Patient-Specific Decrease in Circulating Levels of TGFα is Associated with Lower Pain after Total Knee Arthroplasty

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Introduction

10-30% of patients undergoing Total Knee Arthroplasty (TKA) for osteoarthritis (OA) have poor or no improvement in pain after surgery [1-2] which can lead to reduced work productivity, poorer general health, sleep problems, long-term opioid use, and social isolation for elderly patients [3-4]. Attempts to identify predictors of poor surgical outcome have focused on patient reports of physical limitations and pain prior to surgery, single health traits (e.g. BMI) [1-5], or psychological factors. However, several structural characteristics of OA are thought to contribute to pain prior to surgery. These include increased inflammatory cytokines. In this study we aim to investigate whether:

1. Patient's pain profile (Peri-op, improvement, and Post-op) differ between racial groups.

2. Specific serum cytokine profiles align with differences observed in pain between racial groups.

3. Changes in specific serum cytokines can predict pain after TKA.

Methods

Table 3. Repository composition

Demographic*	n (% population)
White Female	73 (39)
Black Female	49 (26)
White Male	29 (16)
Black Male	18 (10)
Hispanic Female	5 (3)
Hispanic Male	2 (1)
Asian Female	1 (0.5)
Asian Male	0 (0)
Other	8 (4)
Total	185

Blood serum and plasma: Peri-op & 3 month Post-op
Synovium & Synovial Fluid
Femoral condyles (cartilage & subchondral bone)
Tibial Plateau (cartilage & subchondral bone)
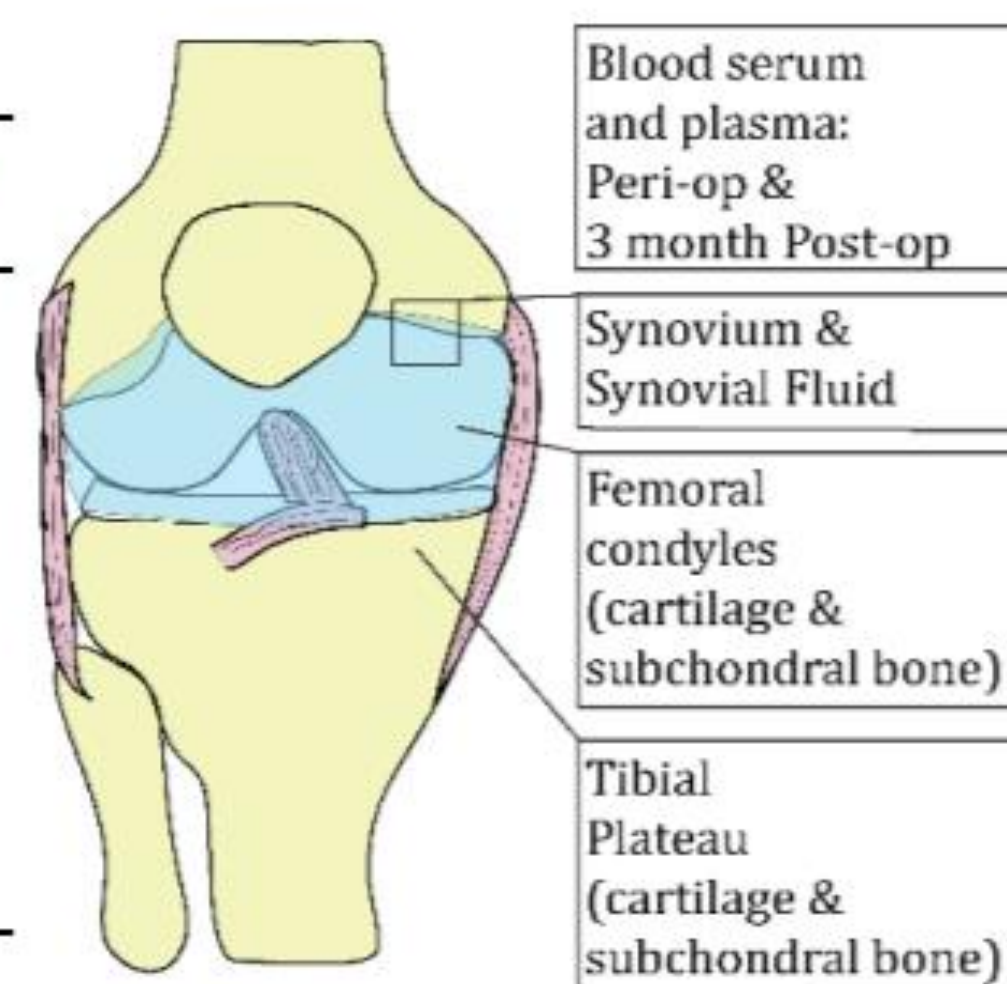
Figure 1. Demographics of the current 185 patients and the tissues housed in the biobank.

KOOS: Knee Osteoarthritis Outcome Scores
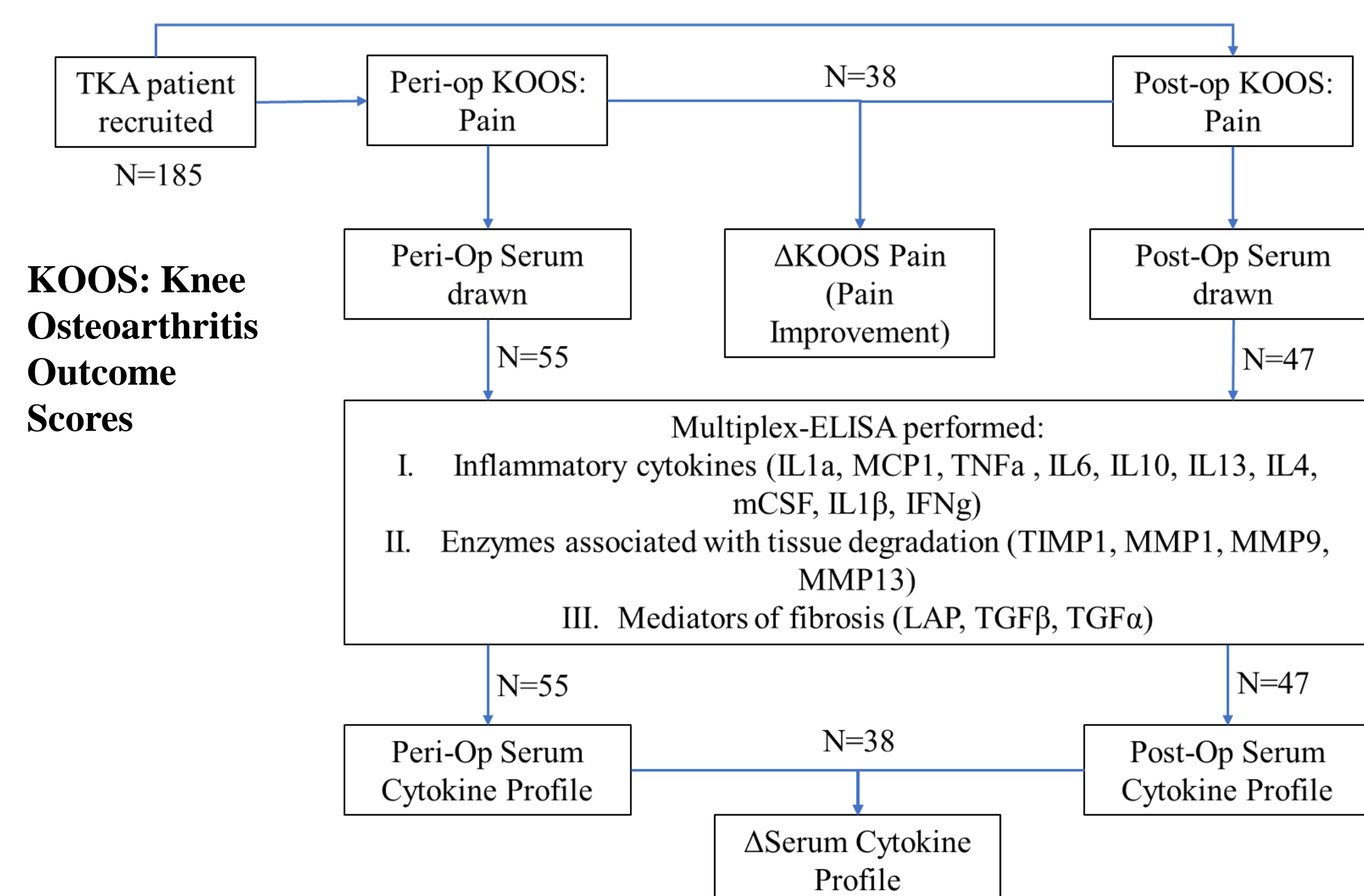
Wilcoxon Mann-Whitney U test, Pearson Correlation (for data with parametric distribution), and Spearman correlation (for data with non-parametric distribution) were used to perform statistical analysis, where P<0.05 was deemed significant.

Variation in KOOS Pain by Race

Figure 2A: Peri-OP KOOS Pain by Race
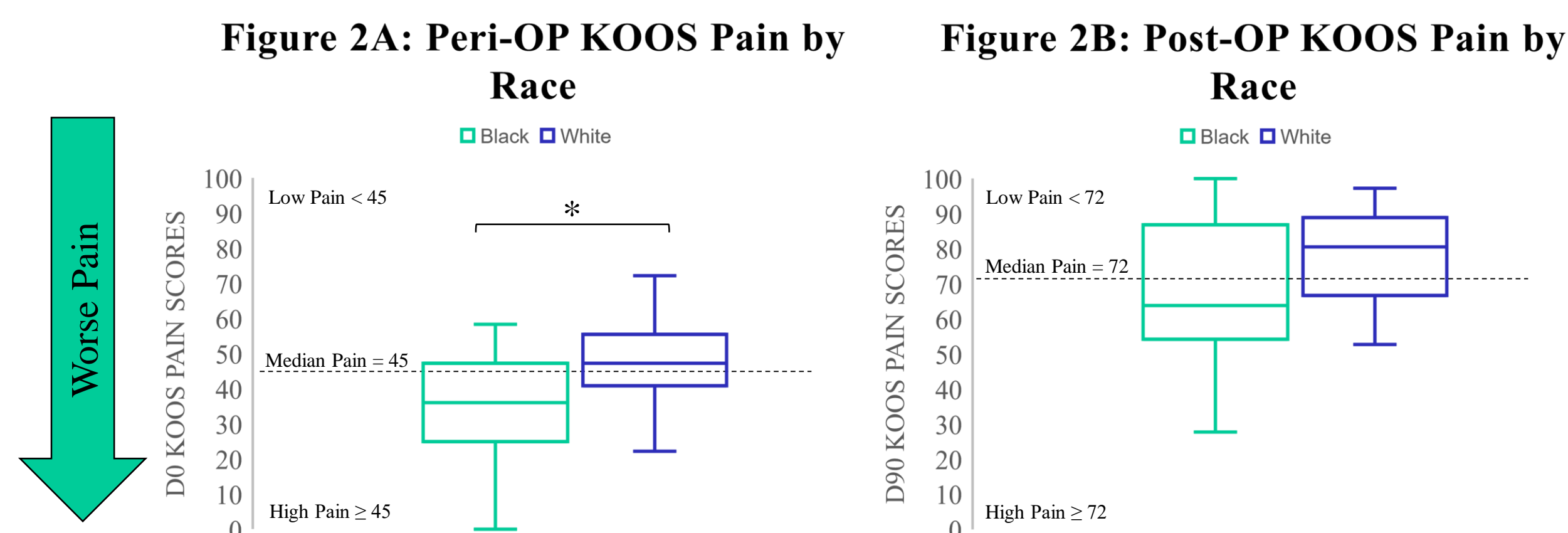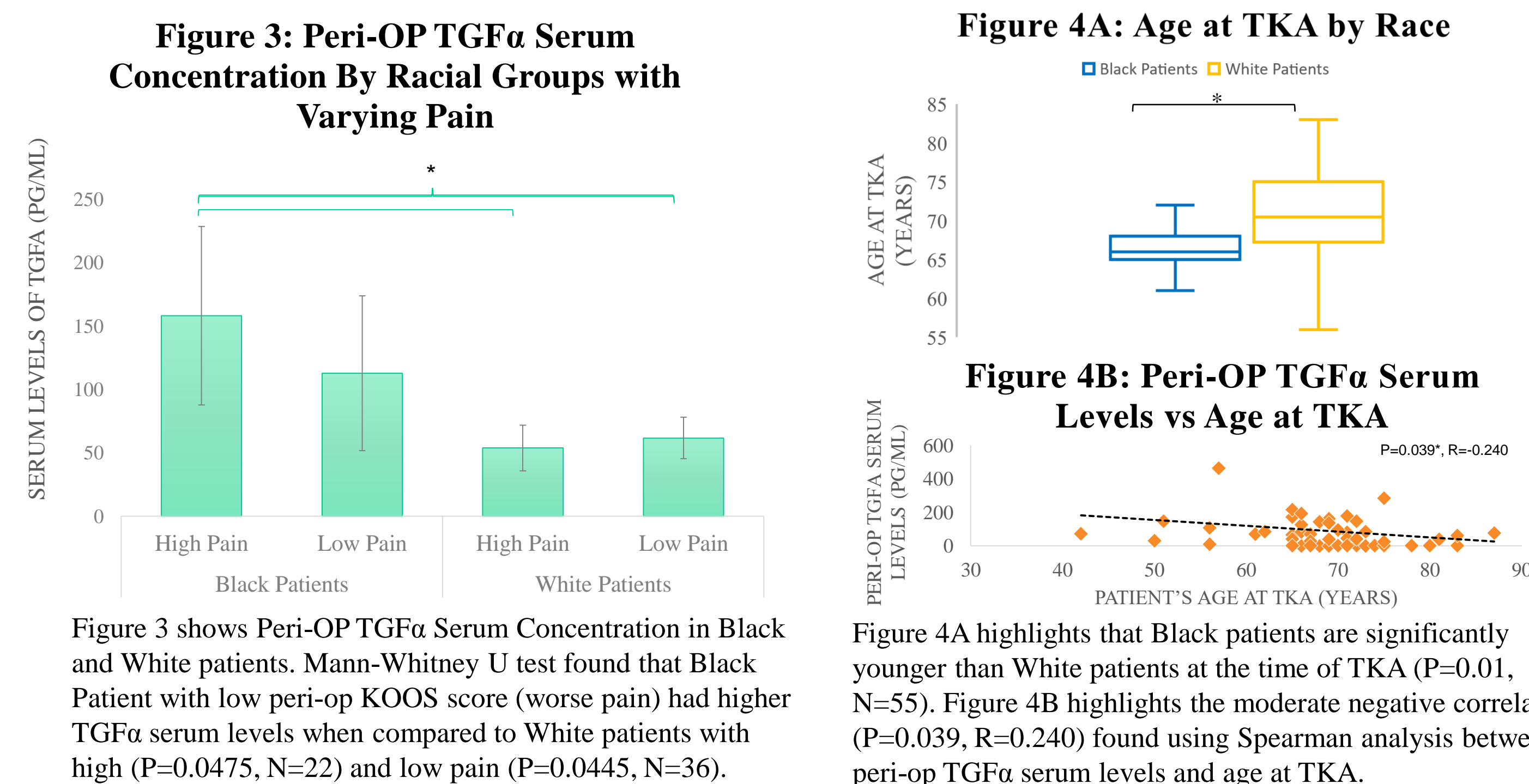
Figure 2B: Post-OP KOOS Pain by Race

Figure 2: Peri-OP KOOS pain (A) and Post-OP KOOS pain (B) distribution by race is depicted. Mann-Whitney U Test detected a significant difference between Black and White patients Peri-OP KOOS Pain (P=0.027, N=55), however, no significant difference was detected for Post-OP KOOS Pain (P=0.278, N=47).

Peri-OP TGFα serum levels Analysis

Figure 3: Peri-OP TGFα Serum Concentration By Racial Groups with Varying Pain

Figure 4A: Age at TKA by Race

Figure 4B: Peri-OP TGFα Serum Levels vs Age at TKA

Figure 3 shows Peri-OP TGFα Serum Concentration in Black and White patients. Mann-Whitney U test found that Black Patient with low peri-op KOOS score (worse pain) had higher TGFα serum levels when compared to White patients with high (P=0.0475, N=22) and low pain (P=0.0445, N=36).

Figure 4A highlights that Black patients are significantly younger than White patients at the time of TKA (P=0.01, N=55). Figure 4B highlights the moderate negative correlation (P=0.039, R=0.240) found using Spearman analysis between peri-op TGFα serum levels and age at TKA.

Pre-OP to Post-OP variation in TGFα

Figure 5A: ΔTGFα by Racial Groups with Varying Improvement
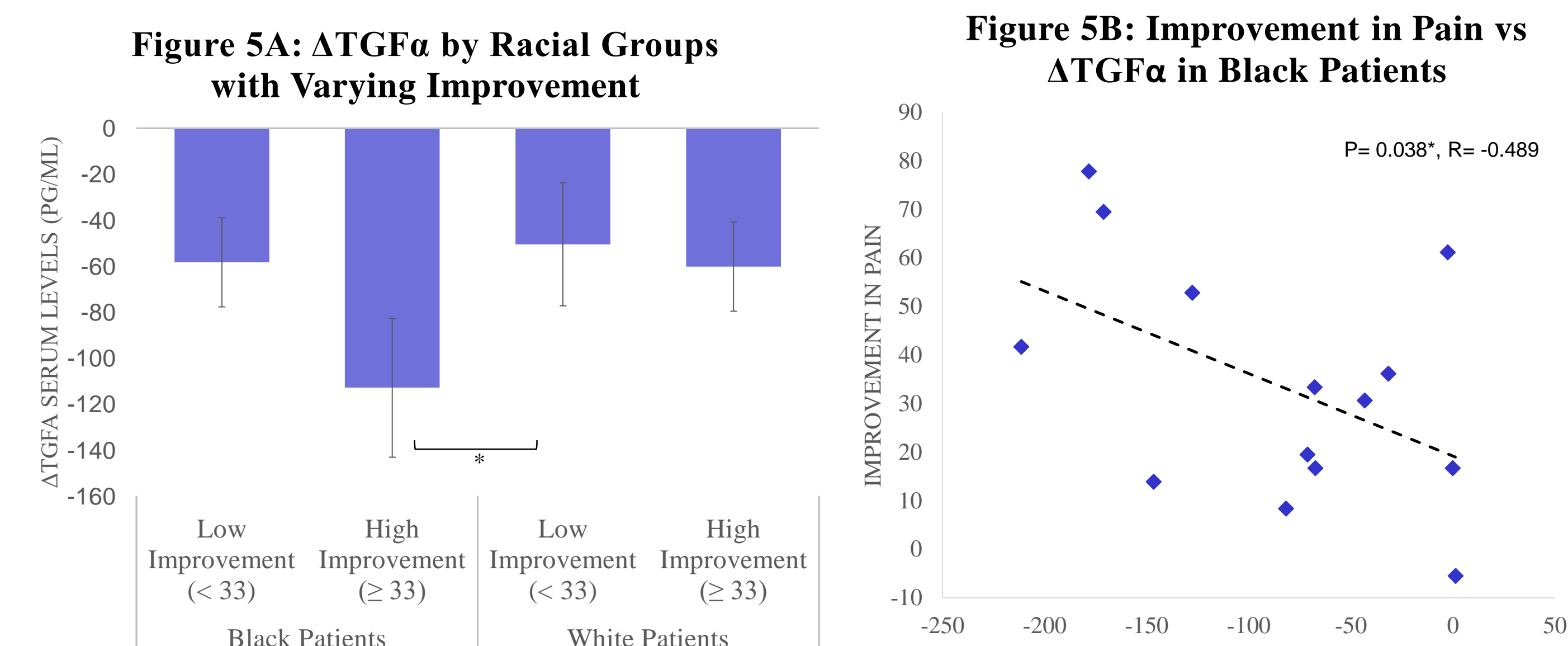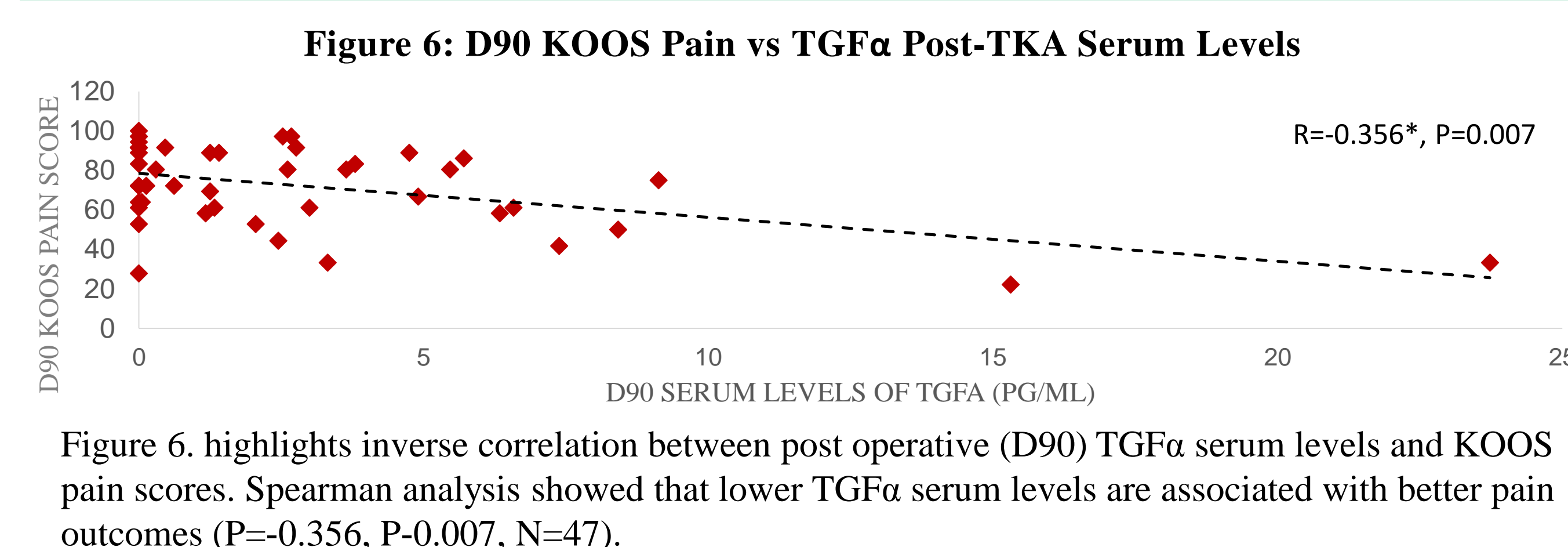
Figure 5B: Improvement in Pain vs ΔTGFα in Black Patients

Figure 5A shows Pre-OP to Post-OP change in TGFα (ΔTGFα) serum levels in Black and White Patients. Statistical Analysis was conducted using a Mann-Whitney U Test. (*) denotes the significant difference between groups highlighted by the bar. Figure 5B highlights the inverse relationship between pain and TGFα found using a Pearson's chi squared test.

Post-OP TGFα serum levels Analysis

Figure 6: D90 KOOS Pain vs TGFα Post-TKA Serum Levels

Figure 6. highlights inverse correlation between post operative (D90) TGFα serum levels and KOOS pain scores. Spearman analysis showed that lower TGFα serum levels are associated with better pain outcomes (P=-0.356, P-0.007, N=47).

Conclusions & Future Direction

Are there Biomarkers to predict high-risk patients?
Are there Biomarkers that tie symptomatic OA to structural OA?
Cytokines in OA
Descriptive: cytokines in TKA
What accounts for the changes in pain observed?
What drives pain after surgery?

➤ Black patients in the United States have a higher prevalence of symptomatic osteoarthritis -- high pain and stiffness [6-8]. Our study found when controlling for hospital, surgeon, and surgical team, Black osteoarthritis patients show equal, if not greater, improvement in pain three months after surgery when compared to White patients.

➤ The primary correlating factor, TGFα, has been previously identified as a potent activator of epidermal growth factor receptor (EGFR), associated with cartilage degeneration and increase in nocifensive behavior in mouse models [9-10]. Thus, the correlation of TGFα with pain warrant further investigation in this biomarker's role in mediation of pain in OA.

➤ The trend observed fits specifically with patients who identify as Black or African American, highlighting the need for patient-specific models that incorporate age, gender, race, and other social determinants of health.

Peri-OP KOOS Pain Score Model for Black TKA Patients

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