Confusing correlation and prediction
Simple approach to evaluate marker accuracy for predicting time-to-event

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1. Background

2. Methodology

3. Calculator

4. Conclusion
Objective of pronostic markers/scores

- To early stratify patients according to their risk for future event.
  - Adaptation of the therapy.
  - Adaptation of the follow-up frequency.
  - Information for patients, etc.

The methodology always used in the past (single marker)

- Kaplan-Meier estimator.
  - High distance between curves = High prognostic capacity.

- Log-Rank statistic.
  - Small p-value = High prognostic capacity.

- Cox model (with possible adjustment).
  - High value of the HR = High prognostic capacity.
Monitoring of donor chimerism in sorted CD34+ peripheral blood cells allows the sensitive detection of imminent relapse after allogeneic stem cell transplantation

Martin Bornhäuser,1 Uta Oelschlaegel,1 Uwe Platzbecker,1 Gesine Bug,2 Karin Lutterbeck,1 Michael G. Kiehl,3 Johannes Schetelig,4 Alexander Kiani,5 Thomas Illmer,1 Markus Schaich,1 Catrin Theuser,1 Brigitte Mohr,1 Cornelia Brendel,4 Axel A. Fauser,3 Stefan Klein,2 Hans Martin,2 Gerhard Ehninger,1 and Christian Thiede1

In summary, the results of this study show for the first time that the serial chimerism analysis in CD34+ cells sorted out of peripheral blood is a sensitive technique to detect residual or reoccurring disease after allogeneic SCT. Its use allows the prediction of relapsing disease in most cases with CD34+ leukemia. The major advantage is the less frequent requirement of bone marrow aspiration and the possibility to start preemptive therapeutic interventions earlier. Since the method is time and labor-intensive, it needs further optimization before entering routine use.
P-values

- P-value depends on the sample size:
  - Small differences between survival curves may be significant for study with large sample size.
  - Great differences between survival curves may not be significant for study with small sample size.
- Small p-value only demonstrates that the correlation is not observed by chance.
- P-value does not inform on prognostic accuracies.
Methodological issues (2)

Hazard Ratio (HR)

- HR does not inform on prognostic accuracy.
- Ex: Fictive data on CD34+ (same follow-up for all patients).

<table>
<thead>
<tr>
<th></th>
<th>Decrease CD34+</th>
<th>Stable CD34+</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapse</td>
<td>19</td>
<td>9</td>
<td>28</td>
</tr>
<tr>
<td>No Relapse</td>
<td>24</td>
<td>38</td>
<td>62</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>43</strong></td>
<td><strong>47</strong></td>
<td><strong>90</strong></td>
</tr>
</tbody>
</table>

\[
HR = \frac{Incidence_{Decrease}}{Incidence_{Stable}} = \frac{19/43}{9/47} = 2.31.
\]

- Sensitivity: \( Pr(\text{Decrease}|\text{Relapse}) = 19/28 = 68\% \).
- Specificity: \( Pr(\text{Stable}|\text{No Relapse}) = 38/62 = 56\% \).
Problem

- A marker can be highly correlated with the risk of event but with low predictive capacities.

The sensitivity and specificity for a prognostic up to time $t$

- $SE_t$ is the proportion of patients that are classified as high risk, among all the patients who experience the event before time $t$.
- $SP_t$ is the proportion of patients that are classified as low risk, among all the patients who do not experience the event before time $t$. 
Problem with censored data

T=0  T=t  
event 
event 
event 
no event 
no event 
no event 
prognostic 
time

event

no event

no event

no event

Time
Problem with censored data

- Over representation of patients with event

![Diagram showing over representation of patients with event](image-url)
• Heagerty et al. * proposed a correction for censored data.

• The authors proposed estimators of time-dependent sensitivity and specificity.

• Method available in a lot of statistical software.

• Nevertheless, the method is not often used in practice....

⇓

We proposed a simple methodology for computing time-dependent sensitivity and specificity by using (already) published survival curves.

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Definitions

Number of low risk individuals
NLR = 47

Number of high risk individuals
NHR = 43

Survival in low risk group
SLR = 55%

Survival in high risk group
SHR = 25%

Prognostic time
t = 6
• The proportion of patients that are correctly classified as high risk (HR), among all the patients who experience the event before \( t \):

\[
SE_t = \frac{(1 - SHR) \times NHR}{(1 - SHR) \times NHR + (1 - SLR) \times NLR}
\]

• Application:

\[
SE_{6 \text{ years}} = \frac{(1 - 0.25) \times 43}{(1 - 0.25) \times 43 + (1 - 0.55) \times 47} = 60\%
\]
Time-dependent specificity

- The proportion of patients that are correctly classified as low risk (LR), among all the patients who do not experience the event before time $t$:

$$SP_t = \frac{SLR \times NLR}{SHR \times NHR + SLR \times NLR}$$

- Application:

$$SP_{6 \text{ years}} = \frac{0.55 \times 47}{0.25 \times 43 + 0.55 \times 47} = 71\%$$
Predictive values

- **$PPV_t$**: The positive predictive value is the proportion of patients who experience the event before $t$, among all the HR patients.

- **$NPV_t$**: The negative predictive value is the proportion of patients who not experience the event before $t$, among all the LR patients.
Predictive values: direct evaluation from the survival curves

Prognostic time \( t = 6 \)

NPV = SLR

PPV = 1 - SHR

\[ PPV_{6\,years} = 100\% - 25\% = 75\% \]

\[ NPV_{6\,years} = 55\% \]
Warning: $PPV_t$ and $NPV_t$ depend on the overall survival

Let $S_t$ be the overall survival at time $t$:

$$PPV_t = \frac{SE_t \times (1 - S_t)}{SE_t \times (1 - S_t) + (1 - SP_t) \times S_t}$$

$$NPV_t = \frac{SP_t \times S_t}{SP_t \times S_t + (1 - SE_t) \times (1 - S_t)}$$

<table>
<thead>
<tr>
<th></th>
<th>Initial study</th>
<th>New population</th>
</tr>
</thead>
<tbody>
<tr>
<td>$S_t$</td>
<td>41%</td>
<td>55%</td>
</tr>
<tr>
<td>$SE_{6\text{ years}}$</td>
<td>60%</td>
<td>60%</td>
</tr>
<tr>
<td>$SP_{6\text{ years}}$</td>
<td>71%</td>
<td>71%</td>
</tr>
<tr>
<td>$PPV_{6\text{ years}}$</td>
<td>75%</td>
<td>63%</td>
</tr>
<tr>
<td>$NPV_{6\text{ years}}$</td>
<td>55%</td>
<td>68%</td>
</tr>
</tbody>
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Calculator : EVALBIOM
(www.divat.fr/en/online-calculators/)

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At 6 years, prognostic biomarker abilities can lead to the following error rates:

⇒ among the patients who should suffer the event, 39.6% may be incorrectly classified as low risk.

⇒ among the patients who should not suffer the event, 29.4% may be incorrectly classified as high risk.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
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</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>60.4 %</td>
</tr>
<tr>
<td>Specificity</td>
<td>70.6 %</td>
</tr>
</tbody>
</table>
Assuming 59.3% of events before 6 years, one can expect that the following error rates:

- HR-classified patients have 25% of risk to not suffer the event.
- LR-classified patients have 45% of risk to suffer the event.
Expected predicted values (in %) according to the population frailty.

Cumulative probability at 6 years (in percentage)

- Positive predicted values
- Negative predicted values
- Observed cumulative probability
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Conclusion

In order to evaluate prognostic capacities of marker from censored data :

- The time-dependent ROC theory have to be used from individual data.
- Other concordance indexes exist.
- If only survival curves are available : you should use the previous formulae for a better interpretation of results.
  1. Compute time-dependent sensitivity and specificity, which do not depend on the event probability.
  2. Compute time-dependent predictive values according to your population.
- If more than two survival curves : you can merge groups together.