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AI Driven Prognosis in Pediatric Bone Marrow Transplantation Survival

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***Abstract*— Pediatric Bone Marrow Transplantation (BMT) is widely used as a treatment innovation that can treat certain types of cancers and hematologic disorders in children. Nevertheless, it is quite worrying that despite all the scientific breakthroughs in medical field, the survival rates for post BMT pediatric patients are still very low. This work aims to improve the probabilistic forecast of pediatric BMT survival rates by applying AI and ML approaches. Having a large dataset of demographic and clinical characteristics of pediatric patients, we subjected the data to an elaborate data cleaning process. This included handling of missing records, converting categorical variables into dummy and dealing with an uneven distribution of the survival status using the Borderline SMOTE method. Then we used mutual information for selecting the features, which helped in the elimination of the non-relevant characteristics. The selected features along with the full features dataset were fed to the ML models namely Random Forest, XGBoost, Logistic Regression, Decision Tree and Support Vector Classifier through Hyperparameter optimization. The results of this study showed that the XGBoost model was the most efficient in identifying the survival status of the pediatric patients after BMT. By facilitating more accurate predictions of survival outcomes, we can equip healthcare professionals with the insights necessary to make more informed clinical decisions, thereby potentially enhancing survival rates for children undergoing BMT.**

Keywords—Machine learning, Pediatric BMT, Borderline SMOTE, Mutual information, Hyperparameter Optimization, XGBoost

I. Introduction

A. Background and Motivation

Cancer is a prominent cause of death globally, characterized by the uncontrolled growth and spread of abnormal cells. Individuals of various ages, including children, might be affected. Pediatric cancer, although uncommon, poses distinct diagnostic and therapy issues. Leukemias are the most common childhood cancers [1].

Any interruption in bone marrow function can have catastrophic consequences, leading to illnesses such as anemia, leukemia, and other immune deficiency disorders [2]. Bone Marrow Transplantation (BMT) has become a source of hope for people affected by some types of cancer including leukemia and many other severe diseases, especially for children. BMT means transplanting of unhealthy or infected bone marrow cells with healthy stem cells which then mature and perform the roles of bone marrow [3]. Before the operation, the patient is prescribed huge chemotherapy dosages and radiation therapy so that possible metastases are eradicated. After that, the bone marrow, which was extracted and transplanted, is utilized to produce good blood cells. These fresh healthy cells will also inhibit the cancer cells, which are already present, from continuing to multiply. BMTs are used with good effect in cancer and non-cancer patients with diseases like adrenoleukodystrophy, Hodgkin's disease, acute leukemia, aplastic anemia, multiple myeloma and neuroblastoma [4].

About 50,000 hematopoietic stem cell transplants (HSCTs), also referred as BMT, annually are carried out globally as a therapy [5]. With the recent development in medical research, BMT has proven to be a life-saving procedure for many pediatric patients. But the prognosis and survival rates can vary considerably. This is so because several factors may come into play like the type of the disease, general condition of the patient, type of transplant, and compatibility between the donor and the recipient among others. Currently available prognostic methods, although valuable, often struggle to incorporate the multifaceted and dynamic nature of the many variables involved.

In the recent past, AI and ML applications in the various sectors including the healthcare sectors have become notable. This is due to a few factors which include heightened availability and accessibility of health care information, improved ability in computation and continuous development of advanced algorithms. At present these technologies are used in almost any sphere of healthcare diagnostics, prognosis or prediction, patient's monitoring and treatment planning [6].

B. Research Contribution

This paper will cover the process of establishing and evaluating an ML model that aims at determining the survival rates of pediatric-BMT patients. The goal of using AI in this case is to help clinicians make better choices and save more young lives through increasing the patients' survival rates and their quality of life.

The salient contributions of our study are:

a) To work with the dataset, we first cleaned, transformed, and then decoded as per the systematic method to deal with the missing values and further check the quality of the data to make it ready for further analysis.

b) Maximized quantitative analysis allowed us to identify major factors affecting the results of bone marrow transplantation and discuss the major factors that define bone marrow transplantation effectiveness.

c) Recognizing the potential impact of class imbalance on model performance, we applied Borderline SMOTE for oversampling, enhancing the model's ability to generalize and improving its performance on minority class predictions.

d) Using mutual information, we ranked the features based on their relevance to the target variable, providing insights into the factors most predictive of survival in pediatric BMT.

e) We incorporated Hyperparameter Optimization (HPO) through the grid search cross-validation into our methodology, tuning the parameters of our machine learning models to optimize their performance.

f) We evaluated various machine learning models on their predictive performance, thereby identifying the most optimal models for use in predictive healthcare in the context of pediatric treatment.

II. Literature Review

HSCT is a crucial and frequently employed technique in many situations in childhood cancer and other diseases. This transplant can treat 85% of children afflicted with very serious blood disorders in middle income countries as low risk and have long term effect on health associated quality of life in the children and is cost effective solution. [7].

Despite its therapeutic potential, HSCT is associated with numerous complications and challenges. These include viral infections due to the patient's immunosuppression, as well as complications related to the high dose chemotherapy regimen. Acute graft versus host disease (GvHD) is the most significant toxicity of allogeneic HSCT that can involve the liver, the skin and the gastrointestinal tract, both the upper and lower segments [8]. A study aimed to design and test index model based on machine learning for the risk stratification of aGVHD in adult HSCT recipients in Japan. Specific to the analysis, models were built using the ADTree machine learning algorithm, and the rates of aGVHD were distinctly separated by ordinal levels of the ADTree scores [9].

A Bayesian network model was created to determine the best first dose of intravenous CsA for the pediatric patients undergoing HSCT. The model passed the 10-fold cross-validation and prediction using the data from the last 2 years. The model displayed reasonable prediction accuracy with an average area of 0.804 under the ROC curve [10]. In many cases, the outcome determination, or the need to predict survival time is challenging because of the interactions between biological, genetic, and environmental aspects. An exploratory study establishes findings on the survival time estimation of children with Acute Lymphoblastic Leukemia applying three algorithms. The study established that support vector regression and multiple linear regression techniques were useful in the computation with an average cross-validated root adjusted mean error of less than 0. 3. It was again concluded that all the prediction models have passed the 70% of the classification accuracy wherein each patient is classified between short survivor and long survivor [11].

Using an effectual classification model, a study assesses the children's survival who receive BMT. On the basis of the Chi-square feature selection method, the first 11 features were extracted from the given dataset. To enhance the accuracy of prediction, hyperparameter tuning employing the grid search cross-validation methodology was applied having a prediction accuracy of 94.73% [12]. Another study was performed on the same dataset using machine learning classifiers to predict patients survival state after BMT using two feature selection methods: Principal Component Analysis (PCA) and Fuzzy Discernibility Matrix (FDM). Top results were presented by ADA Boost, with an accuracy score of 95.23% [13]. The Mud Ring Algorithm (MRA) was proposed as a novel feature selection method for survival prediction. Experiments on 13 real datasets showed that the MRA outdid other techniques with an accuracy of up to 82.6% for test cases [14].

Another research study was also done using the same dataset and the features were selected through Salp swarm optimization, Harris Hawks optimization, and mutual information. LIME, SHAP, and ELI5 were combined with QLattice to improve the interpretability of the model. The four most significant characteristics were relapse, the age of the donor, the age of the recipient, and platelet recovery time [15]. These encouraging results indicate the capacity of AI in aiding the comprehension and enhancement of BMT prognosis in children.

III. Data Preprocessing

A. Dataset Description

This study utilizes the 'Bone Marrow Transplant: Children' dataset, sourced from the UCI Machine Learning Repository [16]. The data involves pediatric patients with different hematologic malignancies and non-malignant disorders who received unmanipulated allogeneic unrelated donor HSCT. The dataset is also multivariate, and it contains 187 records and 39 variables.

B. Data Exploration

Exploratory data analysis is essentially the first step concerning investigation to be conducted on data to identify patterns, outliers, relations, hypothesis and also to check validity of assumptions by using summary statistics and graphics. If the features have many missing values, imputation cannot be performed as the models prove to be undependable. "Extensive_chronic_GvHD" was excluded because most of its values were missing. The median of the other numerical variables was used in their stead. Due to the significant impact of outliers on the missing values in this study, we did not use mean to replace them. Categorical variables that were missing were substituted with their corresponding modes [15].

Most ML models cannot deal with categorical variables. Even if they can like Decision Tree, it is more practical to convert categorical variables to numerical variables, they can decrease memory usage and potentially speed up the computations. One-hot encoding is used in this research as it effectively handles nominal categorical variables by avoiding the introduction of any arbitrary order. The StandardScaler method was used to normalize the dataset for analysis. It maintains the shape of the original distribution and is more resilient to outliers, ensuring that the data is appropriately scaled and less influenced by extreme values. This provides a robust foundation for the subsequent stages of the analysis.

We used box plots to perform a summary analysis on the numerical variables in our dataset. They provide information about the patterns of dispersion of the data and potential data anomalies. In Figure 1, the graph reveals that rates of mortality in BMT patients could rise owing to the age of the donor. Furthermore, one gets the impression that only a few donor patients are within the ages of 30- 40 years. It can be observed that pediatric patients under 10 are most likely to survive after transplantation. The likelihood of survival

declines as the rise of recipient's body mass. It can be inferred that survivability rate is directly proportionality to CD3+ and CD34+ cell dosage. The CD3+ cell to CD34+ cell ratio had a negligible impact on survivability. Interestingly, we found that mortality is positively associated with longer platelet recovery time.

From Figure 2, representing bar charts for some categorical variables, it can be inferred that patients had a higher chance of survival when the donor age was under 35. If the hematopoietic stem cell donor had CMV infection prior to transplantation, the recipient is more likely to survive. A higher level of compatibility of antigens (HLA match) results in a better likelihood that the recipient will survive. The result also implies that ALL (acute lymphoblastic leukemia) was present in most individuals who had BMT. BMT has a lower success rate when used to treat lymphoma patients. Most pediatric patients with this illness died following the transplant. As can be observed, death was higher in high-risk patients. The fact that so few individuals underwent a second consecutive bone marrow transplant after relapse is clear.

C. Data Balancing using Borderline SMOTE Algorithm

Our dataset, employed for prognosticating pediatric Bone Marrow Transplant survival, exhibits a minor imbalance with 102 survival instances and 85 non-survival instances. Such an imbalance could potentially bias our AI model towards over-predicting survival. Considering the potential data loss with under-sampling, we opted for oversampling to address data imbalance in our study. The Synthetic Minority Oversampling Technique (SMOTE) was considered as a potential solution, given its demonstrated superiority over traditional oversampling methods, which replicate existing minority class instances and often causes overfitting. SMOTE employs the K Nearest Neighbor (KNN) algorithm to synthesize new instances within the minority class, creating unique instances until the class distribution is balanced. However, SMOTE is not without limitations. The algorithm may result in the 'line bridge' problem when synthesizing records from the minority class that are proximate to the majority class instances. This issue could potentially lead to misclassification, compromising the model's accuracy. To circumvent this challenge, we leveraged the Borderline SMOTE variant in this study. Borderline-SMOTE refines the original SMOTE algorithm by prioritizing the resampling of instances proximal to both the majority and minority classes when synthesizing new data points. This approach ensures a more precise class balance and mitigates the risk of misclassification [17].

In the Borderline-SMOTE algorithm:

$$PC = \{p_1, p_2, ..., p_{pnum}\},\ NC = \{n_1, n_2, ..., n_{nnum}\}$$

where $pnum$ and $nnum$ are the total number of minority and majority instances.

In Table 1, Step 1 identifies the samples in the minority class that belong to noisy, borderline, and safe regions based on their nearest neighbors. The instances in *DANGER* are the borderline data of the minority class *PC*, and we can see that $DANGER \subseteq PC$. We set $DANGER = \{p'_1, p'_2, ..., p'_{dnum}\}, 0 \leq dnum \leq pnum$. Step 2 calculates the nearest neighbors of the instances in the *DANGER* set, representing the borderline samples. Step 3 generates synthetic minority examples by combining scaled difference vectors between borderline samples and their nearest neighbors. The number of synthetic instances depends upon d_{num} (the number of examples in the DANGER set) and s (the oversampling amount, an integer between 1 and k). Multiplying these values gives us the total count of synthetic examples ($s \times d_{num}$). By drawing out more instances that fall closer to the line from the minority borderline cases to similar instances of the minority class, then it is possible to extend the minority class and balance the classes [18].

D. Feature Selection using Mutual Information

The selection of features is a crucial preprocessing step in machine learning. This entails removing the least important features from the initial feature set and keeping only the most important ones. Many feature selection algorithms emphasize improving important information while reducing redundant information. To further reduce redundant information in assessment measures, we propose a feature selection method that makes use of mutual information [19].

TABLE I. BORDERLINE-SMOTE ALGORITHM

Algorithm:	Borderline-SMOTE
Input:	Training set *TS,* Minority class *PC,* Majority class *NC,* Nearest neighbors count *m* and *k,* Oversampling amount *s*
Output:	Synthetic minority class samples
Initialization:	Initialize the algorithm with the given input parameters.
1.	For each sample p_i in the minority class *PC*: • Calculate the m nearest neighbors of p_i from the training set *TS*. • Denote the count of the majority examples in the m nearest neighbors as m'. • If $m' = m$, ignore p_i as it belongs to a noisy region. • If $m/2 \leq m' < m$, add p_i to the *DANGER* set, indicating that it is in a borderline region. • If $0 \leq m' < m/2$, ignore p_i as it is considered safe.
2.	For every instance in *DANGER* set: • Compute the k nearest neighbors of the examples from the minority class *PC*.
3.	For each p_i' in the *DANGER* set: • *Choose s* nearest neighbors from the k nearest neighbors of p_i' in the minority class *PC.* • Compute the difference vector dif_j between p_i' and each selected neighbor. • Generate *s* new synthetic minority examples by adding a scaled difference vector to p_i', where the scaling factor is a random number between 0 and 1. $synth_j = p_i' + r_j \times dif_j$ (where $j = 1, 2, \ldots, s$)

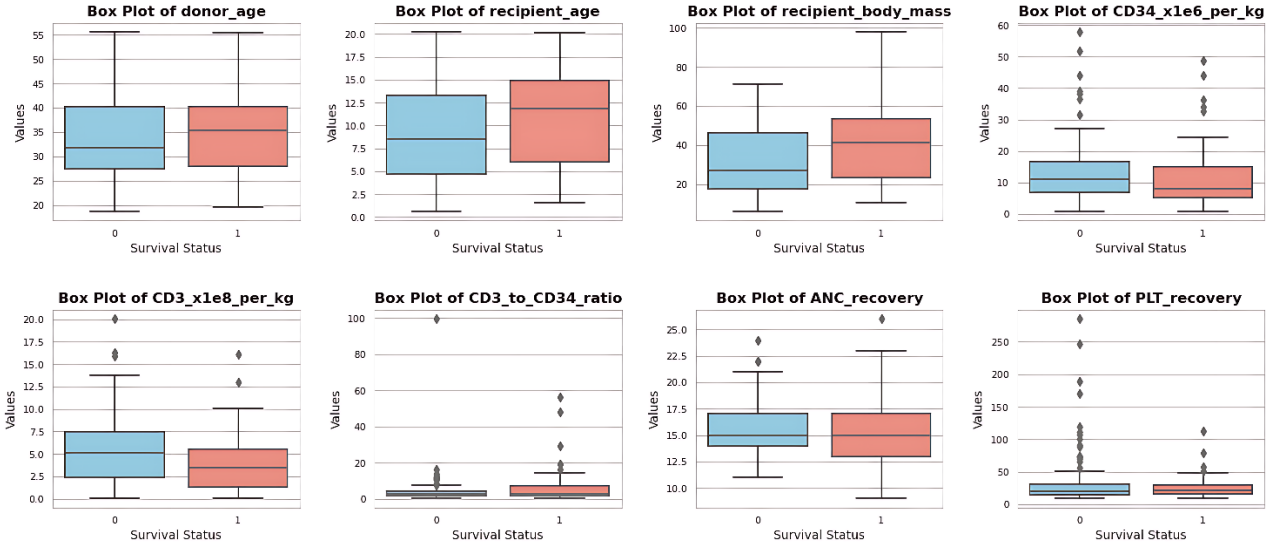
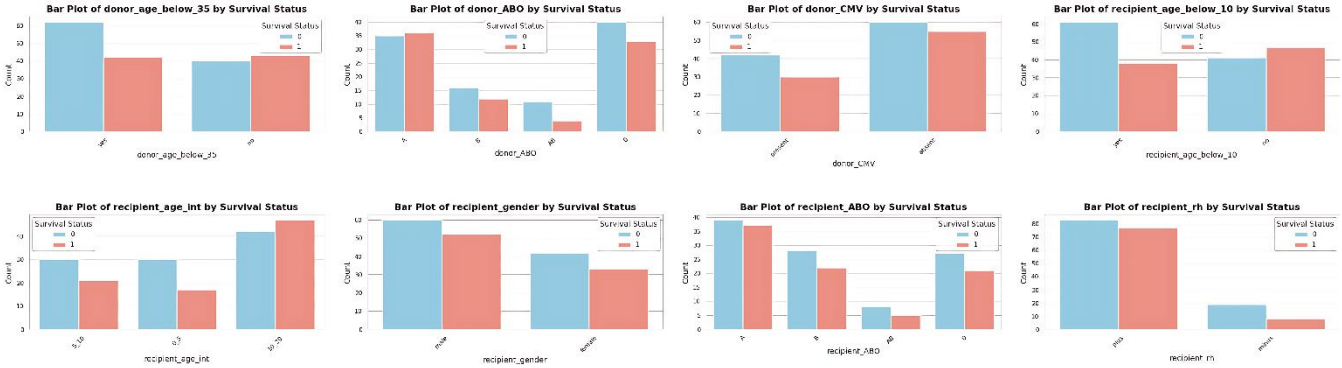


Fig. 1. Box plots of few numeric variables (0 - alive, 1 - dead).



Bar plots of few categorical variables (0 - alive, 1 - dead).

Mutual information is calculated between two variables that captures the number of bits required on average to optimally predict one variable given the value of the other variable known. Formally, the mutual information between two random variables W and Z is as follows.

$$I(W\ ;\ Z)\ =\ H(W)\ -\ H(W\mid Z)$$

where *I (W; Z)* is the mutual information for *W* and *Z*, *H(W)* is the entropy for *W* and *H (W | Z)* is the conditional entropy for *W* given *Z*. The mutual information between two discrete variable *W* and *Z* with $w1, w2, \ldots, wn$ and $z1, z2, \ldots, zm$ distinct values is as follows.

$$I(W\ ;\ Z) = \sum_{i,j} p(w_i, z_i)\, log\, \frac{p(w_i, z_i)}{p(w_i)p(z_i)}$$

where $p(w_i)$ and $p(z_i)$ is the marginal probability mass function of *W* and *Z* [20]. This approach was implemented in Python using the 'mutual-info-classif' package.

TABLE II. SELECTED FEATURES USING MUTUAL INFORMATION

10 features	'survival_time', 'PLT_recovery', 'donor_CMV_present', 'HLA_match_10/10', 'risk_group_high', 'HLA_group_1_three_diffs', 'acute_GvHD_III_IV_yes', 'donor_age_below_35_yes', 'recipient_ABO_A', 'recipient_age_below_10_no'

IV. PROPOSED METHODOLOGY

A. Model Selection

The dataset is split into an 8:2 ratio, implying that 80% of it is utilized for training and the rest of 20% is used for testing. This assures that the models can be evaluated on unseen data to assess their predictive performance.

This research study is divided into eight experiments, each representing a unique combination of feature selection, SMOTE (Synthetic Minority Over-sampling Technique), and Hyperparameter Optimization (HPO). The experiments are categorized into two groups: A and B. Group A Experiments A (1-3) use the full feature set, while Group B Experiments B (1-3) use a selected subset of features we extracted using mutual information. Each experiment within the groups is further differentiated based on the use of SMOTE and HPO. The cross validation of the training dataset was done using Grid Search Cross Validation (GSCV) to get the models' optimum hyper-parameter. In each experiment, we employed five different machine learning algorithms: Random Forest (RF), Decision Trees (DT), Logistic Regression (LR), XGBoost, and Support Vector Classifier (SVC).

The summary of results of each experiment is given in Table 3-8.

TABLE III. FULL FEATURE SET WITH DEFAULT HYPERPARAMETERS

Algorithm	Accuracy	Precision	Recall	F1
RF	0.9473	0.9411	0.9411	0.9411
DT	0.9736	1.0	0.9411	0.9696
LR	0.9210	0.9375	0.8823	0.9090
XGBoost	0.9736	1.0	0.9411	0.9696
SVC	0.8947	0.8823	0.8823	0.8823

TABLE IV. FULL FEATURE SET WITH HYPERPARAMETER OPTIMIZATION

Algorithm	Accuracy	Precision	Recall	F1
RF	0.9736	1.0	0.9411	0.9696
DT	0.9473	0.9411	0.9411	0.9411
LR	0.9473	0.9411	0.9411	0.9411
XGBoost	0.9736	1.0	0.9411	0.9696
SVC	0.9473	0.9411	0.9411	0.9411

TABLE V. FULL FEATURE SET WITH HYPERPARAMETER OPTIMIZATION AND BORDERLINE SMOTE

Algorithm	Accuracy	Precision	Recall	F1
RF	0.9736	1.0	0.9411	0.9696
DT	0.9210	0.8888	0.9411	0.9142
LR	0.9210	0.9375	0.8823	0.9090
XGBoost	0.9736	1.0	0.9411	0.9696
SVC	0.8684	0.8333	0.8823	0.8571

TABLE VI. SELECTED FEATURES WITH DEFAULT HYPERPARAMETERS

Algorithm	Accuracy	Precision	Recall	F1
RF	0.9473	0.9411	0.9411	0.9411
DT	0.8684	0.8	0.9411	0.8648
LR	0.9210	0.85	1.0	0.9189
XGBoost	0.9210	0.8888	0.9411	0.9142
SVC	0.8947	0.8421	0.9411	0.8888

TABLE VII. SELECTED FEATURES WITH HYPERPARAMETER OPTIMIZATION

Algorithm	Accuracy	Precision	Recall	F1
RF	0.9736	1.0	0.9411	0.9696
DT	0.8947	0.8421	0.9411	0.8888
LR	0.9210	0.85	1.0	0.9189
XGBoost	0.9736	1.0	0.9411	0.9696
SVC	0.9210	0.85	1.0	0.9189

TABLE VIII. SELECTED FEATURES WITH HYPERPARAMETER OPTIMIZATION AND BORDERLINE SMOTE

Algorithm	Accuracy	Precision	Recall	F1
RF	0.9473	0.9411	0.9411	0.9411
DT	0.9473	0.9411	0.9411	0.9411
LR	0.9210	0.85	1.0	0.9189
XGBoost	0.9736	1.0	0.9411	0.9696
SVC	0.9210	0.85	1.0	0.9189

B. Model Evaluation

a) Experiment A(1): Full Feature Set with default hyperparameters

Table 3 shows the performance of various algorithms with the full feature set and default hyperparameters. The Decision Tree and XGBoost algorithms showed high performance, while the Logistic Regression and Support Vector Classifier algorithms showed lower performance. This indicates that without hyperparameter optimization, some algorithms may not perform as well as others.

b) Experiment A(2): Full Feature Set with Hyperparameter Optimization

With hyperparameter optimization, the performance of all algorithms improved as shown in Table 4. The Random Forest and XGBoost algorithms maintained their high performance, while the Decision Tree and Support Vector Classifier algorithms showed significant improvement, particularly in terms of accuracy and F1-score.

c) Experiment A (3) : Full Feature Set with hyperparameter Optimization and Borderline SMOTE

As shown in Table 5, Random Forest and XGBoost algorithms achieved the highest accuracy and F1-score, indicating excellent overall performance. The Support Vector Classifier, on the other hand, had the lowest scores among the algorithms, suggesting it may not be the best choice for this dataset when using the full feature set.

d) Experiment B (1): Selected Features with default hyperparameters

The algorithms were run with default hyperparameters, and a selected subset of features extracted using mutual information. The Random Forest algorithm again performed well in accuracy terms. However, the Decision Tree algorithm showed a decrease in performance compared to the full feature set, particularly in terms of precision and F1-score displayed in Table 6.

e) Experiment B (2) : Selected Features with Hyperparameter Optimization

Optimization of the hyperparameters enhanced the performance of all algorithms as observed in Table 7. While the Decision Tree and Support Vector Classifier algorithms significantly improved, notably the accuracy and F1-score, the Random Forest and XGBoost algorithms kept up their strong performance.

f) Experiment B (3) : Selected Features with Hyperparameter Optimization and Borderline SMOTE

It can be inferred in Table 8 that with both hyperparameter optimization and Borderline SMOTE, the XGBoost algorithm achieved the highest scores across all metrics, followed closely by the Random Forest algorithm. The Support Vector Classifier, while improved, still lagged behind other algorithms.

V. RESULTS AND DISSUSSION

In Experiment A, where the full feature set was used with hyperparameter optimization and Borderline SMOTE, the Random Forest and XGBoost model demonstrated the highest accuracy and F1-score. This suggests that these models were able to effectively classify the survival outcomes of pediatric BMT patients using the full feature set. The Support Vector Classifier, on the other hand, performed poorly in comparison, indicating that it may not be the best choice for this dataset when using the full feature set. In Experiment B, where selected features were used, the Random Forest algorithm continued to perform well in terms of accuracy. However, the Decision Tree algorithm showed a decrease in performance compared to the full feature set, particularly F1-score and precision. This suggests that the selected features may not have included some important variables that the Decision Tree algorithm could use to improve its predictions. The introduction of hyperparameter optimization in Experiment B improved the performance of all algorithms. This indicates that tuning the parameters of the models can significantly enhance their predictive capabilities.

The use of Borderline SMOTE in Experiment B did not significantly change the performance of the algorithms. However, it did improve the Decision Tree algorithm results, suggesting that the technique may be beneficial for certain models.

Finally, in Experiment B with both hyperparameter optimization and Borderline SMOTE, the XGBoost algorithm achieved the highest accuracy of 97.36% outperforming previous accuracy score of 95.23% [13] . This suggests that the combination of either full feature set or selected features with hyperparameter optimization and Borderline SMOTE can lead to highly accurate predictions of survival outcomes in pediatric BMT patients.

VI. Future Work

The potential to save lives and enhance the quality of life for pediatric BMT patients is immense, and the predictive models developed in this study represent a significant step forward. However, we must not rest on our laurels. The future of this research holds exciting possibilities that could revolutionize the way we predict survival outcomes in pediatric BMT patients. We envision a future where our models are enriched with a broader spectrum of data, encompassing detailed medical histories, genetic information, and comprehensive post-transplantation care details. This wealth of information could unlock new insights and enhance the predictive power of our models. We also see great promise in exploring alternative feature selection methods and oversampling techniques. By doing so, we could discover hidden patterns and correlations in the data, directing more precise predictions. The use of more complex models, such as artificial neural networks, could further enhance our ability to predict survival outcomes by capturing intricate non-linear relations in the data. By employing ensemble methods, we can harness the strengths of multiple models, leading to more robust and accurate predictions. We plan to validate our models using a variety of cross-validation techniques, external datasets, and temporal splits. This rigorous validation process will affirm that our models are not just theoretically comprehensive, but also practically applicable in varied real-world scenarios.

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