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Comparison of Clinical Outcomes 1 and 5 Years Post-Injury Following Combat Concussion

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Abstract

Objective

To compare 1-year and 5-year clinical outcomes in 2 groups of combat-deployed service members without brain injury to those of 2 groups with combat-related concussion to better understand long-term clinical outcome trajectories.

Methods

This prospective, observational, longitudinal multicohort study examined 4 combat-deployed groups: controls without head injury with or without blast exposure and patients with combat concussion arising from blast or blunt trauma. One-year and 5-year clinical evaluations included identical batteries for neurobehavioral, psychiatric, and cognitive outcomes. A total of 347 participants completed both time points of evaluation. Cross-sectional and longitudinal comparisons were assessed. Overall group effect was modeled as a 4-category variable with rank regression adjusting for demographic factors using a 2-sided significance threshold of 0.05, with post hoc Tukey *p* values calculated for the pairwise comparisons.

Results

Significant group differences in both combat concussion groups were identified cross-sectionally at 5-year follow-up compared to controls in neurobehavioral (Neurobehavioral Rating Scale–Revised [NRS]; Cohen *d*, −1.10 to −1.40, confidence intervals [CIs] [−0.82, −1.32] to [−0.97, −1.83] by group) and psychiatric domains (Clinician-Administered PTSD Scale for DSM-IV [CAPS]; Cohen *d*, −0.91 to −1.19, CIs [−0.63, −1.19] to [−0.76, −1.62] by group) symptoms with minimal differences in cognitive performance. Both combat concussion groups also showed clinically significant decline from 1- to 5-year evaluation (66%–76% neurobehavioral NRS; 41%–54% psychiatric CAPS by group). Both control groups fared better but a subset also had clinically significant decline (37%–50% neurobehavioral NRS; 9%–25% psychiatric CAPS by group).

Conclusions

There was an evolution, not resolution, of symptoms from 1- to 5-year evaluation, challenging the assumption that chronic stages of concussive injury are relatively stable. Even some of the combat-deployed controls worsened. The evidence supports new considerations for chronic trajectories of concussion outcome in combat-deployed service members.

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Glossary

CAPS = Clinician-Administered PTSD Scale for DSM-IV; **CPT-II** = Conner Continuous Performance Test II; **CVLT-II** = California Verbal Learning Test II; **D-KEFS CWI** = Delis–Kaplan Executive Function System Color-Word Interference Test; **GOS-E** = Glasgow Outcome Scale Extended; **HIT** = Headache Impact Test; **MADRS** = Montgomery-Åsberg Depression Rating Scale; **MAST** = Michigan Alcohol Screening Test; **MIDAS** = Migraine Disability Assessment; **NOS-TBI** = Neurologic Outcome Scale for TBI; **NRS** = Neurobehavioral Rating Scale–Revised; **PTSD** = posttraumatic stress disorder; **TBI** = traumatic brain injury.

Questions remain regarding the long-term outcome trajectories of service members who sustain traumatic brain injuries (TBIs) in combat. Recent publications suggest these trajectories are not fully understood in particular for mild TBI.[1,2] One challenge of prior efforts has been the reliance on self-report of brain injury that may have occurred months to years before.[3,4] Furthermore, comprehensive assessments for co-occurring conditions complicating clinical course are often lacking.[5] Substantial research has attempted to elucidate these outcomes, which has provided important insights and paved the way for future efforts. However, it has primarily been reliant upon self-report[6–10] or retrospective records,[8,11] with single time point of assessment,[6,10–13] and combining all chronic injury.[8,12,14]

Some longitudinal studies have been performed but they largely focused on the subacute to early chronic time frame postinjury[15] with remote surveys or focused only on chronic phases of injury[16] more subject to recall bias. Through collaborative efforts in combat, following medical evacuation, and in the United States, we have been provided the opportunity to follow the same service members both with and without blast concussion from the subacute, 1-year, and 5-year outcome. We recently reported varying neuroimaging trajectories in this cohort, where a subset of the patients who experienced concussive blast were found to have secondary worsening of brain white matter microstructure, motivating consideration of the implications on clinical outcomes.[17] The objective of the current study was to compare 1-year and 5-year clinical outcomes in these service members to better understand trajectories of long-term clinical outcome.

Methods

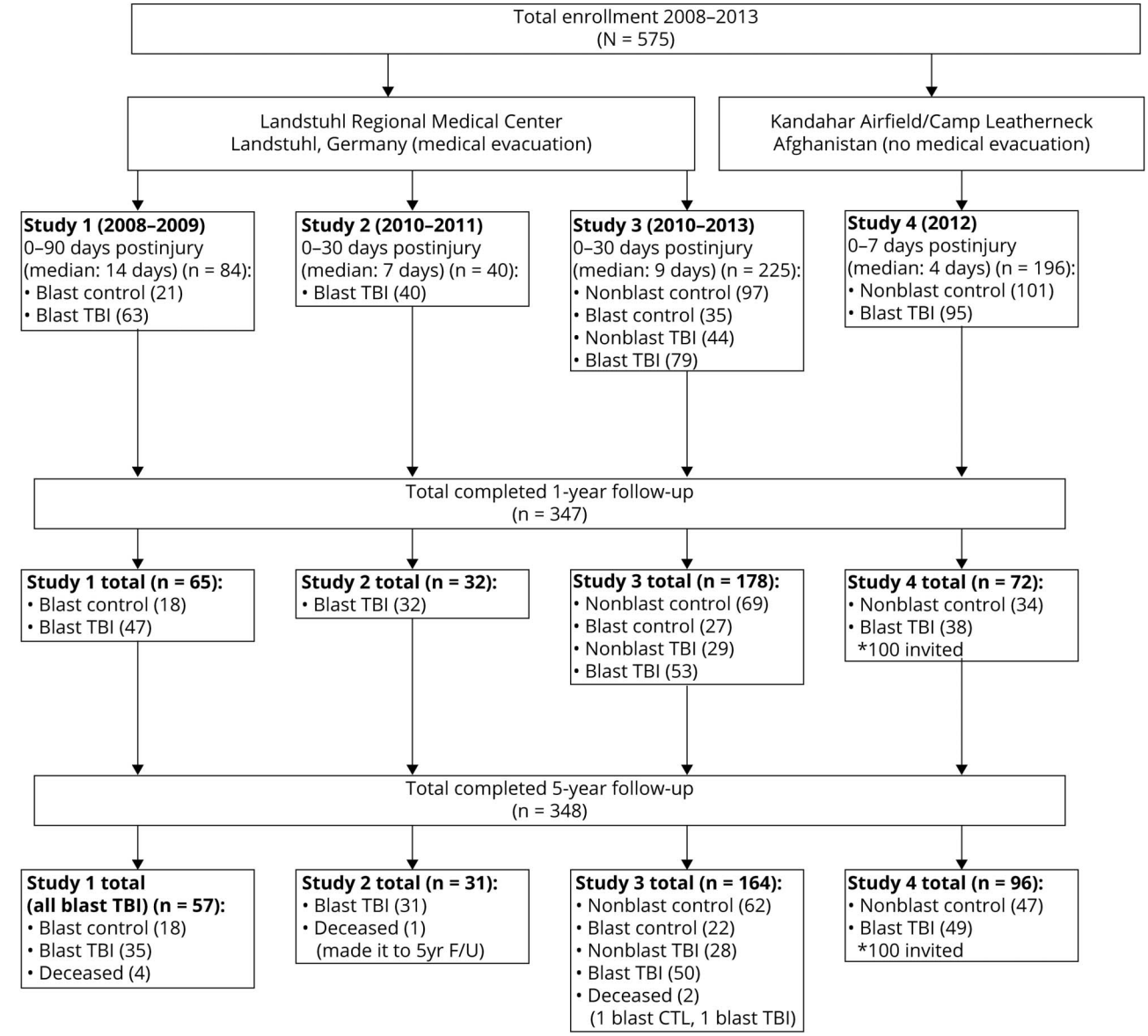
Participants in this study were originally enrolled into 1 of 4 previous cohorts between 2008 and 2013.[17–21] This is the 5-year evaluation in an ongoing prospective, observational, longitudinal research study. In this publication, we report the longitudinal clinical outcomes across our 4 participant groups, 2 primary and 2 exploratory: (1) combat-deployed controls without history of blast exposure (nonblast controls) (primary); (2) patients with concussive blast TBI (primary); (3) combat-deployed controls with history of blast exposure (blast controls) (exploratory); and (4) combat concussion arising not from blast (nonblast TBI) (exploratory). Inclusion criteria have been reported elsewhere.[18,20,21] Briefly, participants were service members deployed to the combat theatre between 2008 and 2013 in whom original enrollment was completed either directly in Afghanistan[20] or following medical evacuation to Landstuhl Regional Medical Center in Germany.[18,21] Diagnosis of head injury was determined by trained medical personnel working in the TBI clinics in Afghanistan or Germany using the same protocol. First, the Military Acute Concussion Evaluation was administered by clinic staff, followed by further examination for diagnosis corroboration by a TBI neurologist. For the concussive blast TBI group, all available clinical histories indicated blast exposure plus another mechanism of head injury such as a fall, motor vehicle crash, or being struck by a blunt object. None had an isolated blast injury. All patients with concussive blast and nonblast TBI met the Department of Defense definition for mild, uncomplicated TBI[22] defined as Glasgow Coma Scale score 13–15, loss of consciousness 0–30 minutes, alteration of consciousness less than 24 hours, posttraumatic amnesia less than 24 hours, and unremarkable CT or MRI at the time of evaluation. All combat-deployed controls were clinically evaluated to be free of signs and symptoms of head injury for both the nonblast and blast control groups and additionally no history of blast exposure was present in the nonblast control group. Prior psychiatric and TBI diagnoses were exclusions for all groups.

Through these efforts, 575 participants have been prospectively enrolled and assessed at the acute (0–7 days, median 4, study 4) and subacute time points (0–30 days, median 7–9, study 2–3; 0–90 days, median 14, study 1), 347 of whom completed further clinical examination at 1 year and 348 at 5 years postinjury, with 281 completing both follow-up evaluations. Due to funding restrictions, only a subset of study 4 could be followed. Reasons for nonparticipation at follow-up primarily were due to continued service responsibilities. It was intentional in the study design to assess both medically evacuated (studies 1–3) and non–medically evacuated (study 4) combat casualties so that direct comparisons in outcome measures could be determined. At the 1-year follow-up, no difference in clinical outcome measures was found comparing the patients with TBI from these groups[21] (medically evacuated vs non–medically evacuated), so their data were combined for further analysis. Figure 1 shows the enrollment flow diagram summarizing enrollment including details of the specific groups evaluated.

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by the University of Washington institutional review board with additional approval from the

Figure 1 CONSORT (Consolidated Standards of Reporting Trials) Diagram of Longitudinal Enrollment



CTL = control; TBI = traumatic brain injury.

US Army Medical Research and Materiel Command Institutional Review Board and carried out in accordance with the approved protocol. Reconsent for each follow-up evaluation was provided by all participants according to the Declaration of Helsinki; no surrogate consent was allowed. Active-duty military were not paid for participation per government guidelines, though travel expenses to the follow-up evaluations were covered.

Clinical Assessments

In-person clinical assessments at the 5-year evaluation included a structured neurobehavioral interview, structured psychiatric evaluation, and neuropsychological battery consisting of 10 cognitive tests identical to the 1-year follow-up with additional self-administered questionnaires. Evaluations lasted approximately 5 hours: 1 hour of standardized neurobehavioral evaluation and 2 hours both for cognitive testing and psychiatric evaluation. During the evaluations, participants took their regularly scheduled medications. All tests were performed between 8 AM and 5 PM in private, quiet, well-lighted rooms. All examiners underwent standardized training for evaluation consistency and were blinded to other clinical information, though during the interviews it often became clear which group participants were in given endorsements of prior events. Per patient, the examiners for each evaluation battery were different, meaning the patient would see 3 different examiners for the 3 different assessments (neurobehavioral, neuropsychological, and psychiatric). In order to evaluate multiple patients on a single day, assessment order for the neurobehavioral and psychiatric evaluations varied,

making sure to always complete the neuropsychological assessment in the first half of the day.

Overall global disability was assessed using the Glasgow Outcome Scale Extended (GOS-E).[23] The GOS-E is scored from 1–8: 1 = dead, 2 = vegetative, 3–4 = severe disability, 5–6 = moderate disability, 7–8 = good recovery. Moderate disability (GOS-E 5–6) is defined as one or more of the following: (1) inability to work to previous capacity, (2) inability to resume much of regular social and leisure activities outside the home, (3) psychological problems that have frequently resulted in ongoing family disruption or disruption of friendships. Severe disability (GOS-E 3–4) is defined as one or more of the following: (1) inability to drive or travel locally without assistance, (2) inability to shop or run errands without assistance, (3) support required for activities of daily living. Standardized, structured interviews were performed per published guidelines.[23] Participants were instructed to consider deployment as the reference point for this interview.

The neurologic assessment included a structured interview designed for patients with TBI (Neurobehavioral Rating Scale–Revised [NRS][24]), 2 headache interviews capturing frequency and intensity (Migraine Disability Assessment [MIDAS],[25] Headache Impact Test [HIT]–6[26]), the Neurologic Outcome Scale for TBI (NOS-TBI),[27] designed to assess focal neurologic deficits associated with TBI, and a TBI history intake interview modified from the Brain Injury Screening Questionnaire,[28] to confirm life history of head injury exposure and identify new head injuries sustained since last evaluation. Participants also completed the Quality of Life after Brain Injury[29] questionnaire capturing life satisfaction.

The psychiatric evaluation included structured interviews and self-administered questionnaires. The Clinician-Administered PTSD Scale for DSM-IV (CAPS)[30] and Montgomery-Åsberg Depression Rating Scale (MADRS)[31] for depression were administered as structured interviews before the participant completed the PTSD Checklist–Military,[32] Beck Depression Inventory,[33] Brief Symptom Inventory–Anxiety module,[34] Insomnia Severity Index,[35] and Michigan Alcohol Screening Test (MAST).[36] The CAPS was scored using the standards from Blake et al.[30]

The neuropsychological test battery assessed cognitive domains of attention, executive functioning, memory, and motor functioning. The Wechsler Test of Adult Reading[37] was used as an estimate of preinjury intellectual abilities. Cognitive measures included the Conner Continuous Performance Test II (CPT-II),[38] a computer-based assessment of attention, impulsivity, reaction time, and vigilance; the California Verbal Learning Test II (CVLT-II),[39] an assessment of verbal declarative memory; the Ruff-Light Trail Learning Test,[40] an assessment of visual-spatial memory; the Trail-Making Test,[41] an assessment of visual scanning and mental flexibility; the Controlled Oral Word Association test,[42] an assessment of verbal fluency; the Iowa Gambling Test, a computer-based assessment of impulsivity and decision-making; the Delis–Kaplan Executive Function System Color-Word Interference Test (D-KEFS CWI),[43] a measure of response inhibition similar to the Stroop test; the Grooved Pegboard test,[44] an assessment of upper extremity motor speed and coordination; and a timed 25-foot walk, an assessment for motor strength, balance, and coordination. Participant effort and engagement was assessed using embedded measures (e.g., CVLT-II forced choice).

Statistical Analysis

Overall differences in characteristics across the 4 groups were assessed for statistical significance using Fisher exact and Kruskal-Wallis tests as appropriate. Five-year cross-sectional analysis considered the entire cohort that completed this follow-up evaluation (n = 348) while longitudinal analysis only considered those who completed both the 1-year and 5-year evaluations (n = 281). Because many of the 5-year outcome measures had skewed distributions, differences among the groups were assessed nonparametrically using rank-regression, in which the actual measured values are replaced by the corresponding within-sample ranks. All outcome models adjusted for age, education, sex, branch of service, and subsequent head injury exposure that may have occurred since last study evaluation. The overall group effect was modeled as a 4-category variable using a 2-sided significance threshold of 0.05, with post hoc Tukey p values calculated for the pairwise comparisons of the 4 groups. All resulting probability values were interpreted for significance across multiple measures within each outcome domain using a 5% false discovery rate per Benjamini-Hochberg.

Data Availability

Data from this study are available through data use agreements submitted by interested parties to the corresponding author. Following study completion, data will also be available and have been submitted to the Federal Interagency Traumatic Brain Injury Research data repository per NIH-NINDS guidelines for funded studies.

Results

At 5-year follow-up, 109 nonblast controls and 170 patients with concussive blast TBI, as well as 41 blast controls and 28 patients with nonblast TBI, completed evaluation, of which 80 nonblast controls, 136 patients with concussive blast TBI, 39 blast controls, and 26 patients with nonblast TBI completed both 1- and 5-year follow-up. Participants across studies by group were combined across original studies 1–4 as there were no demographic differences identified within the groups. Of note, overall the study participants sustained 7 deaths from the 1-year to 5-year follow-up, as reported in figure 1. All of these deaths were in blast-exposed patients, the vast majority of which were deaths by suicide, followed by accidents. Across groups, as shown in table 1, there were significant demographic differences. Specifically, differences were identified in age, education, sex, branch of service, and military rank. As military rank is a surrogate for education, all statistical

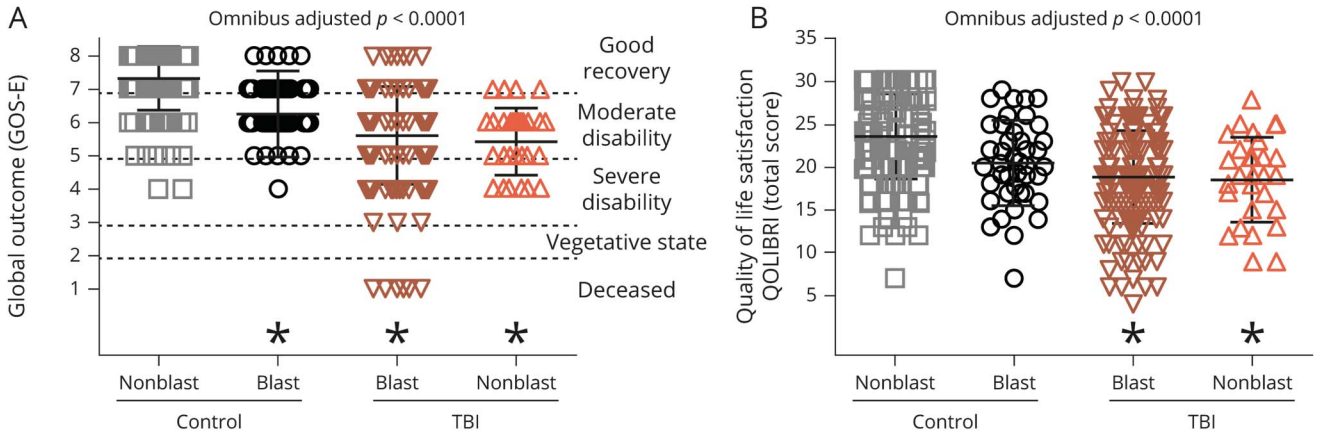
Table 1 Participant Characteristics at 5-Year Follow-up

Characteristic	Nonblast CTL (n = 109)	Blast-exposed CTL (n = 41)	Concussive blast TBI (n = 170)	Nonblast TBI (n = 28)	*p* Value
Age, y	33.6 ± 7.8	38.7 ± 7.9	31.9 ± 6.9	34.9 ± 9.2	<0.001[a,b]
Education, y	16.0 ± 3.1	14.6 ± 2.2	13.7 ± 1.7	14.6 ± 2.0	<0.001[a,c]
Sex					
Male	92 (84)	40 (98)	163 (96)	25 (90)	0.004[a]
Female	17 (16)	1 (2)	7 (4)	3 (10)	
Race/ethnicity					
White	83 (76)	32 (78)	125 (74)	19 (69)	0.82[d]
African American	16 (15)	6 (15)	13 (8)	6 (21)	
Hispanic/Latino	10 (9)	2 (5)	27 (16)	2 (7)	
Asian/Pacific Islander	0 (0)	0 (0)	4 (2)	1 (3)	
Other	0 (0)	1 (2)	1 (1)	0 (0)	
Branch of service					
US Army	61 (56)	36 (88)	145 (85)	24 (86)	<0.001[d]
US Air Force	17 (16)	2 (5)	2 (1)	2 (7)	
US Marine Corps	9 (8)	3 (7)	21 (12)	2 (7)	
US Navy	22 (20)	0 (0)	2 (1)	0 (0)	
Military rank					
Enlisted	86 (79)	36 (88)	163 (96)	27 (97)	<0.001
Officer	23 (21)	5 (12)	7 (4)	1 (3)	
Deployments	2.1 ± 1.6	2.7 ± 2.0	1.8 ± 1.1	2.5 ± 2.3	0.02[b]
Subsequent HIE[e] by 5 y	0.2 ± 0.7	1.2 ± 2.8	0.9 ± 2.3	0.5 ± 0.7	<0.001[a,c]
Service separation					
No	62 (57)	12 (30)	51 (31)	9 (32)	<0.001[a,c,f]
Yes	47 (43)	28 (70)	113 (69)	19 (68)	
Percent disability	32 ± 37.4	55 ± 41.5	69.3 ± 35.9	73.2 ± 37.2	<0.001[a,c,f]

Abbreviations: CTL = control; HIE = head injury exposure; TBI = traumatic brain injury.
Values are mean ± SD or n (%). Statistical significance by Kruskal-Wallis and Fisher exact test as appropriate. Post hoc pairwise significance <0.05 (Tukey). There was no significance for blast control vs nonblast TBI and blast TBI vs nonblast TBI post-hoc comparisons.
[a] Nonblast CTL vs blast TBI.
[b] Blast control vs blast TBI.
[c] Nonblast CTL vs blast CTL.
[d] Dichotomous comparison reported for race (white vs other) and branch (army vs other).
[e] All subsequent exposures met the clinical definition for concussion.
[f] Nonblast CTL vs nonblast TBI.

comparisons were adjusted for age, education, sex, and branch of service, in addition to subsequent head injury exposure sustained between the 1- and 5-year evaluation to account for any possible effect on clinical outcome. All subsequent head injury exposures identified across groups met the clinical criteria for concussion and were primarily due to ground-level falls, low-speed motor vehicle crashes, and fights. At the time of 5-year evaluation, there was also a significant difference in the percent of individuals by group who had separated from the service, with close to 70% of the patients with concussive blast TBI, patients with nonblast TBI, and blast controls already separated, while only 43% of the nonblast controls had completed service separation. Percent disability was also significantly higher in the patients with concussive blast TBI and patients with nonblast TBI but also in the blast controls in comparison to the nonblast controls. In contrast, no patient or participant had separated from the service at 1-year evaluation.

Figure 2 Global Outcome and Quality of Life Satisfaction at 5-Year Follow-up



Overall global disability was significantly different across groups, with greater numbers of patients with concussive blast traumatic brain injury (TBI) and patients with nonblast TBI in the moderate or severe disability range compared to both control groups (A). In parallel, lower quality of life satisfaction was observed in the patients with concussive blast TBI and patients with nonblast TBI compared to both control groups (B). Omnibus test for group comparisons with rank regression adjustment for age, education, sex, branch of service, and subsequent head injury exposure followed by Tukey pairwise post hoc comparison and correction for multiple comparisons. Omnibus and post hoc findings (noted with an asterisk) are only reported as significant if they survived adjustment and correction. GOS-E = Glasgow Outcome Scale Extended; QOLIBRI = Quality of Life after Brain Injury.

5-Year Cross-Sectional Analysis of Global Outcome

Overall 5-year follow-up global outcome and quality of life were substantially impaired in the patients with concussive blast TBI as well as the patients with nonblast TBI in comparison to the nonblast controls as evidenced by the GOS-E and quality of life satisfaction questionnaire (all adjusted post hoc $p < 0.0001$, figure 2). Blast controls were also significantly impaired compared to nonblast controls on global disability but not quality of life after adjustment and statistical correction for multiple comparisons (GOS-E adjusted post hoc $p = 0.002$, quality of life adjusted post hoc $p = 0.09$). A total of 70% of the patients with concussive blast TBI, 86% of patients with nonblast TBI, and 56% of blast controls met criteria for moderate to severe disability on the GOS-E, in contrast to only 16% of nonblast controls.

Longitudinal Comparison Between 1-Year and 5-Year Global Outcome

For comparison to the 1-year follow-up, we defined worse as any GOS-E score that at 5-year follow-up fell into a lower disability bracket than the previous score; better as any GOS-E score that fell into a higher disability bracket than the previous score; no change as any GOS-E score that was in the same disability bracket as the previous score (good recovery, moderate disability, severe disability, death). While the nonblast controls were found to have 72% of participants unchanged, 23% getting better, and 5% getting worse, there was a substantially greater number of patients with blast and nonblast TBI who declined during this same time frame. In fact, 30% of patients with blast TBI and 34% of patients with nonblast TBI declined into a worse disability bracket, which is particularly striking given that at 1 year[21] 79% of patients with blast TBI and 78% of patients with nonblast TBI were already in the moderate to severe disability range. A total of 17% of patients with concussive blast TBI and 7% of patients with nonblast TBI got better by 5-year evaluation. Blast controls were more in line with the TBI groups, with 23% getting worse, 20% getting better, and 57% remaining the same as their 1-year evaluation,[19,21] where 58% already met criteria for moderate to severe disability.

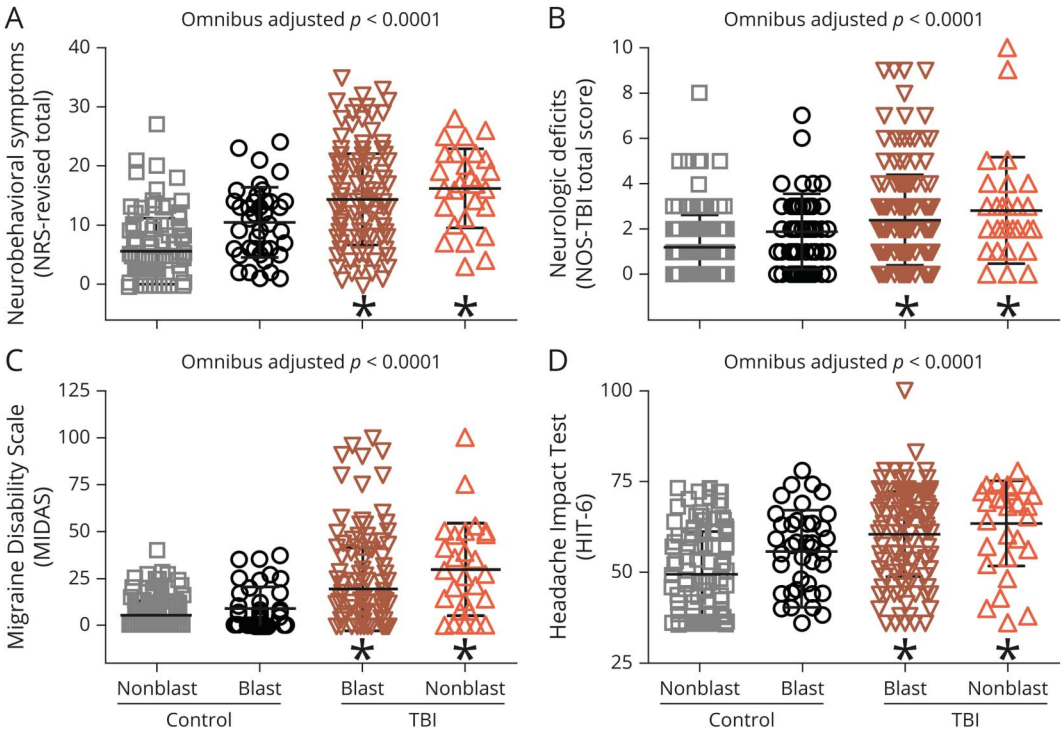
5-Year Cross-Sectional Analysis of Neurobehavior

Overall neurobehavioral symptoms in addition to focal neurologic deficits and headache frequency and intensity were significantly elevated in patients with concussive blast TBI and patients with nonblast TBI compared to nonblast controls at 5-year follow-up (all adjusted post hoc $p < 0.0001$, figure 3). Blast controls were not significantly more impaired in these domains compared to nonblast controls after adjustment and pairwise post hoc analysis followed by correction for multiple comparisons (NRS adjusted post hoc $p = 0.02$, MIDAS adjusted post hoc $p = 0.73$, HIT-6 adjusted post hoc $p = 0.16$, NOS-TBI adjusted post hoc $p = 0.68$).

Longitudinal Comparison Between 1-Year and 5-Year Neurobehavior

In comparison to 1-year follow-up,[19,21] worsening of neurobehavioral symptoms, defined as a 5-point increase or greater, was found in 66% of patients with concussive blast TBI and 76% of patients with nonblast TBI; 50% of blast controls also met this criterion, in contrast to only 37% of nonblast controls. Increases in focal neurologic examination findings were found in 81% of patients with concussive blast TBI, 88% of patients with nonblast TBI, 80% of blast controls, and 55% of nonblast controls during this same time frame and were primarily in domains of hearing, olfaction, and sensory deficits to an extremity. Using the clinical cutoff of 11 for the MIDAS and 50 for the HIT-6, 5-year moderate to severe headache impairment

Figure 3 Neurobehavioral Outcomes and Headache Impairment at 5-Year Follow-up



Patients with concussive blast traumatic brain injury (TBI) and patients with nonblast TBI exhibited significantly more neurobehavioral symptoms than either of the control groups at 5-year follow-up (A). This was also the case for focal neurologic deficits (B) as well as headache frequency (C) and headache intensity (D). Omnibus test for group comparisons with rank regression adjustment for age, education, sex, branch of service, and subsequent head injury exposure followed by Tukey pairwise post hoc comparison and correction for multiple comparisons. Omnibus and post hoc findings (noted with an asterisk) are only reported as significant if they survived adjustment and correction. MIDAS = Migraine Disability Assessment; NOS-TBI = Neurologic Outcome Scale for TBI; NRS = Neurobehavioral Rating Scale–Revised.

was identified in 52% (MIDAS) and 82% (HIT-6) of patients with concussive blast TBI as well as 75% (MIDAS) and 86% (HIT-6) of patients with nonblast TBI in contrast to 15% (MIDAS) and 44% (HIT-6) of nonblast controls. A total of 27% (MIDAS) and 68% (HIT-6) of blast controls were also found to have moderate to severe headache disability at 5-year follow-up. In comparison to the 1-year evaluation,[19,21] all groups were found to have an increase in the number of participants meeting criteria for both the MIDAS (concussive blast TBI, 30% 1 year vs 52% 5 years; nonblast TBI, 64% 1 year vs 75% 5 years; blast controls, 23% 1 year vs 27% 5 years; nonblast controls, 3% 1 year vs 15% 5 years) and HIT-6 (concussive blast TBI, 46% 1 year vs 82% 5 years; nonblast TBI, 78% 1 year vs 86% 5 years; blast controls, 50% 1 year vs 68% 5 years; nonblast controls, 13% 1 year vs 44% 5 years).

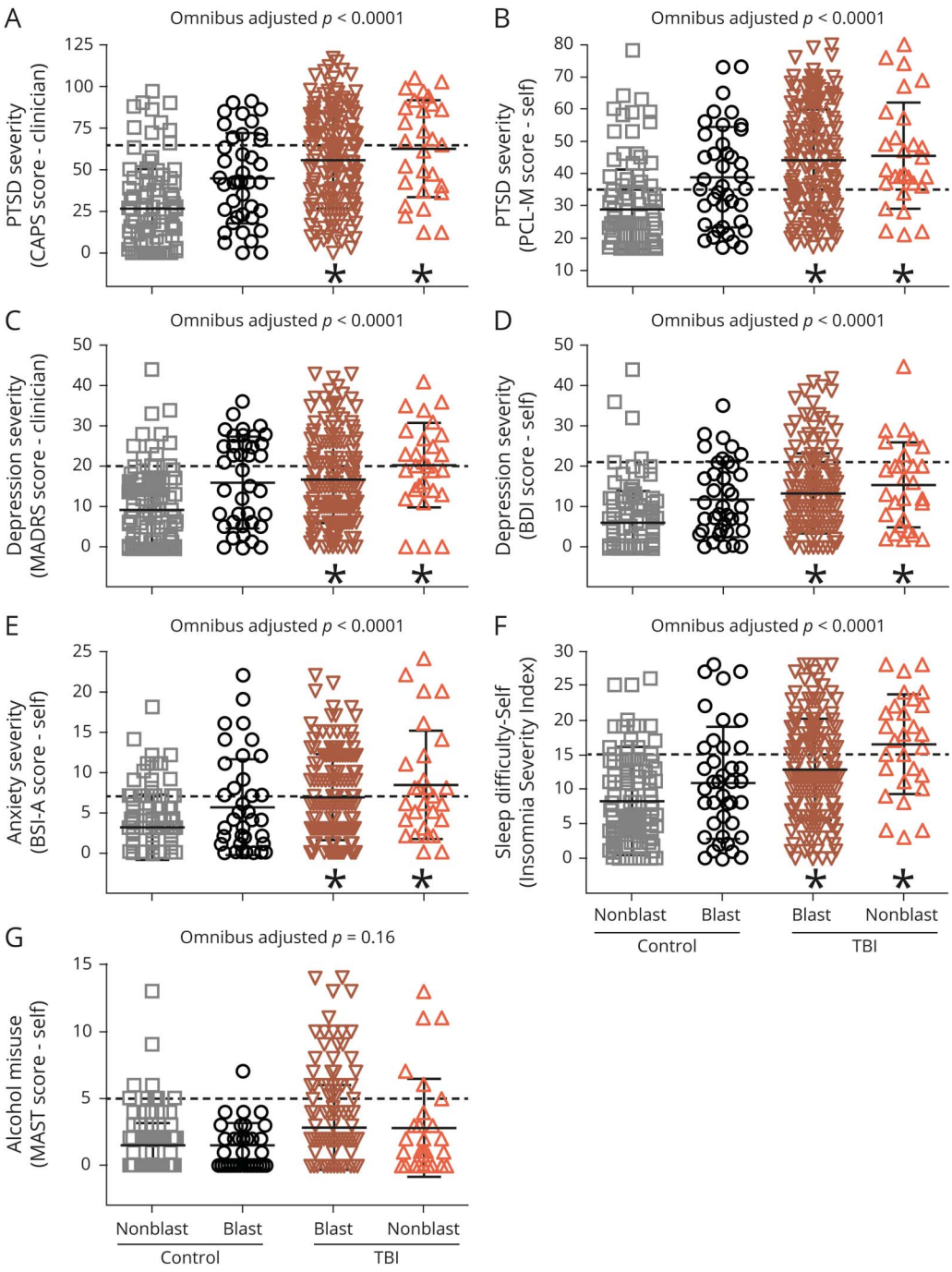
5-Year Cross-Sectional Analysis of Psychiatric Symptoms

There was also significant psychological impairment identified at 5-year follow-up in the domains of posttraumatic stress, depression, and anxiety in both patients with concussive blast TBI and patients with nonblast TBI compared to nonblast controls (all adjusted post hoc $p < 0.0001$, figure 4). Significant impairment was identified by both the structured clinical interview (figure 4A) and self-administered questionnaire (figure 4B) for posttraumatic stress disorder (PTSD) as well as for depression (figure 4, C and D) in both TBI groups but not for the blast controls compared to nonblast controls after statistical adjustment, pairwise post hoc analysis, and correction for multiple comparisons (blast controls vs nonblast controls, adjusted post hoc p values range: 0.02–0.82). While elevated symptoms of anxiety were significantly different between both TBI groups compared to nonblast controls (both adjusted post hoc $p < 0.0001$), there was not a significant difference comparing blast controls to nonblast controls (adjusted post hoc $p = 0.36$, figure 4E). In parallel, sleep impairment followed the same pattern with significant impairment in both TBI groups compared to nonblast controls (both adjusted post hoc $p < 0.001$) while there was no difference comparing blast controls to nonblast controls after proper adjustment, pairwise post hoc analysis, and correction for multiple comparisons (adjusted post hoc $p = 0.82$, figure 4F). In contrast, alcohol misuse was largely similar across groups (omnibus adjusted $p = 0.16$, adjusted post hoc pairwise comparisons p values range 0.23–0.99, figure 4G). This is consistent with the 1-year follow-up, where there were no differences in alcohol misuse across any of the groups.[19,21]

Longitudinal Comparison Between 1-Year and 5-Year Psychiatric Symptoms

Overall comparison of 1-year vs 5-year outcome in these domains identified an increase in the number of patients or

Figure 4 Psychological Health, Sleep, and Alcohol Misuse Outcomes at 5-Year Follow-up



Symptoms of posttraumatic stress were significantly elevated in both traumatic brain injury (TBI) groups compared to both groups of controls observed via clinical evaluation (A) and self-endorsement (B). Symptoms of depression were also significantly elevated in both TBI groups compared to both control groups via clinical evaluation (C) and self-endorsement (D). Symptoms of anxiety (E) and sleep impairment (F) were also significantly increased in both TBI groups compared to both control groups. There was not a significant difference across groups on alcohol misuse (G). Dashed lines indicate clinical cutoff for moderate to severe impairment on each measure. Omnibus test for group comparisons with rank regression adjustment for age, education, sex, branch of service, and subsequent head injury exposure followed by Tukey pairwise post hoc comparison and correction for multiple comparisons. Omnibus and post hoc findings (noted with an asterisk) are only reported as significant if they survived adjustment and correction. BDI = Beck Depression Inventory; BSI-A = Brief Symptom Inventory–Anxiety; CAPS = Clinician-Administered PTSD Scale for DSM-IV; MADRS = Montgomery-Åsberg Depression Rating Scale; MAST = Michigan Alcohol Screening Test; PCL-M = PTSD Checklist–Military; PTSD = posttraumatic stress disorder.

participants meeting criteria for moderate to severe impairment. Using the clinical cutoff of 65 on the CAPS, the percentage of each group, including the nonblast controls but to a lesser extent, meeting criteria for moderate to severe PTSD symptoms was found to noticeably increase during this time frame (concussive blast TBI, 26% 1 year vs 41% 5 years; nonblast TBI, 39% 1 year vs 54% 5 years; blast controls, 25% 1 year vs 39% 5 years; nonblast controls, 0% 1 year vs 9% 5

Table 2 Neuropsychological Test Performance at 5-Year Follow-up

Assessment	Nonblast control (n = 109)	Blast-exposed control (n = 41)	Concussive blast TBI (n = 170)	Nonblast TBI (n = 28)	Adjusted *p* value[a]
Wechsler Test of Adult Reading (standard score), estimate of preinjury verbal intelligence	106.8 ± 11.9	103.2 ± 12.6	104 ± 11.9	103.8 ± 9.8	0.86
Conners Continuous Performance Test II					
Omission errors (*t* score): attention lapses	46.4 ± 4.6	48 ± 6.5	48.1 ± 7.1	47.9 ± 3.4	0.24
Commission errors (*t* score): impulsivity	48.6 ± 9	53 ± 9.7	51.8 ± 9.6	52.5 ± 10.6	0.28
Hit rate (*t* score): reaction time	51.4 ± 7.6	49.8 ± 7.8	51.9 ± 8	53.8 ± 7.1	0.13
Hit rate block change (*t* score): sustained vigilance	52 ± 8.5	51.3 ± 7.3	52.2 ± 10	53.2 ± 8.9	0.85
California Verbal Learning Test II					
Long-Delay Free Recall (standard score): verbal memory	0.3 ± 1	0.1 ± 1.3	−0.2 ± 1.1	−0.2 ± 1.2	0.22
Total intrusions (standard score): falsely recalled items	−0.1 ± 1	0 ± 1.1	0 ± 1	0.3 ± 1.6	0.96
List B vs list A (standard score): proactive memory interference	−0.2 ± 1.2	−0.1 ± 1.1	0 ± 0.9	−0.3 ± 1	0.22
Ruff light trail learning test					
Total trials correct (*t* score): visuospatial learning	51.8 ± 9.6	49.4 ± 10.3	49.2 ± 10	47.3 ± 12.6	0.02
Long delay trial correct: visuospatial memory	14.4 ± 1	14.4 ± 1	14.1 ± 1.4	13.9 ± 1.3	0.39
Trail-Making Test					
Trails A time (s): visual scanning, coordination	22.4 ± 6	22.6 ± 7.4	25.8 ± 10.7	30.1 ± 16.6	0.01
Trails B time (s): mental flexibility	56.1 ± 16.9	60.7 ± 17	64.8 ± 23.9	77.5 ± 46.7	0.16
Controlled Oral Word Association total score: verbal fluency	45.4 ± 11	43 ± 10.7	43.9 ± 11.9	41.2 ± 9.8	0.39
Iowa gambling task net trials (*t* score): monetary decision making	51.1 ± 10.1	51.2 ± 9.9	49.7 ± 10.9	47.7 ± 9.5	0.57
D-KEFS CWI: executive function					
Trial 1 + trial 2 (scaled score): naming, reading	19.7 ± 4.8	19.3 ± 5.6	18.7 ± 5.9	18.3 ± 7	0.84
Trial 3 (scaled score): inhibition	11 ± 2.6	10.3 ± 2.9	10 ± 3.3	8.7 ± 4	0.26
Trial 4 (scaled score): inhibition switching	10.5 ± 2.5	10 ± 2.5	9.3 ± 3.1	9 ± 4	0.71
Grooved Pegboard (motor speed and coordination)					
Average dominant and nondominant time, s	66.8 ± 13	69.6 ± 13.2	71.9 ± 15.3	80.8 ± 20.7	<0.001[b,c,d]
25-Foot walk, s: motor strength, balance, coordination	4.2 ± 0.8	4.4 ± 0.8	4.5 ± 1.1	4.9 ± 1.2	0.004[b]

Abbreviations: CTL = control; D-KEFS CWI = Delis–Kaplan Executive Function System Color-Word Interference Test; TBI = traumatic brain injury.
Values are mean ± SD. Post hoc pairwise significance <0.05 (Tukey). There was no significance for non-blast CTL vs blast TBI, non-blast CTL vs blast CTL, blast control vs blast TBI, and blast TBI vs non-blast TBI post-hoc comparisons.
[a] Omnibus statistical significance with rank regression adjustment for age, education, sex, branch of service, and subsequent head injury exposure.
[b] Significant after adjustment and correction for multiple comparisons.
[c] Nonblast CTL vs nonblast TBI.
[d] Blast control vs nonblast TBI.

years). Using the clinical cutoff of 21 on the MADRS, the percentage of each group, including the nonblast controls but to a lesser extent, meeting criteria for moderate to severe depression symptoms was also found to noticeably increase during this time frame (concussive blast TBI, 23% 1 year vs 32% 5 years; nonblast TBI, 36% 1 year vs 43% 5 years; blast controls, 23% 1 year vs 43% 5 years; nonblast controls, 4% 1 year vs 9% 5 years). It should be noted that these increases in symptoms from 1-year to 5-year follow-up were not for lack of trying to get help on the part of the patient or participant. In fact, 80% of patients with concussive blast TBI, 79% of patients with nonblast TBI, 82% of blast controls, and 48% of nonblast

controls endorsed seeking assistance with a licensed mental health provider. However, only 30% of patients with concussive blast TBI, 45% of patients with nonblast TBI, 34% of blast controls, and 49% of nonblast controls who sought help and completed treatment reported positive benefit with sustained resolution. In contrast, alcohol misuse, which was also collected at both time points, was differentially increased by group. Using the clinical cutoff of 6 for moderate to severe alcohol impairment on the MAST identified preferential increases in impairment in the TBI groups compared to the control groups (concussive blast TBI, 6% 1 year vs 17% 5 years; nonblast TBI, 7% 1 year vs 18% 5 years; blast controls, 7% 1 year vs 3% 5 years, nonblast controls, 5% 1 year vs 4% 5 years) despite no group differences in MAST score at either timepoint.

5-Year Cross-Sectional Analysis of Cognitive Performance

Overall neuropsychological performance was largely similar across the groups at 5-year follow-up (table 2). Only performance on the grooved pegboard and 25-foot walk were found to be significantly different although there is not a good embedded reliability measure for these assessments so we interpret these findings with caution (grooved pegboard omnibus adjusted $p < 0.0001$, 25-foot walk omnibus adjusted $p = 0.004$). Post hoc pairwise analysis followed by correction for multiple comparisons only identified patients with nonblast TBI as performing significantly worse than nonblast controls on the grooved pegboard (adjusted post hoc $p = 0.001$).

Longitudinal Comparison Between 1-Year and 5-Year Cognitive Performance

Comparing 1-year to 5-year neuropsychological function revealed marginal fluctuations in performance for most cognitive measures. The average change in performance for both TBI and both control groups was 0%–10%, meaning there was less than a 10% difference in test performance when comparing the data from each patient between these 2 time points and then taking the average change for each group. There were 2 exceptions: omission errors *t* score indicating attentional lapses on the CPT-II and the scaled score for trial 4 (inhibition switching condition) on the D-KEFS CWI test of executive function. For omission errors *t* score, while both the nonblast control and blast control groups showed on average a 4% worsening in performance, the patients with concussive blast TBI had an average of 25% worsening and the patients with nonblast TBI had a 39% worsening in performance over the same time frame. Examining the D-KEFS CWI trial 4 for inhibition switching, nonblast controls performed on average 3% worse at 5-year verses 1-year follow up, while blast controls performed 4% better in contrast to patients with concussive blast TBI, who performed on average 37% worse, and patients with nonblast TBI, who performed 12% worse comparing this same time frame.

Discussion

Overall, careful examination of the same cohort of service members from the point of injury to 1-year and 5-year follow-up identified an evolution, not resolution, of symptoms, including selective worsening of cognitive performance in 2 domains. While prior efforts examining concussion mostly in collegiate athletes and other civilian cohorts have not predominantly reported lasting cognitive deficits, very little work has been done to understand trajectories in the active duty service population. Our current results challenge the historical consideration of "chronic" injury as one group and underscore the need to consider clinically significant fluctuations even after the 6- to 12-month outcome. Findings from this study support the notion that one should not merely lump all patients with mild TBI who are past 1 year postinjury together as these trajectories of outcome continue to evolve, and can complicate additional conditions unrelated to the brain injury as these service members age. Furthermore, there may be a unique contribution of these concussion exposures to long-term outcome even in the absence of a comorbid mental health condition such as PTSD. Prior evidence of dynamic trajectories in chronic outcome has been reported from large longitudinal studies of moderate to severe civilian brain injury through the TBI Model Systems Study[45] as well as penetrating head injury of veterans from previous conflicts through the Vietnam Head Injury Study.[46] To our knowledge, we provide the first evidence in combat-deployed service members with mild TBI complementing prior work in more severely injured civilian and military patients.

We extend this trajectory comparison to also consider longitudinal outcomes in those who do not sustain a head injury but are combat-deployed. In fact, we also observed worsening trajectories in a proportion of our nonblast controls in particular in the domains of headache impairment, focal neurologic deficits, and mental health problems to a lesser extent than the patients with concussive blast TBI and patients with nonblast TBI but still showing decline. The consistent and comparable findings in both TBI patient groups imply that mechanism of injury in combat may not differentially affect long-term outcome; rather a concussive brain injury in combat by any mechanism may increase a service member's risk for a complicated clinical course with poor outcome. Last, we note that in our parallel neuroimaging study of these same patients and participants, it was striking to find that 20% of the patients with concussive blast TBI also were found to have a delayed worsening in their brain white matter microstructure from 1-year to 5-year follow-up evidenced by diffusion tensor imaging.[17] This supports the notion that these clinical declines may be indicative of continued underlying pathophysiologic changes that may corroborate recent theories regarding accelerated brain aging and early life head injury exposures linking to later life neurodegeneration.[47]

Strengths of the study include the use of a prospectively assessed, longitudinal study design enrolling deployed service members at the point of injury or immediately following medical evacuation from the combat theatre, the relatively robust sample size in our 2 primary groups of nonblast controls and patients with concussive blast TBI, utilization of 2 different control groups to be able to directly examine effect of

combat exposure alone versus combat exposure plus head injury, as well as effect of subconcussive blast injuries in our blast controls, consideration of additional head injury exposures that may have ensued since original enrollment in the study, and examination by trained clinicians blinded to the clinical status of the patient or participant at each time point.

Limitations of the study include the relatively modest group size of our exploratory patient groups of patients with non-blast TBI and blast controls, the heterogeneity of treatment centers in the United States in which our patients and participants sought care, lack of ability to corroborate ensuing medical diagnosis and treatment between the 1-year and 5-year follow-up, lack of comprehensive preinjury clinical data for comparison to long-term outcome, heterogeneity in service separation across groups, and unmeasured covariates that may have influenced the clinical course and findings.

Clinical outcome trajectories following combat concussion were not stable 1 year to 5 years postinjury, with many patients exhibiting continued clinical decline. There are over 18 million US veterans of all previous conflicts alive today with TBI diagnosis from these conflicts[46] and mild TBI in particular from recent conflicts[48] affecting 20%[49]–40%[46] of this population. These findings have direct public health implications as many of these service members have decades of life to live with the hope that these would be good quality years. Understanding varying outcome trajectories will aid clinicians in identifying individuals requiring more targeted screening and treatment in order to help maintain better quality of life for our servicemen and servicewomen throughout their lifetime.

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Christine Mac Donald, PhD	University of Washington	Designed and conceptualized study, interpreted the data, drafted the manuscript, study PI
Jason Barber, MS	University of Washington	Analyzed the data, performed biostatistical review of results, drafted the manuscript for intellectual content
Jana Patterson	University of Washington	Major role in the acquisition of data
Ann Johnson	Washington University	Major role in the acquisition of data
Carolyn Parsey, PhD	University of Washington	Interpreted the data, revised the manuscript for intellectual content
Beverly Scott, MD	University of Washington	Interpreted the data, revised the manuscript for intellectual content
Jesse Fann, MD, MPH	University of Washington	Interpreted the data, revised the manuscript for intellectual content
Nancy Temkin, PhD	University of Washington	Performed biostatistical review of results, revised the manuscript for intellectual content

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Comparison of Clinical Outcomes 1 and 5 Years Post-Injury Following Combat Concussion

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