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Prevalence of Exertional Rhabdomyolysis in Endurance Horses in the Pacific Northwestern United States

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Summary

Reasons for performing study: Exertional rhabdomyolysis (ER) is a reported syndrome in competing endurance horses; however the prevalence and cause of ER in this population has not been defined.

Objectives: To determine the prevalence of ER in a sample of endurance racing horses, and to investigate factors, including relevant genetic defects, contributing to the occurrence of rhabdomyolysis in this group.

Study design: Prospective clinical study

Methods: Riders of 101 horses participating in one of four 50 mile distance races completed a comprehensive questionnaire regarding the medical history, management and performance of their horse. Serum creatine kinase activity (CK) was measured before and four hours after completion of exercise. Hair samples were analysed by PCR for the R309H mutation in the glycogen synthase gene (GYS1) responsible for Type 1 polysaccharide storage myopathy (PSSM) and the C7360G mutation in the ryanodine receptor 1 (RYRI) gene causing malignant hyperthermia (MH).

Results: Samples were obtained from 68 Arabians, 20 half-Arabians, and 13 horses of other breeds. Serum CK was above the resting reference interval (145-633 U/L) in 38 horses after racing (median 883 U/L, range 658–3,739) but was compatible with values previously reported in apparently healthy endurance horses. Pathologic ER was suspected to occur in four horses with serum CK activities exceeding 10,000 U/L four hours after racing (median 84,825 U/L; range 10,846 - 381,790) including three Arabians and one half-Arabian horse. GYS1 and RYRI mutations were not present in hair samples from any horses.

Conclusions: Exertional rhabdomyolysis occurred at a prevalence of 4.0% in a sample of horses participating in 50 mile distance events, and all affected horses were Arabian or half-Arabian.
**Potential Relevance:** The cause of ER in the endurance horse population remains unknown; however, ER in competing Arabian endurance horses is unlikely to be due to Type 1 PSSM or MH.
Introduction

Exertional rhabdomyolysis (ER) is an important cause of impaired performance and financial loss in several equine athletic disciplines.[1] Affected horses typically display reluctance to continue exercise, a stiff gait, excessive sweating, and pigmenturia. Measurable increases in serum creatine kinase activity (CK), reflecting skeletal muscle necrosis, usually occur rapidly in affected horses, with peak activity often reached four to six hours after exercise.[2] Currently it is understood that chronic ER in horses frequently arises from heritable intrinsic defects of muscle metabolism or function, which are heavily influenced by environmental factors including diet and exercise regimens.[3-8] Clinical studies of light breed athletic horses have demonstrated approximate prevalences of ER disorders of 5 to 7% in racing Thoroughbred horses, 6% in racing Standardbred horses, 7 to 9% in polo ponies and 6 to 12% in Quarter horses.[6, 9-12]

Polysaccharide storage myopathy (PSSM), a disorder of skeletal muscle glycogen metabolism, has been identified as the major cause of ER in a variety of equine breeds.[13, 14] In Quarter horse related breeds (Quarter horse, Paint, Appaloosa) the majority of horses with histopathologic evidence of PSSM have a gain of function mutation (R309H) in the glycogen synthase gene (GYS1).[3, 13, 15] This disorder is characterized by accumulation of abnormal amylase-resistant polysaccharide and excessive glycogen within skeletal muscle cells and has been termed ‘Type 1 PSSM’. A small percentage of Quarter horses with the GYS1 mutation also have a concurrent mutation (C7360G) in the ryanodine receptor gene (RYR1) which is associated with a more severe phenotype.[16] In contrast, the specific cause of ER in Thoroughbred and Standardbred horses has not yet been definitively identified, though the disease is believed to be analogous between these breeds and is possibly related to a heritable defect of intracellular calcium regulation in skeletal myocytes.[10, 17, 18, 19] Affected Thoroughbred and Standardbred horses tend to be more prone to episodes of
clinical disease if they are female and possess a nervous temperament. Clinical disease in these horses is also exacerbated by lameness, infrequent exercise regimens and high starch rations.[6, 8, 9, 10]

Research studies of ER in endurance horses are currently lacking, particularly in Arabian horses which represent the major breed participating in endurance racing events.[20] Though some published reports exist describing a small number of Arabian horses with histologic features consistent with PSSM in skeletal muscle tissue, the cause of ER in Arabian endurance horses has not been definitively determined and the prevalence is unknown.[14, 21] Nonetheless, there is evidence to indicate that ER is an important cause of failure of Arabian horses to complete endurance riding competitions.[20]

The purpose of the current study was therefore to establish the prevalence of ER in horses competing in 50 mile distance endurance race events in the Pacific Northwest region of the United States, and to determine the prevalence in this sample of the GYS1 and RYRI mutations associated with Type 1 PSSM. Additionally, riders of horses competing in these events completed a comprehensive questionnaire designed to further evaluate the characteristics of ER in this group.

**Material and Methods**

**Horses**

A total of 156 horse and rider teams were entered to participate in four different 50 mile distance endurance races occurring in Washington and Idaho between May and August 2010. All rides were sanctioned under the American Endurance Ride Conference. Riders willing to participate in the study (n = 101) signed an informed consent form. Procedures associated with the study were approved by the Oregon State University Institutional Animal Care and Use Committee. All horses were determined to be healthy prior to racing via
physical examination procedures performed by the attending veterinarians affiliated with each event.

Prior to events, participating riders completed a questionnaire that requested the age, breed, and gender of their horse, and also requested that riders subjectively classified their horse’s temperament (1=very calm; 2=calm; 3=average; 4=nervous; 5=very nervous) and muscle mass (1=below average, 2=average, 3=above average). Riders also provided basic dietary information including the number of pounds of grain their horse was fed per day, whether or not their horses received any high-fat feeds or supplements, and if supplemental electrolytes are administered during racing.

Riders reported whether their horse had suffered from any lameness in the four weeks prior to the event and also whether their horse had ever been diagnosed with an episode of ER, either presumptively based on observation of relevant clinical signs by the rider and/or a veterinarian, or definitively via measurement of increased serum CK activity after exercise and clinical signs suspected to reflect ER.

After completing their respective event, riders reported whether they had completed the full distance of the race, any reason for the horse and rider not completing the entire race, and the occurrence of any adverse events in their horse during their race event, including lameness, muscle pain, muscle tremors, sweating, discoloured urine, or ‘thumps’ (synchronous diaphragmatic flutter).

Sample Collection

From each horse entered into the study, 2 mL of whole blood were obtained in a serum separator tube\(^a\) by jugular venepuncture approximately 12 hours before the racing event commenced, and again four hours after either successful completion of or removal from the event. After separation from clotted blood by centrifugation 30 minutes after sampling,
serum was immediately stored at -150°C in a liquid nitrogen dry vapour shipper\(^b\), and serum CK activity was measured via automated analyser\(^c\) within 72 hours of collection. Based on previous reports documenting that apparently healthy endurance horses frequently develop serum CK activities of several thousand units per litre after competitive endurance exercise, serum CK activity \(\leq 4000\) U/L four hours after exercise was considered a non-pathologic response for horses participating in the current study.[22-24] At the time of collection of the initial blood sample, 20 to 40 hairs were plucked from the mane of each horse and stored away from direct heat and sunlight. Hair samples were subsequently analysed\(^d\) for \(GYSI\) and \(RYRI\) mutations by PCR and gene sequencing as previously described.[3]

**Statistical Analysis**

Due to departures from normality (as detected by Komogorov-Smirnov normality tests) and heterogeneous variances, serum CK activity before and after racing was log transformed prior to statistical analysis. Simple linear (Pearson’s, or in the case of temperament score, Spearman’s) correlations were performed to evaluate relationships between serum CK before and after racing and meaningfully numeric variables derived from the questionnaire (time taken to complete the race, age, temperament score, and amount of grain in the ration). Two sample t-tests with a Satterthwaite’s approximation for degrees of freedom to account for remaining heterogeneity of variance estimates after the log transformation were utilized to assess the effect of all remaining binary independent variables on the responses. Binary variables included horse gender, race completion, lameness, muscle pain, muscle tremors, discoloured urine, excessive sweating and synchronous diaphragmatic flutter, in addition to electrolyte supplementation, fat supplementation, and history of prior ER. Muscle mass was also analysed as a binary variable since all but three horses were scored as having average (n = 55) or above average (n= 43) muscle mass. Statistical
significance was determined when the p-value was less than 0.05. Data are presented as mean ± SD unless otherwise stated.

**Results**

**Horses and Events**

Ambient temperature ranges on the days of competition were comparable between the four endurance race events, varying from 8.4 to 11.1°C (47 to 52°F) for low temperature extremes and from 24.2 to 27.8°C (76° to 82° F) for high temperature extremes. Information regarding total elevation change of the race course was available for three of the four events, and ranged from 1187 to 1524 meters (3900 to 5000 feet).

Blood and hair samples were obtained from 101 different horses between the four events, including 68 Arabian horses, 20 half-Arabian horses, and 11 horses comprising 8 other breeds [Fox trotter /Fox trotter cross (n=3), Kentucky Mountain Saddle Horse (n=1), Morgan (n=1), mule (n=1), Mustang (n=1), Nez Perce (n=1), Paso Fino (n=2), Thoroughbred (n=1)]. Breed information was not recorded for two horses. The data set included 76 geldings and 25 mares, with an average age of 11.1 ± 3.3 years. A total of 28, 41, 7 and 25 horses were sampled at each of the four events respectively.

Of the 101 horse and rider combinations entered in the study, 92 successfully completed 50 miles of distance in an average time of 6 h 33 min ± 1 h 36 min. Nine horse and rider combinations did not complete 50 miles in distance, of which six abandoned because of lameness and one because of ER diagnosed based on the occurrence of clinical signs of muscle pain and red urine. An additional two horse and rider combinations did not complete their event because the riders voluntarily withdrew from competition with no indication that their horses had developed problems that prevented them from continuing.
Serum CK activity

Mean serum CK activity before competition was within reference interval (145-633 U/L) in 96 horses, with relatively small variation (252 ± 94; median: 232 U/L). Five horses had serum CK activity above the reference interval prior to competition (range: 725-1186; median: 753 U/L). Serum CK activity prior to racing was positively correlated to serum CK activity after racing ($r = 0.2122$, $p = 0.03$, Figure 1). In horses that completed races ($n= 92$), race time was negatively correlated with post-exercise serum CK activity ($r = -0.2047$, $p = 0.05$, Figure 2).

A frequency histogram of serum CK activity in horses four hours after ceasing their event is presented in Figure 3. Serum CK four hours after racing was < 4000 U/L in 97 horses (679 ± 452; range: 658–3,739; median: 497 U/L) and considered normal for the level of activity performed based on previous studies.[22-24] The remaining four horses (three Arabians and one half-Arabian) had serum CK activities exceeding 10,000 U/L (range: 10,846 - 381,790 U/L), which was considered consistent with ER. These horses comprised 3 geldings and one mare, with an average age of 10.3 ± 2.6 years. The three geldings completed their race, although one was reported to produce red urine during the event (CK: 153,333 U/L). The mare was removed from the race due to clinical signs of muscle pain accompanied by red urine (CK: 381,790 U/L).

Serum CK activity before and after racing was not found to be significantly associated with whether horses successfully finished the race ($n= 92$), or displayed lameness ($n = 12$), muscle pain ($n = 7$ horses) or discoloured urine ($n = 3$) during their event (Table 1). Nor was serum CK activity associated with whether horses received ($n = 95$) or did not receive ($n = 6$) electrolyte supplements during their event. No horses were reported to display excessive sweating, muscle tremors or synchronous diaphragmatic flutter during any of the events (Table 1).
Signalment and management variables

No significant correlation was identified between serum CK activity before and after racing and horse age (data not shown). Serum CK activity before and after racing did not differ with gender, muscle mass, or temperament score in this study (data not shown).

Twelve horses (11 Arabians, one half-Arabian) were reported by their owners to have had at least one previous episode of suspected ER, however, serum CK activity in all of these horses was only mildly elevated after racing in the current study (706 ± 402; median 669; range: 246-1263 U/L).

Most horses in the study were fed 5 lbs (2.3 kg) or less of grain per day (n = 98) and the majority (n = 87) also received some form of additional fat supplementation in their diet as well as electrolyte supplementation during racing (n = 96). No significant association was found between dietary variables and serum CK activity except for the finding that post-exercise serum CK activity was significantly higher (p = 0.03) in the group of horses receiving a fat supplement (7,219 ± 44,102 vs. 514 ± 230 U/L), and all four horses with serum CK activities exceeding 10,000 U/L after racing were reportedly receiving a fat supplement in the diet.

Genetic testing

PCR analysis to identify the GYS1 and RYR1 mutations was successfully performed on hair samples from 98 horses. Analysis was unsuccessful in two horses for the GYS1 and RYR1 mutations respectively, and analysis for both mutations failed in a third horse. Neither of the mutations were identified in any of the successfully tested samples.

Discussion
In the current study, 41.6% (42/101) of sampled horses competing in 50 mile endurance events in the Pacific Northwest region displayed serum CK activity above reference interval for resting horses at four hours after racing. However, the majority of these horses had mild to moderate increases in serum CK activity (<4,000 U/L) which were comparable to findings documented in previous studies of apparently healthy endurance horses, as well as in studies of sled dogs and human athletes competing in long-distance running events.[24-26] However, 4% of horses in the current study, representing 4.5% of Arabian horses studied, had increases in serum CK activity after racing which were ten times or more the mean of the remaining sample of horses, and which represented between a 20 to 700 fold increase from pre-race values. These horses were therefore classified as having ER, the prevalence of which in this sample was comparable to that of other equine athletic breeds and disciplines, including Thoroughbred and Standardbred racing, and polo.[6, 10, 11]

Of significant concern is the fact that of the four horses in this study classified with ER, only one horse, with massive serum CK activity (>300,000 U/L), was recognized as diseased during the event and therefore prevented from continuing in the race. The other three horses completed the event with no obvious signs of lameness or muscle pain, though one horse with a serum CK exceeding 150,000 U/L was reported by the owner to have passed noticeably red urine during the race. Although previous reports exist regarding individual endurance horses that successfully complete their events despite subsequently being found to have dramatic elevations in serum CK activity, it must be recognized that endurance races are prolonged and demanding events in which a significant proportion of competing horses routinely develop dehydration and other metabolic abnormalities which may exacerbate, or in turn be exacerbated by, the occurrence of ER.[20, 22, 23, 27] Ultimately this combination of factors can promote severe morbidity and potentially mortality of even highly conditioned
elite horses, and therefore prompt recognition and/or prevention of ER in endurance racing horses is desirable.[20]

Measurement of serum CK activity is not routinely performed during endurance competition in horses, and detection of ER during racing is typically reliant on the relatively insensitive approach of periodic clinical examinations during brief mandatory rest periods. Hence, individual horses may be at significant risk of severe consequences as a result of continued exercise in the face of undetected muscle damage.[22, 27] The findings of the current study support the concept that measured serum CK activity often correlates poorly with the clinical appearance of the rhabdomyolysis-affected individual, a phenomenon previously reported in Thoroughbred and Standardbred horses participating in intense exercise.[1] Complicating matters further is the finding that five out of the seven horses in the current study which riders thought had muscle pain during racing actually had relatively low serum CK activities (< 1,000 U/L). This finding suggests that either perceived or real muscle pain is not a reliable indicator of ER during endurance exercise in horses, and could reflect the occurrence of muscle cramping that is not associated with actual muscle necrosis. Readily available, reliable and clinically practical methods of detecting subclinical or early rhabdomyolysis in horses during endurance racing are currently lacking.

The occurrence of discoloured urine was reported by the riders of three horses in the current study, including two horses with massively increased serum CK activities (153,550 U/L and 381,790 U/L respectively) and presumed myoglobinuria. However, a urine sample was not obtained at the time of these observations and additional clinicopathologic tests to confirm this suspicion were not performed. Discoloured urine (dark but not red) was reported in the third horse which was subsequently found to have only minor elevations in serum CK (825 U/L), indicating that urine discoloration in this horse was unlikely related to myoglobinuria. The rider of this horse attributed the urine colour to greatly reduced water
intake by the horse. Hence although red or discoloured urine is likely an important indicator of severe rhabdomyolysis in endurance horses, it is also a transient phenomenon susceptible to incorrect interpretation. Thus additional clinicopathologic assessments should be considered in any horse suspected of having myoglobinuria associated with ER.[28] Additionally, it is likely that in some individuals or during some episodes of ER, the degree of muscle necrosis may not necessarily be severe enough to generate grossly visible myoglobinuria. Therefore on some occasions, horses may have occult myoglobinuria and may or may not display accompanying signs of muscle pain that would attract investigation.

In the current study, all horses classified as having ER were Arabian (3 horses) or half-Arabian (1 horse). Interestingly, despite the mean age of these horses exceeding 10 years old, their riders reported no prior history of ER. Conversely, another twelve horses (also Arabian or half-Arabian) that were reported by their owners to have had at least one previous episode of ER displayed no more than mild elevations in serum CK activity during the studied race events. Possible explanations for these somewhat paradoxical findings might include the intermittent and often subclinical nature of ER in horses, incorrect classification of horses with ER that actually have muscle cramping without muscle necrosis, or misdiagnosis of ER by riders or veterinarians of horses developing conditions with clinical similarities to ER, such as undifferentiated lameness or metabolic disorders. The method of owner questionnaire to establish a past diagnosis of ER in horses is not an optimal tool, and further evaluation of Arabian horses to identify the definitive cause of ER in this breed must involve a tightly phenotyped, carefully selected sample of horses. Nonetheless, it is likely that at least some of these individuals may truly have an ER disorder, and the prevalence of ER in Arabian endurance horses may therefore exceed the 4.5% predicted by the results of the current study.
The association of nervous temperament and female gender with episodes of clinical disease has been described in Thoroughbred and Standardbred horses with ER, but not in Quarter horses with PSSM.[6, 7, 9, 21] Additionally, lameness, young age, and the feeding of more than five pounds of grain per day also influence the occurrence of ER in Thoroughbred horses.[6] These latter associations were not identified in horses in the current study, however it is also possible that if such associations were to exist they might have been obscured by the greater average age and low grain intake of the relatively small sample of horses evaluated in the current study.

Although a previous report describes a very high prevalence (> 60%) of PSSM in Arabian horses undergoing necropsy for reasons unrelated to muscular disease, the criteria applied for histopathologic diagnosis of PSSM are variable and somewhat controversial.[21, 29] In a more recent study of muscle biopsies obtained specifically to investigate neuromuscular complaints in horses, only 3 of 40 Arabian horses with neuromuscular complaints were classified as having histopathologic changes consistent with PSSM on examination of skeletal muscle tissue, and no Arabian horses were positive for the GYS1 mutation.[14] Similarly, none of the hair samples obtained from Arabian horses in the current study were positive for the relevant GYS1 or RYR1 mutations. Biopsies were not performed to evaluate the skeletal muscle histology of these horses. Another form of PSSM (‘Type 2 PSSM’) is recognized in several equine breeds, particularly Warmblood breeds, and is characterized by accumulation of granular muscle amylase-sensitive glycogen in muscle biopsy samples, in the absence of the GYS1 mutation.[15, 30] Since skeletal muscle biopsies were not within the scope of the current study, currently Type 2 PSSM cannot be excluded as a cause of ER in the Arabian breed. Other possible causes of ER in the Arabian population might include sporadic rhabdomyolysis associated with exertion, impaired thermoregulation or metabolic perturbations; an analogous recurrent ER disorder to that observed in
Thoroughbred and Standardbred horses; or a currently unclassified muscular disease.[20] It is of interest to note that the dam of the most severely affected horse in the current study reportedly had a life-long history of repeated episodes of ER during endurance exercise, suggesting the possibility of a hereditary muscular defect in this individual.

In summary, the current study identified an apparent prevalence of 4.5% of ER in a sample of Arabian endurance horses, which was often associated with minimal clinical indication in most affected horses. A history of ER was reported in an additional 13.6% of horses of this breed, suggesting a clinically intermittent disorder with a prevalence in Arabian endurance horses comparable to other equine breeds and athletic disciplines. Exertional rhabdomyolysis in this group was not associated with known genetic mutations tied to Type 1 PSSM and MH. Hence the underlying cause of ER in the Arabian breed remains currently unknown but warrants further investigation which must include collection and analysis of skeletal muscle biopsies in an appropriately phenotyped sample of horses.
Manufacturer’s detail

a. Corvac serum separator tubes, Tyco Healthcare Group LP, Mansfield, MA, USA
b. MVE SC 4/2V Dry shipper. Reproduction Resources Walworth, WI
c. Hitachi 911, Roche-Boehringer Manheim, Indianapolis, IN
d. University of Minnesota Equine Center Neuromuscular Diagnostic Laboratory, Saint Paul, MN.

Figure 1: A scatter plot of serum CK activity (log transformed) in horses prior to and after ceasing participation in a 50 mile endurance race

Figure 2: A scatter plot of duration of race time (minutes) compared to serum CK activity (log transformed) in horses after ceasing participation in a 50 mile endurance race

Figure 3: Frequency histogram of serum CK activity in 101 horses four hours after ceasing participation in a 50 mile endurance race

References


Exclusion of linkage of the RYR1, CACNA1S, and ATP2A1 genes to recurrent 
Myoplasmic calcium regulation in myotubes from horses with recurrent exertional 
Clinical and biochemical abnormalities in endurance horses eliminated from competition 
for medical complications and requiring emergency medical treatment: 30 cases (2005-
Changes in selected physiological and laboratory measurements in elite horses competing 
(2010). Effect of a 120 km endurance race on plasma and muscular neutrophil elastase 
(2007) Serum chemistry alterations in Alaskan sled dogs during five successive days of 


Table 1: Serum CK activity (mean ± 95% CI; range below) in 101 horses four hours after competing in a 50 mile endurance race

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
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<td><strong>Completed Race</strong></td>
<td>2,607 ± 3,277</td>
<td>43,188 ± 82,959</td>
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<td></td>
<td>188 – 153,550</td>
<td>222 – 381,790</td>
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<tr>
<td></td>
<td>(n = 92)</td>
<td>(n = 9)</td>
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<tr>
<td><strong>Lameness</strong></td>
<td>997 ± 619</td>
<td>6,928 ± 9,010</td>
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<td></td>
<td>222 – 3,739</td>
<td>188 – 381,790</td>
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<td></td>
<td>(n = 12)</td>
<td>(n = 89)</td>
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<td><strong>Muscle Pain</strong></td>
<td>55,347 ± 106,640</td>
<td>2,565 ± 3,209</td>
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<td></td>
<td>402 – 381,790</td>
<td>188 – 153,550</td>
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<tr>
<td></td>
<td>(n = 7)</td>
<td>(n = 94)</td>
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<tr>
<td><strong>Discoloured Urine</strong></td>
<td>178,722 ± 216,958</td>
<td>943 ± 390</td>
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<tr>
<td></td>
<td>825 – 381,790</td>
<td>188 – 16,542</td>
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<td></td>
<td>(n = 3)</td>
<td>(n = 98)</td>
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<td><strong>Electrolyte Supplement</strong></td>
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<td>489 ± 225</td>
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<td>188 – 381,790</td>
<td>241 – 980</td>
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<td>(n = 95)</td>
<td>(n = 6)</td>
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<td>188 - 381,790</td>
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