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Research paper

Circadian variability of the initial Glasgow Coma Scale score in traumatic brain injury patients

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ABSTRACT

Introduction: The Glasgow Coma Scale (GCS) score is the primary method of assessing consciousness after traumatic brain injury (TBI), and the clinical standard for classifying TBI severity. There is scant literature discerning the influence of circadian rhythms or emergency department (ED) arrival hour on this important clinical tool.

Methods: Retrospective cohort analysis of adult patients suffering blunt TBI using the National Sample Program of the National Trauma Data Bank, years 2003–2006. ED arrival GCS score was characterized by midday (10 a.m.–4 p.m.) and midnight (12 a.m.–6 a.m.) cohorts (N=24548). Proportions and standard errors are reported for descriptive data. Multivariable regressions using odds ratios (OR), mean differences (B), and their associated 95% confidence intervals [CI] were performed to assess associations between ED arrival hour and GCS score. Statistical significance was assessed at $p < 0.05$.

Results: Patients were 42.48 ± 0.13-years-old and 69.5% male. GCS score was 12.68 ± 0.13 (77.2% mild, 5.2% moderate, 17.6% severe-TBI). Overall, patients were injured primarily via motor vehicle accidents (52.2%) and falls (24.2%), and 85.7% were admitted to hospital (33.5% ICU). Injury severity score did not differ between day and nighttime admissions.

Nighttime admissions associated with decreased systemic comorbidities ($p < 0.001$) and increased likelihood of alcohol abuse and drug intoxication ($p < 0.001$). GCS score demonstrated circadian rhythmicity with peak at 12 p.m. (13.03 ± 0.08) and nadir at 4am (12.12 ± 0.12). Midnight patients demonstrated lower GCS (12 a.m.–6 a.m.: 12.23 ± 0.04; 10 a.m.–4 p.m.: 12.95 ± 0.03, $p < 0.001$). Multivariable regression adjusted for demographic and injury factors confirmed that midnight-hours independently associated with decreased GCS (B=−0.29 [−0.40, −0.19]).

In patients who did not die in ED or go directly to surgery (N=21862), midnight-hours (multivariable OR 1.73 [1.30–2.31]) associated with increased likelihood of ICU admission; increasing GCS score (per-unit OR 0.82 [0.80–0.83]) associated with decreased odds. Notably, the interaction factor ED GCS score*ED arrival hour independently demonstrated OR 0.96 [0.94–0.98], suggesting that the influence of GCS score on ICU admission odds is less important at night than during the day.

Conclusions: Nighttime TBI patients present with decreased GCS scores and are admitted to ICU at higher rates, yet have fewer prior comorbidities and similar systemic injuries. The interaction between

Abbreviations: CAD, coronary artery disease; CCI, Charlson Comorbidity Index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CRSD, circadian rhythm sleep disorder; ED, emergency department; GABA, gamma-aminobutyric acid; GCS, Glasgow Coma Scale; ICD-9, International Classification of Diseases, 9th Revision; ICU, intensive care unit; IQR, interquartile range; ISS, injury severity score; MVA, motor vehicle accident; NSP, National Sample Program; NTDB, National Trauma Data Bank; OR, odds ratio; REM, rapid eye movement; RHT, reticulohypothalamic tract; SCN, suprachiasmatic nucleus; SD, standard deviation; SE, standard error; TBI, traumatic brain injury

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nighttime hours and decreased GCS score on ICU admissions has important implications for clinical assessment/triage.

1. Introduction

Traumatic brain injury (TBI), defined as an alteration in brain function or other evidence of brain pathology following trauma, is a debilitating disease and public health burden (Manley and Maas, 2013). The incidence of TBI in the USA is at least 1.7 million annually, and 5.3 million people are currently living with TBI-related disability (Faul et al., 2010; Langlois et al., 2006). The Glasgow Coma Scale (GCS), designed as a standardized method for healthcare practitioners to evaluate and describe TBI severity, is the primary method of assessing level of consciousness after TBI. The GCS score comprises three subcategories: eye opening (score of 1–4), verbal response (score of 1–5) and motor response (score of 1–6), with a sum score of 15. It is the current clinical standard for subdividing patients into mild (13–15), moderate (9–12), and severe (3–8) TBI (Maas et al., 2008; McNett, 2007; Saatman et al., 2008; Teasdale et al., 2014).

Accordingly, the GCS score forms the basis for clinical management decisions following TBI, such as the need for computed tomography (CT) scan, serial neurologic exams, medical management and/or surgical intervention (Fischer et al., 2001). A GCS score of less than 15 is an indicator of neurologic deficit and a strong predictor of the need for emergency intervention (e.g. surgery) in TBI patients (Hong et al., 2016). There is an approximately linear relationship between decreasing total GCS scores and increasing mortality following moderate and severe TBI (Reith et al., 2016). The GCS score has also been shown to be a predictor for hospital admission following trauma. One study showed abnormal GCS (score of 13 ± 4) to be the only parameter associated with increased relative risk for hospitalization following motor vehicle accidents (MVA) (Norwood et al., 2002).

Circadian rhythmicity is an endogenous oscillation of alertness/consciousness across a 24-hour period regulated by the suprachiasmatic nucleus (SCN) of the hypothalamus (Leproult and Van Cauter, 2010). The SCN receives input from photosensitive retinal ganglion cells via the reticulohypothalamic tract (RHT); the SCN both self-regulates circadian cycles through gene transcription and sends signals to the pineal gland as well as other hypothalamic nuclei for melatonin and cortisol secretion (Leproult and Van Cauter, 2010). In addition to dysregulation of serotonergic and noradrenergic neurotransmitter circuits (Pappius, 1991; Kawa et al., 2015), studies have demonstrated that circadian rhythm of melatonin production is disrupted following both TBI and ICU admission following trauma (Paul and Lemmer, 2007). Hence it is not unreasonable to extrapolate that nighttime hours may be associated with reduced levels of alertness; indeed, one study of traumatic insults in children found an association between reduced GCS score and admission to the ICU (Onita et al., 2015). However, these admissions were onto both trauma and/or medicine services, and did not extend to adults.

The literature associates TBI with persistent circadian rhythm sleep disorders (CRSD). Schekleton and colleagues report a correlation between melatonin secretion and rapid eye movement (REM) sleep; accordingly, patients with a history of TBI demonstrate lower evening melatonin production compared to controls, and suffer from increased sleep disturbances and higher anxiety and depressive symptoms (Shekleton et al., 2010). Ayalon and colleagues discuss the development of CRSD, e.g. delayed sleep phase syndrome and irregular sleep-wake patterns, following even mild TBI (Ayalon et al., 2007). While most patients exhibit a 24-h rhythmicity of melatonin secretion, patients who have suffered mild TBI experience a 1–2 h delay of the peak (3:40 a.m. -vs - 5:39 a.m.) and 2–3 h delay of the nadir (5:00 a.m. - vs - 7:59 a.m.) compared to controls, associating with increased fatigue and loss of productivity (Ayalon et al., 2007).

There is scant literature discerning the potential influence of circadian rhythms and/or ED arrival hour on the GCS score at the time of injury, and no study exists for adults in the TBI setting. The National Sample Program (NSP) of the National Trauma Data Bank (NTDB) is a prospectively enrolled registry with a purpose of informing trauma care and outcomes in the USA, and draws from a sample size of 100 hospitals to represent the nationwide patient distribution (American College of Surgeons, 2009). Here, we use the NSP to evaluate the effects of emergency department (ED) arrival hour on ED GCS score following blunt TBI in adult patients – controlling for demographics, medical comorbidities, and injury severity factors. We hypothesized that ED arrival hour would associate with GCS score as well as ICU admission. Our data indicate that there is a circadian distribution of GCS score across ED arrival hours, that ED arrival hour is independently associated with GCS score, and that nighttime ED admissions are associated with an increased likelihood of ICU admission.

2. Methods

In this study, we used the NSP of the NTDB from arrival years 2003–2006. The NSP for each year consists of a stratified sample of 100 NTDB participating hospitals based on U.S. census region, trauma care designation, and NTDB reporting status (Aarabi and Bizhan, 2003). Hospitals were drawn by the NTDB from the sampling universe of 453 Level I or II trauma centers, and the sample size of 100 hospitals was determined by prior review indicating it can be extrapolated to represent the national patient distribution (Schoenfeld et al., 2013). Detailed data qualification, selection, cleaning and standardization algorithms have been previously reported (Schoenfeld et al., 2013). As the NSP of the NTDB is a fully de-identified dataset without the 18 federal Health Insurance Portability and Accountability Act (HIPAA) identifiers, the current study was classified as exempt from institutional review board (IRB) review.

The NSP years 2003–2006 were selected because they are the only NSP years in the public domain with the variable "edarrtime" which represents the time of patient arrival to the ED on a 24-h clock. A total of 89541 incidents sustaining TBI were extracted from NSP years 2003–2006 using the International Classification of Diseases, 9th Revision (ICD-9) codes 800-801.99, 803-804.99 and 850-854.19 as previously described (Bekelis et al., 2015; Bowman et al., 2007; Majidi et al., 2013). Adult patients (variable name "age" ≥18, n=72,015) with known hour of arrival (n=58,937), ED GCS (variable name "edgcstotal", n=55,109), gender (variable name "gender", n=55,083), blunt TBI (variable name "injurytype"=blunt, n=52,782; variable name "mech_cdc" ≇ "drowningsubmersion", "cutpierce", "firearm", "fireburn", "poisoning", "suffocation", n=52,645) in stepwise fashion. The 52,645 qualifying patients were analyzed for circadian trends, showing a clear peak in ED GCS score during ED arrival hours of 10 a.m.–4 p.m. (n=13,501) and a clear nadir during arrival hours of 12 a.m.–6 a.m. (n=11,047), with comparable sample sizes between both groups. As the objective of this manuscript was to discern whether circadian variability existed in the initial ED GCS score, these times windows were determined empirically. Accordingly, these two groups were extracted for targeted analysis as mid-day and mid-night circadian cohorts, for a combined subgroup n of 24548 patients (Fig. 1).

Demographic and clinical variables of interest were extracted for multivariable analysis to include age, prior medical history, mechanism of injury, whether injury was work-related, hypotension in the ED (ED

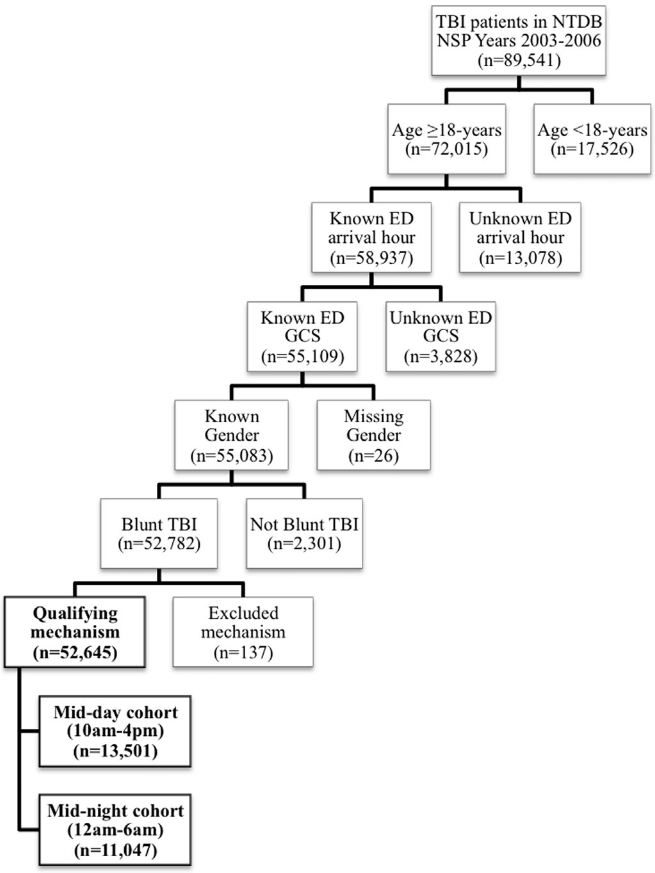

Fig. 1. Flowchart of included patients. Caption**:** Flowchart of included patients with traumatic brain injury. Inclusion criteria were adult patients with blunt trauma, known ED arrival hour, known GCS score, and known gender. Excluded mechanisms were CDC-specified mechanisms of drowning/submersion, cutting/piercing, firearm, burn, poisoning, and/or suffocation. CDC=Centers for Disease Control; ED=Emergency department; GCS=Glasgow Coma Scale.

systolic blood pressure < 90 mmHg), ED toxicology screen results, ED alcohol screen results, and stratified injury severity score (ISS). The Charlson comorbidity index (CCI) was utilized as a summative score of overall comorbidity burden, calculated using the standard comorbidity weights as previously described in large retrospective TBI studies (Charlson et al., 1987; Chen et al., 2012; Winkler et al., 2016; Yue et al., 2016; Zhao et al., 2016). Demographic and clinical variables that were missing and/or marked as not known/not recorded from the NSP were coded as "unknown."

2.1. Statistical analysis

Descriptive variables are presented using proportions for categorical variables, and means and standard errors (SE) for continuous variables. Group differences were assessed using Pearson's chi-squared test (X^2) for categorical variables and analysis of variance (ANOVA) for continuous variables. For analyses with individual cell counts < 5, Fisher's Exact Test was used in place of X^2. Categorical outcome variables (e.g. ICU admission) were assessed using binary logistic regression. Continuous outcome variables (e.g. GCS score) were assessed using linear regression. Multivariable analyses were adjusted for demographic and clinical variables (age, CCI, mechanism of injury, whether injury was work-related, ED SBP, ED toxicology and alcohol screen results, stratified ISS score). Odds ratios (OR) and associated 95% confidence intervals (CI) were reported for logistic regressions, and mean differences (*B*), standard errors (SE), and 95% CI were reported for linear regressions. Statistical significance was assessed at α=0.05. All analyses were performed using the Statistical Package for

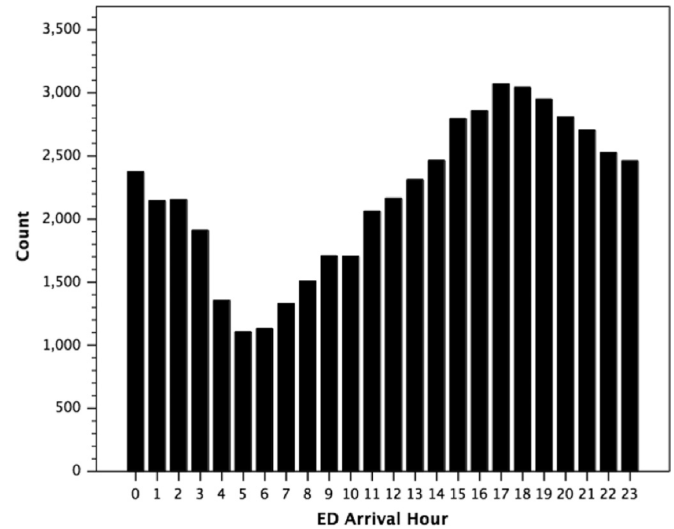

Fig. 2. Number of ED visits by ED arrival hour. Caption: ED arrival hour plotted on the scale of a full 24-h day from 0 (12 a.m.) to 23 (11 p.m). Total sample size=52645. ED=Emergency department.

Social Sciences (SPSS), version 23 (IBM Corporation, Chicago, IL, USA).

3. Results

From admission years 2003–2006, 52645 adult blunt TBIs with documented GCS score and ED arrival hour in the NSP of the NTDB were present and extracted, which represents 248,763 weighted incidents nationally. Patients were aged 43.15 ± 0.09-years, 69.5% male, and 67.1% Caucasian. The overall incidence of ED visits by ED arrival hour showed a clear circadian trend with the nadir at 4–6 a.m. (1100–1400 visits/hr nationwide) and the peak at 3–8 p.m. (2800–3100 visits/hr nationwide) (Fig. 2). An analysis of ED arrival GCS by ED arrival hour yielded largely congruous results, with the nadir at 2–6 a.m. (12.1–12.3) and the peak across 10 a.m.–4 p.m. (12.8–13.1) (Fig. 3). Interestingly, mean age by ED arrival hour yielded parallel results, with the youngest patients arriving between 2–4 a.m. (32–36-years) and the oldest patients between 10 a.m.–3 p.m. (47–49-years) (Fig. 4). Given the clear circadian trends observed across these three markers (injury triage (ED visit), severity (GCS score), and baseline morbidity (age)), we elected to constrain our main analyses to two 6-h

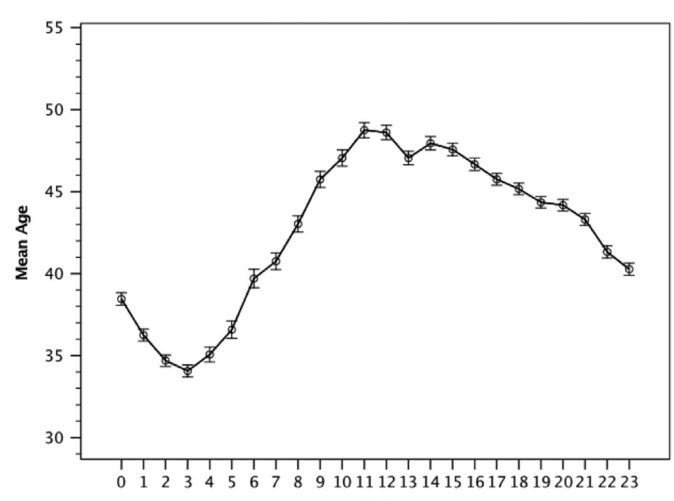

Fig. 3. Age distribution by ED arrival hour. Caption: Mean age plotted on the scale of a full 24-hour day from 0 (12 a.m.) to 23 (11 p.m). Total sample size=52645. Error bars denote standard error. ED=Emergency department.

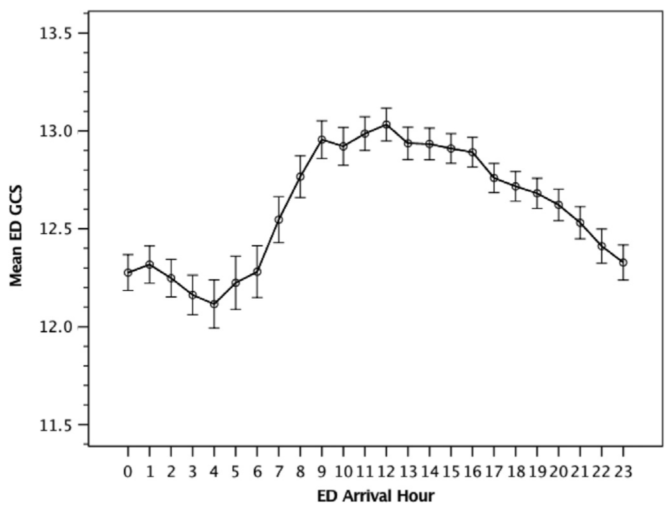

Fig. 4. GCS score distribution by ED arrival hour. Caption: Mean ED GCS score plotted on the scale of a full 24-hour day from 0 (12 a.m.) to 23 (11 p.m.). Total sample size=52645. Error bars denote standard error. ED=Emergency department; GCS=Glasgow Coma Scale.

groups: the mid-night cohort (12 a.m.–6 a.m., n=11047) and the mid-day cohort (10 a.m.–4 p.m., n=13501), in order to better characterize the presentation, risk factors and hospital triage of these two sub-populations to better address their potential circadian differences.

3.1. Demographics and clinical characteristics

Overall, age was 42.48 ± 0.13-years with mid-night TBI patients being younger than their mid-day counterparts (35.93 ± 0.16 vs. 47.84 ± 0.18; $p < 0.001$). There was a higher incidence of male (75.0% vs. 66.7%; $p < 0.001$) and lower incidence of Caucasian (62.8% vs. 70.7%; $p < 0.001$) patients in the mid-night cohort. Mechanisms of injury in order of incidence were motor vehicle accidents (MVA, 52.2%), fall (24.2%), struck by or against object (6.0%), and pedal cyclist/pedestrian not otherwise specified as MVA (1.5%); mid-night hours were associated with a higher incidence of MVA (54.1% vs. 50.7%), struck by/against (7.8% vs. 4.5%), and other unspecified mechanisms (19.7% vs. 13.1%). Mid-day hours were associated with more falls (29.7% vs. 17.5%). In patients with documented injury status as relating or not relating to the workplace (mid-night n=4,056; mid-day n=5,489), a significantly higher proportion of the mid-day cohort suffered work-related injuries (28.3% vs. 18.4%; $p < 0.001$) (Table 1).

Regarding overall trauma injury severity, the incidence of hypotension in the ED was 2.6% and did not differ between night/day cohorts. Mean ISS did not differ between day and night cohorts, while slight differences were observed for ISS group classifications (ISS 16–25: mid-night 27.9%, mid-day 29.6%; ISS 26–75: mid-night 17.6%, mid-day 16.3%; p=0.006) (Table 1).

Regarding ED disposition, 3.0% of TBI patients were discharged home from the ED, 85.8% were admitted to hospital (42.8% floor, 9.4% operating room, 33.5% ICU), 9.6% were other/unspecified, and 1.6% died in the ED. Mid-night TBI patients associated with higher incidence of ICU admissions (35.5% vs. 31.9%), and a lower incidence of floor (41.6% vs. 43.8%) and operating room admissions (8.8% vs. 9.9%) (Table 1).

3.2. Medical comorbidities

The overall Charlson comorbidity index (CCI) was 0.08 ± 0.46 and was significantly higher in the mid-day (10 a.m.–4 p.m.) group (0.11 ± 0.53 vs. 0.05 ± 0.36; $p < 0.001$). As there were 14 medical comorbidities compared across night/day cohorts, the Bonferroni threshold was set at $p < 0.0035$ (0.05÷14). Mid-night admissions were associated

Table 1
Descriptive statistics for mid-night and mid-day circadian cohorts.

Descriptive variable	Total (N=24548)	12 a.m.–6 a.m. (N=11,047)	10 a.m.–4 p.m. (N=13501)	Sig. (p)
Age				< 0.001
Mean ± SE	42.48 ± 0.13	35.93 ± 0.16	47.84 ± 0.18	
Gender				< 0.001
Male	17287 (70.4%)*	8284 (75.0%)	9003 (66.7%)	
Female	7261 (29.6%)*	2763 (25.0%)	4498 (33.3%)	
Race				< 0.001
White, non-Hispanic	16480 (67.1%)*	6934 (62.8%)	9546 (70.7%)	
Hispanic	2708 (11.0%)*	1416 (12.8%)	1292 (9.6%)	
Black	2193 (8.9%)*	1157 (10.5%)	1036 (7.7%)	
Other or unknown	3167 (12.9%)*	1540 (13.9%)	1627 (12.1%)	
Mechanism of Injury				< 0.001
MVA	12817 (52.2%)*	5975 (54.1%)	6842 (50.7%)	
Pedestrian/cyclist	374 (1.5%)*	106 (1.0%)	268 (2.0%)	
Fall	5939 (24.2%)*	1929 (17.5%)	4010 (29.7%)	
Struck by	1471 (6.0%)*	861 (7.8%)	610 (4.5%)	
Other	947 (16.1%)*	2176 (19.7%)	1771 (13.1%)	
ED SBP				0.878
90+	23478 (95.6%)	10560 (95.6%)	12,918 (95.7%)	
< 90	349 (2.6%)	286 (2.6%)	349 (2.6%)	
Unknown	234 (1.7%)	201 (1.8%)	234 (1.7%)	
Work-related injury				< 0.001
No	7246 (29.5%)*	3309 (30.0%)	3937 (29.2%)	
Yes	2,299 (9.4%)*	747 (6.8%)	1552 (11.5%)	
Unknown	15003 (61.1%)*	6991 (63.3%)	8012 (59.3%)	
ED drug screen				< 0.001
Negative	2399 (9.8%)*	1249 (11.3%)	1150 (8.5%)	
Positive	4216 (17.2%)*	2207 (20.0%)	2009 (14.9%)	
Unknown	17933 (73.1%)*	7591 (68.7%)	10342 (76.6%)	
ED alcohol screen				< 0.001
Negative	6005 (24.5%)*	1556 (14.1%)	4449 (33.0%)	
Positive	5711 (23.3%)*	4580 (41.5%)	1131 (8.4%)	
Unknown	12832 (52.3%)*	4911 (44.5%)	7921 (58.7%)	
ED GCS score				< 0.001
Mean ± SE	12.63 ± 0.03	12.23 ± 0.04	12.95 ± 0.03	
ED GCS score group				< 0.001
Mild (13–15)	18947 (77.2%)*	8078 (73.1%)	10869 (80.5%)	
Moderate (9–12)	1267 (5.2%)*	661 (6.0%)	606 (4.5%)	
Severe (3–8)	4,334 (17.7%)*	2308 (20.9%)	2026 (15.0%)	
ISS				0.521
Mean ± SE	15.65 ± 0.07	15.70 ± 0.11	15.60 ± 0.10	
ISS group				0.006
0–8	7140 (29.1%)	3232 (29.3%)	3908 (28.9%)	
9–15	6189 (25.2%)	2797 (25.3%)	3392 (25.1%)	
16–25	7076 (28.8%)*	3077 (27.9%)	3999 (29.6%)	
26–75	2202 (16.3%)*	1941 (17.6%)	2202 (16.3%)	
ED disposition				< 0.001
Home	728 (3.0%)	283 (2.6%)	445 (3.3%)	
Floor	10516 (42.8%)*	4596 (41.6%)	5920 (43.8%)	
Operating room	2310 (9.4%)*	976 (8.8%)	1334 (9.9%)	
Intensive care unit	8229 (33.5%)*	3922 (35.5%)	4307 (31.9%)	
Other	2389 (9.7%)*	1109 (10.0%)	1280 (9.5%)	
Died in ED	376 (1.5%)	161 (1.5%)	215 (1.6%)	

Table 2
Medical comorbidities for mid-night and mid-day circadian cohorts.

Medical comorbidity	Total (N=24548)	12 a.m.–6 a.m. (N=11047)	10 a.m.–4 p.m. (N=13501)	Sig. (p)
Congestive heart failure	130 (0.5%)	43 (0.4%)	87 (0.6%)	0.006
Coronary artery disease	384 (1.6%)	104 (0.9%)	280 (2.1%)	< 0.001
Hypertension	1473 (6.0%)	439 (4.0%)	1034 (7.7%)	< 0.001
Cerebrovascular accident	122 (0.5%)	39 (0.4%)	83 (0.6%)	0.004
Dementia	64 (0.3%)	28 (0.3%)	36 (0.3%)	0.840
Cirrhosis	35 (0.1%)	15 (0.1%)	20 (0.1%)	0.799
COPD	243 (1.0%)	69 (0.6%)	174 (1.3%)	< 0.001
Peptic ulcer disease	11 (0.0%)	3 (0.0%)	8 (0.1%)	0.237
Coagulopathy	183 (0.7%)	51 (0.5%)	132 (1.0%)	< 0.001
Diabetes mellitus	622 (2.5%)	186 (1.7%)	436 (3.2%)	< 0.001
Metastatic cancer	68 (0.3%)	16 (0.1%)	52 (0.4%)	< 0.001
Psychiatric disorder	551 (2.2%)	248 (2.2%)	303 (2.2%)	0.997
Illicit drug use	304 (1.2%)	160 (1.4%)	144 (1.1%)	0.007
Alcohol abuse	749 (3.1%)	490 (4.4%)	259 (1.9%)	< 0.001

Caption: Mid-night (12 a.m.–6 a.m.) and mid-day (10 a.m.–4 p.m.) cohorts of TBI patients are compared by chi-squared test. COPD=Chronic obstructive pulmonary disease.

with decreased incidences of cardiac, pulmonary, vascular/coagulopathic, and oncologic comorbidities ($p < 0.001$) (Table 2). Specifically, the incidences of coronary artery disease (CAD; 0.9% vs. 2.1%), hypertension (4.0% vs. 7.7%), chronic obstructive pulmonary disease (COPD; 0.6% vs. 1.3%), coagulopathy (0.5% vs. 1.0%), diabetes mellitus (1.7% vs. 3.2%), metastatic cancer (0.1% vs. 0.4%) were all, at minimum, 1.8 times higher in the mid-day cohort compared to the mid-night cohort. In contrast, mid-night patients were more likely to have a history of documented alcohol abuse (4.4% vs. 1.9%, p < 0.001). Furthermore, TBI patients during mid-night hours were more likely to have a positive ED toxicology result for illicit drugs (20.0% vs. 14.9% of all ED visits, including those without toxicology results; p < 0.001) and for alcohol (41.5% vs. 8.4% of all ED visits; p < 0.001) (Table 2).

3.3. Circadian influence on Glasgow coma scale

Mean ED GCS score was 12.63 ± 0.03 (median 15, IQR 13–15), and TBI severity by GCS classification was 77.5% mild (GCS 13–15), 4.8% moderate (GCS 9–12), and 17.6% severe (GCS 3–8). GCS was significantly lower in mid-night ED visits compared to mid-day (12.23 ± 0.04 vs. 12.95 ± 0.03; p < 0.001); post-hoc analysis showed statistically significant reductions in all three subcomponent scores of the GCS during mid-night ED visits (eyes 0.21, verbal 0.24, motor 0.27, p < 0.001). Additionally, mid-night ED visits included a lower proportion of mild TBI (73.1% vs. 80.5%) and a higher proportion of moderate TBI (6.0% vs. 4.5%) and severe TBI (20.9% vs. 15.0%) compared to their mid-day counterparts (Table 1). Multivariable regression adjusting for age, CCI, mechanism of injury, work-related injury status, hypotension, ED toxicology (illicit drugs and alcohol), and ISS confirmed that midnight-hours were associated with a mean GCS score decrease of 0.3 (95% CI [−0.4, −0.2]; p < 0.001) (Table 3). ISS (reference group ISS 0–8; ISS 9–15: B=−0.3 [−0.4, −0.2]; ISS 16–25: B=−1.7 [−1.8, −1.6]; ISS 26–75: B=−5.1 [−5.2, −5.0]; p < 0.001), hypotension (reference group SBP 90+; SBP < 90: B=−2.4 [−2.7, −2.1]; SBP unknown: B=−5.1 [−5.5, −4.8]; p < 0.001), presence of illicit drugs (B=−0.3 [−0.5, −0.1]; p < 0.001), and presence of alcohol (B=−0.6 [−0.8, −0.5]; p < 0.001) on ED toxicology were independent predictors of decreased GCS score. Increasing age (per-unit B=0.01 [0.01, 0.02]; p < 0.001) and CCI (per-unit B=0.11 [0.01, 0.21]; p=0.031) were associated with increased GCS (Table 3).

3.4. Circadian influence on ICU admission

As stated previously, there was a higher incidence of ICU admissions in the mid-night cohort compared to mid-day (Table 1); as we have verified a circadian association for GCS score, we performed an analysis of ED arrival hour, GCS, and the interaction factor ED arrival hour*GCS score in order to better address the nuances of circadian rhythms on ICU admission following TBI. In patients who did not die in the ED or go directly to the operating room (N=21,862), multivariable logistic regression for the binarized outcome of admission to ICU (Yes/No) demonstrated that mid-night hours (OR 1.73, 95% CI [1.30, 2.31]; p < 0.001), age (per-unit OR 1.01 [1.01, 1.01]; p < 0.001), ISS (reference group ISS 0–8; ISS 9–15: OR 3.07 [2.79, 3.38]; ISS 16–25: OR 6.63 [6.04, 7.27]; ISS 26–75: OR 9.89 [8.77, 11.16]; p < 0.001), positive ED toxicology screen for illicit drugs (OR 1.33 [1.16, 1.51]; p < 0.001) and alcohol (OR 1.21 [1.09, 1.34]; p < 0.001) were associated with increased odds of ICU admission (Table 4). Increasing GCS score (per-unit OR 0.82 [0.80, 0.83]; p < 0.001) was associated with decreased odds of ICU admission (Table 4). Notably, the interaction factor ED GCS score*ED arrival hour independently demonstrated an OR of 0.96 (95% CI [0.94, 0.98]; p < 0.001), suggesting that the influence of an increase in GCS on ICU admission is *less important* at night than during the day (Table 4).

4. Discussion

Accurate assessment of neurologic injury following TBI is paramount in determining acute triage and management. It logically

Table 3
Multivariable linear regression for the GCS score.

Clinical variable	N	*B*	SE	95% CI	Sig. (p)
ED arrival hour					
10 a.m.–4 p.m.	13501	Reference	–	–	–
12 a.m.–6 a.m.	11047	−0.29	0.05	−0.40, −0.19	< 0.001
Age	24548	0.01	0.00	0.01, 0.02	< 0.001
CCI	24548	0.11	0.05	0.01, 0.21	0.031
Mechanism of injury					
MVA	12817	Reference	–	–	–
Pedestrian/cyclist	374	0.55	0.19	0.17, 0.92	0.004
Fall	5939	−0.10	0.06	−0.22, 0.02	0.108
Struck by	1471	0.14	0.10	−0.06, 0.34	0.168
Other	3947	−0.04	0.07	−0.17, 0.09	0.552
Work-related injury					
No	7246	Reference	–	–	–
Yes	2299	0.14	0.09	−0.04, 0.31	0.119
Unknown	1,5003	−0.14	0.05	−0.24, −0.03	0.010
ED SBP					
90+	23,478	Reference	–	–	–
< 90	635	−2.41	0.15	−2.70, −2.12	< 0.001
Unknown	435	−5.14	0.18	−5.49, −4.80	< 0.001
ED drug screen					
No	2399	Reference	–	–	–
Yes	4216	−0.33	0.09	−0.51, −0.14	< 0.001
Unknown	1,7933	−0.07	0.08	−0.23, 0.09	0.408
ED alcohol screen					
No	6005	Reference	–	–	–
Yes	5711	−0.64	0.07	−0.78, −0.50	< 0.001
Unknown	1,2832	−0.05	0.06	−0.16, 0.07	0.437
ISS group					
0–8	7140	Reference	–	–	–
9–15	6189	−0.29	0.06	−0.42, −0.17	< 0.001
16–25	7076	−1.70	0.06	−1.82, −1.58	< 0.001
26–75	4143	−5.10	0.07	−5.24, −4.96	< 0.001

Caption: Multivariable linear regression analysis is shown with the GCS score as the dependent variable. B denotes the mean increase or decrease of each predictor subcategory compared to the reference category. CCI=Charlson Comorbidity Index; CI=confidence interval; ED=Emergency department; GCS=Glasgow Coma Scale; ISS=Injury severity score; MVA=Motor vehicle accident; SBP=Systolic blood pressure; SE=Standard error.

Table 4
Multivariable logistic regression for ICU admission.

Clinical variable	N	B	OR	95% CI	Sig. (p)
ED arrival hour					
10am-4pm	1,1952	Reference	–	–	–
12am-6am	9910	0.55	1.73	1.30, 2.31	< 0.001
ED GCS score					
Per-unit	2,1862	−0.21	0.82	0.80, 0.83	< 0.001
ED GCS score*ED arrival hour					
Interaction factor	2,1862	−0.04	0.96	0.94, 0.98	< 0.001
Age					
Per-unit	2,1862	0.01	1.01	1.01, 1.01	< 0.001
CCI					
Per-unit	2,1862	0.02	1.02	0.96, 1.09	0.543
Mechanism of injury					< 0.001
MVA	1,1106	Reference	–	–	–
Pedestrian/cyclist	350	−0.18	0.83	0.64, 1.09	0.186
Fall	5446	0.13	1.14	1.05, 1.24	0.003
Struck by	1351	0.07	1.08	0.94, 1.24	0.302
Other	3609	0.20	1.22	1.11, 1.34	< 0.001
Work-related injury					< 0.001
No	6449	Reference	–	–	–
Yes	2036	−0.51	0.60	0.53, 0.68	< 0.001
Unknown	1,3377	−0.24	0.79	0.73, 0.85	< 0.001
ED SBP					0.001
90+	2,1273	Reference	–	–	–
< 90	425	0.21	1.23	0.95, 1.60	0.114
Unknown	164	−0.70	0.50	0.33, 0.75	0.001
ED drug screen					< 0.001
Negative	2139	Reference	–	–	–
Positive	3757	0.28	1.33	1.16, 1.51	< 0.001
Unknown	1,5966	−0.02	0.98	0.88, 1.10	0.783
ED alcohol screen					< 0.001
Negative	5219	Reference	–	–	–
Positive	5188	0.19	1.21	1.09, 1.34	< 0.001
Unknown	1,1455	−0.26	0.77	0.71, 0.84	< 0.001
ISS group					< 0.001
0–8	6965	Reference	–	–	–
9–15	5735	1.12	3.07	2.79, 3.38	< 0.001
16–25	6151	1.89	6.63	6.04, 7.27	< 0.001
26–75	3011	2.29	9.89	8.77, 11.16	< 0.001

Caption: Multivariable logistic regression analysis is shown with ICU admission (Yes/No) as the dependent variable, for patients who did not die in the ED or go directly to the operating room. Odds ratios and associated 95% CIs are reported for each predictor. CCI=Charlson Comorbidity Index; CI=Confidence interval; ED=Emergency department; GCS=Glasgow Coma Scale; ISS=Injury severity score; MVA=motor vehicle accident; OR=Odds ratio; SBP=Systolic blood pressure

follows that the influence of circadian rhythmicity on baseline alertness and consciousness can further complicate evaluation of neurologic deficit and warrants careful consideration during acute traumatic insults to the head. Delineating true neurologic injury from an obtunded response due to an interrupted sleep-wake cycle can better enable the application of appropriate therapies for true TBI versus circadian dysregulation, minimizing misdiagnosis and ineffective health care utilization. To date, however, no study exists on the influence and interaction between neurologic deficit and circadian rhythmicity in the context of emergency department admissions and triage following adult TBI.

In the current study, we utilized the NSP of the NTDB to conduct such an analysis, and found clear, congruous circadian trends for ED admissions, age, and GCS in adult TBI patients across U.S. trauma centers. At 52645 patients overall, this is the largest study to date on circadian rhythms in acute TBI in the ED and the first population-based study to investigate circadian effects on the GCS score. Our data shows that in general, GCS score assessed in the ED reaches a peak for patients admitted during the mid-day hours of 10 a.m.–4 p.m., and a nadir for patients admitted during mid-night hours of 12am-6am. In a subset of 2,4548 patients arriving to the ED during mid-day and mid-night hours, we demonstrate that nighttime TBI patients suffer a comorbidity burden distinct from their daytime counterparts, and nighttime hours are associated with reduced ED GCS score independent of a number of demographic and clinical variables. Further, we find that TBI patients arriving to the ED during mid-night hours are at increased likelihood of being admitted to the ICU independent of their GCS score, and that the influence of GCS score on odds of ICU admission may be less important at night than during the day.

4.1. ED admission trends

Our data for TBI ED admissions supports studies examining overall ED admissions over the course of 24-h, which noted the lowest rates of arrival during mid-night hours of 12 a.m.–7 a.m. (McCarthy et al., 2008; Morzuch and Allen, June 11–14, 2006; Welch et al., 2007). It makes intuitive sense that a greater number of patients are admitted to the ED during mid-day hours, particularly via walk-ins or self-presentation, due to higher levels of daytime activity, which may correlate with quicker response to such injuries by bystanders or EMS. EMS utilization has also been shown to peak at 10 a.m. during daytime hours (Cantwell et al., 2015). Here, circadian rhythms are intertwined with societal organization – more people are active during the day and asleep during the night. In fact, McCarthy and colleagues determined that when temporal, climatic, and patient demographic/clinical factors were assessed, hour-of-day showed the highest predictive power for ED admissions (McCarthy et al., 2008). While trauma and TBI patients are far less likely and/or able to self-present, the increased number of attentive bystanders and the intrinsic circadian alertness of the injured patient during peak daytime hours of trauma enable higher likelihoods of on-scene triage, EMS contact, and successful transport to the ED. In contrast, nighttime traumatic injuries on average have fewer bystanders, overtaxed EMS resources, potentially more severe trauma injuries, and a decreased level of patient alertness that may be complicated by sleepiness or intoxication – all of which can confound the neurologic exam and GCS score. In injuries such as TBI where rapid triage and transport critically impact timing to medical evaluation and surgical intervention, dissection of the contributing clinical, circadian, and injury severity factors as we have done here is highly relevant, especially during nighttime hours where there can be an inherent mismatch between capacity and demand for medical services.

4.2. Medical comorbidities

In our analysis of medical comorbidities, we observed increased systemic comorbidities in the mid-day TBI cohort as compared to the mid-night cohort, a group with a significantly younger patient population (mean age 39 vs. 48-years). These findings are consistent with previous reports indicating that older patients present with higher rates of multiple chronic conditions (Gijsen et al., 2001; Guralnik, 1996). The increased incidences of cardiac, respiratory, coagulopathic, and oncologic conditions as well as diabetes and hypertension observed in the mid-day cohort indicate a distinct comorbidity profile for daytime USA TBI patients and is consistent with the notion that the older demographic is at greater cumulative risk for suffering these chronic conditions. In contrast, the mid-night cohort had a higher incidence of documented alcohol abuse and positive ED toxicology results for both alcohol consumption and illicit drug use – all of which may be in fact underreported in the ED population. The high prevalence of alcohol abuse may be attributable to the phenomenon of young adults consuming alcohol at higher frequencies and amounts than older adults (Carter et al., 2010; Hingson et al., 2009); indeed, Fahimi and colleagues found that younger adults were more likely to present to the ED for alcohol and substance abuse overnight rather than during daytime hours (Fahimi et al., 2015). The confounding effects of intoxication on the neurologic exam have been well-documented in the literature and consequently the influence of nighttime hours/circadian rhythmicity on GCS score independent of known confounders is warranted as performed.

4.3. Circadian influence on GCS

In the present study, we sought to investigate the potential influence of circadian rhythms and/or admission hour on the GCS score. Our data demonstrates significant decreases in mean ED GCS score associated with the mid-night cohort. This finding in both univariate and multivariate analyses demonstrates a clear circadian fluctuation in mental status with peak between 3 and 4 p.m. and nadir at 4–6 a.m. It is important to note that compromising factors to consciousness, such as intoxication and hypotension, per their relation to impaired cerebral perfusion pressure, were significantly greater in the mid-night cohort; these factors have all been shown to negatively influence GCS score and patient outcomes (Thomas et al., 2000; Toschlog et al., 2003). Paradoxically, increased age and CCI was associated with increased GCS score. This can be at least partially explained by the lifestyle choices of younger, less risk-averse patients that can lead to more severe TBIs as is the case with MVA and blunt force trauma (Bruns and Hauser, 2003).

The GCS score has become a ubiquitous bedside assessment of consciousness in any clinical setting (Teasdale et al., 2014). Teasdale and colleagues, the creators of the GCS, remark in 2014 upon the confounding factors which might render one or more components of the GCS score untestable or invalid. These include drugs (e.g. sedative and neuromuscular blockades), cranial nerve injuries, alcohol and recreational drugs, hearing impairments, intubation or tracheostomy, limb or spinal-cord injuries, dysphasia, dementia, ocular trauma, patient native language, and/or orbital swelling. Our data showed a statistically significant effect even when controlling for these well-documented independent predictors, further demonstrating the robust nature of the association between GCS score and time of day. These external factors affect alertness and consciousness (Åkerstedt, 2007), which is manifested in the circadian swings in admission GCS.

The GCS score may be influenced by circadian rhythms via the presence or absence of melatonin, which is predominantly regulated by prevailing light/dark environments; increased melatonin, released from the pineal gland during night hours, correlates with decreased arousal (Reiter, 2003). Since the pineal gland does not store and release melatonin but rather releases it quickly after synthesis – possibly directly into cerebrospinal fluid – circulating concentrations of melatonin may fluctuate based on external stimuli. Generally, increased melatonin during nighttime hours lead to increased sleepiness, and thus reduced baseline alertness and an across-the-board decrease in GCS score during assessment.

Important neurotransmitters responsible for induction and maintenance of the sleep cycle, including serotonin, norepinephrine, acetylcholine, dopamine, are likely also affected by TBI (Kawa et al., 2015; Pappius, 1991; Seigel et al., 2004; Jones et al., 2005; Monti et al., 2011). Most central nervous system neurons functioning in sleep control are GABAergic (GABA: gamma-aminobutyric acid), and are unique in that they increase in activity during sleep onset and non-REM sleep (Seigel et al., 2004). Studies have shown that, in fact, the excitatory actions of GABA following neuronal trauma, e.g. depolarization and calcium ion (Ca^{2+}) influx, may modulate gene expression and enhance outgrowth of regenerating neurites, and on the negative side, contribute to maladaptive signal transmission in GABAergic brain circuits such as circadian sleep cycles (van den Pol et al., 1996).

A number of studies have shown that circadian rhythms significantly influence subjective alertness and cognitive performance; alertness remains stable during a normal 16-h waking day but deteriorates considerably with the trough/nadir of the circadian rhythm, along with a correlative decrease in core body temperature (Czeisler and Gooley, 2007; Dijk et al., 1992; Mundigler et al., 2002) Hence, it is reasonable to assume that a combination of night hours, decreased environmental lighting, and neuronal trauma would decrease overall patient arousability at night. Due to less availability of ambient light, people are no longer able to rely on visuospatial cues and therefore fall more, have more disorientation, leading to decreased GCS score. Decreased eye opening, conversational arousability, and/or spontaneous motor movements, all of which are critical components of the GCS score, can be at the mercy of time of day – a salient observation that should not be ignored when similarly affected clinicians are assessing severity of trauma and triage to higher levels of care, such as the ICU.

4.4. Circadian influence on ICU admission

Previous studies have demonstrated no association between time of day of presentation to the ICU and various outcomes including length of stay and mortality (Asha et al., 2011). Prehospital GCS has been known to significantly impact hospital admission, as a GCS score of 13–14 in over 4000 consecutive MVA patients was associated with increased risk of full trauma code activation as well as a 73% chance of hospital admission (Norwood et al., 2002). Our data adds the novelty of circadian fluctuations as a variable of impact, specifically for ICU admissions following TBI during mid-night hours. The other factors that are associated with increased ICU admission, such as a positive toxicology screen, history of alcohol abuse, and increased age, highlight the fact that patients presenting with equivocal levels of consciousness are inherently "riskier" patients due to an inability to determine the true extent of their TBI. However, after controlling for these confounding factors, nighttime admissions remained associated with increased likelihood of ICU admissions independent of a decreased GCS score. This finding suggests that the trough of the circadian cycle confers an additional level of risk or unknown prognosis at the time of assessment, and that the patient may be better off under high acuity monitoring above that of routine. Furthermore, the interaction factor ED GCS score*ED arrival hour presents another level of complexity in nighttime assessments; with an $OR < 1$, it seems that GCS score at night is less important than GCS score during the day as part of the decision process to admit a TBI patient to the ICU. We acknowledge that it is difficult to understand whether these significant associations can be attributed to TBI severity, institutional preferences, and/or clinical morbidity – likely a combination of these in conjunction with a differential circadian effect. Whether these patients require a higher level of care or if this finding is due to limitations in healthcare delivery during nighttime hours remains to be seen. However, for the clinician of today, extra care and scrutiny during GCS assessment is warranted for nighttime TBI patients in order to differentiate somnolent/obtunded patients at the nadir of their circadian awareness from patients with pathological depression of consciousness secondary to TBI.

4.5. Limitations

Large retrospective studies naturally have inherent limitations. The NTDB database has been reported as having missing values that leads to inaccurate clustering of patient data (Roudsari et al., 2008). More recently, the validity of GCS score in the setting of severe trauma has been questioned. The NTDB manual describes that many patients with severe head injuries may be intubated and sedated prior to arrival at the ED making accurate GCS scoring difficult. This bias should affect both groups of patients in our study equally; however, it is an important factor to consider in interpreting the results described (American College of Surgeons, 2012). While this study may be the first to characterize the relationship of circadian rhythm on the GCS score, different patient presentations based on geographic location and time of day are important factors beyond the scope of the database used. A focus on city versus rural hospitals may bias the results for a specific time of day. Precise categorization of head injury is difficult to capture based off of ICD-9 codes alone and the lack of granularity can introduce potential confounders into the dataset. While we are limited by the inability to identify the specific intracranial injury type due to lack of hierarchical AIS coding within the NSP of the NTDB (American College of Surgeons, 2009), we nevertheless control for ISS, alcohol intoxication, and age – factors cited to be equally as predictive as CT imaging findings (Jacobs et al., 2010) – as well as a number of demographic and injury-specific variables in an effort to reduce bias and confounding. Ideally, the large sample size in the current analysis and population-based sampling techniques used by the NTDB would correct for these factors. Our findings provide a starting point for future studies of similar scale. By using the NSP of the NTDB, we acknowledge that we are yet unable to differentiate whether nighttime TBI patients suffered different types of TBI, i.e. more damage to wake-promoting structures (Imbach et al., 2015) that may impact ED GCS score. Our findings require validation from basic injury models as well as prospective clinical trials to assess the contribution of circadian rhythmicity to the GCS score.

4.6. Conclusions

ED admissions for TBI, and the GCS score, demonstrate circadian rhythmicity with a daytime peak and nighttime trough. Nighttime TBI patients present with decreased GCS score and are admitted to ICU at higher rates, yet have fewer prior comorbidities and similar systemic injuries. The interaction between nighttime hours and decreased GCS score on ICU admissions has important implications for clinical assessment/triage.

Disclosures

The authors declare no conflicts of interest.

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