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RESEARCH ARTICLE

Advancing Precision Medicine: VAE Enhanced Predictions of Pancreatic Cancer Patient Survival in Local Hospital

YUAN WANG[1], CHENBI LI[2], AND ZEHENG WANG[3,4], (Member, IEEE)
[1]Department of Oncology, 3201 Hospital, Hanzhong, Shaanxi 723000, China
[2]Department of ICU, 3201 Hospital, Hanzhong, Shaanxi 723000, China
[3]Data61, CSIRO, Clayton, VIC 3168, Australia
[4]Manufacturing, CSIRO, West Lindfield, NSW 2070, Australia

Corresponding author: Zeheng Wang (zenwang@outlook.com)

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ABSTRACT In this research, we address the urgent need for accurate prediction of in-hospital survival periods for patients diagnosed with pancreatic cancer (PC), a disease notorious for its late-stage diagnosis and dismal survival rates. Utilizing machine learning (ML) technologies, we focus on the application of Variational Autoencoders (VAE) for data augmentation and ensemble learning techniques for enhancing predictive accuracy. Our dataset comprises biochemical blood test (BBT) results from stage II/III PC patients, which is limited in size, making VAE's capability for data augmentation particularly valuable. The study employs several ML models, including Elastic Net (EN), Decision Trees (DT), and Radial Basis Function Support Vector Machine (RBF-SVM), and evaluates their performance using metrics such as Mean Absolute Error (MAE) and Mean Squared Error (MSE). Our findings reveal that EN, DT, and RBF-SVM are the most effective models within a VAE-augmented framework, showing substantial improvements in predictive accuracy. An ensemble learning approach further optimized the results, reducing the MAE to approximately 10 days. These advancements hold significant implications for the field of precision medicine, enabling more targeted therapeutic interventions and optimizing healthcare resource allocation. The study can also serve as a foundational step towards more personalized and effective healthcare solutions for PC patients.

INDEX TERMS Pancreatic cancer, machine learning, bioinformatics, small-scale data, variational auto-encoder.

I. INTRODUCTION

Pancreatic cancer (PC), of which approximately 90% is pancreatic ductal adenocarcinoma (PDAC), ranks among the most lethal malignancies globally, with a dismal 5-year survival rate of less than 11% [1]. Although recent advancements in therapeutic interventions have marginally improved this rate to 17.4% [2], PC continues to account for a significant number of fatalities worldwide as of 2020 [1], [3]. A major contributing factor to these grim clinical outcomes is the diagnostic challenge posed by the non-specific symptoms of PC, which often mimic those of other non-cancerous conditions, leading to delayed diagnosis at early stages [4], [5]. Consequently, by the time of hospital admission, the majority of patients present with tumors that have already progressed to late stages, often characterized by local invasion and distant metastases [6].

In addition to enhancing early-stage diagnosis, there is an urgent need to innovate therapeutic strategies aimed at reducing mortality among late-stage PC patients. Precision medicine (PM) is increasingly recognized as a viable approach and has garnered considerable attention in recent

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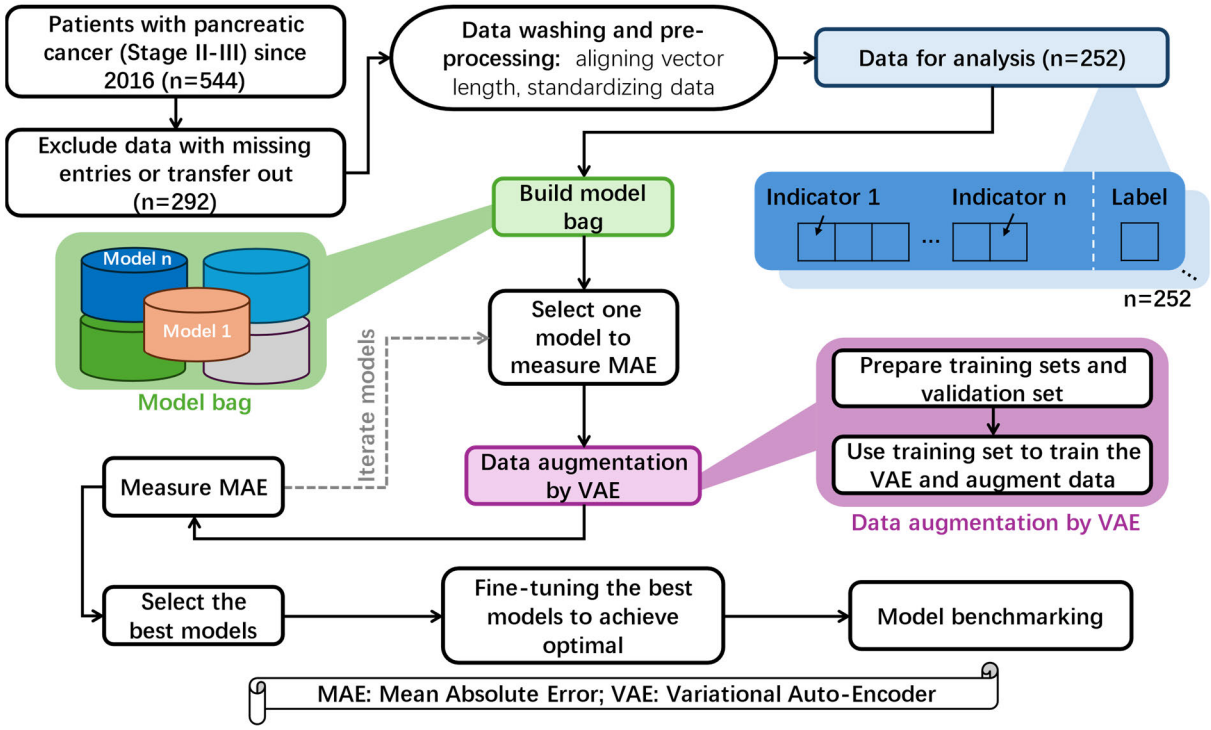

FIGURE 1. The procedure of the data preparation and model training. There are 24 biochemical blood test indicators/items in one record, with a label 0 or 1 indicating the final outcome of that patient. Ten machine learning models have been benchmarked, and four of them have been selected to build the ensemble learning architecture.

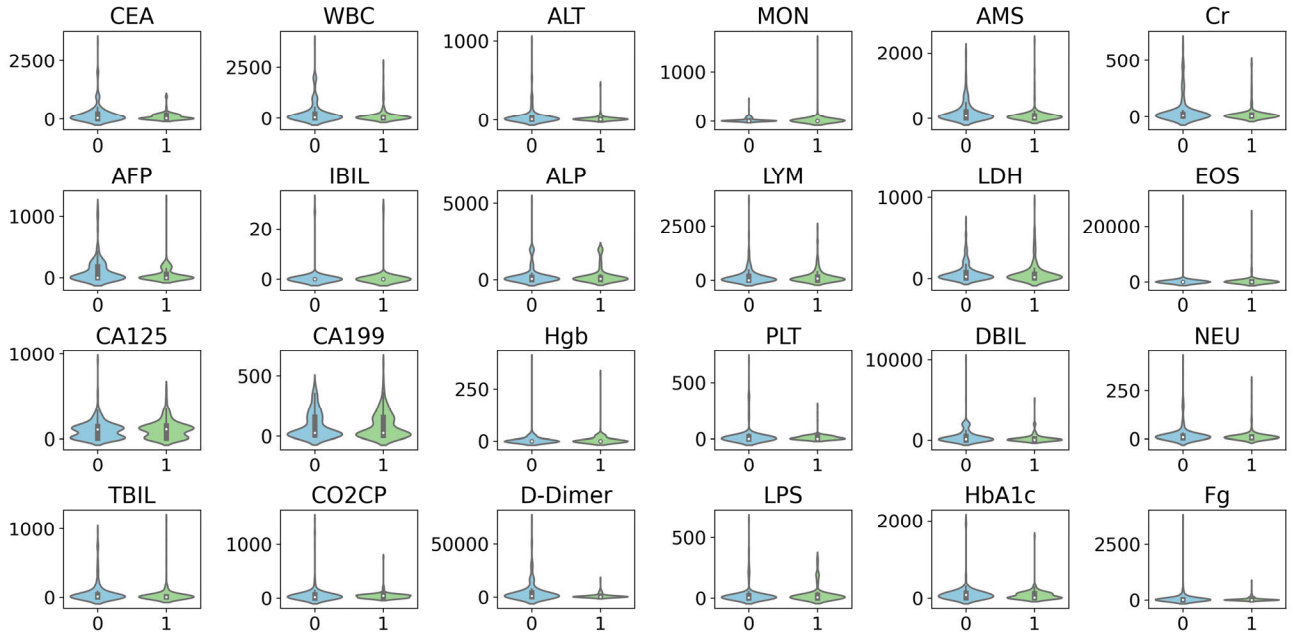

FIGURE 2. The violin plot showing the dataset's structure and the distribution of each variable. Here 0 and 1 on the x-axis respectively represents survived and deceased group. Y-axis indicates the tested value. ALT, Alanine aminotransferase; NEU, Neutrophil; LDH, Lactate dehydrogenase; MON, Monocyte; EOS, Eosinophil; CO2CP, carbon dioxide combining power; TBIL, total bilirubin; AMS, Amylase; LYM, Lymphocyte; AFP, Alpha fetoprotein; CEA, Carcinoembryonic antigen; WBC, white blood cell; DBIL, Direct Bilirubin; ALP, alkaline phosphatase; HbA1c, glycated hemoglobin; CA125, carbohydrate antigen 125; CA199, Carbohydrate antigen199; Fg, Fibrinogen; Cr, creatinine; LPS, Lipase; PLT, platelet; Hgb, Hemoglobin; IBIL, Indirect bilirubin. Note that only the record of the deceased group was used in the analysis of this work.

years [7], [8]. A critical component of implementing PM is the judicious selection of patients who are suitable candidates for novel precision healthcare interventions [9]. For instance, in the context of Patient-derived Organoid Pharmacotyping (PDOP) [10], it becomes imperative to identify patients with an appropriate survival period to mitigate ethical

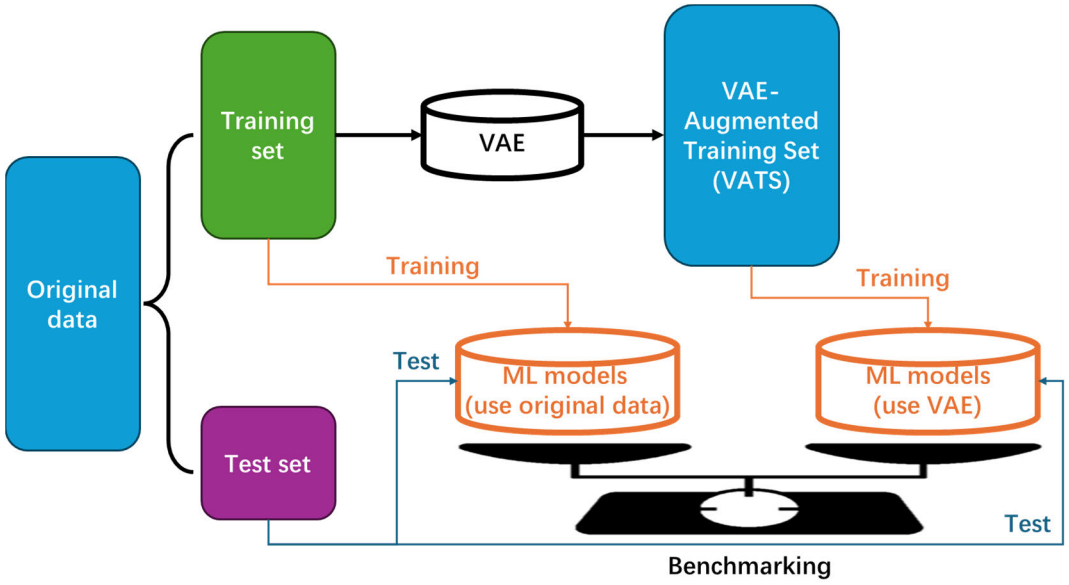

FIGURE 3. The procedure of VAE augmentation.

concerns associated with potential inappropriate treatment or overtreatment [11].

Conversely, machine learning (ML) has increasingly found applications in various medical domains for several years, extending from mitigating COVID-19 [12] to advancing herbal medicine research [13], [14]. In these diverse applications, ML has consistently demonstrated its efficacy in accurately predicting clinical outcomes [15], [16], [17]. This track record strongly suggests that ML could serve as a potential tool for predicting patient clinical statuses, thereby facilitating more targeted interventions in the realm of PM. While there has been a surge in research focusing on the application of ML in pancreatic cancer [11], [18], [19], [20], [21], and Variational Auto-Encoder (VAE)-based data augmentation [22], [23], [24] there remains a conspicuous gap in the literature: no studies have yet reported on leveraging ML to predict the in-hospital survival period of pancreatic cancer patients specifically for the purpose of PM by biochemical blood test (BBT).

Building on the promising capabilities of machine learning in medical applications and the unmet need for precise in-hospital survival prediction in pancreatic cancer, this study takes a practical approach. We employ a Variational Auto-Encoder (VAE) to augment a dataset of biochemical blood test (BBT) results collected from stage II/III pancreatic cancer patients. This augmented data is then used to predict the in-hospital survival period. To validate the efficacy of our approach, we benchmarked the predictive performance

TABLE 1. Specifications of the models.

Model	Specification
EN	alpha=0.1, l1_ratio=0.5
RBF-SVM	kernel='rbf', C=1.0, gamma='scale'
KNC	n_neighbors=3, weights='distance'
DT	max_depth=10, min_samples_split=5
RF	n_estimators=150, max_depth=10, min_samples_split=5
GB	n_estimators=150, learning_rate=0.05, max_depth=5
XGB	objective='reg:squarederror', n_estimators=150, learning_rate=0.05, max_depth=5
AB	n_estimators=100
LightGBM	n_estimators=100, learning_rate=0.05
DL	4 layers, neurons for each layer: 8, 4, 2, 1, epochs=300, lr=0.01, Act. Func.=ReLU

TABLE 2. Specifications of the best models after fine-tuning.

Model	Specification
EN	alpha=1, l1_ratio=0.8
RBF-SVM	kernel='rbf', C=10, gamma=10
DT	max_depth=15, min_samples_split=5

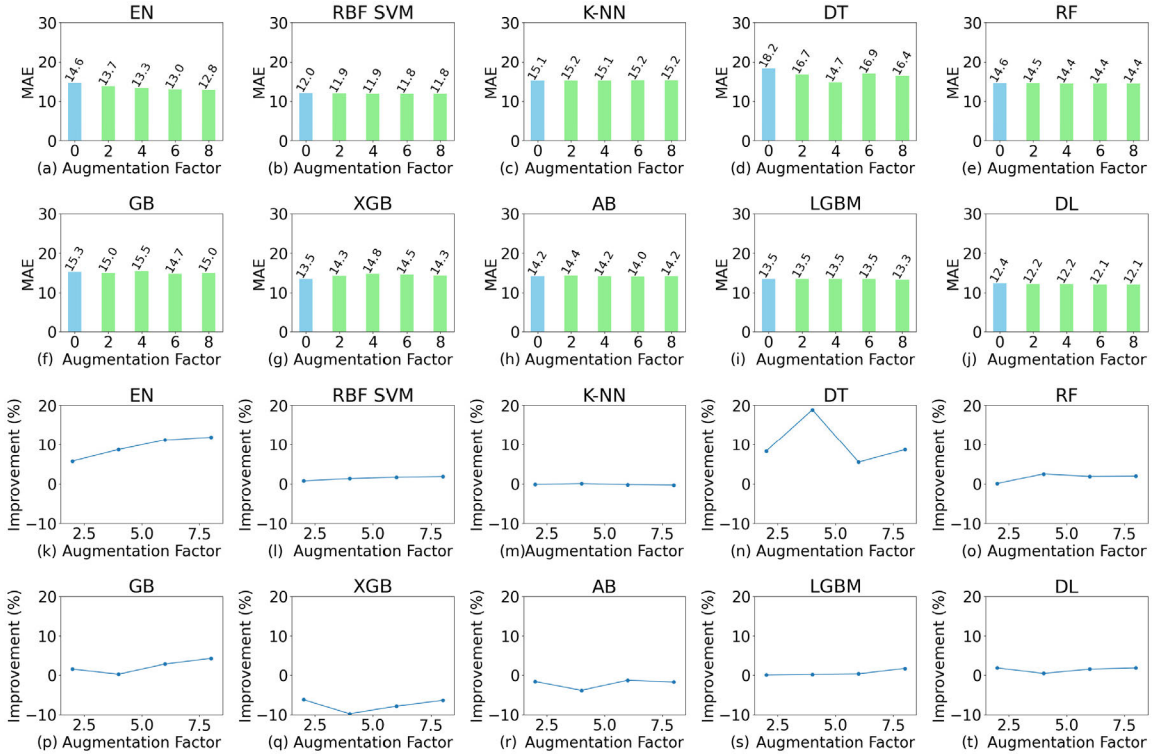

FIGURE 4. The (a)-(j) MAE and (k)-(t) MAE changes of each model before and after VAE augmentation. Augmentation factors indicate the folds of original training data that VAE synthesized. Factor 0 means the data without augmentation.

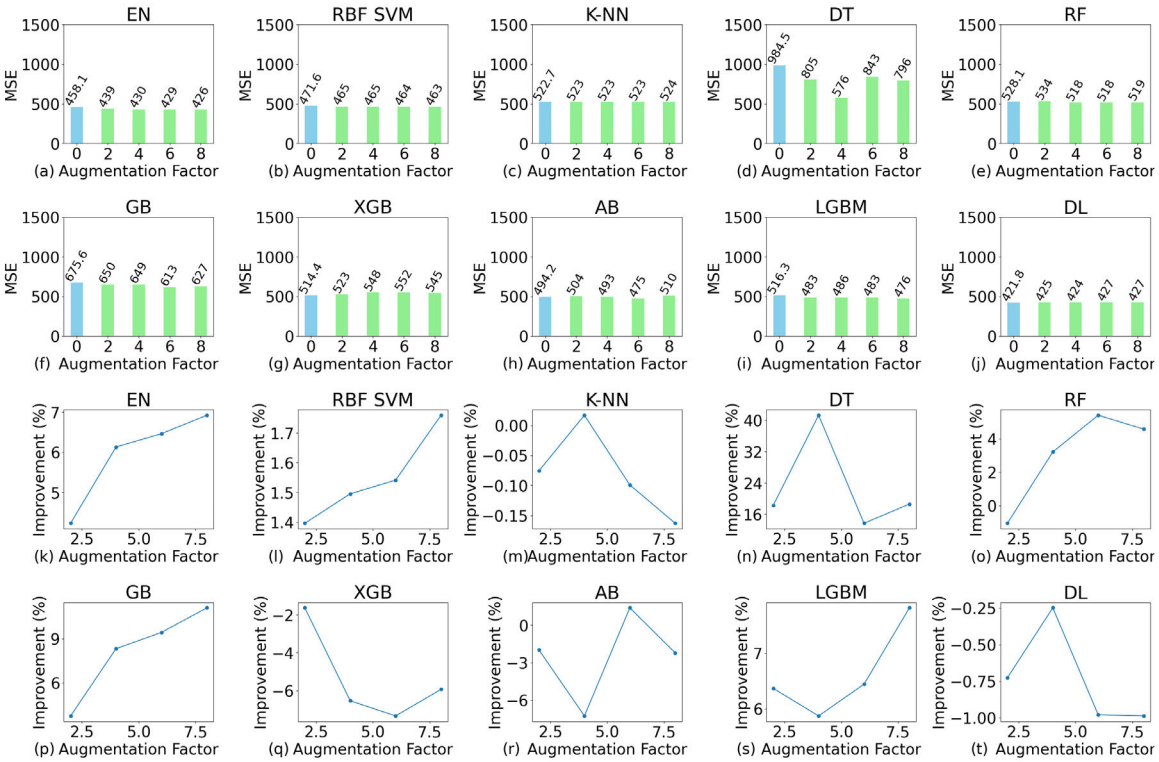

FIGURE 5. The (a)-(j) MSE and (k)-(t) MSE changes of each model before and after VAE augmentation. Augmentation factors indicate the folds of original training data that VAE synthesized. Factor 0 means the data without augmentation.

against ten mainstream machine learning algorithms and subsequently integrated the three best-performing models into an ensemble learning framework. Remarkably, our findings indicate that the ensemble learning approach, when augmented with VAE, can reduce the prediction error by up to 33% compared to using a single conventional model.

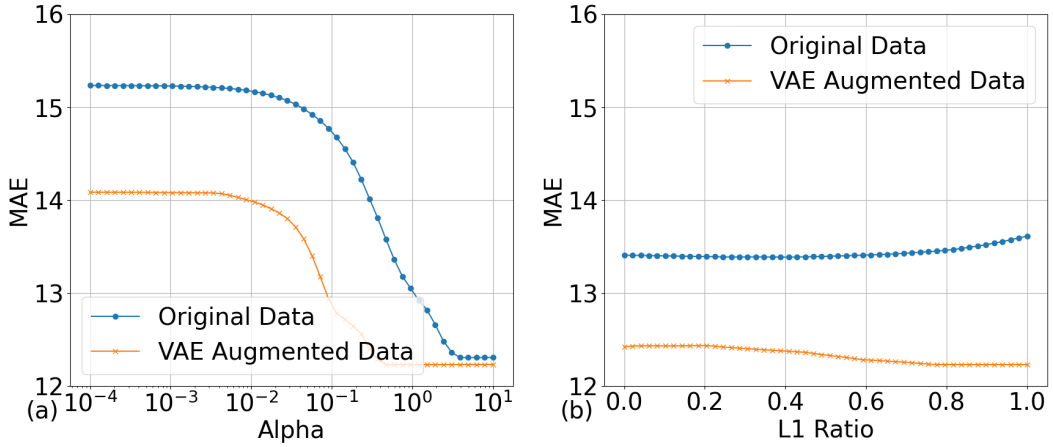

FIGURE 6. The fine-tuning of the EN model's parameters: (a) Alpha when L1 ratio is 0.9, and (b) L1 ratio when Alpha is 0.5.

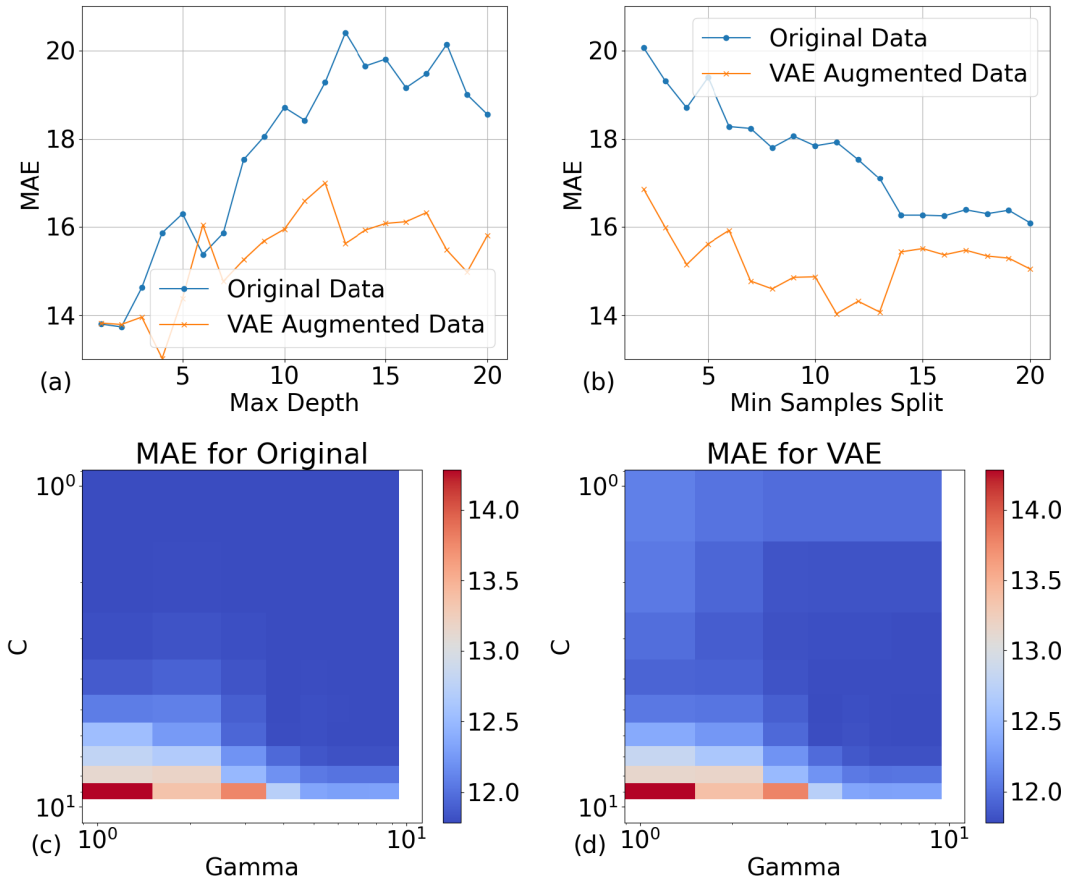

FIGURE 7. The fine-tuning of (a), (b) the DT and (c), (d) the RBF-SVM models' parameters. When scanning one parameter of the model, another parameter stays in default of the Scikit-learn package.

These results underscore the potential of our VAE-assisted ensemble learning strategy in accurately predicting in-hospital clinical outcomes, thereby highlighting its prospective utility in the PM of pancreatic cancer.

II. METHODS

The data was extracted from the medical records of the patients' treatment conducted in 3201 Hospital, Shaanxi, China, in accordance with the principles of the Declaration of Helsinki. The protocol was approved by the Ethics Committee of the 3201 Hospital. Due to the retrospective nature of this study, the Ethics Committee of the 3201 Hospital waived the requirement for informed consent from the patients; however, all patients were informed about the potential use of their de-identified data for research purposes. The data used in this study were fully de-identified to ensure anonymity.

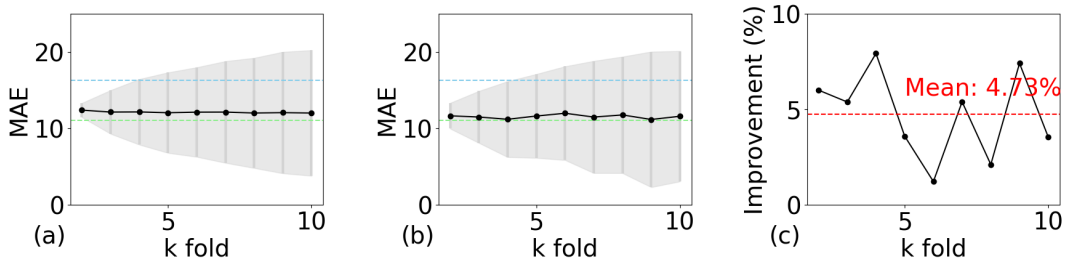

FIGURE 8. K-fold cross validation of the ensemble learning model (EN+DT+RBF-SVM) (a) without VAE and (b) with VAE. The improvement in using VAE is (c). The blue dashed lines indicate the average survival days of the patients upon admission, the green dashed lines are the median survival periods, and the red dashed line is the mean prediction improvement after using VAE. The grey regions indicate the variance. The details of the patients' survival period: count 252; mean 16.3; 50% 11.000000; min 0.0; max 100.0.

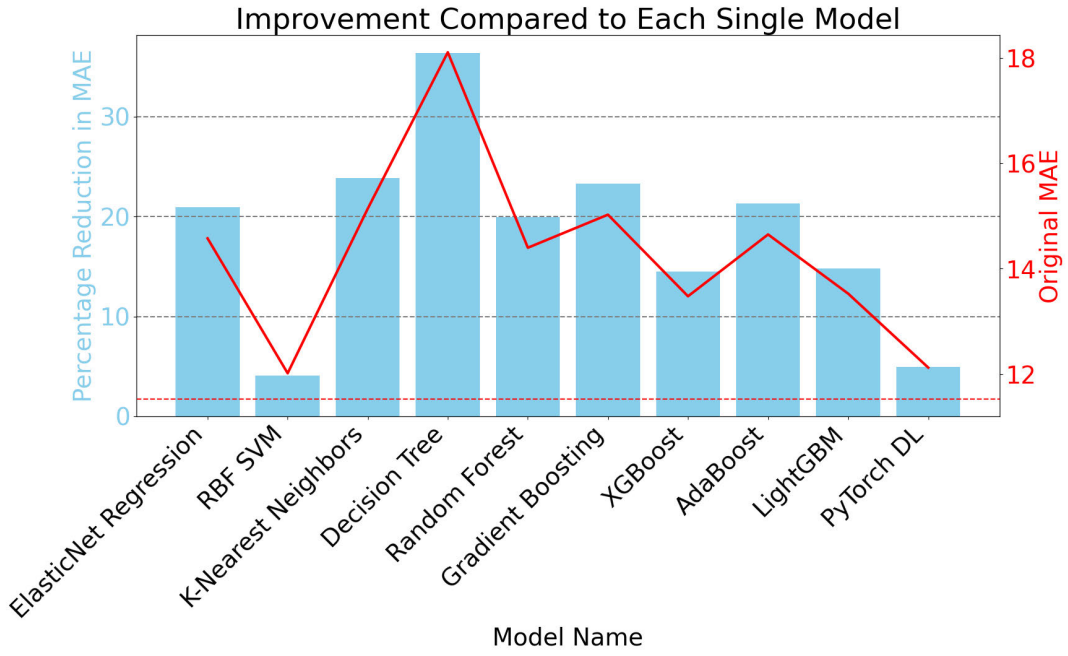

FIGURE 9. The prediction error improvement of the proposed strategy (VAE+ ensemble learning, dash line in red) compared to other individual algorithms (improvement rates are bars and the models' original MAE values are solid lines in red).

Data storage, access, and potential re-use were strictly controlled and in compliance with data protection regulations of the 3201 Hospital.

This study employs a retrospective analysis based on anonymized data. All patient information was fully de-identified prior to inclusion in this research. The dataset comprises BBT data collected from stage II/III pancreatic cancer patients admitted to 3201 Hospital in China since 2016 to present. Initially, a total of 544 records were gathered; however, 292 of these were excluded due to incomplete entries, successful treatment outcomes, or ambiguous final clinical results, as illustrated in Fig. 1. Consequently, the final dataset used for this study consists of 252 records, each containing 24 BBT features such as ALT, NEU, CA199, among others. Detailed information of the BBT markers can be found in the caption of Fig. 2. Note that only the record of the deceased group was used in the analysis of this work.

To prepare the dataset for machine learning experiments, all data vectors were aligned and standardized using the StandardScaler function of Scikit-Learn package by default settings. The dataset was then partitioned into two distinct subsets: an 80% training set and a 20% test set. Machine learning models were initially trained using the training set and subsequently validated using the test set.

Variational Autoencoders (VAE) serve as a key role in machine learning technologies, designed to encode a training dataset into a latent space and synthesize new data [25]. This encoding process is not merely a data compression mechanism; it captures underlying patterns within the dataset that can be leveraged for data augmentation. When a recognizable pattern emerges in the encoded data, VAE has the capability to generate new, synthetic data by sampling from this latent pattern [26]. The efficacy of VAE in augmenting small-scale datasets has been previously demonstrated in the realm of electronics, where it is evident that using VAE was to augment

data of semiconductor devices can improve the performance of ML-based modeling [27].

In our study, the VAE model was initially trained using the existing training set. This VAE model is constructed with a detailed multi-layer architecture. The encoder consists of two fully connected layers with a hidden dimension of 100 units each. The first layer applies a sigmoid activation function, and the second layer uses a tanh activation to enhance their capability of representation. These layers feed into two linear layers that generate the mean and log-variance for the latent space, which has a dimensionality of 2. The decoder mirrors this architecture with a tanh activated layer followed by a sigmoid activated layer, both with a hidden dimension of 100, and culminates in a sigmoid activated output layer that reconstructs the input data. The model is trained over 100 epochs with a batch size of 32. A validation split of 20% is used to monitor and prevent overfitting.

Post-training, the model was deployed to generate synthetic data from the latent space: random points in the latent space were sampled and processed by the decoder to generate data in real space. This synthetic data was not used in isolation but was integrated with the original training set to create a more robust VAE-Augmented Training Set (VATS). Utilizing VATS, we trained our machine learning models and subsequently evaluated their performance metrics, such as Mean Absolute Error (MAE) and Mean Squared Error (MSE), using a separate test set for validation. The entire workflow of this VAE-based data augmentation strategy is illustrated in Fig. 3.

The ML models adopted in this work are: Elastic Net (EN), radical basis function support vector machine (RBF-SVM), k-nearest clustering (KNC), decision tree (DT), random forest (RF), gradient boosting (GB), XGBoost [28] (XGB), AdaBoost [29] (AB), LightGBM [30] (LGB), and deep neural network (DL, realized by Pytorch 2.0.1). Except for the last four models, others were realized by using Scikit-Learn 1.2.2. All codes were compiled by Python 3.10.12 in a personal computer with AMD Ryzen 5600G CPU and 16GB memory. The specifications of the models can be found in Table 1.

III. RESULTS AND DISCUSSION

Fig. 4 serves as an initial overview of the model performances, revealing a wide range of MAE values that span from 18.1 to 12.0 (Augmentation Factors indicate the folds of original training data that VAE synthesized. Factor 0 means the data without augmentation. Same below.) This variation in MAE underscores the importance of model selection, a point further emphasized by the differential impact of VAE augmentation on each model. For example, the EN model sees a 10% improvement in MAE with VAE augmentation, while XGBoost experiences a decline. This suggests that VAE's effectiveness is highly model-dependent. Among the models tested, EN and DT rise to prominence, both showing over a 10% improvement in MAE when augmented with VAE. RBF-SVM also merits attention; although it doesn't benefit from VAE augmentation, it achieves a low MAE, indicating its inherent robustness. The improvement is calculated by Eq.1 as below, where the positive improvement means the model with augmented data overperforms that with the original data.

$$Improvement = \frac{\text{Ori.value} - \text{Aug.value}}{\text{Ori.value}} \times 100\% \quad (1)$$

Fig. 5 builds on these insights again by focusing on MSE, another key performance metric. The data corroborates the MAE findings, reinforcing the notion that EN, DT, and RBF-SVM are the most reliable models for predicting in-hospital survival periods for PC patients. This consistency across different metrics adds a layer of validation to our model selection process.

Fig. 6 dives deeper into the EN model's performance, exploring how different parameters affect its MAE. Fig. 6(a) examines the relationship between MAE and the Alpha parameter when L1_ratio is set at 0.9, and Fig. 6(b) shows the relationship between MAE and the L1_ratio parameter when Alpha is set at 0.5. The results indicate potential higher performance as Alpha increases for both the original and VAE-augmented data, suggesting that more complex models may be more effective to capture the structure of the data in this case. Interestingly, the trends for the original and VAE-augmented data diverge in Fig.6(b), implying that VAE introduces additionally meaningful but sophisticated information that can be mitigated through L1 regularization. This observation is critical for understanding how VAE augmentation affects model complexity and performance: a feature selection step may be helpful to further boost the prediction accuracy.

Fig. 7 extends this analysis to the DT and RBF-SVM models, providing a comprehensive view of how parameter tuning impacts different models. For both data, the algorithm requires shallower trees to provide a closer modeling of the data, as shown in Fig. 7(a), suggesting a simpler DT model is more suitable for capture the features of the data. The opposing trends between the original and VAE-augmented data confirm that VAE introduces a certain level of complexity, inherent to its sampling procedure from the low-dimensional latent space, as shown in Fig. 7(b). Similar to the EN's parameters, RBF-SVM's parameters exhibit the same trends as shown in Fig. 7(c) and (d): The data requires more complex model to capture its hyperfine structures. This complexity could be both a boon and a bane, as demonstrated in Fig. 6's L1 regulation, depending on the model and its parameters, emphasizing the need for careful model selection and tuning. However, although understanding the data structure can help in modeling and predicting unforeseen data, the in-depth analysis of the data distribution in their latent space is not the scope of this study.

In the final analysis that is depicted in Fig. 8, we integrate the top-performing models into an ensemble learning framework, utilizing the "StackingRegressor" method from the Scikit-Learn package. The ensemble consists of three base models: EN, RBF SVR, and DT, each selected for their unique strengths in modeling complex relationships and

performance enhancing after VAE-based data augmentation. These base learners are first trained on the dataset, and then their predictions are stacked and used as input for the final model, known as the meta-learner. This meta-learner integrates the predictions from each base model to produce a final, aggregated prediction. This approach leverages the diverse capabilities of individual models, aiming to enhance the robustness and reliability of predictions, particularly in the context of predicting in-hospital survival for pancreatic cancer patients.

Through k-fold cross-validation, we find that this ensemble approach further narrows down the MAE to just 12 days. With the addition of VAE augmentation, this already impressive figure is further reduced by 4.7% to approximately 11 days. The blue dashed lines of Fig. 8(a) and (b) indicate the average survival days of the patients upon admission, and the green dashed lines are the median survival periods, and the red dashed line is the mean prediction improvement of the ensemble learning model after using VAE. It can be seen that after the VAE+ensemble learning, the average prediction error (as per MAE) is lower than the mean survival days (16.3) – This is a good sign that our strategy can yield an acceptable prediction result even with small-scale dataset from a single local hospital.

Fig. 9 is a summary of the prediction enhancement that was achieved by our strategy compared to the use of each individual model. The red solid line indicates the original MAE of each model, and the red dashed line is the MAE from our strategy. A maximum of 35% reduction was achieved. Additionally, the proposed VAE-based ensemble learning overperforms all individual models. This strengthens our claim again that the proposed strategy can be more powerful in the clinical prediction tasks of PM.

The substantial reduction in MAE, particularly to around 10 days through VAE-augmented ensemble learning, holds significant promise for PM in the context of pancreatic cancer. By achieving such a high level of predictive accuracy, our approach opens the door for more targeted and timely therapeutic interventions. This not only has the potential to improve patient outcomes but also to optimize resource allocation in healthcare settings.

This study is not without its limitations, which warrant discussion for a comprehensive understanding of the results and their applicability. First and foremost, the research is confined to a single-center dataset with a relatively small sample size. This inherently restricts the generalizability of our findings to a broader population of pancreatic cancer (PC) patients. Second, the study focuses exclusively on stage II/III PC patients, thereby limiting the scope of the model's validation across varying disease stages. This could potentially skew the predictive accuracy when applied to a more diverse patient cohort. Third, the limited dataset size compelled us to rely heavily on machine learning (ML) algorithms to discern differences between subgroups, such as those defined by age and gender. This could introduce bias or noise into the predictive model, affecting its performance. However, studies have indeed shown that older patients generally face poorer survival outcomes [31], and there are notable differences in survival rates between genders within certain treatment procedures [32]. These facts are worthy of being considered in future explorations. Additionally, the study does not account for other potential confounding factors like comorbidities or treatment history, which could offer a more nuanced understanding of in-hospital survival period. Also, to our best knowledge, there is no literature so far to ensure our selection of BBT items can represent the definitive set of predictors – Our findings can only suggest a correlation between these chosen markers and patient outcomes.

It's important to note that these limitations were primarily dictated by data availability and scope constraints. Future research endeavors should aim to address these issues by incorporating multi-center data, expanding the patient stage range, and considering additional variables that could influence the model's predictive accuracy. Moreover, with the rapid development of ML technology, more fancy methodologies might also be integrated into our proposed approach to enhance further the performance like MAE, which is, however, out of the scope of the current research and is expected to appear in future research.

IV. CONCLUSION

In this study, we attempt to address the critical challenge of predicting in-hospital survival periods for PC patients by leveraging ML technologies, specifically VAE for data augmentation and ensemble learning for predictive accuracy. Our results highlight the efficacy of models like EN, DT, and RBF-SVM within a VAE-augmented framework. The VAE technology itself was instrumental in enhancing the performance of our ML models, particularly useful for small-scale datasets. The ensemble approach further optimized the results, reducing the MAE to approximately 10 days when augmented with VAE.

These findings have profound implications for PM of PC. The significant reduction in prediction error of the survival periods, especially through VAE-augmented ensemble learning, not only enables more targeted therapeutic interventions but also optimizes healthcare resource allocation. This study serves as a pivotal step towards more personalized and effective healthcare solutions for PC patients.

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YUAN WANG received the M.B.B.S. degree from Xi'an Medical University, Shaanxi, China, in 2016, and the M.S. degree in medicine from Harbin Medical University, Heilongjiang, China, in 2019. She is currently with the Department of Oncology, Hanzhong 3201 Hospital. She mainly engages in the research of radiotherapy, chemotherapy, targeted therapy, and immunotherapy for malignant tumors.

CHENBI LI received the M.B.B.S. degree, in 2014. She is currently with the Department of ICU, Hanzhong 3201 Hospital. Her research interest includes all aspects of ICU.

ZEHENG WANG (Member, IEEE) received the master's and Ph.D. degrees in interdisciplinary subjects. He is currently working on quantum sensing, quantum artificial intelligence, and artificial intelligence for science.