Differentiation Between Primary Lateral Sclerosis and Amyotrophic Lateral Sclerosis

Examination of Symptoms and Signs at Disease Onset and During Follow-up

Maria Carmela Tartaglia, MD; Ann Rowe, RN; Karen Findlater, BScPT; J. B. Orange, PhD; Gloria Grace, PhD; Michael J. Strong, MD

Background: Motor neuron diseases can affect the upper motor neuron and/or the lower motor neuron. Both amyotrophic lateral sclerosis (ALS) and primary lateral sclerosis (PLS) are motor neuron diseases, and there is much debate as to whether these are 2 separate disorders or simply 2 points on a continuum.

Objective: To determine which clinical features at onset and during follow-up could help differentiate between PLS and ALS.

Design: Retrospective study comparing patients with a diagnosis of PLS or ALS for differences in symptoms or signs at disease onset and during follow-up.

Setting: Tertiary referral center.

Patients: Six hundred sixty-one patients with ALS and 43 patients with PLS were included in the study.

Results: At presentation, stiffness was the only symptom that was significantly different between patients with PLS and patients with ALS (observed in 47% and 4% of patients, respectively; \( P < .001 \)). During follow-up, limb wasting was rare in patients with PLS (2%, compared with 100% in patients with ALS; \( P < .001 \)). Disease duration was significantly longer in patients with PLS compared with patients with ALS (mean ± SD, 11.2 ± 6.1 vs 3.8 ± 4.2 years, respectively; \( P < .001 \)). During the 16 years of follow-up, the mortality rate was significantly lower in patients with PLS compared with patients with ALS (only 33% vs 89%, respectively; \( P < .001 \)).

Conclusion: Our findings suggest that a patient presenting with spasticity who does not develop wasting within 3 years most likely has PLS.

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Motor neuron diseases comprise a heterogeneous group of disorders that affect the upper motor neuron (UMN) and/or the lower motor neuron (LMN). Both amyotrophic lateral sclerosis (ALS) and primary lateral sclerosis (PLS) fall under the umbrella of motor neuron diseases. Amyotrophic lateral sclerosis is usually defined as a fatal neurodegenerative disorder that progressively affects both the UMN and LMN, with mean survival between 3 and 5 years, though long-term survival can occur, albeit infrequently. Primary lateral sclerosis is an idiopathic, nonfamilial neurodegenerative disorder of the UMN. In 1992, Pringle et al\(^1\) proposed diagnostic criteria for PLS that included the insidious onset of a symmetric, slowly progressive spastic paresis in adults, usually beginning in the lower extremities and eventually evolving into a tetrapyramidal syndrome with marked pseudobulbar features. The criteria written by Pringle et al\(^1\) demand a disease duration of at least 3 years, and other diagnoses are to be excluded by imaging and laboratory tests. There should be no family history of similar disorders. The absence of lower motor signs is the hallmark of the disease and can be confirmed using neurophysiologic studies.

There is an ongoing debate as to whether ALS and PLS are 2 separate disorders or simply 2 points on a continuum of motor neuron degeneration. Le Forestier et al\(^2\) have observed electrophysiologic evidence of LMN involvement in their patients with PLS, suggesting that PLS is not restricted to the UMN. Their patients had an insidious onset with slow progression, and all but 1 of their patients progressed to debilitating spasticity, though they were free of marked weakness. These authors have argued that PLS may be a slowly progressive form of ALS in which the LMN is affected, but the process is slower or different. In addition, postmortem studies have reported degeneration of

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January 15, 2006. Survival was defined as the period from first symptom onset until death or until January 15, 2006.

Patients with a diagnosis of PLS per criteria by Pringle et al1 or with definite ALS per El Escorial criteria4 reviewed in the Mine features that differentiate these 2 entities. Disease progression is slower in PLS and survival is longer. Because survival is substantially different, it would be prognostically useful if there were clinical criteria in addition to the criteria established by Pringle et al1 that could help differentiate between ALS and PLS early in the disease course. In this study, we have compared patients with PLS with patients with ALS to identify differences in symptoms or signs at disease onset and during follow-up to determine features that differentiate these 2 entities.

METHODS

Patients with a diagnosis of PLS per criteria by Pringle et al1 or with definite ALS per El Escorial criteria4 reviewed in the Motor Neuron Diseases Clinic at the University of Western Ontario from 1990 to 2006 were included in the analysis. All patients underwent electromyography/nerve condition studies (EMG/NCS). Primary lateral sclerosis was diagnosed in patients only if they had no evidence of acute or chronic denervation on EMG/NCS. We evaluated both symptoms and signs at the time of onset (ie, age, dysarthria, dysphagia, paresthesias, fasciculations, cramping, weakness, wasting, fatigability, stiffness, and dyspnea) in addition to symptoms and signs at follow-up (ie, bulbar dysfunction, wasting, pyramidal dysfunction, dementia, parkinsonism, and cerebellar, cortical, and sensory signs) for significant differences between the 2 patient populations. We also assessed the 2 groups for differences in comorbid diseases, including diabetes, epilepsy, cardiovascular disease, trauma, hypothyroidism, respiratory disease, rheumatological disease, malignancy, autoimmune disorder, infection, other neuromuscular disease, stroke/transient ischemic attack, human immunodeficiency virus (HIV) risk, and smoking status. This information was obtained during the initial visit and thus reflects premorbid conditions. Mann-Whitney tests were used to look for significant differences between the 2 groups. Two logistic regressions were run. The first included presenting symptoms and age at onset, and the second included follow-up symptoms and age at onset.

RESULTS

Complete data sets were available for 661 patients with ALS and 43 patients with PLS (Table 1). Patients with PLS demonstrated no evidence of acute or chronic denervation on EMG/NCS. Survival, defined as the period from the first symptom onset until death or until January 15, 2006, could be determined in 83% of patients with PLS and 90% of patients with ALS. Six patients with PLS and 64 patients with ALS were lost to follow-up. There was no significant difference in sex ratios between the 2 groups (49% of the patients were men in the PLS group and 56% were men in the ALS group).

Survival data were available in 36 patients with PLS (83%) and 597 patients with ALS (90%). The mean ± SD of disease duration was significantly longer in patients with PLS compared with patients with ALS (11.2 ± 6.1 vs 3.8 ± 4.2 years, respectively; P < .001). The mortality rate was also significantly different between the 2 groups, with an overall mortality rate of 33% in the PLS group and 89% in the ALS group (Figure). The breakdown of deaths per time interval is presented in Table 2. The median sur-

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Table 1. Patient Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients With PLS (N = 43)</th>
<th>Patients With ALS (N = 661)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset of first symptom, mean ± SD (range), y</td>
<td>54.62 ± 10.9 (33-74)</td>
<td>59.11 ± 13.1 (15-88)</td>
<td>.009</td>
</tr>
<tr>
<td>Sex, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>49</td>
<td>55.5</td>
<td>.39</td>
</tr>
<tr>
<td>F</td>
<td>51</td>
<td>44.5</td>
<td></td>
</tr>
<tr>
<td>Survival, mean ± SD (range), y</td>
<td>11.18 ± 6.1 (2.46-28.41)</td>
<td>3.76 ± 4.2 (0.39-60.63)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Survival, median ± SE, y</td>
<td>9.88 ± 1.0</td>
<td>2.76 ± 0.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Deceased, No. (%)</td>
<td>12 (33)</td>
<td>533 (89)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: ALS, amyotrophic lateral sclerosis; PLS, primary lateral sclerosis.

*Data on survival were available for 36 patients with PLS (83%). One patient was known to have died, but actual date of death could not be determined.

†Data on survival and mortality were available for 597 patients with ALS (90%). Survival was defined as the period from first symptom onset until death or until January 15, 2006.

‡Data on mortality were available for 37 patients with PLS.

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Figure. Kaplan-Meier survival curve for patients with primary lateral sclerosis (PLS) and patients with amyotrophic lateral sclerosis (ALS). Patients with PLS had a significantly longer survival compared with patients with ALS.
vival for the ALS group was 2.79 years. Because of prolonged survival, a median survival for the PLS group could not be calculated. The log-rank test indicated that the 2 survival curves differed significantly (χ² statistic of 70.49; P < .001).

**SYMPTOMS AND SIGNS AT ONSET**

Patients with PLS were significantly younger than patients with ALS at symptom onset (mean age ± SD, 54.6 ± 10.9 vs 59.1 ± 13.1 years, respectively; P = .009). At first presentation to the clinic, stiffness was the only symptom that was significantly different between patients with PLS and patients with ALS (47% vs 4%, respectively; P < .001). Dysphagia was a presenting symptom in 8% of the patients with ALS, while no patient with PLS presented with this problem (P = .51). Fasciculations, cramps, weakness, and limb wasting were more common in ALS, though not statistically significant (Table 3). There was no difference in the occurrence of either paresthesias or dyspnea between the 2 groups.

**SYMPTOMS AND SIGNS AT FOLLOW-UP**

During follow-up the 2 groups also displayed a different incidence for certain signs and symptoms (Table 4). Limb wasting was rare in patients with PLS compared with patients with ALS (2% vs 100%, respectively; P < .001). Bulbar symptoms were significantly less common in patients with PLS than in patients with ALS (74% vs 88%, respectively; P = .01). Cortical signs were slightly more common in PLS compared with ALS (P = .05). Clinically overt dementia, however, was more prevalent in patients with ALS than in patients with PLS (P = .06). Parkinsonism, and cerebellar pyramidal, and sensory occurred very rarely in both patient groups and thus were not significantly different.

**ASSOCIATED MEDICAL CONDITIONS**

Trauma was more commonly encountered in patients with PLS than in patients with ALS (19% vs 8%, respectively; P < .05) (Table 5). Autoimmune disorders were more common in patients with PLS (5% vs <1%; P < .005). There was no significant difference in the incidence of

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**Table 2. Mortality per Interval in Patients With ALS or PLS**

<table>
<thead>
<tr>
<th>Patient Outcome</th>
<th>Time Interval, y</th>
<th>Total</th>
<th>Patients with ALS, No. (%)</th>
<th>Patients with PLS, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-5.00</td>
<td>67</td>
<td>Alive 40 (8)</td>
<td>Alive 5 (83)</td>
</tr>
<tr>
<td></td>
<td>5.01-10.00</td>
<td>87</td>
<td>15 (17)</td>
<td>8 (67)</td>
</tr>
<tr>
<td></td>
<td>10.01-15.00</td>
<td>16</td>
<td>7 (44)</td>
<td>6 (75)</td>
</tr>
<tr>
<td></td>
<td>15.01-20.00</td>
<td>7</td>
<td>3 (43)</td>
<td>6 (75)</td>
</tr>
<tr>
<td></td>
<td>20.01-30.00</td>
<td>3</td>
<td>1 (33)</td>
<td>2 (100)</td>
</tr>
<tr>
<td></td>
<td>&gt;30.00</td>
<td>2</td>
<td>1 (50)</td>
<td>1 (50)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>597</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** ALS, amyotrophic lateral sclerosis; PLS, primary lateral sclerosis; ellipses, no patients applicable.

*Total number of patients during time interval.

**Table 3. Disease Symptoms and Signs at Onset**

<table>
<thead>
<tr>
<th>Disease Characteristic</th>
<th>Patients With PLS (N = 43)</th>
<th>Patients With ALS (N = 661)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site of first symptom or sign, %</td>
<td></td>
<td></td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Both LE</td>
<td>40</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Right LE</td>
<td>19</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Left LE</td>
<td>16</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Bulbar</td>
<td>14</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Left UE</td>
<td>7</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Right UE</td>
<td>2</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>UE + LE</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Both UE</td>
<td>0</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Bulbar + UE + LE</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

**Frequency of symptom and sign at onset, %**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Patients With PLS (N = 43)</th>
<th>Patients With ALS (N = 661)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysarthria</td>
<td>14</td>
<td>25</td>
<td>.09</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>0</td>
<td>8</td>
<td>.05</td>
</tr>
<tr>
<td>Paresthesias</td>
<td>0</td>
<td>1</td>
<td>.44</td>
</tr>
<tr>
<td>Fasciculations</td>
<td>0</td>
<td>7</td>
<td>.07</td>
</tr>
<tr>
<td>Cramps</td>
<td>0</td>
<td>7</td>
<td>.09</td>
</tr>
<tr>
<td>Weakness</td>
<td>42</td>
<td>55</td>
<td>.09</td>
</tr>
<tr>
<td>Wasting</td>
<td>0</td>
<td>7</td>
<td>.08</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0</td>
<td>5</td>
<td>.12</td>
</tr>
<tr>
<td>Stiffness</td>
<td>47</td>
<td>4</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>0</td>
<td>4</td>
<td>.19</td>
</tr>
</tbody>
</table>

**Table 4. Symptoms and Signs During Follow-up**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Patients With PLS (N = 43)</th>
<th>Patients With ALS (N = 661)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bulbar dysfunc</td>
<td>74</td>
<td>88</td>
<td>.01</td>
</tr>
<tr>
<td>Limb wasting</td>
<td>2</td>
<td>100</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Pyramidal signs</td>
<td>100</td>
<td>99</td>
<td>.61</td>
</tr>
<tr>
<td>Cerebellar signs</td>
<td>2</td>
<td>&lt; 1</td>
<td>.19</td>
</tr>
<tr>
<td>Cortical signs</td>
<td>2</td>
<td>&lt; 1</td>
<td>.049</td>
</tr>
<tr>
<td>Dementia</td>
<td>0</td>
<td>8</td>
<td>.06</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>0</td>
<td>&lt; 1</td>
<td>.61</td>
</tr>
<tr>
<td>Sensory signs</td>
<td>7</td>
<td>6</td>
<td>.71</td>
</tr>
</tbody>
</table>

**Abbreviations:** ALS, amyotrophic lateral sclerosis; LE, lower extremity; PLS, primary lateral sclerosis; UE, upper extremity.
respiratory disease, rheumatologic disease, malignancy, epilepsy, hypothyroidism, diabetes, cardiovascular or cerebrovascular disease, infective disease, smoking, or HIV between the 2 groups.

AMYOTROPHIC LATERAL SCLEROSIS

An analysis of presenting symptoms and signs in patients with ALS revealed that those who presented with spasticity (27 of 661 patients) had significantly better survival rates than patients who presented with other signs or symptoms (P = .009). There was, however, no statistically significant difference in disease duration between the 2 groups, though the patients who presented with spasticity had a longer disease duration than those who presented with other signs or symptoms (7.46 ± 13.0 vs 3.61 ± 3.3 years, respectively; P = .08). There was a trend for patients presenting with spasticity to be younger at disease onset than those who presented with other symptoms or signs (mean ± SD, 53.8 ± 15.7 vs 59.3 ± 13 years, respectively; P = .08). There was no difference in disease duration or mortality in patients with ALS who presented with weakness, fatigue, fasciculations, cramps, dyspnea, limb wasting, dysarthria, or dysphagia, as opposed to those who did not.

LOGISTIC REGRESSION

Two logistic regressions were run. The first included presenting symptoms and age at onset and revealed that stiffness is the most important variable for differentiating PLS from ALS (P = .004). Both dysarthria and weakness were also significant but much less so (P = .04 vs P = .03, respectively). In the second logistic regression, which included follow-up symptoms and age at onset, only limb wasting was significantly different between the 2 groups (P < .001).

COMMENT

We have observed that stiffness or spasticity was significantly more common as a presenting sign in patients with PLS than in patients with ALS, while limb wasting was rare in patients with PLS. Only 1 patient with PLS demonstrated limb wasting, while the remaining patients, including a patient observed for 24 years, had none. Sixteen of the patients with PLS studied in this cohort were observed for longer than 10 years, and limb wasting continued to be absent. In contrast to PLS, in which spasticity is ubiquitous, only 27 patients with ALS (4.1%) presented with spasticity and 21 had limb wasting within 3 years (77%). Extending the analysis to 4 years only added one other person. The remaining patients with ALS, in whom limb wasting developed following a spastic presentation, all had very long disease durations, consistent with the UMN-predominant variant of ALS.5 Taken together, our findings suggest that a patient presenting with spasticity who does not develop wasting within 3 years most likely has PLS.

Patients with PLS represent less than 3% of those with motor neuron disease, thus making it quite rare. Similar to ALS, there is no single diagnostic test for PLS. Primary lateral sclerosis remains a clinical diagnosis in which other illnesses must first be excluded.6 The Pringle et al7 criteria suggested that a disease duration of at least 3 years was required before a diagnosis of definite PLS can be made. In attempting to differentiate UMN-predominant variants of ALS from PLS, Gordon and colleagues8 extended disease duration to at least 4 years. We had 2 patients with ALS who had initially been diagnosed with PLS. One had leg weakness as the initial symptom, and 11 years later his EMG/NCS demonstrated acute and chronic denervation. During that time he had developed spasticity and dysarthria, as well as some calf wasting. It may be argued that because there was some calf wasting in the third year, he should have been diagnosed as having ALS. It was mild, however, and he had no electrophysiologic evidence of LMN disease. The second patient was reclassified as having ALS 8 years after disease onset. Her initial symptom was spastic dysarthria. Our study cannot comment on the likelihood of developing PLS or ALS when bulbar signs and symptoms are the presenting problem.

There is an ongoing debate of whether PLS and ALS are distinct disorders or rather different manifestations of a single disease. Modern autopsy cases of patients with PLS have not helped settle this discussion. Many of the pathologic hallmarks of ALS, including ubiquitinated inclusions and Bunina bodies, have also been observed in patients with PLS. However, some of these patients also demonstrated either LMN or diffuse degeneration neuropathologically, including dementia or parkinsonism, suggesting that this is a heterogeneous patient population with considerable overlap.9-11 Imaging studies suggest some differences between ALS and PLS, with ALS being more likely to show corticospinal tract involvement.10,12 whereas PLS is usually associated with varying degrees of cortical atrophy involving the precentral regions.13,14

Table 5. Associated Medical Conditions in Patients With PLS or ALS

<table>
<thead>
<tr>
<th>Condition</th>
<th>Patients With PLS (N = 43)</th>
<th>Patients With ALS* (N = 661)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>12</td>
<td>7</td>
<td>.24</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>12</td>
<td>7</td>
<td>.50</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>0</td>
<td>&lt;1</td>
<td>.001</td>
</tr>
<tr>
<td>Trauma</td>
<td>19</td>
<td>8</td>
<td>.02</td>
</tr>
<tr>
<td>Respiratory disease</td>
<td>2</td>
<td>8</td>
<td>.69</td>
</tr>
<tr>
<td>Rheumatologic disease</td>
<td>0</td>
<td>6</td>
<td>.10</td>
</tr>
<tr>
<td>Malignancy</td>
<td>7</td>
<td>6</td>
<td>.92</td>
</tr>
<tr>
<td>Autoimmune disorder</td>
<td>5</td>
<td>&lt;1</td>
<td>.002</td>
</tr>
<tr>
<td>Infective disease</td>
<td>2</td>
<td>&lt;1</td>
<td>.20</td>
</tr>
<tr>
<td>Other neuromuscular disease</td>
<td>7</td>
<td>4</td>
<td>.34</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>35</td>
<td>33</td>
<td>.87</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>2</td>
<td>4</td>
<td>.62</td>
</tr>
<tr>
<td>Smoking</td>
<td>21</td>
<td>17</td>
<td>.35</td>
</tr>
<tr>
<td>HIV risk</td>
<td>5</td>
<td>1</td>
<td>.46</td>
</tr>
</tbody>
</table>

*Because information on associated medical conditions was not available for all patients with ALS, sample size is included in parentheses.
Our study does not resolve the issue of whether ALS and PLS are distinct disorders. Our findings, however, allow us to state that patients who present with spasticity at onset and do not develop limb wasting within 3 years do not have the profile of classic ALS patients and will likely progress slower and live longer.

A number of studies have suggested that a UMN-dominant syndrome has a better outcome than classic ALS.15-19 Gordon et al4 observed that patients with ALS who retained only UMN signs for at least 4 years had a more benign prognosis. These patients had a prolonged course and high levels of independence for prolonged periods. Our results from comparing survival in patients with ALS based on their initial signs and symptoms confirm these findings. Patients with ALS who presented with spasticity had a significantly longer survival than patients who presented with other signs or symptoms. Patients with ALS presenting with spasticity also had a longer disease duration, but it was not statistically significant.

Although our results suggest that the best clinical pattern that differentiates between PLS and ALS was spasticity and/or stiffness as a presenting symptom and lack of limb wasting during follow-up, this study has a number of limitations. Disease duration could be determined in 83% of patients with PLS and 90% of patients with ALS. Given the dramatically different disease duration and rate of mortality between the 2 groups, we do not feel that the patients who were lost to follow-up would have had a great impact on our results. In our clinic, patients with PLS do not get annual EMG/NCS to determine if there is electrophysiologic evidence of LMN dysfunction consistent with ALS. However, Gordon et al4 reported that clinical signs of LMN disease developed 6 months after EMG/NCS evidence of denervation. Given that we have extensive follow-up in most of our patients with PLS, we feel that if they had signs of LMN disease, we would have detected it clinically. Another limitation is the number of patients lost to follow-up. This is difficult to remedy as this is a tertiary referral center and some patients live far away and come infrequently, and when they become very disabled, they cannot return for follow-up. Last, this study does not provide any insight on bulbar symptom onset in patients with PLS or ALS. This area requires further study as the ability to differentiate between PLS and ALS is important for prognosis and possibly for therapeutic interventions.

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Author Contributions: Dr Tartaglia had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Tartaglia and Strong. Acquisition of data: Tartaglia, Rowe, Findlater, Orange, Grace, and Strong. Analysis and interpretation of data: Tartaglia and Strong. Drafting of the manuscript: Tartaglia. Critical revision of the manuscript for important intellectual content: Tartaglia, Rowe, Findlater, Orange, Grace, and Strong. Statistical analysis: Tartaglia. Administrative, technical, and material support: Rowe, Findlater, and Orange. Study supervision: Strong.

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REFERENCES