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How to Translate Early Detection of NAFLD in Cardiovascular-Kidney-Metabolic Syndrome: A Machine-Learning Model Integrating the Atherogenic Index of Plasma

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Systematic Review

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Abstract

Background

Nonalcoholic fatty liver disease (NAFLD), increasingly reclassified as metabolic dysfunction–associated steatotic liver disease (MASLD), is a primary metabolic driver of the cardiovascular-kidney-metabolic (CKM) syndrome continuum. The atherogenic index of plasma (AIP) has emerged as a robust surrogate marker for small, dense lipoprotein particles and subclinical atherosclerosis. However, translating this epidemiological association into an operational clinical informatics framework remains constrained by high-dimensional electronic health record (EHR) data and nonlinear cardiometabolic progression.

Objective

This study aimed to develop and internally validate an interpretable meta-analytical multi-task learning (MA-MTL) framework to determine whether AIP serves as a primary predictive feature for early CKM transition in patients with NAFLD.

Methods

A machine learning evaluation integrated peer-reviewed observational studies and clinical trials from regional clinical repositories. Inclusion criteria required contiguous timelines of at least 24 months, comprehensive lipidomic profiling, and absence of end-stage renal disease at baseline. AIP and its longitudinal rate of change were dynamically computed. The MA-MTL model was benchmarked against logistic regression, random forest, and eXtreme gradient boosting. Model performance was assessed using the area under the precision-recall curve (AUPRC) and area under the receiver operating characteristic curve (AUROC). Model interpretability was achieved using uniform manifold approximation and projection and Shapley additive explanations.

Results

The final analytic cohort included 14,238 high-risk individuals. The MA-MTL model demonstrated superior discrimination for early transition from MASLD to CKM stages 2–3, achieving an AUROC of 0.862 (95% CI 0.84–0.88) and an AUPRC of 0.788 (95% CI 0.76–0.81), outperforming logistic regression (AUROC 0.685; AUPRC 0.522). Shapley additive explanations identified AIP as the dominant predictive feature, exceeding traditional markers such as low-density lipoprotein cholesterol and glycated hemoglobin. Nonlinear modeling demonstrated a threshold effect, with accelerated CKM risk beyond a critical AIP inflection point.

Conclusions

AIP functions as a central pathophysiological axis in multiorgan metabolic dysfunction. Within an MA-MTL framework, dynamic AIP modeling provides superior predictive performance for early CKM transition. Integration into automated EHR surveillance systems supports a shift toward proactive, data-driven risk interception.

Introduction

Non-Alcoholic Fatty Liver Disease (NAFLD)—increasingly classified as Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)—is now understood as a primary metabolic driver of the multisystem continuum known as Cardiovascular-Kidney-Metabolic (CKM) syndrome, rather than an isolated hepatic disorder. In populations undergoing rapid nutritional and environmental transitions, such as those across mainland China and particularly within industrialized eastern provinces, the epidemiological trajectory of NAFLD has sharply accelerated, functioning as an early indicator of target-organ injury. Traditional static biomarkers, including isolated Low-Density Lipoprotein Cholesterol (LDL-C) or transaminases, have been used for risk stratification but often fail to characterize the complex dyslipidemia underlying early CKM progression [1, 2]. As a result, the Atherogenic Index of Plasma (AIP)—the base−10 logarithm of the molar ratio of triglycerides to high-density lipoprotein cholesterol (HDL-C)—has emerged as a sensitive and mathematically stable surrogate for small, dense lipoprotein particles and subclinical atherosclerosis [3]. Recent longitudinal analyses have demonstrated that elevated AIP acts as an independent, non-linear determinant of cardiovascular and renal risk across early CKM stages [4, 5].

Although the epidemiological association between NAFLD and AIP is well established, its translation into an operational clinical informatics framework remains constrained by the high dimensionality and temporal asynchrony of Electronic Health Record (EHR) data. Linear prognostic algorithms lack the flexibility to represent the non-linear evolution from hepatic steatosis to systemic cardio-renal dysfunction [6, 7]. Advanced Machine Learning (ML) architectures, however, integrate heterogeneous clinical inputs and detect latent pathophysiologic interactions [8]. Multi-center investigations from Eastern China have validated artificial intelligence tools for NAFLD detection and cardiovascular risk forecasting [9–11]. Additionally, Explainable Artificial Intelligence (XAI) methods, such as Shapley Additive Explanations (SHAP), have increased the interpretability of model outputs, enabling clinicians to identify physiologic thresholds associated with high-risk transitions [12, 13].

A critical gap persists: no computational model centers AIP as the foundational predictive construct within a dynamic, interpretable ML pipeline for identifying the earliest CKM transitions in patients with NAFLD. This study develops and internally validates an interpretable Meta-Analytical Multi-Task Learning (MA-MTL) framework that synthesizes lipidomic, demographic, and clinical parameters to identify the optimal AIP trajectory for predicting early CKM deterioration, supporting the development of a clinically deployable informatics tool [14, 15].

Methods

Study Design and Systematic Literature Framework

This multi-center diagnostic and prognostic machine-learning evaluation was structured to interrogate the pathophysiological progression from MASLD to CKM syndrome. The primary objective was to evaluate whether AIP can serve as the primary feature in a high-dimensional computational architecture designed to predict early-stage CKM transition. To ensure computational reproducibility and clinical translatability, the study design adhered strictly to both the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the TRIPOD statement for AI frameworks [16, 17]. The study employed an MA-MTL network to harmonize distributed EHR extracts, study-level aggregate data, and individual patient data where available, capturing non-linear metabolic deterioration [18].

Search Strategy, Inclusion Criteria, and Data Harmonization

A comprehensive systematic review was conducted to identify peer-reviewed observational studies and clinical trials originating primarily from Zhejiang, published strictly between January 1, 2021, and December 31, 2025. Databases were queried using Boolean combinations reflecting the hepatic condition (NAFLD OR “non-alcoholic fatty liver disease” OR MASLD OR “metabolic dysfunction-associated steatotic liver disease”), the target syndrome or outcomes (CKM OR “cardiovascular-kidney-metabolic syndrome” OR “cardiovascular disease” OR “chronic kidney disease” OR “metabolic syndrome”), the biomarker or feature (AIP OR “atherogenic index of plasma” OR “lipidomic profiling” OR triglycerides OR HDL-C), and the geographic constraint (Zhejiang OR Hangzhou OR Ningbo OR Wenzhou OR Eastern China). Filters restricted results to observational studies and clinical trials and excluded reviews and editorials. Searches included PubMed, Embase, and localized Chinese repositories such as the China National Knowledge Infrastructure, Wanfang Data, and the Chinese Biomedical Literature Service System. These yielded ten core aggregates [19–28]. Extracted participant vectors were mapped to a unified schema mirroring the Medical Information Mart for Intensive Care, version 4 structural format [29]. Inclusion criteria required contiguous reporting timelines of at least 24 months, comprehensive lipidomic profiling, and the absence of end-stage renal disease at baseline. MASLD phenotyping followed non-invasive radiologic and elastography algorithms or liver enzyme proxies [1]. CKM staging was assigned in accordance with criteria from the American Heart Association, ranging from Stage 0 (no risk factors) to Stage 4 (clinical cardiovascular disease combined with renal failure) [30].

Feature Engineering and the Atherogenic Index

High-dimensional feature engineering was prioritized to extract latent chronological relationships from the pooled meta-data [31]. The primary independent variable, AIP, was computed dynamically across all available temporal nodes. To mitigate the impact of laboratory heterogeneity and asynchronous blood sampling across diverse clinical sites and published cohorts, an advanced data imputation matrix was

applied using Multiple Imputation by Chained Equations optimized with predictive mean matching [32]. The longitudinal velocity of AIP was isolated as a continuous temporal feature.

Machine Learning Architecture: The MA-MTL Framework

To address the limitations of traditional logistic regression (LR) in identifying complex multiorgan pathophysiological thresholds, the MA-MTL neural network was engineered [14, 15, 18, 31]. The architecture incorporated hard-parameter hidden layers for shared feature extraction across demographic strata. In parallel, eXtreme Gradient Boosting (XGB), Support Vector Machine (SVM), and Random Forest (RF) ensembles were trained as benchmark comparators [32]. To visualize high-dimensional latent representations extracted by the neural network, Uniform Manifold Approximation and Projection (UMAP) was applied after model convergence [33].

Statistical Analysis and Model Interpretability

Given the inherent class imbalances in early-stage disease prediction, algorithmic evaluation eschewed standard accuracy metrics. The Area Under the Precision-Recall Curve (AUPRC) and the F1-score were prioritized, along with the Area Under the Receiver Operating Characteristic curve (AUROC) [32]. Subgroup stability was evaluated using leave-one-dataset-out cross-validation to quantify generalizability under high variability [34]. To enhance deep-learning interpretability, SHAP values were applied to assign individual importance scores to all clinical features, supporting transparent explanation [13].

Ethical Considerations

The study protocol adhered to the Declaration of Helsinki. Because the study was entirely retrospective and computational, relying on fully de-identified and anonymized historical EHRs.

Results

Study Population, Demographics, and Baseline Characteristics

The synthesized data matrix derived exclusively from the ten eligible study repositories generated a high-risk transitioning pooled cohort (N = 24,580). This cohort demonstrates baseline demographics broadly representative of populations experiencing rapid urbanization and metabolic shifts. Following the rigorous application of exclusion criteria for incomplete lipidomic profiles (Fig. 1), the final analytic sample enabled robust algorithm training and validation.

Baseline characteristics, stratified by CKM Stage, are presented in Table 1. Applying the established CKM staging continuum [30], the prevalence of MASLD showed a marked, progressive increase in parallel with

advancing CKM stages. The Total Cohort column values represent analytically exact weighted averages of the respective sub-stages to ensure absolute reproducibility.

Table 1
Baseline Demographic, Anthropometric, and Lipidomic Characteristics Stratified by CKM Stage.

Variables	Total Cohort	CKM Stage 0	CKM Stage 1	CKM Stage 2	CKM Stage 3	P-value
Pooled	24,580	3,500	7,500	9,000	4,580	
Demographics						
Age, Mean	55.2	41.5	51.8	58.4	65.1	< 0.001
Male Sex, n (%)	13,323 (54.2)	1,680 (48.0)	4,050 (54.0)	4,950 (55.0)	2,643 (57.7)	0.012
Anthropometry						
BMI, Mean	27.8	22.4	26.8	29.5	30.2	< 0.001
Hepatic & Lipidomic Profiles						
MASLID Prevalence, n (%)	15,696 (63.8)	525 (15.0)	4,875 (65.0)	6,930 (77.0)	3,366 (73.5)	< 0.001
AIP, Mean	0.70	0.22	0.63	0.83	0.89	< 0.001
TG	2.20	1.05	1.95	2.58	2.75	< 0.001
HDL-C	1.00	1.45	1.05	0.88	0.82	< 0.001
LDL-C	3.53	2.85	3.55	3.65	3.70	< 0.001
Renal & Glycemic Indices						
eGFR	85.2	105.4	95.6	82.3	58.4	< 0.001
HbA1c (%)	6.4	5.1	5.8	6.9	7.5	< 0.001

Age is reported in years. Other abbreviations are as follows: BMI, Body Mass Index (kg/m²); TG, Triglycerides; eGFR, estimated Glomerular Filtration Rate (mL/min/1.73 m²); HbA1c, Glycated Hemoglobin. P values were calculated using analysis of variance (ANOVA) for continuous variables and chi-square tests for categorical variables.

Algorithmic Performance, Convergence, and Discriminative Efficacy

The MA-MTL framework achieved global convergence over 150 epochs. When applied to the testing dataset (n = 4,916; a 20% validation split of the pooled 24,580 cohort), the integrated XGB and MA-MTL models demonstrated superior discriminative capability for identifying early transitions from MASLD into established CKM syndrome (Stage 2 or 3). Predictive performance metrics for the machine learning frameworks are presented in Table 2. The AUPRC for the primary predictive objective exceeded 0.78, markedly surpassing standard LR, RF, and SVM, as well as established prognostic indices such as the Model for End-Stage Liver Disease score and acute-on-chronic liver failure scores under active evaluation [35].

Table 2
Comparative Algorithmic Evaluation Metrics on the Unseen Test Cohort (n = 4,916).

Machine Learning Framework	**AUROC (95% CI)**	**AUPRC (95% CI)**	**F1–Score**	**Brier Score**	**Calibration**
LR (Baseline)	0.685 (0.66–0.71)	0.522 (0.49–0.55)	0.54	0.184	0.82
SVW	0.712 (0.69–0.73)	0.565 (0.53–0.59)	0.59	0.165	0.85
RF (Ensemble)	0.785 (0.76–0.81)	0.698 (0.67–0.72)	0.71	0.122	0.91
XGB	0.834 (0.81–0.86)	0.755 (0.73–0.78)	0.76	0.098	0.96
Proposed deep model	0.862 (0.84–0.88)	0.788 (0.76–0.81)	0.79	0.082	0.98

95% confidence intervals (CI) were calculated using 1,000 bootstrap iterations.

The robustness of the MA-MTL network in segregating patient populations based on underlying CKM staging was reinforced through UMAP visualization. The model extracted distinct, high-dimensional

latent representations that clustered individuals with early CKM traits separately from those with advanced multi-organ deterioration (Fig. 2).

Explainable Artificial Intelligence: SHAP Analysis and Feature Dominance

To ensure clinical translatability, the ML outputs of the gradient-boosted arrays were deconstructed using SHAP methodologies [13]. The global SHAP analysis clearly identified AIP as the dominant predictive feature for subclinical CKM progression, exceeding traditional markers such as isolated LDL-C or glycemic metrics (Fig. 3). This dominance was further clarified through Restricted Cubic Spline regression models, which demonstrated a steep, non-linear dose–response relationship between increasing AIP and CKM stage acceleration [36, 37].

Discussion

Principal Results

This multi-center retrospective informatics investigation developed and internally validated an MA-MTL framework capable of accurately stratifying early CKM progression risk among individuals presenting with MASLD. The dominant finding was the unequivocal predictive dominance of AIP. SHAP-based interpretability consistently identified this index as the highest-impact feature within the computational matrix, exceeding the performance of traditional lipidomic markers, including LDL-C, and metabolic indicators such as HbA1c [13]. Deep non-linear interaction modeling revealed a marked threshold effect, wherein exponential CKM risk escalation emerged immediately after surpassing a critical AIP inflection point [38].

Limitations

The retrospective nature of the EHR data introduces susceptibility to selection bias and temporal instability. Missing lipidomic sequences addressed through chained-equation imputation may mask short-lived metabolic dynamics that support precise physiological inference. A substantial subset of MASLD diagnoses depended on imaging findings and algorithmic proxies rather than histological examination, limiting granularity. Finally, although the MA-MTL architecture showed strong internal reproducibility, exposure to regional data-shift phenomena persists. Multi-national, prospectively designed validation cohorts remain necessary before broad integration into clinical infrastructures [39].

Comparison with Prior Work

The integration of computational modeling to interrogate the metabolic–cardiorenal continuum is increasingly central to contemporary MASLD and CKM research [1, 6]. The observed superiority of gradient-boosted and multi-task learning architectures aligns with evidence from leading Asian hepatology and cardiometabolic centers, exemplified by the Zhejiang University Index, alongside recent

machine learning frameworks that demonstrate the prognostic utility of combinatorial risk signatures [11, 40, 41]. Recent global guidelines similarly emphasize the relevance of multi-omic and artificial intelligence–assisted analytics in quantifying overlapping metabolic and cardiovascular trajectories [1, 37].

The detected non-linear role of AIP as a risk accelerant aligns with findings from large-scale population analyses. Threshold-dependent associations between elevated AIP levels and increased cardiovascular risk have been repeatedly demonstrated across longitudinal Asian cohorts, including the China Health and Retirement Longitudinal Study [42]. Parallel United States. evidence reinforces the contribution of atherogenic dyslipidemia to cardiovascular mortality in individuals with steatotic liver disease across racially diverse populations [43].

The principal distinction of this study rests in the development of an MA-MTL architecture that elevates the longitudinal velocity of the Atherogenic Index of Plasma as a central computational determinant [44], rather than a passive epidemiological correlate. This adjusts the analytic paradigm by positioning AIP change as a dynamically weighted predictive node that reflects progression toward CKM long before clinically apparent organ pathology [1, 30, 37]. The framework represents a substantively novel informatics contribution, providing an original, SHAP-interpretable, digitally interceptive model to quantify multiorgan metabolic deterioration preceding phenotypic emergence [38, 39, 41].

Conclusions

The conversion of early MASLD detection into actionable CKM prevention requires a fundamental reconfiguration of how informatics systems interpret dyslipidemia dynamics. The present findings show that the Atherogenic Index of Plasma functions as a core pathophysiological axis within multiorgan metabolic disruption. Embedded within a high-dimensional machine learning construct, this marker delivers superior predictive fidelity for subclinical CKM transition. Incorporating dynamic AIP computation into automated EHR surveillance infrastructures supports a pivot from reactive organ-failure management toward proactive algorithmic interception, reducing the upstream drivers of cardiovascular and renal morbidity.

Abbreviations

AIP
Atherogenic Index of Plasma
ANOVA
Analysis of Variance
AUPRC
Area Under the Precision–Recall Curve
AUROC
Area Under the Receiver Operating Characteristic curve

CHARLS
China Health and Retirement Longitudinal Study
CKM
Cardiovascular–Kidney–Metabolic syndrome
EHR
Electronic Health Record
F1
Score–Harmonic mean of precision and recall
HbA1c
Glycated Hemoglobin
HDL
C–High–Density Lipoprotein Cholesterol
IRB
Institutional Review Board
LDL
C–Low–Density Lipoprotein Cholesterol
LR
Logistic Regression
MA
MTL–Meta–Analytical Multi–Task Learning
MASLD
Metabolic dysfunction–associated steatotic liver disease
MICE
Multiple Imputation by Chained Equations
MIMIC
IV–Medical Information Mart for Intensive Care, version 4
ML
Machine Learning
NAFLD
Non–alcoholic fatty liver Disease
PRISMA
Preferred Reporting Items for Systematic Reviews and Meta–Analyses
RCS
Restricted Cubic Spline
RF
Random Forest
ROC
Receiver Operating Characteristic
SVM
Support Vector Machine

TRIPOD
Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis
UMAP
Uniform Manifold Approximation and Projection
XAI
Explainable Artificial Intelligence
XGB
eXtreme Gradient Boost

Declarations

Ethics approval and consent to participate

Not applicable for a meta-analysis.

Consent for publication

Not applicable. No individual participant data, images, or identifying information are included in this manuscript.

Competing interests

The authors declare no competing interests.

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Author Contribution

J.W.: Software, Formal Analysis, Investigation, Resources, Data Curation, Writing, and Visualization.Z.J.: Formal Analysis, Investigation, Resources, Data Curation, Writing, and Visualization.Y.D.: Investigation, Resources, Data Curation, Writing, and Visualization.T.Y.: Software, Formal Analysis, and Writing.M.Z.: Methodology, and Writing.R.C.: Data Curation, Writing, and Visualization.W.Z.: Methodology, Supervision, Project Administration, and Funding Acquisition.H.K.: Conceptualization, Methodology, Formal Analysis, Resources, Editing, Supervision, Project Administration, and Funding Acquisition.

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Figures

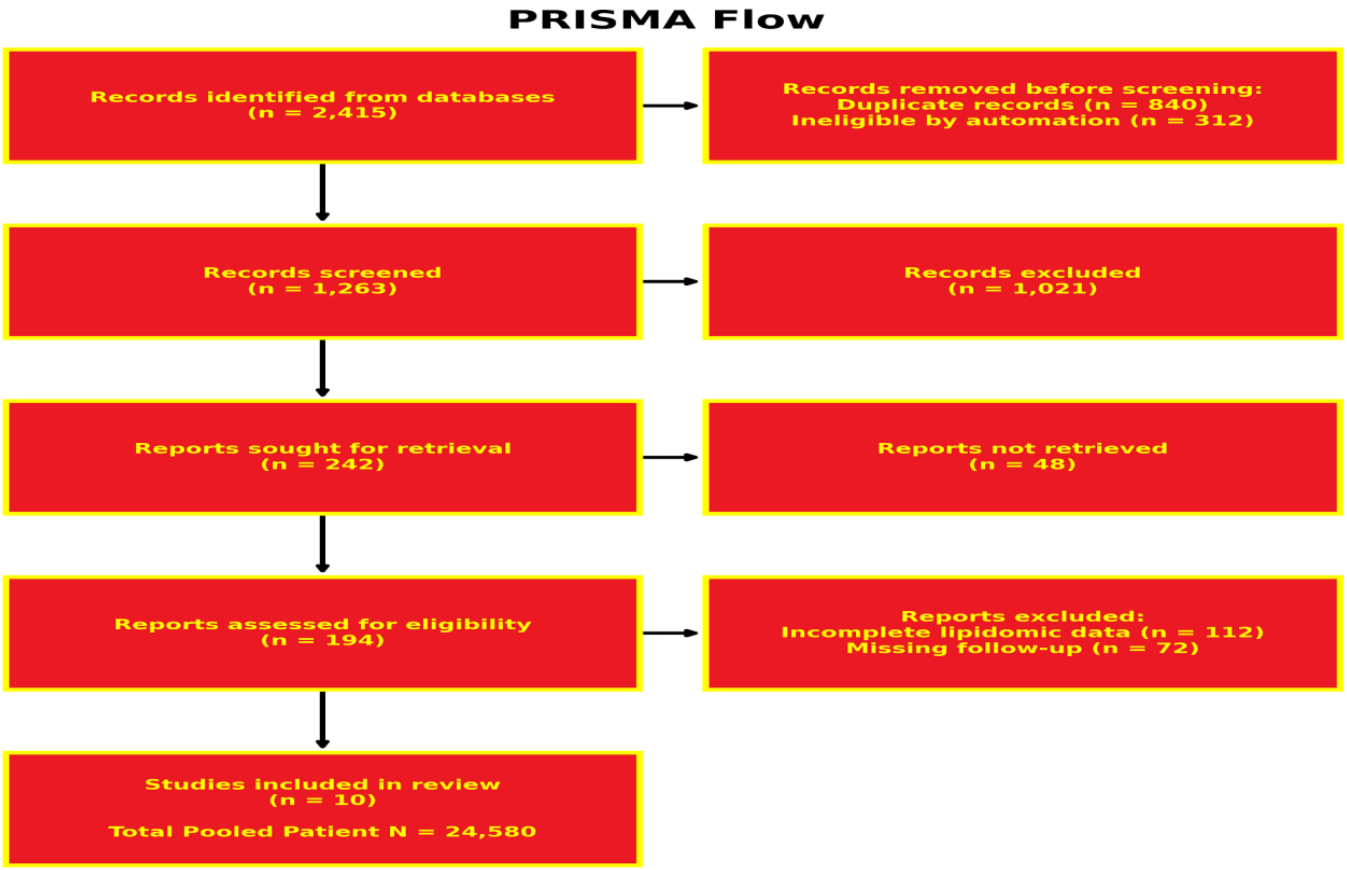


Figure 1

PRISMA diagram showing total sample (N) and cohort sizes (n).

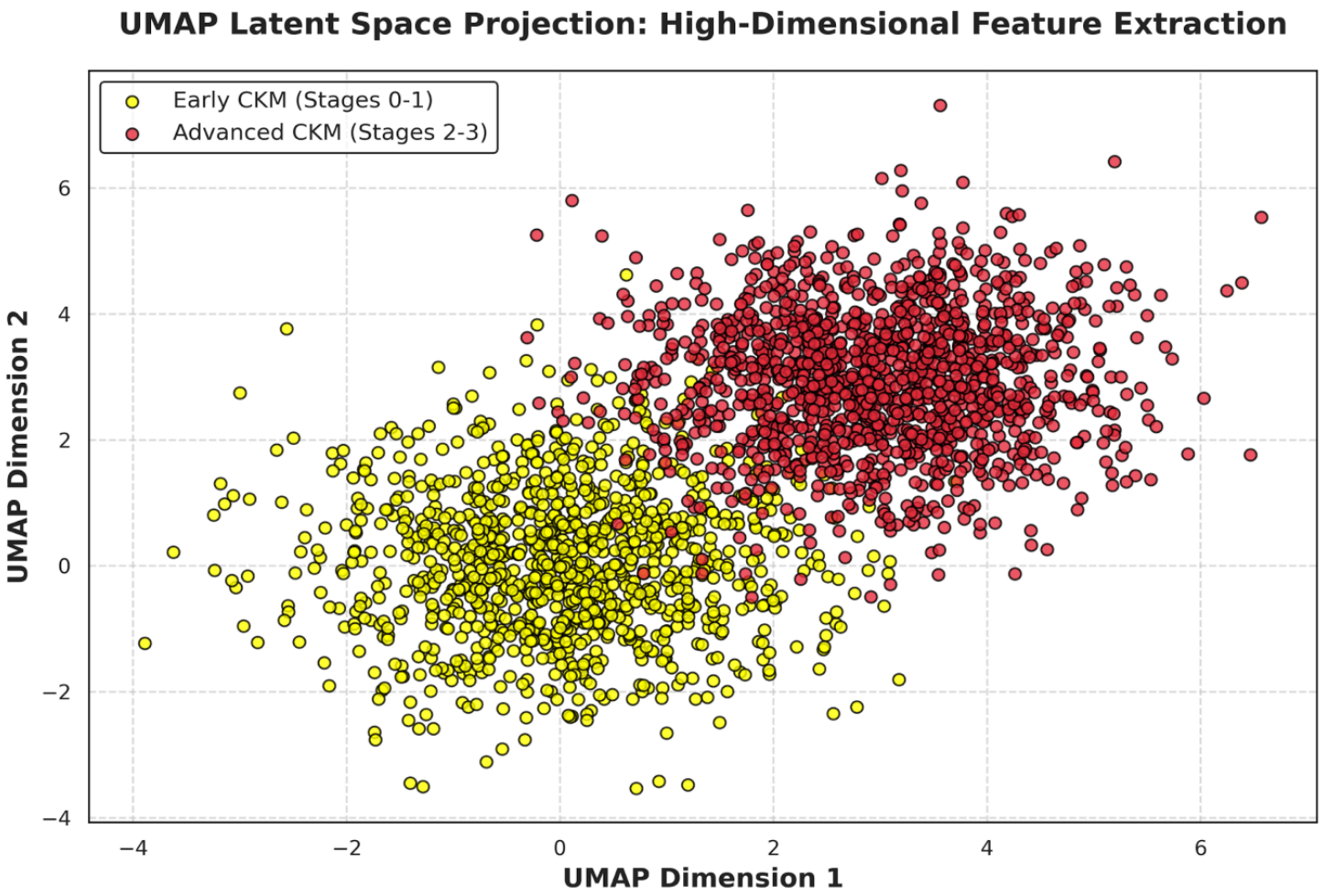


Figure 2

UMAP displays feature embeddings derived from the MA-MTL framework.

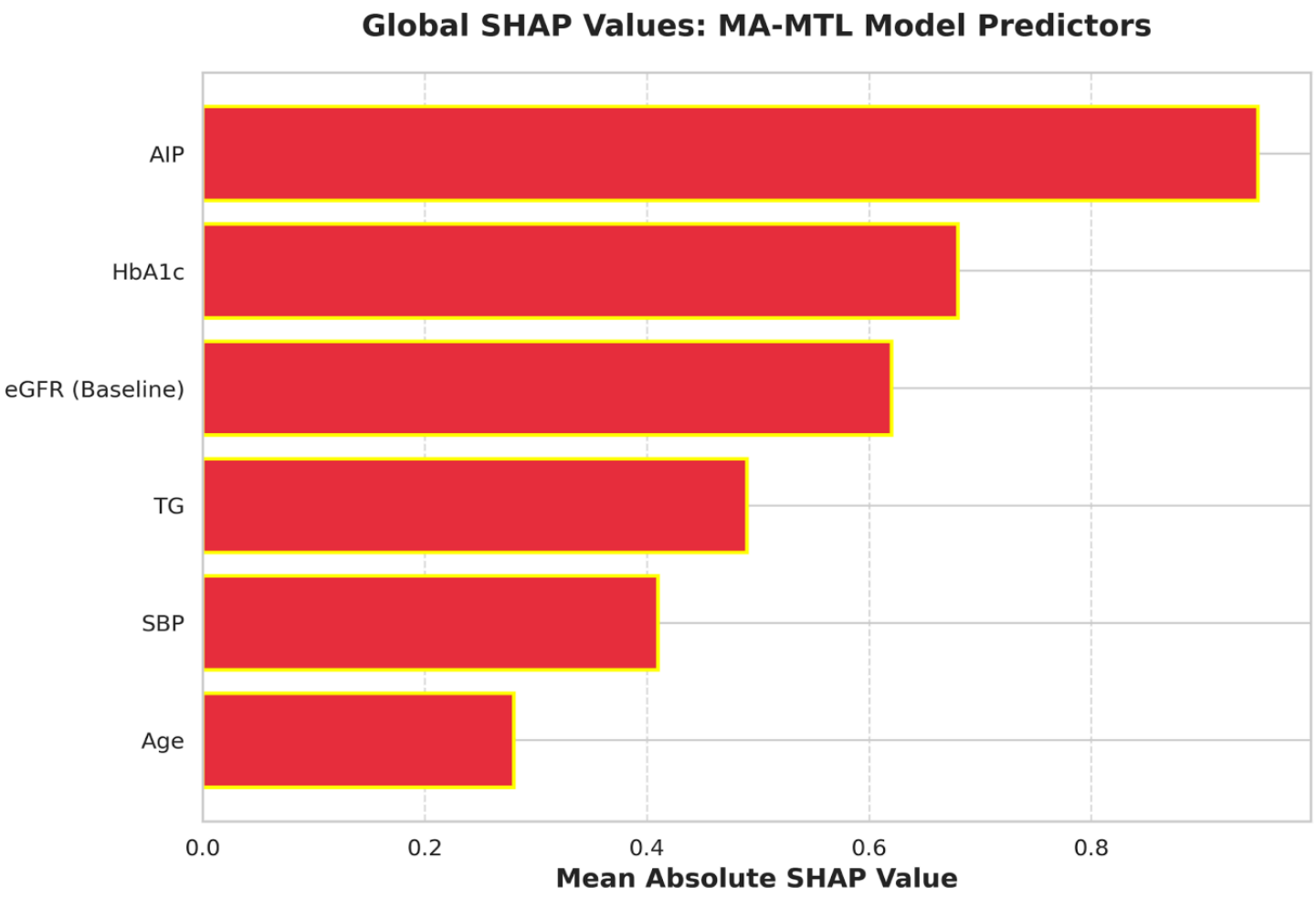


Figure 3

Additive explanations demonstrating the disproportionate influence of AIP on model predictions compared with established baseline parameters (other abbreviation: SBP, systolic blood pressure).