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Predicting non-unions in fifth metatarsal fractures

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PREDICTING NON-UNIONS IN FIFTH METATARSAL FRACTURES

by

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DEDICATION

I would like to dedicate this work to my mom, Jennifer, my dad, Michael, my older brother, Michael, my twin sister, Courtney, and my pets, Scout, Edgar, Logan, and Kinjie. Last but not least, I'd like to dedicate this work to my fiancé, Amelia, who has supported me throughout my academic pursuits and continues to inspire my future career in medicine.

ACKNOWLEDGMENTS

I would like to acknowledge my colleagues in the Foot & Ankle Research Lab (FARIL) for helping me along the way during this project. I would also like to give special recognition to the Chief Scientific Officer of FARIL, Dr. Soheil Ashkani Esfahani, for granting me the opportunity to become a contributing member of this lab. It is amazing to be a part of a group that is so ambitious, dedicated, and innovative.

PREDICTING NON-UNIONS IN FIFTH METATARSAL FRACTURES

BRADLEY A. WEAVER

ABSTRACT

Fractures of the metatarsal bones are among the most common injuries of the foot. Specifically, fifth metatarsal fractures account for 40-75% of all foot fractures. It is common for fifth metatarsal fractures to develop healing complications, including bone non-unions. There is currently no consensus on the optimal choice of treatment and management of these fractures that yield complete bone union. Therefore, non-union healing complications remain a significant problem in orthopedics. A prediction model for the development of non-unions would be a powerful clinical tool to limit modifiable causes for non-union when making decisions about treatment and management for this injury. This study aims to address the gap in a clinical prediction model for non-union by targeting high risk patient features that contribute to non-union. Using correlation analysis, we found 13 high-risk patient features that were significantly correlated with non-union development. These features were found across different categories: patient demographics (2), chronic diseases (6), and medication use (5). This study can provide clinicians with important insight when they are trying to determine the most effective treatment approach and management of fifth metatarsal fractures in patients with specific demographic characteristics, co-morbidities, and medication use.

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LIST OF ABBREVIATIONS

BMI .... Body Mass Index

CDC .... Center for Disease Control

COPD .... Chronic Obstructive Pulmonary Disease

CKD .... Chronic Kidney Disease

CVD .... Cardiovascular Disease

DM .... Diabetes Miletus

GERD .... Gastroesophageal Reflux Disease

IBS .... Irritable Bowel Syndrome

KNN .... K-Nearest Neighbor

MGH .... Massachusetts General Hospital

MICE .... Multivariate Imputation by Chained Equations

NSAID .... Non-steroidal Anti-Inflammatory Drugs

OCP .... Oral Contraceptive Pills

OSA .... Obstructive Sleep Apnea

PVD .... Peripheral Vascular Disease

RPDR .... Research Patient Data Registry

SD .... Standard Deviation

SSRI .... Selective Serotonin Re-Uptake Inhibitors

T1DM .... Type I Diabetes Mellitus

T2DM .... Type 2 Diabetes Mellitus

Vit-D .... Vitamin D

INTRODUCTION

General Bone Anatomy and Epidemiology of Metatarsal Fractures

The metatarsals refer to the five long bones found in each foot, as shown in Figure 1 (Ligaments of the Foot and Ankle, 2019). They are numbered one to five from medial to lateral. Each metatarsal bone includes a proximal base, shaft (or body), neck, and distal head. The metatarsal bones act as an insertion point for many muscles of the lower limb and foot (Lezak & Massel, 2022). Additionally, metatarsals play an important structural role in the arches of the foot, which are important for weight-bearing, walking, and running. The first and fifth metatarsals are unique because they allow for superior-inferior motion to adapt to uneven surfaces, unlike the other metatarsals that are fixed to their proximal base.

Fractures of the metatarsal bones are among the most common injuries of the foot. Out of all metatarsal fractures, the fifth metatarsal bone is the most commonly fractured (Lezak & Massel, 2022). Epidemiological studies found that fifth metatarsal fractures account for 40-75% of all fractures related to the foot (Wang et al., 2020).

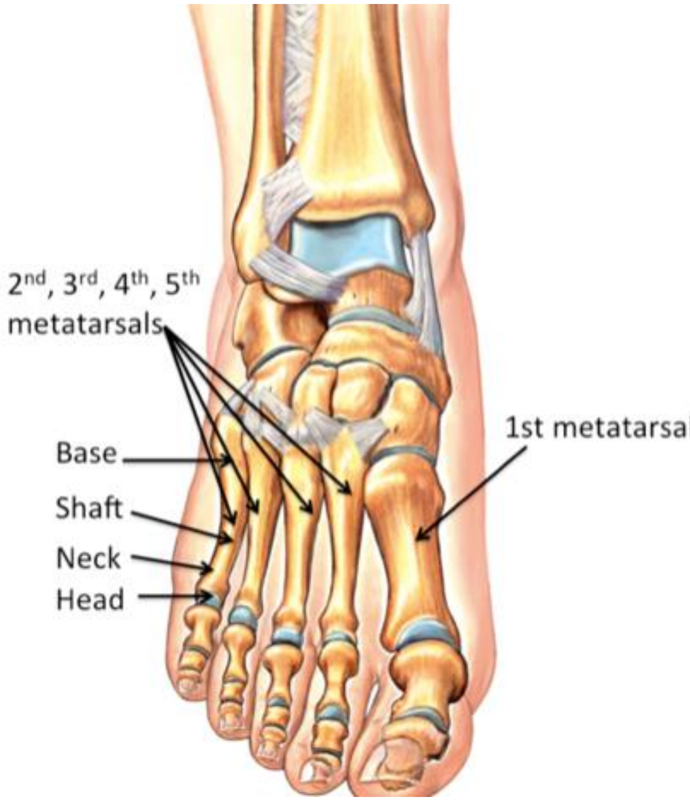

Figure 1: Anatomy of foot metatarsals. Metatarsal bones are numbered 1-5 from medial to lateral. Each metatarsal has a labeled proximal base, shaft, neck, and distal head (Ligaments of the Foot and Ankle, 2019).

There are several risk factors related to patient characteristics that contribute to fifth metatarsal fractures. With respect to age and gender, most fifth metatarsal fractures occur between the ages of 20 and 60 years old (Kane et al., 2015), with males accounting for more fractures in young patients while females account for more fractures in older patients (Aynardi et al., 2013). The increased number of fractures in older, female populations could be a result of post-menopause, which decreases the protective effects of estrogen on bone. In addition, there are certain foot structure characteristics that increase risk of fifth metatarsal fractures. Individuals who have cavovarus (high arch in the foot) and forefoot metatarsus adductus (bone turned inward towards body's midline) have an increased risk of fractures. There are also specific mechanisms of injury that put individuals at a greater risk of fracture. Proximal fifth metatarsal fractures are mainly caused by inversion injuries, falls from height/twisting motions (trauma), overuse, and/or repetitive stress (Cakir et al., 2011).

Healing Outcomes of Fifth Metatarsal Bone Fractures

Different outcomes can occur in the bone healing process after a metatarsal bone fracture. Bone union, or healed bone, is defined as the bridging of two or more cortices via radiographic imaging (Ekegren et al., 2018). However, fractures do not always heal quickly or may not ever heal correctly without surgical intervention, which may result in healing complications. Bone non-union is a fracture outcome which, according to a treating physician, has no possibility of healing without intervention. Additionally, delayed union is defined as a slower progression to healing without further intervention with an increased risk of non-union development (Smidt & Massey, 2022). For diagnosis and analysis purposes, the literature has designated time frames to these healing outcomes. For example, one study defines delayed union as a persistent fracture line on radiographic imaging after 12 weeks, while a non-union is defined as a persistent fracture line after six months (Miller et al., 2019). However, not all studies use these exact time frames, which makes comparing healing outcomes across different studies challenging. In addition, refractures can occur, which means that a previous fracture that has united becomes fractured once again in the same anatomical location.

The Origin of Fifth Metatarsal Fracture Classification Systems

Historically, the phrase “proximal fifth metatarsal bone fracture” was first published in 1902 by a British orthopedic surgeon known as Sir Robert Jones. He simply labeled the fracture as a “Jones fracture.” It became known that some of these fractures resulted in high healing capacity, while other fractures showed prolonged healing and a high rate of healing-related complications. Even a millimeter difference in the proximal fifth metatarsal fracture site could lead to drastically different healing outcomes (Japjec et al., 2015). As a result, many physicians developed classification systems to help diagnose location-specific fractures. Since the first Jones fracture diagnosis, several physicians in subsequent years assigned a more specific location to the Jones fracture. In 1975, Dr. Dameron designated the Jones fracture to the tuberosity. In 1983, Dr. Stewart designated this fracture to the proximal diaphysis. This ever-changing terminology of Jones fractures in scientific literature complicated the diagnoses of fifth metatarsal fractures. The inconsistencies in fracture classifications and diagnoses led to confusion in recommendations regarding treatment, which negatively influenced patient outcomes. Thus, it became necessary to design a standardized classification system for fifth metatarsal fractures. This standardization intended to help avoid inconsistencies in scientific literature. More importantly, the standardization provided physicians guidance on diagnosing these fractures and allowed them to effectively recommend treatment options based on published literature using the same classification system (Polzer et al., 2012).

Classification Systems that are Used in Clinical Practice

The first classification system designed by Lawrence and Botte in 1993 was based on anatomic fracture location and associated prognoses/ treatment options of proximal fifth metatarsal fractures. In Figure 2, an animated diagram and radiographs illustrate the fracture locations of this classification system (Ligaments of the Foot and Ankle, 2019; Pugliese et al., 2020). Lawrence and Botte designated three anatomic zones for fifth metatarsal fractures. Zone 1 includes tuberosity avulsion fractures. Zone 2 includes fractures at the metaphyseal/diaphyseal junction, which is the location formerly known as the Jones fracture from many earlier physicians. Zone 3 includes proximal diaphyseal stress fractures (Zwitser & Breederveld, 2010). For each fracture zone, Lawrence and Botte also advised specific treatments based on data from retrospective case series. While other classification systems exist, the Lawrence and Botte classification is the most used in clinical practice.

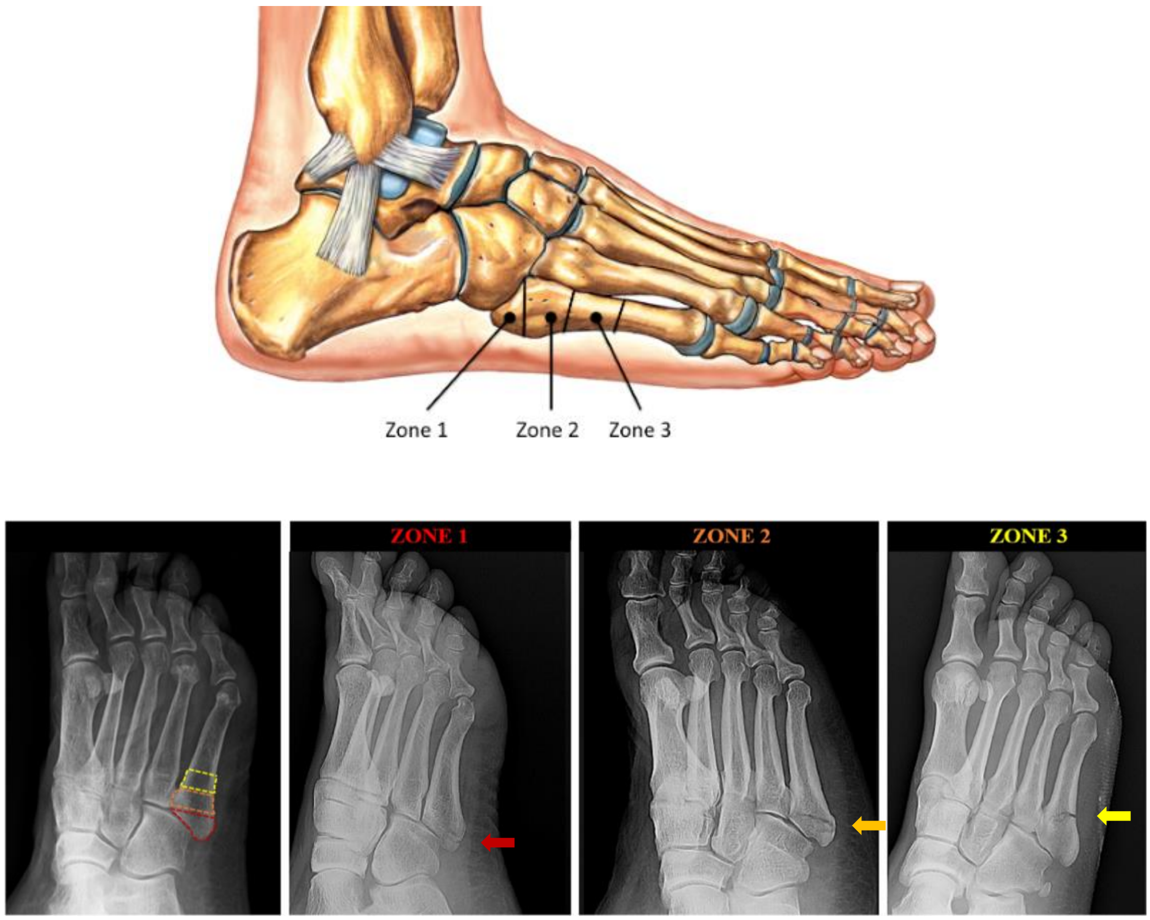

Figure 2: Lawrence and Botte classification of proximal fifth metatarsal fractures. Top: This classification subdivides fractures into three distinct anatomical zones, as labeled on the fifth metatarsal bone. Zone 1= tuberosity avulsion fractures, Zone 2= metaphyseal/diaphyseal junction fractures, and Zone 3= proximal diaphyseal fractures (Ligaments of the Foot and Ankle, 2019). Bottom: Radiographic images for each anatomical fracture zone are labeled. Note that the image on the far left is a non-fractured bone and serves as a reference image for the different zone boundaries (Pugliese et al., 2020).

Other systems, such as the Torg classification, focus on the healing potential of fifth metatarsal fractures. Because Zone 2 and Zone 3 of the Lawrence and Botte classification have a higher susceptibility to healing complications, Torg developed this system to further classify these fracture locations based on healing outcomes. This system classifies bone based on intramedullary sclerosis, which is when radiological evidence shows abnormal bone formation in the medullary cavity of long bones (Cheung & Lui, 2016). In the Torg classification, Type I are acute fractures (Jones fractures) with a narrow fracture line and no intramedullary sclerosis. Type II are fractures with a wide fracture line and intramedullary sclerosis, which result in delayed unions. Type III are fractures that have total obliteration of the medullary canal by the sclerotic bone, which result in non-unions. The Torg classification is also widely used and its associated treatment plan for each classification type have become the standard treatment for Jones and proximal diaphysis fractures (Zwitser & Breederveld, 2010).

Treatment Recommendations within Classification Systems

As previously mentioned, the classification systems have specific treatment regimens based on anatomic location. In the Lawrence and Botte classification, Zone 1 fractures are treated conservatively (non-surgically) because of their high healing union rate. Many studies have shown that functional treatments, including early weight-bearing with orthopedic shoe and Jones bandage, result in better outcomes and earlier return to work compared to non-weight-bearing treatment, including short leg casts (Vorlat et al., 2007). In Zones 2 and 3, union times can result in delayed union with a longer time to return to function, or even progress to non-union, which requires surgical repair. As a result, the Torg classification for Zone 2 and 3 fractures include more nuanced and specific treatment plans (Torg et al., 1984). Type I fractures are treated conservatively, including non-weight-bearing in a short leg cast. Type II fractures can be treated both surgically and non-surgically, depending on the activity levels of the patients. In active patient groups, a surgical approach is recommended since early surgical treatment has shown to reduce the time for bone union and expedite the time needed for return to full activity. In non-active patient groups, a conservative approach is recommended since the need to return to full activity is not as time sensitive. Lastly, it is recommended that Type III fractures should be managed operatively (Cheung & Lui, 2016).

There are several different surgical approaches to treat fifth metatarsal fractures that also include possible post-operative complications. Surgical approaches include intramedullary screws, tension band wiring, differential pitch screw and percutaneous bi-cortical screws (Cheung & Lui, 2016). The most referenced surgical approach is fixation with intramedullary compression screws. While the optimal surgical treatment has not yet been pinpointed definitively, the surgical approach should be an internal fixation device that can allow the bone to undergo torsion, tension, and bending (Zwitser & Breederveld, 2010). While surgical fixation shows promising outcomes in Zones 2 and 3 fractures, there are postoperative risks. There is a chance of wound infection, rupture of peroneus brevis tendon, peroneal nerve irritation, sural nerve injury, impingement by a prominent screw head, the screw missing the medullary canal, iatrogenic fracture of the metatarsal bone, and metatarsalgia (Cheung & Lui, 2016).

Prevalence of Healing Complications by Anatomic Location and Treatment Approach

Since healing complications exist in fifth metatarsal fractures, in part, from the unique intraosseous blood supply of this bone, it is important to consider the prevalence of each fracture zone and the associated healing complications for each fracture location when advising specific treatment plans. In the Lawrence and Botte classification, Zone 1, 2 and 3 fractures account for 93%, 4%, and 3% percent of proximal fifth metatarsal fractures, respectively (Bowes & Buckley, 2016). With respect to healing complications, Zone 1 fractures account for a low non-union rate of 0.5% -1% when treated conservatively. In comparison, conservative treatment of Zones 2 and 3 fractures result in a non-union rate as high as 25-28% (Cheung & Lui, 2016). Patients who ultimately have failed conservative treatment in these zones and progress to non-union will require a surgical procedure to treat this healing complication. It is well known in the literature that fracture Zones 2 and 3 create challenges for proper healing, given the unique intraosseous blood supply of the fifth metatarsal bone (Figure 3). There are numerous metaphyseal vessels that radiate randomly and supply the tuberosity, while the nutrient artery supplies the proximal diaphysis (Smith et al., 1992). Fractures in these zones disrupt the normal blood supply and create an avascular, watershed-region, which can significantly lower the rate of union and result in non-unions, especially using non-operative interventions. Studies have shown that operative interventions can reduce the rate of non-unions, duration of union, duration of return to normal activity, and duration of return to sport. These surgical interventions can preserve retrograde blood supply to the vascular insufficient areas of the fifth metatarsal, which enhance healing outcomes (Wang et al., 2020).

Risk Factors Associated with Healing Complications

There are several risk factors related to patient health characteristics, recovery time, and bone structure characteristics that contribute to healing complications (delayed union, non-union, and refracture) after treatment. In terms of patient health characteristics, increasing age showed the strongest positive correlation with surgical failure, followed by diabetes mellitus and increasing body mass index (Ruta et al., 2020). The recovery time of patients must also be considered to maximize healing capacity after fifth metatarsal fractures. Patients who returned to vigorous activity before complete radiographic union had an increased risk of delayed union and subsequent non-union (Miller et al., 2019). This stresses the importance of post-operative patient compliance and medical clearance from a physician when complete radiographic bone union is evident (Larson et al., 2002). Bone structure characteristics that predispose healing to non-union include cavovarus foot alignment, increasing inter-metatarsal angle between the 4^{th}/5^{th} metatarsals and/or a protruding 5^{th} metatarsal head (Welck et al., 2017). Lastly, plantar gap has been used as another prognostic factor to determine likelihood for post-surgical failure. Plantar gap is the distance between the fracture margins on the plantar lateral side of the fifth metatarsal bone. A linear relationship was found between time for bone union and the degree of plantar gap. Patients who have a plantar gap of greater than 1 mm are at a higher risk of non-union and refracture, as well (Lee et al., 2011).

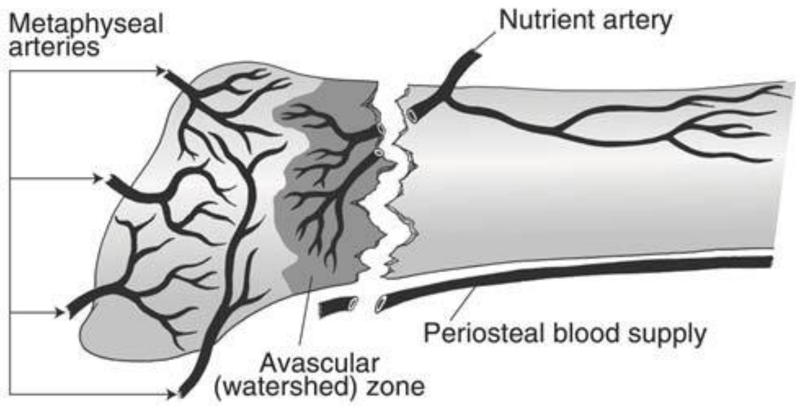

Figure 3: The intraosseous vascular supply of the proximal fifth metatarsal. Metaphyseal arteries supply the tuberosity, and the nutrient artery supplies the proximal diaphysis. A vascular (watershed) zone can be seen in the metaphyseal-diaphyseal region in the event of a fracture (Den Hartog, 2009).

The Need for an Effective Decision-Making Model

Despite the progress made in recent decades relating to the development of both non-surgical and surgical interventions, as well as defining several risk factors relating to healing complications, there still lacks a consensus on the optimal choice of intervention in fifth metatarsal fractures. As a result, this lack of consensus has made it difficult for clinicians to apply an effective decision-making model for choosing interventions and designing treatment plans that yield complete bone union during the fracture healing process (Wang et al., 2020).

Since the risk of non-unions is significant in fifth metatarsal fractures, it would be useful for clinicians to be able to predict which patients are at a high risk of non-union and potentially modify the treatment approach and management of their fracture to avoid this complication. One predictive model for non-union in the literature considered treatment type, co-morbidities, and medication use in a large patient dataset. Regarding treatment type and co-morbidity, it was found that a surgical approach and patients with osteoarthritis have significant associations of developing non-unions. For medication use, anticonvulsants, insulin, osteoporosis treatment, opioids, and opioids with non-steroidal anti-inflammatory drugs (NSAIDs) also had significant associations of resulting in non-unions (Zura et al., 2017). However, the aforementioned study simply grouped all metatarsal fracture outcomes together, which does not specifically focus on the unique blood supply of the fifth metatarsal.

Given the high prevalence of fifth metatarsal fractures and the unique blood supply of this bone, it is important to develop a predictive model for non-unions that is specific to fifth metatarsals. Therefore, this present study aims to address the gap in a prediction model for non-unions in fifth metatarsal fractures to help clinicians make effective decisions during the treatment and management of these fractures. This model will provide insight into the risk factors for the development of non-unions across many different clinical categories, including treatment type (surgical vs. non-surgical), patient demographics, co-morbidities, medication use, and anatomical fracture location.

METHODS

Study Design and Patient Population

This study retrospectively analyzed patients diagnosed with fifth metatarsal fractures from the years 2005 to 2014 at a tertiary medical center in Boston, Massachusetts known as Massachusetts General Hospital (MGH). Both surgically and non-surgically treated patients were included in this dataset. After the Institutional Review Board approved of the research study protocol, a total of 65 patient characteristics, or features, were analyzed based on the outcome variables of healing outcome and healing time. The patient population of this study originally included 1,222 adult patients with fifth metatarsal fractures during this time frame at MGH before applying all inclusion/ exclusion criteria.

Patient Database and Features of Interest for Analysis

The patient data analyzed in this study were extracted from the Research Patient Data Registry (RPDR). The 65 features of interest include patient demographics, such as age, height, weight, body mass index (BMI), gender, race, smoking status, and activity level. Additionally, treatment method (surgical vs. conservative), healing duration, and fracture zone classification were considered in the analysis. Fracture zones were classified according to Lawrence and Botte: Zone 1 = tuberosity avulsion fractures, Zone 2 = also known as Jones fracture, includes the metaphyseal/diaphyseal junction, Zone 3 = proximal diaphyseal stress fracture (Zwitser & Breederveld, 2010). Also, chronic disease and medication use were included in the analysis. The 24 most prevalent chronic diseases and 24 most prevalent medications used in the patient cohort were analyzed.

Inclusion and Exclusion Criteria of Patients

The inclusion criteria for patients analyzed in this study were (1) patients diagnosed with fifth metatarsal fractures at MGH, (2) patients treated and attended follow-up visits at MGH, (3) patients received X-rays of the foot at the time of fracture and during follow-up visits, (4) adults 18 years of age or older. Fracture diagnoses were confirmed with X-ray radiographic imaging by an attending orthopedic surgeon. The exclusion criteria for patients were (1) patients with missing documentation of final healing outcome and/or total healing time, (2) patients with missing X-ray imaging during initial presentation and/or during follow-up visits, and (3) patients with foot deformities. The patient dataset included medical histories, lab data, and medications that patients were taking at the time of fracture diagnosis.

Operationalization of Outcome Measures

The first outcome variable, healing outcome, can be categorized as bone union, delayed union, or non-union. Bone union, or healed bone, is defined as the bridging of two or more cortices via radiographic imaging. For this study analysis, we operationalized healing outcome as either union or non-union. Patients were labeled as "union" if they had complete bone union within 180 days (six months). Patients were labeled as "non-union" if bone union time exceeded 180 days (Miller et al., 2019).

The second outcome variable, healing time, was determined from the dataset based on the date of fracture, date of treatment, and date of follow-up visit, which confirmed if the fracture was completely or incompletely healed via radiographic imaging.

Data Pre-Processing Steps

In the total patient cohort of 1,222 potential subjects, 393 subjects (32% of the dataset) had complete feature sets with no missing data. With respect to patients who had incomplete feature sets, various imputation techniques were used to replace missing data with substituted values. Five methods of imputation were used to compute missing data in the patient cohort. The methods used were mean, median, mode, K-Nearest Neighbor Imputation (KNN) and multivariate imputation by chained equations (MICE). These different techniques were compared to the complete case analysis (with adjusted R^2).

KNN was chosen because this technique can incorporate all patient features and finds the patient in the dataset that has the highest similarity to the patient with missing value to replace the missing value. MICE was chosen because this technique creates multiple imputations, as opposed to single imputations, and accounts for statistical uncertainty in the imputations (Azur et al., 2011).

Data elements that were considered to be extreme outliers were recorded as missing; for example, subjects with a recorded BMI of over 60 were relabeled as missing their BMI, and the data point was imputed. BMI was categorized based on CDC guidelines: underweight <18.5, healthy 18.5-24.9, overweight 25-29.9, obese >30 (CDC, 2021). Finally, patients with missing data related to the outcome variables – healing outcome or healing time – were removed from the dataset. After this data cleaning and applying all inclusion/exclusion criteria, the total number of eligible patients included in the dataset was 1,000 subjects.

Statistical Analysis

The descriptive statistics (mean and standard deviation (SD)) were calculated in Python 3.7 and scikit-learn library for all continuous variables. To assess the associations between variables, Pearson's R correlation was used (alpha level = 0.05).

RESULTS

Between the years of 2005 and 2014, a total of 1,222 patients had fifth metatarsal fractures at MGH. There were 222 patients that were removed after applying all inclusion and exclusion criteria. Therefore, 1,000 patients qualified for this study and were analyzed.

The demographics of our dataset included patients that were a majority females (75%) with over 85% of patients who identified as white (5.1% African American, 3.2% Asian, and 2.1% Hispanic). Additional demographic information including average age, BMI, and gender within union and non-union cohorts can be found in Table 1. Other patient characteristics, such as physical activity level and smoking status, are also recorded in Table 1. Overall, two demographic patient features significantly correlated with non-union (weight and BMI, $P<0.05$).

The healing outcomes extracted from our dataset includes patients with all treatment types for fifth metatarsal fractures, including surgical and non-surgical approaches. In Figure 4, the healing outcome distribution of all patients in our dataset shows 22.4% (224 patients) non-union and 77.6% (776 patients) complete union of fifth metatarsal fractures. Figure 4 also shows that despite the increase of fifth metatarsal fractures year after year, the rate of non-union is decreasing. A visual representation of patient healing times for all complete union cases (within 180 days) can be seen in Figure 5. There were 224 patients not included in Figure 5 because they exceeded the 180-day threshold for complete union and were assigned to the non-union group.

Table 1: Patient Demographics/ Characteristics and Bone Union/ Non-union. For each patient demographic/characteristic and associated union/non-union outcome, Pearson's R test was used. For numerical data and comparison of means, t-test was used. A One-way ANOVA with post-hoc Tukey was performed for age, height, weight, and BMI (mean ± SD listed for each of these variables). P<0.05 was considered statistically significant.

Demographics/Characteristics	Union	Non-Union	P-value
Age (yrs.)	51.2 ± 18.0	52.1 ± 16.5	0.488
Height (cm)	165.2 ± 9.7	166.4 ± 10.7	0.099
Weight (kg)	74.9 ± 18.5	79.4 ± 21.4	0.002
BMI	27.4 ± 6.0	28.5 ± 6.7	0.012
Gender			
Female (n = 746)	78%	22%	0.374
Male (n = 254)	76%	24%	
Race/Ethnicity			
White (n = 853)	78%	22%	0.498
African American (n = 51)	76%	24%	
Asian (n = 32)	69%	31%	
Hispanic (n = 21)	95%	5%	
Other (n = 43)	84%	16%	
Activity Level			
Regular (n = 984)	78%	22%	0.144
Athlete (n = 16)	62%	38%	
Smoking Status			
None (n = 636)	78%	22%	0.429
Former (n = 301)	77%	23%	
Current (n = 63)	75%	25%	

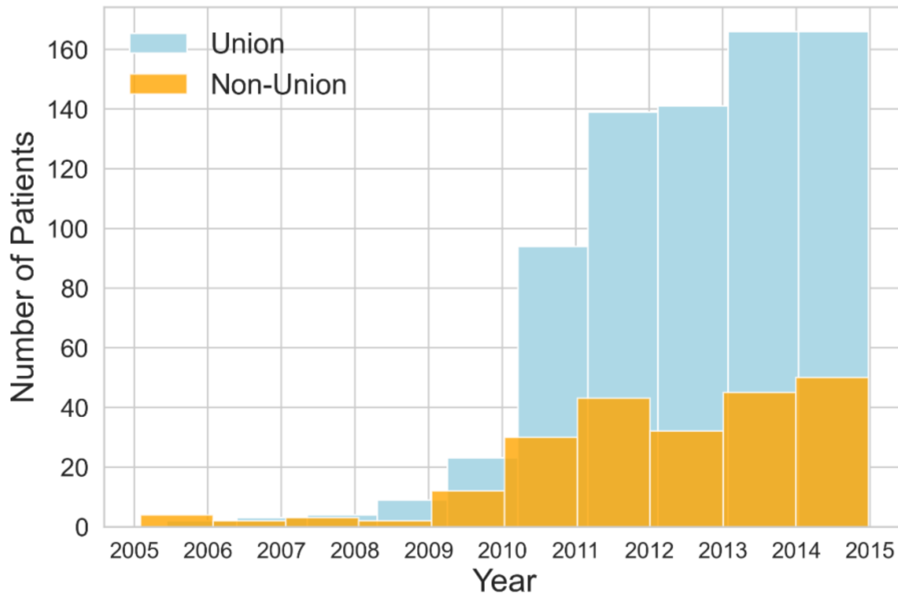

Figure 4: Rate of union and non-union in the patient dataset. The number of fifth metatarsal fractures increased year by year, while the rate of non-union decreased.

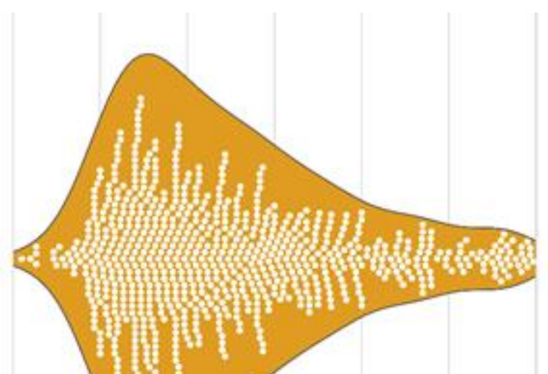

Figure 5: The healing time of all union cases. The outcome variable of healing time was used to define the parameters of 'union' versus 'non-union'. The violin plot above depicts the distribution of the time that each of the union cases was healed within the 0–180-days range. Each data point represents one union case.

The frequency and type of each fifth metatarsal fracture using the Lawrence and Botte classification system were analyzed (Figure 6). Out of the three zones, Zone 2 fractures resulted in the most non-unions (28%), followed by Zone 1 (21.7%) and Zone 3 (16.1%). Using correlation analysis, these fracture zones did not significantly correlate ($P>0.05$) with non-union in our dataset.

The treatment type (conservative vs. operative) of the fractures and the associated healing duration of each approach was also considered in our analysis (Table 2). In correlation analysis, the treatment type did not significantly correlate with non-union ($P>0.05$). However, there was a significant correlation ($P<0.05$) present between the treatment type and the duration of healing. It was found that a longer healing duration is significantly correlated for patients who had an operative treatment.

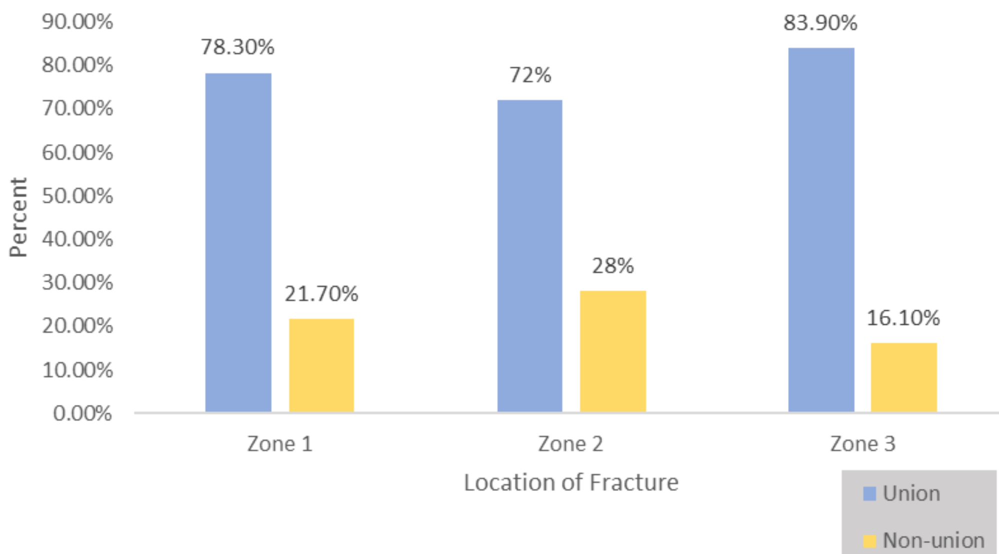

Figure 6: The percentage of union and non-union healing outcomes for each fracture zone (as defined by the Lawrence and Botte classification system). Each zone has unique anatomical characteristics; thus, it is useful to visualize and evaluate non-union rates individually.

Table 2: Treatment Type/ Healing Duration and Bone Union/ Non-Union. Treatment was subdivided into conservative and operative approaches with associated proportions of union and non-union outcomes. Healing duration was also subdivided into conservative and operative approaches with associated length of healing. All healing lengths >180 days were considered non-unions.

	Union	**Non-Union**
Treatment, % (n)		
Conservative (n = 911)	78% (712)	22% (199)
Operative (n = 89)	75% (67)	25% (22)
Healing Duration (days), mean ± SD		
Conservative (n = 911)	95.7 ± 56.0	>180
Operative (n = 89)	121.3 ± 50.0	

Among the chronic diseases that were analyzed, hyperlipidemia (38%), hypertension (37%), gastroesophageal reflux disease (GERD) (22%), and depression (22%) were the most prevalent diseases in our dataset (Figure 7). Out of 24 chronic diseases (and patients with no disease), we found six diseases that were significantly correlated ($P<0.05$) with non-union: thyroid disease, hypertension, GERD, irritable bowel syndrome, obstructive sleep apnea, and glaucoma (Table 3). Patients with diabetes mellitus and obesity showed no significant correlation with non-union. It should be noted that diabetes mellitus includes both type I and type II diabetes, and thus were not considered independently in the analysis.

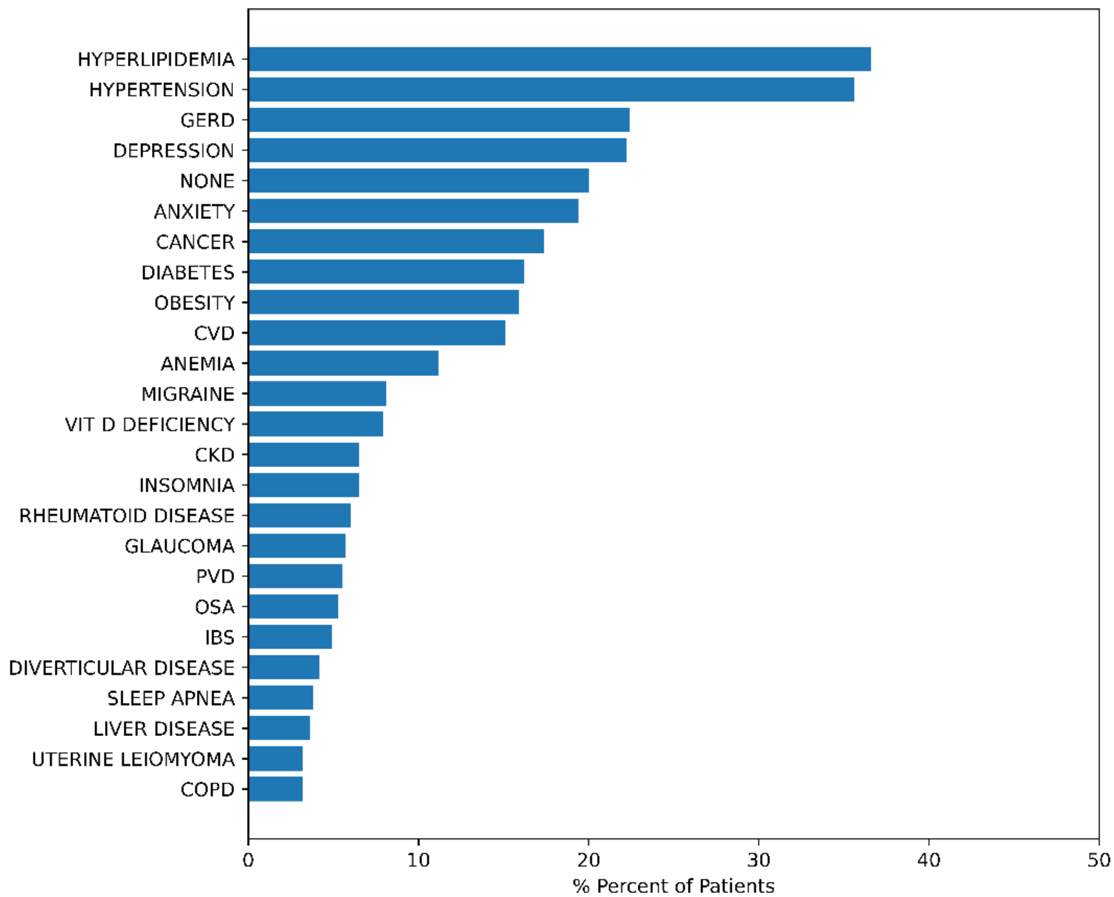

Figure 7: The prevalence of chronic diseases of patients in the dataset. Abbreviations: GERD = gastroesophageal reflux disease, CVD = cardiovascular disease, CKD = chronic kidney disease, PVD = peripheral vascular disease, OSA = obstructive sleep apnea, IBS = irritable bowel syndrome, COPD = chronic obstructive pulmonary disease.

Table 3: Chronic Diseases and Bone Union/Non-Union. For each chronic disease and associated union/non-union proportion, Pearson's R test was used. For numerical data and comparison of means, t-test was used. P<0.05 was considered statistically significant.

	Union	**Non-Union**	**P-value**
Thyroid Disease			
Hyperthyroid (n = 12)	67%	33%	0.019
Hypothyroid (n = 150)	71%	29%	
Euthyroid (n = 838)	79%	21%	
Hypertension			
Yes (n = 405)	73%	27%	0.006
No (n = 595)	81%	19%	
GERD			
Yes (n = 247)	71%	29%	0.008
No (n = 753)	80%	20%	
IBS			
Yes (n = 56)	65%	35%	0.029
No (n = 944)	79%	21%	
OSA			
Yes (n = 54)	66%	34%	0.032
No (n = 946)	79%	21%	
Glaucoma			
Yes (n = 63)	67%	33%	0.035
No (n = 937)	79%	21%	
Diabetes Mellitus			
Yes (n = 162)	72%	28%	0.073
No (n = 838)	79%	21%	
Obesity			
Yes (n = 159)	76%	24%	0.621
No (n = 841)	78%	22%	

Abbreviations: GERD = gastroesophageal reflux disease, IBS = irritable bowel syndrome, OSA = obstructive sleep apnea.

In addition to chronic diseases, current medication use of patients was also considered. The most prevalent medications used in our dataset were Vitamin D (34%), statin (29%), multivitamins (25%), and aspirin (21%) (Figure 8). Out of 24 medications (and patients taking no medications), we found that five medications were significantly correlated with non-union development: levothyroxine, lisinopril, aspirin, steroids, and acetaminophen (Table 4).

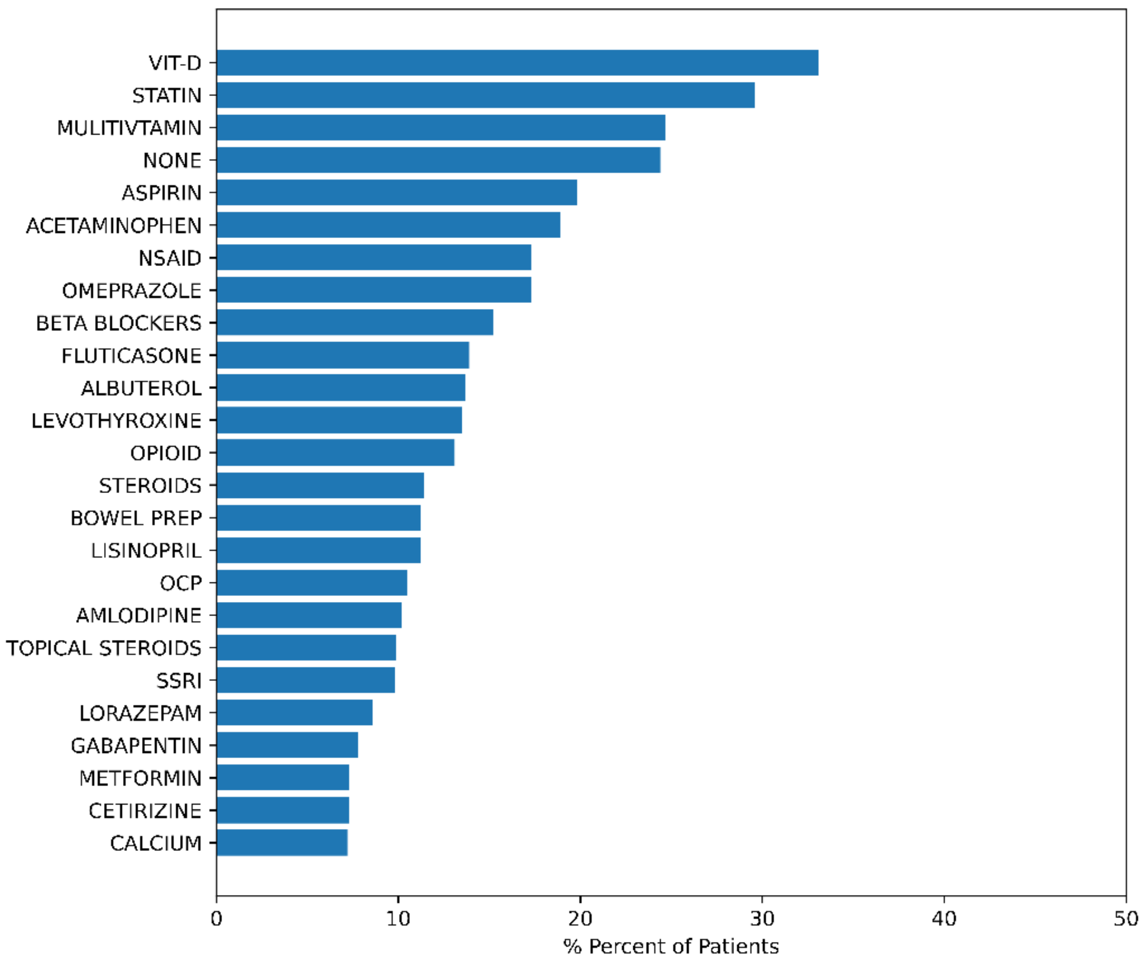

Figure 8: The prevalence of medications used by patients in the dataset. Abbreviations: Vit-D = vitamin D, NSAID = non-steroidal anti-inflammatory drugs, bowel prep = bowel preparation, OCP = oral contraceptive pills, SSRI = selective serotonin re-uptake inhibitors.

Table 4: Medication Prescriptions and Bone Union/Non-Union. For each medication and associated union/non-union proportion, Pearson's R test was used. For numerical data and comparison of means, t-test was used. P<0.05 was considered statistically significant.

	Union	Non-Union	P-Value
Levothyroxine			
Yes (n = 148)	70%	30%	0.013
No (n = 852)	79%	21%	
Lisinopril			
Yes (n = 128)	70%	30%	0.025
No (n = 872)	79%	21%	
Aspirin			
Yes (n = 222)	72%	28%	0.032
No (n = 778)	79%	21%	
Steroids			
Yes (n = 127)	70%	30%	0.035
No (n = 873)	79%	21%	
Acetaminophen			
Yes (n = 208)	72%	28%	0.046
No (n = 792)	79%	21%	

DISCUSSION

In this study, we found 13 high-risk features that were significantly correlated with non-union development in patients with fifth metatarsal fractures. Our model incorporates features from a variety of different patient categories. The statistically significant high-risk features were found in patient demographics (2), chronic diseases (6), and current medications (5). Significant risk factors within patient demographics include weight and BMI. The identified chronic diseases include thyroid disease, hypertension, gastroesophageal reflux disease, irritable bowel syndrome, and glaucoma. Lastly, the identified medications include levothyroxine, lisinopril, aspirin, steroids, and acetaminophen.

The association between BMI, obesity, and non-union have been previously studied in the literature with conflicting results. A 59-patient retrospective study found a significant positive correlation between both high BMI and obesity in the context of non-union after surgical treatment of fifth metatarsal fractures (Ruta et al., 2020). Contrarily, a 48-patient case-control study found no significant association between BMI or morbid obesity and non-union (Thorud et al., 2017). It is evident that these studies have only included a relatively small sample size of patients, which can include error from statistical outliers and may have contributed to the conflicting results. Both studies stated challenges in finding a large enough dataset where a sufficient number of non-union patients were present for analysis. One cohort study that included a large dataset of over 58,000 metatarsal fractures found that there was no significant odds ratio of developing non-union in obese patients (Zura et al., 2017). However, the limitation of this previously mentioned study is that the prevalence of obese individuals in the dataset is underestimated. This is because only clinically diagnosed obesity was analyzed and thus, undiagnosed obese patients who developed non-unions were overlooked in the analysis, which could have altered the results.

Comparatively, our study of 1,000 patients includes a relatively larger patient dataset than most studies analyzing non-unions after fifth metatarsal fractures. Regarding BMI and obesity, we found a significant correlation between higher BMI and non-union. However, no significant correlation was found between obesity and non-union. To eliminate the possibility of inadvertently excluding undiagnosed obese patients from our analysis as shown in the previously mentioned Zura et al. (2017) paper, we categorized normal weight and obese patients based on their BMI. The BMI values and weight classifications (Underweight <18.5, Healthy 18.5-24.9, Overweight 25-29.9, Obese >30) were taken from CDC guidelines (CDC, 2021). While this method ensures that all normal weight and obese patients are included based on their BMI and avoids the need for a clinical diagnosis, there are problems associated with BMI as an index of obesity. More specifically, BMI does not distinguish between body lean mass (fat-free mass) and body fat mass (Nuttall, 2015). Since obesity is a measure of body fat mass, a high BMI does not always mean that a patient is obese. For example, it is common for athletic populations, which are prevalent cohorts in surgically treated fifth metatarsal fracture studies, to show increased values of BMI because of the athlete's high body lean mass and low-fat mass. While their BMI may be above the threshold for obesity according to CDC guidelines, the measure of body fat mass does not qualify as obesity (Weir & Jan, 2022). In addition, there are important BMI differences to consider between males and females. In general, even though females have greater body fat mass than males, females typically have a lower BMI. Therefore, because BMI is not sufficient as the sole measure of weight classifications, our analysis may have inappropriately classified some patients as obese and non-obese, which could have altered the results of this patient feature.

Similar to BMI and obesity, the existing literature on diabetes mellitus (DM) in the context of non-union also shows inconsistent results. A systematic review found that five out of seven studies showed statistical significance that DM is a risk factor for non-union, especially fractures involving the foot and ankle (Zura et al., 2016). Other studies that focused specifically on the fifth metatarsal also showed inconsistent results. Ruta et al. (2020) found a significant positive correlation between DM and the development of non-unions, while Thorud et al. (2017) and Zura et al. (2017) found no significant correlation. While our study also found no significant correlation, we are interested in further breaking down DM into Type 1 DM (T1DM) and Type 2 DM (T2DM), which has not been done in the previously mentioned studies. Mechanistically, T1DM destroys pancreatic beta cells and ceases insulin production. Conversely, T2DM, develops insulin resistance and reduced insulin production (Tan et al., 2019). It is important for future analysis to consider T1DM and T2DM independently because each type of DM has associated risk factors that may influence healing outcomes in different ways. More specifically, T1DM has a higher incidence of cardiovascular disease, while T2DM is often associated with adults and obese individuals. In addition, each type of diabetes has a unique medication treatment regimen. The most common treatment for T1DM is insulin, while the most common treatment for T2DM is metformin. These different medications also have the potential to influence the healing outcome in different ways. For example, it is known that insulin can impede osteogenesis, which contributes to induced bone loss in T2DM patients (Zhang et al., 2020). Similarly, an in vivo experiment analyzing the effect of metformin found adverse effects on the fracture healing process (La Fontaine et al., 2016).

There is an interesting interplay between thyroid disease, osteoporosis, and Vitamin D that are evident in this study and published literature. Thyroid disease includes both hypothyroidism and hyperthyroidism. Hypothyroidism results in low bone turnover with decreased osteoblastic bone formation. However, hyperthyroidism creates high bone turnover and increased bone resorption, which results in brittle bones due to accelerated bone loss and leads to osteoporosis (Williams & Bassett, 2018). Interestingly, our study found a significant correlation ($P<0.05$) between thyroid disease and non-union, but a non-significant correlation between osteoporosis and non-union. Similarly, one published case-control study found that osteoporosis is not a significant risk factor for non-union because they determined that bone mineral density, which tests for osteoporosis, is not predictive of non-union (van Wunnik et al., 2011). Rather, their results indicate that the risk of non-union is most likely involved in bone metabolism and/or bone regeneration capacity. In addition, while Vitamin D is crucial for bone health, our study surprisingly showed that there was no significant correlation ($P>0.05$) between Vitamin D deficient patients and non-union. Contrarily, a review article that focused on thyroid disease and vitamin in-take found that two risk factors for non-union include certain nutritional and hormonal deficiencies, including Vitamin D and thyroid hormone (Hunt & Anderson, 2014).

While our study found no significant correlation between thyroid disease and non-union development, future analysis should consider hyperthyroidism and hypothyroidism as independent features instead of grouping these conditions together as one thyroid disease feature. Because each condition has a different mechanism of action with respect to bone turnover, osteoblastic activity, and bone resorption, the bone presumably behaves in different ways after a fracture. Additionally, each condition has a different treatment regimen. A common medication used for hyperthyroidism treatment is a beta blocker, while a typical medication for hypothyroidism is levothyroxine (Sweeney et al., 2014). Both medications were considered in our analysis for non-union development. However, only levothyroxine was significantly correlated with non-union. Since levothyroxine is specific for hypothyroidism treatment and is acting on a different disease mechanism, this supports our reasoning for future analyses to consider these two types of thyroid disease as independent features.

With respect to anti-inflammatory medications, there is a current lack of consensus in the literature on the effect of NSAIDs on fracture healing. Mechanistically, NSAIDs reduce inflammation by inhibiting cyclooxygenase (COX)-1 and -2. (COX)-2, specifically, is necessary for differentiation of mesenchymal cells to osteoblasts and therefore, these medications can suppress osteoblast formation and impede bone formation (Barnds et al., 2021). A retrospective study found that the use of NSAIDs significantly increased the rate of both delayed union and non-union in patients treated non-operatively for fifth metatarsal fractures. Interestingly, no significance was found between operatively treated patients and non-union. Given that over 25% of the population in the United States is currently taking NSAIDs, our study analyzed aspirin, an NSAID, in relation to healing outcomes. We found a significant correlation ($P<0.05$) between the use of aspirin and non-union development. This drug class, in particular, is challenging to incorporate into study designs other than retrospective studies. More specifically, there are a vast number of medications that fall into this drug class. Additionally, it is difficult for clinicians to control over-the-counter use of NSAIDs. These obstacles complicate the prospect of running future randomized controlled trials to assess the true risk of non-union in patients who are taking NSAIDs. Because of these associated challenges with NSAIDs, our study, and a majority of studies in the literature, are retrospective in design.

Based on the scientific literature, our study found unexpected results when considering the location zone, treatment approach, and healing duration of fifth metatarsal fractures. It is known in the literature that Zone 2 and Zone 3 fractures within the Lawrence and Botte classification system are more susceptible to delayed union and non-union (Cheung & Lui, 2016). Interestingly, our results showed no significant correlation between fracture zone and non-union. In a recently published systematic review that analyzed treatment approach and union rate of proximal fifth metatarsal fractures, it was found that compared to conservative treatment, a surgical approach resulted in a shorter duration to bone union and a higher union rate. Additionally, a surgical approach resulted in a lower rate of delayed union and non-union (Hollander et al., 2021). Contrary to this previously mentioned systematic review, we found no significant correlation ($P<0.05$) between the treatment type (surgical or conservative) and non-union development. Also contrary to the previously mentioned study, we found an unexpected significant correlation between surgical treatment and healing duration. More specifically, patients who received surgical treatment resulted in a longer time to heal than non-surgically treated patients. One possibility that may explain these conflicting results relates to patient compliance with post-operative instructions, which was not captured in our dataset and subsequent analysis. One previous retrospective study found that an early return to vigorous physical activity after surgical treatment of Jones fractures is a predictor of post-surgical failure, including non-union (Larson et al., 2002). More specifically, it was found that the group of patients who had non-union and other treatment failures returned to full physical activity earlier, against the advisement of the clinician, compared to the compliant patient group who had uncomplicated healing outcomes. Furthermore, only 17% of the non-compliant patient group had complete bone union upon their return to full activity compared to 86% in the compliant patient group when they resumed full activity. These results highlight the importance of patient compliance to a clinician's post-surgical guidelines and the need for radiographic evidence of complete bone union before participating in physical activities.

In addition to our study not capturing post-surgical compliance data, another possibility that could explain the prolonged healing duration in surgically treated patients relates to the effects of early weight-bearing after operative treatment. It is imperative to begin weight-bearing after fracture repair since it helps maintain bone and muscle mass, which ultimately helps restore daily activities of living (Quan et al., 2021). Weight-bearing also promotes a process called mechanical transduction that promotes bone healing. A retrospective study compared early weight-bearing, or full weight mobilization in a cast three days after initial treatment, to late weight-bearing, or no full weight mobilization for 6 weeks, in the context of bone regeneration and complete bone union duration (Park et al., 2017). It was found that early weight-bearing in both conservatively and operatively treated patients with fifth metatarsal fractures prevented bone resorption and shortened the duration to bone union. A more recent retrospective comparative study found that regardless of the fracture repair treatment method, early weight-bearing patient cohorts compared to delayed weight-bearing patient cohorts showed fewer cases of bone resorption (Looney et al., 2020). Additionally, it was found that the time to complete bone union was shorter in surgically treated patients with early weight-bearing mobilization. Therefore, because our dataset did not consider the weight-bearing timeframe after conservative or surgical treatment, it is possible that patients in our cohort did not participate in early weight-bearing after their treatment, which could have influenced the healing duration of treated fifth metatarsal fractures.

To improve the effectiveness in comparing healing complications in future research studies, there is a need for standardized definitions of healing outcomes and a standardized imaging modality to determine bone union. Similar to the importance of a standardized fracture classification system for fifth metatarsal fractures, as developed by Lawrence and Botte, standardized definitions of delayed union and non-union are equally as important but have not been addressed in the literature. Therefore, varying definitions are currently being used for both delayed unions and non-unions. Some studies did not even explicitly define these terms in their methodologies. This poses challenges for researchers to effectively compare these healing related outcomes across different studies. For example, it was difficult to make non-union rate comparisons between conservative and surgically treated patient cohort studies with different non-union definitions that were being used. To improve analysis between different healing outcome studies, uniform definitions of these outcomes are needed (Hollander et al., 2021). In addition, while conventional radiographic imaging is mostly used for clinical evaluation of bone fracture healing, some studies in the literature have used computer tomography (CT) and ultrasound imaging (Schwarzenberg et al., 2020). While all of these imaging modalities are assessing for proper fracture healing and bone union, these modalities may have varying sensitivities in detecting the union of bone, which can affect the interpretation of complete bone union, as well as the time needed for this complete union. These discrepancies in interpretation can cause additional problems for future researchers in trying to determine bone union across different studies using different imaging techniques (Hollander et al., 2021). In the context of our study, we ensured that our methodology to determine complete bone union was consistent. Therefore, we used radiographic imaging for all patients.

Further limitations of this study include the binary classifications of union and non-union, as well as surgical and non-surgical treatment. Because of the previously mentioned lack of uniform definitions of healing complications, our analysis did not separate out the terms of delayed union and non-union. Instead, we set a threshold for healing of six months, or 180 days, and used radiographic evidence to designate bone union and non-union for fractures. Fifth metatarsal fractures that healed before this time point were designated as union and those that were not healed within this timeframe were labeled as non-union. It is possible that some of these fractures would have been labeled as “delayed union” and not “non-union,” according to the varying definitions found across the published literature. In addition, the binary classification of treatment (surgical vs. non-surgical) does not consider the various treatment modalities that fall within each category that could alter the healing outcomes of the fractures that were analyzed. Non-surgical treatment modalities include orthopedic shoes, short-leg casts, and Jones bandages (Vorlat et al., 2007). While the most referenced surgical approach is fixation with intramedullary compression screws, other approaches include tension band wiring, differential pitch screws, and percutaneous bi-cortical screws (Cheung & Lui, 2016). Future studies trying to formulate a more comprehensive risk analysis and predictive model for non-union should consider the specifics of the treatment type, including these different modalities within both non-surgical and surgical realms.

In addition to the binary classification that we used to designate a surgical treatment approach, the hardware used in each operation was not considered in our analysis. For example, our dataset did not include the characteristics of the intramedullary compression screws used in intramedullary fixation. Many published studies have attempted to find the most effective screw diameter and length that results in complete bone healing and minimizes healing complications. These screw characteristics are important to consider because inadequate screw diameter and length create an increased risk of delayed union, non-union, refracture, and hardware failure (Ochenjele et al., 2015). Because there are conflicting results in the literature, the type of screw used has changed over the years and remains a controversial and highly debated topic in orthopedics (Ruta et al., 2020). The challenge associated with choosing a screw type is finding the balance between the correct fit and optimal compression at the fracture site while, at the same time, considering the fitment of a screw into a poorly vascularized fifth metatarsal bone with lateroplantar curvature (Nayak et al., 2021). A screw diameter that is too large can result in iatrogenic fracture, while a screw diameter that is too small reduces the thread contact on bone and contributes to fracture instability, leading to delayed union and non-union. Similarly, a screw length that is too long can result in straightening of the bone, creating a cortical gap at the fracture site, which also leads to delayed union and non-union (Ochenjele et al., 2015). In the literature, one study found that a screw diameter of less than 4.5 mm is significantly associated with the development of delayed union and non-union (Den Hartog, 2009). However, a more recent retrospective study that looked at both screw diameter and length found no significant difference in patients who had uncomplicated healing outcomes versus those who had complications (Ruta et al., 2020). Even though there is no clear evidence-based recommendations of screw characteristics, there are general rules of thumb that are used for proper screw diameter and length selection. It was determined that a majority of patients require screw diameters that are larger than 4.5 mm for adequate fixation (Nayak et al., 2021). In addition, the possibility of excessive screw length can be avoided by selecting a screw that is less than 68% of the fifth metatarsal length. Typically, this results in a screw that is 40 mm, which ends proximally before the curvature of the metatarsal and helps avoid complications related to screw length selection (Ochenjele et al., 2015).

Since our study only looked at the Lawrence and Botte classification system for fifth metatarsal fractures, we are interested in running a future analysis with the Torg and plantar gap classification systems to determine if there are significant correlations present between these designations and non-union development. The Torg classification incorporates healing outcomes into their system and specifically focuses on the fracture types within Lawrence and Botte's designations for Zones 2 and 3, which have higher susceptibility to healing complications (Cheung & Lui, 2016). On the other hand, the plantar gap classification focuses on the plantar gap, which is the distance between fracture margins on the plantar lateral side of the fifth metatarsal bone. It was found in a cohort study that patients with a greater than 1mm plantar gap are at a higher risk for non-union (Lee et al., 2011). This same study also compared the efficacy of prognosis in Torg and plantar gap classification systems. Interestingly, different prognoses were determined in patients that had the exact Torg designation. For example, some patients resulted in complete bone union within 6 weeks while other patients with the same Torg designation resulted in non-union. This study showed that Torg classification might be too simplified and insufficient to predict a diverse grouping of prognoses, but more research is needed. Additionally, it was concluded that plantar gap adds value into the clinical decision-making process for surgery indication and non-union prognosis.

Similar to the results of this study, a published systematic review that focuses on the biological risk factors for non-union after bone fracture found a surprisingly high level of ambiguity for many of the factors that were analyzed (Zura et al., 2016). For example, the negative effects of smoking on overall health and fracture repair are frequently cited in the literature. However, only 64% of the studies analyzed in this systematic review found a significant association between current smokers and non-union in long bones. Our current study also found no significant association. This may show that certain individual risk factors are not definitive prognostic tools for predicting non-union. Rather, these individual risk factors combine with other risk factors in multi-faceted ways. More specifically, smoking status most likely cannot predict non-union without other vital information, such as anatomical location of fracture, treatment method (conservative vs. surgical), and other important clinical data that is unique to each patient. Future analysis should use statistical tools, such as advanced regression models, that can not only test for correlational significance from one risk factor but should consider a combination of different risk factors simultaneously. Additionally, there are certain risk factors, such as age, that can act as an aggregate of many different patient features. For example, increasing age means that there is a higher prevalence of comorbidities that may increase the probability of non-union, which include osteoporosis, heart disease, diabetes, obesity, and the use of NSAIDs. Therefore, it is important for future studies to control for potential confounders associated with age to determine if age alone is a risk factor for healing complications.

Similarly, future studies that are attempting to determine risk factors for non-union need to carefully consider the comparisons being made across studies with varying average ages within the patient populations being analyzed. This is because age related factors, such as osteoporosis, heart disease, and obesity have a greater probability of being present in higher average age patient cohorts and may not be applicable in lower average age cohorts (Quan et al., 2021). This may explain why some studies show statistical significance for these age-related risk factors, while other studies with younger patient cohorts do not show this relationship. This point is especially relevant in many published studies relating to surgically treated cases because these patient cohorts are often from high-level athletic populations with a lower average age (Hollander et al., 2021).

Fifth metatarsal fractures not only have significant implications on a patient's health, but there are also potential economic burdens that a patient and society may deal with from significant healthcare-related costs. These costs are especially significant with surgically treated patients. A retrospective cohort study found that surgically treated patients for fifth metatarsal fractures had increased hospitalization costs and double the number of outpatient contacts, which resulted in total healthcare costs that were four times greater than non-surgically treated patients (Monteban et al., 2018). In addition, surgically treated patients not only have to pay for the expensive operation-related costs but also must traverse through the expenses associated with increased opioid prescriptions to control pain levels after surgery (Ekegren et al., 2018). Therefore, our prediction model of non-union development will not only be important for clinicians to consider for effective bone healing, but also help avoid significant healthcare related costs for a patient and society.

As shown in this study, the treatment and management of fifth metatarsal fractures is a multifactorial process that requires further clinical investigations, particularly randomized clinical trials, to limit modifiable causes for non-union development (Barnds et al., 2021). Non-unions and other healing complications remain a particular clinical problem in fifth metatarsal fractures. While our study cannot prove any causal relationships between the analyzed patient features and non-union development, the high-risk patient features that we have identified in our analysis can provide important insights to clinicians. This insight will be especially important when fracture treatment options are being considered, as well as the management of this fracture with other comorbidities and/or current medications that are being used by patients.

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