5-2021

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ABSTRACT

Background: Osteogenesis imperfecta (OI) is a genetic connective tissue disorder affecting quantity and integrity of collagen type I, which is integral for the strength of osseus tissue. OI has a heterogenous molecular inheritance pattern – divided into four major subgroups (I-IV). Defects in collagen protein products lead to poor development of skeletal structures and increased fracture rates. Children with OI suffer from multiple fractures and bone deformities often requiring surgical intervention with osteotomies and intramedullary telescoping rods, most often with Fassier-Duval (FD) rods. Our study–updated cohort from 2018 paper Azzam et al.–looked at the relationship between initial and reoperation indications for femur and tibia FD rodding surgeries based on age, bone, and OI type.

Methods: Retrospective chart review of initial surgeries included 197 bones (femurs and tibias) from 58 patients. Reoperations included 140 bones from 45 patients. Variables included age at first operation (0-24, 24.1-48, 48.1+ months), time to reoperation, operation indications, bone, and OI type. Spearman correlations were used separately for each bone-type to assess associations between age at first surgery and total number of surgeries. To assess dichotomous outcomes (i.e. specific indication), generalized estimating equations were utilized and adjusted for bone-type and side. Hazard ratios and associated 95% confidence intervals were derived from frailty survival models for the time to first reoperation outcome. Kaplan-Meier curves were generated to display time to reoperation, stratified by age at first operation and bone-type. Data was collected from 2003-2018. Analyses were performed using SAS software v9.4.

Results: There was a statistically significant correlation between age at first surgery and indication (bowing and fracture) for initial ($p<0.0001$, $p=0.01$) and reoperation surgeries ($p=0.004$, $p=0.03$), respectively. All bones, except left tibias, showed significant negative correlation between age at first surgery and total number of surgeries. Both older age at first surgery groups (24.1-48, 48.1+ months) had significantly lower risks of needing reoperation relative to the 0-24 months group ($p=0.0003$, $p=0.0004$). Descriptive analyses suggest median survival of FD rods in OI type III was decreased relative to type IV, XV or unknown when initial surgery was between 0-24 months.

Conclusion: Bowing and fractures are the most common causes for initial and reoperation surgeries in children with OI. Patients in older age groups at first surgery need fewer reoperation surgeries. Median survival probabilities of FD rods increased when age at first surgery was after 48.1+ months. OI type may impact median survival of FD rods.

Total Number of Surgeries by Bone-type and Age at First Surgery

Figure 3 illustrates total number of surgeries by bone-type and age at first surgery. Large icons represent mean value of the group and smaller icons represent outliers within the group. Results demonstrate a descriptive graphical analysis of an average decrease by bone-type and age at first surgery when initial surgery was at an older age (i.e. 0-24 months compared to 48.1+ months). Total number of reoperation rodding surgeries included 140 bones from 45 patients.

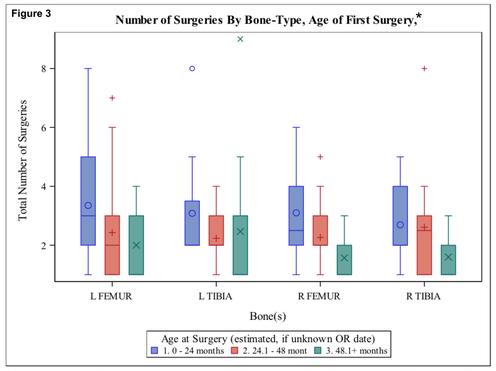
Table 3 displays Spearman correlation values between age of first surgery and total number of surgeries for each bone. This was done to measure the strength and direction of age at first surgery and correlate it to the total number of surgeries. Negative values signify the old a patient is at first surgery the fewer total number of surgeries a patient will have. All bones show significance between as at first surgery and total number of surgeries, except for left tibias.

Table 3

Bone	Spearman Correlation Between Age of First Surgery and Total Number of Surgeries	P-value
Left Femur	-0.36	0.01
Left Tibia	-0.18	0.25
Right Femur	-0.48	0.0003
Right Tibia	-0.35	0.02

For all bones except left tibias, there was a significant negative correlation between age of first surgery and total number of surgerys - patients who were younger at the time of their first surgery tended to have more surgeries.

Figure 3



*Data needs to be corrected with statistical correlation models as an individual may have multiple rodding surgeries on multiple bones at a time. Since data is looking at multiple variables: bone-type, age at initial surgery and total number of surgeries, not using correlational statistics would unequally weight risk factors for an individual undergoing multiple surgeries. Therefore complex statistical correlation models are needed to analyze and stratify data to determine statistical significance between each bone, individual, and age at initial surgery. Graph is present for descriptive purposes.

Median Survival for FD Rods Placed before 24 Months of Age in OI Type III and Type IV

Bone(s)=L FEMUR OI Type=III

Figure 8

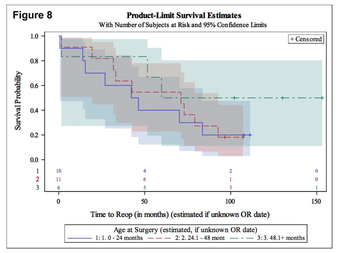


Table 5

Median Survival of FD Rods in OI Type III when Initial Surgery was less than 24 Months

Bone	Number of Patients	Median Survival in Months	Lower CI	Upper CI
L FEMUR	10	44.3	0.6	83.5
L TIBIA	8	16.2	6.4	39.8
R FEMUR	10	44.4	7.0	77.7
R TIBIA	7	15.6	8.0	48.3

Figure 8 Kaplan-Meier curve shows survival probability of left femur for OI type III based on age at initial surgery. Left femur was selected as representative of other bone-types due to greatest total number of patients in subgroup for both type III and combined type IV, XV or unknown. Additionally, Kaplan-Meier curves showed similar trending data for other bone-types and to minimize redundancy those graphs were excluded from the poster. The graph demonstrates group 0-24 months had a median survival of 44.3 months, 24.1-48 months had a median survival of 71.0 months, and 48.1+ months was not able to calculate median survival as less than 50% needed reoperation

Table 5 shows median survival estimates by bone-type in patients with OI type III who had their first surgery prior to 24 months. Left femur and right femur had the same number of patients in each study (10) and had same median survival of 44 months. Left and right tibia had comparable number of patients (8 and 7) and median survival was also comparable at around 16 months. Laterality for femurs and tibias were similar on average however median survivals of FD rods for femurs and tibias differed by 28 months (statistical significance between groups was not assessed).

Bone(s)=L FEMUR OI Type=IV, XV, or Unknown

Figure 9

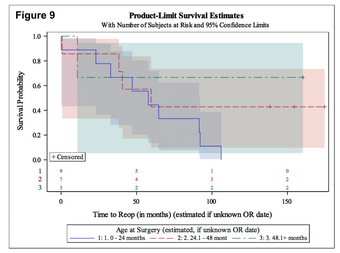


Table 6

Median Survival of FD Rods in OI Type IV, XV, or Unknown when Initial Surgery was less than 24 Months

Bone	Number of Patients	Median Survival in Months	Lower CI	Upper CI
L FEMUR	9	57.8	0.1	92.1
L TIBIA	4	23.9	11.5	64.7
R FEMUR	9	64.4	22.6	94.1
R TIBIA	6	66.6	11.5	.

Figure 9 Kaplan-Meier curve shows survival probability of left femur for OI type IV, XV or unknown based on age at initial surgery. Left femur was selected as representative of other bone-types due to greatest total number of patients in subgroup for both type III and combined type IV, XV or unknown. Additionally, Kaplan-Meier curves showed similar trending data for other bone-types and to minimize redundancy those graphs were excluded from the poster. Figure 9 shows age at surgery for 0-24 months had a median survival of 57.8 months, 24.1-48 months median survival of 59.6 months and 48.1+ months was not able to calculate median survival as less than 50% needed reoperation.

Table 6 shows median survival estimates by bone-type in patients with OI type IV, XV and unknown who had their first surgery prior to 24 months. Left femur and right femur had the same number of patients in each study (9) and with a median survival difference of 6.7 months . Left femur median survival was 57.8 months whereas R femur was 64.4 months. Left and right tibia also had a median survival of 42.7 months as left tibia median survival was 23.9 months and right tibia was 66.6 months (statistical significance between groups was not assessed).

Indications for Initial and Reoperation Femur and Tibia Rodding Surgery by Percentage

Table 1

Indication(s) for Initial Intramedullary Rodding Surgeries by Age in Children with OI

	0 - 24 months	24.1 - 48 months	48.1+ months	P-Value for age (continuous)
Bowing	88.6%	71.4%	43.6%	<.0001
Fracture	22.6%	43.8%	44.0%	0.01

*Percentages are esimtates from generalized estimating equations (one model for each indication) which adjust for bone and side. P-values reflect main effect of surgery age when treated as continuous (i.e. tests for a linear relationship.)

Table 1 shows the top two indications, bowing and fracture, by age of initial surgery in children with OI. Patients who are older at their first surgery, the operative indication for bowing decreases as the incidence of fractures increases. Note that a patient may be counted four times in a cell, if they had a given indication for all four bones in the same age group.

Figure 1 illustrates top four surgical indication(s) for children with OI by percentage separated by bone-type and age. Individuals may have more than one surgical indication listed for operation. The greatest two indications are bowing and fracture. n represents number of patients in each subgroup.

Figure 1

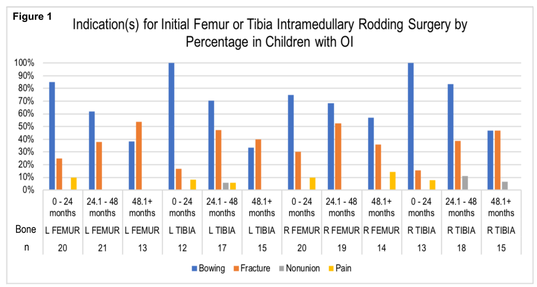


Table 2

Indication(s) for Initial Reoperation Intramedullary Rodding Surgery by Age in Children with OI

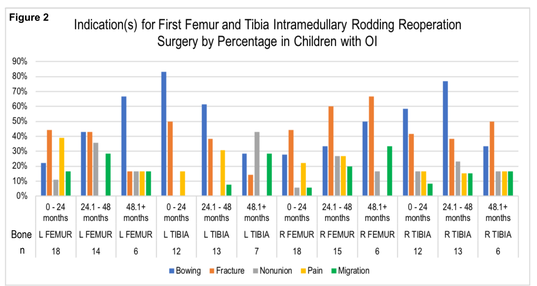
	0 - 24 months	24.1 - 48 months	48.1+ months	P-Value for age (continuous)
Bowing	42.3%	40.2%	17.7%	0.004
Fracture	41.0%	34.5%	15.6%	0.03

*Percentages are estimates from generalized estimating equations (one model for each indication) which adjust for bone and side. P-values reflect main effect of surgery age when treated as continuous (i.e. tests for a linear relationship.)

Table 2 shows the top two indications, bowing and fracture, for initial reoperation in children with OI. Patients that are older at their first surgery have a statistically decreased incidence of reoperations for bowing and fracture. Note that a patient may be counted four times in a cell, if they had a given indication for all four bones in the same age group.

Figure 2 illustrates top five surgical indication(s) for children with OI by percentage. Individuals may have more than one surgical indication listed for operation on bone totaling greater than 100%. The greatest two indications in general are bowing and fracture. The n represents number of patients in each group.

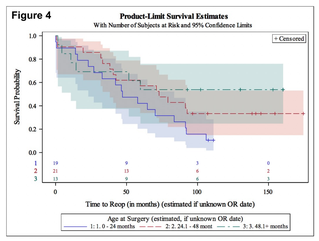
Figure 2



Median Survival Probability of Fassier-Duval Rods Stratified by Age of Operation

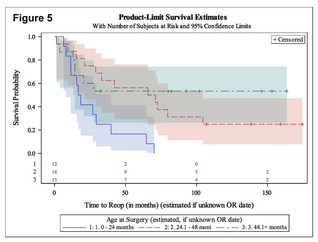
Bone(s)=L FEMUR

Figure 4



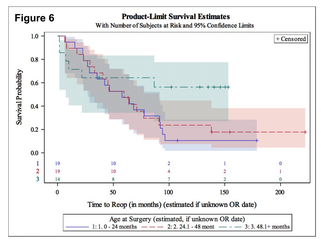
Bone(s)=L TIBIA

Figure 5



Bone(s)=R FEMUR

Figure 6



Bone(s)=R TIBIA

Figure 7

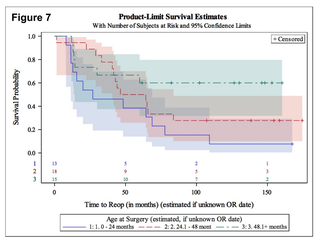


Figure 4, 5, 6 and **7** illustrates Kaplan-Meier curves showing median survival or FD rods in months of left femur, left tibia, right femur and right tibia, respectively. Median survival probability was determined when 50% of subjects needed a reoperation. X-axis represents time in months since reoperation. Numbers above x-axis represent the number of subjects since initial surgery with intact FD rod and no reoperations. In general patients who had initial operation at greater than 48.1 months of age had greater median survival probability than those who had initial surgery at a younger age. 0-24 months group median survival probabilities, from figure 4-7, in months are 47.1 L femur, 17.6 . L tibia, 57.8 R femur and 26.9 R tibia.

Table 4 displays hazard ratios for groups 0-24, 24.1-48, 48.1+ months at initial surgery. 0-24 months was used as the relative reference value for which 24.1-48 months and 48.1+ months were compared . Results show that older groups at first surgery (24.1-48 and 48.1 months) had significantly lower risks of needing reoperation than 0-24 months age group.

Table 4

Age	Hazard Ratio	Adjusted 95% Confidence Interval		P-Value
1. 0 - 24 months	1	Reference		
2. 24.1 - 48 months	0.235	0.089	0.617	0.0003
3. 48.1+ months	0.16	0.047	0.548	0.0004

Hazard ratios were derived from a frailty survival model that accounts for correlated data with a time-to-event outcome and adjusted for bone type and side. Both older age at first surgery groups had significantly lower risks (i.e. hazard ratio less than 1.00) of needing a reoperation than the youngest age at first surgery group.

Conclusion and Future Directions

1. The two most common indication(s) for initial and reoperation surgeries were bowing and fractures
2. Patients who have their first surgery at an older age have decreased surgical indications for bowing compared to those at a younger age, comparatively fracture percentage increases with older age at first surgery
3. All bones, except left tibias, showed significant negative correlation between age at first surgery and total number of surgeries—suggesting patients who have first surgery at a younger age have increased total number of surgeries
4. Femurs had on average longer median survival when compared to tibias prior to first operation at 24 months
5. On average, Type III had lower median survival probability for FD rods than type IV, XV or Unknown
6. Complex statistical correlation models are needed to analyze and stratify data based on OI type and to further determine statistical significance
7. It is probable OI type is a confounding factor for Fassier-Duval rod median survival, bone-type, and time to reoperation
8. Future directions include increasing number of subjects from 58 in the original cohort to the total 135 in the OI database—increasing power to statistically correlate additional variables to OI type
9. Analyze medical management, surgical times, total number of reoperation surgeries, and surgical placement of FD rods in distal and proximal epiphyses to determine potential confounding in FD rod median survival in children with OI

References

1. Azzam KA, Rush ET, Burke BR, Nabower AM, Esposito PW. Mid-term Results of Femoral and Tibial Osteotomies and Fassier-Duval Nailing in Children With Osteogenesis Imperfecta. J Pediatr Orthop. 2018 Jul;38(6):331-336. doi: 10.1097/BPO.0000000000000824. PMID: 27379783.