Multiple Organ Failure Prediction with Classifier-Guided Generative Adversarial Imputation Networks

Xinlu Zhang*
Department of Computer Science, University of California, Santa Barbara
Santa Barbara, USA
xinluzhang@cs.ucsb.edu

Yun Zhao*
Department of Computer Science, University of California, Santa Barbara
Santa Barbara, USA
yunzhao@cs.ucsb.edu

Rachael Callcut
UC, Davis Health
Davis, USA
racallcut@ucdavis.edu

Linda Petzold
Department of Computer Science, University of California, Santa Barbara
Santa Barbara, USA
petzold@cs.ucsb.edu

ABSTRACT

Multiple organ failure (MOF) is a severe syndrome with a high mortality rate among Intensive Care Unit (ICU) patients. Early and precise detection is critical for clinicians to make timely decisions. An essential challenge in applying machine learning models to electronic health records (EHRs) is the pervasiveness of missing values. Most existing imputation methods are involved in the data preprocessing phase, failing to capture the relationship between data and outcome for downstream predictions. In this paper, we propose classifier-guided generative adversarial imputation networks (Classifier-GAIN) for MOF prediction to bridge this gap, by incorporating both observed data and label information. Specifically, the classifier takes imputed values from the generator(imputer) to predict task outcomes and provides additional supervision signals to the generator by joint training. The classifier-guide generator imputes missing values with label-awareness during training, improving the classifier’s performance during inference. We conduct extensive experiments showing that our approach consistently outperforms classical and state-of-art neural baselines across a range of missing data scenarios and evaluation metrics.

CCS CONCEPTS

• Applied computing → Health care information systems;
• Information systems → Data mining.

KEYWORDS

Multiple organ failure; Missing value imputation; GAN;

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1 INTRODUCTION

Multiple organ failure (MOF) is a life-threatening syndrome with variable causes, including sepsis [26], pathogens [10], and complicated pathogenesis [28]. It is a major cause of death in the surgical intensive care unit (ICU) [7]. Care in the first few hours after admission is critical to patient outcomes. This period is also more prone to medical decision errors in ICUs than later times [19]. Thus, an effective and real-time prediction is essential for clinicians to provide appropriate treatment and increase the survival rates for MOF patients.

With the rapid growth of electronic health record (EHR) data availability, machine learning models have drawn increasing attention for MOF prediction. Missing values are a pervasive and serious medical data issue, which could be caused by various reasons such as lost records or inability to collect the data during some time periods [34]. There exist many imputation algorithms, such as mean value imputation [1], multivariate imputation by chained equations (MICE) [5] and generative adversarial imputation nets (GAIN) [31] which impute missing components by adapting generative adversarial networks (GANs). However, these methods focus only on constructing the distribution between the unobserved components and the observed ones, without considering the underlying connections with specific downstream tasks, as is shown in the Figure 1.

Recently, GANs [8] have made significant progress on data generation. Labels can be incorporated in the GAN framework, e.g. CGAN [16] and AC-GAN [18], to generate label-aware outputs. Semi-supervised GAN [17] introduces a classifying discriminator to output either the validity of data or its class. Triple-GAN [14] is further proposed by adding an additional classifier to separate the role of the discriminator in Semi-supervised GAN. These works leverage label information to improve data generation and their generators have to take ground truth labels to generate label-aware data, which is not applicable in classification problems during inference.
The remainder of our paper is organized as follows. Preliminaries are introduced in Section 2, followed by the details of our proposed approach in Section 3. Experimental results are reported in Section 4. In Section 5, we review the existing related work, and conclusions are given in Section 6.

2 PRELIMINARIES

We formulate the MOF prediction as a binary classification problem with missing components in multiple features. In this section, we describe the problem definition in Section 2.1 and review the GAIN imputation algorithm in Section 2.2. The related notations are summarized in Table 1. Specifically, throughout this paper, we utilize lower-case letters, e.g. \( x \), to denote the data vector. \( p(x) \) is the probability distribution function of \( x \). \( \mathbf{1} \) denotes a d-dimensional vector of 1s, and letters with hats such as \( \hat{x} \) denote estimated vectors.

### Table 1: Notation definitions

| Notations | Description |
|-----------|-------------|
| \( i \)   | index of observations |
| \( j \)   | index of observed features |
| \( d \in \mathbb{N} \) | number of observed features |
| \( N \in \mathbb{N} \) | total number of observations |
| \( n \in \mathbb{N} \) | size of minibatch |
| \( x \) | data vector |
| \( y \) | outcome indicator |
| \( m \) | mask vector |
| \( z \) | noise vector |
| \( h \) | hint vector |
| \( b \) | binary vector for calculating hint |
| \( \tilde{x} \) | combination of partially observed data and NA |
| \( \hat{x} \) | combination of partially observed data and noise |
| \( G \) | generator |
| \( C \) | classifier |
| \( D \) | discriminator |
| \( g \) | reconstructed vector, the output of \( G \) |
| \( \hat{m} \) | estimated mask, the output of \( D \) |
| \( \hat{y} \) | estimated label, the output of \( C \) |

2.1 Problem definition

Let \( \mathcal{X}^d \) be a \( d \)-dimensional space and \( x \) a data vector, taking values in \( \mathcal{X}^d \) following distribution \( p(x) \). We denote \( x_j \) as the \( j \)-th feature in \( x \). Binary mask vector \( \mathbf{m} \in \{0,1\}^d \) indicates if the corresponding element in \( x \) is missing or not, where \( x_j \) is observed if \( m_j = 1 \), otherwise it is missing. To clarify the observed and missing components, we define a new vector \( \tilde{x} = (\tilde{x}_1, \cdots, \tilde{x}_d) \) as follows:

\[
\tilde{x}_j \in \{1,2,\ldots,d\} = \begin{cases} x_j, & \text{if } m_j = 1, \\ \text{NA}, & \text{if } m_j = 0. \end{cases}
\]

Supposing that \( y \in \{0,1\} \) is the binary outcome indicator for each sample, we can represent the dataset as a collection of \( N \) i.i.d. samples \( \{(\tilde{x}_i, \mathbf{m}_i), y_i\}_{i=1}^N \). We aim to impute the missing components in every \( \tilde{x}_i \), and predict the outcome \( y \) for all samples by leveraging the imputed data vector.
Formally, we seek to model \( p(y|x) \): the conditional distribution of the task outcome given a partially observed data vector.

### 2.2 Generative adversarial imputation networks (GAIN)

GAIN [31] was proposed to impute missing components with a GAN framework. In GAIN, the generator takes the observed components in \( \mathbf{x} \), mask vector \( \mathbf{m} \) and a noise vector \( \mathbf{z} \) as inputs, and outputs a completed data vector. The discriminator tries to distinguish the observed components and the missing ones. Furthermore, a hint vector \( \mathbf{h} \) is introduced to provide additional missing information for alleviating the diversity of the imputation result.

The generator, \( G \), takes

\[
\hat{x} = \mathbf{m} \odot \hat{x} + (1 - \mathbf{m}) \odot \mathbf{z},
\]

a combination of \( \hat{x} \) and \( \mathbf{z} \) by element-wise multiplication with \( \mathbf{m} \), as input, and outputs \( \mathbf{g} \), the reconstructed vector,

\[
g = G(\hat{x}).
\]

Note that \( \mathbf{g} \) is an output vector for every component, even if values are not missing in the data vector.

Thus, another element-wise multiplication is performed to calculate the imputed data vector via

\[
\tilde{x} = \mathbf{m} \odot \hat{x} + (1 - \mathbf{m}) \odot g,
\]

where \( \tilde{x} \) is obtained by taking the observed part in \( \hat{x} \) and replacing each NA by the corresponding value in \( \mathbf{g} \).

The discriminator serves as an adversarial character to train \( G \) by taking in the imputed data vector \( \tilde{x} \) and the hint vector \( \mathbf{h} \), following the distribution \( p(h|x) \). The output of the discriminator is a distribution to identify which components in \( \tilde{x} \) are observed. To help the discriminator distinguish imputations and observations, \( \mathbf{h} \) provides certain information about \( \mathbf{m} \) and its amount can be controlled by adjusting \( \mathbf{h} \) in different settings. Specifically, a binary random variable \( \mathbf{b} \in \{0,1\}^d \) is randomly drawn with \( P(b_j = 1) = p \). Then, \( \mathbf{h|m} \) is calculated by

\[
\mathbf{h} = \mathbf{m} \odot \mathbf{b} + 0.5(1 - \mathbf{b}),
\]

such that the discriminator will get mask information by \( h_j = m_j \) if \( b_j = 1 \), otherwise, no information provided.

### 3 METHODOLOGY

Notably, conditional distributions such as labels can improve the performance of the generator [16, 18], and the completed data vector can enhance its task prediction result. However, state-of-art imputation methods, e.g. GAIN, do not make use of the relationship between observations and outcome labels, which could provide additional information to help downstream classification tasks. Therefore, we propose Classifier-GAIN to bridge this gap. Figure 2 depicts the overall architecture. We explain each of the components and the training process of Classifier-GAIN in detail in Section 3.1~3.2.
by
\[ \hat{y} = C(\hat{x}). \]
Then \( G \) and \( C \) are jointly trained to obtain the distribution \( p(y, x'|\hat{x}) \), making \( G \) label-aware during imputation, which is ignored by GAIN.

**Discriminator.** In our architecture, the discriminator \( D \) serves as an adversarial character to train \( G \) by receiving the predicted label information from \( C \). We input \( \hat{x}, \hat{y} \) and \( h \) into \( D \) to obtain the probability that each component in \( \hat{x} \) is observed. Here, \( \hat{x} \) and \( \hat{y} \) jointly provide information to enhance \( D \) by learning the relationship between data and task outcomes, which can further strengthen \( G \) and \( C \). We define the estimated mask variable, \( \hat{m} \in [0,1]^d \), by

\[ \hat{m} = D(\hat{x}, \hat{y}, h), \]
with the \( j \)-th item in \( \hat{m} \) corresponding to the probability that the \( j \)-th item in \( \hat{x} \) is not NA in \( \hat{x} \).

### 3.2 Classifier-GAIN training

\( G \), \( C \) and \( D \) are trained as a min-max game by

\[
\min_{G,C,D} \max_{\hat{y}} V(G,C,D) = \mathbb{E}_{x,m,h} \left[ m \log \left( D(G(x), C(G(x)), h) \right) + (1-m) \log \left( 1 - D(G(x), C(G(x)), h) \right) \right],
\]

where \( \log \) is an element-wise logarithm. Specifically, We train \( G \) and \( C \) together to minimize the probability of \( D \) identifying \( m \), maximize the probability of correctly predicting \( y \) and minimize the reconstruction loss of observed components. We train \( D \) to maximize the probability of correctly predicting \( m \).

On each iteration, \( G \) and \( C \) are updated \( k \) times with objective function, \( \mathcal{L}_{C\&G} \), which is a weighted sum of three losses

\[ \mathcal{L}_{C\&G} = \mathcal{L}_G(m, \hat{m}) + \alpha \mathcal{L}_R(x, \hat{x}) + \beta \mathcal{L}_C(y, \hat{y}), \]

where \( \alpha \) and \( \beta \) are hyper-parameters.

The first loss, \( \mathcal{L}_G \), is an adversarial loss, which applies to missing components (\( m_j = 0 \)) by

\[ \mathcal{L}_G(m, \hat{m}) = - \sum_{j=1}^d \left( 1 - m_j \right) \log(h(m_j)). \]

The second loss, \( \mathcal{L}_R \), is a reconstruction loss, which applies to observed components (\( m_j = 1 \)) by

\[ \mathcal{L}_R(x, \hat{x}) = \sum_{j=1}^d m_j \mathcal{L}(x_j, \hat{x}_j), \]

where

\[ \mathcal{L}(x_j, \hat{x}_j) = \begin{cases} \frac{(x_j - \hat{x}_j)^2}{\hat{x}_j^2}, & \text{for numerical variables,} \\ -x_j \log(\hat{x}_j), & \text{for binary variables.} \end{cases} \]

The third loss, \( \mathcal{L}_C \), is a binary cross-entropy loss for task prediction given by

\[ \mathcal{L}_C(y, \hat{y}) = -\left[ y \log(\hat{y}) + (1 - y) \log(1 - \hat{y}) \right]. \]

Note that as \( G \) and \( C \) are updated together via Eq. 2, \( C \)'s performance will influence \( G \)'s parameters to guide the missing component imputation.

\( \mathcal{L}_R \) updates once at each iteration with objective function

\[
\mathcal{L}_D(m, \hat{m}) = - \sum_{j=1}^d \left[ m_j \log(\hat{m}_j) + (1-m_j) \log(1 - \hat{m}_j) \right] + \nabla_y \mathcal{L}_C(m, \hat{y}, \hat{m}), \tag{6}
\]

The detailed training process is shown in Algorithm 1.

**Algorithm 1** Minibatch Classifier-GAIN training

1. **Input:** Original data vector with missing component \( \hat{x} \), mask vector \( m \), ground truth label \( y \), the probability for drawing the hint vector \( p \), hyper-parameters \( \alpha \) and \( \beta \).
2. **repeat**
3. **Generator and Classifier**
4. Sample a batch of \( n \) binary vector \( \{b_i\}^{n}_{i=1} \sim \text{Bern}(p)^d \)
5. **for** \( k \) **steps do**
6. Sample a batch of \( n \) noises \( \{z_i\}^{n}_{i=1} \sim U(0,1)^d \)
7. **for** \( i \) **←** 1 to \( n \) do
8. \( h_i \leftarrow m_i \odot b_i + 0.5(1 - h_i) \)
9. \( \hat{x}_i \leftarrow m_i \odot \hat{x}_i + (1 - m_i) \odot b_i \)
10. Imputed data \( g_i \leftarrow G(\hat{x}_i) \)
11. Obtain \( \hat{y}_i \leftarrow C(\hat{x}_i) \)
12. Obtain \( \hat{m}_i \leftarrow D(\hat{x}_i, \hat{y}_i, h_i) \)
13. **end for**
14. Update generator \( G \) and classifier \( C \) together via stochastic gradient descent (SGD):
15. \( \nabla_G \frac{1}{n} \sum_{i=1}^n \mathcal{L}_G(m_i, \hat{m}_i) + \alpha \mathcal{L}_R(x_i, \hat{x}_i) + \beta \mathcal{L}_C(y_i, \hat{y}_i) \)
16. **end for**
17. **Discriminator**
18. Sample a batch of \( n \) binary vector \( \{b_i\}^{n}_{i=1} \sim \text{Bern}(p)^d \)
19. **for** \( i \) **←** 1 to \( n \) do
20. \( h_i \leftarrow m_i \odot h_i + 0.5(1 - h_i) \)
21. \( \hat{x}_i \leftarrow m_i \odot \hat{x}_i + (1 - m_i) \odot h_i \)
22. Obtain \( \hat{m}_i \leftarrow D(\hat{x}_i, \hat{y}_i, h_i) \)
23. **end for**
24. Update discriminator with fixed \( G \) and \( C \) via SGD
25. **for** \( d \) **←** 1 to \( D \) **do**
26. \( \nabla_D \frac{1}{n} \sum_{i=1}^n \mathcal{L}_D(m_i, \hat{m}_i) \)
27. **until** Classifier-GAIN converges

---

### 4 EXPERIMENTS

In this section, we conduct experiments on two datasets: the PhysioNet sepsis synthetic dataset and the UCSF real-world EHR dataset, introduced in Section 4.1, to evaluate Classifier-GAIN’s performance. Particularly, we investigate

**Q1.** Does the classifier-guided imputation help the downstream MOF prediction?

**Q2.** How does the proposed algorithm perform across different missing ratio scenarios?

We explain the experimental settings in Section 4.2. The performance comparisons of Classifier-GAIN against other imputation algorithms for MOF prediction are shown in Section 4.3, followed
by the visualizations of the imputed missing values of the UCSF MOF dataset in Section 4.4.

4.1 Dataset

For the PhysioNet sepsis dataset, 10,587 patients and 40 features are contained. We randomly select 80% of the instances as the training set, 10% as the development set, and 10% as the testing set. For the UCSF MOF dataset, 2,160 patients and 29 features are contained. We perform a 5-fold cross validation, considering the dataset’s size and models’ training time. The detailed description of datasets as follows:

PhysioNet sepsis synthetic dataset. Sepsis is a severe critical illness syndrome that can result in MOF [26]. Since MOF is the fatal end of sepsis progression[3], early detection of sepsis and antibiotic prescription are critical for improving MOF patient outcomes. We built a synthetic dataset based on the physiological data [25] provided by PhysioNet, sourced from ICU patients. Each patient contains 40 hourly measurements in three categories (vital signs, laboratory values and demographics) and the sepsis outcome in each hour. To obtain the sepsis outcome in the early stages, we focus on the first 6 hours’ records of each feature. We take the first-appearance measurement of each feature in the first six hours after admission. If the value of a feature was not recorded in the first six hours, we assume that value was missing. We exclude the patients whose features were entirely missing in the first six hours. We label a patient with sepsis as 1, otherwise as 0. To obtain a completed synthetic dataset for further experiments, we apply KNN (with \( K = 5 \)) to impute the original missing components and SMOTE to balance the data. After data preprocessing, we obtained 10,587 patients, among which 5,808 patients are with sepsis and 4,779 without sepsis.

UCSF MOF real-world dataset. Our UCSF MOF dataset, collected from the UCSF/San Francisco General Hospital and Trauma Center, contains 2,190 patients admitted to a Level I trauma center. Both demographic information, such as gender, age, BMI (body mass index), and injury measurements, e.g. injury severity score (ISS), traumatic brain injury, and Glasgow Coma Scale (GCS), were measured at the admission time of each patient. Laboratory results (D-Dimer, creatinine, white blood cell etc.) and physical vital signs (for example heart rate, respiratory rate, systolic blood pressure etc.) were recorded at different hours. Unique ICU treatments such as blood transfusion units, fresh frozen plasma transfusion and crystalloids for fluid resuscitation were slotted into time intervals such as 0 to 24 hours. Medical treatments (vasopressor, Heparin and Factor VII et al) were reported daily after admission.

To analyze the MOF states associated with patients’ early-stage status, we select either the first day or the initial hour records manually. We extract features with importance scores higher than 2% using forests of trees in Scikit-learn [22], and remove the patients whose data were utterly missing in the early stage or whose MOF outcome was not recorded. After data preprocessing and removal of abnormal values, we are left with 2,160 patients and 29 measurements. Selected features are categorized by types, and detailed statistics are shown in Appendix A. Two blood test features, D-Dimer and Factor VII, had a missing rate higher than 40%. The body mass index (BMI) missed 17.4%. Factor VII treatment, partial thromboplastin time (PTT), respiratory rate and systolic blood pressure were missing at rates between 5% and 10%. The remainder of the features were missing at rates less than 5%. The rate of missing data for each feature is listed in Table 2, ordered from high to low. Missing values account for 6.42% among all observations and the labelling ratio between No MOF (class 0) and MOF (class 1) is 11 : 1 in the dataset.

4.2 Experimental settings

Evaluation metrics. We measure the performance of Classifier-GAIN and baselines by both macro F1-score and area under the ROC curve (AUC-ROC).

Macro F1-score is defined as the mean of class-wise F1 scores which assigns equal importance to every class. It is low for models that perform well on the common classes, while performing poorly on the rare classes. For the Macro F1-Score calculation, we use 0.5 as the predicted value threshold.

AUC-ROC is also commonly used for MOF prediction [2, 20]. AUC-ROC assesses the overall preference of a classifier by summarizing over all possible classification thresholds. In binary classification problems, the higher the AUC-ROC, the better the model’s performance in identifying the two classes.

Model configurations. We compare Classifier-GAIN with both classical and state-of-art neural baselines for MOF prediction as follows:

(1) Simple imputation: It imputes missing components by mean imputation and most frequent imputation for continuous and categorical variables, respectively.

Table 2: Rates of missing data in the UCSF dataset

| Missing rate | Feature                        |
|--------------|--------------------------------|
| 41.9%        | D-Dimer (blood test)           |
| 41.6%        | Factor VII (blood test)        |
| 17.4%        | BMI                            |
| 5% ≥ & > 5%  | Factor VII treatment, PTT, Respiratory, SBP |
| 5% ≥ & > 0%  | HR, numribfxs, GCS, Vasopressor, Bun, Serumco2, PLTs, Crystalloids, Crystalloids, WBC, HGB, HCT, AIS scores, FFP_units, Blood_units, age, iss, Thromboembolic complication, Heparin_gtt |
| 0%           | Gender                        |

Table 3: Hidden layer setting of different modules in UCSF and Sepsis datasets.

| Dataset     | Network | Hidden layer 1 | Hidden layer 2 | Dropout rate |
|-------------|---------|----------------|----------------|--------------|
| Classifier  | 32      | 16             |                | 0.1          |
| UCSF        | Generator | 64             | 32             | 0.1          |
| Discriminator | 64      | 32             |                | 0.1          |
| Sepsis      | Generator | 64             | 32             | 0.1          |
| Discriminator | 64      | 32             |                | 0.1          |
(2) MICE [5]: It is a multiple imputation method, accounting for the statistical uncertainty in the imputations.

(3) GAIN [31]: It is a deep learning adversarial imputation framework, which we explained in Section 2.2 in detail.

Each of methods (1), (2) and (3) is separated into two steps. First we impute missing components by the corresponding method. Then we utilize a binary classifier to predict the subjects’ outcomes by taking imputed data. For our proposed Classifier-GAIN, we take the partially observed data as input, and output both an imputed data and classification outcomes.

In order to make the performance comparison as fair as possible, we assign the same structure and hidden size for all classifiers. GAIN has exactly the same structure in the generator and the same number of hidden layers in the discriminator as Classifier-GAIN. All of the networks are designed as multi-layer perceptrons with two hidden layers. We use batch normalization to normalize the input layer by re-centering and re-scaling. ReLU activation function and dropout are applied after each hidden linear layer. All of the neural networks utilize Sigmoid activation at the last step for outputs. The hidden layer settings in all of our experiments are listed in Table 3.

We implement our model and its variants using PyTorch [21], and use a GeForce GTX TITAN X 12 GB GPU for training, validation as well as testing. All of the neural networks are trained by using the Adam optimizer [13], whose learning rates are selected by grid search from 0.0005 to 0.002. For the convergence of the MICE imputation, we apply the IterativeImputer in Scikit-learn [22] with mean initial strategy, 100 maximum number of imputation rounds and 0.001 as tolerance of the stopping condition.

4.3 Performance comparison

We conduct each experiment by running 5 times with different random initializations and show the results in the format "mean ± standard deviation" to answer Q1 and Q2. For readers’ convenience, we make the best performance bold in each of the performance tables in this section.

**Synthetic data.** To evaluate Classifier-GAIN’s capability to capture the relationship between clinical records (vital signs and laboratory values) and label outcome for downstream prediction, we randomly remove 20%, 25%, 30%, 35%, 40%, 45% and 50% of all components from clinical records, to simulate missingness resulting from the urgency of the clinical situation. We demonstrate the effectiveness of Classifier-GAIN against other baselines in Table 4. To understand the performance gap between different missing scenarios and the completed data, we train a binary classifier on the completed dataset, which we refer to as the upper bound. As shown in Table 4, Classifier-GAIN consistently outperforms the simple imputation, MICE and GAIN across the entire range of missing rates, for both evaluation metrics. Especially, when the missing rate is 25%, Classifier-GAIN improves 5.2% and 14.6% in AUC-ROC and macro F1-score, respectively, compared with the best baselines.

To quantitatively evaluate the performance of Classifier-GAIN, we derive two additional metrics: (1) the relative improvement rate (RIR),

\[
\text{Classifier-GAIN - best_baseline - best_baseline} \quad \text{RIR},
\]

and (2) the relative gap reduction rate (RGRR),

\[
\frac{\text{Upper bound - best_baseline}}{\text{Upper bound - best_baseline}} \quad \text{RGRR},
\]

to demonstrate how much Classifier-GAIN improves compared to the best baseline.

![Graph](image)

(a) The relative improvement rate (%) (b) The relative gap reduction rate (%)

**Figure 3:** The relative improvement rate (left) and the relative gap reduction rate (right) of Classifier-GAIN on AUC-ROC and macro F1-score for PhysioNet sepsis dataset across different missing ratio scenarios.

The relative improvement rates calculated by Eq. 7 across different settings are shown in Figure 3 (a). For both macro F1-score

| Missing Rate | Classifier-GAIN | Simple imputation | MICE | GAIN | Classifier-GAIN | Simple imputation | MICE | GAIN |
|--------------|-----------------|-------------------|------|------|-----------------|-------------------|------|------|
| 0%           | 88.3 ± 0.6      | 85.7 ± 0.9        | 84.3 ± 1.5 | 83.4 ± 1.4 |
| 25%          | 87.1 ± 0.4      | 81.6 ± 1.2        | 81.6 ± 0.6 | 81.5 ± 1.4 |
| 30%          | 86.4 ± 0.6      | 81.9 ± 1.0        | 81.0 ± 0.9 | 81.8 ± 1.0 |
| 35%          | 84.8 ± 0.4      | 82.4 ± 1.1        | 80.3 ± 1.0 | 81.7 ± 0.8 |
| 40%          | 83.9 ± 0.6      | 80.3 ± 0.4        | 80.0 ± 1.0 | 81.2 ± 0.9 |
| 45%          | 81.1 ± 0.4      | 79.5 ± 0.9        | 79.2 ± 0.9 | 79.0 ± 0.7 |
| 50%          | 82.1 ± 0.7      | 80.5 ± 0.4        | 80.4 ± 0.6 | 80.7 ± 0.6 |

**Table 4:** Model performance (%) on PhysioNet sepsis dataset in different missing ratio settings.
and AUC-ROC, Classifier-GAIN consistently achieves a high relative improvement rate, with 21.62% and 6.16% on average across different scenarios, respectively. Especially, the relative improvement rate of macro F1-score is 25.80% when the missing rate is 25%, and the relative improvement rate of AUC-ROC is 9.91% when the missing rate is 50%. Figure 3 (b) shows the relative gap reduction rate of Classifier-GAIN with different missing ratio settings. Classifier-GAIN significantly reduces the performance gap to the upper bound, with a 75.43% relative reduction rate for macro F1-score and 60.82% and 66.35%, which further validates Classifier-GAIN’s applicability in different missing scenarios.

| Missing Rate | Classifier-GAIN | Simple imputation | MICE | GAIN | Classifier-GAIN | Simple imputation | MICE | GAIN |
|--------------|----------------|-------------------|------|------|----------------|-------------------|------|------|
| 20%          | 68.3 ± 0.4     | 64.9 ± 1.6        | 65.2 ± 1.5  | 66.0 ± 0.9  | 88.9 ± 0.5     | 88.2 ± 0.6 | 89.1 ± 0.2 | 88.7 ± 0.5 |
| 25%          | 67.9 ± 1.0     | 64.3 ± 0.5        | 65.1 ± 1.7  | 66.6 ± 1.7  | 88.5 ± 0.4     | 87.4 ± 0.5 | 88.4 ± 0.2 | 87.8 ± 0.3 |
| 30%          | 70.2 ± 0.7     | 68.2 ± 1.3        | 61.6 ± 2.2  | 65.9 ± 1.0  | 89.5 ± 0.5     | 89.0 ± 0.2 | 87.7 ± 0.2 | 88.7 ± 0.4 |
| 35%          | 67.6 ± 0.8     | 64.5 ± 1.2        | 60.4 ± 2.1  | 65.0 ± 0.4  | 88.5 ± 0.4     | 87.7 ± 0.4 | 87.0 ± 0.6 | 87.4 ± 0.5 |
| 40%          | 65.7 ± 1.4     | 61.9 ± 0.8        | 58.1 ± 3.0  | 63.2 ± 1.2  | 87.8 ± 0.5     | 86.8 ± 0.4 | 85.3 ± 0.2 | 86.5 ± 0.5 |
| 45%          | 65.7 ± 1.0     | 62.5 ± 1.4        | 57.3 ± 2.7  | 61.7 ± 1.7  | 86.8 ± 0.6     | 85.7 ± 0.7 | 84.6 ± 0.2 | 85.0 ± 0.7 |
| 50%          | 65.0 ± 0.2     | 59.4 ± 1.6        | 57.3 ± 3.3  | 60.0 ± 1.7  | 83.9 ± 0.8     | 83.7 ± 0.5 | 84.2 ± 0.1 | 83.5 ± 1.4 |

Table 7: Model performance on UCSF MOF dataset with different additionally simulated missing ratios.

**Real-world data.** We further evaluate our model on the UCSF MOF real-world dataset, including early-stage clinical records for MOF prediction. In addition to the high missing ratio in bio-marker measurements, there is a serious label imbalance issue in this dataset, which is common in real-world clinical data. We evaluate the performance of Classifier-GAIN on the UCSF MOF dataset in the following settings: (1) imputing the original missing components and predicting MOF outcome; (2) adding additional random masks with 20%, 25%, 30%, 35%, 40%, 45% and 50% missing rates to simulate more serious missing situations in real-world data.

Table 6 reports the macro F1-score and AUC-ROC to evaluate Classifier-GAIN’s prediction performance against other methods, on the UCSF MOF dataset with original missing components. (The missing ratio of features is 6.42% among all patients on average.). Classifier-GAIN yields the best prediction performance as measured by both macro F1-score and AUC-ROC. All the three baselines in the original missing scenario have similar performance, and the simple imputation has the best performance in baselines, which may due to the small size and high imbalance of the real-world data. Classifier-GAIN shows better performance reflecting the classifier-guided imputation helps the downstream MOF prediction by making imputed values label-aware.

Table 6: Model performance on UCSF MOF dataset with original missing components.

| Algorithm | macro F1-score | AUC-ROC |
|-----------|----------------|---------|
| Classifier-GAIN | 71.0 ± 1.0 | 90.6 ± 0.5 |
| Simple imputation | 68.9 ± 1.0 | 90.3 ± 0.3 |
| MICE | 68.2 ± 0.8 | 90.0 ± 0.4 |
| GAIN | 68.2 ± 0.9 | 90.2 ± 0.3 |

For more missing ratios in our simulated setting, the corresponding macro F1-score and AUC-ROC are shown in Table 7. For the macro F1-score, Classifier-GAIN consistently outperforms the best baselines more than 2% across the entire range of missing rates. Especially, in the 50% missing scenario, Classifier-GAIN improves 5% comparing to the best baseline, GAIN. For AUC-ROC, Classifier-GAIN outperforms other post-imputation predictions in 25%, 30%, 35%, 40%, 45% missing scenarios, and achieves comparable performance with MICE in 20% and 50% missing conditions.

### 4.4 Imputation results

To further visualize the imputation outcomes of the generator in Classifier-GAIN, we compare the imputation results for the original missing components and other baselines. We select three features: D-Dimer, Factor VII (blood test)\(^1\) and respiratory rate, for the imputation study. Both D-Dimer and Factor VII have more than 40% missing in the original dataset, and the missing rate of respiratory rate is 31%. D-Dimer is an indicator of patients who may develop organ failure in the further course of acute pancreatitis\(^2\). Factor VII and respiratory rate are highly related to pulmonary failure \(\cite{6,29}\).

Figure 4 plots the univariate distributions of selected features for MOF (MOF = 1) and no MOF (MOF = 0) patients, respectively. The blue and orange curves are density curves of observed components of features that need imputation. The blue curves represent the density curves of MOF = 0, and the orange ones represent MOF = 1. Dashed vertical lines are the imputed results of three different imputation methods: red is Classifier-GAIN, green is GAIN, and black is MICE imputation. In the UCSF MOF dataset, the feature values available with maximum density of D-Dimer, Factor VII and respiratory rate for patients who did not develop MOF are 0.86 mg/L, 68.82% and 16.92 breaths per minute, respectively. For MOF

\(^1\)In the remainder of this subsection, we use Factor VII to represent Factor VII (blood test).

\(^2\)In the remainder of this subsection, we use Factor VII to represent Factor VII (blood test).
patients, the feature values available with the maximum density are 7.71 mg/L, 80.69% and 18.75 breaths per minute, respectively.

For panels (a) and (b), Classifier-GAIN predicts correctly for a patient without MOF, while the other classifiers, whose input data are imputed by MICE or GAIN, predict incorrectly. The imputed values of Classifier-GAIN for Factor VII and respiratory rate are relatively closer to the feature values with maximum density for no-MOF’s in both cases. Panel (c) shows a MOF patient whose data was missing the D-Dimer record. MICE and GAIN have very similar imputed value which are 3.38 mg/L and 3.35 mg/L, Classifier-GAIN imputes the D-Dimer as 6.53 mg/L which follows the trend of MOF patients in this dataset. Panel (d) shows a situation that all of the classifiers predict a no-MOF case incorrectly. In this case, all three methods impute the Factor VII closer to the feature value with the maximum density for MOF’s.

![Density plots of features and imputed values.](image)

Figure 4: Density plots of features and imputed values. The blue and orange curves are density curves of observed data points. The blue curve represents MOF = 0, and the orange represents MOF = 1. The dashed vertical lines are the imputation results of three different imputation methods. For (c), GAIN and MICE have similar imputation results, which makes lines overlap.

5 RELATED WORK

**Generative Adversarial Networks (GAN).** GAN, introduced in [8], is a game-theoretic framework for estimating the implicit distribution of data via an adversarial process. CGAN conditions the GAN framework on class labels to direct the data generation process [16]. AC-GAN further improves generation performance by modifying the discriminator to contain an auxiliary decoder network [18]. However, both CGAN and AC-GAN need to feed label information to their generators, which could not be achieved if the final goal is classification and the label information is unknown during inference. Semi-supervised GAN [17] performs GAN in a semi-supervised context to make the discriminator output either data validation or class labels. Triple-GAN facilitates the convergence of both the generator and the discriminator by introducing the “third player” – classifier [14].

Researchers have also applied GANs on missing value imputation. In GAIN [31], the generator imputes the missing components while the discriminator takes a completed vector and attempts to determine which components were actually observed and which were imputed with some additional information in the form of a hint vector. MISGAN learns a complete data generator along with a mask generator that models the missing data distribution and an adversarially trained imputer [15]. However, those existing methods ignore the connection between observations and classification information, which can make use for learning-label-aware imputation during training and help to improve downstream task prediction during inference.

**Multiple Organ Failure (MOF).** MOF is a major threat to the survival of patients with sepsis and is becoming the most common cause of death for surgical ICU patients [4]. According to a recent study of ICU trauma patients, almost half of them developed MOF, and MOF increased the overall risk of death 6.0 times compared to the patients without MOF [27]. Sepsis is viewed as an immune storm that leads to MOF and death, which still is a leading cause of death in critically ill patients, though modern antibiotics and new resuscitation therapies have been used [9]. The Acute Physiology and Chronic Health Evaluation (APACHE) score and the Ranson score are widely used for seriously ill patients, but their empirical utilization for predicting the risk of MOF at an early stage is limited by cumberosness and needs to record some indexes dynamically [23]. Therefore, a prognostic tool that can reliably predict MOF in the early phase is essential for improving patient outcomes. In this work, we have chosen to base our MOF prediction on highly-related vital signs at the initial stage, to predict outcomes with classifier-guided imputation, in order to handle the data sparsity problem.

**Missing Data Mechanisms.** Depending on the underlying reasons, missingness is divided into three categories: missing completely at random (MCAR), missing at random (MAR), and missing not at random (MNAR). MCAR refers to a situation in which the occurrence for a data point to be missing is entirely random. MAR assumes that the missingness does not have any relationship with the missing data but may depend on the observed data. MNAR indicates that the missing elements are related to the reasons for which the data is missing. In general, we assume that the EHR data is MAR data because, in most EHR instances, those collected features would be expected to explain some, but not all, of the variation among patients whose data have missing values [30].

Various methodologies are available to address the missing data problem. Single imputation algorithms only impute missing components in one iteration, which can utilize some unique numbers (e.g., 0) or statistical characteristics, such as mean value imputation [1], median imputation [12] and most common value imputation [11]. MICE [5] is one of the most commonly used multiple imputation algorithms, applying multiple regression models iteratively to impute missing values for different types of variables [33]. Grape
is a graph-based framework with both feature imputation and label prediction, which formulates missing components imputation as an edge-level prediction and downstream label prediction as a node-level prediction [32]. Unlike our work, Grape predicts the downstream task without caring about imputed data and the feature imputation only learns information from partially observed data, which is not label-aware. In this work, we have explored the algorithm with missing components in EHRs datasets to resolve the real-world MOF prediction task.

6 CONCLUSION

In this paper, we present Classifier-GAIN, an end-to-end deep learning framework to improve performance of MOF prediction on datasets with a wide range of missingness ratios. In contrast to most of the label-aware GANs, whose generator takes label information directly, focusing on improving the generator outputs, we design a three-player adversarial imputation network to optimize the downstream prediction while imputing missing values. Classifier-GAIN uses a classifier to provide label supervision signals to the generator in training, and the trained generator to improve the classifier’s downstream prediction performance in inference. Extensive experimental results on both a synthetic sepsis dataset and a real world MOF dataset demonstrate the usefulness of this framework. Although we only demonstrate the effeciveness of Classifier-GAIN in MOF prediction tasks, its applications in other domains are worth exploring, which we leave as future work.

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Appendix A UCSF MOF DATA STATISTICS

For numerical variables, all features except age are list as: feature
name, unit: type, description, mean (standard deviation) of no MOF
patients, mean (standard deviation) of MOF patients. For age, we
show the min-max age for no MOF and MOF patients.
For categorical variable, all features are list as: feature name, unit-
type, description, number and percentage in each level.

Demographic:
Gender, no.(%): categorical, Male = 1, Female = 0, 1608 (81.3%), 157
(86.3%)
Age, year: numerical, age of patients, 37(15.0 - 100.0), 45.5 (19.9 -
99.0)
BMI, kg/m2: numerical, body mass index, 26.50 ± 4.80, 27.02 ± 5.25
TBI, no.(%): categorical, traumatic brain injury, Yes = 1, No = 0, 629
(31.8%), 129(70.9%)

Injury measurement
AIS-Head: numerical, abbreviated injury scale: head, 1.52 ± 2.00,
3.40 ± 4.97
AIS-Chest: numerical, abbreviated injury scale: chest, 0.98 ± 1.53,
2.03 ± 1.77
ISS: numerical, injury severity score, 14.95 ± 14.66, 33.03 ± 13.98
GCS: numerical, GCS (Glasgow Coma Scale), 9.58 ± 5.36, 4.92 ± 6.67

Admission day
Vasopressor, no.(%): categorical, vasopressor utilization Yes = 1, No
= 0, 429 (21.7%), 109 (60.0%)
Heparin_gtt, no.(%): categorical, heparin utilization Yes = 1, No = 0,
84 (4.2%), 43 (23.6%)
Factor VII treatment, no.(%): categorical, factor VII medication given
Yes = 1, No = 0, 12 (0.6%), 14 (7.7%)
Thromboembolic complication, no.(%): categorical, thromboembolic
complication condition Yes = 1, No = 0, 83 (4.2%), 51 (28.0%)
umribfxs: numerical, number of rib fractures, 0.68 ± 1.97, 3.40 ± 4.97

Initial hour measurement
WBC,10^3/mcL: numerical, white blood cell, 10.44 ± 4.76, 11.85 ±
5.47
HCT, %: numerical, hematocrit, 40.99 ± 5.48, 39.69 ± 6.03
HGB, g/dL: numerical, hemoglobin, 13.66 ± 1.74, 13.18 ± 2.12
Bun, mg/dL: numerical, blood urea nitrogen, 15.58 ± 8.06, 19.66 ±
15.25
Creatinine, g/24 hr: numerical, creatinine value, 1.00 ± 0.48, 1.27 ±
1.29
D-Dimer, mg/L: numerical, D-Dimer value, 2.90 ± 5.70, 6.43 ± 9.13
Factor VII, %: numerical, factor VII value, 79.39 ± 37.82, 75.81 ±
32.57
PLTs, 10^4/ mcL: numerical, platelets, 272.08 ± 85.04, 267.12 ± 87.71
PTT, sec: numerical, partial thromboplastin time, 29.66 ± 11.20,
11.08 ± 0.28
Serumco2, mmol/L: numerical, carbon dioxide, 23.66 ± 4.35, 4.83 ±
0.28

Vital signs
HR, beats per minute: numerical, heart rate, 96.44 ± 27.74, 102.14 ±
29.27

Respiratory, breaths per minute: numerical, respiratory rate, 19.67
± 5.43, 20.57 ± 5.96
SBP, mmHg: numerical, systolic blood pressure, 136.53 ± 31.22,
132.57 ± 37.14

ICU first day measurement
Blood_units, unit: numerical, blood units transfusion, 2.41 ± 6.51, 9.28
± 15.65
Crystalloids, ml: numerical, crystalloids for fluids resuscitation,
3856.62 ± 3395.06, 6721.5 ± 4437.48
FFP_Units, unit: numerical, fresh frozen plasma, 1.52 ± 4.71, 7.53 ±
12.91

Appendix B HYPERPARAMETERS

To support the reproducibility of the results in this paper, we provide
the hyperparameters we used in all the experiments.

B.1 PhysioNet sepsis dataset:
Model:
Simple imputation & Classifier: epochs: 30, batch size: 128, learning
rate: 0.0005-0.002, classifier’s weight decay: 5e-4.
MICE & Classifier: initial strategy: mean, maximum number of
imputation iteration: 100, tolerance: 0.001.
GAIN & Classifier: epochs for GAIN: 20, batch size for GAIN: 128,
generator’s learning rate: 0.0005-0.002, discriminator’s learning
rate: 0.0005-0.002, generator’s weight decay: 5e-4, discriminator’s
weight decay: 5e-4, p_hint: 0.9, alpha: 1, epochs for classifier: 30,
batch size for classifier: 128, classifier’s learning rate: 0.0005-0.002,
classifier’s weight decay: 5e-4
Classifier-GAIN: epochs: 50, batch size: 128, generator’s learning
rate: 0.0005-0.002, discriminator’s learning rate: 0.0005-0.002,
classifier’s learning rate: 0.0005-0.002, p_hint: 0.5, alpha: 20, beta:1,
generator’s weight decay: 5e-4, discriminator’s weight decay: 5e-4,
classifier’s weight decay: 5e-4.

B.2 UCSF MOF dataset:
Model:
Simple imputation & Classifier: epochs: 30, batch size: 16, learning
rate: 0.0005-0.002, classifier’s weight decay: 5e-4.
MICE & Classifier: initial strategy: mean, maximum number of
imputation iteration: 100, tolerance: 0.001.
GAIN & Classifier: epochs for GAIN: 50, batch size for GAIN: 128,
generator’s learning rate: 0.0005-0.002, discriminator’s learning
rate: 0.0005-0.002, generator’s weight decay: 5e-4, discriminator’s
weight decay: 5e-4, p_hint: 0.9, alpha: 5, epochs for classifier: 30,
batch size for classifier: 16, classifier’s learning rate: 0.0005-0.002,
classifier’s weight decay: 5e-4.
Classifier-GAIN: epochs: 50, batch size: 128, generator’s learning
rate: 0.0005-0.002, discriminator’s learning rate: 0.0005-0.002,
classifier’s learning rate: 0.0005-0.002, p_hint: 0.9, alpha: 5, beta:1,
generator’s weight decay: 5e-4, discriminator’s weight decay: 5e-4,
classifier’s weight decay: 5e-4.