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Characteristics and Outcomes of Athletes With Slow Recovery From Sport-Related Concussion: A CARE Consortium Study

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ABSTRACT

Background & Objectives: Some athletes experience a slow recovery after sport-related concussion (SRC). There is little agreement on what constitutes slow recovery, however, and minimal data on the prevalence, predictors, or prognosis for this group. The objectives were to apply an operationalized definition of slow recovery and characterize predictors and long-term prognosis of these individuals.

Methods: This is a prospective multi-site observational study of collegiate athletes. Participants underwent multimodal assessments preseason and five additional timepoints following SRC. Time from injury to initiation of return to play progression (*asymptomatic timepoint*), and from injury to return to play (*RTP*) were the primary markers of recovery.

Results: 1,751 concussed male and female collegiate athletes were studied. 80% of participants reached the *asymptomatic* and/or *RTP* timepoints by days 14 and 24, respectively. Slow recovery was thus defined as exceeding one or both of those intervals (n=399). This group was significantly more likely to be female (41.1% versus 35.6%, $p=0.05$), have higher initial post-injury SCAT symptom severity scores (mean [SD]: 36.6 [23.4] versus 25.4 [19.9], $p<0.01$), lower post-injury SAC scores (mean [SD]:25.74 [2.98] versus 26.26 [2.85], p=0.004), perform worse on the post-injury BESS (mean [SD]: 17.8 [8.9] versus 15.9 [8.5], $p<0.01$), have fewer

assessments in the first 14 days after injury (mean [SD]: 48.8 [29.7] versus 67.9 [24.6], $p<0.01$), and be injured in practice (70.7% versus 65.1%, $p=0.04$). 77.6% of the slow recovery group returned to play within 60 days of injury, and 83.4% (n=349) returned to play within 90 days of injury. Only 10.6% had not returned to play 6 months postinjury.

Discussion: This study suggests an overall favorable prognosis for slowly recovering athletes and provides data for athletes and medical teams to consider in calibrating return to play expectations, and making decisions about medical disqualification versus ongoing engagement in their sport.

INTRODUCTION:

Historically, sport-related concussion (SRC) has been considered an injury with a favorable prognosis.[1] However, it has long been acknowledged that a small percentage of individuals experience a longer recovery trajectory, and in some cases, remain symptomatic for months or even years after injury.[2-6] This issue is complicated by varying conceptualizations of "recovered" (e.g. symptom-free vs. minimally symptomatic vs. return to pre-injury baseline),[7-9] different outcome metrics (e.g. cognitive testing only vs. multimodal assessments), and relatively small sample sizes. Furthermore, even when a concussed athlete is asymptomatic measures of brain structure and function may differ from non-concussed athletes, suggesting that resolution of symptoms may not be the final recovery endpoint.[10,11]

Data on the percentage of athletes with SRC who experience slow recovery are scarce and come primarily from American football. McCrea et al.[2] found that while the great majority of a cohort of concussed high school and collegiate football players returned to baseline performance on clinical measures within 7-10 days, ~10% of the cohort had not returned to pre-injury baseline several weeks after injury. The etiology of persisting symptoms has been a subject of debate with some arguing that they reflect ongoing neural dysfunction, and others arguing they are tied to psychological health factors or an interaction of pre- and post-injury factors.[5, 12-14] More recently, concerns have been raised that concussion may trigger a cascade of neurobiological events that degrade cognitive and neurobehavioral function and increase the risk for neurodegenerative disease.[15-17]

There has been little study of the natural history and determinants of outcome of athletes who recover slowly. Such data would be useful to inform medical management, to calibrate the expectations of athletes and coaches for return to play, and to advance our knowledge of concussion recovery. The objectives of this paper were to apply an operationalized definition of slow recovery, and characterize the long-term prognosis for these athletes.

METHODS:

CARE Consortium and Protocol: The NCAA-DoD Concussion Assessment, Research and Education (CARE) Consortium is a 30-site study of the natural history and neurobiology of concussion described previously.[18] In brief, participants completed a pre-season baseline evaluation consisting of demographics, medical history, concussion-like symptoms, postural control, and neurocognitive functioning. All CARE sites used a common definition of concussion[19] with diagnosis made by a local team physician. Concussed participants were reassessed at five additional post-injury time points: within six hours and again 24-48 hours after injury, at clearance to initiate return to participation progression (defined herein as the *asymptomatic* time point), at clearance for unrestricted return to participation (RTP), and six months post-injury. Concussed participants reported symptoms to the medical staff daily, up to 14 days following injury and then weekly if they had not yet returned to unrestricted play. Symptoms were captured using the Sport Concussion Assessment Tool – 3rd Edition (SCAT-3) symptom list, a 22-item inventory with severity ranked on a 0 to 6 scale. Percent completion of the daily symptom reports was used as a metric of clinical care assessment frequency. The presiding clinician's exam served as the gold standard for determining an athlete's readiness to initiate the return to progression protocol[20,21] and for unrestricted RTP.

Standard Protocol Approvals, Registrations, and Patient Consents: Prior to participation, all participants gave written informed consent. The research protocol and consent form were approved by the Institutional Review Board of each participating site, as well as the U.S. Army Human Research Protection Office (HRPO).

Participants: All varsity athletes at 26 civilian universities and all varsity athletes and cadets from four military service academies within the United States were eligible to participate. Between Fall 2014 and Spring 2018, a total of 34,709 athletes and cadets were enrolled in the CARE Consortium and completed a minimum of one baseline evaluation. Following enrollment and intake, 3,361 concussions were recorded. A previous report[22] used this same cohort to characterize the natural history of concussion recovery including median time from injury to initiation of graded exercise and to clearance for return to play.

Slow Recovery Definition: Our previous work[22] found that across all sports, the median time to *asymptomatic* was 6.4 days (IQR 3.7, 11.8), with 80% achieving asymptomatic status by day 14. The median time to *RTP* was 12.8 (IQR 8.7, 20.1) days, with 76% returning to participation by day 21 and 84% by day 28 post-injury. We therefore included athletes in the slow recovery group if they took $\geq$ 14 days to reach the asymptomatic timepoint and/or $\geq$ 24 days to reach the RTP timepoint, thresholds that signified that these were taking longer than 80% of their peers to achieve one or both of the stated recovery mileposts.

Data analysis: Descriptive statistics, means and standard deviations for continuous variables and percentages for categorical variables, were calculated for baseline demographic and examination measures, injury characteristics and post-injury (within 48 hours) measures. Analyses for time to *asymptomatic* and total time to *RTP* was limited to the first concussion for each athlete (N=1,751). Athletes who had not reached the *Asymptomatic* or *RTP* timepoint when the season ended and for whom follow-up was not readily available (e.g. practices were no longer scheduled and/or athletes left campus) were right censored for analysis. Thus, an exact time for RTP or RTP protocol initiation could not be determined. There were 161 athletes with the date of RTP protocol initiation available but not RTP. Similarly, there were 131 athletes with an RTP date but no protocol initiation date. For these 292 athletes the missing time was imputed using the other available time and the mean duration of the RTP protocol. Using time-to-event (survival) analysis techniques, censored observations (73 where *asymptomatic* and full RTP were not captured) are included in the analysis up until the censoring time.

Initial analyses compared the typical and slow recovery cohorts. Statistical comparisons for continuous characteristics between slow and typical recovery were performed using the Wilcoxon rank sum test. Chi square tests were used for the comparisons of categorical variables. Subsequent analyses focused on the recovery trajectory of the slow recovery cohort. The survival trajectory for time to *RTP* was estimated using a Kaplan-Meier curve. Bivariate associations between time to RTP and athlete and injury characteristics were assessed using the Cox proportional hazards model. The best multivariable model among possible predictors, based on the Akaike Information Criterion (AIC), was identified using the characteristics that met the screening criteria of $p \leq 0.2$ from the bivariate proportional hazards models. A p-value of ≤ 0.20

was selected to reduce the number of candidate predictors but allow those that may be important in multivariable models to remain. The Condition Index method was used to check for multicollinearity (indices >30 indicates strong multicollinearity). Additional analyses compared individuals at the far end of the recovery trajectory, defined as having a *RTP* time greater than 74 days (n= 63), to those with *RTP* between 24 and 74 days, using Chi-square and Wilcoxon rank sum tests.

Data Availability: Qualified investigators may obtain access to the data used in this investigation through the Federal Interagency Traumatic Brain Injury Research (FITBIR) Informatics System (https:// fitbir. nih. gov/).

RESULTS:

Concussed Participants: The characteristics of the overall cohort of concussed athletes have been described elsewhere.[22] In brief 1,751 athletes with SRC sustained during the CARE study were included in the analysis. For those with repeat concussions during CARE, only the initial concussion was included (see consort diagram -**Figure 1**).

Concussed participants averaged 19.2 (±1.3) years of age and 63% were male, 37% female. The majority of participants (n=1387; 79%) participated in Contact sports such as football or ice hockey. The remainder participated in Limited Contact sports (n=292; 17%) such as baseball/softball, and Non-Contact sports (n=72, 4%) such as golf or track. Concussed female athletes most commonly participated in soccer (23.4%), volleyball (14.0%), basketball (12.9%),

and lacrosse (8.4%). Concussed males primarily participated in football (54.7%), soccer (10.7%), basketball (6.8%), and wrestling (6.4%).

Slow Recovery Participants: Of the 1,751 concussed individuals, 399 (22.8%) had a slow recovery defined by a delayed *Asymptomatic* timepoint only (n=79), a delayed *RTP* timepoint only (n=71) or both (n=249). There were no significant differences in demographic variables between the three slow recovery groups (*delayed asymptomatic only; delayed RTP only; delayed both*), thus subsequent analyses combined these individuals into a single slow recovery group. Compared to those with typical recovery, the slow recovery group was significantly more likely to be female ($p=0.05$), be injured in practice ($p=0.04$), have higher initial post-injury SCAT symptom severity scores ($p<0.01$) and lower post-injury SAC scores ($p<0.004$), perform worse on the initial post-injury BESS (Total Score, Firm only Score, and Foam only Score; $p<0.01$), have less frequent assessments in the first 14 days after injury ($p<0.01$), and have higher initial post-injury BSI somatic, anxiety, depression and global severity scores ($p< 0.00$; 0.01; 0.00; 0.00 respectively) (see **Table 1**). A large number of post-injury BSI values were missing (n=183, 46% missing) in the slow recovery group thus the BSI findings should be viewed with caution.

Return to Play Within the Slow Recovery Group: Figure 2 shows the Kaplan-Meier curve for the probability of return to play for the slow recovery group. The median time for RTP was 34.7 days (Q_{25},Q_{75}:32.6, 36.7) after injury in the slow recovery group, compared to 12.8 (Q_{25},Q_{75}: 8.7, 20.1) days in the overall concussed group (see Broglio et al. 2021[22]). Based on the Kaplan-Meier cumulative percentage estimates of days to RTP since date of concussion in the

slow recovery group, 77.6% were able to return to play within 60 days of concussion, and 83.4% were able to return to play within ~ three months (88 days) of concussion (see **Table 2**). **Figure 2** shows that the trajectory for the proportion of those able to return to play begins to flatten substantially approximately 60 days after concussion. Of those unable to return to play at approximately 3 months (90 days, n=50) after injury, the median RTP was 187.1 days. Overall, an estimated 10.6% (see **Table 2)** in the slow recovery group did not return to play 180 days after concussion; this represents 2.4% of our overall cohort of 1,751 concussed athletes.

Predictors of Recovery Within the Slow Recovery Group: As noted above, the slow recovery group was more likely to be female, and have indicators of a more severe concussion within 48 hours of injury compared to the typical recovery group. However, other than history of self-reported concussion (p=.05), these characteristics were not strong predictors of RTP within the slow recovery group (e.g. female slow recovery athletes did not differ from male slow recovery athletes with respect to eventual *RTP*). Five variables met the screening criteria for entry into the multivariable model selection (see **Table 3)** - Post injury SCAT severity score, Post injury SAC total score, Post injury BESS firm score, concussion history and Post injury BSI somatic score). All condition indices were < 30. Due to the high rate of missing BSI data, we did not include it in the best multivariable model selection process. The final best model included only the post injury SCAT severity score. However, the hazard ratio was not significantly different from 1 (see **Table 3**).

A further analysis compared those who took >74 days to return to play (n=63; the timepoint at which 80% of the slow recovery group had returned to play) and those whose RTP was between 24 and 74 days after concussion (n=336). There were no statistically significant differences with respect to baseline measures (SCAT; BSI); initial post injury severity measures (SCAT, SAC, BESS, BSI, presence of loss of consciousness or PTA); sex; or number of self-reported previous concussions (data not shown).

DISCUSSION

We studied the characteristics and outcome of a diverse cohort of 399 concussed male and female collegiate athletes from a wide range of NCAA sanctioned varsity sports who demonstrated a slow recovery. Those with a slow recovery were more likely to be female, be injured in non-contact or limited-contact sport activities during practice/training sessions, have a higher symptom burden immediately after injury, and have completed fewer post-injury assessment timepoints. However, once these individuals exceeded the threshold we used to define a slow recovery, these characteristics were not predictors of eventual RTP. This raises the possibility that while neurobiological factors related to sex and injury severity are primary drivers of recovery trajectory within the first four weeks after injury, additional factors may assume a greater role further out in time from the injury. The possibility of a complex interaction between initial neurobiological factors and psychosocial factors was difficult to evaluate definitively in our study, due in part to the significant BSI data missingness, but warrants further investigation. Indeed, Nelson et. al.[5] evaluated factors associated with outcome after mild TBI and noted a similar pattern in which markers of initial injury severity were predictive of acute outcomes, whereas prolonged recovery was more clearly associated with

psychosocial and psychological health variables. This does not mean there is a causal relationship between these measures and outcome. It is equally plausible that certain individuals are more likely to become discouraged by a prolonged and complicated recovery after injury and thus score higher than their peers on some of these measures. The role that frequency of symptom evaluation within the first 14 days after injury plays is not entirely clear. Possibly, more frequent evaluations are associated with earlier determination of readiness to initiate graded exercise protocols and thus shortened RTP intervals. Additionally, concussions occurring near holiday breaks, at the end of semester, or in post-season tournament play may have resulted in student athletes not being seen daily and a longer interval between determination of the asymptomatic or RTP timepoints.

These results add important nuance to the evolving narrative about recovery from SRC. The perception of the "typical" recovery from concussion has been changing over the last 15 years, evolving from a belief that such injuries typically have a short-term (7-10 day) period of signs and symptoms[1] with a highly favorable prognosis for full recovery, to concerns that a single concussion may put an individual at risk for long-term consequences including the possibility of chronic traumatic encephalopathy.[16,23] While not directly contradicting this view, the largely favorable outcomes in the slow to recover athletes is reassuring. While these athletes took longer than 24 days to return to play, it is encouraging that over three-fourths (77.6%) were able to return to play within 60 days of injury, and four-fifths (83.4%) were able to return to play within 88 days of injury. This is an important message to share with slow to recover athletes, who may be worried that they will never return to play.

However, our data does suggest that a slow recovery trajectory does have implications for the athlete and their medical providers. As has been noted for some time, a minority of concussed athletes, as well as individuals with other types of mild TBI, can develop a more chronic symptom pattern, and struggle to fully recover. As noted in **Figure 2**, the rate of return to play diminishes around 60 days post-injury and of those unable to return to play at approximately 3 months (90 days, n=50) after injury, the median RTP was 187.1 days. Taken together, these findings suggest that while the overall prognosis in the slow recovery group is quite good, the longer the recovery period takes, the probability curve for successful return to play flattens and the prognosis becomes less favorable.

Limitations: There are important limitations to consider in interpreting the results of this paper. While this is a large and diverse cohort of athletes with slow recovery, the participants were all collegiate varsity athletes and may not be representative of other age groups or levels of sport, nor are we able to generalize the findings to other types of mild brain injury (e.g. military or civilian trauma). As noted in the methods, both asymptomatic and return to participation data were not available on all of our participants, and 73 of our 1,751 injuries were censored either by the last contact with study personnel, or by the end of the season in which they were injured, which ever was earlier, thus their data may not accurately depict their final recovery trajectories. However, survival analysis methods use all of the available data to best estimate the overall recovery trajectory. It is also important to point out that resolution of symptoms at rest (*asymptomatic* timepoint interval), and return to play interval are not the sole indicators of concussion recovery. It could be considered a limitation that the delayed asymptomatic-only group was included in the RTP analysis; however, they were included because the focus of this

paper was on any delayed recovery and it is important to note that this group was no different from the other two delayed groups with regard to demographic characteristics. It is also noteworthy that additional measures such as a directed physical exam, with more detailed assessment of autonomic nervous system function, oculomotor and vestibular function, and potential neck injury were not part of the CARE protocol for all participants and if carefully assessed in future studies might contribute significantly to our understanding of factors driving slow recovery.

Clinical Implications: The results of this study provide useful data for athletes and medical teams to consider in calibrating RTP expectations and in making difficult decisions about medical disqualification and the value of ongoing engagement in their sport.[24] We found that three-fourths of our slow recovery cohort were able to return to participation if given an additional month beyond what is considered the typical recovery interval. Overall, only 10.6% of our 399 delayed recovery athletes did not return to play by the end of the 6-month follow-up. On balance, this is reassuring and may provide additional information to guide discussions on the risk-benefit ratio of ongoing participation in collegiate-level varsity athletics. Although an athlete may experience a slow or delayed recovery, there is reason to believe recovery is achievable with additional time and injury management. Overall, this is an encouraging message that may help to mitigate some of the dysphoria and discouragement that can be associated with prolonged resolution of symptoms and return to full sport activities.

ETHICS APPROVAL: This study was completed following approval from respective local Institutional Review Boards and the United States Army Human Research Protection Office. This study was conducted in accordance with the Declaration of Helsinki.

WNL-2022-201645_coinvestigator_appendix ---http://links.lww.com/WNL/C596

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Table 1: Comparison of Assessment Measures – Typical vs. Slow Recovery Athletes

		Slow Recovery n=399		Typical Recovery n=1352		P-Value
Variables						
		n	**%**	**n**	**%**	
Sex	Male	235	58.90	871	64.42	0.05
	Female	164	41.10	481	35.58	
Division	I	323	80.95	1076	79.59	0.28
	II	33	8.27	147	10.87	
	III	43	10.78	129	9.54	
Sport category	Contact Sport	305	76.44	1082	80.03	0.12
	Limited Contact Sport	71	17.79	221	16.35	
	Non-contact Sport	23	5.76	49	3.62	
ADHD Diagnosis at	Yes	27	7.01	128	9.70	0.13

Baseline	No	358	92.99	1192	90.30	
Migraine Diagnosis at Baseline	Yes	36	9.30	114	8.62	0.75
	No	351	90.70	1209	91.38	
Injury Situation	Competition	117	29.32	472	34.91	0.04
	Practice	282	70.68	880	65.09	
Loss of Consciousness	Yes	18	4.57	63	4.70	1.00
	No	376	95.43	1277	95.30	
Post Traumatic Amnesia	Yes	49	12.47	129	9.63	0.13
	No	344	87.53	1210	90.37	
		Mean	**SD**	**Mean**	**SD**	
History of Prior Concussions*		0.72	0.99	0.59	0.83	0.03
SCAT Symptom Severity at Baseline		5.75	9.59	4.82	8.53	0.06
BSI Somatic Raw Score at Baseline		0.91	2.04	0.84	1.83	0.44
SCAT Symptom Severity Score Post Injury		36.62	23.4	25.4	19.85	<0.001

(First Score within 48 Hours)		2	1		
SAC Total Score Post Injury (First Score within 48 Hours)	25.74	2.98	26.26	2.85	0.004
BESS Total Score Post Injury (First Score within 48 Hours)	17.81	8.91	15.91	8.50	0.002
BESS Firm Score Post Injury (First Score within 48 Hours)	5.74	4.62	4.92	4.34	0.003
Bess Foam Score Post Injury (First Score within 48 Hours)	12.19	5.41	11.10	5.26	0.004
Percent Compliance with daily checks up to 14 days after Injury	48.84	29.70	67.93	24.64	<0.001
BSI Somatic Raw Score Post Injury	3.94	3.54	2.00	2.62	<0.001
BSI Anxiety Score Post Injury	2.41	3.56	1.15	2.24	<0.001
BSI Depression Score Post Injury	2.20	3.05	1.16	2.29	<0.001
BSI Global Severity Index Score Post Injury	8.55	8.70	4.31	6.12	<0.001

* Refers to athlete self-report of number of concussions sustained prior to study entry.

Table 2: **Cumulative percentage of athletes who return to play in the Slow Recovery Group (n=399)**

Days Since Injury	**% RTP**
≤15	0.00
≤ 18	1.5*
≤ 25	23.0
≤ 32	44.6
≤ 39	59.3
≤ 46	68.7
≤ 53	74.6
≤ 60	77.6
≤ 67	79.6
≤ 74	80.8
≤ 81	81.8
≤ 88	83.4
<180	89.4

*These individuals had a delayed time to Asymptomatic (hence meeting the definition of delayed recovery trajectory), however, progressed rapidly enough through the graded exercise protocol to be returned to play prior to 24 days post injury.

Table 3: Predictors of RTP in the Slow Recovery Group

		N	Hazard Ratio (CI)	P-Value	C-statistic[1]
Gender	Male (ref)	235	--	0.96	0.52
	Female	164	1.00 (0.80-1.24)		
Division	I	323	--	0.56	0.51
	II	33	0.90 (0.60-1.36)		
	III	43	0.84 (0.59-1.19)		
Sport category	Contact (ref)	305	--	0.70	0.52
	Limited Contact	71	0.92 (0.70-1.22)		
	Non-contact	23	0.85 (0.53-1.36)		
ADHD Diagnosis at Baseline	No (ref)	358	--	0.76	0.50
	Yes	27	0.94 (0.61-1.43)		

Migraine Diagnosis at Baseline	No (ref)	351	--	0.36	0.51
	Yes	36	0.83 (0.56-1.24)		
Injury Situation	Competition (ref)	117	--	0.89	0.49
	Practice	282	1.02 (0.80-1.29)		
Loss of Consciousness	No (ref)	376	--	0.21	0.51
	Yes	18	0.70 (0.40-1.22)		
Post Traumatic Amnesia	No (ref)	344	--	0.65	0.51
	Yes	49	1.08 (0.78-1.49)		
SCAT Symptom Severity at Baseline		391	1.00 (0.99-1.01)	0.98	0.49
BSI Somatic Raw Score at Baseline		388	1.00 (0.94-1.06)	0.94	0.50

Daily Post-Injury Symptom Assessment Frequency	270	1.00 (0.99-1.00)	0.56	0.53
SCAT Symptom Severity Score Post Injury	**293**	**1.01 (0.99-1.01)**	**0.06**	**0.53**
SAC Total Score Post Injury	**287**	**0.97 (0.93-1.01)**	**0.10**	**0.52**
BESS Firm Score Post Injury	**265**	**1.02 (0.99-1.05)**	**0.16**	**0.53**
BSI Somatic Score at Post	**216**	**1.03 (0.99-1.07)**	**0.13**	**0.52**
BSI Anxiety Score at Post	216	0.97 (0.93-1.02)	0.21	0.51
BSI Depression Score at Post	216	0.98 (0.94-1.03)	0.46	0.49
BSI GSI Score at Post	216	1.00 (0.98-1.02)	0.83	0.50
History of Previous Concussion[2]	**389**	**0.90 (0.80-1.00)**	**0.05**	**0.51**

Note: Bolded variables met the criteria for inclusion in the multivariable model selection process. Due to the high rate of missing BSI data, it was not included it in the selection process.

[1]C-statistic represents predictive validity. Values < 0.70 suggest low predictive ability. A value of 1 represents perfect prediction while values near 0.50 represent chance (no predictive ability).

[2]Refers to athlete self-report of number of concussions sustained prior to study entry.

Figure 1: Cohort Consort Diagram

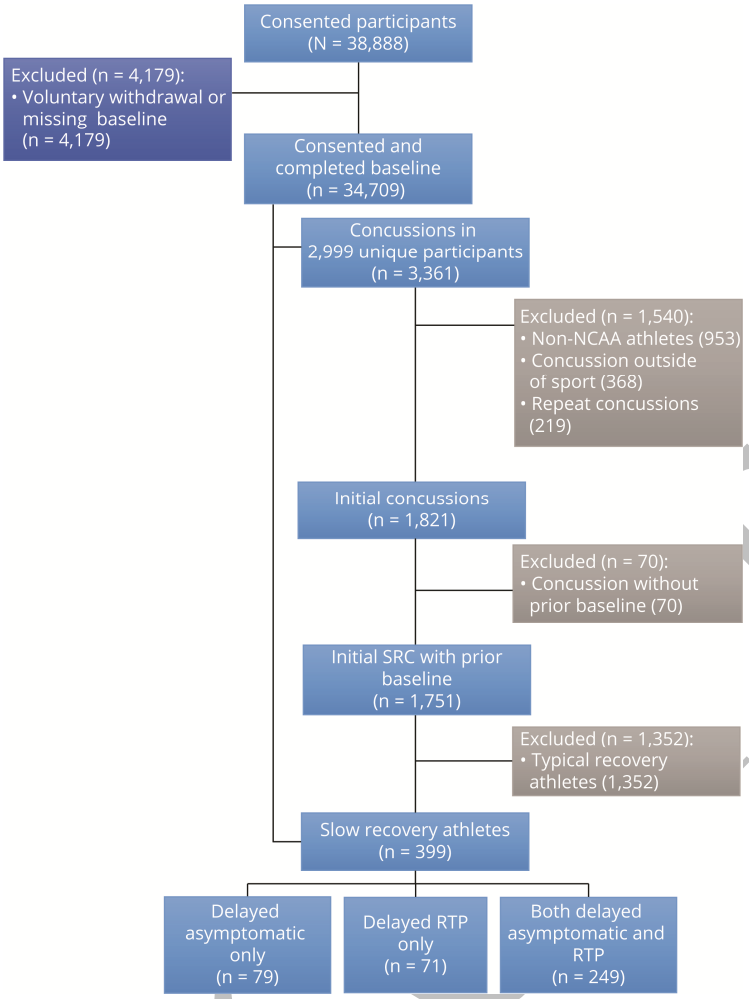

Figure 2: Kaplan-Meier curve for the probability of return to play for the slow recovery group.

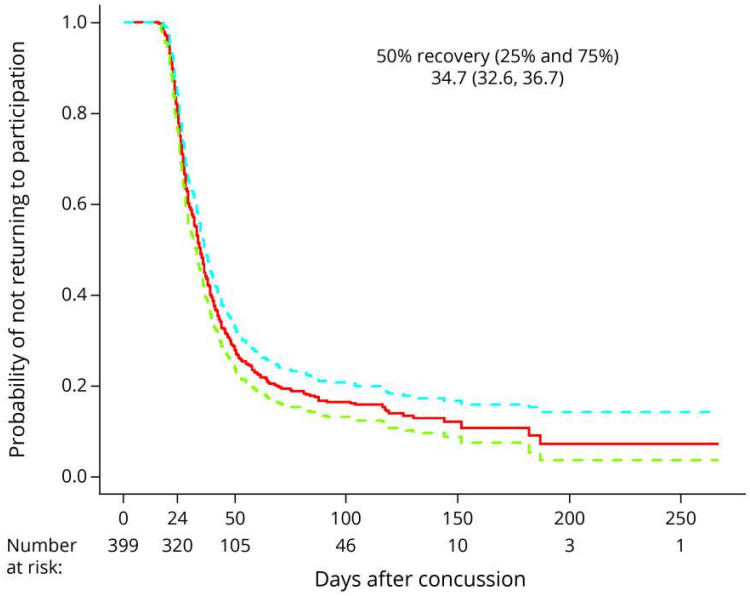

Figure 2 shows the Kaplan-Meier curve (red line) for the probability of return to play for the slow recovery group (n=399). The blue and green lines represent the 95% point-wise confidence intervals for the Kaplan-Meier curve.

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