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Impact of surgery after injury on SDNN and posttraumatic stress disorder development over two years

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This study examined the modifying effects of surgery status on the association between the Standard Deviation of NN Intervals (SDNN) of the heart rate variability and the post-traumatic stress disorder (PTSD) development. Participants with physical injury were recruited from a trauma center and followed for two years. Baseline assessment included SDNN and surgery status. Socio-demographic and clinical covariates were collected. PTSD was diagnosed at 3, 6, 12, and 24 months post-injury using the Clinician-Administered PTSD Scale for DSM-5. Logistic regression analyses were performed. Among 538 participants, 58 (10.8%) developed PTSD during the study, with prevalence rates of 8.4% at 3 months, 6.5% at 6 months, 4.7% at 12 months, and 2.5% at 24 months. A significant modifying effect was found that lower SDNN were significantly associated with PTSD in non-surgical patients but not in surgical patients, with significant interaction terms. This pattern was observed from 3 to 12 months but not at 24 months. Surgery-dependent associations between SDNN and PTSD development were observed, highlighting the need for tailored PTSD prevention strategies considering SDNN and surgery status.

Keywords Posttraumatic stress disorder, Surgery, Heart rate variability, SDNN, Longitudinal study

Post-Traumatic Stress Disorder (PTSD) is a severe psychiatric condition that manifests through a variety of psychological and physiological symptoms. Heart Rate Variability (HRV) serves as a physiological marker reflecting autonomic nervous system function[1]. Generally, reduced HRV indicates diminished cardiovascular adaptability to internal and external stressors, thereby increasing susceptibility to PTSD[2]. Specifically, the Standard Deviation of NN intervals (SDNN) is the most prominent HRV marker, assessing overall heart rate variability and indicating general autonomic nervous system function[3].

Previous research and meta-analyses have demonstrated a significant association between low SDNN and PTSD[2,4–6]. However, there are also studies that report no such association[7–10], indicating a need for further investigation into this relationship.

Physical injuries are a substantial cause of PTSD[11]. Many individuals who suffer physical injuries require surgical interventions. HRV metrics, including SDNN, can be affected after surgery due to the body's response to surgical trauma and anesthesia[12]. Consequently, the effect of SDNN on PTSD development might differ based on whether the patient underwent surgery. Despite its importance, research examining the impact of surgical intervention on the relationship between SDNN and PTSD is lacking.

This study aims to address this gap by conducting a two-year follow-up study in patients with physical injuries to investigate how SDNN influences PTSD development, considering the surgical intervention status.

Materials and methods

Study overview and participants

This analysis is part of the Biomarker-based Diagnostic Algorithm for Post-Traumatic Syndrome (BioPTS) study, aimed at refining PTSD diagnostic and predictive models. The protocol is detailed in a prior publication[13].

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We prospectively enrolled patients admitted to the Trauma Center at Chonnam National University Hospital (CNUH), South Korea, for physical injuries from June 2015 to January 2021. Patients who met the following inclusion and exclusion criteria were invited to to participate in the present study. Inclusion criteria were (i) aged 18 years or older at the time of injury; (ii) hospitalized for more than 24 h following a moderate to severe physical injury (Injury Severity Score, ISS $\geq$ 9)[14]; and (iii) proficient in Korean to understand the study protocol. Exclusion criteria included: (i) moderate or severe brain injury (Glasgow Coma Scale, GCS < 10)[15]; (ii) injuries resulting from suicide attempts; (iii) severe physical conditions preventing comprehensive psychiatric evaluation; (iv) history of psychiatric disorders (psychotic disorders, bipolar disorder, or substance use disorders excluding depression and anxiety); (v) significant cognitive impairments due to organic or neurocognitive disorders; and (vi) pre-existing convulsive disorders or anticonvulsant use. Baseline psychiatric assessments including HRV measures, were conducted within one month of hospitalization, conducted in person and post-surgery if applicable. The mean (SD) duration from injury to baseline assessment was 8.8 (5.3) days. Follow-up evaluations were via telephone at 3, 6, 12, and 24 months post-injury, using Clinician-Administered PTSD Scale for Diagnostic and Statistical Manual of mental disorders 5th edition (DSM-5)[16] (CAPS-5)[17]. The CNUH Institutional Review Board approved the study (CNUH 2015 – 148). Informed consent was obtained from all participants.

SDNN data collection and analysis

SDNN data were collected and analyzed using the SA-6000 HRV analyzer (Medicore Co., Seoul, Korea). Participants rested for 5 min before the test, removing any metal accessories, keeping their eyes open, and lying comfortably. To avoid biases from movement or posture changes, participants remained still, speaking and breathing naturally. Electrode sensors were placed on the insides of both wrists and the left ankle, with a 3-minute recording duration. A trained experimenter supervised the data collection to ensure protocol adherence and data accuracy. To ensure the accuracy and reliability of the data, HRV recordings were initially screened for artifacts using automated algorithms, which identified and marked discrepancies based on physiological thresholds and statistical parameters. Approximately 2.7% of inter-beat intervals (IBIs) were flagged by this automated process. Flagged IBIs were then manually reviewed by trained personnel who evaluated each potential artifact to determine whether adjustments or exclusions were necessary, adhering to standardized criteria that prioritize data integrity without compromising the natural variability in heart rate. Corrections were applied to less than 1% of the total IBIs, either by interpolation of adjacent normal intervals or by exclusion of non-physiological spikes. The SDNN (ms) parameter was derived using the Medicore HRV Analysis System in the SA-6000 device. SDNN data were analyzed as both continuous and categorical variables. The data were dichotomized using the median value due to the absence of established reference values and to ensure an equal distribution of participants across categories.

Operation status

Operation status was determined based on medical records documented by the surgeons. Patients were classified into two categories: those who received an operation and those who did not during the period between the physical injury and the baseline assessment.

Other baseline characteristics

To comprehensively evaluate factors potentially influencing PTSD development and HRV outcomes, a diverse array of variables was assessed as follows.

Socio-demographic characteristics

The following baseline socio-demographic characteristics were recorded: age, sex, duration of education, marital status (categorized as currently married or not), cohabitation status (living alone or not), and occupational state (current employed or not).

Pre-trauma characteristics

Prior histories of psychiatric disorders including depressive disorders, panic disorder, agoraphobia, social phobia, and generalized anxiety disorder, were documented. Participants' experiences of previous lifetime traumatic events were assessed using the Life Events Checklist[18], with the occurrence of at least one type of event being categorized as present for analysis purposes. Childhood abuse experiences were evaluated using the Nemesis Childhood Trauma Interview[19], encompassing emotional/psychological, physical, and sexual abuse before the age of 16. A broad definition of "childhood abuse" (having at least one type of abuse) was utilized for the analysis. The prevalence of physical disorders was assessed via a questionnaire encompassing 15 systems or diseases. Smoking status was categorized as current smoker or not. Alcohol use was screened using the Alcohol Use Disorders Identification Test (AUDIT)[20], where higher scores indicate more severe alcohol-related issues. Body Mass Index (BMI) was also calculated.

Trauma related characteristics

Type of accidental injury was evaluated using the Life Events Checklist[18], to identify the specific type of traumatic event participants experienced. Recognizing that PTSD prevalence and symptom patterns often significantly differ between unintentional (e.g., accidents) and intentional (e.g., violent, interpersonal) traumas[21], injury types were categorized into these two distinct groups. The severity of injuries sustained by participants was assessed using the ISS and GCS as described in the Eligibility criteria above, with higher ISS scores and lower GCS scores indicating more pronounced symptomatology.

Peri-trauma characteristics

During the peri-trauma period spanning from the index injury to the baseline evaluation, participants' symptoms and functional status were assessed. PTSD symptom severity was gauged by summing the frequency and intensity scores of the 20 DSM-5 PTSD symptoms, yielding a total severity score[17]. Anxiety and depressive symptoms were measured using the Hamilton Anxiety Rating Scale (HAMA)[22] and Hamilton Depression Rating Scale[23], respectively, with higher scores indicating more severe symptoms. Baseline physiological status was checked through measurements of vital signs, including systolic and diastolic blood pressures and heart rate.

Follow-up diagnoses of PTSD with CAPS-5

The CAPS-5 is highly reliable and valid, suitable for detailed PTSD assessment, including via telephone[24]. To confirm PTSD, participants must meet DSM-5 criteria across several symptom clusters: one symptom from Cluster B (intrusion), one from Cluster C (avoidance), two from Cluster D (negative alterations in cognition and mood), and two from Cluster E (alterations in arousal and reactivity). The criteria for symptom duration (Cluster F) and functional significance (Cluster G) must also be met. This study's outcome variables included any PTSD diagnosis during follow-up and PTSD presence at 3, 6, 12, and 24 months post-trauma, with the CAPS-5 specifically anchored to the traumatic injury event that led to hospitalization.

Statistical analysis

Participants included those who completed at least one follow-up after baseline, in line with DSM-5 PTSD criteria[16]. Baseline characteristics were categorized by PTSD development, SDNN median value (higher vs. lower), and surgery status (received vs. not received). Continuous and categorical variables were compared using t-tests or χ^2 tests. Covariates for further analysis were chosen based on statistical significance ($P < 0.05$). Logistic regression analyzed individual associations of SDNN and surgery status with PTSD development, adjusting for covariates. To assess the modifying effects of surgery on the SDNN-PTSD relationship, multinomial logistic regression with interaction terms was applied. This method was iteratively used for PTSD occurrences at each follow-up interval. All tests were two-sided with a significance level of $P < 0.05$. Analyses were conducted using SPSS, version 21.0.

Results

Recruitment and baseline data

The recruitment trajectory and PTSD prevalence at each follow-up interval are shown in Fig. S1. Of 1142 patients assessed at baseline, 580 (50.8%) underwent HRV evaluation. Baseline comparisons between those who completed and did not complete HRV evaluation are in Supplementary Table S1. Higher Injury Severity Scores (ISS) were significantly related to non-completion of HRV, but other variables were not. Of those who completed HRV assessment, 42 (7.4%) did not proceed to the 3-month evaluation, leaving 538 patients (92.6%) for analysis. No significant differences in baseline characteristics were found between completers and non-completers (all P-values > 0.05). Within this cohort, 58 patients (10.8%) were diagnosed with PTSD during the 24-month period. Baseline characteristic comparisons between patients with and without PTSD are in Table S2. PTSD diagnosis was significantly associated with female sex, higher education, previous psychiatric disorders, prior traumatic events, and elevated anxiety and depressive symptoms. Lower SDNN (≤ 22 ms) was significantly associated with higher age, female sex, lower education, more physical disorders, higher depressive symptoms, and higher heart rate (Table S3). Received surgery ($N = 268$; 49.8%) was significantly associated with higher depressive symptoms (Table 1). Eight covariates were identified for further analysis: age, sex, education, previous psychiatric disorders, prior traumatic events, number of physical disorders, depressive symptoms, and heart rate.

Individual associations

SDNN levels were not significantly associated with surgery status (Table S3). Neither SDNN levels nor surgery status was associated with any PTSD development after adjustment for covariates (left part of Fig. 1).

Interactive modifying associations

A significant modifying effect was found: lower SDNN levels were significantly associated with PTSD development in patients without surgery, but not in those who underwent surgery, with significant interaction terms (right part of Fig. 1st row of Table 2). The prevalence rates of PTSD at each follow-up interval were 8.4% at 3 months, 6.5% at 6 months, 4.7% at 12 months, and 2.5% at 24 months. The temporal relationship between SDNN levels and PTSD diagnosis over these intervals by surgery status is illustrated in Fig. 2and 2nd ~ 5th rows of Table 2. Consistent with the overarching findings, lower SDNN levels were significantly associated with PTSD diagnoses at the 3, 6, and 12-month intervals, underscored by significant interaction terms. However, this association was not evident at the 24-month evaluation. Similar interactive associations were observed when analyzing SDNN levels as continuous variables. Interactive modifying effects of SDNN on the relationships between post-injury surgical intervention and PTSD status were significant for any PTSD (Wald = 7.119; $p = 0.01$), PTSD at 3 months (Wald = 5.211; $p = 0.012$), PTSD at 6 months (Wald = 7.614; $p = 0.003$), and PTSD at 12 months (Wald = 4.815; $p = 0.027$). However, no significant association was found for PTSD at 24 months (Wald = 1.980; $p = 0.306$).

Discussion

The principal findings of this two-year longitudinal study indicate that the association between lower SDNN and subsequent PTSD development was significant only in patients who did not receive surgery for their physical injury, with significant interaction terms. This pattern was consistent during the follow-up periods from 3 to 12 months post-injury but dissipated at the 24-month follow-up.

	All patients ($N=538$)	Received surgery ($N=268$)	Not received surgery ($N=270$)	Statistical coefficients	P-value[a]
Socio-demographic characteristics					
Age, mean (SD) years	57.0 (16.9)	56.3 (17.1)	57.8 (16.8)	t=-1.020	0.308
Sex, N (%) female	169 (31.4)	94 (35.1)	75 (27.8)	$\chi^2=3.324$	0.068
Education, mean (SD) years	10.7 (4.2)	10.7 (4.3)	10.7 (4.2)	t=+0.003	0.997
Marital status, N (%) unmarried	178 (33.1)	82 (30.6)	96 (35.6)	$\chi^2=1.494$	0.222
Living alone, N (%)	79 (14.7)	36 (13.4)	43 (15.9)	$\chi^2=0.667$	0.414
Unemployed status, N (%)	88 (16.4)	50 (18.7)	38 (14.1)	$\chi^2=2.065$	0.151
Pre-trauma characteristics					
Previous psychiatric disorders, N (%)	41 (7.6)	19 (7.1)	22 (8.1)	$\chi^2=0.214$	0.644
Previous traumatic events, N (%)	29 (5.4)	13 (4.9)	16 (5.9)	$\chi^2=0.305$	0.581
Any childhood abuse, N (%)	37 (6.9)	22 (8.2)	15 (5.6)	$\chi^2=1.479$	0.224
Physical disorders, mean (SD) numbers	2.0 (2.1)	1.9 (2.0)	2.1 (2.1)	t=-1.303	0.193
Current smoker, N (%)	140 (26.0)	75 (28.0)	65 (24.1)	$\chi^2=1.069$	0.301
AUDIT, mean (SD) scores	10.2 (10.0)	10.5 (10.2)	9.9 (9.8)	t=+0.641	0.522
Body mass index, mean (SD)	23.6 (3.5)	23.6 (3.4)	23.7 (3.6)	t=-0.267	0.789
Trauma related characteristics					
Injury type, N (%) intentional	51 (9.5)	23 (8.6)	28 (10.4)	$\chi^2=0.501$	0.479
Injury severity score, mean (SD) scores	14.0 (5.3)	13.8 (5.7)	14.2 (4.7)	t=-0.812	0.417
Glasgow coma scale, mean (SD) scores	14.9 (0.6)	14.9 (0.5)	14.9 (0.6)	t=+0.565	0.572
Peri-trauma assessment scales and measurements, mean (SD)					
HAMA	4.7 (4.7)	5.0 (4.7)	4.4 (4.6)	t=+1.438	0.151
HAMD	6.3 (5.4)	6.8 (5.5)	5.8 (5.3)	t=+2.025	**0.043**
Systolic blood pressure, mmHg	119.1 (14.1)	118.3 (13.5)	120.0 (14.7)	t=-1.374	0.170
Diastolic blood pressure, mmHg	71.9 (9.2)	71.4 (9.0)	72.4 (9.3)	t=-1.298	0.195
Heart rate per minute	78.7 (11.1)	78.7 (11.5)	78.6 (10.6)	t=+0.106	0.915

Table 1. Baseline characteristics by post-injury surgical intervention status in 538 patients with physical injuries. *AUDIT* alcohol use disorders identification test, *HAMA* Hamilton anxiety rating scale, *HAMD* Hamilton depression rating scale. [a] t-tests or χ^2 tests, as appropriate between patients who received surgical intervention and those who did not. Bold style indicates statistical significance ($P < 0.05$).

Previous research on the association between SDNN and PTSD has primarily involved cross-sectional studies of military veterans, where SDNN levels were examined based on PTSD status[4,6–10]. Direct comparisons with the results of this prospective study on patients with physical injuries are therefore challenging. One prior study with a similar design to ours assessed HRV at hospital admission following a traffic accident and evaluated PTSD at 2 and 6 months post-injury[5]. This study found that low SDNN was significantly associated with PTSD at both time points. While these findings partially align with our results, the study did not report whether the participants underwent surgery, and the sample size was relatively small, with approximately 20 participants.

Our study, with a larger cohort and long-term follow-up, reveals that the SDNN-PTSD link varies by surgical intervention status. Several mechanisms may explain these differences. Firstly, surgical interventions and perioperative care can normalize autonomic nervous system function. Surgery typically involves pain management, rehabilitation, and psychological support, stabilizing autonomic responses and HRV metrics like SDNN[12]. This could obscure the low SDNN-PTSD link in surgical patients, making SDNN a less effective biomarker. Secondly, surgery-induced autonomic adjustments during healing can alter HRV measures like SDNN[25], masking SDNN's predictive value for PTSD in surgical patients. Thirdly, intensive follow-up and monitoring in surgical patients can lead to early psychological intervention, reducing PTSD severity and the role of SDNN as a predictor[26]. Lastly, biological recovery differences between surgical and non-surgical patients, involving controlled inflammation, hormonal changes, and neuroplasticity, can disrupt the typical SDNN-PTSD associations.

Notably, the significant modifying effects of surgery status observed from 3 to 12 months post-injury dissipated by the 24-month follow-up. This can be interpreted in several ways. Firstly, the acute and subacute recovery phases involve significant physiological and psychological adjustments, influencing autonomic nervous system function and HRV metrics like SDNN[27]. By 24 months, these processes may have stabilized, reducing the SDNN-PTSD association. Secondly, over time, individuals may develop coping mechanisms and psychological resilience that mitigate initial autonomic dysregulation[26]. Thirdly, other health factors and life events might influence PTSD outcomes more significantly than initial physiological responses by 24 months. New stressors, health changes, and life circumstances can alter PTSD's trajectory, making early biomarkers like SDNN less relevant for long-term predictions[28].

A notable limitation of this study is its exclusive focus on individuals with physical injuries. While relevant to PTSD research due to the strong link between traumatic physical injuries and PTSD, the generalizability to those experiencing other trauma types remains uncertain[11]. Recruitment from a single trauma center aids

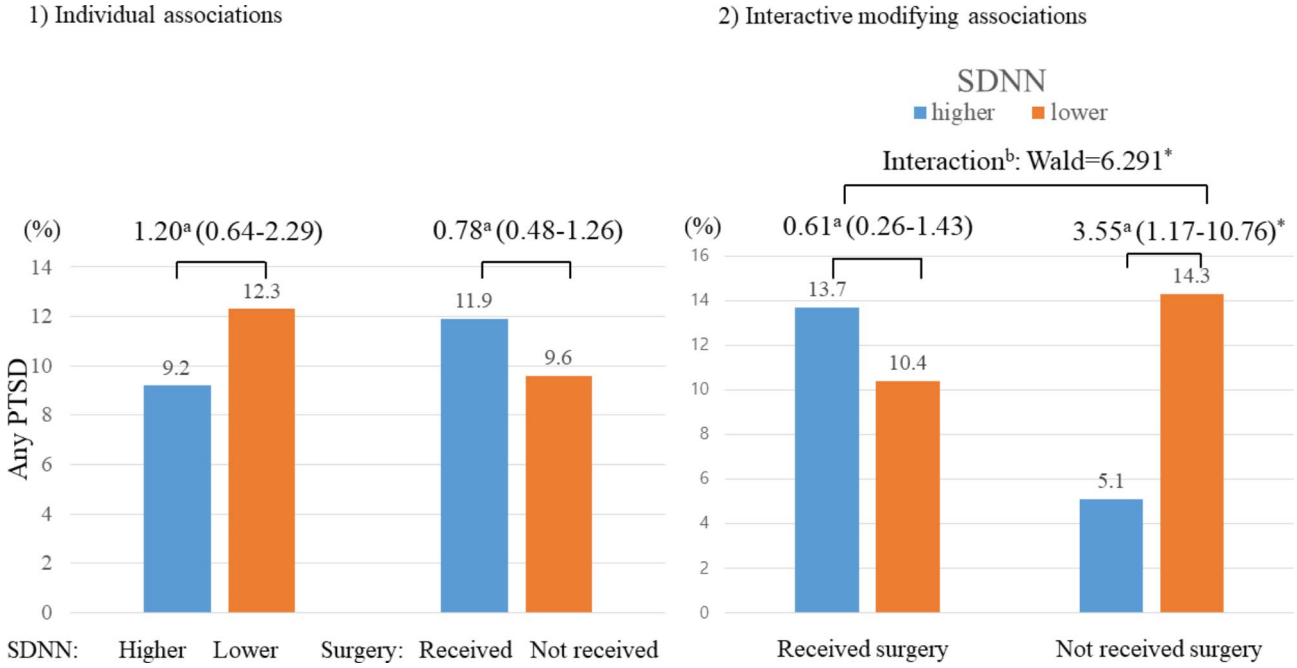

Fig. 1. Individual and interactive modifying associations of SDNN and post-injury surgical intervention status with any posttraumatic stress disorder (PTSD) over 2-years in 538 patients with physical injuries. [a]Odds ratios (95% confidence intervals) were calculated using binary logistic regression; [b]interactive modifying associations were estimated using multinomial logistic regression between higher (> 22 ms) vs. lower (≤ 22 ms) SDNN and/or received vs. not received post-injury surgical interventions at baseline on development of any PTSD over 2-years, adjusted for age, sex, education, previous psychiatric disorders, previous traumatic events, number of physical disorders, scores on Hamilton Depression Rating Scale, and heart rate. *$P < 0.05$.

consistency but may limit broader applicability. The HRV evaluation completion rate was 51%, with non-completion significantly associated with higher Injury Severity Scores (ISS), indicating more severely injured patients were less likely to complete HRV evaluations. This could lead to an underestimation of the HRV-PTSD association. Additionally, follow-up via telephone interviews, though validated, may lack the depth and accuracy of in-person assessments, potentially affecting data reliability[24].

A principal strength of our study is its two-year longitudinal design with a large cohort. Another key advantage is the consecutive recruitment of participants from the entire population of recently injured patients, significantly reducing selection bias and ensuring a representative sample. The structured schedule of regular follow-up evaluations minimizes biases from inconsistent timing. Adherence to a rigorous research protocol ensured uniform evaluations and data collection, enhancing consistency and reliability. Additionally, collecting a wide array of potential baseline covariates for PTSD allowed for a comprehensive analytical framework. Reasonable long-term follow-up rates and analyses showing no evidence of selective attrition further bolster the credibility and reliability of our findings.

In conclusion, our study offers new insights into PTSD etiology, demonstrating surgery-dependent associations between SDNN and PTSD development, along with temporal variations in patients with physical injuries. Identifying individuals at elevated risk based on surgery status enables more precisely tailored interventions, potentially reducing PTSD onset or severity. Clinically, our findings highlight the value of incorporating SDNN measures and surgery status into PTSD diagnostic and treatment plans, emphasizing stress response regulation and coping strategy enhancement. Future research should generalize these results across diverse trauma populations and multi-centers, and investigate the underlying biological mechanisms linking SDNN alterations to PTSD development.

PTSD status	Surgical intervention	SDNN	*N*, Patient	No. (%), PTSD	Odds ratio (95% confidence interval)	
					Unadjusted	Adjusted[a]
Any PTSD	Received	Higher (> 22 ms)	124	17 (13.7)	Ref	Ref
		Lower (≤ 22 ms)	144	15 (10.4)	0.73 (0.35–1.53)	0.61 (0.26–1.43)
	Not received	Higher (> 22 ms)	137	7 (5.1)	Ref	Ref
		Lower (≤ 22 ms)	133	19 (14.3)	3.10 (1.26–7.63)*	3.55 (1.17–10.76)*
PTSD at 3-month	Received	Higher (> 22 ms)	124	15 (11.2)	Ref	Ref
		Lower (≤ 22 ms)	144	13 (9.1)	0.82 (0.32–2.04)	0.78 (0.31–1.95)
	Not received	Higher (> 22 ms)	137	4 (2.9)	Ref	Ref
		Lower (≤ 22 ms)	133	13 (9.8)	3.06 (1.19–7.86)*	3.24 (1.35–8.10)*
PTSD at 6-month	Received	Higher (> 22 ms)	119	10 (8.4)	Ref	Ref
		Lower (≤ 22 ms)	144	7 (4.9)	0.54 (0.21–1.51)	0.56 (0.18–1.73)
	Not received	Higher (> 22 ms)	134	4 (3.0)	Ref	Ref
		Lower (≤ 22 ms)	130	13 (10.1)	3.61 (1.15–11.38)*	6.75 (1.53–29.79)†
PTSD at 12-month	Received	Higher (> 22 ms)	115	7 (6.1)	Ref	Ref
		Lower (≤ 22 ms)	137	6 (4.3)	0.51 (0.16–1.59)	0.58 (0.16–2.13)
	Not received	Higher (> 22 ms)	129	2 (1.6)	Ref	Ref
		Lower (≤ 22 ms)	125	9 (7.2)	3.12 (1.04–11.88)*	3.24 (1.53–10.59)*
PTSD at 24-month	Received	Higher (> 22 ms)	109	4 (3.7)	Ref	Ref
		Lower (≤ 22 ms)	126	3 (1.6)	0.44 (0.16–1.87)	0.40 (0.07–2.36)
	Not received	Higher (> 22 ms)	120	2 (1.7)	Ref	Ref
		Lower (≤ 22 ms)	118	3 (2.6)	2.18 (0.26–27.99)	1.84 (0.34–33.21)

Table 2. Interactive modifying effects of SDNN and post-injury surgical intervention status with posttraumatic stress disorder (PTSD) status in patients with physical injuries. [a]Adjusted for age, sex, education, previous psychiatric disorders, previous traumatic events, number of physical disorders, scores on Hamilton Depression Rating Scale, and heart rate. *$P < 0.05$; †$P < 0.01$.

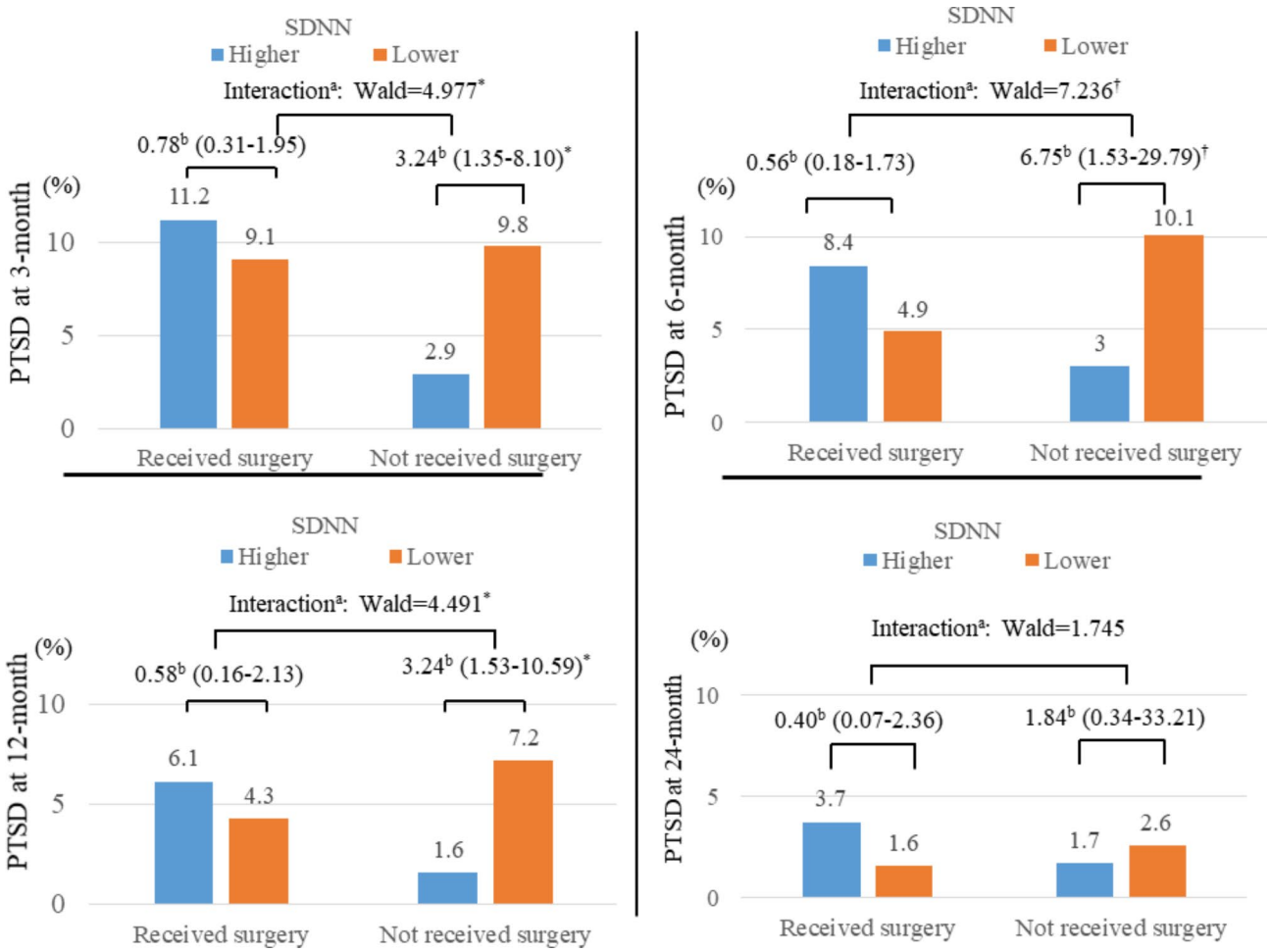

Fig. 2. Interactive modifying associations of SDNN and post-injury surgical intervention status with posttraumatic stress disorder (PTSD) at 3, 6, 12, and -24months in patients with physical injuries. [a]Interactive modifying associations of SDNN and post-injury surgical interventions on PTSD onset were estimated using multinomial logistic regression; and [b]odds ratios (95% confidence intervals) were calculated using binary logistic regression for higher (> 22 ms) vs. lower (≤ 22 ms) SDNN at baseline on development of PTSD at each follow-up, adjusted for age, sex, education, previous psychiatric disorders, previous traumatic events, number of physical disorders, scores on Hamilton Depression Rating Scale, and heart rate. $^{*}P < 0.05$; $^{\dagger}P < 0.01$.

Data availability

The data that support the findings of study are available from the corresponding author (J-M Kim) upon reasonable request.

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Author contributions

Conceptualization: J-MK. Methodology: J-MK, H-JK, JWK, SWK, ISS. Conuction of the study: J-MK, H-JK, JWK, HJ, JCK, JKJ, SWK, ISS. Statistical analysis and Interpretation: J-MK, H-JK. Writing -original draft preparation: J-MK, H-JK. Writing -review and editing: J-MK, H-JK. JWK, HJ, JCK, JKJ, JYL, SWK, ISS. Resources: J-MK. Supervision: J-MK, H-JK. JWK, HJ, JCK, JKJ, JYL, SWK, ISS. All authors contributed to the article and approved the submitted version.

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Declarations

Competing interests

The authors declare no competing interests.

Ethics statement

This study was approved by the Chonnam National University Hospital Institutional Review Board (CNUH 2015 – 148) and complied with all provisions of the Declaration of Helsinki.

Additional information

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