PREDICTION OF SEPSIS USING ARTIFICIAL NEURAL NETWORK AND OPTIMAL BRAIN SURGEON

BY

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ABSTRACT

Sepsis is a severe threat to global health. Approximately, the mortality rate of sepsis in the Intensive Care Unit (ICU) is 42%. In 2017, 11 million sepsis-related deaths were reported among 49 million cases, 20% of all-cause of deaths worldwide. Detection and prediction of sepsis in earlier stage allow patients to get earlier care and better results, but sepsis is often unknown until the late stages. Substantial bodies of research studies on sepsis prediction have mainly focused on rules-based severity scores, which are transparent and straightforward; unfortunately, they have imperfect sensitivity and specificity in identifying and predicting sepsis. Typically, various sepsis predictions approach that would allow for predicting in an earlier stage, which can reduce the mortality rate and treatment cost. So, machine learning algorithms can be a choice for predicting sepsis. Therefore, this current thesis identified the features influencing early sepsis prediction and examining the features impelling the clinical severity scores used for the prediction of sepsis. The thesis also developed a hybrid optimal brain surgeon algorithm for sepsis prediction and tested the proposed algorithm's accuracy. The research methodology adopted for this thesis is an experimental simulation. The datasets used in this research were adopted from MIMIC-III, which comes with vast electronic health records. A systematic literature review was performed, and significant features of the MIMIC-III dataset for sepsis prediction were obtained by applying Automatic Backward Elimination (ABE) algorithm, Generalized Linear Model (GLM), and Correlation Matrix (CM). After that, the research built a hybrid-sepsis prediction model using machine learning techniques to train and test with selected features for model selection. Then Optimal Brain Surgeon (OBS) algorithm was used to simplify the architecture of the neural network for making an explainable deep learning-based sepsis prediction model. This is where hybridization has taken effect. The pruning algorithm OBS uses Hessian information and considers the time delay for measuring the saliency. Second-derivative information is used to compromise between the difficulty of the network and the training set error. The thesis's finding revealed that the AUROC of the predictive model was 0.882. The hybrid OBS algorithm pruned network is 80.0% with the same accuracy of the prediction model. This result indicates that the proposed hybrid model is efficient with high prediction accuracy and slight complexity compared with some previous prediction techniques. Early prediction of sepsis can reduce mortality rates and save treatment costs among ICU patients.

خلاصة البحث

الإنتان تهديد خطير للصحة العالمية؛ إذ يؤدي إلى وفيات في وحدة العناية المركزة بمعدل ٤٢٪، وقد أُبلغ عام 2017 عن ١١ مليون حالة وفاة سببها بالإنتان من بين 49 مليون حالة تمثل 20٪ من جميع أسباب الوفيات في جميع أنحاء العالم، ويؤدي الاكتشاف المبكر للإنتان، أو التنبؤ به؛ إلى رعاية مبكرة ونتائج طيبة، ولكن؛ غالبًا ما يكون الإنتان مجهولاً، ولو في المراحل المتأخرة، وقد ركزت مجموعة من الدراسات في التنبؤ بالإنتان أساسًا على درجات الشدة المستندة إلى القواعد التي على الرغم من أنها واضحة مباشرة؛ تقصر في حساسيتها وخصوصيتها عن التنبؤ به؛ إذ ليس لمنهجية التنبؤ بالإنتان دور في الاكتشاف المبكر له، مما يحدُّ من معدل الوفيات وتكلفة العلاج، ولكن؛ يمكن أن تكون خوارزميات التعلم الآلي خيارًا للتنبؤ بالإنتان، وعليه؛ يتناول هذا البحث سمات التأثير على التنبؤ بالإنتان، وفحص العوامل التي تستدعي درجات الخطورة السريرية المستخدمة للتنبؤ بالإنتان، وقد صمَّم الباحث خوارزمية هجينة لجراحة الدماغ المثلى؛ للتنبؤ بالإنتان، واختبر مدى تعقيد الخوارزمية الهجينة المقترحة ودقَّتها، وتوسَّل الباحث منهج المحاكاة التجريبية، فاعتمد مجموعات بيانات MIMIC-III التي تأتي مع سجل صحي إلكتروني كبير، وذلك بعد مراجعة الدراسات السابقة للحصول على الميزات المهمة لمجموعة بيانات MIMIC-III؛ للتنبؤ بالإنتان من خلال تطبيق خوارزمية الإزالة التلقائية للخلف (ABE)، والنمط الخطي المعمم (GLM)، ومصفوفة الارتباط (CM)، ومن ثم؛ صاغ الباحث أنموذجًا للتنبؤ بالإنتان الهجين؛ باستخدام تقنيات التعلم الآلي للتدريب والاختبار، ثم قوَّم الشبكة باستخدام جراحة الدماغ المثلى (OBS)؛ لتسهيل بنية الشبكة العصبية حيث بدأ التهجين تأثيره، وتستخدم خوارزمية جراحة الدماغ المثلى بيانات مصفوفة ، وتأخذ في الحسبان التأخير الزمني لقياس البروز، كما تُستخدم المعلومات المشتقة الثانية ؛ للتوفيق بين تعقيد الشبكة وخطأ مجموعة التدريب، وقد تبيَّن أن نسبة AUROC للأنموذج المقترح كانت ٠,٨٨ ، وأن خوارزمية (OBS) الهجينة قوَّمت أكثر من ٨٠٪؛ بدقة أنموذج التنبؤ نفسه؛ أي إن الأنموذج كان فعالاً مع دقة تنبؤ عالية وتعقيد طفيف؛ مقارنة ببعض تقنيات التنبؤ السابقة،

APPROVAL PAGE

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DECLARATION

I hereby declare that this thesis is the result of my own investigations, except where otherwise stated. I also declare that it has not been previously or concurrently submitted for any other degrees at IIUM or other institutions.

Mohammed Ashikur Rahman

Signature .... Date 08/08/2021 ....

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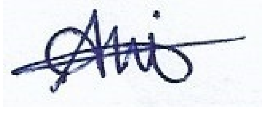

08/08/2021

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Signature Date

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It is my great pleasure to dedicate this work to my respected parents, beloved wife, and dear sons, who have given me the gift of their unwavering trust in my ability to achieve my goal: to thank you all for your patience and encouragement.

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CHAPTER ONE

INTRODUCTION

1.1 OVERVIEW

The Intensive Care Unit (ICU) is a critical unit of the hospital that provides critically ill patients with continuous and wide-ranging care. The intensive care unit, providing thorough care for patients needs a substantial investment in nurses, technology, and other services, all of which raise the cost of treatment. Owing to the complexities of critical care processes and the variability in the number of patients needing intensive care at a given time, managing intensive care services is still tricky (Takala, 2018).

Sepsis is one of the most frequent reasons for decease and admission in the ICU (Alberti et al., 2002; Brun-Buisson, 2006; Perner et al., 2016; Sakr et al., 2018; Tolonen et al., 2018). That is likewise a prevalent cause of sepsis patients being admitted to the hospital again. Annually, sepsis influences between 3 and 10 in every 1000 people in developing countries (Fleischmann et al., 2016). Information is accessible just from the developed country by the World Health Organization (WHO). It is assessed that, out of 31.5 million sepsis cases, the more significant part is severe sepsis (19.4 million with 5.3 million deaths).

Many studies' death rates are around 55.0% and 60.0% in septic shock instances worldwide. In some African nations, there is even 100% mortality from sepsis (WHO, 2018). In May 2017, the World Health Assembly (WHA) and the World Health Organization (WHO) made sepsis a worldwide high priority. They adopted a goal to improve the prevention, diagnosis, and management of sepsis in the 194 United Nations Member States (Kim & Park, 2019).

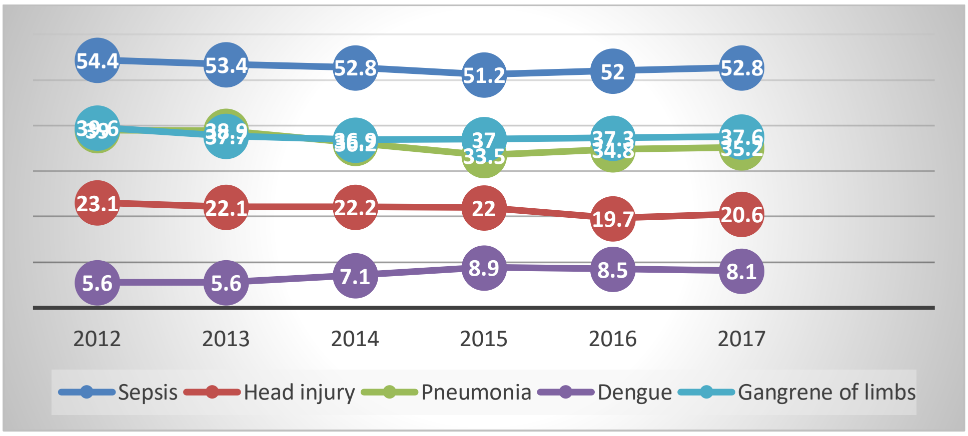

Figure 1.1: In-hospital mortality for the five most common diagnoses in ICU (adapted from MRIC Report, Malaysia)

In Malaysia, according to the Malaysian Registry of Intensive Care Report published in 2016 and 2017, sepsis is the topmost diagnosis leading to ICU admission. About 52.0% and 52.8% in-hospital mortality occurred due to sepsis in 2016 and 2017, respectably. The number of ICU admission was 38196 and 37759 in 2017 and 2016. Among them, male patients were 59.0%. Moreover, the highest numbers of admissions were Malays (59.5%), Chinese (14.7%), and Indians (9.7%). Furthermore, two-thirds (68.9%) of admissions were non-operative and with one or more organ dysfunction. The average SOFA score was 6.4, while the median was 6.0 for Malaysia's last five years. (Ling et al., 2016, 2017). According to Figure 1.1, more than 50.0% died in the hospital during the previous six years because of sepsis.

Currently, in the clinical setting, physicians use Sequential Organ Failure Assessment (SOFA) (Vincent, Moreno, Takala, Willatts, De Mendonca, et al., 1996), quick-SOFA (mentioned in the sepsis-3 definition), the Systemic Inflammatory Response Syndrome (SIRS) (Balk, 2000), criteria to predict sepsis by calculating physiological data, clinical data and laboratory test data (Points, 2019). Moreover, these severity scores required different variables for different scores and different data collection periods for sepsis prediction (Wa, 2004). According to Calvert et al., researchers compared machine learning-based diagnosis (MLD) to predict sepsis with SIRS, quick-SOFA. The area under the receiver operating characteristic (AUROC) curves were 0.917, 0.468, and 0.653 for the developed machine learning-based diagnostic (MLD) model, SIRS, and qSOFA, respectably (Calvert et al., 2019). Another research conducted by Avijit et al. The researcher compared the machine learning-based model with severity score SOFA and qSOFA. The AUROC was 0.62, 0.66, and 0.90 in the SOFA, qSOFA, and ML-based models (Mitra & Ashraf, 2018). In the year 2018, Akash and his colleagues completed research on the comparison between severity scores SIRS and qSOFA using a machine learning-based model based on Decision Tree (DT), Multivariate Logistic Regression (MLR) (Gupta et al., 2018). Still, the AUROC for both is less than 0.70.

Machine learning algorithms are becoming more popular in every sector, especially in the health sector. Healthcare informatics is the current advancement in improving modern health care, contributed by researchers. By investigating sizeable electronic patient healthcare records, it is possible to improve sepsis prediction, which improves the mortality rate in the ICU (Dustin et al., 2015; E, 2016). In 2017, A comparable framework demonstrated much better outcomes in the Johns Hopkins Hospital in Baltimore. The output of this system brings significant changes in health care. For this reason, it is planning to grow it to four different hospitals in the US. In 2018, in Durham, N.C., Duke University Hospital was authoritatively launching Sepsis Watch, an AI-based framework that identifies early sepsis cases and raises the alarm. The medical clinic will send it at first in the emergency department and will, at that point, extend it to the general hospital floor and the intensive care unit. This project aims to catch sepsis early before getting to the ICU (E. Strickland, 2018).

1.2 BACKGROUND OF THE RESEARCH

Sepsis is one of the leading causes of death in ICU (Brun-Buisson, 2006; Xu J, Murphy SL, Kochanek KD, 2016). Early detection and sepsis prediction allow for earlier care and improved results, but sepsis is often unknown until the late stages. Existing methods have low predictive accuracy and often rely on time-consuming laboratory results (Gutierrez, 2020). Though rules-based severity scores are transparent and straightforward, they have low sensitivity and specificity in identifying and predicting sepsis (Calvert et al., 2019). Further implementation of extra measures is required to improve the reliability and precision of SOFA scoring (Arts et al., 2005). The SOFA score is based on organ dysfunction to evaluate morbidity, not only symptoms to predict sepsis (Jeong, 2018).

The first objective was formulated to investigate the significant features (independent features) related to sepsis (Dependent feature). With this objective, it is possible to reduce dependency on physicians for the sepsis prediction as well as data overfitting of the machine learning algorithms. A systematic literature review was conducted to find the features used in the existing research. Then, data was extracted from the MIMIC-III database for the features that were found significant in SLR. After pre-processing the dataset, generalized linear model, backward elimination algorithm, and correlation matrix, these three techniques were applied to find those features which are mostly related to sepsis.

The second objective was developed to examine the machine learning techniques that provide better accuracy than the existing methods and clinical severity scores. The random forest and XGBoost models' accuracy is better than the clinical severity score (Mitra & Ashraf, 2018). Still, the accuracy of a machine learning-based prediction model for sepsis is not up to the mark because of learning features that fit data (Kam & Kim, 2017). Model selection strategies play a vital role in prediction accuracy. From the literature review, it was found that the random forest prediction model for sepsis performs better. In this model selection process, Artificial neural networks, Random Forest were used as ML methods, SIRS, qSOFA, and SOFA were used as clinical severity scores to compare the model's accuracy.

Early diagnosis can reduce the mortality rate and treatment cost (McCoy & Das, 2017; Rothman et al., 2017). Research is required to improve the prediction model's accuracy and inputted data that can predict sepsis more accurately than existing machine learning techniques and clinical severity scores (Kam & Kim, 2017). An optimal brain surgeon algorithm was applied to prune the sepsis prediction model by simplifying the prediction model, one of the biggest problems of machine learning algorithms (Kam & Kim, 2017). Blackbox can be averted through simplification of the neural network. The simplified model will be easy to understand and transparent to the clinicians. A simplified model is also required to implement for commercial purposes at a reduced price. The use of the ML-based prediction model in the intensive care unit can save millions of lives all over the world per year.

1.3 PROBLEM STATEMENT

Machine learning prediction models perform better for sepsis prediction than the traditional scoring system (Fleuren et al., 2020). Yet, machine learning-based prediction models have shortcomings like data overfitting, prediction accuracy, black box, etc. Due to the vast amount of imbalanced electronic health records, Feature selection methodologies are important for clinical prediction modeling (Chowdhury & Turin, 2020). In addition, Accuracy of prediction is mandatory because it is a concern with the mortality of the patients. Clinicians want interpretable and straightforward predictive models (Tonekaboni et al., 2019; Wiens & Shenoy, 2018). For clinicians' adopting the machine learning model, machine learning based prediction model in healthcare should be designed as explainable (Amann et al., 2020; Stiglic et al., 2020).

1.4 RESEARCH QUESTIONS

1. What are the features influencing sepsis prediction?
2. Which machine learning techniques were used for the prediction of sepsis to be most accurate?
3. a) How to build a deep learning model to predict sepsis in an earlier stage?

   b) How to simplify the model for making it explainable to the clinicians?

1.5 RESEARCH OBJECTIVES

Three main research objectives are given below:

1. To identify the features influencing early sepsis prediction.
2. To identify the machine learning models that can predict sepsis with more accuracy.
3. a) To develop a hybrid model for sepsis prediction.

   b) To simplify the proposed model for making it explainable.

1.6 RESEARCH SCOPE

This research focused on developing an improved ML-based prediction model for sepsis among intensive care patients. The disease study reveals that one in five deaths worldwide was caused by sepsis, also known as blood poisoning. According to BBC News, the vast majority of cases (85 percent) are in countries with low and medium incomes. With four out of 10 cases in children under five, they were highly at risk.

Because of the mortality rate, sepsis is a challenge in first-world countries such as the UK, Spain, France, and Canada (Gallagher, 2020).

This is a retrospective cohort study based on the electronic health record, which contains 46520 patients' information of Beth Israel Deaconess Medical Centre between 2001 and 2012. "MIMIC-III, a freely accessible critical care database" paper published in nature.com. MIMIC means Medical Information Mart for Intensive Care, which contains 53,423 distinct hospital admissions. The dataset is briefly described in section 3.4.

This experimental thesis aims to increase knowledge for developing an improved ANN-based predictive model for sepsis.

- To find the features through SLR and apply algorithms to investigate the independent features' significance with dependent features.
- To find ML techniques that can predict SLR accurately and develop the model to test, validate, and compare the accuracy.
- To propose a hybrid deep learning-based prediction model.
- To contribute to the simplification of the ML-based predictive model by pruning the network for explainable AI.

1.7 SIGNIFICANCE OF THE RESEARCH

This research is designed to develop an improved sepsis prediction model that can increase a patient's survival rate and reduce their time of stay in the ICU, ultimately reducing the mortality rate. From an economic point of view, this may reduce the cost for patients, hospitals, and insurance providers. According to the World Health Organization, sepsis is a life-threaten disease resulting from severe organ failure, which is the global health threat of the 21st century. The definition of sepsis-3 was defined recently in 2016. So, more research was required following the sepsis-3 definition.

A lot of research has been conducted on the prediction model using machine learning techniques for sepsis (Biglarbeigi et al., 2019; Du et al., 2019; Lyra et al., 2019; Nakhashi et al., 2019; Narayanaswamy et al., 2019; Nonaka & Seita, 2019; Noorzadeh et al., 2019; Roussel et al., 2019; Zabihi et al., 2019). The maximum number of studies emphasized the accuracy of the prediction (Chang et al., 2019; Gilbertson et al., 2019; B. Lee et al., 2019; Li & Andr, 2019; Morrill et al., 2019; Nirgudkar & Ding, 2019; Pimentel et al., 2019; M. Vollmer et al., 2019; Q. Yu et al., 2019). Few studies proposed a hybrid algorithm for predicting sepsis earlier (Chami & Tavakolian, 2019; Firoozabadi & Babaeizadeh, 2019; He et al., 2019; Vicar et al., 2019; Yang et al., 2019; Yao et al., 2019). This research is worked on the simplification of neural networks for simple and interpretable prediction models, which can attract the investor to develop the ML-based sepsis prediction model commercially at a lower cost. This study also worked on the accuracy that is also remarkable. The proposed ML-based prediction model can be implemented commercially. This model's accuracy rate, simplicity, and interpretability will quickly be adopted by the clinicians, like clinical severity scores. This model can support clinicians in decision-making about sepsis among ICU patients.

The millions of intensive care unit (ICU) patients’ have been suffering sepsis every year. Approximately 50.0% of death in ICU happens because of sepsis. Early prediction and treatment can reduce the mortality rate and treatment cost. Implementing a machine learning-based prediction model in the ICU is possible to save millions of lives and billions of money.

1.8 OPERATIONAL DEFINITIONS

In this section, clinical severity scores and medical definitions for sepsis are described. Researchers' current efforts follow this to compare the developed prediction model using various machine learning and deep learning models among intensive care unit patients.

1.8.1 Definition of Sepsis

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Presently, multiple definitions and terminologies are used for sepsis, septic shock, and organ dysfunction (Singer et al., 2016). Past iterations of the sepsis bundle were presented to give training and improvement identified with sepsis management. This new sepsis "hour-1 bundle," in light of the 2016 rules, ought to be acquainted with the emergency department, floor, and ICU staff as the following emphasis of regularly improving tools being taken care of by patients with sepsis and septic shock as well as a whole work to lessen the global burden of sepsis (Levy et al., 2018). Within 25 years, sepsis was defined multiple times, which specifies that knowledge of sepsis is still limited, and sepsis onset was poorly defined, and onset time was not identified by Singer et al. (Desautels et al., 2016a; Khojandi et al., 2018).

The original definition of sepsis was established at the 1991 ACCP / SCCM consensus conference, known as sepsis one or systemic inflammatory response syndrome (SIRS) to infection. There is no clinical response defined for SIRS, which may occur due to infection, inflammation, or trauma. For SIRS, two or more of the following are required: temperature >38^0C or <36^0C, heart rate >90/min, respiration rate >20/min or Paco2 <32 mm Hg and WBC (white blood cell) count >12,000/mm3 or

<4,000/mm3 or >10% immature bands (Gül et al., 2017). From 1991 through 2001, SIRS was used in clinical practice.

In 2001, due to sepsis prediction's specificity, the concept of sepsis was revised. Infection with sepsis 1 (SIRS) (Levy et al., 2003) was included in the updated definition, renamed sepsis 2. Clinicians and researchers need to have the necessary tools to identify and diagnose sepsis relative to SIRS quickly; effective infection therapies are widely and readily available. As in 1992, both the presence of infection and the systemic inflammatory response in sepsis characterize the clinical condition. The fact that no new concepts for sepsis are introduced in this conference report is notable. This lack of evidence illustrates the difficulty faced by physicians and researchers who were already present in the 2003 diagnosis of sepsis. The three meanings of sepsis are listed in Table 1-1.

Sepsis 3 was identified in 2016 as life-threatening organ dysfunction due to a dysregulated host reaction to new contamination (Singer et al., 2016). Sepsis is a significant burden of health care, and insufficient epidemiological data are available on the demographics of sepsis or chronological patterns in its occurrence and outcome. The epidemiology of sepsis in the US includes a specific study of race and sex, causative species, and patient disposition. In a study of discharge data on nearly 750 million hospitalizations in the United States over the past two decades, 10,319,418 cases of sepsis were found. Sepsis was more prevalent among males than among females and non-whites than among whites. (Arnold et al., 2014).