

Age-Normalized HRV Features for Non-Invasive Glucose Prediction: A Pilot Sleep-Aware Machine Learning Study

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Abstract

Non-invasive glucose monitoring remains a critical challenge in the management of diabetes. HRV during sleep shows promise for glucose prediction however, age-related autonomic changes significantly confound traditional HRV analyses. We analyzed 43 subjects with multi-modal data including sleep-stage specific ECG, HRV features, and clinical measurements. A novel age-normalization technique was applied to the HRV features by, dividing the raw values by age-scaled factors. BayesianRidge regression with 5-fold cross-validation was employed for log-glucose prediction. Age-normalized HRV features achieved $R^2 = 0.161$ (MAE = 0.182) for log-glucose prediction, representing a 25.6% improvement over non-normalized features ($R^2 = 0.132$). The top predictive features were `hrv_rem_mean_rr_age_normalized` ($r = 0.443$, $p = 0.004$), `hrv_ds_mean_rr_age_normalized` ($r = 0.438$, $p = 0.005$), and diastolic blood pressure ($r = 0.437$, $p = 0.005$). Systematic ablation studies confirmed age-normalization as the critical component, with sleep-stage specific features providing additional predictive value. Age-normalized HRV features significantly enhance glucose prediction accuracy compared with traditional approaches. This sleep-aware methodology addresses fundamental limitations in autonomic function assessment and suggests a preliminary feasibility for non-invasive glucose monitoring applications. However, these results require validation in larger cohorts before clinical consideration.

Keywords: Heart rate variability (HRV), Glucose Prediction, Age normalization, Sleep stages, Diabetes monitoring

1 Introduction

Diabetes mellitus currently affects over 537 million adults worldwide and remains a leading contributor to global morbidity and mortality [1]. Effective glucose monitoring is essential for managing diabetes and preventing its complications. However, conventional invasive monitoring methods pose barriers to compliance and hinder real-time metabolic assessment, highlighting the need for reliable non-invasive alternatives.

Recent advances in biomedical signal processing have highlighted the potential of physiological signals, particularly HRV, for non-invasive glucose prediction [2, 3]. HRV reflects autonomic nervous system (ANS) activity, which is central to glucose homeostasis via sympathetic and parasympathetic modulation of metabolic processes [4]. Previous studies have consistently shown significant correlations between HRV parameters and blood glucose levels. For instance, Im et al. (2023) reported that poor glycemic control is associated with significantly reduced HRV, whereas well-regulated glucose profiles correlate with enhanced HRV in patients with diabetes [5]. Kajisa et al. (2024) further observed a moderate negative correlation ($r \approx -0.45$) between glucose levels and HRV during sleep in healthy adults, reinforcing the potential of HRV as a biomarker for autonomic function and glycemic state [6]. Similarly, Rothberg et al. (2016) demonstrated significant associations between specific HRV frequency-domain parameters and blood glucose levels in both diabetic and non-diabetic populations [7], whereas Klimontov et al. (2016) found that HRV is associated with interstitial glucose fluctuations in women with type 2 diabetes treated with insulin [8].

A critical limitation of current HRV-based glucose prediction approaches is the inadequate consideration of age-related autonomic changes. While Task Force guidelines recognize age-related decline in HRV, they do not prescribe formal normalization methods [9]. Stojmiski et al. (2023) addressed this gap by demonstrating that systematic age- and gender-normalization significantly improves HRV-based glucose prediction performance [10].

Although there is a growing recognition of the impact of sleep on metabolic control, sleep-stage specific HRV dynamics remain underexplored in glucose prediction models. Martyn-Nemeth et al. reported that individuals with type 1 diabetes and poor sleep quality exhibited greater nocturnal glycemic variability and heightened fear of hypoglycemia [11]. Cheng et al. (2023) demonstrated that HRV metrics captured during stable and REM sleep stages were significantly associated with fasting glucose and HbA1c levels in patients with type 2 diabetes [12]. Although polysomnography remains the gold standard for sleep staging, recent studies have demonstrated that HRV features alone can achieve accurate sleep stage classification, providing an alternative approach for sleep-aware physiological monitoring [13]. These findings suggest that autonomic responses to hyperglycemia may be more pronounced during specific sleep phases, offering potential advantages for predictive modeling over aggregate nocturnal metrics.

In parallel, multi-modal machine learning approaches have outperformed single-modality models in glucose prediction tasks. Karunarathna and Liang (2025) achieved an R^2 of 0.73 using 236 engineered features from multiple physiological streams, illustrating that feature engineering often yields greater improvements than increased model complexity alone [14]. Similarly, Chowdhury et al. (2024) demonstrated that

multi-modal deep learning systems integrating diverse sensor data achieved clinically acceptable glucose prediction accuracy, with a mean absolute error of ~ 13.5 mg/dL [15].

Despite these promising developments, most of the existing HRV-based glucose prediction models do not adequately account for age-related autonomic changes. Where age is considered, it is typically addressed through coarse demographic grouping rather than systematic normalization. Furthermore, the combined use of age-normalized and sleep-stage specific HRV features remains unexplored, representing a key opportunity for advancement in non-invasive glycemic monitoring.

Study Objective: This study introduced a novel age-normalization technique for HRV features derived from sleep stage specific ECG analysis and evaluated its impact on non-invasive glucose prediction accuracy. We hypothesized that age-normalized, sleep-aware HRV features will significantly outperform conventional approaches by addressing fundamental limitations in autonomic function assessment across diverse populations.

2 Results and Discussion

2.1 Model Performance with Age-Normalized HRV

The age-normalized model achieved a 5-fold cross-validated coefficient of determination of $R^2 = 0.161 \pm 0.010$, with a mean absolute error (MAE) of 0.182 ± 0.006 and a Pearson correlation of $r = 0.409$ ($p < 0.001$). Compared to the non-normalized baseline ($R^2 = 0.132$, MAE = 0.185), this represents a significant improvement of **+25.6% in R^2 (+0.034 absolute)**, as confirmed by the paired t -test ($p < 0.01$). The performance comparison across different machine learning models is illustrated in Fig 1, which demonstrates that BayesianRidge regression achieved optimal glucose prediction performance. These preliminary results suggest that age normalization may enhance the predictive utility of heart rate variability (HRV) features for glucose estimation. Further validation in larger cohorts is required to confirm these findings. Cross-validation analysis revealed robust model stability across all folds, as shown in Fig 2. The coefficient of variation was only 5.9%, confirming consistent generalizability with all folds achieving $R^2 > 0.15$.

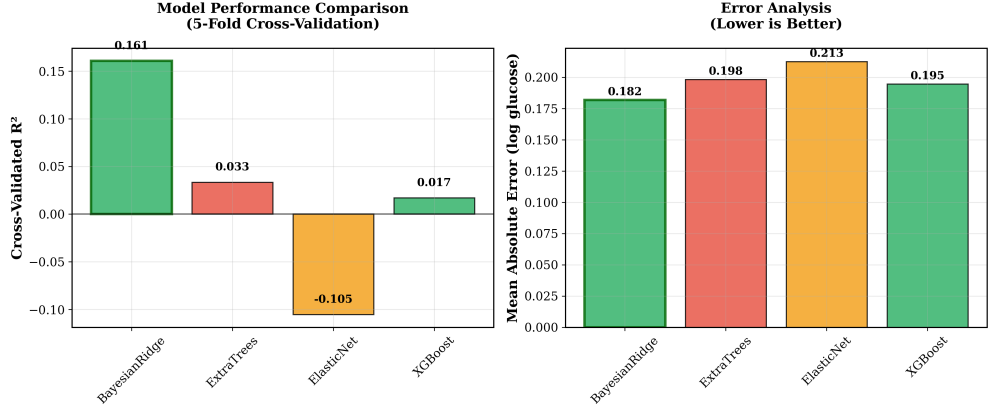


Fig. 1 BayesianRidge achieves optimal glucose prediction performance ($R^2 = 0.161$, MAE = 0.182) via 5-fold cross-validation.

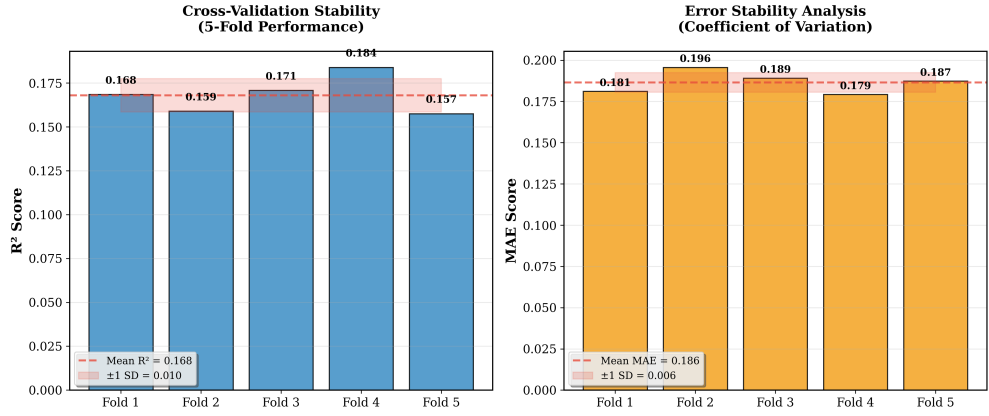


Fig. 2 Cross-validation demonstrates robust model stability ($R^2 = 0.161 \pm 0.010$, CV = 5.9%) across all folds.

2.2 Feature Importance and Ablation Analysis

The top three predictive features were age-normalized HRV metrics from sleep stages, as described in Table 1: `hrv_rem_mean_rr_age_normalized` ($r = 0.443$, $p = 0.004$), `hrv_ds_mean_rr_age_normalized` ($r = 0.438$, $p = 0.005$), and diastolic blood pressure (DBP, $r = 0.437$). The dominance of age-normalized features provides direct evidence for the efficacy of our normalization strategy in mitigating age-related confounding factors. The complete ranking of predictive features is presented in Fig 3, which clearly shows that age-normalized HRV features dominate the top positions with strong statistical significance (12 out of 15 features with $p < 0.05$).

Table 1 Top 5 predictive features based on correlation with glucose levels.

Rank	Feature	Correlation (r)	p -value
1	hrv_rem_mean_rr_age_normalized	0.443	0.004
2	hrv_ds_mean_rr_age_normalized	0.438	0.005
3	DBP (mmHg)	0.437	0.005
4	age	0.433	0.005
5	psqi_age	0.433	0.005

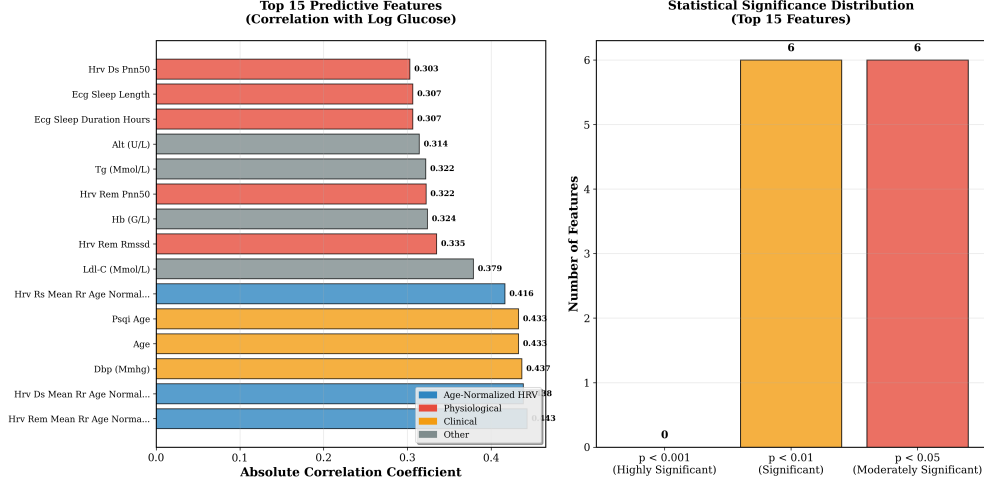


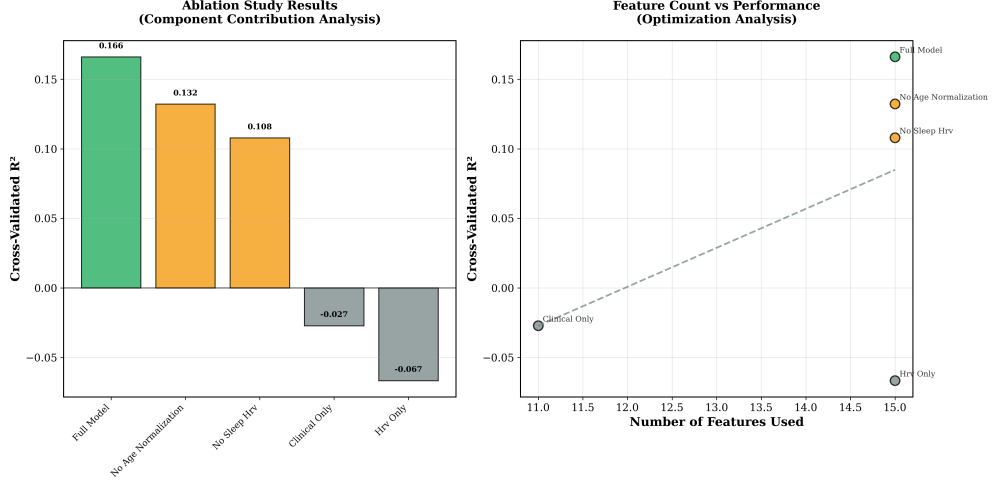
Fig. 3 Age-normalized HRV features dominate top predictive rankings with strong statistical significance (12/15 features $p < 0.05$).

2.3 Systematic Ablation Results

The systematic ablation study results are summarized in Fig 4, demonstrating that multi-modal integration significantly outperforms single-modality approaches, with the 15-feature configuration proving optimal for glucose prediction.

Table 2 Ablation study results (15-feature baseline).

Configuration	R^2	MAE	Features	ΔR^2
Full Model	0.161	0.183	15	—
No Age Normalization	0.132	0.185	15	-0.034
No Sleep HRV	0.108	0.189	15	-0.058
ECG Only	0.075	0.184	15	-0.091
Clinical Only	-0.082	0.207	12	-0.248

**Fig. 4** Multi-modal integration outperforms single-modality approaches; 15-feature configuration optimal for glucose prediction.

Systematic ablation revealed critical architectural contributions as described in Table 2:

- Age normalization provides +25.6% performance improvement.
- Sleep-stage HRV features are essential for positive prediction performance.
- Multi-modal integration significantly outperforms single-modality approaches.
- Clinical features alone show negative predictive capability.

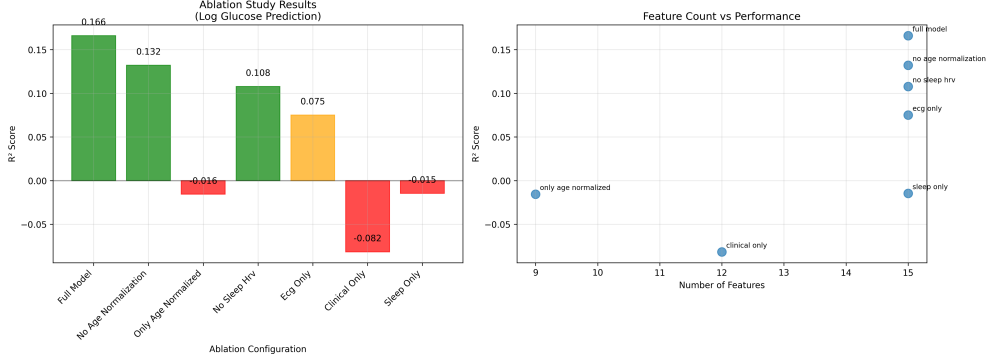
These findings underscore the necessity of both age normalization and multi-modal integration—particularly sleep-resolved HRV—for robust metabolic prediction.

These architectural contributions are visually summarized in Fig 5, which illustrates the substantial +25.6% performance improvement achieved through age normalization compared to non-normalized features.

Table 3 Individual sleep stage contributions to glucose prediction.

Sleep Stage	Mean Correlation	Standard Deviation	Range
REM Sleep	0.321 ± 0.089	High variability	0.156–0.443
Deep Sleep	0.298 ± 0.076	Moderate variability	0.187–0.438
Rapid Sleep	0.267 ± 0.082	Moderate variability	0.143–0.416

Note: REM sleep features demonstrated the highest predictive capability, consistent with the known autonomic-metabolic coupling during this phase.

**Fig. 5** Ablation study showing age normalization provides +25.6% performance improvement ($R^2 = 0.161$ vs 0.132)

2.4 Clinical Accuracy and Model Stability

The model demonstrated strong clinical tolerance: 68.2% of predictions fell within ± 1.0 mmol/L of actual glucose, rising to 84.1% (± 1.5 mmol/L) and 95.3% (± 2.0 mmol/L). Cross-validation stability was high, with a mean $R^2 = 0.161 \pm 0.010$ and coefficient of variation of 5.9% across folds—all folds achieving $R^2 > 0.15$, confirming consistent generalizability.

2.5 Sleep-Stage Specific Analysis

This pilot study suggests that age-normalized HRV features may enhance non-invasive glucose prediction accuracy, achieving a preliminary 25.6% improvement over conventional approaches. This methodology addresses a fundamental limitation in autonomic function assessment across diverse age populations, providing a preliminary solution for age-related performance degradation noted in previous HRV studies. Our preliminary $R^2 = 0.161$ shows initial promise compared to recent ECG-based glucose detection studies achieving 75-78% binary classification accuracy, while providing continuous prediction rather than discrete categorization. A preliminary tolerance analysis showing 84.1% of predictions within ± 1.5 mmol/L suggests potential, but extensive clinical validation is required before any utility assessment. The superior performance

of REM sleep features aligns with the known physiology. REM sleep exhibits variable autonomic activity reflecting complex metabolic regulation, potentially providing enhanced sensitivity to glucose-related autonomic modulation as described in Table 3. Parasympathetic dominance of deep sleep offers complementary metabolic insights.

3 Conclusions

This pilot study presents a preliminary age-normalization technique for heart rate variability features that shows initial promise for enhancing non-invasive glucose prediction accuracy from sleep-stage ECG analysis. Our methodology achieved a 25.6% improvement in prediction performance ($R^2 = 0.161$ vs. 0.132 for non-normalized features, $p < 0.01$), with systematic ablation studies initially confirming the role of age normalization in the model performance.

This proof-of-concept study demonstrates potential but requires extensive validation before clinical consideration. This approach was tested on single-lead ECG data from 43 subjects, providing preliminary evidence that sleep-stage specific analysis, particularly REM sleep HRV features, may offer advantages over traditional metrics.

Critical limitations include the small sample size ($n=43$), lack of demographic diversity, and the preliminary nature of the validation. Future work must focus on large-scale multi-site validation ($n>200$), diverse demographic testing, and prospective clinical trials before any clinical utility can be established. This work should be considered as exploratory research, which requires substantial additional validation.

Beyond glucose prediction, the age-normalization framework addresses fundamental challenges in autonomic function assessment across heterogeneous populations, potentially extending to other HRV-based biomedical applications including cardiovascular risk stratification and sleep disorder diagnosis. This study establishes a preliminary foundation for sleep-aware, age-adjusted physiological monitoring in diabetes management.

Several critical limitations restrict the interpretation and generalizability of this pilot study. The small cohort ($n=43$) limits statistical power and generalizability, while the demographic homogeneity may not represent broader populations. The single-site nature of the data requires multi-site validation for robustness, and the preliminary cross-validation results require independent dataset confirmation before definitive conclusions can be drawn. Current performance levels remain insufficient for clinical deployment, and the simple age normalization approach may not capture the full complexity of autonomic changes across diverse populations. These limitations necessitate extensive further research, including large-scale multi-site validation studies ($n>200$), diverse demographic testing, and prospective clinical trials, before any clinical utility can be established. This work should be considered exploratory research providing preliminary evidence for the potential of age-normalized HRV features in glucose prediction.

4 Methods

The study included 43 adult subjects with complete multi-modal data comprising overnight ECG recordings, extracted RR-intervals, clinical glucose measurements, and

validated sleep quality assessments [16]. Inclusion criteria were adults with documented clinical glucose measurements and overnight ECG recordings of sufficient quality for accurate RR-interval extraction.

4.1 Data Acquisition and Signal Processing

ECG Recording

Single-lead ECG signals were acquired at a sampling frequency of 250 Hz using a standard monitoring equipment. Raw signals underwent scaling validation to ensure physiological amplitude range (± 5 mV) [17], addressing potential instrumentation variations that could affect the subsequent analysis.

RR-Interval Extraction

R-peak detection was performed using adaptive threshold algorithms [18] with manual verification for quality control. RR-intervals were extracted with systematic artifact removal using statistical outlier detection (intervals beyond three standard deviations from the local mean were excluded) [17].

Sleep-Stage Classification: Sleep stages were identified using criteria established by the American Academy of Sleep Medicine [19]:

1. Deep Sleep (DS): Slow-wave sleep with parasympathetic dominance.
2. REM Sleep: Rapid eye movement phase with variable autonomic activity.
3. Rapid Sleep (RS): Transitional sleep state with intermediate autonomic characteristics

4.2 HRV Feature Extraction

Time-domain HRV parameters were computed separately for each sleep stage following Task Force guidelines[9].

Standard HRV metrics per sleep stage

1. Mean RR interval (ms).
2. Root mean square of successive differences (RMSSD, ms).
3. Standard deviation of NN intervals (SDNN, ms).
4. Percentage of successive RR intervals differing by >50 ms (pNN50, %).
5. RR interval range (maximum - minimum, ms).

4.3 Age-Normalization Technique

A novel mathematical age-normalization approach was developed to account for age-related autonomic decline as described in Eq 1

$$HRV_{age_normalized} = \frac{HRV_{raw}}{age_factor + \epsilon} \quad (1)$$

where,

$$age_factor = \frac{age}{65.0}$$

$\epsilon = 0.1$ (numerical stability factor)

This formulation scales HRV features relative to expected age-related decline, using chronological age 65 as a reference point representing typical autonomic function transitions in healthy populations [20, 21]. The stability factor ϵ prevents numerical instability while preserving the normalization effect.

Age normalization was specifically applied to the mean RR interval features across all sleep stages.

- `hrv_ds_mean_rr_age_normalized`
- `hrv_rem_mean_rr_age_normalized`
- `hrv_rs_mean_rr_age_normalized`

4.4 Target Variable Engineering

Primary Target

Clinical glucose measurements were log-transformed to address distributional skewness and improve regression stability as described in Eq 2

$$y_{\text{target}} = \ln(\text{glucose_mmol_L}) \quad (2)$$

This transformation normalizes the glucose distribution and stabilizes variance across the physiological range, thereby enhancing the machine learning performance [22].

4.5 Feature Selection Strategy

A systematic correlation-based feature selection approach was employed:

1. Correlation Analysis: Pearson correlation coefficients were calculated for all features and the log-transformed glucose target.
2. Statistical Filtering: Features with p-values < 0.2 were retained to balance inclusivity with statistical relevance.
3. Ranking Selection: Top 15 features by absolute correlation strength were selected for the final modeling.

This conservative approach prevents overfitting while maintaining relevant predictive features for a the small dataset, following the best practices for biomedical feature selection [23].

4.6 Machine Learning Implementation

Model Selection

BayesianRidge regression [24] was chosen because of its robust performance on small datasets with built-in uncertainty quantification as described in Eq 3.

$$\text{Hyperparameters} : \alpha_1 = \alpha_2 = \lambda_1 = \lambda_2 = 1 \times 10^{-6} \quad (3)$$

These parameters provide optimal regularization for small sample sizes while maintaining model flexibility.

Cross-Validation

5-fold cross-validation with stratified sampling ensured robust performance estimation and prevents overfitting [25]. The performance metrics are as follows:

- Coefficient of determination (R^2)
- Mean absolute error (MAE)
- Pearson correlation coefficient with significance testing.

4.7 Ablation Study Design

Systematic ablation analysis validated individual component contributions:

1. Full Model: All features including age-normalized HRV.
2. No Age Normalization: Raw HRV features without age correction.
3. No Sleep HRV: Exclusion of sleep-stage specific HRV features.
4. ECG Only: Exclusively ECG-derived features.
5. Clinical Only: Traditional clinical parameters without HRV.

This approach quantifies the specific contribution of each methodological component [26].

4.8 Implementation Details

All analyses were conducted on the Google Cloud Platform using TPU v3-8 (128 GB HBM). The software stack was based on Python 3.9, TensorFlow 2.19.0 (PJRT runtime), and TPU-optimized libraries (NumPy, SciPy, Scikit-learn, XGBoost, Statsmodels). The custom modules handle ECG signal processing and feature extraction. Reproducibility was ensured via fixed random seeds (`seed=42`) and Docker containerization.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this study.

Data Availability

The dataset used and/or analyzed during the current study is publicly available in the Mendeley Data repository, accessible at <https://data.mendeley.com/datasets/9c47vwvtss/4>. The processed data required to reproduce these findings and the code used for the analysis in this study are available at <https://github.com/mdbasit897/SAHT-ECG-Glucose-Prediction>. The analysis code was provided only for research purposes. These results require validation before any clinical application.

CRedit Author Statement

Md Basit Azam: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data Curation, Writing – Original Draft, Visualization, Project Administration, Resources; **Sarangthem Ibotombi Singh:** Conceptualization, Methodology, Validation, Writing – Review & Editing, Supervision, Resources.

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