Real-World Data Analysis of Adverse Manifestations Attributable to Arthroplasty Implants

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Abstract

Background: Various adverse events are reported with metal implants. However, their clinical manifestations and underlying mechanisms remain unclear. We initiated a research effort on implant-associated manifestations employing real-world data (RWD) and electronic health records (EHR). Objectives: Outline the scope and risks of clinically consequential adverse device reactions (ADRs) and associated pre- and post-implantation clinical conditions.

Methods: A dataset of >27,000 patients with large joint arthroplasties, including ~27 million diagnoses and ~9 million procedure records, was constructed using EHRs (Lungmark Analytics, 2016–2019). Natural language processing (NLP) was used to link EHR-based surgical supply information to device-specific information (alloy chemistry) from regulatory submissions. Using ICD10 codes, comorbidity analysis was performed in cohorts stratified by arthroplasty types and Adverse Outcomes (AO) including revision as well as patient demographics. Pre/post-implantation occurrence of 71 ICD10 diagnostic categories (pre-selected as immune/inflammatory conditions) was compared with respect to AORevision to identify potential comorbidities representing risk factors or underrecognized complications. Inter-cohort differences were assessed using chi-square tests with odds ratios, relative risks, and time-to-event analysis, and multivariate regression. LASSO regression modeling using ~22,300 ICD10 diagnoses was used to build “unsupervised” prediction models for identifying risk factors/comorbidities and modifying factors.

Results: Compared to Controls (recipients of large joint arthroplasty with no known arthroplasty-related comorbidities), AOResolution cohorts showed higher post-implantation frequencies for some immune/inflammatory conditions as arthroplasty-related complications, with likelihoods being further impacted by patient demographics and device materials.

Conclusion: Use of our transferable analytical/statistical methodology for pre-existing healthcare RWD analysis can provide insights into implant-related factors and complications, thus prompting the informed use and predictive evaluation of implants.

Overall Research Flow

Device-Patient Data Acquisition (Orthopedic Devices)

Electronic Health Records (EHR) for patients with large joint arthroplasty:
- ~27% subjects with hip, knee, or shoulder implants
- ICD10 codes used to characterize large arthroplasties as well as other comorbidities and procedures

Device Matching Engine built to connect EHRs to FDA Medical Device Databases above:
- Standardize manufacturer names
- Very similar formatting to part numbers
- Match EHR data to GUID with standard manufacturer names and part #
- Match EHR data to PMA/S510a with probabilistic matching rules using device models

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Multivariate Logistic Regression Analysis

As a starting point, the cohort of 1,194 patients with large joint arthroplasty was stratified by type of arthroplasty and by presence or absence of arthroplasty-related Revision and Adverse Outcomes such as periprosthetic osteolysis (AO-Hex and Contour, respectively). Multivariate logistic regression analysis was applied to assess the risk of certain pre-selected ICD10-defined inflammatory conditions (mT1) with regards to AO-Hex and patient’s sex and race. An example below shows the higher risk of M5 - MH: Inflammatory Polyarthritis including Rheumatoid Arthritis in patients with Knee arthroplasty (> 16,749), especially in Blacks and Females.

<table>
<thead>
<tr>
<th>M5 - MH: Inflammatory Polyarthritis</th>
<th>Odds Ratio 95% CI p-value</th>
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<tbody>
<tr>
<td>Black</td>
<td>1.53 (1.14,1.85) 0.011</td>
</tr>
<tr>
<td>White</td>
<td>0.63 (0.56,0.71) 0.001</td>
</tr>
<tr>
<td>Female</td>
<td>0.25 0.22</td>
</tr>
<tr>
<td>Outcome</td>
<td>Black Ref.</td>
</tr>
<tr>
<td>Outcome</td>
<td>Female Ref.</td>
</tr>
<tr>
<td>Outcome</td>
<td>Control Ref.</td>
</tr>
<tr>
<td>Outcome</td>
<td>Control Ref.</td>
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Time-to-Event Analysis using Kaplan-Meier Approach

Following our hypothesis that comorbidities with higher AO-Hex vs. Control frequencies may represent potential risk factors or complications correlated with implant reacti

Logistic LASSO Regression Analysis

To complement our comorbidity analyses using pre-selected ICD10 diagnoses and to further study the potential risk factors identified above, we applied a LASSO regression analysis. LASSO penalization helps reduce dimensions of ICD10 feature selection aimed at distinguishing between the AORenew and Controls groups.

For the LASSO-based coefficients and importance rankings of these ICD10 features, the post-implantation appearance of M244. Reactive Dactylitis of Joint (not shown), despite its relatively low p-value of 0.002, was the top LASSO-identified feature. The RWD Acquisition & Analysis Methodology with Respective Examples

Device Alloy Data Acquisition

PMA/S510a Text Mining Algorithm (Natural Language Processing - NLP) built to identify alloy metals from >78K Premarket Approval (PMA) Summaries of Safety and Effectiveness (ISEN) and 510(k) Summaries.

<table>
<thead>
<tr>
<th>PMA</th>
<th>S510a</th>
<th>Summaries</th>
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<tr>
<td>Manual review of the listed references that contain alloy metals in (progress)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selection of PMA and S510a documents referring to larger metal-containing implants</td>
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The image below shows an example of NLP-based identification of nickel-titanium alloy Nitinol as one of device-related alloy/ metal targets (note: the acquired device composition data are not limited to arthroplasty).

Patient Socioeconomic Data Acquisition

An algorithm aimed to:
- Yield dataset that protects privacy but provides censored time specific on specific socio-economic factors:
- Create clusters using variables such as 6-digit zip code and a-k means model
- Create group similar censuses across groups of 50,000 inhabitants

Socio-economic factors included:
| 1. Median Household Income |
| 2. % receiving assisted income |
| 3. % living below Poverty Level |
| 4. % with at least high school education |
| 5. % lacking health coverage |

Summary of RWD Acquisition & Analysis Methodology:

- PMA/S510a Text Mining Algorithm (NLP) built to identify alloy metals from >78K Premarket Approval (PMA) Summaries of Safety and Effectiveness (ISEN) and 510(k) Summaries.
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