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Depression Trajectories during the First Year after Traumatic Brain Injury

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Abstract

Major depression is prevalent after traumatic brain injury (TBI) and associated with poor outcomes. Little is known about the course of depression after TBI. Participants were 559 consecutively admitted patients with mild to severe TBI recruited from inpatient units at Harborview Medical Center, a Level I trauma center in Seattle, WA. Participants were assessed with the Patient Health Questionnaire-9 (PHQ-9) depression measure at months 1–6, 8, 10, and 12 post-injury. We used linear latent class growth mixture modeling (LCGMM) of PHQ-9 total scores to identify homogeneous subgroups with distinct longitudinal trajectories. A four-class LCGMM had good fit indices and clinical interpretability. Trajectory groups were: low depression (70.1%), delayed depression (13.2%), depression recovery (10.4%), and persistent depression (6.3%). Multinomial logistic regression analyses were used to distinguish trajectory classes based on baseline demographic, psychiatric history, and clinical variables. Relative to the low depression group, the other three groups were consistently more likely to have a pre-injury history of other mental health disorders or major depressive disorder, a positive toxicology screen for cocaine or amphetamines at the time of injury, and a history of alcohol dependence. They were less likely to be on Medicare versus commercial insurance. Trajectories based on LCGMM are an empirical and clinically meaningful way to characterize distinct courses of depression after TBI. When combined with baseline predictors, this line of research may improve our ability to predict prognosis and target groups who may benefit from treatment or secondary prevention efforts (e.g., proactive telephone counseling).

Keywords: depression; prognosis; substance abuse; trajectories; traumatic brain injury

Introduction

Major depression is increasingly recognized as an important comorbid condition associated with traumatic brain injury (TBI).[1–6] Multiple studies demonstrate an elevated lifetime prevalence of depression before TBI and then an even greater risk of depression after TBI.[1,3,6] Depression is associated with adverse outcomes including greater physical disability,[2] unemployment,[7] functional dependence,[8] post-concussive symptoms,[8,9] lower quality of life,[2,9] poor psychosocial functioning and community participation,[2,4,10,11] and suicidal ideation.[12–14] Thus far, there is mixed evidence for the efficacy of telephone counseling or antidepressants to prevent[15–17] or treat patients with depression after TBI.[18–20]

A major gap in our knowledge has to do with the course of depressive symptoms after TBI. Cohort studies have produced conflicting results regarding whether depression increases[6,21] or decreases[22–24] over time. Cohort studies suggest that there are subgroups that never become depressed, are only transiently depressed, or are persistently depressed.[1,25,26] Of those who become depressed, some are depressed early and some become depressed in the post-acute phase.[1,25,26] There is speculation that depression that develops soon after TBI may be more biologically determined, while depression that develops during the post-acute phase may be triggered by psychosocial factors.[27,28]

Latent class growth mixture modeling makes it possible to identify relatively homogeneous subgroups that have distinct longitudinal trajectories within a heterogeneous population.[29] This approach has been used extensively to describe psychological responses to trauma exposure and interpersonal loss.[30] Four prototypical distress trajectories have been identified: resilient (consistently low psychological distress), recovery (improving psychological distress), delayed (worsening psychological distress), and persistent (consistently high psychological distress).[30] This method has been used to describe post-traumatic stress symptoms after TBI,[31] and mixed-effects models have been used to identify predictors of rate of change in psychiatric symptoms longitudinally.[32]

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Identification of distinct depression trajectories after TBI could improve our ability to understand causal factors, predict outcomes, and develop targeted interventions. In this study, we sought to identify depression trajectories in a cohort of persons who were followed for 1 year after being hospitalized for TBI. Our research questions were: (1) Can we identify distinct, clinically meaningful depression trajectories? and (2) Are baseline demographic and clinical characteristics drawn from TBI cohort studies predictive of depression trajectory membership?[1,4,24,33] We included as predictors the presence or absence of cerebral contusion, because the previous study on this variable was quite small,[34] and insurance status (with Medicaid being a proxy for low social economic status), because impoverishment is a risk factor for depression in the general population.[35]

Methods

Procedures

We used daily automatic queries of electronic medical records and TBI consultation lists to identify consecutively eligible inpatients with TBI. Research staff obtained consent from eligible patients who were fully oriented before discharge. For patients disoriented at discharge, we obtained assent from legal next of kin to conduct follow-up. Those patients not approached at discharge were recruited via a letter from the attending neurosurgeon and telephone calls. Trained research assistants used structured telephone interviews to assess participants at months 1, 2, 3, 4, 5, 6, 8, 10, and 12 months after injury. Disoriented patients were followed for up to 1 year and were required to pass standardized orientation examination before consenting.[36]

Study procedures were approved by the University of Washington Institutional Review Board and followed guidelines from the Health Insurance Portability and Accountability Act. We obtained a waiver of consent to determine eligibility and retain selected demographic information about nonrecruited patients. Otherwise, participation required written consent.

Participants

This is a reanalysis of data gathered between 2001 and 2006 and published previously.[1] This study was the recruitment phase of a clinical trial investigating the efficacy of sertraline for major depressive disorder (MDD) after TBI. Participants with evidence of acute TBI were recruited from consecutive admissions to Harborview Medical Center. Acute TBI was defined as having radiological evidence of acute, traumatically induced brain abnormality or Glasgow Coma Scale (GCS) score lower than 13 (based on the lowest score within 24 h after admission or the first after paralytic agents were withdrawn). Other inclusion criteria were: at least 18 years old, English speaking, and residing in King, Pierce, Kitsap, Jefferson, Mason, Thurston, or Snohomish counties.

Potential participants were excluded if they had uncomplicated mild TBI (GCS 13–15 and no radiological abnormality)[37] or if they had GCS scores lower than 13, no radiological evidence of TBI, and blood alcohol levels over 199 mg/dL because of diagnostic uncertainty in these groups.[38] Other exclusion criteria were homelessness, having no contact information, pending incarceration, and schizophrenia. We did not exclude persons with a history of other mental health disorders because of the high prevalence of these disorders and the potential importance of psychiatric history in predicting outcomes.[3,4,33,39] Patients were referred for further evaluation and treatment if they reported suicidal ideation with plan or intent.

Measures

We gathered demographic, medical, radiologic, and *International Classification of Diseases, Ninth Revision* (ICD-9) code data from participant interviews, medical record reviews, and the Harborview Trauma Registry. We assessed race via self-report and record review. We based other system injury severity on the Injury Severity Score excluding head injury.[40] Serum blood alcohol level and toxicology screening results (cocaine and amphetamine) were obtained on 80% of the sample.

During the first assessment, we conducted a structured interview to assess pre-injury history of psychiatric disorders and treatment.[1,19] We coded participants as having a pre-injury history of depression if they reported ever receiving a diagnosis of or treatment for depression or making a suicide attempt. We asked participants whether they ever received any of the following mental health diagnoses before injury: post-traumatic stress disorder (PTSD), bipolar disorder or manic depression, generalized anxiety disorder, panic disorder, obsessive-compulsive disorder, any phobia, schizophrenia, schizoaffective disorder, or any psychotic disorder.

Because of the prevalence and salience of PTSD in TBI,[6] we reported those with this disorder separately, while the remainder were grouped into the category of those having a history of ''other mental health disorder.'' Lifetime history of alcohol dependence was based on endorsing at least two items on the CAGE (Cut down? Angered? Guilty? Eye–opener?) questionnaire.[41] Alcohol intoxication was defined as blood alcohol level greater than 79 mg/dL. Other drug use was defined as a positive toxicology screen for cocaine or amphetamine on admission. Participants were asked whether they were involved in or planning a lawsuit related to their injury.

The subsequent assessments focused on assessing symptoms of depression and mental health treatment. Depressive symptoms were assessed using a telephone-based, structured interview of depressive symptoms using the Patient Health Questionnaire 9-item depression scale (PHQ-9).[42] In a subset of this sample, the PHQ-9 has been shown to have excellent interrater reliability ($r = 0.99$) and good diagnostic validity using telephone interviews in persons with TBI.[43] At a cutoff of 10 or higher, the PHQ-9 has a sensitivity of (0.88) and a specificity of (0.90) for independently diagnosed MDD in persons who are within 1 year of sustaining TBI.[43] Therefore, we refer to PHQ-9 scores less than 10 as being in the nondepressed range and scores of 10 or more as being in the depressed range.

To capture use of antidepressants, we asked participants whether they were taking ''any medicine for nerves, stress, depression, or to help you sleep in the last 4 weeks,'' and if the medication was an antidepressant, they were coded as using an antidepressant. To capture use of counseling, we asked whether they were ''currently receiving outpatient mental health treatment.'' PHQ-9 scores were captured from both treatment and control subjects during the trial, because there were no differences in treatment response between the two groups. Participation in the trial, however, was not counted as having received antidepressants because the treatment received was not community-based.

Statistical analyses

We conducted latent class growth mixture models (LCGMM) on total PHQ-9 scores to obtain distinct trajectories of depression over time.[29,44,45] LCGMM is a contemporary longitudinal technique and is an extension of conventional growth modeling.[46] When conducting these conventional analyses, we assume that all persons in the study sample come from a single population. This implies that one (average) trajectory will adequately describe the developmental pattern of the whole sample.

This assumption is relaxed in LCGMM, meaning that persons in the sample need not come from one single underlying population but can come from multiple, underlying (or latent) subpopulations. Identifying the number and characteristics of these underlying subpopulations is the main aim of LCGMM. This is done by identifying k number of

Table 1. Demographic, Clinical, and Mental Health Variables by Class and Total

	Recovery n = *58*	*Persistent* n = *35*	*Low depression* n = *392*	*Delayed* n = *74*	*Total* N = *559*
Age	%	%	%	%	%
18–29 years	36.2	11.4	32.1	32.4	31.3
30–44 years	34.5	45.7	23.7	27.0	26.7
45–59 years	24.1	31.4	23.5	24.3	24.2
60+ years	5.2	11.4	20.7	16.2	17.9
Sex					
Female	39.7	40.0	24.2	36.5	28.4
Race/ethnicity					
Non-Hispanic white	79.3	85.7	90.3	85.1	88.2
Black, African American	10.3	14.3	3.8	5.4	5.4
Other	10.3	0.00	5.9	9.5	6.4
Education					
<High school	19.0	14.3	8.2	13.5	10.4
Insurance					
Commercial	46.6	48.6	21.2	35.1	27.4
Medicaid	13.8	20.0	16.1	16.2	16.1
Medicare	39.7	31.4	62.8	48.6	56.5
Cause of injury					
Fall	31.0	37.1	33.7	28.4	32.9
Vehicle	39.7	45.7	46.9	52.7	46.9
Violence	24.1	11.4	9.2	12.2	11.3
Other	5.2	5.7	10.2	6.8	8.9
Injury characteristics					
Complicated mild (GCS 13–15)	55.2	48.6	53.8	41.9	52.1
Moderate (GCS 9–12)	24.1	20.0	22.7	24.3	22.9
Severe (GCS 3–8)	20.7	31.4	23.5	33.8	25.0
Cerebral contusion (yes)	36.2	20.0	30.8	17.6	29.0
Intracranial hemorrhage (yes)	67.2	74.3	67.9	71.6	68.7
Injury Severity Score (nonhead)					
0	34.5	28.6	27.7	20.3	27.5
1, 2	34.5	40.0	34.9	29.7	34.5
3, 4, 5	31.0	31.4	37.4	50.0	38.1
TBI related litigation (yes)	22.4	25.7	12.2	18.9	18.0
Mental health history					
Depression history (yes)	74.1	77.1	32.4	55.4	42.6
PTSD history (yes)	17.2	28.6	3.1	5.4	6.6
Other mental health disorder history (yes)	20.7	40.0	4.8	21.6	11.1
Alcohol and other drug abuse					
Lifetime alcohol dependence (CAGE ≥2)	59.3	60.0	33.6	50.7	40.7
Alcohol intoxication (BAL ≥80 mg/dL)	37.9	31.4	29.3	33.8	30.9
Positive drug screen*	29.3	34.3	9.9	35.1	16.8
Treatments received					
Used antidepressant**	41.7	58.3	21.8	55.0	29.0
Used counseling**	18.9	39.4	6.5	30.1	12.9
Used either antidepressants or counseling	50.0%	64.3%	23.2%	62.5%	32.4

GCS, Glasgow Coma Scale; PTSD, post-traumatic stress disorder; CAGE, Cut down? Angered? Guilty? Eye-opener?; BAL, blood alcohol level; *Other drug screening included amphetamine, methamphetamine, and cocaine; **Any time during the follow-up year.

distinct latent classes (i.e., subgroups) of trajectories of depression. Each identified class has its own specific growth parameters (intercept, linear slope), which are also assumed to be unobserved, or latent.

To decide on the optimal number of classes, we used the Bayesian Information Criterion (BIC), the Bootstrapped Likelihood Ratio Test (BLRT), and the entropy.[47,48] Lower BIC values, nonsignificant BLRT p values (lower than $p = 0.05$), and entropy values close to 1.00 imply a better fitting model. Clinical interpretation and class sample size were also considered in the decision making process where models with clinically uninterpretable classes and classes with <1% of the study sample were rejected.[49,50]

For the present study, we conducted models with linear slopes including an estimated intercept variance parameter. The variance of the linear slopes only was fixed at zero, implying that all persons within a class have a similar depression trajectory shape. Missing data were adequately handled by the Expectation-Maximization algorithm and treated as missing at random. Solutions with 1–6 classes were run based on previous studies.[50–54]

We tested putative predictors of class membership based on biopsychosocial predictors of incident depression after TBI.[1] We assessed predictors of class membership by conducting multinomial regression analyses through the newly introduced three-step

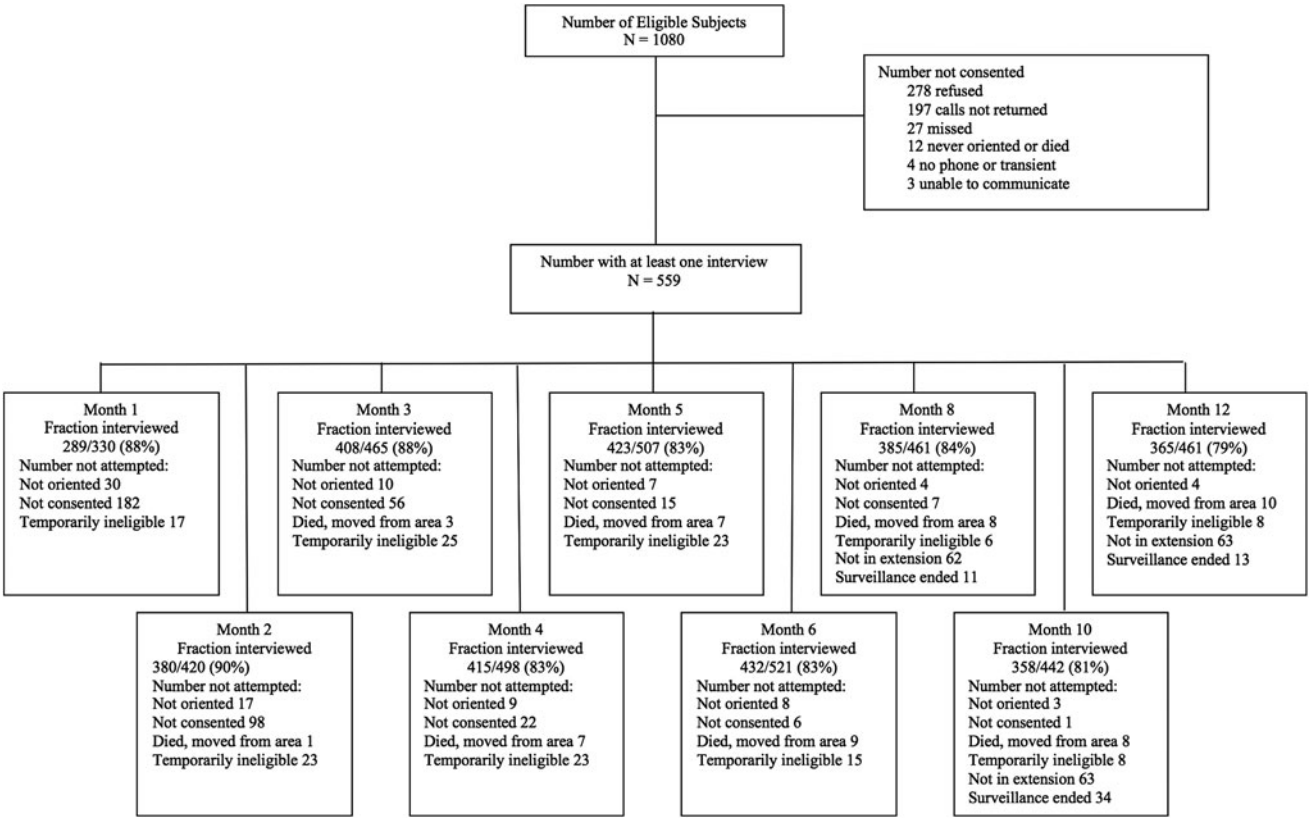

FIG. 1. Participant flow.

approach,[54,55] where class membership was the outcome variable. In this improved approach, the latent classes are formed first (i.e., the predictors are not clouding the interpretation of the classes). In the second step, the most-likely class membership variable was created, which in the third step is used as the outcome variable in the multinomial logistic regression that assesses predictors of class membership while taking into account the measurement error (or uncertainty) in class assignment.

The predictors described in Table 1 (excluding treatments received) were assessed, and odds ratios (OR) with corresponding 95% confidence intervals (CIs) and p values were presented comparing each class with all other classes. Analyses were conducted in Mplus version 7.11,[56] and detailed explanations of the analysis steps can be found elsewhere.[49,50,56,57]

Results

Demographic and clinical characteristics

Of the 1080 eligible patients identified, 559 consented and underwent at least one interview. The two groups were equivalent except that the recruited group was significantly younger (mean [standard deviation, SD] age, 42.5 [17.9] vs. 46.8 [21.5] years), more likely to have completed high school (89% vs. 84%), and less likely to have Medicare insurance (16% vs. 25%) compared with the nonrecruited group. Follow-up rates at each of the nine time points ranged from 79% to 90% (Fig. 1). Fewer participants were interviewed at month 1 ($n = 289$) versus subsequent months ($n = 358$–432), primarily because more participants at month 1 were not eligible for interview, e.g., pending consent ($n = 182$) or not yet oriented ($n = 30$). See Table 1 for detailed demographic and clinical information on the sample.

Trajectory subgroups

Table 2 shows the results of the linear LCGMMs. Model fit indices did not point definitively toward an optimal number of classes. Therefore, we took clinical interpretation of the obtained solutions into account as well. Because the 4- and 5-class model had fairly similar fit, we considered the clinical interpretation of

Table 2. Latent Class Growth Mixture Modeling Results

	Latent class growth mixture models				
Fit index	*1 class*	*2 classes*	*3 classes*	*4 classes*	*5 classes*
BIC	19220.072	19023.042	18838.432	18797.200	18765.433
Entropy	1.00	0.895	0.870	0.868	0.871
BLRT p value	Not available	< 0.001	< 0.001	< 0.001	< 0.001

BIC, Bayesian Information Criterion; BLRT, Bootstrapped Likelihood Ratio Test.

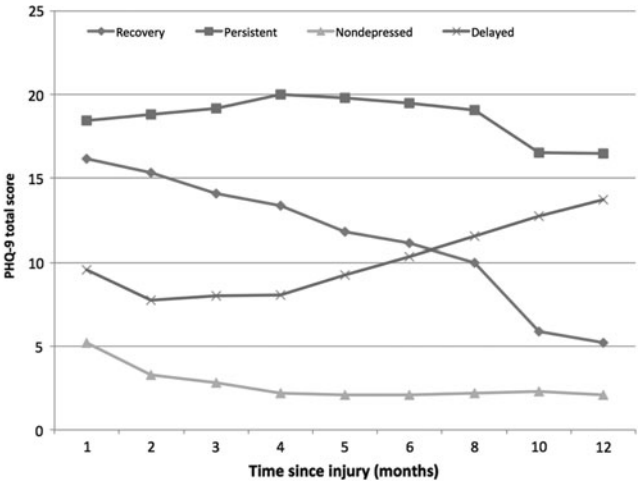

FIG. 2. Mean Patient Health Questionnaire-9 (PHQ-9) scores for the four depression trajectory groups.

these two models in more detail and chose the model with four classes (Fig. 2).

The modal trajectory, low depression, encompassed 70.1% of the sample and was characterized by average PHQ-9 scores in the nondepressed range throughout the follow-up period. This group is referred to as a low depression trajectory because 78.8% of the group never scored in the depressed range, but 21.2% had one or more assessment points with PHQ-9 scores of 10 or more. Next, a delayed depression trajectory (13.2%) was observed with average PHQ-9 scores increasing from the nondepressed range during months 1–5 to the depressed range in months 6–12. Third, 10.4% of the sample was characterized by depression recovery. Average PHQ-9 scores in this group began in the depressed range, but declined over time such that by months 10–12, average scores were well into the nondepressed range. Finally, 6.3% of the sample was persistently depressed, with average PHQ-9 scores remaining in the moderately severe depression range[42] throughout the follow-up period.

Predictors of trajectory groups

Tables 3 and 4 display the results of the multinomial logistic regression analyses. There were numerous consistent differences between the low depression and other groups. Compared with the low depression group, the other three were significantly less likely to be on Medicare versus commercial insurance and more likely to have a pre-injury history of MDD, other mental health disorders, a lifetime history of alcohol dependence, as well as a positive toxicology screen for cocaine or amphetamines at the time of injury. Compared with the low depression group, the delayed depression group was more likely to have a severe TBI and less likely to have a cerebral contusion.

Differences among the other three groups were less pronounced. Compared with the delayed depression group, the persistently depressed group was significantly more likely to be 30–44 years old (vs. 18–29) and report a history of PTSD. There were also nonsignificant trends for the persistently depressed group to have higher pre-injury rates of MDD and other mental health disorders relative to the delayed depression group. The group with persistent depression and depression recovery were similar except that the persistently depressed group displayed nonsignificant trends in the direction of being more likely to be 30–59 and to have a history of other mental health problems. The delayed and recovery groups were also similar except the delayed group was less likely to have a cerebral contusion and more likely to have severe nonhead injuries. There were also nonsignificant trends for the delayed group to be less likely to have a pre-injury history of MDD or PTSD.

Use of treatment in trajectory groups

Overall, 29% of the sample used antidepressants, 12.9% used counseling, and 32.4% used either during the observational period (Table 1). Compared with the low depression group, use of antidepressants was significantly higher in the persistent depression group (21.8% vs. 58.3%; OR, 5.56; 95% CI, 2.10–14.69) and in the delayed depression group (21.8% vs. 55.0%; OR 5.38; 95% CI, 2.69–10.77). Relative to the low depression group, use of counseling was also significantly higher in the persistent depression group (6.5% vs. 39.4%; OR, 11.65, 95% CI, 4.67–29.03) and the delayed depression group (6.5% vs. 30.1%; OR 7.74, 95% CI 3.53–17.00).

Discussion

Through the use of latent class modeling, we were able to differentiate four empirically derived and clinically meaningful depression trajectories during the first year after TBI. The number and type of trajectories as well as the overall proportion in each trajectory are consistent with findings among persons exposed to a wide variety of potentially traumatic experiences[30] including general physical trauma[58] or spinal cord injury.[51]

The present study shows that the modal trajectory during the first year after TBI was low depression, which comprised 70.1% of the sample. This finding is consistent with rates of nondepression reported in previous 1-year prospective prevalence studies in TBI, which ranged from 57–71%.[4,26,25] The rate of low depression in this study also is similar to the proportion of people with ''resilient'' trajectories (35–65%)[26] and low depression[49] in studies of persons exposed to other types of trauma. For comparison purposes, the estimated 12-month prevalence of MDD is 6.7% in the U.S. population.[59]

This study extends our previous work on depression after TBI. Previously, we reported on the high cumulative rate of MDD (53%) within 1 year of TBI. We also noted, however, that 27% of those with an episode of MDD within the first 3 months screened positive for MDD only once during the entire year. Beyond that, we had limited ability to describe the course of these depressive episodes.

The current study, which focuses on depression severity versus MDD, emphasizes that a large proportion of the sample had, on average, a longitudinal course characterized by minimal depressive symptoms. This group is referred to as ''low depression'' rather than nondepressed, in part because while 78.8% within this group never scored in the depressed range on the PHQ-9, the remainder did have one or more episodes when their PHQ-9 score was at least 10. Relative to the three other groups, the low depression group was more likely to have an unremarkable psychiatric and substance use history, and to be on Medicare. A minority of persons in the low depression group received antidepressants (21.8%) or counseling (6.5%).

The next most prevalent trajectory was delayed depression representing 13.2% of the entire sample and 15.9% of the subgroup that had PHQ-9 scores below 10 at 1 month. Despite their initially low PHQ-9 scores, relative to the low depression group, this group was significantly more likely to have several pre-injury mental health and substance use risk factors. In 55.4% of cases, delayed depression represented a recurrence of pre-injury depression. More than 20% had a history of other mental health disorder, half had a history of alcohol dependence, and a third were using other drugs at the time of injury. They were less likely to be on Medicare, and

Table 3. Predictors of Trajectory Membership: Low Depression Versus Others

Variables	*Recovery vs. lowdep OR (95% CI)*	p *value*	*Delayed vs. lowdep OR (95% CI)*	p *value*	*Persistent vs. lowdep OR (95% CI)*	p *value*
Age						
18–29 years	*Reference*		*Reference*		*Reference*	
30–44 years	1.16 (0.50–2.71)	0.73	1.06 (0.48–2.34)	0.89	**8.29 (0.08–815.14)**	**0.02**
45–59 years	0.78 (0.30–2.03)	0.61	0.98 (0.44–2.19)	0.97	5.68 (0.14–226.73)	0.06
60+ years	0.07 (0.00–6.90)	0.25	0.76 (0.32–1.84)	0.54	2.35 (0.46–12.08)	0.40
Sex						
Male	*Reference*		*Reference*		*Reference*	
Female	**2.25 (1.06–4.80)**	**0.04**	1.90 (1.01–3.59)	0.05	2.14 (0.95–4.83)	0.07
Race/ethnicity						
White	*Reference*		*Reference*		*Reference*	
Black, African American	3.43 (0.96–12.26)	0.06	1.38 (0.31–6.23)	0.68	**4.23 (1.31–13.63)**	**0.02**
Other	2.35 (0.77–7.16)	0.13	1.86 (0.67–5.15)	0.23	**0.00 (0.00–0.00)**	**<0.001**
Education						
< High school	*Reference*		*Reference*		*Reference*	
>High school	**0.32 (0.13–0.81)**	**0.02**	0.54 (0.22–1.36)	0.19	0.54 (0.17–1.78)	0.31
Insurance						
Commercial/Private	*Reference*		*Reference*		*Reference*	
Medicaid	0.32 (0.09–1.08)	0.07	0.59 (0.23–1.47)	0.26	0.54 (0.19–1.53)	0.25
Medicare	**0.25 (0.11–0.56)**	**0.00**	**0.45 (0.23–0.89)**	**0.02**	**0.20 (0.08–0.50)**	**0.00**
Cause of injury						
Fall	*Reference*		*Reference*		*Reference*	
Vehicle	0.88 (0.35–2.21)	0.78	1.43 (0.71–2.90)	0.32	0.87 (0.37–2.05)	0.75
Violence	**3.59 (1.34–9.58)**	**0.01**	1.65 (0.56–4.82)	0.36	0.99 (0.22–4.36)	0.99
Other	0.49 (0.07–3.38)	0.47	0.79 (0.22–2.85)	0.72	0.49 (0.09–2.79)	0.43
Injury characteristics						
GCS 13–15	*Reference*		*Reference*		*Reference*	
GCS 9–12	1.03 (0.43–2.47)	0.95	1.48 (0.69–3.20)	0.32	0.96 (0.33–2.80)	0.94
GCS 3–8	0.71 (0.24–2.04)	0.52	**2.08 (1.03–4.18)**	**0.04**	1.57 (0.64–3.84)	0.33
Cerebral contusion (no)	*Reference*		*Reference*		*Reference*	
Cerebral contusion (yes)	1.54 (0.73–3.23)	0.25	**0.40 (0.17–0.94)**	**0.04**	0.50 (0.18–1.42)	0.19
Intracranial hemorrhage (no)	*Reference*		*Reference*		*Reference*	
Intracranial hemorrhage (yes)	0.91 (0.42–1.97)	0.81	1.22 (1.22–1.22)	0.55	1.44 (0.57–3.60)	0.44
Injury severity (nonhead) (0)	*Reference*		*Reference*		*Reference*	
Injury severity (nonhead) (1,2)	0.74 (0.31–1.76)	0.49	1.25 (0.51–3.10)	0.63	1.17 (0.45–3.08)	0.74
Injury severity (nonhead) (3,4,5)	0.58 (0.23–1.46)	0.25	2.20 (0.96–5.00)	0.06	0.83 (0.29–2.32)	0.72
No litigation	*Reference*		*Reference*		*Reference*	
Litigation	1.84 (0.74–4.56)	0.19	1.49 (0.66–3.35)	0.33	2.57 (0.98–6.75)	0.06
Mental health disorder history						
No depression history	*Reference*		*Reference*		*Reference*	
Depression history	**8.37 (3.16–22.18)**	**<0.001**	**2.71 (1.47–5.00)**	**<0.001**	**7.78 (2.97–20.38)**	**<0.01**
No PTSD history	*Reference*		*Reference*		*Reference*	
PTSD history	**7.55 (2.41–23.63)**	**<0.001**	1.36 (0.21–8.93)	0.75	**15.99 (5.70–44.83)**	**<0.001**
No other mental health history	*Reference*		*Reference*		*Reference*	
Other mental health history	**5.33 (1.77–16.03)**	**<0.001**	**6.25 (2.55–15.34)**	**<0.001**	**17.36 (6.79–44.38)**	**<0.001**
Alcohol and drug abuse history						
No alcohol dependence	*Reference*		*Reference*		*Reference*	
Alcohol dependence (CAGE ≥2)	**3.32 (1.51–7.31)**	**<0.001**	**2.15 (1.13–4.07)**	**0.02**	**3.11 (1.28–7.55)**	**0.01**
No alcohol intoxication	*Reference*		*Reference*		*Reference*	
Alcohol intoxication (BAL ≥80 mg/dL)	1.63 (0.77–3.45)	0.20	1.26 (0.67–2.38)	0.48	1.07 (0.45–2.54)	0.88
Negative drug screen	*Reference*		*Reference*		*Reference*	
*Positive drug screen**	**4.21 (1.77–10.03)**	**0.00**	**6.05 (3.00–12.20)**	**<0.001**	**5.28 (2.19–12.72)**	**<0.001**

GCS, Glasgow Coma Scale; PTSD, post-traumatic stress disorder; CAGE, Cut down? Angered? Guilty? Eye–opener?; BAL, blood alcohol level; *Other drug screening included amphetamine, methamphetamine, and cocaine; **Any time during the follow-up year.

there was a nonsignificant trend for this group to have a greater proportion of women compared with the low depression group. The delayed depression group was also more likely to have severe TBI but less likely to have cerebral contusions compared with the low depression group.

The association between delayed depression and injury severity adds to speculation that brain injury type, location, or severity may influence depression outcomes. Jorge and colleagues[26] explored the relationship between depression at 1 month after TBI and lesion characteristics. They found an association between left frontal

Table 4. Predictors of Trajectory Membership: Persistent Versus Delayed Versus Recovery

Variables	*Persistent versus recovery OR (95% CI)*	p *value*	*Persistent versus delayed OR (95% CI)*	p *value*	*Delayed versus recovery OR (95% CI)*	p *value*
Age						
18–29 years	*Reference*		*Reference*		*Reference*	
30–44 years	7.16 (0.92–55.38)	0.06	**7.84 (1.12–54.67)**	**0.04**	0.91 (0.30–2.80)	0.87
45–59 years	7.30 (0.85–62.44)	0.07	5.78 (0.79–41.99)	0.08	1.26 (0.37–4.28)	0.71
60+ years	35.52 (0.18–7142.08)	0.19	3.08 (0.34–27.77)	0.32	11.53 (0.10–1382.05)	0.32
Sex						
Male	*Reference*		*Reference*		*Reference*	
Female	0.95 (0.30–3.02)	0.93	1.13 (0.41–3.07)	0.82	0.84 (0.33–2.17)	0.73
Race/ethnicity						
White	*Reference*		*Reference*		*Reference*	
Black, African American	1.23 (0.23–6.66)	0.81	3.06 (0.40–15.54)	0.22	0.40 (0.06–2.51)	0.33
Other	**0.00 (0.00–0.00)**	**<0.001**	**0.00 (0.00–0.00)**	**<0.001**	0.79 (0.19–3.22)	0.74
Education						
< High school	*Reference*		*Reference*		*Reference*	
>High school	1.69 (0.37–7.76)	0.50	1.00 (0.24–4.19)	0.99	1.70 (0.51–5.60)	0.39
Insurance						
Commercial/private	*Reference*		*Reference*		*Reference*	
Medicaid	1.69 (0.32–9.01)	0.54	0.92 (0.24–3.52)	0.90	1.84 (0.42–8.09)	0.42
Medicare	0.80 (0.22–2.89)	0.73	0.44 (0.14–1.35)	0.15	1.82 (0.66–5.00)	0.25
Cause of injury						
Fall	*Reference*		*Reference*		*Reference*	
Vehicle	0.99 (0.26–3.75)	0.99	0.61 (0.20–1.81)	0.37	1.63 (0.52–5.13)	0.40
Violence	0.27 (0.04–1.71)	0.17	0.60 (0.10–3.63)	0.58	0.46 (0.12–1.80)	0.27
Other	1.02 (0.06–16.58)	0.99	0.63 (0.07–5.45)	0.67	1.62 (0.16–16.83)	0.69
Injury characteristics						
GCS 13–15	*Reference*		*Reference*		*Reference*	
GCS 9–12	0.93 (0.22–4.00)	0.92	0.65 (0.17–2.39)	0.51	1.44 (0.46–4.49)	0.53
GCS 3–8	2.22 (0.51–9.63)	0.29	0.76 (0.25–2.29)	0.62	2.94 (0.84–10.26)	0.09
Cerebral contusion (no)	*Reference*					
Cerebral contusion (yes)	0.32 (0.08–1.24)	0.10	1.25 (0.32–4.83)	0.75	**0.26 (0.09–0.79)**	**0.02**
Intracranial hemorrhage (no)	*Reference*		*Reference*		*Reference*	
Intracranial hemorrhage (yes)	1.58 (0.45–5.59)	0.48	1.17 (0.38–3.62)	0.78	1.31 (0.50–3.64)	0.56
Injury severity (non head) (0)	*Reference*		*Reference*		*Reference*	
Injury severity (nonhead) (1,2)	1.59 (0.41–6.18)	0.50	0.94 (0.25–3.51)	0.92	1.69 (0.49–5.00)	0.40
Injury severity (nonhead) (3,4,5)	1.42 (0.33–6.17)	0.64	0.38 (0.10–1.40)	0.14	**3.79 (1.12–12.75)**	**0.03**
No litigation	*Reference*		Reference		*Reference*	
Litigation	1.40 (0.36–5.45)	0.63	1.72 (0.52–5.76)	0.38	0.81 (0.26–2.56)	0.72
Mental health disorder history						
No depression history	Reference		Reference		*Reference*	
Depression history	0.93 (0.22–4.00)	0.92	2.87 (0.93–8.86)	0.07	0.32 (0.10–1.01)	0.05
No PTSD history	*Reference*		*Reference*		*Reference*	
PTSD history	2.12 (0.55–8.15)	0.28	**11.79 (1.60–86.85)**	**0.02**	0.18 (0.02–1.34)	0.09
No other mental health history	*Reference*		*Reference*		*Reference*	
Other mental health history	3.26 (0.86–12.33)	0.08	2.78 (0.96–8.02)	0.06	1.17 (0.36–3.82)	0.79
Alcohol and drug abuse history						
No alcohol dependence	*Reference*		*Reference*		*Reference*	
Alcohol dependence (CAGE ≥2)	0.94 (0.27–3.23)	0.92	1.45 (0.50–4.21)	0.50	0.65 (0.24–1.71)	0.38
No alcohol intoxication	*Reference*		*Reference*		*Reference*	
Alcohol intoxication (BAL ≥80 mg/dL)	0.66 (0.20–2.19)	0.50	0.85 (0.30–2.45)	0.76	0.77 (0.39–2.22)	0.88
Negative drug screen	Reference		Reference		*Reference*	
Positive drug screen	1.25 (0.37–4.25)	0.72	0.87 (0.32–2.41)	0.79	1.44 (0.53–3.87)	0.47

GCS, Glasgow Coma Scale; PTSD, post-traumatic stress disorder; CAGE, Cut down? Angered? Guilty? Eye–opener?; BAL, blood alcohol level; *Other drug screening included amphetamine, methamphetamine, and cocaine; **Any time during the follow-up year.

injury and major depression. Their study differed from this one in that they had detailed neuroimaging data and excluded persons who were not able to provide reliable responses by 1 month after injury. We suspect that in the present study, the relationship between more severe TBI and delayed depression was confounded by our method of enrollment. We followed cases for the entire year until they passed an orientation test and could be consented and assessed. Those with more severe TBI were disoriented longer, and consented and assessed later in the follow-up period, delaying the detection of depressive symptoms.

Other prospective longitudinal studies have reported delayed depression after TBI. In a 1-year cohort study, Jorge and associates[26] reported that 26% had MDD at 1 month, and an additional 6%, 6%, and 5% met criteria for MDD at 3, 6, and 12 months, respectively. In a later study, Jorge and coworkers[4] reported that 50% of those in whom MDD developed after TBI were diagnosed at the initial assessment, whereas MDD developed in 50% at 3 or 6 months after TBI. Gould and colleagues[25] reported the same phenomenon with regard to psychiatric disorders as a whole. That is, 37% of those in whom psychiatric disorders developed received a diagnosis early (about 61 days after TBI) while 44% received a diagnosis between the initial examination and 6 months, and 19% received a diagnosis between 6–12 months. Of note, MDD developing for the first time as late as 1 year after TBI is rare but does occur,[1,26] suggesting that studies following persons beyond 1 year are needed.

In previous studies, persons with delayed depression were less likely to have a pre-injury psychiatric disorder compared with those with early depression.[25] In addition, psychosocial factors, not injury-related factors, are thought to be associated with later depression onset.[28] For example, Gomez-Hernandez and associates[27] showed that lack of close personal relationships and fear of job loss were related to depression in the post-acute period. In the current study, those with delayed depression had lower likelihood of pre-injury PTSD and were less likely to be in the 30–44 age range relative to the persistent depression group.

Future research should determine whether post-injury psychosocial factors such as difficulties with work, school, or social relationships predict delayed depression. If future research confirms the notion that delayed depression is related to fears of job loss and impaired social relationships, this might support the use of early vocational rehabilitation to address return to work concerns and psychological treatment aimed at preserving social support.[27]

Just over 10% of the sample followed a recovery trajectory. Compared with the group that did not recover, this trajectory group was significantly less likely to have a pre-injury history of other mental health problems. These two groups did not differ with regard to receipt of antidepressants or counseling, although both forms of treatment were somewhat higher in the group with persistent depression. Because other mental disorders such as anxiety are highly comorbid with depression after TBI[1] and can interfere with response to antidepressants,[60] we speculate that having a lower burden of lifetime mental illness permits persons who are initially depressed after TBI to recover or respond to treatment.

Persistent depression was observed in 6.2% of the sample. Compared with the low depression trajectory, this group was more likely to be in the 30–44-year-old age group and have a significantly greater burden of mental health and substance abuse problems before TBI. For 77.1% of this group, persistent depression after TBI represented a recurrence or continuation of pre-injury depression. In previous research, being female and involved in litigation were found to be depression risk factors[61,62]; however, in this study, these variable were not significant predictors of persistent depression.

Persistent depression cannot be attributed entirely to the absence of treatment in this sample. Receipt of mental health treatment was highest in the persistently depressed group, with 64.3% receiving antidepressant medications or counseling. Nevertheless, almost 36% of this group reported receiving no depression treatment. Based on previous research, we would expect that much of the treatment received was inadequate in terms of dose or duration. A population-based study of depressed persons who received treatment has shown that 25% received an inadequate dose or duration of antidepressants and 50% received an inadequate dose of counseling.[63]

Even if persistently depressed persons in this study received adequate treatment, high quality controlled trials of depression treatment in persons with TBI demonstrate that antidepressants[18] and cognitive behavioral therapy[19] have modest efficacy in persons with TBI. To reduce the proportion of persistently depressed people with TBI, greater efforts are needed to improve: depression recognition and treatment initiation, delivery of adequate treatment dose and duration, and research on single or combined therapies that effectively treat persons with MDD in this population.

Limitations

This study is limited by its singular focus on depression. PTSD and other anxiety disorders after TBI are also common and disabling and merit more longitudinal research.[3,25] Next, the study was conducted at a single urban Level 1 trauma center in the Northwest that serves mostly non-Hispanic white persons. It is uncertain whether the findings in this study will generalize to other TBI populations, particularly to other regions of the United States and to other racial and ethnic groups. Therefore, future trajectory research should include data gathered in larger, more diverse samples of TBI survivors and should include measures of other mental health conditions that are highly comorbid with TBI, including other mood disorders, anxiety disorders, and substance use disorders.[25]

We used the PHQ-9 to measure the severity of depressive symptoms, not a diagnostic interview such as the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders* Disorders (SCID) depression module. Albeit, in persons with TBI, the PHQ-9 has good sensitivity and specificity compared with the SCID.[43] Moreover, the PHQ-9 meets item response theory for unidimensionality, and no item exhibited significant differential item functioning when comparing responses from persons with TBI with persons in primary medical care clinics.[64]

The study lacked a robust set of theory-driven, modifiable risk factors. Future research should include early assessment of psychosocial variables that might predict depression trajectory such as social support and fears of job loss,[27] impairment self-appraisals,[65] pain,[66] physical activity,[67] pleasant events,[68] and cognitive distortions.[69] Future research should also include more detailed information on medical and psychological treatment received during the observation period, including timing, type, dose and duration, to better understand factors that might be used to influence depression trajectories.

The longer-term clinical relevance of the trajectory groups we have observed is unknown. While these trajectory groups appear clinically meaningful, it will be crucial to determine whether they are associated with important outcomes such as return to work, quality of life, and social and emotional adjustment at 1 year and beyond. These findings will be the subject of a future publication. Future studies also should address the accuracy with which multivariate predictor models can correctly classify trajectory groups and whether predictor models can be devised that are simple enough to use clinically.

Clinical and research implications

Current mental health care for persons with TBI and depression is far from ideal. In this sample, one third of persons with persistent depression reported receiving no mental health treatment. Current thinking on improving outcomes for persons with TBI emphasizes personalized medicine[70] and the use of proactive, chronic illness management approaches to care.[71]

This study suggests the potential for developing multivariate regression models that could predict a person's likely depression trajectory during the first year after TBI based on information available at the time of injury. If sufficiently accurate and reliable, trajectory classification could identify those in need of early aggressive treatment (persistent and recovery groups), those requiring active prevention and monitoring to determine the need for treatment (delayed group), and those who might not require intensive monitoring, but could benefit from education and advice to seek care if depressive symptoms arise (low depression group). Identification of the low depression group could aid secondary prevention research by permitting the researcher to exclude resilient persons from trials. Doing so would minimize resource expenditure and the probability of null findings from a ''floor effect.''

Conclusions

Latent class growth mixture modeling can be used to classify persons who sustain complicated mild to severe TBI into one of four clinically meaningful depression trajectories. Demographic, clinical, and especially psychiatric and substance use history variables available at or soon after TBI are predictive of trajectory class membership. This line of research will give clinicians and TBI survivors more precise information about prognosis and lead to individualized depression follow-up, prevention, and treatment programs.

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