Comparison of Forgotten Joint Score Between Alignment Techniques for Total Knee Arthroplasty

Doungporn Wiwatanapataphee

Abstract: A concern to improve postoperative and long-term outcomes for patients undergoing total knee arthroplasty (TKR) has led to many different alignment schemes being utilized. Functional alignment (FA) is one of the most effective computer-based osteoarthritis surgery technique aimed to restore neutral knee alignment and improve its functionalities. Two potential alignment schemes for achieving FA in TKA including mechanical axis and kinematic axis. FA with mechanical axis initial plan is designated as FA(m), whereas FA with kinematic axis initial plan is referred as FA(k). Both schemes utilize boundaries expansion of hip-knee-ankle angle (HKA) to 6 degrees of varus and three degrees of valgus. The objective of this study is to determine the optimal alignment technique in FA TKA by investigating the difference in postoperative forgotten joint score (FJS) between FA(m) and FA(k) over time and patient demography. Preoperative, postoperative, and demographic data on 300 patients were collected. The linear mixed effects models will be fitted with FJS as response, including all other preoperative and demographic variables as covariates. The final model is interpreted, and the results and findings are discussed.

1. Introduction

Total knee arthroplasty (TKA), also called total knee replacement (TKR), is recognised as one of the most effective orthopaedical surgery of the twentieth century. Initially, the primary goals of TKA are to reduce pain and improve symptoms for patients with end-stage knee osteoarthritis [1]. Over the past few decades, the goal of TKA has shifted from survivorship alone to optimal function and stable long-term outcomes [2].

Since the first knee replacement was performed in 1968, surgical materials and techniques have been significantly improved. However, about 20% of the patients undergone TKA surgery annually report that they were not satisfied with the postoperative outcomes, which resulted from an improper joint alignment [3]. Poorly aligned TKA can also result in decreased implant survivorship and increased wear. In addition, the rising prevalence of osteoarthritis and TKA procedure implies health care costs and resources; therefore, a new efficient provision of TKA is a priority [4].

Successful TKA depends on the postoperative restoration of the knee to neutral limb alignment and restores native, patient-specific anatomy and knee kinematics. Moreover, implant positioning and soft tissue balancing accuracy during and after TKA are also significant prognostic factors that affect long-term clinical outcomes and implant

survivorship. Many different alignment schemes and surgical techniques have been introduced to achieve these goals, including computer-based navigation and custom cutting guides [1].

Functional Alignment (FA) is one of many possible ways to improve the TKA outcomes by aligning the knee with the soft tissue constraints and reproducing the native joint line-height and obliquity. With FA, the initial position of the knee is based on bony landmarks and resection depths but after quantitative measurement of joint laxity. Manipulation of bone resections and fine-tuning implant positioning are then accomplished to preserve patient-specific anatomy and balance [5].

This study employs two alignment axe schemas for achieving FA in TKA – namely, mechanical axis and kinematic axis. The mechanical axis/alignment is performed by making an initial femoral cut perpendicular to the mechanical axis of the femur, followed by a tibial resection made perpendicular to the mechanical axis of the tibia. On the other hand, the kinematic axis/alignment aims to co-align two transverse axes of the femur to achieve more natural knee kinematics [1]. FA with mechanical axis initial plan is referred to as FA(m), whereas FA with kinematic axis initial plan is referred to as FA(k). Both schemes will utilise boundaries expansion of overall hip-knee-ankle (HKA) alignment up to 6 degrees of varus and 3 degrees of valgus. Although the overall limb alignment in FA is independent of the initial plan, the individual component position and knee joint line obliquity (KJLO) will vary depending on the axis starting point [2].

Other factors affect long-term functional outcomes, including patient-related factors (demographics) and preoperative factors. Patient demographic information such as age, gender, and BMI, and preoperative variables such as Forgotten Joint Score (FJS), visual analogue pain score (VAS), Oxford Knee Score (OKS), Knee Injury and Osteoarthritis Outcome Score for Joint Replacement (KOOS JR), European Quality of Life Measurement – 5 Dimension (EQ5D5l), and Range of movement (ROM) are also considered as essential prognostics factors influencing the clinical outcomes [2], [6].

The main objective of this study is to determine the optimal alignment technique in FA TKA by investigating the difference in postoperative clinical outcomes between FA(m) and FA(k) over two years following surgery and patient-related factors. Forgotten Joint Score (FJS) is used as the primary outcome measure under the null hypothesis that there is no difference in scores between patients undergoing FA(m) and FA(k).

The remainder of this paper is structured as follows. The methodology of the data collection process and statistical modelling technique will be presented in the next section. The results are presented in Section 3, followed by a discussion in Section 4.

2. Methodology

2.1. Data collection and management

Perth Hip and Knee Surgery collected the pre and postoperative data on three hundred knee surgery patients performed by the same surgeon at Subiaco and Midlands branches between 2016 and 2019. All patients who undergone TKA had end-stage knee osteoarthritis that had previously failed non-operative management and was assessed as suitable primary TKA candidates. Prior to the surgery, patient demographic information such as height, weight, BMI, age, and gender was gathered. Each patient will be identifiable with a unique patient identifier number (DAP). In addition, patient-reported outcome measures (PROMs) such as EQ5D5l, FJS, OKS, KOOS JR, and VAS pain were recorded as validation tools for clinical assessment [5].

Computer navigated FA TKA were performed to improve the functional outcomes. The process is considered a blinded randomised control trial where half of the patients undergo a FA(m) and the other half undergo a FA(k). After the surgery, PROMs, especially postoperative FJS at three months, one year and two years, were collected and used to further assess outcomes [5].

2.2. Statistical methods

Numerical and graphical descriptive statistics are firstly obtained to gain better insight into the raw data. Then, a linear mixed-effects model (LMM) with a random intercept to adjust for repeated observation will be fitted with postoperative FJS as the response variable and all other variables (demographic and preoperative PROMs) as covariates to assess any difference in FJS between FA(m) and FA(k) groups after adjusting for the effects of the other covariates. Since the mixed model procedure requires the data to be in longitudinal structure, the original data in wide format was reshaped prior to fitting an LMM.

A step-up modelling strategy will be employed to select the most appropriate and simplest LMM that best fits the observed data. The approach starts with an "unconditional" (means-only) model having only the fixed intercept and random effects associated with the intercept for patients. Then, the model is built by adding fixed effects of covariates measured and their associated random effects at level 1 (time) and level 2 (patient), respectively. The choices concerning the structure of random effects and the fixed effects will be considered at each level.

3. Results

3.1. Data exploration

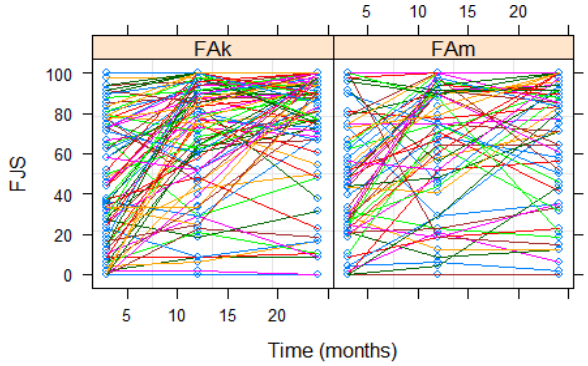

Figure 1. Observed FJS across time (in month) for patients who undergone FA(k) and FA(m)

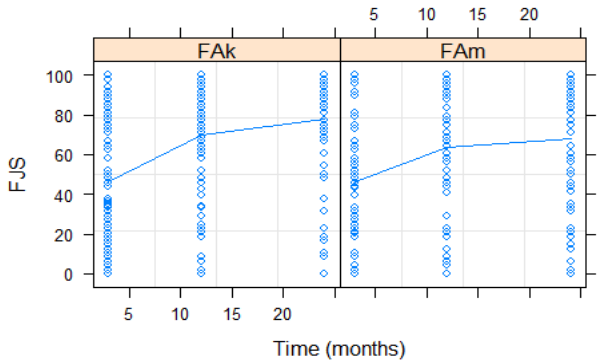

Figure 2. Mean profiles of FJS across time for patients undergone FA(k) and FA(m)

Figure 1 shows substantial variation from patient to patient. However, there is no evidence that the between patient variability in the FJS is varying over time. The FJS mean profiles, shown in Figure 2, tend to increase at a decreasing rate for both alignment groups, suggesting a nonlinear relationship between FJS and time might be considered.

Table 1 contains a statistical summary of FJS by alignment technique and time after TKA. Since the minimum and maximum FJS are 0 and 100 across all times and techniques, these two fields are omitted. It is noticed that the standard deviations remain relatively constant over time and alignment technique, suggesting there is no significant difference between the variances of FJS measurements obtained at different time points.

Table 1. Summary of FJS measurements by alignment technique and time after TKA. The overall summaries, the summary by alignment, and the summary by time are also presented.

		3 month	1 year	2 year	
FA(k)	Q1	18.75	52.08	72.92	37.50
	Median	43.75	79.17	89.58	77.08
	Mean	46.39	69.87	78.09	64.78
	Q3	77.08	93.75	97.92	93.75
	SD	31.75	29.13	28.33	32.57
	n	89	89	89	267
FA(m)	Q1	25.00	42.33	44.79	29.17
	Median	45.83	70.83	81.25	64.58
	Mean	46.51	63.71	67.99	59.40
	Q3	69.80	91.67	93.75	91.67
	SD	30.39	31.49	31.90	32.46
	n	63	63	63	189
	Q1	20.83	47.40	60.42	33.33
	Median	43.75	76.04	87.50	72.92
	Mean	46.44	67.32	73.90	62.55
	Q3	73.44	91.67	97.92	91.67
	SD	31.09	30.18	30.18	32.60
	n	152	152	152	456

3.2. Data analysis

The data were analysed as a linear mixed-effects model with the Forgotten Joint Scores (FJS) response variable. The final model containing only significant fixed and random effects at a 5% significance level is presented in Table 2 and shows the following.

Table 2. Linear mixed model significant (at 5% significance level) covariates with their associated coefficient, standard deviation (SD), and p-value corresponding to Students' t-test

Variable	Coefficient (SD)	p-value
Intercept	-56.97 (17.45)	0.0012
$TIME3^{**}$	3.28 (0.38)	0.0000
$(TIME3)^2$	-0.08 (0.02)	0.0000
$ALIGNMENTFAm$	0.81 (4.39)	0.8538*
Age	1.03 (0.25)	0.0001
$Femoral$	-1.80 (0.73)	0.0154
$PreopEQ5D5L$	0.23 (0.11)	0.0346
$PreopOKS$	1.09 (0.30)	0.0003
$TIME3{:}\,ALIGNMENTFAm$	-0.48 (0.24)	0.0430

*The *ALIGNMENTFAm* covariate is retained in the final model despite being non-significant because its associated interaction term with *TIME3* is significant at 5% level.
** *TIME3* variable is the centred time (in month) at which the postoperative FJS measurements were taken, which is defined as *TIME* minus 3 so that the parameter estimates can be interpreted at 3 month postoperatively instead of 0 month (immediately after the surgery which has no data).

- Usually, the intercept represents the estimated mean FJS measurements for patients after three months of surgery using the FA(k) technique (reference category). However, a negative value of FJS is outside of the observed data and hence should not be interpreted.
- The time parameter estimate is positive, whereas the squared time estimate is negative, indicating the FJS measurements is increasing at a decreasing rate.
- The non-significant alignment effect suggests no overall effect of either FA(m) or FA(k) group. However, a significant interaction term between time and FA(m) group indicates that there are significant differences between FA(m) and FA(k) alignment group over time.
- A negative parameter estimate of the interaction term between time and alignment technique suggests that the FJS of patients who underwent FA(m) TKA is slightly lower than FJS of patients who underwent FA(k) TKA over time.
- The positive parameter estimates of Age, PreopEQ5D5L, and PreopOKS suggest that postoperative FJS measurements increase with these covariates.
- There appears to be a negative effect of a measure of preoperative femoral alignment (Femoral) on FJS after controlling for the effect of time and other covariates.

4. Discussion

The study differs from other published randomised control trials because it utilised the Function alignment (FA) rather than Kinematic alignment (KA) as the intervention group. FA is a new technique, which two alignment axe schemas can be employed– namely, mechanical axis and kinematic axis. The comparison of postoperative Forgotten Joint Score (FJS) of knee osteoarthritis patients operated with different technique was conducted.

The study's most important finding is that the patient's ability to forget about knee joint measured by FJS is comparable between FA(k) and FA(m) TKA. Patients who operated with FA(k) tend to be more "forgetting" about the artificial joint over two years than patients who undergone FA(m).

The significance of patient's demographics such as age, gender and BMI in this study are in line with the results found by Schotanus et al. [7]. They studied the difference in joint awareness after mobile- and fixed-bearing TKA and found that only patients' age between both groups was significant despite the process being randomised. It is also founded that most of the PROMs are not capturing the differences in FJS.

One of the limitations of the study is the limited number of patients with completed records and thus the statistical power of this study. Although the FJS is employed to investigate and evaluate joint awareness after TKA, other clinical outcomes and joint-specific PROMs such as OKS and KOOSKR could also be used.

References

[1] J. J. Cherian, B. H. Kapadia, S. Banerjee, J. J. Jauregui, K. Issa and M. A. Mont, "Mechanical, Anatomical, and Kinematic Axis in TKA: Concepts and Practical Applications," *Curr Rev Musculoskelet Med,* vol. 7, no. 2, pp. 89-95, Jun 2014.

[2] R. Steer, B. Tippett, N. R. Khan, G. Clark and D. Collopy, "A Prospective Randomised Control Trial Comparing Functional with Mechinal Axis Alignment ain Total Knee Arthroplasty: study protocol for an investigator initiated trial," *BioMed Central ,* 2021.

[3] R. B. Bourne, B. M. Chesworth, A. M. Davis, N. N. Mahomed and K. D. J. Charron, "Patient Satisfaction after Total Knee Arthroplasty: Who is Satisfied and Who is Not?," *Clinical Orthopaedics and Related Research,* vol. 468, no. 1, pp. 57-63, 2010.

[4] I. N. Ackerman, M. A. Bohensky, E. Zomer, M. Tacey, A. Gorelik, C. A. Brand and R. d. Steiger, "The projected burden of primary total knee and hip replacement for osteoarthritis in Australia to the year 2030," *BMC Musculoskeletal Disorders,* vol. 20, no. 1, p. 90, 2019.

[5] R. Steer, B. Tippett, N. R. Khan, D. Collopy and G. Clark, "Restoring Joint Line Obliquity in Functional Alignment results in improved PROMs following TKA".

[6] N. A. Hewlett-Smith, R. P. Pope, W. A. Hing, V. P. Simas and J. W. Furness, "Patient and surgical prognostic factors for inpatient functional recovery following THA and TKA: a prospective cohort study," *Journal of Orthopaedic Surgery and Research,* vol. 15, p. 360, 2020.

[7] M. G. M. Schotanus, P. Pilot, R. Vos and N. P. Kort, "No difference in joint awareness after mobile- and fixed-bearing total knee arthroplasty: 3-year follow-up of a randomised controlled trial," *European Journal of Orthopaedic Surgery & Traumatology,* vol. 27, no. 8, pp. 1151-1155, 2017.

Appendix A

This section will outline analysis steps (followed by step-up modelling strategy), models specification, and the associated hypotheses and assumptions. For all analyses, a p-value considered to be statistically significant is at $p \leq 0.05$.

Step 1: Fit the initial "unconditional" model

The analysis step starts with fitting a mean-only model with only the fixed intercept. Since the variation from patient to patient is observed in the exploratory section, the random effects associated with the intercept for patients are included.

The general model specification for an individual response FJS_{ti} on patient i at the t-th visit ($t = 1, 2, 3$ correspondings to time at 3, 12, and 24 months) is given by:

$$FJS_{ti} = \beta_0 + u_{0i} + \varepsilon_{ti} \qquad \text{Model 1}$$

where

- β_0 is the fixed effects associated with the intercept.
- $u_{0i} \sim N(0, \sigma^2_{int:patient})$ represents the patient-specific random intercept.
- $\varepsilon_{ti} \sim N(0, \sigma^2)$ represents the residual variances.
- u_{0i} and ε_{ti} are assumed to be independent of each other.

Step 2: Add level 1 covariates and their associated fixed effects

In this step, the fixed effects associated with the time-level covariates ($TIME3$ and $ALIGNMENT$) are added to Model 1. Considering a nonlinear relationship shows in the mean profiles of FJS, $(TIME3)^2$ the fixed effect is also included. The random effects associated with time are also added to consider the time-specific variation. Since there is no significant difference between the variances of FJS measurements obtained at different time points, the variance structure can also be excluded. The new model specification is:

$$\begin{aligned} FJS_{ti} = {} & \beta_0 + \beta_1 \times TIME3_{ti} + \beta_2 \times (TIME3)^2_{ti} + \beta_3 \times ALIGNMENTFAm_i \\ & + \beta_4 \times TIME3_{ti} \times ALIGNMENTFAm_i \\ & + u_{0i} + u_{1i} \times TIME3_{ti} + \varepsilon_{ti} \end{aligned} \qquad \text{Model 2}$$

where

- $TIME3_{ti}$ is the centred time (in month) at which the FJS was taken. It is defined as $TIME$ minus 3 so that the parameter estimates are easier to interpret.
- $ALIGNMENTFAm_i$ indicates alignment group, which takes value of 1 for FA(m).
- $\beta_1, \beta_2, \beta_3$ and β_4 are fixed effects associated with $TIME3$, $(TIME3)^2$, $ALIGNMENTFAm$, and interaction between $TIME3$ and $ALIGNMENTFAm$.
- u_{0i} and u_{1i} are the random effect associated with the intercept and $TIME3$, which are independent of each other and of ε_{ti}.

$$\mathbf{u}_i = \begin{pmatrix} u_{0i} \\ u_{1i} \end{pmatrix} \sim N(\mathbf{0}, \mathbf{D}), \quad \mathbf{D} = \begin{pmatrix} \sigma^2_{int} & \sigma_{int,time3} \\ \sigma_{int,time3} & \sigma^2_{time3} \end{pmatrix}$$

Then, the test to decide whether the fixed effects of time-level covariates should be added is conducted.

$$H_0: \quad \beta_1 = \beta_2 = \beta_3 = \beta_4 = 0$$
$$H_A: \beta_i \neq \text{for at least one } i = 1, \dots, 4$$

Model 1 vs Model 2

The hypothesis is assessed using a likelihood ratio test (LRT) based on maximum likelihood (ML) estimation. The test statistic is asymptotically a χ_4^2 distributed. The result suggests that the fixed effects associated with time covariates should be added to the model; therefore, Model 2 is preferred.

Also, the test to decide whether the random effects associated with time should be retained is conducted.

$$H_0: \quad \sigma_{time3}^2 = \sigma_{int,time3} = 0$$
$$H_A: \sigma_{time3}^2 \neq 0 \text{ or } \sigma_{int,time3} \neq 0$$

Model 2A vs Model 2

The hypothesis is assessed using LRT with the REML estimation method. The asymptotic null distribution of the test statistic is a mixture of χ_1^2 and χ_2^2 distributions, with equal weights of 0.5. The result suggests that the random time effects in the model should be retained; therefore, Model 2 is preferred at this stage of the analysis.

Step 3: Add level 2 covariates

In this step, the fixed effects of the patient-level covariates (demography and PROMs) are added to Model 2. The variable LOS is excluded from the model because there is no evidence in the literature that LOS affects FJS. Also, the variable HEIGHT and WEIGHT are excluded because they were used to calculated BMI. The new model specification is

Model 3

$$\begin{aligned} FJS_{ti} = {} & \beta_0 + \beta_1 \times TIME3_{ti} + \beta_2 \times (TIME3)_{ti}^2 + \beta_3 \times ALIGNMENTFAm_i \\ & + \beta_4 \times TIME3_{ti} \times ALIGNMENTFAm_i + \beta_5 \times BMI_i + \beta_6 \times AGE_i \\ & + \beta_7 \times GENDER_i + \beta_8 \times TIBIAL_i + \beta_9 \times FEMORAL_i \\ & + \beta_{10} \times PreopROM_i + \beta_{11} \times PreopEQ5D5L_i + \beta_{12} \times PreopFJS \\ & + \beta_{13} \times PreopOKS + \beta_{14} \times PreopKOOSJR + \beta_{15} \times PreopPainVAS \\ & + u_{0i} + u_{1i} \times TIME3_{ti} + \varepsilon_{ti} \end{aligned}$$

The coefficient of the newly added fixed effects should be self-explanatory. Then, eleven hypotheses are tested to decide whether the fixed effects associated with BMI, $AGE, GENDER, TIBIAL, FEMORAL, PreopROM, PreopEQ5D5L, PreopFJS, PreopOKS,$ $PreopKOOSJR$ and $PreopPainVAS$ should be kept. For example, the hypothesis for the fixed effect associated with BMI is

$$H_0: \beta_5 = 0$$
$$H_A: \beta_5 \neq 0$$

The individual t-tests with 139 degrees of freedom is used for each hypothesis. Based on the summary output of Model3, the following fixed effects associated with patient-level covariates are dropped in respective order: $PreopROM, PreopKOOSJR, PreopPainVAS, Tibial, Gender, BMI,$ and $PreopFJS$. Then, the reduced model is

$$\begin{aligned} FJS_{ti} = {} & \beta_0 + \beta_1 \times TIME3_{ti} + \beta_2 \times (TIME3)^2_{ti} + \beta_3 \times ALIGNMENTFAm_i \\ & + \beta_4 \times TIME3_{ti} \times ALIGNMENTFAm_i + \beta_6 \times AGE_i \\ & + \beta_9 \times FEMORAL_i + \beta_{11} \times PreopEQ5D5L_i \\ & + \beta_{13} \times PreopOKS \\ & + u_{0i} + u_{1i} \times TIME3_{ti} + \varepsilon_{ti} \end{aligned}$$

Model 4

The hypothesis test of whether the remaining level 2 covariates should be retained is conducted.

$$H_0: \quad \beta_6 = \beta_9 = \beta_{11} = \beta_{13} = 0$$
$$H_A: \beta_i \neq \text{for at least one } i = 6, 9, 11, 13$$

Model 2 vs Model 4

The LRT based ML estimation is carried out. The test statistic is asymptotically a χ^2_4 distributed. The result suggests that the remaining fixed effects associated with patient covariates should be included in the model; therefore, Model 4 is the final model. The summary output of the model is shown in Appendix B.

Step 4: Model diagnostics

Lastly, four diagnostic plots for the final model- namely the Normal Q-Q plot of standardised residuals, the standardised residuals against fitted values, the Normal Q-Q plot of random effects for intercept and slope, and the plot of observed versus fitted values are considered.

Figure 3 and Figure 4 can be assessed to check the normality assumption and homogeneous variance assumption, respectively. There does not appear to be any significant issue observed from these two plots.

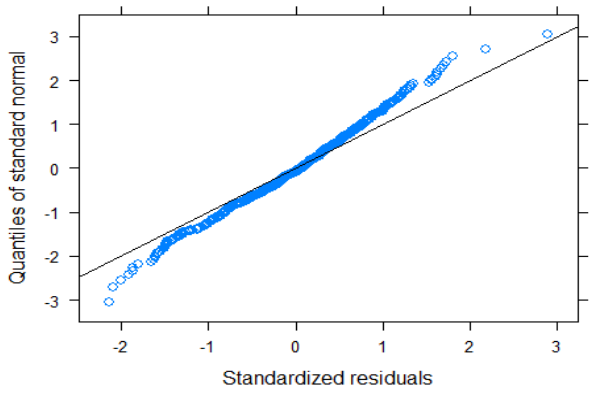

Figure 3. Normal Q-Q plot of standardised residuals.

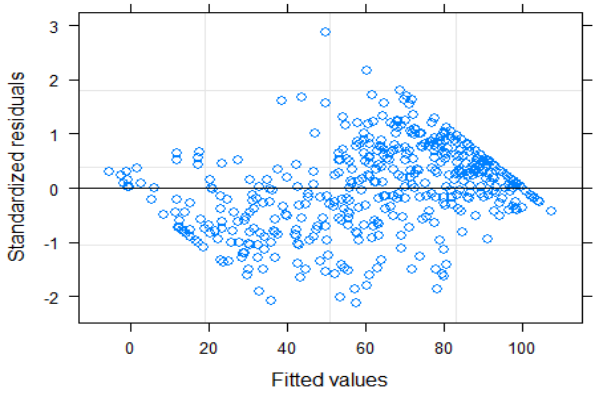

Figure 4. Standardised residuals against fitted values

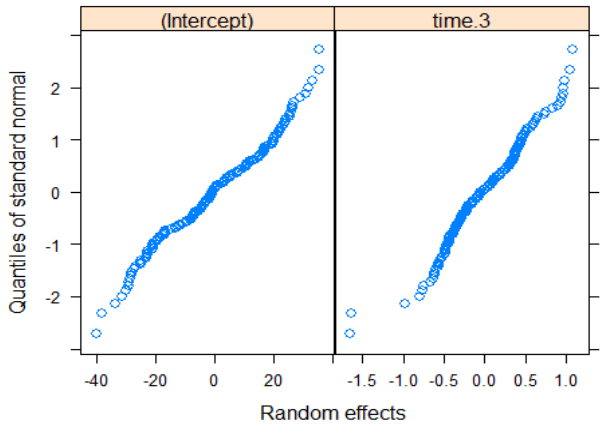

Figure 5. Normal Q-Q plot of random effects for intercept and slope

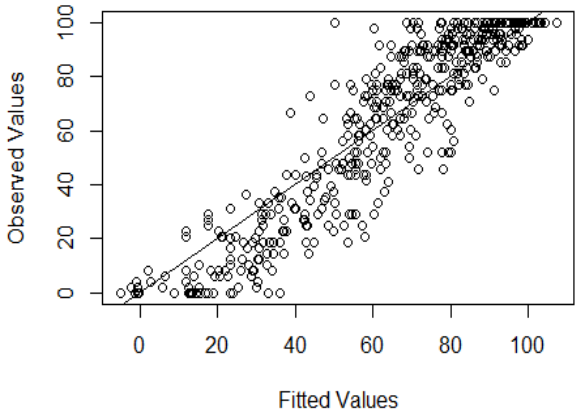

Figure 6. Observed values against fitted values

Figure 5 can be observed to gain insight into the distribution of the random intercept and the slope. The residuals of random slope do not depict an ideal Normal distribution shape, which might raise some concern about the normality of the random slope effects.

Figure 6 shows the observed values against the fitted values. The agreement between observed and fitted values looks quite acceptable.

Appendix B

In this section, annotated R code used to conduct data cleaning (dealing with missing values and reshaping original wide data to longitudinal data), data exploration to obtain numerical and graphical summaries, and data analysis using LMM are provided. The description, hypotheses, and justification are given according to the model specification, hypotheses, and assumption stated in Appendix A.

1. Reshape data to long format

```
library(nlme)
library(nlmeU)
library(lattice)
library(tidyverse)

knee <- read.delim("KneeData.txt", header=TRUE, sep="\t", stringsAsFactors=TRUE)
str(knee)

## 'data.frame':    300 obs. of  20 variables:
##  $ DAP                  : int  1 2 3 4 5 6 7 8 9 10 ...
##  $ Location             : Factor w/ 2 levels "Midland ","Subiaco": 2 2 2 2 2 2 2 2
 2 2 ...
##  $ Alignment            : Factor w/ 2 levels "FAk","FAm": 2 2 2 2 2 2 2 2 2 2 ...
##  $ LOS                  : int  4 3 3 3 3 3 5 6 2 4 ...
##  $ Height               : int  170 186 163 172 190 181 180 154 163 144 ...
##  $ Weight               : num  92 103 101 71 115 ...
##  $ BMI                  : num  31.8 29.8 38 24 31.9 ...
##  $ Age                  : int  59 48 58 55 53 67 76 80 63 56 ...
##  $ Gender               : Factor w/ 2 levels "Female","Male": 2 2 1 1 2 2 2 1 1 1
...
##  $ NativeTibialAlignment: num  NA -8.6 -6 -6.5 -4.5 -0.5 0.1 -7 NA -6 ...
##  $ NativeFemoral        : num  NA 3.5 5.7 3.2 0.9 1.5 4.5 2.5 NA 3.7 ...
##  $ PreopROM             : int  123 134 125 128 115 130 120 110 NA 100 ...
##  $ PreopEQ5D5L          : int  80 70 70 45 50 50 60 65 NA NA ...
##  $ PreopFJS             : num  6.25 22.92 4.17 14.58 39.58 ...
##  $ PreopOKS             : int  32 27 20 22 17 20 16 27 NA 20 ...
##  $ PreopKOOSJR          : num  61.6 50 39.6 50 42.3 ...
##  $ PreopPainVAS         : int  30 69 82 50 83 33 92 71 NA 64 ...
##  $ X3MoFJS              : num  27.1 18.8 22.9 22.9 27.1 ...
##  $ X1YearFJS            : num  77.1 64.6 NA NA 97.9 ...
##  $ X2YearFJS            : num  91.7 64.6 50 60.4 52.1 ...

# Remove all rows with NA
knee <- na.omit(knee)

# reshape to long format
knee.long <- reshape(knee,
                     varying=c("X3MoFJS", "X1YearFJS", "X2YearFJS"),
                     v.names="FJS",
                     direction="long", times=c(3, 12, 24)) # time in month
knee.long$time.f <- as.factor(knee.long$time)
```

2. Data Exploration

2.1. Numerical summaries

```
# overall summary of FJS
summary(knee.long$FJS)

##    Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
##    0.00   33.33   72.92   62.55   91.67  100.00

# overall standard deviation of FJS
sd(knee.long$FJS)

## [1] 32.59826

# summary of FJS by time
knee.long %>%
  group_by(time.f) %>%
  summarise(Min = min(FJS),
            Q1 = quantile(FJS, 0.25),
            Median = quantile(FJS, 0.5),
            Mean = mean(FJS),
            Q3 = quantile(FJS, 0.75),
            Max = max(FJS),
            SD = sd(FJS),
            n = n())

## # A tibble: 3 x 9
##   time.f   Min    Q1 Median  Mean    Q3   Max    SD     n
##   <fct>  <dbl> <dbl>  <dbl> <dbl> <dbl> <dbl> <dbl> <int>
## 1 3          0  20.8   43.8  46.4  73.4   100  31.1   152
## 2 12         0  47.4   76.0  67.3  91.7   100  30.2   152
## 3 24         0  60.4   87.5  73.9  97.9   100  30.2   152
```

- Q1, median, mean, and Q3 increase over time.
- Almost equal standard deviations.

```
# summary of FJS by alignment technique
knee.long %>%
  group_by(Alignment) %>%
  summarise(Min = min(FJS),
            Q1 = quantile(FJS, 0.25),
            Median = quantile(FJS, 0.5),
            Mean = mean(FJS),
            Q3 = quantile(FJS, 0.75),
            Max = max(FJS),
            SD = sd(FJS),
            n = n())

## # A tibble: 2 x 9
##   Alignment   Min    Q1 Median  Mean    Q3   Max    SD     n
##   <fct>     <dbl> <dbl>  <dbl> <dbl> <dbl> <dbl> <dbl> <int>
## 1 FAk           0  37.5   77.1  64.8  93.8   100  32.6   267
## 2 FAm           0  29.2   64.6  59.4  91.7   100  32.5   189
```

- Slightly higher Q1, median, mean, and Q3 in FA(k) group. Equal standard deviation.

```r
# summary of FJS by alignment technique and time
knee.long %>%
  group_by(Alignment, time.f) %>%
  summarise(Min = min(FJS),
            Q1 = quantile(FJS, 0.25),
            Median = quantile(FJS, 0.5),
            Mean = mean(FJS),
            Q3 = quantile(FJS, 0.75),
            Max = max(FJS),
            SD = sd(FJS),
            n = n())
```

```
## # A tibble: 6 x 10
## # Groups:   Alignment [2]
##   Alignment time.f   Min    Q1 Median  Mean    Q3   Max    SD     n
##   <fct>     <fct>  <dbl> <dbl>  <dbl> <dbl> <dbl> <dbl> <dbl> <int>
## 1 FAk       3          0  18.8   43.8  46.4  77.1   100  31.7    89
## 2 FAk       12         0  52.1   79.2  69.9  93.8   100  29.1    89
## 3 FAk       24         0  72.9   89.6  78.1  97.9   100  28.3    89
## 4 FAm       3          0  25     45.8  46.5  69.8   100  30.4    63
## 5 FAm       12         0  42.3   70.8  63.7  91.7   100  31.5    63
## 6 FAm       24         0  44.8   81.2  68.0  93.8   100  31.9    63
```

- FJS tends to increase with time for both alignment groups.
- FJS of patients undergone FA(k) TKA is slightly higher after 1 and 2 years.
- There is no evidence of heterogeneous variance across time or alignment groups.

2.2. Graphical summaries

```r
# Figure 1
knee.g1 <- groupedData(FJS ~ time | DAP, outer = ~Alignment, data = knee.long)
plot(knee.g1, display = "DAP", outer = TRUE, asp = 1, key = FALSE,
     xlab = "Time (month)", ylab = "FJS")
```

```r
# Figure 2
knee.g2 <- groupedData(FJS ~ time | Alignment, order.groups=FALSE, data=knee.long)
plot(knee.g2, display="Alignment", asp=1, key=FALSE, xlab="Time (month)", ylab="FJS")
```

3. Data Analysis

```r
# Create time.3 which is equal to zero at 3 months' time
knee.long$time.3 <- knee.long$time - 3
```

Step 1: Fit the initial "unconditional" (variance components) model

```r
fm1 <- lme(FJS ~ 1, random = ~1 | DAP, data=knee.long, method="REML")
```

Step 2: Add level 1 covariates and their associated fixed effects

```r
fm2 <- lme(FJS ~ time.3 + I(time.3^2) + Alignment + time.3:Alignment,
           random = ~time.3 | DAP,
           data = knee.long)
fm1.ml <- update(fm1, method="ML")
fm2.ml <- update(fm2, method="ML")

anova(fm1.ml, fm2.ml)
```

```
##        Model df      AIC      BIC    logLik   Test  L.Ratio p-value
## fm1.ml     1  3 4393.204 4405.572 -2193.602
## fm2.ml     2  9 4260.708 4297.810 -2121.354 1 vs 2 144.4963  <.0001
```

- Likelihood ratio test (LRT) based on maximum likelihood (ML) estimation to decide whether the fixed effects of time-level covariates are significant.
- The test statistic is chi-squared distributed with 4 degrees of freedom.
- The p-value (<0.0001) is statistically significant at the 5% level, suggesting all the level 1 fixed effects should be added, and model fm2 is preferred.

```
# test of random effect structure
fm2A <- lme(FJS ~ time.3 + I(time.3^2) + Alignment + time.3:Alignment,
            random = ~1 | DAP,
            method = "REML",
            data = knee.long)
anova(fm2A, fm2)

##      Model df      AIC      BIC    logLik   Test  L.Ratio p-value
## fm2A     1  7 4265.052 4293.833 -2125.526
## fm2      2  9 4262.631 4299.635 -2122.316 1 vs 2 6.420881  0.0403
```

- LRT based on REML estimation method to test whether the random effects associated with time should be retained.
- The asymptotic null distribution of the test statistic is a mixture of χ^2_1 and χ^2_2 distributions, with equal weights of 0.5. The test statistic is 6.420881.

```
0.5    * (1 - pchisq(6.420881, 1)) + 0.5 * (1 - pchisq(6.420881, 2))

## [1] 0.02580873
```

- The test statistic is statistically significant (p = 0.0258), so the random time effects in the model should be retained, and fm2 is preferred.

Step 3: Add level 2 covariate

```
fm3 <- lme(FJS ~ time.3 + I(time.3^2) + Alignment + time.3:Alignment +
             BMI + Age + Gender +
             NativeTibialAlignment + NativeFemoral +
             PreopROM + PreopEQ5D5L + PreopFJS + PreopOKS +
             PreopKOOSJR + PreopPainVAS,
           random = ~time.3 | DAP,
           method = "REML",
           data = knee.long)
summary(fm3)

## Linear mixed-effects model fit by REML
##   Data: knee.long
##        AIC      BIC    logLik
##   4233.628 4315.364 -2096.814
##
## Random effects:
##  Formula: ~time.3 | DAP
##  Structure: General positive-definite, Log-Cholesky parametrisation
##             StdDev    Corr
```

```
## (Intercept) 20.873614 (Intr)
## time.3       0.831994 -0.304
## Residual    17.331067
##
## Fixed effects:  FJS ~ time.3 + I(time.3^2) + Alignment + time.3:Alignment + BMI +
     Age + Gender + NativeTibialAlignment + NativeFemoral + PreopROM +      PreopEQ5D
5L + PreopFJS + PreopOKS + PreopKOOSJR + PreopPainVAS
##                            Value Std.Error  DF   t-value p-value
## (Intercept)           -78.08446  32.65245 301 -2.391381  0.0174
## time.3                  3.27689   0.37563 301  8.723645  0.0000
## I(time.3^2)            -0.08432   0.01600 301 -5.271546  0.0000
## AlignmentFAm            0.25730   4.43716 139  0.057987  0.9538
## BMI                     0.46160   0.35155 139  1.313029  0.1913
## Age                     1.05860   0.26200 139  4.040440  0.0001
## GenderMale              4.00886   4.13275 139  0.970022  0.3337
## NativeTibialAlignment   0.47660   0.75940 139  0.627602  0.5313
## NativeFemoral          -1.42648   0.77097 139 -1.850233  0.0664
## PreopROM               -0.01703   0.15401 139 -0.110577  0.9121
## PreopEQ5D5L             0.23304   0.10932 139  2.131717  0.0348
## PreopFJS                0.16095   0.12878 139  1.249845  0.2135
## PreopOKS                0.90300   0.49410 139  1.827552  0.0698
## PreopKOOSJR             0.05240   0.28115 139  0.186387  0.8524
## PreopPainVAS            0.06533   0.12567 139  0.519872  0.6040
## time.3:AlignmentFAm    -0.47847   0.23546 301 -2.032018  0.0430
##  Correlation:
##                       (Intr) time.3 I(.3^2 AlgnFA BMI    Age    GndrMl NtvTbA
## time.3                -0.036
## I(time.3^2)            0.020 -0.915
## AlignmentFAm          -0.029  0.127  0.000
## BMI                   -0.551  0.000  0.000 -0.016
## Age                   -0.472  0.000  0.000  0.090  0.160
## GenderMale            -0.110  0.000  0.000 -0.101  0.272  0.069
## NativeTibialAlignment  0.011  0.000  0.000 -0.093 -0.009  0.061  0.172
## NativeFemoral         -0.153  0.000  0.000  0.045  0.043 -0.040  0.202  0.048
## PreopROM              -0.562  0.000  0.000 -0.045  0.190  0.027  0.006  0.048
## PreopEQ5D5L           -0.011  0.000  0.000 -0.141 -0.041 -0.213 -0.041  0.056
## PreopFJS               0.072  0.000  0.000  0.053  0.055 -0.029 -0.013 -0.010
## PreopOKS              -0.063  0.000  0.000  0.048 -0.044  0.086 -0.165  0.082
## PreopKOOSJR           -0.252  0.000  0.000 -0.012  0.049 -0.168 -0.001 -0.091
## PreopPainVAS          -0.387  0.000  0.000 -0.121 -0.014 -0.119 -0.050  0.079
## time.3:AlignmentFAm    0.027 -0.260  0.000 -0.488  0.000  0.000  0.000  0.000
##                       NtvFmr PrpROM PEQ5D5 PrpFJS PrpOKS PKOOSJ PrPVAS
## time.3
## I(time.3^2)
## AlignmentFAm
## BMI
## Age
## GenderMale
## NativeTibialAlignment
## NativeFemoral
## PreopROM               0.044
## PreopEQ5D5L            0.061 -0.071
## PreopFJS               0.112  0.130 -0.034
## PreopOKS              -0.109 -0.140 -0.135 -0.371
## PreopKOOSJR            0.092  0.020 -0.045 -0.064 -0.543
```

```
## PreopPainVAS           0.102 -0.038  0.076 -0.208  0.276  0.287
## time.3:AlignmentFAm    0.000  0.000  0.000  0.000  0.000  0.000  0.000
##
## Standardized Within-Group Residuals:
##         Min          Q1         Med          Q3         Max
## -2.14822550 -0.50679945  0.06648941  0.51473516  2.84193806
##
## Number of Observations: 456
## Number of Groups: 152
```

- Test whether each of the patient-level covariates should be retained.
- We test each of these hypotheses using t-tests based on the fit of fm3 and decide to drop the following fixed effects in respective order: PreopROM, PreopKOOSJR, PreopPainVAS, NativeTibialAlignment, Gender, BMI, and PreopFJS.

```
# reduced model
fm4 <- lme(FJS ~ time.3 + I(time.3^2) + Alignment + time.3:Alignment +
             Age + NativeFemoral + PreopEQ5D5L + PreopOKS,
           random = ~time.3 | DAP,
           method = "REML",
           data = knee.long)

fm3.ml <- update(fm3, method="ML")
fm4.ml <- update(fm4, method="ML")
anova(fm4.ml, fm3.ml)

##        Model df      AIC      BIC    logLik   Test  L.Ratio p-value
## fm4.ml     1 13 4216.609 4270.201 -2095.304
## fm3.ml     2 20 4225.667 4308.116 -2092.833 1 vs 2 4.942318   0.667
```

- LRT based on ML estimation method to test the significant of covariates PreopROM, PreopKOOSJR, PreopPainVAS, NativeTibialAlignment, Gender, BMI, and PreopFJS.
- The asymptotic null distribution of the test statistic is χ^2_7 with value of 4.942318.
- p-value = 0.667 is not statistically significant at 5% level, suggesting the covariates are significant and fm4 is preferred.

```
anova(fm2.ml, fm4.ml)

##        Model df      AIC      BIC    logLik   Test  L.Ratio p-value
## fm2.ml     1  9 4260.708 4297.810 -2121.354
## fm4.ml     2 13 4216.609 4270.201 -2095.304 1 vs 2 52.09904  <.0001
```

- LRT based on ML estimation method to test the remaining level 2 covariates in fm4 against fm2.
- The asymptotic null distribution of the test statistic is χ^2_4 with the value of 52.09904.
- p-value $< .0001$ is statistically significant, suggesting the level 2 fixed effects remaining in fm4 are significant.
- fm4 is preferred and is our final model, and its summary output is shown as follows:

```
summary(fm4)

## Linear mixed-effects model fit by REML
##   Data: knee.long
```

```
##        AIC      BIC    logLik
##   4222.405 4275.738 -2098.203
##
## Random effects:
##  Formula: ~time.3 | DAP
##  Structure: General positive-definite, Log-Cholesky parametrisation
##             StdDev     Corr
## (Intercept) 21.1372762 (Intr)
## time.3       0.8319956 -0.358
## Residual    17.3310568
##
## Fixed effects:  FJS ~ time.3 + I(time.3^2) + Alignment + time.3:Alignment + Age +
     NativeFemoral + PreopEQ5D5L + PreopOKS
##                          Value Std.Error  DF   t-value p-value
## (Intercept)         -56.96564 17.452565 301 -3.264027  0.0012
## time.3                3.27689  0.375633 301  8.723649  0.0000
## I(time.3^2)          -0.08432  0.015995 301 -5.271549  0.0000
## AlignmentFAm          0.81071  4.392937 146  0.184548  0.8538
## Age                   1.03287  0.250726 146  4.119520  0.0001
## NativeFemoral        -1.79865  0.733701 146 -2.451475  0.0154
## PreopEQ5D5L           0.22897  0.107359 146  2.132709  0.0346
## PreopOKS              1.09274  0.296045 146  3.691108  0.0003
## time.3:AlignmentFAm  -0.47847  0.235465 301 -2.032018  0.0430
##  Correlation:
##                     (Intr) time.3 I(.3^2 AlgnFA Age    NtvFmr PEQ5D5 PrpOKS
## time.3              -0.068
## I(time.3^2)          0.037 -0.915
## AlignmentFAm        -0.199  0.135  0.000
## Age                 -0.860  0.000  0.000  0.092
## NativeFemoral       -0.141  0.000  0.000  0.080 -0.022
## PreopEQ5D5L         -0.079  0.000  0.000 -0.135 -0.220  0.073
## PreopOKS            -0.257  0.000  0.000  0.143  0.016 -0.026 -0.363
## time.3:AlignmentFAm  0.054 -0.260  0.000 -0.520  0.000  0.000  0.000  0.000
##
## Standardized Within-Group Residuals:
##         Min          Q1         Med          Q3         Max
## -2.13057208 -0.51667023  0.06295216  0.52767270  2.88430493
##
## Number of Observations: 456
## Number of Groups: 152
```

Step 4: Model diagnostics

```
# Normal Q-Q plot of standardised residuals
qqnorm(fm4, ~resid(., type = "p"), abline = c(0, 1))

# Stardardised residuals against fitted values
plot(fm4, resid(., type = "p") ~ fitted(.), abline=0)

# Normal Q-Q plot of random effects
qqnorm(fm4, ~ranef(.))

# Observed values against fitted values
plot(fitted(fm4), knee.long$FJS, xlab="Fitted Values", ylab="Observed Values")
abline(0,1)
```