The Impact of Missing Deaths on Survival Analyses Conducted in an Oncology EHR Database


Abstract

Background

- Real-world evidence (RWE) based on data derived from electronic health records (EHRs) is increasingly used in pharmacopoeiologic research.
- In order to fully utilize RWE, high-quality outcomes data are needed, and mortality-based outcomes are particularly important for many disease areas, including oncology.
- However, in RWE sources, mortality data may not capture all deaths.

Objectives

- The aim of this study was to assess the impact of missing death data on survival analyses conducted in an oncology EHR-derived database.
- Specifically, we wanted to examine the results of three main analytic applications in patients with advanced non-small cell lung cancer (aNSCLC) at different mortality sensitivity levels with those obtained using a gold standard data source with an assumed mortality sensitivity of 100%.

Methods

Design:

aNSCLC patients with advanced stage disease diagnosed between 1/1/11 and 12/31/15 in an oncology EHR were included in the study. Three analytic use case scenarios were evaluated: absolute risk estimation, relative risk comparison across external control arm, and a sensitivity analysis to assess the impact of missing death data on survival analyses when using a benchmark gold standard data source.

Population:

The aNSCLC cohort was selected from the Flatiron Health EHR database. National Death Index (NDI) data were obtained on patients in the aNSCLC cohort.

Exposures of Interventions:

The analyses included a number of survival comparisons for groups defined on the basis of drug exposure or clinical characteristics (e.g., biomarker status).

Main Outcome:

The primary outcome was overall survival (OS), defined as time from first line treatment initiation or advanced diagnosis to death. Patients were censored at their last known structured activity date in the EHR prior to the end of the analysis period. The gold standard mortality was death data within the NDI.

Statistical Analysis:

The Kaplan-Meier method was used to estimate median OS (mOS), and Cox proportional hazards models were used to estimate hazard ratios (HRs).

Study Overview

Results

Table 1. Impact of missing deaths on measures of absolute risk (mOS)

<table>
<thead>
<tr>
<th>Group</th>
<th>Overall Survival (mOS) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDI</td>
<td>12.4 (11.7, 13.1)</td>
</tr>
<tr>
<td>Observed</td>
<td>11.7 (11.2, 12.3)</td>
</tr>
<tr>
<td>Relative Risk</td>
<td>1.09 (1.02, 1.16)</td>
</tr>
<tr>
<td>HR (vs. Observed)</td>
<td>1.16 (1.08, 1.25)</td>
</tr>
</tbody>
</table>

Figure 1. Censoring patterns of those patients with missing death dates

Figure 2. Impact on comparative analyses conducted with EHR data

Figure 3. Impact on analyses that use EHR data as an external control arm

Table 2. Impact of missing deaths on measures of relative risk (RR)

<table>
<thead>
<tr>
<th>Group</th>
<th>Median Overall Survival (mOS) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDI</td>
<td>11.8 (11.5, 12.1)</td>
</tr>
<tr>
<td>Observed</td>
<td>11.2 (10.8, 11.6)</td>
</tr>
<tr>
<td>Relative Risk</td>
<td>1.08 (1.05, 1.12)</td>
</tr>
<tr>
<td>HR (vs. Observed)</td>
<td>1.12 (1.09, 1.15)</td>
</tr>
</tbody>
</table>

Limitations

- This study leveraged data from community-based oncology clinics in the US and hence missing data may be different in academic centers in other countries.
- Despite the marginal impact on most conclusions observed in aNSCLC, it is unclear how this would expand to other cancer types with longer mOS.
- This study did not consider the mechanism for missing deaths, further work is needed to describe the presence and degree of informative censoring in these data and understand its impact.

Conclusions

- Overall, small differences were observed in the HRs for the EHR-derived cohort across comparative analyses when compared to HRs obtained from the gold standard data source.
- When only a single treatment was subject to estimation bias (i.e., external control analyses), the bias was slightly more pronounced.
- The magnitude of all observed biases increased when lower censoring levels were generated. The impact was pronounced in high sensitivity scenarios, with no evidence of impact associated with external control arm applications.
- EHR mortality data with high sensitivity limits the potential for missing deaths in bias OS estimates. This enables robust conclusions and decision making based on RWE.

Bibliography