Does the White Cell Matter in septic shock?

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Disclosures

None
Objectives

1. Review limitations of prognostic tools

2. Introduce group-based trajectory analysis, a method to identify variability in a patient’s illness or response to treatment

3. Present research results exploring trajectories of white cells in patients with septic shock
Background

• Infection is the 3rd leading cause of preventable mortality\(^1\)

• Incidence of septic shock ~3/1000 per year\(^2\)

• 2016 Sepsis-3 definition of sepsis:
  – life-threatening organ dysfunction due to a dysregulated host response to infection

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Pathophysiology

• Complex host response
• Balance of pro-inflammatory and anti-inflammatory responses
• WBC play an important role
  – Pro-inflammatory phase (neutrophils/monocytes)
  – Anti-inflammatory phase (lymphocytes)
Prognosis – baseline characteristics

- APACHE II score
  - 12 physiologic variables, max score 71
  - Most abnormal value in first 24 hours of admission

Prognosis – baseline characteristics

- SOFA score
  - 6 organ systems
  - Score 0-4, worse value per day used
  - Possible score 0-24
    - Score >15 associated with mortality of 90%
    - Increase in SOFA score over first 48 hrs associated with >50% mortality

Limitations of current scoring systems

- Assessments are typically static, based on the first 24 hours of ICU admission

- Fail to consider clinical phenotypes, individual genotypes, or response to treatment
Precision Medicine

• An emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle

• Identify “like” groups
  1. Inflammatory biomarkers
  2. Genetic testing or genetic array
Metabolic profiles in SIRS (white) and sepsis (black)
Genetic Array in pediatric sepsis

- Genes corresponding to glucocorticoid receptor signalling
- 28-day mortality 22% (subclass A) vs. 10% (subclass B), p<0.05
Precision Medicine

• An emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle

• Identify “like” groups
  1. Inflammatory biomarkers
  2. Genetic testing or genetic array
  3. Trajectory analysis
Trajectory analysis

• Describes the pattern of a dependent variable over time
  – unique subgroups exist within a population that follow distinct trajectories over time

• Data that evolves over time, such as the temporal trend of the complete blood count

Recidivism trajectories in sex-offenders

• Population separated into risk categories
• Unique, modifiable characteristics of group membership can be explored

Trajectory analysis of HIV virologic outcomes

- Identify and predict HIV ‘career’ trajectories
- Models incorporate social and SES variables
A primer on trajectory analysis

• PROC TRAJ – SAS procedure that estimates multiple groups in a population

• Identifies clusters of individuals following similar progressions over time by fitting a group based model

• Subjects are grouped and assumed that everyone in group follows same trajectory

Nagin DS. Group-Based Modeling of Development. Cambridge, Massachusetts: Harvard University Press; 2005
Methods – Trajectory analysis

1. Determine the maximum number of groups
2. Fit number of groups to data
   – Start at one, then 2, then 3, and so on
3. Select the maximum shape of the pattern of change for each group over time (linear or other)
   – Can model up to 5th order polynomials
Methods – Model choice and diagnostics

• Model choice based on:
  – Bayesian Information Criterion (BIC)
    • Log-likelihood adjusted for number of parameters and sample size
  – Clinical judgment
  – Parsimony

• Model diagnostics
  – Ratio between the probability of group membership to the actual group assignment
  – Average posterior probability
  – Odds of correct classification
White Blood Cell Count and Septic Shock

• CBC very commonly ordered test in ICU
• WBC integrates many parameters that are pertinent to the host response
  – e.g. granulopoiesis, mobilization of white cells from the marrow reserve, margination and egress into tissues, and apoptosis
• Specific changes in WBC over time in septic shock are not well described
White blood cell count derangements and outcomes septic shock

- First 48 hours\(^1\)
  - Initial leukocytosis due to neutrophilia
  - Lymphocyte count low
- Persistent lymphopenia associated with poor outcome\(^2\)
- Baseline WBC <4 associated with increased mortality\(^3\)
  - OR 1.85 (95%CI 1.38-2.48)

Limitations of existing data

• *Modeling the Average WBC*
  – Might not be representative of ANYONE in the population
• Value on first day
• Pre-determined groups based on expert opinion

• Small sample sizes
• Studies are not contemporaneous and to not reflect current standards of care or mortality rates
Hypotheses

- There are distinct clinical of individuals with septic shock with different disease biology, genetics or response to treatment that can be identified using trajectory analysis.

- Identified trajectories will be able to predict mortality.
Objectives our study

• Identify subgroups of patients with septic shock with differing patterns of WBC counts over time

• Identify characteristics of patients and pathogens associated with the unique WBC count trajectories identified

• Evaluate the association between the unique WBC count trajectories and 30-day mortality in patients with septic shock
Study Design: Retrospective Cohort (n = 917)

• **Inclusion criteria:**
  – Adult patients with septic shock at HSC or SBH
  – Identified from CATSS database
  – Linked to LIS for complete study records

• **Exclusion criteria:**
  – Malignancy, HIV, immunosuppression, liver disease, neutropenia
  – ICU length of stay <48 hours
  – <3 WBC measurements
  – Re-admission for septic shock within study period
Results: Trajectory analysis of WBC count

Mean WBC overall recorded every 12 hours.
# Summary of WBC trajectory

<table>
<thead>
<tr>
<th>Group Number</th>
<th>Summary of WBC trajectory</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Normal, flat</td>
</tr>
<tr>
<td>2</td>
<td>Normal, rising</td>
</tr>
<tr>
<td>3</td>
<td>Moderate, gradual decline</td>
</tr>
<tr>
<td>4</td>
<td>High, gradual decline</td>
</tr>
<tr>
<td>5</td>
<td>High, rising</td>
</tr>
<tr>
<td>6</td>
<td>High, rapid decline</td>
</tr>
<tr>
<td>7</td>
<td>Significant elevation</td>
</tr>
</tbody>
</table>
Selecting the best model using the BIC

<table>
<thead>
<tr>
<th>Group</th>
<th>BIC (Observation)</th>
<th>(BIC subjects)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>-24834.8</td>
<td>-24818.6</td>
</tr>
<tr>
<td>3</td>
<td>-24176.8</td>
<td>-24152.3</td>
</tr>
<tr>
<td>4</td>
<td>-23919.4</td>
<td>-23886.9</td>
</tr>
<tr>
<td>5</td>
<td>-23710.1</td>
<td>-23669.4</td>
</tr>
<tr>
<td>6</td>
<td>-23677.5</td>
<td>-23628.6</td>
</tr>
<tr>
<td>7</td>
<td>-23499.2</td>
<td>-23442.2</td>
</tr>
</tbody>
</table>

- \(2^* (\Delta \text{BIC}) = 2^* (-23499.2 - (-23677.5)) = 356.6\)
- Strong evidence to support group 7
### Testing model robustness

<table>
<thead>
<tr>
<th>Trajectory</th>
<th>( \pi_j ) (%)</th>
<th>Actual(%)</th>
<th>ratio</th>
<th>( \pi_j ) odds</th>
<th>AvgPP</th>
<th>AvgPP odds</th>
<th>OCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>35</td>
<td>35.4</td>
<td>0.99</td>
<td>0.54</td>
<td>0.88</td>
<td>7.6</td>
<td>14.1</td>
</tr>
<tr>
<td>2</td>
<td>7.9</td>
<td>6.2</td>
<td>0.82</td>
<td>0.09</td>
<td>0.85</td>
<td>5.6</td>
<td>64.9</td>
</tr>
<tr>
<td>3</td>
<td>34.6</td>
<td>35.8</td>
<td>0.97</td>
<td>0.53</td>
<td>0.83</td>
<td>4.8</td>
<td>9.0</td>
</tr>
<tr>
<td>4</td>
<td>14</td>
<td>14.1</td>
<td>0.99</td>
<td>0.16</td>
<td>0.87</td>
<td>6.7</td>
<td>40.7</td>
</tr>
<tr>
<td>5</td>
<td>3.1</td>
<td>2.9</td>
<td>0.94</td>
<td>0.03</td>
<td>0.95</td>
<td>18.4</td>
<td>572.5</td>
</tr>
<tr>
<td>6</td>
<td>4.5</td>
<td>4.6</td>
<td>0.98</td>
<td>0.05</td>
<td>0.95</td>
<td>19.3</td>
<td>411.0</td>
</tr>
<tr>
<td>7</td>
<td>0.8</td>
<td>0.8</td>
<td>1</td>
<td>0.01</td>
<td>1.00</td>
<td>172412.8</td>
<td>2251348</td>
</tr>
</tbody>
</table>
Final model – 7 groups

• Face validity: meaningful and potentially expected trajectories for patients with septic shock

• BIC value: less negative than the preceding groups

• Predicted group assignment with high probability
Methods - Multinomial regression

• Evaluate patient, illness and pathogen characteristics association with trajectory group
• Trajectory 1 reference group
• Multivariable model
  – Age, sex, APACHEII*WBC, bacteremia, time to antibiotics, use of appropriate antibiotics, number of organ failures at time of ICU admission and baseline platelet count
Creation of new variable APACHEII*WBC

• If WBC >=40 or <= 1, then subtract 4 from APACHE II score
• If WBC 20-39.9 or 1-2.9, then subtract 2 from APACHE II score
• If WBC 15-19.9, then subtract 1 from APACHE II score
• If WBC 3-14.9, then do not alter the APACHE II score
## Results - Multinomial regression

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.99 (0.97, 1.01)</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.89 (0.48, 1.65)</td>
</tr>
<tr>
<td>APACHE II score (excl WBC)</td>
<td>1.02 (0.97, 1.07)</td>
</tr>
<tr>
<td>Time to 1st antibiotic (hours)</td>
<td>1 (0.98, 1.02)</td>
</tr>
<tr>
<td>Appropriate Antibiotic Use</td>
<td>1.26 (0.41, 3.82)</td>
</tr>
<tr>
<td>Number of organ failures on day 1</td>
<td>1.21 (0.96, 1.52)</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>0.98 (0.46, 2.1)</td>
</tr>
<tr>
<td>Platelet count (per 10 increase)</td>
<td>2.01 (0.94, 4.31)</td>
</tr>
</tbody>
</table>
Group Trajectory and mortality outcomes:
Cox proportional hazard model

• Outcome: 30-day mortality
• Variables in multivariable model
  – age, sex, APACHE II*WBC, number of organ failures on day 1 of ICU admission, bacteremia, culture positive or negative, time to first antibiotic, the provision of appropriate antibiotics, combination antibiotics
• Time zero = admission to ICU
Mortality

• Unadjusted overall 30-day mortality 26.3%

P = 0.0013
## Mortality - Cox proportional hazard model

<table>
<thead>
<tr>
<th>Group</th>
<th>Hazard Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>reference</td>
<td>reference</td>
</tr>
<tr>
<td>2</td>
<td>1.46 (0.84, 2.54)</td>
<td>0.184</td>
</tr>
<tr>
<td>3</td>
<td>1.13 (0.81, 1.58)</td>
<td>0.464</td>
</tr>
<tr>
<td>4</td>
<td>0.84 (0.51, 1.38)</td>
<td>0.486</td>
</tr>
<tr>
<td>5</td>
<td><strong>3.48 (1.91, 6.35)</strong></td>
<td><strong>&lt;0.0001</strong></td>
</tr>
<tr>
<td>6</td>
<td>1.43 (0.7, 2.92)</td>
<td>0.329</td>
</tr>
<tr>
<td>7</td>
<td>1.44 (0.35, 6.02)</td>
<td>0.617</td>
</tr>
</tbody>
</table>

Adjusted for age, sex, APACHE*WBC, co-morbidities, type of infection, time to antibiotics, appropriate antibiotics
Strengths

• Novel method of analysis to demonstrate individual variability in sepsis
• Large database; consecutive patients
• Excluded patients with alternative explanation of WBC count abnormalities
Mean WBC overall recorded every 12 hours.

WBC 7 Days – 7 Groups

Group Percents: 35.0 7.9 34.6 14.0 3.1 4.5 0.8
Limitations

• Proof of concept
• Retrospective
  – Unmeasured confounders
• Diverse but finite explanatory variables included
  – e.g. missing: Frailty, immune responses, genomics
• Large database but small overall numbers in the trajectory groups
Conclusions – Septic shock

• Group-based trajectory analyses can segregate patients into distinct and clinically relevant WBC trajectories

• Conventionally recognized patient, treatment and illness characteristics poorly predict trajectory assignment

• A rising WBC is independently associated increased risk of death at 30-days
What’s next?

- Validate in larger database
- Trajectory of neutrophils and lymphocytes
- Trajectory of platelet count, bilirubin
- Create a multivariable trajectory model
What’s the vision?

• Real-time integration of comprehensive health data to create dynamic patient trajectories
  – Inform prognosis
  – Response to treatment
    • When to escalate or de-escalate
"Sepsis and ARDS are biologically heterogenous syndromes: they are not diseases per se with singular mechanisms that are plausibly amenable to singular interventions"

Beyond Critical Care

• Application of trajectory analysis to other areas of medicine are many:
  – Changes in tumor markers
    • e.g. M-protein in myeloma or PSA in prostate cancer
  – Changes in functional ability
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