Leveraging Visual Analytics to Identify Subgroups in Readmitted Patients: Implications for Precision Medicine

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Overview

• Motivation
  – 30-Day Hospital Readmission in Total Hip/Knee Arthroplasty Patients

• Method
  – Data Extraction
  – Visual Analytical Method
  – Results

• Conclusions and Future Research
  – Implications for Precision Medicine and Predictive Modeling
Motivation

• Incidence of Total Hip/Knee Arthroplasty (THA/TKA)
  – Steady increase in the number of THA and TKA in the elderly
  – In 2010 alone, there were 1.6 million THAs and 3.2 million TKAs performed (Kremers et al., 2015)

• Rate and Impact of Hospital Readmission
  – Despite successful procedures, 6.3% of THA/TKA patients have unplanned hospital readmissions (CMS, 2015)
  – Readmissions lead to avoidable mortality, morbidity, and resource consumption

• Predictive Accuracy
  – Current models to predict patient-specific hospital readmissions have marginal predictive accuracy (C-statistic = 0.60-0.65) (CMS, 2015)
  – Do not consider patient subgroups, which could improve predictive accuracy
**Motivation for Precision Medicine**

- **Heterogeneity in Patient Profiles** (e.g., McClellan et al., 2010)
  - Numerous studies on topics ranging from molecular to environmental determinants of health show that most humans share characteristics forming patient subgroups

- **Primary Goal of Precision Medicine** (e.g., Collins et al., 2015)
  - Identify these patient subgroups
  - Infer and validate their underlying causal processes
  - Design interventions targeted to specific patient subgroups to improve outcomes
Three Basic Approaches Used to Analyze Risk of Readmission

1. **Univariable Descriptive Statistics**
   - Risk of readmission with Renal Failure = 1.3
   - Cannot reveal how comorbidities interact

2. **Multivariable Predictive Modeling**
   - Risk of readmission = 0.5 Renal Failure + 0.7 CHF + 0.3 COPD + 0.2 Diab ...
   - Cannot reveal subgroups within cases that have different combinations of comorbidities and associated risk

3. **Combinatorial Methods**
   - Renal Failure + CHF; Renal Failure + COPD; Renal Failure + Diabetes ...
   - Cannot reveal interactions among such combinations (e.g., how a dyad of comorbidities interacts with a triad of a different set of comorbidities)

What’s Missing in These Approaches?

- **Patient Subgroups**: Critical for precision medicine
- **Research Question**: *How do patient characteristics co-occur across subgroups of readmitted patients?*
Method and Results
Method: Data Selection

Data Source
2006-2015 data from the Veteran’s Affairs Clinical Data Warehouse (VA-CDW) representing ~130 medical centers

Cases
- **Included**: 100% cases (THA/TKA patients readmitted within 30 days of hospital discharge)
- **Excluded**: Patients <65 years, died during hospital stay, missing data for DOB/Age

Controls
Equal number of patients not readmitted within 30 days, matched by age, gender, and race

Patient Characteristics
All comorbidities from the Charlson, and CMS-CC indices that were also in the VA-CDW
Vitals, marital status, and frailty

Results
- **THA**: 460 matched pairs each in the training dataset and in the replication dataset (total 1,840)
- **TKA**: 895 matched pairs each in the training dataset and in the replication dataset (total 3,582)

Characteristics: 47 variables (41 binary, 1 cat., 5 cont.)

VA Data provided by Co-PI Dr. Copeland (HCSRN)
Method: Variable Normalization and Selection

• **Feature Selection**
  – Used logistic regression to estimate the significance of each variable for predicting readmission in each dataset, and corrected for multiple testing
  – Selected the top-10 in the training dataset that were also highly-ranked (in the top-20) in the replication dataset

• **Range Normalization of Multiple Datatypes**
  – Clustering methods require uniform ranges and meanings
  – Transformed the value of each variable for each patient into the respective univariable probability (range 0-1) for predicting readmission *(e.g., what is a patient’s probability of readmission based on age alone?)*

• **Dichotomitization**
  – Matched case-control study design results in overall readmission probability to be 0.5
  – Probabilities were therefore dichotomized (*<=.5=*0; *>.5=*1) for the bipartite network analysis
Results: Variable Selection

### THA: Top-10 Replicated Variables

1. Infections (DVT, Pulmonary embolism, etc.)
2. Number of opioid one year pre-surgery
3. Cellulitis, Local Skin Infection
4. Schizophrenia
5. Gait diseases
6. Anemia
7. Acute Renal Failure
8. Fractures
9. Chronic Obstructive Pulmonary Disease
10. Peripheral Vascular Disease

### TKA: Top-10 Replicated Variables

1. Infections (DVT, Pulmonary embolism, etc.)
2. Number of opioids one year pre-surgery
3. Schizophrenia
4. Number days on opioids one year pre-surgery
5. Specified Heart Arrhythmias
6. Gait diseases
7. Peripheral Vascular Disease
8. Cellulitis, Local Skin Infection
9. Other Injuries
10. Body Mass Index (BMI)

6 variables overlapped between the two conditions
Method: Network Analysis

A network is a set of nodes connected in pairs by edges

A. Unipartite Network

B. Bipartite Network

Degree of Clusteredness (Modularity) = Fraction of edges falling within a cluster – the expected fraction of such edges in a network of the same size with randomly assigned edges

Significance of Modularity: Actual modularity compared to modularity from 1000 permutations of the data

Replication of Characteristic Co-occurrence: Rand Index and its significance (proportion of pairs that were and were not in the same cluster in both networks)
ExplodeLayout Algorithm (Bhavnani et al., 2017)

Method: Visualization

Significant but Overlapped Clusters

Optimal circle radius determined through search

Compact Cluster Separation = Non-overlapped area/Total Area

Separated Clusters
Results: Visual Analytics

- **THA**: 7 biclusters, with strong and significant degree of clusteredness ($Q=0.35$, $p<.05$) compared to 1000 random permutations of the network; strong and significant replication ($RI=0.87$, $p<.05$).

- **TKA**: 6 biclusters, with strong and significant degree of clusteredness ($Q=0.28$, $p<.05$) compared to 1000 random permutations of the network; strong and significant replication ($RI=0.91$, $p<.05$).
Implications and Future Research
• **High-Risk Characteristics**

− Majority of patient characteristics that predict readmission are comorbidities (with the exception of BMI, and opioid usage)

− Results agree with observations in other studies

  Most common cause of readmission is non-surgical, suggesting existing comorbidities are associated with a high risk of 30-day readmission (Boockvar, 2003)
Inference by Stakeholders: Cycle of Readmission

- Existing Process Resulting in Hospital Readmission

Patient admitted to the hospital → Patient discharged with “Hip Fracture” in notes → Rehab focused on wound healing & PT

Triggered existing comorbidities ← Dehydration, poor nutrition ← Reduced oral intake, increased bedrest

- Hypothesis to Reduce Risk of Hospital Readmission

Patient admitted to the hospital → Discharge notes indicates “THA + Psych. + Opioids” → Rehab wound healing/PT + targeted interventions

Reduction of Risk for Hospital Readmission ← Early identification and treatment of exacerbation ← Triaging & monitoring of comorbidities
Implications for Design of Interventions

• **Discharge Notes**
  - Monitor high-risk frequently co-occurring comorbidities (e.g., psychiatric disorders and opioid usage)
  - State which of the high-risk comorbidities are present in patient to be discharged

• **Monitoring**
  - Providers (PT, physicians, RN, social workers) should be trained to monitor changes such as reduced oral intake, and exacerbation of a small set of comorbidities for each index condition
Implications for Predictive Modeling

- Automatically identify patient subgroups
- Develop stratified regression models that use information about patient subgroups
- Compare predictive accuracy of patient subgroup models, to overall regression model
Conclusions and Future Research

• **Methodology**
  – Visual analytical method to obtain an integrated understanding of patient subgroups and co-occurring factors that are predictive of an outcome
  – Approach addresses multiple datatypes common in multi-omics datasets

• **Implications**
  – **Precision Medicine**: Discharge planning and monitoring of comorbidities in subgroups of THA/TKA patients
  – **Predictive Modeling**: Stratified regression modeling to improve accuracy of prediction

• **Current and Future Research**
  – **Test generality** of methodology on other outcomes in VA Data
  – **Publication in review**: *Bipartite Network Analysis with Multiple Datatypes: Implications for Precision Medicine in the Age of Multi-omics Data*
  – **Planned RO1 proposal** (pa-17-462): *How Symptom Clusters in Elderly Stroke Patients are Longitudinally Associated with Cognitive and Physical Outcomes*
Leveraging Visual Analytics to Identify Subgroups in Readmitted Patients: Implications for Precision Medicine

Timothy Reistetter OTR PhD, Professor, School of Health Professions University of Texas Health Sciences Center, San Antonio TX
Stroke

• Stroke is a leading cause of disability, institutionalization, readmission, and death…
  – almost 795,000 Americans sustain a stroke (Yang et al 2000; Benjamin et al 2017)

• Many stroke survivors face substantial disease management hurdles once they return to the community (Wolf et al 2017)

• Post-acute hurdles:
  – exacerbation of existing comorbidities,
  – development of chronic conditions,
  – hospital readmissions (Ottenbacher et al, 2014)
• Project Goal

Inform the development and implementation of a *stroke tailored chronic disease management program* for those living in the community

- leverage experience with large data & analytics
- patient-centered stakeholder engagement
- clinical experience
Data Description

- Centers for Medicare & Medicaid Services (CMS) files
- Medicare Provider Analysis and Review (MedPAR)
- Master Beneficiary Summary File
- Data files from 2013 & 2014 (CMS 2018; Kokotailo et al 2005)

<table>
<thead>
<tr>
<th>Initial cohort selection</th>
<th>Train set</th>
<th>Replication set</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>% remained</td>
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<tr>
<td>1. Acute Hospitalization for stroke based on the primary dx in 2013 (train set) or 2014 (replication set)</td>
<td>526,767</td>
<td>92.0</td>
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<td>2. Select the 1st discharge for each patient</td>
<td>484,812</td>
<td>89.8</td>
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<td>3. Age 66 or over at admission</td>
<td>435,483</td>
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<td>4. Survived 90 days post discharge</td>
<td>362,309</td>
<td>82.8</td>
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<td>5. Continuous Part A coverage without HMO in the year before admission and 90 days after discharge</td>
<td>247,254</td>
<td>68.2</td>
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<tr>
<td>6. Exclude those transferred* to another acute care facility</td>
<td>244,612</td>
<td>98.9</td>
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<tr>
<td>7. Exclude those discharged against medical advice (AMA)</td>
<td>243,701</td>
<td>99.6</td>
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</table>

*To qualify as a transfer, (1) The second inpatient admission must occur on the same day or the next calendar day following discharge from the first inpatient admission, and (2) The second inpatient admission had stroke as the primary diagnosis.
Patient and Variable Selection

**Training dataset:** 44,082 cases (stroke patients readmitted within 90 days of discharge), and 191,319 controls (patients not readmitted within 90 days of discharge) matched by age, gender, race, and Stroke type.

**Replication Dataset:** 43,088 cases (stroke patients readmitted within 90 days of discharge), and 183,374 controls (patients not readmitted within 90 days of discharge) matched by age, gender, race, and Stroke type.

**Variables:** Analyzed 96 comorbidities from the Elixhauser, Charlson, and CMS-CC indices that were significant (after BON correction) and replicated in the replication dataset, resulting in 72 significant and replicated comorbidities.

<table>
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<tr>
<th>Variable</th>
<th>OR</th>
<th>Significance</th>
<th>Variable</th>
<th>OR</th>
<th>Significance</th>
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</tbody>
</table>
Results: Patient-Comorbidity Biclusters

- 5 biclusters of readmitted stroke patients and comorbidities
- Strong clusteredness (Q=0.17, z=6.19, p<.001), and significant replication (RI=0.73, z=7.54, p<.001)
- Clusters used to enhance an evidence-based (EBP) self-management program

### Stroke MTT Training

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<th>Condition</th>
<th>Coef</th>
<th>p-value</th>
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<tr>
<td>OtherPsychiatric</td>
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<td>6.99E-52</td>
</tr>
<tr>
<td>PolyMononeuropathy</td>
<td>1.366</td>
<td>5.63E-49</td>
</tr>
</tbody>
</table>

[Diagram showing biclusters and conditions]
Self-management

- Active participation in managing daily health care

- **Chronic Disease Self-Management Program (CDSMP)** is one type of program that has evidence to:
  - Improve quality of life
  - Improve psychosocial outcomes (e.g., self-efficacy)
  - Increase confidence in managing chronic disease

- CDSMP was developed by team of researchers at Stanford University
- It is a program for people who have more than one health condition, whose health problems have begun to interfere with their valued life activities
The program covers a range of topics:
- Techniques to deal with problems such as frustration, fatigue, pain and isolation
- Appropriate exercise for maintaining and improving strength, flexibility and endurance
- Appropriate use of medications
- Communicating effectively with family, friends and health professionals
- Nutrition
- Use of community resources

“Individuals with stroke may have several chronic symptoms … (and) chronic conditions”

“Future studies should explore self-management programs that are more tailored”
Informed Stroke Specific Program

- To bridge the gap between evidence based practice and their real-world use
- To target the above negative outcomes of stroke
- Implement a self-management program adapted for stroke survivors
- Informed by Visual Analytics
• **Session 1**: Introductions, overview to self-management, discussion on stroke.

• **Session 2**: Managing chronic breathing issues and managing mood.

• **Session 3**: Managing diabetes (healthy eating).

• **Session 4**: Managing heart disease and high blood pressure (healthy weight management, medication management).

• **Session 5**: Managing musculoskeletal conditions (physical activity).

• **Session 6**: Communication, making treatment decisions, conclusions and follow up reminders.
Adaptation: Inclusion of Case Vignettes

- For each session we will present a vignette based on the combinations of comorbidities from Aim 1 (visual analytics) and further informed by the stakeholders.

- Concrete scenarios to enable a meaningful discourse with patients about self-management without getting too personal.

Vignette Example: how would you advise Mrs. Smith aged 72, who had a stroke but also suffers from coronary artery disease, high blood pressure, morbid obesity, and congestive heart failure?
Self-Management feasibility study goals

- Test the feasibility of implementing a stroke specific chronic disease self-management program
  - Patient based feasibility
  - Institution based feasibility

- Explore the efficacy of the program
  - Southampton Stroke Self-Management Questionnaire
  - Patient Reported Outcome Measure (PROMIS) self-efficacy
  - PROMIS self disturbance and sleep-related impairment
Feasibility Study Methodology

- Prospective RCT
- Study flow:

  - Intervention: 1.5 hours every week, for 6 weeks
  - Inclusion: Stroke, at least one chronic medical condition, able to consent, over 18 years, alert and oriented x 3
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Thank You
Comments & Questions