Original Investigation

Prospectively Assessed Clinical Outcomes in Concussive Blast vs Nonblast Traumatic Brain Injury Among Evacuated US Military Personnel

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IMPORTANCE Blast injury has been identified as the signature injury in the conflicts in Iraq and Afghanistan. However it remains to be determined whether fundamental differences may exist between blast-related traumatic brain injury (TBI) and TBI due to other mechanisms.

OBJECTIVES To determine similarities and differences between clinical outcomes in US military personnel with blast-related vs. non-blast-related concussive TBI and to identify the specific domains of impairment that best correlate with overall disability.

DESIGN, SETTING, AND PARTICIPANTS Prospective cohort study involving active duty US Military personnel evacuated from Iraq or Afghanistan to Landstuhl Regional Medical Center, in Landstuhl, Germany. Four groups of participants were enrolled from 2010 to 2013: (1) blast plus impact complex TBI (n=53), (2) non-blast related TBI with injury due to other mechanisms (n=29), (3) blast-exposed controls evacuated for other medical reasons (n=27) (4) non-blast-exposed controls evacuated for other medical reasons (n=69). All patients with TBI met Department of Defense criteria for concussive (mild) TBI. The study participants were evaluated 6-12 months after injury at Washington University in St Louis. In total, 255 subjects were enrolled in the study, and 183 participated in follow-up evaluations, 5 of whom were disqualified.

MAIN OUTCOMES AND MEASURES In-person clinical examinations included evaluation for overall disability, a standardized neurological exam, headache questionnaires, neuropsychological test battery, combat exposure and alcohol use surveys, and structured interview evaluations for post-traumatic stress disorder (PTSD) and depression.

RESULTS Global outcomes, headache severity, neuropsychological performance, and surprisingly even PTSD severity and depression were indistinguishable between the two TBI groups, independent of mechanism of injury. Both TBI groups had higher rates of moderate to severe overall disability than the respective control groups: 41/53 (77%) of blast plus impact TBI and 23/29 (79%) of nonblast TBI vs. 16/27 (59%) of blast-exposed controls and 28/69 (41%) of non-blast-exposed controls. In addition, blast-exposed controls had worse headaches and more severe PTSD than non-blast-exposed controls. Self-reported combat exposure intensity was higher in the blast plus impact TBI group than in nonblast TBI group and was higher in blast-exposed controls than in non-blast-exposed controls. However, combat exposure intensity did not correlate with PTSD severity in the TBI groups, but a modest positive correlation was observed in the controls. Overall outcomes were most strongly correlated with depression, headache severity, and number of abnormalities on neuropsychological testing. However a substantial fraction of the variance in overall outcome was not explained by any of the assessed measures.

CONCLUSIONS AND RELEVANCE One potential interpretation of these results is that TBI itself, independent of injury mechanism and combat exposure intensity, is a primary driver of adverse outcomes. Many other important factors may be as yet unmeasured, and adverse outcomes following war-time injuries are difficult to fully explain.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01313130.

JAMA Neurol. doi:10.1001/jamaneurol.2014.1114
Published online June 16, 2014.

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Traumatic brain injury (TBI) affects approximately 3.5 million individuals annually in the United States,[1] and approximately 75% are due to "mild" or concussive events.[2] In the US military, it is estimated that approximately 20% of the deployed force experienced a head injury in the wars in Iraq and Afghanistan,[3] of whom 83.3% endured a mild, uncomplicated TBI or concussion.[4] Blast injury has been identified as the signature injury in these conflicts. However, it remains to be determined whether fundamental differences may exist between blast-related TBI and TBI due to other mechanisms.

Previous studies have attempted to compare blast and nonblast TBI outcomes, with evaluations based largely on self-reporting,[5-12] retrospective medical record review,[13-16] and later stages after injury.[17,18] Findings from previous investigations comparing patients with blast vs nonblast TBI vary. Specifically, similarities have been observed in neurocognitive performance,[14,19,20] symptom complaints,[6,20] and mental health,[5,20] while other investigations have found individuals with blast TBI to be worse compared with individuals with nonblast TBI in all 3 of these domains[13] or solely in mental health.[21] Other studies[22,23] have shown that self-reporting is poorly associated with actual performance on measures such as neuropsychological testing not only in civilian populations but also specifically in the military, motivating further research using thorough clinical examinations in a prospective fashion.

Two main objectives of the present study were (1) to determine similarities and differences between clinical outcomes in US military personnel with blast-related vs non-blast-related concussive TBI and (2) to identify the specific domains of impairment that best correlate with overall disability. We prospectively enrolled and followed up patients with blast and nonblast TBI injured in the wars in Iraq and Afghanistan and then assessed clinical measures at 6 to 12 months. In addition, a blast-exposed control group (hereafter blast control) was compared with a non-blast-exposed control group (hereafter nonblast control) to explore whether blast exposures not resulting in a diagnosis of TBI could also contribute to outcomes. These cohorts were enrolled from October 2010 to May 2013 as part of an ongoing collaborative research effort at Landstuhl Regional Medical Center, Landstuhl, Germany. Results from previous cohorts, enrolled from 2008 to 2010, have been reported elsewhere.[24-27]

Methods

The research protocol was approved by the Human Research Protection Office at Washington University, the Institutional Review Board for Landstuhl Regional Medical Center at Brooke Army Medical Center, and the Clinical Investigation Regulatory and Human Research Protection Offices of the US Army Medical Research and Materiel Command. Written informed consent was obtained from all patients in person at Landstuhl Regional Medical Center; no surrogate consent was allowed by the funding agency. See the supplemental methods on the author's website for additional information (http://neuro.wustl.edu/index.php/download_file/view/2071/1054/). We enrolled 255 patients at Landstuhl Regional Medical Center after medical evacuation from combat theaters. The following 4 groups of active duty US military personnel evacuated from Iraq or Afghanistan were assessed: (1) nonblast control, (2) blast control subjects, (3) nonblast TBI (ie, TBI from mechanisms other than blast), and (4) blast plus impact TBI. See the supplemental methods on the author's website for specific inclusion and exclusion criteria. The mean (SD) times from injury to enrollment were 11.5 (9.6) days (blast plus impact TBI group) and 13.8 (10.1) days (nonblast TBI group), with a total range of 0 to 30 days. Of these patients, 183 were followed up at Washington University in St Louis at 6 to 12 months after injury. Of those who were followed up, 5 patients were disqualified (supplemental methods on the author's website), and data from 178 patients were used for analyses (eTable 1 on the author's website). Most patients were young, white, male enlisted service members in the US Army (**Table 1**), consistent with a previous Landstuhl Regional Medical Center cohort.[26]

For the blast plus impact TBI group, all available clinical histories indicated blast exposure plus another mechanism of head injury such as a fall, motor vehicle crash, or strike by a blunt object. None experienced an isolated blast injury. The mechanisms of injury for the nonblast TBI group were falls (9 of 29), motor vehicle crashes (6 of 29), or strike by a blunt object that did not involve blast exposure (14 of 29). Diagnosis of TBI was typically made based on self-report of alteration of neurological function due to an injury.[28] Medical evacuations of both control groups were mostly for gastrointestinal, dermatological, women's health, and orthopedic reasons. Clinical histories from the control subjects indicated no current or previous diagnoses of TBI, with the blast control group endorsing a history of blast exposure. All clinical histories were verified by study personnel (L.W., E.K., and T.S.) taking additional clinical history and reviewing medical records. None who screened positive for TBI were determined not to have had a TBI on further inspection.

Clinical Assessments

All examiners (C.L.M., E.C.N., N.J.W., and D.L.B.) were blinded to other clinical information and imaging results. However, in the course of the interviews, it often became clear whether the patients were in the TBI or control groups based on their endorsements of prior events.

Overall clinical outcomes were assessed using the Glasgow Outcome Scale–Extended[29,30] by telephone or e-mail monthly for 6 to 12 months. See the supplemental methods on the author's website for additional information.

In-person clinical evaluations included a standardized neurological examination, a neuropsychological test battery, and a psychiatric evaluation. The neuropsychological test battery consisted of 9 standard quantitative tests with well-documented performance norms. See the supplemental methods on the author's website for details. The neurological assessment included a structured interview designed for patients with TBI (Neurobehavioural Rating Scale–Revised[31]), 2 headache interviews capturing recent frequency and intensity (Migraine Disability Assessment [MIDAS] and Headache Impact Test 6,[32,33] and the Neurological Outcome Scale for

Table 1. Characteristics of Study Participants

Variable	Nonblast Control Follow-up (n = 69)	Nonblast Control No Follow-up (n = 28)	Blast Control Follow-up (n = 27)	Blast Control No Follow-up (n = 8)	Nonblast TBI Follow-up (n = 29)	Nonblast TBI No Follow-up (n = 15)	Blast Plus Impact TBI Follow-up (n = 53)	Blast Plus Impact TBI No Follow-up (n = 26)
Age, median (range), y	31 (21-49)	30 (22-49)	34 (22-46)	29 (20-39)	28 (20-50)	24 (22-48)	26 (19-47)[a]	24 (20 43)
Education, median (range), y	14 (9-28)	12 (12-15)	13 (10-19)	12 (12-14)	14 (9-18)	12 (12-14)	12 (12-18)	12 (12-16)
Sex, No. (%)								
Male	63 (91.3)	24 (85.7)	25 (92.6)	6 (75.0)	26 (89.7)	14 (93.3)	51 (96.2)	24 (92.3)
Female	6 (8.7)	4 (14.3)	2 (7.4)	2 (25.0)	3 (10.3)	1 (6.7)	2 (3.8)	2 (7.7)
Race/ethnicity, No. (%)[b]								
White	50 (72.5)	18 (64.3)	20 (74.1)	5 (62.5)	19 (65.5)	12 (80.0)	40 (75.5)	23 (88.5)
African American	16 (23.2)	6 (21.4)	4 (14.8)	1 (12.5)	7 (24.1)	2 (13.3)	4 (7.5)	1 (3.8)
Hispanic or Latino	3 (4.3)	3 (10.7)	2 (7.4)	1 (12.5)	3 (10.3)	0	7 (13.2)	1 (3.8)
Asian	0	1 (3.6)	1 (3.7)	1 (12.5)	1 (3.4)	1 (6.7)	2 (3.8)	2 (7.7)
Branch of service, No. (%)								
US Army	55 (79.7)	25 (89.3)	24 (88.9)	6 (75.0)	26 (89.7)	10 (66.7)	46 (86.8)	20 (76.9)
US Air Force	11 (15.9)	3 (10.7)	0	1 (12.5)	2 (6.9)	1 (6.6)	1 (1.9)	2 (7.7)
US Marine Corps	3 (4.3)	0	3 (11.1)	1 (12.5)	1 (3.4)	3 (20)	5 (9.4)	4 (15.4)
US Navy	0	0	0	0	0	1 (6.7)	1 (1.9)	0
Duty status, No. (%)								
Active	43 (62.3)	16 (57.1)	19 (70.4)	7 (87.5)	20 (69.0)	12 (80.0)	39 (73.6)	21 (80.8)
National Guard	23 (33.3)	7 (25.0)	7 (25.9)	0	4 (17.2)	0	10 (18.9)	4 (15.4)
Reserve	3 (4.3)	5 (17.9)	1 (3.7)	1 (12.5)	5 (17.2)	3 (13.3)	4 (7.5)	1 (3.8)
Military rank, No. (%)								
Enlisted	63 (91.3)	26 (92.9)	24 (88.9)	8 (100.0)	27 (93.1)	15 (100.0)	52 (98.1)	25 (96.2)
Officer	6 (8.7)	2 (7.1)	3 (11.1)	0	2 (6.9)	0	1 (1.9)	1 (3.8)
Theater of operation, No. (%)								
Afghanistan	55 (79.7)	23 (81.1)	21 (77.8)	5 (62.5)	18 (62.1)	13 (86.7)	50 (94.3)	24 (92.3)
Iraq	14 (20.3)	5 (17.9)	6 (22.2)	3 (37.5)	11 (37.9)	2 (13.3)	3 (5.7)	2 (7.7)
Concussion severity MACE score, median (range)	NA	NA	NA	NA	26 (21-30)	26 (10-30)	26 (12-30)	25 (16-30)

Abbreviations: MACE, Military Acute Concussion Evaluation[28]; NA, not applicable; TBI, traumatic brain injury.

[a] $P = .000026$ for blast controls vs blast plus impact TBI by Mann-Whitney test.

[b] Individuals were allowed to choose more than 1 response.

Traumatic Brain Injury (NOS-TBI).[34-36] The Neurobehavioural Rating Scale-Revised was analyzed using a published 5-subdomain model.[37] The psychiatric evaluation included the Clinician-Administered PTSD Scale for *DSM-IV* (CAPS),[38] Montgomery-Åsberg Depression Rating Scale,[39] Combat Exposures Scale (CES),[40] and Michigan Alcoholism Screening Test.[41] The CAPS was scored using standard scoring rules by Blake et al.[42]

Statistical Analysis

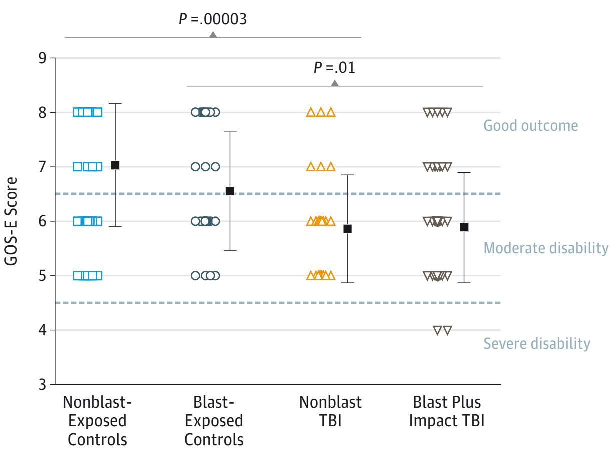
See the supplemental methods on the author's website for complete details on the statistical analyses. Briefly, statistical software (Statistica 10.0; StatSoft Inc) was used for the analyses. Continuous variables are summarized as means (SDs). *t* Test and Mann-Whitney test were used based on the distribution of the data. Uncorrected *P* values are reported but were considered significant only at $P < .05$ after Bonferroni correction for multiple comparisons within each class of variables. The 4 main comparisons of interest were (1) nonblast control group vs nonblast TBI group, (2) nonblast control group vs blast control group, (3) blast control group vs blast plus impact TBI group, and (4) blast plus impact TBI group vs nonblast TBI group, so $P < .0125$ (0.05 divided by 4) was considered significant for most comparisons between groups. Correlations are reported from Spearman rank correlation because of the nature of the data analyzed. Logistic regression analysis was used to explore the relationship between global outcomes and multiple quantitative measures of specific symptoms and impairments.

Results

Global Outcomes

Global outcomes assessed by the Glasgow Outcome Scale-Extended were worse in both TBI groups than in either control group (**Figure 1**). Patients with nonblast TBI were significantly more disabled than nonblast controls ($P = .00003$). Likewise, patients with blast plus impact TBI were significantly worse than blast control subjects ($P = .01$), replicating previous results.[27] No differences in global outcomes were observed between the blast plus impact TBI vs nonblast TBI

Figure 1. Worse Global Outcomes After Traumatic Brain Injury (TBI) Than in Control Subjects Among Evacuated US Military Personnel



Results were assessed at 6 to 12 months after enrollment. *P* values were calculated using 1-tailed Mann-Whitney test and were reported if significant after correction for multiple comparisons at *P* < .0125. GOS-E indicates Glasgow Outcome Scale–Extended.

groups (*P* = .82); similarly, no differences were found between the blast control vs nonblast control groups (*P* = .10). At an individual subject level, 41/53 blast plus impact TBI subjects (77%) and 23/29 nonblast TBI subjects (79%) had moderate to severe disability defined as GOS-E score of 6 or less; 16/27 blast controls (59%) and 28/69 nonblast controls (41%) also met this criteria. The disabled proportion was significantly greater in non-blast TBI subjects in comparison to non-blast controls (p=0.0005, chi-square). Blast-exposed controls and non-blast-exposed controls did not significantly differ (p=0.10, chi-square), nor did blast controls and blast-plus TBI subjects (p=0.09, chi-square) or blast-plus TBI and non-blast TBI subjects (p=0.84, chi-square) in proportion of disabled subjects.

Neuropsychological Testing

In general, all 4 patient groups performed well on neuropsychological testing, and no significant differences were observed across groups (eTable2 on the author's website). However, analysis of individual patients' neuropsychological performance revealed abnormalities that were not apparent at the group level (**Figure 2**A). Abnormal performance for an individual patient was defined as a score that fell 2 SDs outside the mean for the nonblast control group in the direction of worse performance for each assessment. For each individual patient, the number of tests for which performance was abnormal was counted. By chance, of 18 test variables, 66% of patients would be expected to have abnormal performance on 0 tests, 28% would be expected to have abnormal performance on 1 test, and 5% would be expected to have abnormal performance on 2 or more tests. Both the nonblast-exposed TBI (hereafter nonblast TBI) and blast plus impact TBI groups had more patients with abnormalities on neuropsychological testing in 2 or more assessments than would be expected by chance (nonblast TBI, *P* = .0002 and blast plus impact TBI, *P* = .0001; χ^2 test). The proportion of patients with blast plus impact TBI did not differ from the proportion of patients with nonblast TBI. No apparent trend was found in the profiles of test abnormalities within this subset of patients. Blast and nonblast controls did not differ, and neither control group had more patients with abnormal performance on 2 or more neuropsychological tests than would be expected by chance. This result indicates that subsets of patients in both the blast plus impact TBI and nonblast TBI groups were impaired in neuropsychological performance, although the group means were generally not different from those of the controls.

Neurobehavioral Assessment

Clinician ratings in multiple neurobehavioral domains using the Neurobehavioural Rating Scale-Revised revealed more substantial impairments in the patients with TBI compared with the controls. However, no significant differences were observed between the blast plus impact TBI and nonblast TBI groups. More severe neurobehavioral impairments were found in blast controls compared with nonblast controls (eFigure 1 and supplemental results on the author's website).

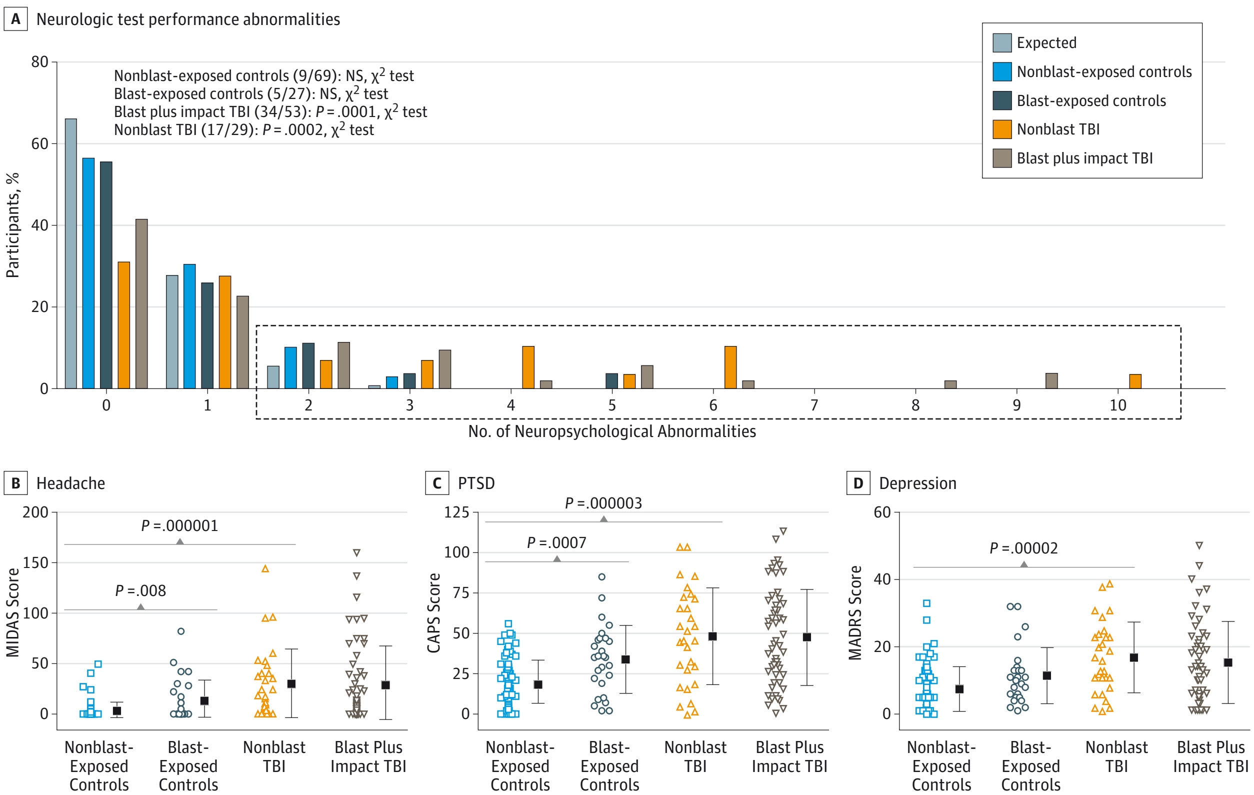
Focal Neurological Examination Findings

As assessed using the NOS-TBI, few focal neurological deficits were observed among the patients across groups overall. The NOS-TBI identified significant impairment only in patients with nonblast TBI compared with nonblast controls (*P* = .008, Mann-Whitney test) (eFigure 2 on the author's website). The most common focal deficits were in the domain of olfaction, found in 11 of 69 nonblast controls (15.9%), 6 of 27 blast controls (22.2%), 15 of 29 patients with nonblast TBI (51.7%), and 9 of 53 patients with blast plus impact TBI (17.0%). This was followed by hearing deficits, observed in 2 of 69 nonblast controls (2.9%), 3 of 27 blast controls (11.1%), 4 of 29 patients with nonblast TBI (13.8%), and 10 of 53 patients with blast plus impact TBI (18.9%). The difference in frequency of olfactory deficits between the nonblast TBI group and the nonblast control group was statistically significant (*P* = .0003, χ^2 test), as was the difference between the nonblast TBI group and blast plus impact TBI group (*P* = .0009, χ^2 test). None of the group comparisons for hearing loss were significant. No difference across groups was observed on the NOS-TBI supplement assessing gait and limb ataxia.

Headache

Headache impairment was substantially higher in patients with TBI compared with controls as assessed using the 2 validated self-report measures of MIDAS (Figure 2B and eFigure 3 on the author's website) and Headache Impact Test 6 (eFigure 4 on the author's website). However, no differences were observed between the blast plus impact TBI and nonblast TBI groups (MIDAS, *P* = .48; MIDAS grade, *P* = .31; MIDAS-A for frequency, *P* = .07; and MIDAS-B for pain severity, *P* = .77; Mann-Whitney test). Patients with nonblast TBI scored significantly higher than nonblast controls on the MIDAS total (*P* = .000001) and each of its subscores (MIDAS grade, *P* = .000001; MIDAS-A, *P* = .000001; and MIDAS-B, *P* = .0005).

Figure 2. Clinical Measures Collected at 6 to 12 Months After Injury



A, Neuropsychological test performance abnormalities were detected in subsets of patients with traumatic brain injury (TBI). The number of patients with neuropsychological test abnormalities (defined as >2 SDs outside the mean for the nonblast control group) is displayed by group compared with what would be expected by chance (blue bars). The percentage of patients is shown to account for the differences in the numbers of patients across groups. The dotted box indicates the group of patients who had poor performance on 2 or more of 18 neuropsychological assessments. *P* values were calculated using χ^2 test between each group vs expected numbers by chance. B, Headache impairment was assessed by the Migraine Disability Assessment (MIDAS) (maximum score, 180). C, Posttraumatic stress disorder (PTSD) severity was assessed by the Clinician-Administered PTSD Scale for *DSM-IV* (CAPS) (maximum score, 136). The CAPS total severity comparison of blast control subjects vs patients with blast plus impact TBI was not significant ($P = .06$). D, Depression severity was assessed by the Montgomery-Åsberg Depression Rating Scale (MADRS) (maximum score, 60). Higher scores indicate worse impairment. *P* values were calculated using 1-tailed Mann-Whitney test and were reported if significant after correction for multiple comparisons at $P < .0125$. NS indicates not significant.

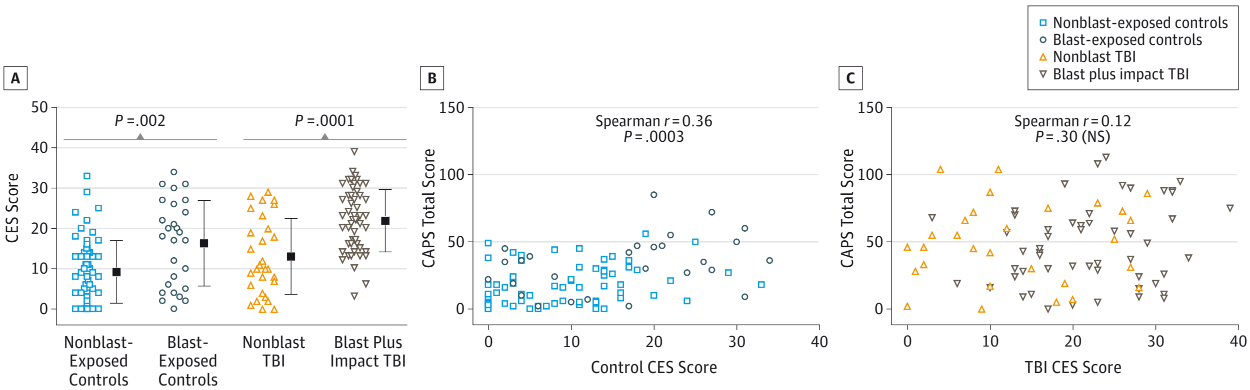
Blast controls also had more impairment than nonblast controls on the MIDAS-A ($P = .0003$). No differences were found between the patients with blast plus impact TBI and the blast controls (MIDAS total, $P = .56$; MIDAS grade, $P = .07$; MIDAS-A, $P = .07$; and MIDAS-B, $P = .39$).

Posttraumatic Stress Disorder and Depression

Psychiatric evaluations revealed worse severity of depression and posttraumatic stress disorder (PTSD) symptoms in both TBI groups than in controls (Figure 2C and D), but surprisingly no differences were observed between the blast plus impact TBI and nonblast TBI groups. Specifically, 41.5% (22 of 53) of patients with blast plus impact TBI and 48.3% (14 of 29) of patients with nonblast TBI met all *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) criteria for PTSD, while 22.2% (6 of 27) of blast controls and only 5.8% (4 of 69) of nonblast controls met these criteria. This outcome represented significantly more patients in the nonblast TBI group compared with the nonblast controls ($P = .0000001$, χ^2 test). Comparing blast controls vs nonblast controls ($P = .018$), blast controls vs patients with blast plus impact TBI ($P = .09$), or patients with blast plus impact TBI vs patients with nonblast TBI ($P = .56$), the differences in the numbers of patients were not significant by χ^2 test after correction for multiple comparisons ($P < .0125$).

Furthermore, no difference was found in any of the PTSD severity scores between the nonblast TBI and blast plus impact TBI groups (Figure 2C and eFigure 5 on the author's website) (CAPS total, $P = .90$; CAPS-B severity–reexperiencing traumatic events, $P = .46$; CAPS-C severity–avoidance and numbing, $P = .55$; and CAPS-D severity–increased arousal and hypervigilance, $P = .76$; Mann-Whitney test). The CAPS total scores for PTSD severity were significantly increased in the nonblast TBI group compared with nonblast controls ($P = .000003$). Of the 3 CAPS subseverity scores, CAPS-D ($P = .00002$) was most affected, followed by CAPS-B ($P = .0001$) and CAPS-C ($P = .0004$). Blast controls were more severely affected than nonblast controls on all measures (CAPS total, $P = .0007$; CAPS-B, $P = .0003$;

Figure 3. Correlations Between Combat Exposure Intensity and Posttraumatic Stress Disorder



A, Combat exposure intensity was assessed by the Combat Exposures Scale (CES). Higher scores indicate greater self-reported combat exposure (maximum score, 41). *P* values were calculated using 1-tailed Mann-Whitney test and were reported if significant after correction for multiple comparisons at *P* < .0125. B, A positive correlation was found between the Clinician-Administered PTSD Scale for *DSM-IV* (CAPS) total score and the combat exposure intensity measured by the CES in control subjects. C, In contrast, no correlation was observed between the CAPS total score and the CES score in the traumatic brain injury (TBI) groups. NS indicates not significant.

CAPS-C, *P* = .004; and CAPS-D, *P* = .003). The difference in PTSD severity between patients with blast plus impact TBI and blast controls was marginal (CAPS total, *P* = .06; CAPS-B, *P* = .05; CAPS-C, *P* = .13; and CAPS-D, *P* = .16).

Likewise, comparing depression severity scores of the blast plus impact TBI group vs the nonblast TBI group (*P* = .38, Mann-Whitney test), no difference was observed (Figure 2D). Depression symptoms were significantly worse in the nonblast TBI group compared with the nonblast controls (*P* = .00002). A trend was observed in blast controls toward worse depression compared with nonblast controls, but it did not reach significance after correction for multiple comparisons (*P* = .014). No difference was observed comparing patients having blast plus impact TBI with blast controls (*P* = .24).

Combat Exposure Intensity

In contrast to psychiatric symptom severity, the intensity of self-reported combat exposure was highest in the blast plus impact TBI group and the blast controls (**Figure** 3A). Blast controls reported significantly higher levels of combat exposure than nonblast controls (*P* = .002), as did the blast plus impact TBI group compared with the nonblast TBI group (*P* = .0001). No difference was found after correction for multiple comparisons between patients with blast plus impact TBI and blast controls (*P* = .03); similarly, no difference was observed between patients with nonblast TBI and nonblast controls (*P* = .08). Therefore, the relationship between group and combat exposure intensity differed substantially from the relationship between group and adverse clinical outcomes.

Alcohol Misuse

No significant differences were found in the scores for any of the groups on the Michigan Alcoholism Screening Test (range, *P* = .04 to *P* = .85 across groups; Mann-Whitney test). See eFigure 6 on the author's website for more details.

Poor Sleep

An index of poor sleep was obtained from subsection D-1 of the CAPS comparing the mean number of hours of sleep reported with the mean number of hours of sleep desired (eFigure 7 on the author's website). We refer to this difference as the Poor Sleep Index. It was found to strongly correlate with total severity scores on the CAPS (*r* = 0.55, *P* < .0001), Montgomery-Åsberg Depression Rating Scale (*r* = 0.55, *P* < .0001), Neurobehavioural Rating Scale–Revised (*r* = 0.42, *P* < .0001), MIDAS (*r* = 0.47, *P* < .0001), and Headache Impact Test 6 (*r* = 0.46, *P* < .0001). It did not correlate with the metrics of combat exposure, alcohol misuse, or neuropsychological testing performance.

Relationship Between Combat Exposure and PTSD Severity

The intensity of self-reported combat exposure was differentially related to PTSD severity in controls and patients with TBI (Figure 3B and C). In controls, a modest but statistically significant correlation was found between the total PTSD severity measured by the CAPS and the combat exposure intensity measured by the CES (*r* = 0.36, *P* = .0003) (Figure 3B). This relationship held for each of the subdomains (eFigure 8 on the author's website), including CAPS-B (*r* = 0.36, *P* = .0003), CAPS-C (*r* = 0.24, *P* = .02), and CAPS-D (*r* = 0.34, *P* = .0007). Surprisingly, this was not the case for the patients with TBI: no correlation was observed between the combat exposure intensity and the CAPS total score (*r* = 0.12, *P* = .30 [not significant]) (Figure 3C) or any of the subdomains, including CAPS-B (*r* = 0.19, *P* = .08 [not significant]), CAPS-C (*r* = 0.09, *P* = .44 [not significant]), and CAPS-D (*r* = 0.07, *P* = .56 [not significant]). In a generalized linear model that included CES and group identity, an almost significant interaction between CES and group identity (*P* = .06) was seen. Therefore, any difference in the relationships between patients with TBI and controls should be considered hypothesis generating rather than definitive.

Table 2. Models With the Best Fit in Logistic Regression Analyses for Global Outcomes

Variable	Estimate (95% CI)	P Value
Model 1[a,b]		
Intercept	−0.9477 (−1.5376 to −0.3576)	.0016
MADRS	0.0689 (0.0199 to 0.1179)	.0059
No. of neuropsychological abnormalities	0.4381 (0.1173 to 0.7589)	.0074
MIDAS	0.02349 (0.00002 to 0.04696)	.0498
Model 2[c]		
Intercept	−0.7573 (−1.3837 to −0.1309)	.0178
MADRS	0.0663 (0.0162 to 0.1163)	.0094
No. of neuropsychological abnormalities	0.4077 (0.0755 to 0.7399)	.0161
MIDAS	0.0182 (−0.0055 to 0.0418)	.1323
TBI vs control groups	−0.3546 (−0.7273 to 0.0182)	.0623

Abbreviations: GOS-E, Glasgow Outcome Scale–Extended; MADRS, Montgomery-Åsberg Depression Rating Scale; MIDAS, Migraine Disability Assessment; TBI, traumatic brain injury.

[a] The overall Akaike information criterion was 202.5, and the likelihood ratio by χ^2 test was 44.04.

[b] Model 1 includes the GOS-E, MADRS, number of neuropsychological abnormalities, and MIDAS.

[c] Model 2 includes the GOS-E, MADRS, number of neuropsychological abnormalities, MIDAS, and TBI vs control groups.

Multivariate Correlates of Global Outcomes

We assessed many possible correlates and found that the number of neuropsychological abnormalities, severity of depression, and extent of headache-related disability were most strongly related to overall disability (**Table 2**). Specifically, we performed logistic regression analysis using the dichotomized Glasgow Outcome Scale–Extended as the dependent variable. Scores of 7 or 8 were defined as good outcomes, and scores of 6 or below were defined as disabled (Figure 1). We entered the following possible correlates into the model: PTSD severity (CAPS), self-reported Poor Sleep Index, combat exposure intensity (CES), headache-related disability (MIDAS), overall headache impairment (Headache Impact Test 6), severity of neurological deficits (NOS-TBI), the number of neuropsychological abnormalities, and depression severity (Montgomery-Åsberg Depression Rating Scale). All possible subsets of models were assessed, and models were ranked based on the Akaike information criterion. The best model by the Akaike information criterion included the number of neuropsychological abnormalities, depression severity, and headache-related disability (model 1 in Table 2).

However, this model accounted for only a moderate proportion of global disability (area under the receiver operating characteristic curve, 0.78) (eFigure 9A on the author's website). To determine whether unmeasured factors associated with TBI provided explanatory power, we added the dichotomous variable TBI vs control groups to the model. In this model, the effect of headache-related disability was no longer significant, and the effect of TBI vs control groups was marginal (P = .06) (model 2 in Table 2). The addition of TBI vs control groups negligibly improved the receiver operating characteristic curve area to 0.79 (eFigure 9B on the author's website). This result indicated very little contribution of unmeasured factors associated with TBI. However, it leaves a substantial fraction of the variance in outcomes still unaccounted for in these patients.

Discussion

In summary, the blast plus impact TBI and nonblast TBI groups were essentially indistinguishable with regard to clinical outcomes at 6 to 12 months after injury. Overall global outcomes, neurobehavioral impairments, neuropsychological performance, headache-related disability, depression, and PTSD were all similar in the blast plus impact TBI and nonblast TBI groups. Although few group-level impairments were found in the neuropsychological testing, subsets of individuals in both TBI groups had worse performance than would be expected by chance. Only a slightly higher rate of olfactory impairment in the patients with nonblast TBI distinguished the groups. However, it must be emphasized that all patients with blast-related TBI in the study had complex mechanisms of injury, including blast plus another type of injury such as a fall, motor vehicle crash, or strike by a blunt object. None had an isolated primary blast injury, suggesting as in previous work[24,26] that such injuries may be rare among evacuated US military personnel.

The exacerbation of depression and PTSD symptoms after concussive brain injury is consistent with investigations examining patients with blast TBI after loss of consciousness,[17] self-report surveys in Operation Enduring Freedom and Operation Iraqi Freedom veterans,[23] and subjective complaint measures comparing predeployment and postdeployment.[43] A recent retrospective study[44] reported similar findings specifically in Marines at 3 months after deployment; however, questions remained about the generalizability to other branches of the military and the longer-term effect on outcomes. A novel finding from our study is that combat exposure intensity did not correlate with PTSD severity in patients with TBI but correlated with PTSD severity in controls. Although this requires replication, the present investigation is the first to date to examine this relationship in a prospectively collected cohort of patients with blast plus impact TBI and nonblast TBI at 6 to 12 months. Among potential explanations for this relationship, the hypothesis that injury to specific brain regions sustained in both TBI groups impaired the extinction of traumatic combat memories and contributed to the chronic effects of posttraumatic stress[45] is perhaps most intriguing. However, definitive evidence for this hypothesis will require detailed correlations between imaging and clinical outcomes, which were beyond the scope of this study.

Logistic regression modeling identified a modest relationship between global outcomes and other clinical measures, most notably depression severity, the number of neuropsychological performance abnormalities, and headache impairment. Negligible improvement in the strength of the model was observed when TBI diagnoses were included. However, the area under the receiver operating characteristic curve was 0.78, which suggests that much of the underlying cause of poor global outcomes is unaccounted for by our present evaluation measures. Clearly, new assessment techniques in additional domains, such as specific duty-related cognitive assessments, social and emotional intelligence testing, and methods to capture disabilities unrelated to head injury, should be explored.

An additional major finding was that blast controls were significantly worse on neurobehavioral outcomes, psychiatric measures, and headache impairment but not neuropsychological test performance compared with nonblast controls. Several possible explanations include that (1) associated increases in combat exposure could negatively influence outcomes, (2) direct structural adverse effects could result from subconcussive blast exposure, (3) some of the blast controls could have been misclassified with respect to TBI, or (4) other events associated with blast exposure may be involved.

Strengths of this study include the prospective design, direct comparison of patients with blast and nonblast TBI, the addition of a blast control group, blinded clinical evaluations completed by trained personnel, and rigorous quantitative analysis techniques. Limitations include the modest sample size, potential selection bias given that these were all patients who were medically evacuated from combat theaters, and a lack of preinjury or early postinjury clinical data for comparison with later outcomes. In addition, we were unable to obtain objective measures of sleep disorders, and we could not control for medication use and current interventions at the time of follow-up evaluations. With regard to headache, we only globally collected headache information and did not explore the underlying causes or chronic pain unrelated to headache. This limitation is discussed in more detail in the supplemental discussion on the author's website.

Conclusions

Based on this prospective study of evacuated US military personnel, we conclude that the clinical outcomes after blast-related concussive TBI are generally similar to those after nonblast-related concussion sustained during deployment. The rate of disability seen after both blast-related and non-blast-related concussive TBI is much higher than that in otherwise comparable civilian studies,[46-54] which may be owing to common elements involved in TBI in a deployed setting rather than the mechanisms of injury per se. However, the finding that the specific domains assessed still do not fully capture overall adverse outcomes indicates substantial room for further investigation into the causes of disability after wartime concussive TBI.

ARTICLE INFORMATION

Accepted for Publication: April 9, 2014.

Published Online: June 16, 2014. doi:10.1001/jamaneurol.2014.1114.

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Obtained funding: Brody.
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Conflict of Interest Disclosures: None reported.

Funding/Support: The study was funded by grant PT090444 from the Congressionally Directed Medical Research Program (Dr Brody, principal investigator).

Role of the Sponsor: The funding source had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: The views expressed in this article are those of the authors and do not reflect the official policy of the Department of the Army, Department of the Air Force, Department of Defense, or US Government.

Additional Contributions: Assistance was provided by the Washington University clinical assessment team, including Leslie French, PhD, Justin Hampton, LCSW, Erick Shumaker, PhD, Kathryn Salmo, MS, Kathryn Stinson, MS, Danielle Marinucci, MSW, April Reupke, MS, Meghan Jenkins, MSW, Natasha Hilts, MSW, Christine Lakey, LCSW, Amanda Hiesele, MS, and Laura Daigh, BS, for whom compensation was given for their contributions to the study. We thank the participants, their families, commanding officers, and clinical providers for making this study possible.

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