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ORIGINAL RESEARCH

Association of Novel Sleep EEG Biomarkers with All-Cause Mortality in a Large Community-Based Cohort

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Background: The prognostic value of sleep depth remains poorly understood. The odds ratio product (ORP) is a novel electroencephalogram-based biomarker of sleep depth. We investigated the association between ORP-derived biomarkers and all-cause mortality in a large community-based cohort.

Methods: We analyzed 5802 Sleep Heart Health Study participants. A suite of ORP biomarkers was derived from baseline polysomnography, including mean ORP values across sleep stages, change in ORP across the night (ΔORP), interhemispheric sleep depth coherence ($ORP_{Icc\ R/L}$), and ORP architecture phenotypes. Cox proportional hazards models with false discovery rate (FDR) correction estimated mortality associations. Prognostic nomograms were constructed based on variables selected through least absolute shrinkage and selection operator (LASSO) and multivariable Cox regression.

Results: During 11.0 years of follow-up, 1305 deaths occurred. After multivariable adjustment and FDR correction, higher ORP_W (HR: 0.54, 95% CI: 0.39–0.73), ORP_{REM} (HR: 0.81, 95% CI: 0.69–0.95), ORP_{N1} (HR: 0.71, 95% CI: 0.59–0.87), $ORP_{ICC\ R/L}$ (HR: 0.49, 95% CI: 0.29–0.81), and ΔORP (HR: 0.70, 95% CI: 0.56–0.87) were associated with lower mortality risk, while higher ORP_{N3} (HR: 1.38, 95% CI: 1.06–1.81) predicted increased risk. ORP architecture phenotypes 1,2 (HR: 1.28, 95% CI: 1.06–1.56), 1,3 (HR: 1.27, 95% CI: 1.05–1.54), and 3,1 (HR: 1.48, 95% CI: 1.19–1.84) conferred higher mortality risk compared to phenotype 2,2. Nonlinear associations and threshold effects were identified for ORP_{N1}, $ORP_{ICC\ R/L}$, and ΔORP. Among ORP parameters examined, ΔORP and ORP architecture phenotypes were identified as the most important predictors through LASSO and multivariable Cox regression. Prognostic nomograms integrating these selected ORP metrics with traditional risk factors demonstrated excellent discrimination (C-index: 0.81).

Conclusion: ORP-derived biomarkers are independently associated with all-cause mortality and complement conventional sleep metrics in refining mortality risk stratification. Identified threshold effects for several ORP parameters may provide potential cutoff points for clinical intervention.

Keywords: EEG biomarkers, sleep depth, odds ratio product, all-cause mortality

Introduction

Extensive research has linked insufficient sleep duration and circadian disruption to cardiometabolic diseases, neurodegenerative disorders, and all-cause mortality.[1–4] However, the electroencephalogram (EEG) signal itself—the primary measure of brain activity during sleep—contains prognostic information that extends beyond simple sleep duration. For instance, prevalent disorders such as obstructive sleep apnea (OSA) may impact neuronal activity through intermittent hypoxia, including a slowing of the waking EEG.[5] This highlights a critical gap: while the EEG reflects neuronal activity levels and theoretically can objectively quantify sleep depth, conventional metrics such as the percentage of stage 3 non-rapid eye movement (NREM) sleep or delta power have proven insufficient for robustly quantifying this key dimension —sleep depth/intensity.[6,7] To date, it follows that traditional PSG metrics have not yet properly assessed sleep depth.

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The odds ratio product (ORP) is a novel quantitative metric derived from the relative EEG power distribution across distinct frequency bands, providing a continuous scale of sleep depth, ranging from 0 (deepest sleep) to 2.5 (full wakefulness).[7–9] Accumulating evidence validates ORP as a reliable indicator of sleep depth/intensity.[6,7,10] Since its development in 2015,[11] ORP has been widely applied in sleep research to: monitor dynamic changes during sleep restriction or deprivation;[7,12] identify arousals;[13,14] correlate with subjective sleepiness, quality-of-life measures, and cognition;[9,15–18] and assess post-arousal recovery patterns.[19,20] A key validation arises from its near-perfect correlation with the probability of spontaneous cortical arousal or awakening in the subsequent 30-second epoch.[11]

Building upon this foundation, several ORP-derived biomarkers have emerged as promising indicators of sleep architecture and neurophysiological function.[6] These include stage-specific ORP values across different sleep phases, the change in ORP across the night (ΔORP), ORP measured within the first 9 seconds following arousal events (ORP-9),[9] ORP architecture phenotypes and interhemispheric coherence measures quantified through the correlation between right and left ORP ($ORP_{ICC\ R/L}$).[21] While existing studies have primarily utilized ORP for phenotyping sleep disorders and elucidating mechanistic insights, its long-term prognostic value remains largely unexplored. The sole study exploring predictive outcomes, conducted by Ali and colleagues, reported that enhanced interhemispheric sleep depth coherence correlated with a reduced risk of motor vehicle accidents in individuals with sleep apnea.[21] This finding highlights the potential of ORP in predicting specific real-world outcomes. However, whether ORP-derived biomarkers hold broader prognostic significance for major health endpoints, such as all-cause mortality in the general population, remains a critical unanswered question. From a public health perspective, establishing this relationship could be valuable for identifying high-risk individuals who might be overlooked by conventional metrics, potentially improving population sleep health outcomes. Such findings may provide epidemiological evidence for the importance of ORP-derived biomarkers in human health and could potentially inform new approaches to sleep health management. Moreover, these objective measures might serve as potential intervention targets, possibly enabling strategies to reduce population mortality risk and enhance public health outcomes.

Against this background, we conducted a comprehensive analysis of the relationship between ORP-derived biomarkers and all-cause mortality in a large community-based cohort of middle-aged and older adults. Our primary objective was to evaluate the prognostic utility of novel sleep EEG indicators in predicting long-term survival outcomes. Additionally, to enhance the clinical utility of our findings, we developed a predictive nomogram incorporating key ORP parameters to enable practical risk stratification in general populations.

Materials and Methods

Study Populations

Data for this analysis were drawn from the Sleep Heart Health Study (SHHS), a large-scale, multicenter prospective cohort originally designed to examine the cardiovascular outcomes of sleep-disordered breathing in middle-aged and older adults.[22,23] Baseline polysomnography (PSG) data from the SHHS are publicly available through the National Sleep Research Resource (www.sleepdata.org). From an initial 6441 eligible participants identified, we excluded those who subsequently withdrew consent (n = 637) and those for whom follow-up data were unavailable (n = 2), yielding a final analytical cohort of 5802 individuals (Supplementary Figure 1). The original SHHS protocol was approved by the institutional review boards of all participating centers, and all participants provided written informed consent. This study was conducted in accordance with the tenets of the Declaration of Helsinki. The requirement for ethical approval for this secondary analysis of anonymized, publicly available data was specifically exempted by the Institutional Review Board of Guangdong Provincial People's Hospital (Approval No. KY2025-775-01), in line with Article 32 of the Chinese national legislation "Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects".

In-Home Overnight PSG and ORP Analysis

Unattended in-home PSG was conducted using Compumedics P-series portable systems, with sensors applied by certified technicians following established protocols.[24] Sleep stages were scored according to standard Rechtshaffen and Kales (R&K) criteria.[23] Detailed methodology has been described previously.[25]

ORP calculation methods are outlined elsewhere.[7,8,11] PSG recordings were analyzed using the Michele Sleep Scoring system. ORP measurement involved spectral analysis of EEG signals from central electrodes (C3 and C4). For each non-overlapping 3-second epoch, fast Fourier transform was applied to extract power across four frequency bands: 0.33–2.33 Hz, 2.67–6.33 Hz, 7.0–14.0 Hz, and 14.3–35.0 Hz.[11] Within each band, spectral power was ranked (0–9) based on its decile position in reference clinical PSG studies. These ranks were concatenated to generate a four-digit label representing power distribution. Using a reference lookup table developed from prior studies, the probability (0%–100%) of each pattern occurring during either wakefulness or arousals was determined. This probability was then divided by 40 (the percentage of epochs scored as wake in development files), yielding ORP values ranging from 0 (never occurring during wakefulness) to 2.5 (never occurring during sleep). The final ORP value for each epoch was the average of measurements from C3 and C4 electrodes.

To align with standard 30-second epoch analysis, consecutive sets of ten 3-second epochs were averaged to produce a single ORP value for each 30-second interval. Mean ORP values were subsequently calculated for each sleep stage, including ORP during wake (ORP_W), stage N1 (ORP_{N1}), stage N2 (ORP_{N2}), stage N3 (ORP_{N3}), rapid eye movement (REM) sleep (ORP_{REM}), non-REM sleep (ORP_{NR}), and over the total recording time (ORP_{TRT}). ΔORP was derived to reflect sleep restoration, calculated as the difference between the mean ORP over the final two hours of NREM sleep and its early nadir.[6] ORP-9 was utilized to quantify the rate of sleep recovery following arousals, defined as the average ORP value during the initial 9-second "fast recovery phase" (comprising three 3-second epochs) immediately following the termination of an American Academy of Sleep Medicine-defined arousal.[6] $ORP_{ICC\ R/L}$ was quantified by comparing ORP signals derived from the right (C4-M1) and left (C3-M2) central electrodes. For each 30-second epoch, we first calculated a mean ORP value for each hemisphere. The agreement between these paired right and left hemispheric averages was then assessed for the entire night's recording using the intra-class correlation coefficient. Epochs with technical artifacts were excluded from this analysis.[21]

ORP architecture phenotypes was characterized using the ORP distribution across ten deciles of the ORP range (0.0–2.5, in 0.25 increments), expressed as the percentage of total recording time spent in each decile.[6] The distribution was categorized into one of nine phenotypes, each represented by a two-digit code (Supplementary Figure 2). The first digit (1, 2, or 3) reflects the participant's quartile for time spent in deep sleep (ORP < 0.50; deciles 1–2)—lowest, interquartile, or upper, respectively—relative to the SHHS community distribution. The second digit (1, 2, or 3) similarly categorizes the percentage of time spent in full wakefulness (ORP > 2.25; decile 10). For example, phenotype 2,2 indicates both deep sleep and full wakefulness are within the interquartile range and is considered normal sleep, while phenotype 1,3 represents minimal deep sleep with excessive full wakefulness.

Outcomes

All-cause mortality was the primary endpoint for this analysis. A comprehensive mortality verification process was implemented throughout the follow-up period, incorporating multiple data sources including participant interviews, annual surveys, telephone contacts, hospital records, obituary tracking, and cross-referencing with the Social Security Death Master File,[25] as described previously.[26]

Covariates Assessment

A broad set of baseline sociodemographic characteristics was evaluated, including age, sex, and body mass index (BMI). Health behaviors were assessed based on smoking status and alcohol consumption.

Comprehensive medical history was documented, including hypertension, diabetes, and cardiovascular diseases (myocardial infarction, heart failure, and stroke). We used standardized spirometry to obtain forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC). From these, the FEV1/FVC ratio was calculated to serve as a measure of airflow limitation, a potential confounder in our mortality analysis.[27]

Key polysomnographic measures were recorded, including TST, wake after sleep onset (WASO), percentage of REM sleep, apnea-hypopnea index (AHI), time below 90% oxygen saturation (T90), and arousal index (AI). These measures served as potential confounders in examining ORP-mortality relationships.[26,28–30]

Statistical Analysis

Descriptive statistics are reported as counts (percentages) for categorical variables and mean ± standard deviation for continuous variables. For inferential comparisons between groups, the Chi-square test was employed for categorical data, while the *t*-test or Mann–Whitney *U*-test was used for continuous data. Spearman correlation was used to analyze the associations between ORP parameters and other PSG metrics.

Survival time was defined from date of baseline PSG until date of death or date of censoring. Censoring time was the last time the patient was known to be alive. We used Cox proportional hazards models to examine associations between ORP parameters and all-cause mortality, reporting hazard ratios (HRs) with 95% confidence intervals (CIs). Schoenfeld residuals were used to verify the proportional hazards assumption. To identify potential confounders, we employed directed acyclic graphs (DAGs) prior to statistical analysis. The minimally sufficient adjustment set was determined using DAGitty software (http://www.dagitty.net). Detailed principles and methodology of the DAG approach are provided in the Statistical Analysis Plan within the Supplementary Materials. We also assessed for collinearity using variance inflation factors (VIF) and excluded any variable with a VIF greater than 2.5. To visually assess non-linear relationships between ORP parameters and all-cause mortality risk, multivariable Cox regression with restricted cubic splines was performed. When non-linear associations were detected, we performed threshold effect analysis using a two-piecewise linear regression approach with the "segmented" R package. Additionally, to assess the clinical impact of key ORP parameters, we calculated 10-year absolute risk reduction (ARR) and number needed to treat (NNT).[31] We then stratified each ORP parameter into tertiles (lowest tertile as reference) and fitted multivariable Cox models to estimate risk across tertiles. Covariate-adjusted survival curves were plotted for visualization. Excluding cases with missing values may bias results (Supplementary Table 1); thus, we used multiple imputation to impute missing data and analyze results.

To validate the robustness of primary findings, several sensitivity analyses were conducted: (1) exclusion of participants with follow-up < 1 year, (2) removal of outliers with ORP parameters > 3 standard deviations from the mean, and (3) re-ran all the analyses restricted to complete cases without missing data for exposure, outcome, and covariates. Subgroup analyses were performed based on age (< 65 vs ≥ 65 years), sex (male vs female), and OSA status (AHI ≥ 5 events/hour for OSA vs AHI < 5 events/hour for non-OSA).

To demonstrate the clinical value and practical utility of ORP parameters, we developed a prognostic nomogram for clinical risk assessment. The study cohort was randomly divided into training (80%) and validation (20%) sets. In the training set, least absolute shrinkage and selection operator (LASSO) regression was employed for variable selection from 29 candidate variables, followed by multivariable Cox regression analysis. A nomogram was then constructed using the selected variables for 5-year and 10-year mortality prediction. Model performance was evaluated using C-index, calibration curves, decision curve analysis, and time-dependent ROC curves. The incremental clinical value of ORP parameters was assessed by comparing models with and without ORP parameters using net classification improvement (NRI) and integrated discrimination improvement (IDI) and DeLong tests.

All statistical analyses were performed using R statistical software, version 4.3.2 (R Foundation for Statistical Computing). Given the exploratory nature of this study examining multiple ORP parameters, the Benjamini-Hochberg procedure was applied to correct for multiple comparisons, with the false discovery rate (FDR) threshold set at 0.05. Both original and FDR-adjusted p-values are presented in the results tables. Statistical significance was defined as $p < 0.05$ for both uncorrected and FDR-corrected analyses. Detailed methodology is provided in the Statistical Analysis Plan within Supplementary Materials.

Results

Participant Characteristics

This study involved 5802 participants (52.3% female; mean age 63.1±11.2 years; BMI 28.2±5.1 kg/m^2) (Table 1). Participants were divided into the deceased group (1305, 22.5%) and the alive group (4497, 77.5%) based on occurrence of death over a mean follow-up period of 11.0±3.2 years. The deceased group was characterized by older age, a higher proportion of males, and a greater prevalence of former smokers compared to the alive group. The burden of comorbidity

Table 1 Baseline Characteristics of Included Participants

	All Subjects (N=5802)	Alive (N=4497)	Deceased (N=1305)	*P*-value
Anthropometric and ethnicity data				
Age (years)	63.1±11.2	60.4±10.2	72.6±9.3	<0.001
Sex, n (%)				<0.001
Male	2765 (47.7)	2063 (45.9)	702 (53.8)	
Female	3037 (52.3)	2434 (54.1)	603 (46.2)	
BMI (kg/m^2)	28.2±5.1	28.3±5.1	27.7±5.0	<0.001
Lifestyle				
Smoke, n (%)				<0.001
Never	2706 (46.6)	2171 (48.3)	535 (41.0)	
Current	560 (9.7)	433 (9.6)	127 (9.7)	
Former	2495 (43.0)	1857 (41.3)	638 (48.9)	
Alcohol, n (%)				<0.001
At least 1 drink per day	2412 (41.6)	1941 (43.2)	471 (36.1)	
None	2977 (51.3)	2195 (48.8)	782 (59.9)	
Medical history				
Diabetes, n (%)	405 (7.0)	210 (4.7)	195 (14.9)	<0.001
Hypertension, n (%)	2069 (35.7)	1411 (31.4)	658 (50.4)	<0.001
CVD, n (%)	535 (9.2)	258 (5.7)	277 (21.2)	<0.001
FEV1/FVC	0.8±0.1	0.8±0.1	0.7±0.1	<0.001
Medication history				
Benzodiazepines	308 (5.3)	210 (4.7)	98 (7.5)	<0.001
Tricyclic anti-depressants	166 (2.9)	116 (2.6)	50 (3.8)	0.049
Anti-hypertensive medication	2318 (40.0)	1539 (34.2)	779 (59.7)	<0.001
Conventional polysomnographic parameters				
AHI, events/h	14.6±15.6	13.8±15.1	17.5±17.1	<0.001
WASO, min	61.4±44.0	57.0±40.3	76.7±52.2	<0.001
AI, events/h	19.2±10.7	18.7±10.1	20.9±12.2	<0.001
TST, min	359.8±64.6	365.1±62.5	341.6±68.3	<0.001
T90 (%)	3.5±10.3	2.7±8.5	6.1±14.8	<0.001
REM (%)	19.8±6.3	20.3±6.1	18.2±6.7	<0.001
ORP parameters				
ORP_{TRT}	1.13±0.27	1.11±0.26	1.21±0.29	<0.001
ORP_{W}	2.11±0.19	2.11±0.18	2.13±0.19	0.001
ORP_{REM}	1.28±0.33	1.28±0.33	1.32±0.35	<0.001
ORP_{NR}	0.84±0.24	0.83±0.23	0.88±0.26	<0.001
ORP_{N1}	1.52±0.28	1.51±0.28	1.54±0.30	0.008
ORP_{N2}	0.89±0.25	0.88±0.24	0.92±0.27	<0.001
ORP_{N3}	0.48±0.18	0.47±0.18	0.50±0.19	<0.001
Orp-9	1.18±0.23	1.17±0.23	1.20±0.25	<0.001
$ORP_{Icc\ R/L}$ (%)	87.6±9.7	87.5±9.7	88.0±9.3	0.129
ΔORP	0.58±0.25	0.58±0.24	0.55±0.27	<0.001
ORP architecture				<0.001

(*Continued*)

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Table 1 (Continued).

	All Subjects (N=5802)	Alive (N=4497)	Deceased (N=1305)	*P*-value
1,1	201 (3.5)	163 (3.6)	38 (2.9)	
1,2	648 (11.2)	489 (10.9)	159 (12.2)	
1,3	571 (9.8)	335 (7.4)	236 (18.1)	
2,1	673 (11.6)	570 (12.7)	103 (7.9)	
2,2	1481 (25.5)	1205 (26.8)	276 (21.1)	
2,3	680 (11.7)	490 (10.9)	190 (14.6)	
3,1	700 (12.1)	581 (12.9)	119 (9.1)	
3,2	706 (12.2)	563 (12.5)	143 (11.0)	
3,3	119 (2.1)	83 (1.8)	36 (2.8)	
Follow-up time, years	11.0±3.2	12.1±1.9	7.0±3.3	<0.001

Notes: Data are presented as n (%) or mean± standard deviation. Numbers may not add to total because of missing values.

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; FEV1/FVC, forced expiratory volume in 1 second/forced vital capacity ratio; AHI, apnea–hypopnea index; WASO, wake after sleep onset; AI, arousal index; TST, total sleep time; T90, percent total sleep duration with below 90% oxygen saturation; REM, percentage of total sleep duration in REM; ORP, odds ratio product; $ORP_{TRT,}$ average ORP over total recording time; $ORP_{W,}$ average ORP during stage wake; $ORP_{REM,}$ average ORP during stage REM; ORP_{NR}, average ORP during stage non-REM; $ORP_{N1,}$ average ORP during stage 1; $ORP_{N2,}$ average ORP during stage N2; $ORP_{N3,}$ average ORP during stage N3; Orp-9, ORP in the first 9 seconds after arousal; $ORP_{Icc\ R/L,}$ interhemispheric sleep depth coherence; ΔORP, change in ORP across the night.

was substantially greater in the deceased group, as well as poorer pulmonary function as measured by FEV1/FVC. In comparison to the alive group, the deceased group also exhibited a significantly higher AHI, WASO, AI, and T90, along with lower TST and percentage of REM sleep. Regarding the ORP parameters, the deceased group displayed elevated values for ORP_{TRT}, ORP_{W}, ORP_{REM}, ORP_{NR}, ORP_{N1}, ORP_{N2}, ORP_{N3}, and Orp-9, but a lower ΔORP.

Given the novelty of the ORP metrics, and to facilitate a more comprehensive understanding of their characteristics, we have provided supplementary data. Specifically, Supplementary Table 2 details the ranges and median (IQR) for the ORP parameters, and Supplementary Figure 3 presents the correlation matrix between these metrics and conventional PSG parameters.

ORP Parameters and All-Cause Mortality

Table 2 presents the Cox regression analysis examining ORP parameters and all-cause mortality. DAG analysis identified a minimally sufficient adjustment set (Supplementary Figure 4): age, gender, BMI, smoking, alcohol, hypertension, diabetes, CVD, FEV1/FVC, anti-hypertensive medication, psychotropic drugs, sleep medications, AHI, AI, REM, T90, TST, and WASO. VIF for all variables in the multivariable models were below 2.5 (Supplementary Table 3), indicating absence of significant multicollinearity. Bootstrap cross-validation with 1000 repetitions demonstrated excellent model stability (C-index coefficient of variation < 1%). After multivariable adjustment and FDR correction, several ORP parameters remained significantly associated with mortality risk. Higher values of ORP_{W} (HR: 0.54, 95% CI: 0.39–0.73, FDR-corrected p = 0.001), ORP_{REM} (HR: 0.81, 95% CI: 0.69–0.95, FDR-corrected p = 0.026), ORP_{N1} (HR: 0.71, 95% CI: 0.59–0.87, FDR-corrected p = 0.004), $ORP_{Icc\ R/L}$ (HR: 0.49, 95% CI: 0.29–0.81, FDR-corrected p = 0.016), and ΔORP (HR: 0.70, 95% CI: 0.56–0.87, FDR-corrected p = 0.004) were significantly associated with lower mortality risk. Conversely, higher ORP_{N3} (HR: 1.38, 95% CI: 1.06–1.81, FDR-corrected p = 0.033) was associated with increased mortality risk. For ORP architecture, phenotypes 1,2 (HR: 1.28, 95% CI: 1.06–1.56, FDR-corrected p = 0.040), 1,3 (HR: 1.27, 95% CI: 1.05–1.54, FDR-corrected p = 0.040), and 3,1 (HR: 1.48, 95% CI: 1.19–1.84, FDR-corrected p = 0.004) demonstrated significantly higher mortality risk compared to the reference phenotype 2,2. To assess the clinical impact of

Table 2 Association of ORP Parameters and All-Cause Mortality

	Univariate Analysis		Multivariate Analysis		
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**	**FDR-Corrected p value**
ORP_{TRT}	3.01(2.47,3.66)	<0.001	0.80(0.61,1.04)	0.090	0.110
ORP_{W}	1.63(1.19,2.24)	0.002	0.54(0.39,0.73)	<0.001	0.001
ORP_{REM}	1.4(1.2,1.65)	<0.001	0.81(0.69,0.95)	0.012	0.026
ORP_{NR}	2.14(1.73,2.64)	<0.001	1.00(0.79,1.27)	0.996	0.996
ORP_{N1}	1.3(1.08,1.58)	0.006	0.71(0.59,0.87)	0.001	0.004
ORP_{N2}	1.72(1.4,2.11)	<0.001	0.93(0.75,1.17)	0.537	0.591
ORP_{N3}	2.41(1.88,3.09)	<0.001	1.38(1.06,1.81)	0.018	0.033
Orp-9	1.74(1.39,2.18)	<0.001	0.80(0.64,1.01)	0.063	0.087
$ORP_{Icc\ R/L}$	1.36(0.77,2.4)	0.290	0.49(0.29,0.81)	0.006	0.016
ΔORP	0.64(0.51,0.8)	<0.001	0.70(0.56,0.87)	0.001	0.004
ORP architecture					
1,1	1.05(0.75,1.47)	0.77	1.27(0.90,1.79)	0.170	0.227
1,2	1.38(1.14,1.68)	0.001	1.28(1.06,1.56)	0.013	0.040
1,3	2.54(2.14,3.03)	<0.001	1.27(1.05,1.54)	0.015	0.040
2,1	0.81(0.65,1.02)	0.073	1.22(0.97,1.53)	0.097	0.194
2,2	ref	ref	ref	ref	
2,3	1.61(1.34,1.93)	<0.001	1.09(0.89,1.33)	0.425	0.486
3,1	0.92(0.74,1.14)	0.447	1.48(1.19,1.84)	<0.001	0.004
3,2	1.11(0.91,1.35)	0.320	1.16(0.94,1.42)	0.160	0.227
3,3	1.69(1.19,2.39)	0.003	0.99(0.69,1.42)	0.960	0.960

Notes: Univariate analysis: without adjustment. Multivariable analysis adjusted for covariates selected a priori using a DAG: age, sex, BMI, smoking status, alcohol use, hypertension, diabetes, CVD, FEV1/FVC, antihypertensive medication, psychotropic drugs (antidepressants), sleep medications (benzodiazepines), AHI, AI, REM, T90, TST, and WASO.
Abbreviations: BMI, body mass index; CVD, cardiovascular disease; FEV1/FVC, forced expiratory volume in 1 second/forced vital capacity ratio; AHI, apnea–hypopnea index; WASO, wake after sleep onset; AI, arousal index; TST, total sleep time; T90, percent total sleep duration with below 90% oxygen saturation; REM, percentage of total sleep duration in REM; ORP, odds ratio product; $ORP_{TRT,}$ average ORP over total recording time; $ORP_{W,}$ average ORP during stage wake; $ORP_{REM,}$ average ORP during stage REM; $ORP_{NR,}$ average ORP during stage non-REM; $ORP_{N1,}$ average ORP during stage 1; $ORP_{N2,}$ average ORP during stage N2; $ORP_{N3,}$ average ORP during stage N3; Orp-9, ORP in the first 9 seconds after arousal; $ORP_{Icc\ R/L,}$ interhemispheric sleep depth coherence; ΔORP, change in ORP across the night.

key ORP parameters, we calculated 10-year ARR and NNT. The ARR ranged from 2.1% to 4.1%, with corresponding NNT ranging from 24 to 47 (Supplementary Table 4).

Sensitivity analyses showed generally consistent results with the primary analysis, though some variations were observed. Complete case analysis (Supplementary Table 5) and analyses excluding early deaths or extreme values (Supplementary Table 6) yielded largely similar associations, with most key ORP parameters maintaining their prognostic significance. Subgroup analyses stratified by age, sex, and OSA status are presented in Supplementary Tables 7–9, with no significant interactions detected.

Non-Linear Association and Threshold Effects of ORP on Mortality

Multivariable-adjusted restricted cubic spline analysis revealed significant non-linear associations between all-cause mortality and several ORP parameters, including ORP_{N1} (P for non-linearity = 0.039), $ORP_{Icc\ R/L}$ (P for non-linearity < 0.001) and ΔORP (P for non-linearity = 0.005) (Figure 1).

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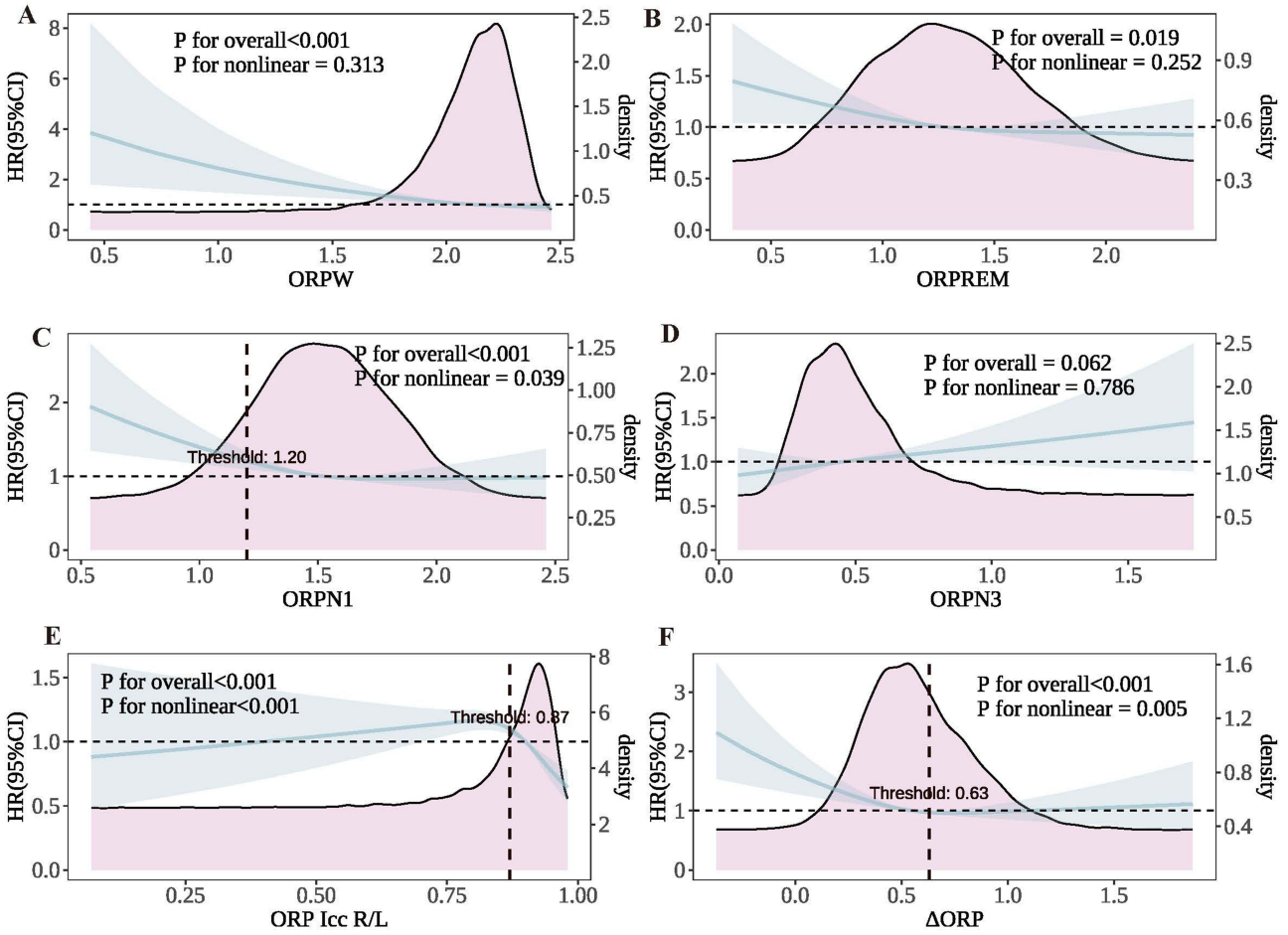

Figure 1 Exposure-Response Associations of ORP Parameters with All-Cause Mortality. The potential nonlinear association of ORP parameters with all-cause mortality were assessed by restricted cubic splines, adjusted for age, sex, BMI, smoking status, alcohol use, hypertension, diabetes, CVD, FEV1/FVC, antihypertensive medication, psychotropic drugs (antidepressants), sleep medications (benzodiazepines), AHI, AI, REM, T90, TST, and WASO. Panels show associations for: (**A**) ORP_{W}, (**B**) ORP_{REM}, (**C**) ORP_{N1}, (**D**) ORP_{N3}, (**E**) ORP $_{Icc\ R/L}$, and (**F**) ΔORP. The solid blue line represents the multivariable-adjusted hazard ratio (HR) and the shaded blue area represents the corresponding 95% confidence interval (CI). The shaded pink area illustrates the density distribution of ORP parameters within the study population.

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; FEV1/FVC, forced expiratory volume in 1 second/forced vital capacity ratio; AHI, apnea–hypopnea index; WASO, wake after sleep onset; AI, arousal index; TST, total sleep time; T90, percent total sleep duration with below 90% oxygen saturation; REM, percentage of total sleep duration in REM; ORP, odds ratio product; ORP_{W}, average ORP during stage wake; ORP_{REM}, average ORP during stage REM; ORP_{N1}, average ORP during stage 1; ORP_{N3}, average ORP during stage N3; ORP $_{Icc\ R/L}$, interhemispheric sleep depth coherence; ΔORP, change in ORP across the night.

To characterize these non-linear relationships, two-piecewise linear regression identified significant inflection points for ORP_{N1} (1.20), ORP $_{Icc\ R/L}$ (0.87) and ΔORP (0.63) (P for likelihood ratio tests = 0.022, <0.001, and 0.004, respectively; Table 3). Below their respective thresholds, ORP_{N1} (HR: 0.27, 95% CI: 0.12–0.61) and ΔORP (HR: 0.44, 95% CI: 0.30–0.64) showed stronger protective associations with mortality. For ORP $_{Icc\ R/L}$, significant protection emerged only above the threshold of 0.87 (HR: 0.004, 95% CI: 0.001–0.033).

Tertiles of ORP Parameters and All-Cause Mortality

In a multivariable-adjusted analysis that categorized ORP parameters by tertiles (Figure 2), the middle and high tertiles of ORP_{W}, ORP_{N1}, ORP $_{Icc\ R/L}$ and ΔORP were each associated with a lower risk of mortality compared to the reference (lowest) tertile. No significant associations were observed for ORP_{REM} or ORP_{N3} across tertiles. Multivariable-adjusted survival curves stratified by tertiles are presented in Figure 3.

Table 3 Threshold Effects Analysis of ORP Parameters on All-Cause Mortality

	HR (95% CI)	P value
ORP_{N1}		
Model 1 Fitting model by standard linear regression	0.71(0.59, 0.87)	0.001
Model 2 Fitting model by two-piecewise linear regression		
Inflection point		
<1.20	0.27(0.12, 0.61)	0.002
≥1.20	0.83(0.66, 1.05)	0.114
P for likelihood ratio test		0.022
$ORP_{Icc\ R/L}$		
Model 1 Fitting model by standard linear regression	0.49(0.29, 0.81)	0.006
Model 2 Fitting model by two-piecewise linear regression		
Inflection point		
<0.87	1.40(0.66, 2.98)	0.377
≥0.87	0.004(0.001, 0.033)	<0.001
P for likelihood ratio test		<0.001
ΔORP		
Model 1 Fitting model by standard linear regression	0.70(0.56, 0.87)	0.001
Model 2 Fitting model by two-piecewise linear regression		
Inflection point		
<0.63	0.44(0.30, 0.64)	<0.001
≥0.63	1.18(0.78, 1.78)	0.433
P for likelihood ratio test		0.004

Notes: Adjusted for age, sex, BMI, smoking status, alcohol use, hypertension, diabetes, CVD, FEV1/FVC, antihypertensive medication, psychotropic drugs (antidepressants), sleep medications (benzodiazepines), AHI, AI, REM, T90, TST, and WASO. HR (95% CI): Hazard ratios (95% confidence interval).

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; FEV1/FVC, forced expiratory volume in 1 second/forced vital capacity ratio; AHI, apnea–hypopnea index; WASO, wake after sleep onset; AI, arousal index; TST, total sleep time; T90, percent total sleep duration with below 90% oxygen saturation; REM, percentage of total sleep duration in REM; ORP, odds ratio product; ORP_{N1}, average ORP during stage 1; $ORP_{Icc\ R/L}$, interhemispheric sleep depth coherence; ΔORP, change in ORP across the night.

Variable Selection and Model Construction

Participants were randomly divided into training and validation sets at an 8:2 ratio, with no significant differences in baseline characteristics between the two datasets (all $P > 0.05$) (Supplementary Table 10). To identify the optimal variables for predictive model construction, we employed LASSO regression followed by multivariable Cox regression analysis. LASSO regression was performed on 29 candidate variables to assess their associations with all-cause mortality, with variable selection based on "lambda.1se". This procedure yielded an optimal model with 14 non-zero coefficients (Supplementary Figure 5), including ORP architecture 1,3 phenotype, ΔORP, ORP_{N3}, CVD, diabetes, anti-hypertensive medication, age, current smoker, T90, WASO, TST, REM, female sex, and FEV1/FVC (Figure 4). These variables were subsequently entered into multivariable Cox regression analysis, which identified 10 variables significantly associated with all-cause mortality risk (Supplementary Table 11), notably including ORP architecture and ΔORP. Based on these prognostic factors, we constructed nomograms for predicting 5-year and 10-year overall survival (Figure 5).

Nomogram Performance and Validation

The C-index of the nomogram was 0.805 (95% CI: 0.791–0.818) in the training set and 0.811 (95% CI: 0.787–0.835) in the validation set, demonstrating good discriminative ability and stability. Calibration curves (Supplementary Figure 6) showed good agreement between predicted and observed 5-year and 10-year mortality risks in both sets, particularly for 10-year prediction, indicating satisfactory calibration and discrimination. Decision curve analysis (Supplementary Figure 7) demonstrated favorable net benefit and clinical utility, especially for 10-year risk prediction.

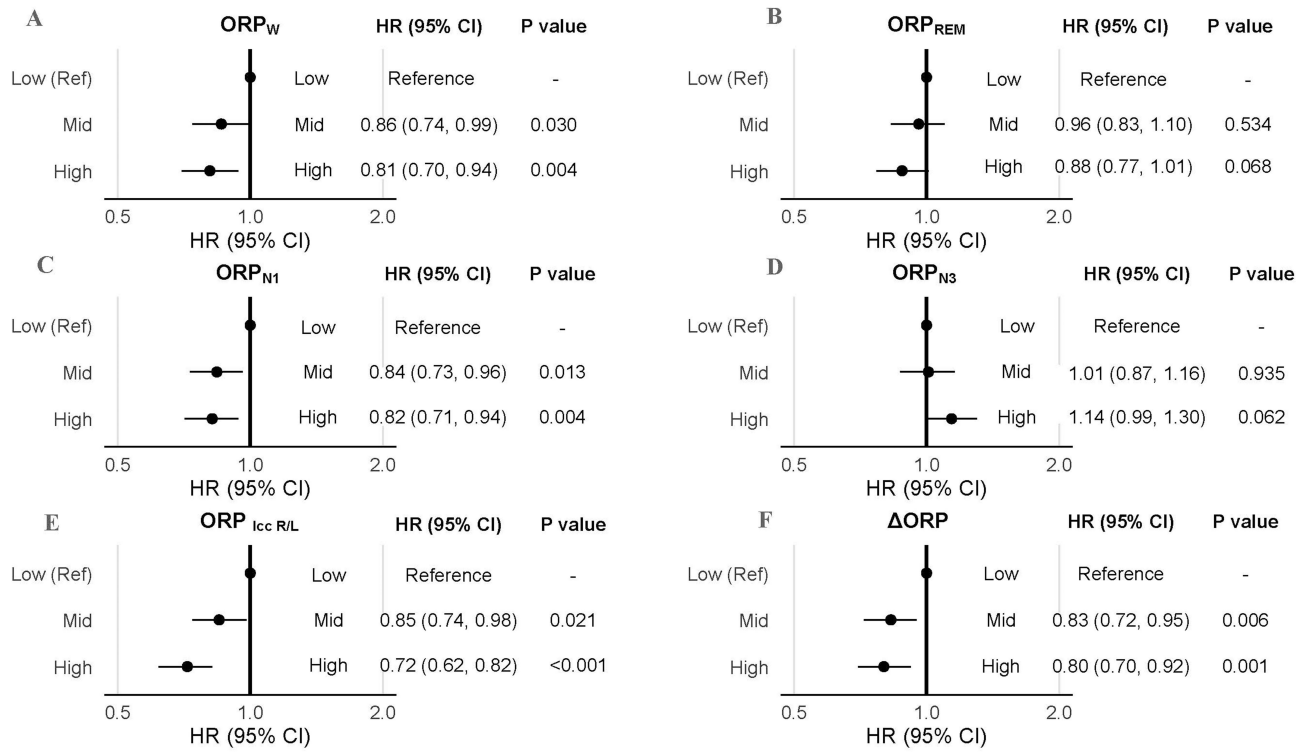

Figure 2 Tertiles of Key ORP Parameters and All-Cause Mortality. Multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause mortality across tertiles of ORP parameters: (**A**) ORP_W, (**B**) ORP_{REM}, (**C**) ORP_{N1}, (**D**) ORP_{N3}, (**E**) ORP $_{Icc\ R/L}$, and (**F**) ΔORP. The lowest tertile serves as the reference category. Adjusted for age, sex, BMI, smoking status, alcohol use, hypertension, diabetes, CVD, FEV1/FVC, antihypertensive medication, psychotropic drugs (antidepressants), sleep medications (benzodiazepines), AHI, AI, REM, T90, TST, and WASO.

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; FEV1/FVC, forced expiratory volume in 1 second/forced vital capacity ratio; AHI, apnea–hypopnea index; WASO, wake after sleep onset; AI, arousal index; TST, total sleep time; T90, percent total sleep duration with below 90% oxygen saturation; REM, percentage of total sleep duration in REM; ORP, odds ratio product; ORP_W, average ORP during stage wake; ORP_{REM}, average ORP during stage REM; ORP_{N1}, average ORP during stage 1; ORP_{N3}, average ORP during stage N3; ORP $_{Icc\ R/L}$, interhemispheric sleep depth coherence; ΔORP, change in ORP across the night.

To evaluate the incremental value of ORP parameters, we compared three models for 10-year mortality prediction (Supplementary Figure 8): Model 1 (traditional risk factors, AUC: 0.826), Model 2 (Model 1 + T90, AUC: 0.828), and Model 3 (Model 2 + ORP architecture + ΔORP, AUC: 0.830). Model 3 showed significantly higher AUC compared to Model 1 (p = 0.001) and Model 2 (p = 0.035). Time-dependent AUC curves for the three models in training and validation sets are presented in Supplementary Figures 9 and 10. Furthermore, compared to Model 2, the nomogram demonstrated improved 10-year mortality prediction with IDI of 0.004 (95% CI: 0.001–0.011, p = 0.004) and NRI of 0.053 (95% CI: 0.002–0.118, p = 0.040).

Risk Stratification Performance

Using the surv_cutpoint function, an optimal cut-off value of 92.0 was identified in the training set. Participants were stratified into high-risk (score >92.0) and low-risk (score ≤92.0) groups. Kaplan-Meier analysis revealed significant survival differences between risk groups in both training and validation sets (both P < 0.001) (Supplementary Figures 11 and 12), demonstrating that the nomogram successfully identifies high-risk individuals.

Discussion

This study demonstrates for the first time that novel ORP-derived sleep EEG biomarkers are independently associated with all-cause mortality in a community-based population. After rigorous adjustment and correction for multiple comparisons, higher ORP_W, ORP_{REM}, ORP_{N1}, ORP $_{ICC\ R/L}$, and ΔORP were associated with reduced mortality risk, while elevated ORP_{N3} predicted increased risk. Regarding ORP architecture, phenotypes 1,2, 1,3, and 3,1 were associated with higher mortality compared to the reference phenotype 2,2. Through LASSO regression and multivariable

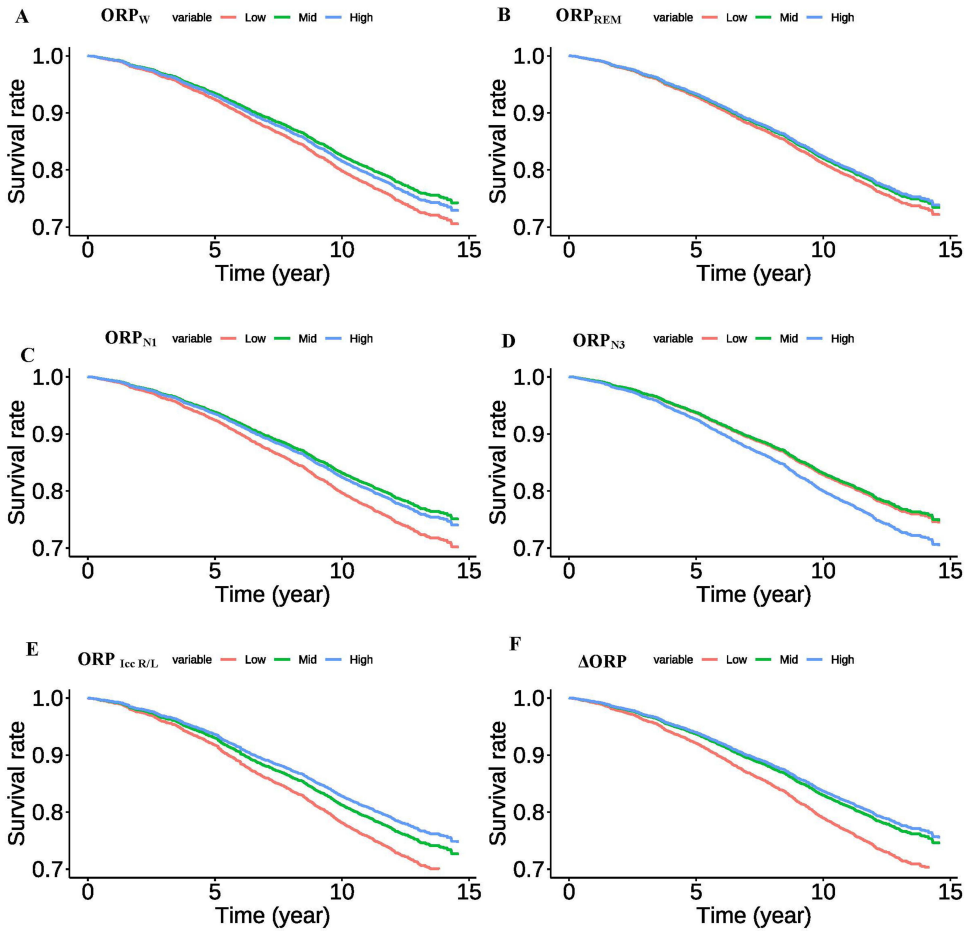

Figure 3 Adjusted Survival Curves for All-Cause Mortality According to Tertiles of ORP Parameters. Covariate-adjusted survival curves stratified by tertiles of ORP parameters: (**A**) ORP$_W$, (**B**) ORP$_{REM}$, (**C**) ORP$_{N1}$, (**D**) ORP$_{N3}$, (**E**) ORP $_{Icc\ R/L}$, and (**F**) ΔORP. Adjusted for age, sex, BMI, smoking status, alcohol use, hypertension, diabetes, CVD, FEV1/FVC, antihypertensive medication, psychotropic drugs (antidepressants), sleep medications (benzodiazepines), AHI, AI, REM, T90, TST, and WASO.
Abbreviations: BMI, body mass index; CVD, cardiovascular disease; FEV1/FVC, forced expiratory volume in 1 second/forced vital capacity ratio; AHI, apnea–hypopnea index; WASO, wake after sleep onset; AI, arousal index; TST, total sleep time; T90, percent total sleep duration with below 90% oxygen saturation; REM, percentage of total sleep duration in REM; ORP, odds ratio product; ORP$_W$, average ORP during stage wake; ORP$_{REM}$, average ORP during stage REM; ORP$_{N1}$, average ORP during stage 1; ORP$_{N3}$, average ORP during stage N3; ORP $_{Icc\ R/L}$, interhemispheric sleep depth coherence; ΔORP, change in ORP across the night.

Cox regression for variable selection, we developed 5-year and 10-year prognostic nomograms incorporating traditional risk factors along with ΔORP and ORP architecture to enhance clinical utility. The nomogram demonstrated robust discriminative ability, and importantly, the model incorporating ORP parameters provided superior predictive performance compared to models using traditional risk factors alone. These findings establish the important prognostic value of ORP-derived biomarkers for long-term mortality outcomes and underscore the clinical significance of quantitative sleep depth assessment.

ORP$_W$ reflects sleep propensity and is largely influenced by sleep pressure. A low ORP$_W$ indicates elevated sleep pressure and reduced vigilance.[8] Previous studies demonstrate that low ORP$_W$ is likely due to: (i) chronic sleep deprivation; (ii) intrinsic excessive sleep need (eg, specific idiopathic hypersomnia); or (iii) disorders that interfere with progression to deep sleep (eg, OSA).[8] Prior research suggests that ORP$_W$ progressively decreases with increasing OSA severity.[8] Notably, our finding linking lower ORP$_W$ to increased all-cause mortality may be attributable to these underlying conditions (chronic sleep deficiency, hypersomnia, or OSA) captured by low ORP$_W$, as they constitute established mortality risks.[26,32–34]

ORP$_{REM}$ is a robust and highly repeatable trait.[15] Distinctively, this parameter shows no significant variation across gender groups or different disease phenotypes, contrasting with other ORP measurements.[8] A preliminary study[35] has suggested potential links between elevated ORP$_{REM}$ values and both reduced REM time and heightened REM sleep

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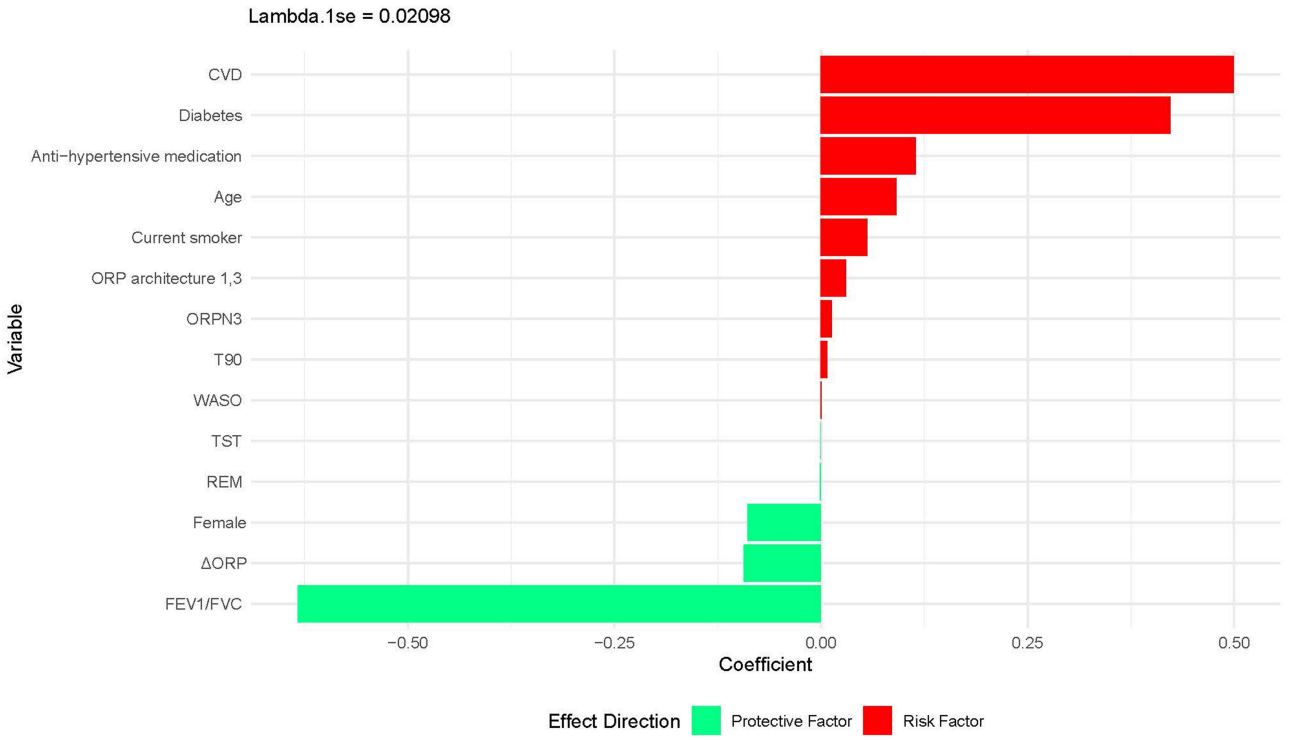

Figure 4 Variables Selected by LASSO Regression for All-cause Mortality Prediction. LASSO regression was used to identify the optimal set of predictors for all-cause mortality. This method removes redundant and irrelevant variables by penalizing the regression coefficients of less important predictors to zero. A total of twenty-nine candidate variables were entered into this selection process, including demographics, comorbidities, and both conventional and ORP-derived polysomnography metrics (as listed in Table 1). The tuning parameter (lambda) was optimized using 10-fold cross-validation based on the one-standard-error rule. This resulted in an optimal model with 14 non-zero coefficients. Notably, among all the ORP-derived biomarkers evaluated, the ORP architecture 1,3 phenotype, ΔORP and ORP_{N3} were selected as significant predictors.

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; FEV1/FVC, forced expiratory volume in 1 second/forced vital capacity ratio; AHI, apnea–hypopnea index; WASO, wake after sleep onset; AI, arousal index; TST, total sleep time; T90, percent total sleep duration with below 90% oxygen saturation; REM, percentage of total sleep duration in REM; ORP, odds ratio product; ORP_{N3}, average ORP during stage N3; ΔORP, change in ORP across the night.

fragmentation, phenomena that could relate to abnormal dream states and mood disorders—conditions potentially considered risk factors for adverse health outcomes.[6,36,37] Our study, however, revealed a paradoxical association: higher ORP_{REM} was independently linked to a lower risk of all-cause mortality. Currently, detailed information regarding ORP_{REM} remains limited, and our observed association lacks supporting biological evidence. We propose a hypothesis rooted in sleep homeostatic regulation. As homeostatic sleep pressure is progressively discharged during the initial deep NREM sleep stages, the sleep architecture naturally shifts towards a predominance of REM and lighter sleep in the latter part of the night. Within this physiological context, a higher ORP_{REM} may not represent pathological fragmentation, but could instead be a marker of the successful release of sleep pressure. Nevertheless, interpretation of this finding requires caution. Stratified analyses revealed that associations were primarily concentrated in participants aged ≥65 years, females, and those with OSA. However, interaction tests were non-significant, precluding definitive conclusions about effect modification. Some methodological considerations warrant attention: 1) Residual confounding—despite adjustment for psychotropic medication use, unmeasured confounders such as specific medication effects on REM sleep, or REM behavior disorders could influence the association. 2) ORP_{REM} may reflect unmeasured neurophysiological processes. This finding requires validation in independent cohorts, along with mechanistic studies to elucidate the biological basis of ORP_{REM} variability and its potential relationship to mortality outcomes.

Our study revealed divergent mortality associations for stage-specific ORP values: higher ORP_{N1} was associated with reduced mortality risk, whereas elevated ORP_{N3} predicted increased mortality. Consistent with our findings, Alen et al reported a positive association between ORP_{N3} and the probability of cardiovascular death.[38] As ORP progressively decreases from wakefulness to stage N3 (Supplementary Table 2),[11] ORP_{N1} represents the transitional state between wakefulness and deeper NREM sleep. Higher ORP_{N1} may reflect preserved alertness and appropriate sleep-wake

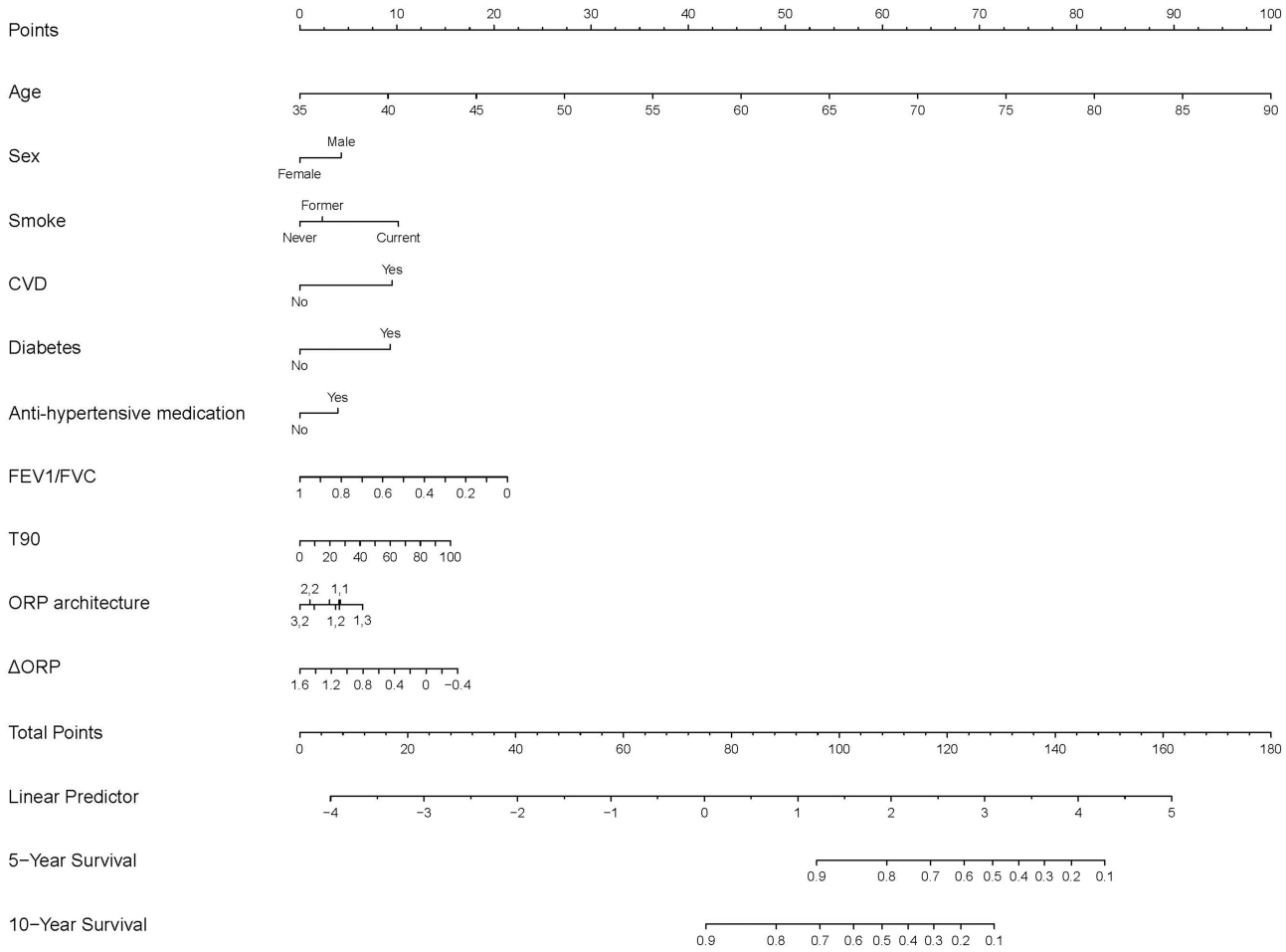

Figure 5 Nomogram for predicting 5- and 10-year overall survival in community-dwelling middle-aged and older adults.
Abbreviations: BMI, body mass index; CVD, cardiovascular disease; FEV1/FVC, forced expiratory volume in 1 second/forced vital capacity ratio; AHI, apnea–hypopnea index; WASO, wake after sleep onset; AI, arousal index; TST, total sleep time; T90, percent total sleep duration with below 90% oxygen saturation; REM, percentage of total sleep duration in REM; ORP, odds ratio product; ΔORP, change in ORP across the night.

transition capacity, whereas abnormally low ORP_{N1} approaching deeper sleep stages could potentially signal excessive sleep pressure or pathological hypersomnia. Conversely, higher ORP_{N3} values signify reduced N3 sleep depth and intensity,[7] potentially reflecting compromised sleep quality. Supporting the pathological nature of elevated $ORP_{N3,}$ our correlation analyses demonstrated that ORP_{N3} negatively correlated with the functional outcomes of sleep questionnaire (FOSQ) score (Supplementary Figure 13), indicating impaired daytime functioning. Notably, ORP_{N3} showed no significant correlation with slow-wave sleep duration (Supplementary Figure 13), suggesting it captures sleep depth intensity rather than quantity—a dimension not assessed by traditional metrics that have linked reduced N3 duration to adverse outcomes.[39,40] However, the physiological significance of stage-specific ORP values remains largely unexplored, and we also cannot exclude unmeasured confounding. Future studies are needed to validate these associations and elucidate the underlying biological mechanisms.

Our study found that higher $ORP_{ICC\ R/L}$, reflecting greater interhemispheric sleep depth coherence, was associated with reduced all-cause mortality risk. Limited prior research has examined the clinical significance of this parameter. Ali and colleagues[21] reported that higher $ORP_{ICC\ R/L}$ was associated with lower motor vehicle crash risk in OSA patients; the authors speculated that high interhemispheric sleep depth coherence may be a marker of reduced susceptibility to OSA-related adverse neurocognitive outcomes. In critically ill patients requiring mechanical ventilation, most patients with $ORP_{ICC\ R/L}$ >0.7 successfully passed weaning trials, whereas most patients with lower correlation values failed.[41] It must be acknowledged that any mechanistic insights regarding the relationship between $ORP_{ICC\ R/L}$ and all-cause

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mortality in our study remain speculative. Ali et al[21] proposed potential mechanisms underlying interhemispheric coherence disruption in the context of OSA and driving safety outcomes, suggesting that reduced coherence may result from interhemispheric differences in autonomic EEG arousal responses to respiratory events, and that frequent respiratory events in OSA patients likely lead to sleep deprivation, which in turn may deteriorate interhemispheric coherence. Whether similar mechanisms operate in the mortality context remains unknown. Notably, our stratified analyses revealed that the protective association of high ORP $_{\text{ICC R/L}}$ was primarily observed in participants with OSA, which may suggest some mechanistic overlap. Additionally, unpublished observations demonstrate deterioration of ORP $_{\text{ICC R/L}}$ in healthy individuals following: (1) 36 hours of sleep deprivation, (2) four consecutive nights of sleep restriction to 5 hours, or (3) exposure to frequent noise transients during sleep.[21] Collectively, these findings suggest that low ORP $_{\text{ICC R/L}}$ may serve as a marker of poor prognosis, potentially reflecting cumulative sleep disruption, though the precise biological pathways linking interhemispheric coherence to mortality risk require further investigation.

Our study found that higher ΔORP was associated with reduced all-cause mortality, though this relationship exhibited a non-linear pattern. ΔORP represents the change in sleep depth from early night to late night, quantifying the restoration process as homeostatic sleep pressure is discharged.[6] As restorative processes unfold and sleep pressure diminishes, ORP progressively increases across the night, with the magnitude of this increase (ΔORP) varying considerably among individuals.[6] Alen et al reported that ΔORP was negatively associated with the probability of cardiovascular death.[38] Furthermore, ΔORP has been validated against objective sleepiness measures, demonstrating a significant positive correlation with next-day mean sleep latency on the Multiple Sleep Latency Test (MSLT),[7] indicating that greater ΔORP reflects more effective sleep restoration. Notably, through rigorous variable selection procedures including LASSO and multivariable Cox regression, ΔORP was retained as one of the key predictors in our final prognostic nomogram model. These observations suggest that ΔORP may capture a functionally meaningful dimension of sleep quality—the degree of homeostatic restoration achieved during sleep—that potentially influences long-term health outcomes, though the underlying biological mechanisms require further elucidation.

Our analysis of ORP architecture revealed that phenotypes 1,2, 1,3, and 3,1 were associated with higher all-cause mortality compared to the normative 2,2 phenotype. These findings are consistent with prior work linking these specific sleep patterns to underlying pathologies.[9] The 1,2 phenotype, characterized by minimal deep sleep combined with moderate wakefulness, has been previously associated with poor sleep quality and reduced quality of life,[9] supporting its potential role as a marker of adverse health outcomes. The 1,3 phenotype, characterized by minimal deep sleep combined with maximal wakefulness, was identified as a key predictor in our LASSO regression. This phenotype reflects a state of low sleep pressure or hyperarousal[9] and has been previously associated with insomnia with short sleep duration and significantly reduced quality of life.[9] Our finding reinforces the clinical importance of this uniquely detrimental sleep pattern. The 3,1 phenotype, characterized by abundant deep sleep with minimal wakefulness, presented a distinct pattern: while this phenotype is common in healthy young adults and rare in older individuals,[9] the mortality association in our study was observed exclusively in participants aged ≥65 years, although the interaction test was not statistically significant. This pattern has been previously suggested to potentially reflect prior sleep deprivation or insufficient sleep.

These findings have several important clinical implications. First, ORP-derived biomarkers provide prognostic information that is independent of and incremental to traditional sleep and clinical parameters, as evidenced by significantly improved 10-year mortality prediction with positive IDI and NRI. Second, ORP measurements can be obtained through simplified, automated monitoring, lowering barriers for broader clinical application.[11,42] Third, specific ORP parameters—particularly ORP architecture phenotypes (eg, 1,3) and ΔORP—enable identification of "hidden" high-risk individuals who may appear to have normal sleep on conventional metrics, facilitating targeted interventions and closer monitoring. Fourth, our nomograms provide practical tools for individualized risk stratification, with demonstrated excellent discrimination (C-index:0.81) and successful separation of high- versus low-risk groups. Fifth, the identified threshold effects for ORP_{N1}, ORP $_{\text{ICC R/L}}$, and ΔORP may serve as potential intervention targets to improve long-term survival outcomes. Finally, the low NNT values (24–47) indicate high clinical utility, suggesting that population-level implementation of these objective ORP biomarkers could substantially reduce mortality burden among individuals with sleep disorders.

This study has several notable strengths. First, this is the first large-scale, prospective investigation evaluating ORP-derived biomarkers for all-cause mortality in a community-based population. Second, we employed rigorous analytical approaches including DAG analysis, comprehensive confounder adjustment, FDR correction, and extensive sensitivity analyses to ensure robustness. Third, we developed practical prognostic nomograms with excellent discrimination. Finally, the minimal additional cost, negligible training requirements, and demonstrated incremental prognostic value suggest that ORP metrics are well-positioned for clinical translation.

Despite these strengths, several limitations warrant consideration. First, the study population consisted primarily of middle-aged and older adults from community-dwelling populations in the United States, and the participants were predominantly White. This may limit the generalizability of our findings to younger adults, more ethnically diverse populations, or different socioeconomic strata. Second, despite DAG-guided confounder adjustment,[43] unmeasured factors such as psychosocial stress and healthcare accessibility may still confound our findings.[44] Third, while we excluded participants who died within the first year to minimize reverse causation, the possibility remains that subclinical illness or declining health status at baseline could have influenced sleep architecture parameters.[45,46] Sleep disturbances may be early manifestations of systemic illness that subsequently leads to mortality, potentially creating spurious associations. Fourth, our study relied on single-night PSG recordings to assess ORP parameters, which may not adequately represent participants' habitual sleep architecture. Single-night measurements of PSG are susceptible to various influences including first-night effects, pre-monitoring sleep restriction, dietary factors, and physical activity patterns, which may alter sleep depth and architecture, thereby affecting stage-specific ORP values and other ORP-derived metrics. Additionally, temporal changes in sleep patterns over the 11-year follow-up period could further impact the precision and validity of our findings. Future studies incorporating longitudinal ORP assessments (repeated measurements, trajectory analysis, and wearable technology integration) would provide more robust evidence for these associations. Fifth, while we employed multiple imputation under the missing at random assumption and conducted sensitivity analyses, potential bias from missing data cannot be entirely eliminated. If missing data were related to unobserved factors (missing not at random), our estimates could be biased. Sixth, the all-cause mortality endpoint does not allow us to determine which specific diseases contribute most to the observed mortality differences or which diseases are most susceptible to the influence of ORP parameters. Without cause-specific mortality data, we cannot identify whether cardiovascular diseases, cancers, respiratory illnesses, or other conditions are the primary drivers of the ORP-mortality associations, limiting our ability to develop disease-specific prevention strategies.

Our findings lay the groundwork for several critical avenues of future research. First, the prognostic utility of key ORP markers—such as the ORP architecture 1,3 phenotype—should be validated for cause-specific outcomes, particularly cardiovascular mortality and cardiovascular events, to determine which diseases are most strongly associated with ORP parameters and most amenable to sleep-based interventions. Second, research is needed to elucidate the specific pathophysiological pathways that connect these novel ORP metrics to all-cause mortality. Third, external validation in younger, more ethnically diverse, and socioeconomically varied populations is essential to establish the generalizability of our findings across different demographic groups. Finally, randomized controlled trials are warranted to determine whether modifying high-risk ORP profiles through sleep interventions translates into improved long-term health outcomes and reduced mortality risk.

Conclusions

This study demonstrates that ORP-derived biomarkers are independently associated with all-cause mortality in a community-based population. Nomograms incorporating ΔORP and ORP architecture showed excellent discrimination and provided incremental prognostic value beyond traditional risk factors. These automated metrics may complement conventional assessment to refine mortality risk stratification. However, given the observational and exploratory nature of this study, the findings should be interpreted with caution. Replication in independent, more ethnically and demographically diverse cohorts is essential to confirm these associations and to assess their generalizability. Furthermore, interventional studies are needed to determine whether modifying ORP-related sleep characteristics can translate into improved long-term health outcomes before these biomarkers can be adopted in clinical practice.

Data Sharing Statement

The data utilized in this research may be obtained by contacting the corresponding author, Longlong Wang, at wanglonglong@gdph.org.cn, upon reasonable request.

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Author Contributions

Conceptualization: Jinhuan Huang, Longlong Wang; Methodology: Jinhuan Huang, Longlong Wang; Data Curation: Jinhuan Huang, Longlong Wang; Formal Analysis: Jinhuan Huang; Investigation: Jinhuan Huang, Longlong Wang; Writing – Original Draft: Jinhuan Huang; Writing – Review & Editing: Longlong Wang; Supervision: Longlong Wang; Funding Acquisition: Longlong Wang; Project Administration: Longlong Wang.

All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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