Equitable Post-HCT Survival Prediction: A Systems Engineering Approach to Fair Machine Learning in Healthcare

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***Abstract*—Hematopoietic cell transplantation (HCT) is a life-saving procedure for severe blood disorders, yet predicting post-transplant survival remains challenging due to complex clinical, genetic, and demographic interactions. Current prediction models often exhibit disparities across patient populations, disadvantaging certain demographic groups. This paper presents a comprehensive systems engineering approach to develop equitable survival prediction models for the CIBMTR Kaggle competition. Our modular architecture addresses both accuracy and fairness requirements through seven interconnected components: data preprocessing, equity analysis, feature selection, predictive modeling, fairness calibration, uncertainty quantification, and interpretable outputs. System analysis reveals extreme sensitivity to parameters such as age, disease risk indices, and HLA compatibility, with small variations causing significant outcome differences. We propose a technical stack integrating survival analysis libraries (Lifelines, Scikit-survival), ensemble methods (XGBoost, LightGBM, CatBoost), and fairness tools (AIF360, Fairlearn) to address the stratified C-index evaluation metric. Our framework provides a foundation for developing machine learning systems that deliver both clinically accurate and demographically equitable predictions in healthcare.**

***Index Terms*—Hematopoietic cell transplantation, healthcare equity, survival prediction, fairness-aware machine learning, systems engineering, stratified C-index**

I. Introduction

A. Medical Context and Motivation

Allogeneic hematopoietic cell transplantation (HCT) represents a critical therapeutic intervention for patients with severe hematological malignancies and immune disorders [1]. The procedure involves replacing a patient's damaged bone marrow with healthy stem cells from a compatible donor, potentially curing conditions such as acute and chronic leukemias, lymphomas, multiple myeloma, and severe aplastic anemia [2]. Despite significant advances in transplantation protocols, HCT remains associated with substantial morbidity and mortality risks, including graft-versus-host disease (GVHD), infections, and graft failure [3].

Accurate survival prediction following HCT serves multiple critical functions: guiding transplant candidacy decisions, enabling personalized treatment protocols, optimizing resource allocation, and supporting shared decision-making between clinicians and patients [4]. However, current predictive models frequently exhibit systematic disparities across demographic groups, with certain populations receiving less accurate or less reliable predictions [5]. These inequities can perpetuate existing healthcare disparities and compromise care quality for underrepresented patient groups.

B. The CIBMTR Competition

The Center for International Blood and Marrow Transplant Research (CIBMTR) Kaggle competition addresses this critical challenge by requiring participants to develop machine learning models that are both accurate and equitable [6]. The competition distinguishes itself through a dual evaluation framework: models must achieve high predictive accuracy while maintaining consistent performance across different racial and socioeconomic patient groups. This approach directly confronts a fundamental limitation of traditional machine learning evaluation, which often focuses exclusively on aggregate metrics that can mask poor performance for specific subpopulations.

The competition employs a stratified concordance index (C-index) as its primary evaluation metric, calculating performance separately within demographic subgroups before aggregating results [6]. This methodology ensures that models cannot achieve high scores by optimizing for majority populations at the expense of minority groups. The dataset provided includes comprehensive clinical, genetic, demographic, and temporal variables for thousands of transplant patients, enabling sophisticated modeling approaches while restricting participants to authorized data sources.

C. Previous Work

Recent advances in machine learning for healthcare have demonstrated both the potential and pitfalls of predictive modeling in clinical contexts. Ensemble methods such as XGBoost and gradient boosting machines have shown strong performance in survival analysis tasks [7], while deep learning architectures have captured complex non-linear relationships

in medical data [8]. However, numerous studies have documented algorithmic bias in healthcare prediction systems, where models trained on historical data reproduce and amplify existing disparities [5].

Fairness-aware machine learning approaches have emerged to address these concerns, employing techniques such as demographic parity constraints, equalized odds optimization, and calibration across groups [9]. In the context of survival analysis, researchers have developed methods to ensure consistent calibration of time-to-event predictions across demographic strata [7]. The integration of explainable AI techniques such as SHAP (SHapley Additive exPlanations) values has enhanced model interpretability, enabling clinicians to understand and validate prediction rationale [8].

D. Research Objectives

This paper presents a comprehensive systems engineering approach to the CIBMTR equity challenge, with the following objectives:

1) Conduct a thorough systems analysis of post-HCT survival prediction, identifying key components, relationships, and constraints
2) Characterize system complexity and sensitivity to input parameters
3) Design a modular architecture that explicitly addresses both accuracy and equity requirements
4) Propose a comprehensive technical implementation strategy integrating state-of-the-art tools for survival analysis, machine learning, and fairness evaluation
5) Establish a framework for developing trustworthy, equitable healthcare prediction systems

The remainder of this paper is organized as follows: Section II describes our systems analysis methodology and findings; Section III presents the proposed modular architecture and technical stack; Section IV discusses results including sensitivity analysis and design validation; and Section V concludes with implications and future directions.

II. Methods and Materials

A. Systems Analysis Methodology

We conducted a comprehensive systems analysis of the CIBMTR prediction challenge following established systems engineering principles. Our analysis examined four key dimensions: (1) system inputs, encompassing disease characteristics, transplant-specific factors, demographic variables, and temporal elements; (2) system architecture and processing modules; (3) system outputs including predictions, equity metrics, and interpretability artifacts; and (4) system constraints arising from data limitations, fairness requirements, and clinical validity needs.

The analysis employed multiple techniques to characterize system behavior. We reviewed medical literature on HCT outcomes to identify clinically relevant variables and their relationships [1], [2], [10]. We examined the competition dataset structure and evaluation methodology to understand technical constraints [6]. We applied complexity analysis methods to identify non-linear interactions and sensitivity parameters. Finally, we mapped user requirements from multiple stakeholder perspectives including transplant physicians, clinical researchers, healthcare administrators, and patients.

B. Modular System Architecture

Based on our analysis, we designed a seven-module architecture that addresses both prediction accuracy and demographic equity throughout the processing pipeline (Fig. 1). Each module serves a specific function while maintaining interfaces that enable information flow and feedback mechanisms.

Module 1: Data Preprocessing handles initial data ingestion, validation, missing value imputation, normalization, and basic feature engineering. The module employs equity-aware imputation methods to ensure missing data handling does not introduce systematic biases across demographic groups. Continuous variables undergo standardization while preserving demographic-related variations that might indicate disparities.

Module 2: Equity Analysis performs stratified analysis across demographic subgroups to identify potential biases in data quality, feature availability, and baseline outcome rates. The module implements bias detection algorithms and applies fairness-aware preprocessing techniques such as sample reweighting to balance representation while preserving clinical validity.

Module 3: Feature Selection and Importance determines which variables contribute most to survival predictions using multiple complementary strategies: clinical domain knowledge integration, statistical significance testing, and machine learning-based importance rankings. The module ensures that predictive features are available equitably across all patient populations and avoids features that might be systematically missing for certain demographic groups.

Module 4: Predictive Modeling Core represents the central prediction engine, employing an ensemble approach that combines survival analysis models (Cox proportional hazards, accelerated failure time), machine learning algorithms (gradient boosting machines, random forests), and potentially deep learning architectures for capturing complex non-linear relationships. Cross-validation is specifically designed for survival data with demographic stratification to ensure robust performance evaluation.

Module 5: Fairness Calibration adjusts model predictions to ensure equitable performance across demographic groups. The module implements post-processing calibration techniques that maintain similar prediction accuracy for all patient populations, optimizes risk classification thresholds considering fairness metrics alongside traditional performance measures, and quantifies disparity impact.

Module 6: Uncertainty Quantification provides confidence intervals and prediction uncertainties appropriate for survival analysis. The module generates prediction intervals using bootstrap or other suitable techniques, associates uncertainty bounds with risk stratification categories, and identifies

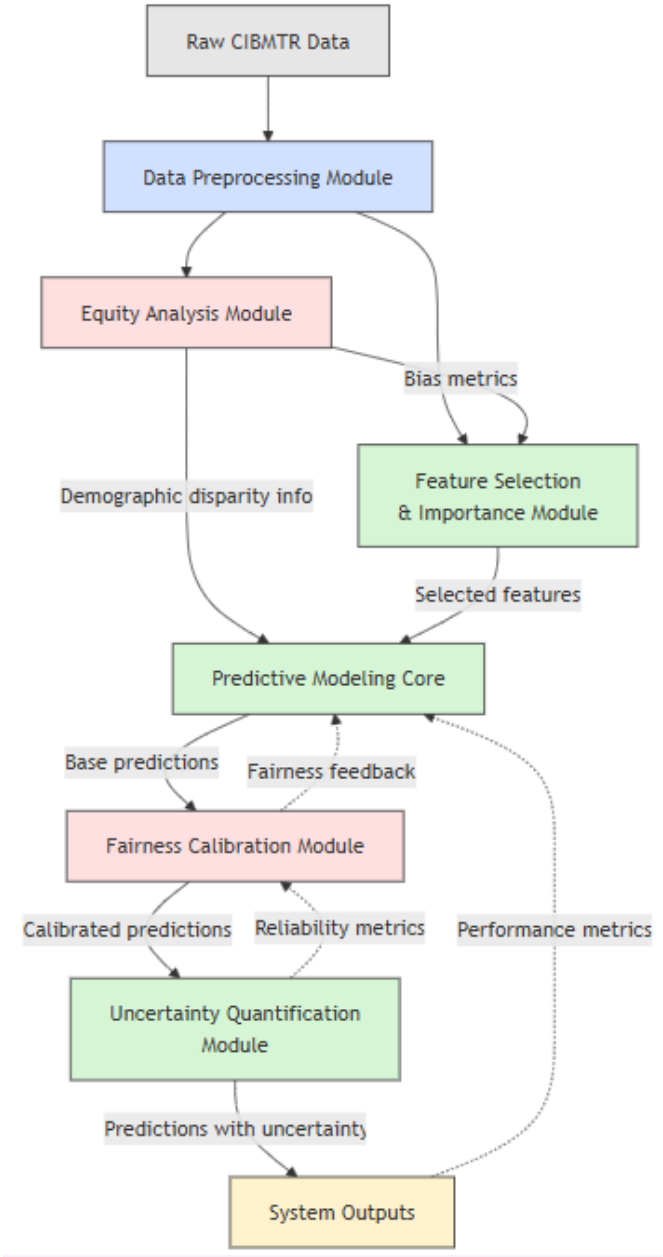

Fig. 1. Modular system architecture showing seven core components and information flow. Blue modules handle data preparation, red modules address equity concerns, green modules perform modeling, and yellow modules generate outputs.

cases where predictions might be less reliable due to data limitations or characteristics.

Module 7: System Outputs generates comprehensive results for clinical decision support and equity monitoring. Primary outputs include time-dependent survival probabilities at key clinical milestones (100 days, 1 year, 2 years, 5 years post-transplant) and risk stratification categories. Secondary outputs include equity metrics dashboards, clinical decision support information with individualized risk factors, model interpretability artifacts (feature importance, SHAP values), and quality assurance reports.

C. Complexity and Sensitivity Analysis

Post-HCT survival prediction presents a fundamentally complex system characterized by multiple interacting factors operating across different scales [7]. The system exhibits characteristics of chaotic behavior where small variations in initial conditions can lead to dramatically different outcomes [11]. This ”butterfly effect” manifests in several specific ways relevant to our prediction task:

Parameter Sensitivity: We identified four critical parameters exhibiting extreme sensitivity where minor variations cause substantial prediction changes:

1) **Patient Age:** A single-year age difference can shift risk categorization significantly, particularly near clinical threshold ages where treatment protocols change
2) **Disease Risk Indices:** Small changes in composite risk scores can alter prognosis dramatically and affect treatment eligibility
3) **HLA Matching Degree:** Subtle differences in genetic compatibility substantially affect graft rejection rates and survival
4) **Comorbidity Presence:** The presence or absence of specific severe comorbidities can double or drastically reduce projected survival

Fig. 2 visualizes this sensitivity for the age parameter, demonstrating how a minimal 0.1-year difference can lead to significantly different risk categories and survival probability estimates.

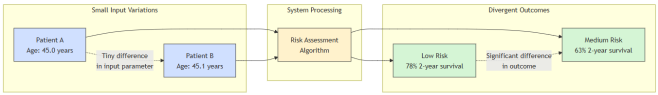

Fig. 2. Sensitivity analysis showing how minimal age differences can lead to substantially different survival predictions and risk categorization. This extreme sensitivity necessitates robust modeling approaches with uncertainty quantification.

Chaotic Dynamics: Several biological processes in post-HCT outcomes exhibit characteristics of deterministic chaos [8]: immune reconstitution dynamics where small variations in initial T-cell populations lead to dramatically different recovery trajectories; GVHD emergence following complex non-linear patterns despite identical prophylaxis regimens; infection susceptibility displaying extreme sensitivity to timing and environmental factors; and relapse dynamics influenced by minimal residual disease and immune escape mechanisms.

Inherent Randomness: Beyond deterministic complexity, the system contains elements of true stochasticity arising from biological diversity, incomplete medical records, and unknown confounding factors [11]. Two patients with apparently identical risk profiles may experience completely different outcomes due to unmeasured genetic or environmental variables.

This complexity analysis directly informed our architectural decisions, particularly the emphasis on ensemble methods to

capture multiple possible outcome trajectories, explicit uncertainty quantification to acknowledge inherent unpredictability, fairness calibration to ensure robust performance despite data quality variations across groups, and interpretability mechanisms to enable clinical validation of predictions.

D. Evaluation Metric: Stratified C-Index

The competition employs a stratified concordance index as its primary evaluation metric, specifically designed to ensure equitable performance across demographic groups [6]. The C-index measures a survival model's ability to correctly order risk among pairs of patients, with values ranging from 0.5 (random predictions) to 1.0 (perfect ordering).

In the stratified version, the C-index is calculated separately within each racial/ethnic subgroup, then aggregated with dispersion adjustment. This methodology ensures that models must achieve consistent performance across all demographic strata, preventing optimization strategies that achieve high aggregate scores by maximizing performance for majority populations at the expense of minority groups.

Fig. 3 illustrates the stratified evaluation workflow, showing how patient populations are first stratified by demographic characteristics, C-index is calculated within each stratum, and results are weighted and aggregated to produce the final metric. This evaluation approach directly addresses the competition's dual requirements for accuracy and equity.

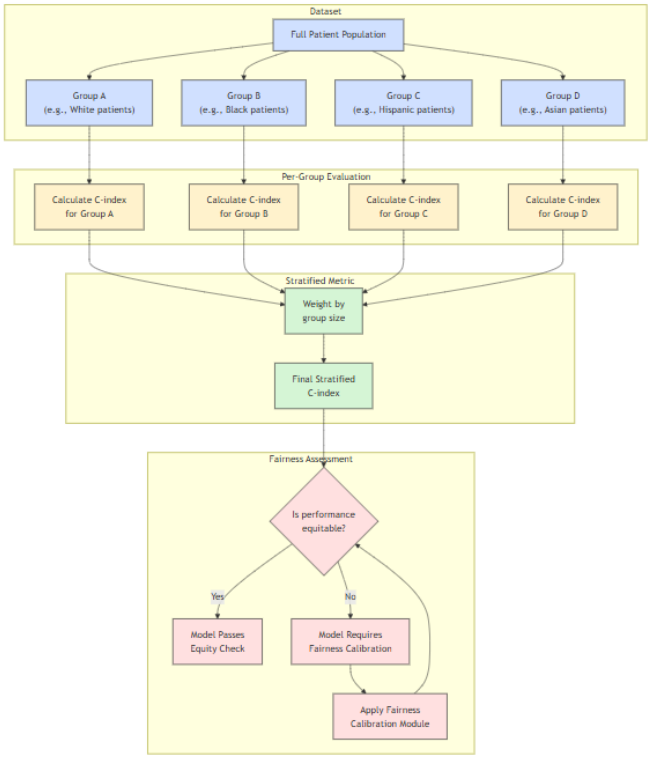

Fig. 3. Stratified C-index calculation workflow showing demographic stratification, within-group evaluation, and fairness-aware aggregation. The iterative fairness assessment loop ensures equitable performance across all patient populations.

E. Technical Implementation Stack

We selected a comprehensive technical stack balancing state-of-the-art capabilities with practical implementation concerns:

Data Processing: Pandas for efficient tabular data manipulation, NumPy for numerical computations, and Scikit-learn for preprocessing utilities including imputation, scaling, and train-test splitting.

Survival Analysis: Lifelines for Cox proportional hazards and accelerated failure time models, and Scikit-survival for machine learning-enhanced survival prediction with seamless integration into the broader ecosystem.

Machine Learning: XGBoost, LightGBM, and CatBoost for gradient boosting implementations, each offering specific advantages: XGBoost provides robust handling of missing values, LightGBM offers superior computational efficiency for large datasets, and CatBoost enables direct use of categorical features without preprocessing.

Fairness and Bias Mitigation: AIF360 (IBM) for comprehensive fairness metrics and bias reduction techniques applicable at different pipeline stages, and Fairlearn (Microsoft) for fairness constraints during model training and threshold optimization.

Model Interpretation: SHAP for generating additive feature importance explanations at both global and local levels, enabling clinical validation of model predictions.

Visualization: Matplotlib for core plotting functionality and Seaborn for statistical graphics including survival curves and calibration plots.

Infrastructure: Docker for reproducible computational environments, PostgreSQL for data management, and MLflow for experiment tracking and model versioning.

III. Results and Discussion

A. Requirements Analysis and Traceability

We identified user requirements through stakeholder analysis, considering needs of transplant physicians (accurate, demographically stratified predictions for equitable prognostic information), clinical researchers (understanding of influential factors for intervention development), healthcare administrators (performance metrics demonstrating equitable care delivery), model developers (robust evaluation frameworks for algorithm verification), and patients (trustworthy survival estimates with appropriate uncertainty bounds for informed decision-making).

Using the MoSCoW prioritization framework, we classified requirements into four categories. **Must Have** requirements include equity across demographic groups (measured by stratified C-index), accurate survival predictions (minimum C-index of 0.70), clinical validity of identified risk factors, and appropriate uncertainty quantification. **Should Have** requirements include interpretability of model predictions, efficient computational performance, handling of complex missing data patterns, and identification of potential biases in input data. **Could Have** requirements include integration capabilities with

clinical workflows, advanced visualization of prediction uncertainty, personalization of risk thresholds, and continuous learning capabilities. **Won't Have** (in this version) includes integration with electronic health records, real-time prediction updates, patient-facing interfaces, and external data augmentation.

Table I shows our requirements traceability matrix, mapping each critical requirement to specific system modules that address it. This ensures comprehensive coverage of all stakeholder needs within the proposed architecture.

TABLE I
REQUIREMENTS TRACEABILITY MATRIX

Requirement	Prep	Equity	Feature	Model	Fair	Out
Equity across groups	✓	✓	✓	✓	✓	✓
Clinical validity	✓		✓			✓
Missing data	✓	✓				
Uncertainty				✓	✓	✓
Fairness	✓	✓	✓		✓	✓

B. Risk-Impact Analysis of Prediction Features

We conducted a risk-impact analysis positioning key prediction features according to their predictive power (impact) and potential for introducing bias (risk). Fig. 4 presents this analysis, revealing several important patterns.

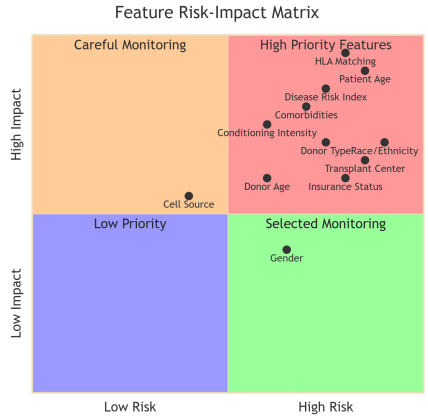

Fig. 4. Risk-impact matrix for key prediction features. High-impact, high-risk features (upper right quadrant) such as age and HLA matching require careful handling to balance predictive power with equity concerns.

Features in the high-impact, high-risk quadrant—including patient age, HLA matching degree, and certain comorbidities—require particular attention in our fairness calibration process. These variables provide strong predictive signal but may be differentially available or measured across demographic groups. Our architecture addresses this through the Equity Analysis module (identifying systematic differences in feature availability) and Fairness Calibration module (adjusting for bias without sacrificing predictive accuracy).

Features in the high-impact, low-risk quadrant such as disease stage and conditioning regimen intensity can be leveraged more directly for prediction with less concern about introducing systematic bias. Features in the low-impact quadrants may be candidates for removal to simplify the model and improve computational efficiency.

C. Design Validation

We validated our architectural design against competition requirements and systems engineering principles along multiple dimensions:

Completeness: The traceability matrix (Table I) demonstrates that all "Must Have" and "Should Have" requirements are addressed by at least one system module, with critical requirements such as equity and fairness covered by multiple redundant mechanisms.

Modularity and Maintainability: The seven-module architecture enables independent development and testing of components. For example, different survival analysis algorithms can be substituted in Module 4 without affecting upstream preprocessing or downstream calibration modules. This separation of concerns facilitates iterative refinement and adaptation to new medical knowledge.

Scalability: The pipeline design supports both horizontal scaling (processing more patients in parallel) and vertical scaling (incorporating more complex models). The choice of technologies such as LightGBM and efficient survival analysis libraries ensures computational feasibility even for large datasets.

Robustness: Multiple mechanisms address the chaotic and sensitive nature of the prediction task identified in our complexity analysis. The ensemble approach in Module 4 captures multiple possible outcome trajectories. Module 6 explicitly quantifies prediction uncertainty. Module 5 ensures calibration across demographic groups despite potential data quality variations. Module 2 identifies and flags potential bias issues early in the pipeline.

Clinical Validity: Module 3's integration of clinical domain knowledge ensures that selected features align with medical understanding of transplant outcomes. Module 7's interpretability outputs (particularly SHAP values) enable clinicians to validate that predictions rely on medically meaningful factors rather than spurious correlations.

D. Limitations and Considerations

Despite the comprehensive nature of our design, several important limitations must be acknowledged:

Data Constraints: Working exclusively with the competition dataset limits our ability to incorporate potentially valuable external information. While our preprocessing module includes sophisticated missing data handling, it cannot entirely overcome fundamental data limitations or systematic measurement differences across sites.

Complexity-Interpretability Trade-off: Ensemble methods and advanced machine learning techniques provide superior predictive performance but reduce interpretability compared to simpler models. We attempt to balance these concerns

through SHAP-based explanations, but this tension remains fundamental to the problem domain.

Computational Resources: The sophisticated modeling approaches necessary for addressing the complex and chaotic nature of post-HCT outcomes require significant computational resources. This may limit real-time application in resource-constrained clinical settings, though batch prediction workflows remain feasible.

Generalizability: Models trained on historical CIBMTR data may not generalize perfectly to future patients or different healthcare systems. Medical practices in HCT continue to evolve, requiring regular model updates. Geographic and institutional variations may affect model performance when deployed in new settings.

Ethical Dimensions Beyond Technical Fairness: While our design emphasizes statistical equity across demographic groups, broader ethical considerations in healthcare prediction extend beyond what can be addressed through technical means alone. Questions about appropriate use of predictions, patient autonomy, and potential for systematic exclusion require ongoing multidisciplinary engagement.

IV. Conclusions

This paper presented a comprehensive systems engineering approach to developing equitable survival prediction models for post-HCT patients. Our work makes several key contributions:

Systems Analysis: We conducted a thorough characterization of the prediction challenge, identifying it as a complex, sensitive, and partially chaotic system where small parameter variations can produce dramatic outcome differences. This analysis revealed critical sensitivity parameters (age, disease risk indices, HLA compatibility, comorbidities) and characterized the inherent unpredictability arising from biological stochasticity and feedback mechanisms.

Modular Architecture: We designed a seven-module pipeline that explicitly addresses both prediction accuracy and demographic equity throughout the processing workflow. Each module serves a specific function while maintaining interfaces enabling information flow and adaptation. The architecture embodies key systems engineering principles: modularity for independent component development, scalability for handling complex datasets, maintainability through clear separation of concerns, and robustness through multiple redundant mechanisms addressing sensitivity and bias.

Technical Implementation Strategy: We proposed a comprehensive technology stack integrating state-of-the-art tools for survival analysis, machine learning, fairness evaluation, and interpretability. The selection balances sophisticated capabilities necessary for the complex prediction task with practical implementation concerns including computational efficiency and reproducibility.

Fairness Integration: Unlike many machine learning approaches that treat fairness as an afterthought, our architecture integrates equity considerations throughout the pipeline from initial data preprocessing through final output generation. The stratified C-index evaluation metric is addressed through dedicated modules for equity analysis, fairness-aware feature selection, and explicit calibration across demographic groups.

Clinical Validity: The design emphasizes medical meaningfulness alongside statistical performance, incorporating clinical domain knowledge in feature selection, providing interpretability artifacts for validation, and quantifying uncertainty to support shared decision-making.

A. Future Work

Several promising directions for future enhancement emerge from this work:

Continuous Learning: Implementing feedback loops that incorporate new patient outcomes to continuously refine predictions, adapting to evolving medical practices while monitoring for performance drift or emerging biases.

Expanded Equity Analysis: Extending fairness considerations beyond racial/ethnic groups to address additional dimensions of potential healthcare disparities including socioeconomic status, geographic access to care, insurance coverage, and intersectional identities.

Federated Learning: Developing techniques that allow model training across multiple transplant centers while preserving data privacy, significantly expanding available training data and potentially improving generalizability.

Temporal Dynamics: Incorporating more sophisticated approaches to capture time-dependent nature of post-transplant complications, intermediate events, and evolving patient states.

Clinical Integration: Creating interfaces between the prediction system and clinical workflows to facilitate seamless integration into transplant decision-making processes, with appropriate safeguards against automation bias and provision for human oversight.

In conclusion, this work demonstrates that systems engineering principles provide a powerful framework for developing machine learning systems that address complex, high-stakes healthcare challenges while maintaining commitments to both accuracy and equity. The CIBMTR competition represents an important step toward fair, trustworthy AI in medicine, and our proposed approach offers a roadmap for principled development of equitable healthcare prediction systems.

Acknowledgments

This work was conducted as part of the Systems Analysis & Design course at Universidad Distrital Francisco José de Caldas under the guidance of Eng. Carlos Andrés Sierra, M.Sc. We thank CIBMTR and Kaggle for providing the competition framework and dataset that motivated this research.

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