Accurate detection of sepsis at ED triage using machine learning with clinical natural language processing

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Abstract

Background

Sepsis is a life-threatening condition with organ dysfunction and is a leading cause of death and critical illness worldwide. Accurate detection of sepsis during emergency department triage would allow early initiation of lab analysis, antibiotic administration, and other sepsis treatment protocols. The purpose of this study was to determine whether EHR data can be extracted and synthesized with the latest machine learning algorithms (KATE Sepsis) and clinical natural language processing to produce highly accurate sepsis predictive models, and compare KATE Sepsis performance with existing sepsis screening protocols, such as SIRS and qSOFA.

Method

A machine learning model (KATE Sepsis) was developed using patient encounters with triage data from 16 participating hospitals. KATE Sepsis, SIRS, standard screening (SIRS with source of infection) and qSOFA were tested in three settings. Cohort-A was a retrospective analysis on medical records from a single Site 1. Cohort-B was a prospective analysis of Site 1. Cohort-C was a retrospective analysis on Site 1 with 15 additional sites.

Result

Across all cohorts, KATE Sepsis demonstrates an AUC of 0.94-0.963 with 73-74.87% TPR and 3.76-7.17% FPR. Standard screening demonstrates an AUC of 0.682-0.726 with 39.39-51.19% TPR and 2.9-6.02% FPR. The qSOFA protocol demonstrates an AUC of 0.544-0.56, with 10.52-13.18% TPR and 1.22-1.68% FPR. For severe sepsis, across all cohorts, KATE Sepsis demonstrates an AUC of 0.935-0.972 with 70-82.26% TPR and 4.64-8.62% FPR. For septic shock, across all cohorts, KATE Sepsis demonstrates an AUC of 0.96-0.981 with 85.71-89.66% TPR and 4.85-8.8% FPR. SIRS, standard screening, and qSOFA demonstrate low AUC and TPR for severe sepsis and septic shock detection.
Conclusion

KATE Sepsis provided substantially better sepsis detection performance in triage than commonly used screening protocols. Future research should focus on the impact of KATE Sepsis on administration of antibiotics, readmission rate, morbidity and mortality.

Keywords: Sepsis; Severe Sepsis; Septic Shock; Emergency Department; Emergency Nursing; Machine Learning; ED Triage; SIRS; qSOFA; Natural Language Processing

1. Background

Sepsis is a life-threatening condition with organ dysfunction caused by a dysregulated host response to infection (Singer et al. 2016) and is a leading cause of death and critical illness worldwide (Angus et al. 2001, Vincent et al. 2014, Fleischmann et al. 2015, Liu et al. 2014, Fleischmann-Struzek et al. 2020, Vincent et al. 2020).

The global incidence of sepsis is estimated at 32 million with 5.3 million deaths per year (Fleischmann, 2016). In the United States alone more than 1.7 million patients are diagnosed with sepsis annually and nearly 270,000 die from sepsis (CDC, 2021). In 2017, the United States spent over $38 billion on sepsis treatment, making it the most expensive condition to treat (Liang, 2020). Patients who survive sepsis often have long-term health and social consequences (Iwashyna et al. 2010). Despite advances in medical treatment, the reported incidence of sepsis has failed to decrease (Iwashyna et al. 2012, Gaieski et al. 2013, Rhee et al. 2017), and sepsis remains the primary cause of death from infection (Singer et al. 2016).

The difficulty of treating sepsis arises from challenges in early identification, with subtle and heterogeneous symptoms at the onset of the disease and often quick progression to life-threatening stages of severe sepsis and septic shock (Vincent, 2016, de Grooth et al. 2018). Even a few hours of delay in the treatment of sepsis
results in increased mortality (Seymour et al. 2017, Liu et al. 2017, Ferrer 2014, Kumar et al. 2006). Early detection of sepsis allows for close monitoring, early testing and treatment, and has been shown to reduce mortality, morbidity and cost of care (Rivers et al. 2001, Nguyen et al. 2007, Seymour et al. 2017). The Surviving Sepsis Campaign International Guidelines recommend that administration of IV antimicrobials be initiated immediately, ideally within 1 hour of recognition for both sepsis and septic shock onset (Evans et al. 2021).

Early and accurate detection of sepsis is critical to reduce the negative impacts of sepsis on the population. Despite high prevalence, early and accurate identification of sepsis remains elusive. Existing rule-based methods for early identification of sepsis, such as systemic inflammatory response syndrome (SIRS) criteria and quick sequential organ failure assessment score (qSOFA) have low sensitivity and specificity (Islam et al. 2019, Filbin et al. 2018) and do not show significant change in clinical outcomes (Nelson et al. 2011, Hooper et al. 2012, Nguyen et al. 2014).

Machine learning (ML) has been increasingly studied as a promising tool to identify sepsis (Schinkel et al. 2019, Islam et al. 2019, Fleuren et al. 2020, Teng et al. 2020, Giacobbe et al. 2021). The majority of research is focused on applying ML to predict sepsis within hospital intensive care units (ICU). Some studies used ML to predict sepsis for patients throughout their stay in the ED using vital signs and lab results as model features (Haug and Ferraro, 2016, Delahanty et al. 2019) for severe sepsis or septic shock (Jones et al. 2012, Brown et al. 2016, Nachimuthu and Haug, 2012, McCoy and Das, 2017). Notwithstanding, sepsis, or the infection causing sepsis, starts outside of the hospital in nearly 87% of cases (CDC, 2021). Ideally sepsis is detected when a patient arrives at an Emergency Department (ED) during triage. Accurate detection of sepsis during the triage assessment would allow early initiation of lab analysis, antibiotic administration, and other sepsis treatment protocols.

During the initial triage assessment, pertinent information regarding the patient's presenting complaint and past medical history typically occurs concurrently with obtaining vital signs by ED triage teams. While additional information about the patient, such as active problems, medications, family history, surgeries, and social risk
factors, that is available through an electronic health record (EHR) should be considered, it is often overlooked. Our study examined whether access to information about a patient's condition and full medical history at triage is sufficient to accurately predict sepsis. The vast amount of extant literature for ML in sepsis focuses on ICU patients, and to the best of our knowledge, there are no publications with ML models that focus on undifferentiated patients with minimal diagnostics, or predict sepsis at ED triage. The primary goal of this study was to develop an accurate ML model, which we call “KATE Sepsis”, to detect sepsis with the limited information available at ED triage, where no lab results are present, and compare its performance to standard screening protocols.

2. Methods

2.1. Data Collection

Human subjects protection and conflicts of interest: Prior to data collection, IRB exemption was obtained from the WCG IRB (IRB registration number: 13574120). All protected health information (PHI) was redacted from the datasets, in accordance with 45 CFR § 164.514 for de-identifying PHI to safe-harbor standards. De-identified raw text files were mapped and consolidated to a multi-hospital hierarchical data model, preserving the differences between sites.

2.2. Study Sites

The primary study site (Site 1) is a community emergency department in an urban setting in the state of California with approximately 65,000 annual visits where retrospective and prospective analysis was initially conducted. Fifteen additional sites across California, Oregon, and Hawaii were also analyzed in a one year retrospective period. During triage, nurses used standard screening (defined in Section 2.6) for sepsis risk
The data in this study were split into three Cohorts:

- **Cohort-A**: retrospective analysis of Site 1 from Feb 2015 to May 2018, 174,739 medical records with 2,849 sepsis diagnoses.
- **Cohort-B**: prospective analysis of Site 1 from Jul 2020 to May 2021, 26,963 medical records with 713 sepsis diagnoses.
- **Cohort-C**: retrospective analysis on 16 sites (Site 1 through 16) from Feb 2015 to Jul 2021, 607,739 medical records with 9,333 sepsis diagnoses.
Clinical information of Cohort-A and Cohort-C medical records was in the free text form. Clinical information of Cohort-B medical records was in the form of HL7 ED triage nurse notes and patient histories.

### 2.3. Sepsis diagnosis definition

Cohort-A and Cohort-C medical records, which were used for retrospective KATE Sepsis model training, had diagnoses written as free text from ED provider notes. Cohort-B medical records, which we used for prospective analysis of the KATE Sepsis model, had diagnosis in the form of ICD-10 codes extracted from EHR problem lists. We extracted a sepsis diagnosis from Cohort-A and Cohort-C records using Clinical Natural Language Processing (C-NLP) described in Section 2.4.2. These extracted sepsis diagnoses were verified through sampling by Emergency Department clinicians participating in this study. Sepsis diagnoses from Cohort-B medical records were extracted using ICD-10 codes. We considered sepsis, severe sepsis, and septic shock diagnoses as a “sepsis” diagnosis for the model. We also considered SIRS with a documented source of infection in diagnosis as sepsis.

### 2.4. Machine Learning

#### 2.4.1. Features overview

A model feature is equivalent to a clinical data point. For reference, “difficulty breathing”, “non-labored respiration”, and “history of diabetes” would represent three unique features in the KATE Sepsis model. In this study, numerical, categorical, and free text data were used. Numerical data are represented by age, vital signs, pain scores, Glasgow Coma Scale score, and other triage assessments. Numerical data were transformed into features after removing physiologically impossible outliers. Categorical data are represented by sex, arrival mode, arrived from, and risk factors such as alcohol and drug abuse. Overall, information that was available at...
Triage was used as model features. Post-triage data, such as labs or vitals signs after triage, were not used as model features. Clinical terms were extracted from chief complaints, and patient histories (medical, social, family, surgical, and medication data) using Clinical Natural Language Processing (C-NLP).

2.4.2. Clinical Natural Language Processing (C-NLP)

Accurate extraction of clinical terms from patient record free text is a prerequisite to form a complete understanding of each patient and can enhance ML-based clinical decision models (Ivanov et al. 2020). This has been a primary challenge in building ML-based clinical decision support tools for clinicians which leverage clinical raw text evidence. We developed C-NLP technology to accurately extract medical terms from free text. The details of the algorithm are presented in prior research (Ivanov et al. 2020). C-NLP algorithm demonstrates 99.7% TPR and 0.992 F1-score in extracting clinical terms from free text (Ivanov et al. 2020).

2.4.3. Feature Engineering

Clinical feature engineering was undertaken to derive new composite features from the study EHR data and public datasets, which improved predictive value for sepsis detection. The following feature engineering methods were applied:

- UMLS dictionaries of normalized clinical terms were used to derive consolidated features based on features extracted from free text data fields in nurses triage forms using C-NLP. UMLS is a collection of dictionaries, many of which have a primary term for medical terms (Bodenreider, 2004). For example, “radiating chest pain” is related to “chest pain”.

- Social and environmental risk factors were binned into risk and non-risk categories
● Duration of symptoms features were created based on time references in reason for visit (e.g., hours, days, weeks)
● Count of the number of features extracted from the reason of visit using C-NLP
● Count of Number of NAs in vital signs
● Count of the number of vital signs in risk zones

2.4.4. Machine Learning Algorithms

XGBoost was selected as the ML algorithm used for this study. XGBoost is a method from the gradient tree boosting family. Gradient boosting is a method of sequential building of decision trees in which each subsequent tree is built on the subset of data where previous trees made the most mistakes in classification (Chen, 2016). XGBoost was designed to have an efficient model training performance for large sparse datasets (Chen, 2016) which is common for clinical data.

2.4.5. Software

Java 8.0 and OpenNLP Java library were used to develop C-NLP. Python 3.8 was used for ML pipeline development. XGBoost 1.4 library was used to build KATE Sepsis. Sklearn and Scipy libraries were used for model evaluation and statistical analysis.

2.5. Training and evaluation sets

KATE Sepsis, SIRS, standard screening, and qSOFA were evaluated on three cohorts of data (see Section 2.2 for Cohorts details):

● Cohort-A: retrospective analysis of Site 1. The KATE Sepsis model was trained on a random sample of 80% of data, 137,564 medical records. KATE Sepsis, SIRS, standard screening, and qSOFA were
evaluated on a 20% test set of 34,391 remaining medical records with 561 positive sepsis diagnoses. Results are presented in Section 3.1.

- Cohort-B: prospective analysis of Site 1 from Jul 2020 to May 2021. KATE Sepsis, SIRS, standard screening, and qSOFA were evaluated on 26,963 medical records with 713 positive sepsis diagnoses. Results are presented in Section 3.2.

- Cohort-C: retrospective analysis on 16 sites (Site 1 through 16). The KATE Sepsis model was trained on 80% of data, 486,191 medical records. KATE Sepsis, SIRS, standard screening, and qSOFA were evaluated on 20% of data, 121,548 medical records with 1,867 positive sepsis diagnoses. Results are presented in Section 3.3.

2.6. Sepsis screening protocols

We also evaluated common sepsis detection protocols in the three cohorts mentioned above. The commonly used sepsis detection and related mortality protocols we evaluated during triage are:

- **SIRS**: 2 or more SIRS vitals (temperature < 36 or > 38 °C, pulse rate > 90, or respiratory rate > 20) (Bone et al. 1992). Note: The SIRS protocol also includes white blood cell labs but we omitted this because labs are not available during triage.

- **Standard screening protocol**: 2 or more SIRS vitals and a source of infection documented anywhere in the triage assessment (Bone et al. 1992). See Supplementary Table 1 for infection types.

- **qSOFA**: respiratory rate ≥ 22, systolic blood pressure ≤ 100, and altered mentation (Singer et al. 2016)

Results for the common sepsis screening protocols are presented in Section 3 and compared to the KATE Sepsis model.

Additionally, we evaluated the KATE Sepsis model versus common sepsis rule-based protocols on each ability to
detect patients with a final diagnosis of severe sepsis (Section 3.6) or septic shock (Section 3.7.) at the time of ED triage.

3. Results

3.1 Results for Cohort-A

Results on the test set of Cohort-A for KATE Sepsis, SIRS, standard screening, and qSOFA are presented in Table 2. Common rule-based protocols such as SIRS, standard screening, and qSOFA demonstrate low predictive power for sepsis at triage. At the same time KATE Sepsis demonstrates high predictive power and significantly higher scores than the common protocols. Specifically, the KATE Sepsis model AUC is 0.963, and SIRS, standard screening, and qSOFA protocol AUC scores are 0.703, 0.682 and 0.544 respectively. KATE Sepsis TPR (true positive rate or sensitivity) is 74.87%, and SIRS, standard screening, and qSOFA sensitivities are 44.39%, 39.39% and 10.52% respectively. All the protocols have a similar FPR (false positive rate) of 3.76% for KATE Sepsis, 3.79% for SIRS, 2.9% for standard screening, with the exception of qSOFA with lower FPR of 1.68%. All the protocols also have high accuracy but due to the strong class imbalance for sepsis (patients diagnosed with any form of bacterial sepsis comprise 1.63% of Cohort-A population), accuracy alone is not an objective measure of model performance. KATE Sepsis also demonstrates significantly higher F1-score than SIRS, standard screening, and qSOFA (0.37 vs 0.24, 0.25 and 0.10 respectively), and higher precision (0.25 vs 0.16, 0.18, 0.09 respectively).
Table 2. Retrospective performance metrics and 95% confidence intervals (in parentheses) for Cohort-A (Feb 2015 to May 2018) of KATE Sepsis, SIRS, standard screening and qSOFA trained on 80% of data, 137,564 medical records, and evaluated on 20% test set of 34,391 medical records with 561 sepsis diagnoses.

| Group         | AUC         | TPR        | FPR        | F1-score   | Accuracy    | Precision   |
|---------------|-------------|------------|------------|------------|-------------|-------------|
| KATE Sepsis   | 0.96337 (0.9576 - 0.9684) | 0.7487 (0.7078 - 0.7785) | 0.0376 (0.0354 - 0.0388) | 0.373 (0.3497 - 0.3929) | 0.95894 (0.9575 - 0.9609) | 0.24837 (0.231 - 0.2645) |
| SIRS          | 0.70296 (0.6796 - 0.7234) | 0.4439 (0.3969 - 0.4839) | 0.0379 (0.0359 - 0.0398) | 0.23794 (0.2094 - 0.2623) | 0.95362 (0.9516 - 0.9553) | 0.16253 (0.14 - 0.1771) |
| Standard      | 0.68246 (0.6604 - 0.7028) | 0.3939 (0.3507 - 0.4354) | 0.029 (0.0273 - 0.0305) | 0.25057 (0.2197 - 0.2758) | 0.96156 (0.9595 - 0.9633) | 0.18371 (0.1582 - 0.2034) |
| Screening     |             |            |            |            |             |             |
| qSOFA         | 0.5442 (0.5314 - 0.5571) | 0.1052 (0.0792 - 0.1309) | 0.0168 (0.0155 - 0.0183) | 0.09941 (0.0761 - 0.1208) | 0.96892 (0.9675 - 0.9707) | 0.09425 (0.0703 - 0.1153) |

3.2 Results for Cohort-B

Prospective results of KATE Sepsis, SIRS, standard screening, and qSOFA evaluated on Cohort-B at triage for 26,963 medical records are presented in Table 3. KATE Sepsis, SIRS, standard screening, and qSOFA results are in concordance with the retrospective results presented in Table 2. Specifically, the KATE Sepsis ML model demonstrates an AUC of 0.94 with TPR of 74.33% and FPR of 7.17%. Comparatively, in Cohort-A analysis, SIRS, standard screening, and qSOFA demonstrates low AUC scores (0.76, 0.73 and 0.56 respectively) and TPR (0.58, 0.51 and 0.13 respectively) compared to KATE Sepsis. All demonstrate similar FPR with 7.17% for KATE Sepsis, 7.24% for SIRS, 6.02% for standard screening, with the exception of qSOFA with lower FPR of 1.22%. All except qSOFA demonstrate significantly higher FPR (false positive rates), compared to retrospective analysis. This difference in FPR between cohorts is analyzed in Section 3.5.

All the methods demonstrate high accuracy. KATE Sepsis also demonstrates higher F1-score than SIRS, standard screening, and qSOFA (0.34 vs 0.30, 0.27, 0.27 and 0.17 respectively), and higher precision (0.22 vs 0.18, 0.19, and 0.23 respectively).
### Table 3.
Prospective performance metrics and 95% confidence intervals (in parentheses) for Cohort-B (Jul 2020 to May 2021) of KATE Sepsis, SIRS, standard screening, and qSOFA evaluated on 26,963 medical records with 713 sepsis diagnoses.

| Group            | AUC       | TPR       | FPR       | F1-score  | Accuracy  | Precision  |
|------------------|-----------|-----------|-----------|-----------|-----------|------------|
| KATE Sepsis      | 0.94008   | (0.9329 - 0.9463) | 0.7433   | (0.7119 - 0.7715) | 0.0717    | (0.068 - 0.0742) | 0.33931   | (0.3167 - 0.3589) | 0.92345   | (0.9207 - 0.9271) | 0.21983   | (0.2014 - 0.2354) |
| SIRS             | 0.75552   | (0.7387 - 0.7719) | 0.5835   | (0.5471 - 0.6168) | 0.0724    | (0.0694 - 0.0755) | 0.27459   | (0.2526 - 0.2936) | 0.91848   | (0.915 - 0.9214) | 0.17954   | (0.1616 - 0.1942) |
| Standard screening | 0.72588   | (0.7071 - 0.746) | 0.5119   | (0.4738 - 0.5524) | 0.0602    | (0.0574 - 0.0627) | 0.27475   | (0.249 - 0.2956) | 0.92853   | (0.9255 - 0.9313) | 0.18776   | (0.1677 - 0.2016) |
| qSOFA            | 0.5598    | (0.5445 - 0.5723) | 0.1318   | (0.1003 - 0.1567) | 0.0122    | (0.0108 - 0.0137) | 0.16667   | (0.1325 - 0.1921) | 0.96514   | (0.9626 - 0.9669) | 0.22651   | (0.1856 - 0.2814) |

### 3.3. Results on Cohort-C

Results on the test set for Cohort-C for KATE Sepsis, SIRS, standard screening, and qSOFA are presented in Table 4. As in the case of the Cohort-A and Cohort-B, KATE Sepsis demonstrates high predictive power and significantly higher scores than the common rule based protocols. Specifically, the KATE Sepsis model AUC is 0.95, and SIRS, standard screening, and qSOFA AUC scores are 0.71, 0.69 and 0.55 respectively. KATE Sepsis TPR is 73%, and SIRS, standard screening, and qSOFA TPR of 47.3%, 41.94% and 12.21% respectively. FPR is 4.76% for KATE Sepsis, 5.03% for SIRS, 3.85% for standard screening, and 1.35% for qSOFA. KATE Sepsis also demonstrates significantly higher F1-score than SIRS, standard screening, and qSOFA (0.31 vs 0.20, 0.22 and 0.12 respectively), and higher precision (0.19 vs 0.13, 0.15, 0.12 respectively).
Table 4. Performance metrics and 95% confidence intervals (in parentheses) for Cohort-C (Feb 2015 to Jul 2021) of KATE Sepsis, SIRS, standard screening, and qSOFA trained on 80% of data, 486,191 medical records, and evaluated on 20% of data, 121,548 medical records with 1,867 sepsis diagnoses.

| Group          | AUC         | TPR         | FPR         | F1-score     | Accuracy     | Precision    |
|----------------|-------------|-------------|-------------|--------------|--------------|--------------|
| KATE Sepsis    | 0.95051     | 0.73        | 0.0476      | 0.30554      | 0.94902      | 0.1932       |
|                | (0.9461 - 0.9546) | (0.7115 - 0.7503) | (0.0464 - 0.0487) | (0.2938 - 0.317) | (0.9477 - 0.95) | (0.1844 - 0.202) |
| SIRS           | 0.71134     | 0.473       | 0.0503      | 0.20146      | 0.94241      | 0.12799      |
|                | (0.6986 - 0.72)  | (0.448 - 0.49) | (0.0493 - 0.0512) | (0.1908 - 0.2095) | (0.9412 - 0.9432) | (0.1207 - 0.1339) |
| Standard screening | 0.69045     | 0.4194      | 0.0385      | 0.21579      | 0.95318      | 0.14527      |
|                | (0.6806 - 0.6991) | (0.3991 - 0.4366) | (0.0377 - 0.0394) | (0.2026 - 0.2253) | (0.952 - 0.954) | (0.1356 - 0.1525) |
| qSOFA         | 0.55431     | 0.1221      | 0.0135      | 0.12284      | 0.97321      | 0.12358      |
|                | (0.5471 - 0.5615) | (0.1073 - 0.1364) | (0.0128 - 0.0141) | (0.1075 - 0.136) | (0.9723 - 0.9741) | (0.1086 - 0.1378) |

3.4. The overlap between KATE Sepsis and standard screening

All study sites prior to the research had adopted the standard screening process as a sepsis screening protocol at ED Triage. KATE Sepsis has a similar FPR to standard screening but significantly outperforms in TPR. We compared the percentage of correct sepsis diagnosis predictions of standard screening versus KATE Sepsis. For Cohorts-A,B,C, the overlap of true positive predictions of standard screening with KATE Sepsis was 92.17%, 85.75%, and 92.21% respectively.

3.5. Influence of COVID-19 on sepsis predictions

Cohort-B analysis was conducted on a population of ED visits that occurred after the onset of the COVID-19 viral outbreak (July 2020 to May 2021). We noted that compared to Cohorts A and C, both KATE Sepsis, SIRS and standard screening have significantly higher FPR for identifying bacterial sepsis which they were designed to predict (Tables 3-5). Figure 1 demonstrates the relation between the fraction of COVID-19 patients with FPR of KATE Sepsis and standard screening. Panel A of Figure 1 demonstrates time series by month of fraction of COVID-19 patients for Cohort-B, KATE Sepsis and standard screening FPR. The FPR of KATE Sepsis and standard
screening follows COVID-19, which is illustrated by the relation between FPR for these two models and the fraction of COVID-19 patients on panel B. Pearson correlation coefficient for KATE Sepsis FPR with the fraction of COVID-19 patients is 0.982 (p<10^{-5}). Pearson correlation coefficient for standard screening is 0.958 (p<10^{-4}).

![Figure 1](image_url)

**Figure 1.** The influence of COVID-19 on FPR for KATE Sepsis and standard screening for Cohort-B. **Panel A:** Time series by month of fraction of COVID-19 patients, KATE Sepsis FPR and standard screening FPR for Cohort-B. **Panel B:** The relation between the fraction of COVID-19 patients and KATE Sepsis and standard screening FPRs. Pearson correlation coefficient for KATE Sepsis FPR with the fraction of COVID-19 patients is 0.982 (p < 10^{-5}). Pearson correlation coefficient for standard screening is 0.958 (p < 10^{-4}).

We also studied TPR and FPR on the subset of patients with and without COVID-19 diagnosis (Table 5). KATE Sepsis and standard screening without COVID-19 diagnosis have similar FPRs to the corresponding pre-COVID-19 datasets of Cohort-A and Cohort-C (Table 2 and Table 4), whereas for the patients with COVID-19 diagnosis the corresponding FPRs are 29.25% and 29.69%. Therefore, both sepsis detection methods confuse...
COVID-19 symptoms with sepsis at triage.

| Data subset          | Source of infection (%) | Temperature > 38 or ≤ 36 (%) | Pulse rate > 90 (%) | Respiratory rate > 20 (%) |
|----------------------|-------------------------|------------------------------|---------------------|---------------------------|
| Cohort-A, no COVID-19| 56.91% (56.68% - 57.1%) | 6.16% (6.28 - 0.06.49)     | 44.52% (44.33% - 44.75%) | 14.1% (13.94 - 14.21%)   |
| Cohort-B, no COVID-19| 56.56% (55.94% - 57.13%)| 3.6% (3.51% - 0.0395%)     | 44.11% (43.27 - 0.44.66) | 8.18% (7.86 - 0.08.51)    |
| Cohort-B, with COVID-19 | 87.45% (86.09% - 88.49%) | 20.73% (19.31% - 22.15%)  | 61.86% (60.28% - 6336%) | 33.56% (32.37% - 35.28%) |

3.6. Severe sepsis

KATE Sepsis demonstrates high performance for detecting sepsis for patients diagnosed with severe sepsis. Common sepsis screening protocols demonstrate low predicting power for detecting sepsis for patients...
diagnosed with severe sepsis.

For Cohort-A sepsis predictions for patients diagnosed with severe sepsis (Supplementary Table 2), KATE Sepsis demonstrates an AUC of 0.972 with TPR of 82.26% and FPR 4.64%. SIRS, standard screening, and qSOFA demonstrate low AUC scores (0.696, 0.673 and 0.588 respectively) and low TPR (43.55%, 37.9% and 19.35% respectively) compared to KATE Sepsis. The FPR is similar to KATE Sepsis with 4.31% for SIRS, 3.37% for standard screening, and qSOFA with lower FPR of 1.76%.

For Cohort-B sepsis predictions for patients diagnosed with severe sepsis (Supplementary Table 3), KATE Sepsis demonstrates an AUC of 0.935 with TPR of 70.5% and FPR of 8.62%. SIRS, standard screening, and qSOFA demonstrate low AUC scores (0.761, 0.742 and 0.59 respectively) and low TPR (60.43%, 55.4% and 19.42% respectively) compared to KATE Sepsis. The FPR is similar to KATE Sepsis with 8.32% for SIRS, 6.96% for standard screening, and qSOFA with lower FPR of 1.45%.

For Cohort-C sepsis predictions for patients diagnosed with severe sepsis (Supplementary Table 4), KATE Sepsis demonstrates an AUC of 0.96, with TPR of 77.78% and FPR of 5.6%. SIRS, standard screening, and qSOFA demonstrate low AUC scores (0.74, 0.713 and 0.59 respectively) and low sensitivities (53.56%, 47.01%, and 19.37% respectively). The FPR is similar to KATE Sepsis with 5.54% for SIRS, 4.31% for standard screening, and qSOFA with lower FPR of 1.47%.

3.7. Septic shock

The KATE Sepsis model demonstrates high predictive power for predicting sepsis in patients diagnosed with septic shock, whereas common sepsis screening protocols demonstrate low predicting power.

For Cohort-A sepsis predictions for patients diagnosed with septic shock (Supplementary Table 5), KATE Sepsis demonstrates an AUC of 0.981, with TPR of 89.66% and FPR of 4.85%. SIRS, standard screening, and qSOFA
demonstrate low AUC scores (0.685, 0.672 and 0.629 respectively) and low sensitivities (41.38%, 37.93%, and 27.59% respectively). The FPR is similar to KATE Sepsis with 4.42% for SIRS, 3.47% for standard screening, and qSOFA with lower FPR of 1.8%.

For Cohort-B sepsis predictions for patients diagnosed with septic shock (Supplementary Table 6), KATE Sepsis demonstrates an AUC of 0.96 with TPR of 85.71% and FPR of 8.8%. SIRS, standard screening, and qSOFA demonstrate low AUC scores (0.743, 0.699 and 0.686 respectively) and low TPR (57.14%, 46.94% and 38.78% respectively). The FPR is similar to KATE Sepsis with 8.5% for SIRS, 7.14% for standard screening, and qSOFA with lower FPR of 1.47%.

For Cohort-C sepsis predictions for patients diagnosed with septic shock (Supplementary Table 7), KATE Sepsis demonstrates an AUC of 0.974 with TPR of 87.41% and FPR of 5.71%. SIRS, standard screening, and qSOFA demonstrate low AUC scores (0.713, 0.681 and 0.671 correspondingly) and low sensitivities (48.25%, 40.56% and 35.66% respectively). The FPR is similar to KATE Sepsis with 5.63% for SIRS, 4.39% for standard screening, and qSOFA with lower FPR of 1.48%.

4. Discussion

Sepsis is a leading cause of death in hospitals (Liu et al. 2014), hospital readmissions (Fingar and Washington, 2015), and cost of care (Buchman et al. 2020). Early and accurate screening is critical for rapid treatment, potentially improving the patient's outcomes, and reducing the patient's mortality risk. Nurses at triage have an important role in recognizing high risk patients and prioritizing patients for rapid intervention.

The purpose of this study was to determine whether EHR data could be extracted and synthesized with clinical natural language processing (C-NLP) and the latest ML algorithms (KATE Sepsis) to produce highly accurate predictive models of sepsis detection at triage prior to the use of laboratory diagnostics.
This study demonstrates with both retrospective and prospective results, for all cohorts, that an ML approach (KATE Sepsis) can generate highly accurate predictions of sepsis diagnosis with data available at triage, prior to diagnostic results such as labs. Across all the cohorts, KATE Sepsis demonstrates an AUC of 0.94-0.963 with 73-74.87% TPR and 3.76-7.17% FPR. Common rule-based sepsis protocols, such as SIRS and qSOFA, demonstrate low performance in detecting sepsis at triage. Standard screening has an AUC of 0.682-0.726 AUC with 39.39-51.19% TPR and 2.9-6.02% FPR. The qSOFA protocol demonstrates the lowest performance in detection of sepsis at triage with an AUC of 0.544-0.56, 10.52-13.18% TPR and 1.22-1.68% FPR.

Nurse accuracy in triage for patients with sepsis is 41.7% using standard screening (Ivanov et al. 2020). The lack of predictive power of the standard screening protocol results in significant underdetection of patients with sepsis at triage and with delays in treatments and potential deterioration of patients conditions. Machine learning algorithms, such as KATE Sepsis, can significantly increase detection rate of patients with sepsis at triage and therefore demonstrate a promise to reduce time to treatment, morbidity and mortality.

Since KATE Sepsis provides 85.3% better TPR than standard screening, with a similar specificity, the follow up question is whether standard screening can be replaced with KATE Sepsis. Although KATE Sepsis cannot fully replace standard screening protocol, it predicts the majority of all sepsis diagnoses that standard screening detects in the studied cohorts. Standard screening true positive cases are detected 85.75-92.21% of the time by the KATE Sepsis model (Section 3.4).

Detection of patients with severe sepsis or septic shock at triage is crucial, because such patients are at high risk of morbidity and mortality (Schoenberg et al. 1998, Bauer et al. 2020). The KATE Sepsis model predicts sepsis with high accuracy especially for patients diagnosed in the ED with severe sepsis (Section 3.6) and septic shock (Section 3.7). For severe sepsis, across the cohorts, KATE Sepsis demonstrates an AUC of 0.935-0.972 with 70-82.26% TPR and 4.64-8.62% FPR. For septic shock, across the cohorts, KATE Sepsis demonstrates an AUC of 0.96-0.981 with 85.71-89.66% TPR and 4.85-8.8% FPR. SIRS, standard screening and qSOFA demonstrate
low performance for severe sepsis and septic shock detection.

For each cohort, KATE Sepsis, SIRS, standard screening, and qSOFA demonstrate similar results in terms of AUC, TPR, FPR, F1 score, precision and other measures. The only difference was significantly higher FPR for each in Cohort-B. Cohort-B analysis was conducted during the onset of the COVID-19 viral pandemic. COVID-19 has a strong influence on FPR for KATE Sepsis and standard screening, which is demonstrated by high Pearson correlation coefficient between the fraction of COVID-19 patients with KATE Sepsis FPR (0.982) and standard screening FPR (0.958). These strong correlations are explained by the fact that patients with COVID-19 diagnosis present with similar symptoms to bacterial sepsis at triage. Such patients have a significantly higher percentage of source of infection, high temperature, pulse rate and respiratory rate compared to patients without COVID-19 diagnosis (Section 3.5).

Traditionally, sepsis caused by bacterial infection has been the focus of identification and management algorithms (Martin et al. 2003). However, the recent COVID-19 pandemic has brought viral sepsis to the forefront of pharmaceutical development and viral sepsis identification (Zhou et al. 2020). Research conducted prior to COVID-19 reported respiratory viral infections were often underdiagnosed in patients with severe sepsis and septic shock (Ljungstrom et al. 2013, Lin et al. 2018). Therefore, an increase of FPR by KATE Sepsis, SIRS and standard screening during COVID-19 pandemic can be explained both by the similarity of symptoms of viral and bacterial sepsis at triage, and the fact that viral sepsis may be underdiagnosed in COVID-19 patients. Patients presenting with viral sepsis, especially susceptible populations, may require timely intervention to prevent poor outcomes (Lin et al. 2018), so rapid identification of both types of sepsis will become more critical as new therapies are implemented for viral sepsis (Gu et al. 2020). The KATE Sepsis ML algorithm, with high sensitivity for detecting sepsis of any etiology at triage (prior to diagnostic studies), facilitates earlier clinician recognition and initiation of targeted sepsis treatment protocols, including timely antibiotics or antiviral therapy.
5. Limitations and future perspectives

We used each hospital site's EHR documented diagnosis as a true label for training of KATE Sepsis and evaluation of KATE Sepsis and other protocols. Sepsis diagnosis may not have been recorded in the patient's diagnosis but the patient actually met the criteria of sepsis. We did not manually audit each patient chart to see if the patient met technical criteria of sepsis due to the study's large population size.

The definition of sepsis changes over time (Gül et al. 2017). The hospital sites in this study use the definition of sepsis as SIRS with a source of infection, called Sepsis-2 (Bone et al. 1992). In 2016 a new definition of sepsis, Sepsis-3, was introduced based on Sequential [Sepsis-related] Organ Failure Assessment (SOFA) (Singer et al. 2016). Future research should focus on training and evaluation of ML models using Sepsis-3 as a true label and measuring clinical outcomes of such models.

During the course of study outcomes data, such as antibiotics administration, length of stay, mortality, readmission rate was not available. Future prospective research will focus on the impact of KATE Sepsis and other screening methods on clinical decision making and patient outcomes.

In this study we used information available at triage, i.e. without labs. Future research will study how the availability of data during patient stay at ED can improve sepsis detection.

6. Conclusions

Sepsis is a life threatening condition which requires rapid intervention to prevent deterioration of patient condition. Ideally sepsis is detected when a patient arrives at an Emergency Department (ED) and is triaged. Accurate detection of sepsis during the triage assessment would allow early initiation of lab analysis, antibiotic administration, emerging antiviral therapies, and other sepsis treatment protocols. Current sepsis screening
protocols, such as SIRS, SIRS with source of infection, and qSOFA demonstrate low sensitivity at triage. KATE Sepsis, an ML model, has been shown to provide significantly higher performance for sepsis detection, without a significant increase in false positive predictions compared to standard screening protocols. Moreover, KATE Sepsis demonstrates high sensitivity in detecting both bacterial and viral sepsis for patients with severe sepsis or septic shock at triage.

Future research should focus on the impact of KATE Sepsis on patient’s outcomes, including time to antibiotics administration, readmission rate and mortality. Future research should also focus on performance of KATE Sepsis during a patient’s stay in the ED with data including labs, additional vital signs taken, and treatments and assessments during the ED course.

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Supplementary data

Supplementary Table 1. Example potential infection signs and symptoms for various systems used in the standard screening algorithm

| System         | Examples                                      |
|----------------|-----------------------------------------------|
| Respiratory    | Cough, pneumonia                              |
| GI/GU          | UTI, gastroenteritis                          |
| Skin           | Cellulitis, abscess, petechiae                |
| Neurological   | Nuchal rigidity, photophobia, Altered level of consciousness with fever |
| Oral Maxillofacial | Facial swelling, periorbital cellulitis      |
| Oncological    | Neutropenia with fever, central line infection |
| Other          | Fever status post surgery, postpartum        |

Supplementary Table 2. Retrospective performance metrics and 95% confidence intervals (in parentheses) for Cohort-A (Feb 2015 to May 2018) for predicting sepsis for patients with severe sepsis diagnosis of KATE Sepsis, SIRS, standard screening and qSOFA trained on 80% of data, 137,564 medical records, and evaluated on 20% test set of 34,391 medical records with 124 severe sepsis diagnoses.

| Group          | AUC         | TPR           | FPR           | F1-score       | Accuracy       | Precision       |
|----------------|-------------|---------------|---------------|----------------|----------------|-----------------|
| KATE Sepsis    | 0.97217     | 0.8226        | 0.0464        | 0.1124         | 0.95316        | 0.06032         |
|                | (0.9653 - 0.9779) | (0.7537 - 0.8807) | (0.0442 - 0.0479) | (0.0906 - 0.1335) | (0.9511 - 0.9551) | (0.0483 - 0.0725) |
| SIRS           | 0.69618     | 0.4355        | 0.0431        | 0.06522        | 0.95499        | 0.03525         |
|                | (0.6571 - 0.7424) | (0.3583 - 0.5312) | (0.0409 - 0.045) | (0.0498 - 0.084) | (0.953 - 0.957) | (0.0266 - 0.0456) |
| Standard screening | 0.67265     | 0.379         | 0.0337        | 0.07084        | 0.96415        | 0.03907         |
|                | (0.631 - 0.7212) | (0.2943 - 0.4779) | (0.0318 - 0.0354) | (0.0467 - 0.0926) | (0.962 - 0.9658) | (0.0255 - 0.0516) |
| qSOFA          | 0.58799     | 0.1935        | 0.0176        | 0.064          | 0.97959        | 0.03834         |
|                | (0.5511 - 0.6311) | (0.1186 - 0.2798) | (0.0163 - 0.0188) | (0.0391 - 0.0917) | (0.9782 - 0.9809) | (0.0225 - 0.0574) |
### Supplementary Table 3. Prospective performance metrics and 95% confidence intervals (in parentheses) for Cohort-B (Jul 2020 to May 2021) for predicting sepsis for patients with severe sepsis diagnosis of KATE Sepsis, SIRS, standard screening, and qSOFA evaluated on 26,963 medical records with 139 severe sepsis diagnoses.

| Group          | AUC               | TPR               | FPR               | F1-score          | Accuracy        | Precision        |
|----------------|-------------------|-------------------|-------------------|-------------------|-----------------|------------------|
| KATE Sepsis    | 0.93491 (0.9259 - 0.9452) | 0.705 (0.6507 - 0.7683) | 0.0862 (0.0824 - 0.089) | 0.07686 (0.0645 - 0.0903) | 0.9127 (0.9097 - 0.9163) | 0.04065 (0.0339 - 0.048) |
| SIRS           | 0.76054 (0.7223 - 0.7984) | 0.6043 (0.5283 - 0.6788) | 0.0832 (0.0801 - 0.0863) | 0.0684 (0.0561 - 0.0786) | 0.91514 (0.912 - 0.9181) | 0.03625 (0.0296 - 0.0417) |
| Standard screening | 0.74218 (0.6981 - 0.7759) | 0.554 (0.4664 - 0.6217) | 0.0696 (0.0665 - 0.0725) | 0.07393 (0.0597 - 0.0868) | 0.92846 (0.9254 - 0.9315) | 0.03961 (0.0316 - 0.0468) |
| qSOFA          | 0.58989 (0.5575 - 0.6224) | 0.1942 (0.1296 - 0.2588) | 0.0145 (0.0131 - 0.0159) | 0.09747 (0.0624 - 0.1296) | 0.98146 (0.9797 - 0.9831) | 0.06506 (0.041 - 0.0861) |

### Supplementary Table 4. Performance metrics and 95% confidence intervals (in parentheses) for Cohort-C (Feb 2015 to Jul 2021) for predicting sepsis for patients with severe sepsis diagnosis of KATE Sepsis, SIRS, standard screening, and qSOFA trained on 80% of data, 486,191 medical records, and evaluated on 20% of data, 121,548 medical records with 351 severe sepsis diagnoses.

| Group          | AUC               | TPR               | FPR               | F1-score          | Accuracy        | Precision        |
|----------------|-------------------|-------------------|-------------------|-------------------|-----------------|------------------|
| KATE Sepsis    | 0.95998 (0.9529 - 0.9665) | 0.7778 (0.7237 - 0.8182) | 0.056 (0.0546 - 0.0571) | 0.07372 (0.0663 - 0.0824) | 0.94356 (0.9424 - 0.9447) | 0.0387 (0.0347 - 0.0434) |
| SIRS           | 0.74012 (0.7081 - 0.7646) | 0.5356 (0.4717 - 0.5853) | 0.0554 (0.0545 - 0.0564) | 0.05186 (0.0447 - 0.0582) | 0.94345 (0.9423 - 0.9443) | 0.02725 (0.0234 - 0.0306) |
| Standard screening | 0.71349 (0.6814 - 0.7365) | 0.4701 (0.4056 - 0.516) | 0.0431 (0.0422 - 0.0442) | 0.05748 (0.0495 - 0.0649) | 0.95548 (0.9544 - 0.9563) | 0.03061 (0.0263 - 0.0348) |
| qSOFA          | 0.58954 (0.5699 - 0.6093) | 0.1937 (0.1546 - 0.2336) | 0.0147 (0.0141 - 0.0153) | 0.06193 (0.0495 - 0.0736) | 0.98305 (0.9823 - 0.9837) | 0.03686 (0.0296 - 0.0445) |
### Supplementary Table 5. Retrospective performance metrics and 95% confidence intervals (in parentheses) for Cohort-A (Feb 2015 to May 2018) for predicting sepsis for patients with septic shock diagnosis of KATE Sepsis, SIRS, standard screening and qSOFA trained on 80% of data, 137,564 medical records, and evaluated on 20% test set of 34,391 medical records with 29 septic shock diagnoses.

| Group            | AUC     | TPR     | FPR    | F1-score | Accuracy | Precision |
|------------------|---------|---------|--------|----------|----------|-----------|
|                  | (AUC)   | (TPR)   | (FPR)  | (F1-score) | (Accuracy) | (Precision) |
| **KATE Sepsis**  | 0.98138 | 0.8966  | 0.0485 | 0.03023  | 0.9515   | 0.01538   |
|                  | (0.9748 - 0.9887) | (0.75 - 1.0) | (0.046 - 0.0503) | (0.019 - 0.0404) | (0.9496 - 0.9539) | (0.0096 - 0.0207) |
| **SIRS**         | 0.68478 | 0.4138  | 0.0442 | 0.01537  | 0.95531  | 0.00783   |
|                  | (0.5735 - 0.7731) | (0.1901 - 0.5889) | (0.0419 - 0.0463) | (0.0064 - 0.024) | (0.9532 - 0.9572) | (0.0033 - 0.0123) |
| **Standard screening** | 0.67231 | 0.3793  | 0.0347 | 0.01786  | 0.96482  | 0.00914   |
|                  | (0.5779 - 0.7689) | (0.1894 - 0.5717) | (0.0327 - 0.0365) | (0.0068 - 0.0275) | (0.9628 - 0.9666) | (0.0035 - 0.0142) |
| **qSOFA**        | 0.62894 | 0.2759  | 0.018  | 0.02443  | 0.98142  | 0.01278   |
|                  | (0.5409 - 0.7131) | (0.0997 - 0.4448) | (0.0166 - 0.0193) | (0.0092 - 0.0459) | (0.9801 - 0.9828) | (0.0048 - 0.0244) |

### Supplementary Table 6. Prospective performance metrics and 95% confidence intervals (in parentheses) for Cohort-B (Jul 2020 to May 2021) for predicting sepsis for patients with septic shock diagnosis of KATE Sepsis, SIRS, standard screening, and qSOFA evaluated on 26,963 medical records with 49 septic shock diagnoses.

| Group            | AUC     | TPR     | FPR    | F1-score | Accuracy | Precision |
|------------------|---------|---------|--------|----------|----------|-----------|
|                  | (AUC)   | (TPR)   | (FPR)  | (F1-score) | (Accuracy) | (Precision) |
| **KATE Sepsis**  | 0.95959 | 0.8571  | 0.088  | 0.03415  | 0.91188  | 0.01742   |
|                  | (0.9334 - 0.9718) | (0.7592 - 0.9425) | (0.0845 - 0.0908) | (0.0255 - 0.0428) | (0.909 - 0.9153) | (0.0129 - 0.0219) |
| **SIRS**         | 0.74319 | 0.5714  | 0.085  | 0.02367  | 0.91433  | 0.01208   |
|                  | (0.6546 - 0.8112) | (0.3946 - 0.7066) | (0.0819 - 0.0881) | (0.0139 - 0.0326) | (0.9108 - 0.9177) | (0.0071 - 0.0167) |
| **Standard screening** | 0.69901 | 0.4694  | 0.0714 | 0.02308  | 0.92779  | 0.01183   |
|                  | (0.6161 - 0.7686) | (0.3017 - 0.6089) | (0.068 - 0.0745) | (0.0121 - 0.0327) | (0.9246 - 0.9309) | (0.0062 - 0.0168) |
| **qSOFA**        | 0.68652 | 0.3878  | 0.0147 | 0.0819   | 0.9842 (0.9825 - 0.9857) | 0.04578   |
|                  | (0.618 - 0.7585) | (0.25 - 0.5322) | (0.0133 - 0.0161) | (0.0487 - 0.1203) | (0.9842 - 0.9857) | (0.0266 - 0.0685) |
| Group         | AUC               | TPR               | FPR               | F1-score          | Accuracy          | Precision          |
|---------------|-------------------|-------------------|-------------------|-------------------|-------------------|--------------------|
| KATE Sepsis   | 0.97351 (0.9683 - 0.9784) | 0.8741 (0.8213 - 0.9162) | 0.0571 (0.0558 - 0.0582) | 0.03473 (0.0299 - 0.0409) | 0.94284 (0.9416 - 0.9441) | 0.01772 (0.0152 - 0.0209) |
| SIRS          | 0.71313 (0.6693 - 0.7578) | 0.4825 (0.3945 - 0.5725) | 0.0563 (0.0554 - 0.0573) | 0.0196 (0.0153 - 0.0247) | 0.9432 (0.9421 - 0.9441) | 0.01 (0.0078 - 0.0126) |
| Standard screening | 0.68084 (0.639 - 0.7188) | 0.4056 (0.3213 - 0.482) | 0.0439 (0.043 - 0.0449) | 0.02097 (0.0155 - 0.0261) | 0.95543 (0.9544 - 0.9564) | 0.01076 (0.008 - 0.0135) |
| qSOFA         | 0.67093 (0.627 - 0.7182) | 0.3566 (0.2687 - 0.451) | 0.0148 (0.0142 - 0.0155) | 0.05131 (0.037 - 0.0647) | 0.98448 (0.9837 - 0.9851) | 0.02764 (0.0199 - 0.0348) |