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The smell of sepsis: Electronic nose measurements improve early recognition of sepsis in the ED☆,☆☆

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ABSTRACT

Objective: Early recognition of sepsis is essential for timely initiation of adequate care. However, this is challenging as signs and symptoms may be absent or nonspecific. The cascade of events leading to organ failure in sepsis is characterized by immune-metabolic alterations. Volatile organic compounds (VOCs) are metabolic byproducts released in expired air. We hypothesize that measuring the VOC profile using electronic nose technology (eNose) could improve early recognition of sepsis.

Material and methods: In this cohort study, bedside eNose measurements were collected prospectively from ED patients with suspected infections. Sepsis diagnosis was retrospectively defined based on Sepsis-3 criteria. eNose sensor data were used in a discriminant analysis to evaluate the predictive performance for early sepsis recognition. The dataset was randomly split into training (67 %) and validation (33 %) subsets. The derived discriminant function from the training subset was then applied to classify new observations in the validation subset. Model performance was evaluated using receiver operating characteristic (ROC) curves and predictive values.

Results: We analyzed a total of 160 eNose measurements. The eNose measurements had an area under the ROC (AUROC) of 0.78 (95 % CI: 0.69–0.87) for diagnosing sepsis, with a sensitivity of 72 %, specificity of 73 %, and an overall accuracy of 73 %. The validation model showed an AUC of 0.83 (95 % CI: 0.71–0.94), sensitivity of 71 %, specificity of 83 %, and an accuracy of 80 %.

Conclusion: eNose measurements can identify sepsis among patients with a suspected infection at the ED.

Clinical trial registration: The study is embedded in the Acutelines data-biobank (www.acutelines.nl), registered in Clinicaltrials.gov (NCT04615065).

1. Introduction

Sepsis, a life-threatening response to an infection, is responsible for 20 % of all deaths worldwide [1]. Despite advancements in medical care, the in-hospital mortality rate remains around 25–35 % in high-income countries [2-5]. Current sepsis management involves promptly administering broad-spectrum antibiotics, ensuring source control, and providing supportive care. Early recognition and timely initiation of treatment could improve sepsis care [6-8]. However, up to 40 % of sepsis cases at the emergency department (ED) are not recognized, as signs and symptoms may be absent or nonspecific [9]. Moreover, distinguishing sepsis from an uncomplicated infection early is crucial to deliver appropriate care in a timely manner, preventing organ failure while also avoiding unnecessary use of broad-spectrum antibiotics and hospital admissions. The cascade of events leading to organ failure

Abbreviations: AUC, Area Under the Curve; COPD, Chronic Obstructive Pulmonary Disease; DKA, Diabetic ketoacidosis; eNose, electronic Nose; ED, Emergency Department; ICU, Intensive Care Unit; MOS, Metal Oxide Semiconductor; NEWS, National Early Warning Score; ROC, Receiver Operating Characteristic; SIRS, Systemic Inflammatory Response Syndrome; qSOFA, quick Sequential Organ Failure Assessment; SOFA, Sequential Organ Failure Assessment; VOC, Volatile Organic Compound.

☆ This study involved a collaboration with a commercial entity, which provided logistical support for the use of their eNose device. The company had no involvement in the funding of the study, the definition of study endpoints, data analysis, or the interpretation and formulation of the study's results and conclusions.

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in sepsis is characterized by immune-metabolic alterations [10]. Volatile organic compounds (VOCs), metabolic byproducts released in expired air, may provide critical insights. We hypothesize that using electronic nose (eNose) technology to measure the VOC profile could enhance early sepsis detection.

Although the precise pathophysiology of sepsis remains to be unraveled, mitochondrial dysfunction and alterations in cellular metabolism seem to play a key role [11-13]. Excessive production of reactive species, such as nitric oxide and reactive oxygen species, inhibits mitochondrial respiration and damages mitochondrial structures, leading to reduced ATP generation [11,14]. As a compensatory response, cells increase glycolytic activity, releasing specific VOCs in expired air. These VOCs reflect metabolic and pathophysiological changes during sepsis [15]. Studies have shown that eNose technology can measure these VOCs and has identified specific VOCs associated with particular pathogens [16], inflammation [17], and infection [18]. These findings collectively emphasize the promise of VOC analysis for early detection of sepsis.

To date, no studies have prospectively utilized eNose measurements to analyze the VOC profile for sepsis diagnosis in clinical settings. We propose that the eNose devices are suitable diagnostic tools for sepsis due to their capacity to analyze complex gas mixtures. Furthermore, the non-invasive and real-time nature of eNose measurements aligns with the practical requirements for diagnostics in emergency medicine. In this study, we aimed to use bedside eNose measurements to diagnose sepsis in the ED.

2. Study design and methods

2.1. Study design and population

For this cohort study, eNose measurements and other data were prospectively collected from patients presenting at the ED from April 2022 until April 2023 between 9 AM and 9 PM by the Acutelines research team. Acutelines is a multi-disciplinary prospective hospital-based data-biobank at the ED of the University Medical Centre Groningen (UMCG), a tertiary care teaching hospital in the Northern Netherlands. Of note, due to the health care infrastructure, the ED in In the Netherlands, general practitioners and emergency medical services are the primary sources of referrals and self-referred patients constitute the minority of ED patients. Potential participants were asked written informed consent prior to inclusion in the study. If patients were unable to provide consent themselves, then their next of kin was asked to provide consent on their behalf. The Acutelines cohort is approved by the institutional review board of the UMCG and registered under trial registration number NCT04615065 at ClinicalTrials.gov [19]. Acutelines' complete protocol and data dictionary are available via www.acutelines.nl [20]. This study is conducted in accordance with the Helsinki declaration.

2.2. Inclusion and exclusion criteria

Adult patients (≥18 years) referred to the ED for internal medicine, nephrology, geriatric medicine, oncology, hematology, pulmonology, rheumatology, gastrointestinal/liver medicine, urology, or emergency medicine (non-trauma), with a suspicion of an infection, were eligible for participation. Suspicion of infection was defined either as determined by the physician upon initial contact, based on focal symptoms suggestive of an infection [e.g. productive cough, dyspnoea, dysuria, pollakisuria, abdominal pain, erythema]) and/or fever (≥38 °C, either at home or upon triage in the ED). Patients were excluded from participation if they were pregnant or if they had one or more of the following contra-indications for use of the eNose: (suspected) pneumothorax, thoracic surgery one week prior to ED admission, vomiting, wounds in or around mouth with active bleeding, intoxication with alcohol and inability to follow instructions. Moreover, in consultation with ED physicians, it was determined not to enroll patients exhibiting signs of respiratory insufficiency (defined as a respiratory rate > 30/min, requiring oxygen supplementation >2 L/min, or invasive ventilation) due to the prioritization of patient oxygenation over research objectives and a high probability of inability to perform the measurement correctly.

2.3. eNose

Measurements were performed using a cloud-connected eNose (SpiroNose; Breathomix, Leiden, The Netherlands, Fig. 1). The SpiroNose is a validated eNose device containing seven different types of cross-reactive metal oxide semiconductor (MOS) sensors with varied particle sensitivities, facilitating comprehensive analysis of the entire gaseous mixture [21-23]. These sensors are present in duplicate in sensor arrays on both the inside of the device to measure the full mixture of VOCs in exhaled breath and on the outside of the SpiroNose, for background VOC correction. The MOS sensors measure the full VOC mixture inside and outside the device by detecting changes in metal oxide resistance due to gas adsorption. Through this technique, both ambient air and breath VOCs can be measured and differentiated. A detailed description of the SpiroNose measurement technology and breath sampling methods is provided by De Vries et al. [21,23].

2.4. Data collection

Breath profile measurements were obtained with the eNose by trained research assistants who completed the comprehensive training program outlined by Breathomix to ensure competence in data collection. Demographic and clinical data was collected by trained researchers from Acutelines and managed using REDCap [24,25]. The database is enriched by data from the electronic health records of the hospital. The eNose measurements were conducted at bedside in the ED of the UMCG by a trained researcher. Patients were breathing via a bacteria and virus filter (Pulmosafe V3/2, Lemon Medical, Germany) and performed five tidal breaths, followed by a maximum inhalation with 5 s breath hold and a slow full expiration that was finalized by a complete inhalation. Performance metrics were visualized real time at bedside in the online BreathBase analysis platform (Breathomix, Leiden, The Netherlands) which includes the secured online database of Breathomix (ISO27001 and NEN7510 certified). The presence and site of infection were post hoc determined by an expert adjudication committee as part of Acutelines, based on the Centers for Disease Control and Prevention consensus definitions [26].

2.5. Primary outcome

The primary outcome was sepsis defined as the simultaneous presence of an infection and organ failure represented by a deterioration

Fig. 1. Demonstration of SpiroNose device by Breathomix (Leiden).

of two or more Sequential Organ Failure Assessment (SOFA) points. The baseline SOFA score was determined using the most recent information from the year prior to presentation as present in our health records, which was available for 75 % of patients [27]. When no information on organ function was available the baseline SOFA score was assumed to be 0 [28].

2.6. Data analysis

All statistical analyses were performed using IBM SPSS statistics version 28 (Armonk, IBM Corp) and R Studio version 4.3.1 (Vienna; R Core Team). Prior to analysis, eNose sensor signals were pre-processed by filtering, detrending, ambient correction, peak detection and parameter selection as described by *De Vries* et al. [21-23]. From each type of sensor, two variables were determined: (1) the sensor peak normalized to the most stable sensor (S2), to reduce inter-array differences (S1, S3-S7) and (2) the ratio between the sensor peak and the breath hold (BH) point (S1BH-S7BH). Sensor peak values and ratios between peak value and breath hold were both used for analysis. The dataset was split 2:1 into a training dataset ($N = 106$; 66.2 %) and validation dataset ($N = 54$; 33.8 %) at random. Baseline characteristics were analyzed using a combination of non-parametric and parametric tests, including Student's *t*-tests for normally distributed data and Mann-Whitney *U* tests. The association between eNose measurements and sepsis was assessed using Student's t-tests and Mann-Whitney U tests. Thereafter, stepwise discriminant analysis was used to assess the classification of sepsis including cross-validation, whereafter a multivariable model was constructed with optimal discrimination between patients with and without sepsis. The classification was represented by discriminant scores derived from the discriminant analysis. A Receiver Operating Characteristic (ROC) curve was used to assess the diagnostic performance of the models. The optimal cutoff to diagnose sepsis was assessed using the Youden's J statistic, calculated using the training dataset and applied in the validation dataset. The discriminant function was utilized to classify new cases in the validation cohort. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy were determined in both the training and validation dataset respectively. We compared the AUCROC of our model to that of the national early warning score 2 (NEWS2) score, the recommended tool for sepsis recognition according to the NICE-guideline on suspected sepsis detection [29]. In subsequent stratified analyses, differences in diagnostic accuracy were assessed by generating ROC curves after stratifying the dataset into groups based on potential confounders: sex, smoking habits, pulmonary infection, COPD, diabetes mellitus, corticosteroid use and use of inhalation medication. Significant differences between ROC curves were assessed using the DeLong's test. Statistical significance was defined as $P < 0.05$ for all analyses.

3. Results

Between April 2021–2022, 1098 patients were screened at the ED for inclusion in the study of which 499 patients were eligible (Fig. 2). At bedside in the ED, eNose measurements of 199 patients were performed. There were 33 measurements of insufficient quality for analysis due to erroneous performance of the breath measurement or environmental disturbances and 9 patients retracted their consent. Therefore, 160 (83 %) measurements were analyzed. As judged by post-hoc chart review, 50 patients (31 %) had sepsis according to the sepsis-3 criteria ($N = 36$ training and $N = 14$ validation), 71 (44 %) had an infection and 39 (24 %) did not have an infection within 48 h of ED admission. The population was split 2:1 into a training ($N = 106$, 66 %) and validation ($N = 54$, 34 %) cohort at random.

The characteristics of the training and validation cohorts are shown in Table 1. Females comprised roughly half of the participants (42 % and 54 %). A minority smoked or had quit smoking in the past year (19 % and 20 %). The site of infection in both the training and validation cohort was mainly pulmonary (40 % and 28 %), followed by urogenital (10 % and 17 %) and abdominal (8 % and 6 %). In total six patients (4 %) were admitted to the ICU within 72 h, and nine patients (6 %) died within 30 days. The ICU admission and 30-day mortality rate did not differ significantly between the training and validation cohort.

Within the cohorts, patients with sepsis were on average older in both the training and validation cohort (*Training;* median 65 vs. 61 years; $P = 0.23$), more frequently had diabetes mellitus (*Training;* 33 % vs. 13 %; $P = 0.01$), and had a higher median SOFA score upon presentation to the ED (*Training;* median 3 vs. 1; $P < 0.001$). There were no significant differences in the presence of other comorbidities, the use of corticosteroid medication or inhalation medication in either cohort.

3.1. eNose analysis

To determine whether eNose measurements can identify sepsis, we first performed a discriminant analysis using the training cohort. First, individual Students *t*-tests and Mann Whitney *U* tests were used to determine possible significant associations of eNose variables with sepsis (eTable 1). In stepwise discriminant analysis variables S1BH, S2BH, S3BH and S7BH were included in the discriminant model (eTable 2). The discriminant model correctly classified 72.6 % of cases and 69.8 % of cases in cross validation. The training model showed an area under the curve (AUC) of 0.78 (95 % CI: 0.69–0.87). Using Youden's index, the optimal performance of the model was identified with a cut-off for a positive test set at ≤ −0.18. This resulted in a sensitivity of 72 %, specificity of 73 %, positive predictive value (PPV) of 58 %, negative predictive value (NPV) of 84 %, and an overall accuracy of 73 % (Table 2, Fig. 3). The coefficients for the discriminant score were extracted to create the discriminant score equation:

$$\text{Discriminant score} = \text{S1BH} \times 1.582 + \text{S2BH} \times -4.914 + \text{S3BH} \times 4.806 + \text{S7BH} \times 1.866 - 1.565$$

Next, discriminant scores for the validation cohort were computed using the coefficients derived from the training cohort. The previously established cut-off of ≤ −0.18 was then applied to evaluate the diagnostic accuracy of the discriminant scores derived from the validation cohort. The validation model showed an AUC of 0.83 (95 % CI: 0.71–0.83), sensitivity of 71 %, specificity of 83 %, PPV of 59 %, NPV of 89 %, and an accuracy of 80 %.

3.2. Comparison to NEWS2 score

NEWS2 scores significantly differed between sepsis and non-sepsis groups ($P = 0.03$). NEWS2 achieved a cross-validation accuracy of 66 % and an AUC of 0.55 (95 % CI, 0.44–0.68) in discriminant analysis. Which was significantly different compared to the training dataset (DeLong's *P* value = 0.004; eFig. 1).

3.3. Sensitivity analysis

To obtain insight in the diagnostic performance of the eNose to recognize sepsis among different subsets of patients, we calculated the diagnostic performance in stratified analysis based on sex, smoking, site of infection, diabetes mellitus, COPD, corticosteroid use and use of inhalation medication (Table 3, eFig. 2). The performance of eNose measurements to diagnose sepsis is different in patients with COPD (AUC 1.00 [1.00–1.00]) as compared to patients without COPD (AUC 0.74 [0.63–0.85]; DeLong's $P < 0.001$) as determined by a significant DeLong's test. The VOC prediction model showed a decrease in AUC for subgroups with pulmonary infection and diabetes; however, the DeLong's test yielded non-significant *p*-values, indicating that these decreases were not statistically significant. No participants with diabetic ketoacidosis (DKA) were included (eTable 3). Consequently, while this

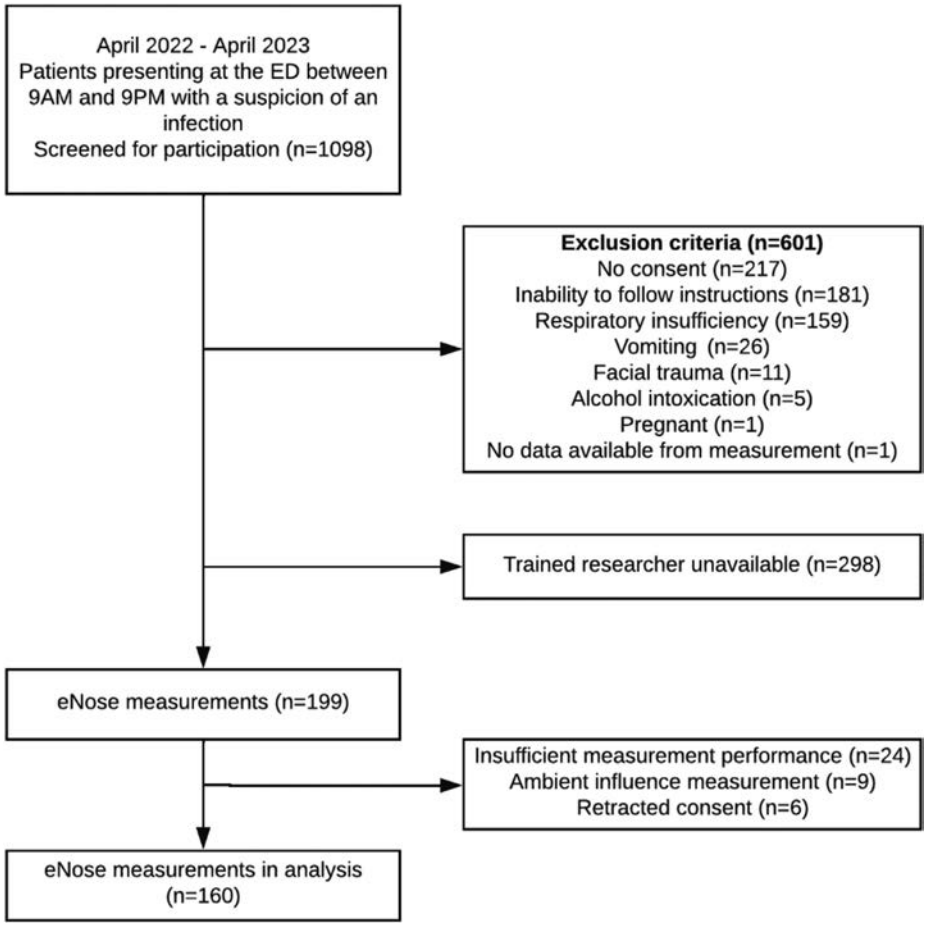

Fig. 2. Flowchart of patient selection.

study does not provide sufficient evidence to conclude that model performance is significantly affected by diabetes or pulmonary infection, further research is needed to fully understand their on VOC measurements.

4. Discussion

In this proof-of-concept study, we demonstrated that eNose measurements can accurately identify sepsis among patients with a suspected infection in the ED with an AUC of 0.78 (validation cohort: AUC 0.83), a sensitivity of 72 % and a specificity of 73 %. Our study specifically focused on patients suspected of having an infection who were not obviously septic, with the overarching aim to enhance early sepsis recognition. We demonstrated that this device can detect differences that may not be apparent through traditional clinical assessments and scoring systems. Notably, our predictive model demonstrated significantly better performance compared to the NEWS2 score (AUC 0.55; DeLong's $P = 0.004$), indicating that our approach may enhance early detection of sepsis in an ED population with suspected infection. The diagnostic accuracy was consistent regardless of sex, smoking habits, pulmonary site of infection, or use of inhalation medication or corticosteroids. To the best of our knowledge, this is the first study to explore the use of an eNose device for early sepsis detection at the bedside in the ED. Our findings demonstrate that measurement of the VOC profile, which reflects changes in cellular metabolism, can differentiate sepsis from an uncomplicated infection upon first clinical presentation. Not only are these findings of relevance to improve early recognition of sepsis, but also support the role of metabolic changes in early sepsis leading to organ failure.

The SOFA score is currently the gold standard for diagnosing sepsis. However, it is not ideally suited for use in the ED because it depends on changes in the SOFA score over 48 h after ED admission, which requires baseline values that may be unavailable or confounded by co-morbidity [30-32]. Alternative scoring systems such as the quick SOFA (qSOFA) score, systemic inflammatory response syndrome (SIRS) and NEWS2 are practically more useful for the ED [33], as the vital parameters and the few lab values it contains are routinely measured. Yet, their diagnostic accuracy in the early phase is insufficient to differentiate sepsis from infection and safely support clinical decision making [34,35]. For instance, the qSOFA is designed to facilitate sepsis and severe outcome screening rather than provide a definitive diagnosis [36]. Also, while prior studies reported good predictive value of the NEWS2 for severe sepsis and septic shock (AUC 0.78–0.81), identifying sepsis in the early phase decreases performance of the NEWS2 score significantly (AUC 0.55, DeLong's $P = 0.004$). These findings suggest that current screening tools may not be sufficient to detect early-stage sepsis in the ED, when cardinal signs of an infection are absent and vital parameters may be normal [9,37]. Incorporating our approach into a decision support tool could enhance the early detection of sepsis in patients with suspected infections.

Metabolic disturbances due to mitochondrial dysfunction seem to play an important role in the processes leading to organ failure and sepsis in patients with an infection [10]. VOCs, as metabolic byproducts, reflect both host and pathogen metabolism [16]. These VOCs are dissolved in the blood and can diffuse into the lung alveoli where they are exhaled into the breath. Previous animal and clinical studies have shown specific VOCs to be affected by inflammation, infection and sepsis [15-18,38,39]. Specifically for sepsis, the VOCs profile reflects the altered fatty acid and

Table 1
Baseline characteristics of the training and validation cohorts stratified by sepsis. $P < 0.05$ is shown in bold. Normally distributed data is shown as mean (SD), non-normally distributed data is shown as median [IQR], observations of cases is shown as n (%). BMI Body Mass Index, COPD Chronic Obstructive Pulmonary Disease, MAP Mean Arterial Pressure, GCS Glasgow Coma Scale, SOFA Sequential Organ Failure Assessment, NEWS National Early Warning Score, ICU Intensive Care Unit.

	Training dataset ($N = 106$)			Validation dataset (M = 54)		
	Suspected infection $N = 70$	Sepsis N = 36	P-value	Suspected infection $N = 40$	Sepsis $N = 14$	P-value
Baseline characteristics						
Age	61 [45–69]	65 [57–69]	0.23	50 [33–67]	68 [65–74]	0.04
Sex, Female	29 (41)	15 (42)	0.98	20 (50)	9 (64)	0.36
BMI	25 [21–28]	26 [24–29]	0.47	26 [22–28]	26 [24–30]	0.48
Smoker*	15 (21)	5 (14)	0.35	9 (23)	2 (14)	0.51
Comorbidities N (%)						
Diabetes Mellitus	9 (13)	12 (33)	0.01	1 (3)	7 (50)	<0.001
Cardiovascular illness	14 (20)	10 (28)	0.37	10 (25)	7 (50)	0.08
COPD	11 (16)	5 (14)	0.80	2 (20)	3 (21)	0.91
Malignancy	31 (44)	14 (39)	0.59	9 (23)	6 (43)	0.14
Transplant history	15 (21)	12 (33)	0.18	6 (15)	3 (21)	0.58
Medication N (%)						
Oral corticosteroids	15 (23)	12 (35)	0.20	14 (38)	5 (36)	0.89
Inhalation medication	13 (19)	7 (21)	0.80	11 (28)	3 (21)	0.62
Presentation ED						
Heart frequency	100 (19)	101 (17)	0.75	99 (15)	92 (16)	0.15
MAP	95.2 (15.3)	91.3 (14.8)	0.22	96.4 (13.9)	90.2 (24.8)	0.24
Temperature	98.8 [98.2–99.7]	99.5 [98.6–100.6]	0.14	99.0 [98.4–100.4]	99.0 [98.4–99.9	0.72
GCS <15	0	3 (8)	0.01	0	0	
Respiratory rate	19 [17–23]	19 [17–24]	0.88	18 [14–22]	22 [18–24]	0.07
O2 suppletion	2 (3)	5 (14)	0.03	1 (3)	3 (21)	0.02
SOFA score ED	1 [0–2]	3 [2–4]	<0.001	1 [0–2]	4 [3–4]	<0.001
NEWS2 score ED	2 [1–4]	3 [1–5]	0.32	2 [1–3]	4 [2–5]	0.02
Laboratory values ED						
Hb (g/dL)	12.3 (2.3)	12.2 (2.3)	0.79	12.2 (2.3)	11.1 (2.4)	0.14
Leukocytes (x 10^3 L)	9.1 [5.8–13.0]	7.1 [3.8–10.7]	0.03	7.1 [3.8–10.7]	8.1 [5.7–14.2]	0.24
CRP mg/dL	6.6 [1.8–13.7]	8.9 [5.2–22.3]	0.02	8.9 [5.2–22.3]	11.3 [3.2–18.7]	0.03
Lactate (mmol/L)	1.4 [1.1–2.0]	1.3 [0.9–1.6]	0.18	1.3 [0.9–1.6]	1.4 [1.1–2.3]	0.44
Diagnosis ED						
Pulmonary infection	23 (33)	19 (53)		9 (23)	6 (43)	
Urogenital infection	8 (11)	3 (8)		7 (18)	2 (14)	
Abdominal infection	3 (4)	6 (17)		1 (3)	2 (14)	
Infection other	11 (16)			9 (23)		
Cardiovascular disease[1]	4 (6)			2 (5)		
Respiratory disease[2]	2 (3)			3 (8)		
GI disease[3]	4 (6)			3 (8)		
Generalized pain[4]	3 (4)			1 (3)		
Other non-infection[5]	12 (17)			5 (13)		
Outcome						
ICU admission <72 h	1 (1)	1 (3)	0.63	4 (10)	0	0.22
Length of hospital stay	4 [2–6]	5 [3–6]	0.41	4 [2–5]	5 [4–12]	0.09
30-day mortality	3 (4)	3 (8)	0.39	2 (5)	1 (7)	0.76

* Smoker; Self-reported current tobacco or e-cigarette users, including recent ex-smokers (<1 year).
[1] Pericarditis carcinomatosis (N = 2), auto-immune-mediated hemolysis (N = 1), vasovagal collapse(N = 1), atrial fibrillation with decompensated heart failure(N = 1), dyspnea with cardiac disease ($N = 2$).
[2] Pulmonary embolism (N = 2), stent-related dyspnea status after lung transplantation ($N = 1$), COPD exacerbation (N = 1), dyspnea eci (N = 1).
[3] Gastrointestinal bleeding (N = 1), varices (N = 1), abdominal pain without alarm symptoms (N = 1), inflammatory bowel disease (N = 1), proctitis (N = 1), rectal bleeding (N = 1), obstipation (N = 1).
[4] Generalized pain episode eci (N = 1), chest pain without alarm symptoms (N = 2), shoulder pain (N = 1).
[5] Medication-induced (N = 3), endocrine (N = 2), allergic reaction (N = 2), progression malignancy (N = 4), nephrolithiasis (N = 1), fever eci (N = 1), IgA nephropathy(N = 1), gout (N = 1), anemia (N = 1), M.femoralis weakness (N = 1).

protein metabolism [40,41]. However, VOCs are also affected by pathological states other than sepsis, such as hemorrhagic shock or diabetes [42-44]. We observed a non-statistically significant diminished performance of the eNose model in detecting sepsis in patients with diabetes. Impaired performance was hypothesized due to the increased fatty acid metabolism and glycolysis that are characteristic of both

Table 2
Performance diagnostic eNose model stratified by training (67 %) and validation (33 %) cohort. Discriminant analysis on the preprocessed sensor data from the 13 eNose sensors, of which a set of four sensors showed best discriminatory performance (S1BH, S2BH, S3BH, S7BH). Cut-off was based on Youden's J index and validated. Area under the curve (AUC) with corresponding 95 % CI are provided. AUC, area under the curve; PPV, positive predictive value; NPV, negative predictive value.

	Cut-off*	AUC (95 % CI)	Sensitivity (95 % CI)	Specificity (95 % CI)	PPV (95 % CI)	NPV (95 % CI)	Accuracy (95 % CI)
Model training	−0.18	0.78 (0.69–0.87)	72 (55–86)	73 (61–83)	58 (47–68)	84 (75–90)	73 (63–81)
Model validation	−0.18	0.83 (0.71–0.94)	71 (42–93)	83 (67–93)	59 (40–75)	89 (78–95)	80 (66–89)

* Positive test if discrimination score from S1BH, S2BH, S3BH and S7BH ≤ −0.1781751.

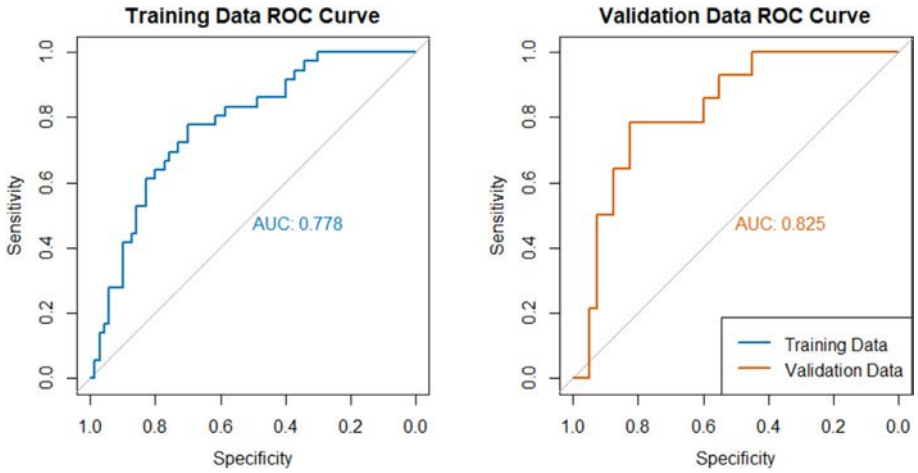

Fig. 3. eNose AUROC for diagnosing sepsis.

sepsis and diabetes [44-46]. This effect was not observed in our study, potentially due to the small sample size, and may become more evident in the presence of DKA, which none of the patients in this study exhibited. To accurately capture the complex and heterogeneous alterations in cellular respiration during sepsis, a comprehensive VOC profile is essential. The eNose utilized in this study was equipped with cross-reactive, nonspecific sensor arrays, enabling multiple VOCs to bind to the same sensor. This approach generated a sensor-activation pattern based on the entire mixture of VOCs present in exhaled air. By focusing on these collective VOC patterns, we can encompass the multifaceted nature of sepsis, effectively identifying it as a volatile biomarker.

Timely and accurate recognition of sepsis is vital to allow timely initiation of adequate treatment tailored to the individual's needs, which could benefit not only the patient but also have broader societal implications [7,8,47,48]. First, the incidence of sepsis is rising, placing a heightened burden on the healthcare system [49-51]. Early recognition of sepsis could decrease time at the ED [52], aiding patient flow from the ED to designated care destinations [53,54], and reduce health care costs [55]. Second, precise discrimination of non-septic cases is equally important to prevent unnecessary hospitalization and antibiotic use. Effective antimicrobial stewardship is essential, since misuse and overuse of antimicrobials are the main drivers in the development of drug resistant pathogens [56]. Antimicrobial resistance is one of the top global public health threats [56]. Last, we speculate that the eNose could advance precision medicine for sepsis by measuring VOC profiles indicative of metabolic -sub-phenotypes that could benefit from specific, targeted treatments that mitigate metabolic disturbances and potentially prevent organ failure.

Our study is the first to use the eNose as a dynamic bedside diagnostic tool, which provokes interest about its feasibility and relevance in less controlled environments. In this study, after a relatively brief training program, the technical feasibility of the eNose measurements was 84 %. The primary challenge faced was insufficient measurement quality due to insufficient performance. When a diagnostic test requires active patient participation, the patient's ability to perform the required actions becomes a limiting factor. Although experience in coaching breath measurements can enhance patient performance, this limitation is inherent and will persist to some extent. Despite this challenge, our study demonstrated that screening at-risk populations in the ED is feasible. Extending this screening approach beyond the hospital—through emergency medical services or general practitioners—also appears to be a promising prospect. Currently, efforts are made to integrate eNose technology into ventilatory devises [57], thereby making it possible to not only conduct these measurements in severely ill patients, but also to build a reference database to assess the VOC fingerprint of septic patients.

Potential limitations constitute its single-center design in a tertiary care hospital with a referral of patients for academic specialist care, potentially limiting generalizability. Yet our hospital has a substantial geographical spread in a rural area, ensuring a diverse population in need of either academic (tertiary) or non-academic (secondary) hospital acute care. Our emergency department's unique

Table 3
Diagnostic performance stratified by possible confounders in the training dataset. COPD, chronic obstructive pulmonary disease.

Stratification	N (%*)	AUC (95 % CI)	P-value ROC	DeLong's test *P*-value
Male	62 (58)	0.77 (0.65–0.89)	<0.001	0.93
Female	44 (42)	0.77 (0.64–0.92)	<0.001	
Pulmonary infection	42 (40)	0.66 (0.49–0.83)	0.06	0.06
Extrapulmonary infection	64 (60)	0.85 (0.75–0.96)	<0.001	
Diabetes Mellitus	21 (20)	0.57 (0.29–0.85)	0.59	0.10
No diabetes mellitus	85 (80)	0.83 (0.74–0.92)	<0.001	
Smoker[c]	20 (19)	0.85 (0.68–1.00)	<0.001	0.32
Non-smoker	86 (81)	0.75 (0.65–0.86)	<0.001	
Inhalation medication use	20 (20)	0.87 (0.70–1.00)	<0.001	0.23
No inhalation medication use	81 (80)	0.74 (0.63–0.86)	<0.001	
Oral corticosteroid use	27 (27)	0.87 (0.74–1.00)	<0.001	0.13
No oral corticosteroid use	72 (73)	0.73 (0.61–0.85)	<0.001	
COPD	16 (15)	1.00 (1.00–1.00)	<0.001	<0.001
No COPD	90 (85)	0.74 (0.63–0.84)	<0.001	

* Valid percentage in case of missing variables.
[c] Self-reported current tobacco or e-cigarette users, including recent ex-smokers (<1 year).

infrastructure, as outlined in the Acutelines protocol [19,20], allows us to work with a relatively unbiased ED patient population. However, surgical patients were not screened for this study, which may limit the generalizability of our findings to post-operative sepsis. Yet, the majority of patients with community-acquired sepsis are referred to the medical specializations participating in Acutelines (e.g., internal medicine, rheumatology, pulmonology, gastroenterology, emergency medicine, urology). While the study had sufficient power to assess the primary study aim, whether eNose can enhance the early recognition of sepsis, the smaller sample sizes of the sub analyses have a lower statistical power and therefore, these findings should be considered exploratory. Lastly, patients who were unable to perform the eNose measurement were not included in the study. This exclusion criterion specifically targeted patients exhibiting signs of neurological or respiratory organ failure as defined by the SOFA criteria by excluding patients with signs of respiratory insufficiency and neurological impairment. It is important to note that these exclusion factors are integral components of various early warning scores, including the NEWS, MEWS, and qSOFA, indicating that these patients are readily identifiable as high-risk for developing sepsis.

5. Conclusion

Our study demonstrates the potential of eNose technology in identifying sepsis in patients presenting to the emergency department with a suspected infection based on VOC measurement at the bedside. Our predictive model demonstrated superior performance compared to current sepsis screening tools, indicating that our approach may enhance early detection of sepsis at the bedside in an ED population with suspected infection. Further research is warranted to explore the broader applicability of eNose technology in identifying sepsis across diverse patient populations and different clinical settings.

CRediT authorship contribution statement

T.J. van der Aart: Conceptualization, Methodology, Software, Formal analysis, Investigation, Writing – original draft, Visualization, Project administration. **M. Visser:** Methodology, Investigation, Writing – review & editing. **M. van Londen:** Validation, Writing – review & editing, Supervision. **K.M.H. van de Wetering:** Investigation, Writing – review & editing. **J.C. Ter Maaten:** Methodology, Data curation, Writing – review & editing, Supervision. **H.R. Bouma:** Conceptualization, Methodology, Software, Validation, Data curation, Writing – review & editing, Supervision, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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