Wearable-Derived Autonomic Metrics for Predicting Metabolic and Hepatic Risk: Insights from AI-READI

Capstone Project

Paul Kalnins, ND, MS

NLM T-15 Postdoctoral Fellow
Division of Informatics, Clinical Epidemiology, and Translational Data Science (DICE)
Oregon Health & Science University (OHSU)

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Abstract

This study evaluated the predictive value of wearable-derived autonomic function metrics (WOMAFs) for two important metabolic outcomes: Type 2 Diabetes Mellitus (T2DM) and liver fibrosis associated with Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD). Leveraging the AI-READI dataset, which integrates clinical, laboratory, and wearable data, we assessed whether autonomic markers from wearable devices and resting electrocardiograms (ECGs)—including adjusted heart rate variability (HRV) measures (SDNN, RMSSD), Garmin stress scores, pulse-respiratory quotient (PRQ), and sleep efficiency ratio (SER)—could identify individuals at risk for T2DM and liver fibrosis, the latter estimated via the Steatosis-Associated Fibrosis Estimator (SAFE) score. Participants were categorized into low- and intermediate-high-risk groups based on SAFE scores. Logistic regression models combining WOMAFs, ECG-HRV, and anthropometric measures (body mass index, waist-hip ratio, and waist circumference) demonstrated moderate accuracy in predicting both outcomes. While WOMAFs alone showed limited predictive capacity, their integration with traditional clinical markers improved non-invasive risk stratification. These findings highlight the potential of combining wearable and clinical data to enhance screening for T2DM and MASLD-related liver fibrosis.

1. Introduction

Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disorder marked by insulin resistance and progressive beta-cell dysfunction, leading to hyperglycemia and widespread systemic complications.1 T2DM affects over 38 million Americans—approximately one in ten—and accounts for 95% of all diabetes cases.2 Its prevalence continues to grow globally, driven by factors such as obesity, sedentary lifestyles, poor diet, environmental exposures, and chronic stress, all of which contribute to cardiometabolic dysfunction.3 T2DM significantly increases the risk of macro- and microvascular complications, including cardiovascular disease (CVD), chronic kidney disease (CKD), neuropathy, retinopathy, and impaired wound healing.4–6

An often-overlooked complication of T2DM is metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as non-alcoholic fatty liver disease (NAFLD).[7,8] MASLD represents the hepatic manifestation of metabolic syndrome and affects nearly 38% of adults worldwide, increasing the risk for cirrhosis, liver cancer, and the need for liver transplantation.[9,10] MASLD is defined by hepatic steatosis in the absence of significant alcohol consumption, typically co-occurring with cardiometabolic risk factors such as obesity, hypertension, or dyslipidemia.[8] Notably, MASLD can also affect individuals with a normal body mass index ("lean MASLD"), likely due to visceral adiposity and insulin resistance.[11]

While simple hepatic steatosis is often benign, approximately 20% of MASLD cases progress to steatohepatitis (MASH) and liver fibrosis, substantially increasing the risk of cirrhosis and hepatocellular carcinoma.[10] Both MASLD and T2DM independently elevate the risk of CVD, CKD, and premature mortality.[12,13] Although fibrosis progression may be reversible with lifestyle modifications or emerging pharmacotherapies, current diagnostic tools often lack sensitivity for early detection.[14–16] The presence of T2DM further accelerates fibrotic progression, which points to the need for improved risk stratification.[17]

Dysfunction in the autonomic nervous system (ANS) is increasingly recognized as a shared pathophysiological mechanism in both T2DM and MASLD. Autonomic imbalance characterized by heightened sympathetic activity and diminished parasympathetic tone is associated with insulin resistance, systemic inflammation, and cardiometabolic complications.[18,19] Advances in

wearable technologies now allow for the non-invasive assessment of autonomic function through metrics such as heart rate variability (HRV), pulse-respiratory quotient (PRQ), and sleep efficiency.[20,21]

This capstone project evaluates whether wearable-obtained autonomic metrics (WOMAFs) can enhance risk prediction for T2DM and liver fibrosis using clinical and wearable data from the NIH-funded AI-READI dataset.[22] Specifically, we examine associations between WOMAFs—including ECG-derived HRV, Garmin stress scores, PRQ, and sleep efficiency—and validated indices such as the Steatosis-Associated Fibrosis Estimator (SAFE) score. Logistic regression models are used to assess whether these non-invasive, physiological signals can improve identification of individuals at risk. This work contributes to a salutogenic digital health paradigm, emphasizing early detection and resilience-oriented prevention strategies.[23,24]

2. Background

2.1 Pathophysiology of T2DM and MASLD Progression

The rising prevalence of T2DM, MASLD and MASH is largely driven by obesogenic environments characterized by high-calorie, ultra-processed diets, sedentary lifestyles, urbanization, exposure to environmental toxins, and chronic psychological stress—often compounded by disrupted sleep patterns.[25,26] T2DM and MASLD are increasingly recognized as systemic metabolic disorders, closely linked to insulin resistance, chronic inflammation, and dysregulated lipid metabolism.[27]

In MASLD, progression from simple steatosis to fibrosis is driven by a constellation of interconnected mechanisms, collectively described by the "multiple-hit hypothesis." These include genetic predisposition, epigenetic modifications, neuroendocrine-immune dysregulation, altered hepatic lipid metabolism, and gut microbiome disturbances.[28–30] Together, these factors promote hepatic lipid accumulation, immune activation, and fibrogenesis.

Insulin resistance play a central role in the development of MASLD by enhancing hepatic de novo lipogenesis and impairing lipid oxidation, leading to excessive buildup of triglycerides and free fatty acids within hepatocytes.[31,32] This lipid overload promotes the formation of toxic lipid

species—such as diacylglycerols (DAGs) and ceramides—which trigger lipotoxicity, oxidative stress, endoplasmic reticulum (ER) stress, mitochondrial dysfunction, and ferroptosis.[33,34] These cellular stressors activate the immune system, recruiting both innate (e.g., Kupffer cells, macrophages, and natural killer (NK) cells) and adaptive (T and B lymphocytes) immune cells that release pro-inflammatory cytokines, including TNF-α, IL-1, IL-6, and IL-17A.[35,36]

This chronic inflammatory state is further exacerbated by gut-liver axis dysfunction. Increased intestinal permeability allows endotoxins and microbial metabolites to enter the portal circulation, stimulating hepatic immune responses.[37] These overlapping inflammatory pathways converge to activate hepatic stellate cells (HSCs), promoting their transdifferentiation into myofibroblasts that secrete extracellular matrix (ECM) proteins, ultimately leading to fibrosis, hepatocellular injury, and progressive liver dysfunction.[28,38,39]

2.2 Autonomic Nervous System (ANS) Dysregulation in T2DM and MASLD

Beyond metabolic disturbances, dysfunction of the autonomic nervous system (ANS) is increasingly recognized as a contributor to the progression of both T2DM and MASLD.[33] The ANS, a key regulator of the gut-liver-brain axis, orchestrates neuroendocrine, immune, and metabolic processes through its afferent (sensory) and efferent (motor) pathways. Afferent fibers relay visceral signals—such as hormones, cytokines, nutrients—to the hypothalamus, while efferent sympathetic (via the celiac ganglion) and parasympathetic (via the vagus nerve) fibers modulate hepatic metabolism, immune activity, detoxification, and regeneration.[33,40,41] Disruption of this liver-brain communication, as seen in hepatic denervation following liver transplantation, has been linked to obesity, dyslipidemia, and increased incidence of T2DM, underscoring the ANS's essential role in maintaining metabolic homeostasis.[33,42,43]

Dysautonomia—marked by sympathetic overactivity and diminished vagal tone—is commonly observed in both T2DM and MASLD and has been linked to the progression of liver fibrosis.[44] Insulin resistance and obesogenic signals stimulate hypothalamic centers, increasing sympathetic nervous system (SNS) activity and norepinephrine release, which in turn exacerbate hepatic steatosis, lipotoxicity, inflammation, and oxidative stress.[33] In animal models hepatic sympathetic denervation reverses obesity-induced steatosis and reduces liver triglyceride

accumulation in the context of high-fat diet-induced obesity, highlighting the pathological role of SNS overactivation. Conversely, parasympathetic activation—via vagus nerve stimulation or cholinergic agonists—attenuates hepatic inflammation and lipid accumulation through the cholinergic anti-inflammatory response.[45]

Sleep disturbances are increasingly recognized as markers of ANS imbalance and are closely associated with both T2DM and MASLD.[46] Normal sleep architecture is characterized by parasympathetic predominance during non-rapid-eye-movement (NREM) sleep—marked by reduced heart rate and blood pressure—followed by sympathetic dominance during rapid-eye-movement (REM) sleep.[46] In individuals with T2DM and MASLD, disrupted sleep patterns—including poor sleep quality, fragmentation, and reduced sleep efficiency—further exacerbate ANS dysregulation, contributing to hepatic inflammation and fibrosis.[47,48]

2.3 Wearable-Obtained Metrics of Autonomic Function (WOMAFs)

Given the prominent role of autonomic imbalance in the progression of T2DM and MASLD—characterized by increased sympathetic activity, reduced vagal tone, and disrupted sleep—physiological markers of autonomic function may offer valuable insight into disease severity and fibrosis risk. Advances in wearable technology now allow for continuous, non-invasive monitoring of autonomic indicators such as heart rate variability (HRV), pulse-respiratory quotient (PRQ), sleep quality. These wearable-obtained metrics of autonomic function (WOMAFs) provide a unique opportunity to assess real-time autonomic regulation in both active and resting states. Notably, they may serve as early indicators of insulin resistance, hepatic dysfunction, and fibrosis progression.

Heart Rate Variability (HRV)

HRV is a widely used non-invasive index of ANS function, representing the dynamic balance between sympathetic (SNS) and parasympathetic (PNS) activity.[49] Unlike the regular ticking of a metronome, a healthy heart exhibits beat-to-beat variability, indicating a flexible autonomic system capable of adapting to internal and external stressors.[50,51] Reduced HRV reflects diminished adaptability and has been consistently associated with chronic stress, systemic inflammation, and autonomic dysfunction in metabolic disease.[52,53]

HRV is derived from variability in the R-R intervals (the time between successive heartbeats) and can be quantified using time-domain (e.g., SDNN, RMSSD), frequency domain (e.g., LF, HF, LF/HF ratio), and nonlinear methods.[50] While clinical and research settings often rely on 24-hour Holter monitoring, wearable devices enable ultra-short recordings, making HRV a scalable tool for population health surveillance.[49] In both T2DM and MASLD, reduced HRV—particularly in parasympathetic indices like RMSSD and HF—is associated with greater insulin resistance, elevated fibrosis scores, and worse cardiovascular outcomes.[54,55]

Sleep Metrics

Sleep disturbances—including fragmentation, poor efficiency, and circadian misalignment—are closely tied to ANS dysregulation and may accelerate progression of MASLD and T2DM. Wearables now offer validated proxies for sleep architecture using actigraphy and photoplethysmography.[56] Patients with MASLD often exhibit increased nocturnal awakenings and altered sleep-wake cycles, which promote sympathetic overactivity, hepatic inflammation, and fibrotic remodeling.[47] Similarly, individuals with T2DM frequently demonstrate abnormal sleep patterns, especially reduced REM sleep and increased sleep apnea, which impair glycemic control and exacerbate insulin resistance.[57]

The bidirectional relationship between sleep and autonomic regulation, where poor sleep worsens ANS dysfunction and autonomic imbalance disrupts sleep quality, underscores the importance of sleep metrics as a core component of WOMAFs for metabolic liver disease risk assessment.

Pulse-Respiratory Quotient (PRQ)

The PRQ, defined as the ratio of heart rate to respiratory rate, is an emerging biomarker for assessing autonomic tone and cardiopulmonary coupling in real time.[58] Unlike HRV, PRQ responds rapidly to changes in posture and breathing patterns, making it well-suited for capturing short-term shifts in sympathetic and parasympathetic balance.[58,59]

While direct evidence linking PRQ to T2DM or MASLD is limited, its physiological

relevance—particularly in detecting acute autonomic fluctuations—positions it as a promising candidate for non-invasive fibrosis risk stratification. In MASLD, sympathetic overactivation and reduced vagal tone are central features of fibrotic progression and PRQ may detect these changes more dynamically than HRV alone.[60] Likewise, in T2DM, where autonomic dysregulation exacerbates glycemic variability and inflammation, PRQ could serve as an early warning signal of metabolic instability.[61]

2.4 Assessment of Fibrosis in MASLD

Fibrosis severity in MASLD is graded histologically from F0 (no fibrosis) to F4 (cirrhosis), with stages F2 and above (F2+) representing clinically significant fibrosis.[62] F2+ fibrosis is the strongest predictor of liver-related complications and cardiovascular mortality.[10] Notably, an estimated 40–50% of individuals with T2DM exhibit advanced fibrosis, emphasizing the urgent need for early detection and accurate risk stratification to reduce morbidity and mortality.[63]

While liver biopsy remains the diagnostic gold standard for assessing MASLD and MASH, its invasiveness, sampling variability, and limited scalability make it impractical for routine or large-scale screening.[64] These limitations have spurred the development of reliable, non-invasive alternatives.

Imaging-Based Modalities

Vibration-Controlled Transient Elastography (VCTE), commonly performed using FibroScan, is widely used for non-invasive fibrosis assessment.[65] It measures liver stiffness as a surrogate for fibrosis severity and demonstrates strong diagnostic accuracy, with an area under the curve (AUC) of 0.83 for detecting F2+ fibrosis.[64] Magnetic Resonance Imaging-Proton Density Fat Fraction (MRI-PDFF), which quantifies hepatic fat and metabolic dysfunction, achieves even higher AUCs (>0.93) in validation studies.[64] However, both imaging approaches face barriers to routine implementation due to high cost and limited accessibility, limiting their feasibly for widespread screening and longitudinal monitoring.

Serum-Based Biomarkers

Serologic models have gained favor for their accessibility, low cost, and scalability. These include indirect markers (e.g., APRI, FIB-4, NAFLD Fibrosis Score, and Steatosis-Associated Fibrosis Estimator [SAFE]) and direct markers of extracellular matrix turnover and fibrogenesis.[66] While direct markers may offer mechanistic insights, they are less frequently used due to higher costs and limited availability.[67] Indirect panels, though more widely used, can produce false positives in low-prevalence populations.[68]

Among these, the SAFE score stands out as a robust multivariable logistic regression model designed to estimate the probability of clinically significant fibrosis.[69,70] It multiple clinical and laboratory variables—including age, BMI (capped at 40), diabetes status, AST, ALT, globulin, and platelet count—providing a comprehensive risk estimate. Validation studies report AUCs ranging between 0.84 and 0.88, with SAFE scores <0.00 showing strong negative predictive value (>90%) for excluding significant fibrosis across diverse populations.[70]

This study adopts the SAFE score as a non-invasive, scalable tool for fibrosis risk estimation in populations at elevated cardiometabolic risk. By integrating the SAFE score with wearable-obtained metrics of autonomic function (WOMAFs)—including heart rate variability (HRV), stress indictors, and sleep efficiency—this work seeks proposes a novel framework for early fibrosis risk stratification. Such integration may enhance detection of high-risk individuals and inform more personalized, preventive strategies for MASLD and its complications.

3. Methods

3.1 Study Design and Population

This retrospective, cross-sectional study involved a secondary analysis of the publicly available portion of the AI-READI dataset. The primary objective was to evaluate the association between autonomic function metrics—derived from wearable devices and resting ECG recordings—and the risk of type 2 diabetes mellitus (T2DM) and clinically significant liver fibrosis in individuals with metabolic dysfunction-associated steatotic liver disease (MASLD).

T2DM status was based on documented clinical diagnoses, while fibrosis risk was assessed using the Steatosis-Associated Fibrosis Estimator (SAFE) score. No new data collection or participant interaction was performed in this analysis.

The AI-READI dataset was developed under the NIH Bridge2AI Program to support artificial intelligence and machine learning (AI/ML) research in metabolic health. The publicly accessible dataset includes survey data (demographics, lifestyle, environmental exposures), laboratory results (blood and urine), wearable-derived metrics (e.g., Garmin stress score, sleep efficiency, heart and respiratory rate), 10-second resting ECG recordings, retinal images, and environmental air quality data. Restricted-access elements—such as zip codes, detailed demographics (sex, race, ethnicity), medication history, and full medical records—were not available. Birth years were provided that allowed estimation of participant age within ±6 months.

A total of 1,077 participants were recruited from three U.S. sites by March 2025. Eligible individuals were aged ≥40 years, English-speaking, capable of providing informed consent, and either diagnosed with T2DM or at elevated risk for developing it. Exclusion criteria included pregnancy, gestational diabetes, type 1 diabetes, and missing wearable data. Participants with incomplete key variables or physiologically implausible heart rate variability (HRV) values—defined as SDNN or RMSSD < 100 milliseconds, likely due to ectopic beats in the short ECG recordings—were also excluded. The final analytic sample included 740 participants (Figure 1).

Participants were stratified into low- and high-risk groups for both T2DM and liver fibrosis. T2DM status was classified based on clinical diagnosis. Fibrosis risk was categorized using the

SAFE score: low risk (< 0.00) and high risk (≥ 0.00). Ethical approval and informed consent were obtained in the original AI-READI study protocol.

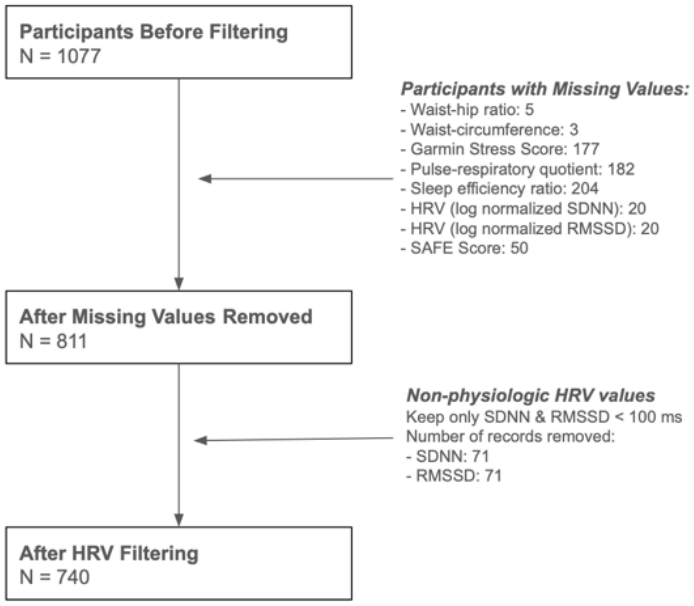


Figure 1. Flow diagram of participant selection. Of 1,077 participants, those missing values for key variables (e.g., waist-hip ratio, waist circumference, Garmin stress score, pulse-respiratory quotient, sleep efficiency ratio, HRV metrics [log-transformed SDNN and RMSSD], and SAFE score) were excluded (n = 266), yielding 811 participants. After removing records with non-physiologic HRV values (SDNN and RMSSD < 100 ms), 740 participants remained in the final analytic sample.

3.2 Data Acquisition, Preprocessing, Variable Calculation

This study integrated wearable-derived autonomic metrics, ECG-based heart rate variability measures, and clinical/laboratory data to evaluate associations with type 2 diabetes (T2DM) and liver fibrosis risk. Variables were derived through standardized preprocessing and calculation pipelines, detailed below.

Wearable-Obtained Autonomic Metrics (WOMAFs)

Autonomic data were obtained from the Garmin Vivosmart 5 device, which uses the proprietary Firstbeat Analytics algorithm. The following metrics were extracted and averaged across days:

- **Garmin Stress Score**: Quantifies autonomic balance on a scale from 0 to 100, with scores >25 indicating increased sympathetic activity. Values of -1 or -2, representing motion or uncertainty artifacts, were excluded.

- **Pulse Respiratory Quotient (PRQ)**: Calculated as the daily average ratio of heart rate to respiratory rate. Higher PRQ values indicate sympathetic predominance while lower values suggest increased parasympathetic tone.

- **Sleep Efficiency Ratio (SER)**: Computed from actigraphy-based sleep staging using the following formula:

  SER = [(Light + Deep + REM) / (Light + Deep + REM + Awake)]×100

  Higher SER values reflect improved sleep quality and increased parasympathetic activity.

Wearable JSON data were parsed using Python's orjson library (v3.10.15). Participants with fewer than two valid days of data were excluded. Multi-day averages were used to reduce intra-individual variability.

ECG-Derived Metrics

Resting ECG data were recorded using the Philips PageWriter TC30 system in a supine or 30° semi-reclined position. Raw XML files were converted to WFDB format and analyzed using wfdb (v4.1.2) and NeuroKit2 (v0.2.10) Python libraries. Lead XI was selected for analysis based on signal consistency.

SDNN and **RMSSD** were computed from the 10-second ECG segments, with the final second excluded to minimize motion artifacts. Values >100 ms—likely due to ectopic beats or signal noise—were removed. Both measures were log-transformed and normalized to resting heart rate to approximate a Gaussian distribution.

Liver Fibrosis Risk Estimation (SAFE Score)

The Steatosis-Associated Fibrosis Estimator (SAFE) score was calculated the following validated formula:

$$SAFE = 2.97(age) + 5.99(BMI) + 62.85(diabetes) + 154.85\ln(AST) - 58.23\ln(ALT) + 195.48\ln(globulin) - 141.61\ln(platelets) - 75$$

Participants were categorized as either low risk (<0.00) or intermediate-to-high risk (≥0.00) for clinically significant fibrosis.

Summary of Variables

Table 2 outlines all predictor and outcome variables used in this analysis, including their data sources and definitions.

Table 2: Predictor and Target Variables

Variable	Source	Type	Description
Garmin Stress Score	Wearable device	Predictor	Average daily HRV-derived stress score
Pulse Respiratory Quotient (PRQ)	Wearable device	Predictor	Average HR-to-respiratory rate ratio
Sleep Efficiency Ratio (SER)	Wearable device	Predictor	Sleep efficiency percentage
SDNN (log-normalized)	Resting ECG	Predictor	Standard deviation of NN intervals
RMSSD (log-normalized)	Resting ECG	Predictor	Root mean square of successive NN intervals
T2DM Diagnosis	Medical record	Target (outcome)	Presence or absence of T2DM diagnosis
SAFE Score	Clinical/lab measures	Target (outcome)	Estimated liver fibrosis risk

3.3 Statistical Analysis

All analyses were conducted to ensure data quality, reduce bias, and explore associations between autonomic function metrics and metabolic outcomes. After excluding participants with missing key variables or invalid sensor data (see Figure 1), the final analytic sample included 740 participants.

Descriptive statistics were generated for all variables. Continuous variables were summarized as means and standard deviations; categorical variables were presented as frequencies and percentages. Group comparisons were stratified by T2DM status (diagnosed vs. non-diagnosed) and liver fibrosis risk (SAFE score < 0.00 vs. ≥ 0.00).

Distributions of continuous variables—including body mass index (BMI), waist-hip ratio (WHR), waist circumference, Garmin stress score, pulse-respiratory quotient (PRQ), sleep efficiency ratio (SER), and log-transformed SDNN and RMSSD—were visualized using histograms overlaid with kernel density estimates. Target outcomes such as hemoglobin A1c (HbA1c) and SAFE score were similarly assessed for distributional characteristics and normality.

Bivariate relationships between predictors and continuous outcomes (HbA1c, SAFE score) were assessed using simple linear regression. Multivariable logistic regression was used to evaluate associations between predictors and binary outcomes (T2DM diagnosis and SAFE risk category), adjusting for relevant clinical covariates where applicable. Model performance was evaluated using the area under the receiver operating characteristic curve (ROC-AUC), as well as classification metrics including accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

To minimize overfitting and improve generalizability, we applied an 80/20 train-test split followed by 5-fold stratified cross-validation. Outcome class imbalance was addressed through stratified sampling within each fold to preserve class proportions.

All analyses were conducted in Python (v3.9.21) using the following libraries: NumPy (v26.4), pandas (v2.2.3), SciPy (v1.13.1), scikit-learn (v1.6.0), statsmodels (v0.14.4), and matplotlib

(v3.9.2). Statistical significance was defined as two-tailed $p < 0.05$. All analyses were exploratory in nature and intended to inform future hypothesis-driven studies.

4. Results

4.1 Participant Characteristics

Table 1 presents the summary of participant characteristics stratified by Type 2 Diabetes Mellitus (T2DM) and liver fibrosis risk, as determined by the SAFE score. The final analytic sample included 740 participants, with 39% classified as having Type 2 Diabetes Mellitus (T2DM) and 49% classified as having high liver fibrosis risk based on the SAFE score.

Participants with T2DM were slightly older (61.4 ± 11.0 years vs. 59.4 ± 10.8 years, $p = 0.013$), exhibited higher rates of obesity (52.1% vs. 31.2%, $p < 0.001$), metabolic syndrome (61.5% vs. 26.1%, $p < 0.001$), and hypertension (73.6% vs. 38.9%, $p < 0.001$) compared to those without T2DM. Anthropometric measures, including BMI (33.0 ± 8.5 kg/m² vs. 29.2 ± 7.0 kg/m²), waist-hip ratio (0.94 ± 0.08 vs. 0.90 ± 0.10), and waist circumference (108.3 ± 16.9 cm vs. 97.0 ± 16.7 cm), were significantly higher in the T2DM group (all $p < 0.001$).

Laboratory biomarkers demonstrated worse glycemic profiles among participants with T2DM, including higher glucose (128.6 ± 56.9 mg/dL vs. 94.1 ± 25.2 mg/dL) and hemoglobin A1c (6.73 ± 1.32% vs. 5.63 ± 0.57%) levels ($p < 0.001$ for both). Similarly, participants with high fibrosis risk had older age (64.3 ± 10.4 years vs. 56.2 ± 10.0 years, $p < 0.001$), higher rates of obesity (51.2% vs. 27.9%, $p < 0.001$), and worse cardiometabolic profiles.

Regarding autonomic function, participants with T2DM exhibited significantly higher Garmin stress scores (58.5 ± 18.7 vs. 49.3 ± 15.9, $p < 0.001$) and lower sleep efficiency ratios (74.9% ± 10.5 vs. 78.2% ± 9.5, $p < 0.001$). Both SDNN and RMSSD (log-normalized) were markedly lower in the T2DM and high fibrosis risk groups ($p < 0.001$ for all comparisons), indicating impaired heart rate variability among individuals with adverse metabolic profiles.

SAFE scores were notably higher among participants with T2DM (53.8 ± 78.1 vs. –32.5 ± 74.3, $p < 0.001$) and in those with high fibrosis risk compared to those with low fibrosis risk (72.1 ± 56.1 vs. –67.2 ± 46.7, $p < 0.001$).

Table 1: Summary of Participants Grouped by T2DM and SAFE Scores

	T2DM Category			SAFE Score Category		
	No T2DM[1]	**T2DM**[1]	**p-value**[2]	**Low Fibrosis Risk**[1]	**High Fibrosis Risk**[1]	**p-value**[2]
Counts (Total n = 740)	**452** (61%)	**288** (39%)		**377** (51%)	**363** (49%)	
General Characteristics						
Age (years)	59.38 (10.82)	61.40 (10.96)	0.013	56.23 (9.95)	64.26 (10.36)	<0.001
Systolic BP (mmHg)	127.84 (15.22)	129.29 (17.06)	0.341	125.03 (14.86)	131.90 (16.33)	<0.001
Diastolic BP (mmHg)	77.33 (9.21)	75.95 (8.84)	0.042	76.39 (8.88)	77.21 (9.28)	0.149
Obesity	141 (31.19%)	150 (52.08%)	<0.001	105 (27.85%)	186 (51.24%)	<0.001
Metabolic Syndrome	118 (26.11%)	177 (61.46%)	<0.001	95 (25.20%)	200 (55.10%)	<0.001
Hypertension	176 (38.94%)	212 (73.61%)	<0.001	149 (39.52%)	239 (65.84%)	<0.001
Type 2 Diabetes[3]	0 (0.00%)	288 (100.00%)	<0.001	68 (18.04%)	220 (60.61%)	<0.001
Insulin Use	2 (0.44%)	82 (28.47%)	<0.001	16 (4.24%)	68 (18.73%)	<0.001
Anthropomorphic Metrics						
BMI (kg/m^2)	29.17 (6.98)	33.03 (8.51)	<0.001	28.05 (6.34)	33.39 (8.30)	<0.001
Waist-Hip Ratio	0.90 (0.10)	0.94 (0.08)	<0.001	0.89 (0.09)	0.94 (0.09)	<0.001
Waist Circumference (cm)	96.96 (16.66)	108.25 (16.93)	<0.001	94.14 (15.57)	108.85 (16.50)	<0.001
Laboratory Biomarkers						
Glucose (mg/dL)	94.13 (25.20)	128.57 (56.91)	<0.001	99.28 (32.03)	116.11 (52.20)	<0.001
Hemoglobin A1c (%)	5.63 (0.57)	6.73 (1.32)	<0.001	5.78 (0.89)	6.35 (1.18)	<0.001
Insulin (ng/mL)	0.89 (1.06)	1.13 (1.14)	<0.001	0.82 (0.90)	1.16 (1.25)	<0.001
hs-CRP (mg/L)	2.87 (4.94)	4.99 (8.49)	<0.001	2.70 (4.85)	4.74 (7.95)	<0.001
Total Cholesterol (mg/dL)	185.83 (39.48)	153.07 (41.89)	<0.001	183.12 (41.90)	162.65 (42.62)	<0.001
Triglycerides (mg/dL)	144.45 (83.16)	163.71 (130.50)	0.092	147.25 (102.99)	156.82 (105.99)	0.213
HDL-Cholesterol (mg/dL)	59.43 (16.41)	50.22 (13.90)	<0.001	58.50 (16.11)	53.09 (15.66)	<0.001
LDL-Cholesterol (mg/dL)	101.14 (33.49)	75.05 (34.24)	<0.001	99.04 (35.45)	82.63 (34.84)	<0.001
NT-proBNP (pg/mL)	227.71 (3303.25)	149.82 (591.54)	0.719	264.82 (3621.40)	127.38 (493.05)	<0.001
Blood-Urea Nitrogen (mg/dL)	15.44 (5.03)	17.84 (7.98)	<0.001	15.21 (5.49)	17.58 (7.11)	<0.001
Creatinine (mg/dL)	0.86 (0.35)	1.00 (0.49)	<0.001	0.87 (0.40)	0.97 (0.43)	<0.001
Wearable-Obtained Autonomic Metrics						
Garmin Stress Score	49.26 (15.92)	58.53 (18.73)	<0.001	51.43 (16.89)	54.37 (18.30)	0.025
Pulse-Respiratory Quotient (PRQ)	5.28 (0.60)	5.46 (0.67)	<0.001	5.37 (0.58)	5.33 (0.68)	0.382
Sleep Efficiency Ratio (SER) (%)	78.21 (9.52)	74.92 (10.52)	<0.001	78.66 (9.44)	75.13 (10.34)	<0.001
SDNN (Log-Normalized)	-1.09 (0.72)	-1.52 (0.84)	<0.001	-1.12 (0.76)	-1.40 (0.82)	<0.001
RMSSD (Log-Normalized)	-1.09 (0.75)	-1.52 (0.86)	<0.001	-1.15 (0.78)	-1.36 (0.85)	<0.001
Fibrosis Metric						
SAFE Score	-32.46 (74.28)	53.82 (78.09)	<0.001	-67.19 (46.74)	72.07 (56.11)	<0.001

[1]Mean (SD); n (%)
[2] Wilcoxon rank sum test; Pearson's Chi-squared test
[3] T2DM status determined by using the clinical record

4.2 Ranges and Distributions of Predictor and Outcome Variables

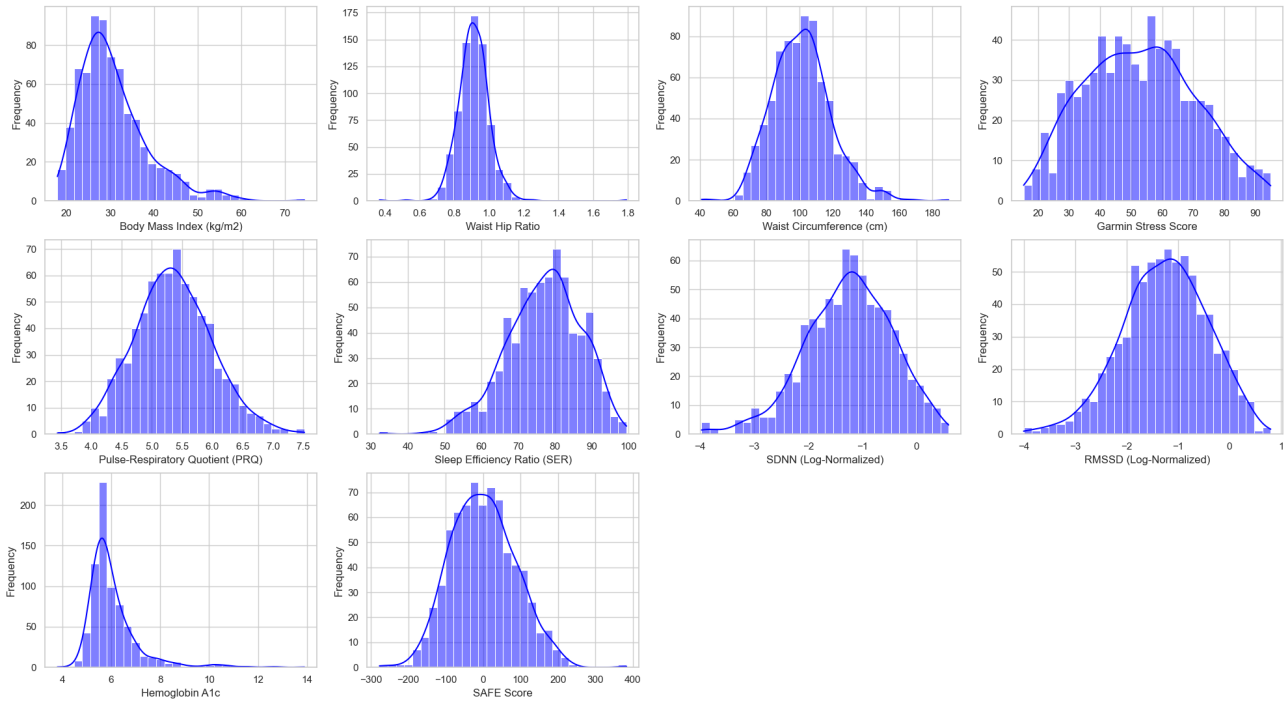
The distributions of the predictor and outcome variables were assessed for normality using the Shapiro-Wilk test (table 3) and are plotted as histograms (figure 2). For the anthropometric metrics, all variables—Body Mass Index (BMI), Waist-Hip Ratio, and Waist Circumference—showed significant deviations from normality ($p < 0.0001$). The Garmin Stress Score, Sleep Efficiency Ratio (SER), SDNN (log-normalized), and RMSSD (log-normalized) also exhibited non-normal distributions with p-values less than 0.05. In contrast, the Pulse-Respiratory Quotient (PRQ) was normally distributed ($p = 0.172$).

Regarding the outcome variables, both Hemoglobin A1c and the SAFE Score did not follow a normal distribution, with p-values indicating significant departures from normality ($p < 0.05$). In summary, while the PRQ was normally distributed, most other predictor and outcome variables showed significant deviations from normality.

Table 3: Distributions of Predictor and Outcome Variables

	Missing (n)	Minimum	Maximum	Shapiro-Wilk p-value	Normal Distribution
Anthropomorphic Metrics					
Body Mass Index (kg/m2)	0	17.88	74.53	0.0000	No
Waist Hip Ratio	0	0.37	1.79	0.0000	No
Waist Circumference (cm)	0	41.00	190.00	0.0000	No
WOMAFs					
Garmin Stress Score	0	15.38	94.95	0.0000	No
Pulse-Respiratory Quotient (PRQ)	0	3.44	7.52	0.1720	Yes
Sleep Efficiency Ratio (SER)	0	32.32	99.42	0.0000	No
SDNN (Log-Normalized)	0	-3.97	0.59	0.0000	No
RMSSD (Log-Normalized)	0	-4.00	0.80	0.0055	No
Outcome Variables					
Hemoglobin A1c	6	3.80	13.90	0.0000	No
SAFE Score	0	-277.08	382.86	0.0057	No

Figure 2: Distributions of Predictors (WOMAFs) and Target Variables



4.3 Linear Regression

Figure 3 displays the associations between various anthropomorphic and wearable-obtained autonomic function metrics (WOMAFs) and glycated hemoglobin (HbA1c) using simple linear regression models. The R^2 values indicate the proportion of variance in HbA1c explained by each predictor, with regression lines (in red) and 95% confidence intervals (gray shaded areas) included.

Among the anthropomorphic predictors, waist circumference demonstrated the highest R^2 value (0.097), followed by body mass index (BMI) with an R^2 of 0.063, while waist-hip ratio explained only 3.3% of the variance ($R^2 = 0.033$). Similarly, Garmin Stress Score ($R^2 = 0.067$) was the strongest autonomic predictor of HbA1c, albeit with modest explanatory power. Other autonomic metrics, including Pulse-Respiratory Quotient (PRQ), Sleep Efficiency Ratio (SER), log-normalized SDNN, and log-normalized RMSSD, demonstrated minimal associations with HbA1c, with R^2 values ranging from 0.021 to 0.026.

Overall, these findings highlight weak associations between HbA1c and both anthropomorphic and autonomic predictors, suggesting that these metrics, while relevant, explain only a small proportion of the variability in glycemic control. The relatively low R^2 values underscore the complexity of factors influencing HbA1c and suggest the need for incorporating additional clinical and behavioral covariates to improve model performance.

Figure 3: Scatterplots of Wearable-Derived Metrics vs. hba1c

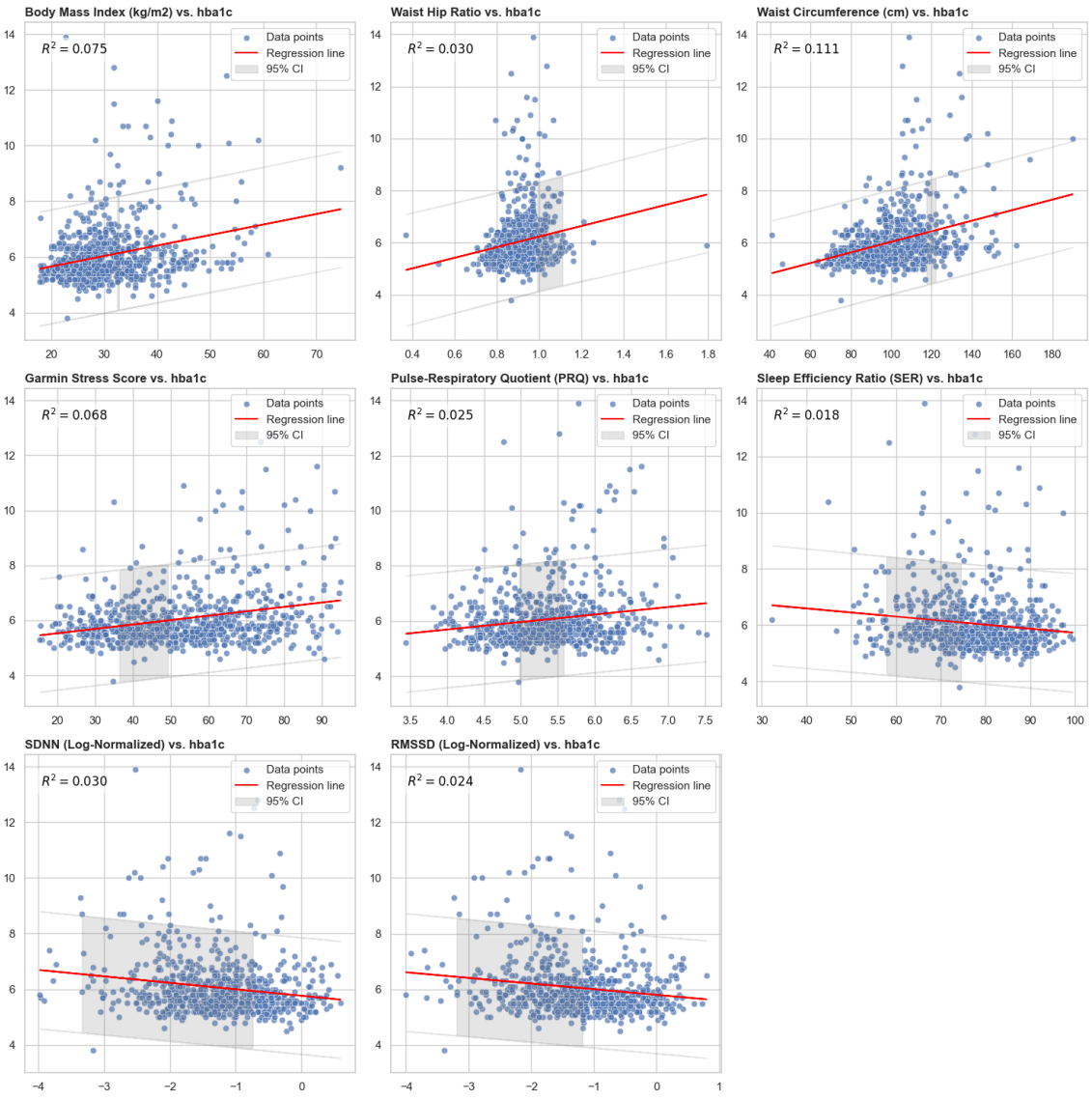
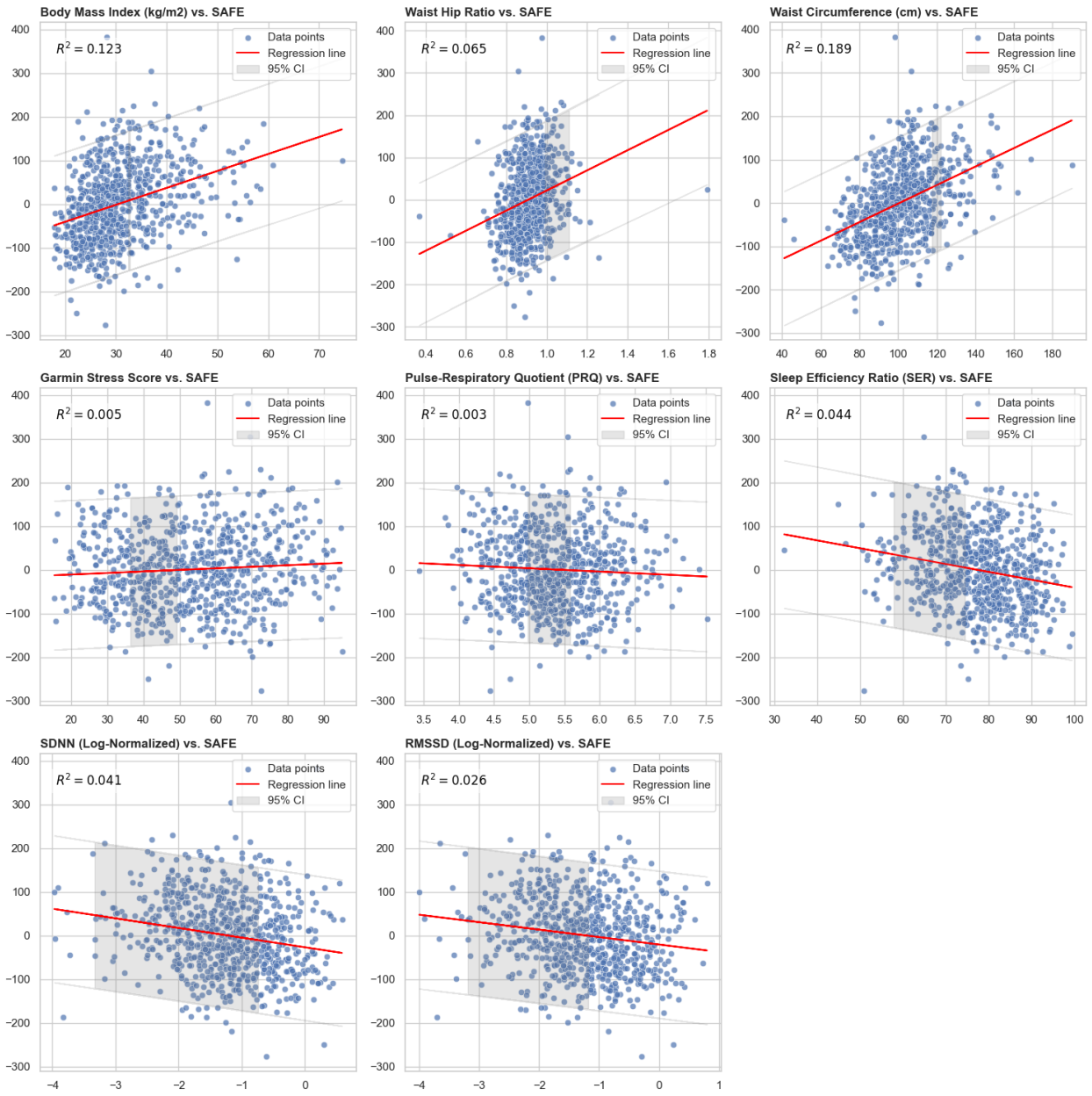


Figure 4 presents the results of simple linear regression models examining the relationships between various anthropomorphic and autonomic predictors with the Steatosis-Associated Fibrosis Estimator (SAFE) score. Each scatter plot depicts the distribution of data points (blue dots) for a given predictor relative to the SAFE score, overlaid with a red regression line and a shaded 95% confidence interval (CI). The R^2 values, shown in the top-left corner of each plot, indicate the proportion of variance in the SAFE score explained by each predictor.

Among the anthropomorphic predictors, waist circumference demonstrated the strongest association with the SAFE score, explaining 17.0% of the variance ($R^2 = 0.170$), followed by body mass index (BMI) with an R^2 of 0.108. Waist-hip ratio exhibited a weaker association, accounting for only 5.8% of the variance. Conversely, most autonomic predictors showed minimal associations with the SAFE score. Garmin Stress Score ($R^2 = 0.002$), Pulse-Respiratory Quotient (PRQ) ($R^2 = 0.005$), and log-normalized RMSSD ($R^2 = 0.011$) all exhibited negligible explanatory power. Sleep Efficiency Ratio (SER) and log-normalized SDNN demonstrated slightly stronger but still weak associations, with R^2 values of 0.042 and 0.024, respectively.

Overall, these results suggest that anthropomorphic metrics, particularly waist circumference and BMI, have stronger associations with SAFE scores compared to autonomic metrics, which displayed minimal explanatory power. The weak associations observed with autonomic predictors reinforce the complexity of the pathophysiological mechanisms underlying liver fibrosis and emphasize the need for incorporating additional clinical and molecular covariates to enhance predictive model performance.

Figure 4: Scatterplots of Wearable-Derived Metrics vs. SAFE Score



4.4 Logistic Regression Analysis

Logistic regression models were developed to evaluate predictors of Type 2 Diabetes Mellitus (T2DM) and liver fibrosis risk (as measured by the SAFE score) in the study population (n = 740) (Table 4). In the T2DM model, 39% of participants had T2DM, while 61% did not, with a McFadden's R^2 of 0.144, indicating modest model fit. For liver fibrosis risk, 49% of participants were classified as high risk and 51% as low risk, with a McFadden's R^2 of 0.175.

In the T2DM model, higher Garmin Stress Score (OR = 1.022, p = 0.003), lower Sleep Efficiency Ratio (OR = 0.983, p = 0.041), and lower SDNN (log-normalized) (OR = 0.573, p = 0.049) were significantly associated with higher odds of T2DM. Waist circumference showed a borderline association (p = 0.067), while Body Mass Index (BMI), Waist-Hip Ratio, Pulse-Respiratory Quotient (PRQ), and RMSSD were not significantly associated.
In the liver fibrosis risk model, higher Waist Circumference (OR = 1.053, p = 0.001), lower Sleep Efficiency Ratio (OR = 0.975, p = 0.004), lower SDNN (log-normalized) (OR = 0.359, p < 0.001), and higher RMSSD (log-normalized) (OR = 1.919, p = 0.022) were significantly associated with high SAFE scores. Garmin Stress Score and PRQ were not significantly associated with liver fibrosis risk in this model.

Overall, measures of autonomic function, particularly stress, sleep efficiency, and HRV metrics, demonstrated modest but significant associations with metabolic and liver health outcomes

Table 4: Logistic Regression Analysis

	T2DM			SAFE Score		
	Total Samples: 740 - No T2DM: **452** (61%) - T2DM: **288** (39%) **McFadden's R^2: 0.144**			**Total Samples: 740** - Low Liver Fibrosis Risk: **377** (51%) - High Liver Fibrosis Risk: **363** (49%) **McFadden's R^2: 0.175**		
	Odds Ratio	**95% CI**	**p-value**	**Odds Ratio**	**95% CI**	**p-value**
Intercept	0.004	[0.00, 0.08]	< 0.001	0.021	[0.00, 0.50]	0.017
Anthropomorphic Metrics						
Body Mass Index	0.999	[0.95, 1.05]	0.959	1.011	[0.95, 1.07]	0.723
Waist-Hip Ratio	16.958	[0.79, 365.79]	0.071	3.766	[0.15, 95.00]	0.421
Waist Circumference (cm)	1.027	[1.00, 1.06]	0.067	1.053	[1.02, 1.09]	**0.001**
WOMAFs						
Garmin Stress Score	1.022	[1.01, 1.04]	**0.003**	0.998	[0.98, 1.01]	0.839
Pulse-Respiratory Quotient	0.891	[0.61, 1.31]	0.557	0.778	[0.53, 1.15]	0.205
Sleep Efficiency Ratio (%)	0.983	[0.97, 1.00]	**0.041**	0.975	[0.96, 0.99]	**0.004**
ECG-Derived HRV						
SDNN (log-normalized)	0.573	[0.33, 1.00]	**0.049**	0.359	[0.20, 0.63]	**< 0.001**
RMSSD (log-normalized)	1.01	[0.58, 1.75]	0.971	1.919	[1.10, 3.35]	**0.022**

4.5 Logistic Regression Prediction Models

Logistic regression models were developed to predict T2DM status and liver fibrosis risk (SAFE score category) using different sets of predictors: anthropomorphic metrics alone, wearable-obtained metrics of autonomic function (WOMAFs) alone, ECG-derived HRV metrics alone, and a combined model incorporating all predictors (Table 5, Figure 5). Models were evaluated using 5-fold stratified cross-validation with an 80%/20% train-test split.

In models using only anthropomorphic metrics (BMI, waist-hip ratio, and waist circumference), prediction performance was moderate for both T2DM (accuracy = 0.643; ROC-AUC = 0.692) and liver fibrosis risk (accuracy = 0.700; ROC-AUC = 0.743).

Models using WOMAFs alone (Garmin stress score, PRQ, and sleep efficiency ratio) demonstrated lower predictive performance, with an accuracy of 0.618 (ROC-AUC = 0.656) for T2DM and 0.597 (ROC-AUC = 0.622) for liver fibrosis risk.

Similarly, models using ECG-derived HRV metrics alone (log-normalized SDNN and RMSSD) achieved moderate but slightly lower predictive performance (T2DM accuracy = 0.628; ROC-AUC = 0.655 and liver fibrosis risk accuracy = 0.592; ROC-AUC = 0.610).

The combined model, incorporating all metrics, yielded the best performance across outcomes. For T2DM prediction, the combined model achieved an accuracy of 0.672 and a ROC-AUC of 0.743. For liver fibrosis risk, the model achieved an accuracy of 0.712 and a ROC-AUC of 0.760. These results suggest that integrating wearable-derived autonomic function metrics with anthropomorphic variables modestly improves prediction compared to using either type of data alone.

These findings suggest that wearable-derived autonomic function metrics alone offer modest predictive value for identifying risk of T2DM and liver fibrosis. However, combining these metrics with traditional anthropomorphic measures substantially improves model performance, highlighting the potential utility of integrated, multimodal approaches for risk stratification in clinical and digital health settings.

Table 5: Logistic Regression Prediction Models[1] Results

Total Samples	T2DM *No*	T2DM *Yes*	Liver Fibrosis Risk *Low*	Liver Fibrosis Risk *Intermediate-High*
740	452 (61%)	288 (39%)	377 (51%)	363 (49%)

Model 1: Anthropomorphic Metrics Only

Predictors: BMI (kg/m^2), Waist-Hip Ratio, Waist circumference

	Accuracy	Sensitivity	Specificity	PPV[2]	NPV[3]	ROC-AUC[4]
T2DM Category	0.643	0.667	0.628	0.534	0.748	0.692
Liver Fibrosis Risk (SAFE Score Category)	0.700	0.705	0.695	0.692	0.710	0.743

Model 2: WOMAFs Only

Predictors: Garmin Stress Score, PRQ, Sleep Efficiency Ratio (%)

	Accuracy	Sensitivity	Specificity	PPV[2]	NPV[3]	ROC-AUC[4]
T2DM Category	0.618	0.597	0.631	0.509	0.710	0.656
Liver Fibrosis Risk (SAFE Score Category)	0.597	0.576	0.618	0.593	0.601	0.622

Model 3: ECG-HRV Metrics Only

Predictors: SDNN (log-normalized), RMSSD (log-normalized)

	Accuracy	Sensitivity	Specificity	PPV[2]	NPV[3]	ROC-AUC[4]
T2DM Category	0.628	0.601	0.646	0.522	0.717	0.655
Liver Fibrosis Risk (SAFE Score Category)	0.592	0.587	0.597	0.583	0.601	0.610

Model 4: All Metrics

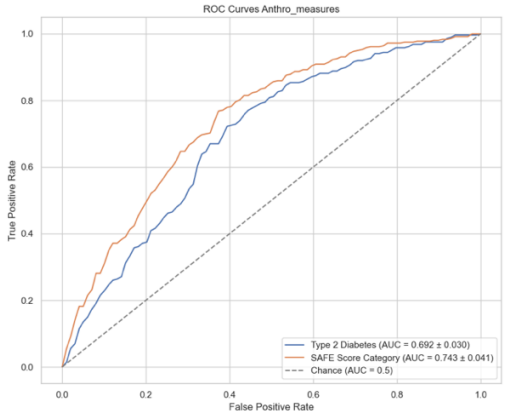
Predictors:

- *Anthropomorphic Metrics*: BMI (kg/m^2), Waist-Hip Ratio, Waist circumference
- *WOMAFs:* Garmin Stress Score, PRQ, Sleep Efficiency Ratio (%)
- ECG-HRV Metrics: SDNN (log-normalized), RMSSD (log-normalized)

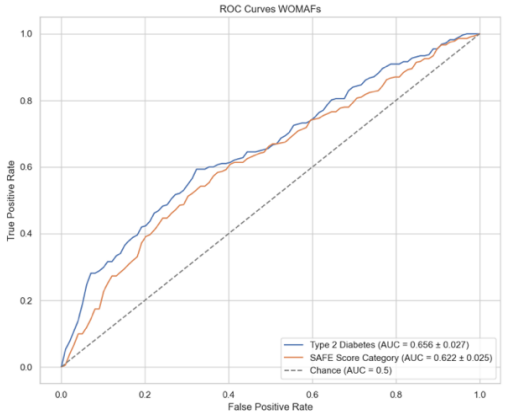
	Accuracy	Sensitivity	Specificity	PPV[2]	NPV[3]	ROC-AUC[4]
T2DM Category	0.672	0.632	0.697	0.574	0.749	0.743
Liver Fibrosis Risk (SAFE Score Category)	0.712	0.716	0.708	0.703	0.722	0.760

[1]Models employed 5-fold stratified cross-validation, with 80%/20% train-test split
[2] PPV = Positive Predictive Value | [3] NPV = Negative Predictive Value |
[4] ROC-AUC = Receiver Operating Characteristic – Area Under the Curve

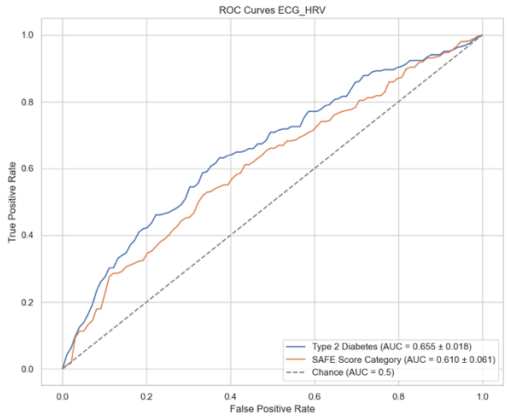
Figure 5: ROC-AUC Curves for Logistic Regression Models



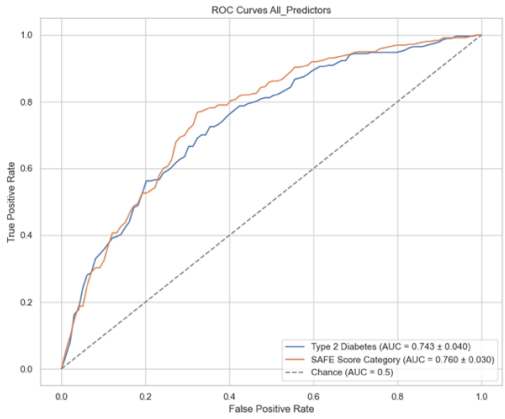
Anthropomorphic Measures Only



WOMAFs Only



ECG-HRV Only



All Predictors Combined

5. Discussion

5.1 Principal Findings

This study evaluated whether wearable-derived autonomic function metrics (WOMAFs) could predict two key metabolic outcomes: Type 2 Diabetes Mellitus (T2DM) and liver fibrosis risk. The principal findings were as follows: (1) WOMAFs alone demonstrated limited predictive capacity; (2) predictive performance improved substantially with the addition of anthropometric measures; and (3) combined models achieved moderate discrimination. These results highlight both the emerging utility and current limitations of wearable-based approaches in cardiometabolic and hepatic risk assessment.

Predictive Performance of WOMAFs Alone

Logistic regression models using only wearable-derived and ECG-based heart rate variability (HRV) metrics—Garmin stress score, pulse-respiratory quotient (PRQ), sleep efficiency ratio (SER), and log-transformed SDNN and RMSSD—yielded modest performance. The WOMAF-only model yielded ROC-AUCs of 0.656 for T2DM and 0.622 for liver fibrosis risk, with corresponding accuracies of 61.8% and 59.7%. These results suggest that while autonomic function metrics capture physiologically relevant variation, they may be insufficient on their own for reliable clinical risk stratification.

Impact of Adding Anthropometric Measures

Incorporating anthropometric predictors—BMI, waist-hip ratio (WHR), and waist circumference—significantly enhanced model performance. ROC-AUC values increased to 0.692 for T2DM and 0.743 for fibrosis risk. Waist circumference emerged as a particularly strong predictor of liver fibrosis, consistent with prior research linking central adiposity to hepatic steatosis and fibrosis.[71] These gains underscore the continued value of conventional clinical markers that reflect underlying metabolic dysfunction, including chronic inflammation and insulin resistance.[72]

Combined Models and Overall Predictive Capacity

The strongest models combined WOMAFs with anthropometric measures. The T2DM model achieved an ROC-AUC of 0.743 and 67.2% accuracy, while the fibrosis model reached an ROC-

AUC of 0.760 with 71.2% accuracy. While these results are encouraging, they remain moderate, suggesting that meaningful gains in predictive performance may require integration with additional modalities—such as biochemical, genomic, or imaging data—to build clinically actionable tools.

5.2 Limitations and Strengths

This study has several important limitations. First, the cross-sectional study design precludes causal inference. Second, some wearable-derived variables rely on proprietary algorithms with limited validation. For example, the Garmin stress score depends on accurate detection of rest periods and lacks benchmarking against established HRV measurement protocols, which typically require seated, resting assessments lasting ≥ 1 minute.[51] Third, the use of ultra-short (10-second) ECG recordings may reduce the reliability of HRV estimates due to susceptibility to motion artifacts and ectopic beats. Longer recordings (≥ 5 minutes) would enable more robust frequency-domain analysis, yielding more information about autonomic function.[73] Fourth, potential inaccuracies in wearable-derived sleep staging algorithms may have affected the validity of the sleep efficiency ratio (SER).[74] Finally, liver fibrosis categorization using the SAFE score without confirmatory imaging may have led to misclassification.[75]

Nonetheless, the study has notable strengths. It leverages a large, demographically diverse cohort (AI-READI), incorporates a range of autonomic function metrics, and applies rigorous analytic methods including cross-validation, enhancing both generalizability and model robustness.

5.3 Clinical Implications and Future Directions

The modest standalone performance of WOMAFs suggests that they are not yet suitable for use in isolation for clinical risk stratification of metabolic or hepatic disease. However, when combined with standard clinical variables, they enhance predictive accuracy, supporting their integration into multi-modal risk models. Future research should prioritize longitudinal validation, incorporate additional biomarkers of inflammation and neuroendocrine function (e.g., hs-CRP, cortisol, DHEA-S, melatonin),[76–78] and explore wearable technologies with higher fidelity and continuous monitoring capabilities. The application of machine learning may further

enable the synthesis of wearable, clinical, and biochemical data to facilitate early identification of individuals at elevated cardiometabolic and hepatic risk.

In sum, this study highlights the potential role of wearable-derived autonomic metrics in clinical informatics. Realizing their full utility will require continued advances in data quality, integration with complementary biomarkers, and the development of sophisticated modeling frameworks within a precision medicine paradigm.

Conclusion

This study highlights the emerging potential of wearable-derived autonomic function metrics in cardiometabolic and hepatic risk assessment. While these metrics alone offer limited predictive value for Type 2 Diabetes Mellitus and liver fibrosis risk, their integration with established anthropometric measures modestly improves model performance. These findings support the value of wearables as complementary tools within multi-modal, personalized risk frameworks. Realizing their full clinical utility will require continued advances in wearable sensor fidelity, standardized measurement protocols, and integration with clinical, biochemical, and computational tools. As such, wearables hold promise as a scalable component of precision health—particularly when embedded in robust, data-driven models of disease risk.

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