ICU length of stay:
A new approach to a challenging outcome

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Various outcome measures in Critical Care RCTs

Table 1. Proportion of ICU-based RCTs using different outcome measures

<table>
<thead>
<tr>
<th>Outcome</th>
<th>% RCTs using measure as a primary or secondary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU length of stay</td>
<td>60.0</td>
</tr>
<tr>
<td>Mortality over a specified time-period</td>
<td>59.9</td>
</tr>
<tr>
<td>Hospital length of stay</td>
<td>44.1</td>
</tr>
<tr>
<td>Duration of mechanical ventilation</td>
<td>38.6</td>
</tr>
<tr>
<td>Healthcare associated infections</td>
<td>37.8</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>33.9</td>
</tr>
<tr>
<td>Ventilator-free days</td>
<td>20.5</td>
</tr>
</tbody>
</table>

Systematic review of all ICU RCTs using clinical outcomes published in 16 top journals from 2007-2012

Harhay MO, et al. (in preparation)
CC RCTs are typically negative on mortality

Among 39 RCTs with sufficient data, 3 were positive (7.7%); 12% positive overall

Scales et al. systematic review: 17% RCTs with mortality endpoint (1995 - 2008) were positive

Harhay MO, et al. (in preparation)
RCTs’ power for absolute mortality differences

Number of trials with sufficient power (80%)

N = 37 RCTs

Minimum clinically important difference (% decline in cumulative incidence of mortality)

Note: (alpha = 0.05)

Harhay MO, et al. (in preparation)
We lack good endpoints for ICU RCTs

1. Efficient
   - Mortality, Long-term QOL

2. Patient-centered
   - VFDs, Nosocomial infections

3. May be analyzed validly
   - Numerous challenges...

Length of stay
- Continuous variable
- Readily available data
- For patients who live or die
- For families
- For future patients
Challenges in estimating effects on LOS

1. “Immutable time”: most interventions could not alter ICU time right after admission or right before discharge

2. Because many ICU patients die, an intervention’s effects on LOS are inextricably related to its effects on mortality
“Immutable time” in ICU length of stay

Figure 2. Immutable Time

- Early Immutable Time
  - ICU admission
  - "Eligible" for ICU discharge

- ICU Length of Stay

- Late Immutable Time
  - Deemed ready to leave ICU
  - Discharged from ICU
We don’t discharge patients on 1st calendar day

Data from 268,824 patients admitted to 138 U.S. ICUs from 2001-2008 in Project Impact
Floor bed availability influences ICU LOS

Median difference = 6.7 hours, a 15% increase in the median time to bed request.

Figure 3. Difference between time-to-bed-request and time-to-discharge among 1,149 ICU patients discharged from the ICU to a general ward.

Median: 40.1 (20.5 – 84.5) hours
Median: 46.8 (27.4 – 91.2) hours
Limited floor bed availability would affect most ICU patients’ LOS

<table>
<thead>
<tr>
<th>Discharge Location</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Floor</td>
<td>167,253</td>
<td>62.2%</td>
</tr>
<tr>
<td>Step-down/Intermediate Care</td>
<td>41,090</td>
<td>15.3%</td>
</tr>
<tr>
<td>Died in ICU</td>
<td>22,781</td>
<td>8.5%</td>
</tr>
<tr>
<td>Home</td>
<td>15,619</td>
<td>5.8%</td>
</tr>
<tr>
<td>Another Hospital</td>
<td>3,603</td>
<td>1.3%</td>
</tr>
<tr>
<td>Other facility</td>
<td>18,486</td>
<td>6.9%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>268,824</strong></td>
<td><strong>100.0%</strong></td>
</tr>
</tbody>
</table>
Traditional ways to deal with death

- **Ignore it**: intervention could reduce ICU LOS by killing more patients or allowing them to die more quickly.

- **Stratify on it**: interventions that save lives typically do so for patients ‘on the margin’ → increase in survivors’ LOS.

- **Censor it**: assumes that patients who die would have had a LOS distribution equal to that among “similar” patients who lived; but death and LOS are related to acuity (informative censoring).
A new way to deal with death

- Compare entire treatment group with entire control group

- **Rank death** relative to possible values of LOS. For example:
  - Death = worst possible outcome (longest LOS in distribution)
  - Death = specific # days or %ile (e.g., 30 days, 80\textsuperscript{th} percentile of distribution)

- Use non-parametric tests to estimate intervention’s effect on median or other quantiles (e.g., ‘tails’)

Applying the new method: an example

• Suppose that an intervention truly saves the lives of 5% of patients, and has no effects on the LOS of the other 95%:
  - 5% are “responders” who would die in the ICU with usual care, but would survive with the intervention
  - 15% would die either way (“never survivors”)
  - 80% would survive either way (“always survivors”)

Penn Medicine  FIELDS
Simulating an RCT

- 2,000 real patients randomly selected from ~400,000 in Project IMPACT from 2001-2008.

- Randomly assigned 50% to intervention / 50% to control.

- Replicated random assignment 1,000 times and assessed the frequencies with which each method concluded that the intervention: provided benefit, provided harm, or had no statistically significant effect (using $\alpha = 0.10$).
## Results for conventional methods

<table>
<thead>
<tr>
<th>Model</th>
<th>Expected %:</th>
<th>Conclude benefit</th>
<th>Effect not statistically significant</th>
<th>Conclude harm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linear (no accounting for death)</td>
<td>5%</td>
<td>1%</td>
<td>84%</td>
<td>15%</td>
</tr>
<tr>
<td>Linear (survivors only)</td>
<td>90%</td>
<td>0%</td>
<td>84%</td>
<td>16%</td>
</tr>
<tr>
<td>Cox time-to-event (no accounting for death)</td>
<td>5%</td>
<td>0%</td>
<td>79%</td>
<td>21%</td>
</tr>
<tr>
<td>Cox time-to-event (censoring by death)</td>
<td></td>
<td><strong>12%</strong></td>
<td></td>
<td>2%</td>
</tr>
</tbody>
</table>
# Results for new method

<table>
<thead>
<tr>
<th></th>
<th>True positive</th>
<th>Type II error</th>
<th>Wrong (by chance)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Conclude benefit</td>
<td>Effect not statistically significant</td>
<td>Conclude harm</td>
</tr>
<tr>
<td><strong>Death = worst outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effect on median</td>
<td>10%</td>
<td>89%</td>
<td>1%</td>
</tr>
<tr>
<td>Effect on 75\textsuperscript{th} percentile</td>
<td>69%</td>
<td>31%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Death = 30 days in ICU</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effect on median</td>
<td>10%</td>
<td>88%</td>
<td>2%</td>
</tr>
<tr>
<td>Effect on 75\textsuperscript{th} percentile</td>
<td>64%</td>
<td>36%</td>
<td>0%</td>
</tr>
</tbody>
</table>

- Low power for effect on median due to small effect on median (< 0.2 days) in this scenario
- Results reasonably stable over other placements of death
What the new method can and can’t do

• Can estimate effects on a composite measure of ICU LOS and death with low rates of false conclusions

• Investigators cannot declare 1 ‘right’ placement of death
  o But can conduct sensitivity analyses
  o And can inform placements by assessments of how patients (e.g., ICU survivors) value death vs. prolonged ICU stay (‘fate worse than death’?)

• Cannot isolate effects on ICU LOS per se. This is not what patients and providers really care about anyway.
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The simulation’s assumptions about LOS

- “Always-survivors”: median ICU LOS = 2 days (range 0 – 47), not affected by the intervention
  - 95th percentile: 11 days
  - 99th percentile: 22 days
- “Never-survivors”: LOS is similar to always-survivors, also not affected by intervention
- “Responders”: higher LOS – a median of 3.5 days with the intervention