Temporal Trends in Synovial Biomarker Levels Following Acute ACL Injury

Emily A Berzolla, Vishal Sundaram, Nicole Rynecki Baker, Daniel J Kaplan, Thorsten Kirsch, Eric Jason Strauss

INTRODUCTION:

Anterior cruciate ligament (ACL) injury initiates a cascade of inflammatory and reparative responses within the joint that may influence cartilage health, healing potential, and long-term outcomes such as osteoarthritis. While synovial fluid (SF) biomarker levels have been associated with post-injury progression, few studies have characterized how these biomarkers evolve over time. Understanding the temporal dynamics of intra-articular inflammation and repair is critical to identifying therapeutic windows and stratifying patients for targeted biologic interventions.

METHODS:

A retrospective analysis of a prospectively collected cohort was performed, including patients with native ACL tears who underwent preoperative SF aspiration. Nine biomarkers involved in immune regulation, tissue remodeling, and vascular signaling were quantified. Baseline demographics, injury characteristics, and time from injury to aspiration were recorded. Multivariable linear regression was used to assess associations between time from injury and log-transformed biomarker concentrations, adjusting for age, sex, and BMI. ANOVA was used to compare biomarker levels across five post-injury time intervals: <1 week, 1–2 weeks, 2 weeks–1 month, 1–2 months, and 2–3 months.

RESULTS:

A total of 306 patients were included (mean age 32.1±10.1 years, mean BMI 25.5±4.2 kg/m², 54% male). The average time from injury to SF aspiration was 1.50 ± 1.29 months. Multivariable linear regression analyses demonstrated a significant inverse association (p<.001) between time from injury and the concentrations of IL-6 (β = -.572), MCP-1 (β = -.316), MIP-1β (β = -.322), IL-1Ra (β = -.443), and VEGF (β = - .421), after adjusting for baseline demographics and injury characteristics. Conversely, bFGF levels significantly increased with time from injury (β = .349, p<.001). Temporal biomarker trends revealed that IL-6, MIP-1β, VEGF, and IL-1Ra peaked within the first week post-injury, whereas MCP-1 reached its highest level between weeks 1 and 2 before declining. BFGF concentrations were lowest in the first week and rose progressively through the post injury period.

DISCUSSION AND CONCLUSION:

Biomarker expression in the synovial fluid changes significantly over time following ACL injury, with early inflammatory peaks followed by later increases in reparative markers. These findings highlight the need to consider timing when interpreting biomarker data and support the importance of characterizing temporal trends when designing studies or interventions. Rather than assuming fixed roles for individual biomarkers, future work should focus on understanding their time-dependent behavior and interactions, which may provide insight into optimal windows for therapeutic intervention and improve biologic stratification of patients.

Table 1. Multivariable Linear Regression of Biomarker Concentration by Time Since ACL Injury, Adjusted for Age, Sex, and BMI

	Time After Injury		Age		Sex		BMI	
	β	P value	β	P value	β	P value	β	P value
IL-6	**-.572**	**<.001**	.055	.272	.104	.048	.113	.035
MCP-1	**-.316**	**<.001**	.102	.061	.051	.375	-.100	.086
MIP-1B	**-.322**	**<.001**	**.151**	**.015**	.084	.203	.057	.395
RANTES	.005	.934	-.036	.533	-.056	.358	.112	.069
MMP-3	-.077	.222	-.022	.729	.056	.404	.114	.089
IL-1Ra	**-.443**	**<.001**	-.043	.478	.038	.555	.102	.113
TIMP-1	-.089	.159	-.119	.057	.067	.312	-.102	.127
VEGF	**-.421**	**<.001**	.086	.103	.061	**.271**	**.045**	.429
bFGF	**.349**	**<.001**	-.055	.347	-.083	.183	-.083	.185

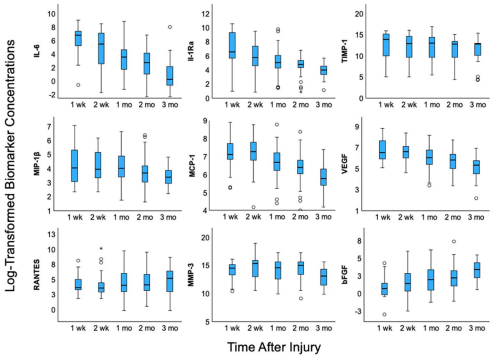

Figure 1. Log-transformed synovial fluid biomarker concentrations over time following Anterior Cruciate Ligament injury. Box and whisker plots display concentrations for each biomarker across five post-injury time bins: <1 week, 1–2 weeks, 2 weeks–1 month, 1–2 months, and 2–3 months. The horizontal line within each box represents the sample median; box edges indicate the first and third quartiles. Whiskers extend to the most extreme values not considered outliers, and circles represent statistical outliers. Each subplot shows log-normalized concentrations of a specific biomarker over time.