# Forecasting of Sepsis in ICU patients using Deep Learning AI


A thesis submitted in partial fulfilment of the requirement for the degree of Master of Science in Bioinformatics

By

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# *Dedication*

***I dedicate this work to my family for their constant***

***love and support***

# Certificate of Originality

I declare that this thesis is a result of my research and struggle. Furthermore, none of its contents has been plagiarised or submitted for a higher degree. Finally, other people's contributions to this project are acknowledged and referenced.

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**Muhammad Huzaifa Arshad**

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Muhammad Huzaifa Arshad

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# List of Abbreviation

| | |
|---|---|
| WHO | World Health Organization |
| ICU | Intensive Care Unit |
| DL | Deep-learning |
| LOCF | Last Observation Carried Forward |
| LSTM | Long short-term memory |
| GRUs | Gated recurrent units |
| AUROC | Area Under the Receiver Operating Characteristic curve |
| ICULOS | Intensive Care Unit Length of Stay |
| SCCM | Society of Critical Care Medicine |
| ACCP | American College of Chest Physicians |
| SIRS | Systemic Inflammatory Response Syndrome |
| MODS | Multiple Organ Dysfunction Syndrome |
| ESICM | European Society of Intensive Care Medicine |
| SIS | Surgical Infection Society |
| ATS | American Thoracic Society |
| SOFA | Sequential Organ Failure Assessment |
| qSOFA | quick SOFA |
| $PaO_2$ | Partial pressure of oxygen in the arterial blood |
| $FiO_2$ | Fraction of inspired oxygen |
| GCS | Glasgow Coma Scale |
| MAP | Mean Arterial Pressure |
| SBP | Systolic blood pressure |

| | |
|---|---|
| NK Cells | Natural Killer Cells |
| PRRs | Pattern-Recognition Receptors |
| TLRs | Toll-Like Receptors |
| NOD | Nucleotide-binding oligomerisation domain |
| RIG-1 | Retinoic acid-inducible gene-1 |
| MD-2 | Myeloid differentiation factor-2 |
| LPS | Lipopolysaccharide |
| PAMPs | Pathogen-Associated Molecular Patterns |
| DNA | Deoxyribonucleic acid |
| LPA | Lysophosphatidic acid |
| SPE | Streptococcal Pyrogenic Exotoxins |
| RNA | Ribonucleic acid |
| DAMPs | Damage/Danger-Associated Molecular Patterns |
| HMGB1 | High-mobility group box 1 |
| mtDNA | Mitochondrial DNA |
| ATP | Adenosine triphosphate |
| IL-6 | Interleukin-6 |
| IL-1 | Interleukin-1 |
| TNF-α | Tumour Necrosis Factor-α |
| IL-18 | Interleukin-18 |
| IL-1β | Interleukin-1-beta |
| C5a | Complement factor 5a |
| DIC | Disseminated Intravascular Coagulation |
| RBCs | Red Blood Cells |

| | |
|---|---|
| ROS | Reactive oxygen species |
| MOFS | Multiple Organ Failure Syndrome |
| USA | United States of America |
| CDC | Centres for Disease Control |
| Octogenarians | Between 80-90 years of age |
| Sexagenarian | Between 60-69 years of age |
| CRP | C-reactive protein |
| PCT | Procalcitonin |
| sTREM-1 | Soluble form of Triggering Receptor Expressed on Myeloid cells-1 |
| LBP | Lipopolysaccharide-binding protein |
| suPAR | Soluble form of Urokinase Plasminogen Activator Receptor |
| Pro-ADM | Proadrenomedullin |
| sCD14-ST | Soluble form of Cluster of Differentiation 14 subtype |
| Pro-ANP | Pro-atrial natriuretic peptide |
| IFN-ɣ | Interferon-ɣ |
| IL-27 | Interleukin-27 |
| Ang-1 | Angiopoietin-1 |
| Ang-2 | Angiopoietin-2 |
| M | Mannan |
| AM | Antimannan |
| miRNAs | MicroRNAs |

| | |
|---|---|
| circRNAs | Circular RNAs |
| lncRNAs | Long non-coding RNAs |
| FDA | Food and Drug Administration |
| NEWS2 | National Early Warning Score 2 |
| WBCs | White Blood Cells |
| RCPL | Royal College of Physicians of London |
| NEWS | National Early Warning Score |
| Bpm | Breath per minute |
| HR | Heart Rate |
| BC | Blood Culture |
| LBC | Laboratory Blood Culture |
| SBC | Satellite Blood Culture |
| SF | SeptiFast |
| PCR | Polymerase Chain Reaction |
| SICU | Surgical ICU |
| CD64 | Cluster of Differentiation 64 |
| GEO | Gene Expression Omnibus |
| DEGs | Differentially Expressed Genes |
| TRIM25 | Tripartite Motif Containing 25 |
| RNF4 | Ring Finger Protein 4 |
| EMR | Electronic Medical Record |
| ED | Emergency Department |
| CI | Confidence Interval |
| SBP | Systolic Blood Pressure |

| | |
|---|---|
| MAP | Mean Arterial Pressure |
| $O_2$Sat | Oxygen Saturation |
| DBP | Diastolic Blood Pressure |
| Resp | Respiration Rate |
| Temp | Temperature |
| ML | Machine Learning |
| SL | Supervised Learning |
| UL | Unsupervised Learning |
| RL | Reinforcement Learning |
| NN | Neural Networks |
| k-NN | k-Nearest Neighbours |
| LR | Logistic Regression |
| SVM | Support Vector Machine |
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-analysis |
| MEWS | Modified Early Warning System |
| MIMIC | Medical Information Mart for Intensive Care |
| UCSF | University of California, San Francisco |
| SAPS-II | Simplified Acute Physiology Score-II |
| AISE | Artificial Intelligent Sepsis Expert |
| WCPH | Weibull Cox proportional hazards |
| AIDEx | Artificial Intelligence Decompensation Expert |
| GUI | Graphical User Interface |
| SERA | Sepsis Early Risk Assessment |

| | |
|---|---|
| CDR | Clinical Decision Rule |
| RF | Random Forest |
| LR | Logistic Regression |
| CURB-65 | Confusion, Uremia, Respiratory Rate, Blood Pressure, Age > 65 years |
| MEDS | Mortality in Emergency Department Sepsis |
| mREMS | Modified Rapid Emergency Medicine Score |
| CART | Classification And Regression Tree |
| CNN-LSTM | Convolutional Long Short-Term Memory Neural Network |
| ESM | Epic Sepsis Model |
| EHR | Electronic Healthcare Record |
| COMPOSER | Conformal Multidimensional Prediction of Sepsis Risk |
| DeepAISE | Deep Artificial Intelligence Sepsis Expert |
| SSP | Smart Sepsis Predictor |
| CNN | Convolutional Neural Networks |
| TREWScore | Targeted Real-time Early Warning Score |
| PSV | Pipe-Separated Value format |
| NaN | Not a number |
| CSV | Comma-Separated Value format |
| P_ID | Patient ID |
| EDA | Exploratory Data Analysis |
| FFILL | Forward Fill |

| | |
|---|---|
| RNN | Recurrent Neural Network |
| API | Application Programming Interface |
| SMOTE | Synthetic Minority Over-sampling Technique |

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# Abstract

Sepsis is the body's abnormal and dysregulated response to an infection due to septicaemia. It causes multiple organ damage, and eventually, the patient dies. The worldwide mortality ratio of sepsis is exceptionally high, with an estimated 11 million deaths according to 2017 global sepsis statistics. In Pakistan, an estimated 60-80% of intensive care unit (ICU) deaths are due to sepsis, which might reach 90% soon. Due to limited resources and inflation, early sepsis detection is imperative to lower mortality. Several machine learning-based sepsis prediction tools have been developed, and many studies have been conducted for sepsis prediction. However, these tools cannot predict sepsis as it is a time-series problem but treat it as a binary classification problem. Deep-learning (DL) algorithm-based methods can better deal with the time-series data due to their robustness, allowing better insights into the data and performance. Therefore, in this study, a novel DL-based approach is opted to forecast the sepsis mortality risk in ICU patients. MissForest and Last Observation Carried Forward (LOCF)-zero (FFILL-0) imputation methods were used to impute Not a Number (NaN) values (missing values) in the data, and the patient data was converted to fixed-length tensors, which were then used for model training and evaluation. Among the DL algorithms, Long short-term memory (LSTM) and Gated recurrent units (GRUs) were selected for model building. Finally, four models were trained on MissForest, and FFILL-0 imputed data, and to check the effectiveness, the models were evaluated on the hold-out datasets and the Area Under the Receiver Operating Characteristic curve (AUROC) was calculated for each model. LSTM model outperformed GRU, and the highest AUROC achieved in this study was 0.758. In short, DL algorithms can accurately forecast sepsis risk in ICU patients and can help reduce Intensive Care Unit Length of Stay (ICULOS) and sepsis mortality risk.

# Introduction

## 1.1. Insights to sepsis

Sepsis is the earliest known illness that dates back to ancient Greeks, who defined sepsis as "σῆψις" or "putrefaction" [1, 2]. However, the modern context of sepsis is different. Sepsis is the lethal condition that ensues when the body fights against blood poisoning due to microbes, a condition called septicaemia [3]. The body's organs and tissues get damaged so much that it causes the individual's death [4]. The appropriate description of sepsis was ambiguous before 1991. Some researchers defined sepsis as a clinical syndrome, a systemic response to infection [5].

However, the Chicago consensus conference held in August of 1991 by the Society of Critical Care Medicine (SCCM) together with the American College of Chest Physicians (ACCP) specified the first definition of sepsis (Sepsis-1) as "The infection commencing the onset of SIRS". Furthermore, it defined SIRS as "Systemic Inflammatory Response Syndrome" [6, 7], and the SIRS criteria consist of heart rate (tachycardia), respiration rate (tachypnea), temperature (hyperthermia, hypothermia), and white blood cells (leukocytosis, leukopenia) [2, 5, 6, 8]. Sepsis is aggressive and deadly, and severe sepsis and septic shock are responsible for sepsis-related deaths.

Severe sepsis involves organ dysfunction, including hypotension and tissue hypoperfusion caused by sepsis. On the other hand, septic shock is sepsis with persistent hypoperfusion and hypotension even with fluid resuscitation [9, 10]. All these (SIRS, Sepsis, Severe Sepsis, Septic shock) along with Multiple Organ Dysfunction Syndrome (MODS) lead to the death of the patient [11] (Figure. 1).

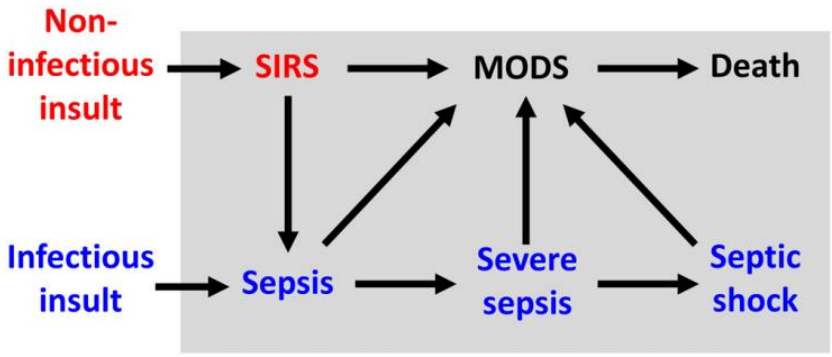



*Figure 1: The infectious and non-infectious relationship between SIRS, Sepsis, Severe Sepsis, Septic shock, and MODS leading to death* [12]

However, the European Society of Intensive Care Medicine (ESICM), ACCP, SCCM, the Surgical Infection Society (SIS), and the American Thoracic Society (ATS) revised the definition of sepsis (Sepsis-2) in the second consensus conference in 2001. They defined sepsis as the existence of two (or more) SIRS criteria concurrently with the infection [13]. The third consensus conference of 2016 reviewed the definition of Sepsis (Sepsis-3) and described sepsis as the dysregulated and escalated response of the host toward an infection [14, 15]. The consensus defined the Sequential Organ Failure Assessment (SOFA) Score and introduced quick SOFA (qSOFA), the modified version of SOFA. In addition, it redefined sepsis based on SOFA and qSOFA instead of SIRS [16]. Figure 2 compares sepsis definitions described in the Surviving Sepsis Campaign Guidelines and consensus conferences [17].

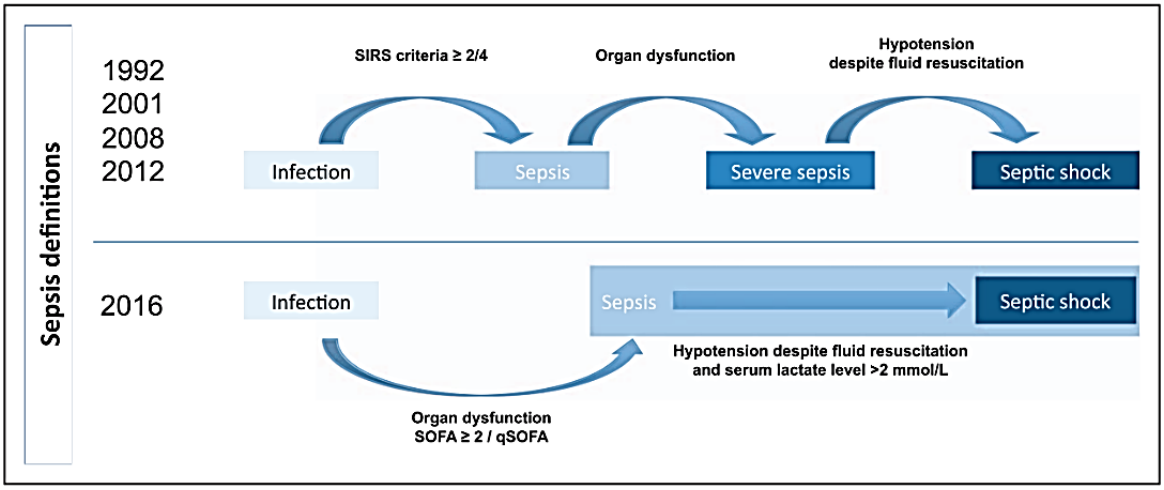



*Figure 2: Graphical representation of sepsis definitions from 1992 to 2016*

The SOFA score criteria comprise of Respiratory system (Partial pressure of oxygen in the arterial blood ($PaO_2$), Fraction of inspired oxygen ($FiO_2$)), Nervous system (Glasgow Coma Scale (GCS)), Cardiovascular system (Mean Arterial Pressure (MAP) and Dopamine), Liver (Bilirubin), Coagulation (Platelets), and Kidneys (Creatinine) [8, 18]. Now, physicians and doctors worldwide mostly use qSOFA to diagnose septic patients quickly. qSOFA criteria are Respiration rate, GCS, and Systolic Blood Pressure (SBP) [8].

## 1.1. Pathophysiology of Sepsis

When pathogens enter the host (patient) body, the patient's defence mechanism is activated, which protects against the microbes [19]. The most prevalent infectious sites for the onset of sepsis are the urinary tract, bloodstream, lungs, and abdominal

cavity [14]. Immune cells like monocytes, macrophages, Natural Killer (NK) Cells, and neutrophils are released that attacks the invading pathogens [20]. How these cells recognise and attack only the invading pathogens is a fascinating capability of the immune system. On the surface of these immune cells are specialised receptor molecules called Pattern-Recognition Receptors (PRRs), such as Toll-Like Receptors (TLRs), Nucleotide-binding oligomerisation domain-like (NOD-like) receptors, Retinoic acid-inducible gene-1-like (RIG-1-like) receptors, and C-type lectin receptors [20-22]. Figure 3 shows the structure of a TLR type 4 and Myeloid differentiation factor-2 (MD-2) complex, which is bound to bacterial Lipopolysaccharide (LPS).

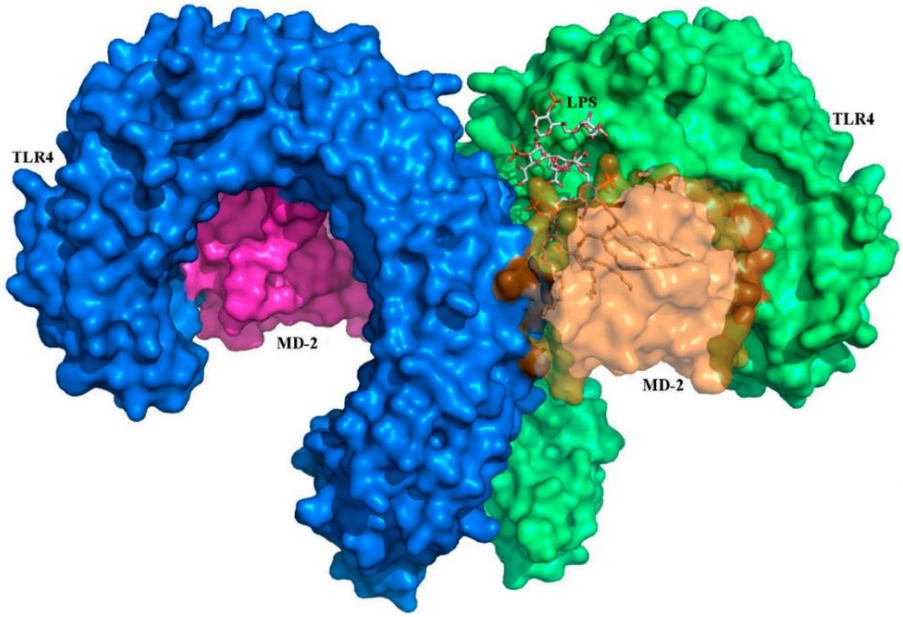



*Figure 3: Structure of a hexamer complex of a Toll-Like Receptor 4 and Myeloid differentiation factor-2 attached to bacterial LPS [23]*

When pathogens enter the host body, they release some molecules known as Pathogen-Associated Molecular Patterns (PAMPs), such as β-glucans (in the case of fungi), bacterial endotoxins, Deoxyribonucleic acid (DNA), flagellin, Lysophosphatidic acid (LPA), LPS, and superantigens like Streptococcal Pyrogenic Exotoxin (SPE) and double or single-stranded viral Ribonucleic acid (RNA). [20, 21, 24, 25]. PRRs recognise these PAMPs and activate innate immune cell responses. Immune cells interact with pathogens, phagocytise them, and sometimes get damaged or killed during the encounter, thus releasing alarmins or Damage/Danger-Associated Molecular Patterns (DAMPs) such as heat-shock proteins, High-mobility group box 1 (HMGB1), histones, lipoproteins, Mitochondrial DNA (mtDNA), and Adenosine

triphosphate (ATP) molecules. PAMPs and DAMPs, when recognised by PRRs on immune cells, activate signalling pathways within the immune cells [22], resulting in the production of pro-inflammatory proteins known as Cytokines, like Interleukin-6 (IL-6), Interleukin-1 (IL-1), and Tumour Necrosis Factor-α (TNF-α), which promote inflammation.

TNF-α is one of the earliest releasing cytokines during the onset of sepsis [25]. Aggregated NOD-like receptors (Inflammasomes) (Figure. 4) produce cytokines (caspases, Interleukin-18 (IL-18), and Interleukin-1-beta (IL-1β)) that participate in apoptosis. Pro-inflammatory cytokines are responsible for the activation of leucocytes, production of tissue factors, Nitric oxide release, inhibition of fibrinolysis, and decrease in thrombomodulin. Conversely, anti-inflammatory cytokines impede inflammation by hindering pro-inflammatory cytokine functions [25]. Pro-inflammatory and anti-inflammatory cytokines cancel each other's effects [26], thus maintaining the balance in the body. However, the excessive production of pro-inflammatory cytokines along with cellular dysfunction disrupts this balance in case of sepsis.

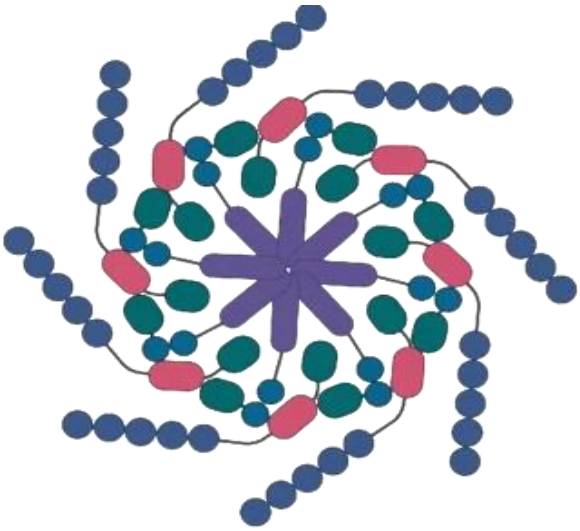


*Figure 4: The structure of the NLRP3 Inflammasome complex [27].*

When the infection is severe, immature neutrophils are released by bone marrow through the short maturation of granulocytes, consequently exhibiting decreased oxidative burst and phagocytosis capability [24]. Also, Lymphocytes undergo apoptosis because they lose their ability to produce cytokines owing to the overproduction of Complement factor 5a (C5a) protein due to infection [28] and thus exhibit reduced

function [29]. The endothelium plays a crucial role in sepsis pathophysiology. It releases pro-inflammatory cytokines and recruits inflammatory cells.

In addition, endothelium vasodilation, leucocyte adhesion, and barrier functionality loss result in tissue oedema [30]. Furthermore, the loss of anticoagulant function due to cytokine storm stimulates coagulation [24]. Antithrombin deficiency causes prolonged blood clotting, and Disseminated Intravascular Coagulation (DIC) is evident in cases of sepsis [26, 29]. Bacterial endotoxins or LPS induce apoptosis in the endothelium, leading to microvascular thrombosis due to the release of intracellular histones. This abnormality of excessive bleeding and clotting favours coagulopathy and increases mortality risk [31].

Moreover, endothelium also produces nitric oxide and its production upsurges due to the pro-inflammatory cytokines. This unregulated nitric oxide release results in vasodilation [32], which results in hypotension [33]. Peroxynitrite and nitric oxide are also accountable for endothelial mitochondrial dysfunction and cause cellular and tissue hypoxia because of poor oxygen utilisation [34, 35]. Due to hypoxia, Red Blood Cells (RBCs) release nitric oxide and promote vasodilation and perfusion of blood vessels. RBCs also become rigid, and they aggregate. Also, leucocytes produce Reactive oxygen species (ROS) that destroy cellular interactions and coagulation function, leading to oedema and cellular distress [35]. These phenomena fail multiple vital organs – a condition called Multiple Organ Failure Syndrome (MOFS) or MODS [36, 37].

Lungs are the first organ affected in MODS due to capillary leakage and alveolar flooding, followed by myocardial dysfunction due to excessive nitric oxide production. The third organ most affected in MODS is the kidneys because of catecholamine production, even after fluid resuscitation [38]. The neurological dysfunction due to MODS is polyneuropathy and polymyopathy because of hyperglycaemia and bacteraemia. Also, gastrointestinal system dysfunction due to MODS can be pancreatitis and ulcers [39]. In sepsis, MODS-related multiple organ dysfunction increases the in-hospital mortality risk and causes the patient's death [36, 37].

## 1.4. Challenges

Due to the unavailability of local patient data from the Pakistani population till now, no study has been published on sepsis prediction and forecasting based on

Pakistani data. Thus, this study is limited to using open-source patient data from the United States of America (USA) population.

## 1.5. Problem Statement

The currently used predictive algorithm-based tools for predicting sepsis in patients predict sepsis as binary classification of “Yes” (septic patient) and “No” (non-septic patient) as in at one instance the patient might classify as septic and later the same might be classified as non-septic. However, when a patient is admitted to the hospital, the data is collected over regular time intervals (primarily hourly base), thus making it a time-series analysis and problem, and simple prediction-based tools for sepsis detection are not suitable. Thus, this study uses time series forecasting to predict the probability of sepsis occurring.

## 1.6. Proposed Strategy

Forecasting sepsis using Deep Learning (DL) algorithms is efficient because DL algorithms work best with time-series data. As a result, time series forecasting is used in this study to deal with the data. This technique will accurately assess a patient’s risk for sepsis and minimise in-hospital patient mortality and ICULOS.

## 1.7. Objectives

Following are the objectives of this research:

1. To find out the appropriate Deep Learning models for sepsis forecasting.
2. To select the best features for building the sepsis forecasting model.
3. To prepare and pre-process the data for model building.
4. To develop, optimize, and evaluate the sepsis forecasting model.

# Literature Review

## 2.1. Sepsis Epidemiology

Sepsis is lethal and has a high mortality and morbidity ratio globally. The epidemiological study conducted in the USA in the 1990s by the Centres for Disease Control (CDC) on sepsis using hospital data revealed that from 1979 to 1989, the sepsis rate per 100,000 patients increased from 73.6 to 175.9 [40]. Per the 2019 Global Sepsis Alliance, 60-80% of ICU deaths in Pakistan are due to sepsis [41], which might approach 90% soon [42]. According to the 2017 study [43] (Figure. 5), 48.9 million people were diagnosed with sepsis globally, and 11 million died, representing 20% worldwide deaths.

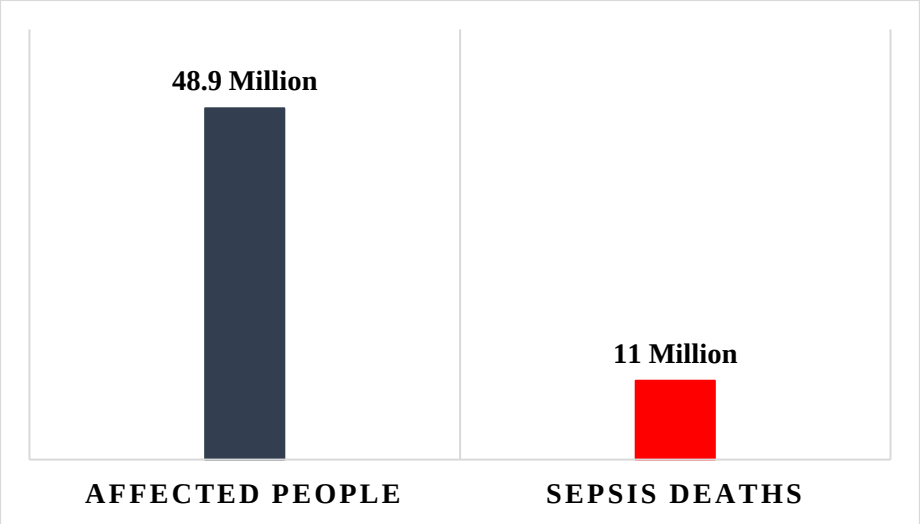



*Figure 5: Global Sepsis Statistics in 2017.*

Sepsis and severe sepsis put an estimated burden of 17 billion dollars annually in the USA [44], 36.4 million dollars to 72.9 million dollars in Canada [45], and 2.16 billion dollars in Australia [46]. The rate of sepsis varies age-wise, and the average age of sepsis patients is allegedly between 55 to 68 years, and it is more common in men than women [44, 47]. The rate of sepsis is 5 per 1000 patients in infants, <5 per 1000 patients in children, and 15 per 1000 patients in octogenarians. In sexagenarian patients, 58% of sepsis cases and 71% of sepsis-related deaths are reported in developed countries [48].

Also, a study conducted in 2017 [43] acknowledged that the percentage of age-related sepsis deaths from infections or injuries worldwide fluctuates among

individuals. It surged in early infancy, plunged amongst young adults, and spiked again among mature adults (Figure. 6).

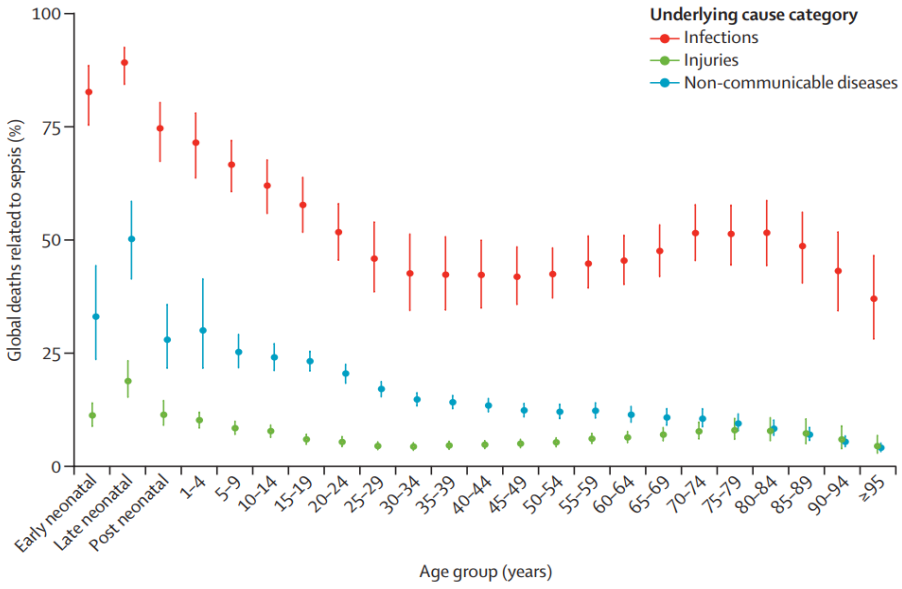



*Figure 6: Percentage of global sepsis-related deaths in 2017 age-category-wise*

Over the past decade, the sepsis mortality rate decreased in high-income countries, but the mortality rate in middle- and low-income countries has increased. For example, septic patients in ICU in Brazil has a mortality rate of 55.7% [42]. In Brazil, from 2006 to 2015, there was a spike of 50% in sepsis incidence from 31.5 to 47.4 per 100,000 people and a spike of 85% in sepsis mortality from 13.3 to 24.6 per 100,000 people (Figure. 7).

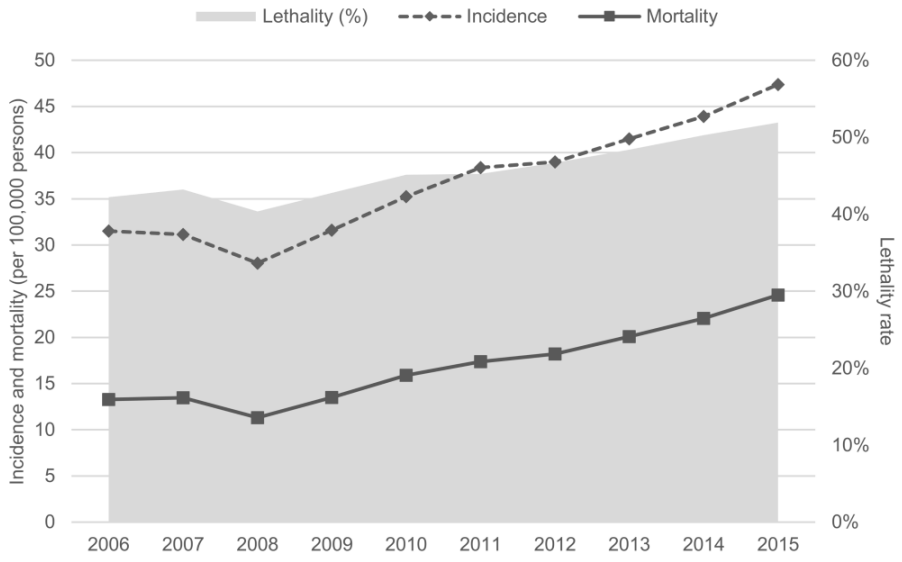



*Figure 7: Sepsis Mortality, Incidence, Lethality from 2006 to 2015 in Brazil [49]*

From 2000 to 2013 in Spain, sepsis-related in-hospital deaths increased from 18% to 29%, and sepsis-related hospital admissions increased from 3.6% to 5.8% (Figure. 8).

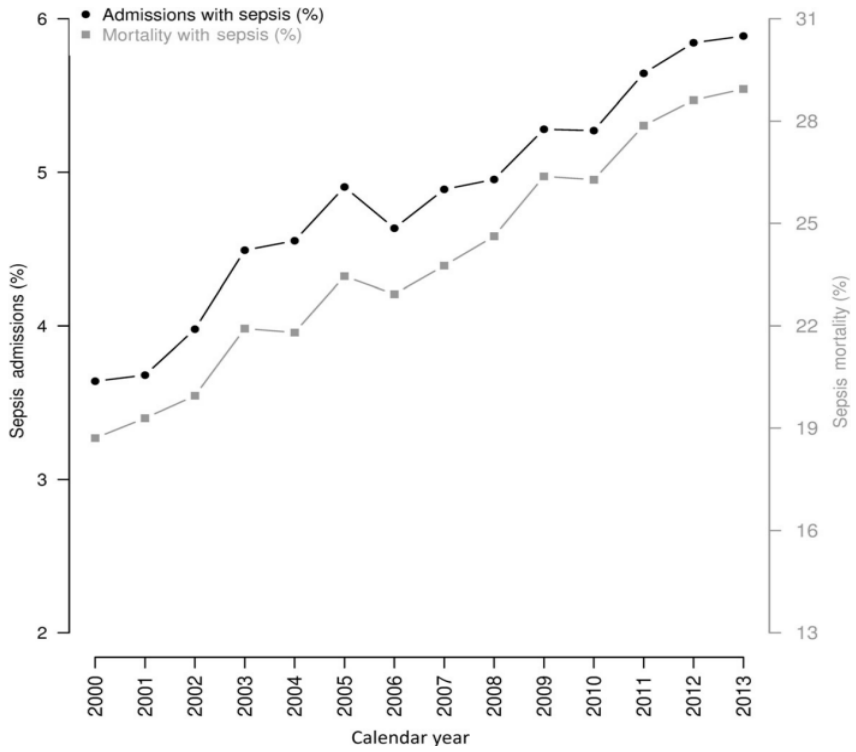



*Figure 8: Sepsis-related hospital admission and mortality in Spain [50]*

## 2.2. Assessment of Sepsis

Regardless of the top-notch healthcare system worldwide, sepsis assessment is still complicated. Early sepsis evaluation is the key to saving the patient's life. Nevertheless, diagnosing sepsis is challenging due to non-infectious inflammation in the body. So, physicians relied on using biomarkers to properly diagnose the patient as septic or non-septic [51].

A biomarker characterises a biological entity that anticipates the outcomes of a standard or abnormal process (like a disease) inside humans that is difficult to observe [52]. The use of biomarkers is extensive to diagnose heart-related issues, immune disorders, infections, disease screening and monitoring, drug reaction prediction, identification of cell types, measuring drug efficacy in clinical trials, and studying tumours and cancers [52, 53].

Proteins like C-reactive protein (CRP), Procalcitonin (PCT), IL-6, Soluble form of Triggering Receptor Expressed on Myeloid cells-1 (sTREM-1), Lipopolysaccharide-Binding Protein (LBP), Soluble form of Urokinase Plasminogen Activator Receptor (suPAR), Proadrenomedullin (Pro-ADM), Soluble form of Cluster of Differentiation 14 subtype (sCD14-ST) or presepsin, Pro-atrial natriuretic peptide (pro-ANP), Interferon-ɣ (IFN-ɣ), resistin, Interleukin-27 (IL-27), Angiopoietin-1 (Ang-1) and Angiopoietin-2 (Ang-2), antibodies like Mannan (M), Antimannan (AM), Lactate, non-coding RNAs like MicroRNAs (miRNAs), Circular RNAs (circRNAs), Long non-coding RNAs (lncRNAs) are the potential biomarkers used to diagnose sepsis [54-56].

Among these biomarkers, PCT, CRP, IL-6, and Lactate are widely used for sepsis diagnosis [57, 58]. Doctors use different scoring systems and criteria for sepsis diagnosis when patients are admitted to the ICU after an accident or surgery. They order Food and Drug Administration-approved (FDA-approved) lab tests such as PCT, Lactate, CRP, and Cytokines to confirm whether the patient is septic or non-septic [59]. Although these lab tests are efficient enough to diagnose sepsis properly, some of these tests take time.

Patients with septic shock have an 8% increase in mortality each passing hour if there is any delay in administering antibiotics to the patients [60]. So, doctors use qSOFA and National Early Warning Score 2 (NEWS2) alongside SOFA and SIRS to quickly check a patient's mortality risk and ensure the timely administration of antibiotics [61]. Following is the detail of the scoring systems with their criteria:

### 2.2.1. SIRS

If a patient meets two (or more) out of these four SIRS criteria, their condition is said to be sepsis [8]:

- Tachycardia - Heart rate greater than 90 beats per minute
- Tachypnea - Respiration rate of more than 20 breaths/minute
- Hyperthermia or Hypothermia - Temperature more than 38°C or less than 36°C
- Leukocytosis or Leukopenia - Abnormal White blood cells (WBCs) count of more than 12,000/mL or less than 4000/mL

### 2.2.2. SOFA

Table 1 represents the SOFA criteria [8]. Each organ system or variable that comprises SOFA is given a score from “0” to “4”.

*Table 1: Sequential Organ Failure Assessment (SOFA) score [8]*

| *Organ System / Variable* | *SOFA Score* | | | | |
|---|---|---|---|---|---|
| | ***0*** | ***1*** | ***2*** | ***3*** | ***4*** |
| *Respiration* $PaO_2$ *mmHg* $FiO_2$ *(kPa)* | *> 400* | *< 400* | *< 300* | *< 200 with respiratory support* | *< 100 with respiratory support* |
| *Coagulation* *Platelets,* $10^3$ */* $mm^3$ | *> 150* | *< 150* | *< 100* | *< 50* | *< 20* |
| *Liver* *Bilirubin (mg/dL)* | *<102* | *1.2 - 1.9* | *2.0 - 5.9* | *6.0 - 11.9* | *> 12.0* |
| *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* *GCS* | *15* | *13 - 14* | *10 - 12* | *6 - 9* | *< 6* |
| *Renal* *Creatinine (mg/dL)* | *< 1.2* | *1.2 - 1.9* | *2.0 - 3.4* | *3.5 - 4.9 < 500* | *> 5.0 < 200* |

A SOFA score of “0” means normal, and a SOFA score of “4” means exceptionally abnormal. The score is calculated for each variable separately based on that variable’s value, and a patient with a combined SOFA score of 2 or more is considered septic with organ dysfunction [13] and needs immediate care.

### 2.2.3. qSOFA

A patient with a qSOFA score of 2 or more indicates sepsis and organ dysfunction [8, 62] and needs urgent care; otherwise, there is a mortality risk for the patient. qSOFA criteria are shown in Table 2.

*Table 2: Quick Sequential Organ Failure Assessment (qSOFA) score*

| *qSOFA score criteria* | *Score* |
|---|---|
| *Respiration Rate ≥ 22 per minute* | *1* |
| *Level of Consciousness (GCS)* | *1* |
| *SBP ≤ 100 mmHg* | *1* |

### 2.2.4. NEWS2

In 2012, the Royal College of Physicians of London (RCPL) proposed a National Early Warning Score (NEWS) composed of six vital signs: Respiration Rate, Oxygen Saturation, Temperature, SBP, Heart Rate, and GCS. Each vital sign is assigned a score from 0 - 3.

Later in 2017, RCPL proposed NEWS2, a modified version of NEWS. The modifications were made in each vital sign score weightage [63]. Table 3 shows the NEWS2 criteria [64]. A score is assigned to each vital sign value, and a combined score of 5 or more indicates sepsis and the patient needs urgent care.

*Table 3: National Early Warning Score 2 (NEWS2) [64]*

| *Vital Sign / Parameter* | *NEWS2 Score* | | | | | | |
|---|---|---|---|---|---|---|---|
| | ***3*** | ***2*** | ***1*** | ***0*** | ***1*** | ***2*** | ***3*** |
| *Respiration (bpm)* | *≤ 8* | | *9 - 11* | *12 - 20* | | *21 - 24* | *≥ 25* |
| *$SpO_2$ Scale 1 (%)* | *≤ 91* | *92 - 93* | *94 - 95* | *≥ 96* | | | |
| *$SpO_2$ Scale 2 (%)* | *≤ 83* | *84 - 85* | *86 - 87* | *88 - 92 ≥ 93 on air* | *93 - 94 on oxygen* | *95 - 96 on oxygen* | *≥ 97 on oxygen* |
| *Air or Oxygen?* | | *Oxygen* | | *Air* | | | |
| *SBP (mmHg)* | *≤ 90* | *91 - 100* | *101 - 110* | *111 - 219* | | | *≥ 220* |
| *Pulse / HR (per minute)* | *≤ 40* | | *41 - 50* | *51 - 90* | *91 - 110* | *111 - 130* | *≥ 131* |
| *Consciousness* | | | | *Alert* | | | *CVPU* |
| *Temperature (°C)* | *≤ 35.0* | | *35.1 - 36.0* | *36.1 - 38.0* | *38.1 - 39.0* | *≥ 39.1* | |

## 2.3. Invasive methods based sepsis detection

The microbial infection is the *sine qua non* for sepsis [65], and the earliest symptom of sepsis observed in hospital patients is fever [66]. Initially, researchers focused on early sepsis detection based on biomarkers using blood cultures (BC). Martin *et al.* [67] studied IL-6 and TNF-α patterns in critically ill patients. Their study involved 60 patients with multiple trauma and 25 septic shock patients without trauma. The serum concentrations of these cytokines were studied, and they reported that septic shock patients have a high concentration of both TNF-α and IL-6 and high mortality risk. Moreover, higher IL-6 concentrations in trauma patients are linked to the onset of nosocomial infections, which can lead to sepsis.

BC is the most effective way to detect the pathogens inside a patient's blood. However, specific BC conditions are required for the pathogen to grow, making them tedious [68]. Ziqi *et al.* [69] conducted a study on ICU patients from the Chinese population to lower the time a BC-based patient lab report takes. Patients were divided into two groups; Laboratory Blood Culture (LBC), BCs cultured within the hospital microbiology lab, and Satellite Blood Culture (SBC), BCs cultured at the collection site, typically in the ICU. The authors reported no considerable difference between the BC protocol of these two groups. However, the culture time was significantly shorter for SBC than for LBC.

Lodes *et al.* [70] evaluated SeptiFast (SF), a multiplex real-time Polymerase Chain Reaction based (PCR-based) sepsis detection kit for early detection of pathogens in abdominal sepsis patients' blood. Blood samples were taken from surgical ICU (SICU) patients in Germany, and 77 pathogens were identified. Out of which, BC confirmed 25 pathogens. Therefore, it is concluded that PCR-based sepsis detection is a suitable method for helping doctors better care for patients. Christian *et al.* [71] also used SF for sepsis diagnosis based on BC. Data from 258 sick patients were collected from the Italy population, and the purpose of the study was to get a higher probability of pathogen detection.

Instead of using BC-based methods, which are time-consuming, or PCR-based methods, which might fail due to abundant human DNA and low pathogenic DNA in the samples, Trung *et al.* [68] developed Sepsis@Quick – a sepsis diagnosis kit. This kit helps in the real-time removal of human DNA from the PCR samples and can detect more pathogens in blood samples than BC-based or other PCR-based methods. Another sepsis detection kit was developed by Zhang Ye *et al.* [72]. Blood samples were obtained from critically ill patients, and sepsis was diagnosed based on Cluster of Differentiation 64 (CD64) expression measurement using the microfluidic cell separation device. This sepsis chip is cost-effective, and the approach is proven precise for sepsis detection.

Christopher *et al.* [73] introduced a mechanism for the detection of IL-6 electrochemically. They developed a needle-shaped microelectrode for real-time detection of IL-6 to diagnose sepsis in the affected person. Moreover, Zupančič *et al.* [74] developed a graphene oxide nanoparticle-based multi-biomarker detection sensor

system, which can detect PCT, CRP, and PAMPs simultaneously. This system can quickly achieve parallel detection of multiple biomarkers from whole blood, which is otherwise challenging in electrochemical systems [75]. A bioinformatics-based study for finding biomarkers associated with sepsis was carried out by Jianhua *et al.* [76]. The microarray data were obtained from Gene Expression Omnibus (GEO) database, and differentially expressed genes (DEGs) were identified. Many DEGs were involved in the cell cycle and activation of neutrophils, and genes like Tripartite Motif Containing 25 (TRIM25), MYC, and Ring Finger Protein 4 (RNF4) were identified as potential DEGs critical biomarkers for sepsis.

## 2.4. Non-Invasive methods based sepsis detection

However, blood culture-based detection usually takes 12-72 hours [73], and a one-hour delay increases mortality risk by 6-10% [60, 77]. So, researchers focused on more reliable ways to detect sepsis. Nguyen *et al.* [78] evaluated the accuracy and performance of an automated Electronic Medical Report (EMR) system for sepsis detection in the emergency department (ED) of hospitals. This system collects data like vital signs and lab tests of all patients in ED and generates an alert for sepsis based on SIRS. Out of 795 sepsis alerts, 355 were actual alerts for sepsis. Among these alerts, 38% were for patients with respiratory tract infections, and 32.7% were for urinary tract infections. The EMR system also generated false sepsis alerts for patients with trauma and heart-related issues.

SIRS, qSOFA and NEWS are the best tools for sepsis diagnosis. A statistical analysis-based study was conducted by Usman *et al.* [79], who performed a retrospective study to compare SIRS, qSOFA, and NEWS to detect severe sepsis and septic shock. Data was obtained from ED, and they calculated AUROC, sensitivity, and specificity. NEWS was the most accurate scoring system than SIRS or qSOFA. In terms of sensitivity, NEWS achieved similar sensitivity 84.2% (Confidence Interval (CI): 81.5% - 86.5%) to SIRS 86.1% (CI: 83.6% - 88.2%) as it is based on vital signs only. However, qSOFA is a poor choice for sepsis diagnosis for ED patients, with a sensitivity of 28.5% (CI: 25.6% - 31.7%). Brink *et al.* [80] also compared the SIRS, qSOFA, and NEWS for sepsis detection in ED patients. They carried out a retrospective study using a total of 8204 patients. 3.5% (286) patients died within ten days of ICU admission, and 6% (490) died within 30 days after ICU admission. AUC was calculated for 10-days and 30-days. Ten days AUC achieved for NEWS is 0.837, qSOFA 0.744,

and SIRS 0.646. Similarly, 30 days AUC achieved for NEWS is 0.779, qSOFA 0.697, and SIRS 0.631. NEWS outperformed qSOFA and SIRS in predicting ten days and 30 days of patient mortality in ED.

Another statistics-based study was carried out by Shashikumar *et al.* [81]. They included vital signs like Heart Rate (HR), Systolic Blood Pressure (SBP), Mean Arterial Pressure (MAP), Oxygen Saturation ($O_2$Sat), Diastolic Blood Pressure (DBP), Respiration Rate (Resp), GCS, and Temperature (Temp) as essential features in their study. Using a multivariate modelling approach for early sepsis detection in ICU patients, they concluded that blood pressure and HR dynamics are valuable predictors for detecting sepsis four hours before the onset. Also, AUROC increased from 0.67 to 0.78 when demographics and other data like surgical history were added to the model.

### 2.4.1. Machine learning based Sepsis detection

Early detection of sepsis is the key to minimising in-hospital patient mortality. However, relying only on invasive methods is not a good approach, even though BC, PCR, and biomarkers-based studies are proven reliable for sepsis detection. Non-invasive methods are more efficient than invasive methods [82]. Relying only on continuously available vital signs and incorporating Machine Learning (ML) algorithms is another way to diagnose sepsis effectively. There is a gradual increase in the use of ML for disease prediction due to improved algorithms that enable the early detection of deadly diseases and helps doctors control patient mortality [83-85].

Various ML techniques such as Supervised Learning (SL), Unsupervised Learning (UL), Reinforcement Learning (RL), and Deep Learning (DL) are used for disease prediction [86]. In addition, algorithms such as Neural Networks (NN), k-Nearest Neighbours (k-NN), Logistic Regression (LR), Support Vector Machine (SVM), and Gradient boosting have been used for sepsis detection [87-89]. Islam *et al.* [90] performed a meta-analysis to evaluate ML models' performance with available scoring systems used for sepsis prediction. They did an extensive literature review using electronic databases like Google Scholar, PubMed, and others. They found out that out of 135 studies, only 7 met their inclusion criteria based on the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA). 3-4 hours before the onset of sepsis, ML models achieved the pooled AUROC of 0.89, the sensitivity of 0.81, and specificity of 0.72, as compared to pooled AUROC of SIRS (0.70), Modified Early

Warning System (MEWS) (0.50), and SOFA (0.78). So, ML-based sepsis detection methods proved to be more efficient than other scoring system-based methods.

Jacob *et al.* [91] developed *InSight*, an efficient tool for sepsis detection ahead of time, typically up to three hours. They trained the model using Medical Information Mart for Intensive Care (MIMIC) data. *InSight* achieved an AUROC of 0.83, a sensitivity of 0.90, and a specificity of 0.81 when tested on unseen data (test data). It outperformed biomarker-based methods for sepsis detection. Figure 9 compares the specificity and sensitivity of *InSight* and other sepsis detection methods.

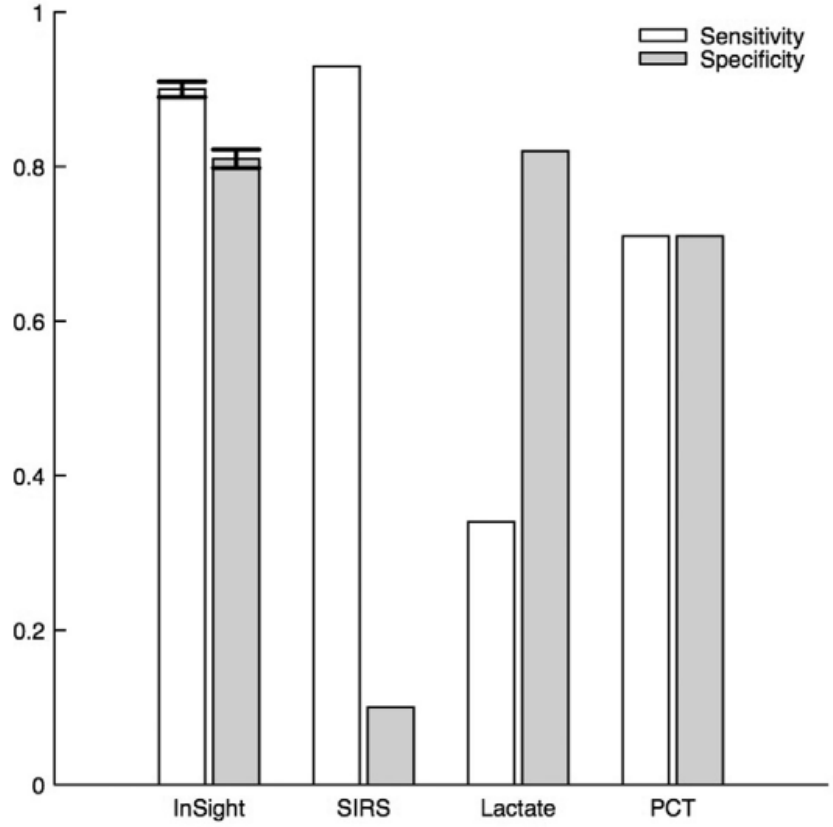



*Figure 9: Comparison of Sensitivity and specificity among InSight, SIRS, Lactate, and PCT tests [91]*

Qingqinq *et al.* [92] evaluated the performance of the *InSight* tool by using data from the University of California, San Francisco (UCSF) for training and MIMIC data for transfer learning. *InSight* is based on a gradient tree boosting algorithm and uses only six vital signs as features with one outcome and achieved AUROC of 0.92 for sepsis and 0.87 for severe sepsis. Also, it achieved an AUROC of 0.85 for severe sepsis and 0.96 for septic shock four hours before the onset of sepsis. This method is prone to NaN values in the data and can outperform other sepsis detection algorithms.

Desautels *et al.* [93] also used the *InSight* algorithm and compared it with other sepsis detection tools and scoring systems. Using MIMIC-III data, they trained the model and calculated the AUROC on the hold-out dataset. Figure 10 compares the AUROC of *InSight* with other methods. It is evident that for sepsis onset, *InSight* achieved the highest AUROC (0.88), MEWS (0.803), qSOFA (0.77), SOFA (0.73), SAPS-II (0.70), and SIRS (0.61). Moreover, when 60% of the input data was randomly deleted, *InSight* outperformed other methods and attained an AUROC of 0.781.

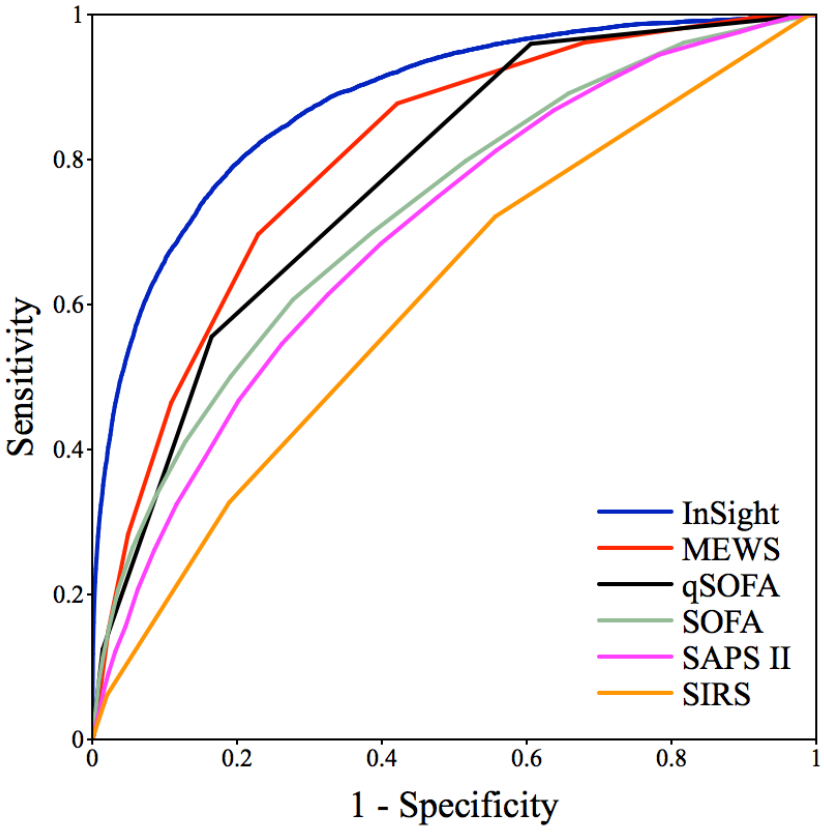



*Figure 10: AUROC of InSight algorithm with other sepsis prediction methods [93]*

Nemati *et al.* [94] developed an Artificial Intelligent Sepsis Expert (AISE) algorithm based on Weibull Cox proportional hazards (WCPH) model. Time-series data from two different hospitals of Emory University was used for model training, and MIMIC data was used to validate the model. A total of 65 features were used in the model building, and AISE predicted sepsis onset before 4, 6, 8, and 12 hours of clinical confirmation, achieving AUROC of 0.83 to 0.85. This system can predict the onset of sepsis ahead of time. Another important AISE-based sepsis detection platform is Artificial Intelligence Decompensation Expert (AIDEx) (Figure. 11), designed by Amrollahi *et al.* [95]. The platform consists of three modules: The first module consists

of Healthcare Application Programming Interface (API) linked to EMR data. The second module consists of a Data Wrangler, MongoDB, and AIDEx APIs. Inside AIDEx API, a sepsis predictor algorithm (AISE) predicts the sepsis, and the results are stored in the MongoDB database. Finally, the third module hosts a graphical user interface (GUI) dashboard, which shows the prediction results.

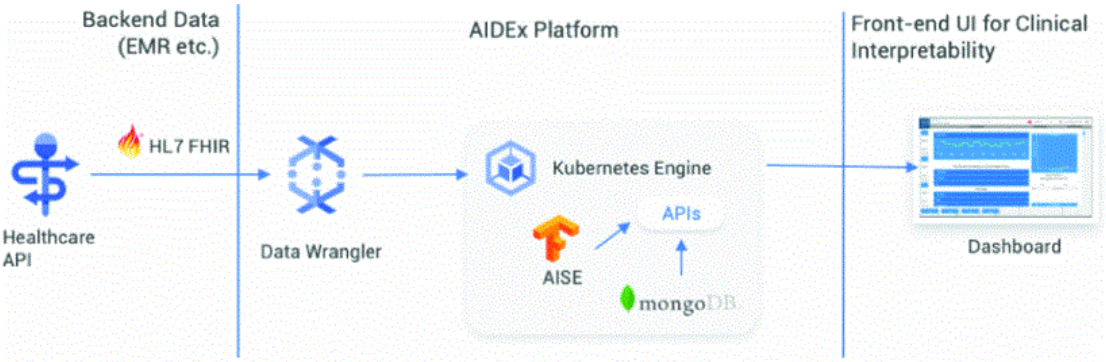



*Figure 11: Architecture of AIDEx platform [95]*

Likewise, Goh *et al.* [96] developed a Sepsis Early Risk Assessment (SERA) algorithm for early sepsis prediction. This study used two data types: Structured and Unstructured data. Structured data consisted of vital signs, patient treatment history, and Investigations. Similarly, unstructured data consisted of notes like patient recovery progress, medication, and ICU consultation, made by nurses or doctors. LR and RF models were trained and evaluated on validation data based on the ensemble method for model training. SERA achieved an AUROC of 0.94 with 0.87 sensitivity and specificity. It also reduced false positives by 17% and increased early detection of sepsis up to 32%, compared to doctors' confirmation of sepsis.

Taylor *et al.* [97] performed a retrospective study on ED patients and proposed a novel sepsis prediction model which outperformed available clinical decision rules (CDR) models for sepsis detection. They predicted in-hospital patient mortality using a Random Forest-based (RF-based) model. A total of 500 features, including demographics, lab reports, medication history, vital signs, ED diagnosis, patients' history, and nursing interventions, were involved, and an 80-20 split ratio was used for model training and validation. Finally, model results were compared with other ML models and sepsis prediction tools, including the Logistic Regression (LR) model, Confusion, Uremia, Respiratory Rate, Blood Pressure, Age > 65 years (CURB-65), Mortality in Emergency Department Sepsis (MEDS), Modified Rapid Emergency

Medicine Score (mREMS), and Classification And Regression Tree (CART) in terms of AUROC. RF model achieved highest AUROC (0.86) as compared to LR (0.76), CURB-65 (0.73), mREMS (0.72), MEDS (0.71), and CART (0.69) (Figure. 12).

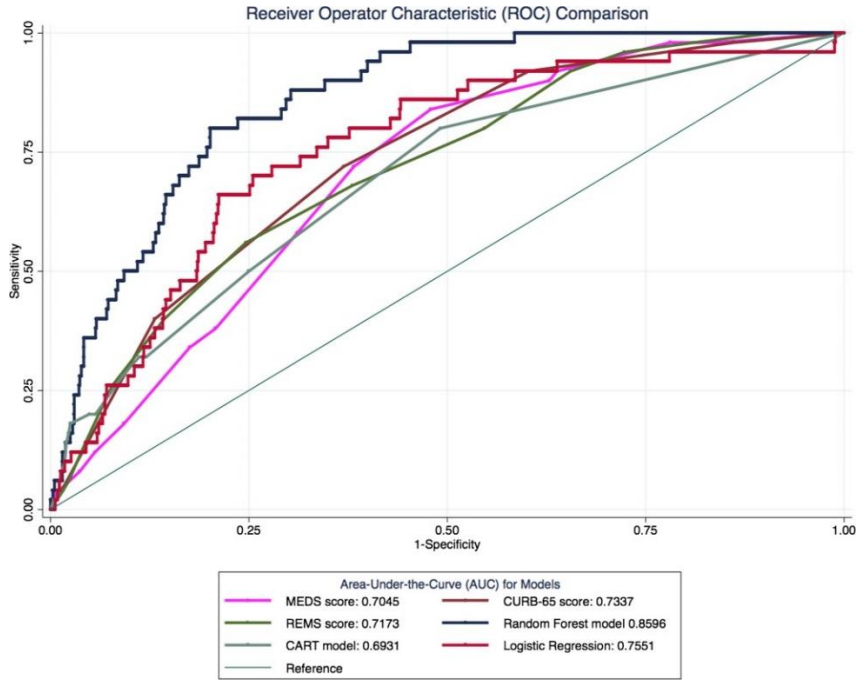



*Figure 12: AUROC of RF model with existing CDRs for sepsis detection [97]*

Hou *et al.* [98] developed an XGboost-based ML model to predict 30-day mortality for sepsis patients using MIMIC-III data. The model was trained on 4559 patients, and they compared their model with LR and SAPS-II score-based prediction models. Among them, the XGboost-based model achieved the highest AUROC (0.857) as compared to SAPS-II (0.797) and LR (0.819). Thus, the model was capable of predicting 30-day patient mortality. The Separatrix team of Zabihi *et al.* [99] scored third in the PhysioNet Cardiology Challenge 2019 for sepsis detection. They proposed an XGboost-based ensemble model to predict sepsis and achieved a utility score of 0.339 on hold-out data.

Li *et al.* [100] also used PhysioNet data to make a Time-Phased ML model for sepsis prediction, using LightGBM as a candidate algorithm. Through feature engineering, a total of 312 features were generated out of 40 available clinical variables present in the data, which were used for model training, and achieved the utility score of 0.354 when the model was evaluated on the test data. The Sepsis ReSepsion team

[101] also participated in this challenge and achieved a utility score of 0.076 with their DL-based Convolutional Long Short-Term Memory Neural Network (CNN-LSTM) algorithm.

Although ML-based methods can efficiently and effectively predict sepsis, they can fail to detect sepsis properly. Habib *et al.* [102] reported such incidence in their work. They studied Epic Sepsis Model (ESM) – a tool for sepsis detection based on Electronic Healthcare Record (EHR) data. As per the developers of ESM, it achieved an AUROC of 0.76-0.83. Nevertheless, when the tool was tested, it failed to detect 67% of septic patients and only generated alerts for 18% of patients. Also, the AUROC achieved was only 0.63, which was way too low, as claimed by developers.

Topiwala *et al.* [103] examined the *InSight* tool for identifying sepsis by carrying out a retrospective study and proposed that the tool failed to identify a significant number of positive sepsis cases. Out of 269 sepsis cases, *InSight* generated positive alerts for 77 cases with a sensitivity of 28.6%, of which six alerts were generated prior to clinical suspicion. Moreover, *InSight* generated 126 false positive alerts for Diabetes, Gastrointestinal Bleeding, End-Stage Renal Disease, Hypertension, and Alcoholic Cirrhosis.

However, the EHR data is a time series that doctors or nurses collect and maintain regularly [104]. Furthermore, many studies have proved that DL algorithms can better work with time-series data [105-109]. Many researchers used DL for sepsis detection and proposed various tools. Shashikumar *et al.* [110] proposed a DL-based sepsis detection tool Conformal Multidimensional Prediction of Sepsis Risk (COMPOSER). The primary purpose of this tool is to reduce the number of false alerts for sepsis. Instead of labelling these alerts as final, it marks them as intermediate, thus reducing the false predictions. They trained a DL model based on 515,720 ICU and ED patients from the USA population. Finally, the COMPOSER achieved AUROC of 0.925-0.953 in ICU patients and 0.938-0.945 in ED patients. Moreover, 20% of intermediate alerts were generated for non-septic patients and 8% for septic patients.

Another important DL-based sepsis detection method Deep Artificial Intelligence Sepsis Expert (DeepAISE), was introduced by Shashikumar *et al.* [111]. They used data from two cohorts: the Emory cohort, which incorporates ICU data from two hospitals, and the MIMIC cohort, which has MIMIC-III data. The Emory cohort

data were used for model training, and the MIMIC cohort data was used to evaluate the model performance. DeepAISE is based on Gated Recurrent Units (GRU) and WCPH methods to predict sepsis. In addition, this model can learn the data's temporal patterns and essential features present in the dataset. When tested, DeepAISE achieved an AUROC of 0.90, and it can generate real-time sepsis predictions.

Lauritsen *et al.* [112] proposed a hybrid DL model (Figure. 13) based on CNN-LSTM for sepsis detection and classification. The study is based on 3126 patients' data from the Danish population. The input data goes to five convolutional layers in the model architecture and is processed within. Lastly, the output goes to the LSTM layer that outputs the final prediction for sepsis. The model evaluation shows that it achieved the AUROC of 0.856 and 0.756 three hours and 24 hours before the onset of sepsis. Furthermore, this model outperformed gradient-boosting algorithms for sepsis prediction, as it can efficiently work with time-series data.

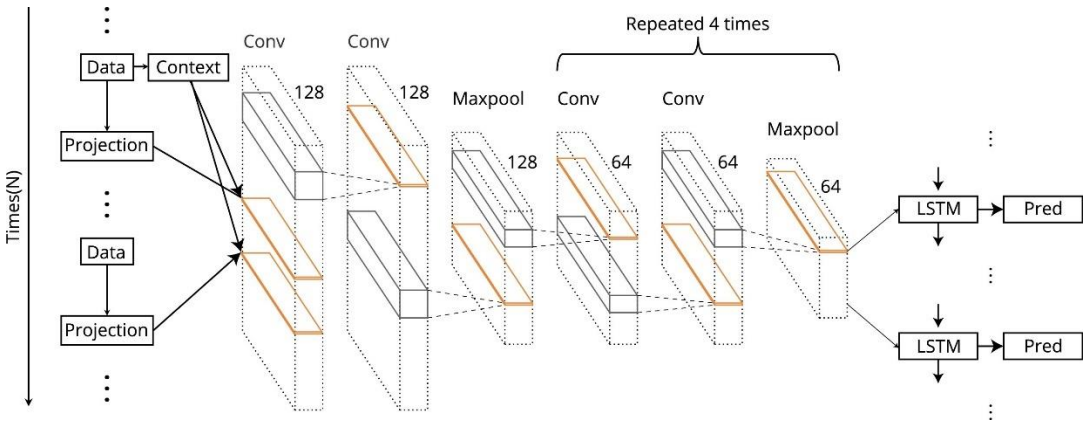



*Figure 13: A hybrid CNN-LSTM model architecture for sepsis prediction [112]*

Another similar LSTM-CNN hybrid model approach for sepsis detection was used by Rafiei *et al.* [113], who proposed Smart Sepsis Predictor (SSP), which is an early sepsis prediction tool (Figure. 14). The study is based on the PhysioNet Cardiology Challenge 2019 data. SSP hosts two modes. Mode 1 works by using vital signs along with patients' demographics, and mode 2 includes laboratory tests alongside vital signs and demographics. After processing the data per the inclusion criteria, data is fed to the Deep Network block. Inside this block are the LSTM and Convolutional Neural Networks (CNN) model layers alongside dense layers. The data goes through the layers, and the final probabilities are calculated. Finally, sepsis probability is calculated based on the pre-defined probability threshold. To evaluate the

model, AUROC was calculated for each mode. The SSP achieved 0.89 AUROC for mode 1 and 0.92 for mode two, four hours before sepsis onset.

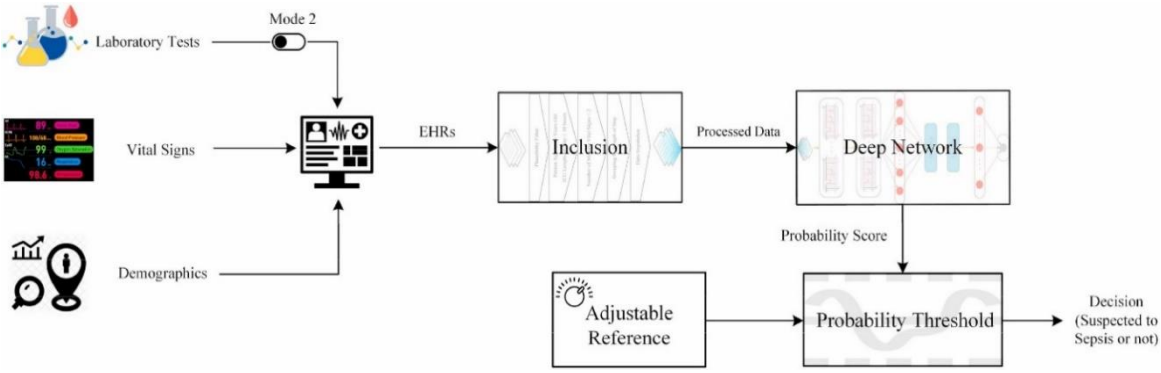



*Figure 14: Structure of Smart Sepsis Predictor (SSP) tool [113]*

Henry *et al.* [114] developed a Targeted Real-time Early Warning Score (TREWScore) system for septic shock prediction, which predicted septic shock patients with an AUROC of 0.83 before septic shock onset. Fagerström *et al.* [88] proposed a LiSep LSTM septic shock prediction tool based on the LSTM model. The study is based on the MIMIC-III data and incorporates vital signs and lab values as model-building features. The model achieved the AUROC of 0.8306 (Figure. 15) and can outperform other models like *InSight* and TREWScore with high confidence intervals.

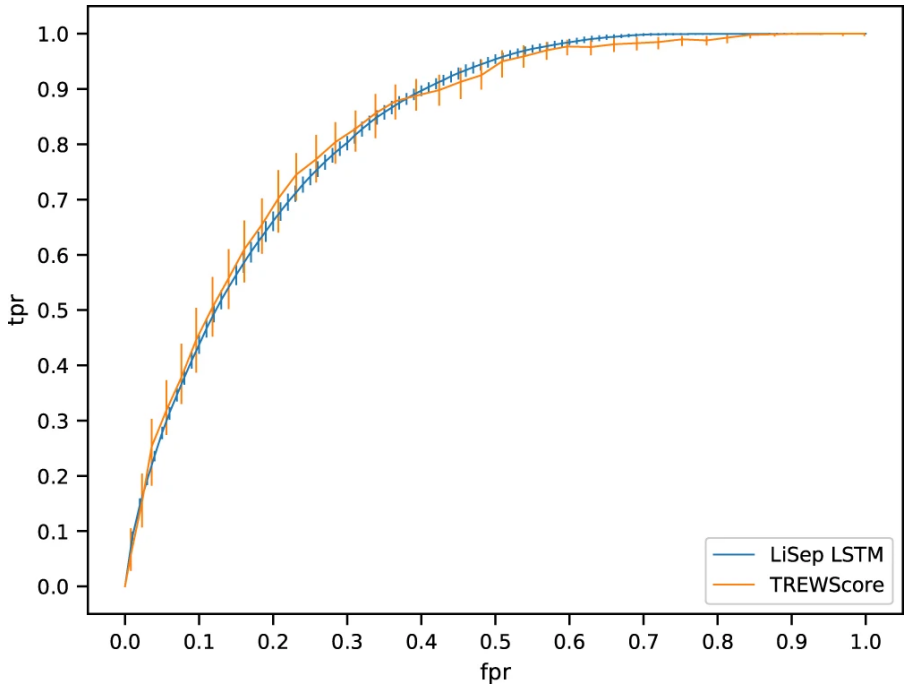



*Figure 15: AUROC of LiSep LSTM and TREWScore [88]*

# Methodology

This study aims to find an optimal way to forecast sepsis and its risk using DL, eventually helping doctors and health care specialists control mortality and ICULOS. The overall methodology followed in this research project to achieve this goal is provided in figure 16.

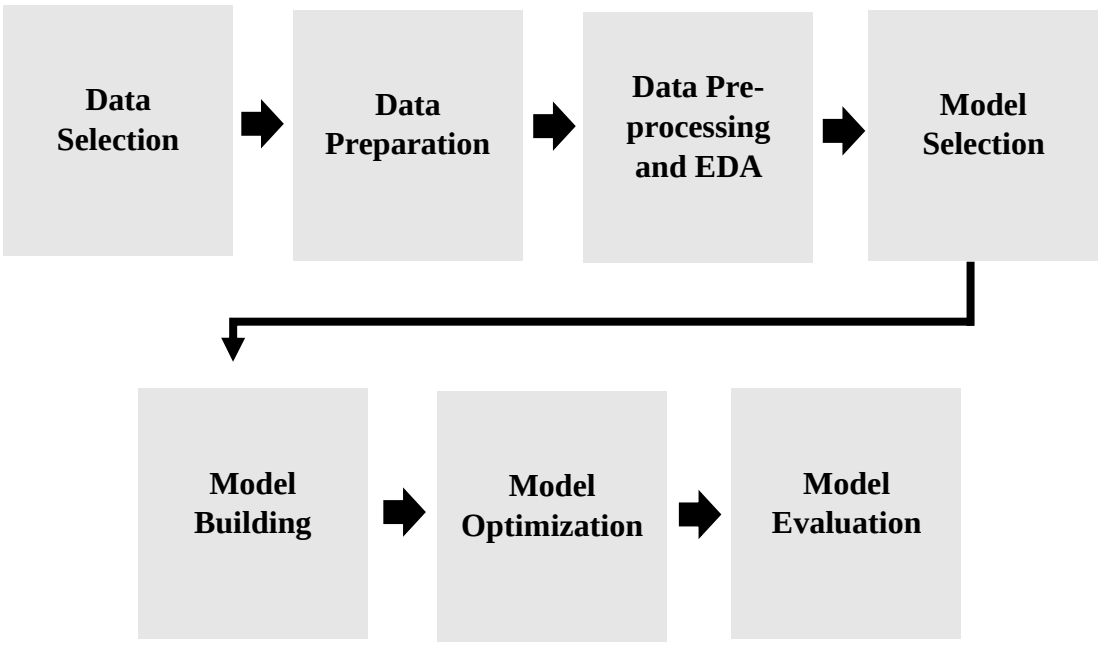



*Figure 16: Overall methodology followed in this research project*

## 3.1. Data Collection

The data is collected from the PhysioNet Challenge 2019 [115], consisting of ICU patients from two US hospitals. The data of hospital A contains 20,336 patients, and the data of hospital B includes 20,000 patients. Each patient file is a pipe-separated value (PSV) file with ".psv extension" and consists of 41 variables: eight vital signs, 26 laboratory values, six demographics, and one outcome variable (Table 4). The outcome variable is "SepsisLabel", in which "0" indicates "no sepsis" and "1" means "sepsis". Variable values having NaN indicate no measurement was taken for the corresponding variable at that time interval.

*Table 4: Data description*

| | |
|---|---|
| **Vital Signs** | |
| HR | Heart rate (bpm) |
| $O_2$Sat | Oxygen Saturation (%) |
| Temp | Temperature (°C) |
| SBP | Systolic blood pressure (mmHg) |
| MAP | Mean arterial pressure (mmHg) |
| DBP | Diastolic Blood Pressure (mmHg) |
| Resp | Respiration rate (breaths per minute) |
| EtCO2 | End-tidal carbon dioxide (mmHg) |
| **Laboratory Values** | |
| BaseExcess | The measure of excess bicarbonate (mmol/L) |
| HCO3 | Bicarbonate (mmol/L) |
| FiO2 | Fraction of inspired oxygen (%) |
| pH | N/A |
| PaCO2 | The partial pressure of carbon dioxide from arterial blood (mmHg) |
| SaO2 | Oxygen Saturation in arterial blood (%) |
| AST | Aspartate transaminase (IU/L) |
| BUN | Blood urea nitrogen (mg/dL) |
| Alkalinephos | Alkaline phosphate (IU/L) |
| Calcium | mg/dL |
| Chloride | mmol/L |
| Creatinine | mg/dL |
| Bilirubin_direct | mg/dL |
| Glucose | Serum glucose (mg/dL) |
| Lactate | Lactic acid (mg/dL) |
| Magnesium | mmol/L |
| Phosphate | mg/dL |
| Potassium | mmol/L |
| Bilirubin_total | mg/dL |
| TroponinI | Troponin I (ng/mL) |

| | |
|---|---|
| Hct | Hematocrit (%) |
| Hgb | Haemoglobin (g/dL) |
| PTT | Partial thromboplastin time (seconds) |
| WBC | White blood cell count (count*10^3/µL) |
| Fibrinogen | mg/dL |
| Platelets | count*10^3/µL |
| **Demographics** | |
| Age | In years |
| Gender | Male (1) and Female (0) |
| Unit1 | Medical ICU |
| Unit2 | Surgical ICU |
| HospAdmTime | Hours between hospital admission and ICU admission |
| ICULOS | Hours since ICU admission |
| **Outcome** | |
| SepsisLabel | Sepsis patients (1) and non-sepsis patients (0) |

## 3.2. Data Preparation

As the data from two different hospitals is in the form of individual patient files (.psv files), it must be combined into a single file for the research. Each PSV file is converted to a single comma-separated value (CSV) file using the Python language "glob" function [116] and "for loop" [117]. Also, each patient is assigned a unique Patient ID (P_ID) during the process. The CSV file format is preferred because it is the most commonly used and user-friendly [118, 119].

## 3.3. Python libraries

Instead of writing the code from scratch, built-in Python libraries are used to conduct the research. Following are some essential libraries used in this study:

- OS [120]: This module allows dealing with directories.
- Random [120]: This module allows the creation of random numbers.
- Pandas [121]: This library is used for data analysis and manipulation.
- NumPy [122]: This library allows one to work with arrays.

- Seaborn [123]: Data visualisation library that allows the creation of beautiful graphs.
- Matplotlib [124]: This library creates static plots and graphs.
- Tqdm [125]: This library allows the creation of progress bars.
- Sklearn [126]: An ML library for classification, regression, and clustering algorithms.
- MissForest [127]: This is an ML-based missing value imputation method.
- itertools [128]: This library allows permutations and combinations.
- TensorFlow [129]: An open-source platform for building ML models.
- Keras [130]: This library allows for the training and develop DL models and is built on top of TensorFlow.

## 3.4. Data Pre-processing and Exploratory Data Analysis (EDA)

The most crucial phase of an ML-based study is how the data is pre-processed [131] because well pre-processed and cleaned data ensures the desired output of an ML or DL model. Also, EDA analysis was performed on the data to check for patterns and missing values using plots and graphs. Below are some of the steps performed in this study for data pre-processing and EDA.

### 3.4.1. Dealing with Missing values

A data frame is created after importing required packages and libraries [132]. After creating a data frame, the first step is checking for missing values (NaN values) inside the data. If NaN values present in the data are deleted, there is a risk of losing critical information, and if the ML (or DL) model is trained, the algorithm might fail, and we might end up with a biased model that will provide invalid output and low accuracy [133]. Therefore, the percentage of missing values in the data was calculated and then visualised by making plots enabling a quick overview of the NaN values present in the data and allowing us to impute them.

### 3.4.2. Correlation Analysis

Not all the variables present in the data are used in model building. Some variables are more important than others. Correlation analysis is used to check the relatedness of variables with each other, and it helps avoid multicollinearity problems and helps in the feature selection process. The correlation of the variables was

calculated using the Python “corr” function and then visualised using a seaborn heatmap [134].

### 3.4.3. Feature Selection

The feature selection process is one of the most critical steps of an ML-based study. It helps remove irrelevant variables from the data and helps minimise the computational time and resources during model training [135]. Important features were selected based on the correlation heatmap, and the variables having a NaN value percentage of more than 70% were removed from the data.

### 3.4.4. Outlier Detection

One of the primary steps of data pre-processing involves outlier detection and removal. Outliers are the measurement of variables that deviates from other observations of the same variable, raising uncertainty [136] and can affect model accuracy and performance. Boxplots [137] are one of the outlier detection methods used in data pre-processing. They help to check for any ambiguity in the variable observations. In this study, the feature range (Table 5) provided by Fagerström *et al.* [88] was used for outlier detection, and the data were plotted using the seaborn “boxplot” function.

*Table 5: Feature range for outlier detection*

| Feature | Range (min-max) |
|---|---|
| HR | 1 - 320 |
| $O_2Sat$ | 1 - 100 |
| SBP | 1 - 400 |
| DBP | 1 - 300 |
| Resp | 1 - 150 |
| Age | 15 - 90 |

### 3.4.5. Age Analysis

The definition of sepsis varies for adults and children [138]. To check if the age of patients in the data is more or less as provided in the feature range, age analysis was

performed using Python “min” and “max” functions. Patient count age-wise and age category-wise was visualised using a pandas bar plot [139]. Also, gender analysis was performed by plotting the gender count of male and female patients and septic and non-septic patient count gender-wise, respectively.

### 3.4.6. ICULOS Analysis

Patients whose ICULOS was not starting from 1$^{st}$ hour were removed from the data as they were considered ambiguous. Any effort to impute the first-hour observations of those particular patients was considered data corruption. Next, the patient ICULOS count was plotted, and those patients whose total ICULOS count was less than eight hours and more than 72 hours were removed from the data. Finally, the remaining patient data was used for model building.

### 3.4.7. Patient Separation

Imputation of septic and non-septic patient data separately is more meaningful than imputing the actual data. Therefore, the entire septic and non-septic patient count was calculated, and based on the total number of septic patients, the same number of non-septic patients were randomly selected. The data was then stored in separate data frames for imputation.

### 3.4.8. Data Imputation

Data imputation is crucial while pre-processing the data because NaN values in the data affect the model training and performance. For imputing the NaN values in the data, two methods were used in this study:

- MissForest Imputation
- Forward Fill and Zero (FFILL-0) Imputation

#### *3.4.8.1. MissForest Imputation*

MissForest is a Random Forest (RF) based method for data imputation. Initially, the algorithm imputes the NaN values based on the mean of the data variables; then, it imputes the NaN using the RF model on the data columns. It first imputes NaN in the column with the least missing values and then moves to the column with the second least number of missing values. The process continues until it meets the stopping criteria and all the NaN values in the data are imputed [140]. In this study, MissForest imputation was carried out on septic and non-septic patients separately with the following parameters:

- max_iters: 12
- n_jobs: -1
- criterion: squared_error

*3.4.8.2. FFILL-0 Imputation*

Another method of NaN values imputation used in this study is FFILL-0 imputation. In this technique, missing values are imputed using the value previous to the NaN value. This process is carried out using Python's “ffill” function. This method is known as the Last Observation Carried Forward (LOCF) and is widely used for time-series EHR data [141]. All the remaining missing values are imputed using “zero”.

### 3.4.9. Train-Validation Data Split

After data imputation through MissForest and FFILL-0, septic and non-septic patient data were concatenated, and patients were shuffled. The shuffling was done so that the septic and non-septic patients could distribute randomly in the data. Two separate files were generated: one file had MissForest imputed septic and non-septic patients, while the second file had FFILL-0 imputed patients. Afterwards, the data were split into an 80-20 ratio (80% patients for training and 20% for validation). This process was done for both imputed files.

### 3.4.10. Creating multi-index data frame and Tensors

Another crucial step in this study is the creation of multi-index data frames (data frames with more than one index). This method aims to create a fixed-length tensor or array used for model training, which is achieved by padding each patient record with zeros. It ensures that each patient record has a fixed length and becomes a fixed-length tensor. These tensors are stored in NumPy arrays (.npy extension). The criteria used for padding are given below:

- maxlen: 72
- dtype: float32
- padding: post
- truncating: post

## 3.5. Model building and optimisation

The foremost step of an ML-based study is model building and optimisation. The choice of an ML algorithm for building the model depends on the data. Since this

research project's data is time-series, using traditional ML algorithms would be a poor approach because they might fail for sepsis detection [102]. To avoid dire outcomes, the approach used in this study focused on DL algorithms like Recurrent Neural Networks (RNN) because they can easily handle time-series data and thus can help forecast sepsis risk.

### 3.5.1. Selected Algorithms

Following DL algorithms were selected for this study:

- Long Short-Term Memory (LSTM) Networks
- Gated Recurrent Units (GRU) Networks

Figure 17 shows the LSTM and GRU model architecture used in this study.

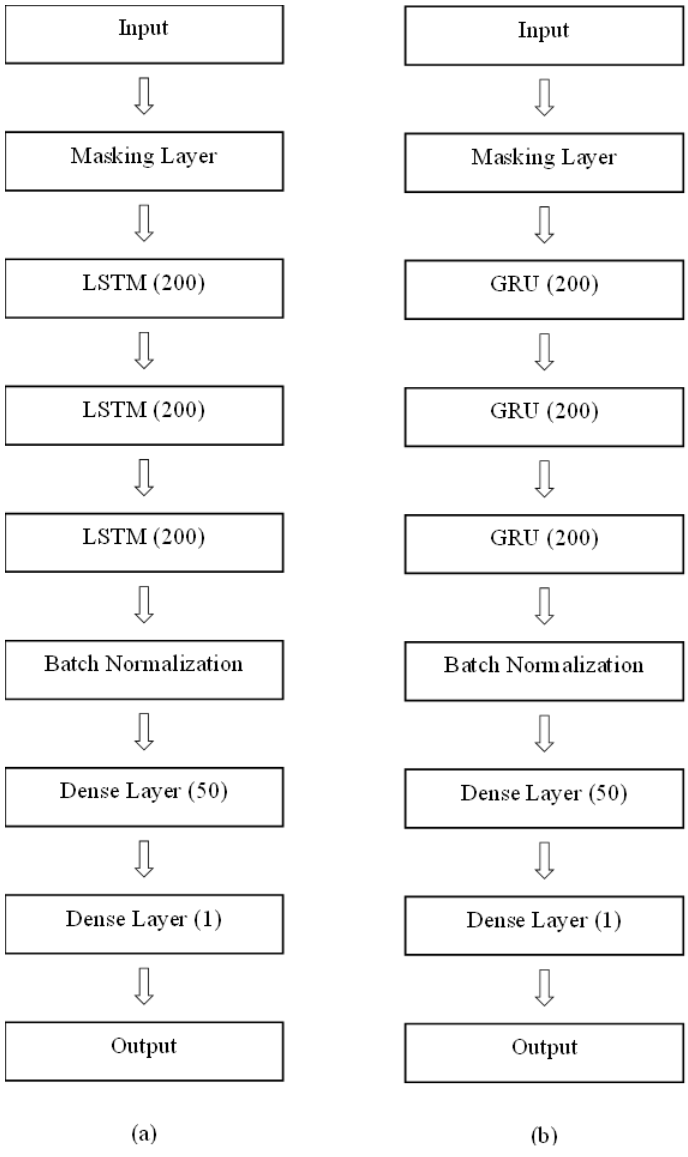



*Figure 17: The proposed architecture of (a) LSTM and (b) GRU networks used in this research project.*

*3.5.1.1. LSTM Networks*

One of the most broadly used RNNs is an LSTM network. Figure 18 (a) shows a simple LSTM network architecture. It has one input, one hidden, and one output gate. As a result, they can learn long-term dependencies and solve problems like Vanishing and Exploding gradients confronted in RNN [142].

*3.5.1.2. GRU Networks*

GRU is another widely used RNN type. It is also capable of solving vanishing and exploding gradient problems. However, the difference lies in the number of gates. In LSTM, there are three gates, while in GRU, there are two gates: update and reset. Figure 18 (b) shows a simple GRU network architecture

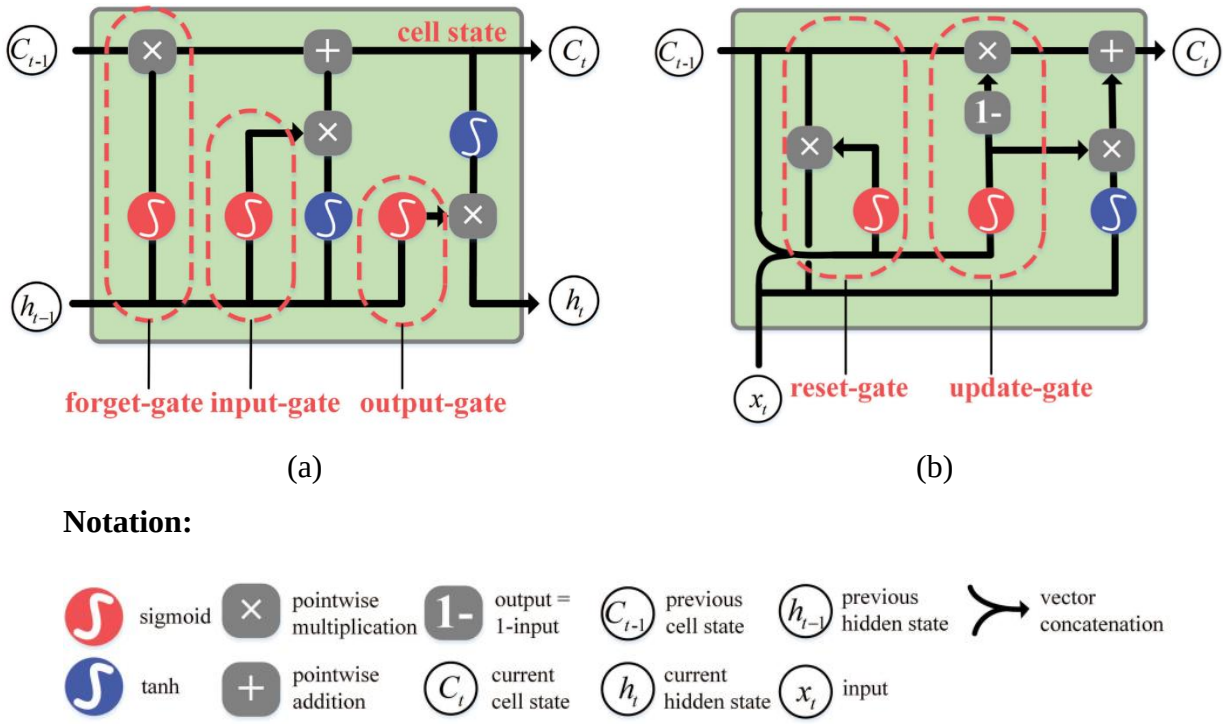



*Figure 18: A simple architecture of (a) LSTM and (b) GRU networks [143]*

### 3.5.2. Model Architecture Decisions

Keras Functional API is used for this study to build stacked LSTM and GRU models instead of Sequential API as it provides more flexibility [129]. The model architecture is the same for LSTM and GRU; however, the only difference lies in the layers. One model used LSTM layers, and the other used GRU layers.

*3.5.2.1. Masking layer*

Since the data is processed by padding to make it a fixed-length tensor, the masking layer is added after the input layer. Therefore, it will force the model to ignore the padding, and the model will drop those time steps where all the feature's value is equal to the value assigned in the masking layer.

*3.5.2.2. LSTM / GRU layer*

For this study, the following parameters are used to build LSTM and GRU models:

- layers: Three layers
- units: 200 units in each layer
- dropout: 0.20
- recurrent_dropout: 0.1
- return_sequences: True
- implementation: 2

*3.5.2.3. Output layer*

The output layer has a dense layer wrapped in a TimeDistributed wrapper. The parameters are:

- units: 1
- activation: sigmoid

*3.5.2.4. Model Compilation*

After adding all the layers, the last step in building the model is to compile it. The following parameters are used in the model compilation step:

- optimizer: RMSprop
- learning_rate: 0.001
- loss: binary_crossentropy

*3.5.2.5. Model Training*

After completing all the model-building steps, the model was trained using the Keras "fit" API. Following are the parameters used for model training:

- x: train data (fixed-length tensor)
- y: test data (fixed-length tensor)

- sample_weight: 1-D array of ones
- batch_size: 128
- epochs: 500
- verbose: 1

## 3.6. Model Evaluation

After building and training the model, the final step of the analysis is to check its effectiveness in forecasting the sepsis risk by using the hold-out (or validation) dataset. The Keras “predict” API evaluated the model on the validation dataset. The results were visualised using the Matplotlib “pcolor” function [144], which creates a heat map-like plot of the prediction array. The mortality risk was visualised in the form of a Python line plot. Finally, the model is evaluated by calculating AUROC (Area under the Receiver Operating Characteristics Curve).

# Results

## 4.1. Data collection and preparation

The data was collected from PhysioNet, and each patient file in PSV format was converted to a single CSV file with both hospital patients (40336 patients). The “glob” function reads the path and retrieves all files matching the file pattern mentioned in the glob, and the “for loop” iterate over each file, reads it, assigns the patient ID, and appends it to a data frame. This data frame is then saved to the CSV using the Pandas “to_csv” function.

## 4.2. Data Pre-processing and EDA

Data pre-processing is a necessary step in ML-based study. Below are the results of the data pre-processing and EDA performed in the study.

### 4.2.1. Missing (NaN) values

NaN value analysis was performed to check for missing data. Missing values were calculated in the data frame and plotted using the Matplotlib bar plot. Figure 19 shows the bar plot of the NaN values percentage present in the dataset. The x-axis shows the variables, and the y-axis shows the percentage. The variable names are present as legends on the upper left. NaN values were also plotted as a heatmap (Figure. 20). The khaki colour represents the NaN values, and the green-cyan colour represents the non-missing values.

### 4.2.2. Correlation analysis

Correlation analysis was performed to check the relationship of the variables, and the correlation matrix was plotted using a seaborn heatmap (Figure. 21). Most variables have negligible to weak positive and negative correlations. Also, some of the variables have a strong positive and negative correlation.

### 4.2.3. Feature Selection

Key features were selected based on the correlation heatmap and NaN value percentage threshold of 70%. Out of all the variables, six vital signs, three demographics, and one outcome variable were considered the best features for this analysis and these features are used for model building. Table 6 shows the selected features.

*Table 6: The finalised set of features chosen for model building*

| Feature No. | Type | Features |
|---|---|---|
| 1 | Vital Sign | HR |
| 2 | | $O_2$Sat |
| 3 | | Temp |
| 4 | | SBP |
| 5 | | DBP |
| 6 | | Resp |
| 7 | Demographics | Age |
| 8 | | Gender |
| 9 | | ICULOS |
| 10 | Outcome | SepsisLabel |

### 4.2.4. Outlier detection and removal

Data was plotted as a boxplot to check for outliers, and abnormal values were removed based on the feature range. Figure 22 shows the boxplot used for outlier detection in this study. All the variables were within the feature range except the age, which was then processed further.

### 4.2.5. Age and Gender Analysis

Patient count based on age was plotted as a bar plot to check how many patients share the same age (Figure. 23). Also, a bar plot was plotted for patient count age category-wise (Figure. 24). Since the minimum age range is 15 and the maximum is 90, all those patients whose age was less than 15 years and more than 90 years were removed from the data. Moreover, patient counts were plotted based on gender (Figure. 25), and septic and non-septic patient counts were also plotted based on gender (Figure. 26). After removing the patients based on age conditions, the following is the patient count:

- Original patient count in the dataset: 40336
- Patient count after applying age conditions: 39942

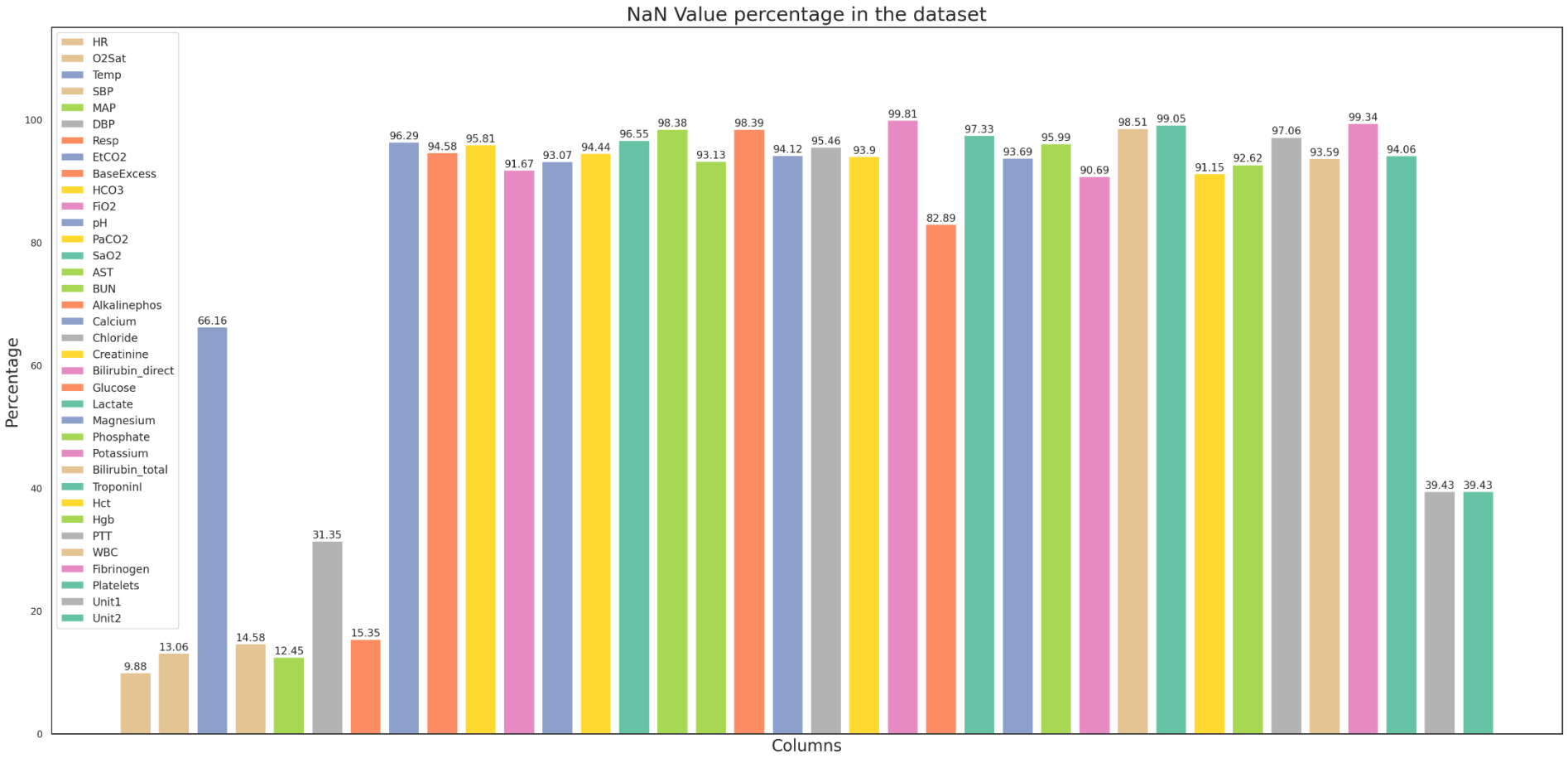



*Figure 19: Percentage of NaN values in the dataset*

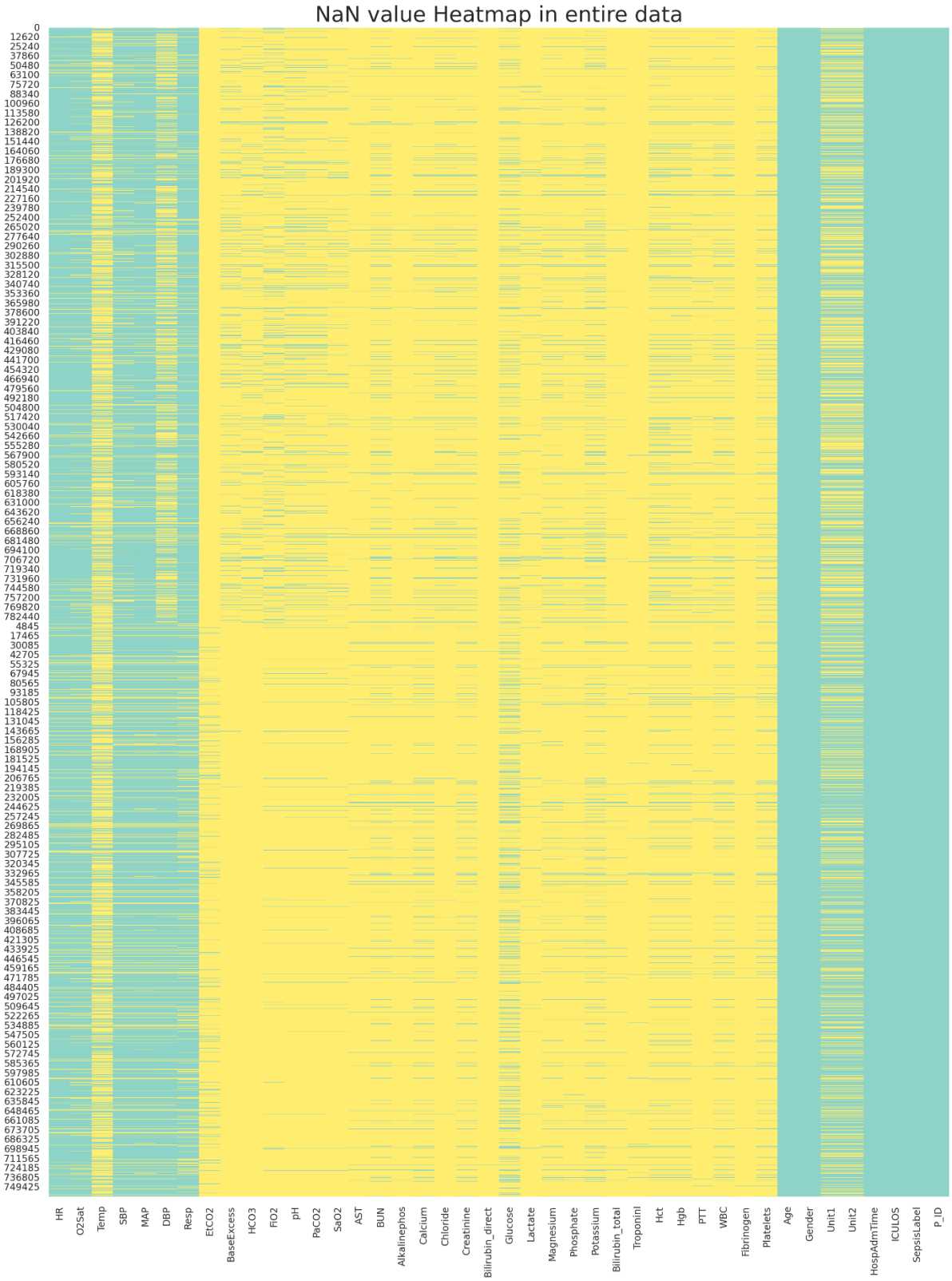



*Figure 20: Missing value heatmap of the dataset*

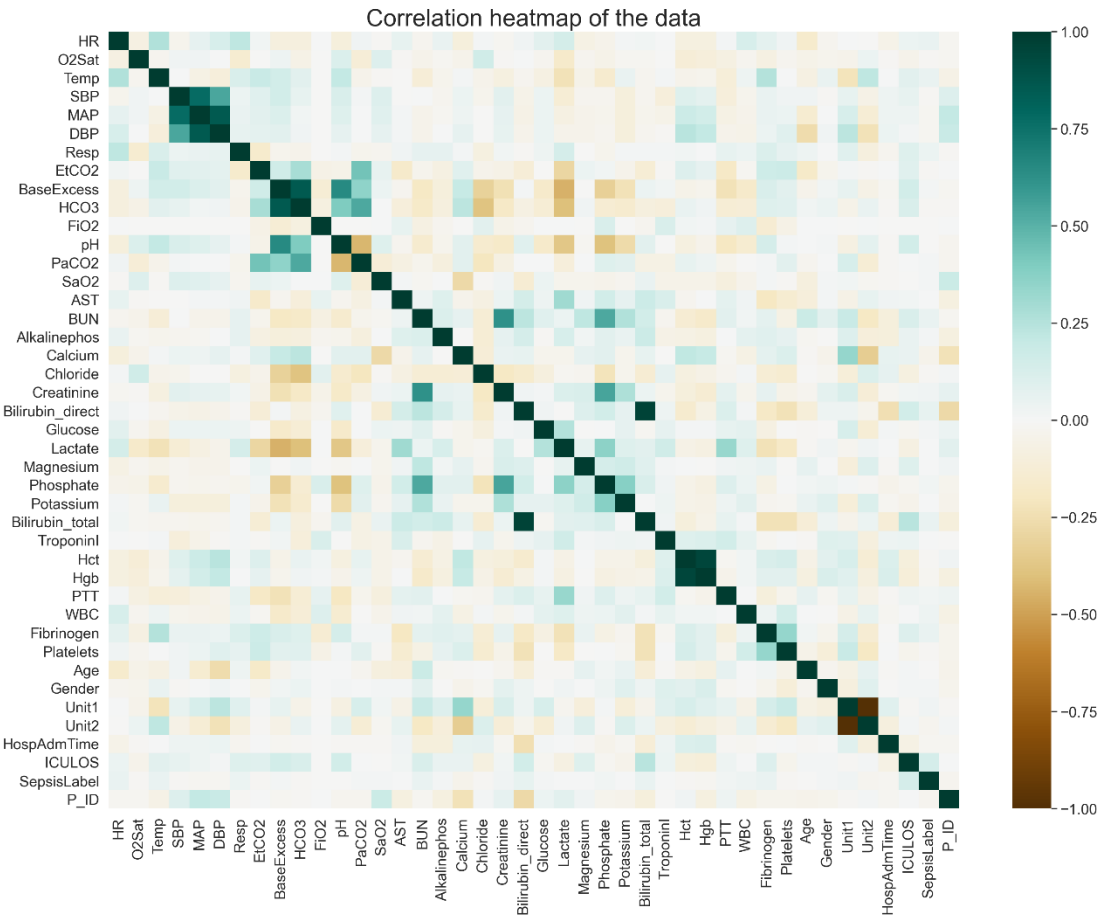



*Figure 21: Correlation heatmap of the dataset*

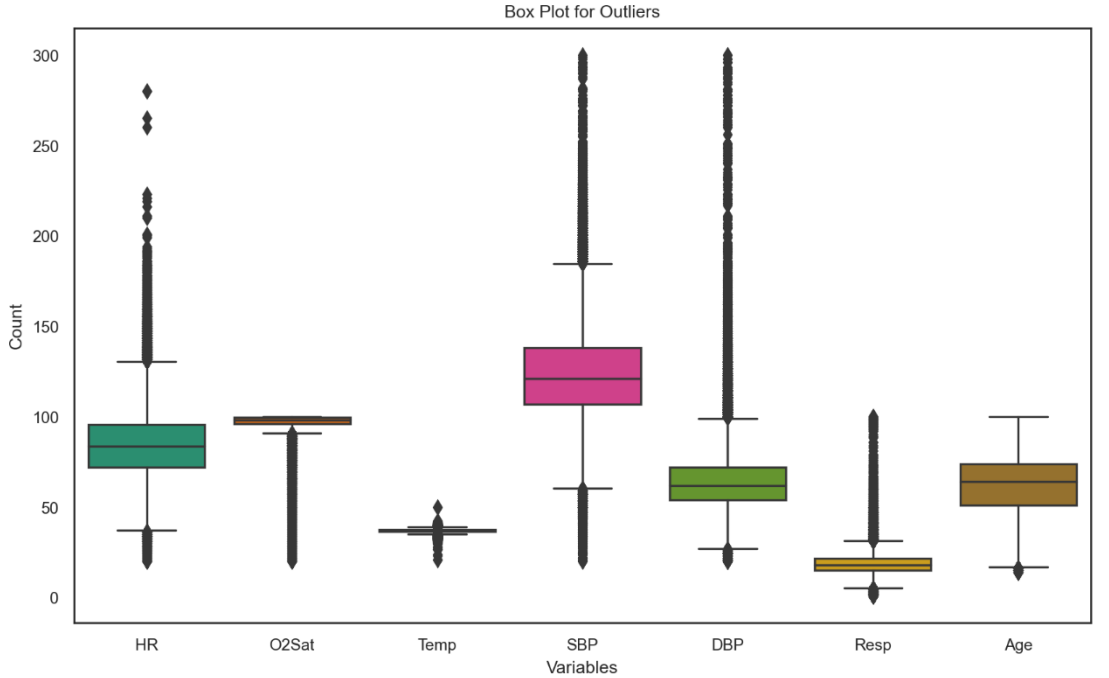



*Figure 22: Boxplot for outlier detection*

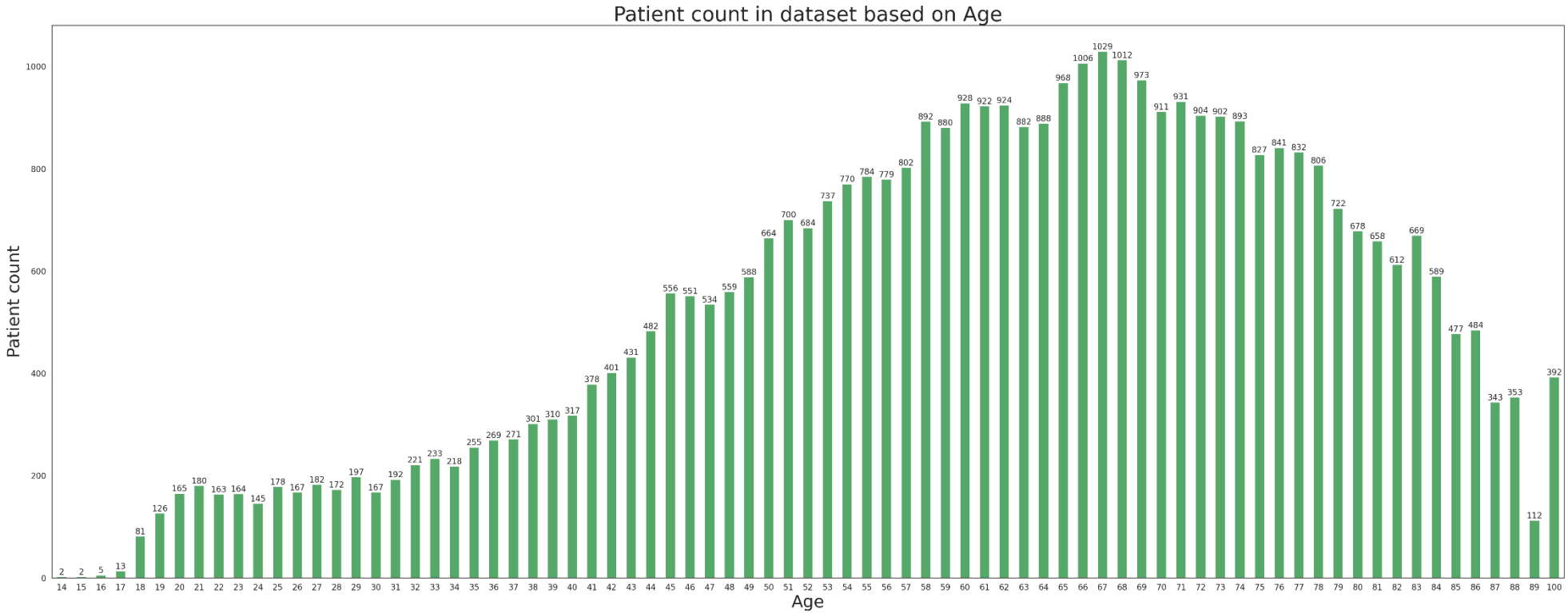



*Figure 23: Patient count Age-wise in the dataset*

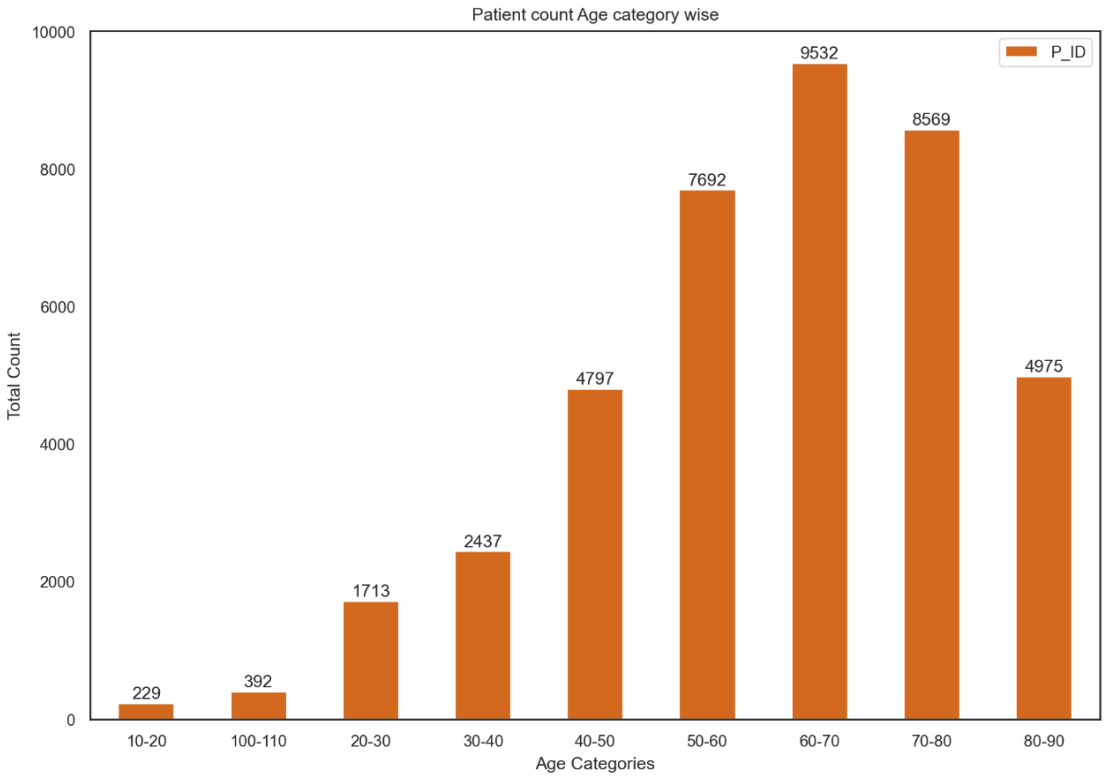



*Figure 24: Patient count in the dataset Age-category-wise*

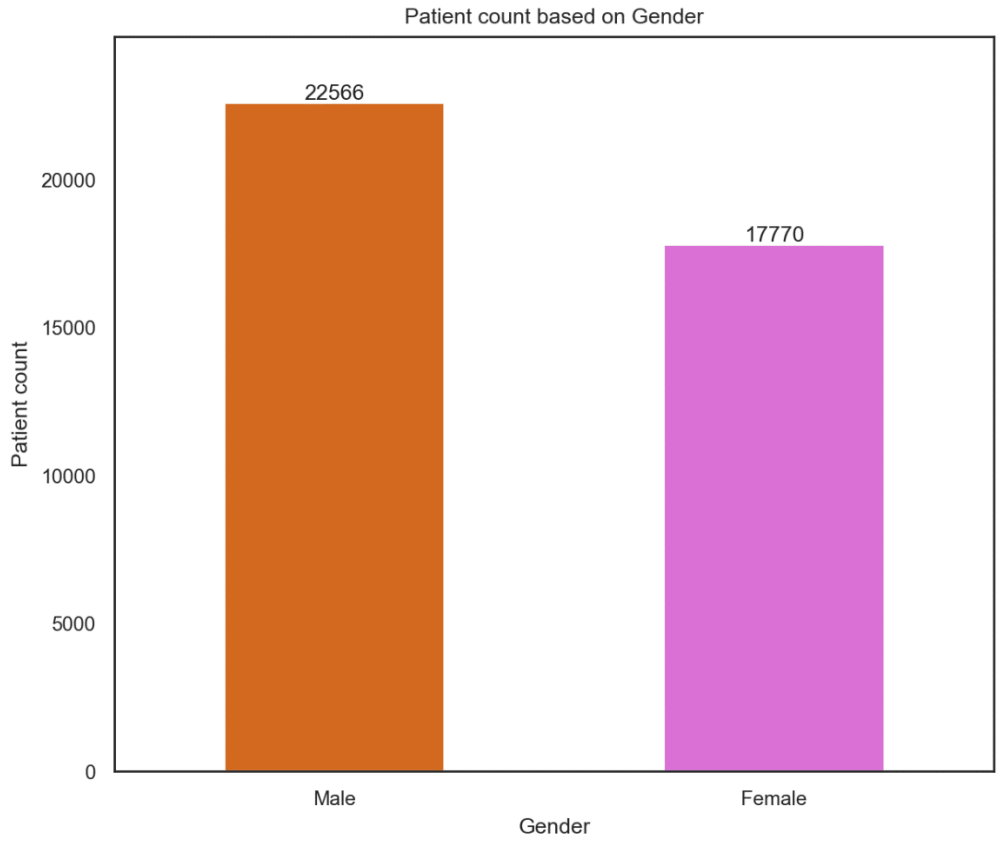



*Figure 25: Patient count based on gender in the dataset*

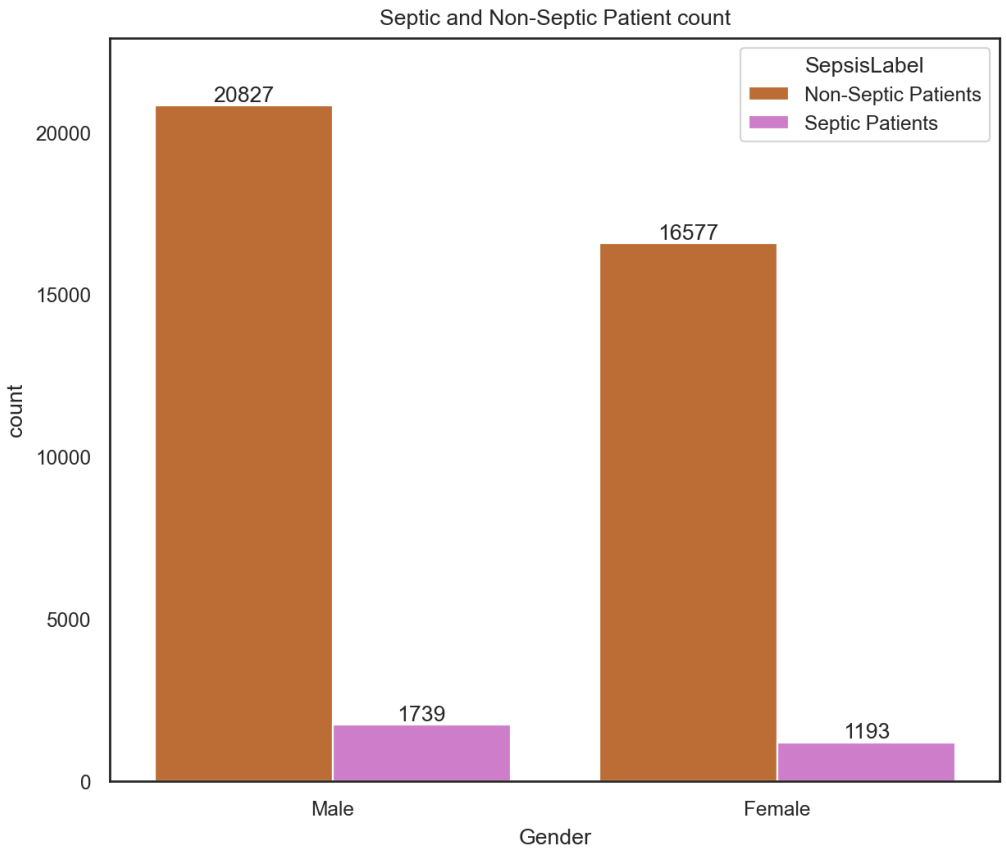



*Figure 26: Septic and Non-septic patient count based on Gender*

### 4.2.6. ICULOS Analysis

ICULOS is a crucial factor in the dataset and was focused on because it represents the number of hours since ICU patient admission. The more the ICULOS of a patient is, the higher burden it puts on hospitals. In this study, those patients with ICULOS not starting from one were removed. Following is the patient count before and after the first ICULOS condition:

- Before first ICULOS condition: 39942
- After first ICULOS condition: 31162

Following this, a second ICULOS condition was applied. ICULOS count was calculated for each patient and stored in a separate column in the data frame. Patients with an ICULOS count of less than eight and more than 72 were removed. Following is the patient count before and after applying the second condition:

- Before the second condition: 31162
- After the second condition: 30361

Moreover, the final patient count was visualised as a bar plot (Figure. 27).

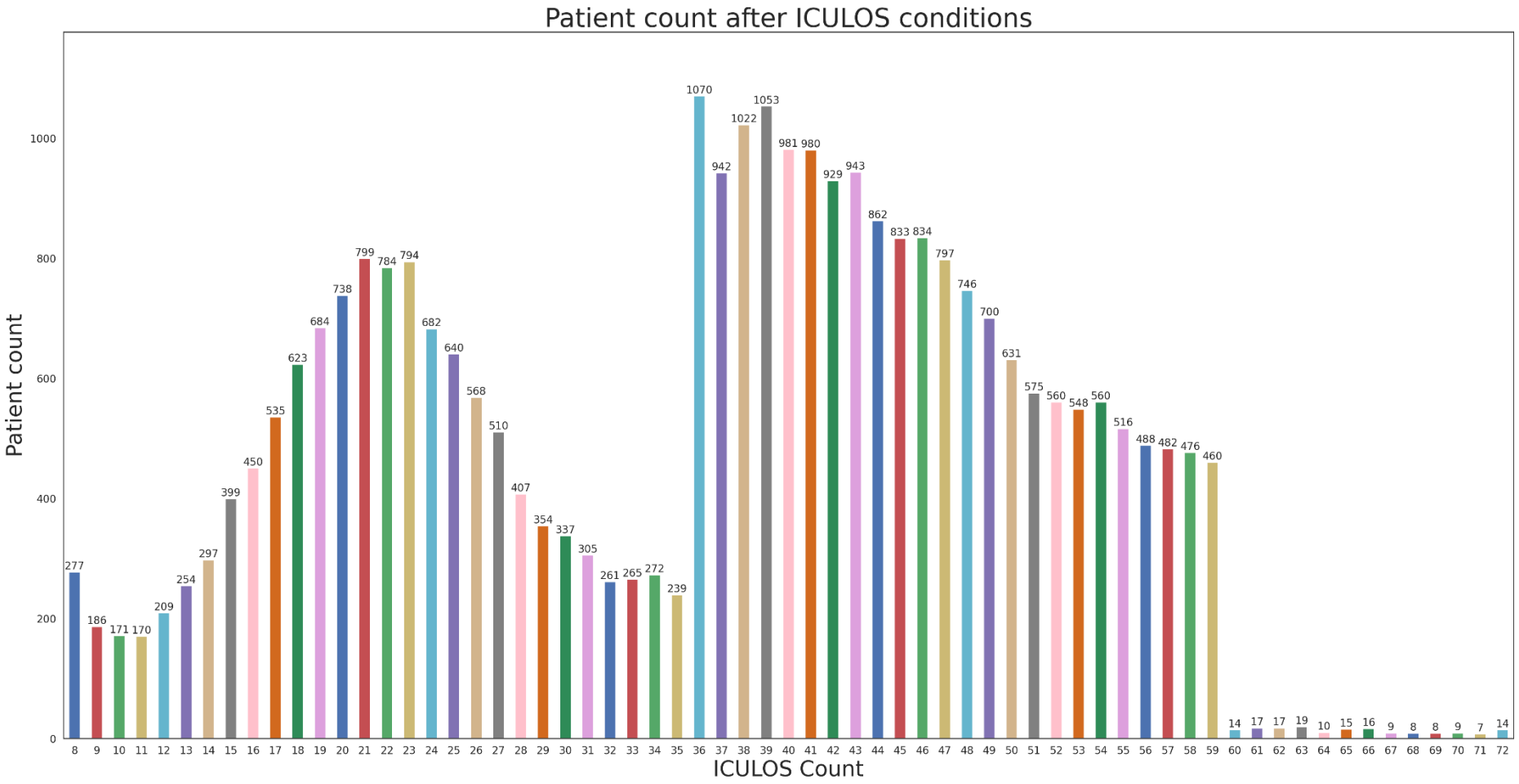



*Figure 27: Patient count after ICULOS conditions*

### 4.2.7. Septic and non-septic patient separation

For imputing missing values in the data, septic and non-septic patients were separated. First, the septic and the non-septic patient count were plotted as a bar chart (Figure. 28). Then, based on the total septic patients, non-septic patients were down-sampled, and the same number of non-septic patients were randomly selected. Also, gender-based septic and non-septic patient count were plotted (Figure. 29). Following is the septic and non-septic patient count:

- Total number of septic patients: 1614
- Number of non-septic patients before down sampling: 28747
- Non-septic patient count after random down-sampling: 1614

Patient data was then stored in separate CSV files so they could be imputed.

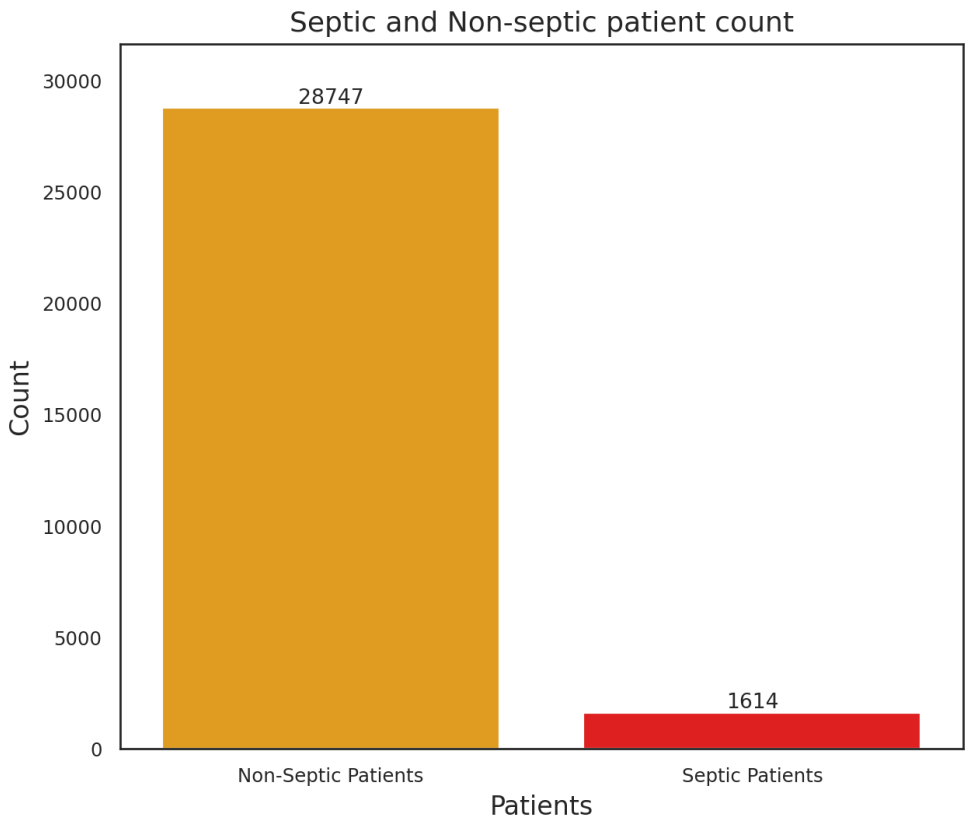



*Figure 28: Septic and non-septic patient count in the final dataset*

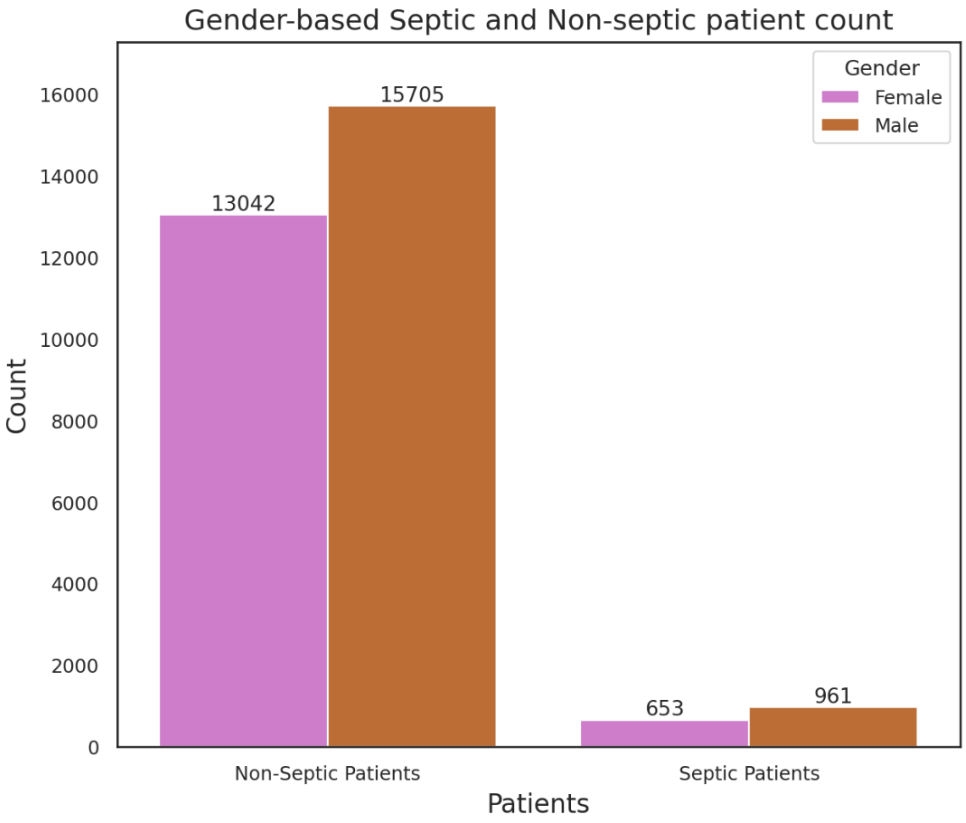



*Figure 29: Gender-based Septic and Non-septic patient count in the final dataset*

### 4.2.8. Missing data imputation

Missing values present in the septic and non-septic patients were imputed separately using the MissForest algorithm and FFILL-0 imputation.

#### *4.2.8.1. NaN imputation through MissForest*

The MissForest algorithm was implemented using the Python "fit_transform" function. This function fits the MissForest imputer on the data frame. After completion, the output was an array, which was then converted to a data frame. The variable values were rounded off like original values using Python "round" function, and the data types of some variables, which were converted to "float", were changed back to "int" using Python "astype" function. Finally, the data frame was then saved as a CSV file.

#### *4.2.8.2. NaN imputation through FFILL-0 method*

Figure 30 illustrates the visual representation of the FFILL-0 method. In this method, the imputation was done for each patient separately using the Python "groupby" function based on the P_ID column. NaN values were then imputed using

Python “ffill” function, and the remaining NaN values were imputed with zero using Python “fillna” function. Finally, the data was saved as a CSV file.

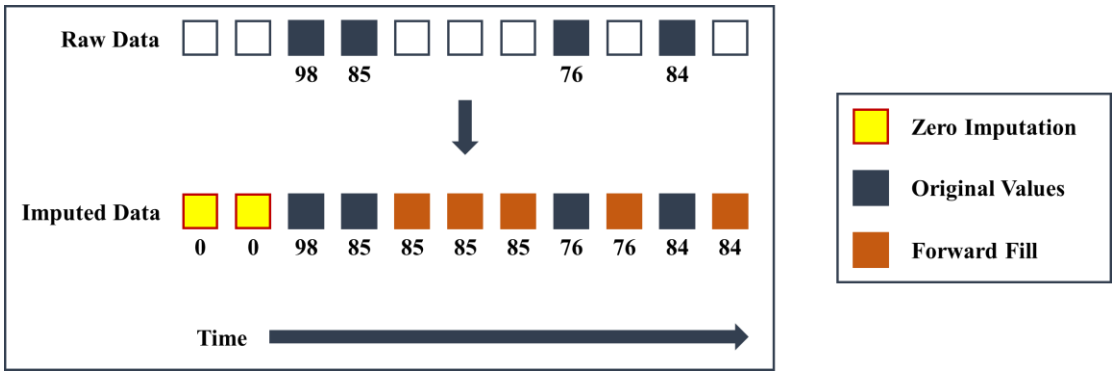



*Figure 30: Visual representation of working of FFILL-0 imputation method*

### 4.2.9. Data Splitting

For model training, the patient data was split into an 80-20 ratio. Of the total 3228 patients’ data, 80% was used in model training, and 20% was reserved for model validation as hold-out data. They were further split into “x” and “y” training and validation datasets.

### 4.2.10. Multi-indexing and padding

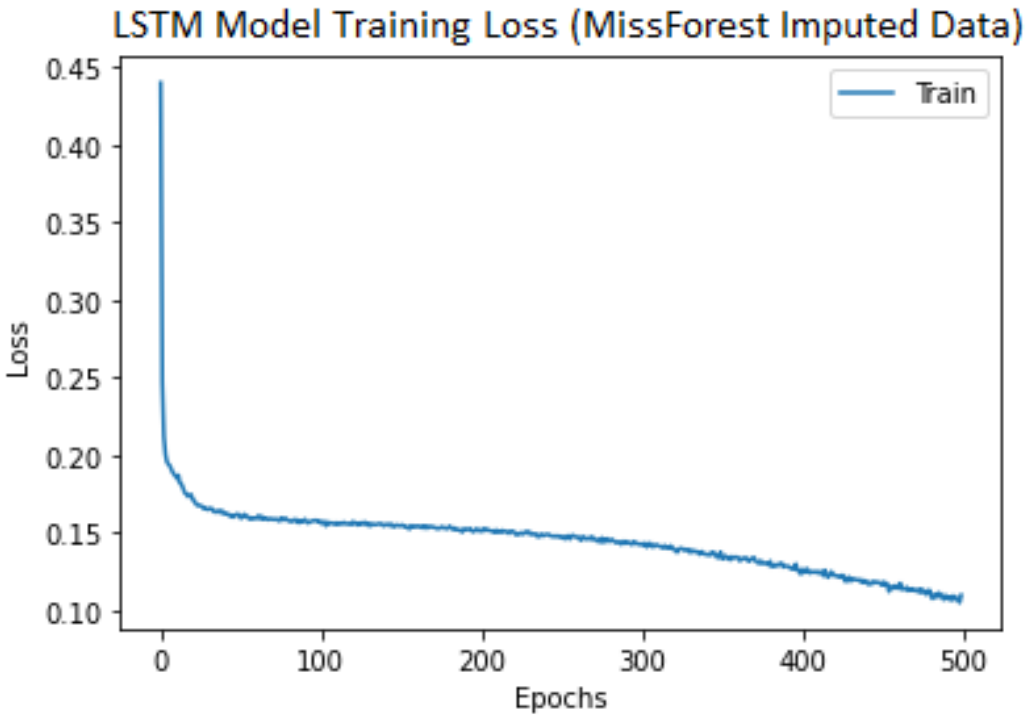
After data splitting, the training and validation datasets were converted to multi-index data frames. Then the files were converted to tensors and saved as arrays. These fixed-length tensors were then used for model training and validation.

## 4.3. Model training and evaluation

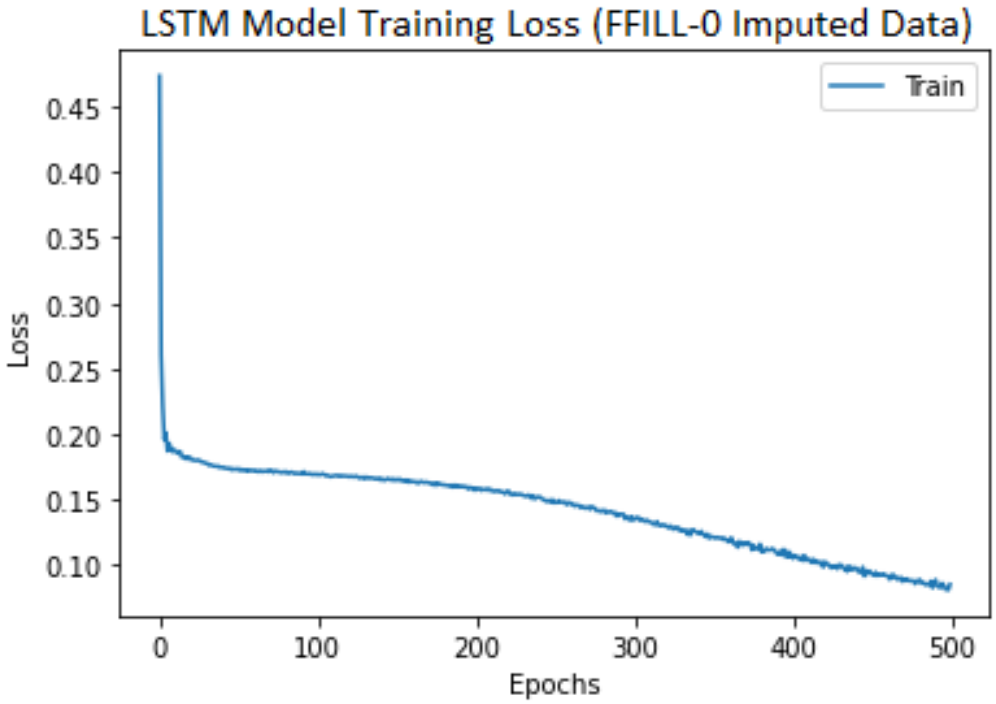
This study trained LSTM and GRU models on MissForest and FFILL-0 imputed data. Thus, a total of four models were trained for 500 epochs each. The model architecture used three LSTM and GRU layers with 200 units each. The batch size of 128 means the parameters are updated every 128 time-steps. A dropout of 0.20 was used to prevent model overfitting as a regularisation method, which means it randomly drops 20% of input vectors in each time step.

Also, a recurrent dropout of 0.1 was applied to the model, which means it drops 10% of the units. Moreover, as we dealt with the binary classification problem in our study to find the mortality risk, binary cross-entropy was used as a loss function, and a small

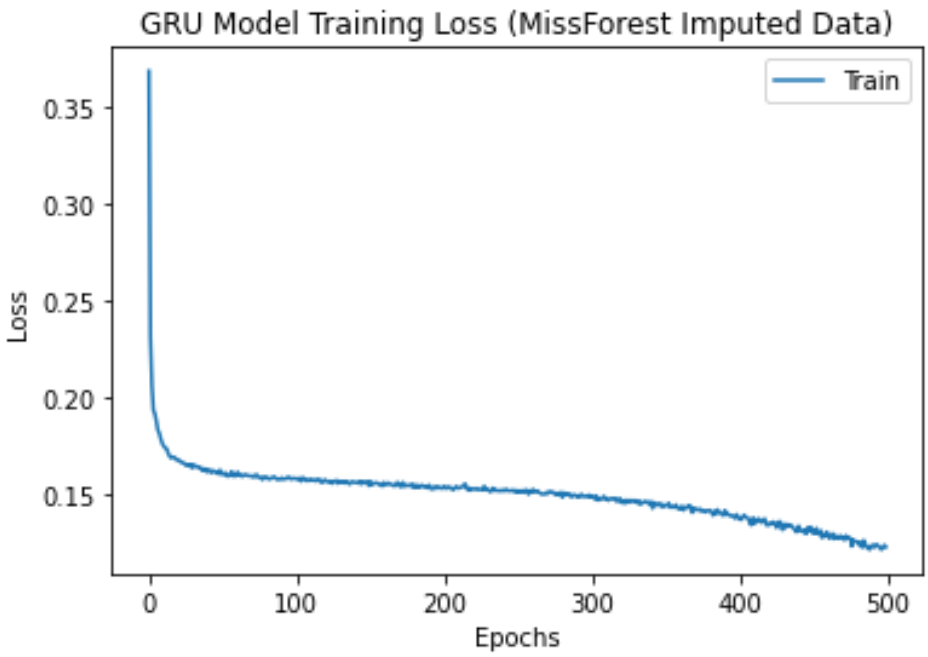
learning rate of 0.001 was used in the RMSprop optimiser. The smaller the learning rate, the more accurate the training is. Figure 31 shows the training loss of each model.



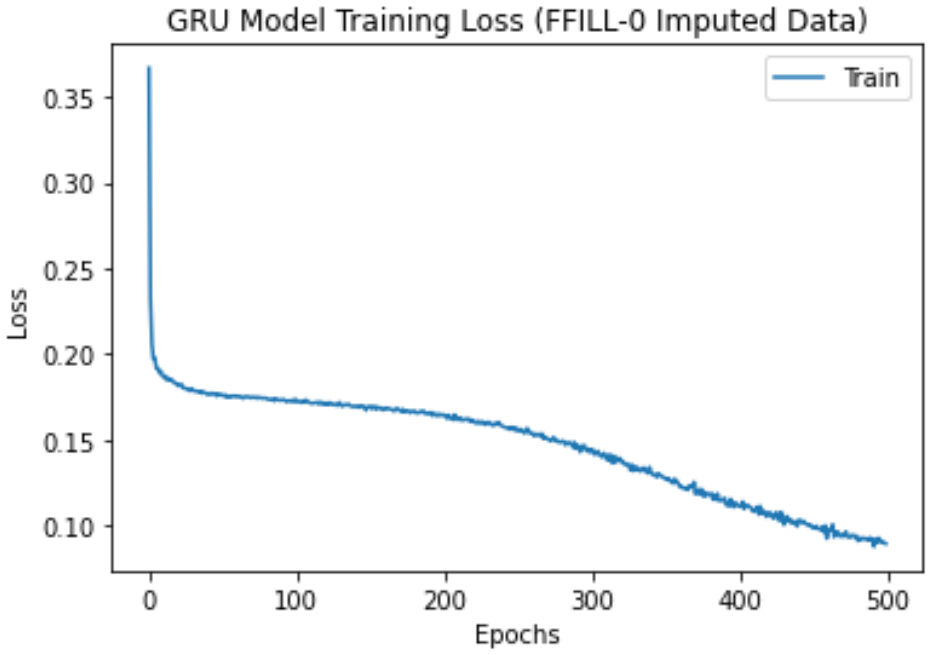

(a)




(b)



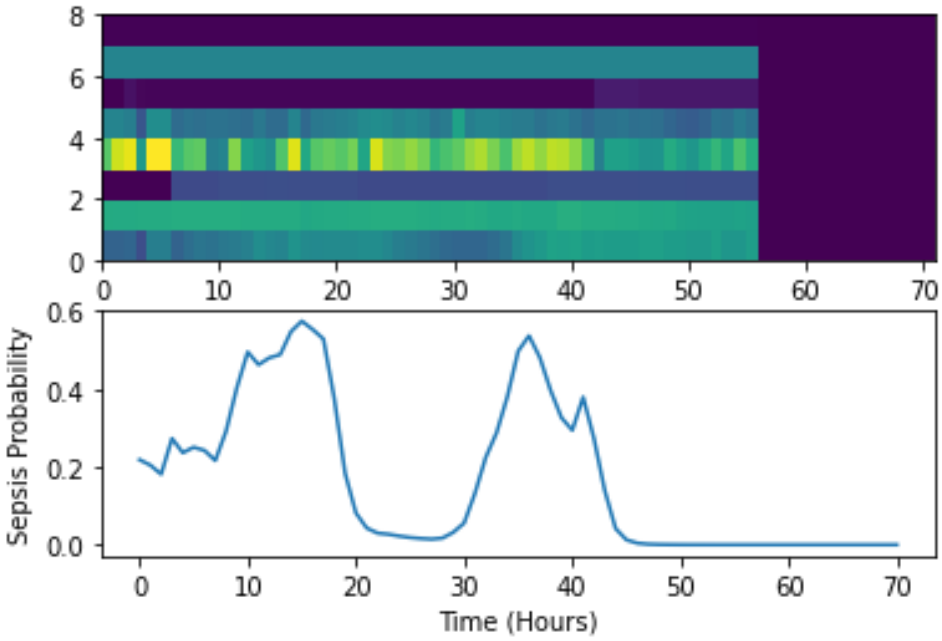

(c)



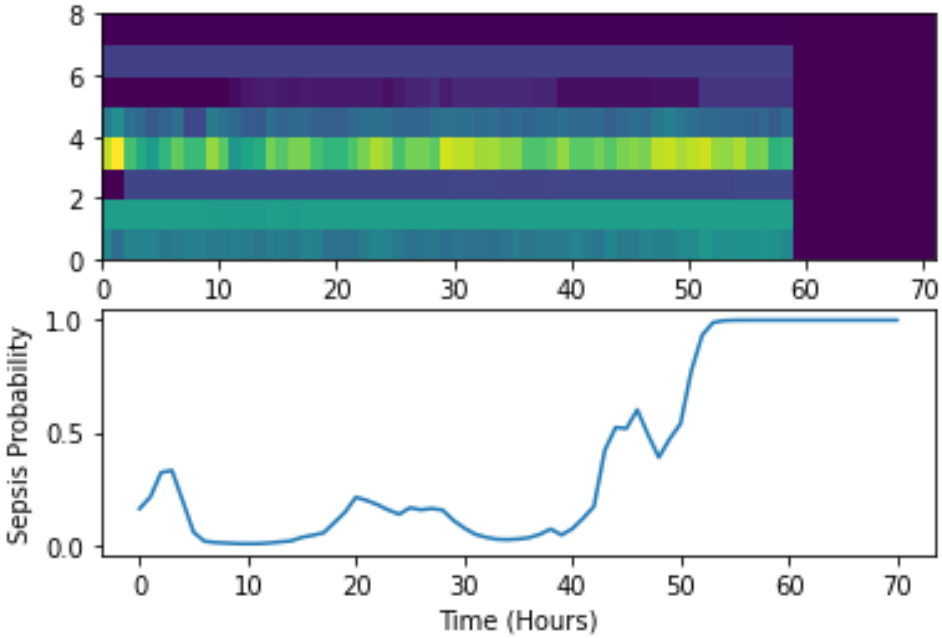

(d)

*Figure 31: Model Training Loss. The x-axis represents the number of epochs, and the y-axis shows the loss. (a) LSTM model training loss on MissForest imputed data (0.1097). (b) LSTM model training loss on FFILL-0 imputed data (0.0854). (c) GRU model training loss on MissForest imputed data (0.1225). (d) GRU model training loss on FFILL-0 imputed data (0.0892)*

The models were then evaluated on the hold-out datasets to check their effectiveness. Random patient predictions were also plotted as line and matrix plots (Figure. 32).




(a)




(b)

*Figure 32: Sepsis mortality risk calculation. (a) Patients with a low sepsis probability and mortality risk. (b) Patients with a high sepsis probability and mortality risk.*

Finally, the AUROC was calculated for each model (Figure. 33).

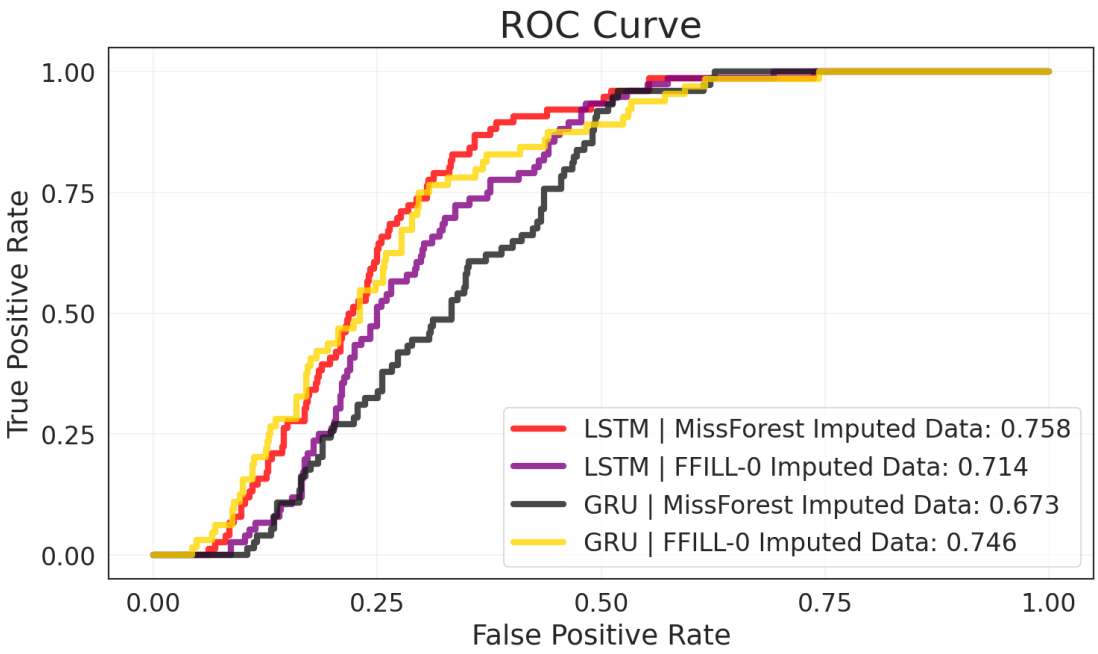



*Figure 33: ROC curve for LSTM and GRU models on MissForest and FFILL-0 imputed data.*

# Discussion

There is no permanent solution to stop sepsis progression in ED or ICU patients. However, the only solution to stop patient mortality and sepsis risk is the early and fast detection of sepsis. Microbial infections are the leading cause of sepsis in critically ill patients, with most sepsis incidences related to septicaemia. Conventional sepsis treatment approaches involve antibiotics and drug administration [145]. However, it is difficult to diagnose due to non-specific symptoms of sepsis.

Also, whether the patient's condition is due to sepsis or some other disease is difficult to determine, which can delay the treatment of the patient [146]. Initial sepsis detection methods are based on BCs, PCRs, and biomarkers. However, specific growth conditions are required for pathogens to grow in BCs, making them tedious. Moreover, unwanted sample noise can hinder the efficiency of PCR methods [68].

Sepsis is detected based on SIRS, SOFA, qSOFA, NEWS2, and MEWS scoring systems. For SIRS, if a patient meets two out of four conditions, it is said to be septic. Likewise, for SOFA and qSOFA, if a patient has a score of two or more is said to be septic. A NEWS2 score of five or more indicates the onset of sepsis in patients. Also, a patient with MEWS score of more than or equal to four is said to be septic [79, 147, 148].

These scoring systems are widely used for sepsis detection in hospitals; still, they are not enough. The involvement of blood sampling to test for the abnormal values of biomarkers in the blood in case of SOFA takes time, and each passing hour without treatment can risk the patient's life expectancy [77].

ML and DL-based approaches can precisely predict sepsis onset and even predict patient mortality with a high probability [149]. Some studies incorporate laboratory values alongside vital signs and demographics as essential features to train the model and achieve higher AUROC, which means their method can effectively predict sepsis. However, they have certain limitations regarding data availability, pre-processing, or model architecture.

The current research focused on non-invasive methods and used vital signs and demographics to build a DL-based sepsis risk forecasting system. However, this study

differs from other published studies on sepsis detection in data pre-processing and model architecture. For NaN values imputation in the data, MissForest [127] and LOCF (FFILL-0) [141] methods are used. First, the percentage of the missing data was calculated and plotted as a bar plot (Figure. 19) and heatmap (Figure. 20), which allowed us to check the percentage of NaN values in each variable, enabling the choice of a threshold of 70% for NaN values. Also, correlation analysis was performed and plotted as a heatmap to check for multicollinearity.

Features were then selected based on the correlation and the NaN values threshold. Those variables with a NaN percentage greater than or equal to the threshold were excluded from the data, and the features were finalised. The finalised feature set included six vital signs (HR, $O_2$Sat, Temp, SBP, DBP, Resp), three demographics (Age, Gender, ICULOS), and one outcome variable (SepsisLabel). Finally, data were plotted as a boxplot to check for any outliers in the finalised feature set, and outliers were removed based on feature range (Table 5).

Since the definition of sepsis differs in children and adults, age analysis was performed to see if the patient's age is outside the 15 – 90 (years) age range, as provided in Table 5. The total number of patients in the data was 40336. Gender analysis was also performed to see how many patients were male and female. Of the 40336 patients, 22566 were male, and 17770 were female (Figure. 25). Also, out of 22566 male patients, 20827 were non-septic, and 1739 were septic. Similarly, out of 17770 female patients, 16577 were non-septic, and 1193 were septic (Figure. 26), which indicates that the male population is more prone to sepsis than females.

Moreover, out of 40336 patients, 394 patients had ages outside the feature range. Out of which two patients were 14 years old, 392 were 100 years old and were removed from the data. The total number of patients left after removing patients was 39942. Then ICULOS analysis was performed, and those patients removed whose ICULOS was not starting from one, followed by those patients who had ICULOS count less than eight hours and more than 72 hours, leaving behind 30361 patients, which was then visualized as a bar plot (Figure. 27).

After that, data was plotted to visualize the septic and non-septic patient count (Figure. 28). Out of 30361 remaining patients, 28747 were non-septic, and 1614 were septic. Of 28747 non-septic patients, 13042 were female, and 15705 were male.

Likewise, out of 1614 septic patients, 653 were females, and 961 were males. This analysis helped down-sample the non-septic patients to match septic patients in number since the number of septic patients was less than non-septic patients. The purpose of this technique was to avoid using artificial data generation methods such as Synthetic Minority Over-sampling Technique (SMOTE) to up-sample septic patients [150].

Afterwards, NaN values were imputed in the data using MissForest and LOCF-0 (FFILL-0) methods. Finally, the data was converted to fixed-length tensors or arrays, which make model training easier, and then fed to LSTM and GRU models as input. Four models were trained based on MissForest and FFILL-0 imputed data, and sepsis mortality risk was forecasted (Figure. 32). The prediction array was plotted as a heat map-like plot along with the line plot illustrating the forecasted sepsis probability of the patient. A probability threshold of 0.5 was selected. Patients with a probability less than the threshold represent a low risk of becoming septic and have a low mortality risk, while the probability greater than the threshold indicates the patient has a higher risk of becoming a septic patient with a higher mortality risk.

Finally, the AUROC was calculated and visualized (Figure.33), and the highest AUROC was achieved by the LSTM model trained on MissForest-imputed data (0.758) as compared to the LSTM model trained on FFILL-0 imputed data (0.714), GRU model trained on MissForest imputed data (0.673), and GRU model trained on FFILL-0 imputed data (0.746). No work, to our knowledge, has been published yet that used a similar data pre-processing and model architecture for sepsis risk forecasting using non-invasive methods based on vital signs and demographics only.

# Conclusion and Future Perspectives

The study aims to forecast the sepsis mortality risk using the DL-based method. A novel data pre-processing method is introduced in this study, and a unique model architecture is used. The study used data from PhysioNet Cardiology Challenge 2019, and an 80-20 split ratio was used for training and validating the model. The MissForest algorithm and LOCF (FFILL-0) imputation methods were used to impute NaN values in the data, and MissForest imputed data outperformed LOCF (FFILL-0) imputation when models were evaluated on validation data. LSTM achieved the highest AUROC of 0.758 and 0.714 on MissForest data compared to GRU, which achieved AUROC of 0.673 and 0.746 on FFILL-0 imputed data.

Though the present study is limited to publicly available data of the USA population, it has very few septic patients, and the non-septic patients are down-sampled to match the number of septic patients. For a future perspective, the study aims to use the local data from the Pakistani population as a validation cohort in order to test the effectiveness of the model, and by using the transfer learning approach, the model will be trained on local data with a more significant number of septic patients. It is surmised that the model will achieve even greater AUROC and can forecast sepsis risk more efficiently.

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