RESEARCH ARTICLE

Factors Associated with Non-Unions of Fifth Metatarsal Fractures

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Abstract

Objectives: Metatarsal fractures account for 5-6% of all fractures presenting to emergency care centers with 68% being fifth metatarsal (5MT) fractures. While most heal uneventfully, non-union is one of the most common complications regardless of treatment modality. Predicting the risk for non-union would potentially change treatment decisions thus lowering burden on patients and the healthcare system. The aim of this study was to identify factors associated with non-union in 5MT fractures.

Methods: In this retrospective case-control study, 731 patients met inclusion criteria. Radiographs and clinical documentation were utilized to determine fracture characteristics and final healing status. 547 were assigned to the union group and 184 to the non-union group. Patients' data were gathered and analyzed using machine learning methods, as well as Mann-Whitney U, Pearson R chi-square test, and multivariable logistic regression analysis. P<0.05 was considered statistically significant.

Results: The overall radiographic non-union rate was 25.2%. The highest incidence of non-union was observed for Zone 3 fractures (31.2%). Fracture displacement (P=0.03) was found to have an independent correlation with healing. Several chronic conditions such as osteoporosis (P=0.03), irritable bowel syndrome (P=0.01), cardiovascular disease (P=0.01) and sleep apnea (P=0.03), were found to have an independent correlation with healing. Beta-blockers (P=0.047) and topical steroids (P=0.04) were also found to be associated with 5MT non-union.

Conclusion: In this study, we identified several non-traditional factors associated with 5MT fracture non-union that warrant further consideration and may assist clinicians during the decision-making process. The relationship between non-fracture related factors with non-union needs to be further examined via larger clinical studies before causality can be determined and designation of those variables as risk factors.

Level of evidence: III

Keywords: Fifth metatarsus, Jones fracture, Metatarsal fractures, Nonunion

Introduction

Approximately 6% of all fracture cases presenting to emergency care settings are metatarsal fractures. Fifth metatarsal (5MT) fractures account for about two-thirds.[1] One-third of these fractures affect the base of the 5MT.[2–4] Poor osseous healing, including delayed or non-union, is one of the most common complications and can lead to poor functional outcomes.[5]

It has been well established that the risk of poor healing tends to be higher at the watershed area of the metaphysis-diaphysis junction.[6] However, other factors such as age, obesity, diabetes, cardiovascular diseases, and certain medications such as anticonvulsants, osteoporosis medications, opioids, and non-steroidal anti-inflammatory drugs (NSAIDs) have been reported to be associated with non-union and should be considered when evaluating patients.[7,8-10] The understanding of whether associated

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factors are causal for non-union may help clinicians to better optimize treatment plans. Despite advancements in treatment modalities, there still lacks a population- or patient-specific prediction method that can objectively and quantitatively take into account numerous variables to assist clinicians in choosing the optimal intervention.[2] In order to develop such a prediction model, factors associated with 5MT non-union need to be further elucidated.

In this study, we aimed to establish possible correlations between cited risk factors and the incidence of healing complications in a large cohort of patients sustaining 5MT fractures.

Materials and Methods

The study protocol (2015P000464) was approved by the Institutional Review Board. Patient data were de-identified in accordance with Health Insurance Portability and Accountability Act of 1996 (HIPAA) compliance.

A total of 1,222 patients with 5MT fractures were identified using International Classification of Diseases codes and the Research Patient Data Registry system. The cohort was screened by two orthopedic researchers. Primary inclusion criteria for the study cohort were 1) age ≥ 18 years old and 2) 5MT fracture with available imaging. The exclusion criteria were 1) missing data on final healing status or treatment method, 2) presence of another traumatic injury to the foot, 3) lack of radiologic imaging demonstrating healing or non-healing. After application of inclusion and exclusion criteria, 731 remaining patients were divided into two groups according to their healing status: union group (n=547) and non-union group (n=184), the later of which included both delayed (incomplete healing at 6 months) and non-union (no healing at 6 months).

Medical records were analyzed for patient and fracture-specific variables. Additionally, demographic data including age, height, weight, body mass index (BMI), gender, race, smoking habits, and activity level were analyzed. Clinical data included healing time, fracture zone, displacement, treatment method, medications taken for more than 6 months, and chronic medical conditions and comorbidities was obtained. The top 25 most frequently prescribed medications and the top 25 most common chronic medical conditions and comorbidities in the cohort were analyzed [Appendix 1, Appendix 2]. Type 1 and Type 2 diabetes were categorized together under the general heading of diabetes mellitus for data analysis. Healing time was determined based on the date of diagnosis and the date that the fracture was deemed healed. Union was defined as a clinical determination by the treating clinician and/or based on radiographic confirmation as these were two consistent and reliable determinants for all patients. Non-union was defined as no healing or incomplete healing after six months post injury.[7] Additionally, patients were sub-classified based on fracture location according to the Lawrence-Botte classification. Zone 1 includes tuberosity avulsion fractures; Zone 2 (Jones Fracture) includes metaphyseal/diaphyseal junction fractures; and Zone 3 includes proximal diaphyseal stress fractures.[8,9]

A python-based algorithm was used to extract, clean, and classify the data automatically; however, after extraction, all data were additionally analyzed by researchers to ensure accuracy and quality. Five methods of imputation were used (mean, median, mode, nearest neighbor and multivariate) to compute the missing values in the cohort.[10,11] These different techniques were compared to the complete case analysis (with adjusted R^2), and lastly the K-Nearest Neighbor Imputation (k=2) was selected to predict value substitutes for the missing data and complete the dataset.

Descriptive statistics were calculated for both quantitative (mean and standard deviation [SD]) and categorical (number of samples and percents) data. The Shapiro-Wilks normality test was used to assess distribution of continuous quantitative data [Appendix 3]. The Mann-Whitney U test was used to compare continuous variables (age, height, weight, and BMI) between cohorts. Pearson's R chi-square was used to compare distribution of categorical variables between cohorts. To assess correlation between all variables and healing, a multivariable binary logistic regression analysis was used with $P<0.05$ considered statistically significant. Given the retrospective nature and inclusion of all patients with a 5MT fracture in the given timeframe, a post-hoc power analysis was utilized, yielding a overall study power of 0.91. Additionally, a post-hoc power analysis was conducted for each individual variable. Variables with a power less than 0.80 were not considered adequately powered to confidently assess correlation.

Results

Demographic data for both cases and controls was obtained and assessed for differences [Table 1]. The only difference observed between the non-union and union groups was a higher proportion of patients with BMI >30 in the non-union group ($P=0.042$). The mean healing time among the union group was 76.1 ± 39.9 days (Median = 66; IQR = 57).

Table 1. The demographic data of the cohort of patients with fifth metatarsal fractures stratified into union and non-union groups. The mean value or percent distribution of each variable is provided for each cohort (union & non-union). Statistical analysis was conducted to determine any significant differences between the two cohorts

Factor	Population (n = 731)	Union (n = 547)	Non-Union (n = 184)	p-value
Age (yrs.)*	51.3 ± 17.7	51.0 ± 18.0	52.1 ± 16.6	0.414
Height (cm)*	165.9 ± 10.1	165.7 ± 9.9	166.6 ± 10.9	0.214
Weight (kg)*	77.2 ±19.9	76.2 ± 19.0	80.1 ± 22.2	0.053
Body Mass Index (BMI)*	27.9 ± 6.3	27.6 ± 6.0	28.7 ± 7.0	0.091

Table 1. Continued					
Obese (BMI>30) †	*Yes (n = 225)*	29%	27.4%	35.3%	0.042
	No (n = 516)	71%	72.6%	64.7%	
Gender†	*Female (n = 746)*	73%	73.3%	71.7%	0.679
	Male (n = 254)	27%	26.7%	28.3%	
Race †	*White (n = 622)*	85%	84.6%	86.4%	0.434
	African- American (n = 41)	6%	5.5%	6.0%	
	Hispanic (n = 26)	2%	2.7%	0.5%	
	Asian (n = 23)	3%	2.9%	3.8%	
	Others (n = 29)	4%	4.2%	3.3%	
Activity Level†	*Regular (n = 718)*	98%	98.4%	97.8%	0.639
	Athlete (n = 13)	2%	1.6%	2.2%	
Smoking†	*Never (n = 462)*	63%	64.2%	60.3%	0.596
	Former (n = 225)	31%	30.2%	32.6%	
	Current (n = 44)	6%	5.7%	7.1%	

* Mann-Whitney U test was used; p<0.05 considered statistically significant
† Pearson's R Chi-Square test was used; p<0.05 considered statistically significant

Fracture characteristics, treatment method and healing outcome were recorded [Table 2]. Overall, no difference was found in the outcome between non-operative (24.8% non-union rate) and operative (28.6% non-union rate) treatments (multivariable regression: *P=0.628*, Pearson R Chi-square: *P=0.467*); however, the power for this variable was found to be 0.16, given the small sample size of the operative group. Given this no definitive conclusion on difference in outcomes between operative and non-operative treatment can be made. A chi-square test also found no difference in outcome for non-operative versus operative treatments for each of the fracture zones (Zone 1: *P=0.588*; Zone 2: *P=0.111*; Zone 3: *P=0.064*). Union and non-union rates were calculated for each fracture zone [Figure 1]. The relationship between fracture zone and healing status was not significant based on both the outcome of multivariable logistic regression (*P=0.324*) and specific Pearson R Chi-sqiare test (*P=0.163*) [Table 3]. The post-hoc power for fracture zone was limited by the sample size of Zone 2 fractures, which resulted in a power of 0.40. Again, given this power, no definitive conclusion on correlation can be made. The multivariable logistic regression data on healing outcomes for displaced and non-displaced 5MT fractures for both non-operative and operative treatment methods was calculated [Table 3]. Displaced fractures were found to have an increased risk for non-union (standardized coefficient=0.432; *P=0.033*). For both displaced and non-displaced fractures, treatment method did not demonstrate an association with outcomes.

Table 2. Healing status (union or non-union) and healing duration of 5MT fractures broken down by treatment method (non-operative or operative) and presence of displacement on radiographs. Overall, 547 patients went on to a union and 184 developed a non-union. The union rate in the conservative (non-surgical) group was 75%, in comparison to 71% in the operative group. The healing duration for the conservative group was shorter than the operative group but was not found to be statistically significant

	Treatment	Union (n = 547)			Non-Union (n=184)		
Fracture Zone	*Zone 1*	277 (77.4%)			81 (22.7%)		
	Zone 2	201 (73.9%)			71 (26.1%)		
	Zone 3	69 (68.3%)			32 (31.7%)		
Treatment Method by Anatomic Fracture Location	*Non-operative (n=654)*	492 (75.2%)			162 (24.8%)		
		Zone 1	Zone 2	Zone 3	Zone 1	Zone 2	Zone 3
		267	179	46	76	58	27
	Operative (n=77)	55 (71.4%)			22 (28.6%)		
		Zone 1	Zone 2	Zone 3	Zone 1	Zone 2	Zone 3
		10	22	23	4	13	5

Table 2. Continued				
Healing Duration (days) [mean ± SD]		*Non-operative*	72.9 ± 39.0 (n =492)	>180*
		Operative	104.6 ± 36.5 (n=55)	
Fracture Alignment	**Displaced**	*Non-operative*	179 (71.9%)	70 (28.1%)
		Operative	15 (62.5%)	9 (37.5%)
	Non-Displaced	*Non-operative*	313 (77.3%)	92 (22.7%)
		Operative	40 (75.5%)	13 (24.5%)

*Mean healing time was not reported for the nonunion group, as healing was not achieved for all patients in this group

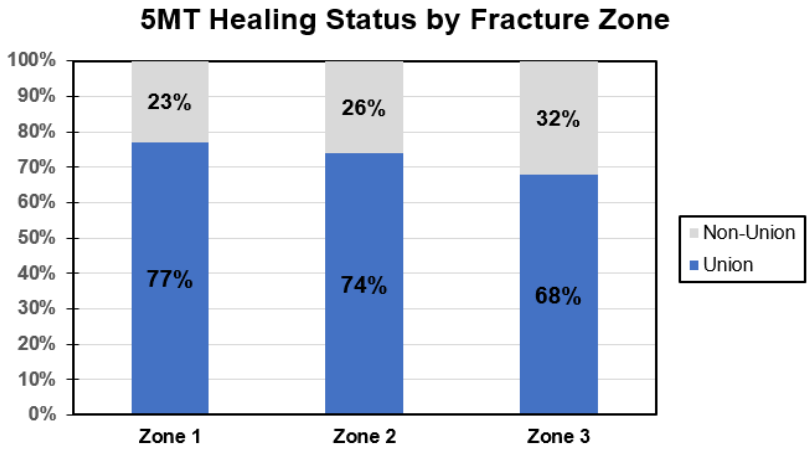

Figure 1. The percentage of union and non-union healing outcomes for each of the fracture zones (as defined by the Lawrence and Botte classification system) are illustrated. The three zones have unique anatomical characteristics; thus, it is useful to visualize and evaluate non-union rates for each zone individually

Table 3. Multivariable logistic regression analysis: demographic data, fracture characteristics, the top 25 most common medications and the top 25 most common medical conditions were included. The variables significantly correlated with non-union, the associated correlation coefficient, and p-value are shown below			
Variables		**Correlation Coefficient**	**p-value**
Displacement	*Yes*	0.115	**0.033**
	No	--	--
Bone Density	*Osteoporosis*	0.149	**0.028**
	Osteopenia	-0.010	0.878
	None	--	--
Irritable Bowel Syndrome	*Yes*	0.122	**0.012**
	No	--	--
Cardiovascular Disease	*Yes*	-0.183	**0.009**
	No	--	--
Sleep Apnea	*Yes*	0.122	**0.029**
	No	--	--
Beta-Blockers	*Yes*	-0.135	**0.047**
	No		
Topical Steroids	*Yes*	-0.125	**0.038**
	No	--	--

Multivariable binary logistic regression; p-value<0.05 was considered statistically significant

Among the 25 most common comorbidities and chronic conditions present in our population, significant correlation was found between non-union and osteoporosis (R=0.149, *P=0.028*), irritable bowel syndrome (IBS) (R=0.122, *P=0.012*), cardiovascular disease (CVD) (R=-0.183, *P=0.009*), and sleep apnea (R=0.122, *P=0.029*). All four of those variables demonstrated a power greater than or equal to 0.80 [Table 4]. Among the 25 most frequently prescribed medications, beta-blockers (R=-0.135, *P=0.047*) and topical steroids (R=-0.125, *P=0.038*) were found to be associated with 5MT non-union. These two medications also demonstrated a power great than or qual to 0.80 [Table 4]. The remainder or the results of the power analysis are shown [Table 4].

Additionally, there were several factors commonly associated with non-union in the previous literature that notably did not demonstrate association in our investigation. In terms of demographic data, neither BMI (*P=0.091*) nor smoking (*P=0.596*) were associated with an increased rate of non-union. Similarly, diabetes mellitus (*P= 0.560*), thyroid disease (*P=0.311*), and Vitamin D deficiency (*P=0.274*) were not found to be associated with non-union. Several medications, including NSAIDs (*P=0.738*), acetaminophen (*P=0.599*), and oral steroids (*P=0.484*), also demonstrated no associated with non-union. All of these variables listed were found to have a power less than 0.80 [Table 4].

Table 4. Power analysis for factors commonly reported to be associated with 5MT non-union

Variable		Power
Age		0.91
Weight		0.91
Height		0.91
BMI		0.05
Fracture Zone	*Zone 1*	---
	Zone 2	0.40
	Zone 3	0.72
Gender	*Female*	0.24
	Male	---
Race	*African American*	0.06
	Asian	0.06
	Hispanic	0.05
	White	0.07
	Other	---
Displacement		0.87
Treatment Method	*Conservative*	0.16
	Operative	---
Activity Level	*Athlete*	0.05
	Non-Athlete	---
Bone Quality	*Osteopenia*	0.08
	Osteoporosis	0.97
	None	---
Smoking Status	*Current*	0.12
	Former	0.14
	None	---
Thyroid Disease	Hyperthyroid	0.29
	Hypothyroid	0.07
	None	---

Table 4. Continued

Medications	*Oral Steroids*	0.22
	Topical Steroids	0.90
	NSAIDs	0.11
	Aspirin	0.66
	Acetaminophen	0.19
	Vitamin D	0.17
	Calcium	0.11
	Beta-Blockers	0.94
Chronic Conditions	*Peripheral Vascular Disease*	0.25
	Rheumatoid Arthritis	0.06
	Chronic Kidney Disease	0.53
	Vitamin D Deficiency	0.38
	Cardiovascular Disease	0.99
	Obesity	0.15
	Diabetes	0.26
	Irritable Bowel Syndrome	0.80
	Sleep Apnea	0.86

Discussion

This study aimed to determine the patient-specific factors associated with 5MT fracture non-union using available electronic health records of a large patient cohort. In addition to evaluating the effect of fracture characteristics, this study aimed to assess the effect of demographics, medications and chronic conditions on non-union. Factors that correlated significantly with 5MT non-unions included: displacement, osteoporosis, IBS, cardiovascular disease, beta-blockers amd topical steroids. Although correlation does not indicate a causal relationship, these factors may be utilized for developing predictive models and therefore may aid clinicians in making decisions regarding treatment. Awareness of these factors can also inform patients of their predicted prognosis.

According to the multivariable logistic regression, no demographic variables were found to be correlated with non-union. There was a significant difference (P=0.04) in the prevalence of obesity between the union and non-union groups; however, the results of the multivariable logistic regression suggest this may be due to confounding. The impact of BMI, age, and level of activity on the rate of 5MT non-union lacks consensus based on previous studies.[12–14] Regarding obesity specifically, one retrospective study of 59 patients by Ruta et al. identified a positive correlation with obesity and non-union.[15] In contrast, a case-controlled study including 48 patients by Thorud et al. found no association between non-union and BMI which was consistent with our results.[16] In contrast, increasing patient age was reported to have a strong positive correlation with delayed and non-union in a study on the surgical management of Jones fractures.[15] With respect to activity level, a previous study reported a significantly higher proportion of elite athletes that experienced non-union and refracture compared to non-athletes.[17] While this conflicts with our results, this may be due to differences in how "athlete" is defined as Larson et al. only included elite level athletes. Another demographic variable frequently associated with decreased bone healing propensity is tobacco use.[18–20] This study found no association between tobacco use, both former and current, and non-union. This is consistent with two prior studies, one specific to 5MT fractures and one related to general bone healing.[21,22] While there is variability within the literature, the present study demonstrated no correlation between demographic variables and non-unions. This may be a result of individual variables being underpowered.

Of the clinical and radiologic variables, fracture displacement was found to have a significant correlation with non-union. Regarding displaced 5MT fractures, the literature suggests that cases with displacement of greater than 2 mm should be recommended for operative treatment due to the increased risk of non-union.[13] This recommendation is supported by Zwister and Breederveld, who stated that a higher degree of misalignment increases non-union risk without operative fixation.[9] The results of the present study are consistent with the finding that fracture displacement coincides with greater non-union risk. However, the treatment method did not yield a significant correlation with non-union for either displacement or fracture zone. In terms of treatment method, no significant correlation was found between operative and conservative treatment and non-union rates. However, operative interventions for 5MT fractures have been reported to reduce the rate of non-union, duration of healing time, and the amount of time required for return to normal activity and sport.[2,23,24] Le et al. specifically investigated Zone 2 and Zone 3 fractures and demonstrated the same correlation, concluding that operative treatment resulted in decreased

non-union rates, lower refracture risk and an earlier return to sport.[25] In contrast to those findings, a recent study by Pettersen et al. demonstrated union rates of 96.2%-97.3% with non-operative treatment in a cohort of 834 5MT fractures composed of all three fracture zones suggesting satisfactory outcomes of conservative treatment.[26] Our study demonstrated a union rate of 75% in patients treated non-operatively and 71% in patients treated operatively which is lower than reported by Pettersen et al. Our study also contrasts with other previous studies that found a significant association between healing outcome and treatment method. These discrepancies may be due to possible confounding factors, such as patient selection for operative management, fracture zone, or differences in treatment protocols. While this study utilized a multivariable logistic regression to minimize confounding effects, the operative group only consisted of 77 patients. Again, based upon the power analysis, the non-significant variables mentioned here are individually underpowered, despite the overall study demonstrating a power of 0.91. Therefore, future studies with larger sample sizes to allow for stratification by fracture zone and analysis that addresses confounding variables are needed.

Interestingly, there was no association demonstrated in our investigation with fracture zone and non-union (limited by a minimum power 0.40 for Zone 3). However, although not statistically significant, there was a difference in non-union rates for each fracture zone: Zone 1 – 22.7%, Zone 2 – 26.1%, and Zone 3 – 31.7% [Figure 1]. These percentages are consistent with previous studies reporting increased rates of non-union in Zone 2 and Zone 3 fractures.[3,5] No previous studies were identified that reported a statistical comparison of fracture zones that included both operative and non-operative treatment. Pettersen et al. conducted an analysis of non-operative treatment of 5MT fractures and found a difference in time to union between Zone 1 and Zone 3 fractures.[26] This is consistent with the results of this study, as non-operative treatment of Zone 1 fractures resulted in a non-union rates of 22% versus a corresponding non-union rates of 37% in Zone 3 fractures.

Regarding the chronic conditions investigated in this analysis, osteoporosis, CVD, IBS and sleep apnea were significantly correlated with 5MT fracture non-union. Osteoporosis is commonly associated with increased risk of fracture and non-union, due to the decreased osteoblastic activity. The results of this study are consistent with this widely accepted association. Conditions that directly affect metabolism, such as diabetes and thyroid disease, also garner significant attention in regard to association with non-union in the orthopedic literature. Several studies have reported a correlation between diabetes and higher non-union rates, citing decreased overall bone health and diminished healing capacity as root causes.[12,16,19,22,27] Other studies have suggested that impaired bone metabolism in thyroid disease may be associated with nonunion.[28,29] Conversely, Moore et al. found no association between non-union and diabetes (P=0.1) or thyroid disease (P=0.67) in a study of 58 patients undergoing elective foot and ankle reconstruction.[30] The findings from this study are consistent with the results reported by Moore et al., which mention that diabetes and thyroid disease were not shown to be correlated with non-union. However, while these studies do provide some insight into risk factors for non-union in foot and ankle surgery, they are not specific to 5MT fractures. Additionally, both diabetes and thyroid disease were underpowered as individual variables in this study. Another chronic condition frequently discussed in relation to non-union due to its direct effect on bone metabolism is Vitamin D deficiency. Despite being regarded for an association with increased risk of both fracture and non-union, Vitamin D deficiency was not found to be associated with 5MT non-union in this study.[31,32] This may be due to a small sample size, as only 55 patients out of the 731 total had Vitamin D deficiency, resulting in a power of 0.38.

Cardiovascular disease, irritable bowel syndrome, and sleep apnea are categorized separately from these metabolic conditions; however, they may also play an important role in inhibiting physiologic bone healing. IBS has been reported to negatively impact bone health through mechanisms such as decreased bone mineral density and inherent imbalances in the bone remodeling process, along with poor nutrition secondary to malabsorption.[33] Literature on the direct impact of cardiovascular disease on 5MT fracture non-union is limited; however, Monteban et al. demonstrated that general cardiovascular risk factors correlated with worse functional outcomes following 5MT fracture regardless of treatment method.[34] Similarly, literature on sleep apnea's relationship to non-union is sparse; however, several pathophysiologic mechanisms have been put forth, including changes in bone metabolism due to interruption of the circadian rhythm of hormone release.[35] Overall, cardiovascular disease, IBS, and sleep apnea are clinical factors that should be included in future studies of 5MT fractures and non-typical risk factors for consideration.

In terms of medications associated with non-union, the results of this study found beta-blockers and topical steroids to be correlated with non-union. No prior studies were identified that discussed these specific medications and a correlation with 5MT non-union or fracture non-union in general. The correlation found in this study may be due to the underlying condition that the medication is treating, rather than the medication itself. The multivariable logistic regression was used to minimize such effects; however, only an randomized control trial can truly differentiate between correlation and causation.

The two classes of medications that are discussed most frequently in the literature in the context of bone healing are corticosteroids and NSAIDs, both of which affect bone metabolism [36,37,38,39–41] Our analysis of NSAIDs and corticosteroids do not align with previous reports, which may be due to inconsistencies in reporting of these medications. NSAIDs are available over the counter and therefore may not be accurately recorded in electronic medical records. Similarly, corticosteroids are available in variety of doses and durations of administration; therefore, the differences in outcomes may be due to exact definition of

corticosteroids with regards to details of administration. Additionally, the power analysis of this study for corticosertoids and NSAIDs was 0.22 and 0.11, respectively, suggesting each individual variable was underpowered. These discrepancies along with the results of the power analysis suggest the need for further research into medications that may play a role in increased risk of 5MT non-union.

There are several limitations to consider. One limitation is the retrospective nature of the study, which impacts the completeness and reliability of data collected. Other limitations were that healing status was determined based upon plain radiographs and that cases of delayed union were combined with non-union cases due to the small delayed-union sample size. While computed tomography is more optimal to assess bony union, post-treatment CT imaging for the routine care of patients sustaining 5MT fractures is impractical and uncommonly indicated. Additionally, treatment options were described in binary terms: operative or non-operative. Within each of these two treatment paths, there are many different approaches. For example, one intervention commonly utilized for the nonoperative treatment of nonunion is bone stimulation which was not captured in this study.

Finally and most importantly, this investigation was underpowered for many variables assessed despite an overall study power of 0.91. This was despite having a study cohort of 731 patients, 184 of which had nonunion. The fact that this retrospective investigation reports on one of the largest cohorts in the current literature examining this topic illustrates common methodologic difficulties when investigation such topics. Needless to say, larger studies which are appropriately powered for subgroup analysis are required to definitively assess correlation between variables. In particular a study with a larger operative group to allow for a separate analysis of operative and non-operaritve groups would be beneficial.

Conclusion

This study helps identify several variables including fracture displacement, osteoporosis, cardiovascular disease, irritable bowel syndrome, sleep apnea, beta-blockers and topical steroids that may influence union in 5MT fractures. Such variables can be utilized to develop predictive models based on patients' specific comprehensive datasets to aid physicians in clinical decision-making and selecting the best approach in treating these patients.

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Appendix

Appendix 1. Medications: 25 Most Common Amongst Included Patients
Acetaminophen
Albuterol
Amlodipine
Aspirin
Beta-Blocker
Bowel Prep/Regimen
Calcium
Cetirizine
Fluticasone
Gabapentin
Levothyroxine
Lisinopril
Lorazepam
Metformin
Multivitamin
No Medications
Non-Steroidal Anti-Inflammatory Drug (NSAID)
Omeprazole
Opioids
Oral Contraceptive Pill (OCP)
Oral Steroids
Selective Serotonin Reuptake Inhibitor (SSRI)
Statin
Topical Steroids
Vitamin D

Appendix 2.Chronic Medical Conditions: 25 Most Common Amongst Included Patients
Anemia
Anxiety
Cancer
Cardiovascular Disease (CVD)
Chronic Kidney Disease (CKD)
Chronic Obstructive Pulmonary Disease (COPD)
Depression
Diabetes
Diverticulitis
Gastroesophageal Reflux Disease (GERD)
Glaucoma
Hyperlipidemia
Hypertension
Insomnia
Irritable Bowel Syndrome (IBS)
Liver Disease
Migraine
No Known Chronic Disease
Obesity
Peripheral Vascular Disease
Rheumatoid Disease
Sleep Apnea
Thyroid Disease
Uterine Leiomyoma
Vitamin D Deficiency

Appendix 3. Shapiro-Wilk normality test results for all quantitative variables. A p<0.05 was considered statistically significant. Bolded p-values indicate samples that demonstrate a non-normal distribution

Variable	Cohort	p-value
Age	*Union*	<0.001
	Nonunion	0.00
Height	*Union*	<0.001
	Nonunion	0.032
Weight	*Union*	<0.001
	Nonunion	<0.001
BMI	*Union*	<0.001
	Nonunion	<0.001

Shapiro-Wilks normality test; p<0.05 considered statistically significant