Real-World Data Analysis of Adverse Events Attributable to Large Joint Arthroplasty Implants

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Abstract

Background: With various adverse events reportedly associated with metal implants, their clinical manifestations and biological underpinnings remain unclear. We employed a comprehensive analysis using real-world data (RWD) from electronic health records (EHR) to explore arthroplasty implant-related adverse outcomes with respect to device/patient characteristics.

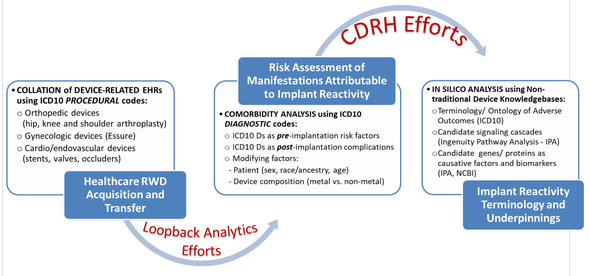
Purpose: This research aims to: 1) outline the scope, frequency, and underlying nature of clinically relevant adverse outcomes potentially attributable to arthroplasty implants; 2) explore pre-implantation risk factors and post-implantation complications likely associated with arthroplasty implant reactivity; and 3) develop device-oriented RWD analysis/ visualization algorithms.

Methods: This research focused on large joint arthroplasty, utilized an EHR dataset of ~27,000 patients who had an arthroplasty encounter (2016 - 2019) that was collated by Loopback Analytics LLC for FDA. Cohorts with hip, knee, or shoulder arthroplasty were established using standardized ICD-10 codes. Comorbidity analysis with respect to the implantation time was performed in subjects with Revision and known arthroplasty-related Adverse Outcomes (AO+Rev) versus those without these outcomes (Control). Inter-cohort differences were assessed using chi-square test with odds ratios, relative risk ratios, and multivariate regression. Time-to-event analysis using Kaplan-Meier approach, log-rank test, and Cox proportional hazards regression were applied to evaluate the inter-cohort differences in pre-selected conditions representing potential implant-related immune/inflammatory responses. LASSO regression modelling was conducted as an unsupervised assessment of diagnoses that may predict AO+Rev. The co-occurrence and correlations between diagnoses pairs were assessed and visualized by network analysis; comorbidity score was introduced to quantify the correlations pertaining to diagnoses that may represent arthroplasty implant reactivity. Hierarchical clustering and correlation heatmaps were applied to visualize the intergroup differences in AO+Rev vs. Control comorbidity patterns and relationships between diagnoses of interest.

Results: Per our preliminary analysis, the AO+Rev vs. Controls cohort showed distinct likelihoods of different diagnoses that potentially represent arthroplasty-related underlying patient conditions (pre-implantation) or underrecognized complications (post-implantation), including some allergic and immune/inflammatory conditions. Different RWD analysis/visualization approaches with the respective results will be illustrated.

Conclusion: The developed RWD algorithm can be applied to provide insights into the risk factors and complications pertaining to various arthroplasty implants, thereby leading to a more predictive evaluation of implant safety in the real-world setting.

Overall Research Flow



RWD Acquisition and Linking (Orthopedic Devices)

Current: Use of EHRs pertaining to large joint arthroplasty

- ~27,000 subjects with hip, knee, or shoulder implants
- ICD10 codes were used to characterize target arthroplasties as well as other comorbidities and procedures
- Study cohorts were created per presence or absence of arthroplasty-related Revision and Adverse Outcomes such as periprosthetic osteolysis (AO+Rev and Controls, respectively) and stratified by arthroplasty type and patient demographics

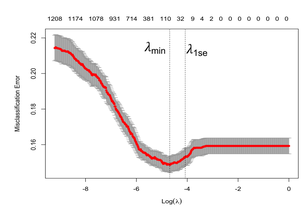
Next Step: Device Matching Engine to connect EHRs to medical device databases

- Standardize manufacturer names
- Apply standard formatting to part numbers
- Match EHR data to Global Unique Device Identification Database (GUDID) with standard manufacturer names and part numbers as well as to PMA/510(k) with probabilistic matching rules using device names

Results: An Algorithm for Inter-Cohort Comorbidity Analysis in AO+Revision vs Controls

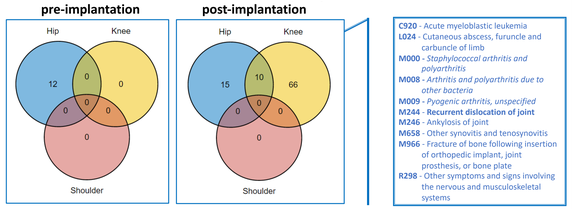
1. Logistic LASSO Regression Analysis with Non-Preselected Assessment of Diagnoses Aimed to Identify Potential Variables Predicting AO+Revision

After incorporating diagnoses from the main ICD10 diagnostic categories as candidate variables, we applied a penalized logistic regression using Least Absolute Shrinkage and Selection Operator (LASSO) to help reduce dimensions of ICD10 feature selection which was aimed at distinguishing between the AO+Rev and Control groups.



The Figure on the left is an example of ICD10 variable selection (regardless of pre- or post-implantation) using LASSO logistic regression in subjects with knee arthroplasty. Dotted vertical lines indicate the optimal values based on the minimum criteria (λ_{min}) and one standard error of the minimum criteria (λ_{1se}). Use of λ_{min}, as the value of λ (lambda) that gives minimum cross-validation mean squared error, resulted in 72 ICD10 codes as potential predictor variables out of a total of 1,241 ICD10 variables initially included in the full LASSO model (note: the latter number of distinguished codes was based on first four characters of all ICD10 codes which were drawn from the main (14 out of 22) ICD10 chapter codes observed in knee arthroplasty subjects.

LASSO-selected ICD10 features in different arthroplasty cohorts:



C920 - Acute myeloblastic leukemia
L024 - Cutaneous abscess, furuncle and carbuncle of limb
M000 - *Staphylococcal arthritis and polyarthritis*
M008 - *Arthritis and polyarthritis due to other bacteria*
M009 - *Pyogenic arthritis, unspecified*
M244 - **Recurrent dislocation of joint**
M246 - Ankylosis of joint
M658 - Other synovitis and tenosynovitis
M966 - Fracture of bone following insertion of orthopedic implant, joint prosthesis, or bone plate
R298 - Other symptoms and signs involving the nervous and musculoskeletal systems

The Venn diagrams above show the numbers and overlap of LASSO-selected ICD10 features in different arthroplasty cohorts; the Table details the variables (n=10) shared by hip and knee cohorts as post-implantation ICD10 features that may distinguish between AO+Rev and Control subjects in these two cohorts. Per LASSO coefficients and importance rankings of these features, the post-implantation appearance of M244: Recurrent Dislocation of Joint (in bold), despite its rarity, was the top LASSO discriminator between AO+Rev and Control subjects in Hip and Knee Arthroplasty cohorts. The AO+Rev subjects in these two cohorts also had much higher odds of post-implantation diagnoses of bacterial/ pyogenic arthritis (italicized) and other joint/bone conditions such as periprosthetic fracture (M966). As shown in the Venn diagram on the left, a total of 12 *pre-implantation* ICD10 codes were identified as potential risk factors for *post-implantation* AO/ Revision in Hip arthroplasty (note: no similar predictors were found for Knee or Shoulder cohorts). *Most notably, none of the LASSO-based distinguishers between AO+Rev and Control groups indicated (auto)immune/ inflammatory conditions as either pre-implantation predisposing factors or post-implantation manifestations of implant reactivity, thereby suggesting their rarity in the overall population with large joint arthroplasty.*

2. Logistic Multivariate Regression for Assessing Inter-Cohort Differences of Pre-Selected Diagnoses

Risk for *pre-selected* ICD-defined immune/ inflammatory conditions (n=71) with regards to AO+Rev was assessed by multivariate logistic regression analysis. As shown in the example below, *the overall higher risk in association with AO+Rev was identified for M05-M14: Inflammatory Polyarthropathies, including Rheumatoid Arthritis, in Knee arthroplasty subjects (n=16,749), especially in Blacks and Females.*

M05 - M14 Inflammatory Polyarthropathies

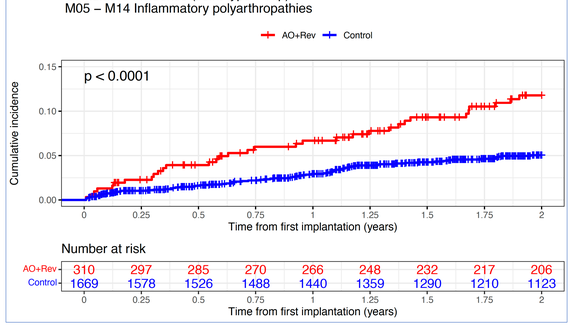
	Adj OR	95% CI	p-value
Race:			
Black	*1.53*	*(1.41, 1.65)*	*< 0.001*
Other	0.69	(0.56, 0.85)	< 0.001
White	Ref		
Sex:			
Female	1.0032	(0.94, 1.07)	0.924
Male	Ref		
Outcome:			
AO+Rev	**1.67**	**(1.53, 1.82)**	**< 0.001**
Control	Ref		

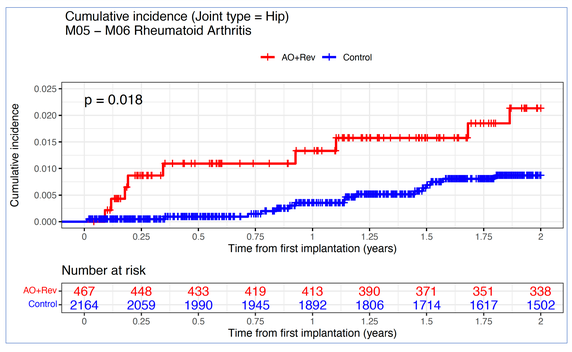
M05 - M06 Rheumatoid Arthritis

	Adj OR	95% CI	p-value
Race:			
Black	*1.22*	*(1.06, 1.39)*	*0.004*
Other	1.21	(0.87, 1.7)	0.258
White	Ref		
Sex:			
Female	*1.84*	*(1.62, 2.1)*	*< 0.001*
Male	Ref		
Outcome:			
AO+Rev	**1.5**	**(1.3, 1.73)**	**< 0.001**
Control	Ref		

3. Time-to-Event Analysis for Assessment of Inter-Cohort Differences in Inflammatory/ Immune Conditions with Respect to the Implantation Time

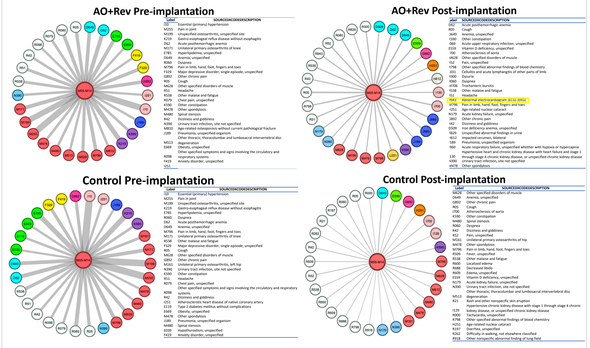
Following our hypothesis that comorbidities with higher AO+Rev vs. Control frequencies may represent potential risk factors or complications related to implant reactivity, we further compared the occurrences of pre-selected immune/inflammatory conditions in the two study groups using Kaplan-Meier estimator, log-rank test, and Cox Proportional Hazards (PH) model. First, comorbidities in each subject were characterized per their first appearance as: 1) *pre*-implantation ICD10 diagnoses dated *prior or on the same day* as first joint replacement procedure, and 2) *post*-implantation ICD10 diagnoses dated *after* first joint replacement procedure. In both AO+Rev and Control groups, most ICD10 code frequencies peaked around the implantation time, likely reflecting a more thorough patient evaluation in this period (not shown). Next, the Kaplan-Meier based time-to-event analysis with log-rank test was used to assess the differences in *post-implantation* cumulative incidences at 2 years (with the first appearance of selected diagnoses as failure variables and with the end of follow-up or death as censored observations). As shown below, *cumulative Incidences of M05-M14: Inflammatory Polyarthropathies, including Rheumatoid Arthritis, were higher in AO+Rev vs. Controls, indicating that these diagnoses may represent post-implantation sequelae of clinically consequential implant reactivity in hip arthroplasty subjects.* Per further Cox PH regression analysis (not shown) aimed to assess potential relationships between the appearance time of immune/ inflammatory conditions as well as AO+Rev and demographic variables such as sex and race, *the post-implantation appearance of M05-M14: Inflammatory Polyarthropathies was associated with the AO+Rev and Female sex.*





4. Network Analysis for Visualization of the Co-occurrence and Correlations between Diagnoses Including Immune/ Inflammatory Conditions

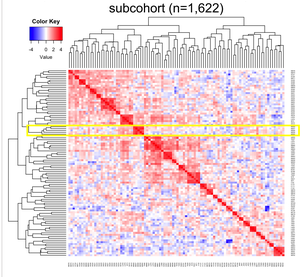
To further explore the immune/ inflammatory conditions presumably associated with implant reactivity, we applied network analysis which was based on disease comorbidity scores and was aimed, in particular, to assess the comorbidities that co-occur with M05-M014. As shown below, *there were differences in comorbidities most closely associated with M05-M14 (central nodes) in the subcohorts stratified by AO+Rev/ Controls and Pre/ Post-implantation. For example, R943: Abnormal Electrocardiogram (in yellow) was found among the most M05-M14 co-associated diagnoses in AO+Rev post-implantation but not in other subcohorts, suggesting these subjects may have more detectable cardiac manifestations.*



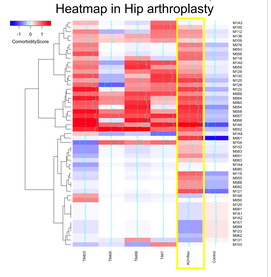
5. Heatmaps for Quantification and Visualization of Diagnosis Correlations Potentially Relevant to Implant Reactivity in AO+Revision versus Controls

Next, we utilized the comorbidity score based hierarchical clustering heatmaps to quantify disease associations in different study cohorts and visualize potential differences in comorbidity patterns. As shown in the examples below, *in addition to the M05-M06: Rheumatoid Arthritis cluster (highlighted on the left), Hip AO+Rev subcohort showed the most distinct M05-M014 comorbidity pattern (highlighted on the right) compared to Controls as well as other subcohorts with individual arthroplasty-related adverse outcomes (T84*).*

Top 100 ICD10 comorbidity pairs in Hip AO+Rev subcohort (n=1,622)



M05-M014 Associated Comorbidity Score Heatmap in Hip arthroplasty



Conclusions

Our analytic algorithm illustrates different methodological approaches to large-scale healthcare RWD analysis/ visualization which can:

- ✓ **provide insights into implant-related *pre*-implantation risk factors and *post*-implantation sequelae with respect to both implant characteristics and patient demographics**
- ✓ **be reapplied to RWD projects aimed to promote predictive evaluation and informed use of different implants in patient subpopulations**

Note: This poster presents the examples of some preliminary analysis results of our on-going research. Currently, we continue developing and testing statistical methods for the cohort creation and outcome analysis using large-scale healthcare RWD. Our next research steps include structured data analyses using codes other than ICD10 as well as verification of the results incorporating unstructured data such as lab tests and physician notes.