Diagnosis-based cohort augmentation using laboratory (lab) data in the FDA Sentinel Initiative: The case of chronic kidney disease (CKD)

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Chronic Kidney Disease (CKD)

- Important health **outcome** of interest for drug safety studies
  - Examples include
    - Non-steroidal anti-inflammatory drugs (NSAIDS)

- Important **population** for drug safety studies
  - Examples include
    - Angiotensin converting enzyme inhibitors (ACEI)
Identification of CKD in database studies

- Diagnosis based
  - ICD9 (e.g. 585)
  - ICD10 (e.g. N18)

- Laboratory findings
  - Estimated glomerular filtration rate (eGFR)
    - Serum creatinine based and also includes age, sex, race
    - CKD-EPI equation
  - To qualify as ‘Chronic’ the National Kidney Foundation guidelines require 2 eGFR <60 ml/min/1.73m²
  - Many studies use a single low eGFR
Study Context

- Incorporating laboratory findings into drug safety databases

Objective:
- To assess how augmenting a diagnosis-based CKD cohort with patients identified through lab results impacts cohort characteristics and outcomes.

Data Source
- FDA’s Sentinel Distributed Database
Study Design

- **Setting:** Two Sentinel Data Partners with diagnosis and laboratory data
  - Kaiser Permanente Colorado and Kaiser Permanente Northern California

- **Cohort Study**
  - During 2012, look for first “indication” of CKD
    - ICD9 code for CKD
    - eGFR <60 ml/min/1.73m²
  - Required 365 days of KP membership prior to first indication of CKD for collection of baseline characteristics
Study Groups

- First CKD indication in 2012 (diagnosis or eGFR<60)
- Look back 365 days (including index date) and assign mutually exclusive groups hierarchically
  - 1\textsuperscript{st}: DxGroup
    - N=107,607 (97% also had serum creatinine)
  - 2\textsuperscript{nd}: 2-LabGroup (2 or more eGFR <60)
    - N=33,542
  - 3\textsuperscript{rd}: 1-LabGroup (1 eGFR <60)
    - N=87,678
Statistical Analyses

- Compare pairwise standardized differences across cohorts
  - Standardized differences >0.2
- Cox regression
  - 1 year follow-up mortality = f(CKD_group, baseline characteristics)
  - P<0.05
Characteristics compared

- Age, sex, race, stage of CKD
- Comorbidity score (Gagne modification of Charlson and Elixhauser)
- Comorbidities:
  - alcohol abuse, anemia, arrhythmia, coagulation disorder, heart failure, diabetes, dementia, fluid/electrolyte disorders, HIV/AIDS, hypertension, hemiplegia, liver disease, cancer mets, psychosis, pulmonary disease, pulmonary circulation disorder, peripheral vascular disease, tumor, weight loss, myocardial infarction/stroke

- Health care utilization
  - Ambulatory visits, emergency department visits, hospital stays, institutional stays
### Characteristics with Std Differences >0.2

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DxGroup</th>
<th>2-LabGroup</th>
<th>1-LabGroup</th>
<th>Std Diff Dx v 2-Lab</th>
<th>Std Diff Dx v 1-lab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>72.6</td>
<td>74.4</td>
<td>69.2</td>
<td>0.18</td>
<td>0.30</td>
</tr>
<tr>
<td>&lt;65 (%)</td>
<td>19.4</td>
<td>16.7</td>
<td>23.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>65-74</td>
<td>31.3</td>
<td>29.3</td>
<td>31.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>75-89</td>
<td>49.3</td>
<td>54.0</td>
<td>44.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black (%)</td>
<td>9.6</td>
<td>4.6</td>
<td>5.7</td>
<td>0.23</td>
<td>0.17</td>
</tr>
<tr>
<td>Stage 4 CKD (%)</td>
<td>10</td>
<td>1.8</td>
<td>1.7</td>
<td>0.38</td>
<td>0.39</td>
</tr>
<tr>
<td>Heart failure (%)</td>
<td>17.1</td>
<td>11.4</td>
<td>8.6</td>
<td>0.16</td>
<td>0.26</td>
</tr>
<tr>
<td>Diabetes* (%)</td>
<td>40.8</td>
<td>17.4</td>
<td>11.2</td>
<td>0.53</td>
<td>0.72</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>45.6</td>
<td>32.1</td>
<td>23.1</td>
<td>0.28</td>
<td>0.49</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>84.4</td>
<td>78.8</td>
<td>64.4</td>
<td>0.15</td>
<td>0.47</td>
</tr>
</tbody>
</table>

*complicated diabetes
Are there mortality differences between the CKD groups?

- Cox regression findings, adjusted for age only

<table>
<thead>
<tr>
<th>Group</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>DxGroup</td>
<td>reference</td>
<td></td>
</tr>
<tr>
<td>1-LabGroup</td>
<td>0.61</td>
<td>(0.59, 0.65)</td>
</tr>
<tr>
<td>2-LabGroup</td>
<td>0.51</td>
<td>(0.48, 0.55)</td>
</tr>
</tbody>
</table>

- Cox regression findings, fully adjusted

<table>
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<th>95% CI</th>
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</thead>
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<tr>
<td>DxGroup</td>
<td>reference</td>
<td></td>
</tr>
<tr>
<td>1-LabGroup</td>
<td>0.99</td>
<td>(0.95, 1.06)</td>
</tr>
<tr>
<td>2-LabGroup</td>
<td>0.84</td>
<td>(0.78, 0.90)</td>
</tr>
</tbody>
</table>
Conclusion

▪ Augmenting a diagnosis-based CKD cohort with laboratory data more than doubled the population

▪ Our cohort with diagnosis based-CKD had a greater comorbidity load and more black patients

▪ Many of the ‘excess’ comorbidities were physiologically related to CKD
  • Stage of CKD, heart failure, diabetes and hypertension

▪ After adjustment, 1 year mortality was greater for the DxGroup
Conclusion

- When augmenting a diagnosis based cohort with laboratory identification, investigators should consider subgroup or stratified analysis

- Next steps:
  - Explore by-site interactions