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Risk Factors for High Symptom Burden Three Months after Traumatic Brain Injury and Implications for Clinical Trial Design: A Transforming Research and Clinical Knowledge in Traumatic Brain Injury Study

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Abstract

More than 75% of patients presenting to level I trauma centers in the United States with suspicion of TBI sufficient to require a clinical computed tomography scan report injury-related symptoms 3 months later. There are currently no approved treatments, and few clinical trials have evaluated possible treatments. Efficient trials will require subject inclusion and exclusion criteria that balance cost-effective recruitment with enrolling individuals with a higher chance of benefiting from the interventions. Using data from the Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) study, we examined the relationship of 3-month symptoms to pre-injury, demographic, and acute characteristics as well as 2-week symptoms and blood-based biomarkers to identify and evaluate factors that may be used for sample enrichment for clinical trials. Many of the risk factors for TBI symptoms reported in the literature were supported, but the effect sizes of each were small or moderate (< 0.5). The only factors with large effect sizes when predicting 3-month symptom burden were TBI-related (i.e., post-concussive) and post-traumatic stress symptom levels at 2 weeks (respective effect sizes 1.13 and 1.34). TBI severity was not significantly associated with 3-month symptom burden ($p = 0.37$). Using simulated data to evaluate the effect of enrichment, we showed that including only people with high symptom burden at 2 weeks would permit trials to reduce the sample size by half, with minimal increase in screening, as compared with enrolling an unenriched sample. Clinical trials aimed at reducing symptoms after TBI can be efficiently conducted by enriching the included sample with people reporting a high early symptom burden.

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Introduction

Symptoms, whether physical, psychological, or functional, are commonly reported after traumatic brain injury (TBI). In the Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) study conducted at 18 United States level I trauma centers, 75% of TBI participants for whom a clinical computed tomography (CT) scan had been ordered upon presentation reported at least one current TBI-related symptom at 3 months post-injury. Nearly 60% reported three or more symptoms.[1] There is controversy about the prevalence of symptoms ≥3 months post-injury,[2] especially for those classified as having mild TBI (Glasgow Coma Scale [GCS] 13–15). However, findings are consistent that symptoms (across TBI severity and time [3 months to 10 years post-TBI]) are associated with adverse functional outcomes such as impaired quality of life,[3–6] lower levels of life satisfaction,[7 8] worse functional status,[9–16] and lower levels of community participation.[17,18] These associations make development of effective treatments targeted at reducing symptom burden especially important.

Many risk factors for predicting chronic post-TBI symptoms have been identified, including pre-existing psychiatric illness, biological factors (e.g., biomarkers, neuroimaging findings), and demographic, social, and personality variables,[2] but there is no consensus about which variables are most predictive.[19] A systematic review of multivariable predictive models found that none adequately predicts individual outcomes from mild TBI (mTBI).[19] A recent study[20] attempted to validate prior mTBI prediction models from the TRACK-TBI Pilot, UPFRONT,[21] and Nijmegen[22] studies with Rivermead Post Concussion Symptoms Questionnaire (RPQ)[23] data obtained at 6 months post-injury from the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study. The results showed that none of the prediction models performed well for predicting individual clinical outcome, although the best-performing models included symptom report at 2 weeks post-injury. None of these articles evaluated the models for clinical trial patient enrichment.

A recent review of treatment interventions for the consequences of TBI determined that only 16% were focused on symptom relief or improvement.[24] These studies were limited by small sample sizes,[25–29] high dropout rates,[28] and TBI diagnoses based on self-report only[30,31] or were restricted to military personnel.[25,27–30] In addition, Polinder and colleagues'[2] extensive review concluded that therapy development has been hindered by lack of clear information about who is likely to develop persistent symptoms.

Efficient trial design will require subject inclusion and exclusion criteria that yield a sample with high probability of detecting an effective treatment (i.e., high-risk individuals), that nonetheless is sufficiently common to make recruitment cost effective. There is currently no published literature to guide enrichment strategies for clinical trials targeting post-TBI symptoms. To inform the design of efficient patient-centered clinical trials to mitigate post-TBI symptom burden, we examined the relationship of symptoms to pre-injury, demographic, and acute risk factors for post-TBI symptoms previously identified in the literature,[2] as well as subacute symptoms and TBI-related blood-based biomarkers, to identify factors that may be used for sample enrichment for clinical trials. We then simulated data incorporating a treatment effect and evaluated sample enrichment strategies using these factors to determine their effect on the efficiency of clinical trials aimed at ameliorating post-TBI symptoms.

Methods

Participants

The TRACK-TBI prospective cohort study enrolled 2697 participants with TBI from 18 level I trauma centers in the United States. They were enrolled from February 26, 2014 to July 3, 2018 and evaluated at 2 weeks and 3, 6, and 12 months post-injury. All TBI participants had sustained a TBI <24 h prior to enrollment and received an acute head CT for clinical care. The current analysis included data from 1718 TBI participants ≥17 years of age who completed the RPQ themselves at 3 months post-injury. Proxies did not complete the RPQ for participants unable to complete it for themselves. For more information about inclusion and exclusion criteria of the study see McCrea and coworkers.[32]

Primary outcome measure

The RPQ is a measure of post-TBI symptoms and lists 16 symptoms that the participant rates to indicate how problematic the symptom has been in the past 7 days compared with before the injury. Each symptom is rated as: not experienced at all (0), no more of a problem than before the injury (1), a mild problem (2), a moderate problem (3), or a severe problem (4). To calculate the total burden of injury-related symptoms, items rated 1 were recoded to 0 prior to summing across all symptoms. The RPQ total score ranges from 0 to 64, with a higher number representing greater symptom burden.

Potential enrichment factors

Predictive measures were chosen from results of previous research identifying pre-injury, demographic, and acute

or subacute risk factors related to post-TBI symptom reporting,[2] and TBI biomarkers that relate to TBI severity or outcomes.[2,19] Potential enrichment factors measured on a continuous scale were categorized to evaluate the effect on needed sample size and screening of potential participants if only those in the high-risk category were included in a clinical trial. The categories chosen were based on the literature where available but were not optimized to maximize differences in symptom burden among categories within the TRACK-TBI study.

Participants' pre-existing conditions were classified as positive for psychiatric history if they or their proxy reported a pre-injury diagnosis of anxiety, depression, sleep disorder, bipolar disorder, schizophrenia, post-traumatic stress disorder (PTSD), or other psychiatric illness; they indicated that they had been hospitalized for emotional or psychiatric problems before the injury; or they took psychiatric medication regularly before the injury.

A history of previous TBI was assessed using the Ohio State University TBI Identification Method[33] grouped as none versus ≥1 prior to the study TBI. Prior TBI was rated positive if it involved loss of consciousness or a dazed feeling and resulted in a visit to the emergency department (ED) and/or hospitalization.

The severity of peripheral injuries was assessed using the maximum Abbreviated Injury Scale[34] (AIS) for regions below the neck (i.e., chest, abdomen, extremity, and external areas). Hospitalized participants were divided into those with a score of ≥3 versus those with a score of ≤2. Those not hospitalized were grouped with those with AIS scores ≤2.

RPQ total score at 2 weeks post-injury was classified as <16 versus ≥16. This division has been suggested as the optimal cutoff for separating people with persistent post-concussion symptoms from healthy adults in the general population,[35] and here was considered indicative of high symptom burden representing, for example, reporting at least half of the symptoms as a mild problem.

Subacute post-traumatic stress symptoms were evaluated with the PTSD Checklist for the *Diagnostic and Statistical Manual of Mental Disorders, 5th edition* (DSM-5) (PCL-5)[36] at 2 weeks post injury. The PCL-5 is a self-report rating scale of 20 symptoms of PTSD each rated from 0 (not at all) to 4 (extremely). Total scores range from 0 to 80. PCL-5 scores were classified as <33 versus ≥33 as per our previous work.[37]

Blood-based biomarkers were obtained within 24 h of injury and included glial fibrillary acidic protein (GFAP),[38–41] ubiquitin carboxyl-terminal hydrolase L1 (UCH-L1),[39,41] neuron-specific enolase (NSE),[41–43] S100 calcium binding protein B (S100b),[40,41 43] and highly sensitive C-reactive protein (hsCRP).[41,44] Plasma GFAP and UCH-L1 were measured based on two platforms (iSTAT and ARCH, Abbott Laboratories) and calibrated to reflect values on the iSTAT platform.[45] Biomarkers were grouped into tertiles as we found no published studies with usable cutoffs for suggesting high symptom burden.

Statistical analysis

Mean RPQ total score at 3 months was calculated for subgroups within the TBI cohort and compared using independent samples *t* tests or analysis of variance (ANOVA). The 3-month RPQ total score was examined because most symptom recovery occurred by then[1] and because that would be a likely time to evaluate outcome for a clinical trial to prevent persistent symptoms after TBI. Magnitude of the difference in symptom burden between subgroups was summarized using standardized mean differences (SMD),[46] also known as Cohen's *d*,[47] with the group having the lowest total score as the reference group so that the maximum difference could be readily seen.

To calculate the impact of enrichment on the sample size needed to detect a fixed treatment effect and the number needed to screen to obtain that sample size, we used individual data from the TRACK-TBI study and simulated data with a treatment effect by assuming that the treatment has a 20% chance of resolving each symptom individually, independently of its effect on other symptoms for the same participant. To get a more stable estimate, we repeated this 10 times for each participant in the data set. For each trial enrichment strategy, we calculated the mean and standard deviation of the 3-month RPQ total score for the participants meeting the inclusion criteria for that strategy in both the original data set (representing the control condition) and the simulated data set with the 20% chance of resolving each reported symptom (representing the treatment condition). These means and standard deviations were input to a sample size calculator[48] for a two-sample *t* test with unequal standard deviations to get the sample size per group for a trial using that enrichment strategy. We further calculated the number of patients with TBI who would need to be screened to achieve the required sample by dividing the sample size needed by the percentage of cases in the analyzed TRACK-TBI sample who satisfied that enrichment criterion. For example, if the trial requires 100 cases meeting the inclusion criterion and 25% of cases within the study sample meet the inclusion criterion, 400 TBI cases would need to be screened to enroll the required sample size in the study. Only participants who completed the measure at 2 weeks were included in the simulations for calculating the number needed to enroll when evaluating high PCL or RPQ scores as potential enrichment factors. However, when calculating the percentage of cases that met a hypothetical trial enrichment criterion (and hence the number needed to screen) related to 2-week symptom

scores, we included individuals who did not complete the questionnaire at 2 weeks in the denominator; that is, we treated them as persons ineligible for trial.

Sensitivity analyses calculated sample sizes based on ranks and assuming a zero-inflated negative binomial distribution (Supplementary Methods). Analyses were performed using SAS, version 9.4 and SPSS, version 19.

Results

Figure 1 presents the participant flow diagram. Of 2310 participants eligible for this analysis, 1718 who completed the RPQ at 3 months were analyzed; 124 participants were excluded because they were too impaired to take the RPQ at 3 months. Sample characteristics for the cohort and the corresponding mean RPQ scores at 3 months are shown in Table 1. The sample was primarily male with GCS 13–15. The mean RPQ score at 3 months was 14.

Risk factors for high symptom burden among those with TBI

Many of the previously published risk factors for post-TBI symptoms such as female sex, lower education, black race, and psychiatric history, were supported, but SMDs were small or moderate (≤ 0.65)[47] (Table 1). RPQ and PCL-5 symptom levels at 2 weeks had large SMD (> 0.65).[47] Symptom levels reported by tertile of GFAP, UCH-L1, and S100b levels differed significantly, with the lowest tertile of each of these biomarkers reporting significantly more symptoms than the other tertiles (small SMDs between 0.18 and 0.34). TBI severity was not significantly related to post-TBI symptoms at 3 months.

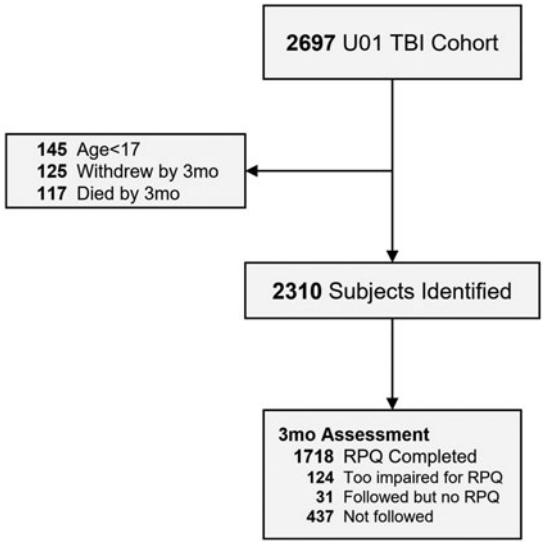

FIG. 1. Participant flow diagram.

Table 1. Potential Risk Factors for High Symptom Reporting at 3 Months

	3 months post-injury			
	n	*Mean (SD) RPQ total score*	p	*SMD (95% CI)*
Age			<0.001	
17-39	933	13.30 (14.28)		0.27 (0.11, 0.43)
40-64	603	16.78 (15.15)		0.52 (0.35, 0.68)
≥ 65	182	9.74 (11.98)		ref
Gender			<0.001	
Male	1165	12.58 (13.84)		ref
Female	553	17.44 (15.39)		0.33 (0.23, 0.43)
Education			<0.001	
Did not complete high school	194	15.99 (15.35)		0.42 (0.25, 0.59)
High school diploma/GED	441	16.93 (15.58)		0.48 (0.35, 0.61)
Some college	535	15.21 (14.47)		0.38 (0.25, 0.50)
4-year college degree	520	10.12 (12.48)		ref
Race			<0.001	
White	1320	13.21 (13.78)		0.24 (0.04, 0.44)
Black	287	19.68 (17.26)		0.65 (0.42, 0.87)
Other	103	10.20 (11.57)		ref
Psychiatric history			<0.001	
Yes	615	17.45 (15.92)		0.35 (0.25, 0.45)
No	1103	12.30 (13.35)		ref
TBI history			<0.001	
Yes	339	17.51 (16.31)		0.28 (0.16, 0.40)
No	1360	13.29 (13.96)		ref
TBI severity			0.365	
GCS 3-8	145	14.25 (12.74)		0.17 (-0.12, 0.47)
GCS 9-12	63	12.03 (12.91)		ref
GCS 13-15, CT positive	507	13.39 (13.92)		0.10 (-0.16, 0.36)
GCS 13 to 15, CT negative	936	14.50 (15.24)		0.17 (-0.08, 0.43)
Maximum AIS below neck			0.598	
≥3	295	13.77 (13.14)		ref
≤2	1423	14.22 (14.80)		0.03 (-0.09, 0.16)
2-week PCL			<0.001	
≤32	1114	10.09 (11.68)		ref
≥33	336	26.04 (16.24)		1.13 (1.00, 1.26)
2-week RPQ total score			<0.001	
≤15	738	5.62 (8.00)		ref
≥16	763	21.82 (15.04)		1.34 (1.23, 1.46)
Blood-based biomarker tertile				
GFAP (pg/mL)			<0.001	
0-143	524	17.28 (16.17)		0.34 (0.22, 0.46)
143-738	538	12.16 (13.87)		ref
738-43,055	524	13.43 (13.45)		0.09 (-0.03, 0.21)
UCH-L1 (pg/mL)			0.008	
1-125	525	15.87 (15.84)		0.17 (0.05, 0.30)
125-294	539	13.64 (14.56)		0.02 (-0.10, 0.14)
294-7299	525	13.30 (13.46)		ref
NSE (ng/mL)			0.846	
0.894-15.260	510	14.68 (15.06)		0.03 (-0.09, 0.15)
15.260-26.102	528	14.21 (14.99)		ref
26.102-370.000	511	14.22 (14.10)		0.00 (-0.12, 0.12)
S100b (μg/L)			0.008	
0.005-0.088	509	15.89 (15.92)		0.18 (0.06, 0.31)
0.088-0.176	527	13.08 (14.75)		ref
0.176-21.030	513	14.17 (13.27)		0.08 (-0.04, 0.20)

(*continued*)

Table 1. (Continued)

	3 months post-injury			
	n	Mean (SD) RPQ total score	p	SMD (95% CI)
hsCRP (mg/L)			0.711	
-.0.383-3.794	482	13.96 (15.33)		0.01 (-0.11, 0.14)
3.794-22.906	497	14.52 (14.54)		0.05 (-0.07, 0.18)
22.906-304.321	482	13.78 (14.02)		ref

For each variable, the category with the lowest mean post-TBI symptom score is considered the reference category (marked ''ref'') and the standardized mean difference (SMD) for the comparison of each other category to the reference category is shown.

SD, standard deviation; CI, confidence interval; GED, general educational diploma; TBI, traumatic brain injury; GCS, Glasgow Coma Scale; CT, computed tomography; AIS, Abbreviated Injury Scale; RPQ; Rivermead Post Concussion Symptoms Questionnaire; PCL, Post-Traumatic Stress Disorder (PTSD) Checklist for the *Diagnostic and Statistical Manual for Mental Disorders, 5th edition* (DSM-5); GFAP, glial fibrillary acidic protein; UCH-L1, ubiquitin carboxyl-terminal hydrolase L1; NSE, neuron-specific enolase; S100b, S100 Calcium Binding Protein B; hsCRP, highly sensitive C-reactive protein.

Sample enrichment and clinical trial efficiency

Table 2 illustrates the simulated effect of enrichment of the population for a clinical trial by limiting enrollment to different high-risk groups. Enrolling only those with PCL ≥33 or RPQ total score ≥16 was associated with simulated sample size reductions of 63% and 45% respectively, whereas enrolling only females had a reduction of 26%. Those factors have different frequencies in the population; therefore, the increase in the number needed to screen was 83% for PCL, 4% for RPQ, and 132% for female. Similar effects were found in the sensitivity analyses based on the ranks of the RPQ score or a zero-inflated negative binomial distribution (Tables S1 and S2). We also examined several factors using a dichotomized RPQ total score (RPQ <16 vs. RPQ ≥16) as 3-month outcome (Table S3). Most of these factors then provided little or even negative enrichment, the exceptions being RPQ total score of ≥16 at 2 weeks, educational attainment, and psychiatric history.

Discussion

This study evaluated risk factors for high post-TBI symptom reporting at 3 months, and the effects on clinical trial efficiency of limiting clinical trial enrollment to high-risk subgroups. In this study of a large TBI cohort including participants across the injury spectrum, as expected, medical/psychiatric history (e.g., pre-existing psychiatric disorder) and demographic (e.g., female gender) characteristics were highly predictive risk factors for significant post-TBI symptom burden at 3 months. However, neither these variables nor the TBI blood-based biomarkers constituted useful enrichment elements when simulated as inclusion criteria for a clinical trial. The sample size reduction achieved (6–32%) would be modest, and would be offset by an increased number of patients who would need to be screened to identify a sufficient sample (122–214%, except 24% for education). Requiring clinical trial participants to have high symptom reporting on the RPQ or PCL-5 in the weeks after their injury would allow for much more efficient trials, yielding a substantially smaller sample size in the trial without a large increase in the number of people with TBI screened.

Consistent with the literature on characteristics associated with post-TBI symptoms, our results found

Table 2. Enrichment Table for 3-Month RPQ Total Score Based on *t* Test

	Placebo 3-month total RPQ score Mean (SD)	Active treatment 3-month total RPQ score Mean (SD)	Mean difference	Number needed to enroll	% reduction in sample size	% cases that meet criterion	Number needed to screen	% increase in number needed to screen
Overall	14.15 (14.53)	11.32 (11.89)	2.83	694			694	
Age 40-64	16.78 (15.14)	13.43 (12.46)	3.35	540	**22**	35	1543	**122**
Female	17.44 (15.38)	13.96 (12.62)	3.48	516	**26**	32	1612	**132**
Education <4-year college degree	15.99 (15.05)	12.80 (12.34)	3.19	586	**16**	68	862	**24**
Black race	19.68 (17.23)	15.62 (13.98)	4.06	470	**32**	17	2765	**298**
Psych history	17.45 (15.91)	13.97 (13.04)	3.48	550	**21**	36	1528	**120**
TBI history	17.51 (16.29)	13.96 (13.30)	3.55	562	**19**	20	2810	**305**
2-week PCL ≥33	26.04 (16.22)	20.78 (13.41)	5.26	254	**63**	20[a]	1270	**83**
2-week RPQ total score ≥16	21.82 (15.04)	17.47 (12.43)	4.35	318	**54**	44[a]	723	**4**
Low GFAP	17.28 (16.15)	13.81 (13.24)	3.47	570	**18**	30	1900	**174**
Low UCH-L1	15.87 (15.83)	12.65 (12.88)	3.22	632	**9**	30	2107	**204**
Low s100b	15.90 (15.90)	12.71 (13.04)	3.19	654	**6**	30	2180	**214**

For example, if only females who had a TBI were included in the trial, a sample size of 516 would be sufficient, a 26% reduction from the 694 needed if the study included males as well. However, because females make up only 32% of the TBI population, 1612 (=516/0.32) TBI cases would have to be considered to identify the needed sample size.

[a]Percentage of cases that meet criterion was recalculated from Table 1 as (number in high-risk group)/1718, treating individuals with missing 2-week questionnaire data as ineligible for the hypothetical trial when enriching on 2-week questionnaire scores.

Bold indicates findings of interest.

SD, standard deviation; RPQ, Rivermead Post Concussion Symptoms Questionnaire; Psych, psychiatric; TBI, traumatic brain injury; PCL, Post-Traumatic Stress Disorder (PTSD) Checklist for the *Diagnostic and Statistical Manual for Mental Disorders, 5th edition* (DSM-5); GFAP, glial fibrillary acidic protein; UCH-L1, ubiquitin carboxyl-terminal hydrolase L1; s100b, S100 calcium binding protein B.

significant relationships between 3-month symptoms and pre-existing difficulties (e.g., prior psychological conditions and prior TBI) and demographic factors (e.g., female gender, black race, lower education). The SMDs for these risk factors are small to moderate: ≤0.51.

This is one of the first articles to examine the association of blood-based biomarkers and symptoms.[49] We found a significant and perhaps counterintuitive relationship between some biomarkers (GFAP, UCH-L1, and S100b) and symptoms, with participants in the *lowest* third for biomarker levels reporting more symptoms than those with higher levels. Lower biomarker levels are generally associated with milder injuries; for example, those with no acute intracranial findings on CT, but there was no significant association when looking at the severity directly. The explanation for greater symptom burden in those with lower biomarker levels is unclear. SMDs for the biomarkers examined were small (< 0.35), and the dynamic nature of peripheral biomarkers makes these results particularly tentative. Two published studies that we identified found higher symptoms in those with higher biomarkers; however, one of the studies was small and the other was in children.[50,51] Of the factors we examined, the only one with a large effect size[47] was high symptom burden at the 2-week assessment (total RPQ score ≥16 or PCL-5 score ≥33; Cohen's $d = 1.34$ and 1.13, respectively).

Enrichment of a trial sample can make the trial more efficient by allowing the trial to have a smaller sample size to detect an effective treatment. This usually comes at a cost of having to screen more potential participants to find those who meet the restricted inclusion criteria. Screening patients for eligibility and taking an enrolled participant through the study both have costs. The screening of individual patients to include only females may appear to be ''free,'' because the medical record contains that information. However, with a minority of hospitalized trauma patients being female,[52] even with the reduced sample size, a study would need $\sim$2.3 times the number of sites or 2.3 times the recruitment time to get enough cases, which can be costly. Screening to determine RPQ or PCL-5 score requires making contact, and also requires that the prospective participant be cognitively capable of reporting symptoms at 2 weeks, thereby excluding some with severe TBI. A study that uses expensive treatments or requires many in-person visits is more costly for each enrolled participant than one that provides an inexpensive treatment and evaluates outcome by telephone. Depending on, among other things, the relative cost of screening and taking an enrolled participant through a trial, different enrichment strategies may be more practical and cost effective.

Using different inclusion criteria for a clinical trial yields different enrichment characteristics. Restricting enrollment based on demographic, history, and biomarker variables yielded expected sample size reductions <30%, with most requiring screening of more than double the number of potential participants. An exception is limiting enrollment to those without a college degree, yielding a 16% decrease in sample size with screening just an extra 24%. Although this was not the sociodemographic factor with the largest reduction in trial sample size, the high prevalence made it more efficient for screening. On the other hand, requiring high post-TBI symptom burden at 2 weeks allows a sample size reduction of >50%, with only a 4% increase in the number screened. Requiring 2-week PCL ≥33 allows an even smaller sample size, but more potential participants would need to be screened.

The numbers reported in the main analysis (Table 2) are based on analyzing the trial using a *t* test, with its assumption of normality. The RPQ total scores are not normally distributed, having a long tail to the right. Although *t* tests are generally robust to some skewness, we also modeled a trial using ranks, as is done with a Mann–Whitney test to make sure that the results are not dependent on the analysis method selected. Using a ranked analysis generally requires a larger sample size, but the effect of enrichment based on early symptom reporting using this method is comparable or stronger than estimates based on parametric statistics. We also analyzed the RPQ score based on a zero-inflated negative binomial distribution and again got comparable results. When we looked at enrichment in a trial using the dichotomous outcome of RPQ at 3 months of ≥16, we got limited enrichment by requiring a RPQ of ≥16 at 2 weeks, and negative enrichment (i.e., a larger sample size) for approximately half of the characteristics examined, including PCL ≥33.

Adaptive population enrichment designs[53] provide an alternative approach to enriching the study population for a clinical trial by restricting enrollment to a specified subgroup as considered here. These designs start with recruiting from the full population and at an interim analysis, look at pre-specified subgroups using pre-specified methods, and may then either continue with the full population, restrict further recruitment to the specified subgroup, or increase the proportion of future recruits from the subpopulation. Adaptive population enrichment designs require a larger sample size than would be achieved by restricting the population from the start, but in their favor, they can give an estimate of the treatment effect in the full population, which provides an indication of the generalizability or applicability of the findings to the broader group. Although not used that way here, the findings of the current study could be used by someone planning an adaptive population enrichment trial to decide what subgroups to pre-specify for evaluation at the interim analysis.

This study has several strengths. TRACK -TBI is a longitudinal study that recruited almost 2700 TBI cases from 18 level I trauma centers in the United States.

Blood samples were collected within 24 h of injury, allowing us to examine whether biomarkers associated with TBI are risk factors for persistent post-TBI symptoms and useful in clinical trial enrichment.

The study also has limitations. TRACK-TBI did not collect data on symptoms reported prior to 2 weeks post-injury. Some trials may want to enroll participants earlier than that. Future studies should collect information on symptoms when the patient is in the ED or soon after. TRACK-TBI did not include people whose TBI did not require a CT scan for clinical care and also did not request symptom information from a proxy when a participant was too impaired to take the RPQ, both of which may have lessened the relationship of TBI severity with 3-month symptom burden. We did not perform comprehensive simulations of potential clinical trials, but rather chose one time point, one model of treatment effect, one set of cutoffs for continuous predictors, one outcome, and three analytic methods as examples to examine enrichment of a population for a clinical trial. We also did not evaluate enrichment for trials of individual symptoms such as headache or cognitive difficulties. With these choices, early symptom reporting based on the RPQ or PCL-5 provides the best enrichment characteristics of the factors evaluated. However, simulations are best constructed according to the choices most relevant to each trial.

Conclusion

Post-injury symptoms may persist for many patients who have sustained a TBI of any severity. Randomized clinical trials are needed to evaluate treatments for general as well as specific symptoms. This study provides foundational data to support the design of clinical trials targeting post-TBI symptoms, including examples of the influence of different sample enrichment strategies on clinical trial efficiency. When designing such trials, investigators should evaluate potential enrichment factors based on the outcome and treatment effect that they are using for designing the trial, including measures of early symptom reporting if this is feasible to collect

TRACK-TBI Investigators

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Author Disclosure Statement

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Supplementary Material

Supplementary Table S1
Supplementary Table S2
Supplementary Table S3
Supplementary Methods

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