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# ARTIFICIAL INTELLIGENCE (AI) APPROACHES IN PATIENTS WITH FEBRILE NEUTROPENIA

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## ABSTRACT

Sepsis and septic shock are the most common complications in patients with febrile neutropenia. Early detection and treatment are key components that can improve patient outcomes. The latest digital health technology, such as remote patient monitoring devices integrated with AI-based models, showed promising results in sepsis identification. The goal of the study is to review the application of an artificial intelligence-based early warning scoring system using a contactless remote patient monitoring device for early identification of sepsis syndrome.

### Highlights

- Patients with febrile neutropenia are at a high risk of sepsis related mortality.
- Clinical deterioration can be identified early with the use of an early warning score.
- Remote patient monitoring (RPM) technologies that provide continuous monitoring over extended periods of time may be more effective in identifying early changes in patients.
- Predictive Artificial Intelligence based algorithms helps in more accurate sepsis prediction
- A novel Early Warning Scoring system can be developed through integrating AI-based algorithms with remote patient monitoring devices.

**KEYWORDS:** Artificial intelligence, Febrile neutropenia, Early Warning Scoring, Sepsis, Remote patient monitoring devices.

## INTRODUCTION

Neutropenia accompanied by fever is known as febrile neutropenia. Neutropenia is characterized by abnormally low neutrophil numbers. Neutrophils are the type of agranulocytes that act as a first line of defense in our body. Patients receiving high-dose chemotherapy during active cancer treatment might develop febrile neutropenia. The incidence of febrile neutropenia is between 10 to 50% in solid tumors and around 80% in hematological malignancies.[1]

Neutrophils play a critical role in the defense against bacteria, fungi, viruses, and other organisms. Patients undergoing intensive cytotoxic therapy will develop blunted immune responses due to neutropenia that can cause bacterial and fungal infections. Hence patients with febrile neutropenia may progress to sepsis syndrome which is the common cause of mortality. Sepsis and septic shock result in a fatality incidence of more than 36% in febrile neutropenia.[2] Early identification of sepsis syndrome is essential in this patient population to improve the outcomes.

Many researchers have created a variety of early warning scoring systems that were composed of vital signs and lab results for predicting the clinical worsening of patients. These scoring systems have been gradually adopted as a sepsis screening tool. However, the application of these scoring systems in oncology settings has been limited.[3,4]

Artificial intelligence is an emerging field in medicine that helps clinicians in decision-making by utilizing enormous patient data. It has demonstrated significant promise in forecasting a patient's clinical state and supporting clinical judgment. Research studies recently

suggest the integration of digital health technology which provides continuous vital signs of the patients with an AI-based algorithm can be applied to different phases of sepsis, including prompt prediction, outcome evaluation, and effective treatment.[5] The review article aims to summarize the application of an AI-based Early Warning Scoring system using a contactless remote patient monitoring system for the early detection of sepsis.

**Febrile neutropenia**

Febrile neutropenia is a frequent complication in patients receiving high-dose chemotherapy or radiation for hematological cancers. It is defined as a single oral temperature measurement of >101ºF (>38.3ºC) or a temperature of ≥100.4ºF (≥38.0ºC) sustained over 1 hour, with an absolute neutrophil count (ANC) of <1000 cells/microliter, or an ANC that is expected to decrease to <500 cells/microliter over the next 48 hours.[6] Absolute Neutrophil Count is the number of neutrophils present in the blood.

**Pathophysiology of febrile neutropenia**

Febrile neutropenia is treated as a medical emergency because the combination of a weakened immune system and the presence of fever shows a higher risk of severe infections. Patients with neutropenia may only experience fever as a sign of a major infection. Unidentified fever and untreated infections can lead to progressive sepsis and adverse outcomes.

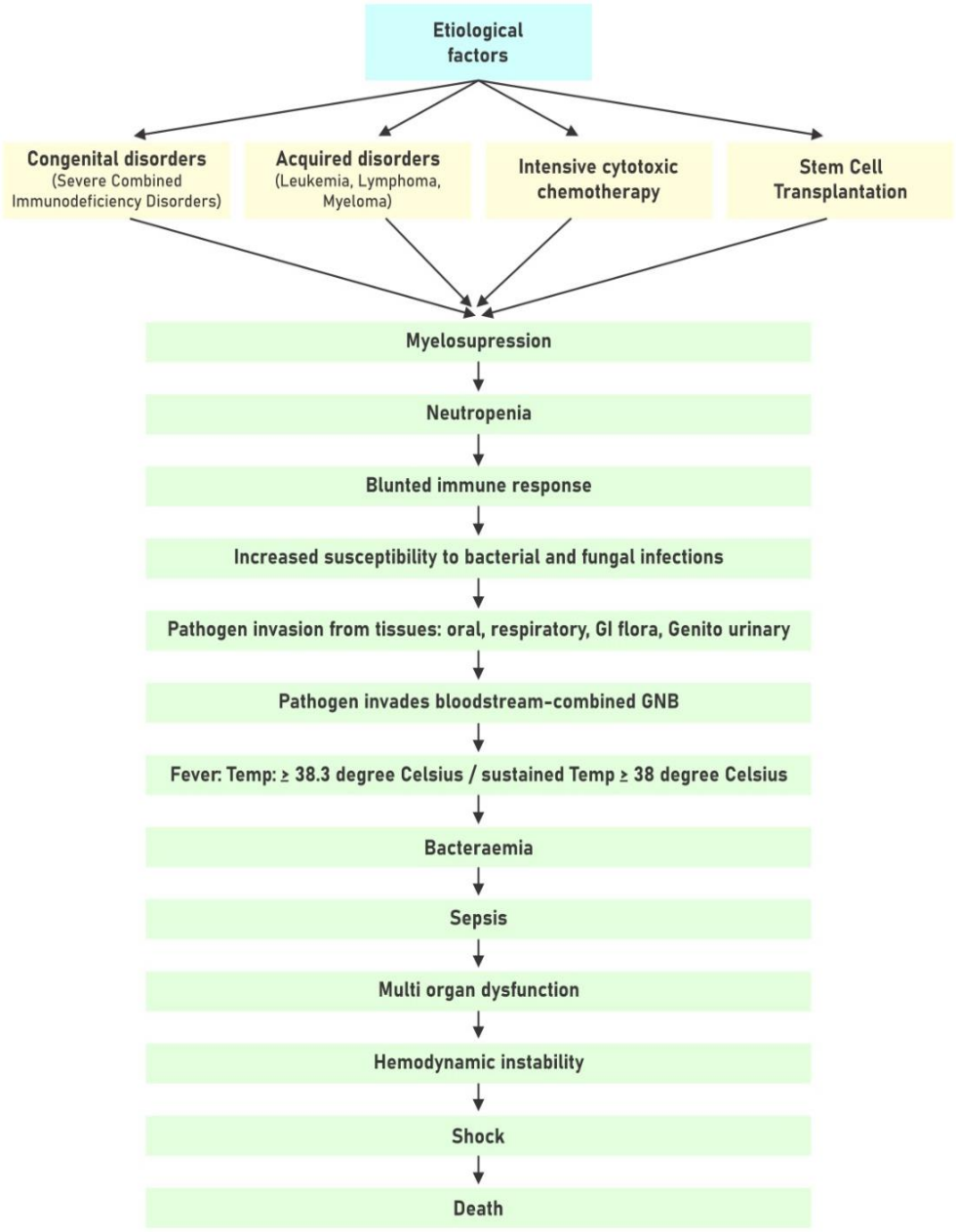


**Figure 1: Pathophysiology of febrile neutropenia.**

**Sepsis syndrome**

Sepsis syndrome refers to an increasingly severe stage of sepsis and septic shock. Sepsis is a medical emergency and a leading cause of death. Worldwide, around 49 million patients are diagnosed with sepsis every year and the mortality rate is about 19.7%.[7] Rapid detection and timely initiation of antibiotics have been proven to better patient outcomes.[8] Based on sepsis.3 criteria, it is defined as a sudden increase in Sequential Organ failure assessment (SOFA) score of ≥ 2 points, attributing life-threatening organ dysfunction due to assumed infection. Standards for Sepsis shock include sepsis along with the need for vasopressor therapy to raise mean arterial pressure to more than or equal to 65 mm of Hg and serum lactate more than 2.0 mmol/L despite sufficient fluid resuscitation.[9] Early identification of sepsis is difficult in patients presenting with different clinical phenotypes. As per international guidelines, the administration of intravenous antimicrobials is recommended within 1 hour of identification of sepsis and fluid resuscitation within 3 hours to stabilize tissue hypoperfusion.[10] With each one-hour delay in sepsis management guidelines, there will be a significant increase in the fatality rate. Early recognition of the patients who are at risk for sepsis syndrome is crucial to modify the therapy and prevent adverse outcomes. Nurses who are at the bedside are in a key position for rapid identification of sepsis, the start of antibiotics, and early intensive care unit transfer of patients with febrile neutropenia which can decrease morbidity and mortality.

**Early warning scoring system for sepsis**

Research studies have shown that significant clinical and physiological changes can be seen several hours earlier before adverse events like code emergencies, unplanned intensive care unit transfers, or death. These changes, meanwhile, are not usually identified or taken into consideration at the appropriate time which can frequently obtain clinical data, such as vital signs or the results of lab tests. This is commonly seen in patients with severe infections or sepsis, which can lead to more than 50% of mortality. Early Warning Scores (EWS) were developed to detect slight changes in vital signs hours to days before an unfavourable incident occurs, allowing for a prompt response and minimizing an adverse event.

Commonly used early warning scoring systems for the identification of sepsis are quick Sequential Organ Failure Assessment (qSOFA), Modified Early Warning Score (MEWS), and National Early Warning Score (NEWS). Many hospitals have started using these EWS for sepsis screening without ensuring validation of their performance.[3] However, the current EWS, has several limitations, including frequency of assessment and response, incorporation into practice, healthcare professionals' inaccurate estimations, and an apparent discrepancy with patient evaluation. It is still unclear whether a generic risk score generated in an undifferentiated inpatient population will perform similarly to scores obtained from systems focused specifically on patients with suspected infections.[11] With regard to other vulnerable oncology populations, these EWS have been shown to have low to moderate predictive power, despite not being developed or validated in patients with febrile neutropenia.[12] Additionally, using these EWS, it is uncertain primarily how well sepsis predicts immunocompromised populations. The scores are based on the present risk of the patient by considering the periodic vital signs but do not consider the patterns nor provide information about the possible adverse trend. Therefore, the assessment is not able to predict the rate at which the patient is getting better or worse. In addition, as the value of each parameter can be obtained independently through simple addition, these results do not account for any relationships between the parameters (for example, HR or RR can be looked at separately when body temperature is considered).[13]

**Artificial Intelligence (AI) in Sepsis Syndrome**

The concept of artificial intelligence was first introduced during the Dartmouth Summer Research Project conference in 1956. Artificial intelligence is a technology that creates software programs that imitate human cognitive functions including thinking and decision-making processes with the help of a vast amount of data. AI has revolutionized the healthcare sector with its ability to predict, diagnose, and augment the treatment of various diseases. There are several subdomains of AI that could potentially have clinical applications. (Figure 2). Among these subdomains, machine learning is most widely used in sepsis.

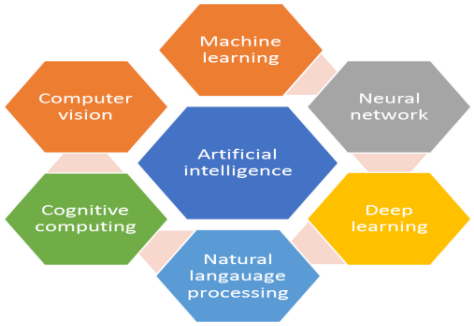


**Figure 2: Subdomains of AI.**

Machine learning (ML) explains and uses models and algorithms to address prediction, classification, and regression problems. To learn and analyze, machine learning (ML) relies significantly on data. Data is used to "teach" a framework, followed by repeated analysis of the algorithm's internal variables using "validation" data. ML models can use a wide range of designs, including regressions (linear and logistic), decision trees, support vector machines, naïve Bayesian classifiers, and numerous others. There are several different types of machine learning, including unsupervised, semi-supervised, and supervised at the beginning. Later, more types including reinforcement learning, deep learning, and integrated learning were developed.[14]

**AI-based EWS for prediction of sepsis syndrome in febrile neutropenia**

The AI-based machine learning (ML) algorithm is a more recent approach to EWS. ML models promptly recognize relationships and patterns from data, instead of relying on a rule-based approach. It can be modified for different care settings and populations, consider changes in risk assessment, take into consideration several clinical variables, and compensate for these aspects. AI algorithms have recently demonstrated promising results in the detection and early warning of sepsis. Aggregate-weighted systems cannot include patterns and detect relationships between variables as these models can.[15,16]

Sepsis is a fatal condition caused by an infection that requires early identification and treatment to reduce mortality and improve patient outcomes. Prediction and diagnosis of sepsis remain challenging due to differences in pathophysiological changes and clinical presentation. As a result, providing adequate treatment may be delayed.

However early identification of sepsis is challenging in patients with febrile neutropenia as they are immunocompromised with less clinical presentations, and subtle clinical findings and progress more rapidly than the general population. Currently, available early warning scoring systems for sepsis such as quick sequential organ failure assessment score (qSOFA), Modified Early Warning Score (MEWS) and National Early Warning Score (NEWS) developed for the general population and have limited prognostic value in a specific population. This necessitates the researchers to adopt cutting-edge analytical methods, such as artificial intelligence (AI), to build automated systems for early identification of sepsis.[17,18]

**Contact-less remote patient monitoring devices for sepsis**

Remote patient monitoring (RPM) is a augmenting field of medicine that uses flexible materials for wearable sensors to support the healthcare team. This is accomplished through implementing innovative Internet of Things (IoT) approaches in the medical sector such as wearable sensors, telemedical programs, and contact-based devices. RPM is widely used to evaluate physiological variables like vital signs, an activity that can aid in therapeutic decisions or treatment strategies for challenges like movement disorders or psychological conditions.[19]

Nurses regularly monitor the patient's vitals and keep manual records of the same in a hospital. Monitoring of the vital signs in a unit depends upon factors such as the availability of nurses, clinical workload, patient diagnosis, clinical leadership, and national guidelines. This will affect the early identification of clinical deterioration of a patient.

Moreover, patient monitoring with invasive equipment requires skin contact to estimate vital signs. The healthcare sector has been revolutionized by technological developments in data transmission that have allowed for continuous patient monitoring and non-invasive devices that do not touch patients' bodies. The advancements have changed the conventional methods of monitoring patients' health conditions and made it possible to monitor patients remotely in hospitals.[19]

Febrile neutropenia is one of the frequent oncological emergencies which leads to frequent hospitalization in patients receiving cancer treatment. The complications such as sepsis, and multi-organ dysfunction can be prevented through early identification and proper antimicrobial therapy. Intensive care unit admissions are commonly seen in these patients. All of this causes a significant economic burden.

According to the Society of Critical Care Medicine, delays in the identification and diagnosis of sepsis and delays in initiating antimicrobial therapy led to a high mortality rate in sepsis. Sepsis is challenging to diagnose, especially in the early stages, because its symptoms (Such as high temperature, low blood pressure, etc.) are like those of many other illnesses. Due to this, sepsis lacks a simple diagnostic test or symptoms that may be used to easily recognize its onset. The automated electronic patient monitoring system is becoming more common for the identification of early sepsis symptoms. These systems will continuously analyze data from patient monitoring devices and alert the healthcare team. After verifying the alerts and evaluating the patient, clinicians will determine whether the patient has sepsis. Once the diagnosis is confirmed will start treatment immediately to improve patient outcomes.[20] Research studies have shown that continuous remote patient monitoring (RPM) systems support clinical teams for early identification and timely intervention of sepsis.[21,22]

**Application of Artificial Intelligence (AI) based Early Warning Scoring system using a contact-less remote patient monitoring device**

Artificial intelligence (AI) is increasingly being used in healthcare. One of the popular healthcare apps, remote

patient monitoring (RPM), helps clinicians to monitor patients with acute or chronic conditions in far-flung locales and even patients who are hospitalized. The utility of manual patient monitoring systems depends on the clinical workload and time management of nursing staff. Invasive techniques that necessitate skin contact are used in conventional patient monitoring to keep track of health status.

As seen in Figure 3, machine learning (ML) and AI designs can be utilized to help healthcare professionals evaluate a patient's health status based on vital signs and activity monitoring. Applications of such data can provide information for recognizing and predicting patient health status as well as supporting clinical judgment.

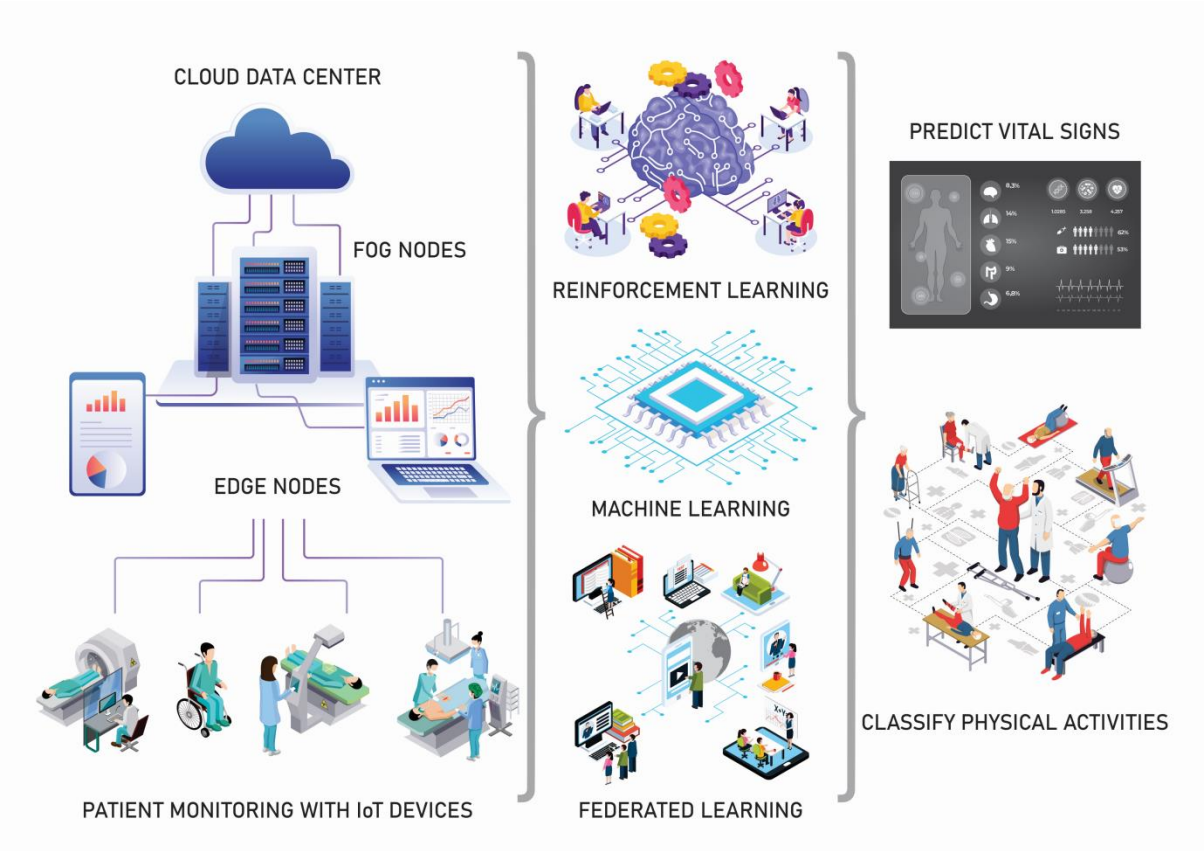


**Figure 3: Designs for remote patient monitoring with artificial intelligence.**

Instead of conventional monitoring over a brief period, continuous monitoring over longer periods using remote patient monitoring (RPM) platforms with information being transmitted into algorithm-based computer programs may be better able to detect early changes and notify of various complications. Currently, the available early warning system based on periodically monitored vital signs has failed to deliver reasonable specificity.[21]

The performance of the current EWS, such as qSOFA, MEWS, and NEWS, is suboptimal, and they still depend on episodic monitoring by staff nurses. The integration of a novel digital health technology such as remote patient monitoring which provides continuous vital signs of the patients with an AI-based algorithm can be applied to create an Early Warning Scoring system.[5]

## CONCLUSION

Numerous studies have demonstrated that each hour in delay of the treatment may increase the risk of mortality in sepsis with febrile neutropenia. Nurses use EWS based on vital signs to monitor patients' clinical status and escalate care as necessary. The existing scores are mainly based on vital sign data that nursing staff obtain on average every four hours to determine the sepsis risk. The significance of these scores is restricted. There may be limited adherence to sepsis treatment recommendations because the vital sign recording is delayed or missed due to workload or staff shortage. Studies showed that AI-based prediction models integrated with remote patient monitoring technologies have helped clinical teams reduce the fatality rate of sepsis in the general population.[5] This showed that AI-based EWS models integrated with remote patient monitoring can be developed for early identification of sepsis, however, more research is required to evaluate the application in patients with febrile neutropenia.

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