Prospective Cohort Study

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Autonomic function effects on postoperative sleep disorder: a prospective cohort study

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Background: Early identification of patients at risk of developing postoperative sleep disorders (PSD), which is a common complication after surgery, is an essential step in reducing surgical stress and is an important part of enhanced recovery after surgery.

Objective: In this study, we used a smart patch to explore heart rate variability (HRV), reflecting autonomic nervous system regulation, as potential PSD digital biomarkers and develop a prognostic model for the early identification of PSD.

Methods: We assessed 120 h of continuous HRV in a separate sample of 51 patients who underwent radical surgery for gastrointestinal cancer with and without PSD.

Results: By analyzing the 120-h HRV data of the two groups, we found that patients with PSD exhibited lower parasympathetic tone and longer dysregulated autonomic circadian rhythms. The area under the curve of the risk factor prediction model established by HRV parameters was 0.815; sensitivity was 0.909; specificity was 0.621; and the Youden index was 0.530.

Conclusion: This research supports the utility of HRV as a non-invasive diagnostic tool, emphasizing its importance in perioperative management of sleep quality and potential to expand its use during the perioperative period.

Keywords: autonomic nervous system, digital biomarker, enhanced recovery after surgery, heart rate variability, postoperative sleep disorder

Introduction

Background

sleep, a vital physiological process regulated by circadian rhythms and autonomic nervous system (ANS) activity, plays a pivotal role in tissue repair, immune function, and cognitive recovery[1]. However, the perioperative period, marked by surgical trauma, anesthesia exposure, and environmental disruptions, often destabilizes these regulatory mechanisms, leading to transient or prolonged sleep disturbances, a condition termed postoperative sleep disorders (PSD)[2]. Increased evidence suggests that PSD is a significant risk factor for adverse outcomes, including delirium, prolonged hospitalization, and impaired functional recovery[3]. Despite its clinical relevance, the pathophysiology and management of PSD remain poorly understood, underscoring the need for interdisciplinary research to bridge this knowledge gap.

Due to the lack of suitable indicators and measurement tools, it is still difficult to objectively diagnose and assess postoperative sleep quality at present. Autonomic function changes during different sleep stages are marked by a higher parasympathetic tone during non-rapid eye movement sleep (REM) and sympathetic predominance during REM[4,5]. But it still lacks clinical studies correlating perioperative autonomic tone measured with PSD. Therefore, continuous assessment of autonomic balance through sympathetic tone monitoring may serve as a valuable predictive biomarker for identifying high-risk individuals prone to PSD.

Recent advancements in wearable technology and digital medicine have facilitated the development of patches designed for long-term heart rate variability (HRV) monitoring, enabling real-time

HIGHLIGHTS

- Smart patches link heart rate variability (HRV) to postoperative sleep disorders as a novel digital biomarker.
- Postoperative sleep disorder (PSD) patients show lower parasympathetic tone and prolonged autonomic dysregulation.
- HRV parameters establish a PSD prediction model with an area under the curve of 0.815.
- HRV offers non-invasive monitoring for perioperative sleep quality management.

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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visual assessment of fluctuations in autonomic nerve tone. In this study, we used a smart HRV patch to explore the mechanisms of autonomic function in PSD and establish HRV parameters as potential digital biomarkers for predicting PSD. Understanding these mechanisms could lead to more effective interventions, improving postoperative recovery and reducing associated complications. Future research should focus on developing comprehensive, evidence-based approaches to address PSD, ultimately enhancing patient outcomes and reducing healthcare burdens.

Material and methods

Participants

This single-center and prospective cohort study recruited patients who underwent Da Vinci robotic/laparoscopic radical surgery for gastrointestinal cancer between September 2020 and December 2022. All patients were managed perioperatively in the enhanced recovery after surgery (ERAS) programs (preoperative patient education, no intestinal preparation for non-constipated patients, preoperative oral carbohydrate administration, multimodal analgesia, avoidance of perioperative fluid overload, no routine use of nasogastric tubes, and early oral feeding)[6]. All patients were treated by the same team. The study was approved by the hospital's Institutional Review Boards. Written informed consent was obtained from all patients prior to enrollment. All patients were asked to complete the same Pittsburgh Sleep Quality Index (PSQI) questionnaire during the clinical follow-up visits at 6 months postoperatively. This retrospective study has been reported in line with the STROCSS criteria[7].

Inclusion criteria

Inclusion criteria were as follows: (1) gastrointestinal malignant tumor diagnosed by biopsy; (2) clinical stage T1-4A, N0-3, M0; (3) receiving laparoscopic or robotic surgery; (4) American Society of Anesthesiologists (ASA) grades I–III; (5) intraoperative continuous infusion, fentanyl and propofol maintained anesthesia; and (6) age >18 years old.

Exclusion criteria

Exclusion criteria were as follows: (1) emergency surgery; (2) combined major visceral resection or palliative surgery; (3) postoperative pathological examination diagnosed benign tumors, gastrointestinal stromal tumors, etc.; (4) history of severe cardiac and neurological related diseases; and (5) PSQI score > 5 before hospitalization.

Shedding criteria

Shedding criteria were as follows: (1) adverse reactions such as redness and skin rash and (2) incomplete data and presence of artifacts.

Measurement

PSQI

The PSQI is a validated, self-administered sleep quality assessment questionnaire. It provides an accessible and reliable tool for evaluating sleep patterns, with a reliability coefficient of 0.82–0.83[8]. A PSQI score above 5 indicates poor sleep quality, with a sensitivity of 89.6% and a specificity of 86.5%[9].

Smart HRV patch

The smart HRV patch with the recorder (Fig. 1a) and three ECG electrodes inside, considered the gold standard for HRV monitoring[10], can continuously record 120 h of ECG for HRV analysis (Fig. 1b). The researchers cleaned the skin of the precardiac area and attached the registered smart HRV patch (THOTH, http://www.thothhealth.com) to the skin in the shape of T (Fig. 1c). Then, the full course heart rate and HRV were monitored from the preoperative day (Pre) to postoperative day 3 (POD3). After data collection, the information was uploaded automatically through the gateway (Fig. 1d) to the cloud (Fig. 1e) and analyzed by the Holter System software (Fig. 1f). Patients fitted with HRV patches were continuously monitored for 120 h from the Pre to POD3 (Fig. 2).

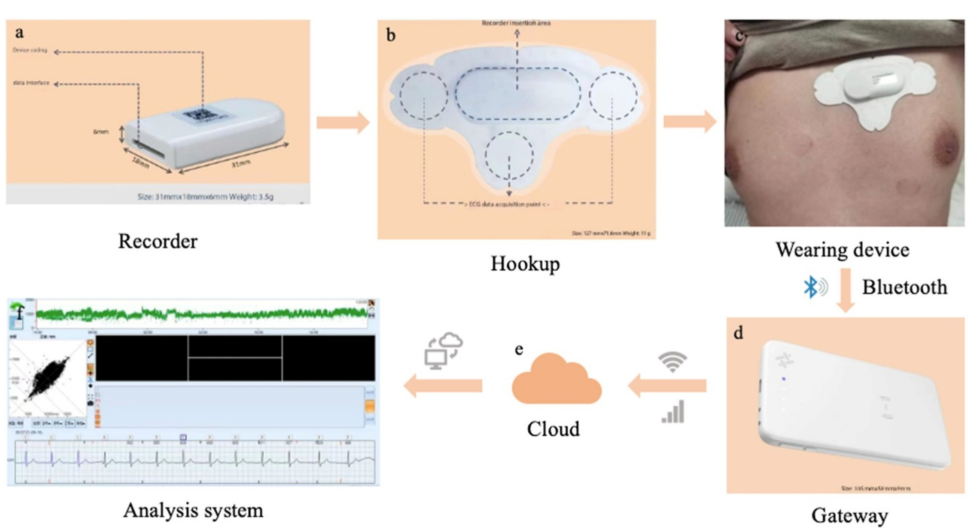

Figure 1. Smart HRV patch.

HRV analysis

In this study, HRV was analyzed using time domain and frequency domain methods, which are widely used in clinical practice for their computational simplicity and interpretability[11]. The time-domain parameters comprised percentage of difference between adjacent normal R–R intervals exceeding 50 ms (pNN50), standard deviation of all NN intervals (SDNN), standard deviation of 5 min average normal R–R intervals (SDANN), mean of the standard deviation of all NN intervals for all 5-min segment (SDNN IDX), and frequency domain (Fig. 2). The frequency domain parameters included: low frequency (LF), high frequency (HF), and LF/HF. PNN50 and HF are associated with parasympathetic nervous system (PNS) activity[12]. SDNN, SDANN, and LF, influenced by both sympathetic and PNSs, indicate the overall regulatory capacity of the sympathetic and PNSs, but SDANN and LF mainly reflect the sympathetic tone. SDNN IDX is negatively correlated with the tension level of the sympathetic nerve. LF/HF reflects the balance between sympathetic nervous system activity and PNS activity[13,14].

Consumer sleep-tracking device

Consumer sleep-tracking devices, which are promising potential alternatives to the current mobile sleep monitoring standard of actigraphy, show excellent validity and reliability when compared with polysomnography[15]. The consumer sleep-tracking device (HUAWEI Band 4, Huawei Device Co., Ltd, Dongguan, China)

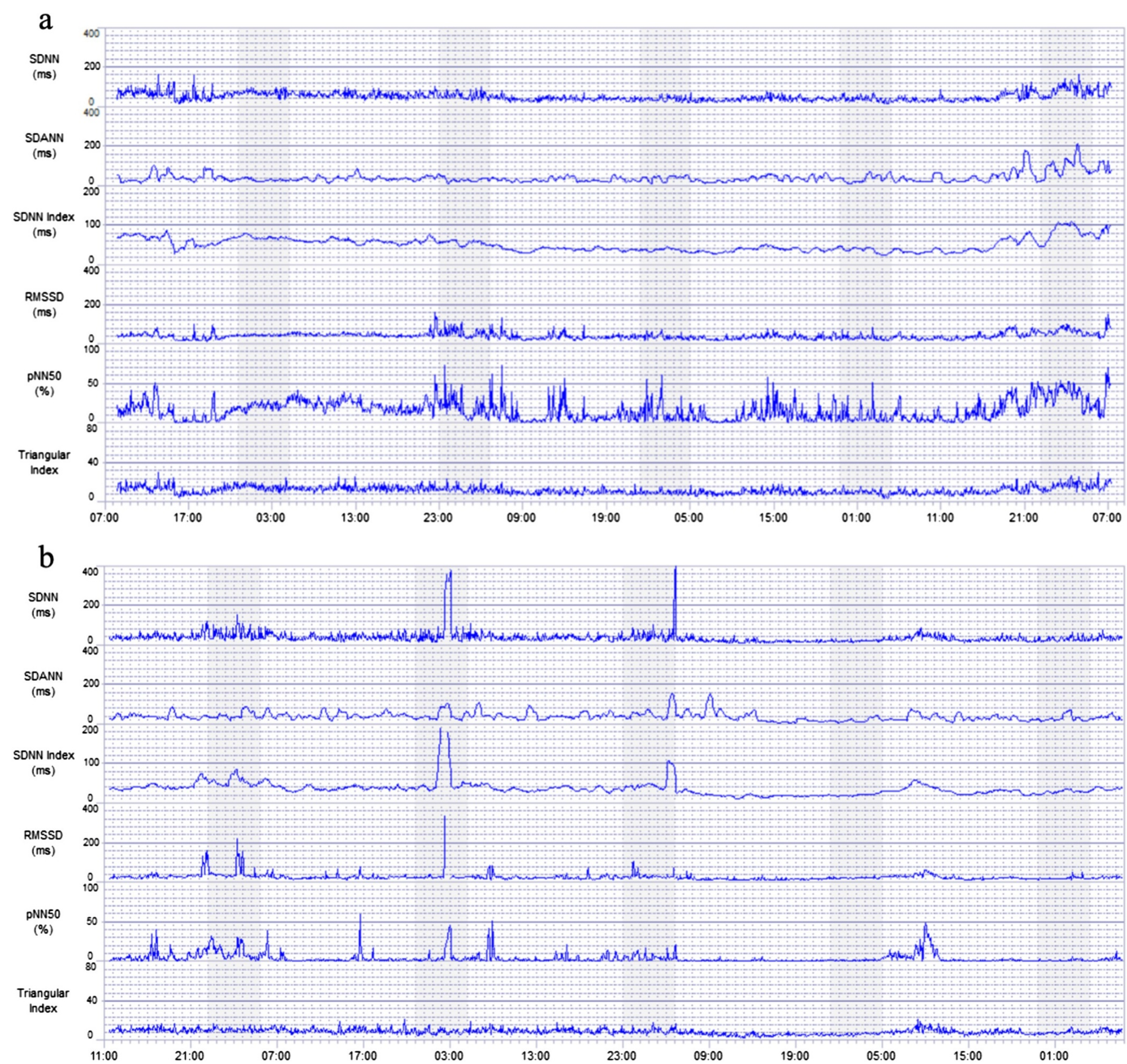

Figure 2. 120 h HRV trend charts of patients in the normal sleep group (a) and the insomnia group (b).

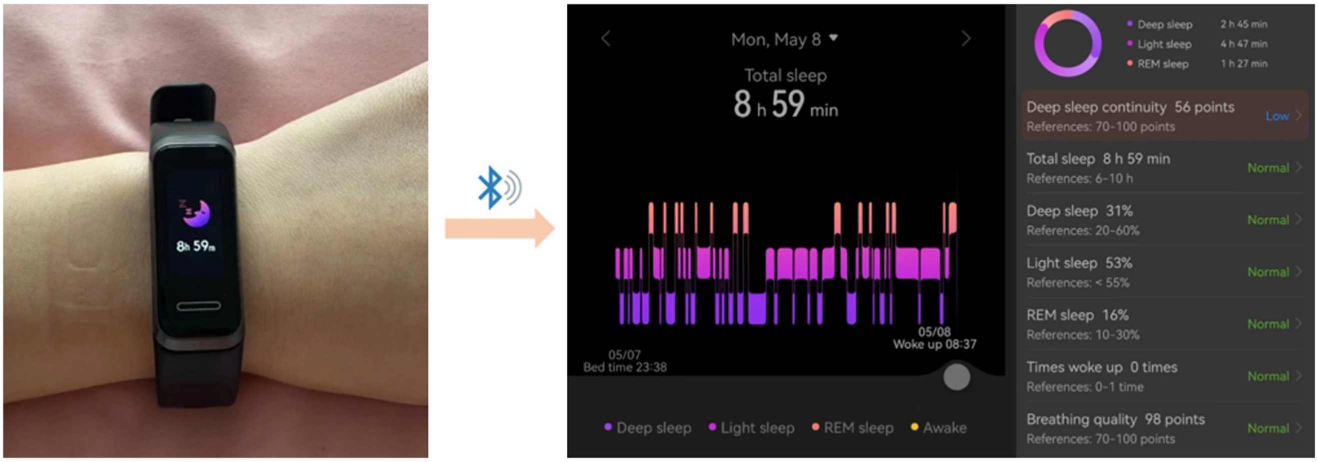

Figure 3. Consumer sleep-tracking device.

used in this study can present recorded data in digital and pictorial forms by transferring to smart devices via Bluetooth (Fig. 3).

Statistical analysis

Statistical analyses were performed using SPSS 26.0 (SPSS, Inc., Chicago, IL, USA) and GraphPad Prism software (version 10.1.1). Normally distributed data are expressed as the mean ± SD. Paired *t*-tests were used for comparisons within the normally distributed groups. An independent two-sample *t*-test was used for intergroup comparison. Non-normally distributed data are expressed as the median (25th–75th percentile), *M* (Q1, Q3). Taking into account the high variability of the HRV parameters, we used the median and interquartile range to describe them. The Wilcoxon rank-sum test was used for measurement data that did not conform to a normal distribution. A chi-squared test or Fisher's exact test was used for categorized data as appropriate. Receiver operating characteristic (ROC) curves were drawn, and the predicted value of the linear predictor of the model was used as a variable for the area under the curve (AUC) calculation. $P < 0.05$ was considered statistically significant.

Results

We assessed 81 patients for eligibility to participate in this study initially. Among them, nine patients did not meet the inclusion criteria. The remaining 72 patients were enrolled in the study. Later, 21 patients were excluded because of adverse reactions

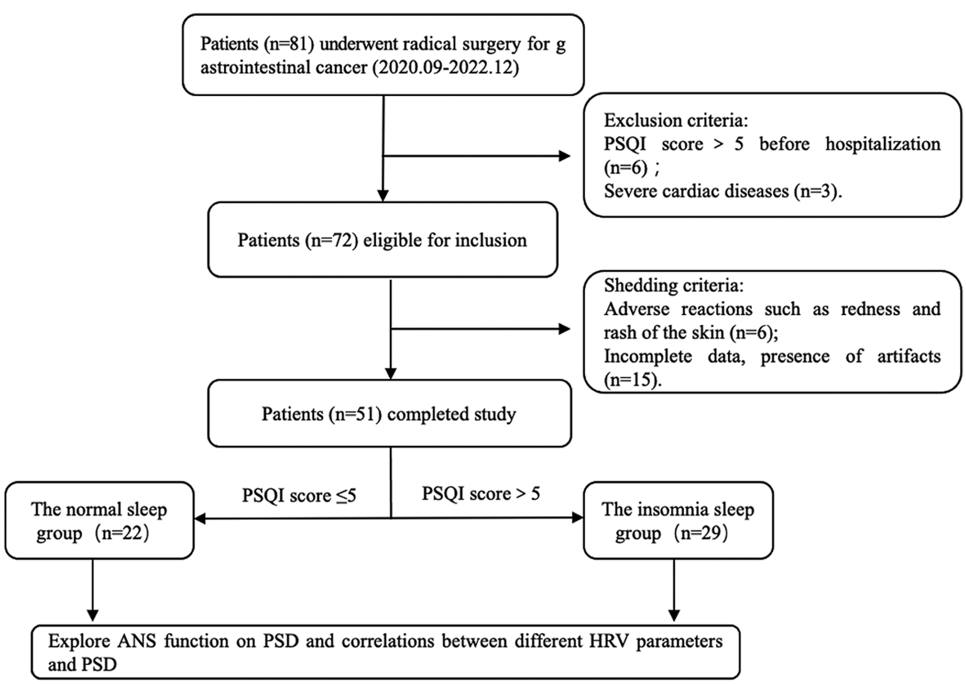

Figure 4. Study flow diagram.

such as redness and rash of the skin, incomplete data, or presence of artifacts. The recruitment and follow-up of the trial participants are presented in Figure 4.

Characteristics of enrolled subjects

After the 120-h continuous monitoring period, 22 patients' PSQI scores were ≤5 (normal sleep group), with the others' (insomnia group) PSQI scores being >5. The incidence of postoperative sleep disturbance was 43.137% (22/51).

As shown in Table 1, no significant differences were found between the two groups in the age, gender, BMI, surgical site, surgical method, operative time, operative period, pathologic stage, postoperative hospital days, postoperative complications, and tumor size ($P > 0.05$). Patients in the insomnia group were more likely to be transferred to the intensive care unit (ICU) postoperatively ($P = 0.012$) than those in the normal sleep group. Sleep disorders were noted in patients on the night of surgery (5/22), POD1 (8/22), POD2 (6/22), and POD3 (9/22). Of the 22 patients with sleep disorders, six patients developed 2-day sleep disturbance postoperatively, four patients developed 3-day sleep disturbance, and two patients remained suggestive of sleep disturbance at the 6-month postoperative follow-up.

Table 1

Baseline characteristics of the patients

Variables	Normal sleep group (n = 29)	Insomnia group (n = 22)	t/χ^2	P-value
Age (year)	62.28 ± 10.54	63 ± 11.06	0.494	0.198
Gender			0.639	0.424
Male	18	16		
Female	11	6		
BMI (kg/m^2)	23.76 ± 3.3	24.53 ± 3.63	0.844	0.585
Surgical site			1.58	0.812
Proximal stomach	6	2		
Distal stomach	4	4		
Whole stomach	6	4		
Colon	5	4		
Rectum	8	8		
Surgical method			0.028	0.737
Da Vinci Robert	22	18		
Laparoscopic	7	4		
Operative time (min)	255 (220, 280)	242.5 (218.75, 276.25)	−0.314	0.753
Operative period			0.473	0.492
Mourning	11	14		
Afternoon	13	13		
ICU			6.297	0.012*
No	25	12		
Yes	4	10		
Pathologic stage			3.519	0.172
I	11	6		
II	13	7		
III	5	9		
Tumor size (cm)	3.8 (2.2, 5.75)	3.4 (1.8, 4.6)	−1.458	0.145
Postoperative hospital days	6 (5, 7)	6.5 (6, 8)	1.127	0.26
Complications			0.64	0.383
None	27	18		
Grade II	2	4		

*P < 0 .05.

Table 2

Nocturnal (22:00–6:00 the next day) HRV parameters of the patients in the normal sleep and insomnia groups

Variables	Normal sleep group (n = 29)	Insomnia group (n = 22)	t/χ^2	P-value
Preoperative day				
pNN50 (%)	4.13 (1.73, 8.42)	3.47 (2.1, 7.5)	−0.428	0.669
SDNN (ms)	90.58 (76.97, 121)	100 (80, 120.75)	0.599	0.549
SDANN (ms)	70 (58.29, 100)	77.5 (65, 87.25)	0.266	0.79
SDNN IDX (ms)	47.88 (35.5, 61)	50.5 (41.25, 63.5)	1.037	0.3
LF (ms^2)	313 (212.65, 557.18)	327.75 (221.5, 708)	−0.257	0.797
HF (ms^2)	232.4 (177.41, 401.65)	231.78 (93, 552.28)	−0.723	0.47
LF/HF	1.16 (0.71, 1.83)	1.65 (0.92, 2.82)	1.911	0.056
Surgery day				
pNN50 (%)	5.21 (0.68, 16.81)	1.99 (1.09, 9.32)	−1.046	0.296
SDNN (ms)	56.75 (47.83, 70.5)	52 (43.63, 81.5)	−0.675	0.499
SDANN (ms)	34 (28.36, 50.5)	39.5 (27,53.5)	−0.038	0.97
SDNN IDX (ms)	40 (24.75, 58.89)	38.43 (25.5, 56.25)	−0.114	0.909
LF (ms^2)	388 (134.51, 894.5)	371.97 (132.47, 906.93)	−0.133	0.894
HF (ms^2)	392.62 (164.5, 716.5)	225.835 (104.75, 497.5)	−1.369	0.171
LF/HF	0.97 (0.65, 1.33)	1.315 (1.01, 2.30)	2.739	0.006**
Postoperative day 1				
pNN50 (%)	9.66 (1.21, 15.56)	3.94 (0.61, 7.84)	−2.111	0.035*
SDNN (ms)	70.76 (54, 97.5)	68.5 (58.93, 82.5)	−0.2	0.842
SDANN (ms)	46.03 (32.5, 68)	51 (46.25, 59)	1.065	0.287
SDNN IDX (ms)	47.25 (32.96, 64.5)	41.5 (34, 49.5)	−0.98	0.327
LF (ms^2)	342 (193, 813.8)	357.65 (261.11, 763)	−0.342	0.732
HF (ms^2)	437.66 (211.83, 691.31)	199.56 (122.3, 315.25)	−2.71	0.007**
LF/HF	0.93 (0.64, 1.39)	1.46 (0.91, 4.28)	3.148	0.002**
Postoperative day 2				
pNN50 (%)	5.46 (2.53, 14.52)	3.55 (1.23, 8.46)	−1.179	0.238
SDNN (ms)	79.64 (63.95, 113.94)	82 (65.25, 92.25)	−0.285	0.775
SDANN (ms)	56.28 (41, 89.83)	55 (43.5, 72)	−0.247	0.805
SDNN IDX (ms)	48.86 (41, 65.5)	50 (37.94, 60.25)	−0.447	0.655
LF (ms^2)	514.81 (213.23, 1021)	392 (223.13, 533.43)	−0.666	0.506
HF (ms^2)	376 (206.49, 766)	225.66 (120.25, 422.83)	−2.453	0.014*
LF/HF	0.99 (0.67, 1.39)	1.61 (0.98,2.77)	3.072	0.002**
Postoperative day 3				
pNN50 (%)	9.03 (3.68, 10.97)	3.18 (1.05, 9.63)	−2.187	0.029*
SDNN (ms)	80 (70.91, 104)	77.49 (61.75, 100)	−0.685	0.493
SDANN (ms)	61 (46.83, 83.64)	57.04 (45.25, 68.25)	−0.732	0.464
SDNN IDX (ms)	50 (42, 62)	46 (38, 69.5)	−0.618	0.536
LF (ms^2)	454.61 (180.5, 808)	397.25 (217.5, 634.23)	−0.456	0.648
HF (ms^2)	402 (238.4, 746.51)	232.14 (97.75, 300.78)	−3.195	0.001**
LF/HF	0.84 (0.76, 1.28)	2.2 (1.47, 2.84)	3.728	0.001***

*P < 0 .05.
**P < 0 .01.
‡P < 0.001.

Comparison of HRV parameters in different time periods

After continuous monitoring of 51 patients' HRV parameters during the perioperative period for 120 h for data analysis, no significant difference was found in all HRV parameters between both groups at Pre ($P > 0.05$). Among the nocturnal (22:00–6:00 the next day) HRV parameters, LF/HF was significantly higher in the insomnia group than in the normal sleep group at surgery day, POD1, POD2, and POD3, while pNN50 in the insomnia group was statistically lower than that in the normal sleep group at POD1 and POD3. HF in the insomnia group was statistically lower ($P < 0.05$) than that in the normal sleep group at POD1, POD2, and POD3. Among the daytime (6:00–22:00) HRV parameters, SDNN, SDANN, SDNN IDX, and LF were not significantly different between the two groups. LF/HF was significantly higher in the insomnia group than in

Table 3

Daytime (6:00–22:00) HRV parameters of the patients in the normal sleep and insomnia groups

Variables	Normal sleep group (*n* = 29)	Insomnia group (*n* = 22)	t/χ^2	*P*-value
Preoperative day				
pNN50 (%)	2.96 (1.16, 8.11)	2.11 (1.35, 5.99)	−0.552	0.581
SDNN (ms)	85 (75.11, 102.5)	82.5 (69, 103.73)	−0.495	0.621
SDANN (ms)	75.93 (54.5,108)	70 (51.65, 86.5)	−0.923	0.356
SDNN IDX (ms)	41 (35, 51.84)	43 (35, 52)	0.105	0.917
LF (ms^2)	226.5 (158.33, 405)	232.85 (152.85, 401.95)	0.048	0.962
HF (ms^2)	181.9 (102, 336.18)	184 (92, 280.7)	−0.685	0.494
LF/HF	1.44 (0.77, 1.93)	1.62 (0.89, 2.13)	0.675	0.5
Surgery day				
pNN50 (%)	2.96 (1.16, 8.11)	2.11 (1.35, 5.99)	−0.903	0.366
SDNN (ms)	120.47 (98, 134.66)	116.5 (97.25, 144.16)	0.418	0.676
SDANN (ms)	114 (87.25, 126)	111 (93.75, 143.25)	0.333	0.739
SDNN IDX (ms)	42 (30, 55.86)	36.81 (32, 43.5)	−0.79	0.43
LF (ms^2)	352 (167, 641.45)	349 (172.17, 519)	−0.342	0.732
HF (ms^2)	227.24 (122.64, 653.5)	197.82 (108.07, 317.25)	−1.35	0.177
LF/HF	1.37 (0.81, 1.64)	1.65 (1.24, 2.29)	2.397	0.017*
Postoperative day 1				
pNN50 (%)	9.66 (1.21, 15.56)	3.94 (0.61, 7.84)	−1.483	0.138
SDNN (ms)	79.94 (53.22, 101)	69.5 (53, 92.5)	−0.847	0.397
SDANN (ms)	65.17 (46.55, 88)	56 (43.13, 83.75)	−0.732	0.464
SDNN IDX (ms)	39.51 (26.5, 58.1)	34 (25.5, 40.25)	−1.227	0.22
LF (ms^2)	250 (143.23, 751.86)	243.91 (110.97, 491.2)	−0.799	0.424
HF (ms^2)	231 (172.69, 524)	137.54 (92.75, 233.45)	−2.558	0.011*
LF/HF	1.16 (0.71, 1.52)	1.52 (1.02, 2.15)	2.064	0.039*
Postoperative day 2				
pNN50 (%)	3.75 (0.73, 9.22)	2.29 (1.12, 4.83)	−0.875	0.382
SDNN (ms)	81 (61, 93)	73.87 (59.78, 90.5)	−0.723	0.47
SDANN (ms)	61 (50.5, 76.45)	57.5 (40, 75.5)	−0.837	0.403
SDNN IDX (ms)	38.2 (29.61, 55.32)	38 (36, 45.25)	0.285	0.775
LF (ms^2)	284.73 (182, 740)	303.35 (212.5, 467.15)	0	1
HF (ms^2)	272.88 (164, 489.5)	181 (93, 257.37)	−2.187	0.029*
LF/HF	1.31 (0.75, 1.6)	1.84 (1.26, 2.77)	2.996	0.003**
Postoperative day 3				
pNN50 (%)	6.99 (1.34, 9.47)	2.15 (0.42, 5.5)	−2.206	0.027*
SDNN (ms)	90.4 (66.34, 107.5)	80.5 (67.75, 93.25)	−1.151	0.25
SDANN (ms)	77 (50.5, 89.06)	69 (50.29, 82.75)	−0.827	0.408
SDNN IDX (ms)	44.68 (35.23, 55.5)	38.5 (34.75, 46)	−1.313	0.189
LF (ms^2)	292.81 (172, 514.29)	386.78 (173.79, 644.59)	0.647	0.518
HF (ms^2)	259.78 (169, 492)	176.94 (105.75, 270.93)	−2.14	0.032*
LF/HF	1.2 (0.9, 1.56)	2.31 (1.44, 3.42)	3.89	0.001***

*$P < 0\ .05$.
**$P < 0\ .01$.
***$P < 0.001$.

the normal sleep group at POD1, POD2, and POD3 ($P < 0.05$), while pNN50 in the insomnia group was statistically lower than that in the normal sleep group at surgery day and POD2. HF in the insomnia group was statistically lower than that in the normal sleep group at POD1, POD2, and POD3.

Compared with the normal sleep group, among 120 h HRV parameters, pNN50, SDANN, SDNN IDX, and LF were not significantly different between the two groups. LF/HF was significantly higher in the insomnia group than in the normal sleep group, while SDNN and HF in the insomnia group were statistically lower than those in the normal sleep group.

All results are summarized in Tables 2–4 and shown in Figures 5 and 6.

Binary logistic regression analysis on risk factors of PSD

Given that the observed differences in the LF/HF ratio are predominantly influenced by variations in HF, while LF remains relatively stable, we concentrated exclusively on HF for diagnostic evaluation within the frequency domain indicators. Finally, in the multivariable logistic regression model, considering the collinearity between some variables, 14 variables were identified as independent variables: 120 h pNN50, 120 h SDANN, 120 h SDNN, 120 h HF, POD1,3 nocturnal pNN50, surgery daytime pNN50, POD2,3 daytime pNN50, POD1–3 daytime HF, and POD1–3 nocturnal HF ($P < 0.10$). After binary logistic regression (backward LR algorithm), three variables

Table 4

120 h HRV parameters of the patients in the normal sleep and insomnia groups

Variables	Normal sleep group (n = 29)	Insomnia group (n = 22)	t/χ^2	P-value
pNN50 (%)	5.69 (2.82, 10.34)	3.65 (1.31, 7.15)	−1.931	0.054
SDNN (ms)	126 (113.43, 138.5)	101 (96.5, 126.5)	−2.626	0.009**
SDANN (ms)	119 (99.5 135.47)	96 (90.25, 112.25)	−2.645	0.008*
SDNN IDX (ms)	42.42 (36.5, 57.37)	39.93 (36, 45.75)	−0.961	0.337
LF (ms^2)	335.21 (224.11, 686.93)	375.73 (260.8, 555.75)	−0.133	0.894
HF (ms^2)	338.12 (190, 544.62)	180.74 (128, 308.59)	−2.739	0.006**
LF/HF	1.12 (0.9, 1.31)	1.91 (1.37, 2.69)	4.641	0.000****

*P < 0 .05.
**P < 0 .01.
****P < 0.001.

retained diagnostic significance for PSD. The regression equation was as follows: Logit(P) = 6.101 – 0.043 * 120 h SDANN – 0.009 * POD2 daytime HF + 0.552 * POD2 daytime pNN50, and statistical significance was found in the regression equation. The Hosmer–Lemeshow fit index was P > 0.05, indicating good matching in this equation. 120 h SDANN, surgery daytime

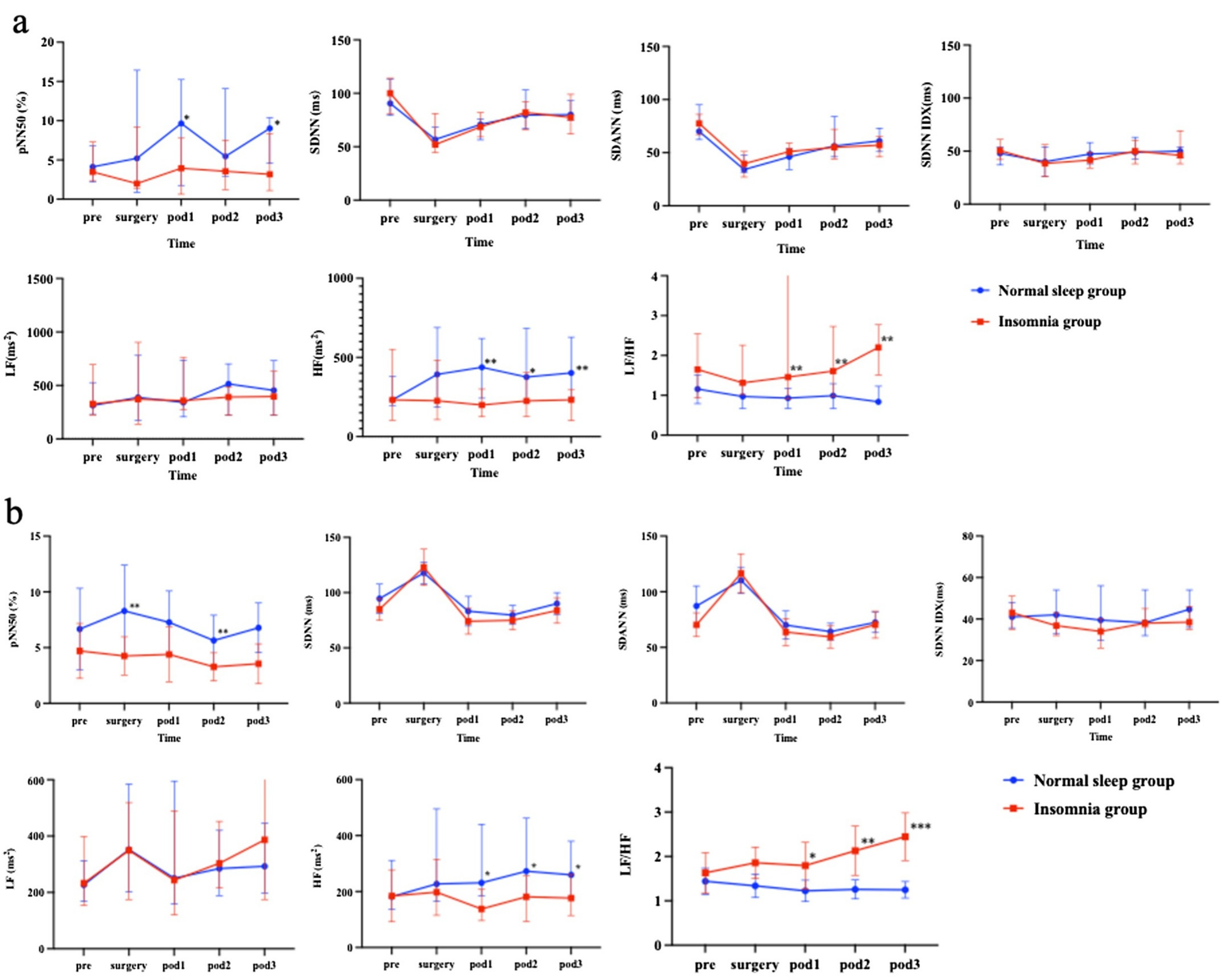

Figure 5. Nocturnal (a) and daytime (b) HRV parameters of patients in the normal sleep and insomnia groups. Data were presented as median ± 95% CI. *P < 0.05, **P < 0 .01, ***P < 0.001.

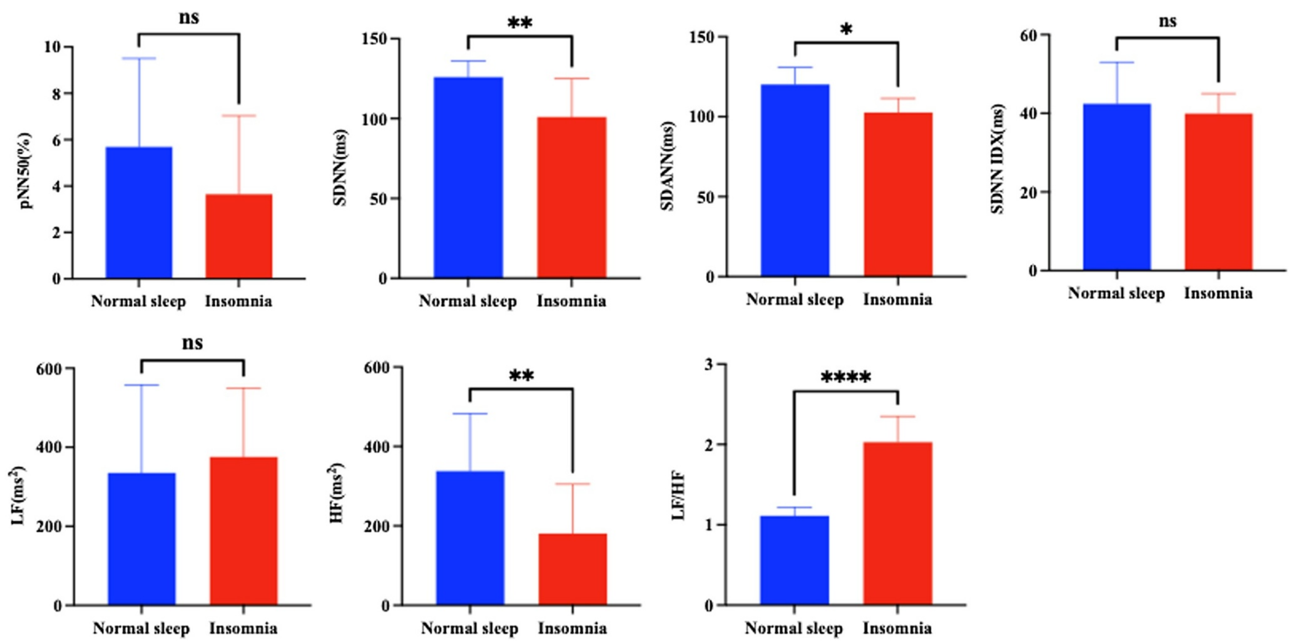

Figure 6. 120 h HRV parameters of patients in the normal sleep and insomnia groups. Data were presented as median ± 95% confidence interval. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, ****$P < 0.0001$.

pNN50, POD2,3 daytime pNN50, and POD2 daytime HF were independent risk factors for PSD in patients undergoing radical surgery for gastrointestinal cancer. The results are summarized in Table 5.

Determination of the best models for diagnosing PSD

The ROC curve for predicting PSD in patients undergoing radical surgery for gastrointestinal cancer are summarized in Table 6 and are displayed in Figure 7. Among the three single indicators, 120 h SDANN had the best diagnostic efficacy based on the area under the ROC curve, sensitivity, and specificity of the diagnosis. The two-joint indicator with the best diagnostic efficacy was POD2 daytime HF + 120 h SDANN. The multiple-joint indicator with the best diagnostic efficacy was 120 h SDANN + POD2 daytime HF + surgery daytime pNN50 + POD2 daytime pNN50 + POD3 daytime pNN50. The AUC of the 120 h SDANN was 0.718 [95% confidence interval (CI): 0.573–0.862, $P < 0.001$][16]. With the largest Youden index, sensitivity was 0.7 and specificity 0.966, corresponding to 0.5 as the cutoff. The AUC of 120 h SDANN + POD2 daytime HF was 0.785 (95% CI: 0.661–0.909, $P < 0.001$). With the largest Youden index, sensitivity was 0.909 and specificity 0.828. The AUC of 120 h SDANN + POD2 daytime HF + surgery daytime pNN50 + POD2 daytime pNN50 + POD3 daytime pNN50 was 0.815 (95% CI: 0.701–0.929, $P < 0.0001$). With the largest Youden index, sensitivity was 0.909 and specificity 0.621.

In summary, our results found that patients with PSD exhibited lower parasympathetic tone and longer dysregulated autonomic circadian rhythms. The feasibility of HRV as a digital biomarker to predict PSD was confirmed by 120 h long-term HRV measurement in surgical patients during the perioperative

Table 5

Binary logistic regression analysis on risk factors of PSD

Variable	β	SE	Ward	Sig.	OR	95% confidence interval Lower limit	Upper limit
120 h SDANN	−0.043	0.017	6.099	0.014	0.958	0.926	0.991
Surgery daytime pNN50	−0.087	0.064	1.851	0.174	0.917	0.809	1.039
POD3 daytime pNN50	0.052	0.263	4.392	0.036	1.736	1.036	2.908
POD3 daytime pNN50	−0.188	0.134	1.972	0.16	0.828	0.637	1.077
POD2 daytime HF	−0.009	0.005	3.979	0.046	0.991	0.982	1
Constant	6.101	2.096	8.478	0.004	446.519		

SE = Standard error; sig. = level of significance; OR = odds ratio.
*$P < 0.05$.
**$P < 0.01$.

Table 6

Multifactorial analysis of each factor and ROC curve results of the joint diagnostic model

Variable	AUC	SE	P	Sensitivity	Specificity	Youden	Cutoff
120 h SDANN	0.718	0.074	0.008***	0.621	0.773	0.394	109.44
POD2 daytime HF	0.574	0.08	0.366	0.517	0.818	0.335	267.44
Surgery daytime pNN50	0.572	0.08	0.382	0.276	1	0.276	12.255
POD2 daytime pNN50	0.682	0.076	0.027*	0.345	0.909	0.254	7.195
POD3 daytime pNN50	0.680	0.074	0.029*	0.517	0.818	0.335	6.38
120 h SDANN + POD2 daytime HF	0.785	0.063	0.001***	0.773	0.69	0.463	0.438
120 h SDANN + POD2 daytime HF + surgery daytime pNN50 + POD2,3 daytime pNN50	0.815	0.058	0.000****	0.909	0.621	0.53	0.33

*$P < 0.05$.
***$P < 0.001$.
****$P < 0.0001$.

period. In addition, the high variability of HRV supports its wider and timely application in perioperative health monitoring.

Discussion

PSD belongs to the category of acute sleep disorders, which are associated with increased sympathetic outflow, irregularity of the ANS, and dysregulation of the hypothalamic–pituitary–adrenal axis[17]. Therefore, we used a smart HRV patch, smart actigraphy, and PSQI in this study to obtain 120 h HRV and sleep data, and then comprehensively understand the perioperative autonomic nerve activity and sleep quality of patients.

As the results showed, there was no statistically significant difference in general clinical data and preoperative HRV parameters between the two groups ($P > 0.05$), indicating comparability. Anesthesia and surgery significantly disrupted HRV data, affecting both time-domain and frequency-domain parameters in both groups. The disruption manifested as significant increase of SDNN and SDANN at daytime and significant decrease at night, and gradually recovered to preoperative levels at POD1–3. LF/HF (night and daytime) was significantly higher in the insomnia group than in the normal sleep group at POD1–3. These results indicated that surgery and anesthesia have disrupted the balance of ANS. With rehabilitation, the balance also gradually recovered. In addition, we found that preoperative daytime LF/HF was higher than preoperative nocturnal LF/HF in the normal sleep group, and LF/HF was gradually reduced at POD1–3, which may correlate with postoperative sleepiness. Otherwise, preoperative daytime LF/HF was basically the same with preoperative nocturnal LF/HF in the insomnia group, and LF/HF was gradually increase at POD1–3. The circadian rhythm of LF/HF in both groups did not recover at POD3, suggesting that circadian rhythm disorder of ANS induced by general anesthesia and surgery may play an important role in PSD mechanisms.

Our study results found no significant difference in LF and SDNN IDX (night, daytime, and 120 h) during perioperative period between the two groups. However, 120 h SDNN, 120 h SDANN, nocturnal pNN50 at POD1,3, and HF at POD1–3 were significantly lower in the insomnia group compared with the normal sleep group, suggesting that the PNS activity, especially the vagus nerve, had an impact on the sleep quality at night. With postoperative rehabilitation, the pNN50 in the sleep normal group was restored to the preoperative level and increased at POD3, while the pNN50 in the insomnia group basically returned to the preoperative stage. These results proved that good sleep and rest are important for the recovery of ANS, which might benefit from our ERAS program. Vagus nerve is the longest nerve of the ANS and the key component of PNS[18]. In a previous study, we applied transcutaneous electrical acupoint stimulation in the perioperative period and successfully improved postoperative sleep quality, reduced postoperative pain, and alleviated postoperative

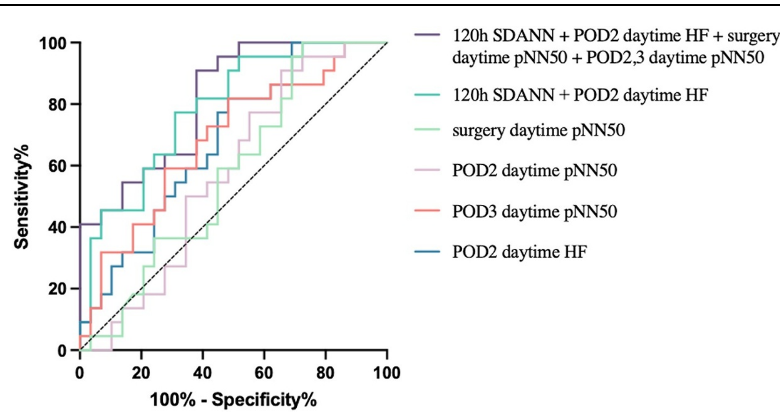

Figure 7. The results of ROC curves for multi-factor regression analysis of risk factors and joint model.

adverse effects in patients who underwent laparoscopic gastrointestinal tumor surgery resection[19]. In this study, the 120 h SDANN model exhibited the best performance for single-model prediction, whereas the 120 h SDANN + POD2 daytime HF + surgery daytime pNN50 + POD2 daytime pNN50 + POD3 daytime pNN50 model exhibited the greatest AUC among the models we tested. These results showed that HRV has potential as a digital biomarker that can help predict PSD and may prove useful in clinical management during the perioperative period.

Several studies suggested that HRV may provide insights into acute pain, inflammation, and other perioperative complications that may be difficult to predict in clinic[20–22]. Our previous study also demonstrated that HRV is a more precise indicator of postoperative stress compared to cortisol, enabling surgeons to comprehensively and accurately assess changes in surgical stress among patients[23]. Although advances in anesthesia and the development of minimally invasive operations have made day surgery a viable and safe option, the risk of adverse events remains, many of which are potentially preventable[24]. Therefore, measurement of HRV based on remote measurement technology and long-range monitoring should become part of perioperative routine monitoring, which can help patients obtain timely medical care in case of complications or problems developed at home.

However, our study does have some limitations. The small sample size may be the first limitation. Future research in larger study populations is required to establish the value of HRV as a predictive clinical tool. Meanwhile, the insomnia cohort showed a higher proportion of advanced pathological stages ($P > 0.05$) and increased ICU transfers ($P < 0.05$), possibly resulting in a biased result. Second, the low completion rate, which is approximately only 70%, in this study was primarily due to the material of the HRV patch. Although we have used skin-friendly and breathable materials, it is still inevitable to produce sweat and cause allergic reactions, leading to data artifacts, skin allergy, and subsequent high dropout rate.

Conclusion

PSD, a common complication after surgery, is associated with the circadian rhythm of ANS and the PNS activity, especially the vagus nerve. Providing surgery patients with preoperative vagal reinforcement as a part of prehabilitation might be a beneficial strategy against PSD. HRV based on remote measurement technology and long-range monitoring is a convenient and effective tool for monitoring ANS activity, and has potential as a digital biomarker that can help predict PSD and may prove useful in clinical sleep management during the perioperative period.

Ethical approval

Ethical approval for this study was provided by the Ethical Committee on 23 July 2020. Ethical approval for this study was granted by the ethics committee of Jiangsu Province Hospital of Chinese Medicine (2020NL-098-02). The study protocol was registered with the Chinese Clinical Trial Registry (http://www.chictr.org.cn/index.aspx, ChiCTR2100054971). This study was conducted in accordance with the Declaration of Helsinki.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author contributions

F.Y.D., Z.L., D.Z.M., and J.Z.W. contributed to study design. F.Y.D., Z.Y., W.G., G.J.J., W.H.F., and S.M.Y. contributed to acquisition and analysis of the data. F.Y.D., Z.Y., and W.G. contributed to drafting of the manuscript. D.Z.M. and J.Z.W. contributed to critical revision of the manuscript. All authors had access to the data in the study, contributed to, and approved the final manuscript, and had final responsibility for the decision to submit for publication.

Conflicts of interest disclosure

The authors declare that they have no affiliations with or involvement in any organization or entity with any financial interest in the subject matter or materials discussed in this manuscript.

Research registration unique identifying number (UIN)

This study was registered in the Chinese clinical trial registry (ChiCTR2100054971).

Guarantor

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Provenance and peer review

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Data availability statement

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

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