1,12,15-21] Other studies such as Burns et. al. show perhaps not all patients undergoing DC have good outcomes.[22]

The advent of machine learning and artificial intelligence have created the possibility for better prognostication following a wide range of injuries especially TBIs. When compared to traditional statistical models, machine learning and artificial neural networks have proven to be superior tools for prognostication in patients following TBI.[3-8] Within pediatric patients with TBI, Hale et. al. found success utilizing an artificial neural network to predict 6-month outcome. The artificial neural network outperformed traditional prognostic models including the computed tomography scoring systems Rotterdam, Marshal, and Helsinki.[5] Despite the successes in predicting outcome following TBIs, little has been done to utilize the new technology to prognosticate outcomes following DC. Hanko et. al. utilized classification random forest and survival random forest to predict survival and 6-month outcome. The study had success with an area under the receiver operating curve (ROC AUC) of 0.811 and 0.873 for the survival random forest classification random forest respectively When running the model on their hand-picked variables, the ROC AUC slightly decreased to 0.787 and 0.846 respectively.[9] This indicates the possibility of utilizing machine learning to predict outcomes following DCs. This study aims to build upon previous literature by utilizing classification random forest and survival random forest algorithms to predict outcomes in pediatric patients undergoing decompressive craniectomies.

II. Research Questions

- Can machine learning and artificial intelligence create algorithms with more accurate predictive power on outcome following pediatric decompressive craniectomy than conventional statistical methods?
- Are classification random forest algorithms or artificial neural networks more predictive of outcome following pediatric decompressive craniectomy.

III. Objectives (including specific aims)

- Identify all pediatric patients undergoing a primary decompressive craniectomy over the 3-year time span.
- Ensure the needed blood tests are ran and documents prior to the procedure as well as accurate documentation of all data points within the chart and data sheet.
- Follow up with the surviving patients at 6-month and 1-year intervals with careful clinician calculation of Glasgow Outcome Scale-Extended Pediatric Revision (GOS-E Peds).
- Complete descriptive and traditional statistical analysis of data collected.
- Create classification random forest and artificial neural network for prediction of discharge and 1-year outcome measures. Determine the most prognostic factors associate with outcome.
- Compare accuracy and predictability between classification random forest, artificial neural networks, and traditional linear regression. Determine the most prognostic.

IV. Hypothesis

- Our hypothesis is that with the subjective and objective data collected at the time of operation, the classification random forest algorithm and artificial networks will be able to accurately predict outcome at discharge and 1 year.
- We further predict the classification random forest will prove superior to the artificial neural network.

V. Preliminary Data

- The existing preliminary data is limited to a retrospective study in which survival random forest and classification random forest were utilized for prediction of outcome in 40 pediatric patients with decompressive craniectomies. Within the study, the classification random forest showed moderate success at predicting 6-month outcome measured as GOS and the survival random forest showed moderate success at predicting survival witch a ROC AUC of 0.75. Prognostic models on good and bad outcome are still under creation. The study was limited by low patient numbers and the unavailability of all data points desired for the algorithm creation. The preliminary data is currently in the manuscript writing phase and not yet published; however, was presented at the 2023 Congress of Neurological Surgeons and will be presented at the North Texas American College of Surgeons conference in 2024.

VI. Methods

- Study Sites: University Medical Center, Covenant Woman and Children's Hospital, The University of Oklahoma Medical Center
- Design
    - This is a 3-year prospective, observational study in which pediatric patients undergoing decompressive craniectomy will be enrolled. Patient data that has been carefully decided upon will be documented prior to decompressive craniectomy will be documented. Following surgery, patient outcome will be document at discharge utilizing the GOS-E Peds

in which 1-4 will be considered a good outcome whereas 5-8 will be considered a poor outcome. This is the standard scoring system within neurosurgical research. Following discharge, patients will be followed for a year in order to document a 1-year outcome at their 1-year follow up appointment utilizing the GOS-E Peds. GOS-E Peds scores will be carefully calculated by the attending or resident neurosurgeon seeing the patient. Following completion of the study, descriptive statistics will be utilized to describe the data set. Following traditional statistical models will be utilized to generate a predictive model. Furthermore, classification random forest models and artificial neural networks will be generated to predict patient outcome at discharge and 1 year follow up. The models will be compared between each other in search of the most predictive model.

- Recruitment:
    - Inclusion criteria:
        - Age less than 18 years old
        - Undergoing a primary decompressive craniectomy for TBI
    - Exclusion criteria:
        - Age 18 years or older
        - DC for indication other than TBI
        - DC at an unaffiliated facility
        - Patient who is pregnant
        - Any patient with previous neurological surgery
- Measurement
    - Demographic data will be collected including age, sex, ethnicity, height, weight, body mass index, and mechanism of injury.
    - Clinical data measured will include blood pressure, pulse, oxygen saturation, mean arterial pressure, temperature, Glasgow coma scale (GCS), pupil size and reactivity, and the use of mechanical ventilation. For continuous variables such as blood pressure, pulse, oxygen, mean arterial pressure, and temperature that will have more than 1 value, the value closest to the time of surgery will be utilized. GCS, pupil size, and reactivity will be documented by the attending or resident neurosurgeon and in the case of more than 1 input, the values closest to the time of surgery will be utilized. Furthermore, the use of ICP lowering agents such as mannitol and hypertonic saline will be documented.
    - Radiologic data will be collected including scoring systems such as Rotterdam, Helsinki, and Marshal, status of ambient cisterns, midline shift, herniation and the type and size of hemorrhagic lesions. Typically, only 1 CT scan will be present prior to surgery, but in the case of more, the imaging study closest to the operation will be utilized.
    - Lastly preoperative laboratory data will be collected including classic coagulation metrics (PT/INR, aPTT, fibrinogen, D-dimer), complete blood count and comprehensive metabolic panel. If a laboratory study is collected more than once (i.e. CBC or CMP), then the laboratory studies closest to the time of the operation will be utilized. Coagulation metrics

will not typically be collected more than once before the operation. If they are, then the values closest to the operation will be used.
    - Not measured will be standard measurements of ICP and cerebral perfusion pressure as this model is being constructed for outcome prediction prior to primary surgical decompression.
- Randomization
    - As this is an observational study with machine learning and artificial intelligence application no randomization is appropriate.
- Intervention
    - All patients will undergo the primary intervention of a decompressive craniectomy. Other interventions will be subject to neurosurgeon discretion following the guidelines set forth by Kochanek et. al.[23] These interventions include the usage of sedatives/analgesics, hypertonic saline/mannitol, and external ventricular drains/lumbar drains.
- Analysis
    - Immediately following collection of the data, data preprocessing will commence which will include exclusion of data entries with incomplete patient information, the removal of identifiable/sensitive patient information non-relevant to the study, the transformation of categorical variables, and the handling of censored information to fit the requirements of analysis.
    - Following this, Descriptive statistics including mean age and sex will be tabulated. Differences between groups in demographics will be assessed using chi-squared or Fisher's exact test for categorical variables, and Student's t test or Wilcoxon rank-sum for numerical/continuous variables. Other potential confounders will be used to calculate the adjusted effects. Results will be presented as odds ratio with 95% confidence intervals.
    - In Rstudio, a traditional logistic regression model will be created for outcome prediction. The classification random forest and artificial neural networks will be created in python and MATLAB respectively. The random forest model will utilize the RandomForestClassifier from the Python scikit-learn library. The artificial neural network will be created within MATLAB. The data will be split into an 80-20 ratio for training and testing, ensuring a substantial representation for model learning and validation. A fixed random seed will be employed for reproducibility. Model training will involve tuning 1000 decision trees. Thee model's performance will be evaluated using standard metrics such as accuracy, recall, the f-1 score, and the receiver operator characteristics area under the curve.

VII. Expected Results

- The results expected at the conclusion of this study is generally a good outcome for pediatric patients undergoing decompressive craniectomy. We expect that at the 1-year time mark, most survivors will have a GOS-E Peds of 1-4 (what is

considered a good outcome). Furthermore, we predict a total mortality rate in the 30s based on previous literature and our current preliminary data.

- We believe that the classification random forest will outperform the artificial neural network. This is based upon the previous studies and the nature of the study being performed. We also expect that both algorithms will perform well at outcome prognostication based upon the careful and thorough decision for the data collected.
- We expect coagulopathy, admission GCS, Helsinki scoring system, status of cisterns, pupil reactivity, neutrophil/leukocyte ratio, and albumin, to emerge as the most predictive of patient outcome.

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Key Personnel

[redacted] Medical Student/Researcher, BS

- Prior to matriculation of medical school, I spent a year working in a laboratory in biochemistry at Texas Tech University. I worked as a research technician preparing samples and running the LC/MS. It was here I discovered my deep interest in research; an interest that has continued throughout my career as a medical student. My research interests are centered on neurosurgery and specifically traumatic brain injury. This is evident through my research both in the lab and clinical research. Much of my research has centered on the detection and treatment of severe traumatic brain injuries. While pursuing my interests in clinical research I have obtained experience in data collection, curation, and analyzation. I have progressed in my ability to write manuscripts and present the data and results from the topics. As I have progressed, I have received experience with the creation of my own research questions and experiments within my areas of interest. Conducting the study proposed herein would further propagate my goal of continuing to improve upon the care patients receive.
- Professional Position
    - Third year medical student at Texas Tech University Health Sciences Center
    - Professional Memberships:
        - Congress of Neurological Surgeons
        - American Association of Neurological Surgeons
        - Association For Academic Surgery
        - North Texas American College of Surgeons
        - American Medical Association
        - Texas Medical Association

- Selected Peer Reviewed Articles (see CV for full list)

Facilities

- University Medical Center
- Covenant Women and Children's Hospital
- University of Oklahoma Healtch Sciences Center

Environment

- This study will be all clinical with all research taking place in either the hospital or clinical setting.
- The resources required will already be present at the hospital and we will require no extra recources. We should not require any extra recources not already attributed to treating these patients.

Budget

- Budget: $5,000

- Justification: This $5,000 will be utilized to aid in the publication costs of the final manuscript and conference submissions. Due to the observational nature of this study no extra monetary rescources are required. The algorithm should be easily applicable so no data collected is anything that is not already routinely collected as standard of care.