Platelet Recovery Rate at Day 5 of Therapeutic Plasma Exchange for Acquired Thrombotic Thrombocytopenic Purpura Can Aid in Identifying Risk of Disease Exacerbation

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Presentation Outline

- Disease Background
- Previous research on platelet recovery rate
- Goal of our study
- Methods
- Results
- Limitations
- Conclusions
Acquired TTP

- Autoimmune disease
- Many patients have severe, antibody-induced deficiency of ADAMTS13
  - von Willebrand factor cleaving protease
  - Activity levels ≤10%
- Classically characterized by pentad of findings
  - Thrombocytopenia
  - Microangiopathic hemolytic anemia
  - Fever
  - Nervous system and kidney dysfunction
- Now only dyad of thrombocytopenia and hemolytic anemia used to consider diagnosis
Acquired TTP

- **Standard of care**
  - Emergent therapeutic plasma exchange (TPE)
  - Plasma used as replacement fluid
  - Daily treatment until
    - PLT counts normal x 2 days
    - LDH normalizing

- **Despite prompt treatment, exacerbations occur in ~50% patients**
  - Disease recurrence within 30 days of achieving remission and stopping TPE
  - Currently no well-characterized metrics of distinguishing exacerbators vs. non-exacerbators
Platelet Recovery Rate (PRR)

- Hypothesized as a potential marker of TTP recurrence
- PRR defined as the linear rate of change in platelet count per day

\[
PRR3 = \frac{\Delta \text{Platelet count (day 3 – day 0)}}{3}
\]

- PRR3 ≥ 5,000/µL/day previously identified as a potential marker of disease exacerbation
  - Correctly classified 94% exacerbators
  - Misclassified 67% non-exacerbators

Previous PRR Research

• That TTP patient population had
  » ~60% patients with >10% ADAMTS13 activity
  » ~50% patients with associated diagnoses that could cause thrombotic microangiopathy (TMA) and confound diagnosis of acquired TTP

• Based on our previous analyses of our TTP patient population, we know that our patients with clinical diagnoses of acquired TTP had almost exclusively
  » Severe ADAMTS13 deficiency
  » No associated diagnoses which could cause TMA
Goal of Our Study

• Analyze PRR as a marker of disease exacerbation in our TTP patient population
• Determine if PRR is a generalizable metric of disease exacerbation in different TTP patient populations
Methods

• IRB-approved 16-year retrospective study
• Patient records analyzed between 1/1999 – 12/2014

• Inclusion Criteria
  » Diagnosis of TTP
  » Severe ADAMTS13 deficiency (<10%)
  » First episode of disease

• Exclusion criteria
  » Plasma exchange was not exclusively performed at UNC
  » Other diagnoses which could cause TMA and possibly confound diagnosis of acquired TTP
    • Drugs, pregnancy, malignancy, etc.
Methods

• Patient demographic and laboratory data gathered
  » Age
  » Race
  » Gender
  » Platelet counts
    • Pre-treatment
    • First measurement each day for the first 5 days after treatment
  » Exacerbation status (Yes/No)
Methods

• PRR3 from previous study applied to our TTP patient cohort to determine how this threshold performed
  » PRR3 ≥ 5,000/µL/day

• Analyzed our TTP patient data
  » Calculated PRR1, 2, 3, 4, and 5
  » Stratified data by exacerbators vs. non-exacerbators
  » For any significant PRR differences identified
    • Receiver operator characteristic (ROC) curve analysis subsequently performed to identify optimal cut-point for distinguishing exacerbators vs. non-exacerbators
# Results

<table>
<thead>
<tr>
<th>Cohort</th>
<th>N</th>
<th>Mean age (years)</th>
<th>% Female</th>
<th>% Black</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exacerbation</td>
<td>35</td>
<td>46</td>
<td>77</td>
<td>63</td>
</tr>
<tr>
<td>Non-exacerbation</td>
<td>38</td>
<td>45</td>
<td>82</td>
<td>68</td>
</tr>
<tr>
<td>P value</td>
<td>---</td>
<td>0.78</td>
<td>0.54</td>
<td>0.61</td>
</tr>
</tbody>
</table>

*Statistical significance was defined as p<0.05*
Results

• When previously described threshold of PRR3 ≥ 5,000/µL/day was applied to our TTP patient population
  » Correctly classified 86% exacerbators
  » Mis-classified 100% of non-exacerbators
## Results

<table>
<thead>
<tr>
<th>PRR Day</th>
<th>Exacerbator</th>
<th>Non-Exacerbator</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRR1</td>
<td>5 000</td>
<td>10 000</td>
<td>0.20</td>
</tr>
<tr>
<td>PRR2</td>
<td>22 000</td>
<td>22 000</td>
<td>0.89</td>
</tr>
<tr>
<td>PRR3</td>
<td>27 000</td>
<td>30 000</td>
<td>0.40</td>
</tr>
<tr>
<td>PRR4</td>
<td>26 000</td>
<td>32 000</td>
<td>0.18</td>
</tr>
<tr>
<td><strong>PRR5</strong></td>
<td><strong>19 000</strong></td>
<td><strong>31 000</strong></td>
<td><strong>0.004</strong></td>
</tr>
</tbody>
</table>

*PRR units in /μL/day

*Statistical significance was defined as p<0.05
ROC Curve Analysis

Optimal cut-point = 9,000/µL/day
- Sensitivity = 40%
- Specificity = 97%

PRR5

AUC = 0.726
Limitations

• Retrospective study
  » Designed to generate hypotheses
  » Not powered or appropriate for proving them

• Relatively small sample size

• “Day” defined as starting at 12:00AM (midnight) and ending at 11:59PM
  » This definition may differentially influence the impact of TPE on PLT counts early in treatment
  » E.g., Patient A had 1st TPE at 11:00PM and PLT count drawn next day at 4:00AM (Δ5 hrs)
  » May be different from Patient B, who had 1st TPE at 5:00AM and PLT count drawn next day at 4:00AM (Δ23 hrs)
Conclusions

• Previously published threshold of PRR3 ≥ 5,000/µL/day was not a strong distinguisher of exacerbators vs. non-exacerbators in our TTP population

• Only PRR5 demonstrated a statistically significant difference between exacerbators and non-exacerbators in our TTP patients
  » But additional test performance characteristics revealed this metric to be a poor distinguisher of exacerbators vs. non-exacerbators as well

• As a marker of exacerbation, PRR needs further characterization via larger studies of TTP patients from different centers around the U.S.
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