Cross-center Early Sepsis Recognition by Medical Knowledge Guided Collaborative Learning for Data-scarce Hospitals

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ABSTRACT

There are significant regional inequities in health resources around the world. It has become one of the most focused topics to improve health services for data-scarce hospitals and promote health equity through knowledge sharing among medical institutions. Because electronic medical records (EMRs) contain sensitive personal information, privacy protection is unavoidable and essential for multi-hospital collaboration. In this paper, for a common disease in ICU patients, sepsis, we propose a novel cross-center collaborative learning framework guided by medical knowledge, *SofaNet*, to achieve early recognition of this disease. The Sepsis-3 guideline, published in 2016, defines that sepsis can be diagnosed by satisfying both suspicion of infection and Sequential Organ Failure Assessment (SOFA) greater than or equal to 2. Based on this knowledge, *SofaNet* adopts a multi-channel GRU structure to predict SOFA values of different systems, which can be seen as an auxiliary task to generate better health status representations for sepsis recognition. Moreover, we only achieve feature distribution alignment in the hidden space during cross-center collaborative learning, which ensures secure and compliant knowledge transfer without raw data exchange. Extensive experiments on two open clinical datasets, MIMIC-III and Challenge, demonstrate that *SofaNet* can benefit early sepsis recognition when hospitals only have limited EMRs.

CCS CONCEPTS

• **Applied computing** → **Health informatics**; • **Security and privacy** → Privacy protections.

KEYWORDS

healthcare representation learning, collaborative learning, early sepsis recognition

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1 INTRODUCTION

Significant disparities in health resources have always existed, not only in developed and developing countries but even in different areas and among different ethnicities within the same country. Because of the restriction of health resources and service level, it is overwhelming for medical institutions in less developed areas to early diagnosis and timely clinical management of some noncommunicable diseases, e.g., sepsis, diabetes, and heart diseases. Enhancing health services in less developed regions is important to promote health equity.[1] By leveraging web and AI techniques, recent efforts have attempted to connect multiple medical institutions for knowledge sharing to improve the service for data-scarce hospitals [10, 13, 17, 38]. However, medical data involves individuals' private and sensitive information, and thus directly transmitting these datasets will inevitably lead to severe privacy violations [25, 31]. In essence, enhancing health equity for medical institutions lacking data resources remains a critical issue on a global scale.

In this paper, we use *early sepsis recognition* as the representative task to study how to improve health equity for medical institutions without sufficient data, considering that sepsis is one of the most serious medical conditions causing millions of deaths with significant regional disparity. Sepsis is a life-threatening organ dysfunction resulting from a dysregulated host response to infection [35]. If not detected early and treated promptly, it can result in septic shock, multiple organ failure, and even death. Owing to the complexity and importance of clinical sepsis diagnosis and treatment, there are multiple versions of sepsis consensus definitions and diagnosis guidelines, including Sepsis-1 (1991) [27], Sepsis-2 (2001) [19] and Sepsis-3 (2016) [35]. It was estimated that there were 48.9 million cases and 11 million sepsis-related deaths worldwide in 2017, accounting for almost 20% of all global deaths [33]. Moreover, significant regional disparities exist in sepsis incidence and mortality — approximately 85% of sepsis cases and sepsis-related deaths occurred in low- and middle-income countries, specifically with the highest burden in sub-Saharan Africa, Oceania, south Asia, east Asia, and southeast Asia [33]. Prior research has suggested that the sepsis mortality rate may increase by 7% for every one-hour delay

[1]https://www.who.int/health-topics/health-equity

in the administration of antibiotic treatment [16]. Therefore, early recognition is a crucial first step in the management of sepsis.

Nowadays, machine learning techniques are broadly studied in early sepsis recognition and diagnosis, such as the linear model [34], neural network [7], GBDT [20], etc. These methods require a large amount of training data to guarantee performance. Unfortunately, a prior worldwide data challenge [32] has revealed that the early sepsis recognition model learned from a hospital's data may not work well for another hospital. However, it is unrealistic to have large-scale electronic medical records for every hospital, especially for sparsely populated areas where the admitted patients are limited. To cope with the limitations of small data, some academic studies have built models with data from multiple hospitals, called multicenter study [5, 39]. Nevertheless, most multicenter studies do not consider the potential privacy leakage when different centers' patient data are gathered.

In this research, to strengthen the ability of early sepsis recognition for medical institutions without sufficient data, we investigate two possible strategies: (i) incorporating domain knowledge in healthcare model design to relieve the data limitation, and (ii) enabling cross-center collaborations between medical institutions in a privacy-preserving manner. Accordingly, we propose a cross-center collaborative learning framework, *SofaNet*, to realize early sepsis recognition with two main components: (i) *the multi-channel recurrent neural network structure* to predict SOFA (Sequential Organ Failure Assessment) scores of multiple systems which are highly associated with sepsis diagnosis (according to the guidelines of Sepsis-3 [35]), and (ii) *the cross-center feature distribution alignment component* to achieve effective knowledge transfer without raw data sharing. Our contributions are as follows:

(i) To the best of our knowledge, this is one of the pioneering studies to design a privacy-preserving cross-center collaboration mechanism for early sepsis recognition by explicitly considering domain knowledge (i.e., multi-system SOFA scores).

(ii) By conducting the transfer experiments on two open clinical datasets, MIMIC-III and Challenge, we have validated taht *SofaNet* significantly and consistently outperforms the start-of-the-art methods without raw clinical data exchange. We release our code at https://doi.org/10.5281/zenodo.7625404.

2 RELATED WORK

Machine learning techniques are excellent at analyzing complex signals in data-rich environments which promise the effectiveness of early sepsis recognition. Most studies are carried out in the ICU [6, 14]. The systematic review and meta-analysis indicate that individual machine learning models can accurately predict the onset of sepsis in advance on retrospective data [20, 37]. The PhysioNet/Computing in Cardiology (CinC) Challenge 2019 focused on this issue and promoted the development of open-source AI algorithms for real-time and early recognition of sepsis [32]. However, there are few studies that concentrate on sepsis recognition without sufficient data and the common method is centralized learning (i.e., put data together to analysis [39]). Recently, transfer learning and multi-task learning are becoming popular to utilize knowledge shared by different datasets or tasks to achieve better model performance [29]. In healthcare, some work focuses on a specific disease to design transfer methods, such as blood pressure [18], heart disease [13], Covid-19 [22], etc.; there are also work focusing on privacy issues and designing corresponding algorithms [12].

3 PROBLEM FORMULATION

Early Sepsis Recognition. The objective is to use patients' electronic medical records (EMRs) to predict the risk of sepsis. Considering the early warning of sepsis is potentially life-saving, we recognize sepsis onset in the next 6 hours with patients' last 6-hour EMRs, including vital variables, laboratory variables and demographic information (details in Appendix). This setting is consistent with the PhysioNet Computing in Cardiology Challenge 2019 [9, 32] on *Early Prediction of Sepsis from Clinical Data*[2]. In brief, given n patients' variables, $\{\mathcal{X}_1, \mathcal{X}_2, \cdots, \mathcal{X}_n\}$, where the i-th patient's data is $\mathcal{X}_i = \{\boldsymbol{x}_{i,1}, \boldsymbol{x}_{i,2}, \cdots, \boldsymbol{x}_{i,m}\}$, $\boldsymbol{x}_{i,j}$ is the clinical features of j-th hour since patient i entered ICU. For each 6-hour records, $\{\boldsymbol{x}_{i,k}, \boldsymbol{x}_{i,k+1}, \cdots, \boldsymbol{x}_{i,k+5}\}$, we aim to predict whether sepsis will occur for patient i in the next 6 hours ,i.e., before $(k + 11)$-th hour.

Cross-center Early Sepsis Recognition. When there are only limited EMRs per hospital, it is difficult to guarantee the model performance. In this paper, we focus on the collaborative learning of two participants (i.e., hospitals), to generate better health status representations for sepsis recognition. From the machine learning perspective, it can be viewed as a multi-task learning task [41].

4 METHODOLOGY

4.1 Overview

SofaNet is proposed to achieve secure and compliant knowledge transfer when there is limited data in each hospital. Figure 1 shows the overall framework, which contains two key parts, (i) *Multi-channel GRU for health status representation learning* and (ii) *Privacy-preserving Cross-center Collaborative Learning*.

4.2 Health Status Representation Learning

Existing machine learning methods for early sepsis recognition usually input EMR variables and output a binary label on whether sepsis would occur [6, 34]. For hospitals with limited patients' EMRs, this learning strategy may not perform well as the supervision signals are restricted to the small number of sepsis labels.

To increase the supervision signals for such hospitals without sufficient data, our proposed *SofaNet* includes a novel set of auxiliary tasks by incorporating the medical expert knowledge from the sepsis diagnosis guideline [35]. Specifically, since SOFA >= 2 is one of the key conditions for sepsis diagnosis, SOFA score prediction has the potential to become an auxiliary task for early sepsis recognition. Furthermore, SOFA scores can be calculated for six criteria including respiratory, cardiovascular, hepatic, renal, coagulation, and neurological systems. Hence, multiple new supervision signals on SOFA scores can be provided.

With this prior medical knowledge, we adopt a multi-channel GRU structure to embed the health status of each system individually. Also, the dynamic changes of vital signs and laboratory

[2] https://physionet.org/content/challenge-2019/1.0.0/

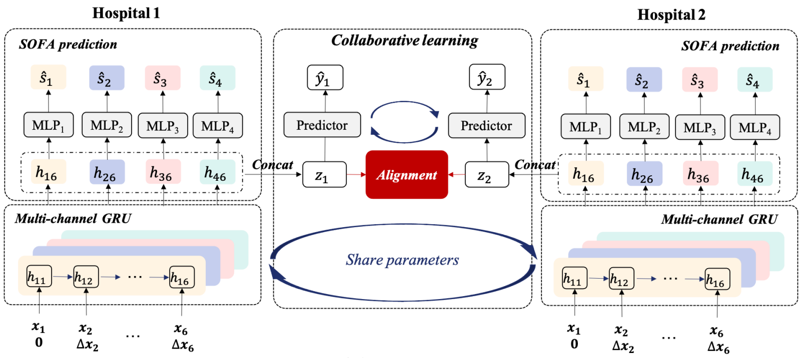


Figure 1: The *SofaNet* framework: (1) health status representation learning with SOFA prediction as the auxiliary task; (2) cross-center collaborative learning with model parameters sharing and feature distribution alignment in hidden space.

	MIMIC-III	Challenge
# patients	13379	4717
# septic patients	2688	1441
Sepsis prevalence (%)	20.09	30.55
# records	69946	18616
# records occur Sepsis in next 6 hours	8751	2476
records with sepsis (%)	12.51	13.30
missing rate (%)	20.83	63.07

Table 1: The Statistics of Datasets

variables can acutely reflect changes of a patient's status [23]. Therefore, given a 6-hour record of a patient, $\{x_1, x_2, \cdots, x_6\}$, we compute the differential features with $\Delta x_i = x_i - x_{i-1}$ when $i > 1$ and set $\Delta x_1 = \mathbf{0}$. As shown in Figure 1, we take the concatenation of original features and differential features as the input, i.e., $\{(x_1, \mathbf{0}), (x_2, \Delta x_2), \cdots, (x_6, \Delta x_6)\}$. Due to the missing variables in the datasets, SOFA scores can be precisely calculated for four systems (out of six), including coagulation, liver, cardiovascular, and renal [3]. Therefore, we build a 4-channel GRU feature extractor with the same input. For each channel, we take the last hidden state of GRU as the output, i.e., $\{h_{16}, h_{26}, h_{36}, h_{46}\}$. As the SOFA score prediction is the auxiliary task, the loss function for each hospital can be written as

$$\mathcal{L}_{local} = \mathcal{L}_{sepsis} + \alpha * \sum_{i=1}^{4} \mathcal{L}_{sofa_i} \tag{1}$$

where $\mathcal{L}_{sepsis}$ and $\mathcal{L}_{sofa_i}$ are cross entropy, and α is set to 0.5 [4]. In brief, in addition to the supervision signal of sepsis ($\mathcal{L}_{sepsis}$), we add four new supervision signals of SOFA scores ($\mathcal{L}_{sofa_i}, i = 1...4$) to improve the learning robustness for hospitals with scarce data.

4.3 Cross-center Collaborative Learning

In addition to auxiliary tasks on SOFA prediction, we introduce a cross-center collaborative learning procedure for multiple hospitals. Specifically, we expect that this collaborative procedure can enable data-scarce hospitals to benefit each other, so that they can be motivated to participate. Note that as direct data sharing may violate data protection regulations such as GDPR, we need to ensure that knowledge is shared while raw data is well protected.

Based on this idea, we design a cross-center collaborative learning mechanism, which achieves knowledge sharing by two ways: (i) *model parameter sharing* in each iteration, which can be seen as the simplified version of the privacy-preserving federated learning algorithm, *FedAvg* [24], since there are only two participants and the central server is unnecessary; (ii) *feature distribution alignment* in hidden space, like domain adaptation [28], to avoid diverged distributions between two hospitals, which may result in negative knowledge transfer. Various alignment methods can be implemented, such as maximum mean discrepancy (MMD) [36] and adversarial training [8, 30]. In our current implementation, we use the MMD method (denoted as $SofaNet_{mmd}$) as it performs generally well in our experiments. The loss function of $SofaNet_{mmd}$ is

$$\mathcal{L} = \mathcal{L}_{local_1} + \mathcal{L}_{local_2} + \mathcal{L}_{mmd} \tag{2}$$

Privacy Protection. In training $SofaNet_{mmd}$, two hospitals only need to transfer intermediate results (i.e.,, model parameters and hidden representations) instead of raw data, which follows the privacy protection criteria in state-of-the-art federated domain adaptation methods [30]. Meanwhile, recent studies show that such intermediate results may also indirectly reveal raw data under certain conditions [42]. In our future work, we plan to add advanced techniques, such as homomorphic encryption and differential privacy, to further protect the intermediate training results [21].

5 EXPERIMENTS

5.1 Experiment Setup

We conduct our experiments on two widely-used real-life Sepsis recognition datasets, **MIMIC-III** [11] and the PhysioNet Computing in Cardiology Challenge 2019 (**Challenge**) [32]. As some patients' records have a large number of missing values, we screen out the patients whose missing value ratio is less than 80%. For missing values, we fill in with data from the previous time point. If a feature at the initial time point is missing, we fill in with the mean value. Through such preprocessing, we obtain the final data for experiments and keep the records of 10% patients as test data. Some basic statistic information is enumerated in Table 1. We list the detailed features in Table 3 (Appendix), including 3 demographic variables, 6 vital sign variables and 18 laboratory variables. The experiment environment is described in Appendix.

5.2 Baselines

In our experiments, we assume that there is only x% ($x = 1$ by default) patients' records from MIMIC or Challenge for two hospitals, respectively, to simulate a data-scarce scenario. To compare with our method *SofaNet*, we implement two types of methods.

[3]The features and SOFA scoring standard can refer to Table 3 and Table 4 respectively in Appendix.

[4]This hyperparameter is determined according to the experimental results, and the difference is small when using different values (from 0.5 to 1.0).

- *Local Learning*: each hospital trains a classifier only with its local medical records.
- *Collaborative Learning*: two hospitals collaborate by techniques such as parameter sharing and finetuning.

For *local learning*, we introduce several classical models widely used for sepsis recognition, including, *Logistic Regression* (*LR*) [34], *Neural Network* (*NN*) [7], *XGBoost*[40], and *GRU*[2]. For *collaborative learning*, we mainly compare with the state-of-the-art finetuning methods without raw data exchange [13, 18, 22]. Following previous research using EMR data [1, 22, 23], model performance is assessed by the area under the receiver operating characteristic curve (AUROC), area under the precision-recall curve (AUPRC), and the minimum of precision and sensitivity (Min(Se,P+)).

5.3 Experimental Results

5.3.1 Main Result. As shown in Table 2, *SofaNet* outperforms in most metrics (except for the AUROC on MIMIC-III), demonstrating *SofaNet* can learn a better representation through knowledge transfer while protecting the raw data. Concretely, compared to the best local methods, *SofaNet* achieves a 0.9% higher AUROC, a 5.39% higher AUPRC, a 2.56% higher min(Se,P+) on MIMIC-III dataset, and achieves a 7.70% higher AUROC, a 50.22% higher AUPRC and a 25.39% higher min(Se, P+) on Challenge dataset.

Effectiveness of Collaborative Learning: By comparing the local methods and collaborative methods, we can conclude that learning knowledge from each other between different datasets can promote the prediction performance for their respective tasks. Also, we can observe that the improvement is more obvious on Challenge dataset, because of the relatively poorer data quality (i.e., smaller data size and higher missing rate shown in Table 1).

Effectiveness of Knowledge-guide Multi-channel GRU: Compared to *GRU* and $SofaNet_{lc}$ *w.o. MC* model, $SofaNet_{lc}$ achieves a better performance during local training on two datasets. This indicates that taking SOFA values prediction as the auxiliary task is helpful for data-scarce hospitals' early sepsis recognition.

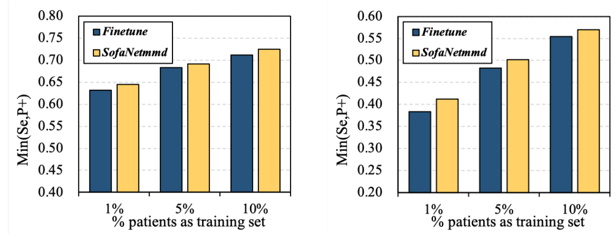
Future direction on combining *XGBoost* and *SofaNet*: Among local methods, *XGBoost* performs the best, outperforming all the deep learning methods including $SofaNet_{lc}$. This is actually consistent with the competition results of the PhysioNet Challenge, where the top three teams all use *XGBoost*-like ensemble methods [4, 26, 40]. A promising direction would be how to combine the local learning capacity of *XGBoost* and the collaboration power of $SofaNet_{mmd}$. We have attempted to use *XGBoost* on the collaboratively aligned representations of $SofaNet_{mmd}$ (i.e., z_1 and z_2 in Figure 1) and observed certain improvements (although not stable). This confirms the feasibility of combining these two methods, and we highly believe that more advanced combination techniques can be developed in the future for significant improvements.

5.3.2 Varying the Size of Training Set. Fixing the test data, we adjust the data size of training set, i.e., sample 1%, 5%, 10% patients and use their medical records as the training data. Figure 2 shows the Min(Se, P+) values of MIMIC-III and Challenge test data under different training data sizes respectively. The Min(Se, P+) values rise as the training data size increases, and $SofaNet_{mmd}$ consistently outperforms *Finetune*. The performance gap between *SofaNet* and *Finetune* is more considerable in smaller datasets, which indicates the capability of our proposed collaborative learning mechanism to alleviate the data insufficiency problem.

Table 2: Early Sepsis Recognition Performance with Only 1% Patients as the Training Set

	MIMIC-III			Challenge		
	AUROC	AUPRC	Min(Se, P+)	AUROC	AUPRC	Min(Se, P+)
Local Learning						
LR	0.8987 (0.002)	0.6583 (0.003)	0.6022 (0.001)	0.5724 (0.002)	0.1715 (0.001)	0.2279 (0.002)
NN	0.8625 (0.008)	0.5986 (0.014)	0.5452 (0.006)	0.4745 (0.009)	0.1334 (0.004)	0.1457 (0.007)
XGBoost	0.9107 (0.003)	0.6829 (0.006)	0.6285 (0.009)	0.7588 (0.009)	0.2676 (0.007)	0.3292 (0.008)
GRU	0.8992 (0.006)	0.6639 (0.012)	0.5994 (0.008)	0.6283 (0.044)	0.2247 (0.019)	0.2667 (0.025)
$SofaNet_{lc}$ *w.o. MC*	0.9046 (0.006)	0.6726 (0.104)	0.6004 (0.009)	0.6647 (0.052)	0.2476 (0.043)	0.2941 (0.063)
$SofaNet_{lc}$	0.9067 (0.006)	0.6807 (0.017)	0.6171 (0.009)	0.6895 (0.036)	0.2609 (0.019)	0.2982 (0.015)
Collaborative Learning						
Finetune	**0.9216** (0.006)	0.7113 (0.028)	0.6314 (0.026)	0.7955 (0.010)	0.3161 (0.016)	0.3831 (0.020)
$SofaNet_{mmd}$	0.9187 (0.006)	**0.7197** (0.016)	**0.6446** (0.008)	**0.8172** (0.007)	**0.4020** (0.023)	**0.4128** (0.025)

1. Values in "( )" denote the standard deviation of five experiments' results;
2. **Bold** denotes the best-performed ones of the task;
3. Underline denotes the best-performed ones in local learning;
4. $SofaNet_{lc}$ means *SofaNet* without collaborative training;
5. $SofaNet_{lc}$ *w.o. MC* means $SofaNet_{lc}$ without multi-channel GRU.



(a) MIMIC-III (b) Challenge

Figure 2: Performance under different training data volume.

6 CONCLUSION

In this paper, we propose a privacy-preserving cross-center collaborative learning method, *SofaNet*, for early sepsis recognition. The experimental results on two datasets show the effectiveness of *SofaNet*, especially for hospitals with scarce data. We mainly achieve raw data protection through parameters sharing and health status representation alignment. Also, we find that *XGBoost* performs well in local training. It is worth thinking about how to further integrate *XGBoost* into *SofaNet* to get better results.

Limitation & Future Work. We focus on early sepsis recognition by two-hospital collaborative learning. However, this method can be easily extended to n-hospital scenario: first, every two hospitals can do collaborative learning for a better health status representation; second, one hospital can combine (e.g., concatenation) all the collaboratively learned representations with other hospitals for its own patients' early sepsis recognition. For the representative disease, sepsis, we used the Sepsis-3 guideline [35] to guide our method design. There are also diagnostic guidelines for different diseases, like KDIGO for acute kidney injury [3]. With the corresponding knowledge, we can design models like *SofaNet*. This idea to inject domain knowledge can be generalized to other domains.

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A SUPPLEMENT INFORMATION

In this section, we list the feature description in detail in Table 3 and the standard of Sequential Organ Failure Assessment (SOFA) in Table 4 which is given in Sepsis-3 [35].

Table 3: Feature Description

Type	Features
Demographic variables	Age, Gender, ICU_hours
Vital sign variables	Heart rates, Temperature, Systolic BP, Mean arterial pressure, Diastolic BP, Respiration rate
Laboratory variables	FiO_2, SaO_2, pH, AST, BUN, Calcium, Chloride, Creatinine, Glucose, Potassium, Total Bilirubin, Hct, Hgb, PTT, WBC, Platelets, BUN/CR, SaO_2/FiO_2

Table 4: Sequential [Sepsis-Related] Organ Failure Assessment Score [35]

System	Score				
	0	**1**	**2**	**3**	**4**
Respiration PaO_2/FiO_2, mmHg (kPa)	>= 400(53.3)	< 400(52.3)	< 300(40)	<200(26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation Platelets, $\times 10^3/\mu L$	>=150	< 150	< 100	<50	<20
Liver Total Bilirubin, mg/dL ($\mu mol/L$)	<1.2(20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	> 12.0 (204)
Cardiovascular	MAP >= 70 mmHg	MAP <70 mmHg	Dopamine < 5 or dobutamine (any dose)	Dopamine 5.1-15 or epinephrine <= 0.1 or norepinephrine <= 0.1	Dopamine > 15 or epinephrine > 0.1 or norepinephrine > 0.1
Central nervous system Glasgow Coma Scale score	15	13-14	10-12	6-9	<6
Renal Creatinine, mg/dL ($\mu mol/L$) Urine output, mL/d	< 1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440) < 500	>5.0 (440) < 200

B EXPERIMENT ENVIRONMENT

The experiment is conducted on a server with AMD Ryzen 9 3900X 12-Core Processor, 64 GB RAM and GeForce RTX 3090. The code is implemented based on Pytorch 1.8.0. To train the model, we use Adam [15] with the batch size of 32, and the learning rate is set to 1e-3. We repeat each experiment for 5 times (i.e., 5 seeds) and record the average results.