Clinical predictors of symptom resolution for children and adolescents with sport-related concussion

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OBJECTIVE The goal of this study was to determine which variables assessed during an initial clinical evaluation for concussion are independently associated with time until symptom resolution among pediatric patients.

METHODS Data collected from a prospective clinical registry of pediatric patients with concussion were analyzed. The primary outcome variable was time from injury until symptom resolution. Predictor variables assessed within 10 days after injury included preinjury factors, Health and Behavior Inventory scores, headache severity, and balance, vestibular, and oculomotor test performances. The researchers used univariate Cox proportional models to identify potential predictors of symptom resolution time and constructed a multivariate Cox proportional hazards model in which total duration of concussion symptoms remained the outcome variable.

RESULTS The sample consisted of 351 patients (33% female, mean age 14.6 ± 2.2 years, evaluated 5.6 ± 2.6 days after concussion). Univariate Cox proportional hazards models indicated that several variables were associated with a longer duration of symptoms, including headache severity (hazard ratio [HR] 0.90 [95% CI 0.85–0.96]), headache frequency (HR 0.83 [95% CI 0.71–0.96]), confusion (HR 0.79 [95% CI 0.69–0.92]), forgetfulness (HR 0.79 [95% CI 0.68–0.92]), attention difficulties (HR 0.83 [95% CI 0.72–0.96]), trouble remembering (HR 0.84 [95% CI 0.72–0.98]), getting tired often (HR 0.86 [95% CI 0.76–0.97]), getting tired easily (HR 0.86 [95% CI 0.76–0.98]), dizziness (HR 0.86 [95% CI 0.75–0.99]), and abnormal performance on the Romberg test (HR 0.59 [95% CI 0.40–0.85]). A multivariate Cox proportional hazards model indicated that an abnormal performance on the Romberg test was independently associated with a longer duration of symptoms (HR 0.65 [95% CI 0.44–0.98]; p = 0.038).

CONCLUSIONS For children and adolescents evaluated within 10 days after receiving a concussion, abnormal performance on the Romberg test was independently associated with a longer duration of symptoms during recovery. In line with findings of other recent studies investigating predictors of symptom resolution, postural stability tests may provide useful prognostic information for sports medicine clinicians.

Identifying a set of ecologically valid variables that can be used to predict symptom recovery as well as expected timelines for returning to play or to school can help facilitate early intervention pathways. This is a challenging concept, particularly with regard to children and adolescents, since these patients may be more vulnerable to prolonged recovery than adults3,19 and because recovery timelines have primarily been established using cohorts of adult participants.31 Previously, in the pediatric emergency department (ED) setting, researchers have observed that a combination of demographic, medical history, symptom, and postural control variables can be used successfully to...
predict those patients who are likely to experience concussion symptoms longer than 28 days after injury. In addition, recently investigators applied this approach to the sports medicine setting and were able to successfully identify those patients at risk for persistent symptoms.

A particularly vulnerable time in life for developing persistent symptoms after a concussion is the teenage years, during which girls may carry a higher risk than boys. Several other noninjury factors that have been associated with concussion recovery time include previous concussions, attention-deficit/hyperactivity disorder (ADHD), learning disability, prior psychiatric history, and migraine history. In addition, some variables identified during initial clinical evaluations, such as acute headache, acute diziness, poor initial balance, and acute neuropsychological deficits, are associated with symptom duration. While total symptom severity has been noted as a predictor of symptom recovery time, few studies have evaluated whether the frequency of symptoms experienced after a concussion can be used to predict symptom resolution. The Health and Behavior Inventory (HBI) is included as a common data element for sport concussion and pediatric TBI, and it has been developed specifically for the pediatric population by assessing the frequency of different symptoms associated with an mTBI. In addition to symptom frequency and noninjury factors, postural stability assessments and tests of vestibular-oculomotor abilities may also provide predictive value to determine the length of time that will be required for symptom resolution.

The purpose of this investigation was to determine which variables assessed as a part of a routine clinical concussion evaluation would be independently associated with the duration of symptom resolution among pediatric patients who were evaluated after sport-related concussion by a sports medicine physician. We hypothesized that patients’ preinjury mental health conditions and prior concussion histories as well as a greater frequency of concussion symptoms within the first 10 days after a concussion would be independently associated with symptom duration.

Methods

Study Design and Participants

We conducted an analysis of data collected from a prospective clinical registry of children and adolescents with concussion who had been seen for care at the Children’s Hospital Colorado Sports Medicine Center between January 1, 2015, and August 31, 2017, and returned for care according to their individual clinical needs until they no longer required it or were referred to a different specialist. Patients were required to complete standardized questionnaires at each clinical visit and to undergo a variety of standardized tests administered by their physician. Responses to the questions and test results were reviewed with the family at the evaluation, which minimized missing data. Data were input into the electronic medical record immediately following the visit. We then reviewed each medical record to input relevant data, ensuring data quality. Inclusion criteria consisted of being seen and evaluated within the first 10 days after concussion and being 18 years of age or younger. We excluded patients who sustained a concussion from a non-sport-related mechanism involving a high-velocity impact (for example, a motor vehicle accident or fall from a height), presented with traumatic abnormalities on neuroimaging, or returned for care following a second head injury before clearance from the initial injury. All diagnoses of concussion were made by a board-certified sports medicine physician and were consistent with guidelines expressed in the international consensus statement on concussion in sport. Management decisions during recovery were also consistent with those outlined in these consensus guidelines, in which patients were given individualized recommendations about school, physical activity, and cognitive activity based on the type of symptoms present and the activities that exacerbated their symptoms. Patients did not receive clearance from the physician to return to full sport participation until they no longer reported concussion symptoms and had completed a stepwise return-to-play protocol. Prior to our conducting this study, the local institutional review board approved the protocol.

Clinical Evaluation

All patients completed a standardized intake form and a clinical evaluation that included several vestibular and ocular motor tests. The intake form required patients to report whether they had previously experienced a diagnosed concussion in their lifetime, the sport they were competing in at the time of injury (if applicable), and previous diagnoses of ADHD, learning disabilities, anxiety, depression, and migraine. Also recorded was whether patients received neuroimaging as a part of their clinical evaluation. Patients responded to several questions pertaining to their current status, including whether they were currently experiencing a headache (and if so, the severity ranked on a Likert-like scale ranging from 0 indicating no pain to 10 indicating the most severe pain) and if they had been experiencing sleep difficulties since the injury occurred; they also filled out the HBI. The HBI is a 20-item scale that measures the frequency of different symptoms that are associated with concussion. Youths completed the child version of the HBI by rating the frequency of symptoms experienced on a 4-point Likert scale as 0 (never), 1 (rarely), 2 (sometimes), and 3 (often). In addition to individual symptom ratings, a total symptom score was calculated as the sum of all items, in which higher scores indicate more frequent symptoms.

To assess balance, vestibular, and ocular function, the clinicians administered the Balance Error Scoring System (BESS), Romberg tandem gait, gaze stability, and near point of convergence (NPC) tests. During the BESS, patients completed three different stance conditions (double-leg, single-leg, and tandem) on firm ground and on a foam pad for 20 seconds. During the double-leg stance, patients stood with their feet positioned side by side. For the single-leg stance, participants stood on the foot that they identified as their nondominant kicking leg. During the tandem stance, participants stood with their feet positioned so that the nondominant foot was placed directly behind the dominant foot. The patients were instructed to remain with their eyes closed and their hands on their hips for the duration of the trial. Physicians or certified athletic trainers administering the test counted the total number of
errors committed during the trial, with a maximum of 10 errors per condition.

The tandem gait, Romberg, gaze stability, and NPC test results were analyzed as dichotomous variables (normal vs abnormal). During the tandem gait test, patients were instructed to walk heel to toe in a straight line across the examination room or down a hallway. A normal test performance was identified as being able to walk without significant loss of balance and to maintain heel-to-toe contact throughout the test. Excessive upper-body movement observed while lower extremities successfully completed the task was identified as an abnormal test performance, as this may indicate exaggeration and symptom feigning.

During the Romberg test, patients stood with feet together and eyes closed while the clinician monitored their stance. A normal Romberg test performance was defined as patients being able to hold still without significant loss of balance (signified by opening eyes, lifting foot, or falling out of position). An abnormal test result was defined as loss of balance or an exaggerated movement during the test. As with the tandem gait test, increased upper-body movement observed while the feet remained still was classified as an abnormal test result.

During the gaze stability test, patients held their thumb at arm’s length in front of their faces. They were instructed to focus on the thumb and turn their heads from side to side horizontally while their eyes maintained focus on the thumb. This process was then repeated with the head moving in the vertical plane of movement. An abnormal test result was recorded if patients reported an increase in dizziness, nausea, headache, or visual problems with either task, while a normal test result was recorded if they experienced no increase in concussion symptoms. Finally, to determine NPC, patients focused on a target such as a pen tip. The target was slowly brought to the tip of the patient’s nose from a distance; once patients reported diplopia or the clinician observed outward deviation of the eye, movement of the target was stopped and the distance was measured. Consistent with prior work, an NPC of > 5 cm was considered abnormal.18,41

Outcome and Predictor Variables

Our primary outcome variable was time from concussi

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Continuous variables are presented as means ± standard deviations and categorical variables are presented as percentages. We assessed demographic factors, medical history, injury characteristics, symptom frequency, and balance, vestibular, and ocular function of patients using descriptive statistics. For the univariate analysis of time to symptom resolution, we constructed univariate Cox proportional models with time to symptom resolution as the outcome and each clinical variable as a separate predictor variable. To adjust for confounders, we selected predictor variables with an a priori determined univariate significance level of p < 0.05 to construct a multivariate Cox proportional hazards model in which total duration of concussion symptoms remained the outcome variable. We assessed collinearity using condition indices and corresponding variance inflation factors (VIFs). A condition index > 30 was determined to require individual collinearity assessments, which were performed using VIFs. Collinearity between two variables was detected using a VIF > 2.5.35,37 Finally, we performed a sensitivity multivariable analysis with Romberg test performance as the predictor variable, and sex, preinjury mental health conditions, history of prior concussion, and age as covariates in the model. Statistical significance was set at α < 0.05 and all tests were two-sided. Statistical analyses were performed using Stata version 15 (StataCorp).

Results

During the study period, 934 patients were seen by clinicians for a potential concussion. We excluded 583 participants after we had applied inclusion and exclusion criteria to ensure a relatively homogeneous sample of children and adolescents in our sample (excluded: 7 patients without concussion diagnosis; 318 patients seen by a clinician > 10 days postinjury; 1 patient > 18 years of age; 229 patients whose concussion was due to a non—sport-related injury mechanism; 2 patients in whom a traumatic abnormality was evident on neuroimaging; 10 patients who returned for care following a second head injury prior to clearance from the initial injury; and 32 patients who were asymptomatic at the time of initial evaluation [some patients were excluded for more than one reason]). Thus, 351 participants were included in our analysis. The most common sports activity during which patients reported sustaining a concussion included American football (25%), soccer (24%), lacrosse (9%), basketball (8%), ice hockey (5%), baseball (4%), and volleyball (3%). Sixty-eight patients (19%) underwent neuroimaging, including 56 (16%) who received a CT scan and 14 (4%) who received an MRI. The children and adolescents included in the study (median age 14.9 years [interquartile range (IQR) 13.1–16.1
years) were evaluated at a median of 6 days (IQR 3–8 days) after concussion and reported that their symptoms had resolved at a median of 23 days (IQR 16–32 days) postinjury. Almost half of the patients reported a history of concussion, while other preinjury health conditions were reported less often (Table 1). The most commonly reported preinjury health conditions were history of concussion, while other preinjury health conditions were reported less often (Table 1). The most commonly reported symptoms by patients at the initial visit were headaches, difficulty paying attention, difficulty concentrating, and getting distracted easily (Tables 2 and 3). The most common abnormal vestibular or oculomotor test result was symptom provocation brought on by gaze stability testing, while fewer patients exhibited an abnormal Romberg test performance, demonstrated an abnormal tandem stance of the BESS test, is associated with prolonged symptom duration in patients seen in both the ED and sports medicine clinic settings. In addition to postural instability assessment, the Romberg test may also serve as a method to determine if patients are exaggerating or feigning symptoms after concussion has been studied in the context of neuropsychological testing and symptom reporting, but it has not received substantial

### Discussion

In the current study we examined the relationship between a comprehensive set of pragmatic variables collected during a clinical sports medicine evaluation and duration of postconcussion symptoms. Romberg test performance was the strongest predictor of symptom duration among all of the noninjury, symptom frequency, vestibular function, oculomotor function, and postural stability factors that we examined. This finding is interesting in light of previous research that showed that the Romberg test may not be sensitive enough to identify vestibular dysfunction. However, in our sample, patients were classified as having abnormal test performance when they demonstrated significant loss of balance or increased upper-body movement, which can be a sign of exaggeration or feigning of symptoms. Thus, it is difficult to determine whether patients who demonstrated abnormal performance on the Romberg test had postural instability due to a physiological deficit, noncredible effort, or exaggerated movements during the test. Therefore, there may be multiple reasons underlying the independent association between abnormal Romberg test performance and longer symptom duration in our cohort of youths with concussion. Regardless, the results suggest that clinicians may consider implementing the Romberg test as a screen for potential prolonged recovery in child and adolescent athletes.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of Patients (%)</th>
<th>Univariate Cox HR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (female)</td>
<td>116 (33)</td>
<td>1.37 (0.99–1.89)</td>
<td>0.06</td>
</tr>
<tr>
<td>Age (yrs)*</td>
<td>14.6 ± 2.2</td>
<td>0.97 (0.91–1.03)</td>
<td>0.35</td>
</tr>
<tr>
<td>LOC at time of injury</td>
<td>56 (16)</td>
<td>0.87 (0.58–1.30)</td>
<td>0.50</td>
</tr>
<tr>
<td>Pre-existing history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concussion</td>
<td>163 (46)</td>
<td>0.89 (0.66–1.20)</td>
<td>0.45</td>
</tr>
<tr>
<td>ADHD</td>
<td>44 (13)</td>
<td>1.38 (0.89–2.13)</td>
<td>0.15</td>
</tr>
<tr>
<td>Learning disability</td>
<td>31 (9)</td>
<td>0.82 (0.49–1.37)</td>
<td>0.45</td>
</tr>
<tr>
<td>Anxiety</td>
<td>18 (5)</td>
<td>1.08 (0.60–1.94)</td>
<td>0.80</td>
</tr>
<tr>
<td>Depression</td>
<td>6 (2)</td>
<td>0.65 (0.16–2.64)</td>
<td>0.55</td>
</tr>
<tr>
<td>Migraine or headaches</td>
<td>96 (27)</td>
<td>1.05 (0.76–1.46)</td>
<td>0.76</td>
</tr>
</tbody>
</table>

LOC = loss of consciousness.
* Continuous variable presented as mean ± SD.
noncredible effort. The Romberg test may not necessarily be particularly useful in detecting and beginning to address consideration of neuroimaging. Neuropsychology may be a neurological injury or exaggeration or feigning of symptoms is key to making appropriate referrals, including the Romberg test may not necessarily be particularly useful in detecting and beginning to address consideration of neuroimaging. Neuropsychology may be a neurological injury or exaggeration or feigning of symptoms is key to making appropriate referrals, including the Romberg test, while others may have exaggerated their movements. Regardless, both sets of individuals may require special attention soon after concussion, as they may be at an increased risk for experiencing prolonged symptoms. Clinical screening using the Romberg test soon after concussion may allow clinicians to identify those patients who may experience persistent symptoms. Identifying these high-risk individuals early after injury may allow for their referral to physical therapy or a mental health provider, depending on the clinical scenario, to reduce concussion symptoms, as has been observed previously. Of course, understanding whether the abnormality represents a neurological injury or exaggeration or feigning of symptoms is key to making appropriate referrals, including the consideration of neuroimaging. Neuropsychology may be particularly useful in detecting and beginning to address noncredible effort. The Romberg test may not necessarily indicate an intentional exaggeration of postinjury deficits, as it may indicate neurological injury resulting in postural instability or external factors that affect injury presentation. After identification of an abnormal test result, clinical expertise should guide management strategies related to potential mechanisms for the abnormal performance.

In comparison to other studies of patients seen for care in specialty concussion programs, our results indicate similar durations of symptom resolution among children and adolescents. Heyer and colleagues described a median symptom recovery time of 18 days, but also reported that female sex, loss of consciousness at the time of injury, symptom severity, premorbid headache, and days from injury to evaluation were each associated with protracted recovery. Interestingly, none of these factors were associated with prolonged recovery in our sample of individuals. This may be due to the timeline differences between studies, as Heyer and colleagues included individuals up to 30 days from injury to evaluation demonstrating clinical balance and corresponding univariate associations with symptom duration.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median Score (IQR)</th>
<th>Range</th>
<th>Univariate Cox HR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Firm surface double stance</td>
<td>0 (0–0)</td>
<td>0–10</td>
<td>0.97 (0.89–1.06)</td>
<td>0.54</td>
</tr>
<tr>
<td>Firm surface single stance</td>
<td>4 (2–7)</td>
<td>0–10</td>
<td>0.97 (0.93–1.02)</td>
<td>0.23</td>
</tr>
<tr>
<td>Firm surface tandem stance</td>
<td>2 (1–4)</td>
<td>0–10</td>
<td>0.98 (0.94–1.03)</td>
<td>0.51</td>
</tr>
<tr>
<td>Foam surface double stance</td>
<td>0 (0–1)</td>
<td>0–10</td>
<td>0.96 (0.86–1.04)</td>
<td>0.29</td>
</tr>
<tr>
<td>Foam surface single stance</td>
<td>8 (6–10)</td>
<td>0–10</td>
<td>1.00 (0.97–1.04)</td>
<td>0.82</td>
</tr>
<tr>
<td>Foam surface tandem stance</td>
<td>5 (3–9)</td>
<td>0–10</td>
<td>1.01 (0.98–1.06)</td>
<td>0.47</td>
</tr>
</tbody>
</table>

Unless otherwise indicated, values represent numbers of patients (%). Boldface type indicates statistical significance (p < 0.05).
days after injury, while we only examined those seen within the first 10 days of injury. In patients evaluated within 14 days after injury, Master and colleagues found that balance deficits during tandem gait testing were associated with prolonged recovery.30 Thus, balance deficits may be more readily predictive of prolonged recovery when tested sooner after injury (2 weeks in that study). Furthermore, our results suggest that almost all patients report symptom resolution within approximately 4 months after injury, which is valuable for clinicians to recognize as they provide counseling for patients regarding the expected duration of recovery. Of course, 4 months likely represents a biased population seen in a concussion specialty clinic, so it may not represent the natural history of concussion.

Although previous work has identified several prognostic factors for concussion recovery,22,30,37,44 our results did not indicate that premorbid conditions, injury characteristics, or functional factors relate to symptom resolution time. This may be due to the fact that we focused only on sport-related injuries that were evaluated in a specialty care sports medicine clinic. As such, postinjury presentation of the patients in our investigation may differ from that of patients seen in an ED setting, for example. Although not significant on the multivariate tests, there were several symptoms that were associated with symptom duration on the univariate evaluation. Specifically, both headache severity and frequency as well as dizziness were associated with longer symptom duration. Previous work has also documented that acute headache39,44 and dizziness9,11,27 are associated with longer symptom duration. As such, determining individual symptoms associated with prolonged recovery may allow for a more individualized approach to identifying patients at risk for developing persistent post-concussion symptoms and for tailoring treatments around their most bothersome findings. Interestingly, we did not find an association between several established predictors of prolonged recovery and symptom duration time, such as female sex,4,44 anxiety,20 ADHD,40 prior concussions,36,46 or younger age.29,45 Our findings may reflect the specific population of individuals seen in our clinic and should be placed in the context of the overall body of literature. As preinjury mental health conditions, prior concussions, and being a teenager or female seem to be the most consistent predictors of persistent concussion symptom risk,22 future studies should continue to develop prospective methods to better understand individual factors related to recovery time following concussion.

Limitations

Our study had several limitations, and our findings should be considered in light of them.

The analysis of data collected from a prospective clinical registry of children reduces our ability to control for factors related to postinjury treatment and the timing of when clinical visits occurred. Furthermore, as we drew from a sample of athletes who presented to a sports medicine specialty clinic, the injuries sustained by our sample of patients may not accurately represent similar injuries that occur within the immediate geographic area or in other geographic areas.

We applied a strict set of inclusion and exclusion criteria in an attempt to ensure some level of homogeneity among patients, but our results may not be generalizable to other populations, such as older or younger individuals, those who sustained an injury as a result of a non–sport-related event, or those seen for care in other clinical settings.

Conclusions

For adolescent and child patients assessed within 10 days after concussion, an abnormal performance on the Romberg test was independently associated with longer symptom duration during recovery. This is in line with findings of other recent studies investigating early predictors of symptom resolution, which demonstrate that postural instability appears to provide valuable prognostic information for sports medicine clinicians. As the Romberg test may identify both those patients who are experiencing

<table>
<thead>
<tr>
<th>Test</th>
<th>No. of Tests w/ Abnormal Performance</th>
<th>% Abnormal Performances</th>
<th>Univariate Cox HR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tandem gait</td>
<td>49</td>
<td>14</td>
<td>0.67 (0.44–1.02)</td>
<td>0.07</td>
</tr>
<tr>
<td>Romberg</td>
<td>68</td>
<td>19</td>
<td>0.59 (0.40–0.85)</td>
<td>0.006</td>
</tr>
<tr>
<td>Gaze stability</td>
<td>162</td>
<td>46</td>
<td>0.76 (0.56–1.02)</td>
<td>0.07</td>
</tr>
<tr>
<td>Near point of convergence</td>
<td>53</td>
<td>15</td>
<td>0.75 (0.49–1.14)</td>
<td>0.18</td>
</tr>
</tbody>
</table>

Boldface type indicates statistical significance (p < 0.05).

<table>
<thead>
<tr>
<th>Predictor Variable</th>
<th>HR</th>
<th>SE</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache severity</td>
<td>0.94</td>
<td>0.03</td>
<td>0.88–1.01</td>
<td>0.08</td>
</tr>
<tr>
<td>Abnormal performance on Romberg test</td>
<td>0.65</td>
<td>0.13</td>
<td>0.44–0.98</td>
<td>0.04</td>
</tr>
<tr>
<td>“I get confused” frequency rating</td>
<td>0.89</td>
<td>0.10</td>
<td>0.72–1.11</td>
<td>0.31</td>
</tr>
<tr>
<td>“I forget things” frequency rating</td>
<td>0.92</td>
<td>0.12</td>
<td>0.71–1.19</td>
<td>0.53</td>
</tr>
<tr>
<td>“I have trouble paying attention” frequency rating</td>
<td>0.97</td>
<td>0.09</td>
<td>0.81–1.16</td>
<td>0.73</td>
</tr>
<tr>
<td>“I get tired a lot” frequency rating</td>
<td>0.99</td>
<td>0.08</td>
<td>0.85–1.15</td>
<td>0.85</td>
</tr>
<tr>
<td>“I have problems remembering what people tell me” frequency rating</td>
<td>1.02</td>
<td>0.13</td>
<td>0.80–1.30</td>
<td>0.90</td>
</tr>
<tr>
<td>“I feel dizzy” frequency rating</td>
<td>1.02</td>
<td>0.09</td>
<td>0.86–1.21</td>
<td>0.80</td>
</tr>
</tbody>
</table>

An abnormal finding on the Romberg test was independently associated with longer symptom duration. Boldface type indicates statistical significance (p < 0.05).
postural instability and those who are exaggerating their symptoms, abnormal test performance within the first 10 days after a concussion may alert clinicians to recognize pediatric patients who are at risk for developing persistent symptoms.

References


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**Author Contributions**

Conception and design: all authors. Acquisition of data: Howell, Potter, Provance, JC Wilson. Analysis and interpretation of data: all authors. Statistical analysis: Howell. Drafting the article: Howell, JC Wilson. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Howell. Administrative/technical/material support: all authors. Approved the final version of the manuscript on behalf of all authors: Howell. Administrative/technical/material support: all authors. Approved the final version of the manuscript on behalf of all authors: Howell. Administrative/technical/material support: all authors.

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