Prognosis

VCU School of Medicine
M1 Population Medicine Class

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The physician who cannot inform his patient what would be the probable issue of his complaint, if allowed to follow its natural course, is not qualified to prescribe any rational treatment for its cure.

Hippocrates 460-375 BC
Extent and determinants of error in doctor’s prognoses in terminally ill patients: prospective cohort study

Christakis N, Lamont E. BMJ. Vol 329,469-73.2000
Extent and determinants of error in doctors' prognoses in terminally ill patients: prospective cohort study

• Objective
  – To describe doctors' prognostic accuracy in terminally ill patients and to evaluate the determinants of that accuracy.

• Design
  – Prospective cohort study in five outpatient hospice programs in Chicago

• Participants
  – 343 doctors provided survival estimates for 468 terminally ill patients at the time of hospice referral

Extent and determinants of error in doctors' prognoses in terminally ill patients: prospective cohort study

• Cohort
  – Five outpatient hospice programs in Chicago in 1996
• Referring doctors were contacted and administered a four minute telephone survey
  – Estimate of how long the patient had to live
• Additional data collected
  – Patient demographic, diagnoses
  – Physician specialty, years in practice, and board certification from public records.
  – Dates of patients' deaths obtained from public death registries or the hospices

Christakis N, Lamont E. BMJ. 2000 February 19; 320(7233): 469–473
Extent and determinants of error in doctors' prognoses in terminally ill patients: prospective cohort study

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Survival</td>
<td>24 days</td>
</tr>
<tr>
<td>Accurate Prediction</td>
<td>20% (92/468)</td>
</tr>
<tr>
<td>Over-optimistic</td>
<td>63% (295/468)</td>
</tr>
<tr>
<td>Over-pessimistic</td>
<td>17% (81/468)</td>
</tr>
<tr>
<td>Physicians overestimated survival by a factor of 5.3</td>
<td></td>
</tr>
<tr>
<td>Few patient or doctor characteristics were associated with prognostic accuracy</td>
<td></td>
</tr>
</tbody>
</table>

Predicted versus observed survival in 468 terminally ill hospice patients. Diagonal line represents perfect prediction. Patients above diagonal are those in whom survival was overestimated; patients below line are those in whom survival was underestimated.
Extent and determinants of error in doctors' prognoses in terminally ill patients: prospective cohort study

- Doctors are inaccurate in their prognoses for terminally ill patients and the error is systematically optimistic.
- The prognostic inaccuracy is, in general, not restricted to certain kinds of doctors or patients.
- This may be adversely affecting the quality of care given to patients near the end of life.

Christakis N, Lamont E. BMJ. 2000 February 19; 320(7233): 469–473
Commentary: Prognoses should be based on proved indices not intuition

- The accurate prediction of survival is important for several reasons. Excessive optimism may cause us to wait too long to refer people for palliative care, we may delay the use of narcotic drugs for pain relief, and we may persist in unpleasant and pointless treatments aimed at curing or prolonging life when it would be kinder to stop.

Christakis N, Lamont E. BMJ. 2000 February 19; 320(7233): 469–473
Commentary: Prognoses should be based on proved indices not intuition

- *In the long term it may be possible to extract from the research those criteria that will enable us to make more reliable clinical predictions. Until that time arrives we would do better to stop guessing and, when predictions are needed, to make use of these indices.*

Christakis N, Lamont E. BMJ. 2000 February 19; 320(7233): 469–473
Doctors' prognostic estimates are a central element of both patient and physician decision making, especially at the end of life.

How can medicine scientifically address the issue of prognosis such that both physicians and patients are better informed?
Studies of Prognosis
Prognostic factors for outcome

Disease Onset

Risk Factors

Outcomes
- Morbidity
- Mortality
- Recovery

Study Types
- Case control studies
- Cohort studies
Elements of Prognostic Studies

• Population based
  – Representative sample of people afflicted with a disease
    • Unbiased

• Zero time
  – Time of onset of disease or symptoms
    • Must be well defined
  – Participants should all be enrolled and observed from the same time
    • Maximizes precision
  – Inception cohort
    • Group of people assembled at the onset, or inception of a disease
Elements of Prognostic Studies

• Follow up
  – Appropriate length of follow up depends upon the disease and anticipated outcomes
    • Patients must be followed long enough for the clinically important outcome events to occur
    • Inadequate follow up time
      – Observed rate of a given outcome will likely underestimate its true rate
Important Definitions

• Clinical course
  – The evolution (prognosis) of a disease has come under medical care and has been treated in a variety of ways that affect the subsequent course of events.

• Natural History
  – The evolution (prognosis) of disease without medical intervention.
## Differences in Risk and Prognostic Factors

<table>
<thead>
<tr>
<th></th>
<th>Risk factors</th>
<th>Prognostic factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Population</td>
<td>Healthy Population</td>
<td>Sick Population</td>
</tr>
<tr>
<td>Outcome</td>
<td>Disease onset</td>
<td>Morbidity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mortality</td>
</tr>
<tr>
<td>Rates</td>
<td>Rare event</td>
<td>Relatively Frequent events</td>
</tr>
</tbody>
</table>
Risk and Prognostic Factors

Outcomes of Disease: The 5 D’s

- Important Clinical Outcomes of Concern:
  - Death
  - Disease
  - Discomfort
  - Disability
  - Dissatisfaction
Important Rates Used to Describe Prognosis

• 5 year survival: percent of patients surviving 5 years from some point in the course of their disease

• Case fatality: percent of patients with a disease who die with it

• Disease-specific mortality: number of people per 100,000 population dying of a specific disease
Important Rates Used to Describe Prognosis

- **Response**: percent of patients showing a clinical improvement following a therapeutic intervention.
- **Remission**: percent of patients entering a phase in which disease is no longer detectable.
- **Recurrence**: percent of patients entering a phase in which disease is no longer undetectable.
Survival Analysis
Survival Analysis

• Survival analysis is another name for time to event analysis.
• Survival analysis is used predominately in biomedical sciences where the interest is in observing time to death
• Time to event can be used for many other applications
  – time to discontinuation of a contraceptive,
  – time to cancer recurrence
  – time to cure of an infection
  – time for a leg fracture to heal
Survival Analysis

Some real life examples....
Case 1

- 63 year old Caucasian man
- HTN and DM
- Palpable abdominal mass confirmed by CT scan
- AAA 8 cm in size
- What is his prognosis?
Rupture rate of large abdominal aortic aneurysms in patients refusing or unfit for elective repair

• Background:
  – Among patients with abdominal aortic aneurysm (AAA) who have high operative risk, repair is usually deferred until the AAA reaches a diameter at which rupture risk is thought to outweigh operative risk
  – Few data exist on rupture risk of large AAA

• Objective:
  – To determine the incidence of rupture in patients with large AAA

Lederle FA et al. JAMA. 2002 Jun 12;287(22):2968-72
Rupture rate of large abdominal aortic aneurysms in patients refusing or unfit for elective repair

• Method and Outcomes
  – Prospective cohort study in 47 Veterans Affairs medical centers
  – Veterans (n = 198) with AAA of at least 5.5 cm for whom elective AAA repair was not planned because of medical contraindication or patient refusal
  – Incidence of AAA rupture by strata of initial and attained diameter

Lederle FA et al. JAMA. 2002 Jun 12;287(22):2968-72
Cumulative Incidence of Probable Rupture by Attained AAA Diameter

Rupture rate of large abdominal aortic aneurysms in patients refusing or unfit for elective repair

• Conclusion
  – The rupture rate is substantial in high-operative-risk patients with AAA of at least 5.5 cm in diameter and increases with larger diameter

Lederle FA et al. JAMA. 2002 Jun 12;287(22):2968-72
Case 2

- 23 year old woman, IVDA
- Admitted to the hospital for bacterial pneumonia.
- Diagnosed with HIV
- What is her prognosis?
- When should HIV therapy be started?
Time Course of HIV Infection: Immunological and Virological

### When To Start Treatment? – Summary of Current Guidelines

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>symptoms or CD4 &lt;200</th>
<th>CD4 200-350</th>
<th>CD4 &gt;350</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DHHS:</strong> 7/14/03 update</td>
<td>treat</td>
<td>offer treatment</td>
<td>defer if VL &lt;55K; treat or defer if VL &gt;55K</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;www.aidsinfo.nih.gov&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>IAS-USA:</strong> JAMA 2002</td>
<td>treat</td>
<td>consider treatment</td>
<td>consider if VL &gt;50-100K</td>
</tr>
</tbody>
</table>
Case 3

- 87 year old caucasian man
- HTN
- Recently admitted for an ischemic stroke
- Will the addition of lipid lowering therapy affect prognosis?
High-Dose Atorvastatin after Stroke or Transient Ischemic Attack

- Statins reduce the incidence of strokes among patients at increased risk for cardiovascular disease; whether they reduce the risk of stroke after a recent stroke or transient ischemic attack (TIA) remains unknown.

High-Dose Atorvastatin after Stroke or Transient Ischemic Attack

• Method
  – 4731 patients with prior stroke or TIA within one to six months before study entry, low-density lipoprotein (LDL) cholesterol levels of 100 to 190 mg per deciliter (2.6 to 4.9 mmol per liter), and no known coronary heart disease were randomly assigned to double-blind treatment with 80 mg of atorvastatin per day or placebo.
  – Primary end point- first nonfatal or fatal stroke

Stroke or TIA

Cardiovascular Events

High-Dose Atorvastatin after Stroke or Transient Ischemic Attack

• Conclusion
  – In patients with recent stroke or TIA and without known coronary heart disease, 80 mg of atorvastatin per day reduced the overall incidence of strokes and of cardiovascular events

Clinical Prediction Rules

• Prediction rules estimate the probability of outcomes according to a set of patient characteristics
  – Outcomes include
    • Morbidity, mortality, adverse events etc
Predicting Mortality Among Patients Hospitalized for Heart Failure

• A predictive model of mortality in heart failure may be useful for clinicians to improve communication with and care of hospitalized patients

• Objective:
  – To identify predictors of mortality and to develop and validate a model using information available at hospital presentation

Predicting Mortality Among Patients Hospitalized for Heart Failure

• Retrospective study of 4031 community-based patients presenting with heart failure at multiple hospitals in Ontario, Canada
  – 2624 patients in the derivation cohort from 1999-2001
  – 1407 patients in the validation cohort from 1997-1999

Clinical Prediction Rules

Table 4. Heart Failure Risk Scoring System*

<table>
<thead>
<tr>
<th>Variable</th>
<th>30-Day Score†</th>
<th>1-Year Score‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>+Age (in years)</td>
<td>+Age (in years)</td>
</tr>
<tr>
<td>Respiratory rate, min (minimal 20; maximum 45)§</td>
<td>+Rate (in breaths/min)</td>
<td>+Rate (in breaths/min)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥180</td>
<td>-60</td>
<td>-50</td>
</tr>
<tr>
<td>160-179</td>
<td>-55</td>
<td>-45</td>
</tr>
<tr>
<td>140-159</td>
<td>-50</td>
<td>-40</td>
</tr>
<tr>
<td>120-139</td>
<td>-45</td>
<td>-35</td>
</tr>
<tr>
<td>100-119</td>
<td>-40</td>
<td>-30</td>
</tr>
<tr>
<td>90-99</td>
<td>-35</td>
<td>-25</td>
</tr>
<tr>
<td>&lt;90</td>
<td>-30</td>
<td>-20</td>
</tr>
<tr>
<td>Urea nitrogen (maximum, 60 mg/dL)§¶</td>
<td>+Level (in mg/dL)</td>
<td>+Level (in mg/dL)</td>
</tr>
<tr>
<td>Sodium concentration &lt;136 mEq/L</td>
<td>+10</td>
<td>+10</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>+10</td>
<td>+10</td>
</tr>
<tr>
<td>Dementia</td>
<td>+20</td>
<td>+15</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>+10</td>
<td>+10</td>
</tr>
<tr>
<td>Hepatic cirrhosis</td>
<td>+25</td>
<td>+35</td>
</tr>
<tr>
<td>Cancer</td>
<td>+15</td>
<td>+15</td>
</tr>
<tr>
<td>Hemoglobin &lt;10.0 g/dL (&lt;100 g/L)</td>
<td>NA</td>
<td>+10</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not applicable to 30-day model.
*An electronic version of the risk scoring system is available at: http://www.ccort.ca/CHFriskmodel.asp.
†Calculated as age + respiratory rate + systolic blood pressure + urea nitrogen + sodium points + cerebrovascular disease points + dementia points + chronic obstructive pulmonary disease points + hepatic cirrhosis points.
‡Calculated as age + respiratory rate + systolic blood pressure + urea nitrogen + sodium points + cerebrovascular disease points + dementia points + chronic obstructive pulmonary disease points + hepatic cirrhosis points + cancer points.
§Values higher than maximum or lower than minimum are assigned the listed maximum or minimum values.
¶Increases were protective in both mortality models. Points are subtracted for higher blood pressure measurements.
Maximum value is equivalent to 21 mmol/L. Score calculated using value in mg/dL.

Clinical Prediction Rules

A Prediction Rule to Identify Low-Risk Patients with Community-Acquired Pneumonia

• There is considerable variability in rates of hospitalization of patients with community-acquired pneumonia, in part because of physicians' uncertainty in assessing the severity of illness at presentation

• Purpose
  – to develop a prediction rule for prognosis that would accurately identify patients with community-acquired pneumonia who are at low risk of dying within 30 days of presentation and to assess the predictive accuracy of this rule for clinically relevant major outcomes

A Prediction Rule to Identify Low-Risk Patients with Community-Acquired Pneumonia

- Data collected on 14,199 adult inpatients with community-acquired pneumonia.
- A prediction rule was derived that stratified patients into five classes with respect to the risk of death within 30 days.
- The rule was validated with 1991 data on 38,039 inpatients and with data on 2287 inpatients and outpatients in the Pneumonia Patient Outcomes Research Team (PORT) cohort study.

### Pneumonia Severity Index

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Points assigned</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic factor</strong></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Age (yrs)</td>
</tr>
<tr>
<td>Men</td>
<td>Age (yrs) - 10</td>
</tr>
<tr>
<td>Women</td>
<td></td>
</tr>
<tr>
<td>Nursing-home resident</td>
<td>+10</td>
</tr>
<tr>
<td><strong>Co-existing illnesses</strong></td>
<td></td>
</tr>
<tr>
<td>Neoplastic disease</td>
<td>+30</td>
</tr>
<tr>
<td>Liver disease</td>
<td>+20</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>+10</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>+10</td>
</tr>
<tr>
<td>Renal disease</td>
<td>+10</td>
</tr>
<tr>
<td><strong>Physical examination findings</strong></td>
<td></td>
</tr>
<tr>
<td>Altered mental status</td>
<td>+20</td>
</tr>
<tr>
<td>Respiratory rate ≥30 breaths/min</td>
<td>+20</td>
</tr>
<tr>
<td>Systolic blood pressure &lt; 90 mm Hg</td>
<td>+20</td>
</tr>
<tr>
<td>Temperature &lt; 35°C (95°F) or ≥40°C(104°F)</td>
<td>+15</td>
</tr>
<tr>
<td>Pulse ≥125 beats/min</td>
<td>+10</td>
</tr>
<tr>
<td><strong>Laboratory and radiographic findings</strong></td>
<td></td>
</tr>
<tr>
<td>(if study performed)</td>
<td></td>
</tr>
<tr>
<td>Arterial blood pH &lt; 7.35</td>
<td>+30</td>
</tr>
<tr>
<td>Blood urea nitrogen level ≥30 mg/dL</td>
<td>+20</td>
</tr>
<tr>
<td>Sodium level &lt; 130 mmol/L</td>
<td>+20</td>
</tr>
<tr>
<td>Glucose level ≥250 mg/dL</td>
<td>+10</td>
</tr>
<tr>
<td>Hematocrit &lt; 30%</td>
<td>+10</td>
</tr>
<tr>
<td>Partial pressure of arterial O₂ &lt; 60 mm Hg or O₂ Sat &lt; 90%</td>
<td>+10</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>+10</td>
</tr>
</tbody>
</table>
## Pneumonia Severity Index

<table>
<thead>
<tr>
<th>Class</th>
<th>Points</th>
<th>Mortality*</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>&lt;51</td>
<td>0.1%</td>
</tr>
<tr>
<td>II</td>
<td>51-70</td>
<td>0.6%</td>
</tr>
<tr>
<td>III</td>
<td>71-90</td>
<td>0.9%</td>
</tr>
<tr>
<td>IV</td>
<td>91-130</td>
<td>9.5%</td>
</tr>
<tr>
<td>V</td>
<td>&gt;130</td>
<td>26.7%</td>
</tr>
</tbody>
</table>

* From the PORT study validation cohort


Prediction rule accurately identified the patients with community-acquired pneumonia at low risk for death and other adverse outcomes.

The prediction rule may help physicians make more rational decisions about hospitalization for patients with pneumonia.

Bias in cohort studies: impact on prognosis
Remember......

• Bias:
  – The introduction of error that produces deviations or distortions of data that are predominantly in one direction, as opposed to random error.
Bias in cohort studies

• In cohort studies concerned with risk or prognosis:
  – Bias can create an apparent difference between groups when it does not exist or can obscure a difference when it does truly exists.
  – The result is a false measure or association
Examples of bias in cohort studies

- **Susceptibility/assembly bias**
  - Groups being compared are not equally susceptible to the outcome of interest for reasons other than the factor under study.

- **Cohort differences**
  - Different levels of diseases severity
  - Different treatments
  - Presence of other comorbid illnesses
  - Duration of illness at time of enrollment
Examples of bias in cohort studies

• Migration bias
  – Patients in different subgroups drop out or switch to another group.
  – If the number of changes is sufficient in a given direction, this will impact the measure of association and conclusion
Examples of bias in cohort studies

• Measurement bias
  – Different methods in which an outcome is sought or classified.
    • Subclinical disease
    • Side effects
    • Disability
  – Careful rules must be set up to define an ‘event’ and must be applied consistently throughout the study
Examples of bias in cohort studies

### Controlling for bias in cohort studies

<table>
<thead>
<tr>
<th>Method</th>
<th>Description</th>
<th>Study Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomization</td>
<td>Assignment resulting in equal chance to fall into a given study group</td>
<td>Design</td>
</tr>
<tr>
<td>Restriction</td>
<td>Limit the range of patient characteristics in a study</td>
<td>Design</td>
</tr>
<tr>
<td>Matching</td>
<td>For each study patient, select a comparator with the same characteristics (except the outcome of interest)</td>
<td>Design and Analysis</td>
</tr>
<tr>
<td>Stratification</td>
<td>Compare rates within subgroups</td>
<td>Analysis</td>
</tr>
<tr>
<td>Multivariable analysis</td>
<td>Adjust for differences in a large number of factors using mathematical modeling techniques</td>
<td>Analysis</td>
</tr>
</tbody>
</table>
Conclusion

- Doctors' prognostic estimates are a central element of both patient and physician decision making
- Doctors are inaccurate in their prognoses, especially if they rely on intuition and not evidence based practice
- Studies of prognosis are important for accurate decision making
- Prognostic factors can be different than risk factors
Conclusion

• Prognostic (cohort studies) should be:
  – Population based
  – A representative sample of people afflicted with a disease
  – Of similar time onset of disease or symptoms
  – Unbiased
    • Should have minimal
      – Assembly bias
      – Migration bias
      – Measurement bias
Conclusion

• Important analyses of prognosis include:
  – Survival analysis (Kaplan-Meier analysis)
  – Clinical prediction rules

• Important prognostic outcomes of interest include
  – Death
  – Disease
  – Discomfort
  – Disability
  – Dissatisfaction
Conclusion

• Important methods to control for bias in studies of prognosis include
  – Randomization
  – Restriction
  – Matching
  – Stratification
  – Multivariable analysis
The End