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Improving the Performance of Clinical Decision Support for Early Detection of Sepsis: A Retrospective Observational Cohort Study

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Abstract

Sepsis remains a significant global health problem. It is a life-threatening, but poorly defined and recognized condition. Early recognition and intervention are essential to optimize patient outcomes. Automated clinical decision support systems (CDS) may be particularly beneficial for early detection of sepsis. The aim of this study was to use retrospective data to develop and evaluate seven revised versions of an electronic sepsis alert rule to assess their performance in detecting sepsis cases and patient deterioration (in-hospital mortality or ICU admission). Four revised options had higher sensitivity but lower specificity than the original rule. After discussion with clinical experts, two revised options with the highest sensitivity were selected. Further analysis on the number of alerts and time intervals between alerts and patient outcomes was conducted to decide the option to be implemented. This study has provided a data-driven approach to improve the CDS on early detection of sepsis.

Keywords:

Sepsis, Clinical Decision Support Systems, Early Diagnosis

Introduction

Sepsis is a life-threatening condition that arises when the body's response to an infection injures its own tissues and organs [1; 2]. Despite advances in care, existing epidemiological studies suggest that sepsis remains a huge burden. A recent systematic review extrapolated data from high-income countries to suggest global estimates of 31.5 million sepsis and 19.4 million severe sepsis cases, with potentially 5.3 million deaths annually [3].

Sepsis is one of the most pervasive, but poorly defined and recognized conditions. It has been called "one of the oldest and most elusive syndromes in medicine" [4]. Early recognition and intervention are essential to optimize patient outcomes. To improve early sepsis detection, several automated sepsis alert systems using electronic medical record (eMR) data have been developed for use in hospital intensive care units (ICU) and in non-critical care settings [5]. The St. John Sepsis Surveillance Agent is one such system. It was developed by Cerner Corporation, an American supplier of health information technology solutions, services, devices and hardware. The St. John Sepsis Surveillance Agent has been implemented in more than 550 hospitals in the United States [6; 7].

An updated version, the Modified St. John Rule, was developed by the Clinical Excellence Commission (CEC) in New South Wales (NSW), Australia. It includes additional clinical criteria for activating sepsis alerts in addition to SIRS (systemic inflammatory response syndrome) alerts. There are three panels in the Modified St. John Rule as shown in Figure 1: i) CEC – a sepsis alert if any of two clinical criteria are satisfied; ii) SIRS – a SIRS alert if three or more modified SIRS criteria are met; iii) Organ dysfunction – a sepsis alert if two or more SIRS criteria and at least one organ dysfunction criteria are satisfied. An alert would be triggered if any clinical criterion is satisfied when all relevant measurement(s) within the specified lookback time period (Figure 1) is(are) available.

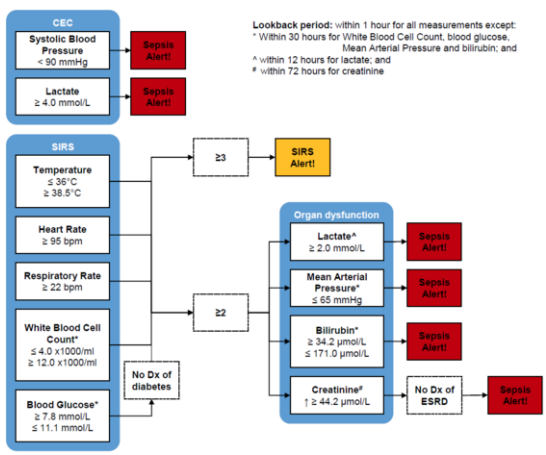

Figure 1 – Simplified Flow Diagram for the Modified St. John Rule. Note: ESRD=End-stage Renal Disease and Dx=Diagnoses.

The modified SIRS criteria used in the Modified St. John Rule were adapted from the original SIRS definition, which was introduced in the first two consensus sepsis definitions [8; 9]. The original SIRS criteria have been criticized for their poor specificity, with 90% of ICU patients and 50% of general ward patients meeting the criteria at some point during their hospitalization [2; 10]. These criticisms are consistent with our findings based on the evaluation of the Modified St John Rule [11], where more than half of the alerts were SIRS alerts. Of patients who experienced a SIRS alert, nearly half of them had two or more SIRS alerts during their hospital stay. The most recent sepsis definition (Sepsis-3) was developed in 2016 and has abandoned SIRS entirely. Sepsis-3 defines organ dysfunction as

an increase in total quick Sequential Organ Function Assessment (qSOFA) score of ≥ 2 [12; 13].

The Adult Sepsis Pathway is a paper-based tool developed for early detection of sepsis in adult patients and currently in practice in hospitals throughout NSW, the most populous state in Australia. The Adult Sepsis Pathway is part of the SEPSIS KILLS program [14; 15], aiming to reduce preventable harm to patients through improved recognition and management of severe infection and sepsis in NSW hospitals. This program has been associated with improved patient outcomes [16]. In this study, we proposed seven revised options of the Modified St John Rule by: i) removing the SIRS alerts and ii) incorporating clinical criteria and threshold values from the qSOFA criteria and the Adult Sepsis Pathway (details in the Methods section). For example, the clinical threshold for heart rate was "≥95 beats/minute" as per the Modified St. John Rule. In the revised options, we included the heart rate clinical thresholds as "≥ 95 beats/minute or ≤50 beats/minute", which was used in the Adult Sepsis Pathway. The aim of this study was to develop and evaluate a set of revised versions of the Modified St. John Rule in order to improve the early identification of patients with sepsis.

Methods

Study Design, Setting and Population

This retrospective observational cohort study included all adult patients (aged 18 years and over) admitted to an acute care teaching hospital in Sydney between December 2014 and June 2016. The hospital is a 570-bed tertiary urban hospital with 24,500 inpatient admissions annually. Sepsis cases were identified based on sepsis-related diagnosis codes based on the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification (ICD-10-AM) and assigned after discharge. The Classification of Hospital Acquired Diagnoses (CHADx) [17] was applied to patients' diagnoses to identify sepsis cases. Ethics approval was obtained from the Macquarie University Human Research Ethics Committee.

Revised Modified St. John Rules

Seven revised options were proposed to improve the performance of the Modified St. John Rule (Figure 2). The changes in these options were:

- Removing the SIRS alert (all seven options)
- Including at least one of five modified SIRS criteria satisfied plus at least one organ dysfunction as a trigger for a sepsis alert (options 2, 4, 5, and 7)
- Including base excess <-5.0 mEq/L as an immediate trigger for a sepsis alert (options 3, 4, 6 and 7)
- Including lactate ≥2 mmol/L as an immediate trigger for a sepsis alert (options 1, 5, 6 and 7)
- Adopting different clinical threshold values:
  - systolic blood pressure ≤100 mmHg (options 1, 5, 6, and 7)
  - heart rate≥ 95 beats/minute or ≤50 beats/minute (options 1, 5, 6 and 7)

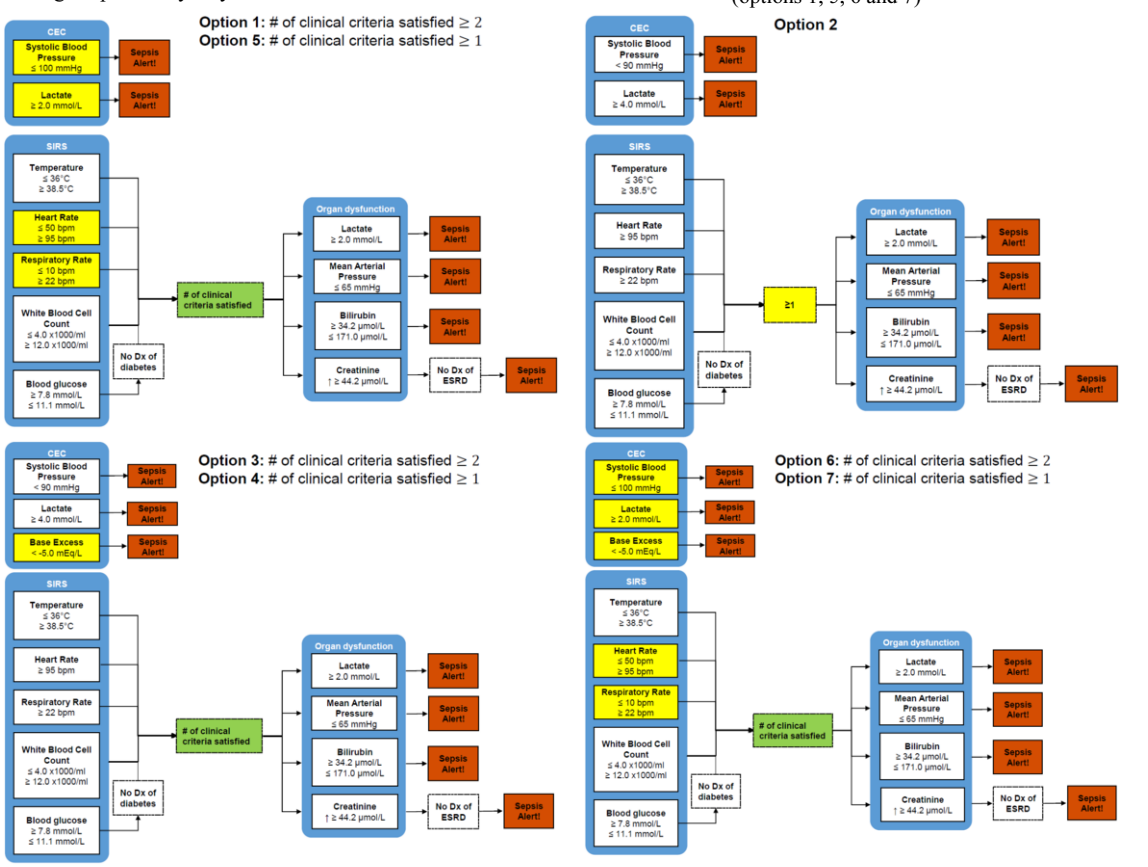

Figure 2 – Simplified Flow Diagrams of Seven Revised Versions of the Modified St. John Rule. Yellow and Green Highlights Indicate the Changes in Each Option. Note:#=Number, ESRD=End-stage Renal Disease and Dx=Diagnoses. See Figure 1 for the Lookback Periods.

- respiratory rate ≥ 22 breaths/minute or ≤10 breaths /minute (options 1, 5, 6 and 7)

Data Sources, Linkage and Management

Patient demographic data and admission related data, including vital signs, laboratory results and ICU admissions were extracted from different clinical information systems. Vital signs and laboratory tests were time-stamped. Data sets from different sources were linked using de-identified medical record numbers and related time stamps. ICD-10-AM diagnosis codes were used to identify patients with diabetes (E10 to E14) and end-stage renal disease (ESRD; N18.5).

Data Analysis

Two patient outcomes were used for assessing the performance of each revised option: i) ICD-10-AM coded sepsis and ii) In-hospital mortality or ICU admission. Performance metrics of seven options and the original Modified St John Rule were calculated, including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and the area under the receiver-operating characteristic curve (AUROC). After discussion with clinical experts, two options with the highest sensitivity were chosen as best options for screening. Further analysis was conducted based on these two options to compare three different time intervals: i) time from admission to the first sepsis alert, ii) time from the first sepsis alert to the ICU admission, and iii) time from the first sepsis alert to death in hospital. Analyses were performed using R (version 3.5.0) and SAS (version 9.4).

Results

A total of 36,065 patient admissions for 28,957 unique patients were included in the study. Patients' median age was 55 years (inter-quartile range [IQR]: 38-71) and 41.3% (N=11,946) of these patients were male. Among these patient admissions, 3.9% (n=1,402) involved admissions to ICUs during their hospital stays and a total of 483 patients died in hospital during the study period. The median length of stay (LOS) was 1.9 days (IQR: 0.3-4.9). A total of 3.5% of admissions (N=1,279) involved an ICD-10-AM coded case of sepsis during their hospital stay.

Detection of ICD-10-AM Coded Sepsis Cases

ICD-10-AM coded sepsis cases were used to assess the performance of these revised options for detecting sepsis (Table 1). Options 2, 3 and 4 had an increased specificity and PPV compared to the original Modified St John Rule. Option 2 had the highest specificity (96.26%) among all options. Option 3 flagged 30 false positives (FP) for every ten true positives (TP, i.e., FP/TP=1,529/502), compared to 40 for the original rule (i.e., FP/TP=2,492/611).

Options 1, 5, 6 and 7 identified more sepsis cases, i.e., true positives than the original Modified St. John Rule. Option 7 had the highest sensitivity (64.97%) among all options, closely followed by Option 6 (64.43%). Options 6 and 7 would correctly identify at least six sepsis cases for every ten admissions with a sepsis alert, compared to less than five out of ten for the original rule (sensitivity 47.77%). Both options 6 and 7 had the highest NPVs (98.39% and 98.40%).

Although these options generated more false positives resulting in lower specificity (Option 6: 79.76% and Option 7: 79.31%) than the original rule (92.84%), fewer false negatives (FN) meant fewer sepsis cases would have been missed than the other options and the original rule. For every ten correctly identified sepsis cases, five cases might be missed (i.e., FN/TP=448/831) for Option 7. In contrast, Option 2 would miss 20 false negatives, i.e., sepsis cases, for every ten correctly identified sepsis case (i.e., FN/TP=865/414); the original rule would miss 10 sepsis cases (i.e., FN/TP=668/611).

Detection of Deteriorating Patients

Death in hospital or ICU admission was used to assess the performance of these seven revised options for detecting patients' deterioration (Table 1). Similar to results for detecting sepsis cases, Option 2 had the highest specificity (97.01%) and Option 3 had the highest PPV (43.57%). Options 1, 5, 6 and 7 had higher sensitivity and AUROC than the original Modified St. John Rule. Options 6 and 7 had much higher sensitivity (71.74% and 72.56%) than the original Modified St John Rule (50.99%). For patients who experienced a sepsis alert based on options 6 or 7 during their hospital stays, at least seven out of ten patients would have died or been admitted to an ICU compared to five out of ten patients if based on the original rule.

Table 1–Revised Modified St. John Rule Options for Detecting i) ICD-10-AM Coded Sepsis and ii) In-hospital Mortality or ICU Admission (N=36,065). Note: PPV=Positive Predictive Value; NPV=Negative Predictive Value; AUROC= Area Under the Receiver-Operating Characteristic Curve; CI=Confidence Interval; Original: the Assessment Based on the Modified St. John Rule (Figure 1)

Options	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	PPV (%, 95% CI)	NPV (%, 95% CI)	AUROC (%, 95% CI)
	i) ICD-10-AM coded sepsis				
Option 1	62.16 (59.44-64.82)	80.07 (79.65-80.49)	10.29 (9.86-10.74)	98.29 (98.17-98.41)	71.12 (70.74-71.49)
Option 2	32.37 (29.81-35.01)	96.26 (96.05-96.45)	24.13 (22.42-25.92)	97.48 (97.39-97.57)	64.32 (63.92-64.71)
Option 3	39.25 (36.56-41.99)	95.60 (95.38-95.82)	24.72 (23.19-26.31)	97.72 (97.62-97.81)	67.43 (67.04-67.81)
Option 4	42.92 (40.19-45.69)	94.18 (93.92-94.42)	21.32 (20.07-22.62)	97.82 (97.72-97.92)	68.55 (68.16-68.94)
Option 5	62.86 (60.15-65.52)	79.59 (79.16-80.01)	10.17 (9.75-10.61)	98.31 (98.19-98.43)	71.23 (70.85-71.60)
Option 6	64.43 (61.73-67.05)	79.76 (79.34-80.19)	10.48 (10.06-10.92)	98.39 (98.26-98.50)	72.10 (71.73-72.46)
Option 7	64.97 (62.29-67.59)	79.31 (78.88-79.73)	10.35 (9.94-10.78)	98.40 (98.28-98.52)	72.14 (71.77-72.51)
Original	47.77 (45.00-50.55)	92.84 (92.56-93.11)	19.69 (18.63-20.80)	97.97 (97.87-98.08)	70.31 (69.93-70.68)
	ii)In-hospital mortality or ICU admission				
Option 1	67.38 (65.11-69.60)	80.87 (80.45-81.29)	15.00 (14.50-15.51)	98.02 (97.88-98.15)	74.13 (73.77-74.48)
Option 2	40.06 (37.73-42.42)	97.01 (96.82-97.19)	40.15 (38.16-42.17)	97.00 (96.88-97.11)	68.54 (68.15-68.92)
Option 3	51.45 (49.06-53.84)	96.66 (96.47-96.85)	43.57 (41.79-45.38)	97.55 (97.43-97.66)	74.06 (73.70-74.41)
Option 4	59.30 (56.94-61.64)	95.47 (95.25-95.69)	39.61 (38.13-41.11)	97.91 (97.79-98.02)	77.39 (77.04-77.73)
Option 5	68.60 (66.35-70.79)	80.42 (80.00-80.84)	14.93 (14.45-15.42)	98.08 (97.95-98.21)	74.51 (74.15-74.87)
Option 6	71.74 (69.55-73.86)	80.70 (80.28-81.12)	15.69 (15.21-16.19)	98.28 (98.14-98.40)	76.22 (75.87-76.57)
Option 7	72.56 (70.38-74.66)	80.26 (79.83-80.68)	15.54 (15.08-16.02)	98.32 (98.18-98.44)	76.41 (76.06-76.76)
Original	50.99 (48.60-53.38)	93.52 (93.25-93.78)	28.26 (27.04-29.52)	97.44 (97.32-97.56)	72.26 (71.89-72.62)

Table 2–Comparison between Options 6 and 7 on the Number of Sepsis Alerts and the Timing of the First Sepsis Alert during the Admission. Note: IQR=Inter-quartile Range and CI= Confidence Interval

Characteristics	Option 6	Option 7
Total number of alerts	37,170	43,616
Total number of admissions with at least one alert	7,863	8,029
Number of alerts per 100 admissions, mean (95% CI)	103 (98-108)	121 (115-127)
Admission to the first alert (hours), Median (IQR)	23.9 (10.1-60.3)	24.1(10.2-60.3)
Time from the first alert to death (hours), Median (IQR)	149.4 (41.4-315.3)	149.2 (46.5-314.3)
Time from the first alert to the first ICU admission (hours), Median (IQR)	233.3 (111.0-428.6)	235.7 (113.6-425.8)
Time from the first alert to death or ICU admission (hours), Median (IQR)	221.8 (98.1-391.1)	223.0 (101.8-390.5)

Further Comparison of Two Options with the Highest Sensitivity

Across the two study outcomes, options 6 and 7 had the highest sensitivity and AUROC. The only difference between two options was the number of SIRS criteria required to trigger a sepsis alert: at least two for Options 6 and at least one for Option 7 (Figure 2). As a result, more alerts would be triggered for more patients using Option 7 than that for Option 6 (Table 2). Option 7 had 121 sepsis alerts per 100 admissions (95% CI: 115-127) compared to many fewer alerts from Option 6 (103 alerts/100 admission, 95% CI: 98-108). In addition, 8,029 admissions would have experienced a sepsis alert if Option 7 was implemented compared to 7,863 admissions if Option 6 was in place.

Both options had very similar alert timing patterns. The median hours from admission to the first alert was around 24 hours and the median hours from the first alert to death in hospital or an ICU admission was around 220 hours (~9.2 days).

Discussion

Automatic clinical decision support systems (CDS) have the potential to provide notifications to clinicians to facilitate real-time early detection of sepsis cases. Following our previous evaluation of one such system [11], i.e. the Modified St John Rule, we proposed seven revised options to improve early identification of patients with sepsis. Using retrospective data, two of the revised options were found to have much higher sensitivities and AUROC in identifying both sepsis cases and deteriorating patients than the original Modified St John Rule. These two options would correctly identify at least six sepsis cases for every ten admissions with a sepsis alert compared to less than five out of ten for the original rule. Similarly, for every ten admissions with a sepsis alert, at least seven patients would be correctly identified as either dying or having an ICU admission compared to five out of ten for the original rule.

The study results were presented to a panel of clinical experts to decide which options should be selected for further implementation in the clinical information system. Given there is a tradeoff between sensitivity and specificity, the high sensitivity options had relatively low specificity. However, a highly sensitive test also means that there are few false negative results, and thus fewer sepsis cases would be missed. Sepsis is a life-threatening complication and any delay in treatment with effective antibiotics increases the risk of organ failure and death. Choosing the options with high sensitivity would save lives. The recommended option, i.e. Option 6, has been adopted by the Clinical Excellence Commission in New South Wales for further implementation and evaluation.

One strength of this study is that we used the composite outcome of in-hospital mortality or ICU admission in addition to ICD coded sepsis cases given the known limitation of ICD coding [18]. A major United States study recently published in the Journal of the American Medical Association found that estimates of the sepsis incidence based on ICD coding ranged between half and twice the actual clinical rate [18].

In medical informatics, large data have been collected for different purposes, including clinical care, administration, and research. We developed algorithms to retrospectively evaluate the performance of seven revised options using data collected routinely from different clinical information systems. This data driven approach allowed us to test different scenarios without utilizing resources and time to develop and implement the CDS.

Previous studies have demonstrated that Big Data techniques, such as machine learning, can be incorporated into electronic health records to predict clinically relevant outcomes in patients with sepsis [19]. Although early identification of sepsis is still challenging, Big Data techniques make it possible to utilize these large volumes of heterogeneous data to provide deeper insights and better understanding of poorly defined and recognized conditions, such as sepsis.

Conclusions

Sepsis remains a significant global health problem. This study has provided a data-driven approach to improve the CDS for early detection of sepsis patients. CDS for early detection of sepsis can be improved and assessed using routinely collected data from different clinical information systems. This data-driven approach would save valuable resources in the health care system and potentially save lives.

It is essential to combine early recognition of sepsis patients with early intervention in order to optimize patient outcomes. The CDS may integrate the early warning systems with the availability of rapid response teams designed to achieve earlier intervention [20]. However, it is important to note that rigorous studies are lacking to evaluate the benefits of these CDS systems [21].

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